PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 C.F.R. §1.53(c).

INVENTOR(S)		
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Additional inventors are being named on the 0 separately numbered sheets attached hereto

TITLE OF THE INVENTION (500 characters max)

CYCLOPROPANE COMPOUNDS

CORRESPONDENCE ADDRESS

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☒ Customer Number: **26211**

OR

☐ Firm *or* Individual Name					
Address					
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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Application Data Sheet.	See 37 C.F.R. § 1.76.	☐ CD(s), Number
☒ Specification	*Number of Pages* ***198***	☐ Other (specify):
☐ Drawing(s)	*Number of Sheets* _____	

Application Size Fee: If the specification and drawings exceed 100 sheets of paper, the application size fee due is $270 ($135 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. § 41(a)(1)(G) and 37 C.F.R § 1.16(s)

METHOD OF PAYMENT OF FILING FEES AND APPLICATION SIZE FEE FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant Claims small entity status. See 37 C.F.R.§ 1.27.

☐ A check or money order is enclosed to cover the filing fees.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Director is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number 06-1050 A copy of this form is enclosed for fee processing.

TOTAL FEE AMOUNT ($)

$490.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

_____

Respectfully submitted,

Signature: _____ Date: September 22, 2010

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Docket No: 25724-0005P01 / W5545-01

Date of Deposit: _____

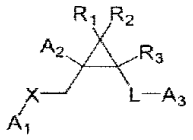
30565266.doc

Cyclopropane Compounds

シクロプロパン化合物

【書類名】明細書
【発明の名称】シクロプロパン化合物
【技術分野】
【０００１】
本発明は、オレキシン受容体拮抗作用を有する、シクロプロパン化合物又はその医薬上許容される塩及びその医薬用途に関するものである。更に詳細には、オレキシン受容体拮抗作用による不眠症等の睡眠異常の治療に有効なシクロプロパン化合物及びそれを有効成分として含有する医薬組成物に関する。
【背景技術】
【０００２】
脳視床下部に局在する２種の脳内神経ペプチド、オレキシンＡ（ＯＸ－Ａ，３３個のアミノ酸ペプチド）及びオレキシンＢ（ＯＸ－Ｂ，２８個のアミノ酸ペプチド）は、主として脳内に存在するＧタンパク質共役型受容体、即ちオレキシン受容体（特許文献１－４）の内在性リガンドとして発見された（特許文献５、非特許文献１）。オレキシン受容体には、２種のサブタイプ、１型サブタイプであるOX_1受容体（ＯＸ１）及び２型サブタイプであるOX_2受容体（ＯＸ２）が存在することが知られている。ＯＸ１はＯＸ－Ａに選択的であり、ＯＸ２はＯＸ－Ｂと同様にＯＸ－Ａも結合することができる。オレキシンは、ラットの食物消費を刺激することが見出されており、摂食行動を調節する中枢フィードバック機構における、これらペプチドのメディエーターとしての生理学的役割が示唆されている（非特許文献１）。一方、また、オレキシンが睡眠覚醒状態を調節することが観察され、不眠症および他の睡眠障害と同様にナルコレプシーへの潜在的に目新しい治療のアプローチを開くと考えられる（非特許文献２）。更に、麻薬依存症及びニコチン依存症に関連している神経可塑性における腹側被蓋領域でのオレキシンシグナルが生体内で重要な役割を果たしていることが示唆されている（非特許文献３；非特許文献４）。更に、オレキシンシグナルは、うつ病と不安症に関係であるCRF（corticotropin-releasing factor）シグナルと相互作用し、及びストレスの影響のため、オレキシンmRNAの発現が増加することが知られている（非特許文献５）。
したがって、オレキシン受容体は、気分変調、気分、精神病や不安障害などの疾患；糖尿病、食欲不振や、味覚、摂食、飲酒などにおける障害；視床下部疾患；不眠症；生物学的な概日リズム障害；神経学的疾患、神経因性疼痛、むずむず脚症候群などの疾患に関連した睡眠障害；精神疾患に関連した不眠症；睡眠時無呼吸症；ナルコレプシー；特発性不眠症；睡眠時随伴症；麻薬依存症；ニコチン依存症；うつ病、双極性障害；不安障害；前立腺肥大症；健常人、精神や神経疾患患者、オレキシン系機能障害に関連した他の疾患患者などの認知症や認知機能障害等において多くの病理学的意義を持つものとされている。
最近では、オレキシン受容体アンタゴニストとして機能する化合物である（２Ｒ）－２－｛（１Ｓ）－６，７－ジメトキシ－１－［２－（４－トリフルオロメチル－フェニル）－エチル］－３，４－ジヒドロ－１Ｈ－イソキノリン－２－イル｝－Ｎ－メチル－２－フェニル－アセトアミドが不眠症治療薬として臨床開発されている（特許文献６）。この化合物は、ラットにおいて、目覚めと歩行での機能低下で特徴付けられる覚醒低下を示し、また、レム睡眠およびノンレム睡眠時間の両者を用量依存的に上昇させることが示されている（非特許文献６）。更には、この化合物は、モデルラットの記憶機能を向上させ（特許文献７）、心的外傷後のストレス障害に有効である（特許文献８）も示されている。
【先行技術文献】
【特許文献】
【０００３】
【特許文献１】国際公開第１９９６／３４８７７号パンフレット
【特許文献２】特開平１０－３２７８８８号公報
【特許文献３】特開平１０－３２７８８９号公報
【特許文献４】特開平１１－１７８５８８号公報
【特許文献５】特開平１０－２２９８８７号公報

【特許文献６】国際公開第２００５／１１８５４８号パンフレット
【特許文献７】国際公開第２００７／１０５１７７号パンフレット
【特許文献８】国際公開第２００９／０４７７２３号パンフレット
【非特許文献】
【０００４】
【非特許文献１】Ｓａｋｕｒａｉ　Ｔ．ｅｔ　ａｌ．，Ｃｅｌｌ，１９９８，９２，５７３－５８５
【非特許文献２】Ｃｈｅｍｅｌｌｉ　Ｒ．Ｍ．ｅｔ　ａｌ，Ｃｅｌｌ，１９９９，９８，４３７－４５１
【非特許文献３】Ｓ．Ｌ．Ｂｏｒｇｌａｎｄ　ｅｔ　ａｌ．Ｎｅｕｒｏｎ，２００６，４９，５８９－６０１
【非特許文献４】Ｃ．Ｊ．Ｗｉｎｒｏｗ　ｅｔ　ａｌ．Ｎｅｕｒｏｐｈａｒｍａｃｏｌｏｇｙ，２０１０，５８，１８５－１９４
【非特許文献５】Ｔ．Ｉｄａ　ｅｔ　ａｌ．Ｂｉｏｃｈｅｍｉｃａｌ　ａｎｄ　Ｂｉｏｐｈｙｓｉｃａｌ　Ｒｅｓｅａｒｃｈ　Ｃｏｍｍｕｎｉｃａｔｉｏｎｓ，２０００，２７０，３１８－３２３
【非特許文献６】Ｆ．Ｊｅｎｃｋ　ｅｔ　ａｌ．，Ｎａｔｕｒｅ　Ｍｅｄｉｃｉｎｅ　２００７，１３，１５０－１５５
【発明の概要】
【発明が解決しようとする課題】
【０００５】
本発明の課題は、オレキシン受容体拮抗作用を有し、オレキシン受容体に起因する、不眠症に代表される睡眠異常の治療剤として有用なシクロプロパン化合物及びその医薬用途を提供することにある。
【課題を解決するための手段】
【０００６】
本発明は、
［１］式（Ｉ）：
【化１】



（Ｉ）

［式中、
A_1はそれぞれ置換基群αから選択される１乃至３個の置換基を有していてもよいピリミジニル基又はＮ－オキシドピリミジニル基であり、
A_2及びA_3は独立して置換基群αから選択される１乃至３個の置換基を有していてもよいグループ１から選択されるアリール基、又は置換基群βから選択される１乃至３個の置換基を有してもよいグループ３から選択される複素環基であり、
R_1、R_2及びR_3は独立して水素原子、ハロゲン原子、置換基群βから選択される１ないし３の置換基を有してもよいC_{1-6}アルキル基又は置換基群βから選択される１ないし３の置換基を有してもよいC_{3-8}シクロアルキル基であり、
Ｘは、酸素原子、C_{1-6}アルキレン基、式－NR_4－（式中、R_4は水素原子又はC_{1-6}アルキル基である。）、－Ｓ－、－ＳＯ－又は－SO_2－であり、
Ｌは、結合又は式－ＣＯNR_5－（R_5は水素原子、C_{1-6}アルキル基又はC_{3-8}アルキル基である。）である。
置換基群α：シアノ基、ハロゲン原子、水酸基、オキソ基、式－NR_6R_7（式中、R_6およびR_7は独立して水素原子又はC_{1-6}アルキル基である。）、置換基群βから選択される１乃至３個の置換基を有していてもよいC_{1-5}アルキル基、置換基群βから選

択される１乃至３個の置換基を有していてもよいC_{1-6}アルコキシ基、置換基群βから選択される１乃至３個の置換基を有していてもよいC_{1-6}アルキルカルボニル基、置換基群βから選択される１乃至３個の置換基を有していてもよいC_{1-6}アルキルスルホニル基、置換基群βから選択される１乃至３個の置換基を有していてもよいグループ１から選択されるアリール基及び置換基群βから選択される１乃至３個の置換基を有していてもよいグループ２から選択されるヘテロアリール基。

置換基群β：シアノ基、ハロゲン原子、水酸基、C_{3-8}シクロアルキル基及びC_{1-6}アルコキシ基。

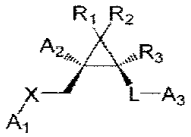
グループ１：フェニル基、ナフチル基、アズレニル基、アントリル基及びフェナントリル基。

グループ２：フリル基、チエニル基、ピロリル基、イミダゾリル基、トリアゾリル基、テトラゾリル基、チアゾリル基、ピラゾリル基、オキサゾリル基、イソオキサゾリル基、イソチアゾリル基、フラザニル基、チアジアゾリル基、オキサジアゾリル基、ピリジル基、ピラジニル基、ピリダジニル基、トリアジニル基、インドリル基、イソインドリル基、インダゾリル基、ベンゾオキサゾリル基、ベンゾイソオキサジアゾリル基、ベンゾチアゾリル基、ベンゾイソチアゾリル基、キノリル基及びイソキノリル基。

グループ３：フリル基、チエニル基、ピロリル基、イミダゾリル基、トリアゾリル基、テトラゾリル基、チアゾリル基、ピラゾリル基、オキサゾリル基、イソオキサゾリル基、イソチアゾリル基、フラザニル基、チアジアゾリル基、オキサジアゾリル基、ピリジル基、ピラジニル基、ピリダジニル基、ピリミジニル基、トリアジニル基、２－ピリドニル基、４－ピリドニル基、ピリダジドニル基、ピリミジドニル基、プリニル基、プテリジニル基、キノリル基、イソキノリル基、ナフチリジル基、キノキサリル基、シンノリル基、キナゾリル基、フタラジル基、イミダゾピリジル基、イミダゾチアゾリル基、イミダゾオキサゾリル基、ベンゾイミダゾリル基、インドリル基、イソインドリル基、インダゾリル基、ピロロピリジル基、チエノピリジル基、フロピリジル基、ベンゾオキサゾリル基、ベンゾイソオキサジアゾリル基、ベンゾチアゾリル基、ベンゾイソチアゾリル基、ピリドピリミジニル基、オキソジヒドロピリドピリミジニル基、ベンゾフリル基、ベンゾチエニル基、ベンゾチアジアゾリル基、ベンゾ［１，３］ジオキソリル基、チエノフリル基、ジヒドロイソベンゾフラニル基、クロマニル基、イソクロマニル基、１，３－ジオキサインダニル基、１，４－ジオキサテトラリニル基及びジヒドロベンゾ［１，４］オキサジニル基。］で示される化合物又はその医薬上許容される塩；

［２］式（ＩＩ）：

【化２】



（ＩＩ）

［式中、A_1、A_2、A_3、R_1、R_2、R_3、Ｘ及びＬは請求項１に記載の定義と同義である。］で示される上記［１］記載の化合物又はその医薬上許容される塩；

［３］R_1、R_2及びR_3が水素原子である、上記［１］又は［２］に記載の化合物又はその医薬上許容される塩；

［４］Ｌが式－ＣＯＮＨ－である、上記［３］に記載の化合物又はその医薬上許容される塩；

［５］Ｘが酸素原子である、上記［４］に記載の化合物又はその医薬上許容される塩；

［６］A_2及びA_3は独立して、それぞれシアノ基、ハロゲン原子、C_{1-6}アルキル基、ハロC_{1-6}アルキル基及びC_{1-6}アルコキシ基から選択される１乃至３個の置換基を有していてもよい、アリール基又はヘテロアリール基である、上記［５］に記載の化合物又はその医薬上許容される塩；

［７］A_2及びA_3は独立して、それぞれシアノ基、ハロゲン原子、C_{1-6}アルキル基

、ハロC_{1-6}アルキル基及びC_{1-6}アルコキシ基から選択される１乃至３個の置換基を有していてもよい、フェニル基、ナフチル基、ピリジル基、ピラジニル基、ピリダジニル基、ピリミジニル基、キノリル基又はイソキノリル基である、上記［６］に記載の化合物又はその医薬上許容される塩；
［８］A_2がシアノ基、ハロゲン原子、C_{1-6}アルキル基、ハロC_{1-6}アルキル基及びC_{1-6}アルコキシ基から選択される１乃至３個の置換基を有していてもよいフェニル基である、上記［７］に記載の化合物又はその医薬上許容される塩；
［９］A_3がシアノ基、ハロゲン原子、水酸基、C_{1-6}アルキル基、ハロC_{1-6}アルキル基及びC_{1-6}アルコキシ基から選択される１乃至３個の置換基を有していてもよいフェニル基又はピリジル基である、上記［８］に記載の化合物又はその医薬上許容される塩；
［１０］A_1がハロゲン原子、C_{1-6}アルキル基、ハロC_{1-6}アルキル基、C_{1-6}アルコキシ基C_{1-6}アルキル基、C_{3-8}シクロアルキル基及びC_{1-6}アルコキシ基から選択される１乃至３個の置換基を有していてもよい５－ピリミジニル基である、上記［９］に記載の化合物又はその医薬上許容される塩；
［１１］A_1がメチル基、ヒドロキシメチル基、メトキシメチル基及びメトキシエチル基から選択される１乃至２個の置換基を有していてもよい５－ピリミジニル基である、上記［１０］に記載の化合物又はその医薬上許容される塩；
［１２］以下の化合物から選ばれる、上記［１］乃至［１１］の何れかに記載の化合物又はその医薬上許容される塩：
１）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド、
２）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド、
３）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロ－４－メチルピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
４）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド、
５）　（１Ｒ，２Ｓ）－Ｎ－（６－フルオロピリジン－３－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
６）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（６－フルオロ－５－メチルピリジン－３－イル）－２－フェニルシクロプロパンカルボキサミド、
７）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－メトキシピリジン－３－イル）－２－フェニルシクロプロパンカルボキサミド、
８）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ，２－ジフェニルシクロプロパンカルボキサミド、
９）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－メチルピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド、
１０）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－［５－フルオロ－４－（メトキシメチル）ピリジン－２－イル］－２－フェニルシクロプロパンカルボキサミド、
１１）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（２－メトキシピリジン－４－イル）－２－フェニルシクロプロパンカルボキサミド、
１２）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－

２－フェニル－Ｎ－［５－（トリフルオロメチル）ピリジン－２－イル］シクロプロパンカルボキサミド、
１３）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニル－Ｎ－［４－（トリフルオロメチル）ピリジン－２－イル］シクロプロパンカルボキサミド、
１４）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－［４－（メトキシメチル）ピリジン－２－イル］－２－フェニルシクロプロパンカルボキサミド、
１５）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
１６）　（１Ｒ，２Ｓ）－Ｎ－［３－（ジメチルアミノ）フェニル］－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
１７）　（１Ｒ，２Ｓ）－Ｎ－（３－クロロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
１８）　（１Ｒ，２Ｓ）－Ｎ－（３－シアノ－４－フルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
１９）　（１Ｒ，２Ｓ）－Ｎ－（４－クロロ－３－シアノフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
２０）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－［３－（メチルスルフォニル）フェニル］－２－フェニルシクロプロパンカルボキサミド、
２１）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
２２）　（１Ｒ，２Ｓ）－Ｎ－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
２３）　（１Ｒ，２Ｓ）－Ｎ－（３－クロロ－４－フルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
２４）　（１Ｒ，２Ｓ）－Ｎ－（３－シアノ－５－フルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
２５）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（３－メトキシフェニル）－２－フェニルシクロプロパンカルボキサミド、
２６）　（１Ｒ，２Ｓ）－Ｎ－［３－（シアノメチル）フェニル］－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
２７）　（１Ｒ，２Ｓ）－Ｎ－（２－シアノピリジン－４－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
２８）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニル－Ｎ－［３－（トリフルオロメチル）フェニル］シクロプロパンカルボキサミド、
２９）　（１Ｒ，２Ｓ）－Ｎ－（４－シアノピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサ

ミド、
３０）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（４－メトキシピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド、
３１）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
３２）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
３３）　（１Ｒ，２Ｓ）－Ｎ－（５－シアノピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
３４）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
３５）　（１Ｒ，２Ｓ）－Ｎ－（４－クロロピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
３６）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシメチルピリジン－２－イル）－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
３７）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシメチルピリジン－２－イル）－２－（３－フルオロフェニル）シクロプロパンカルボキサミド
３８）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）－Ｎ－（４－フルオロフェニル）シクロプロパンカルボキサミド、
３９）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）－Ｎ－フェニルシクロプロパンカルボキサミド、
４０）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシピリジン－２－イル）－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
４１）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（４－フルオロフェニル）－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
４２）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ，２－ビス（４－フルオフェニル）シクロプロパンカルボキサミド、
４３）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシメチルピリジン－２－イル）－２－（４－フルオロフェニル）シクロプロパンカルボキサミド、
４４）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（４－フルオロフェニル）シクロプロパンカルボキサミド、
４５）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシピリジン－２－イル）－２－（４－フルオロフェニル）シクロプロパンカルボキサミド、
４６）　（１Ｒ，２Ｓ）－２－（３－シアノフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（４－フルオロフェニル）シクロプロパンカルボキサミド、
４７）　（１Ｒ，２Ｓ）－２－（３－シアノフェニル）－２－［（２，４－ジメチルピリミジン

－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
４８）　（１Ｒ，２Ｓ）－２－（３－シアノフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）シクロプロパンカルボキサミド、
４９）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニル－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド、
５０）　（１Ｒ，２Ｓ）－２－［（４エチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド、
５１）　（１Ｒ，２Ｓ）－Ｎ－（５－シアノピリジン－２－イル）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
５２）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
５３）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド、
５４）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－（４－フルオロフェニル）－２－フェニルシクロプロパンカルボキサミド、
５５）　（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）シクロプロパンカルボキサミド、
５６）　（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（４－フルオロフェニル）シクロプロパンカルボキサミド、
５７）　（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド、
５８）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
５９）　（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
６０）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
６１）　（１Ｒ，２Ｓ）－Ｎ－（２，４－ジフルオロフェニル）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
６２）　（１Ｒ，２Ｓ）－Ｎ－（５－シアノピリジン－２－イル）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
６３）　（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシピリジン－２－イル）シクロプロパンカルボキサミド、
６４）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－｛［（４－（メトキシメチル）－２－メチルピリミジン－５－イル）オキシ］メチル｝－２－フェニルシクロプロパンカルボキサミド、
６５）　（１Ｒ，２Ｓ）－Ｎ－（５－シアノピリジン－２－イル）－２－｛［（４－（メトキシメチル）－２－メチルピリミジン－５－イル）オキシ］メチル｝－２－フェニルシクロプロパン

カルボキサミド、
６６）　（１Ｒ，２Ｓ）－Ｎ－（５－フルオロピリジン－２－イル）－２－｛［（４－（メトキシメチル）－２－メチルピリミジン－５－イル）オキシ］メチル｝－２－フェニルシクロプロパンカルボキサミド、
６７）　（１Ｒ，２Ｓ）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニル－Ｎ－［５－（トリフルオロメチル）ピリジン－２－イル］シクロプロパンカルボキサミド、
６８）　（１Ｒ，２Ｓ）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
６９）　（１Ｒ，２Ｓ）－Ｎ－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
７０）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
７１）　（１Ｒ，２Ｓ）－２－（４－クロロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
７２）　（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）シクロプロパンカルボキサミド、
７３）　（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（４－フルオロフェニル）シクロプロパンカルボキサミド、
７４）　（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド、
７５）　（１Ｒ，２Ｓ）－Ｎ－（５－シアノピリジン－２－イル）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
７６）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
７７）　（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
７８）　（１Ｒ，２Ｓ）－Ｎ，２－ビス（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
７９）　（１Ｒ，２Ｓ）－Ｎ－（２，４－ジフルオロフェニル）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
８０）　（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシピリジン－２－イル）シクロプロパンカルボキサミド、
８１）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）－２－（３－メトキシフェニル）シクロプロパンカルボキサミド、
８２）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（４－フルオロフェニルル）－２－（３－メトキシフェニル）シクロプロパンカルボキサミ

ド、
８３）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（３－メトキシフェニル）シクロプロパンカルボキサミド、
８４）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－メトキシフェニル）シクロプロパンカルボキサミド
８５）　（１Ｒ，２Ｓ）－２－（３－フルオロフェニル）－Ｎ－（５－フルオロピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
８６）　（１Ｒ，２Ｓ）－２－（３－フルオロフェニル）－Ｎ－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
８７）　（１Ｒ，２Ｓ）－２－（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－（ピリジン－２－イル）シクロプロパンカルボキサミド、
８８）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
８９）　（１Ｒ，２Ｓ）－Ｎ，２－ビス（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９０）　（１Ｒ，２Ｓ）－Ｎ－（２，４－ジフルオロフェニル）－２－（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９１）　（１Ｒ，２Ｓ）－Ｎ－（２，５－ジフルオロフェニル）－２－（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９２）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９３）　（１Ｒ，２Ｓ）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９４）　（１Ｒ，２Ｓ）－Ｎ－（５－シアノピリジン－２－イル）－２－（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９５）　（１Ｒ，２Ｓ）－２－（３－フルオロフェニル）－２－（［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－［５－（トリフルオロメチル）ピリジン－２－イル］シクロプロパンカルボキサミド、
９６）　（１Ｒ，２Ｓ）－２－（４－フルオロフェニル）－Ｎ－（５－フルオロピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９７）　（１Ｒ，２Ｓ）－Ｎ，２－ビス（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９８）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９９）　（１Ｒ，２Ｓ）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、

１００）　（１Ｒ，２Ｓ）－２－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド、
１０１）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１０２）　（１Ｒ，２Ｓ）－Ｎ－（３－フルオロフェニル）－２－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１０３）　（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－２－（［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－（ピリジン－２－イル）シクロプロパンカルボキサミド、
１０４）　（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１０５）　（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－Ｎ－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１０６）　（１Ｒ，２Ｓ）－Ｎ，２－ビス（３，４－ジフルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１０７）　（１Ｒ，２Ｓ）－Ｎ－（２，５－ジフルオロフェニル）－２－（３，４－ジフルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１０８）　（１Ｒ，２Ｓ）－Ｎ－（２，４－ジフルオロフェニル）－２－（３，４－ジフルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１０９）　（１Ｒ，２Ｓ）－Ｎ－（２，３－ジフルオロフェニル）－２－（３，４－ジフルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１１０）　（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド、
１１１）　（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－Ｎ－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１１２）　（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１１３）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－（３，５－ジフルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１１４）　（１Ｒ，２Ｓ）－２－（３－クロロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド、
１１５）　（１Ｒ，２Ｓ）－２－（３－クロロフェニル）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１１６）　（１Ｒ，２Ｓ）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（３－フルオロフェニル）－２－（｛［４－（メトキシエチル）－２－メチルピリミジン－５－イル

］オキシ］メチル）シクロプロパンカルボキサミド、
１１７）　（１Ｒ，２Ｓ）－２－（３－フルオロ－５－メトキシフェニル）－Ｎ－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１１８）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－（３－フルオロ－５－メトキシフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１１９）　（１Ｒ，２Ｓ）－２－（３－フルオロ－５－メトキシフェニル）－Ｎ－（５－フルオロピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１２０）　（１Ｒ，２Ｓ）－２－（３－フルオロ－５－メトキシフェニル）－Ｎ－（５－フルオロ－４－メトキシピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１２１）　（１Ｒ，２Ｓ）－２－（３－フルオロ－５－メトキシフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド、
１２２）　（１Ｒ，２Ｓ）－２－（３－フルオロ－５－メトキシフェニル）－Ｎ－（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１２３）　（１Ｒ，２Ｓ）－２－（４－フルオロ－３－メトキシフェニル）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１２４）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド、
１２５）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
１２６）　（１Ｒ，２Ｓ）－Ｎ－（５－シアノピリジン－２－イル）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
１２７）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
１２８）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
１２９）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（４－フルオロフェニル）－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド、
１３０）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（４－フルオロフェニル）－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
１３１）　（１Ｒ，２Ｓ）－Ｎ－（４－クロロピリジン－２－イル）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（４－フルオロフェニル）シクロプロパンカルボキサミド、
１３２）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（４－フルオロフェニル）シクロプロパンカルボキサミド、
１３３）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オ

キシメチル］－Ｎ－（３－フルオロフェニル）－２－（４－フルオロフェニル）シクロプロパンカルボキサミド、
１３４）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ，２－ビス（４－フルオロフェニル）シクロプロパンカルボキサミド、
１３５）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロ－５－メトキシフェニル）－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
１３６）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロ－５－メトキシフェニル）シクロプロパンカルボキサミド、
１３８）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロ－５－メトキシフェニル）－Ｎ－（５－フルオロ－４－メチルピリミジン－２－イル）シクロプロパンカルボキサミド、
１３９）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）－２－（３－トリフルオロメチルフェニル）シクロプロパンカルボキサミド、
１４０）　（１Ｒ，２Ｒ）－２－（４－ブロモフェニル）－Ｎ－（５－クロロピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１４１）　（１Ｒ，２Ｒ）－２－（４－ブロモフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
１４２）　（１Ｒ，２Ｓ）－２－（３－クロロフェニル）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（｛［４－（メトキシメチル）－２－メチルピリミジン－５－イル］オキシ｝メチル）シクロプロパンカルボキサミド、
１４３）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロメチルピリジン－２－イル）－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
１４４）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）－２－（３－ヨードフェニル）シクロプロパンカルボキサミド、および
１４５）　（１Ｒ，２Ｓ）－Ｎ－（５－フルオロピリジン－２－イル）－２－［（４－ヒドロキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）シクロプロパンカルボキサミド；
［１３］上記［１］乃至［１２］の何れか一項に記載の化合物又はその医薬上許容される塩を有効成分として含有する医薬組成物；
［１４］不眠症、ナルコレプシー（発作性睡眠）および過剰の眠気、睡眠関連ジストニア、下肢静止不能症候群、睡眠時無呼吸、時差ぼけ症候群、交代勤務症候群、遅延睡眠相症候群又は睡眠相前進症候群のその他の疾患を含む睡眠障害の治療のための、上記［１３］に記載の医薬組成物、
［１５］気分変調性障害、気分障害、精神及び不安障害；糖尿病及び食欲、味覚、摂食、又は摂飲障害；視床下部疾患；生物学的及び概日リズム障害；神経疾患、神経因性疼痛及び下肢静止不能症候群から選ばれる疾病に不随する睡眠障害；精神障害に関連した不眠症；うつ病とうつ病に関連した不眠症；双極性障害と双極性障害に関連した不眠症；不安障害と不安障害に関連した不眠症；パーキンソン症に関連した不眠症；統合失調症に関連した不眠症；睡眠時無呼吸；ナルコレプシー；特発性不眠症；睡眠時随伴症；良性前立腺肥大症；麻薬依存症；ニコチン依存症；健康な集団における並びに精神及び神経疾患における全認知症及び認知機能障害；並びに全身のオレキシン系機能不全に関連した他の疾病からなる群から選択される疾病の予防又は治療のための、上記［１３］に記載の医薬組成物、

に関する。

【発明の効果】

【０００７】

本発明によれば、一般式（Ｉ）で表されるシクロプロパン化合物又はその医薬上許容される塩は、オレキシン受容体拮抗作用によるナルコレプシー等の睡眠異常の治療に有効である。より具体的には、一般式（Ｉ）で表されるシクロプロパン化合物又はその医薬上許容される塩は、不眠症、ナルコレプシー（発作性睡眠）および過剰の眠気、睡眠関連ジストニア、下肢静止不能症候群、睡眠時無呼吸、時差ぼけ症候群、交代勤務症候群、遅延睡眠相症候群又は睡眠相前進症候群のその他の疾患などの睡眠障害の治療に有効である。更には、気分変調性障害、気分障害、精神及び不安障害；糖尿病及び食欲、味覚、摂食、又は摂飲障害；視床下部疾患；生物学的及び概日リズム障害；神経疾患、神経因性疼痛及び下肢静止不能症候群から選ばれる疾病に不随する睡眠障害；精神障害に関連した不眠症；うつ病とうつ病に関連した不眠症；双極性障害と双極性障害に関連した不眠症；不安障害と不安障害に関連した不眠症；パーキンソン症に関連した不眠症；統合失調症に関連した不眠症；睡眠時無呼吸；ナルコレプシー；特発性不眠症；睡眠時随伴症；良性前立腺肥大症；麻薬依存症；ニコチン依存症；健康な集団における並びに精神及び神経疾患における全認知症及び認知機能障害；並びに全身のオレキシン系機能不全に関連した他の疾病などの疾病の予防又は治療に有効である。

【発明を実施するための形態】

【０００８】

以下に、本願明細書において記載する記号、用語等の意義を説明し、本発明を詳細に説明する。

【０００９】

本願明細書中においては、化合物の構造式が便宜上一定の異性体を表すことがあるが、本発明には化合物の構造上生ずる総ての幾何異性体、不斉炭素に基づく光学異性体、立体異性体、互変異性体等の異性体及び異性体混合物を含み、便宜上の式の記載に限定されるものではなく、いずれか一方の異性体でも混合物でもよい。したがって、分子内に不斉炭素原子を有し光学活性体及びラセミ体が存在することがあり得るが、本発明においてはそれらに限定されず、いずれもが含まれる。さらに結晶多形が存在することもあるが同様に限定されず、いずれかの単一結晶形またはそれらの混合物であってもよく、無水物以外に水和物であってもよく、いずれも本願明細書の特許請求の範囲に含まれる。

本発明には、式（Ｉ）の化合物の同位体標識された化合物も含まれる、これは１つ又はそれ以上の原子が自然界に通常見出される原子質量か質量数と異なった原子質量か質量数を有する原子で置き換えられていること以外、式（Ｉ）の化合物と同一である。本発明の化合物に組み入れることができる同位元素は、例えば、水素、炭素、窒素、酸素、リン、フッ素、沃素、および塩素の同位元素であり、^{2}Ｈ、^{3}Ｈ、^{11}Ｃ、^{14}Ｃ、^{18}Ｆ、^{35}Ｓ、^{123}Ｉ、および^{125}Ｉ等が含まれる。

前述の同位元素および／または他の同位元素を含む本発明の化合物とその薬学的に許容できる誘導体（例えば、塩）は本願明細書の特許請求の範囲内にある。本発明の同位体標識化合物、例えば、^{3}Ｈおよび／または^{14}Ｃなどの放射性同位元素が組み入れられた化合物、は医薬および／または基質の組織分布アッセイに有用である。^{3}Ｈと^{14}Ｃはそれらの調製と検出の容易さのため有用と考えられている。同位元素^{11}Ｃおよび^{18}ＦはＰＥＴ（陽電子放射断層撮影）で有用と考えられており、同位元素^{125}ＩはＳＰＥＣＴ（単光子放出コンピュータ断層撮影）で有用と考えられており、脳イメージングですべて有用である。^{2}Ｈなどのより重い同位元素による置換は、より高い代謝的安定性による生体内半減期を増加又は必要用量の減少等のある種の治療上の利点を生じさせ、それ故に、ある状況下では有用と考えられている。本発明の式（Ｉ）の同位体標識化合物は容易に利用可能な同位体ラベルされた試薬を非同位体ラベルされた試薬の代わりに用いて、以下の図式および／または実施例に開示された手順を行うことによって、一様に調製することができる。

【００１０】

本明細書において、「ハロゲン原子」とは、フッ素原子、塩素原子、臭素原子、ヨウ素原子等を示し、好ましくはフッ素原子、塩素原子である。

【００１１】

「C_{1-6}アルキル基」とは、炭素数が１乃至６個のアルキル基を示し、好ましい基としては、例えばメチル基、エチル基、ｎ－プロピル基、イソプロピル基、ｎ－ブチル基、イソブチル基、ｔ－ブチル基、ｎ－ペンチル基、イソペンチル基、ネオペンチル基、ｎ－ヘキシル基、１－メチルプロピル基、１，２－ジメチルプロピル基、１－エチルプロピル基、１－メチル－２－エチルプロピル基、１－エチル－２－メチルプロピル基、１，１，２－トリメチルプロピル基、１－メチルブチル基、２－メチルブチル基、１，１－ジメチルブチル基、２，２－ジメチルブチル基、２－エチルブチル基、１，３－ジメチルブチル基、２－メチルペンチル基、３－メチルペンチル基等の直鎖又は分枝状アルキル基が挙げられ、より好ましくは、メチル基、エチル基、ｎ－プロピル基が挙げられる。

【００１２】

「C_{1-6}アルキレン基」とは、炭素数が１乃至６個のアルキレン基を示し、好ましい基としては、例えばメチレン基、エチレン基、ｎ－プロピレン基、イソプロピレン基、ｎ－ブチレン基、イソブチレン基、ｎ－ペンチレン基、イソペンチレン基、ネオペンチレン基等の直鎖又は分枝状アルキレン基が挙げられ、より好ましくは、メチレン基、エチレン基、ｎ－プロピレン基が挙げられる。

【００１３】

「C_{1-6}アルコキシ基」とは、炭素数１乃至６個のアルキル基において、一つの水素原子が酸素原子に置換された基を示し、例えばメトキシ基、エトキシ基、ｎ－プロポキシ基、イソプロポキシ基、ｎ－ブトキシ基、イソブトキシ基、ｓｅｃ－ブトキシ基、ｔ－ブトキシ基、ｎ－ペントキシ基、イソペントキシ基、ｓｅｃ－ペントキシ基、ｔ－ペントキシ基、ｎ－ヘキソキシ基、イソヘキソキシ基、１，２－ジメチルプロポキシ基、２－エチルプロポキシ基、１－メチル－２－エチルプロポキシ基、１－エチル－２－メチルプロポキシ基、１，１，２－トリメチルプロポキシ基、１，１－ジメチルブトキシ基、２，２－ジメチルブトキシ基、２－エチルブトキシ基、１，３－ジメチルブトキシ基、２－メチルペントキシ基、３－メチルペントキシ基、ヘキシルオキシ基等が挙げられる。

【００１４】

「C_{1-6}アルキルカルボニル基」とは、炭素数１乃至６個のアルキル基において一つの水素原子がカルボニル基で置換された基を示し、好ましくは、例えばアセチル基、プロピオニル基、ブチリル基などが挙げられる。

【００１５】

「C_{1-6}アルキルスルホニル基」とは、炭素数１乃至６のアルキル基において、１つの水素原子がスルホニル基に置換された基を示し、例えばメチルスルホニル基、エチルスルホニル基、ｎ－プロピルスルホニル基、イソプロピルスルホニル基、ｎ－ブチルスルホニル基、イソブチルスルホニル基、ｔ－ブチルスルホニル基、ｎ－ペンチルスルホニル基、イソペンチルスルホニル基、ネオペンチルスルホニル基、ｎ－ヘキシルスルホニル基、１－メチルプロピルスルホニル基等が挙げられる。

【００１６】

「C_{3-8}シクロアルキル基」とは、炭素数３乃至８の環状アルキル基を示し、当該基における好ましい基としては、例えばシクロプロピル基、シクロブチル基、シクロペンチル基、シクロヘキシル基、シクロヘプチル基、シクロオクチル基等が挙げられる。

【００１７】

「アリール基」とは、グループ１から選択されるアリール基であり、グループ１は、フェニル基、ナフチル基、アズレニル基、アントリル基及びフェナントリル基からなる。

【００１８】

「ヘテロアリール基」とは、グループ２から選択されるヘテロアリール基であり、グループ２は、フリル基、チエニル基、ピロリル基、イミダゾリル基、トリアゾリル基、テト

ラゾリル基、チアゾリル基、ピラゾリル基、オキサゾリル基、イソオキサゾリル基、イソチアゾリル基、フラザニル基、チアジアゾリル基、オキサジアゾリル基、ピリジル基、ピラジニル基、ピリダジニル基、トリアジニル基、インドリル基、イソインドリル基、インダゾリル基、ベンゾオキサゾリル基、ベンゾイソオキサジアゾリル基、ベンゾチアゾリル基、ベンゾイソチアゾリル基、キノリル基及びイソキノリル基からなる。

【００１９】

「複素環基」とは、グループ３から選択されるアリール基であり、グループ３は、フリル基、チエニル基、ピロリル基、イミダゾリル基、トリアゾリル基、テトラゾリル基、チアゾリル基、ピラゾリル基、オキサゾリル基、イソオキサゾリル基、イソチアゾリル基、フラザニル基、チアジアゾリル基、オキサジアゾリル基、ピリジル基、ピラジニル基、ピリダジニル基、ピリミジニル基、トリアジニル基、２－ピリドニル基、４－ピリドニル基、ピリダジドニル基、ピリミジドニル基、プリニル基、プテリジニル基、キノリル基、イソキノリル基、ナフチリジル基、キノキサリル基、シンノリル基、キナゾリル基、フタラジル基、イミダゾピリジル基、イミダゾチアゾリル基、イミダゾオキサゾリル基、ベンゾイミダゾリル基、インドリル基、イソインドリル基、インダゾリル基、ピロロピリジル基、チエノピリジル基、フロピリジル基、ベンゾオキサゾリル基、ベンゾイソオキサジアゾリル基、ベンゾチアゾリル基、ベンゾイソチアゾリル基、ピリドピリミジニル基、オキソジヒドロピリドピリミジニル基、ベンゾフリル基、ベンゾチエニル基、ベンゾチアジアゾリル基、ベンゾ［１，３］ジオキソリル基、チエノフリル基、ジヒドロイソベンゾフラニル基、クロマニル基、イソクロマニル基、１，３－ジオキサインダニル基、１，４－ジオキサテトラリニル基及びジヒドロベンゾ［１，４］オキサジニル基からなる。

【００２０】

「置換基群α」とは、シアノ基、ハロゲン原子、水酸基、オキソ基、式－NR_6R_7（式中、R_6およびR_7は独立して水素原子又はC_{1-6}アルキル基である。）、置換基群βから選択される１乃至３個の置換基を有していてもよいC_{1-6}アルキル基、置換基群βから選択される１乃至３個の置換基を有していてもよいC_{1-6}アルコキシ基、置換基群βから選択される１乃至３個の置換基を有していてもよいC_{1-6}アルキルカルボニル基、置換基群βから選択される１乃至３個の置換基を有していてもよいC_{1-6}アルキルスルホニル基、置換基群βから選択される１乃至３個の置換基を有していてもよいグループ１から選択されるアリール基及び置換基群βから選択される１乃至３個の置換基を有していてもよいグループ２から選択されるヘテロアリール基を意味する。

【００２１】

「置換基群β」とは、シアノ基、ハロゲン原子、水酸基、C_{3-8}シクロアルキル基及びC_{1-6}アルコキシ基を意味する。

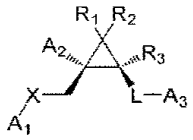
【００２２】

本発明の式（Ｉ）のシクロプロパン化合物は、医薬上許容される塩でもよい。医薬上許容される塩としては、具体的には、例えば無機酸塩（例えば硫酸塩、硝酸塩、過塩素酸塩、リン酸塩、炭酸塩、重炭酸塩、フッ化水素酸塩、塩酸塩、臭化水素酸塩、ヨウ化水素酸塩など）、有機カルボン酸塩（例えば酢酸塩、シュウ酸塩、マレイン酸塩、酒石酸塩、フマル酸塩、クエン酸塩など）、有機スルホン酸塩（例えばメタンスルホン酸塩、トリフルオロメタンスルホン酸塩、エタンスルホン酸塩、ベンゼンスルホン酸塩、トルエンスルホン酸塩、カンファースルホン酸塩など）、アミノ酸塩（例えばアスパラギン酸塩、グルタミン酸塩など）、四級アミン塩、アルカリ金属塩（例えばナトリウム塩、カリウム塩など）、アルカリ土類金属塩（例えばマグネシウム塩、カルシウム塩など）などが挙げられる。

【００２３】

本発明の式（Ｉ）のシクロプロパン化合物又はその医薬上許容される塩としては、式（ＩＩ）：

【化３】



（ＩＩ）

［式中、A_1、A_2、A_3、R_1、R_2、R_3、Ｘ及びＬは上記の定義と同義である。］で示されるシクロプロパン化合物又はその医薬上許容される塩が好ましい。

【００２４】

また、本発明のシクロプロパン化合物又はその医薬上許容される塩としては、式（Ｉ）または式（ＩＩ）において、R_1、R_2及びR_3が水素原子である、シクロプロパン化合物又はその医薬上許容される塩が好ましい。

更に、式（Ｉ）または式（ＩＩ）において、Ｌが式－ＣＯＮＨ－である、シクロプロパン化合物又はその医薬上許容される塩が好ましく、特に、Ｘが酸素原子である、シクロプロパン化合物又はその医薬上許容される塩が好ましい。

【００２５】

本発明のシクロプロパン化合物又はその医薬上許容される塩としては、式（Ｉ）または式（ＩＩ）において、A_2及びA_3は独立して、それぞれシアノ基、ハロゲン原子、C_{1-6}アルキル基、ハロC_{1-6}アルキル基及びC_{1-6}アルコキシ基から選択される１乃至３個の置換基を有していてもよい、アリール基又はヘテロアリール基である、シクロプロパン化合物又はその医薬上許容される塩が好ましい。

更に、A_2及びA_3は独立して、それぞれシアノ基、ハロゲン原子、C_{1-6}アルキル基、ハロC_{1-6}アルキル基及びC_{1-6}アルコキシ基から選択される１乃至３個の置換基を有していてもよい、アリール基又はヘテロアリール基である、シクロプロパン化合物又はその医薬上許容される塩が好ましく、特に、A_2及びA_3は独立して、それぞれシアノ基、ハロゲン原子、C_{1-6}アルキル基、ハロC_{1-6}アルキル基及びC_{1-6}アルコキシ基から選択される１乃至３個の置換基を有していてもよい、フェニル基、ナフチル基、ピリジル基、ピラジニル基、ピリダジニル基、ピリミジニル基、キノリル基又はイソキノリル基である、シクロプロパン化合物又はその医薬上許容される塩が好ましい。

【００２６】

なかでも特に、A_2がシアノ基、ハロゲン原子、C_{1-6}アルキル基、ハロC_{1-6}アルキル基及びC_{1-6}アルコキシ基から選択される１乃至３個の置換基を有していてもよいフェニル基である、シクロプロパン化合物又はその医薬上許容される塩；A_3がシアノ基、ハロゲン原子、水酸基、C_{1-6}アルキル基、ハロC_{1-6}アルキル基及びC_{1-6}アルコキシ基から選択される１乃至３個の置換基を有していてもよいフェニル基又はピリジル基である、シクロプロパン化合物又はその医薬上許容される塩；A_1がハロゲン原子、C_{1-6}アルキル基、ハロC_{1-6}アルキル基、C_{1-6}アルコキシ基C_{1-6}アルキル基、C_{3-8}シクロアルキル基及びC_{1-6}アルコキシ基から選択される１乃至３個の置換基を有していてもよい５－ピリミジニル基である、シクロプロパン化合物又はその医薬上許容される塩；特に、A_1がメチル基、ヒドロキシメチル基、メトキシメチル基及びメトキシエチル基から選択される１乃至２個の置換基を有していてもよい５－ピリミジニル基である、シクロプロパン化合物又はその医薬上許容される塩が好ましい。

【００２７】

具体的には、本発明のシクロプロパン化合物又はその医薬上許容される塩としては、以下の化合物から選ばれる、シクロプロパン化合物又はその医薬上許容される塩が好ましい。

１）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド、

２）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル

］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド、
３）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロ－４－メチルピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
４）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド、
５）　（１Ｒ，２Ｓ）－Ｎ－（６－フルオロピリジン－３－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
６）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（６－フルオロ－５－メチルピリジン－３－イル）－２－フェニルシクロプロパンカルボキサミド、
７）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－メトキシピリジン－３－イル）－２－フェニルシクロプロパンカルボキサミド、
８）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ，２－ジフェニルシクロプロパンカルボキサミド、
９）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－メチルピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド、
１０）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－［５－フルオロ－４－（メトキシメチル）ピリジン－２－イル］－２－フェニルシクロプロパンカルボキサミド、
１１）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（２－メトキシピリジン－４－イル）－２－フェニルシクロプロパンカルボキサミド、
１２）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニル－Ｎ－［５－（トリフルオロメチル）ピリジン－２－イル］シクロプロパンカルボキサミド、
１３）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニル－Ｎ－［４－（トリフルオロメチル）ピリジン－２－イル］シクロプロパンカルボキサミド、
１４）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－［４－（メトキシメチル）ピリジン－２－イル］－２－フェニルシクロプロパンカルボキサミド、
１５）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
１６）　（１Ｒ，２Ｓ）－Ｎ－［３－（ジメチルアミノ）フェニル］－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
１７）　（１Ｒ，２Ｓ）－Ｎ－（３－クロロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
１８）　（１Ｒ，２Ｓ）－Ｎ－（３－シアノ－４－フルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
１９）　（１Ｒ，２Ｓ）－Ｎ－（４－クロロ－３－シアノフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
２０）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－［３－（メチルスルフォニル）フェニル］－２－フェニルシクロプロパンカル

ボキサミド、
２１）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
２２）　（１Ｒ，２Ｓ）－Ｎ－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
２３）　（１Ｒ，２Ｓ）－Ｎ－（３－クロロ－４－フルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
２４）　（１Ｒ，２Ｓ）－Ｎ－（３－シアノ－５－フルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
２５）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（３－メトキシフェニル）－２－フェニルシクロプロパンカルボキサミド、
２６）　（１Ｒ，２Ｓ）－Ｎ－［３－（シアノメチル）フェニル］－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
２７）　（１Ｒ，２Ｓ）－Ｎ－（２－シアノピリジン－４－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
２８）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニル－Ｎ－［３－（トリフルオロメチル）フェニル］シクロプロパンカルボキサミド、
２９）　（１Ｒ，２Ｓ）－Ｎ－（４－シアノピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
３０）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（４－メトキシピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド、
３１）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
３２）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
３３）　（１Ｒ，２Ｓ）－Ｎ－（５－シアノピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
３４）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
３５）　（１Ｒ，２Ｓ）－Ｎ－（４－クロロピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
３６）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシメチルピリジン－２－イル）－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
３７）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシメチルピリジン－２－イル）－２－（３－フルオロフェニル

）シクロプロパンカルボキサミド
３８）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）－Ｎ－（４－フルオロフェニル）シクロプロパンカルボキサミド、
３９）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）－Ｎ－フェニルシクロプロパンカルボキサミド、
４０）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシピリジン－２－イル）－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
４１）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（４－フルオロフェニル）－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
４２）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ，２－ビス（４－フルオフェニル）シクロプロパンカルボキサミド、
４３）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシメチルピリジン－２－イル）－２－（４－フルオロフェニル）シクロプロパンカルボキサミド、
４４）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（４－フルオロフェニル）シクロプロパンカルボキサミド、
４５）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシピリジン－２－イル）－２－（４－フルオロフェニル）シクロプロパンカルボキサミド、
４６）　（１Ｒ，２Ｓ）－２－（３－シアノフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（４－フルオロフェニル）シクロプロパンカルボキサミド、
４７）　（１Ｒ，２Ｓ）－２－（３－シアノフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
４８）　（１Ｒ，２Ｓ）－２－（３－シアノフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）シクロプロパンカルボキサミド、
４９）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニル－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド、
５０）　（１Ｒ，２Ｓ）－２－［（４エチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド、
５１）　（１Ｒ，２Ｓ）－Ｎ－（５－シアノピリジン－２－イル）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
５２）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
５３）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド、
５４）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－（４－フルオロフェニル）－２－フェニルシクロプロパンカルボキサミド、
５５）　（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）シクロプロパンカルボキサミド、
５６）　（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（４－フルオロフェニル）シクロプロパンカルボキサミド、

５７）　（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド、
５８）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
５９）　（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
６０）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
６１）　（１Ｒ，２Ｓ）－Ｎ－（２，４－ジフルオロフェニル）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
６２）　（１Ｒ，２Ｓ）－Ｎ－（５－シアノピリジン－２－イル）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
６３）　（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシピリジン－２－イル）シクロプロパンカルボキサミド、
６４）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－｛［（４－（メトキシメチル）－２－メチルピリミジン－５－イル）オキシ］メチル｝－２－フェニルシクロプロパンカルボキサミド、
６５）　（１Ｒ，２Ｓ）－Ｎ－（５－シアノピリジン－２－イル）－２－｛［（４－（メトキシメチル）－２－メチルピリミジン－５－イル）オキシ］メチル｝－２－フェニルシクロプロパンカルボキサミド、
６６）　（１Ｒ，２Ｓ）－Ｎ－（５－フルオロピリジン－２－イル）－２－｛［（４－（メトキシメチル）－２－メチルピリミジン－５－イル）オキシ］メチル｝－２－フェニルシクロプロパンカルボキサミド、
６７）　（１Ｒ，２Ｓ）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニル－Ｎ－［５－（トリフルオロメチル）ピリジン－２－イル］シクロプロパンカルボキサミド、
６８）　（１Ｒ，２Ｓ）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
６９）　（１Ｒ，２Ｓ）－Ｎ－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
７０）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
７１）　（１Ｒ，２Ｓ）－２－（４－クロロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
７２）　（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）シクロプロパンカルボキサミド、
７３）　（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（４－フルオロフェニル）シクロプロパンカルボキ

サミド、
７４）　（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド、
７５）　（１Ｒ，２Ｓ）－Ｎ－（５－シアノピリジン－２－イル）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
７６）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
７７）　（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
７８）　（１Ｒ，２Ｓ）－Ｎ，２－ビス（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
７９）　（１Ｒ，２Ｓ）－Ｎ－（２，４－ジフルオロフェニル）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
８０）　（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシピリジン－２－イル）シクロプロパンカルボキサミド、
８１）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）－２－（３－メトキシフェニル）シクロプロパンカルボキサミド、
８２）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（４－フルオロフェニルル）－２－（３－メトキシフェニル）シクロプロパンカルボキサミド、
８３）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（３－メトキシフェニル）シクロプロパンカルボキサミド、
８４）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－メトキシフェニル）シクロプロパンカルボキサミド
８５）　（１Ｒ，２Ｓ）－２－（３－フルオロフェニル）－Ｎ－（５－フルオロピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
８６）　（１Ｒ，２Ｓ）－２－（３－フルオロフェニル）－Ｎ－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
８７）　（１Ｒ，２Ｓ）－２－（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－（ピリジン－２－イル）シクロプロパンカルボキサミド、
８８）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
８９）　（１Ｒ，２Ｓ）－Ｎ，２－ビス（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９０）　（１Ｒ，２Ｓ）－Ｎ－（２，４－ジフルオロフェニル）－２－（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、

９１）　（１Ｒ，２Ｓ）－Ｎ－（２，５－ジフルオロフェニル）－２－（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９２）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９３）　（１Ｒ，２Ｓ）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９４）　（１Ｒ，２Ｓ）－Ｎ－（５－シアノピリジン－２－イル）－２－（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９５）　（１Ｒ，２Ｓ）－２－（３－フルオロフェニル）－２－（［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－［５－（トリフルオロメチル）ピリジン－２－イル］シクロプロパンカルボキサミド、
９６）　（１Ｒ，２Ｓ）－２－（４－フルオロフェニル）－Ｎ－（５－フルオロピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９７）　（１Ｒ，２Ｓ）－Ｎ，２－ビス（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９８）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９９）　（１Ｒ，２Ｓ）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１００）　（１Ｒ，２Ｓ）－２－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド、
１０１）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１０２）　（１Ｒ，２Ｓ）－Ｎ－（３－フルオロフェニル）－２－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１０３）　（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－２－（［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－（ピリジン－２－イル）シクロプロパンカルボキサミド、
１０４）　（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１０５）　（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－Ｎ－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１０６）　（１Ｒ，２Ｓ）－Ｎ，２－ビス（３，４－ジフルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１０７）　（１Ｒ，２Ｓ）－Ｎ－（２，５－ジフルオロフェニル）－２－（３，４－ジフルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、

１０８）　（１Ｒ，２Ｓ）－Ｎ－（２，４－ジフルオロフェニル）－２－（３，４－ジフルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１０９）　（１Ｒ，２Ｓ）－Ｎ－（２，３－ジフルオロフェニル）－２－（３，４－ジフルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１１０）　（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド、
１１１）　（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－Ｎ－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１１２）　（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１１３）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－（３，５－ジフルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１１４）　（１Ｒ，２Ｓ）－２－（３－クロロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド、
１１５）　（１Ｒ，２Ｓ）－２－（３－クロロフェニル）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１１６）　（１Ｒ，２Ｓ）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（３－フルオロフェニル）－２－（｛［４－（メトキシエチル）－２－メチルピリミジン－５－イル］オキシ｝メチル）シクロプロパンカルボキサミド、
１１７）　（１Ｒ，２Ｓ）－２－（３－フルオロ－５－メトキシフェニル）－Ｎ－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１１８）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－（３－フルオロ－５－メトキシフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１１９）　（１Ｒ，２Ｓ）－２－（３－フルオロ－５－メトキシフェニル）－Ｎ－（５－フルオロピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１２０）　（１Ｒ，２Ｓ）－２－（３－フルオロ－５－メトキシフェニル）－Ｎ－（５－フルオロ－４－メトキシピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１２１）　（１Ｒ，２Ｓ）－２－（３－フルオロ－５－メトキシフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド、
１２２）　（１Ｒ，２Ｓ）－２－（３－フルオロ－５－メトキシフェニル）－Ｎ－（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１２３）　（１Ｒ，２Ｓ）－２－（４－フルオロ－３－メトキシフェニル）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１２４）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）－Ｎ－ピリジン－２－イルシクロプロパン

カルボキサミド、
１２５）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
１２６）　（１Ｒ，２Ｓ）－Ｎ－（５－シアノピリジン－２－イル）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
１２７）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
１２８）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
１２９）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（４－フルオロフェニル）－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド、
１３０）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（４－フルオロフェニル）－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
１３１）　（１Ｒ，２Ｓ）－Ｎ－（４－クロロピリジン－２－イル）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（４－フルオロフェニル）シクロプロパンカルボキサミド、
１３２）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（４－フルオロフェニル）シクロプロパンカルボキサミド、
１３３）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－（３－フルオロフェニル）－２－（４－フルオロフェニル）シクロプロパンカルボキサミド、
１３４）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ，２－ビス（４－フルオロフェニル）シクロプロパンカルボキサミド、
１３５）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロ－５－メトキシフェニル）－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
１３６）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロ－５－メトキシフェニル）シクロプロパンカルボキサミド、
１３８）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロ－５－メトキシフェニル）－Ｎ－（５－フルオロ－４－メチルピリミジン－２－イル）シクロプロパンカルボキサミド、
１３９）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）－２－（３－トリフルオロメチルフェニル）シクロプロパンカルボキサミド、
１４０）　（１Ｒ，２Ｒ）－２－（４－ブロモフェニル）－Ｎ－（５－クロロピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１４１）　（１Ｒ，２Ｒ）－２－（４－ブロモフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
１４２）　（１Ｒ，２Ｓ）－２－（３－クロロフェニル）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（｛［４－（メトキシメチル）－２－メチルピリミジン－５－イル］

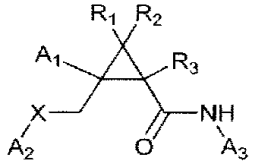
オキシ｝メチル）シクロプロパンカルボキサミド、
１４３）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロメチルピリジン－２－イル）－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
１４４）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）－２－（３－ヨードフェニル）シクロプロパンカルボキサミド、および
１４５）　（１Ｒ，２Ｓ）－Ｎ－（５－フルオロピリジン－２－イル）－２－［（４－ヒドロキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）シクロプロパンカルボキサミド。

【００２８】

次に、本発明の式（Ｉ）の化合物［以下、化合物（Ｉ）という、他式で表される化合物についても同様に表記する］又はその医薬上許容される塩の製造法について説明する。
式（Ｉ）において、Ｌが式－ＣＯＮＨ－の場合は以下の方法によって製造することが出来る。

式（Ｉ－１）：

【化４】



（Ｉ－１）

［式中、Ａ１、Ａ２、Ａ３、Ｒ１、Ｒ２、Ｒ３およびＸは前記と同じ意味を示す。］で示される化合物（Ｉ）およびその中間体は、例えば以下の一般的製造法に記載の方法並びに製造例、実施例に記載の方法等に従って合成される。

【００２９】

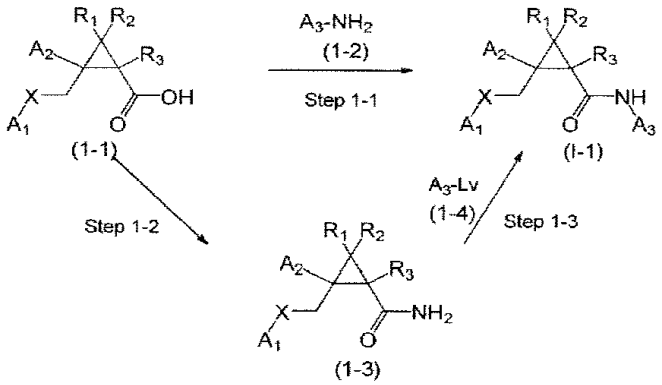
本発明の化合物（Ｉ）を製造する際に用いる原料化合物における「脱離基」とは、求核置換反応に利用される脱離基であればいずれでもよく、好ましくは、例えばハロゲン原子、上記の置換基群αで置換されてもよいＣ$_{1-6}$アルキルスルホニルオキシ基、上記の置換基群αで置換されてもよいアリールスルホニルオキシ基等が挙げられ、具体的には、塩素原子、臭素原子、ヨウ素原子、メタンスルホニルオキシ基、トリフルオロメタンスルホニルオキシ基、ｐ－トルエンスルホニルオキシ基等が挙げられる。

【００３０】

１．一般的製造法１：

【化５】

Scheme 1



［式中、R_1、R_2およびR_3は水素であり、Ｌｖは、脱離基であり、例えばハロゲン原子（塩素原子、臭素原子、ヨウ素原子等）、例えばメタンスルホニルオキシ基、ｐ－トルエンスルホニルオキシ基、トリフルオロメタンスルホニルオキシ基（式中、ＴｆＯで表す。）等のスルホニルオキシ基等を示し、A_1、A_2、A_3およびＸは前記と同じ意味を示す。］

【００３１】

工程１－１：

本工程は、化合物（１－１）を直接（方法１）或いは酸ハロゲン化物（方法２）、混合酸無水物（方法３）又は活性エステル（方法４）等に導いた後、化合物（１－２）と縮合させることにより化合物（Ｉ－１）を得る工程である。

【００３２】

方法１：

化合物（１－１）を直接化合物（１－２）と縮合させる場合には、縮合剤を用いるが、その縮合反応は、以下の文献に記載された通常用いられている条件と同様の条件で行うことができる。公知の方法として、例えばＲｏｓｏｗｓｋｙ，Ａ．；Ｆｏｒｓｃｈ，Ｒ．Ａ．；Ｍｏｒａｎ，Ｒ．Ｇ．；Ｆｒｅｉｓｈｅｉｍ，Ｊ．Ｈ．；Ｊ．Ｍｅｄ．Ｃｈｅｍ．，３４（１），２２７－２３４（１９９１），Ｂｒｚｏｓｔｗｓｋａ，Ｍ．；Ｂｒｏｓｓｉ，Ａ．；Ｆｌｉｐｐｅｎ－Ａｎｄｅｒｓｏｎ，Ｊ．Ｌ．；Ｈｅｔｅｒｏｃｙｃｌｅｓ，３２（１０），１９６８－１９７２（１９９１），Ｒｏｍｅｒｏ，Ｄ．Ｌ．；Ｍｏｒｇｅ，Ｒ．Ａ．；Ｂｉｌｅｓ，Ｃ．；Ｂｅｒｒｉｏｓ－Ｐｅｎａ，Ｎ．；Ｍａｙ，Ｐ．Ｄ．；Ｐａｌｍｅｒ，Ｊ．Ｒ．；Ｊｏｈｎｓｏｎ，Ｐ．Ｄ．；Ｓｍｉｔｈ，Ｈ．Ｗ．；Ｂｕｓｓｏ，Ｍ．；Ｔａｎ，Ｃ．－Ｋ．；Ｖｏｏｒｍａｎ，Ｒ．Ｌ．；Ｒｅｕｓｓｅｒ，Ｆ．；Ａｌｔｈａｕｓ，Ｉ．Ｗ．；Ｄｏｗｎｅｙ，Ｋ．Ｍ．；Ｓｏ，Ａ．Ｇ．；Ｒｅｓｎｉｃｋ，Ｌ．；Ｔａｒｐｌｅｙ，Ｗ．Ｇ．，Ａｒｉｓｔｏｆｆ，Ｐ．Ａ．；Ｊ．Ｍｅｄ．Ｃｈｅｍ．，３７（７），９９８－１０１４（１９９４）等が挙げられる。

化合物（１－１）はフリー体であっても塩であってもよい。

【００３３】

本反応の溶媒は、反応を阻害しないものであれば特に限定されないが、例えばテトラヒドロフラン、１，４－ジオキサン、酢酸エチル、酢酸メチル、ジクロロメタン、クロロホルム、Ｎ，Ｎ－ジメチルホルムアミド、トルエン、キシレン等があげられる。縮合剤としては、ＣＤＩ（Ｎ，Ｎ’－カルボニルジイミダゾール）、Ｂｏｐ（１Ｈ－１，２，３－ベンゾトリアゾール－１－イルオキシ（トリ（ジメチルアミノ））ホスホニウム　ヘキサフルオロホスフェート）、ＷＳＣ（１－エチル－３－（３－ジメチルアミノプロピル）カルボジイミド・塩酸塩）、ＤＣＣ（Ｎ，Ｎ－ジシクロヘキシルカルボジイミド）、ジエチルホスホリルシアニド、ＰｙＢＯＰ（ベンゾトリアゾール－１－イルオキシトリス（ピロリジノ）ホスホニウムヘキサフルオロホスフェート）等が挙げられる。化合物（１－２）は化合物（１－１）に対して１当量から大過剰用いる。また必要に応じて１当量から大過剰の有機塩基、例えばトリエチルアミン等を加えてもよい。

反応時間は、特に限定されないが、通常、０．５から４８時間であり、好ましくは０．５から２４時間である。反応温度は、使用する原料、溶媒等により異なり特に限定されないが、好ましくは氷冷～溶媒の還流温度である。

【００３４】

方法２：（酸ハロゲン化物を用いる合成方法）

本反応は、当業者に公知の方法により化合物（１－１）を対応する酸ハロゲン化物とした後、化合物（１－２）と反応させて化合物（Ｉ－１）を得ることができる。

反応に使用される塩基としては、例えばトリエチルアミン、ピリジン、炭酸カリウム、ジイソプロピルエチルアミン等が挙げられる。反応温度は特に限定されないが、通常、－７８℃～溶媒の還流温度であり、好ましくは－２０℃～室温である。反応に使用される溶媒は、反応を阻害せず出発物質をある程度溶解するものであれば特に限定されないが、好適には、例えば、テトラヒドロフラン、エーテル、トルエン、ジクロロメタン等があげら

れる。

【００３５】

方法３：（酸無水物を用いる合成方法）

化合物（１－１）を混合酸無水物とした後、該混合酸無水物と化合物（１－２）とを反応させて化合物（Ｉ－１）を得ることができる。混合酸無水物は、当業者に公知の手段により合成できるが、例えばトリエチルアミン等の塩基存在下、化合物（１－１）および例えばクロロギ酸エチル等のクロロギ酸エステル類を反応させることで行われる。クロロギ酸エステル類および塩基は、化合物（１－１）に対して１当量から２当量用いる。反応温度は－３０℃～室温であり、好ましくは－２０℃～室温である。

混合酸無水物と化合物（１－２）を縮合させる工程は、例えばジクロロメタン、テトラヒドロフラン、Ｎ，Ｎ－ジメチルホルムアミド等の溶媒中、混合酸無水物と化合物（１－２）とを反応させることにより行われる。化合物（１－２）は、混合酸無水物に対して１当量から大過剰を用いる。

反応時間は、特に限定されないが、通常、０．５から４８時間であり、好ましくは０．５から１２時間である。反応温度は－２０℃～５０℃であり、好ましくは－２０℃から室温である。

【００３６】

方法４：（活性エステルを用いる合成方法）

化合物（１－１）を活性エステルとした後、該活性エステルと化合物（１－２）とを反応させて化合物（Ｉ－１）を得ることができる。活性エステルを得る工程は、例えば１，４－ジオキサン、テトラヒドロフラン、Ｎ，Ｎ－ジメチルホルムアミド等の溶媒中、例えばＤＣＣ等の縮合剤存在下、化合物（１－１）および活性エステル合成試薬を反応させることにより行われる。活性エステル合成試薬としては、例えばＮ－ヒドロキシスクシンイミド等が挙げられる。活性エステル合成試薬および縮合剤は化合物（１－１）に対して１当量から１．５当量用いる。反応時間は、特に限定されないが、通常、０．５から４８時間であり、好ましくは０．５から２４時間である。

反応温度は－２０℃～５０℃であり、好ましくは－２０℃から室温である。

活性エステルと化合物（１－２）を縮合させる工程は、例えばジクロロメタン、テトラヒドロフラン、Ｎ，Ｎ－ジメチルホルムアミド等の溶媒中、活性エステルと化合物（１－２）とを反応させることにより行われる。化合物（１－２）は、活性エステルに対して１当量から大過剰を用いる。反応時間は、特に限定されないが、通常、０．５から４８時間であり、好ましくは０．５から２４時間である。反応温度は－２０℃～５０℃であり、好ましくは－２０℃から室温である。

【００３７】

工程１－２：

本工程は、化合物（１－２）から化合物（１－３）を得る工程である。

本工程は化合物（１－１）を前記方法２および方法３で示した方法により、対応する酸ハロゲン化物または酸無水物とした後、アンモニアと反応させて化合物（１－３）を得る工程である。反応に用いるアンモニアはガスでも水溶液でも良く、さらにアンモニアの塩であってもよい。また、ヘキサメチルジシラザンを酸ハロゲン化物と反応させた後、メタノールを加え酸処理することでも化合物（１－３）を製造することが出来る（Ｒ．Ｐｅｌｌｅｇａｔａら、Ｓｙｎｔｈｅｓｉｓ，１９８５，５１７）。

また、化合物（１－１）を尿素と加熱することでも化合物（１－３）を製造することができる。

【００３８】

工程１－３：

本工程は化合物（１－３）から化合物（Ｉ－１）を得る工程である。

化合物（１－３）と化合物（１－４）とを遷移金属を用いたカップリング反応させて化合物（Ｉ－１）を得る工程である。

本工程は遷移金属を用いるアリールハライドまたはアリールボロン酸と酸アミドとのカ

ップリング反応に通常用いられている条件で反応を行うことができる。

銅を用いるカップリング反応として、例えば、Ｈａｎｈｕｉ Ｘｕ，Ｃｈｒｉｓｔｉａｎ Ｗｏｌｆ，Ｃｈｅｍ．Ｃｏｍｍｕｎ，２００９，１７１５；Ｓｕｒｉｂａｂｕ Ｊａｍｍｉ ｅｔ ａｌ．Ｓｙｎｌｅｔｔ，２００９（２０），３３２３等の文献を挙げることができる。本反応に用いられる銅試薬としては特に限定されないが、好ましくはヨウ化第一銅、酸化第一銅、トリフルオロメタンスルホン酸銅（ＩＩ）等を挙げることができる。

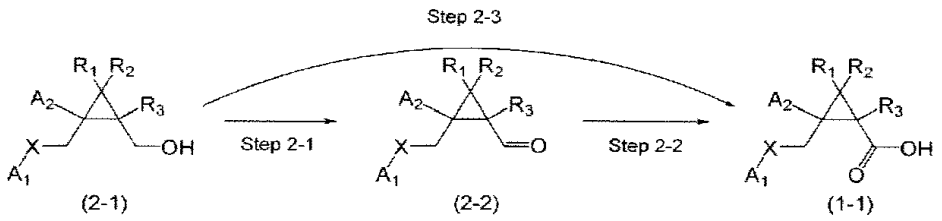
パラジウム錯体を用いるカップリング反応として、例えば、Ｖａｎ ｄｅｎ Ｈｏｏｇｅｎｂａｎｄ，Ａ ｅｔ ａｌ，Ｔｅｔｒａｈｅｄｒｏｎ Ｌｅｔｔ．２００４，４５，８５３５；Ｇｈｏｓｈ，Ａ ｅｔ ａｌ，Ｏｒｇ．Ｌｅｔｔ．２００３，５，２２０７等の文献を挙げることができる。本反応に用いられるパラジウム試薬としては特に限定されないが、好ましくは、例えばトリス（ジベンジリデンアセトン）ジパラジウム、塩化パラジウム、酢酸パラジウム（ＩＩ）等をあげることができる。本反応に用いられるリガンドとしては、例えば、ＸａｎｔＰｈｏｓ（４，５－ビス（ジフェニルホスフィノ）－９，９－ジメチルキサンテン）、Ｘ－Ｐｈｏｓ（２－ジシクロヘキシルホスフィノ－２’，４’，６’－トリイソプロピルビフェニル）、ＢＩＮＡＰ（２，２’－ビス（ジフェニルホスフィノ）－１，１’－ビナフチル）、ＤＰＰＦ（１，１’－ビス（ジフェニルホスフィノ）フェロセン）、トリス（ｔｅｒｔ－ブチルオキシ）ホスフィン等が挙げられる。遷移金属試薬の使用量は、原料に対して約０．００１～０．１当量である。本反応に用いられる溶媒は、反応を阻害しないものであれば特に限定されないが、好ましくは、例えばベンゼン、トルエン、キシレン、Ｎ，Ｎ－ジメチルホルムアミド、１－メチル－２－ピロリドン、テトラヒドロフラン、１，４－ジオキサン、アセトニトリル、プロピオニトリル等をあげることができる。反応温度は特に限定されないが、通常、氷冷～溶媒の還流温度であり、好ましくは、例えば室温～溶媒の還流温度である。反応時間は、特に限定されないが、通常、０．５～４８時間であり、好ましくは０．５～２４時間である。

【００３９】

一般的製造法２：

【化６】

Scheme 2



［式中、A_1、A_2、R_1、R_2、R_3およびＸは前記と同じ意味を示す。］

【００４０】

一般的製造法２は、化合物（２－１）を原料として［工程２－１］および［工程２－２］または［工程２－３］を経由する本発明にかかる化合物（Ｉ－１）の合成中間体である化合物（１－１）を製造する方法である。

化合物（２－１）は、市販品から当業者に公知の方法で製造することもでき、更に実施例中の製造例の記載の方法を用いて製造することもできる。

【００４１】

工程２－１：

本工程は、化合物（２－１）を酸化反応に付し、化合物（２－２）を得る工程である。当業者に公知の方法により、アルコール化合物からアルデヒド化合物を得ることができる。

反応に使用される公知の酸化方法としては、例えばスワン酸化（Ｓｗｅｒｎ酸化）、コーリー－キム酸化（Ｃｏｒｅｙ－Ｋｉｍ酸化）、モファット酸化（Ｍｏｆｆａｔｔ酸化）

、ＰＣＣ酸化、ＰＤＣ酸化、デスーマーチン酸化（Ｄｅｓｓ－Ｍａｒｔｉｎ酸化）、ＳＯ$_3$－ｐｙｒｉｄｉｎｅ酸化、ＴＥＭＰＯ酸化等を挙げることができる。

反応に使用される溶媒は、反応を阻害せず出発物質をある程度溶解するものであれば特に限定されないが、例えばジメチルスルホキシド、テトラヒドロフラン、トルエン、ジクロロメタン、クロロホルム等があげられる。

反応温度は特に限定されないが、通常、－７８℃～溶媒の還流温度であり、好ましくは－７８℃～室温である。反応時間は、特に限定されないが、通常、５分～４８時間であり、好ましくは５分～２４時間である。

【００４２】

工程２－２：

本工程は、化合物（２－３）を酸化反応に付し、化合物（１－１）を得る工程である。当業者に公知の方法により、アルデヒド化合物からカルボン酸化合物を得ることができる。

酸化法としては、通常用いられているものを用いることが出来るが、例えば実施例中の製造例の記載の方法を用いることが出来る。

【００４３】

工程２－３：

本工程は、化合物（２－１）を酸化反応に付し、化合物（１－１）を得る工程である。酸化条件としては通常用いられているものを用いることが出来るが、例えばＴＥＭＰＯ－ビスアセチルヨードベンゼンにより行える。反応に使用される溶媒は、反応を阻害せず出発物質をある程度溶解するものであれば特に限定されないが、例えばジクロロメタン、クロロホルム、アセトニトリル、トルエン等と水を混合させ用いることが出来る。

反応温度は特に限定されないが、通常、０℃～溶媒の還流温度である。反応時間は、特に限定されないが、通常、５分～４８時間であり、好ましくは５分～２４時間である。

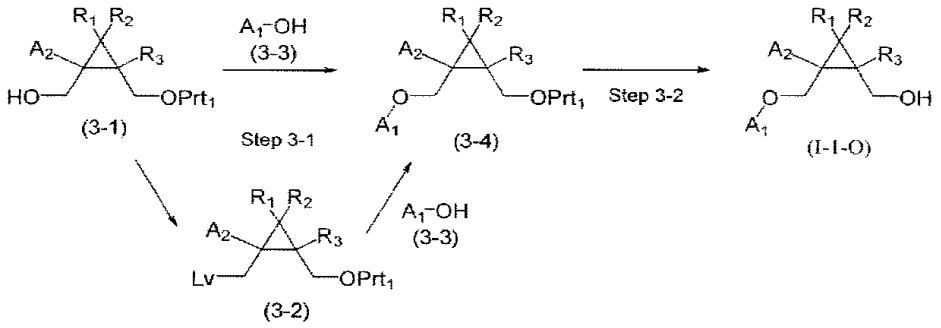
また、実施例中の製造例の記載の方法を用いることが出来る。

【００４４】

一般的製造法３：

【化７】

Scheme 3



［式中、Ｌｖは、脱離基であり、例えばハロゲン原子（塩素原子、臭素原子、ヨウ素原子等）、例えばメタンスルホニルオキシ基、ｐ－トルエンスルホニルオキシ基、トリフルオロメタンスルホニルオキシ基等のスルホニルオキシ基等を示し、Ｐｒｔ$_1$は水酸基の保護基を示し、Ａ$_1$、Ａ$_2$、Ｒ$_1$、Ｒ$_2$およびＲ$_3$は前記と同じ意味を示す。］

【００４５】

一般的製造法３は、化合物（３－１）を原料として［工程３－１］および［工程３－２］を経由する本発明にかかる化合物（Ｉ）の合成中間体である化合物（Ｉ－１－Ｏ）を製造する方法である。

化合物（Ｉ－１－Ｏ）は、市販品から当業者に公知の方法で製造することもでき、更に実施例中の製造例の記載の方法を用いて製造することもできる。

【００４６】

工程３－１：

本工程は、化合物（３－１）を直接或いは化合物（３－２）に変換した後、化合物（３－３）と反応させて、化合物（３－４）を得る工程である。

化合物（３－１）を直接、化合物（３－３）と反応させる場合、本反応は、光延反応に通常用いられている条件（例えば、Ｏ．Ｍｉｔｓｕｎｏｂｕ，Ｓｙｎｔｈｅｓｉｓ，１（１９８１）、Ｄ．Ｌ．Ｈｕｇｈｅｓ，Ｏｒｇａｎｉｃ　Ｒｅａｃｔｉｏｎｓ，４２，３３５（１９９２）等に記載の条件）と同様の条件で反応を行うことができる。

反応はトリフェニルホスフィン等のホスフィン誘導体及びアゾジカルボン酸ジエチル、アゾジカルボン酸ジイソプロピル等のアゾジカルボン酸ジエステルを用いて行う。反応に使用する溶媒としては反応を阻害せず出発物質をある程度溶解するものであれば特に限定されないが、例えばテトラヒドロフラン、ベンゼン、トルエン、Ｎ、Ｎ－ジメチルホルムアミド等を用いることができる。反応温度は特に限定されないが、通常、氷冷～室温である。

また、化合物（３－４）は化合物（３－１）から脱離基を有する化合物（３－２）に変換した後、化合物（３－３）との求核置換反応により、製造することができる。具体的には例えば、化合物（３－３）に塩基を作用させてアニオンとした後、化合物（３－２）と反応させ化合物（３－４）を得ることができる。

本反応の溶媒は反応を阻害しないものであれば特に限定されないが、ジエチルエーテル、テトラヒドロフラン、１，４－ジオキサン、Ｎ，Ｎ－ジメチルホルムアミド、ジメチルスルホキシド等の有機溶媒中で、適当な塩基を１当量～大過剰作用させて行うことができる。使用する塩基としては、水酸化ナトリウム、水酸化カリウム、水素化ナトリウム、水素化カリウム、ナトリウムメトキシド、ナトリウムエトキシド、カリウム　ｔｅｒｔ－ブトキシド等があげられる。

反応温度は特に限定されないが、通常、－７８℃～溶媒の還流温度であり、好ましくは氷冷～１００℃である。

化合物（３－２）は化合物（３－１）の水酸基を脱離基に変換することで製造することができる。

脱離基としてはハロゲン原子（塩素原子、臭素原子、ヨウ素原子）、メタンスルホニルオキシ基、ｐ－トルエンスルホニルオキシ基、トリフルオロメタンスルホニルオキシ基等のスルホニルオキシ基をあげることができる。

水酸基をこれらの脱離基に変換する反応に通常用いられている条件（例えば、Ｒ．Ｋ．Ｃｒｏｓｓｌａｎｄ　ａｎｄ　Ｋ．Ｌ．Ｓｅｒｖｉｓ，Ｊｏｕｒｎａｌ　ｏｆ　Ｏｒｇａｎｉｃ　Ｃｈｅｍｉｓｔｒｙ，３５，３１９５（１９７０）、Ｙ．Ｙｏｓｈｉｄａ，Ｙ．Ｓａｋａｋｕｒａ，Ｎ．Ａｓｏ，Ｓ．Ｏｋａｄａ，ａｎｄ　Ｙ．Ｔａｎａｂｅ，Ｔｅｔｒａｈｅｄｒｏｎ，５５，２１８３（１９９９）等に記載の条件）と同様の条件で反応を行うことができる。

例えば、脱離基がハロゲン原子の場合には、化合物（３－１）を塩化チオニル、臭化チオニル、三臭化リンあるいはテトラハロゲノメタン－トリフェニルホスフィンと反応させることにより製造することができる。反応に使用する溶媒としては、反応を阻害せず出発物質をある程度溶解するものであれば特に限定されないが、好ましくはベンゼン、トルエン、キシレン、ジクロロメタン、クロロホルム等があげられる。さらに塩基の添加により収率向上等の良好な結果を得ることがある。用いる塩基は反応を阻害しない限りにおいて特に限定されないが、好ましくは炭酸ナトリウム、炭酸カリウム、トリエチルアミン、ピリジン、ジイソプロピルエチルアミン等があげられる。反応温度は、通常、－７８℃～溶媒の還流温度であり、好ましくは氷冷～溶媒の還流温度である。

また、脱離基がスルホニルオキシ基の場合には、化合物（３－１）をメタンスルホニルクロリド、ｐ－トルエンスルホニル　クロリド、無水トリフルオロメタンスルホン酸等と反応させて、製造することができる。反応に使用する溶媒としては、反応を阻害せず出発物質をある程度溶解するものであれば特に限定されないが、好ましくはテトラヒドロフ

ラン、トルエン、キシレン、ジクロロメタン、クロロホルム、Ｎ，Ｎ－ジメチルホルムアミド等があげられる。反応温度は、通常、－７８℃～溶媒の還流温度であり、好ましくは氷冷～室温である。さらに塩基の添加により収率向上等の良好な結果を得ることがある。用いる塩基は反応を阻害しない限りにおいて特に限定されないが、好ましくは炭酸ナトリウム、炭酸カリウム、トリエチルアミン、ピリジン、ジイソプロピルエチルアミン等があげられる。

【００４７】

工程３－２：

本工程は、化合物（３－４）を脱保護して、化合物（Ｉ－１－Ｏ）を得る工程である。

Ｐｒｔ１がｔｅｒｔ－ブチルジメチルシリル基、ｔｅｒｔ－ブチルジフェニルシリル基の場合、シリル基の脱保護反応に一般に用いられる条件（例えば、Ｔ．Ｗ．Ｇｒｅｅｎ ａｎｄ Ｐ．Ｇ．Ｍ．Ｗｕｔｓ，“Ｐｒｏｔｅｃｔｉｖｅ Ｇｒｏｕｐｓ ｉｎ Ｏｒｇａｎｉｃ Ｃｈｅｍｉｓｔｒｙ，Ｔｈｉｒｄ Ｅｄｉｔｉｏｎ”，Ｊｏｈｎ Ｗｉｌｅｙ＆Ｓｏｎｓ（１９９９，ｐ．１１３－１４８等の文献に記載の条件）と同様の条件で反応を行うことができる。具体的には例えば、テトラヒドロフランなどの有機溶媒中でフッ化テトラｎ－ブチルアンモニウムを作用させるか、エタノール中で塩酸を作用させることで化合物（Ｉ－１－Ｏ）を得ることができる。本反応に使用する溶媒は反応を阻害しないものであれば特に限定されないが、ジクロロメタン、メタノール、エタノール、プロパノール、酢酸エチル、テトラヒドロフラン、１，４－ジオキサン等が好ましい。また、酢酸の添加により収率向上等に良好な結果を得られる場合がある。

Ｐｒｔ１がベンジル基の場合、ベンジル基の脱保護反応に一般に用いられる条件（例えば、Ｔ．Ｗ．Ｇｒｅｅｎ ａｎｄ Ｐ．Ｇ．Ｍ．Ｗｕｔｓ，“Ｐｒｏｔｅｃｔｉｖｅ Ｇｒｏｕｐｓ ｉｎ Ｏｒｇａｎｉｃ Ｃｈｅｍｉｓｔｒｙ，Ｔｈｉｒｄ Ｅｄｉｔｉｏｎ”，Ｊｏｈｎ Ｗｉｌｅｙ＆Ｓｏｎｓ（１９９９），ｐ．７６－８６等の文献に記載の条件）と同様の条件で反応を行うことができる。具体的には例えば、エタノールなどの有機溶媒中でパラジウム－炭素、水酸化パラジウム－炭素等を触媒とする水素雰囲気下での接触還元法によって行うことができる。

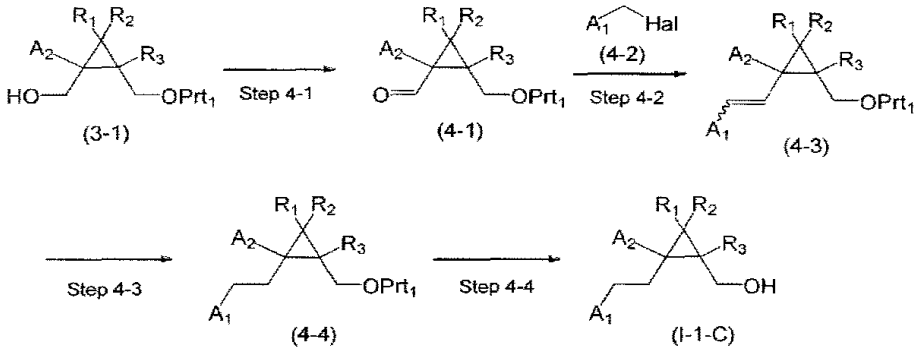
本反応に使用する溶媒は反応を阻害しないものであれば特に限定されないが、メタノール、エタノール、プロパノール、酢酸エチル、テトラヒドロフラン、１，４－ジオキサン等があげられる。反応条件は、特に限定されないが、室温～溶媒の還流温度、常圧から１５０気圧、好ましくは室温～６０℃、常圧～５気圧で行うことができる。

【００４８】

一般製造法４：

【化８】

Scheme 4



［式中、Ｐｒｔ１、Ａ１、Ａ２、Ｒ１、Ｒ２およびＲ３は前記と同じ意味を示す。］

一般的製造法４は、化合物（３－１）を原料として［工程４－１］から［工程４－４］の４工程を経由する本発明にかかる化合物（Ｉ）の合成中間体である化合物（Ｉ－１－Ｃ

）を製造する方法である。

化合物（Ｉ－１－Ｃ）は、市販品から当業者に公知の方法で製造することもでき、更に実施例中の製造例の記載の方法を用いて製造することもできる。

【００４９】

工程４－１

本工程は化合物（３－１）のアルコールを酸化しアルデヒド体（４－１）を得る工程である。本工程は工程２－１と同様の条件で、反応を行うことができる。

【００５０】

工程４－２

本工程は、アルデヒド（４－１）からオレフィン（４－３）を得る工程である。本反応は、通常用いられている条件で反応を行うことができる。具体的には、例えば、化合物（４－２）とトリフェニルホスフィンから合成されるＷｉｔｔｉｇ試薬を用い、塩基存在下に化合物（４－１）と反応させて化合物（４－３）を製造することができる。

【００５１】

工程４－３

本工程は、接触水素還元でオレフィンを還元する工程である。本反応は、通常用いられている条件で反応を行うことができる

【００５２】

工程４－４

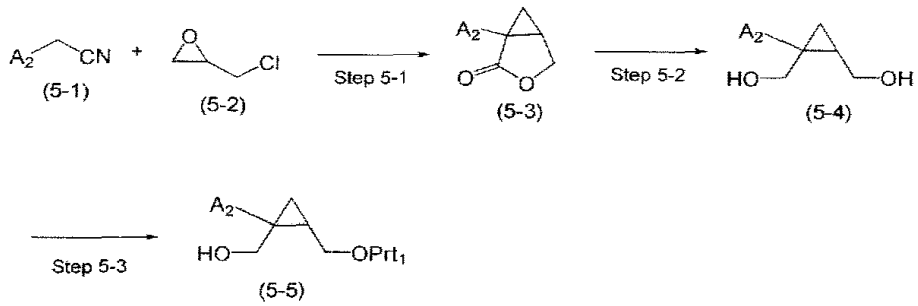
本工程は、化合物（４－３）を脱保護して、化合物（Ｉ－１－Ｃ）を得る工程である。工程３－２と同様の方法で行うことができる。

【００５３】

５．一般的製造法５：

【化９】

Scheme 5



［式中、Ｐｒｔ１およびＡ１は前記と同じ意味を示す。］

一般的製造法５は、化合物（５－１）を原料として［工程５－１］から［工程５－３］を経由する本発明にかかる化合物（Ｉ）の合成中間体である化合物（５－５）を製造する方法である。

化合物（５－５）は、市販品から当業者に公知の方法で製造することもでき、更に実施例中の製造例の記載の方法を用いて製造することもできる。

【００５４】

工程５－１

本工程は、アセトニトリル誘導体（５－１）とエピクロロヒドリン（５－２）を反応させ、化合物（５－３）を得る工程である。反応条件は、通常用いられている条件（例えば、Ｓ，Ｓｈｕｔｏ，Ｂｉｏｏｒｇａｎｉｃ　＆　Ｍｅｄｉｃｉｎａｌ　Ｃｈｅｍｉｓｔｒｙ，１０（２００２）３８２９）、あるいは実施例中の製造例の記載の方法を用いて製造することができる。また、光学活性なエピクロロヒドリンを用いることにより、（５－３）の光学活性体が得ることができる。

【００５５】

工程５－２

本工程は、ラクトン（５－３）を還元し、化合物（５－４）を得る工程である。反応に使用される還元剤としては、例えばソジウムボロハイドライド、リチウムボロハイドライド、リチウムアルミニウムハイドライド等を挙げることができる。

反応に使用される溶媒は、反応を阻害せず出発物質をある程度溶解するものであれば特に限定されないが、例えばテトラヒドロフラン、ジエチルエーテル、等があげられ、場合によってはメタノールなどのアルコール系溶媒を混合させる。反応温度は特に限定されないが、通常、－７８℃～溶媒の還流温度であり、好ましくは－７８℃～室温である。反応時間は、特に限定されないが、通常、５分～４８時間であり、好ましくは５分～２４時間である。

【００５６】

工程５－３

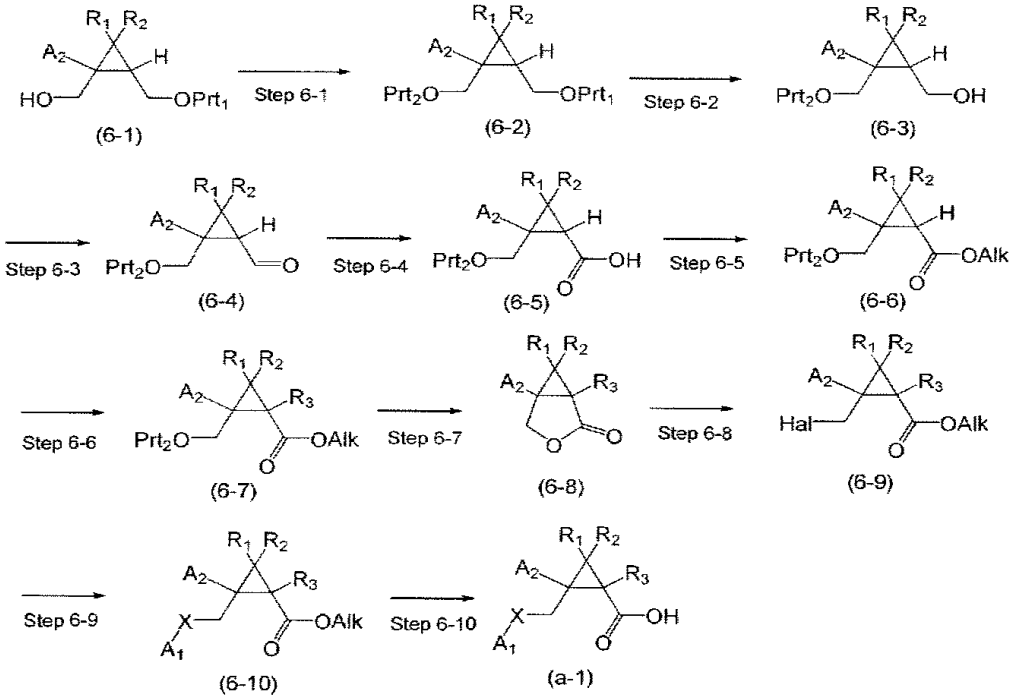
本工程は、化合物（５－４）の水酸基を保護する工程である。用いる保護基としては、例えばアセチル基、メトキシメチル基、トリチル基、ベンジル基、ｔ－ブチルジフェニルシリル基、トリイソプロピルシリル基などである。本反応は、水酸基の保護基導入に一般的に用いられる条件（例えば、Ｔ．Ｗ．Ｇｒｅｅｎ　ａｎｄ　Ｐ．Ｇ．Ｍ．Ｗｕｔｓ，“Ｐｒｏｔｅｃｔｉｖｅ　Ｇｒｏｕｐｓ　ｉｎ　Ｏｒｇａｎｉｃ　Ｃｈｅｍｉｓｔｒｙ，Ｔｈｉｒｄ　Ｅｄｉｔｉｏｎ”，Ｊｏｈｎ　Ｗｉｌｅｙ＆Ｓｏｎｓ（１９９９），ｐ．１７－２４５等の文献に記載の条件）と同様の条件で反応を行うことができる。また、実施例４９にあるように、酵素を用いたアセチル化によっても行うことが出来る。

【００５７】

６．一般的製造法６：

【化１０】

Scheme 6



［式中、ＡｌｋはＣ１－６アルキル基を示し、Ｈａｌはハロゲン原子を示し、であり、Ｐｒｔ１はｔ－ブチルジメチルシリル基、ｔ－ブチルジフェニルシリル基、トリイソプロピルシリル基などのシリル基であり、Ｐｒｔ２はシリル基以外の水酸基の保護基を示し、Ｘ、Ｒ１、Ｒ２、Ｒ３、Ａ１およびＡ２は前記と同じ意味を示す。］

一般的製造法６は、化合物（６－１）を原料として［工程６－１］から［工程６－１０］

の１０工程を経由する本発明にかかる化合物（Ｉ）の合成中間体である化合物（ａ－１）を製造する方法である。

【００５８】

工程６－１

本工程は、化合物（６－１）の水酸基を保護する工程である。用いる保護基としては、例えばメトキシメチル基、トリチル基、ベンジル基などであり、工程５－３に記載した通常用いられる条件によって保護基を導入することが出来る。

【００５９】

工程６－２

本工程は、化合物（６－２）の保護基を選択的に脱保護する工程である。脱保護の条件は、通常用いられる条件で行える。

【００６０】

工程６－３、６－４

本工程は一般製造法２の工程２－１，工程２－２と同様の方法により、化合物（６－３）からカルボン酸（６－５）を得る工程である。

【００６１】

工程６－５

本工程は、カルボン酸（６－５）をエステル化して化合物（６－６）を得る工程である。エステル化は、通常用いられる条件で行える。

【００６２】

工程６－６

本工程は、エステル体（６－６）のカルボニルα位炭素に置換基（Ｒ３）を導入する工程である。用いる塩基としては例えば、リチウムジイソプロピルアミドが良く、アルキル化剤としては、アルキルハライド、アルデヒド、ケトンなどが用いられる。反応に使用される溶媒は、反応を阻害せず出発物質をある程度溶解するものであれば特に限定されないが、例えばテトラヒドロフラン、ジエチルエーテル、等があげられる。反応温度は特に限定されないが、通常、－７８℃～溶媒の還流温度であり、好ましくは－７８℃～室温である。反応時間は、特に限定されないが、通常、５分～４８時間であり、好ましくは５分～２４時間である。

【００６３】

工程６－７

本工程は、化合物（６－７）の保護基を選択的に脱保護する工程である。通常、脱保護と同時に分子内でのラクトンへの環化も進行する。脱保護の条件は、通常用いられる条件で行える。

【００６４】

工程６－８

本工程は、化合物（６－８）をアルコール溶媒中、チオニルハライドと反応させ、ハロエステル（６－９）を得る工程である。反応に使用されるチオニルハライドとしてはチオニルブロマイドが良く、溶媒はメタノールやエタノールが好ましい。反応温度は特に限定されないが、通常、－７８℃～溶媒の還流温度であり、好ましくは－７８℃～室温である。反応時間は、特に限定されないが、通常、５分～４８時間であり、好ましくは５分～４８時間である。

【００６５】

工程６－９

本工程は、化合物（６－９）から、化合物（３－３）との求核置換反応により化合物（６－１０）を得る工程である。反応条件は一般的製造法３の化合物（３－２）から化合物（３－４）を製造する方法で良い。

【００６６】

工程６－１０

本工程は、化合物（６－１０）のエステル加水分解により、化合物（ａ－１）を得る工

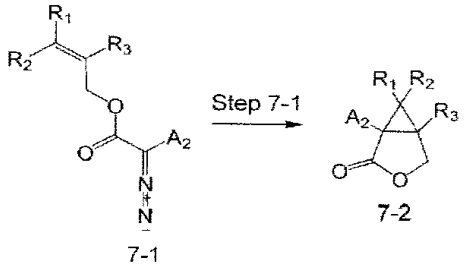
程である。反応条件としては、例えば水酸化ナトリウム水溶液や水酸化カリウム水溶液を用いることができ、必要に応じてメタノールやエタノールなどの有機溶媒を用いる。反応温度は特に限定されないが、通常、－７８℃～溶媒の還流温度であり、好ましくは室温～溶媒の還流温度である。反応時間は、特に限定されないが、通常、５分～４８時間である。

【００６７】

一般的製造法７：

一般的製造法７は、化合物（７－１）を原料として［工程７－１］を経由する本発明にかかる化合物（Ｉ）の合成中間体である化合物（７－２）を製造する方法である。化合物（７－１）は、市販品から当業者に公知の方法で製造することもでき、更に実施例中の製造例の記載の方法を用いて製造することもできる。

【化１１】



【００６８】

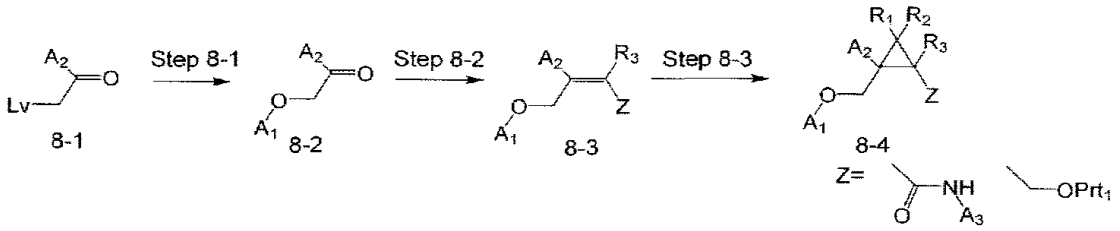
工程７－１

本工程はジアゾ化合物（７－１）から分子内環化を経て、化合物（７－２）を得る工程である。反応は、通常用いられる、ジアゾ化合物からカルベンを発生させることのできる条件で行うことができ、例えば、（Ｄｏｙｌｅ，Ｍ．Ｐ．，Ｏｒｇａｎｉｃ　Ｌｅｔｔｅｒｓ　２（８）１１４５－；Ｃｈｅｎ，Ｃ．，Ｂｉｏｏｒｇａｎｉｃ&Ｍｅｄｉｃｉｎａｌ　Ｃｈｅｍｉｓｔｒｙ　Ｌｅｔｔｅｒｓ，１８（２００８）３３２８－）に記載の方法で行える。

【００６９】

一般的合成法８：

【化１２】



一般的製造法８は、化合物（８－１）から［工程８－１］［工程８－２］および［工程８－３］を経由し、化合物（８－４）を製造する方法である。化合物（８－１）は、市販品から当業者に公知の方法で製造することができる。

【００７０】

工程８－１

本工程は一般的製造法３の化合物（３－２）から化合物（３－４）を製造する方法を用いて、化合物（８－１）から化合物（８－２）を製造する工程である。

【００７１】

工程８－２

本工程は、ｗｉｔｔｉｇあるいはＨｏｒｎｅｒ－Ｗａｄｓｗｏｒｔｈ－Ｅｍｍｏｎｓ反応により、ケトン体（８－２）からオレフィン（８－３）を得る工程である。本反応は、

通常用いられている条件で反応を行うことができる。

【００７２】

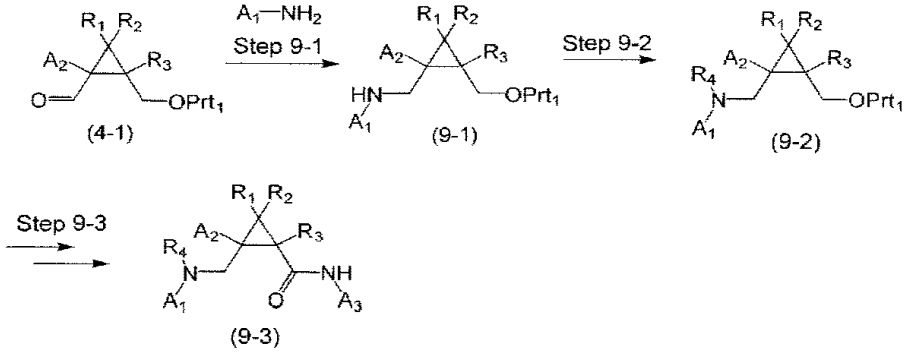
工程８－３

本工程はオレフィン（８－３）をシクロプロパン化することにより、化合物（８－４）を得る工程である。シクロプロパン化は、例えばＳｉｍｍｏｎｓ－Ｓｍｉｔｈ反応、あるいはジアゾ化合物とロジウムアセテートなどの金属触媒を組み合わせた条件でも行える。

【００７３】

一般的製造法９：

【化１３】



【００７４】

工程９－１

本工程は、化合物（４－１）から還元的アミノ化により化合物（９－１）を製造する工程である。反応条件は通常の還元的アミノ化の条件を用いることが出来るが、例えば還元剤としては、ソジウムボロハイドライド、ソジウムトリアセトキシボロハイドライド等を挙げることができる。

反応に使用される溶媒は、反応を阻害せず出発物質をある程度溶解するものであれば特に限定されないが、例えばテトラヒドロフラン、ＤＭＦ等があげられ、場合によっては酢酸などの酸を混合させる。反応温度は特に限定されないが、通常、－７８℃～溶媒の還流温度であり、好ましくは０℃～室温である。反応時間は、特に限定されないが、通常、５分～４８時間であり、好ましくは５分～２４時間である。

【００７５】

工程９－２

本工程は、化合物（９－１）から還元的アミノ化により化合物（９－２）を製造する工程である。反応条件は、工程９－１に準ずる。

【００７６】

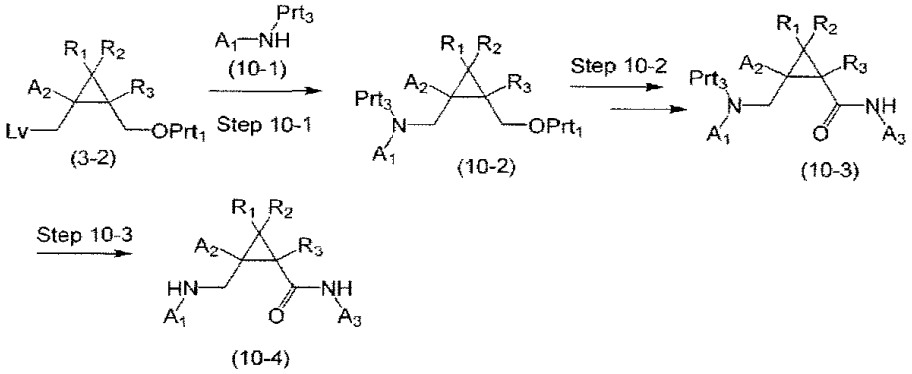
工程９－３

本工程は、化合物（９－２）から、工程３－２，工程２－１，工程２－２および一般的製造法１の方法に準じて化合物（９－３）を製造する工程である。

【００７７】

一般的製造法１０：

【化１４】



【００７８】

工程１０－１

本工程は化合物（３－２）と、アミドやカーバメートで保護されたアミン（１０－１）を塩基存在下で反応させ、化合物（１０－２）を製造する工程である。用いる塩基としては例えば、水素化ナトリウムや炭酸セシウム、水酸化ナトリウムなどが良く、反応に使用される溶媒は、反応を阻害せず出発物質をある程度溶解するものであれば特に限定されないが、例えばテトラヒドロフラン、アセトニトリル、ＤＭＦ等があげられる。反応温度は特に限定されないが、通常、０℃～溶媒の還流温度である。反応時間は、特に限定されないが、通常、５分～４８時間であり、好ましくは５分～２４時間である。また、保護基Ｐｒｔ$_3$としては例えばトリフルオロアセチル基のようなアミド系保護基、あるいはｔ－ブチルカーバーメートのようなカーバメート系保護基が好ましい。

【００７９】

工程１０－２

本工程は、化合物（１０－２）から工程９－３の方法に準じて、化合物（１０－３）を製造する工程である。

【００８０】

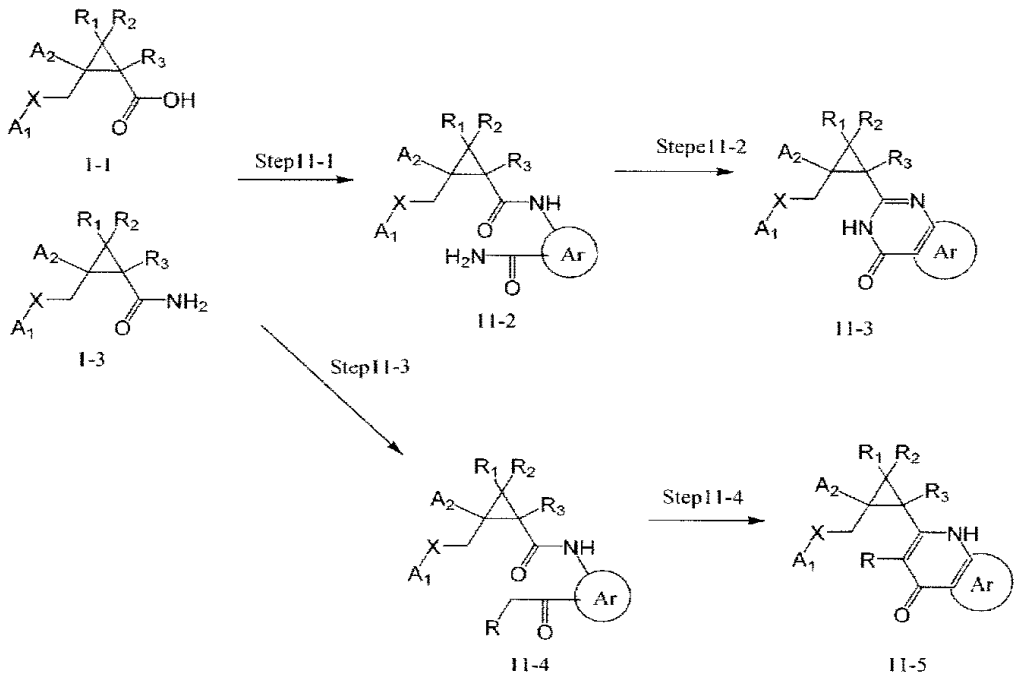
工程１０－３

本工程は、化合物（１０－３）から脱保護により化合物（１０－４）を製造する工程である。脱保護は、通常用いられている条件で行える。

【００８１】

一般的製造法１１

【化１５】



【００８２】

工程１１－１

本工程は、化合物（１－１）あるいは化合物（１－３）から、一般的製造法１に記載した条件によってアリールアミド体（１１－２）を合成する工程である。

【００８３】

工程１１－２

本工程は、化合物（１１－２）から塩基を用いた分子内環化反応により、縮環ピリミドン誘導体（１１－３）を合成する工程である。用いる塩基としては例えば、カリウムｔｅｒｔ－ブトキシド、水素化ナトリウム、炭酸セシウム、炭酸カリウム、ナトリウムエトキシドなどが好ましい。反応に使用される溶媒は、反応を阻害せず出発物質をある程度溶解するものであれば特に限定されないが、例えばテトラヒドロフラン、１，４－ジオキサン、ＤＭＦ、ＮＭＰ、アセトニトリル、エタノール、２－プロパノール等があげられる。反応温度は特に限定されないが、通常、０℃～溶媒の還流温度であり、好ましくは室温～溶媒の還流温度である。反応時間は、特に限定されないが、通常、５分～４８時間であり、好ましくは５分～２４時間である。

【００８４】

工程１１－３

本工程は、化合物（１－１）あるいは化合物（１－３）から、一般的製造法１に記載した条件によってアリールアミド体（１１－４）を合成する工程である。

【００８５】

工程１１－４

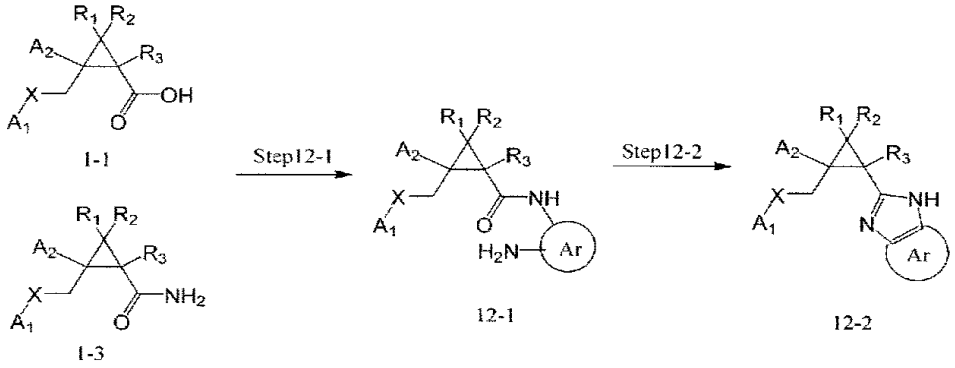
本工程は、化合物（１１－４）から塩基を用いた分子内環化反応により、縮環ピリドン誘導体（１１－５）を合成する工程である。用いる塩基としては例えば、カリウムｔｅｒｔ－ブトキシド、水素化ナトリウム、炭酸セシウム、炭酸カリウム、ナトリウムエトキシドなどが好ましい。反応に使用される溶媒は、反応を阻害せず出発物質をある程度溶解するものであれば特に限定されないが、例えばテトラヒドロフラン、１，４－ジオキサン、ＤＭＦ、ＮＭＰ、アセトニトリル、エタノール、２－プロパノール等があげられる。反応温度は特に限定されないが、通常、０℃～溶媒の還流温度であり、好ましくは室温～溶

媒の還流温度である。反応時間は、特に限定されないが、通常、５分～４８時間であり、好ましくは５分～２４時間である。

【００８６】

一般的製造法１２：

【化１６】



【００８７】

工程１２－１

本工程は、化合物（１－１）あるいは化合物（１－３）から、一般的製造法１に記載した条件によってアリールアミド体（１２－１）を合成する工程である。

【００８８】

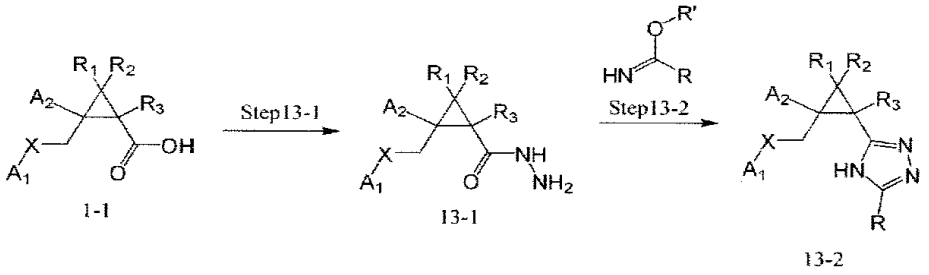
工程１２－２

本工程は、化合物（１２－１）から酸を用いた分子内環化反応により、縮環イミダゾール誘導体（１２－２）を合成する工程である。用いる酸としては例えば、酢酸、トリフルオロ酢酸、塩酸、ｐ－トルエンスルホン酸などが好ましい。反応に使用される溶媒は、反応を阻害せず出発物質をある程度溶解するものであれば特に限定されないが、例えば酢酸を溶媒として用いるか、あるいは、テトラヒドロフラン、１，４－ジオキサン、ＤＭＦ、ＮＭＰ、アセトニトリル、エタノール、２－プロパノール等があげられる。反応温度は特に限定されないが、通常、０℃～溶媒の還流温度であり、好ましくは室温～溶媒の還流温度である。反応時間は、特に限定されないが、通常、５分～４８時間であり、好ましくは５分～２４時間である

【００８９】

一般的製造法１３：

【化１７】



【００９０】

工程１３－１

本工程は、化合物（１－１）から、ヒドラジド（１３－１）を合成する工程である。用いる合成条件としては、一般的に知られている方法で行うことが出来るが、例えばモノ保護ヒドラジンと化合物（１－１）をアミド縮合後、脱保護することによって合成することができる。アミド化は工程（１－１）記載の方法で行うことが出来る。ヒドラジンの保護

基としては、特に限定されないが、例えば、ｔｅｒｔ－ブトキシカルボニル、ベンジルオキシカルボニル、トリフルオロアセチルなどが挙げられる。

【００９１】

工程１３－２

本工程は、化合物（１３－１）とイミデート誘導体を反応させトリアゾール誘導体（１３－２）を合成する工程である。反応は中性条件、あるいは酸や塩基を加えて行うことが出来る。用いる酸としては、酢酸、塩酸などが良く、塩基としては、イミダゾール、トリエチルアミン、炭酸カリウムなどが良い。反応に使用される溶媒は、反応を阻害せず出発物質をある程度溶解するものであれば特に限定されないが、例えば酢酸を溶媒として用いるか、あるいは、テトラヒドロフラン、１，４－ジオキサン、ＤＭＦ、ＮＭＰ、アセトニトリル、エタノール、２－プロパノール等があげられる。反応温度は特に限定されないが、通常、０℃～溶媒の還流温度であり、好ましくは室温～溶媒の還流温度である。反応時間は、特に限定されないが、通常、５分～４８時間であり、好ましくは５分～２４時間である。

【００９２】

かくして得られる本発明の式（Ｉ）の化合物は、必要に応じて、常法により、医薬上許容される塩とすることができる。その製造法は、有機合成化学分野で通常用いられる方法などを適宜組み合わせて行うことができる。具体的には、本発明化合物の遊離型の溶液を酸溶液で中和滴定することなどが挙げられる。また、必要に応じて、それ自体周知の溶媒和物形成反応に付すことにより、本発明の式（Ｉ）の化合物を溶媒和物に変換することができる。

【００９３】

本発明に係るシクロプロパン化合物又はその医薬上許容される塩あるいはそれらの溶媒和物は、極めて優れたオレキシン２受容体阻害作用を有し、オレキシンに起因する、不眠症に代表される睡眠障害の予防剤または治療剤として極めて有用である。具体的には、不眠症、ナルコレプシー（発作性睡眠）および過剰の眠気、睡眠関連ジストニア、下肢静止不能症候群、睡眠時無呼吸、時差ぼけ症候群、交代勤務症候群、遅延睡眠相症候群又は睡眠相前進症候群のその他の疾患などの睡眠障害の予防または治療に有効である。更には、気分変調性障害、気分障害、精神及び不安障害；糖尿病及び食欲、味覚、摂食、又は摂飲障害；視床下部疾患；生物学的及び概日リズム障害；神経疾患、神経因性疼痛及び下肢静止不能症候群から選ばれる疾病に不随する睡眠障害；精神障害に関連した不眠症；うつ病とうつ病に関連した不眠症；双極性障害と双極性障害に関連した不眠症；不安障害と不安障害に関連した不眠症；パーキンソン症に関連した不眠症；統合失調症に関連した不眠症；睡眠時無呼吸；麻薬依存症；ニコチン依存症；ナルコレプシー；特発性不眠症；睡眠時随伴症；良性前立腺肥大症；健康な集団における並びに精神及び神経疾患における全認知症及び認知機能障害；並びに全身のオレキシン系機能不全に関連した他の疾病などの疾病の予防又は治療に有効である。

【００９４】

本発明に係るシクロプロパン化合物又はその医薬上許容される塩あるいはそれらの溶媒和物は、通常の方法により製剤化が可能であり、好ましい剤形としては、例えば、錠剤、フィルム錠や糖衣錠等の被覆錠剤、細粒剤、顆粒剤、散剤、カプセル剤、シロップ剤、トローチ剤、吸入剤、坐剤、注射剤、軟膏剤、点眼剤、点鼻剤、点耳剤、パップ剤、ローション剤等が挙げられる。

これらの錠剤、カプセル剤、顆粒剤、粉末などの固形製剤は、一般的には０．０１～１００重量％、好ましくは０．１～１００重量％の有効成分である本発明に係るシクロプロパンカルボン酸誘導体又はその医薬上許容される塩あるいはそれらの溶媒和物を含むことができる。

【００９５】

製剤化には、一般に医薬品製剤の原料として用いられる成分を配合し、例えば、通常用いられる賦形剤、崩壊剤、結合剤、滑沢剤、着色剤、矯味矯臭剤や、必要により安定化剤

、乳化剤、吸収促進剤、界面活性剤、ｐＨ調整剤、防腐剤、抗酸化剤等を添加して常法により製剤化を行う。これらの成分としては、例えば、大豆油、牛脂、合成グリセライド等の動植物油；流動パラフィン、スクワラン、固形パラフィン等の炭化水素；ミリスチン酸オクチルドデシル、ミリスチン酸イソプロピル等のエステル油；セトステアリルアルコール、ベヘニルアルコール等の高級アルコール；シリコン樹脂；シリコン油；ポリオキシエチレン脂肪酸エステル、ソルビタン脂肪酸エステル、グリセリン脂肪酸エステル、ポリオキシエチレンソルビタン脂肪酸エステル、ポリオキシエチレン硬化ひまし油、ポリオキシエチレンポリオキシプロピレンブロックコポリマー等の界面活性剤；ヒドロキシエチルセルロース、ポリアクリル酸、カルボキシビニルポリマー、ポリエチレングリコール、ポリビニルピロリドン、メチルセルロース等の水溶性高分子；エタノール、イソプロパノール等の低級アルコール；グリセリン、プロピレングリコール、ジプロピレングリコール、ソルビトール等の多価アルコール；グルコース、ショ糖等の糖；無水ケイ酸、ケイ酸アルミニウムマグネシウム、ケイ酸アルミニウム等の無機粉体、精製水等が挙げられる。賦形剤としては、例えば乳糖、コーンスターチ、白糖、ブドウ糖、マンニトール、ソルビット、結晶セルロース、二酸化ケイ素等が、結合剤としては、例えばポリビニルアルコール、ポリビニルエーテル、メチルセルロース、エチルセルロース、アラビアゴム、トラガント、ゼラチン、シェラック、ヒドロキシプロピルメチルセルロース、ヒドロキシプロピルセルロース、ポリビニルピロリドン、ポリプロピレングリコール・ポリオキシエチレン・ブロックポリマー、メグルミン等が、崩壊剤としては、例えば澱粉、寒天、ゼラチン末、結晶セルロース、炭酸カルシウム、炭酸水素ナトリウム、クエン酸カルシウム、デキストリン、ペクチン、カルボキシメチルセルロース・カルシウム等が、滑沢剤としては、例えばステアリン酸マグネシウム、タルク、ポリエチレングリコール、シリカ、硬化植物油等が、着色剤としては医薬品に添加することが許可されているものが、矯味矯臭剤としては、ココア末、ハッカ脳、芳香散、ハッカ油、竜脳、桂皮末等が用いられる。もちろん、これらの添加剤成分に限定される訳ではないことは言うまでもない。

【００９６】

例えば経口製剤は、有効成分である本発明に係るシクロプロパン化合物又はその医薬上許容される塩あるいはそれらの溶媒和物と賦形剤、さらに必要に応じて結合剤、崩壊剤、滑沢剤、着色剤、矯味矯臭剤等を加えた後、常法により散剤、細粒剤、顆粒剤、錠剤、被覆錠剤、カプセル剤等とする。錠剤・顆粒剤の場合には、糖衣、その他必要により適宜コーティングすることはもちろん差支えない。

例えばシロップ剤や注射用製剤等の場合は、ｐＨ調整剤、溶解剤、等張化剤等と、必要に応じて溶解補助剤、安定化剤等を加えて、常法により製剤化する。また、これらの注射剤は予め溶解したものの他、粉末のままたは適当な添加物を加えたものを用時溶解する形態も取ることができる。これらの注射液は、通常０．０１～１００重量％、好ましくは０．１～１００重量％等の有効成分を含むことができる。さらには、経口投与の懸濁剤またはシロップ剤等の液剤は、通常０．０１～１００重量％、好ましくは０．１～１００重量％等の有効成分を含むことができる。

例えば、外用剤の場合は、特に製法が限定されず、常法により製造することができる。使用する基剤原料としては、医薬品、医薬部外品、化粧品等に通常使用される各種原料を用いることが可能で、例えば動植物油、鉱物油、エステル油、ワックス類、高級アルコール類、脂肪酸類、シリコン油、界面活性剤、リン脂質類、アルコール類、多価アルコール類、水溶性高分子類、粘土鉱物類、精製水等の原料が挙げられ、必要に応じ、ｐＨ調整剤、抗酸化剤、キレート剤、防腐防黴剤、着色料、香料等を添加することができる。さらに、必要に応じて分化誘導作用を有する成分、血流促進剤、殺菌剤、消炎剤、細胞賦活剤、ビタミン類、アミノ酸、保湿剤、角質溶解剤等の成分を配合することもできる。

【００９７】

本発明に係るシクロプロパン化合物又はその医薬上許容される塩あるいはそれらの溶媒和物の投与量は、症状の程度、年齢、性別、体重、投与形態・塩の種類、疾患の具体的な種類等に応じて異なるが、通常、成人の場合は１日あたり経口投与で約３０μｇ～１０ｇ

、好ましくは１００μｇ～５ｇ、さらに好ましくは１００μｇ～１ｇを、注射投与で約３０μｇ～１ｇ、好ましくは１００μｇ～５００ｍｇ、さらに好ましくは１００μｇ～３００ｍｇをそれぞれ１回又は数回に分けて投与する。

【００９８】

本発明の化合物は生理活性低分子化合物の標的タンパクを捕捉するためのケミカルプローブとすることができる。すなわち、本発明の化合物は、当該化合物の活性発現に必須な構造部分とは異なる部分に、Ｊ．Ｍａｓｓ　Ｓｐｅｃｔｒｕｍ．Ｓｏｃ．Ｊｐｎ．Ｖｏｌ．５１，Ｎｏ．５，２００３，ｐ４９２－４９８または　ＷＯ２００７／１３９１４９等に記載の手法で標識基、リンカー等を導入することでアフィニティークロマトグラフィープローブ、フォトアフィニティープローブ等に変換することができる。

ケミカルプローブに用いる標識基、リンカー等は、例えば以下の（１）ないし（５）からなる群に示される基が挙げられる。

（１）光親和性標識基（例えば、ベンゾイル基、ベンゾフェノン基、アジド基、カルボニルアジド基、ジアジリジン基、エノン基、ジアゾ基およびニトロ基等）および化学親和性基（例えば、アルファー炭素原子がハロゲン原子で置換されたケトン基、カルバモイル基、エステル基、アルキルチオ基、α、βー不飽和ケトン、エステル等のマイケル受容体、およびオキシラン基等）等のタンパク質標識基、

（２）－Ｓ－Ｓ－、－Ｏ－Ｓｉ－Ｏ－、単糖（グルコース基、ガラクトース基等）または二糖（ラクトース等）等の開裂可能なリンカー、および酵素反応で開裂可能なオリゴペプチドリンカー、

（３）ビオチン、３－（４，４－ジフルオロ－５，７－ジメチル－４Ｈ－３ａ，４ａ－ジアザ－４－ボラ－ｓ－インダセン－３－イル）プロピオニル基等のフィッシングタグ基、

（４）^{125}Ｉ、^{32}Ｐ、^{3}Ｈ、^{14}Ｃなどの放射性標識基；フルオレセイン、ローダミン、ダンシル、ウンベリフェロン、７－ニトロフラザニル、３－（４，４－ジフルオロ－５，７－ジメチル－４Ｈ－３ａ，４ａ－ジアザ－４－ボラ－ｓ－インダセン－３－イル）プロピオニル基等の蛍光標識基；ルミフェリン、ルミノール等の化学発光基；ランタノイド金属イオン、ラジウムイオン等の重金属イオン等の検出可能なマーカー、または

（５）ガラスビーズ、ガラスベット、マイクロタイタープレート、アガロースビーズ、アガロースベッド、ポリスチレンビーズ、ポリスチレンベッド、ナイロンビーズ、ナイロンベッド等の固相担体と結合させる基等。

上記の（１）ないし（５）からなる群より選択される標識基等を上記文献に記載の方法等に準じて本発明の化合物に導入して調製されるプローブは、新たな創薬ターゲットの探索等に有用な標識タンパクの同定のためのケミカルプローブとして用いることができる。

【００９９】

以下、本発明を実施例、製造例及び試験例により詳細に説明する。しかし、本発明はこれらに限定されることはない。また、実施例において使用される略語は当業者に周知の慣用的な略語である、いくつかの略語は以下に示す。

ＴＨＦ；テトラヒドロフラン

ＤＭＦ；Ｎ，Ｎ－ジメチルホルムアミド

ＴＦＡ；トリフルオロ酢酸

ＥＤＣ・ＨＣｌ；１－エチル－３－（３－ジメチルアミノプロピル）カルボジイミド塩酸塩

ＨＡＴＵ；Ｏ－（７－アザベンゾトリアゾール－１－イル）－Ｎ，Ｎ，Ｎ’，Ｎ’－テトラメチルウロニウム　ヘキサフルオルホスフェート

ＨＢＴＵ；Ｏ－ベンゾトリアゾール－１－イル－Ｎ，Ｎ，Ｎ’，Ｎ’－テトラメチルウロニウム　ヘキサフルオルホスフェート

ｐＴＬＣ；分取薄層クロマトグラフィー

ＬＣ－ＭＳ；液体クロマトグラフィー－マススペクトルメトリー

ＰｙＢＯＰ；ベンゾトリアゾール－１－イルオキシトリス（ピロリジノ）ホスホニウムヘ

キサフルオロホスフェート
Pd_2DBA_3；トリス（ジベンジリデンアセトン）ジパラジウム
$Pd(t-Bu_3P)_2$；ビス（トリ－ｔ－ブチルホスフィン）パラジウム
プロトン核磁気共鳴スペクトルの化学シフトは、テトラメチルシランに対するδ単位（ｐｐｍ）で記録、カップリング定数はヘルツ（Ｈｚ）で記録されている。パターンは、ｓ；シングレット、ｄ；ダブレット、ｔ；トリプレット、ｑ；カルテット、ｂｒ；ブロード。

【０１００】

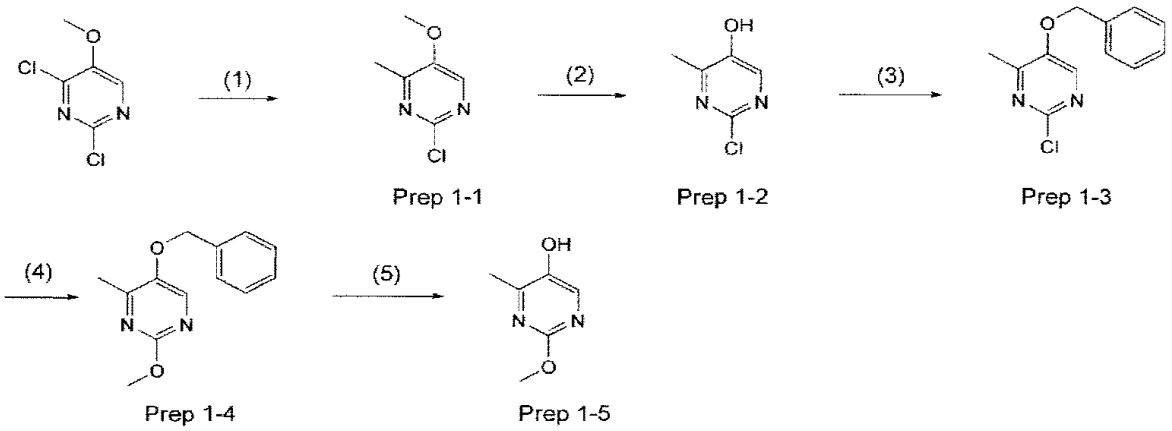
以下の実施例及び製造例中の「室温」は通常約１０℃から約３５℃を示す。％は特記しない限り重量パーセントを示す。

【０１０１】

製造例１

２－メトキシ－４－メチルピリミジン－５－オール（Ｐｒｅｐ１－５）の合成

【化１８】



【０１０２】

（１）２－クロロ－５－メトキシ－４－メチルピリミジン（Ｐｒｅｐ１－１）

２，４－ジクロロ－５－メトキシピリミジン（１０ｇ）をＴＨＦ（１００ｍｌ）に溶解し、冷却下鉄（III）アセチルアセトン（１．９７ｇ）、メチルマグネシウムクロリド（Ａｌｄｒｉｃｈ，３．０Ｍ：２２．４ｍｌ）を加えた。室温で終夜撹拌させた。さらに２回、鉄（III）アセチルアセトン（１．９７ｇ）、メチルマグネシウムクロリド（Ａｌｄｒｉｃｈ，３．０Ｍ：２２．４ｍｌ）を加えた。反応系に１Ｎ塩酸水溶液を加えジエチルエーテルにて分液抽出した。有機層を硫酸マグネシウムで乾燥し、溶媒を減圧下濃縮した。得られた残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，溶出溶媒：ｎ－ヘプタン：酢酸エチル）で精製して標記化合物（６．６ｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，$CDCl_3$）δ（ｐｐｍ）：２．４６（ｓ，３Ｈ），３．９２（ｓ，３Ｈ），８．０６（ｓ，１Ｈ）．

【０１０３】

（２）２－クロロ－４－メチルピリミジン－５－オール（Ｐｒｅｐ１－２）

ボロントリブロミドのジクロロメタン溶液（Ａｌｄｒｉｃｈ，１．０Ｍ：１００ｍｌ）に化合物Ｐｒｅｐ１－１（６．６ｇ）のジクロロメタン（５０ｍｌ）溶液を滴下し室温で４日間撹拌させた。反応系にメタノールを加え５Ｎ水酸化ナトリウム水溶液を加え中和し、ｐＨが２～３程度でクロロホルム、酢酸エチルで順次分液抽出した。有機層を硫酸マグネシウムで乾燥し、溶媒を減圧下濃縮した。得られた残渣にジエチルエーテルを加え固化させ、濾取乾燥して標記化合物を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，$DMSO-d_6$）δ（ｐｐｍ）：２．３２（ｓ，３Ｈ），８．０９（ｓ，１Ｈ），１０．６１（ｓ，１Ｈ）．

【０１０４】

（３）５－ベンジルオキシ－２－クロロ－４－メチルピリミジン（Ｐｒｅｐ１－３）

化合物Ｐｒｅｐ１－２（２００ｍｇ）のＴＨＦ（４．０ｍｌ）溶液にＮａＨを加え室温で１０分間撹拌させた後、ベンジルブロミド（１９７μｌ）を加えた。２時間室温で撹拌させた後、ＤＭＦ（２．０ｍｌ）を加え４時間撹拌させた。反応系に飽和塩化アンモニウム水溶液を加えジエチルエーテルで分液抽出した。得られた有機層を硫酸マグネシウムで乾燥し、溶媒を減圧下濃縮した。得られた残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，溶出溶媒：ｎ－ヘプタン：酢酸エチル）で精製して標記化合物（３１７ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：２．５１（ｓ，３Ｈ），５．１５（ｓ，２Ｈ），７．３７－７．４０（ｍ，５Ｈ），８．１０（ｓ，１Ｈ）．

【０１０５】

（４）５－ベンジルオキシ－２－メトキシ－４－メチルピリミジン（Ｐｒｅｐ１－４）

Ｐｒｅｐ１－３（３１０ｍｇ）のＤＭＦ（４．０ｍｌ）溶液にソディウムメトキシド（１４３ｍｇ）を加え７０℃にて２時間撹拌させた。反応系を放冷し１Ｎ塩酸水溶液を加え、ジエチルエーテルにて分液抽出した。得られた有機層を硫酸マグネシウムで乾燥し、溶媒を減圧下濃縮した。得られた残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，溶出溶媒：ｎ－ヘプタン：酢酸エチル）で精製して標記化合物（２２０ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：２．４４（ｓ，３Ｈ），３．９３（ｓ，１Ｈ），５．０７（ｓ，２Ｈ），７．３５－７．４１（ｍ，５Ｈ），７．９９（ｓ，１Ｈ）．

【０１０６】

（５）２－メトキシ－４－メチルピリミジン－５－オール（Ｐｒｅｐ１－５）

化合物Ｐｒｅｐ１－４（２２０ｍｇ）のメタノール（８．０ｍｌ）溶液に、水酸化パラジウムを加え水素雰囲気下２時間３０分間撹拌させた。反応混合物をセライトろ過し、得られたろ液を減圧濃縮して、粗標記化合物（１３０ｍｇ）を得た。

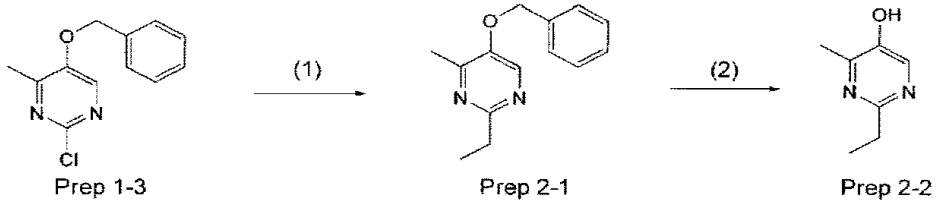
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＤＭＳＯ－ｄ$_6$）δ（ｐｐｍ）：２．２６（ｓ，３Ｈ），３．７７（ｓ，１Ｈ），７．９５（ｓ，１Ｈ）．

【０１０７】

製造例２

２－エチル－４－メチルピリミジン－５－オール（Ｐｒｅｐ２－２）の合成

【化１９】



Prep 1-3　　Prep 2-1　　Prep 2-2

【０１０８】

（１）５－ベンジルオキシ－２－エチル－４－メチルピリミジン（Ｐｒｅｐ２－１）

化合物Ｐｒｅｐ１－３（７９３ｍｇ）のＴＨＦ溶液（１０ｍｌ）に炭酸カリウム（１．４ｇ）、１，１－ビス（ジフェニルフォスフィノ）フェロセンパラジウム（II），ジクロロメタン（２７６ｍｇ）を加えた後ジエチル亜鉛（ＫＡＮＴＯ，１Ｍ：３．７２ｍｌ）を加え６５℃にて終夜撹拌させた。反応系に水を加え酢酸エチルで分液抽出。得られた有機層を硫酸マグネシウムで乾燥し、溶媒を減圧下濃縮した。得られた残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，溶出溶媒：ｎ－ヘプタン：酢酸エチル）で精製して標記化合物（４００ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．３２（ｔ，Ｊ＝８．０Ｈｚ，１Ｈ），２．４９（ｓ，３Ｈ），２．８６（ｄ，Ｊ＝８．０Ｈｚ，１Ｈ），２．９０

（ｄ，Ｊ＝７．６Ｈｚ，１Ｈ），５．１３（ｓ，２Ｈ），７．３３－７．４３（ｍ，５Ｈ），８．１６（ｓ，１Ｈ）．

【０１０９】

（２）２－エチル－４－メチルピリミジン－５－オール（Ｐｒｅｐ２－２）

化合物Ｐｒｅｐ２－１（２２０ｍｇ）のメタノール（８．０ｍｌ）溶液に、水酸化パラジウムを加え水素雰囲気下２時間３０分間撹拌させた。反応混合物をセライトろ過し、得られたろ液を減圧濃縮して、粗標記化合物（１３０ｍｇ）を得た。

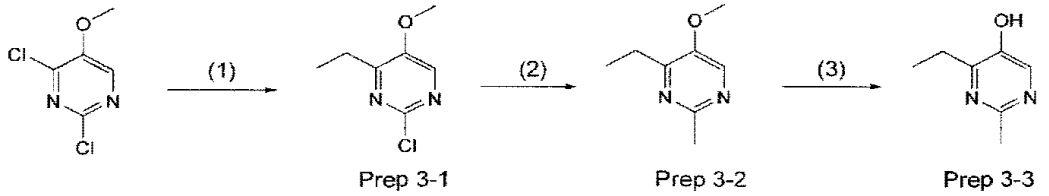
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．３０（ｔ，Ｊ＝８．０Ｈｚ，１Ｈ），２．４８（ｓ，３Ｈ），２．８３（ｄ，Ｊ＝８．０Ｈｚ，１Ｈ），２．８８（ｄ，Ｊ＝８．０Ｈｚ，１Ｈ），８．０４（ｓ，１Ｈ）．

【０１１０】

製造例３

４－エチル－２－メチルピリミジン－５－オール（Ｐｒｅｐ３－３）の合成

【化２０】



【０１１１】

（１）２－クロロ－４－エチル－５－メトキシピリミジン（Ｐｒｅｐ３－１）

２，４－ジクロロ－５－メトキシピリミジン（５ｇ）をＴＨＦ（５０ｍｌ）に溶解し、冷却下鉄（III）アセチルアセトン（９８５ｍｇ）、エチルマグネシウムクロリド（ＫＡＮＴＯ，０．９１Ｍ：３６．９ｍｌ）を加えた。室温で終夜撹拌させた。さらに２回、鉄（III）アセチルアセトン（９８５ｍｇ）、メチルマグネシウムクロリド（ＫＡＮＴＯ，０．９１Ｍ：３６．９ｍｌ）を加えた。反応系に１Ｎ塩酸水溶液を加えジエチルエーテルにて分液抽出した。有機層を硫酸マグネシウムで乾燥し、溶媒を減圧下濃縮した。得られた残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，溶出溶媒：ｎ－ヘプタン：酢酸エチル）で精製して標記化合物（１ｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．２５（ｔ，Ｊ＝８．０Ｈｚ，１Ｈ），２．７８（ｄ，Ｊ＝７．６Ｈｚ，１Ｈ），２．８２（ｄ，Ｊ＝８．０Ｈｚ，１Ｈ），３．９２（ｓ，３Ｈ），８．０６（ｓ，１Ｈ）．

【０１１２】

（２）４－エチル－５－メトキシ－２－メチルピリミジン（Ｐｒｅｐ３－２）

化合物Ｐｒｅｐ３－１（１．０ｇ）のＴＨＦ（１５．０ｍｌ）溶液に、トリメチルアルミウム（ＡＬＤＲＩＣＨ，２．０Ｍ：６．９５ｍｌ）、テトラキストリフェニルフォスフィンパラジウム（０）（３３５ｍｇ）を加え７０℃にて２日間撹拌させた。反応液を氷水に滴下した後、１Ｎ塩酸で中性～弱酸性にし、酢酸エチルで分液抽出した。有機層を硫酸マグネシウムで乾燥し、溶媒を減圧下濃縮した。得られた残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，溶出溶媒：ｎ－ヘプタン：酢酸エチル）で精製して標記化合物（７３６ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．２４（ｔ，Ｊ＝７．６Ｈｚ，１Ｈ），２．６４（ｓ，３Ｈ），２．７６（ｄ，Ｊ＝７．６Ｈｚ，１Ｈ），２．８０（ｄ，Ｊ＝７．６Ｈｚ，１Ｈ），３．８９（ｓ，１Ｈ），８．１０（ｓ，１Ｈ）．

【０１１３】

（３）４－エチル－２－メチルピリミジン－５－オール（Ｐｒｅｐ３－３）

化合物Ｐｒｅｐ３－２（５．１２ｇ）のジクロロメタン溶液（６９．６ｍｌ）に、ボロントリブロミド（ＴＣＩ－ＪＰ；１．０Ｍ，１１８ｍｌ）を滴下した。室温で４日間撹拌

させた後、アンモニア／メタノールを加えクエンチした。中性～弱酸性にした反応液をろ過し、ろ液を減圧濃縮し、得られた残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，溶出溶媒：酢酸エチル→酢酸エチル：メタノール）で精製して標記化合物（４．０ｇ）を得た。

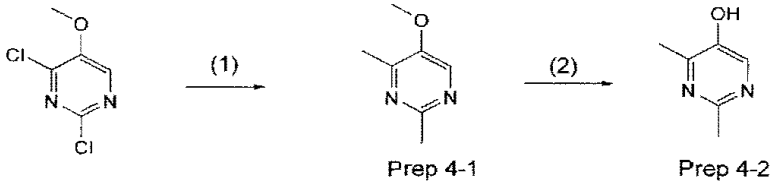
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．１３（ｔ，Ｊ＝８．０Ｈｚ，１Ｈ），２．４３（ｓ，３Ｈ），２．６１（ｄ，Ｊ＝８．０Ｈｚ，１Ｈ），２．６５（ｄ，Ｊ＝７．６Ｈｚ，１Ｈ），８．０４（ｓ，１Ｈ），９．８５（ｓ，１Ｈ）．

【０１１４】

製造例４

２，４－ジメチルピリミジン－５－オール（Ｐｒｅｐ４－２）の合成

【化２１】



【０１１５】

（１）５－メトキシ－２，４－ジメチルピリミジン（Ｐｒｅｐ４－１）

２，４－ジクロロ－５－メトキシピリミジン（５．３ｇ）をＴＨＦ（５１．３ｍｌ）に溶解し、テトラキストリフェニルフォスフィンパラジウム（０）（１．７１ｇ）、トリメチルアルミニウム（Ａｌｄｒｉｃｈ，２．０Ｍ：５１．８ｍｌ）を加えた。７５℃に昇温させ終夜撹拌させた。さらに１当量のトリメチルアルミニウムを加え６時間撹拌させた後、氷冷下飽和塩化アンモニウムを滴下し、クロロホルムにて分液抽出した。有機層を硫酸マグネシウムで乾燥し、溶媒を減圧下濃縮した。得られた残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，溶出溶媒：ｎ－ヘプタン：酢酸エチル→酢酸エチル）で精製して標記化合物（４．２ｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：２．４２（ｓ，３Ｈ），２．６３（ｓ，３Ｈ），３．８８（ｓ，３Ｈ），８．０８（ｓ，１Ｈ）．

【０１１６】

（２）２，４－ジメチルピリミジン－５－オール（Ｐｒｅｐ４－２）

ボロントリブロミド（ＴＣＩ－ＪＰ；１．０Ｍ，４００．０ｍｌ）溶液に化合物Ｐｒｅｐ４－１（１５．５ｇ）のジクロロメタン溶液（１００．０ｍｌ）を滴下した。室温で４日間撹拌させた後、メタノールでクエンチした。アンモニア／メタノールを加え中性～弱酸性にした反応液をろ過し、ろ液を減圧濃縮し、得られた残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，溶出溶媒：酢酸エチル→エタノール）で精製して標記化合物（１０．１ｇ）を得た。

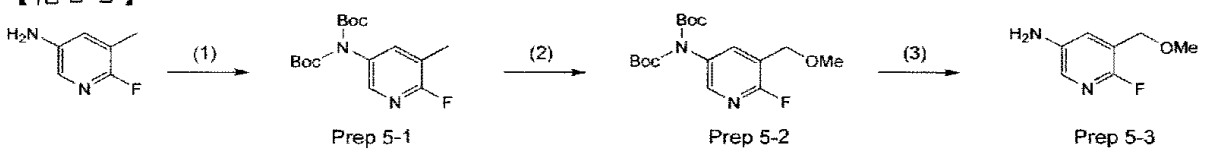
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＤＭＳＯ－ｄ$_6$）δ（ｐｐｍ）：２．２６（ｓ，３Ｈ），２．４１（ｓ，３Ｈ），８．０２（ｓ，１Ｈ）．

【０１１７】

製造例５

６－フルオロ－５－メトキシメチルピリジン－３－アミン（Ｐｒｅｐ５－３）の合成

【化２２】



【０１１８】

（１）ジ－ｔｅｒｔ－ブチル（６－フルオロ－５－メチルピリジン－３－イル）－イミド

ジカルボネート（Ｐｒｅｐ　５－１）

５－アミノ－２－フルオロ－３－ピコリン（０．５ｇ）のＴＨＦ（１０ｍｌ）溶液に、ジ－ｔｅｒｔ－ブチルカルボネート（２．５９ｇ）と触媒量の４－ジメチルアミノピリジン（０．０１ｇ）を加え、室温で６７時間攪拌した。反応液に水を加え、酢酸エチル（ｘ３）で抽出した。水で洗浄し、無水硫酸ナトリウムで乾燥した。溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィー（クロロホルム）で精製して標記化合物（１．１４ｇ）を得た。

【０１１９】

（２）ジ－ｔｅｒｔ－ブチル［６－フルオロ－５－メトキシメチルピリジン－３－イル］－イミドジカルボネート（Ｐｒｅｐ５－２）

化合物Ｐｒｅｐ５－１（５００ｍｇ）とＮ－ブロモスクシンイミド（２７２ｍｇ）をテトラクロロメタン（５ｍｌ）に溶解し、２，２’－アゾビス（イソブチルナイトレイト）（２５．１ｍｇ）を加えた後、８０℃で５時間攪拌した。反応液に水を加え、酢酸エチル（ｘ３）で抽出した。水で洗浄し、無水硫酸ナトリウムで乾燥した。溶媒を減圧下留去した後、残渣をメタノール（５ｍｌ）に溶解し、ナトリウムメトキシド（４１３ｍｇ）を加え、室温にて１時間攪拌した。反応液に水を加え、酢酸エチル（ｘ３）で抽出した。水で洗浄し、無水硫酸ナトリウムで乾燥した。溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝２０：１から２：１）で標記化合物を得た。

【０１２０】

（３）６－フルオロ－５－メトキシメチルピリジン－３－アミン（Ｐｒｅｐ５－３）

化合物Ｐｒｅｐ５－２のジクロロメタン（５ｍｌ）溶液にトリフルオロ酢酸（１ｍｌ）を加え、室温にて１時間攪拌した。反応液に飽和炭酸水素ナトリウム水溶液を加え、ジクロロメタン（ｘ３）で抽出した。水で洗浄し、無水硫酸ナトリウムで乾燥した。溶媒を減圧下留去し、標的化合物（６０ｍｇ）を得た。

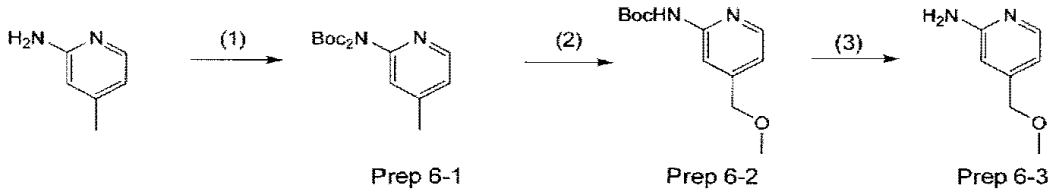
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：３．４３（ｓ，３Ｈ），４．４３（ｓ，３Ｈ），７．２０（ｄｄｔ，Ｊ＝８．０，２．４，０．８Ｈｚ，１Ｈ），７．５３（ｔ，Ｊ＝２．４，Ｈｚ，１Ｈ）．

【０１２１】

製造例６

４－メトキシメチルピリジン－２－アミン（Ｐｒｅｐ６－３）の合成

【化２３】



【０１２２】

（１）ジ－ｔｅｒｔ－ブチル（４－メチルピリジン－２－イル）イミドジカルボネート（Ｐｒｅｐ６－１）

２－アミノ－４－メチルピリジン（１．０ｇ）のジクロロメタン（５０ｍｌ）溶液に、ジ－ｔｅｒｔ－ブチルカルボネート（４．０４ｇ）、４－ジメチルアミノピリジン（２２６ｍｇ）およびトリエチルアミン（５．１７ｍｌ）を加え、室温で７２時間攪拌した。反応液に水を加え、酢酸エチル（ｘ１）で抽出した。有機層を水、飽和食塩水溶液で順次洗浄後、無水硫酸マグネシウムで乾燥し、濾過した。濾液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチルで精製し標記化合物（１．７ｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．４５（ｓ，１８Ｈ），２．３７（ｓ，３Ｈ），７．０３（ｄｄ，Ｊ＝０．８，５．２Ｈｚ，１Ｈ），７．０５（ｄ

，Ｊ＝０．８Ｈ，１Ｈ），８．３４（ｄ，Ｊ＝５．２Ｈｚ，１Ｈ）．
ＭＳ［Ｍ＋Ｈ］$^{+}$＝３０９

【０１２３】

（２）ｔｅｒｔ－ブチル（４－メトキシメチルピリジン－２－イル）カルバメート（Ｐｒｅｐ６－２）

化合物Ｐｒｅｐ６－１（３００ｍｇ）、Ｎ－ブロモスクシンイミド（１７３ｍｇ）のテトラクロロメタン（１０ｍｌ）溶液に、ベンゾイルパーオキサイド（２３．６ｍｇ）を加えた。１時間加熱還流させた後、２，２’－アゾビス（イソブチルナイトレイト）（１６．０ｍｇ）を加え、さらに５時間加熱還流させた。反応液を室温まで冷却後、セライト濾過した。濾液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル）で精製し対応するベンジルブロマイド体を得た。

得られたブロマイド体のメタノール（３ｍｌ）溶液に、ナトリウムメトキシド（Ａｌｄｒｉｃｈ，２５％メタノール溶液：１ｍｌ）を加え、室温にて１９時間攪拌した。反応溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝４：１から３：２）で精製し標記化合物（６２ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：１．５３（ｓ，９Ｈ），３．４２（ｓ，３Ｈ），４．４６（ｓ，２Ｈ），６．９６－６．９７（ｍ，１Ｈ），７．９１（ｂｒｓ，１Ｈ），８．２４－８．２５（ｍ，１Ｈ）．
ＭＳ［Ｍ＋Ｈ］$^{+}$＝２３９

【０１２４】

（３）４－メトキシメチルピリジン－２－アミン（Ｐｒｅｐ６－３）

化合物Ｐｒｅｐ６－２（６２ｍｇ）のジクロロメタン（３ｍｌ）溶液にトリフルオロ酢酸（１ｍｌ）を加え、室温にて３時間攪拌した。反応液に５Ｎ水酸化ナトリウム水溶液を加え、酢酸エチル（ｘ１）で抽出した。有機層を飽和食塩水溶液で洗浄後、無水硫酸マグネシウムで乾燥し濾過した。濾液を減圧濃縮し、標的化合物（３５ｍｇ）を得た。

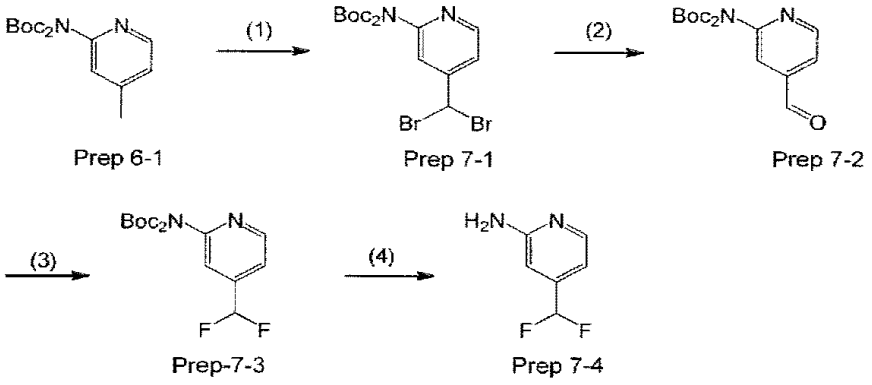
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：３．４１（ｓ，３Ｈ），４．３７（ｓ，２Ｈ），４．６６（ｂｒｓ，２Ｈ），６．５１（ｓ，１Ｈ），６．５９（ｄ，Ｊ＝５．６Ｈｚ，１Ｈ），７．９９（ｄ，Ｊ＝５．６Ｈｚ，１Ｈ）．

【０１２５】

製造例７

４－（ジフルオロメチル）ピリジン－２－アミン（Ｐｒｅｐ７－４）の合成

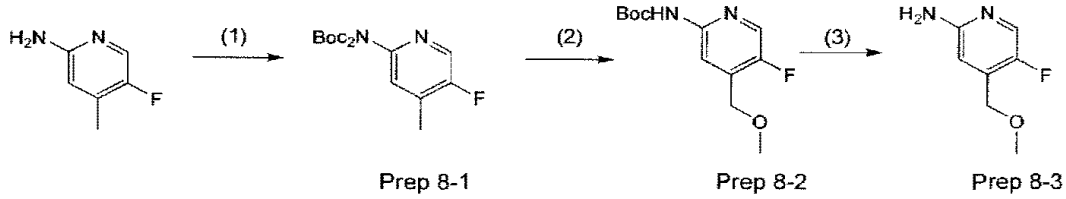
【化２４】



【０１２６】

（１）ジ－ｔｅｒｔ－ブチル［４－（ジブロモメチル）ピリジン－２－イル］イミドジカルボネート（Ｐｒｅｐ７－１）

化合物Ｐｒｅｐ６－１（１．４ｇ）、Ｎ－ブロモスクシンイミド（８０７ｍｇ）のテトラクロロメタン（４７ｍｌ）溶液に、２，２’－アゾビス（イソブチルナイトレイト）（７４．７ｍｇ）を加えた後、４時間加熱還流させた。反応液を室温まで冷却後、セライト

濾過した。濾液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル）で精製し標記化合物（２１０ｍｇ）を得た。
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．４６（ｓ，１８Ｈ），６．５４（ｓ，１Ｈ），７．３６（ｄｄ，Ｊ＝１．６，５．２Ｈｚ，１Ｈ），７．４５（ｄ，Ｊ＝１．６Ｈ，１Ｈ），８．４８（ｄ，Ｊ＝５．２Ｈｚ，１Ｈ）．
ＭＳ［Ｍ＋Ｈ］$^+$＝４６７
【０１２７】
（２）ジ－ｔｅｒｔ－ブチル（４－ホルミルピリジン－２－イル）イミドジカルボネート（Ｐｒｅｐ７－２）
化合物Ｐｒｅｐ７－１（２１０ｍｇ）のトルエン（５ｍｌ）溶液にジメチルスルホキシド（５００μｌ）および亜硝酸銀（６９２ｍｇ）を加え、６０℃で２時間撹拌した。８０℃に昇温し、さらに１９時間撹拌後、反応液を室温まで冷却し、シリカゲル濾過した。濾液を減圧濃縮し、標記化合物（１００ｍｇ）を得た。
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．４７（ｓ，１８Ｈ），７．６１（ｄｄ，Ｊ＝１．２，５．２Ｈｚ，１Ｈ），７．７４（ｄ，Ｊ＝１．２Ｈ，１Ｈ），８．７０（ｄ，Ｊ＝５．２Ｈｚ，１Ｈ），１０．０８（ｓ，１Ｈ）．
【０１２８】
（３）ジ－ｔｅｒｔ－ブチル（４－ジフルオロメチルピリジン－２－イル）イミドジカルボネート（Ｐｒｅｐ７－３）
化合物Ｐｒｅｐ７－２（１００ｍｇ）のジクロロメタン（３ｍｌ）溶液に、ジエチルアミノサルファートリフルオライド（１２２μｌ）を０℃にて加えた。反応液を室温まで昇温し、３．５時間撹拌した。反応液に飽和炭酸水素ナトリウム水溶液を加え、酢酸エチル（ｘ１）で抽出した。有機層を水、飽和食塩水溶液で順次洗浄後、無水硫酸マグネシウムで乾燥し、濾過した。濾液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル）で精製し標記化合物（７８ｍｇ）を得た
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．４６（ｓ，１８Ｈ），６．６５（ｔ，Ｊ＝５５．６Ｈｚ，１Ｈ），７．３２（ｄ，Ｊ＝５．２Ｈｚ，１Ｈ），７．４３（ｓ，１Ｈ），８．５８（ｄ，Ｊ＝５．２Ｈｚ，１Ｈ）．
ＭＳ［２Ｍ＋Ｎａ］$^+$＝７１１
【０１２９】
（４）４－ジフルオロメチルピリジン－２－アミン（Ｐｒｅｐ７－４）
化合物Ｐｒｅｐ７－３（７８ｍｇ）のジクロロメタン（２ｍｌ）溶液にトリフルオロ酢酸（０．５ｍｌ）を加え、室温にて３時間撹拌した。反応液に５Ｎ水酸化ナトリウム水溶液を加え、クロロホルム（ｘ３）で抽出した。有機層を飽和食塩水溶液で洗浄後、無水硫酸マグネシウムで乾燥し濾過した。濾液を減圧濃縮し、標的化合物（３０ｍｇ）を得た。
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：４．６１（ｂｒｓ，２Ｈ），６．５１（ｔ，Ｊ＝５６．０Ｈｚ，１Ｈ），６．６０（ｂｒｓ，１Ｈ），６．７４－６．７６（ｍ，１Ｈ），８．１７（ｄ，Ｊ＝５．２Ｈｚ，１Ｈ）．
【０１３０】
製造例８
５－フルオロ－４－メトキシメチルピリジン－２－アミン（Ｐｒｅｐ８－３）の合成
【化２５】


【０１３１】
（１）ジ－ｔｅｒｔ－ブチル（５－フルオロ－４－メチルピリジン－２－イル）イミドジ

カルボネート（Ｐｒｅｐ８－１）

２－アミノ－５－フルオロ－４－メチルピリジン（５００ｍｇ）のジクロロメタン（５０ｍｌ）溶液に、ジ－ｔｅｒｔ－ブチルカルボネート（１．７３ｇ）、４－ジメチルアミノピリジン（２４２ｍｇ）およびトリエチルアミン（１．６６ｍｌ）を加え、室温で６日間攪拌した。反応液に水を加え、酢酸エチル（ｘ１）で抽出した。有機層を水、飽和食塩水溶液で順次洗浄後、無水硫酸マグネシウムで乾燥し濾過した。濾液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル）で精製し標記化合物（７３７ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：１．４５（ｓ，１８Ｈ），２．３２－２．３３（ｍ，３Ｈ），７．０８（ｂｒｄ，Ｊ＝５．６Ｈｚ，１Ｈ），８．２３（ｄ，Ｊ＝１．２Ｈｚ，１Ｈ）．

ＭＳ［２Ｍ＋Ｎａ］$^{+}$＝６７５

【０１３２】

（２）ｔｅｒｔ－ブチル（５－フルオロ－４－メトキシメチルピリジン－２－イル）カルバメート（Ｐｒｅｐ８－２）

化合物Ｐｒｅｐ８－１（６３０ｍｇ）、Ｎ－ブロモスクシンイミド（３７７ｍｇ）のテトラクロロメタン（２０ｍｌ）溶液に、２，２’－アゾビス（イソブチルナイトレイト）（１５８ｍｇ）を加え、１１時間加熱還流させた。反応液を室温まで冷却後、セライト濾過した。濾液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル）で精製し対応するブロマイド体を得た。

得られたブロマイド体のメタノール（１０ｍｌ）溶液に、ナトリウムメトキシド（１０４ｍｇ）を加え、室温にて３時間攪拌した。反応液に水を加え、酢酸エチル（ｘ２）で抽出した。有機層を無水硫酸マグネシウムで乾燥後、濾過した。濾液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル）で精製し標記化合物（１８０ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：１・５３（ｓ，９Ｈ），３．４６（ｓ，３Ｈ），４．５２（ｂｒｓ，２Ｈ），７．２１（ｂｒｓ，１Ｈ），８．０２－８．０３（ｍ，２Ｈ）．

ＭＳ［Ｍ－ｔＢｕ＋Ｈ］$^{+}$＝２０１

【０１３３】

（３）５－フルオロ－４－メトキシメチルピリジン－２－アミン（Ｐｒｅｐ８－３）

化合物Ｐｒｅｐ８－２（１８０ｍｇ）のジクロロメタン（６ｍｌ）溶液にトリフルオロ酢酸（２ｍｌ）を加え、室温にて１７時間攪拌した。反応液に５Ｎ水酸化ナトリウム水溶液を加え、クロロホルム（ｘ２）で抽出した。有機層を無水硫酸マグネシウムで乾燥後、濾過した。濾液を減圧濃縮し、標的化合物（９０ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：３．４５（ｓ，３Ｈ），４．３２（ｂｒｓ，２Ｈ），４．４７（ｓ，２Ｈ），６．５８（ｄ，Ｊ＝４．８Ｈｚ，１Ｈ），７．８６（ｄ，Ｊ＝１．６Ｈｚ，１Ｈ）．

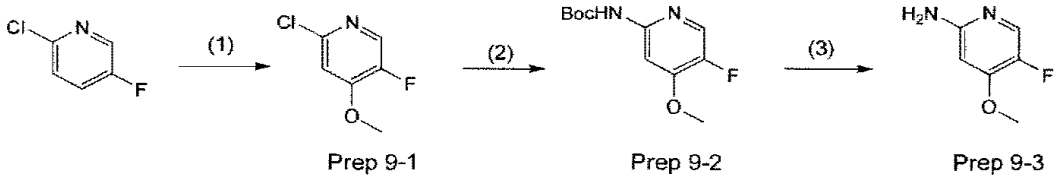
ＭＳ［Ｍ＋Ｈ］$^{+}$＝１５７

【０１３４】

製造例９

５－フルオロ－４－メトキシピリジン－２－アミン（Ｐｒｅｐ９－３）の合成

【化２６】



Prep 9-1　Prep 9-2　Prep 9-3

【０１３５】

（１）２－クロロ－５－フルオロ－４－メトキシピリジン（Ｐｒｅｐ９－１）

ｎ－ブチルリチウム（２．６４Ｍ　ｎ－ヘキサン溶液：１０．４ｍｌ）のＴＨＦ（２０ｍｌ）溶液を－７８℃に冷却し、２－クロロ－５－フルオロピリジン（３．０ｇ）、Ｎ，Ｎ－ジイソプロピルエチルアミン（４．４９ｍｌ）のＴＨＦ（２０ｍｌ）溶液を滴下した。そのままの温度で２時間攪拌後、トリメチルボレート（４．７４ｇ）のＴＨＦ（１０ｍｌ）溶液を加え、室温まで昇温し、１．５時間攪拌した。反応液を０℃に冷却し、酢酸（３．９２ｍｌ）を加え２０分攪拌後、過酸化水素（３０％水溶液；７．０５ｍｌ）を加え、再び室温まで昇温し１５時間攪拌した。反応液を０℃に冷却し、飽和チオ硫酸ナトリウム水溶液を加え２時間攪拌後、５Ｎ塩酸を加え酢酸エチル（ｘ２）、クロロホルム（ｘ１）で抽出した。有機相を硫酸マグネシウムで乾燥後、濾過した。溶媒を減圧下濃縮し、対応するアルコールを得た。

得られたアルコール、炭酸銀（１６．４ｇ）のクロロホルム（１００ｍｌ）溶液に、ヨードメタン（４．１８ｍｌ）を加え、４０℃まで昇温し４時間攪拌した。反応液を室温まで冷却後、セライト－シリカゲル濾過した。濾液を減圧下濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル）で精製し標記化合物（１．９ｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：３．９５（ｓ，３Ｈ），６．９１（ｄ，Ｊ＝６．０Ｈｚ，１Ｈ），８．１１（ｄ，Ｊ＝２．４Ｈｚ，１Ｈ）．

ＭＳ［Ｍ＋Ｈ］$^+$＝１６２

【０１３６】

（２）ｔｅｒｔ－ブチル（５－フルオロ－４－メトキシピリジン－２－イル）カルバメート（Ｐｒｅｐ９－２）

化合物Ｐｒｅｐ９－１（１．０ｇ）、ｔｅｒｔ－ブチルカルバメート（８７０ｍｇ）、ザントホス（１．０７ｇ）、カリウム三リン酸（１．９７ｇ）およびトリス（ジベンジリデン）ジパラジウム（５６７ｍｇ）の１，４－ジオキサン（５０ｍｌ）溶液を１００℃まで昇温し、３．５時間攪拌した。反応液を室温まで冷却後、セライト濾過した。濾液を減圧下濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル）で精製し標記化合物（４７０ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．５３（ｓ，９Ｈ），３．９７（ｓ，３Ｈ），７．５１（ｂｒｓ，１Ｈ），７．６９（ｄ，Ｊ＝６．４Ｈｚ，１Ｈ），７．９６（ｄ，Ｊ＝３．２Ｈｚ，１Ｈ）．

ＭＳ［Ｍ＋Ｈ］$^+$＝２４３

【０１３７】

（３）５－フルオロ－４－メトキシピリジン－２－アミン（Ｐｒｅｐ９－３）

化合物Ｐｒｅｐ９－２（２００ｍｇ）のジクロロメタン（２ｍｌ）溶液にトリフルオロ酢酸（１ｍｌ）を加え、室温にて１．５時間攪拌した。反応液に５Ｎ水酸化ナトリウム水溶液を加え、酢酸エチル（ｘ２）で抽出した。有機層を無水硫酸マグネシウムで乾燥後、濾過した。濾液を減圧濃縮し、標的化合物（１１０ｍｇ）を得た。

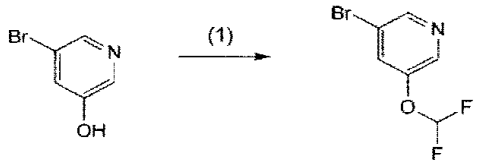
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：３．８７（ｓ，３Ｈ），４．２７（ｂｒｓ，２Ｈ），６．０６（ｄ，Ｊ＝５．６Ｈｚ，１Ｈ），７．８０（ｄ，Ｊ＝３．２Ｈｚ，１Ｈ）．

【０１３８】

製造例１０

３－ブロモ－５－（ジフルオロメトキシ）ピリジン（Ｐｒｅｐ１０）の合成

【化２７】



Prep 10

【０１３９】

（１）（３－ブロモ－５－（ジフルオロメトキシ）ピリジン（Ｐｒｅｐ１０）

３－ブロモ－５－ヒドロキシピリジン（３．０ｇ）のＤＭＦ（４０ｍｌ）溶液に、炭酸カリウム（７．１３ｇ）およびクロロジフルオロ酢酸（１．７５ｍｌ）を加え、１００℃に昇温し２４時間攪拌した。反応液に水を加え、ジエチルエーテル（ｘ１）で抽出した。有機層を飽和炭酸水素ナトリウム水溶液、飽和食塩水で順次洗浄後、硫酸マグネシウムで乾燥し、濾過した。溶媒を減圧下濃縮後、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘキサン：ジエチルエーテル）で精製して標記化合物（６７０ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：６．５６（ｔ，Ｊ＝７２．０Ｈｚ，１Ｈ），７．６７－７．６８（ｍ，１Ｈ），８．４３（ｄ，Ｊ＝２．４Ｈｚ，１Ｈ），８．５６（ｄ，Ｊ＝２．０Ｈｚ，１Ｈ）．

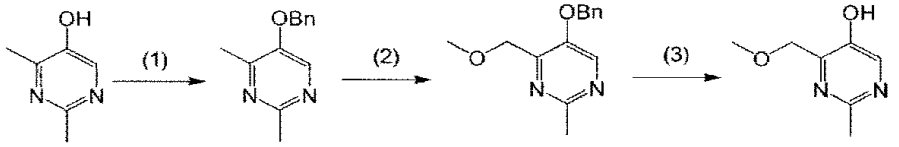
ＭＳ［Ｍ＋Ｈ］$^+$＝２２４

【０１４０】

製造例１１

４－メトキシメチル－２－メチルピリミジン－５－オール（Ｐｒｅｐ１１－３）の合成

【化２８】



Prep 4-2　Prep 11-1　Prep 11-2　Prep 11-3

【０１４１】

（１）５－ベンジルオキシ－２，４－ジメチルピリミジン（Ｐｒｅｐ１１－１）

Ｐｒｅｐ４－２（５．０ｇ）のＴＨＦ（８０ｍｌ）溶液を０℃に冷却し、カリウムｔｅｒｔ－ブトキシド（５．４３ｇ）を加え、０℃にて３０分攪拌した。そのままの温度でベンジルブロマイド（５．７３ｍｌ）を加え、室温まで昇温し２０時間攪拌した。反応液に水を加え、酢酸エチル（ｘ２）で抽出した。有機層を無水硫酸マグネシウムで乾燥後、濾過した。濾液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル～酢酸エチル）で精製し標記化合物（６．０ｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：２．４８（ｓ，３Ｈ），２．６２（ｓ，３Ｈ），５．１３（ｓ，２Ｈ），７．３３－７．４２（ｍ，５Ｈ），８．１３（ｓ，１Ｈ）．

ＭＳ［Ｍ＋Ｈ］$^+$＝２１５

【０１４２】

（２）５－ベンジルオキシ－４－メトキシメチル－２－メチルピリミジン（Ｐｒｅｐ１１－２）

化合物Ｐｒｅｐ１１－１（１３ｇ）のクロロホルム（２００ｍｌ）溶液を０℃に冷却し、ブロミン（３．１１ｍｌ）をゆっくり滴下した。反応液を室温まで昇温し、１８時間攪拌した。反応液に飽和炭酸水素ナトリウム水溶液を加え、クロロホルム（ｘ２）で抽出した。有機層を無水硫酸マグネシウムで乾燥後、濾過した。濾液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル～酢酸エチル）で精製し対応するブロマイド体を得た。

得られたブロマイド体のメタノール（１８０ｍｌ）溶液にナトリウムメトキシド（２．５６ｇ）を加え、２１時間加熱還流させた。反応液を減圧濃縮後、酢酸エチルと水を加え、酢酸エチル（ｘ２）で抽出した。有機層を無水硫酸マグネシウムで乾燥後、濾過した。濾液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル）で精製し標記化合物（９．０ｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：２．７０（ｓ，３Ｈ），３．５２（ｓ，３Ｈ），４．６３（ｓ，２Ｈ），５．１６（ｓ，２Ｈ），７．３４－７．４１（ｍ，５Ｈ），８．２４（ｓ，１Ｈ）．

ＭＳ［Ｍ＋Ｈ］$^+$＝２４５

【０１４３】

（３）（４－メトキシメチル－２－メチルピリミジン－５－オール（Ｐｒｅｐ１１－３）

化合物Ｐｒｅｐ１１－２（８．８ｇ）の酢酸エチル（３００ｍｌ）溶液に１０％パラジウム－カーボン（９００ｍｇ）を加え、水素雰囲気下、室温で２時間撹拌した。反応溶液をセライト濾過し、濾液を減圧濃縮して標記化合物（５．３ｇ）を得た。

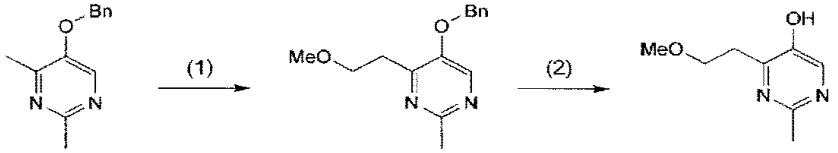
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：２．６１（ｓ，３Ｈ），３．５６（ｓ，３Ｈ），４．７９（ｓ，２Ｈ），７．９０（ｂｒｓ，１Ｈ），８．２５（ｓ，１Ｈ）．

【０１４４】

製造例１２

４－（２－メトキシエチル）－２－メチルピリミジン－５－オール（Ｐｒｅｐ１２－２）の合成

【化２９】



Prep 12-1　　Prep 12-2

【０１４５】

（１）５－ベンジルオキシ－４－（２－メトキシエチル）－２－メチルピリミジン（Ｐｒｅｐ１２－１）

化合物Ｐｒｅｐ１１－１（１．６６ｇ）をＴＨＦ（１３０ｍｌ）に溶解し、０℃に冷却した。１ＮのＬＤＡのＴＨＦ溶液（８．５ｍｌ）を滴下し、３０分撹拌した後、クロロメチルメチルエーテル（０．８８ｍｌ）を加えた。さらに室温で１２時間撹拌した後、反応液に水を加え、酢酸エチル（ｘ３）で抽出した。水で洗浄し、無水硫酸ナトリウムで乾燥した。溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル）で精製して標記化合物（０．６５ｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：２．６３（ｓ，３Ｈ），３．１１（ｔ，Ｊ＝７．２Ｈｚ，２Ｈ），３．３５（ｓ，３Ｈ），３．７９（ｔ，Ｊ＝７．２Ｈｚ，２Ｈ），５．１３（ｓ，２Ｈ），７．３３－７．４２（ｍ，５Ｈ），８．１６（ｓ，１Ｈ）．

【０１４６】

（２）４－（２－メトキシエチル）－２－メチルピリミジン－５－オール（Ｐｒｅｐ１２－２）

化合物Ｐｒｅｐ１２－１（０．６５ｇ）を酢酸エチル（９ｍｌ）に溶解し、０℃に冷却した。５％パラジウムカーボン（０．３１ｇ）加え、水素置換した後、室温で２時間撹拌した。反応溶液をろ過した後、溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル－酢酸エチル：メタノール）で精製して標記化合物（０．３６ｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：２．６１（ｓ，３Ｈ），３．

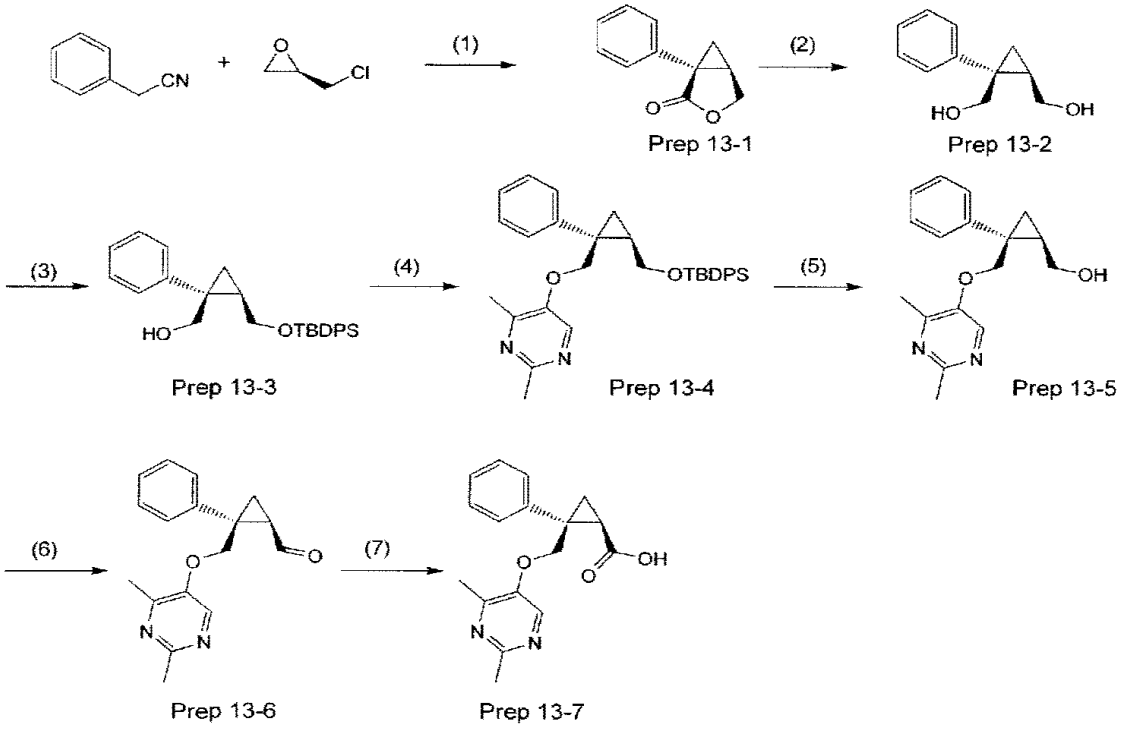
０９（ｔ，Ｊ＝５．６Ｈｚ，２Ｈ），３．６４（ｓ，３Ｈ），３．８０（ｔ，Ｊ＝５．６Ｈｚ，２Ｈ），８．２４（ｓ，１Ｈ），８．３９（ｂｒｓ，１Ｈ）．

【０１４７】

製造例１３

（１Ｒ，２Ｓ）－２－（２，４－ジメチルピリミジン－５－イル）オキシメチル－２－フェニルシクロプロパンカルボン酸（Ｐｒｅｐ１３－７）の合成

【化３０】



【０１４８】

（１）（１Ｓ，５Ｒ）－１－フェニル－３－オキサビシクロ［３．１．０］ヘキサン－２－オン（Ｐｒｅｐ１３－１）

フェニルアセトニトリル（２０ｇ）をＴＨＦ（５００ｍｌ）に溶解し、氷－塩バス冷却下ＮａＨＭＤＳ（３２３ｍｌ、１．０６Ｍ）を滴下した。そのまま２時間撹拌した後、Ｒ－（－）－エピクロロヒドリン（１５．８ｇ）を滴下した（３時間、０℃）。そのまま２時間撹拌（内温０℃前後に維持）した後、室温で一晩撹拌した。反応液を氷冷し少量の水を滴下した。反応液を減圧下濃縮し、残渣にエタノール（２００ｍｌ）、１Ｎ水酸化カリウム水溶液（２００ｍｌ）を加え、８時間加熱還流した。室温に戻した後、濃塩酸を加え、ｐＨ＜２に調整した後０℃で２時間撹拌した。その後室温で１時間撹拌した。反応液を減圧濃縮した後、酢酸エチルと水を加え分液を行った。有機層を飽和炭酸水素ナトリウム水溶液、飽和食塩水で順次洗浄した。硫酸マグネシウムで乾燥し、溶媒を減圧下濃縮した。残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，Ｓｉｚｅ：３Ｌｘ２，ｎ－ヘプタン：酢酸エチル）で精製して標記化合物（２４．７ｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．３７（ｔ，１Ｈ，Ｊ＝４．８Ｈｚ），１．６５（ｄｄ，Ｊ＝７．８，４．４，１Ｈ），２．５４－２．５８（ｍ，１Ｈ），４．３０（ｄ，
Ｊ＝９．２，１Ｈ），４．４７（ｄｄ，Ｊ＝９．４，４．４Ｈｚ，１Ｈ），７．２５－７．４５（ｍ，５Ｈ）．

【０１４９】

（２）（１Ｓ，２Ｒ）－１－フェニルシクロプロパン－１，２－ジメタノール（Ｐｒｅｐ１３－２）

製化合物Ｐｒｅｐ１３－１（２４．７ｇ）のＴＨＦ－メタノール（２００ｍｌ－１００ｍｌ）溶液に水素化ホウ素ナトリウム（１０．７ｇ）を０℃で加えて、室温で１時間撹拌した。氷冷下、反応液に水を加えて減圧濃縮し酢酸エチルで抽出した。有機相を飽和食塩水で洗浄後、硫酸マグネシウムで乾燥した。溶媒を減圧下濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，Ｓｉｚｅ：３Ｌｘ２，ｎ－ヘプタン：酢酸エチル）で精製して標記化合物（２０．５ｇ）を得た。
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：０．７８（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），１．８７（ｄｄ，Ｊ＝８．６，５．２，１Ｈ），１．６０－１．７６（ｍ，１Ｈ），３．４２（ｔ，Ｊ＝１１．６，１Ｈ），３．５７（ｄｄ，Ｊ＝９．４，４．４Ｈｚ，１Ｈ），４．１４－４．２８（ｍ，２Ｈ）７．２２－７．４４（ｍ，５Ｈ）．

【０１５０】

（３）（１Ｓ，２Ｒ）－２－（ｔｅｒｔ－ブチルジフェニルシリルオキシメチル）－１－フェニルシクロプロピルメタノール（Ｐｒｅｐ１３－３）

化合物Ｐｒｅｐ１３－２（１０ｇ）とイミダゾール（４．０１ｇ）をＤＭＦ（９０ｍｌ）に溶解し、－１５℃に冷却した。ｔｅｒｔ－ブチルジフェニルシリルクロリドのＤＭＦ溶液（２０ｍｌ）を滴下した（約３０分、滴下終了とほぼ同時に不溶物が析出する）。１時間撹拌した後、反応液にメタノールを加え、室温で３０分撹拌した。有機層に水を加え、酢酸エチルで抽出した。飽和塩化アンモニウム水溶液、水、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥した。溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，Ｓｉｚｅ：３Ｌｘ２，ｎ－ヘプタン：酢酸エチル）で精製して標記化合物（１０．５ｇ）を得た。
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：０．７１（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），１．０４（ｄｄ，Ｊ＝９．６，５．２Ｈｚ，１Ｈ），１．５－１．５８（ｍ，１Ｈ），３．５０（ｄｄ，Ｊ＝１２．４，１．６Ｈｚ，１Ｈ），３．５３（ｄｄ，Ｊ＝１１．６Ｈｚ，１Ｈ），３．７１（ｄｄ，Ｊ＝１２．４，１．６Ｈｚ，１Ｈ），４．１０（ｔ，Ｊ＝１２．０Ｈｚ，１Ｈ），４．２０（ｄｄ，Ｊ＝１２．０，５．６Ｈｚ，１Ｈ），７．２１－７．４６（ｍ，１０Ｈ），７．７－７．７６（ｍ，５Ｈ）

【０１５１】

（４）５－［（１Ｓ，２Ｒ）－２－（ｔｅｒｔ－ブチルジフェニルシリルオキシメチル）－１－フェニルシクロプロピルメトキシ］－２，４－ジメチルピリミジン（Ｐｒｅｐ１３－４）

化合物Ｐｒｅｐ１３－３（１．５０ｇ）、トリフェニルホスフィン（１．４２ｇ）および製造例４で得た２，４－ジメチル－５－ピリミジノール（０．５８ｇ）のＴＨＦ（１５ｍｌ）溶液にジイソプロピルアゾジカルボキシラート（１．１３ｍｌ）を０℃で滴下し、室温で１日間撹拌した。反応液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，溶出溶媒：ｎ－ヘプタン：酢酸エチル）で精製して標記化合物（１．７６ｇ）を得た。
ＭＳ［Ｍ＋Ｎａ］$^+$＝５４５．

【０１５２】

（５）［（１Ｒ，２Ｓ）－２－（２，４－ジメチルピリミジン－５－イル）オキシメチル－２－フェニルシクロプロピル］メタノール（Ｐｒｅｐ１３－５）

化合物Ｐｒｅｐ１３－４（１．７６ｇ）のＴＨＦ（２１ｍｌ）溶液にテトラブチルアンモニウム　フロリド（１Ｍ－ＴＨＦ溶液：４．２４ｍｌ）を室温で滴下し、室温で１７時間撹拌した。反応液を減圧濃縮し、残渣をＮＨ－シリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，溶出溶媒：ｎ－ヘプタン：酢酸エチル→酢酸エチル）で精製して標記化合物（０．９８ｇ）を得た。

ＭＳ［Ｍ＋Ｈ］$^{+}$＝２８５．

【０１５３】

（６）［（１Ｒ，２Ｓ）－２－（２，４－ジメチルピリミジン－５－イル）オキシメチル－２－フェニル］シクロプロパンカルバルデヒド（Ｐｒｅｐ１３－６）

オキサリルクロリド（５９３μｌ）のジクロロメタン溶液（１０ｍｌ）を－７８℃に冷却し、そこにジメチルスルホキシド（９８１μｌ）のジクロロメタン溶液（２ｍｌ）を滴下した。１５分後、反応液に化合物Ｐｒｅｐ１３－５（９８１ｍｇ）のジクロロメタン（３ｍｌ）溶液を－７８℃で滴下し、同温で７５分撹拌した。反応液にトリエチルアミン（３．８３ｍｌ）を加えて０℃に昇温した。反応液に水と飽和塩化アンモニウム水溶液を加え、ジクロロメタン（ｘ２）で抽出した。有機層を無水硫酸マグネシウムで乾燥し、濾過した。濾液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ^{TM} ｃｏｌｕｍｎ，溶出溶媒：ｎ－ヘプタン：酢酸エチル→酢酸エチル）で精製して標記化合物（７５３．４ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：１．６９（ｄｄ，Ｊ＝４．８Ｈｚ，８．０Ｈｚ，１Ｈ）、１．９７（ｄｄ，Ｊ＝５．２Ｈｚ，６．０Ｈｚ，１Ｈ）、２．３５（ｓ，３Ｈ），２．５０－２．５３（ｍ，１Ｈ），２．５９（ｓ，３Ｈ）、４．１９（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ）、４．４５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ）、７．２５－７．５２（ｍ，５Ｈ）、７．９４（ｓ，１Ｈ）、９．８６（ｄ，Ｊ＝３．６Ｈｚ，１Ｈ）．

【０１５４】

（７）（１Ｒ，２Ｓ）－２－（２，４－ジメチルピリミジン－５－イル）オキシメチル－２－フェニルシクロプロパンカルボン酸（Ｐｒｅｐ１３－７）

化合物Ｐｒｅｐ１３－６のアセトン－水（１２ｍｌ）溶液に室温で２－メチル－２－ブテン（２．２５ｍｌ）、無水りん酸二水素ナトリウム（３１８ｍｇ）および亜塩素酸ナトリウム（４８２ｍｇ）を加え、１００分撹拌した。反応液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ^{TM} ｃｏｌｕｍｎ，溶出溶媒：ｎ－ヘプタン：酢酸エチル＝１：１～クロロホルム：メタノール＝１０：１）で精製して標記化合物（６３９ｍｇ）を得た。

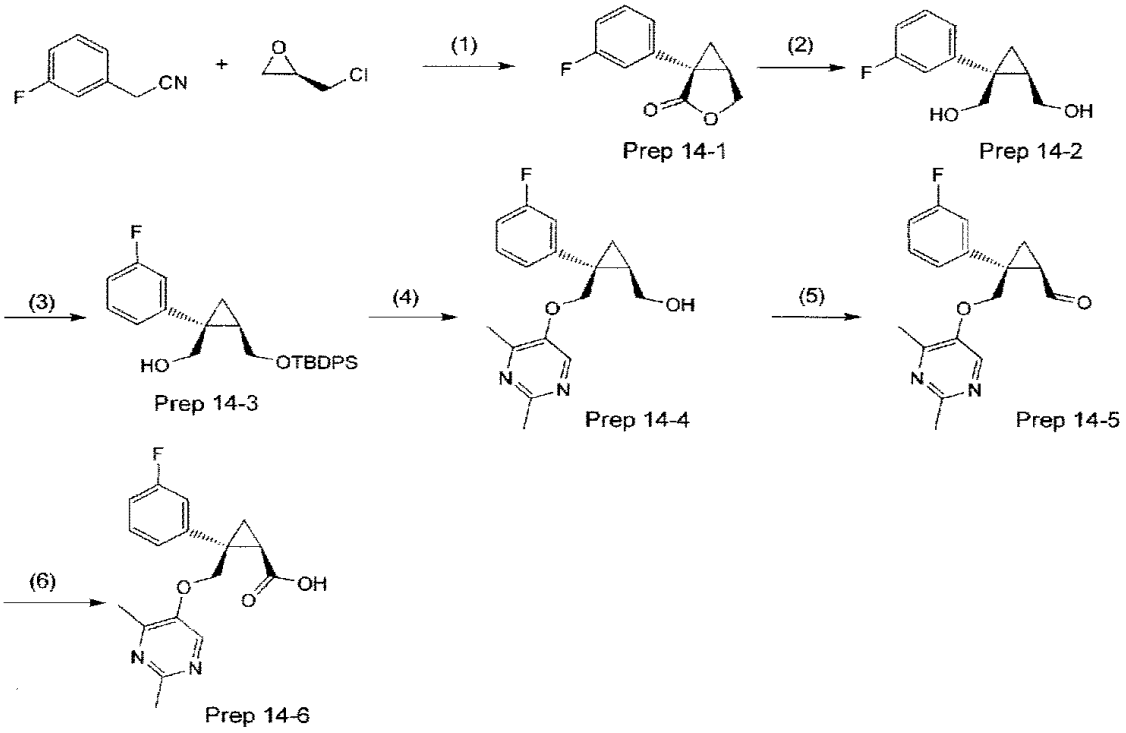
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：１．５７（ｄｄ，Ｊ＝４．８Ｈｚ，８．０Ｈｚ，１Ｈ），１．７５（ｔ，Ｊ＝４．８Ｈｚ，１Ｈ），２．２７（ｄｄ，Ｊ＝５．６Ｈｚ，８．０Ｈｚ，１Ｈ），２．３３（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），４．４５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ）、４．５０（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），７．２６－７．５２（ｍ，５Ｈ），８．１６（ｓ，１Ｈ）．

【０１５５】

製造例１４

（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）シクロプロパンカルボン酸（Ｐｒｅｐ１４－６）の合成

【化３１】



【０１５６】

（１）（１Ｓ，５Ｒ）－１－（３－フルオロフェニル）－３－オキサビシクロ［３．１．０］ヘキサン－２－オン（Ｐｒｅｐ１４－１）

３－フルオロフェニルアセトニトリル（７０ｇ）をＴＨＦ（５００ｍｌ）に溶解し、氷－塩バス冷却下、ＮａＨＭＤＳ（１０００ｍｌ、１．０６Ｍ）を滴下した。そのまま１時間撹拌した後、Ｒ－（－）－エピクロロヒドリン（４０．６ｍｌ）を滴下した（約１０分、内温＜１０℃）。そのまま２時間撹拌（内温０℃前後に維持）した後、室温で１４時間撹拌した。反応液を氷冷し少量の水を滴下した。反応液を減圧下濃縮し、残渣にエタノール（７００ｍｌ）、１Ｎ水酸化カリウム水溶液（１０００ｍｌ）を加え、５時間加熱還流した。室温に戻した後、５Ｎ塩酸（４００ｍｌ）を加え、６０℃で１時間撹拌した。反応液を減圧濃縮した後、酢酸エチルと水を加え分液を行った。有機層を飽和炭酸水素ナトリウム水溶液、飽和食塩水で順次洗浄した。硫酸マグネシウムで乾燥し、溶媒を減圧下濃縮した。残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，ｎ－ヘプタン：酢酸エチル）で精製して標記化合物（８４．９ｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：１．４１（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），１．６４（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），２．５６－２．６３（ｍ，１Ｈ），４．３０（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），４．４７（ｄｄ，Ｊ＝９．２，４．８Ｈｚ，１Ｈ），６．９６－７．０２（ｍ，１Ｈ），７．１６－７．２１（ｍ，２Ｈ），７．２８－７．３５（ｍ，１Ｈ）．

【０１５７】

（２）（１Ｓ，２Ｒ）－１－（３－フルオロフェニル）シクロプロパン－１，２－ジメタノール（Ｐｒｅｐ１４－２）

化合物Ｐｒｅｐ１４－１（７２．７ｇ）のＴＨＦ－メタノール（４４０ｍｌ－２２０ｍｌ）溶液に水素化ホウ素ナトリウム（２５ｇ）を０℃で加えて、室温で６５時間攪拌した。氷冷下、反応液に水と５Ｎ塩酸を加え、酢酸エチルで抽出した。有機相を飽和食塩水で洗浄後、硫酸マグネシウムで乾燥した。溶媒を減圧下濃縮し、残渣をシリカゲルカラムク

ロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，ｎ－ヘプタン：酢酸エチル）で精製して標記化合物（７２．７ｇ）を得た。
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：０．８０（ｔ，Ｊ＝５．０Ｈｚ，１Ｈ），１．１０（ｄｄ，Ｊ＝８．６，５．０，１Ｈ），１．６２－１．７１（ｍ，１Ｈ），３．４１（ｔ，Ｊ＝１１．４Ｈｚ，１Ｈ），３．５８（ｄ，Ｊ＝１２．０Ｈｚ，１Ｈ），４．１２－４．２５（ｍ，２Ｈ），６．９０－６．９６（ｍ，１Ｈ），７．０８－７．１４（ｍ，１Ｈ），７．１６－７．２１（ｍ，１Ｈ）７．２４－７．３２（ｍ，１Ｈ）．
【０１５８】
（３）｛（１Ｓ，２Ｒ）－［２－（ｔｅｒｔ－ブチルジフェニルシリルオキシメチル）－１－（３－フルオロフェニル）シクロプロピル］｝メタノール（Ｐｒｅｐ１４－３）
化合物Ｐｒｅｐ１４－２（４２．４ｇ）とトリエチルアミン（３３．０ｍｌ）をジクロロメタン（２１６ｍｌ）に溶解し、－２０℃に冷却した後、ｔｅｒｔ－ブチルジフェニルシリルクロリド（５６．３ｍｌ）を滴下した（約３０分、滴下終了とほぼ同時に不溶物が析出する）。１時間撹拌した後、さらに室温で２０時間撹拌した。反応液に水を加え、ジクロロメタン（ｘ３）で抽出した。水で洗浄し、無水硫酸マグネシウムで乾燥した。溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル）で精製して標記化合物（６７．８ｇ）を得た。
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：０．７３（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），１．０４（ｄｄ，Ｊ＝８．４，５．２Ｈｚ，１Ｈ），１．０９（ｓ，９Ｈ），１．４８－１．５３（ｍ，１Ｈ），３．５２（ｔ，Ｊ＝１２．０Ｈｚ，１Ｈ），３．５６（ｄｄ，Ｊ＝９．６，１．６Ｈｚ，１Ｈ），３．７０（ｄｄ，Ｊ＝９．６，１．６Ｈｚ，１Ｈ），４．１８（ｔ，Ｊ＝１２．０Ｈｚ，１Ｈ），４．２０（ｄｄ，Ｊ＝１２．０，５．２Ｈｚ，１Ｈ），６．９３（ｔｄｄ，Ｊ＝８．０，２．４，１．２Ｈｚ，１Ｈ），７．１１（ｄｔ，Ｊ＝９．６，２．４Ｈｚ，１Ｈ），７．２０（ｄｔ，Ｊ＝８．０，１．２Ｈｚ，１Ｈ），７．２８（ｔｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），７．３７－７．４９（ｍ，６Ｈ），７．６９－７．７４（ｍ，４Ｈ）．
【０１５９】
（４）｛（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）シクロプロピル｝メタノール（Ｐｒｅｐ１４－４）
化合物Ｐｒｅｐ１４－３（５８１ｍｇ）、トリフェニルホスフィン（１．３ｇ）および製造例４で得た２，４－ジメチル－５－ピリミジノール（１８３ｍｇ）のＴＨＦ（１０ｍｌ）溶液にジイソプロピルアゾジカルボキシラート（０．３１６ｍｌ）を０℃で滴下し、室温で２日間撹拌した。反応液を減圧濃縮し、シリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，Ｓｉｚｅ：Ｌ，ｎ－ヘプタン：酢酸エチル５％→３０％）で精製した。得られた（１Ｓ，２Ｒ）－２－（ｔｅｒｔ－ブチルジフェニルシリルオキシメチル）－１－（２，４－ジメチルピリミジン－５－イル）オキシメチル－１－（３－フルオロフェニル）シクロプロパンをＴＨＦ（１５ｍｌ）に溶解し、テトラブチルアンモニウム　フロリド（１Ｍ－ＴＨＦ溶液：１．６１ｍｌ）を室温で滴下し、室温で１４時間撹拌した。反応液を減圧濃縮し、シリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，Ｓｉｚｅ：Ｍ，ｎ－ヘプタン：酢酸エチル１０％→１００％）で精製し標記化合物（２３８ｍｇ）を得た。
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．００（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），１．２５－１．３３（ｍ，１Ｈ），１．７８－１．８８（ｍ，１Ｈ），２．３９（ｓ，３Ｈ），２．６１（ｓ，３Ｈ），３．５８（ｄｄ，Ｊ＝１２．０，９．６Ｈｚ，１Ｈ），４．０２－４．１１（ｍ，１Ｈ），４．１２（ｄ，Ｊ＝１０．４Ｈｚ，１Ｈ），４．４３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．９２－６．９８（ｍ，１Ｈ），７．１０－７．１６（ｍ，１Ｈ），７．１８－７．２３（ｍ，１Ｈ），７．２９（ｔｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），８．００（ｓ，１Ｈ）．
【０１６０】

（４－別法）

｛（１Ｒ，２Ｓ）－［２－（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）シクロプロピル｝メタノール（Ｐｒｅｐ１４－４）（別法）

化合物Ｐｒｅｐ１４－３（４１．３ｇ）のジクロロメタン（２００ｍｌ）溶液にトリエチルアミン（１４．５ｍｌ）を加え、０℃に冷却した。メタンスルホニル　クロライド（７．３４ｍｌ）を滴下し、１時間攪拌した。反応液に水を加え、ジクロロメタン（ｘ３）で抽出した。無水硫酸ナトリウムで乾燥し、溶媒を減圧下留去した。得られた残渣のアセトニトリル（２００ｍｌ）溶液に製造例４－（２）で得た２，４－ジメチル－５－ピリミジノール（１４．１ｇ）と炭酸セシウム（６１．８ｇ）を加え、７０℃に加熱した。７０℃で４時間攪拌した後、反応液を０℃に冷却し、テトラブチルアンモニウム　フロリド（１Ｍ－ＴＨＦ溶液：１９０ｍｌ）を滴下し、室温で１時間攪拌した。反応液に水を加え、酢酸エチル（ｘ３）で抽出した。無水硫酸ナトリウムで乾燥し、溶媒を減圧下留去した。残渣をＮＨ－シリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝９：１から１：１）で精製して標記化合物（２０．７ｇ）を得た。

【０１６１】

（５）（１Ｒ，２Ｓ）－［２－（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）シクロプロパンカルバルデヒドの（Ｐｒｅｐ１４－５）

オキサリルクロリド（１３７ｕｌ）のジクロロメタン溶液（７ｍｌ）を－７８℃に冷却し、そこにジメチルスルホキシド（２２６ｕｌ）を滴下した（内温　－６０℃以下）。同温度で１０分攪拌後、反応液に化合物Ｐｒｅｐ１４－４（２３８ｍｇ）のジクロロメタン（３ｍｌ）溶液を－７８℃で滴下し、同温で３０分撹拌した。反応液にトリエチルアミン（６７１ｕｌ）を加えて１５分攪拌後、室温に昇温した。反応液に飽和食塩水を加え、酢酸エチルで抽出した。有機層を無水硫酸マグネシウムで乾燥後減圧濃縮し、標記化合物粗精製物（２３６ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．６７（ｄｄ，Ｊ＝８．０，４．８Ｈｚ，１Ｈ），１．９６－２．００（ｍ，１Ｈ），２．３６（ｓ，３Ｈ），２．４９－２．５５（ｍ，１Ｈ），２．５９（ｓ，３Ｈ），４．１９（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４４（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），６．９７－７．０４（ｍ，１Ｈ），７．１４－７．２０（ｍ，１Ｈ），７．２１－７．２５（ｍ，１Ｈ），７．３０－７．３７（ｍ，１Ｈ），７．９５（ｓ，１Ｈ），９．８７（ｄ，Ｊ＝３．２Ｈｚ，１Ｈ）．

【０１６２】

（６）（１Ｒ，２Ｓ）－［２－（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）シクロプロパンカルボン酸（Ｐｒｅｐ１４－６）

化合物Ｐｒｅｐ１４－５（１８．９ｇ）と２－メチル２－ブテン（２６．１ｍｌ）、リン酸二水素ナトリウム（９．０７ｇ）をアセトン・水混合溶媒（２００ｍｌ・４０ｍｌ）に溶解させ、亜塩素酸ナトリウム（６．２６ｇ）を少しずつ加えた。室温で２時間撹拌した後、反応溶液を減圧濃縮した。析出した固体をろ別し、ジクロロメタンで洗浄した後、溶媒を減圧下留去した。残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝１：１から０：１の後、酢酸エチル：メタノール＝１０：１）で精製して標記化合物（１６．２ｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．５５（ｄｄ，Ｊ＝８．４，５．６Ｈｚ，１Ｈ），１．７６（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．２５（ｄｄ，Ｊ＝８．４，６．４Ｈｚ，１Ｈ），２．３３（ｓ，３Ｈ），２．５５（ｓ，３Ｈ），４．４７（ｔ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５０（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．９９（ｔｄｄ，Ｊ＝８．０，２．４，１．２Ｈｚ，１Ｈ），７．２１（ｄｔ，Ｊ＝９．６，２．４Ｈｚ，１Ｈ），７．２６（ｔｄ，Ｊ＝８．０，１．２Ｈｚ，１Ｈ），７．３２（ｔｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），８．２１（ｓ，１Ｈ）．

化合物Ｐｒｅｐ１４－６は化合物Ｐｒｅｐ１４－４から以下の方法により直接製造する

ことができる。

化合物Ｐｒｅｐ１４－４（３００ｍｇ）とＴＥＭＰＯ（５ｍｏｌ％、７．７４ｍｇ）をアセトニトリル・ｐＨ６．４のリン酸緩衝液（５ｍｌ・５ｍｌ）に溶解させ、２Ｎ－ＨＣｌ（１５０μＬ）、亜塩素酸ナトリウム（１８０ｍｇ）を加えた。４０度に加熱した後、５ｗ％の次亜塩素酸水溶液（２ｍｏｌ％、２６．５μＬ）を加え、２時間撹拌した。室温に冷却し、反応液に過剰量の２－メチル－２－ブテンを加え５分間撹拌した。反応液をジクロロメタン（ｘ３）用いて分液抽出した後、溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝１：１から０：１の後、酢酸エチル：メタノール＝９：１)で精製して標記化合物（２１５ｍｇ）を得た。

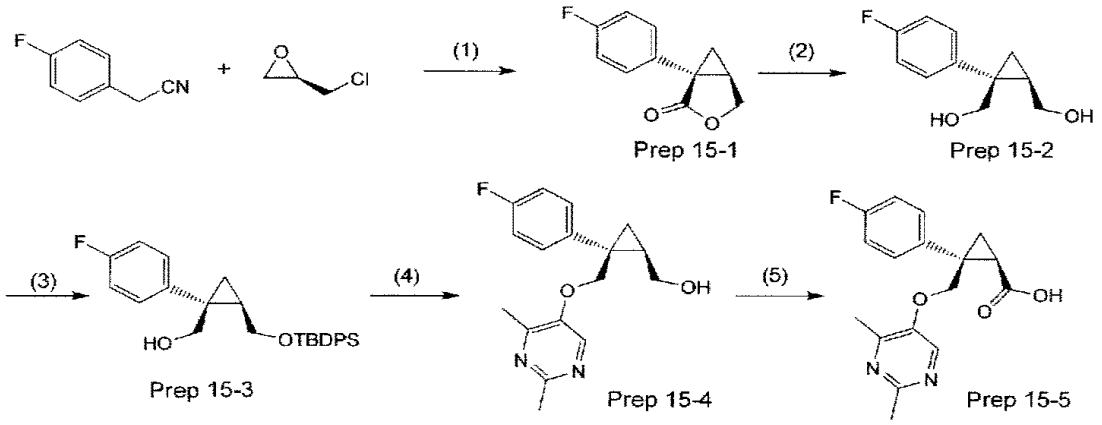
【０１６３】

製造例１５

（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（４－フルオロフェニル）シクロプロパンカルボン酸（Ｐｒｅｐ１５－５）の合成

４－フルオロフェニルアセトニトリルから製造例１３と同様の方法により合成した。

【化３２】



【０１６４】

【表１－１】

化合物番号	化合物名	データ（NMR又は／及びMS）
Ｐｒｅｐ１５－１	（１Ｓ，５Ｒ）－１－（４－フルオロフェニル）－３－オキサビシクロ［３．１．０］ヘキサン－２－オン	^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．３７（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），１．６０（ｄｄ，Ｊ＝４．８，８．０Ｈｚ，１Ｈ），２．５０－２．６０（ｍ，１Ｈ），４．３０（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４８（ｄｄ，Ｊ＝４．８，９．６Ｈｚ，１Ｈ），６．９６－７．１８（ｍ，２Ｈ），７．３０－７．４６（ｍ，２Ｈ）．
Ｐｒｅｐ１５－２	（１Ｓ，２Ｒ）－１－（４－フルオロフェニル）シクロプロパン－１，２－ジメタノール	^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：０．７８（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），１．０６（ｄｄ，Ｊ＝５．２，８．８Ｈｚ，１Ｈ），１．５４－１．７２（ｍ，１Ｈ），３．４２（ｄｄ，Ｊ＝１０．８，１１．６Ｈｚ，１Ｈ），３．５７（ｄ，Ｊ＝１２．０Ｈｚ，１Ｈ），３．９８－４．２６（ｍ，２Ｈ），６．９４－７．０９（ｍ，２Ｈ），７．３３－７．４６（ｍ，２Ｈ）．
Ｐｒｅｐ１５－３	｛（１Ｓ，２Ｒ）－２－［（ｔｅｒｔ－ブチルジフェニルシリル）オキシメチル］－１－（４－フルオロフェニル）シクロプロピル｝メタノール	^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：０．７０（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），０．９２－１．１６（ｍ，１０Ｈ），１．４０－１．６０（ｍ，１Ｈ），３．４２－３．５８（ｍ，２Ｈ），３．６９（ｄｄ，Ｊ＝１．６，１２．４Ｈｚ，１Ｈ），４．０３（ｔ，Ｊ＝１１．６Ｈｚ，１Ｈ），４．２０（ｄｄ，Ｊ＝５．２，１１．６Ｈｚ，１Ｈ），６．９４－７．０６（ｍ，２Ｈ），７．２０－７．５３（ｍ，８Ｈ），７．６６－７．７８（ｍ，４Ｈ）．
Ｐｒｅｐ１５－４	｛（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（４－フルオロフェニル）シクロプロピル｝メタノール	^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：０．９７（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），１．２０－１．３０（ｍ，１Ｈ），１．７２－１．８６（ｍ，１Ｈ），２．１４－２．２６（ｍ，１Ｈ），２．３８（ｓ，３Ｈ），２．６０（ｓ，３Ｈ），３．５０－３．６２（ｍ，１Ｈ），４．００－４．１６（ｍ，２Ｈ），４．３９（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），６．９４－７．１２（ｍ，２Ｈ），７．３２－７．４６（ｍ，２Ｈ），７．９８（ｓ，１Ｈ）．

【表１－２】

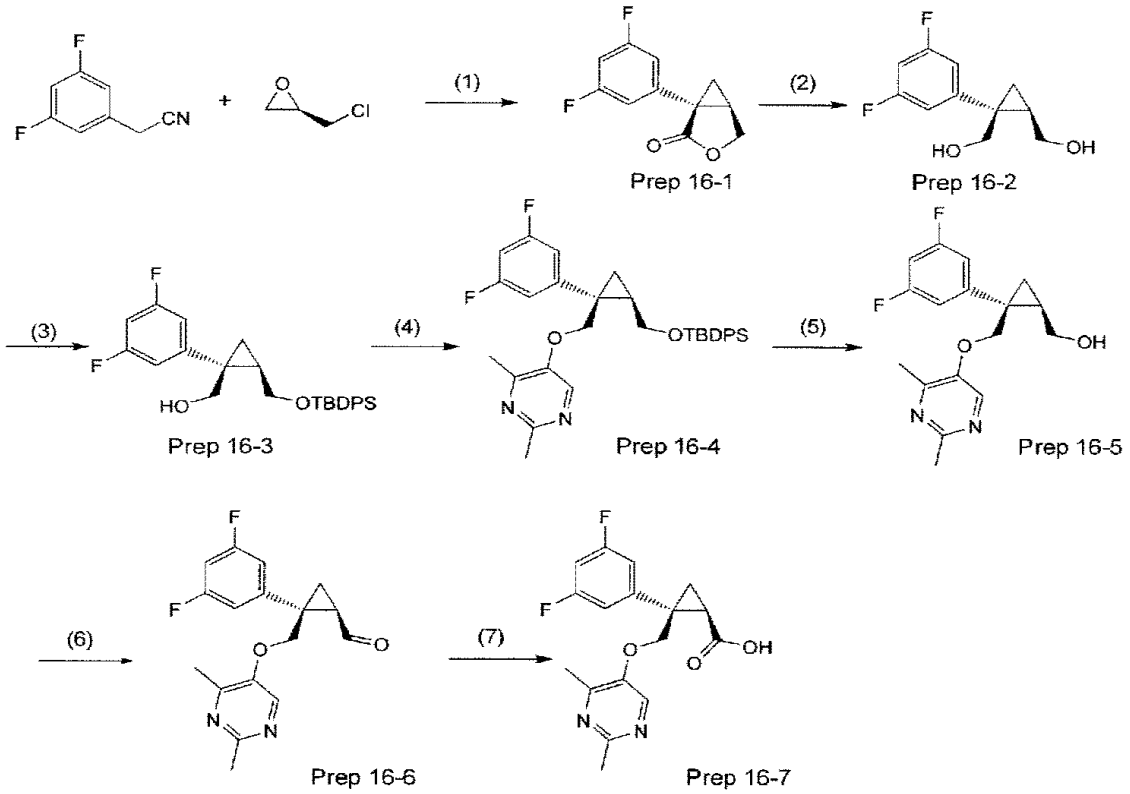
Ｐｒｅｐ１５－５	（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（４－フルオロフェニル）シクロプロパンカルボン酸	^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．５２（ｄｄ，Ｊ＝４．８，８．０Ｈｚ，１Ｈ），１．７４（ｄｄ，Ｊ＝５．２，５．６Ｈｚ，１Ｈ），２．２２（ｄｄ，Ｊ＝６．０，８．４Ｈｚ，１Ｈ），２．３３（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），４．３６－４．５０（ｍ，２Ｈ），６．９６－７．１２（ｍ，２Ｈ），７．３２－７．５４（ｍ，２Ｈ），８．１８（ｓ，１Ｈ）．ＭＳ［Ｍ＋Ｈ］$^+$＝３１７．

【０１６５】

製造例１６

（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボン酸（Ｐｒｅｐ１６－７）の合成

【化３３】



【０１６６】

３，５－ジフルオロフェニルアセトニトリルから製造例１３と同様の方法により合成した。

【０１６７】

【表２－１】

化合物番号	化合物名	データ（NMR又は／及びMS）
Ｐｒｅｐ１６－１	（１Ｓ，５Ｒ）－１－（３，５－ジフルオロフェニル）－３－オキサビシクロ［３．１．０］ヘキサン－２－オン	^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．４５（ｔ，Ｊ＝４．８Ｈｚ，１Ｈ），１．６３（ｄｄ，Ｊ＝５．２，８．４Ｈｚ，１Ｈ），２．５８－２．６３（ｍ，１Ｈ），４．３０（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），４．４６（ｄｄ，Ｊ＝４．４，９．２Ｈｚ，１Ｈ），６．７１－６．７７（ｍ，１Ｈ），６．９７－７．０２（ｍ，２Ｈ）．
Ｐｒｅｐ１６－２	（１Ｓ，２Ｒ）－１－（３，５－ジフルオロフェニル）－１，２－シクロプロパンジメタノール	ＭＳ［Ｍ＋Ｎａ］$^+$＝２３７．
Ｐｒｅｐ１６－３	（１Ｓ，２Ｒ）－２－（ｔｅｒｔ－ブチルジフェニルシリルオキシメチル）－１－（３，５－ジフルオロフェニル）シクロプロピルメタノール	^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：０．７４（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），１．０３（ｄｄ，Ｊ＝５．２，８．４Ｈｚ，１Ｈ），１．０９（ｓ，９Ｈ），１．４２－１．５０（ｍ，１Ｈ），３．５１（ｔ，Ｊ＝１１．６Ｈｚ，１Ｈ），３．５９－３．７０（ｍ，２Ｈ），４．０８－４．２２（ｍ，２Ｈ），６．６５－６．７１（ｍ，１Ｈ），６．９１－６．９５（ｍ，２Ｈ），７．３６－７．４９（ｍ，６Ｈ），７．４９－７．７３（ｍ，４Ｈ）．
Ｐｒｅｐ１６－４	５－［（１Ｓ，２Ｒ）－２－（ｔｅｒｔ－ブチルジフェニルシリルオキシメチル）－１－（３，５－ジフルオロフェニル）シクロプロピルメチルオキシ］－２，４－ジメチルピリミジン	ＭＳ［Ｍ＋Ｎａ］$^+$＝５５９．
Ｐｒｅｐ１６－５	（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロピルメタノール	ＭＳ［Ｍ＋Ｈ］$^+$＝３２１．

【表２－２】

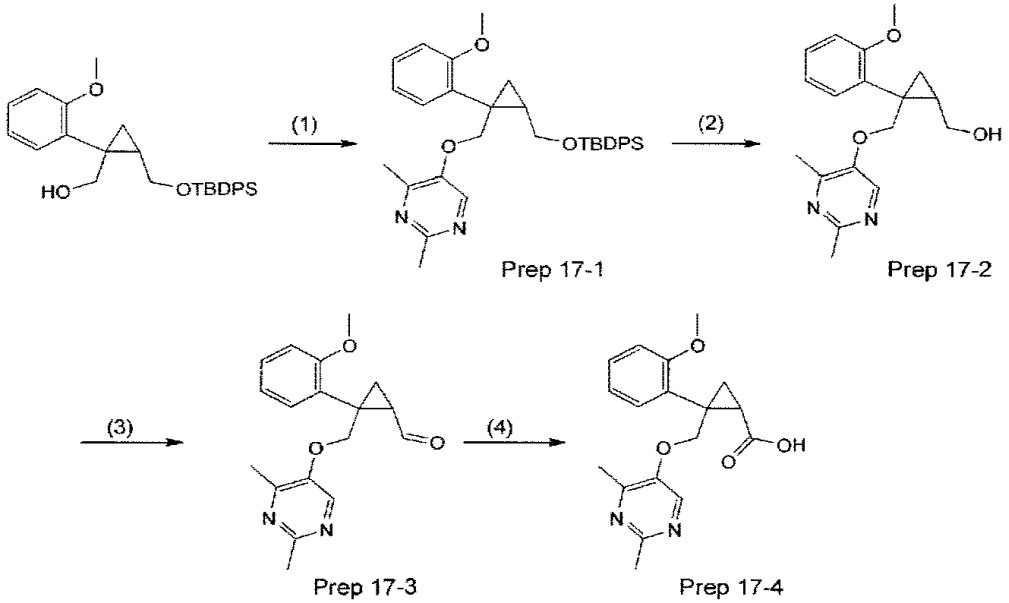
Ｐｒｅｐ１６－６	（１Ｒ，１Ｓ）－２－（３，５－ジフルオロフェニル）－２－（２，４－ジメチルピリミジン－５－イル）オキシメチルシクロプロパンカルバルデヒド	^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．６６（ｄｄ，Ｊ＝５．２，８．４Ｈｚ，１Ｈ），１．９８（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．３６（ｓ，３Ｈ），２．４９－２．５３（ｍ，１Ｈ），２．６０（ｓ，３Ｈ），４．１７（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．７３－６．８０（ｍ，１Ｈ），６．９６－７．００（ｍ，２Ｈ），７．９６（ｓ，１Ｈ），９．８８（ｄ，Ｊ＝３．２Ｈｚ，１Ｈ）．
Ｐｒｅｐ１６－７	（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－（２，４－ジメチルピリミジン－５－イル）オキシメチルシクロプロパンカルボン酸	^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．５９（ｄｄ，Ｊ＝６．０Ｈｚ，８．４Ｈｚ，１Ｈ），１．７４（ｔ，Ｊ＝６．０Ｈｚ，１Ｈ），２．２２（ｄｄ，Ｊ＝６．０Ｈｚ，８．０Ｈｚ，１Ｈ），２．３９（ｓ，３Ｈ），２．５９（ｓ，３Ｈ），４．４４（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５８（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．７５（ｔ，Ｊ＝９．２Ｈｚ，１Ｈ），６．９９－７．０３（ｍ，２Ｈ），８．２８（ｓ，１Ｈ）．ＭＳ［Ｍ＋Ｈ］$^+$＝３３５

【０１６８】

製造例１７

２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（２－メトキシフェニル）シクロプロパンカルボン酸（Ｐｒｅｐ１７－４）の合成

【化３４】



【０１６９】

（１）５－｛（１Ｓ，２Ｒ）－２－［ｔｅｒｔ－ブチル（ジフェニル）シリルオキシメチル］－１－（２－メトキシフェニル）シクロプロピル｝メトキシ－２，４－ジメチルピリミジン（Ｐｒｅｐ１７－１）

（２－メトキシフェニル）アセトニトリルとエピクロロヒドリンより、製造例１３の方

法に準じて合成した［２－（｛［ｔｅｒｔ－ブチル（ジフェニル）シリル］オキシ｝メチル）－１－（２－メトキシフェニル）シクロプロピル］メタノール（８００ｍｇ）、テトラブロモメタン（７７２ｍｇ）のトルエン（１５ｍｌ）溶液にトリフェニルホスフィン（６１０ｍｇ）を室温で加え、４０℃に昇温し２時間撹拌した。反応液に飽和炭酸水素ナトリウム水溶液を加え、酢酸エチル（ｘ１）で抽出した。有機層を水、飽和食塩水溶液で順次洗浄後、無水硫酸マグネシウムで乾燥し、濾過した。濾液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝１９：１～９：１）で精製し対応するブロマイド体を得た。

得られたブロマイド体を、化合物Ｐｒｅｐ４－２（１１３ｍｇ）のＤＭＦ（１０ｍｌ）溶液に炭酸カリウム（２１０ｍｇ）を室温で加え、５０℃に昇温し２時間撹拌した。７０℃に昇温しさらに１１時間撹拌後、反応液に水を加え、酢酸エチル（ｘ１）で抽出した。有機層を水、飽和食塩水溶液で順次洗浄後、無水硫酸マグネシウムで乾燥し、濾過した。濾液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝９：１～１：４）で精製し標記化合物（１４８ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：０．９４（ｄｄ，Ｊ＝５．２，６．２Ｈｚ，１Ｈ），１．０７（ｓ，９Ｈ），１．１０（ｄｄ，Ｊ＝５．２，８．８Ｈｚ，１Ｈ），１．５４－１．６１（ｍ，１Ｈ），２．２１（ｓ，３Ｈ），２．５８（ｓ，３Ｈ），３．８０（ｓ，３Ｈ），３．９５（ｄ，Ｊ＝６．８Ｈｚ，２Ｈ），４．１１（ｄ，Ｊ＝９．８Ｈｚ，１Ｈ），４．２５（ｄ，Ｊ＝９．８Ｈｚ，１Ｈ），６．８２－６．９１（ｍ，２Ｈ），７．１９－７．４２（ｍ，８Ｈ），７．６５－７．６９（ｍ，４Ｈ），７．８７（ｓ，１Ｈ）．

ＭＳ［Ｍ＋Ｎａ］$^+$＝５７５

【０１７０】

（２）｛２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（２－メトキシフェニル）シクロプロピル｝メタノール（Ｐｒｅｐ１７－２）

化合物Ｐｒｅｐ１７－１（１４８ｍｇ）のＴＨＦ（１．３ｍｌ）溶液にテトラブチルアンモニウム　フロリド（１Ｍ－ＴＨＦ溶液：３２２μｌ）を室温で滴下し、室温で２３時間撹拌した。反応液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝１：１～酢酸エチル～酢酸エチル：メタノール＝９：１）で精製し標記化合物（７５ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：０．９９（ｄｄ，Ｊ＝５．２，６．２Ｈｚ，１Ｈ），１．２１（ｄｄ，Ｊ＝５．２，８．８Ｈｚ，１Ｈ），１．６８－１．７６（ｍ，１Ｈ），２．３２（ｓ，３Ｈ），２．４５（ｄｄ，Ｊ＝２．４，８．８Ｈｚ，１Ｈ），２．５８（ｓ，３Ｈ），３．４８－３．５４（ｍ，１Ｈ），３．８８（ｓ，３Ｈ），４．１３（ｄｔ，８．８，６．４Ｈｚ，１Ｈ），４．１８（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），４．３３（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），６．８７（ｄｄ，Ｊ＝１．２，８．０Ｈｚ，１Ｈ），６．９４（ｄｔ，Ｊ＝１．２，８．０Ｈｚ，１Ｈ），７．２４－７．２９（ｍ，１Ｈ），７．３４（ｄｄ，Ｊ＝１．６，８．０Ｈｚ，１Ｈ），７．９４（ｓ，１Ｈ）．

【０１７１】

（３）２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（２－メトキシフェニル）シクロプロパンカルバルデヒド（Ｐｒｅｐ１７－３）

オキサリルクロリド（８２μｌ）のジクロロメタン（０．５ｍｌ）溶液を－７８℃に冷却し、そこにジメチルスルホキシド（１３６μｌ）のジクロロメタン（０．５ｍｌ）溶液を滴下した。１０分後、反応液に化合物Ｐｒｅｐ－２（７５ｍｇ）のジクロロメタン（１ｍｌ）溶液を－７８℃で滴下し、同温で４０分撹拌した。反応液にトリエチルアミン（５３４μｌ）を加えて０℃に昇温し１５分撹拌した。反応液に水を加え、酢酸エチル（ｘ１）で抽出した。有機層を水、飽和食塩水溶液で洗浄後、無水硫酸マグネシウムで乾燥し、濾過した。濾液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝９：１～酢酸エチル）で精製し標記化合物（４１ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．５５（ｄｄ，Ｊ＝５．２，８．４Ｈｚ，１Ｈ），１．９７（ｄｄ，Ｊ＝５．２，６．２Ｈｚ，１Ｈ），２．２８（ｓ，３Ｈ），２．４２（ｄｄｄ，Ｊ＝４．０，６．２，８．４Ｈｚ，１Ｈ），２．５６（ｓ，３Ｈ），３．８７（ｓ，３Ｈ），４．１７（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．８８（ｄｄ，Ｊ＝０．８，８．０Ｈｚ，１Ｈ），６．９４（ｄｔ，Ｊ＝０．８，８．０Ｈｚ，１Ｈ），７．２６－７．３０（ｍ，１Ｈ），７．３７（ｄｄ，Ｊ＝１．８，８．０Ｈｚ，１Ｈ），７．９０（ｓ，１Ｈ），９．８２（ｄ，Ｊ＝４．０Ｈｚ，１Ｈ）．

【０１７２】

（４）２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（２－メトキシフェニル）シクロプロパンカルボン酸（Ｐｒｅｐ１７－４）

化合物Ｐｒｅｐ１７－３（４１ｍｇ）のアセトン－水（１．３ｍｌ）溶液に室温で２－メチル－２－ブテン（１３９μｌ）、無水リン酸二水素ナトリウム（２３．６ｍｇ）および亜塩素酸ナトリウム（４４．４ｍｇ）を加え、２．５時間撹拌した。反応液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝１：１～クロロホルム：メタノール＝９：１）で精製して標記化合物（３５ｍｇ）を得た。

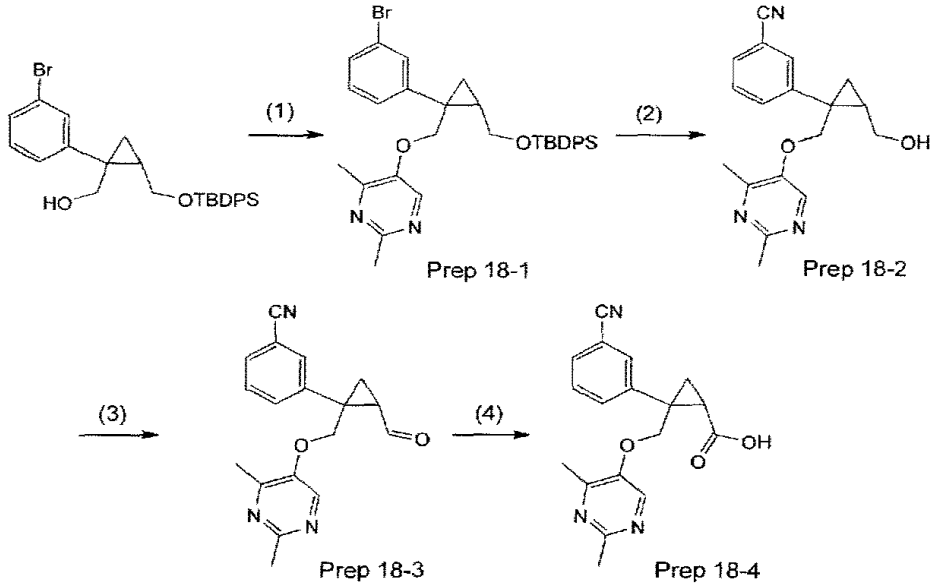
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．５０（ｄｄ，Ｊ＝５．２，８．０Ｈｚ，１Ｈ），１．７０（ｄｄ，Ｊ＝５．２，６．４Ｈｚ，１Ｈ），２．１３（ｄｄ，Ｊ＝６．４，８．０Ｈｚ，１Ｈ），２．３１（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），３．８９（ｓ，３Ｈ），４．４０（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），４．５７（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），６．８９（ｄｄ，Ｊ＝１．２，８．０Ｈｚ，１Ｈ），６．９５（ｄｔ，Ｊ＝１．２，８．０Ｈｚ，１Ｈ），７．２７－７．３０（ｍ，１Ｈ），７．４２（ｄｄ，Ｊ＝１．２，８．０Ｈｚ，１Ｈ），８．１９（ｓ，１Ｈ）．

【０１７３】

製造例１８

２－（３－シアノフェニル）－２－（２，４－ジメチルピリミジン－５－イル）オキシメチルシクロプロパンカルボン酸（Ｐｒｅｐ１８－４）の合成

【化３５】



【０１７４】

（１）５－［１－（３－ブロモフェニル）－２－（ｔｅｒｔ－ブチルジフェニルシリルオキシメチル）シクロプロピルメトキシ－２、４－ジメチルピリミジン（Ｐｒｅｐ１８－１）

（３－ブロモフェニル）アセトニトリルとエピクロロヒドリンより、製造例１３と同様の手法により合成した［１－（３－ブロモフェニル）－２－（ｔｅｒｔ－ブチルジフェニルシリルオキシメチル）］シクロプロピルメタノール（１．３ｇ）、トリフェニルホスフィン（８９３ｍｇ）および製造例４－（２）で合成した２，４－ジメチル－５－ピリミジノール（３９０ｍｇ）のＴＨＦ（１３ｍｌ）溶液にジイソプロピルアゾジカルボキシラート（０．７０６ｍｌ）を０℃で滴下し、室温で１４時間攪拌した。反応液に水を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄後、硫酸マグネシウムで乾燥し、減圧下濃縮した。残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，Ｓｉｚｅ：２Ｌ，ｎ－ヘプタン：酢酸エチル０％→４０％）で精製し、標記化合物（８８０ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：０．９５（ｔ，Ｊ＝５．８Ｈｚ，１Ｈ），１．０８（ｓ，９Ｈ），１．１７－１．３５（ｍ，１Ｈ），１．５５－１．６５（ｍ，１Ｈ），２．３０（ｓ，３Ｈ），２．６１（ｓ，３Ｈ），３．７５（ｄｄ，Ｊ＝１１．２，８．０Ｈｚ，１Ｈ），４．０４（ｄｄ，１Ｈ，Ｊ＝１１．２，５．４Ｈｚ，１Ｈ），４．１１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．１９（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．１７（ｔ，Ｊ＝７．８Ｈｚ，１Ｈ），７．３１－７．３９（ｍ，６Ｈ），７．４０－７．４６（ｍ，２Ｈ），７．５９（ｔ，Ｊ＝２．０Ｈｚ，１Ｈ），７．６２－７．６８（ｍ，４Ｈ），７．８８（ｓ，１Ｈ）．

【０１７５】

（２）３－｛１－［（２、４－ジメチルピリミジン－５－イル）オキシメチル］－２－ヒドロキシメチルシクロプロパン－１－イル｝ベンゾニトリル（Ｐｒｅｐ１８－２）

化合物Ｐｒｅｐ１８－１（８８０ｍｇ）のＤＭＦ（２０ｍｌ）溶液に、シアン化亜鉛（１７２ｍｇ）、テトラキストリフェニルホスフィンパラジウム（１６９ｍｇ）を加え、窒素雰囲気下、９０℃で７時間攪拌した。反応液を室温に戻し、飽和炭酸水素ナトリウム水溶液を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄後、硫酸マグネシウムで乾燥し、減圧下濃縮した。残渣をＴＨＦ（１０ｍｌ）に溶解し、テトラブチルアンモニウム　フロリド（Ａｌｄｒｉｃｈ，１Ｍ－ＴＨＦ溶液：２．１９ｍｌ）を室温で滴下し、室温で５時間攪拌した。反応液を減圧下濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，Ｓｉｚｅ：Ｌ，ｎ－ヘプタン：酢酸エチル０％→１００％→酢酸エチル：メタノール１０％）で精製し、標記化合物（４１５ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．０７（ｔ，Ｊ＝６．０Ｈｚ，１Ｈ），１．３１（ｄｄ，Ｊ＝８．６，５．４Ｈｚ，１Ｈ），１．７４－１．８４（ｍ，１Ｈ），２．３８（ｓ，３Ｈ），２．６０（ｓ，３Ｈ），３．６３（ｄｄ，Ｊ＝１２．０，９．２Ｈｚ，１Ｈ），４．０９（ｄｄ，Ｊ＝１２．０，５．４Ｈｚ，１Ｈ），４．１６（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），４．３８（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），７．４５（ｔ，Ｊ＝７．６Ｈｚ，１Ｈ），７．５４－７．５８（ｍ，１Ｈ），７．６８－７．７２（ｍ，１Ｈ），７．７３－７．７５（ｍ，１Ｈ），８．０１（ｓ，１Ｈ）．

【０１７６】

（３）３－｛１－［（２、４－ジメチルピリミジン－５－イル）オキシメチル］－２－ホルミルシクロプロパン－１－イル｝ベンゾニトリル（Ｐｒｅｐ１８－３）

オキサリルクロリド（２３９ｕｌ）のジクロロメタン溶液（７ｍｌ）を－７８℃に冷却し、そこにジメチルスルホキシド（３９４ｕｌ）を滴下した（内温－６０℃以下）。同温度で１０分攪拌後、反応液に化合物Ｐｒｅｐ１８－２（４１５ｍｇ）のジクロロメタン（７ｍｌ）溶液を－７８℃で滴下し、同温で３０分撹拌した。反応液にトリエチルアミン（１．１７ｍｌ）を加えて１５分攪拌後、室温に昇温した。反応液に飽和食塩水を加え、酢酸エチルで抽出した。有機層を無水硫酸マグネシウムで乾燥後減圧濃縮し、標記化合物粗精製物（２３６ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．４１（ｔ，Ｊ＝７．２Ｈｚ，１Ｈ），１．６９（ｄｄ，Ｊ＝８．４，５．２Ｈｚ，１Ｈ），２．０３（ｔ，Ｊ＝５

．８Ｈｚ，１Ｈ），２．３５（ｓ，３Ｈ），２．５９（ｓ，３Ｈ），４．２２（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），４．４２（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），７．５０（ｔ，Ｊ＝８．２Ｈｚ，１Ｈ），７．５９－７．６５（ｍ，１Ｈ），７．７０－７．７５（ｍ，１Ｈ），７．７６－７．７９（ｍ，１Ｈ），７．９６（ｓ，１Ｈ），９．９２（ｄ，Ｊ＝２．８Ｈｚ，１Ｈ）．

【０１７７】

（４）２－（３－シアノフェニル）－２－｛１－［（２、４－ジメチルピリミジン－５－イル）オキシメチル］｝シクロプロパンカルボン酸（Ｐｒｅｐ１８－４）

化合物Ｐｒｅｐ１８－３（４１５ｍｇ）と２－メチル２－ブテン（０．７１７ｍｌ）、リン酸二水素ナトリウム（２４３ｍｇ）をアセトン・水混合溶媒（１０ｍｌ・２ｍｌ）に溶解させ、亜塩素酸ナトリウム（２４４ｍｇ）を少しずつ加えた。室温で１４時間撹拌した後、反応溶液を減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，Ｓｉｚｅ：Ｍ，酢酸エチル：メタノール０％→１５％）で精製して標記化合物（２６５ｍｇ）を得た。

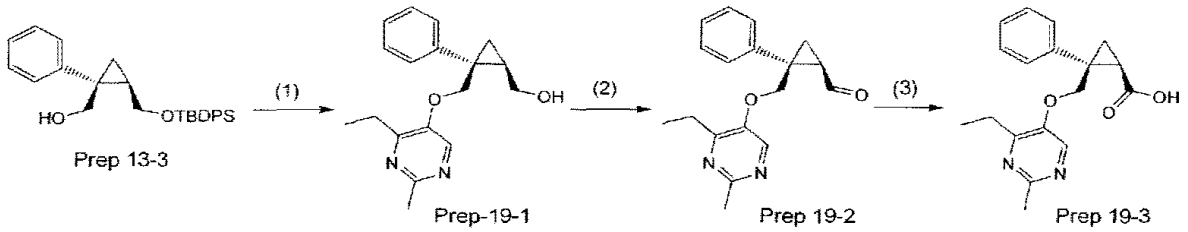
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．６１（ｄｄ，Ｊ＝８．４，５．６Ｈｚ，１Ｈ），１．７９（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．２０－２．２７（ｍ，１Ｈ），２．３７（ｓ，３Ｈ），２．６０（ｓ，３Ｈ），４．４６（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５９（ｄ，Ｊ－９．６Ｈｚ，１Ｈ），７．４９（ｔ，Ｊ＝７．８Ｈｚ，１Ｈ），７．５９－７．６３（ｍ，１Ｈ），７．７２－７．７７（ｍ，１Ｈ），７．８０（ｔ，Ｊ＝１．８Ｈｚ，１Ｈ），８．２８（ｓ，１Ｈ）．

【０１７８】

製造例１９

（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボン酸（Ｐｒｅｐ１９－３）の合成

【化３６】



【０１７９】

化合物Ｐｒｅｐ１３－３から製造例１３と同様の方法により合成した。

【０１８０】

【表３】

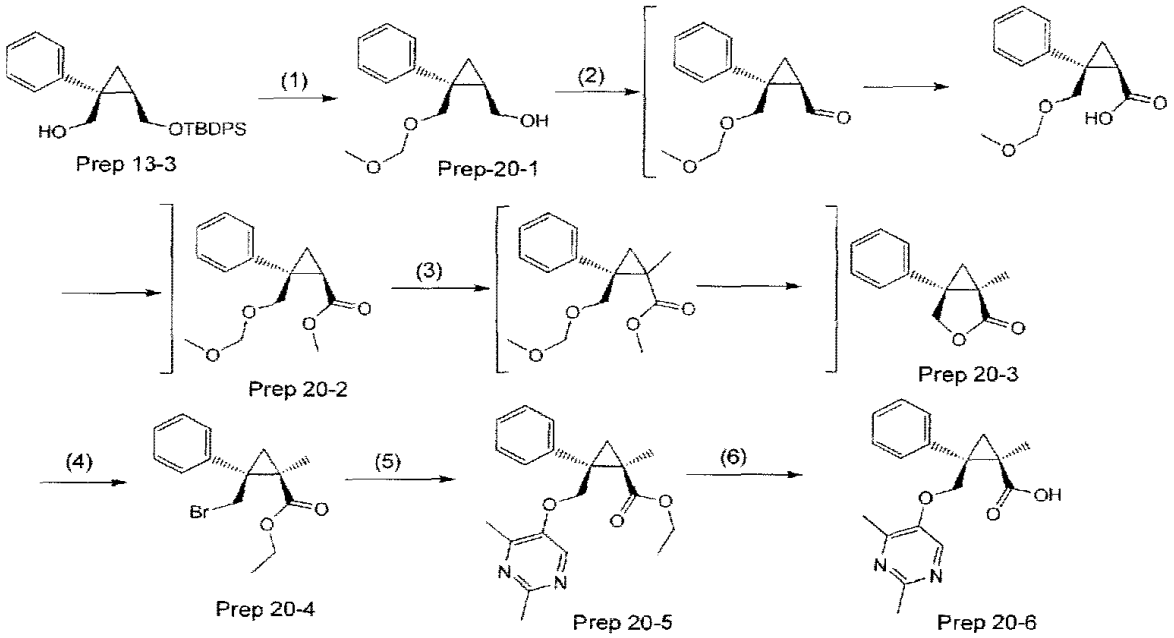
化合物番号	化合物名	データ（ＮＭＲ又は／及びＭＳ）
Ｐｒｅｐ１９－１	（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロピルメタノール	^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：０．９７（ｔ，Ｊ＝５．４Ｈｚ，１Ｈ），１．１５（ｔ，Ｊ＝７．８Ｈｚ，３Ｈ），１．２７（ｄｄ，Ｊ＝８．８，５．２Ｈｚ，１Ｈ），１．８０－１．９０（ｍ，１Ｈ），２．１９（ｄｄ，Ｊ＝９．６，３．２Ｈｚ，１Ｈ），２．６０（ｓ，３Ｈ），２．７０（ｄｄｄ，Ｊ＝１５．２，７．６，３．２Ｈｚ，２Ｈ），３．５４－３．６３（ｍ，１Ｈ），４．０３－４．１５（ｍ，１Ｈ），４．１１（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），４．４４（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．２１－７．２９（ｍ，１Ｈ），７．２９－７．３６（ｍ，２Ｈ），７．４２－７．４６（ｍ，２Ｈ），７．９９（ｓ，１Ｈ）．
Ｐｒｅｐ１９－２	（１Ｒ，２Ｓ）－２－｛［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパン－１－イル｝カルバルデヒド	^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．１６（ｔ，Ｊ＝７．６Ｈｚ，３Ｈ），１．６４－１．７４（ｍ，１Ｈ），１．９７（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．５０－２．５５（ｍ，１Ｈ），２．６０（ｓ，３Ｈ），２．７０（ｑ，Ｊ＝７．６Ｈｚ，２Ｈ），４．２０（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），４．４４（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．２７－７．３８（ｍ，３Ｈ），７．４２－７．４７（ｍ，２Ｈ），７．９５（ｓ，１Ｈ），９．８６（ｄ，Ｊ＝３．６Ｈｚ，１Ｈ）．
Ｐｒｅｐ１９－３	（１Ｒ，２Ｓ）－２－｛［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボン酸	^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．０８（ｔ，Ｊ＝７．４Ｈｚ，３Ｈ），１．５３－１．５８（ｍ，１Ｈ），１．７６（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．２４－２．２９（ｍ，１Ｈ），２．５７（ｓ，３Ｈ），２．６０－２．７１（ｍ，２Ｈ），４．４９（ｄｄ，Ｊ＝１３．２，９．２Ｈｚ，２Ｈ），７．２５－７．３２（ｍ，１Ｈ），７．３２－７．３９（ｍ，２Ｈ），７．４６－７．５２（ｍ，２Ｈ），８．２３（ｓ，１Ｈ）．

【０１８１】

製造例２０

（１Ｒ，２Ｒ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボン酸（Ｐｒｅｐ２０－６）の合成

【化３７】



【０１８２】

（１）［（１Ｒ，２Ｓ）－２－（メトキシメトキシメチル）－２－フェニルシクロプロピル］メタノール（Ｐｒｅｐ２０－１）

化合物Ｐｒｅｐ１３－３（４ｇ）のジクロロメタン（４０ｍｌ）溶液に、氷冷撹拌下、Ｎ，Ｎ－ジイソプロピルエチルアミン（４．３５ｍｌ）とクロロメチルメチルエーテル（１．５２ｍｌ）を加えた。室温で１４時間撹拌した後、反応液に水を加えた。ジクロロメタンで抽出し、有機層を硫酸マグネシウムで乾燥後、減圧下にて溶媒を留去した。得られた残渣をＴＨＦ（４０ｍｌ）に溶解し、テトラブチルアンモニウム　フロリド（１Ｍ－ＴＨＦ溶液：１．６１ｍｌ）を室温で加え、室温で２時間撹拌した。反応液を減圧下濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，Ｓｉｚｅ：２Ｌ，ｎ－ヘプタン：酢酸エチル１０％→５０％）で精製して標記化合物（１．９３ｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：０．７９（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），１．１１（ｄｄ，Ｊ＝８．８，５．２Ｈｚ，１Ｈ），１．７０－１．８０（ｍ，１Ｈ），３．１９（ｓ，３Ｈ），３．３５－３．４５（ｍ，１Ｈ），３．５７（ｄ，Ｊ＝１０．４Ｈｚ，１Ｈ），４．０４－４．１６（ｍ，２Ｈ），４．５２（ｄ，Ｊ＝６．４Ｈｚ，１Ｈ），４．５９（ｄ，Ｊ＝６．８Ｈｚ，１Ｈ），７．１８－７．２４（ｍ，１Ｈ），７．２５－７．３４（ｍ，２Ｈ），７．３５－７．４２（ｍ，２Ｈ）．

【０１８３】

（２）メチル（１Ｒ，２Ｓ）－２－メトキシメトキシメチル－２－フェニルシクロプロパンカルボキシラート（Ｐｒｅｐ２０－２）

オキサリルクロリド（１．５ｍｌ）のジクロロメタン溶液（１５ｍｌ）を－７８℃に冷却し、そこにジメチルスルホキシド（２．４９ｍｌ）のジクロロメタン（５ｍｌ）溶液を滴下した（内温－６５℃以下）。同温度で５分撹拌後、反応液に化合物Ｐｒｅｐ２０－１（１．９３ｇ）のジクロロメタン（２０ｍｌ）溶液を－７８℃で滴下し、同温で３０分撹拌した。反応液にトリエチルアミン（７．３３ｍｌ）を加えて１５分撹拌後、室温に昇温した。反応液に飽和食塩水を加え、酢酸エチルで抽出した。有機層を無水硫酸マグネシウムで乾燥後減圧濃縮し、アルデヒド体（１．９３ｇ）を得た。得られたアルデヒド体（１．９３ｇ）と２－メチル２－ブテン（４．６５ｍｌ）、リン酸二水素ナトリウム（１．０５ｇ）をアセトン・水混合溶媒（６０ｍｌ・１５ｍｌ）に溶解させ、氷冷撹拌下、亜塩素

酸ナトリウム（１．５８ｇ）を少しずつ加えた。室温で５時間撹拌した後、反応液に水を加え、酢酸エチル（ｘ３）で抽出した。有機層を飽和食塩水で洗浄後、硫酸マグネシウムで乾燥し、減圧濃縮した。残渣をメタノール・ＴＨＦ混合溶媒（２０ｍｌ・２０ｍｌ）に溶解し、室温撹拌下、トリメチルシリルジアゾメタン（Ａｌｄｒｉｃｈ，２Ｍ－ヘキサン溶液：８．７６ｍｌ）を加えた。室温で１４時間撹拌した後、少量の酢酸を加え過剰のトリメチルシリルジアゾメタンを分解した。減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，Ｓｉｚｅ：Ｍ，ｎ－ヘプタン：酢酸エチル０％→２０％）で精製して標記化合物（１．６５ｇ）を得た。
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．４３（ｄｄ，Ｊ＝８．０，４．８Ｈｚ，１Ｈ），１．６０（ｄｄ，Ｊ＝６．２，４．８Ｈｚ，１Ｈ），２．１２（ｄｄ，Ｊ＝８．０，６．２Ｈｚ，１Ｈ），３．１４（ｓ，３Ｈ），３．７５（ｓ，３Ｈ），３．８５（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），３．９８（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４８（ｓ，２Ｈ），７．２１－７．２８（ｍ，１Ｈ），７．２９－７．３４（ｍ，２Ｈ），７．３７－７．４２（ｍ，２Ｈ）．

【０１８４】

（３）（１Ｓ，５Ｒ）－１－メチル－５－フェニル－３－オキサビシクロ［３．１．０］ヘキサン－２－オン（Ｐｒｅｐ２０－３）

ジイソプロピルアミン（１．２５ｍｌ）のＴＨＦ（２２ｍｌ）溶液に、－７８℃撹拌下で、ｎ－ブチルリチウム（２．６９Ｍ－ヘキサン溶液：３．３ｍｌ）を加えた。－７８℃で３０分間撹拌した後に、化合物Ｐｒｅｐ２０－２（１．１１ｇ）のＴＨＦ（１１ｍｌ）溶液を加え、－７８℃で１時間撹拌した。ヨードメタン（７０３ｕｌ）を加えて、室温まで昇温させながら３時間撹拌した。反応液に飽和塩化アンモニウム水溶液を加え、酢酸エチルで抽出した。得られた有機層を飽和食塩水で洗浄後、硫酸マグネシウムで乾燥し、減圧濃縮した。残渣をＴＨＦ（１０ｍｌ）に溶解し、室温撹拌下、７．５Ｎ塩酸（１０ｍｌ）を加えた。室温で２時間撹拌した後、水を加え、酢酸エチルで抽出した。得られ有機層を飽和炭酸水素ナトリウム水溶液、飽和食塩水で順次洗浄後、硫酸マグネシウムで乾燥した。減圧濃縮後、残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－ＦｌｕｓｈＴＭｃｏｌｕｍｎ，Ｓｉｚｅ：Ｍ，ｎ－ヘプタン：酢酸エチル０％→２０％）で精製して、標記化合物（３１４ｍｇ）を得た。
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．１５（ｓ，３Ｈ），１．３６（ｄ，Ｊ＝５．２Ｈｚ，１Ｈ），１．５１（ｄ，Ｊ＝４．８Ｈｚ，１Ｈ），４．３８（ｄｄ，Ｊ＝１２．４，９．２Ｈｚ，２Ｈ），７．２０－７．４４（ｍ，５Ｈ）．

【０１８５】

（４）エチル（１Ｒ，２Ｒ）－２－ブロモメチル－１－メチル－２－フェニルシクロプロパンカルボキシラート（Ｐｒｅｐ２０－４）

エタノール（２ｍｌ）に、－１５℃撹拌下、チオニルブロマイド（２４７ｕｌ）を滴下した。その後、化合物Ｐｒｅｐ２０－３（１５０ｍｇ）を加え、－１５℃で一終夜撹拌した。反応液を減圧濃縮し、シリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，Ｓｉｚｅ：Ｍ，ｎ－ヘプタン：酢酸エチル０％→８５％）で精製して、標記化合物（１３１ｍｇ）を得た。
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．０２（ｓ、３Ｈ），１．３１－１．３７（ｍ，１Ｈ），１．３４（ｔ，Ｊ＝７．０Ｈｚ，３Ｈ），１．９１（ｄ，Ｊ＝５．２Ｈｚ，１Ｈ），３．７９（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），３．８７（ｄｄ，Ｊ＝１０．０，１．０Ｈｚ，１Ｈ），４．２４（ｑ，Ｊ＝７．０Ｈｚ，２Ｈ），７．２６－７．４３（ｍ，５Ｈ）．

【０１８６】

（５）エチル（１Ｒ，２Ｒ）－２－［（２、４－ジメチルピリミジン－５－イル）オキシメチル］－１－メチル－２－フェニルシクロプロパンカルボキシラート（Ｐｒｅｐ２０－５）

化合物Ｐｒｅｐ２０－４（１３１ｍｇ）のＤＭＦ（３ｍｌ）溶液に、炭酸カリウム（９

１．４ｍｇ）、製造例４－（２）で合成される２，４－ジメチル－５－ピリミジノール（７１．２ｍｇ）、テトラブチルアンモニウムヨージド（８１．４ｍｇ）を加えた。反応液を７０℃で５時間攪拌した後、室温に戻した。反応液に水を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、硫酸マグネシウムで乾燥後、減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，Ｓｉｚｅ：Ｍ，ｎ－ヘプタン：酢酸エチル５％→６０％）で精製して、標記化合物（１３３ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．０８（ｓ，３Ｈ），１．２２（ｔ，Ｊ＝７．０Ｈｚ，３Ｈ），１．３０（ｄ，Ｊ＝４．８Ｈｚ，１Ｈ），１．９６（ｄ，Ｊ＝４．８Ｈｚ，１Ｈ），２．４０（ｓ，３Ｈ），２．５８（ｓ，３Ｈ），４．０４－４．１７（ｍ，２Ｈ），４．３０（ｄｄ，Ｊ＝１２．２，５．４Ｈｚ，２Ｈ），７．２６－７．４８（ｍ，５Ｈ），７．９０（ｓ，１Ｈ）．

【０１８７】

（６）（１Ｒ，２Ｒ）－２－［（２、４－ジメチルピリミジン－５－イル）オキシメチル］－１－メチル－２－フェニルシクロプロパンカルボン酸（Ｐｒｅｐ２０－６）

化合物Ｐｒｅｐ２０－５（１３３ｍｇ）のエタノール（２ｍｌ）溶液に、５Ｎ水酸化ナトリウム水溶液（２３５ｕｌ）を加え、８０℃で５時間攪拌した。室温に戻してから、５Ｎ塩酸で中和し、減圧濃縮をした。残渣をＴＨＦで良く洗浄し、ろ過を行った。ろ液を硫酸マグネシウムで乾燥後、減圧濃縮することにより、標記化合物（１４４ｍｇ）を得た。

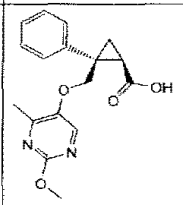
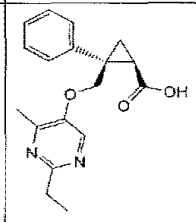
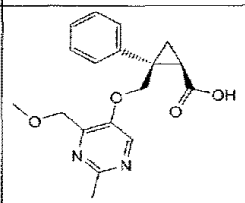
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．１０（ｓ，３Ｈ），１．２４－１．３４（ｍ，１Ｈ），１．９５（ｂｒｄ，Ｊ＝４．４Ｈｚ，１Ｈ），２．３４（ｓ，３Ｈ），２．５１（ｓ，３Ｈ），４．３６（ｂｒｄ，Ｊ＝９．２Ｈｚ，１Ｈ），４．４４（ｂｒｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．２６－７．４７（ｍ，５Ｈ），８．０４（ｓ，１Ｈ）．

【０１８８】

製造例２１－４７のカルボン酸は、製造例１３と同様の方法により合成した。但し、ラセミ体はＲ－（－）－エピクロロヒドリンの代わりに、（±）－エピクロルヒドリンを用いて合成した。

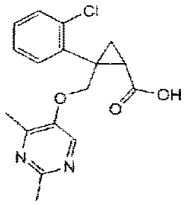
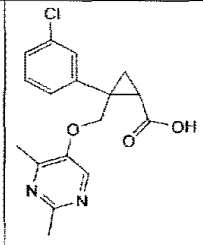
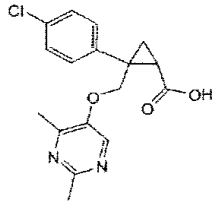
【０１８９】

【表４】

製造例	構造式	化合物名	データ（ＭＳ）
Ｐｒｅｐ２１		（１Ｒ，２Ｓ）－２－[（２，４－ジメチルピリミジン－５－イル）オキシメチル]－２－フェニルシクロプロパンカルボン酸	ＭＳ［Ｍ＋Ｈ］$^{+}$＝３１５
Ｐｒｅｐ２２		（１Ｒ，２Ｓ）－２－[（２－エチル－４－メチルピリミジン－５－イル）オキシメチル]－２－フェニルシクロプロパンカルボン酸	ＭＳ［Ｍ＋Ｈ］$^{+}$＝３１３
Ｐｒｅｐ２３		（１Ｒ，２Ｓ）－２－（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル－２－フェニルシクロプロパンカルボン酸	ＭＳ［Ｍ＋Ｈ］$^{+}$＝３２９

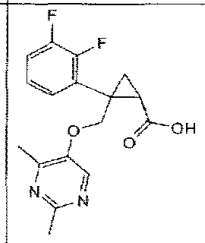
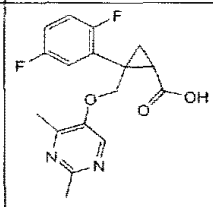
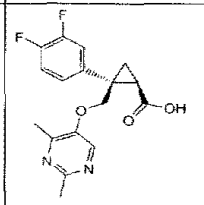
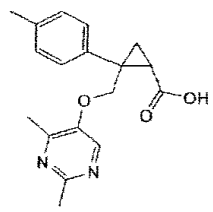
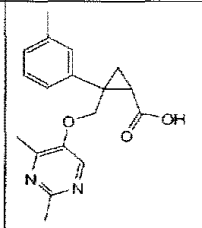
【０１９０】

【表５】

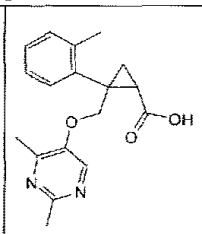
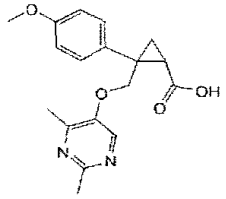
製造例	構造式、MS	製造例	構造式、MS	製造例	構造式、MS
Prep 24	 MS[M+H]$^{+}$= 333	Prep 25	 MS[M+H]$^{+}$= 333	Prep 26	 MS[M+H]$^{+}$= 333

【０１９１】

【表６－１】

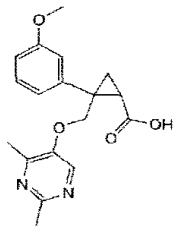
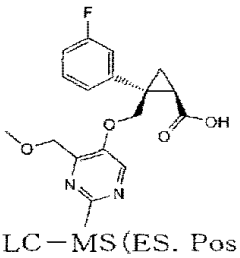
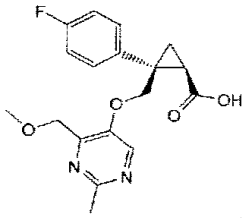
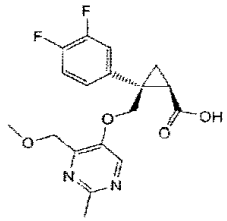
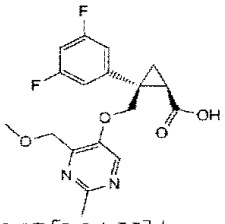
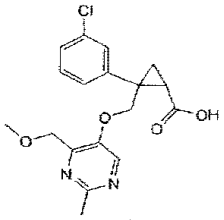
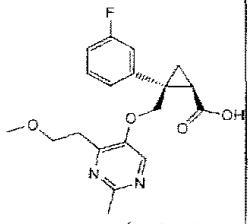
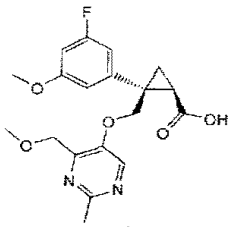
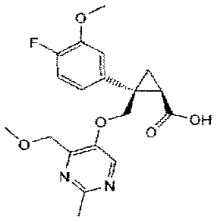
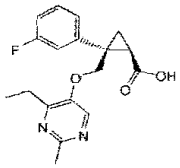
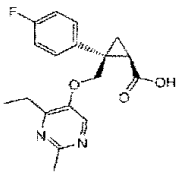
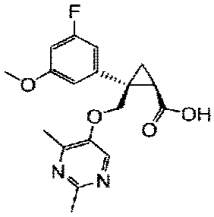
製造例	構造式	NMR及び／又はMS
Ｐｒｅｐ２７		^{1}H－NMR（４００MHｚ，CDCｌ$_3$）δ（ｐｐｍ）：１．５９（ｄｄ，Ｊ＝５．２Ｈｚ，８．４Ｈｚ，１Ｈ），１．７７（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．２０－２．２５（ｍ，１Ｈ），２．３３（ｓ，３Ｈ），２．５９（ｓ，３Ｈ），４．４３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．６１（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），７．０１－７．３０（ｍ，３Ｈ），８．２６（ｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝３３５
Ｐｒｅｐ２８		^{1}H－NMR（４００MHｚ，CDCｌ$_3$）δ（ｐｐｍ）：１．５８（ｄｄ，Ｊ＝５．６Ｈｚ，８．４Ｈｚ，１Ｈ），１．７６（ｔ，Ｊ＝６．０Ｈｚ，１Ｈ），２．２１（ｄｄ，Ｊ＝６．４Ｈｚ，８．４Ｈｚ，１Ｈ），２．３５（ｓ，３Ｈ），２．５９（ｓ，３Ｈ），４．４３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．６１（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），６．９５－７．２０（ｍ，３Ｈ），８．２８（ｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝３３５
Ｐｒｅｐ２９		^{1}H－NMR（４００MHｚ，CDCｌ$_3$）δ（ｐｐｍ）：１．５６（ｄｄ，Ｊ＝５．６Ｈｚ，８．０Ｈｚ，１Ｈ），１．７２（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．２０（ｄｄ，Ｊ＝６．０Ｈｚ，８．４Ｈｚ，１Ｈ），２．３８（ｓ，３Ｈ），２．５８（ｓ，３Ｈ），４．４１（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），４．５５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．１１－７．３４（ｍ，３Ｈ），８．２６（ｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝３３５
Ｐｒｅｐ３０		^{1}H－NMR（４００MHｚ，CDCｌ$_3$）δ（ｐｐｍ）：１．４８－１．６０（ｍ，１Ｈ），１．７０（ｄｄ，Ｊ＝５．２，６．０Ｈｚ，１Ｈ），２．２２（ｄｄ，Ｊ＝６．０，８．４Ｈｚ，１Ｈ），２．２８－２．４４（ｍ，６Ｈ），２．５７（ｓ，３Ｈ），４．３２－４．６２（ｍ，２Ｈ），７．１０－７．４４（ｍ，４Ｈ），８．２０（ｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝３１３
Ｐｒｅｐ３１		^{1}H－NMR（４００MHｚ，CDCｌ$_3$）δ（ｐｐｍ）：１．５９（ｄｄ，Ｊ＝７．６，５．２Ｈｚ，１Ｈ），１．７１（ｄｄ，Ｊ＝５．８，５．０Ｈｚ，１Ｈ），２．２４（ｄｄ，Ｊ＝８．２，６．２Ｈｚ，１Ｈ），２．３７（ｓ，３Ｈ），２．３８（ｓ，３Ｈ），２．５９（ｓ，３Ｈ），４．４３（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），４．５７（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．０８－７．１３（ｍ，１Ｈ），７．２１－７．３３（ｍ，３Ｈ），８．２２（ｓ，１Ｈ）．

【表６－２】

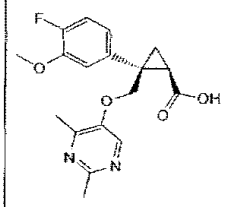
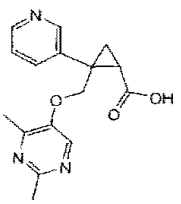
Ｐｒｅｐ３２		^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．５５（ｄｄ，Ｊ＝８．２，４．６Ｈｚ，１Ｈ），１．７８（ｄｄ，Ｊ＝６．０，５．２Ｈｚ，１Ｈ），２．２１（ｄｄ，Ｊ＝８．２，６．２Ｈｚ，１Ｈ），２．３５（ｓ，３Ｈ），２．５２（ｓ，３Ｈ），２．５９（ｓ，３Ｈ），４．３７（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５５（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），７．１６－７．２３（ｍ，３Ｈ），７．４３－７．４９（ｍ，１Ｈ），８．２２（ｓ，１Ｈ）．
Ｐｒｅｐ３３		^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．４６－１．５８（ｍ，１Ｈ），１．６９（ｔ，Ｊ＝４．８Ｈｚ，１Ｈ），２．１４－２．２８（ｍ，１Ｈ），２．３７（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），３．８１（ｓ，３Ｈ），４．３０－４．５６（ｍ，２Ｈ），６．７８－６．９６（ｍ，２Ｈ），７．２０－７．４６（ｍ，２Ｈ），８．１７（ｓ，１Ｈ）．ＭＳ［Ｍ＋Ｈ］$^+$＝３２９

【０１９２】

【表７－１】

製造例	構造式、MS	製造例	構造式、MS	製造例	構造式、MS
Prep 34	 MS[M+H]$^+$= 329	Prep 35	 LC－MS(ES. Pos):347[M+H+]／346	Prep 36	 LC－MS(ES. Pos):347[M+H+]／346
Prep 37	 MS[M+H]$^+$= 365	Prep 38	 MS[M+H]$^+$= 365	Prep 39	 LC－MS(ES. Pos):363[M+H+]／362
Prep 40	 LC－MS(ES. Pos):361[M+H+]／360	Prep 41	 LC－MS(ES. Pos):377[M+H+]／376	Prep 42	 MS[M+H]$^+$=377
Prep 43	 MS[M+H]$^+$= 331	Prep 44	 MS[M+H]$^+$= 331	Prep 45	 MS[M+H]$^+$= 347

【表７－２】

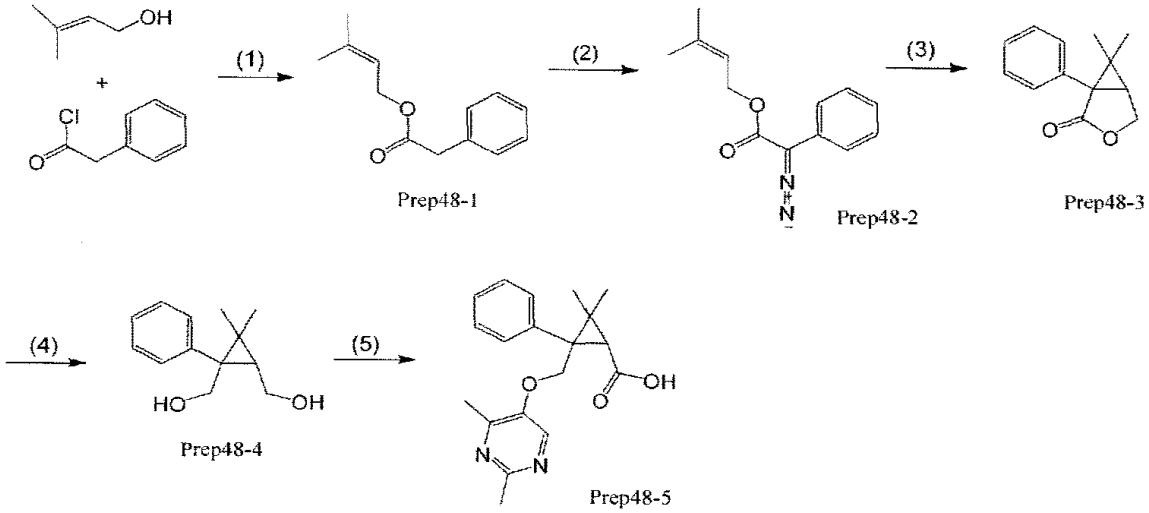
Prep 46	 MS[M+H]$^+$= 347	Prep 47	 MS[M+H]$^+$= 300		

【０１９３】

製造例４８

２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－３，３－ジメチル－２－フェニルシクロプロパンカルボン酸（Ｐｒｅｐ４８－５）の合成

【化３８】



【０１９４】

（１）３－メチル－２－ブテン－１－イル　フェニルアセテート（Ｐｒｅｐ４８－１）

３－メチル－２－ブテン－１－オール（５ｇ）のジクロロメタン（５０ｍｌ）溶液に、氷冷攪拌下でトリエチルアミン（９．７ｍｌ）とフェニルアセチルクロライド（７．６７ｍｌ）を加えた。氷冷下で３時間攪拌した後、水を加えてジクロロメタンで抽出した。得られた有機層を硫酸マグネシウムで乾燥し、減圧下で濃縮した。残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ^{TM} ｃｏｌｕｍｎ，Ｓｉｚｅ：３Ｌ，ｎ－ヘプタン：酢酸エチル０％→５％）で精製し、標記化合物（１１．５ｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．６９（ｓ，３Ｈ），１．７５（ｓ，３Ｈ），３．６３（ｓ，２Ｈ），４．５９（ｄ，Ｊ＝７．２Ｈｚ，２Ｈ），５．３０－５．３７（ｍ，１Ｈ），７．２３－７．３６（ｍ，５Ｈ）．

【０１９５】

（２）３－メチル－２－ブテン－１－イル　ジアゾフェニルアセテート（Ｐｒｅｐ４８－２）

Ｐｒｅｐ４８－１

化合物Ｐｒｅｐ４８－１（１１．５ｇ）のアセトニトリル（１００ｍｌ）溶液に、氷冷攪拌下で、ＤＢＵ（９．２６ｍｌ）と４－アセタミドベンゼンスルホニルアジド（１３．

５ｇ）を加え、室温で１５時間撹拌した。反応液を減圧濃縮し、水を加え、酢酸エチルで抽出した。得られら有機層を、飽和食塩水で洗浄後、硫酸マグネシウムで乾燥し、減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ^{TM} ｃｏｌｕｍｎ，Ｓｉｚｅ：３Ｌ，ｎ－ヘプタン：酢酸エチル０％→５％）で精製し、標記化合物（８．４５ｇ）を得た。
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：１．７５（ｓ，３Ｈ），１．７８（ｓ，３Ｈ），４．７７（ｄ，Ｊ＝７．６Ｈｚ，２Ｈ），５．３６－５．４４（ｍ，１Ｈ），７．１５－７．２０（ｍ，１Ｈ），７．３５－７．４１（ｍ，２Ｈ），７．４５－７．５１（ｍ，２Ｈ）．

【０１９６】

（３）６，６－ジメチル－１－フェニル－３－オキサビシクロ［３．１．０］ヘキサン－２－オン（Ｐｒｅｐ４８－３）

ロジウム（ＩＩ）アセテート　ダイマー（３２４ｍｇ）のジクロロメタン（３６０ｍｌ）溶液に、５０℃で撹拌下にて、Ｐｒｅｐ４８－２（８．４５ｇ）のジクロロメタン（１８０ｍｌ）溶液を２時間かけて滴下した。その後、反応液を５０℃で１時間撹拌した。反応液を室温まで冷却後、減圧濃縮することにより標記化合物粗精製物（８ｇ）を得た。
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：０．８８（ｓ，３Ｈ），１．３２（ｓ，３Ｈ），２．３９（ｄ，Ｊ＝５．２Ｈｚ，１Ｈ），４．２５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５３（ｄｄ，Ｊ＝９．６，５．２Ｈｚ，１Ｈ），７．２７－７．３９（ｍ，５Ｈ）．

【０１９７】

（４）（３，３－ジメチル－１－フェニルシクロプロパン－１，２－ジイル）ジメタノール（Ｐｒｅｐ４８－４）

Ｐｒｅｐ４８－３（８ｇ）のＴＨＦ（１００ｍｌ）溶液に、氷冷撹拌下でリチウムアルミニウムハイドライド（１．５ｇ）を加え、１時間撹拌した。反応液に氷と少量の２７％アンモニア水溶液を加え、室温で１０分間撹拌した。その後、反応液にセライトと硫酸マグネシウムを加え、１０分間撹拌した。反応液をろ過し、ろ液を減圧濃縮することにより、標記化合物（６．５２ｇ）を得た。
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：０．７８（ｓ，３Ｈ），１．２５（ｓ，３Ｈ），１．４９（ｄｄ，Ｊ＝７．０，５．８Ｈｚ，１Ｈ），３．７２（ｄｄ，Ｊ＝１２．２，１１．０Ｈｚ，１Ｈ），３．８９（ｄ，Ｊ＝１２．０Ｈｚ，１Ｈ），４．０３（ｄ，Ｊ＝１２．２Ｈｚ，１Ｈ），４．１０（ｄｄ、Ｊ＝１１．８，５．８Ｈｚ，１Ｈ），７．２１－７．３７（ｍ，５Ｈ）．

【０１９８】

（５）２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－３，３－ジメチル－２－フェニルシクロプロパンカルボン酸（Ｐｒｅｐ４８－５）

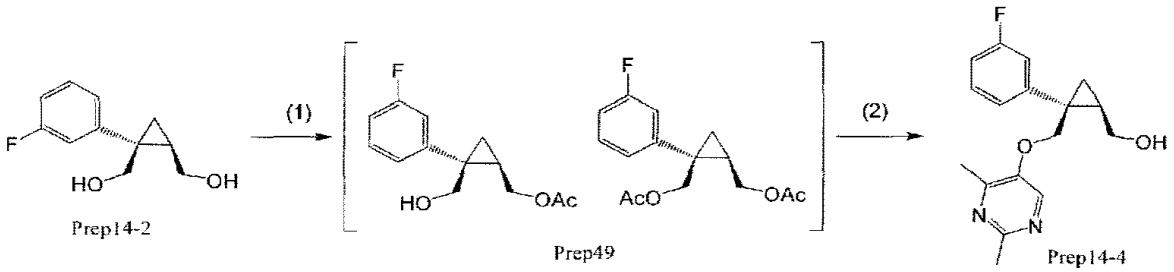
Ｐｒｅｐ４８－４から、製造例１３－（７）の方法に準じて合成した。
ＭＳ［Ｍ＋Ｈ］$^{+}$＝３２７

【０１９９】

製造例４９

（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニルシクロプロピル）メタノール（Ｐｒｅｐ１４－４）の合成

【化３９】



【０２００】

（１）［（１Ｒ，２Ｓ）－２－（３－フルオロフェニル）－２－（ヒドロキシメチル）シクロプロピル］メチルアセテート、［（１Ｓ，２Ｒ）－１－（３－フルオロフェニル）－１，２－ジイル］ビス（メチレン）ジアセテート混合物（Ｐｒｅｐ４９）

化合物Ｐｒｅｐ１４－２（３５．５ｇ）のＴＨＦ（１１０ｍｌ）－酢酸ビニル（２５ｍｌ）溶液に対して氷冷下、ＮＯＶＯＺＹＭＥ４３５（ＳＩＧＭＡ、１．７８ｇ）を加えて室温で１７時間攪拌した。その後、反応液を桐山ろ過し、得られた濾液を濃縮し標記化合物（４３．７ｇ）を得た。

ＭＳ［Ｍ＋Ｈ］$^{+}$＝２３９，２８１

【０２０１】

（２）（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニルシクロプロピル）メタノール（Ｐｒｅｐ１４－４）

化合物Ｐｒｅｐ４９（４３．７ｇ）、トリフェニルホスフィン（５７ｇ）および２，４－ジメチル－５－ピリミジノール（Ｐｒｅｐ４－２、２４．７ｇ）のＴＨＦ（４００ｍｌ）溶液にジイソプロピルアゾジカルボキシラート（４５．８ｍｌ）を０℃で滴下し、室温で１５時間攪拌させた。反応液に飽和炭酸水素ナトリウム水溶液を加えて、酢酸エチルで抽出した。有機相を飽和食塩水で洗浄後、硫酸マグネシウムで乾燥し、濃縮した。得られた反応物をＥｔＯＨ－１規定水酸化ナトリウム水溶液（２００ｍｌ－２００ｍｌ）に溶解させ室温で１時間攪拌した。５規定水酸化ナトリウム水溶液（１００ｍｌ）を加えて室温で１時間攪拌した。その後反応液を室温で減圧下濃縮し、得られた残渣を酢酸エチルで抽出した。有機相を飽和食塩水で洗浄後、硫酸マグネシウムで乾燥した。溶媒を減圧下濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ヘプタン：酢酸エチル＝１：４～酢酸エチル：メタノール＝１：１）、得られた残渣をＮＨ－Ｓｉｌｉｃａでろ過カラム精製して標記化合物（３９．３ｇ）を得た。

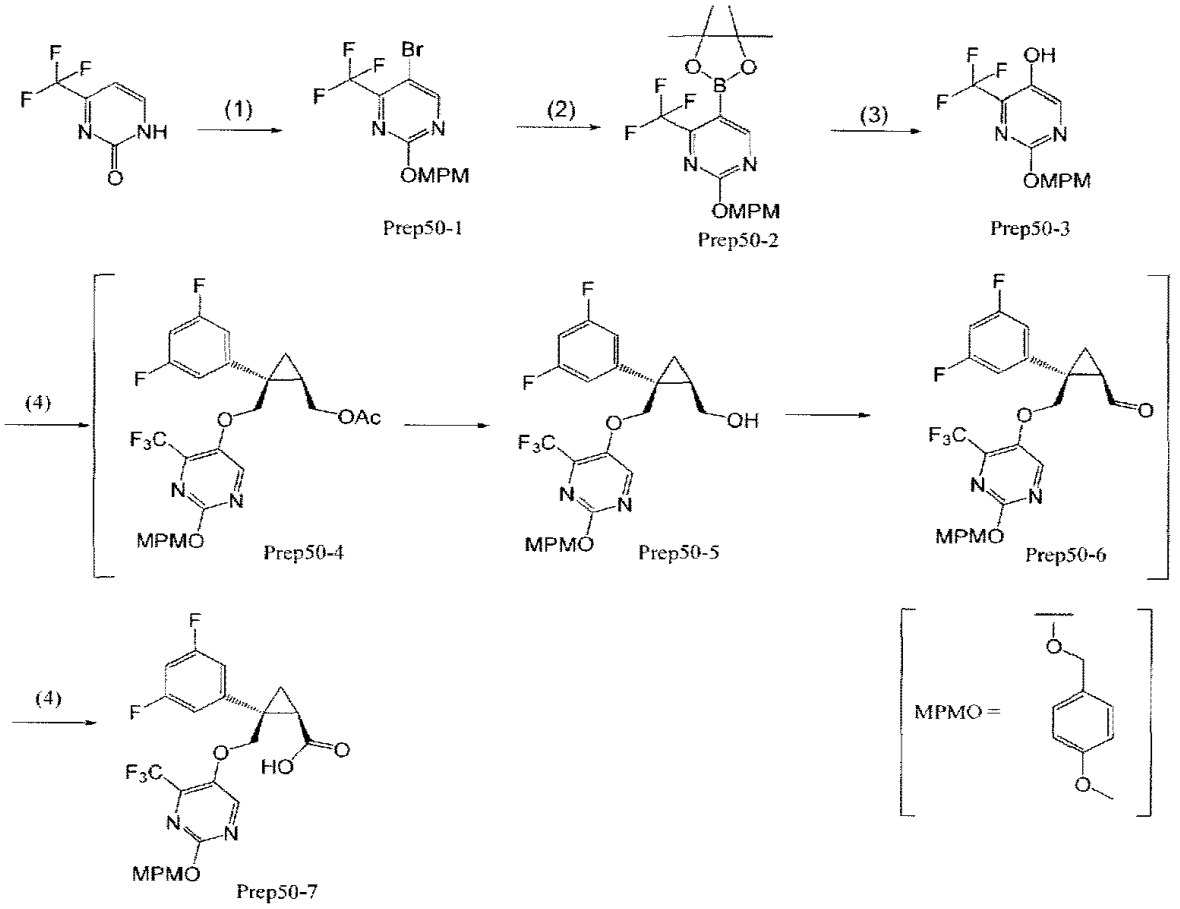
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：１．００（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），１．２４－１．３０（ｍ，１Ｈ），１．７９－１．８５（ｍ，１Ｈ），２．３９（ｓ，３Ｈ），２．６０（ｓ，３Ｈ），３．５５－３．６１（ｍ，１Ｈ），４．０３－４．１３（ｍ，１Ｈ），４．１２（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．９２－６．９８（ｍ，１Ｈ），７．１１－７．１５（ｍ，１Ｈ），７．１９－７．２２（ｍ，１Ｈ），７．２５－７．３１（ｍ，１Ｈ），８．００（ｓ，１Ｈ）．

【０２０２】

製造例５０

（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［２－（４－メトキシベンジルオキシ）－４－（トリフルオロメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボン酸（Ｐｒｅｐ５０－７）の合成

【化４０】



【０２０３】

（１）５－ブロモ－２－（４－メトキシベンジルオキシ）－４－トリフルオロメチルピリミジン（Ｐｒｅｐ５０－１）

４－（トリフルオロメチル）ピリミジン－２（１Ｈ）－オン（ＣＡＳ　Ｎｏ．１０４０４８－９２－２；８．４ｇ）の酢酸溶液（５０ｍｌ）に酢酸カリウム（１５．３ｇ）を加え４０℃にて臭素（２．６ｍｌ）を滴下した。７０℃で１時間３０分間撹拌させた。反応系を減圧濃縮した。残渣に水、酢酸エチルを加え分液抽出した。得られた有機層を硫酸マグネシウムで乾燥させ減圧濃縮。得られた残渣にオキシ塩化リン（４０ｍｌ）を加え加熱還流下１時間３０分間撹拌した。反応系を減圧濃縮しオキシ塩化リンを留去した。残渣に氷を加えヘキサンで分液抽出した。得られた有機層を硫酸マグネシウムで乾燥した。減圧濃縮し粗生成物を得た。

４－メトキシベンジルアルコール（７．０７ｇ）のＴＨＦ溶液（１５０ｍｌ）にＮａＨを加え室温で３０分間撹拌させた。反応系に先ほど得られた粗生成物のＴＨＦ溶液を滴下し終夜撹拌させた。反応系に飽和塩化アンモニウム水溶液を加えクエンチした。ＴＨＦを減圧下留去し、酢酸エチルで分液抽出した。得られた有機層を硫酸マグネシウムで乾燥させ、減圧濃縮した。得られた残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，溶出溶媒：ｎ－ヘプタン：酢酸エチル＝１９：１→３：１）で精製して標記化合物（１２．５ｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：３．８１（ｓ，３Ｈ），５．４０（ｓ，２Ｈ），６．８７－６．９０（ｍ，２Ｈ），７．４３（ｂｒｄｄ，Ｊ＝７．６Ｈｚ，２Ｈ），８．７６（ｓ，１Ｈ）．

【０２０４】

（２）２－（４－メトキシベンジルオキシ）－５－（４，４，５，５－テトラメチル－１，３，２－ジオキサボロラン－２－イル）－４－トリフルオロメチルピリミジン（Ｐｒｅｐ５０－２）

化合物Ｐｒｅｐ５０－１（１１．５ｇ）の１，４－ジオキサン溶液（１３０ｍｌ）に、酢酸カリウム（９．３ｇ）、ビス（ピナコラト）ジボロン（９．６３ｇ）を加えた後、脱気し窒素で置換した。１，１－ビス（ジフェニルホスフィノ）フェロセンジクロロパラジウム（II）を加え１１０℃で６時間加熱還流した。反応系を軽く減圧濃縮し１，４－ジオキサンを留去し酢酸エチルを加え桐山ろ過した。ろ液を減圧濃縮し、得られた残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，溶出溶媒：ｎ－ヘプタン：酢酸エチル＝１９：１→１：２）で精製して標記化合物（８．０ｇ）を得た。

ＭＳ［Ｍ＋Ｈ］$^{+}$＝４３３．

【０２０５】

（３）２－（４－メトキシベンジルオキシ）－４－トリフルオロメチルピリミジン－５－オール（Ｐｒｅｐ５０－３）

化合物Ｐｒｅｐ５０－２（２ｇ）のＴＨＦ溶液（２０ｍｌ）に、氷冷下３０％過酸化水素水（５０２μｌ）、２Ｎ水酸化ナトリウム水溶液（２．４４ｍｌ）を加え１５分撹拌させた後、室温でさらに３０分間撹拌させた。反応系に１Ｎ塩酸水溶液を加えｐＨを５程度に調整し、ジエチルエーテルで分液抽出した。得られた有機層を硫酸マグネシウムで乾燥させ減圧濃縮した。得られた残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，ｎ－ヘプタン：酢酸エチル＝９：１→１：１）で精製して標記化合物（９８０ｍｇ）を得た。

ＭＳ［Ｍ＋Ｎａ］$^{+}$＝３２３．

【０２０６】

（４）（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［２－（４－メトキシベンジルキシ）］－４－（トリフルオロメチルピリミジン－５－イル）オキシメチル）シクロプロパンカルボン酸（Ｐｒｅｐ５０－７）

化合物Ｐｒｅｐ４９と化合物Ｐｒｅｐ５０－３から製造例１３－（４）乃至１３－（７）の方法に準じて標題化合物を得た。

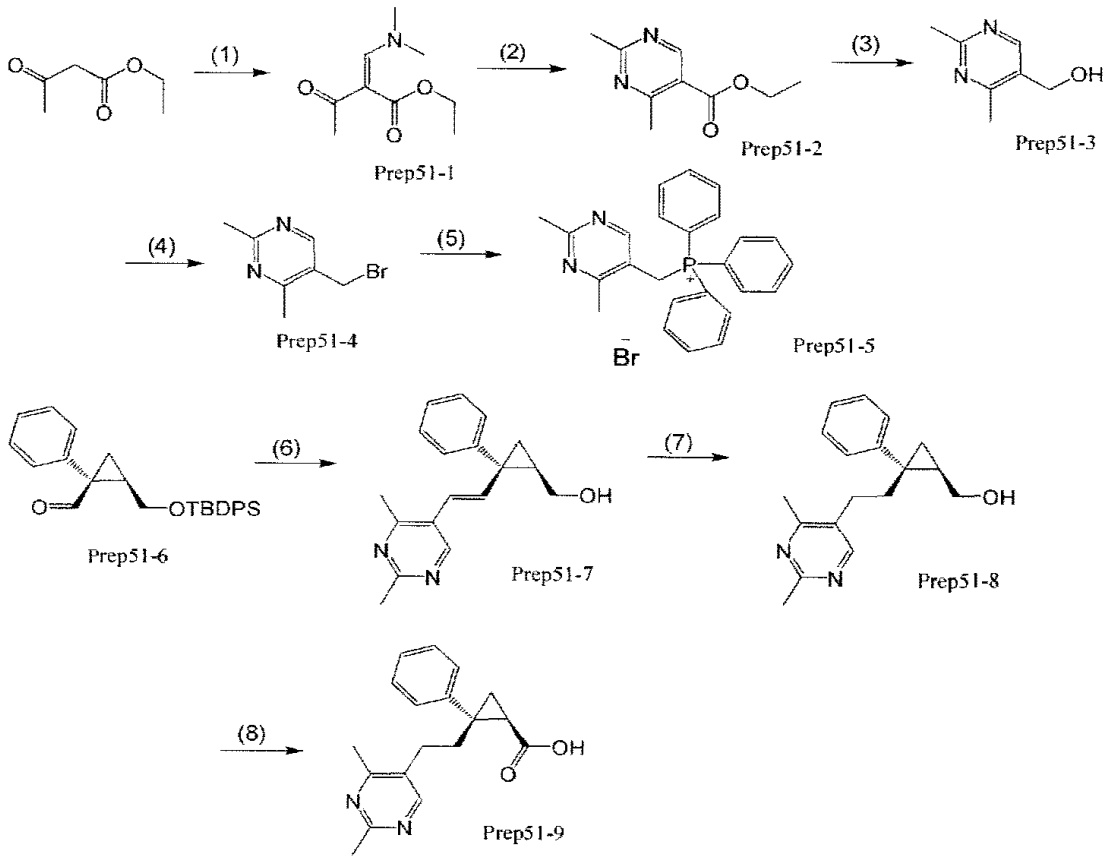
ＭＳ［Ｍ＋Ｎａ］$^{+}$＝５３３．

【０２０７】

製造例５１

（１Ｒ，２Ｓ）－２－［２－（２，４－ジメチルピリミジン－５－イル）エチル］－２－フェニルシクロプロパンカルボン酸（Ｐｒｅｐ５１－９）の合成

【化４１】



【０２０８】

（１）エチル　２－［（ジメチルアミノ）メチレン］－３－オキソブタノエート（Ｐｒｅｐ５１－１）

Ｎ，Ｎ－ジメチルホルムアミド　ジメチルアセタール（８０．４ｍｌ）を、エチルアセトアセテート（６３ｇ）に滴下し、室温で１４時間撹拌した。反応溶液を減圧濃縮した後、トルエン共沸を３回行い、標記化合物粗精製物（８９ｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．３３（ｔ，Ｊ＝７．２Ｈｚ，３Ｈ），２．３３（ｓ，３Ｈ），３．０７（ｂｒｓ，６Ｈ），４．２３（ｑ，Ｊ＝７．２Ｈｚ，２Ｈ），７．６８（ｓ，１Ｈ）．

【０２０９】

（２）エチル　２，４－ジメチルピリミジン－５－カルボキシラート（Ｐｒｅｐ５１－２）

化合物Ｐｒｅｐ５１－１（１０ｇ）、アセトアミジンハイドロクロライド（５．１１ｇ）およびナトリウムエトキシド（３．６７ｇ）をエタノール（１００ｍｌ）に溶解し、１００℃で５時間撹拌した。反応液を室温に戻し、減圧濃縮した。残渣に水を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄後、硫酸マグネシウムで乾燥し、減圧濃縮することにより、標記化合物粗精製物（８．７６ｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．４１（ｔ，Ｊ＝７．０Ｈｚ，３Ｈ），２．７５（ｓ，３Ｈ），２．８０（ｓ，３Ｈ），４．４０（ｑ，Ｊ＝７．０Ｈｚ，２Ｈ），９．０５（ｓ，１Ｈ）．

【０２１０】

（３）（２，４－ジメチルピリミジン－５－イル）メタノール（Ｐｒｅｐ５１－３）

リチウムアルミニウムハイドライド（１．８４ｇ）のＴＨＦ（５０ｍｌ）けん濁液に、

氷冷撹拌下で化合物Ｐｒｅｐ５１－２（８．７６ｇ）のＴＨＦ（３０ｍｌ）溶液を滴下した。室温で３時間撹拌した後、氷冷撹拌下で反応液に氷、２７％アンモニア水溶液、セライトを順次加え、室温で３０分間撹拌した。反応液に硫酸マグネシウムを加えてからろ過をし、ろ液を減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，Ｓｉｚｅ：２Ｌ，ｎ－ヘプタン：酢酸エチル１０％→４０％→酢酸エチル：メタノール１０％）で精製し、標記化合物（６７０ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：２．５２（ｓ，３Ｈ），２．６８（ｓ，３Ｈ），４．７１（ｓ，２Ｈ），８．５０（ｓ，１Ｈ）．

【０２１１】

（４）５－ブロモメチル－２，４－ジメチルピリミジン（Ｐｒｅｐ５１－４）

化合物Ｐｒｅｐ５１－３（６７０ｍｇ）のトルエン－ジクロロメタン（１０ｍｌ－５ｍｌ）溶液に、三臭化リン（０．９１２ｍｌ）を加え、室温で３時間撹拌した。反応液に氷冷撹拌下で氷を加えた後、飽和炭酸水素ナトリウム水溶液を加え、酢酸エチルで抽出した。得られた有機層を飽和食塩水で洗浄後、硫酸マグネシウムで乾燥し、減圧濃縮することにより、標記化合物粗精製物（３５４ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：２．５８（ｓ，３Ｈ），２．７０（ｓ，３Ｈ），４．４４（ｓ，２Ｈ），８．４８（ｓ，１Ｈ）．

【０２１２】

（５）［（２，４－ジメチルピリミジン－５－イル）メチル］トリフェニルホスホニウムブロミド（Ｐｒｅｐ５１－５）

化合物Ｐｒｅｐ５１－４（３５４ｍｇ）のトルエン（１５ｍｌ）溶液に、トリフェニルホスフィン（４６２ｍｇ）を加え、１４０℃で５時間撹拌した。反応液を室温に戻し、析出した固体をろ取し、ｔｅｒｔ－ブチルメチルエーテルで洗浄することにより、標記化合物（６１０ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．８７（ｄ，Ｊ＝１．２Ｈｚ，３Ｈ），２．６２（ｄ，Ｊ＝１．６Ｈｚ，３Ｈ），５．６８（ｄ，Ｊ＝１４．４Ｈｚ，２Ｈ），７．６４－７．７５（ｍ，６Ｈ），７．７７－７．８８（ｍ，９Ｈ），８．３６（ｄ，Ｊ＝２．４Ｈｚ，１Ｈ）．

【０２１３】

（６）（１Ｒ，２Ｓ）－２－［（Ｅ，Ｚ）－２－（２，４－ジメチルピリミジン－５－イル）ビニル］－２－フェニルシクロプロピルメタノール（Ｐｒｅｐ５１－７）

化合物Ｐｒｅｐ５１－５（６１０ｍｇ）のＴＨＦ（７ｍｌ）溶液に、－７８℃で撹拌下、ｎ－ブチルリチウム（２．６４Ｍ　ｎ－ヘキサン溶液：０．５ｍｌ）を加え、そのままの温度で３０分間撹拌した。化合物Ｐｒｅｐ１３－３から製造例５３－（１）に準じて得られる（１Ｓ，２Ｒ）－２－（ｔｅｒｔ－ブチルジフェニルシリルオキシメチル）－１－フェニルシクロプロパンカルバルデヒド（Ｐｒｅｐ５１－６、６０２ｍｇ）のＴＨＦ（４ｍｌ）溶液を反応液に加えた後、０℃で４時間撹拌した。反応液に水と少量の酢酸を加え、酢酸エチルで抽出した。得られた有機層を飽和食塩水で洗浄し、硫酸マグネシウムで乾燥後、減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，Ｓｉｚｅ：Ｌ，ｎ－ヘプタン：酢酸エチル０％→２０％）で精製した。得られた化合物をＴＨＦ（１０ｍｌ）に溶解し、テトラブチルアンモニウムフルオリド（１Ｍ　ＴＨＦ溶液：２．６４ｍｌ）を加え、室温で１２時間撹拌した。反応液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，Ｓｉｚｅ：Ｌ，ｎ－ヘプタン：酢酸エチル１０％→１００％→酢酸エチル：メタノール５％）で精製し、標記化合物（１１３ｍｇ）を得た。

ＭＳ［Ｍ＋Ｈ］$^+$＝２８１

【０２１４】

（７）（１Ｒ，２Ｓ）－２－［２－（２，４－ジメチルピリミジン－５－イル）エチル］－２－フェニルシクロプロピルメタノール（Ｐｒｅｐ５１－８）

化合物Ｐｒｅｐ５１－７（１１３ｍｇ）の酢酸エチル（２０ｍｌ）溶液に、１０％パラジウム－炭素（５０％含水：１００ｍｇ）を加え、室温、常圧で３０分間接触水素還元を行った。反応液をセライトろ過し、ろ液を減圧濃縮することにより、標記化合物粗精製物（８０ｍｇ）を得た。

ＭＳ［Ｍ＋Ｈ］$^{+}$＝２８３

【０２１５】

（８）（１Ｒ，２Ｓ）－２－［２－（２，４－ジメチルピリミジン－５－イル）エチル］－２－フェニルシクロプロパンカルボン酸（Ｐｒｅｐ５１－９）

化合物Ｐｒｅｐ５１－８から、製造例１３－（７）の方法に準じて合成した。

ＭＳ［Ｍ＋Ｈ］$^{+}$＝２９７

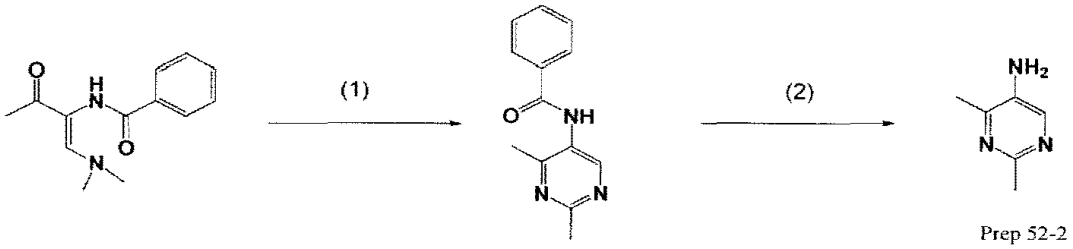
【０２１６】

製造例５２

２，４－ジメチルピリミジン－５－アミン（Ｐｒｅｐ５２－２）の合成

出発物質は文献、Ｈｅｔｅｒｏｃｙｃｌｅｓ，５７（１１），２０４５－２０６４，２００２に記載の方法に準じて合成した。

【化４２】



【０２１７】

（１）Ｎ－（２，４－ジメチルピリミジン－５－イル）ベンズアミド（Ｐｒｅｐ５２－１）

Ｎ－｛（１Ｚ）－１［（ジメチルアミノ）メチレン］－２－オキソプロピル｝ベンズアミド（６．８ｇ）のエタノール溶液（５５．６ｍｌ）にアセトアミジンハイドロクロライド（８．３１ｇ）、炭酸カリウム（６．０６ｇ）を加えて７０℃に昇温し１５時間攪拌した。反応液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝４：１～０：１０）で精製して標記化合物（４．１ｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：２．５３（ｓ，３Ｈ），２．７２（ｓ，３Ｈ），７．４４－７．６４（ｍ，３Ｈ），７．８９－７．９２（ｍ，２Ｈ），８．０１（ｓ，１Ｈ）．

【０２１８】

（２）２，４－ジメチルピリミジン－５－アミン（Ｐｒｅｐ５２－２）

化合物Ｐｒｅｐ５２－１（４．１ｇ）のエタノール（５５．６ｍｌ）－１Ｎ水酸化ナトリウム水溶液に溶解させ、７０℃で２日間攪拌した。反応液を酢酸エチル、クロロホルムで抽出し、有機層を硫酸マグネシウムで乾燥し、濾過した。有機層を減圧濃縮し、標記化合物（２．１ｇ）を得た。

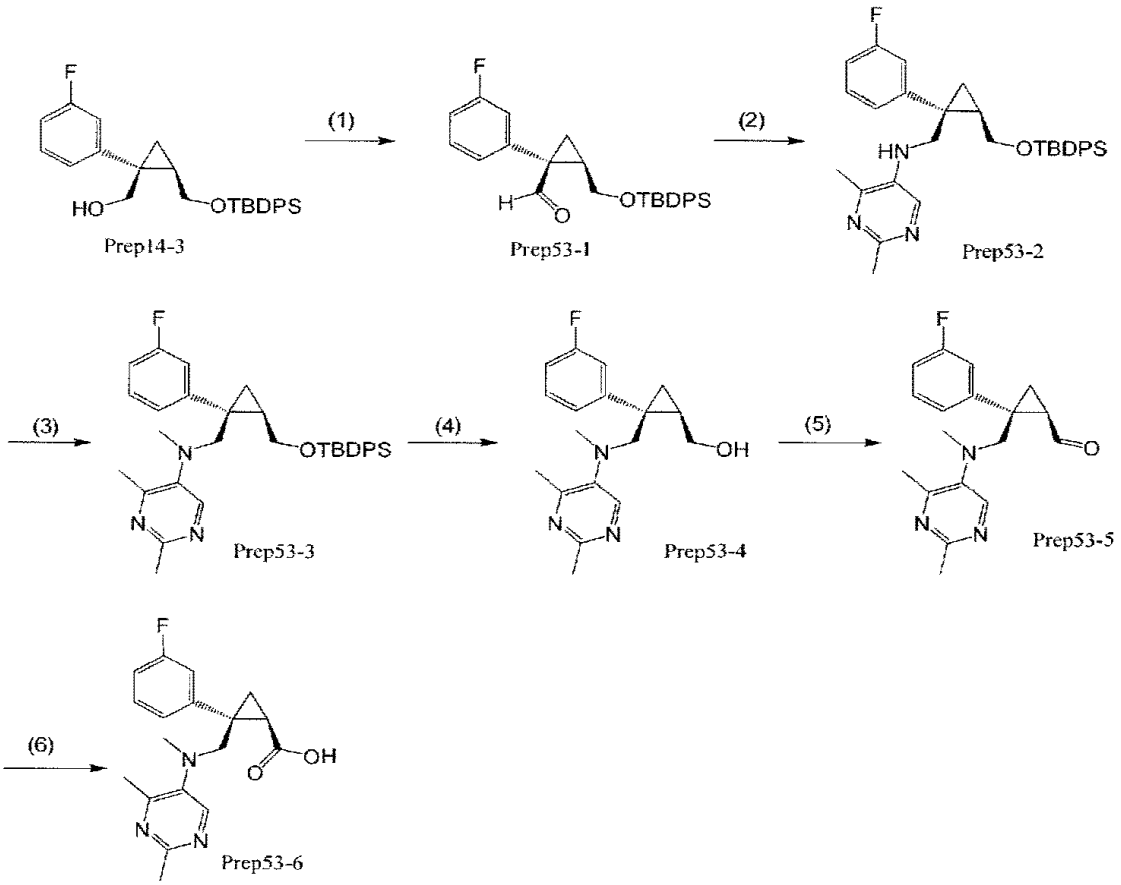
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：２．３８（ｓ，３Ｈ），２．５９（ｓ，３Ｈ），３．５２（ｂｒｓ，２Ｈ），８．０１（ｓ，１Ｈ）．

【０２１９】

製造例５３

（１Ｒ，２Ｓ）－２－｛［（２，４－ジメチルピリミジン－５－イル）（メチル）アミノ］メチル｝－２－（３－フルオロフェニル）シクロプロパンカルボン酸（Ｐｒｅｐ５３－６）の合成

【化４３】



【０２２０】

（１）（１Ｒ，２Ｓ）－２－（ｔｅｒｔ－ブチルジフェニルシリルオキシメチル）－１－（３－フルオロフェニル）シクロプロパンカルバルデヒド（Ｐｒｅｐ５３－１）

オキサリルクロリド（１．２６ｍｌ）のジクロロメタン溶液（５０ｍｌ）を－７８℃に冷却し、そこにジメチルスルホキシド（２．０４ｍｌ）のジクロロメタン溶液（１０ｍｌ）を滴下した。１５分後、反応液に化合物Ｐｒｅｐ１４－３（３．０ｇ）のジクロロメタン（１２ｍｌ）溶液を－７８℃で滴下し、同温で６０分撹拌した。反応液にトリエチルアミン（８．０３ｍｌ）を加えて０℃に昇温し２時間撹拌した。反応液に飽和塩化アンモニウム水溶液を加えて酢酸エチルで抽出し、有機層を飽和炭酸水素ナトリウム溶液、飽和塩化ナトリウム水溶液で洗浄した。有機層を無水硫酸マグネシウムで乾燥し、濾過した。濾液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝１０：０～４：１）で精製して標記化合物（３．７ｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．５３（ｄｄ，１Ｈ，Ｊ＝８．２，４．８Ｈｚ），１．７６（ｄｄ，Ｊ＝７．２，５．２Ｈｚ），１．９０－２．１０（ｍ，１Ｈ），３，６８（ｄｄ，Ｊ＝１２．４，９．６Ｈｚ，１Ｈ），４．０８（ｄｄ，Ｊ＝１１．６，９．６Ｈｚ，１Ｈ），６．９８－７．１６（ｍ，３Ｈ），７．４６－７．６３（ｍ，７Ｈ），７．６４－７．７３（ｍ，４Ｈ），９．５９（ｓ，１Ｈ）．

【０２２１】

（２）Ｎ－［（１Ｓ，２Ｒ）－２－（ｔｅｒｔ－ブチルジフェニルシリルオキシメチル）－１－（３－フルオロフェニル）シクロプロピルメチル］－２，４－ジメチルピリミジン－５－アミン（Ｐｒｅｐ５３－２）

化合物Ｐｒｅｐ５３－１（３．７ｇ）、化合物Ｐｒｅｐ５２－２（１．３７ｇ）のクロロホルム溶液に（６０ｍｌ）に酢酸（１．５ｍｌ）を加えて室温で３０分撹拌し、トリアセトキシボロハイドライドナトリウム（５．４４ｇ）を加えて１５時間撹拌した。反応液に飽和炭酸水素ナトリウム水溶液を加え、酢酸エチル（ｘ２）で抽出した。無水硫酸マグネシウムで乾燥した。溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝９：１～０：１０）で精製して標記化合物（４．２６ｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：０．７５（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），１．０９－１．１３（ｍ，１Ｈ），１．１１（ｓ，９Ｈ），１．５７（ｍ，１Ｈ），２．０８（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），３，３２（ｄ，Ｊ＝１２．８Ｈｚ，１Ｈ），３．５０（ｄ，Ｊ＝１２．８Ｈｚ，１Ｈ），３．５９（ｄｄ，Ｊ＝１１．６，１０．０Ｈｚ，１Ｈ），４．１６（ｄｄ，Ｊ＝１１．６，６．０Ｈｚ，１Ｈ），６．９０－６．９６（ｍ，１Ｈ），７．０４－７．０８（ｍ，１Ｈ），７．１３－７．１６（ｍ，１Ｈ），７．２５－７．４７（ｍ，７Ｈ），７．６３－７．６９（ｍ、４Ｈ），７．７９（ｓ，１Ｈ）．

【０２２２】

（３）Ｎ－｛［（１Ｓ，２Ｒ）－２－（ｔｅｒｔ－ブチルジフェニルシリルオキシメチル）－１－（３－フルオロフェニル）シクロプロピルメチル｝－Ｎ，２，４－トリメチルピリミジン－５－アミン（Ｐｒｅｐ５３－３）

化合物Ｐｒｅｐ５３－２（４．６２ｇ）のアセトニトリル（３０ｍｌ）溶液に対してホルムアルデヒド（１．５９ｍｌ）トリアセトキシボロハイドライドナトリウム（３．７１ｇ）を加えて１時間撹拌した。さらに反応液にホルムアルデヒド（１．５９ｍｌ）トリアセトキシボロハイドライドナトリウム（３．７１ｇ）を加えて３０分撹拌し、飽和炭酸水素ナトリウム水溶液を加え、酢酸エチル（ｘ２）で抽出した。無水硫酸マグネシウムで乾燥した。溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝９：１～０：１０）で精製して標記化合物（４．２６ｇ）を得た。

ＭＳ［Ｍ＋Ｈ］$^+$＝５５５

【０２２３】

（４）［（１Ｒ，２Ｓ）－２－｛［（２，４－ジメチルピリミジン－５－イル）（メチル）アミノ］メチル｝－２－（３－フルオロフェニル）シクロプロピル］メタノール（Ｐｒｅｐ５３－４）

化合物Ｐｒｅｐ５３－３（３．２３ｇ）のＴＨＦ（３０ｍｌ）溶液にテトラブチルアンモニウムフロリド（ＴＣＩ－ＪＰ，１Ｍ－ＴＨＦ溶液：１７．５ｍｌ）を室温で滴下し、室温で１７時間撹拌した。反応液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝１：１～０：１０）で精製して標記化合物（１．８４ｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：０．８０（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），１．１８（ｄｄ，Ｊ＝９．２，５．２Ｈｚ），１．５４－１．６４（ｍ，１Ｈ），２．２０（ｓ，３Ｈ），２．５７（ｓ，３Ｈ），２．６９（ｓ，３Ｈ），３，３５（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），３．４７（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），３．６０（ｄｄ，Ｊ＝１１．６，９．２Ｈｚ，１Ｈ），４．０３（ｄｄ，Ｊ＝１１．６，９．２Ｈｚ，１Ｈ），６．８２－６．８７（ｍ，１Ｈ），６．９２－６．９６（ｍ，１Ｈ），７．０１－７．０４（ｍ，１Ｈ），７．１３－７．１９（ｍ，１Ｈ），８．１０（ｓ，１Ｈ）．

【０２２４】

（５）［（１Ｒ，２Ｓ）－２－｛［（２，４－ジメチルピリミジン－５－イル）（メチル）アミノ］メチル｝－２－（３－フルオロフェニル）シクロプロパンカルバルデヒド（Ｐｒｅｐ５３－５）

オキサリルクロリド（３４３μｌ）のジクロロメタン溶液（４０ｍｌ）を－７８℃に冷却し、そこにジメチルスルホキシド（５６０μｌ）のジクロロメタン溶液（１０ｍｌ）を

滴下した。３０分後、反応液に化合物Ｐｒｅｐ５３－４（６２０ｍｇ）のジクロロメタン（９．６ｍｌ）溶液を－７８℃で滴下し、同温で３０分撹拌した。反応液にトリエチルアミン（８．０３ｍｌ）を加えて３０分攪拌した後、０℃に昇温し２時間攪拌した。反応液に飽和炭酸水素ナトリウム溶液を加えて酢酸エチルで抽出し、有機層を、飽和塩化ナトリウムで洗浄した。有機層を無水硫酸マグネシウムで乾燥し、濾過した。濾液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝２：３～０：１０）で精製して標記化合物（６１７ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．６０－１．６７（ｍ，１Ｈ），１．７８（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０８（ｓ，３Ｈ），２，２６（ｍ，１Ｈ），２．５８（ｓ，３Ｈ），２．６６（ｓ，３Ｈ），３，４２（ｄ，Ｊ＝１４．０Ｈｚ，１Ｈ），３．５３（ｄ，Ｊ＝１４．０Ｈｚ，１Ｈ）６．９１－７．０６（ｍ，３Ｈ），７．２１－７．２７（ｍ，１Ｈ），８．０７（ｓ，１Ｈ），９．７４（ｄ，Ｊ＝４．０Ｈｚ，１Ｈ）．

【０２２５】

（６）（１Ｒ，２Ｓ）－２－｛［（２，４－ジメチルピリミジン－５－イル）（メチル）アミノ］メチル｝－２－（３－フルオロフェニル）シクロプロパンカルボン酸（Ｐｒｅｐ５３－６）

化合物Ｐｒｅｐ５３－５（６１７ｍｇ）のアセトン－水（１０ｍｌ）溶液に室温で２－メチル－２－ブテン（１．０８ｍｌ）、無水りん酸二水素ナトリウム（７３１ｍｇ）および亜塩素酸ナトリウム（３６７ｍｇ）を加え、２時間撹拌した。反応液を酢酸エチルで抽出し、有機層を飽和塩化ナトリウム水溶液で洗浄した。有機層を無水硫酸マグネシウムで乾燥し、濾過した。濾液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝１：４～酢酸エチル＝４：１）で精製して標記化合物（６３２ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．６０－１．６３（ｍ，２Ｈ），２．０３－２．０８（ｍ，１Ｈ），２．０８（ｓ，３Ｈ），２．６０（ｓ，３Ｈ），２．６６（ｓ，３Ｈ），３，５６（ｄ，Ｊ＝１２．８Ｈｚ，１Ｈ），３．６４（ｄ，Ｊ＝１２．８Ｈｚ，１Ｈ），６．９１－６．９７（ｍ，１Ｈ），７．０４－７．０８（ｍ，１Ｈ），７．１１－７．１４（ｍ，１Ｈ），７．２３－７．２９（ｍ，１Ｈ），８．３９（ｓ，１Ｈ）．

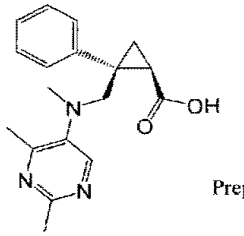
【０２２６】

製造例５４

（１Ｒ，２Ｓ）－２－［（２，４－ジメトキシピリミジン－５－イル）（メチル）アミノ］メチル－２－フェニルシクロプロパンカルボン酸（Ｐｒｅｐ５４）の合成

製造例５３と同様にして合成した

【化４４】



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【０２２７】

ＭＳ［Ｍ＋Ｈ］$^+$＝３１２

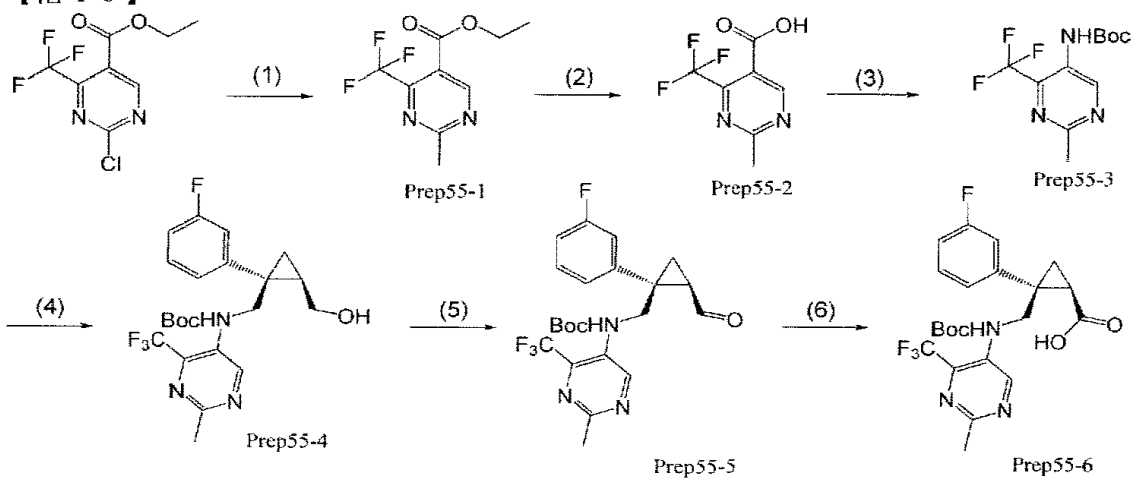
【０２２８】

製造例５５

（１Ｓ，２Ｒ）－２－［（ｔｅｒｔ－ブトキシカルボニル）（２－メチル－４－トリフルオロメチルピリミジン－５－イル）アミノ］メチル－２－（３－フルオロフェニル）シクロ

ペンタンカルボン酸（Ｐｒｅｐ５５－６）の合成

【化４５】



【０２２９】

（１）エチル　２－メチル－４－トリフルオロメチルピリミジンカルボキシラート（Ｐｒｅｐ５５－１）

エチル　２－クロロ－４－（トリフルオロメチル）ピリミジン－５－カルボキシラート（９．７ｇ）をＴＨＦ（１００ｍｌ）に溶解し、トリメチルアルミ（３８．１ｍｌ、２Ｍ）、テトラキス（トリフェニルホスフィン）パラジウム（０）を加え７０℃にて終夜撹拌させた。反応系を室温まで放冷した後、氷冷下飽和塩化アンモニウム水溶液、５Ｎ塩酸水溶液を滴下していった。発泡がなくなった時点で水を加え酢酸エチルで分液抽出。有機層を硫酸マグネシウムで乾燥し、溶媒を減圧下濃縮した。残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，ｎ－ヘプタン：酢酸エチル＝１９／１→２／１）で精製して標記化合物（８．１ｇ）を得た。

ＭＳ［Ｍ＋Ｈ］$^{+}$＝２３５．

【０２３０】

（２）２－メチル－４－トリフルオロメチルピリミジン－５－カルボン酸（Ｐｒｅｐ５５－２）

化合物Ｐｒｅｐ５５－１（８．１ｇ）のＴＨＦ－エタノール（８０ｍｌ－２０ｍｌ）溶液に、２Ｎ水酸化ナトリウム水溶液（２６ｍｌ）を加え室温で２時間撹拌させた。反応終了をＬＣ－ＭＳで確認後、１Ｎ塩酸水溶液を加え中性にして減圧濃縮しＴＨＦとエタノールを留去した。残渣に２Ｎ塩酸水溶液を加えｐＨを２～３程度にし酢酸エチルで分液抽出した。有機層を硫酸マグネシウムで乾燥した。溶媒を減圧下濃縮し、標記化合物（６．２ｇ）の粗生成物を得た。

ＭＳ［Ｍ＋Ｈ］$^{+}$＝２０７．

【０２３１】

（３）ｔｅｒｔ－ブチル（２－メチル－４－トリフルオロメチルピリミジン－５－イル）カーバメート（Ｐｒｅｐ５５－３）

化合物Ｐｒｅｐ５５－２（６．２ｇ）のトルエン－ｔｅｒｔ－ブタノール（５０ｍｌ－５０ｍｌ）溶液にトリエチルアミン（１０．３ｍｌ）、ジフェニルホスホリルアジド（９．５５ｍｌ）を加えた。１００℃にて終夜撹拌させた。反応系を放冷し水を加え減圧濃縮し、残渣に飽和炭酸水素ナトリウム水溶液を加え酢酸エチルで分液抽出した。得られた有機層を硫酸マグネシウムで乾燥させ減圧濃縮した。得られた残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，ｎ－ヘプタン：酢酸エチル＝１９：１→３：１）で精製して標記化合物（８．０ｇ）を得た。

ＭＳ［Ｍ＋Ｈ］$^{+}$＝２７８．

【０２３２】

（４）ｔｅｒｔ－ブチル｛［（１Ｓ，２Ｒ）－１－（３－フルオロフェニル）－２－ヒドロキシメチルシクロプロピル］メチル｝（２－メチル－４－トリフルオロメチルピリミジン－５－イル）カーバメート（Ｐｒｅｐ５５－４）

化合物Ｐｒｅｐ１４－３（５００ｍｇ）のジクロロメタン溶液（６．０ｍｌ）に氷冷下、トリエチルアミン（３２２μｌ）、メタンスルホニルクロリド（１７１μｌ）を加え室温で１時間撹拌させた。反応系に水を加えジクロロメタンで分液抽出した。得られた有機層を硫酸マグネシウムで乾燥させ、減圧濃縮し粗生成物を得た。粗生成物のアセトニトリル溶液（１０ｍｌ）に炭酸セシウム、化合物Ｐｒｅｐ５５－３（６９９ｍｇ）を加え８０℃にて終夜撹拌させた。反応系を放冷し、水を加え酢酸エチルで分液抽出した。得られた有機層を硫酸マグネシウムで乾燥させ減圧濃縮した。得られた残渣をメタノール（５ｍｌ）に溶解させ１Ｎ水酸化ナトリウム水溶液（１．２６ｍｌ）を加え室温で３０分間撹拌させた。反応系に水を加え酢酸エチルで分液抽出した。得られた有機層を硫酸マグネシウムで乾燥させた。減圧濃縮。残渣をシリカゲルカラムクロマトグラフィー（（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ^{TM} ｃｏｌｕｍｎ，溶出溶媒：ｎ－ヘプタン：酢酸エチル＝１９：１→１：１）で精製して標記化合物（２００ｍｇ）を得た。

ＭＳ［Ｍ＋Ｎａ］$^{+}$＝４７８．

【０２３３】

（５）ｔｅｒｔ－ブチル｛［（１Ｓ，２Ｒ）－１－（３－フルオロフェニル）－２－ホルミルシクロプロピル］メチル｝（２－メチル－４－トリフルオロメチルピリミジン－５－イル）カーバメート（Ｐｒｅｐ５５－５）

化合物Ｐｒｅｐ５５－４（２００ｍｇ）のジクロロメタン（５ｍｌ）溶液に、氷冷下Ｄｅｓｓ－Ｍａｒｔｉｎ試薬を加えた。そのまま１時間撹拌させた後、反応系に炭酸水素ナトリウム水溶液－Na_2SO_3の混合溶液を加え透明になるまで撹拌した。反応系をジクロロメタンで分液抽出した。得られた有機層を硫酸マグネシウムで乾燥させ減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ^{TM} ｃｏｌｕｍｎ，溶出溶媒：ｎ－ヘプタン：酢酸エチル＝４：１→１：１）で精製して標記化合物（１８０ｍｇ）を得た。

ＭＳ［Ｍ＋Ｎａ］$^{+}$＝４７６．

【０２３４】

（６）（１Ｓ，２Ｒ）－２－［（ｔｅｒｔ－ブトキシカルボニル）（２－メチル－４－トリフルオロメチルピリミジン－５－イル）アミノ］メチル－２－（３－フルオロフェニル）シクロプロパンカルボン酸（Ｐｒｅｐ５５－６）

化合物Ｐｒｅｐ５５－５（１８０ｍｇ）のアセトン－水混合溶媒（４ｍｌ－２ｍｌ）に２－メチル２－ブテン（２１０μｌ）、リン酸二水素ナトリウム（５７．２ｍｇ）、亜塩素酸ナトリウム（５３．９ｍｇ）を加えた。室温で１時間撹拌した後、反応溶液に水を加えジクロロメタンにて分液抽出した。得られた有機層を硫酸マグネシウムで乾燥し。有機層を無水硫酸マグネシウムで乾燥し濾過した。濾液を減圧濃縮し、標記化合物の粗生成物（１８６ｍｇ）を得た。

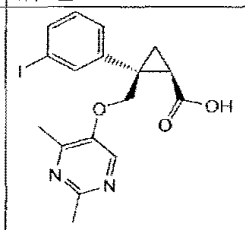
ＭＳ［Ｍ＋Ｎａ］$^{+}$＝４９２．

【０２３５】

製造例５６（Ｐｒｅｐ５６）は製造例１３の手法に準じて製造した。但し、Ｐｒｅｐ１３－２に対応するジオールからＰｒｅｐ１３－５に対応するアルコール体の合成は製造例４９の方法に基づいて行った。

【０２３６】

【表８】

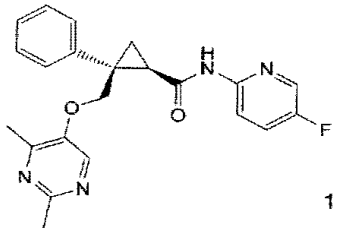
製造例	構造式	NMR（４００MHz，CDCl$_3$）及び／又はMS
Ｐｒｅｐ５６		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．５２－１．５９（ｍ，１Ｈ），１．７３－１．７８（ｍ，１Ｈ），２．２２－２．２７（ｍ，１Ｈ），２．３７（ｓ，３Ｈ），２．５８（ｓ，３Ｈ），４．４７（ｓ，２Ｈ），７．１１（ｔ，Ｊ＝７．８Ｈｚ，１Ｈ），７．４３－７．４８（ｍ，１Ｈ），７．６２－７．６７（ｍ，１Ｈ），７．８９（ｔ，Ｊ＝１．６Ｈｚ，１Ｈ），８．２２（ｓ，１Ｈ） ＭＳ［Ｍ＋Ｈ］$^+$＝４２５

【０２３７】

実施例１

（１Ｒ，２Ｓ）－Ｎ－（５－フルオロピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド（１）の合成

【化４６】



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【０２３８】

カルボン酸Ｐｒｅｐ１３－７（６３９ｍｇ）をジクロロメタン（１０ｍｌ）に溶解させ、この溶液にオキザリルクロリド（３６７μｌ）、ＤＭＦ（触媒量）を加えた。この反応液を室温で１時間撹拌した。反応液を減圧濃縮し、粗酸クロライドを得た。２－アミノ－５－フルオロピリジン（３６０ｍｇ）のＴＨＦ（１０．０ｍｌ）溶液にジイソプロピルエチルアミン（８４８μｌ）を加え６０℃に昇温し、粗酸クロライドのＴＨＦ（５．０ｍｌ）溶液を滴下し、同度で１時間撹拌させた。反応系を室温まで放冷し１時間撹拌させた後、反応液を減圧濃縮した後、酢酸エチルと水に分配し、有機層を分離した。有機層を無水硫酸マグネシウムで乾燥させ、濾液を減圧濃縮した。残渣をＮＨ－シリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ^{TM} ｃｏｌｕｍｎ，溶出溶媒：ｎ－ヘプタン：酢酸エチル＝１９：１→３：２）で精製し、得られた目的物にジエチルエーテルを加えた。析出した固体を濾取乾燥して、標記化合物（４１８ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．６０－１．６４（ｍ，１Ｈ），１．９０（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１２（ｂｒｄｔ，１Ｈ），２．２０（ｓ，３Ｈ），２．５４（ｓ，３Ｈ），４．４０（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），４．５１（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），７．２６－７．４７（ｍ，６Ｈ），７．９６（ｓ，１Ｈ），８，０６－８．１２（ｍ，２Ｈ），８．３３（ｂｒｄｓ，１Ｈ）．

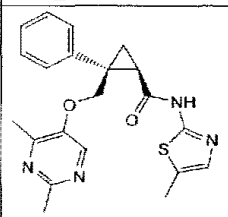
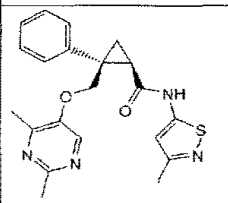
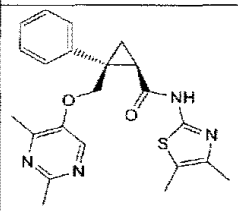
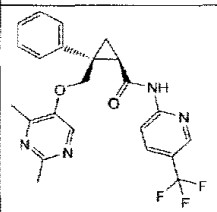
ＭＳ［Ｍ＋Ｈ］$^+$＝３９３

【０２３９】

＊実施例２－４５は、カルボン酸Ｐｒｅｐ１３－７と任意のアミンを実施例１と同様の手法により合成した。

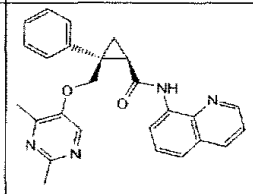
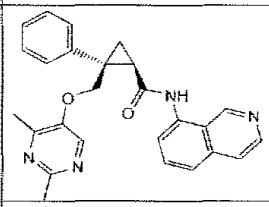
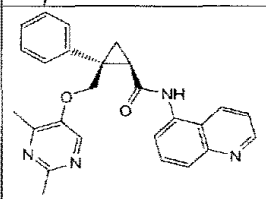
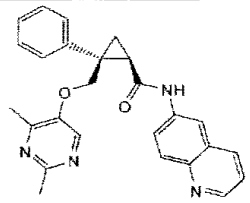
【０２４０】

【表９】

実施例	構造式	NMR（４００MHz，$CDCl_3$）及び／又はMS
2		^{1}H－NMR δ（ppm）：1．78（dd，J＝5．6，8．0Hz，1H），2．01（t，J＝5．6Hz，1H），2．17（s，3H），2．18（s，3H），2．25（brt，1H），2．57（s，3H），4．44（d，J＝9．6Hz，1H），4．63（d，J＝9．6Hz，1H），6．46（brs，1H），7．32－7．41（m，3H），7．44－7．47（m，2H），8．02（s，1H）． MS［M+H］$^+$＝395
3		^{1}H－NMR δ（ppm）：1．72（dd，J＝5．6，8．0Hz，1H），1．98（t，J＝5．6Hz，1H），2．16（dd，J＝5．6，8．0Hz，1H），2．20（s，3H），2．41（s，3H），2．56（s，3H），4．43（d，J＝9．6Hz，1H），4．52（d，J＝9．6Hz，1H），6．59（s，1H），7．30－7．38（m，3H），7．42－7．45（m，2H），7．98（s，1H），8．91（brs，1H）． MS［M+H］$^+$＝395
4		^{1}H－NMR δ（ppm）：1．66（dd，J＝5．6，8．0Hz，1H），1．94（t，J＝5．6Hz，1H），2．09（dd，J＝5．6，8．0Hz，1H），2．15（brs，3H），2．21（s，3H），2．23（s，3H），2．55（s，3H），4．40（d，J＝9．6Hz，1H），4．50（d，J＝9．6Hz，1H），7．29－7．42（m，5H），7．97（s，1H）． MS［M+H］$^+$＝409
5		^{1}H－NMR δ（ppm）：1．67（dd，J＝5．6，8．0Hz，1H），1．94（t，J＝5．6Hz，1H），2．16（dd，J＝5．6，8．0Hz，1H），2．22（s，3H），2．55（s，3H），4．41（d，J＝9．6Hz，1H），4．51（d，J＝9．6Hz，1H），7．36－7．40（m，3H），7．46－7．48（m，2H），7．88（dd，J＝2．4，8．6Hz，1H），7．97（s，1H），8．21（d，J＝8．6Hz，1H），8．41（brs，1H），8．54－8．55（m，1H）． MS［M+H］$^+$＝443

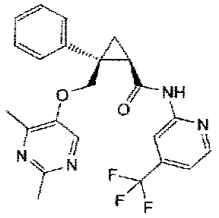
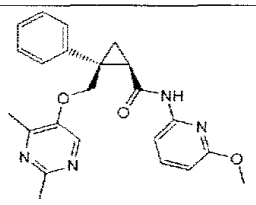
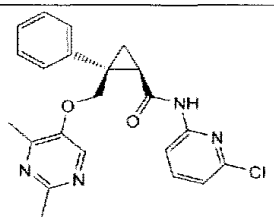
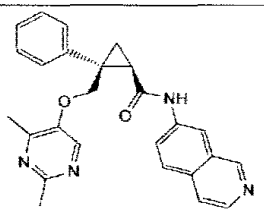
【０２４１】

【表１０】

実施例	構造式	NMR（４００MHz，$CDCl_3$）及び／又はMS
6		^{1}H－NMR（δ（ppm）：1．66（dd，J＝5．0，8．2Hz，1H），1．97（dd，J＝5．0，5．8Hz，1H），2．08（s，3H），2．40（dd，J＝5．8，8．2Hz，1H），2．51（s，3H），4．51（d，J＝9．6Hz，1H），4．59（d，J＝9．6Hz，1H），7．29－7．34（m，1H），7．37－7．42（m，2H），7．47－7．55（m，5H），7．99（s，1H），8．18（dd，J＝1．8，8．2Hz，1H），8．62（dd，J＝2．6，6．2Hz，1H），8．84（dd，J＝1．8，4．2Hz，1H），10．21（brs，1H）． MS［M＋Na］$^+$＝447
7		MS［M＋H］$^+$＝425
8		^{1}H－NMR（δ（ppm）：1．67（dd，J＝5．6，8．0Hz，1H），1．96（t，J＝5．6Hz，1H），2．15（dd，J＝5．6，8．0Hz，1H），2．21（s，3H），2．53（s，3H），4．52（d，J＝9．6Hz，1H），4．59（d，J＝9．6Hz，1H），7．29－7．40（m，4H），7．47－7．49（m，2H），7．54（dd，J＝2．4，8．8Hz，1H），7．90（brs，1H），8．02－8．08（m，3H），8．27（d，J＝1．8Hz，1H），8．83（dd，J＝1．8，4．0Hz，1H）． MS［M＋Na］$^+$＝447
9		MS［M＋H］$^+$＝425

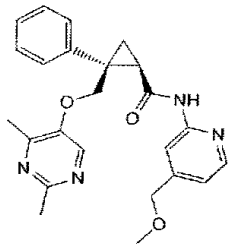
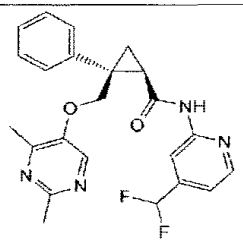
【０２４２】

【表１１】

実施例	構造式	NMR（４００MHz，CDCl$_3$）及び／又はMS
１０		^{1}H－NMR δ（ppm）：1．６６（ｄｄ，Ｊ＝5．６，８．０Ｈｚ，１Ｈ），１．９３（ｔ，Ｊ＝5．６Ｈｚ，１Ｈ），２．１５（ｄｄ，Ｊ＝5．６，８．０Ｈｚ，１Ｈ），２．２０（ｓ，３Ｈ），２．５４（ｓ，３Ｈ），４．４２（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．２４－７．３９（ｍ，４Ｈ），７．４５－７．４８（ｍ，２Ｈ），７．９７（ｓ，１Ｈ），８．３６（ｂｒｓ，１Ｈ），８．４３－８．４４（ｍ，２Ｈ）．
１１		^{1}H－NMR δ（ppm）：1．６３（ｄｄ，Ｊ＝5．６，８．０Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝5．６Ｈｚ，１Ｈ），２．１１－２．１５（ｍ，１Ｈ），２．２３（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），３．８７（ｓ，３Ｈ），４．４３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．４８（ｄ，Ｊ＝８．８Ｈｚ，１Ｈ），７．２８－７．３９（ｍ，３Ｈ），７．４６－７．５６（ｍ，４Ｈ），７．９８－８．００（ｍ，２Ｈ）． MS［M+H］$^+$＝４０５
１２		^{1}H－NMR δ（ppm）：1．６２（ｄｄ，Ｊ＝5．２，８．０Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝5．２Ｈｚ，１Ｈ），２．０９（ｂｒｔ，１Ｈ），２．２２（ｓ，３Ｈ），２．５５（ｓ，３Ｈ），４．３８（ｄ，Ｊ＝９．４Ｈｚ，１Ｈ），４．４７（ｄ，Ｊ＝９．４Ｈｚ，１Ｈ），７．０６（ｄ，Ｊ＝８．０Ｈｚ，１Ｈ），７．３０－７．３８（ｍ，３Ｈ），７．４５－７．４６（ｍ，２Ｈ），７．６２（ｔ，Ｊ＝８．０Ｈｚ，１Ｈ），７．９５（ｓ，１Ｈ），７．９９（ｄ，Ｊ＝８．０Ｈｚ，１Ｈ），８．２５（ｂｒｓ，１Ｈ）． MS［M+H］$^+$＝４０９
１３		^{1}H－NMR δ（ppm）：1．６５（ｔ，Ｊ＝６．０Ｈｚ，１Ｈ），１．９５（ｔ，Ｊ＝６．０Ｈｚ，１Ｈ），２．１６（ｔ，Ｊ＝６．０Ｈｚ，１Ｈ），２．２１（ｓ，３Ｈ），２．５２（ｓ，３Ｈ），４．５０（ｄ，Ｊ＝９．４Ｈｚ，１Ｈ），４．５８（ｄ，Ｊ＝９．４Ｈｚ，１Ｈ），７．２８－７．３６（ｍ，３Ｈ），７．４４－７．４６（ｍ，２Ｈ），７．５８（ｄ，Ｊ＝５．８Ｈｚ，１Ｈ），７．６４－７．６６（ｍ，１Ｈ），７．７６（ｄ，Ｊ＝８．８Ｈｚ，１Ｈ），８．０１（ｓ，１Ｈ），８．２７（ｂｒｓ，１Ｈ），８．４５（ｄ，Ｊ＝５．８Ｈｚ，１Ｈ），９．１４（ｂｒｓ，１Ｈ）．

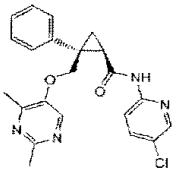
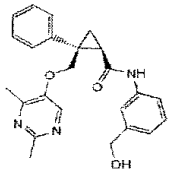
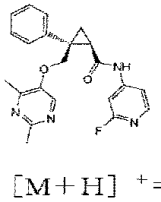
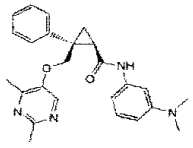
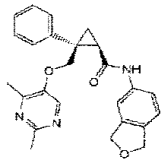
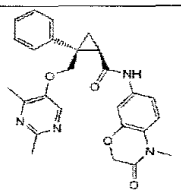
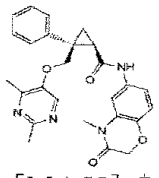
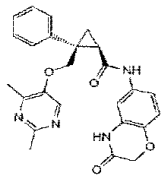
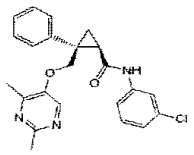
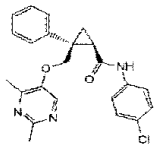
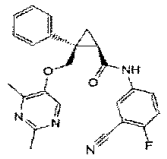
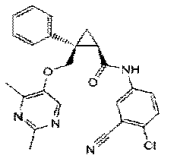
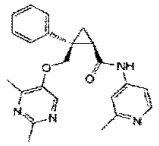
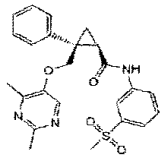
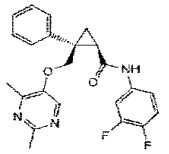
【０２４３】

【表１２】

実施例	構造式	NMR（４００MHz，$CDCl_3$）及び／又はMS
１４		^{1}H－NMR　δ（ｐｐｍ）：１．６２（ｄｄ，Ｊ＝５．２，８．０Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１２－２．１５（ｍ，１Ｈ），２．２０（ｓ，３Ｈ），２．５４（ｓ，３Ｈ），３．３９（ｓ，３Ｈ），４．４１－４．４３（ｍ，３Ｈ），４．５１（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），７．０３－７．０４（ｍ，１Ｈ），７．２７－７．３８（ｍ，３Ｈ），７．４４－７．４７（ｍ，２Ｈ），７．９７（ｓ，１Ｈ），８．００（ｂｒｓ，１Ｈ），８．２２（ｄ，Ｊ＝５．２Ｈｚ，１Ｈ），８．４８（ｂｒｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４１９
１５		^{1}H－NMR　δ（ｐｐｍ）：１．６４（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），１．９２（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．１５（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），２．２０（ｓ，３Ｈ），２．５４（ｓ，３Ｈ），４．４１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５０（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．５６（ｔ，Ｊ＝５６．０Ｈｚ，１Ｈ），７．１８－７．３９（ｍ，４Ｈ），７．４６－７．４８（ｍ，２Ｈ），７．９６（ｓ，１Ｈ），８．２１（ｂｒｓ，１Ｈ），８．３８－８．４０（ｍ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４２５

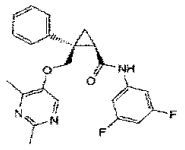
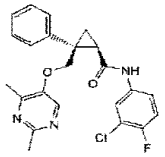
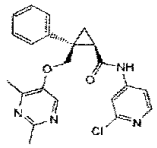
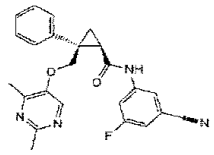
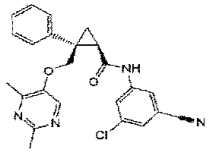
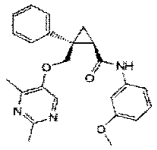
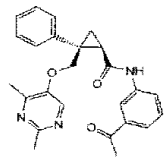
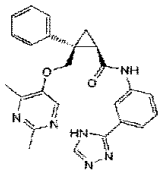
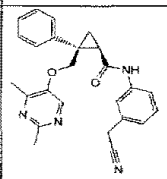
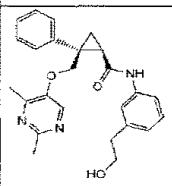
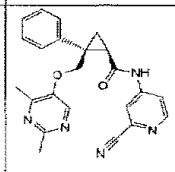
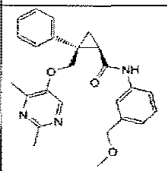
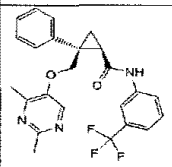
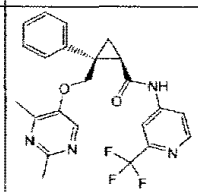
【０２４４】

【表１３】

実施例	構造式、ＭＳ	実施例	構造式、ＭＳ	実施例	構造式、ＭＳ
１６	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４０９	１７	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４０４	１８	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝３９３
１９	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４１７	２０	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４１６	２１	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４５９
２２	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４５９	２３	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４４５	２４	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４０８
２５	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４０８	２６	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４１７	２７	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４３３
Ｅ２８	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝３８９	２９	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４５２	３０	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４１０

【０２４５】

【表１４】

実施例	構造式、ＭＳ	実施例	構造式、ＭＳ	実施例	構造式、ＭＳ
３１	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４１０	３２	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４２６	３３	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４０９
３４	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４１７	３５	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４３３	３６	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４０４
３７	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４１６	３８	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４４１	３９	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４１３
４０	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４１８	４１	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４００	４２	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４１８
４３	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４４２	４４	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４４３		

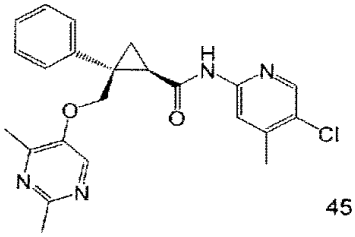
【０２４６】

実施例４５

（１Ｒ，２Ｓ）－Ｎ－（５－クロロ－４－メチルピリジン－２－イル）－２－［（２，４

ージメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド（４５）の合成

【化４７】



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【０２４７】

カルボン酸Ｐｒｅｐ１３－７（５００ｍｇ）をジクロロメタン（５ｍｌ）に溶解させ、オキザリルクロリド（２８８μｌ）、ＤＭＦ（数滴）を加え室温で２時間撹拌した。反応液を減圧濃縮し、粗酸クロライドを得た。２－アミノ－５－クロロ－４－メチルピリジン（３５９ｍｇ）の１，４－ジオキサン（４．５ｍｌ）溶液にＮ，Ｎ－ジイソプロピルエチルアミン（６６４μｌ）を加え１２５℃に昇温し、粗酸クロライドの１，４－ジオキサン（３ｍｌ）溶液を滴下しそのままの温度で１時間撹拌させた。反応系を室温まで放冷し１２時間撹拌させた後、反応液に水を数滴加えて減圧濃縮し、残渣をＮＨ－シリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，Ｓｉｚｅ：Ｍ＋Ｌ，ｎ－ヘプタン：酢酸エチル）で精製し、得られた目的物をエーテルで洗浄し、濾取乾燥して、標記化合物（９５．５ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：１．５４－１．６８（ｍ，１Ｈ），１．９０（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０７－２．１６（ｍ，１Ｈ），２．２１（ｓ，３Ｈ），２．３５（ｓ，３Ｈ），２．５５（ｓ，３Ｈ），４．４０（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．２０－７．５０（ｍ，５Ｈ），７．９７（ｓ，１Ｈ），７．９８（ｓ，１Ｈ），８．１６（ｓ，１Ｈ），８．２７（ｓ，１Ｈ）．

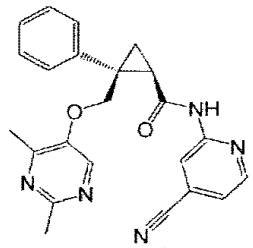
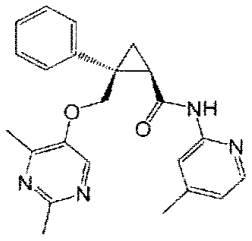
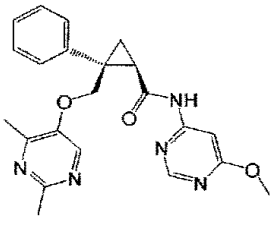
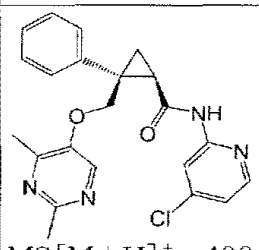
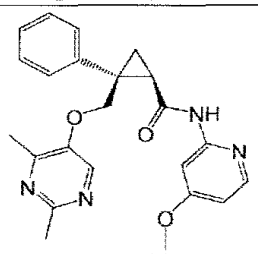
ＭＳ［Ｍ＋Ｈ］$^{+}$＝４２３

【０２４８】

＊実施例４６－５０は、カルボン酸Ｐｒｅｐ１３－７と任意のアミンを実施例４５と同様の手法で反応させ合成した。精製はＬＣ－ＭＳで行った。

【０２４９】

【表１５】

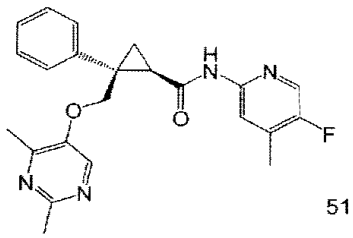
実施例	構造式、MS	実施例	構造式、MS	実施例	構造式、MS
46	 MS[M+H]$^+$=400	47	 MS[M+H]$^+$=389	48	 MS[M+H]$^+$=406
49	 MS[M+H]$^+$=409	50	 MS[M+H]$^+$=405		

【０２５０】

実施例５１

（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド（５１）の合成

【化４８】



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【０２５１】

カルボン酸Ｐｒｅｐ１３－７（２．８６ｇ）をＮ，Ｎ－ジメチルホルムアミド（５７ｍｌ）に溶解させ、この溶液に２－アミノ－５－フルオロ－４－ピコリン（１．４５ｇ）、Ｎ，Ｎ－ジイソプロピルエチルアミン（２ｍｌ）を加えた後、氷冷下でＨＡＴＵ（４．３８ｇ）を加えて、窒素雰囲気下において室温下３時間撹拌した。その後、２－アミノ－５－フルオロ－４－ピコリン（２４２ｍｇ）を追加して、更に１５時間撹拌した。その後、２－アミノ－５－フルオロ－４－ピコリン（３００ｍｇ）を追加して、更に２４時間半撹拌した。その後、反応液に水を加えて、酢酸エチルで抽出（ｘ３）した。有機層を飽和食塩水で洗浄後、無水硫酸マグネシウムで乾燥させ、濾液を減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー｛ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，Ｓｉｚｅ：Ｌ（ＮＨ－インジェクトカラム）＋３Ｌ，ｎ－ヘプタン：酢酸エチル｝で精製し、得られた目的物を６０℃で酢酸エチル（２ｍｌ）とヘキサン（２４ｍｌ）に溶かして、徐々に室温まで放冷しながら一晩放置し、析出した固体を濾取乾燥して、標記化合物（２．４ｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．５６－１．６６（ｍ，１Ｈ），１．９０（ｔ，Ｊ＝４．８Ｈｚ，１Ｈ），２．１０（ｄｄ，Ｊ＝６．０，８．０Ｈｚ，１Ｈ），２．２１（ｓ，３Ｈ），２．２４－２．３０（ｍ，３Ｈ），２．５５（ｓ，３Ｈ），４．４１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．２０－７．５４（ｍ，５Ｈ），７．９０－８．０４（ｍ，３Ｈ），８．２５（ｓ，１Ｈ）．

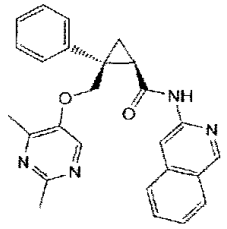
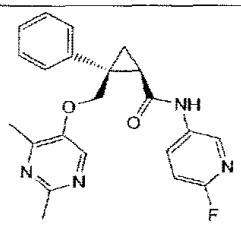
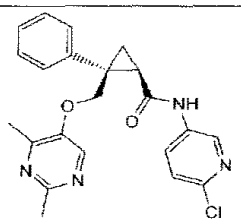
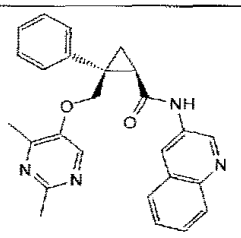
ＭＳ［Ｍ＋Ｈ］$^+$＝４０７

【０２５２】

＊実施例５２－７２は、カルボン酸Ｐｒｅｐ１３－７と、任意のアミンを実施例５１と同様の手法で反応させ合成した。

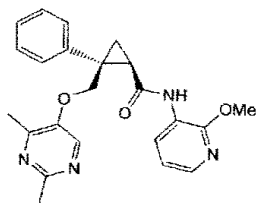
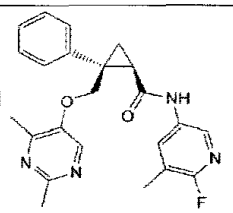
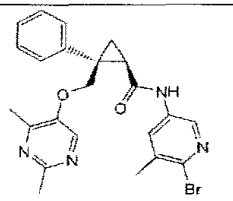
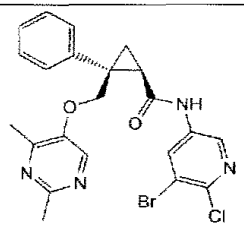
【０２５３】

【表１６】

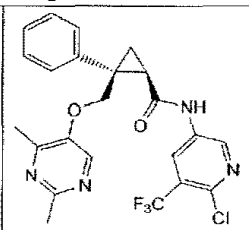
実施例	構造式	NMR（４００MHz，CDCl$_3$）及び／又はMS
５２		^{1}H－NMR δ（ｐｐｍ）：１．６１（ｄｄ，Ｊ＝８．０，４．８Ｈｚ），１．９５（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１９－２．２５（ｍ，１Ｈ），２．２１（ｓ，３Ｈ），２．５２（ｓ，３Ｈ），４．４５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．２５－７．７０（ｍ，６Ｈ），７．６２－７．６７（ｍ，１Ｈ），７．５－７．８１（ｍ，１Ｈ），７．８２－７．９４（ｍ，１Ｈ），７．９９（ｓ，１Ｈ），８．１１－８．１３（ｍ，１Ｈ），８．２２－８．２７（ｍ，１Ｈ），８．８９－８．０４（ｂｒｓ，１Ｈ）．
５３		^{1}H－NMR δ（ｐｐｍ）：１．６４（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１２（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．２４（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），４．４７（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．８９（ｄｄ，Ｊ＝９．２，２．８Ｈｚ，１Ｈ），７．２９（ｔ，Ｊ＝７．２Ｈｚ，１Ｈ），７．３５（ｔ，Ｊ＝７．２Ｈｚ，２Ｈ），７．４４（ｄ，Ｊ＝７．２Ｈｚ，２Ｈ），７．９３（ｂｒｓ，１Ｈ），７．９９（ｓ，１Ｈ），８．１２－８．１７（ｍ，２Ｈ）．
５４		^{1}H－NMR δ（ｐｐｍ）：１．６４（ｄｄ，Ｊ＝８．４，５．２Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１２（ｄｄ，Ｊ＝８．４，６．０Ｈｚ，１Ｈ），２．２３（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），４．４６（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．２６（ｔ，Ｊ＝８．８Ｈｚ，１Ｈ），７．２９（ｔ，Ｊ＝７．２Ｈｚ，１Ｈ），７．３４（ｄ，Ｊ＝７．２Ｈｚ，２Ｈ），７．４３（ｄ，Ｊ＝７．２Ｈｚ，２Ｈ），７．９９（ｓ，１Ｈ），８．１０（ｄｄ，Ｊ＝８．８，２．８Ｈｚ，１Ｈ），８．１１（ｂｒｓ，１Ｈ），８．３４（ｄ，Ｊ＝２．８Ｈｚ，１Ｈ）．
５５		^{1}H－NMR δ（ｐｐｍ）：１．６７（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９６（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１９（ｄｄ，Ｊ＝８．０，５．６Ｈｚ，１Ｈ），２．２０（ｓ，３Ｈ），２．５２（ｓ，３Ｈ），４．５２（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５８（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．２９（ｔ，Ｊ＝７．２Ｈｚ，１Ｈ），７．３６（ｔ，Ｊ＝７．２Ｈｚ，２Ｈ），７．４７（ｄ，Ｊ＝７．２Ｈｚ，２Ｈ），７．５３（ｔ，Ｊ＝８．０Ｈｚ，１Ｈ），７．６３（ｔ，Ｊ＝８．０Ｈｚ，１Ｈ），７．７５（ｄ，Ｊ＝８．０Ｈｚ，１Ｈ），８．０２（ｓ，１Ｈ），８．０４（ｄ，Ｊ＝８．０Ｈｚ，１Ｈ），８．１７（ｂｒｓ，１Ｈ），８．６９（ｄ，Ｊ＝２．０Ｈｚ，１Ｈ），８．７５（ｄ，Ｊ＝２．０Ｈｚ，１Ｈ）．

【０２５４】

【表１７－１】

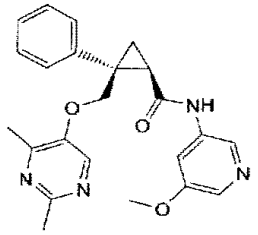
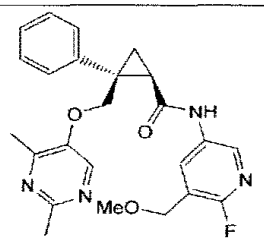
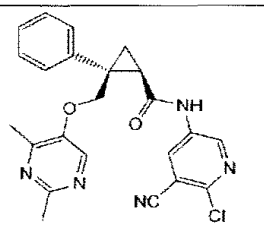
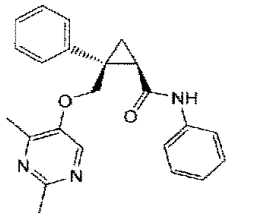
実施例	構造式	NMR（４００MHz，$CDCl_3$）及び／又はMS
５６		^{1}H－NMR δ（ppm）：1．６３（dd，J＝８．０，５．２Hz，１H），１．９０（t，J＝５．２Hz，１H），２．１５（dd，J＝８．０，５．６Hz，１H），２．２１（s，３H），２．５５（s，３H），４．０４（s，３H），４．４６（d，J＝９．２Hz，１H），４．５５（d，J＝９．２Hz，１H），６．８５（dd，J＝７．６，４．８Hz，１H），７．３０（t，J＝７．６Hz，１H），７．３８（t，J＝７．６Hz，２H），７．４７（d，J＝７．６Hz，２H），７．８５（d，J＝４．８Hz，１H），７．９９（s，１H），８．０１（brs，１H），８．４３（d，J＝７．６Hz，１H）．
５７		^{1}H－NMR δ（ppm）：1．６５（dd，J＝８．０，５．２Hz，１H），１．９０（t，J＝５．２Hz，１H），２．０９（dd，J＝８．０，６．０Hz，１H），２．２５（s，６H），２．５７（s，３H），４．４７（d，J＝９．６Hz，１H），４．５３（d，J＝９．６Hz，１H），７．３０（t，J＝７．２Hz，１H），７．３６（t，J＝７．２Hz，２H），７．４５（d，J＝７．２Hz，２H），７．７４（brs，１H），７．９３（s，１H），７．９７－７．９９（m，２H）．
５８		^{1}H－NMR δ（ppm）：1．６４（dd，J＝８．０，５．２Hz，１H），１．９０（t，J＝５．２Hz，１H），２．１１（dd，J＝８．０，５．６Hz，１H），２．２３（s，３H），２．３４（s，３H），２．５６（s，３H），４．４６（d，J＝９．６Hz，１H），４．５３（d，J＝９．６Hz，１H），７．２８（t，J＝７．２Hz，１H），７．３４（t，J＝７．２Hz，２H），７．４３（d，J＝７．２Hz，２H），７．９３－８．００（m，３H），８．１４（d，J＝２．８Hz，１H）．
５９		^{1}H－NMR δ（ppm）：1．６６（dd，J＝８．０，５．２Hz，１H），１．９１（t，J＝５．２Hz，１H），２．１０（dd，J＝８．０，５．６Hz，１H），２．２４（s，３H），２．５７（s，３H），４．４５（d，J＝９．６Hz，１H），４．５２（d，J＝９．６Hz，１H），７．２９（t，J＝７．２Hz，１H），７．３５（t，J＝７．２Hz，２H），７．４２（d，J＝７．２Hz，２H），７．９９（s，１H），８．０４（brs，１H），８．３０（d，J＝２．４Hz，１H），８．４７（d，J＝２．４Hz，１H）．

【表１７－２】

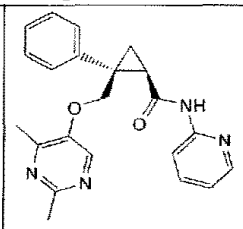
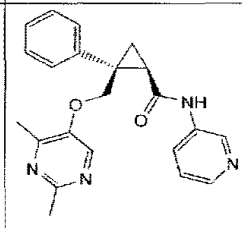
６０		^{1}H－NMR δ（ｐｐｍ）：１．６８（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９３（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１２（ｄｄ，Ｊ＝８．０，５．６Ｈｚ，１Ｈ），２．２４（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），４．４６（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５２（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．３０（ｔ，Ｊ＝７．２Ｈｚ，１Ｈ），７．３６（ｔ，Ｊ＝７．２Ｈｚ，２Ｈ），７．４４（ｄ，Ｊ＝７．２Ｈｚ，２Ｈ），７．９９（ｓ，１Ｈ），８．０１（ｂｒｓ，１Ｈ），８．４６（ｄ，Ｊ＝２．８Ｈｚ，１Ｈ），８．５７（ｄ，Ｊ＝２．８Ｈｚ，１Ｈ）．

【０２５５】

【表１８－１】

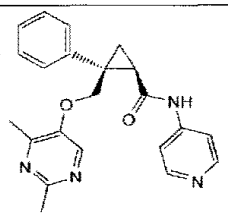
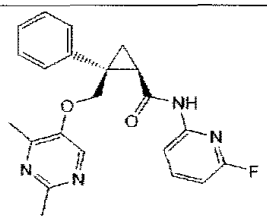
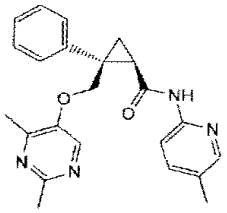
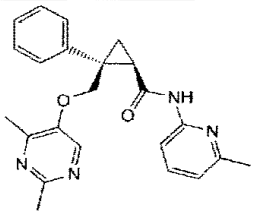
実施例	構造式	NMR（４００MHz，$CDCl_3$）及び／又はMS
６１		^{1}H－NMR δ（ppm）：１．６４（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１４（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．２３（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），３．７９（ｓ，３Ｈ），４．４７（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５４（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．２９（ｔ，Ｊ＝７．６Ｈｚ，１Ｈ），７．３４（ｔ，Ｊ＝７．６Ｈｚ，２Ｈ），７．４５（ｄ，Ｊ＝７．６Ｈｚ，２Ｈ），７．８５（ｂｒｓ，１Ｈ），８．００（ｓ，１Ｈ），８．０４－８．０７（ｍ，３Ｈ）．
６２		^{1}H－NMR δ（ppm）：１．６５（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０９（ｄｄ，Ｊ＝８．０，５．６Ｈｚ，１Ｈ），２．２５（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），３．４２（ｓ，３Ｈ），４．４６（ｓ，２Ｈ），４．４７（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５２（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．３０（ｔ，Ｊ＝７．２Ｈｚ，１Ｈ），７．３６（ｔ，Ｊ＝７．２Ｈｚ，２Ｈ），７．４５（ｄ，Ｊ＝７．２Ｈｚ，２Ｈ），７．６５（ｂｒｓ，１Ｈ），７．９９（ｓ，１Ｈ），８．１１（ｄｄ，Ｊ＝８．４，２．８Ｈｚ，１Ｈ），８．１５（ｄ，Ｊ＝２．８Ｈｚ，１Ｈ）．
６３		^{1}H－NMR δ（ppm）：１．７０（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９４（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１１（ｄｄ，Ｊ＝８．０，５．６Ｈｚ，１Ｈ），２．２３（ｓ，３Ｈ），２．５７（ｓ，３Ｈ），４．４５（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），４．５１（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），７．３１（ｔ，Ｊ＝７．２Ｈｚ，１Ｈ），７．３６（ｔ，Ｊ＝７．２Ｈｚ，２Ｈ），７．４４（ｄ，Ｊ＝７．２Ｈｚ，２Ｈ），７．９３（ｂｒｓ，１Ｈ），７．９９（ｓ，１Ｈ），８．５２（ｄ，Ｊ＝２．８Ｈｚ，１Ｈ），８．５５（ｄ，Ｊ＝２．８Ｈｚ，１Ｈ）．
６４		^{1}H－NMR δ（ppm）：１．６０（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），１．９０（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０６（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），２．２３（ｓ，３Ｈ），２．５５（ｓ，３Ｈ），４．４７（ｄ，Ｊ＝９．４Ｈｚ，１Ｈ），４．５４（ｄ，Ｊ＝９．４Ｈｚ，１Ｈ），７．０８－７．１２（ｍ，１Ｈ），７．２８－７．３７（ｍ，５Ｈ），７．４３－７．４６（ｍ，４Ｈ），７．５８（ｂｒｓ，１Ｈ），７．９９（ｓ，１Ｈ）． MS［M＋H］$^+$＝３７４

【表１８－２】

６５		^{1}H－NMR δ（ｐｐｍ）：１．６２（ｄｄ，Ｊ＝５．２，８．０Ｈｚ，１Ｈ），１．９２（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１５（ｂｒｔ，１Ｈ），２．１９（ｓ，３Ｈ），２．５５（ｓ，３Ｈ），４．４３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５４（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．９４－６．９８（ｍ，１Ｈ），７．２７－７．３８（ｍ，３Ｈ），７．４４－７．４６（ｍ，２Ｈ），７．９９（ｓ，１Ｈ），８．０４（ｂｒｄ，１Ｈ），８．２０（ｂｒｓ，１Ｈ），８．８１－８．９３（ｍ，１Ｈ）．ＭＳ［Ｍ＋Ｈ］$^+$＝３７５
６６		^{1}H－NMR δ（ｐｐｍ）：１．６２（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．１４（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），２．２２（ｓ，３Ｈ），２．５５（ｓ，３Ｈ），４．４８（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５４（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．２１－７．４３（ｍ，６Ｈ），７．９９（ｓ，１Ｈ），８．１２（ｂｒｄ，１Ｈ），８．２２－８．４５（ｍ，２Ｈ），８．５２（ｄ，Ｊ＝２．０Ｈｚ，１Ｈ）．ＭＳ［Ｍ＋Ｈ］$^+$＝３７５．

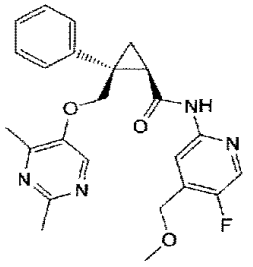
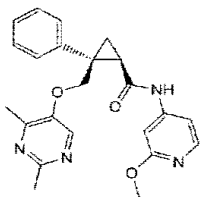
【０２５６】

【表１９】

実施例	構造式	NMR（４００MHz，$CDCl_3$）及び／又はMS
６７		^{1}H－NMR δ（ppm）：１．６２－１．６５（m，１H），１．９２（t，J＝５．４Hz，１H），２．１１－２．１５（m，１H），２．２１（s，３H），２．５６（s，３H），４．４５（d，J＝９．６Hz，１H），４．５４（d，J＝９．６Hz，１H），７．２７－７．４５（m，７H），８．００（s，１H），８．４６（ｂｒｓ，２H）． MS［M+H］$^+$＝３７５
６８		^{1}H－NMR δ（ppm）：１．６３（ｄｄ，J＝５．２，８．０Hz，１H），１．９１（t，J＝５．２Hz，１H），２．１１（ｂｒｔ，１H），２．２１（s，３H），２．５５（s，３H），４．３９（d，J＝９．４Hz，１H），４．４９（d，J＝９．４Hz，１H），６．６６（ｄｄ，J＝２．６，８．０Hz，１H），７．２８－７．３９（m，３H），７．４５－７．４７（m，２H），７．７４（q，J＝８．０Hz，１H），７．９２（ｂｒｄ，１H），７．９６（s，１H），８．１７－８．１９（m，１H）． MS［M+H］$^+$＝３９３
６９		^{1}H－NMR δ（ppm）：１．６０（ｄｄ，J＝５．２，８．０Hz，１H），１．９０（t，J＝５．２Hz，１H），２．１１（ｂｒｔ，１H），２．２０（s，３H），２．２８（s，３H），２．５４（s，３H），４．４０（d，J＝９．４Hz，１H），４．５１（d，J＝９．４Hz，１H），７．２７－７．３８（m，３H），７．４５－７．４８（m，３H），７．９４（ｂｒｄ，１H），７．９６（s，１H），８．０８（q，J＝０．８Hz，１H），８．２７（ｂｒｓ，１H）．
７０		^{1}H－NMR δ（ppm）：１．６０（ｄｄ，J＝５．２，７．６Hz，１H），１．９０（t，J＝５．２Hz，１H），２．１３（ｂｒｔ，１H），２．２１（s，３H），２．４７（s，３H），２．５４（s，３H），４．４０（d，J＝９．６Hz，１H），４．５０（d，J＝９．６Hz，１H），６．９０（d，J＝７．２Hz，１H），７．２７－７．３８（m，３H），７．４６－７．４８（m，２H），７．５５（ｂｒｔ，１H），７．８６（ｂｒｄ，１H），７．９６（s，１H）． MS［M+H］$^+$＝３８９

【０２５７】

【表２０】

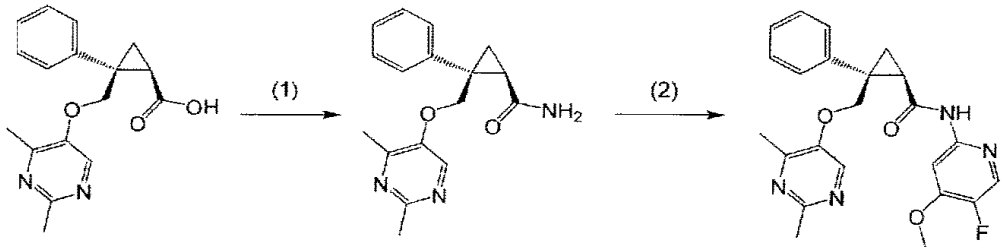
実施例	構造式	NMR（４００MHz，CDCl$_3$及び／又はMS
７１		^{1}H－NMR　δ（ｐｐｍ）：１．６２（ｄｄ，Ｊ＝５．２，８．０Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１２（ｄｄ，Ｊ＝５．２，８．０Ｈｚ，１Ｈ），２．２１（ｓ，３Ｈ），２．５５（ｓ，３Ｈ），３．４１（ｓ，３Ｈ），４．４１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４５－４．５４（ｍ，３Ｈ），７．３０－７．３９（ｍ，３Ｈ），７．４５－７．４８（ｍ，２Ｈ），７．９６（ｓ，１Ｈ），８．０７（ｄ，Ｊ＝１．２Ｈｚ，１Ｈ），８．１７－８．１８（ｍ，１Ｈ），８．２５（ｂｒｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４３７
７２		ＭＳ［Ｍ＋Ｈ］$^+$＝４０５

【０２５８】

実施例７３

（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド（７３－２）の合成

【化４９】



【０２５９】

（１）（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド（７３－１）

カルボン酸Ｐｒｅｐ１３－７（１．０ｇ）、ＨＯＢｔ（６７９ｍｇ）、ＷＳＣ（９６３ｍｇ）および塩化アンモニウム（３５８ｍｇ）のＤＭＦ（１５ｍｌ）溶液にＮ，Ｎ－ジイソプロピルエチルアミンを室温で加え、７日間撹拌した。反応液に飽和炭酸水素ナトリウム水溶液を加え、酢酸エチル（ｘ２）で抽出した。有機層を無水硫酸マグネシウムで乾燥し、濾過した。濾液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝９：１～１：４）で精製した。得られた粗生成物を酢酸エチルに溶解後、ｎ－ヘキサンを加えた。析出した固体を濾取乾燥させ化合物７４－１（６０６ｍｇ

）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．５３（ｄｄ，Ｊ＝４．８，８．４Ｈｚ，１Ｈ），１．７９（ｄｄ，Ｊ＝４．８，６．０Ｈｚ，１Ｈ），１．９９（ｄｄ，Ｊ＝６．０，８．４Ｈｚ，１Ｈ），２．３５（ｓ，３Ｈ），２．５８（ｓ，３Ｈ），４．４５（ｓ，２Ｈ），５．４０（ｂｒｓ，１Ｈ），５．７７（ｂｒｓ，１Ｈ），７．２７－７．３６（ｍ，３Ｈ），７．４２－７．４５（ｍ，２Ｈ），７．９８（ｓ，１Ｈ）．

ＭＳ［Ｍ＋Ｈ］$^+$＝２９８

【０２６０】

（２）（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド（７３－２）

化合物７３－１（３００ｍｇ）、製造例９－（１）で得た２－クロロ－５－フルオロ－４－メトキシピリジン（２４５ｍｇ）、ザントホス（３５１ｍｇ）、カリウム三リン酸（４２９ｍｇ）およびトリス（ジベンジリデン）ジパラジウム（１８５ｍｇ）の１，４－ジオキサン（２０ｍｌ）溶液を９５℃まで昇温し、２６時間攪拌した。反応液に水を加え、酢酸エチル（ｘ１）で抽出した。有機層を水、飽和食塩水で順次洗浄後、無水硫酸マグネシウムで乾燥し、濾過した。濾液を減圧下濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝７：３～酢酸エチル）、次いでＮＨ－シリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝４：１～２：３）で精製した。得られた粗生成物をクロロホルムに溶解後、ｎ－ヘキサンを加えた。析出した固体を濾取乾燥させ化合物７３－２（３０４ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．６３（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），１．８９（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．１１（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），２．２３（ｓ，３Ｈ），２．５５（ｓ，３Ｈ），３．８８（ｓ，３Ｈ），４．４１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．２８－７．３９（ｍ，３Ｈ），７．４５－７．４８（ｍ，２Ｈ），７．８２（ｄ，Ｊ＝６．４Ｈｚ，１Ｈ），７．９７（ｄ，Ｊ＝２．８Ｈｚ，１Ｈ），７．９８（ｓ，１Ｈ），８．３０（ｂｒｓ，１Ｈ）．

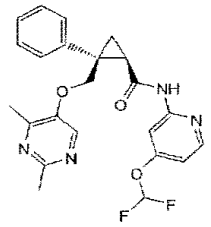
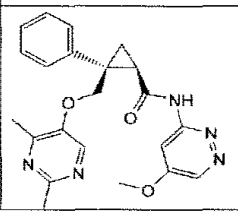
ＭＳ［Ｍ＋Ｎａ］$^+$＝４４５

【０２６１】

＊実施例７４－７５は、実施例７４－１で得られたカルボン酸アミドから、実施例７３と同様の手法で合成した。

【０２６２】

【表２１】

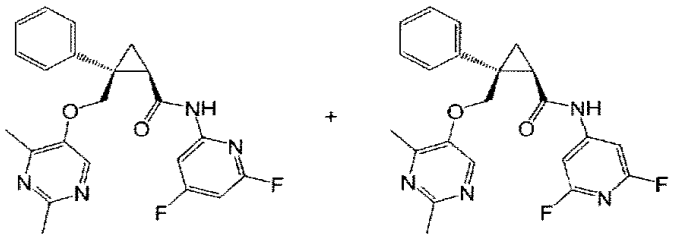
実施例	構造式	NMR（４００MHz，CDCl$_3$）及び／又はMS
７４		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６７（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），１．９３（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．１１（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），２．２３（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），４．４６（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．５３（ｔ，Ｊ＝７２．６Ｈｚ，１Ｈ），７．２８－７．３９（ｍ，３Ｈ），７．４４－７．４６（ｍ，２Ｈ），７．７９（ｂｒｓ，１Ｈ），７．９９（ｓ，１Ｈ），８．０６（ｂｒｓ，１Ｈ），８．２３（ｄ，Ｊ＝２．０Ｈｚ，１Ｈ），８．３７（ｄ，Ｊ＝２．０Ｈｚ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４４１
７５		ＭＳ［Ｍ＋Ｈ］$^+$＝４０６

【０２６３】

実施例７６

（１Ｒ，２Ｓ）－Ｎ－（４，６－ジフルオロピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド（７６－１）及び（１Ｒ，２Ｓ）－Ｎ－（２，６－ジフルオロピリジン－４－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド（７６－２）の合成

【化５０】



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【０２６４】

化合物７３－１（１００ｍｇ）のＮＭＰ（５ｍｌ）溶液に水素化ナトリウム（６０％、２６．９ｍｇ）を加え、室温で１０分間撹拌後、２，４，６－トリフルオロピリジン（８９．４ｍｇ）を加えた。反応液を１００℃に昇温し、４日間撹拌した。反応液に水を加え、酢酸エチル（ｘ１）で抽出した。有機層を水、飽和食塩水で順次洗浄後、無水硫酸マグネシウムで乾燥し、濾過した。濾液を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝４：１～１：９）で精製し標記化合物７６－１（１１．１ｍｇ）および化合物７６－２（２３．４ｍｇ）を得た。

【０２６５】

７６－１

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．６４（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０９（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），２．２２（ｓ，３Ｈ），２．５５（ｓ，３Ｈ），４．３７（ｄ，Ｊ＝９．８Ｈｚ，１Ｈ），４．４８（ｄ，Ｊ＝９．８Ｈｚ，１Ｈ），６．３９（ｄｔ，Ｊ＝７．６，１．６Ｈｚ，１Ｈ），７．２８－７．３９（ｍ，３Ｈ），７．４３－７．４６（ｍ，２Ｈ），７．７４（ｄｄ，Ｊ＝１．６，１０．０Ｈｚ，１Ｈ），７．９５（ｓ，１Ｈ），８．２１（ｂｒｓ，１Ｈ）．

ＭＳ［Ｍ＋Ｈ］$^+$＝４１１

【０２６６】

７６－２

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．７０（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），１．９４（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０７（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），２．２２（ｓ，３Ｈ），２．５７（ｓ，３Ｈ），４．４２（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．００（ｓ，２Ｈ），７．３１－７．３９（ｍ，３Ｈ），７．４２－７．４５（ｍ，２Ｈ），７．８６（ｂｒｓ，１Ｈ），７．９８（ｓ，１Ｈ）．

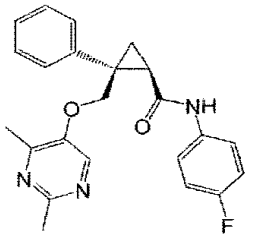
ＭＳ［Ｍ＋Ｈ］$^+$＝４１１

【０２６７】

実施例７７

（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（４－フルオロフェニル）－２－フェニルシクロプロパンカルボキサミド　（７７）の合成

【化５１】



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【０２６８】

カルボン酸Ｐｒｅｐ１３－７（３０ｍｇ）をＮ，Ｎ－ジメチルホルムアミド（１ｍｌ）に溶解させ、４－フルオロアニリン（３３．７ｍｇ）、Ｎ，Ｎ－ジイソプロピルエチルアミン（１７６ｕｌ）、ＨＯＢｔ（４０．９ｍｇ）を加えた後、室温下でＷＳＣ（５８．１ｍｇ）を加えて、室温下２１時間撹拌した。その後、ＬＣ－ＭＳ（Ｗａｔｅｒｓ、カラム：ＣＡＰＣＥＬＬ　ＰＡＫ、Ｃ１８、ＡＣＲ、Ｓ－５、２０ｍｍＩ．Ｄ．×５０ｍｍ、ＡＧＥＥ０１１１４、移動相：メタノール－水－ＴＦＡ）で精製分取し、標記化合物（１０．３４ｍｇ）を得た。

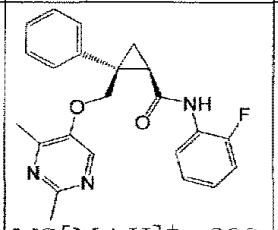
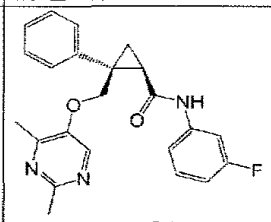
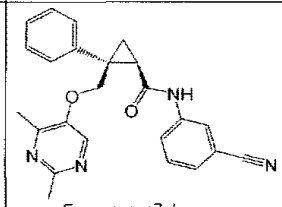
ＭＳ［Ｍ＋Ｈ］$^+$＝３９２

【０２６９】

＊実施例７８－８０はカルボン酸Ｐｒｅｐ１３－７と任意のアミンを実施例７７と同様の手法で反応させ合成した。精製はＬＣ－ＭＳで行った。

【０２７０】

【表２２】

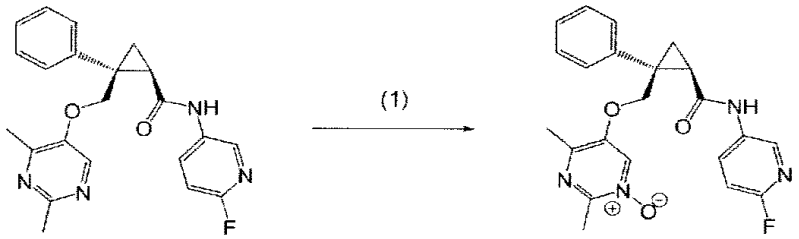
実施例	構造式、MS	実施例	構造式、MS	実施例	構造式、MS
78	 MS[M+H]$^+$=392	79	 MS[M+H]$^+$=392	80	 MS[M+H]$^+$=399

【０２７１】

実施例８１

（１Ｒ，２Ｓ）－２－［（２，４－ジメチル－１－オキソピリミジン－５－イル）オキシメチル］－Ｎ－（６－フルオロピリジン－３－イル）－２－フェニルシクロプロパンカルボキサミド（８１）の合成

【化５２】



【０２７２】

化合物５４（４０ｍｇ）をジクロロメタン（５ｍｌ）に溶解し、３－クロロペルオキシベンゾイックアシッド（２６．４ｍｇ）を加えた。１８時間撹拌した後、反応液に炭酸カリウム（５０ｍｇ）を加え、さらに１時間撹拌した。ろ過後、溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝３：１から０：１の後、酢酸エチル：メタノール＝８：１）で精製して標記化合物（２５．０ｍｇ）を得た。

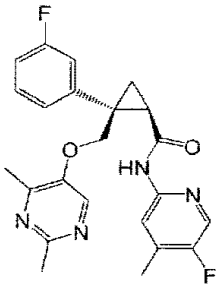
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．６２（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．８６（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．２３（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．２４（ｓ，３Ｈ），２．５４（ｓ，３Ｈ），４．３８（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．８９（ｄｄ，Ｊ＝９．２，２．８Ｈｚ，１Ｈ），７．２７（ｔ，Ｊ＝７．２Ｈｚ，１Ｈ），７．３２（ｔ，Ｊ＝７．２Ｈｚ，２Ｈ），７．４２（ｄ，Ｊ＝７．２Ｈｚ，２Ｈ），７．９１（ｓ，１Ｈ），８．１８－８．２２（ｍ，２Ｈ），８．６２（ｂｒｓ，１Ｈ）．

【０２７３】

実施例８２

（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（３－フルオロフェニル）シクロプロパンカルボキサミド（８２）の合成

【化５３】



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【０２７４】

カルボン酸Ｐｒｅｐ１４－６（３８８ｍｇ）と２－アミノ－５－フルオロ－４－ピコリン（１５４ｍｇ）のＤＭＦ（９．７ｍｌ）溶液に、室温攪拌下、Ｎ，Ｎ－ジイソプロピルエチルアミン（２７８ｕｌ）とＨＡＴＵ（６０４ｍｇ）を加えた。室温で６時間攪拌した後、反応液に水を加え、酢酸エチルで抽出した。有機相を硫酸マグネシウムで乾燥後、減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ^{TM} ｃｏｌｕｍｎ，Ｓｉｚｅ：Ｌ，ｎ－ヘプタン：酢酸エチル１０％→６０％）で精製した。ＴＨＦ－ヘプタンを用いて固体を析出させろ取することにより標記化合物（２８９ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：１．５５－１．６５（ｍ，１Ｈ），１．９１（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０５－２．１３（ｍ，１Ｈ），２．２２（ｓ，３Ｈ），２．２７（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），４．４１（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），４．５０（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），６．９７－７．０４（ｍ，１Ｈ），７．１４－７．２０（ｍ，１Ｈ），７．２２－７．２８（ｍ，１Ｈ），７．３３（ｔｄ，Ｊ＝８．０，５．８Ｈｚ，１Ｈ），７．９３（ｄ，Ｊ＝５．２Ｈｚ，１Ｈ），７．９９（ｓ，１Ｈ），８．００（ｓ，１Ｈ），８．２４（ｂｒｓ，１Ｈ）．

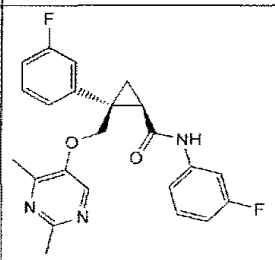
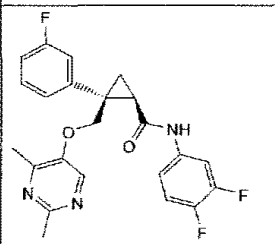
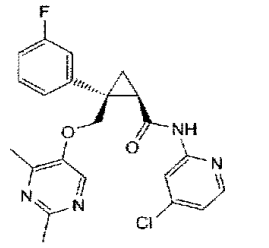
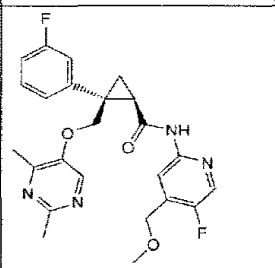
ＭＳ［Ｍ＋Ｎａ］$^{+}$＝４４７

【０２７５】

＊実施例８３－９４はカルボン酸Ｐｒｅｐ１４－６と、任意のアミンを実施例８２と同様の手法により合成した。

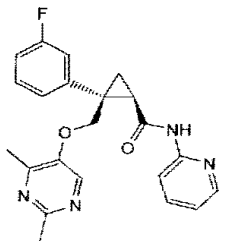
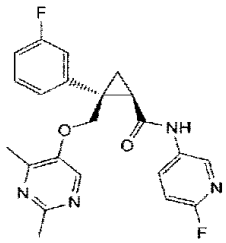
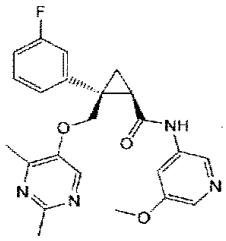
【０２７６】

【表２３】

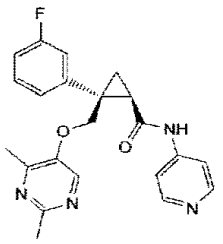
実施例	構造式	NMR（４００MHz，$CDCl_3$）及び／又はMS
８３		^{1}H－NMR δ（ppm）：1．６２（dd，J＝5．６，８．０Hz，１H），１．９２（t，J＝5．６Hz，１H），２．０５（dd，J＝5．６，８．０Hz，１H），２．２３（s，３H），２．５７（s，３H），４．４６（d，J＝９．６Hz，１H），４．５３（d，J＝９．６Hz，１H），６．７９－６．８３（m，１H），６．９８－７．０２（m，１H），７．０９－７．１２（m，１H），７．１５－７．４０（m，５H），７．６４（brs，１H），８．０１（s，１H）． MS［M+H］$^+$＝４１０
８４		^{1}H－NMR δ（ppm）：1．６３（dd，J＝5．６，８．２Hz，１H），１．９２（t，J＝5．６Hz，１H），２．０３（dd，J＝5．６，８．２Hz，１H），２．２４（s，３H），２．５８（s，３H），４．４５（d，J＝９．６Hz，１H），４．５２（d，J＝９．６Hz，１H），６．９８－７．３６（m，６H），７．４９－７．５４（m，２H），８．０１（s，１H）． MS［M+H］$^+$＝４２８
８５		^{1}H－NMR δ（ppm）：1．６３（dd，J＝5．６，８．０Hz，１H），１．９３（t，J＝5．６Hz，１H），２．１３（dd，J＝5．６，８．０Hz，１H），２．２２（s，３H），２．５６（s，３H），４．４０（d，J＝９．８Hz，１H），４．５０（d，J＝９．８Hz，１H），６．９８－７．０６（m，２H），７．１６－７．２０（m，１H），７．２３－７．３６（m，２H），７．９８（s，１H），８．１３（brs，１H），８．１６（d，J＝５．６Hz，１H），８．４２（brs，１H）． MS［M+H］$^+$＝４２７
８６		^{1}H－NMR δ（ppm）：1．６２（dd，J＝5．２，８．０Hz，１H），１．９２（t，J＝5．２Hz，１H），２．０９－２．１３（m，１H），２．２２（s，３H），２．５５（s，３H），３．４１（s，３H），４．４１（d，J＝９．６Hz，１H），４．４５－４．５４（m，３H），６．９８－７．０３（m，１H），７．１６－７．１９（m，１H），７．２３－７．３６（m，２H），７．９８（s，１H），８．０７（brs，１H），８．１６－８．１７（m，１H），８．２６（brs，１H）． MS［M+H］$^+$＝４５５

【０２７７】

【表２４－１】

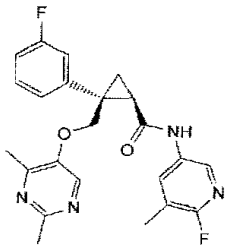
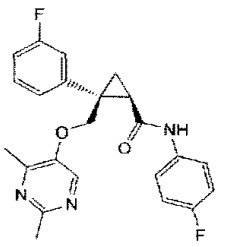
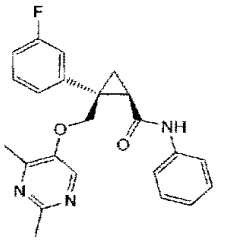
実施例	構造式	NMR（４００MHz，CDCl$_3$）及び／又はMS
８７		^{1}H－NMR δ（ppm）：１．６２（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９３（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１０－２．１９（ｍ，１Ｈ），２．２１（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），４．４１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５０（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．９７－７．０７（ｍ，２Ｈ），７．１５－７．２１（ｍ，１Ｈ），７．２３－７．２９（ｍ，１Ｈ），７．３３（ｔｄ，Ｊ＝８．０，５．６Ｈｚ，１Ｈ），７．６５－７．７１（ｍ，１Ｈ），７．９８（ｓ，１Ｈ），８．０６（ｂｒｄ，Ｊ＝８．４Ｈｚ，１Ｈ），８．２４－８．２８（ｍ，１Ｈ），８．５６（ｂｒｓ，１Ｈ）．
８８		^{1}H－NMR δ（ｐｐｍ）：１．６６（ｄｄ，Ｊ＝８．４，５．２Ｈｚ，１Ｈ），１．９３（ｔ，Ｊ＝５．４Ｈｚ，１Ｈ），２．０９（ｄｄ，Ｊ＝８．４，５．６Ｈｚ，１Ｈ），２．２６（ｓ，３Ｈ），２．５８（ｓ，３Ｈ），４．５０（ｄｄ，Ｊ＝１９．８，９．４Ｈｚ，２Ｈ），６．８７－６．９３（ｍ，１Ｈ），６．９７－７．０５（ｍ，１Ｈ），７．１４－７．３７（ｍ，３Ｈ），７．６５（ｂｒｓ，１Ｈ），８．０１（ｓ，１Ｈ），８．１０－８．１８（ｍ，２Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４１１
８９		^{1}H－NMR δ（ｐｐｍ）：１．６２（ｄｄ，Ｊ＝７．８，５．４Ｈｚ，１Ｈ），１．９２（ｔ，Ｊ＝５．４Ｈｚ，１Ｈ），２．１４（ｄｄ，Ｊ＝８．２，５．８Ｈｚ，１Ｈ），２．２４（ｓ，３Ｈ），２．５７（ｓ，３Ｈ），３．７８（ｓ，３Ｈ），４．４７（ｄ，Ｊ＝９．４Ｈｚ，１Ｈ），４．５３（ｄ，Ｊ＝９．４Ｈｚ，１Ｈ），６．９６－７．０２（ｍ，１Ｈ），７．１２－７．１９（ｍ，１Ｈ），７．２０－７．２４（ｍ，１Ｈ），７．３１（ｔｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），７．８５（ｂｒｓ，１Ｈ），８．００－８．０５（ｍ，２Ｈ），８．０８（ｄ，Ｊ＝１．６Ｈｚ，１Ｈ），８．３３（ｂｒｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４２３

【表２４－２】

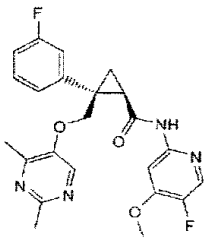
９０		^{1}H－NMR δ（ｐｐｍ）：１．６４（ｄｄ，Ｊ＝８．２，５．０Ｈｚ，１Ｈ），１．９４（ｔ，Ｊ＝５．８Ｈｚ，１Ｈ），２．１３（ｄｄ，Ｊ＝８．２，５．８Ｈｚ，１Ｈ），２．２２（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），４．４４（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），４．５２（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），６．９５－７．０２（ｍ，１Ｈ），７．１１－７．１６（ｍ，１Ｈ），７．１８－７．２３（ｍ，１Ｈ），７．２７－７．３４（ｍ，１Ｈ），７．４３－７．４７（ｍ，２Ｈ），８．０１（ｓ，１Ｈ），８．３９（ｂｒｓ，１Ｈ），８．４４－８．４９（ｍ，２Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝３９３

【０２７８】

【表２５－１】

実施例	構造式	NMR（４００MHz，$CDCl_3$）及び／又はMS
９１		^{1}H－NMR δ（ppm）：１．６３（ｄｄ，Ｊ＝８．２，５．４Ｈｚ，１Ｈ），１．９２（ｔ，Ｊ＝５．４Ｈｚ，１Ｈ），２．１１（ｄｄ，Ｊ＝８．２，５．８Ｈｚ，１Ｈ），２．２４（ｓ，３Ｈ），２．２６（ｓ，３Ｈ），２．５８（ｓ，３Ｈ），４．４７（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５２（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．９６－７．０３（ｍ，１Ｈ），７．１４－７．２０（ｍ，１Ｈ），７．２０－７．２５（ｍ，１Ｈ），７．３２（ｔｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），７．９０－８．０４（ｍ，４Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４２５
９２		^{1}H－NMR δ（ppm）：１．５５－１．７０（ｍ，１Ｈ），１．９１（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０５（ｄｄ，Ｊ＝７．８，６．２Ｈｚ，１Ｈ），２．２６（ｓ，３Ｈ），２．５８（ｓ，３Ｈ），４．４７（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．９４－７．０４（ｍ，３Ｈ），７．１７（ｄｔ，Ｊ＝１０．４，２．０Ｈｚ，１Ｈ），７．２１－７．２７（ｍ，１Ｈ），７．２９－７．３６（ｍ，１Ｈ），７．３７－７．４４（ｍ，２Ｈ），７．５６（ｂｒｓ，１Ｈ），８．０１（ｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４１０
９３		^{1}H－NMR δ（ppm）：１．５５－１．６９（ｍ，１Ｈ），１．９２（ｔ，Ｊ＝５．４Ｈｚ，１Ｈ），２．０６（ｄｄ，Ｊ＝８．２，５．８Ｈｚ，１Ｈ），２．２５（ｓ，３Ｈ），２．５７（ｓ，３Ｈ），４．４８（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），４．５４（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．９６－７．０３（ｍ，１Ｈ），７．０８－７．１４（ｍ，１Ｈ），７．１４－７．２０（ｍ，１Ｈ），７．２０－７．３７（ｍ，４Ｈ），７．４４（ｄ，Ｊ＝７．６Ｈｚ，２Ｈ），７．５６（ｂｒｓ，１Ｈ），８．０１（ｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝３９２

【表２５－２】

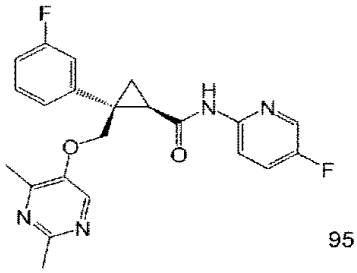
９４		^{1}H－NMR δ（ｐｐｍ）：１．６３（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．１０（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），２．２３（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），３．８７（ｓ，３Ｈ），４．４１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．９９－７．０３（ｍ，１Ｈ），７．１６－７．２６（ｍ，２Ｈ），７．３１－７．３６（ｍ，１Ｈ），７．８０（ｄ，Ｊ＝６．４Ｈｚ，１Ｈ），７．９８（ｄ，Ｊ＝２．８Ｈｚ，１Ｈ），７．９９（ｓ，１Ｈ），８．２８（ｂｒｓ，１Ｈ）． ＭＳ［Ｍ＋Ｎａ］$^+$＝４６３

【０２７９】

実施例９５

（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド（９５）の合成

【化５４】



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【０２８０】

カルボン酸Ｐｒｅｐ１４－６（２２６ｍｇ）をジクロロメタン（１０ｍｌ）に溶解させ、オキザリルクロリド（１２２μｌ）、ＤＭＦ（数滴）を加え室温で１時間撹拌した。反応液を減圧濃縮し、粗酸クロライドを得た。２－アミノ－５－フルオロピリジン（９６．１ｍｇ）のＴＨＦ（１０ｍｌ）溶液にＮ，Ｎ－ジイソプロピルエチルアミン（２８３μｌ）を加え６０℃に昇温し、粗酸クロライドのＴＨＦ溶液を滴下しそのままの温度で１時間撹拌させた。反応系を室温まで放冷し１時間撹拌させた後、反応液を減圧濃縮した後、酢酸エチルと水に分配し、有機層を分離した。有機層を無水硫酸マグネシウムで乾燥させ、濾液を減圧濃縮した。残渣をＮＨ－シリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝２：１）で精製し、得られた目的物にジエチルエーテルを加えた。析出した固体を濾取乾燥して、標記化合物（１３０ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ｄ－ＤＭＳＯ）δ（ｐｐｍ）：１．４６－１．５０（ｍ，１Ｈ），１．６８（ｔ，Ｊ＝６．０Ｈｚ，１Ｈ），２．０１（ｓ，３Ｈ），２．３６（ｓ，３Ｈ），２．５９－２．６３（ｍ，１Ｈ），４．２７（ｄ，Ｊ＝１０．４Ｈｚ，１Ｈ），４．６６（ｄ，Ｊ＝１０．４Ｈｚ，１Ｈ），７．０６－７．１１（ｍ，１Ｈ），７．３７－７．４４（ｍ，３Ｈ），７．６０－７．６５（ｍ，１Ｈ），７．８５－７．８９（ｍ，１Ｈ），８．１１（ｓ，１Ｈ），８．３０（ｄ，Ｊ＝３．２Ｈｚ，１Ｈ），１１．２０（ｂｒｄｓ，１Ｈ）

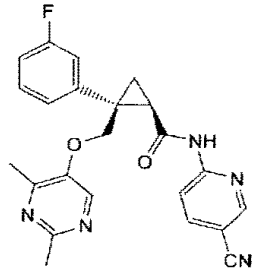
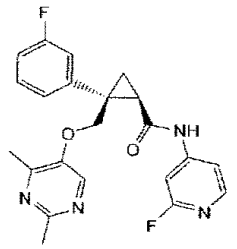
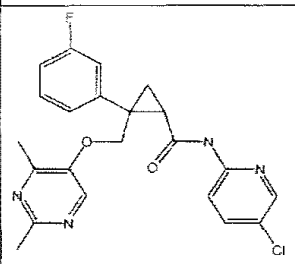
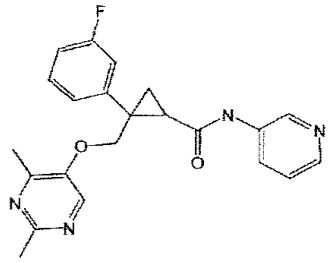
ＭＳ［Ｍ＋Ｈ］$^+$＝４１１

【０２８１】

＊実施例９６－９９は、カルボン酸Ｐｒｅｐ１４－６またはそのラセミ体と、任意のアミンとを実施例９５と同様の手法により合成した。

【０２８２】

【表２６】

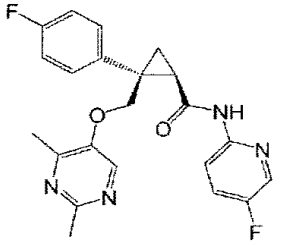
実施例	構造式	NMR（４００MHz，CDCl$_3$）及び／又はMS
９６		^{1}H－NMR　δ（ｐｐｍ）：１．６８（ｄｄ，Ｊ＝８．０，５．６Ｈｚ，１Ｈ），１．９５（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．１６（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．２１（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），４．３９（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５０（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．０２（ｔｄｄ，Ｊ＝８．０，２．４，１．２Ｈｚ，１Ｈ），７．１７（ｄｔ，Ｊ＝１０．０，２．４Ｈｚ，１Ｈ），７．２４（ｄｔ，Ｊ＝８．０，１．２Ｈｚ，１Ｈ），７．３４（ｔｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），７．９０（ｄｄ，Ｊ＝８．８，２．４Ｈｚ，１Ｈ），７．９８（ｓ，１Ｈ），８．２０（ｄ，Ｊ＝８．８Ｈｚ，１Ｈ），８．４８（ｂｒｓ，１Ｈ），８．５６（ｄｄ，Ｊ＝２．４，０．８Ｈｚ，１Ｈ）．
９７		^{1}H－NMR　δ（ｐｐｍ）：１．６９（ｄｄ，Ｊ＝８．２，５．４Ｈｚ，１Ｈ），１．９５（ｔ，Ｊ＝５．４Ｈｚ，１Ｈ），２．０７（ｄｄ，Ｊ＝７．８，５．８Ｈｚ，１Ｈ），２．２３（ｓ，３Ｈ），２．５７（ｓ，３Ｈ），４．４４（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５２（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．９８－７．０５（ｍ，１Ｈ），７．１４－７．２０（ｍ，２Ｈ），７．２０－７．３１（ｍ，２Ｈ），７．３１－７．３８（ｍ，１Ｈ），７．７８（ｂｒｓ，１Ｈ），８．０１（ｓ，１Ｈ），８．１０（ｄ，Ｊ＝５．２Ｈｚ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４１１
９８		ＭＳ［Ｍ＋Ｈ］$^+$＝４２８
９９		ＭＳ［Ｍ＋Ｈ］$^+$＝３９３

【０２８３】

実施例１００

（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（４－フルオロフェニル）－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド（１００）の合成

【化５５】



100

【０２８４】

カルボン酸Ｐｒｅｐ１５－５（２００ｍｇ）をジクロロメタン（１０ｍｌ）に溶解させ、オキザリルクロリド（１０８μｌ）、ＤＭＦ（数滴）を加え室温で１時間撹拌した。反応液を減圧濃縮し、粗酸クロライドを得た。２－アミノ－５－フルオロピリジン（８５ｍｇ）のＴＨＦ（１０ｍｌ）溶液にＮ，Ｎ－ジイソプロピルエチルアミン（２５０μｌ）を加え６０℃に昇温し、粗酸クロライドのＴＨＦ溶液を滴下しそのままの温度で１時間撹拌させた。反応系を室温まで放冷し１時間撹拌させた後、反応液を減圧濃縮した後、酢酸エチルと水に分配し、有機層を分離した。有機層を無水硫酸マグネシウムで乾燥させ、濾液を減圧濃縮した。残渣をＮＨ－シリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝２：１）で精製し、得られた目的物にジエチルエーテルを加えた。析出した固体を濾取乾燥して、標記化合物（１０２ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ｄ－ＤＭＳＯ）δ（ｐｐｍ）：１．４３－１．４５（ｍ，１Ｈ），１．６６（ｔ，Ｊ＝４．４Ｈｚ，１Ｈ），２．０２（ｓ，３Ｈ），２．３６（ｓ，３Ｈ），２．５５－２．５８（ｍ，１Ｈ），４．２６（ｄ，Ｊ＝１０．４Ｈｚ，１Ｈ），４．５９（ｄ，Ｊ＝１０．４Ｈｚ，１Ｈ），７．１５－７．２０（ｍ，２Ｈ），７．５７－７．６５（ｍ，３Ｈ），７．８６－７．８９（ｍ，１Ｈ），８．０９（ｓ，１Ｈ），８．３０（ｄ，Ｊ＝３．２Ｈｚ，１Ｈ），１１．１８（ｂｒｄｓ，１Ｈ）

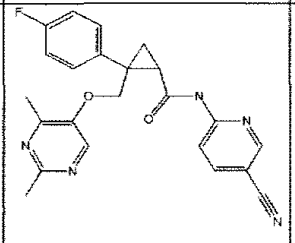
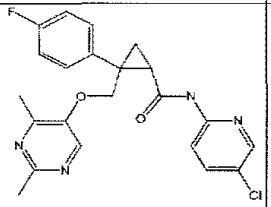
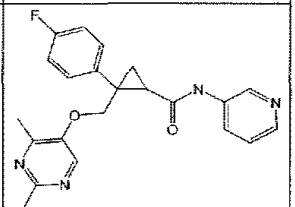
ＭＳ［Ｍ＋Ｈ］$^+$＝４１１

【０２８５】

＊実施例１０１－１０４は、製造例１５においてラセミのエピクロロヒドリンを用いることにより合成できる２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（４－フルオロフェニル）シクロプロパンカルボン酸または製造例１５－（５）で得たカルボン酸Ｐｒｅｐ１５－５を用いて、実施例１００と同様の手法で合成した。精製はＬＣ－ＭＳで行った。

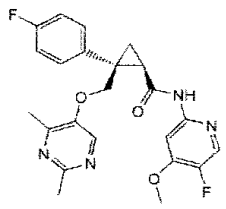
【０２８６】

【表２７】

実施例	構造式、MS	実施例	構造式、MS	実施例	構造式、MS
101	 MS[M+H]$^+$=418	102	 MS[M+H]$^+$=427	103	 MS[M+H]$^+$=393

【０２８７】

【表２８】

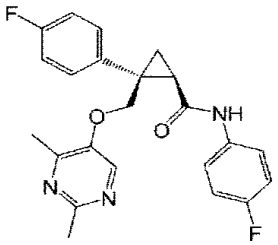
実施例	構造式	NMR及び／又はMS
１０４		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６０（ｄｄ，Ｊ＝５．２，８．０Ｈｚ，１Ｈ），１．８９（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０６（ｄｄ，Ｊ＝５．２，８．０Ｈｚ，１Ｈ），２．２３（ｓ，３Ｈ），２．５５（ｓ，３Ｈ），３．８８（ｓ，３Ｈ），４．４０（ｄ，Ｊ＝９．４Ｈｚ，１Ｈ），４．４６（ｄ，Ｊ＝９．４Ｈｚ，１Ｈ），７．０３－７．０８（ｍ，２Ｈ），７．４２－７．４６（ｍ，２Ｈ），７．８１（ｄ，Ｊ＝６．８Ｈｚ，１Ｈ），７．９７－７．９８（ｍ，２Ｈ），８．２４（ｂｒｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４４１

【０２８８】

実施例１０５

（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ，２－ビス（４－フルオロフェニル）シクロプロパンカルボキサミド（１０５）の合成

【化５６】



105

【０２８９】

カルボン酸Ｐｒｅｐ１５－５（３３ｍｇ）をＤＭＦ（２ｍｌ）に溶解させ、４－フルオロアニリン（１５ｍｇ）、Ｎ，Ｎ－ジイソプロピルエチルアミン（２３．５ｕｌ）、ＨＡＴＵ（５１．３ｍｇ）を加えて室温で２０時間撹拌した。反応液に水を加えて、酢酸エチルで抽出し、有機層を濃縮した。残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ^{TM} ｃｏｌｕｍｎ，Ｓｉｚｅ：Ｓ（ＮＨ－インジェクトカラム），ｎ－ヘプタン：酢酸エチル１０％→６０％）で精製し、標記化合物（２２．１ｍｇ）を得た。

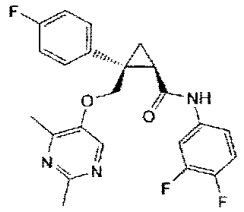
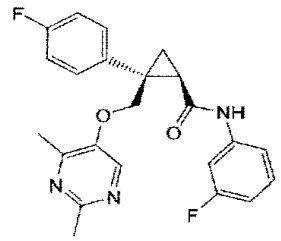
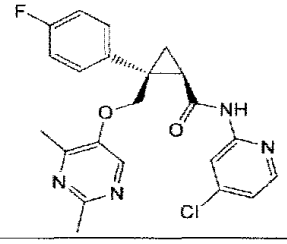
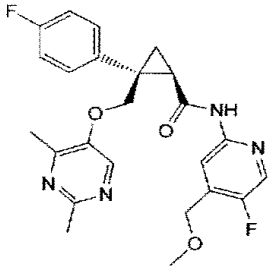
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．５３－１．６２（ｍ，１Ｈ），１．８９（ｔ，Ｊ＝５．４Ｈｚ，１Ｈ），２．０１（ｄｄ，Ｊ＝８．２，５．８Ｈｚ，１Ｈ），２．２５（ｓ，３Ｈ），２．５７（ｓ，３Ｈ），４．４７（ｄｄ，Ｊ＝１２．４，９．６Ｈｚ，２Ｈ），６．９７－７．０８（ｍ，４Ｈ），７．３７－７．４６（ｍ，４Ｈ），７．５０（ｂｒｓ，１Ｈ），７．９９（ｓ，１Ｈ）．

【０２９０】

＊実施例１０６－１１２は、カルボン酸Ｐｒｅｐ１５－５と任意のアミンを、実施例１０５と同様の手法で合成した。

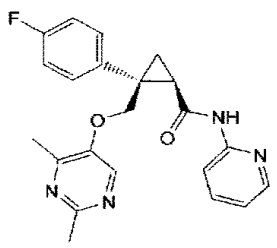
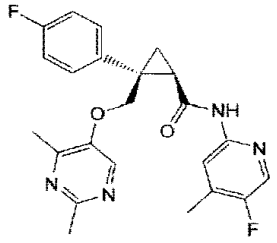
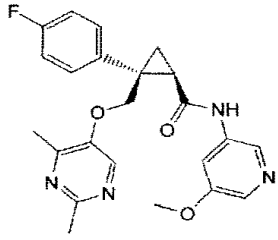
【０２９１】

【表２９－１】

実施例	構造式	NMR及び／又はMS
１０６		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．５８（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．８９（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．００（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．２４（ｓ，３Ｈ），２．５７（ｓ，３Ｈ），４．４４（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４８（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．０１－７．１２（ｍ，４Ｈ），７．３９－７．３６（ｍ，２Ｈ），７．４８－７．５５（ｍ，１Ｈ），７．６８（ｂｒ，１Ｈ），７．９９（ｓ，１Ｈ）．
１０７		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．５８（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．８９（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０２（ｄｄ，Ｊ＝８．６，６．０Ｈｚ，１Ｈ），２．２３（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），４．４４（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４８（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．７６－６．８４（ｍ，１Ｈ），７．０１－７．１２（ｍ，３Ｈ），７．２１－７．２８（ｍ，２Ｈ），７．３６－７．４５（ｍ，１Ｈ），７．７９（ｂｒ，１Ｈ），７．９９（ｓ，１Ｈ）．
１０８		ＭＳ［Ｍ＋Ｈ］$^+$＝４２８
１０９		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．５９（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０８（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），２．２２（ｓ，３Ｈ），２．５５（ｓ，３Ｈ），３．４１（ｓ，３Ｈ），４．４０（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４８（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），４．５２（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），７．０２－７．０８（ｍ，２Ｈ），７．４２－７．４６（ｍ，２Ｈ），７．９７（ｓ，１Ｈ），８．０７（ｄ，Ｊ＝１．２Ｈｚ，１Ｈ），８．１８（ｂｒｄ，Ｊ＝５．２Ｈｚ，１Ｈ），８．２６（ｂｒｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４５５

【０２９２】

【表３０】

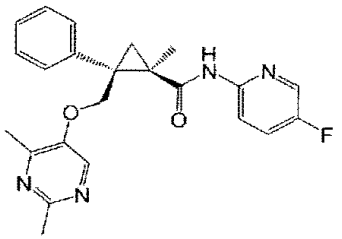
実施例	構造式	NMR及び／又はMS
１１０		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．５８（ｄｄ，Ｊ＝８．２，５．０Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝５．４Ｈｚ，１Ｈ），２．０６－２．１３（ｍ，１Ｈ），２．２０（ｓ，３Ｈ），２．５５（ｓ，３Ｈ），４．４０（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），４．４６（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．００－７．０８（ｍ，３Ｈ），７．４１－７．４８（ｍ，２Ｈ），７．６６（ｔｄ，Ｊ＝７．８，１．８Ｈｚ，１Ｈ），７．９７（ｓ，１Ｈ），８．０５（ｂｒｄ，Ｊ＝１０．４Ｈｚ，１Ｈ），８．２６（ｄｑ，Ｊ＝４．４，０．８Ｈｚ，１Ｈ），８．４１（ｂｒｓ，１Ｈ）
１１１		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．５８（ｄｄ，Ｊ＝７．６，５．２Ｈｚ，１Ｈ），１．８９（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０３－２．０９（ｍ，１Ｈ），２．２２（ｓ，３Ｈ），２．２８（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），４．４０（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），４．４６（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．０１－７．１２（ｍ，２Ｈ），７．４０－７．４７（ｍ，２Ｈ），７．９４（ｂｒｄ，Ｊ＝６．０Ｈｚ，１Ｈ），７．９７（ｓ，１Ｈ），８．００（ｄ，Ｊ＝１．２Ｈｚ，１Ｈ），８．２８（ｂｒｓ，１Ｈ）
１１２		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６２（ｄｄ，Ｊ＝８．４，５．２Ｈｚ，１Ｈ），１．９０（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０６－２．１４（ｍ，１Ｈ），２．２４（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），３．７９（ｓ，３Ｈ），４．４７（ｄｄ，Ｊ＝１３．６，９．６Ｈｚ，２Ｈ），７．０１－７．０８（ｍ，２Ｈ），７．４１－７．４８（ｍ，２Ｈ），７．８６（ｂｒｓ，１Ｈ），８．００（ｓ，２Ｈ），８．０３－８．１１（ｍ，２Ｈ）．

【０２９３】

実施例１１３

（１Ｒ，２Ｒ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）－１－メチル－２－フェニルシクロプロパンカルボキサミド（１１３）の合成

【化５７】



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【０２９４】

カルボン酸Ｐｒｅｐ２０－６（４１．５ｍｇ）のジクロロメタン（１．５ｍｌ）溶液に、氷冷攪拌下、オキサリルクロリド（２２．８ｕｌ）を加えた。室温で２時間攪拌した後、減圧濃縮した。残渣をジクロロメタン（１ｍｌ）に溶解し、氷冷攪拌下、２－アミノ－５－フルオロピリジン（２２．３ｍｇ）のジクロロメタン（１ｍｌ）溶液とＮ，Ｎ－ジイソプロピルエチルアミン（６９．４ｕｌ）を加え、室温で４時間攪拌した。反応液に水を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、硫酸マグネシウムで乾燥後、減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー（１回目：ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，Ｓｉｚｅ：Ｍ，ｎ－ヘプタン：酢酸エチル０％→１００％）（２回目：ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ ａｍｉｎｏ，Ｓｉｚｅ：Ｓ，ｎ－ヘプタン：酢酸エチル０％→５０％）で精製し、標記化合物（８．０ｍｇ）を得た。

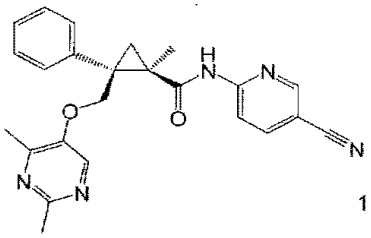
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．２５（ｓ，３Ｈ），１．３４（ｄ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０８（ｄ，Ｊ＝５．２Ｈｚ，１Ｈ），２．２５（ｓ，３Ｈ），２．５３（ｓ，３Ｈ），４．２９（ｄｄ，Ｊ＝１５．６，９．６Ｈｚ，２Ｈ），７．２８－７．４２（ｍ，４Ｈ），７．４２－７．４８（ｍ，２Ｈ），７．８７（ｓ，１Ｈ），８．０７－８．１３（ｍ，２Ｈ），８．３２（ｂｒｓ，１Ｈ）．

【０２９５】

実施例１１４

（１Ｒ，２Ｒ）－Ｎ－（５－シアノピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－１－メチル－２－フェニルシクロプロパンカルボキサミド（１１４）の合成

【化５８】



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【０２９６】

カルボン酸Ｐｒｅｐ２０－６（４５ｍｇ）のジクロロメタン（１．５ｍｌ）溶液に、氷冷攪拌下、オキサリルクロリド（２４．７ｕｌ）を加えた。室温で２時間攪拌した後、減圧濃縮した。残渣をジクロロメタン（１．５ｍｌ）に溶解し、氷冷攪拌下、２－アミノ－５－シアノピリジン（２２．３ｍｇ）のＴＨＦ（１ｍｌ）溶液とＮ，Ｎ－ジイソプロピルエチルアミン（７５．３ｕｌ）を加え、室温で３時間攪拌した。反応液に水を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、硫酸マグネシウムで乾燥後、減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー（１回目：ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ ａｍｉｎｏ，Ｓｉｚｅ：Ｍ，ｎ－ヘプタン：酢酸エチル０％→１００％）で精製し、標記化合物（２８．２ｍｇ）を得た。

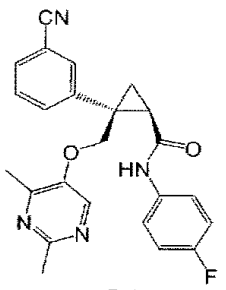
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．２６（ｓ，３Ｈ），１．３８（ｄ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１２（ｄ，Ｊ＝５．２Ｈｚ，１Ｈ），２．２５（ｓ，３Ｈ），２．５３（ｓ，３Ｈ），４．２５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．３２（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．３０－７．４２（ｍ，３Ｈ），７．４３－７．４８（ｍ，２Ｈ），７．８５－７．９１（ｍ，２Ｈ），８．２３（ｄｄ，Ｊ＝８．６，１．０Ｈｚ，１Ｈ），８．５０（ｂｒｓ，１Ｈ），８．５３－８．５６（ｍ，１Ｈ）．

【０２９７】

実施例１１５

（１Ｒ，２Ｓ）－２－（３－シアノフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（４－フルオロフェニル）シクロプロパンカルボキサミド（１１５－１）及び（１Ｓ，２Ｒ）－２－（３－シアノフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（４－フルオロフェニル）シクロプロパンカルボキサミド（１１５－２）の合成

【化５９】



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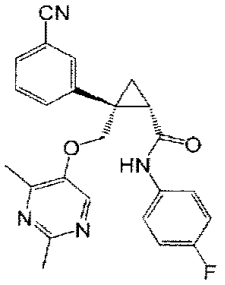

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【０２９８】

カルボン酸Ｐｒｅｐ１８－４（４０ｍｇ）と４－フルオロアニリン（１８．２ｍｇ）のＤＭＦ（１ｍｌ）溶液に、室温撹拌下、Ｎ，Ｎ－ジイソプロピルエチルアミン（２８．５ｕｌ）とＨＡＴＵ（６２．２ｍｇ）を加えた。室温で８時間撹拌した後、反応液に水を加え、酢酸エチルで抽出し、有機相を減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ^{TM} ｃｏｌｕｍｎ，Ｓｉｚｅ：Ｍ，ｎ－ヘプタン：酢酸エチル１０％→６０％）で精製した。次に、ＨＰＬＣ（Ｄａｉｃｅｌ Ｃｈｉｒａｌｐａｋ ＩＡ ｃｏｌｕｍｎ，ｎ－ヘキサン：エタノール３０％）でキラル分割することにより、標記化合物（ｆｒｏｎｔ ｐｅａｋ：１３．１ｍｇ，ｂａｃｋ ｐｅａｋ：１２．４ｍｇ）を得た。

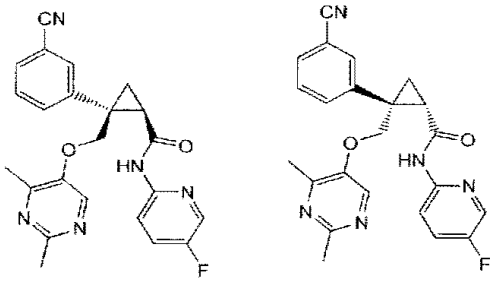
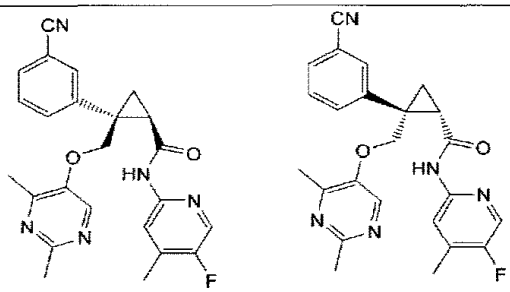
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．５９（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９６（ｔ，Ｊ＝５．４Ｈｚ，１Ｈ），２．０８（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．２５（ｓ，３Ｈ），２．５７（ｓ，３Ｈ），４．４９（ｓ，２Ｈ），６．９６－７．０４（ｍ，２Ｈ），７．４０－７．４６（ｍ，２Ｈ），７．４９（ｔ，Ｊ＝７．８Ｈｚ，１Ｈ），７．６１（ｂｒｄ，Ｊ＝７．６Ｈｚ，１Ｈ），７．７２（ｂｒｄ，Ｊ＝７．６Ｈｚ，１Ｈ），７．８４（ｂｒｄ，Ｊ＝８．０Ｈｚ，２Ｈ），８．００（ｓ，１Ｈ）．

【０２９９】

＊実施例１１６－１１７は、カルボン酸Ｐｒｅｐ１８－４と任意のアミンを実施例１１５と同様の手法で縮合し合成した。

【０３００】

【表３１】

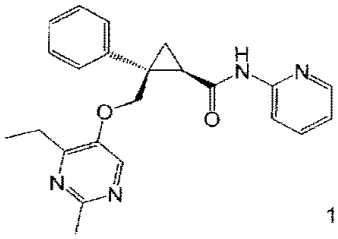
実施例	構造式	NMR及び／又はMS
１１６		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ppm）：1．６０－1．７０（m，１H），1．９７（t，J＝5．５Hz，１H），２．０８－２．１６（m，１H），２．２１（s，３H），２．５７（s，３H），４．４７（dd，J＝１７．２，９．８Hz，２H），７．３７－７．４４（m，１H），７．５０（t，J＝７．８Hz，１H），７．６２（dt，J＝７．８，１．６Hz，１H），７．７１－７．７５（m，１H），７．７８（brs，１H），７．９９（s，１H），８．０４－８．１１（m，１H），８．１３（d，J＝３．１Hz，１H），８．４３（brs，１H）．
１１７		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ppm）：1．６０－1．７０（m，１H），1．９６（t，J＝７．４Hz，１H），２．０７－２．１５（m，１H），２．２２（s，３H），２．２８（s，３H），２．５６（s，３H），４．４４（d，J＝９．２Hz，１H），４．４９（d，J＝１０．０Hz，１H），７．５０（t，J＝８．０Hz，１H），７．６２（dt，J＝８．０，１．２Hz，１H），７．７３（dt，J＝７．６，１．６Hz，１H），７．７７（brs，１H），７．９３（brd，J＝４．８Hz，１H），７．９９（s，１H），８．０１（brs，１H），８．３６（brs，１H）．

【０３０１】

実施例１１８

（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニル－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド（１１８）の合成

【化６０】



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【０３０２】

カルボン酸Ｐｒｅｐ１９－３（３０ｍｇ）と２－アミノピリジン（８．９ｍｇ）のＤＭＦ（０．７５ｍｌ）溶液に、室温攪拌下、Ｎ，Ｎ－ジイソプロピルエチルアミン（２１．４ｕｌ）とＨＡＴＵ（４６．８ｍｇ）を加えた。室温で３時間攪拌した後、反応液に水を加え、酢酸エチルで抽出した。有機相を濃縮し、残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ^{TM} ｃｏｌｕｍｎ，Ｓｉｚｅ：Ｓ，ｎ－ヘプタン：酢酸エチル１０％→６０％）で精製し、標記化合物（３２．１ｍｇ）を得た。

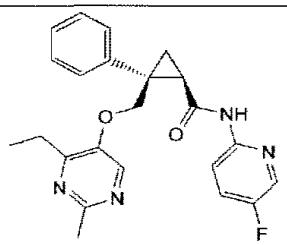
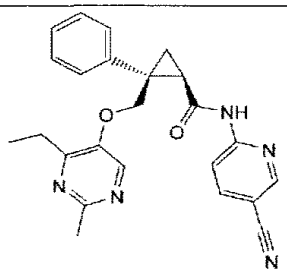
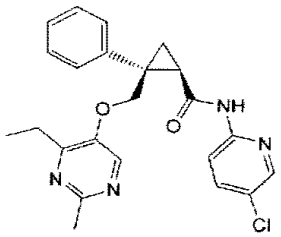
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：０．９７（ｔ，Ｊ＝７．６Ｈｚ，３Ｈ），１．６２（ｄｄ，Ｊ＝８．２，５．０Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝５．４Ｈｚ，１Ｈ），２．１０－２．１８（ｍ，１Ｈ），２．５０－２．６５（ｍ，２Ｈ），２．５６（ｓ，３Ｈ），４．４４（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），４．５１（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），６．９６－７．０２（ｍ，１Ｈ），７．２５－７．３９（ｍ，３Ｈ），７．４３－７．４８（ｍ，２Ｈ）．７．６２－７．６８（ｍ，１Ｈ），７．９９（ｓ，１Ｈ），８．０７（ｂｒｄ，Ｊ＝８．８Ｈｚ，１Ｈ），８．２３（ｄｑ，Ｊ＝４．８，０．８Ｈｚ，１Ｈ），８．６５（ｂｒｓ，１Ｈ）．

【０３０３】

＊実施例１１９－１２１は、カルボン酸Ｐｒｅｐ１９－３と任意のアミンを実施例１１８と同様の手法により縮合し合成した。

【０３０４】

【表３２】

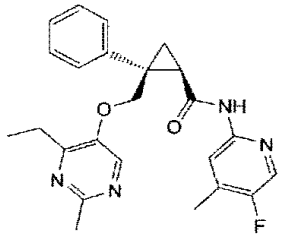
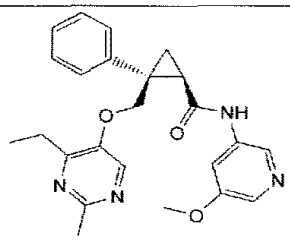
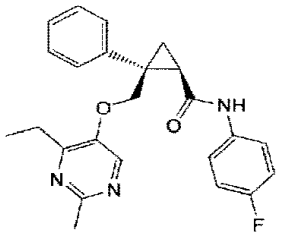
実施例	構造式	NMR及び／又はMS
１１９		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：０．９８５（ｔ，Ｊ＝７．６Ｈｚ，３Ｈ），１．６０－１．６３（ｍ，１Ｈ），１．９０（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１１（ｂｒｄｔ，１Ｈ），２．５１－２．６２（ｍ，５Ｈ），４．４２（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），４．４８（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），７．２７－７．５１（ｍ，６Ｈ）、７．９１（ｓ，１Ｈ），８．０８（ｍ，２Ｈ），８．２６（ｂｒｄｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４０７
１２０		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：０．９７（ｔ，Ｊ＝８．０Ｈｚ，３Ｈ），１．６７（ｄｄ，Ｊ＝８．４Ｈｚ，５．２Ｈｚ，１Ｈ），１．９３（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１６（ｄｄ，Ｊ＝８．０Ｈｚ，５．６Ｈｚ，１Ｈ），２．５０－２．６０（ｍ，５Ｈ），４．４０（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４８（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．２９－７．４６（ｍ，５Ｈ）、７．８９（ｄｄ，Ｊ＝２．４Ｈｚ，８．８Ｈｚ，１Ｈ），７．９７（ｓ，１Ｈ），８．２３（ｄ，Ｊ＝８．８Ｈｚ，１Ｈ），８．５３－８．５５（ｍ，２Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４１４
１２１		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：０．９９（ｔ，Ｊ＝７．６Ｈｚ，３Ｈ），１．６３（ｄｄ，Ｊ＝８．０Ｈｚ，５．２Ｈｚ，１Ｈ），１．９３（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．１２（ｂｒｄｔ，Ｊ＝８．０Ｈｚ，１Ｈ），２．５１－２．６０（ｍ，５Ｈ），４．４１（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），４．４８（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．２６－７．４７（ｍ，５Ｈ）、７．６１（ｄｄ，Ｊ＝２．８Ｈｚ，９．２Ｈｚ，１Ｈ），７．９７（ｓ，１Ｈ），８．０６（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），８．２２（ｄ，Ｊ＝２．８Ｈｚ，１Ｈ）８．２９（ｂｒｄｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４２３

【０３０５】

＊実施例１２２－１２４は、カルボン酸Ｐｒｅｐ１９－３と任意のアミンを実施例５１と同様の手法により合成した。

【０３０６】

【表３３】

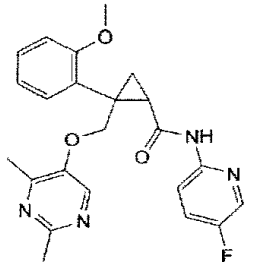
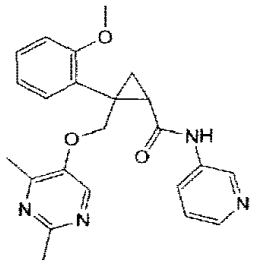
実施例	構造式	NMR及び／又はMS
１２２		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：０．９９（ｔ，Ｊ＝７．４Ｈｚ，３Ｈ），１．６２（ｄｄ，Ｊ＝７．８，５．０Ｈｚ，１Ｈ），１．８９（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．１１（ｄｄ，Ｊ＝７．８，５．８Ｈｚ，１Ｈ），２．２７（ｓ，３Ｈ），２．５０－２．６５（ｍ，２Ｈ），２．５７（ｓ，３Ｈ），４．４３（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），４．５０（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），７．２５－７．３２（ｍ，１Ｈ），７．３３－７．３９（ｍ，２Ｈ），７．４３－７．４７（ｍ，２Ｈ），７．９６（ｂｒｄ，Ｊ＝６．０Ｈｚ，１Ｈ），７．９７－８．０１（ｍ，２Ｈ），８．４０（ｂｒｓ，１Ｈ）．
１２３		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．０２（ｔ，Ｊ＝７．２Ｈｚ，３Ｈ），１．６３（ｄｄ，Ｊ＝７．６，５．２Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝５．４Ｈｚ，１Ｈ），２．１４（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．５４－２．６７（ｍ，２Ｈ），２．５７（ｓ，３Ｈ），３．７８（ｓ，３Ｈ），４．５０（ｄｄ，Ｊ＝１９．２，９．６Ｈｚ，２Ｈ），７．２５－７．３１（ｍ，１Ｈ），７．３１－７．３８（ｍ，２Ｈ），７．４１－７．４７（ｍ，２Ｈ），７．８６（ｔ，Ｊ＝２．２Ｈｚ，１Ｈ），７．９８－８．０８（ｍ，３Ｈ），８．２０（ｂｒｓ，１Ｈ）．
１２４		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．０４（ｔ，Ｊ＝７．８Ｈｚ，３Ｈ），１．５８－１．６７（ｍ，１Ｈ），１．８９（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０３－２．０９（ｍ，１Ｈ），２．５５－２．６６（ｍ，２Ｈ），２．５８（ｓ，３Ｈ），４．５０（ｄｄ，Ｊ＝１４．６，９．４Ｈｚ，２Ｈ），６．９５－７．０３（ｍ，２Ｈ），７．２６－７．３２（ｍ，１Ｈ），７．３３－７．４８（ｍ，６Ｈ），７．５７（ｂｒｓ，１Ｈ），８．００（ｓ，１Ｈ）．

【０３０７】

＊実施例１２５－１２６はカルボン酸Ｐｒｅｐ１７－４と任意のアミンとを、実施例１の手法により合成した。

【０３０８】

【表３４】

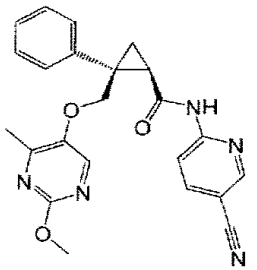
実施例	構造式	NMR及び／又はMS
１２５		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ppm）：１．４７（dd，J＝５．２，８．０Hz，１H），１．８３（dd，J＝５．２，６．４Hz，１H），２．１２（dd，J＝６．４，８．０Hz，１H），２．２３（s，３H），２．５４（s，３H），４．０３（s，３H），４．２１（d，J＝９．４Hz，１H），４．２７（d，J＝９．４Hz，１H），６．９３－６．９９（m，２H），７．２８－７．４５（m，３H），７．８７（s，１H），８．１４（d，J＝３．２Hz，１H），８．１７（dd，J＝４．４，９．６Hz，１H），８．６０（brs，１H）．
１２６		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ppm）：１．４９（dd，J＝５．６，８．０Hz，１H），１．８５（dd，J＝５．６，６．２Hz，１H），２．１２（dd，J＝６．２，８．０Hz，１H），２．２２（s，３H），２．５４（s，３H），３．９８（s，３H），４．２７（d，J＝９．６Hz，１H），４．３２（d，J＝９．６Hz，１H），６．９３－７．００（m，２H），７．２９－７．３３（m，２H），７．３８－７．４０（m，１H），７．８９（s，１H），７．９６（brs，１H），８．２４（brd，１H），８．３６（dd，J＝１．４，４．６Hz，１H），８．５７（d，J＝２．０Hz，１H）． MS［M＋H］$^+$＝４０５

【０３０９】

実施例１２７

（１R，２S）－N－（５－シアノピリジン－２－イル）－２－［（２－メトキシ－４－メチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド（１２７）の合成

【化６１】



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【０３１０】

カルボン酸Ｐｒｅｐ２１を実施例１と同様の手法でアミド化することにより合成した。

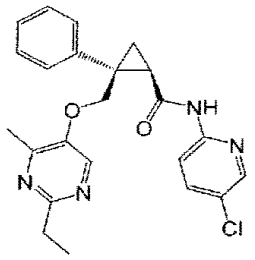
ＭＳ［Ｍ＋Ｈ］$^+$＝４１６

【０３１１】

実施例１２８

（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－［（２－エチル－４－メチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド（１２８）の合成

【化６２】



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【０３１２】

製造例２２のカルボン酸Ｐｒｅｐ２２を実施例１と同様の手法でアミド化することにより合成した。

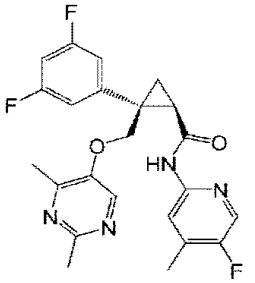
ＭＳ［Ｍ＋Ｈ］$^{+}$＝４２３

【０３１３】

実施例１２９

（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）シクロプロパンカルボキサミド（１２９）の合成

【化６３】



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【０３１４】

カルボン酸Ｐｒｅｐ１６－７（１．０ｇ）のＤＭＦ溶液（２０ｍｌ）に２－アミノ－５－フルオロ－４－ピコリン（４１５ｍｇ）、ＨＡＴＵ（１．７１ｇ）、Ｎ，Ｎ－ジイソプロピルエチルアミン（１．５６ｍｌ）を加えた。室温で２日間攪拌した後、反応液に水を加え、ジエチルエーテルで抽出した。有機層を無水硫酸マグネシウムで乾燥し濾過した。濾液を減圧濃縮し、残渣をＮＨ－シリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ^{TM} ｃｏｌｕｍｎ，溶出溶媒：ｎ－ヘプタン：酢酸エチル＝４：１→１：２）×２で精製して標記化合物（８８０ｍｇ）を得た。

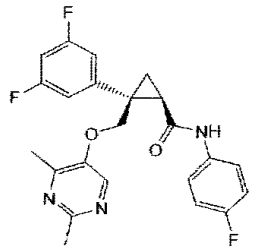
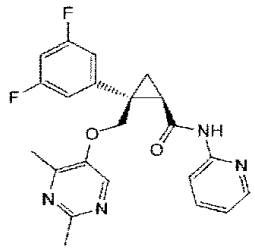
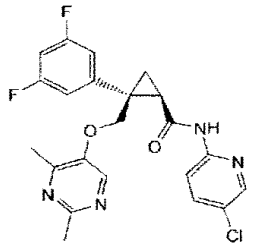
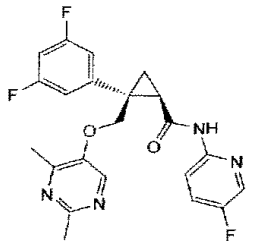
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：１．６０－１．６３（ｍ，１Ｈ），１．９２（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０７（ｂｒｄｔ，Ｊ＝８．０Ｈｚ，１Ｈ），２．２２（ｓ，３Ｈ），２．２７（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），４．４１（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），４．４９（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．７６（ｔ，Ｊ＝８．８Ｈｚ，１Ｈ），６．９７－６．９９（ｂｒｄ，２Ｈ），７．９０（ｄ，Ｊ＝６．４Ｈｚ，１Ｈ），７．９９（ｓ，２Ｈ），８．２７（ｂｒｄｓ，１Ｈ）．

【０３１５】

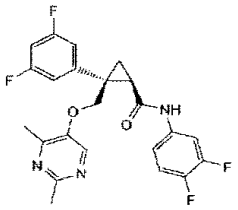
＊実施例１３０－１３８はカルボン酸Ｐｒｅｐ１６－７と任意のアミンとを、実施例１の手法により合成した。

【０３１６】

【表３５－１】

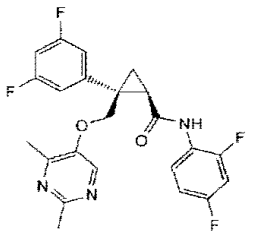
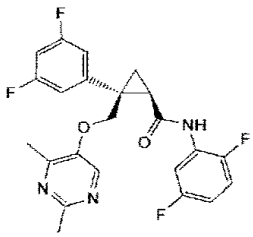
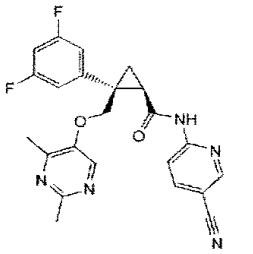
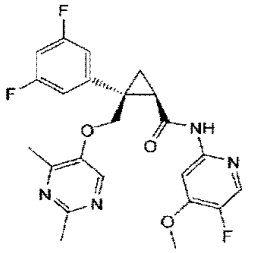
実施例	構造式	NMR（４００MHz，CDCl$_3$）及び／又はMS
１３０		^{1}H－NMR δ（ppm）：1．６０（ｄｄ，Ｊ＝5．２Ｈｚ、８．０Ｈｚ，１Ｈ），１．９２（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０３（ｂｒｄｔ，Ｊ＝７．６Ｈｚ，１Ｈ），２．２５（ｓ，３Ｈ），２．５７（ｓ，３Ｈ），４．４６（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５１（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），６．７５（ｔ，Ｊ＝６．８Ｈｚ，１Ｈ），６．９７－７．０１（ｍ，４Ｈ），７．３８－７．４０（ｍ，２Ｈ），７．６２（ｓ，１Ｈ），８．０１（ｓ，１Ｈ）． MS［M＋H］$^+$＝４２８
１３１		^{1}H－NMR δ（ｐｐｍ）：１．５９－１．６２（ｍ，１Ｈ），１．９４（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１１（ｂｒｄｔ，Ｊ＝８．０Ｈｚ，１Ｈ），２．２１（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），４．４１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５０（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．７６（ｔ，Ｊ＝６．８Ｈｚ，１Ｈ），６．９８－７．０４（ｍ，３Ｈ），７．６５（ｔ，Ｊ＝７．６Ｈｚ，１Ｈ），７．９９－８．０３（ｍ，２Ｈ），８．２６（ｄ，Ｊ＝４．０Ｈｚ，１Ｈ），８．４７（ｓ，１Ｈ）． MS［M＋H］$^+$＝４１１
１３２		^{1}H－NMR δ（ｐｐｍ）：１．６２（ｄｄ，Ｊ＝５．６Ｈｚ、８．４Ｈｚ，１Ｈ），１．９３（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１０（ｂｒｄｔ，Ｊ＝７．６Ｈｚ，１Ｈ），２．２２（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），４．４０（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），４．４９（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），６．７６（ｔ，Ｊ＝８．８Ｈｚ，１Ｈ），６．９６－７．００（ｍ，２Ｈ），７．６１（ｄｄ，Ｊ＝２．８Ｈｚ，９．２Ｈｚ，１Ｈ），７．９９－８．０２（ｍ，２Ｈ），８．２１（ｄ，Ｊ＝２．０Ｈｚ，１Ｈ），８．４５（ｓ，１Ｈ）． MS［M＋H］$^+$＝４４５
１３３		^{1}H－NMR δ（ｐｐｍ）：１．６１－１．６４（ｍ，１Ｈ），１．９３（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０９（ｂｒｄｔ，Ｊ＝８．０Ｈｚ，１Ｈ），２．２２（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），４．４０（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４９（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．７４－６．７９（ｍ，１Ｈ），６．９８（ｄ，Ｊ＝６．０Ｈｚ，２Ｈ），７．３６－７．４１（ｍ，１Ｈ），７．９９（ｓ，１Ｈ），８．０５（ｄｄ，Ｊ＝３．６Ｈｚ，９．２Ｈｚ，１Ｈ）、８．１１（ｄ，Ｊ＝２．８Ｈｚ，１Ｈ），８．３５（ｂｒｄｓ，１Ｈ）． MS［M＋H］$^+$＝４２９

【表３５－２】

１３４		^{1}H－NMR δ（ｐｐｍ）：１．６１－１．６３（ｍ，１Ｈ），１．９２（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０２（ｄｄ，Ｊ＝５．６Ｈｚ，８．４Ｈｚ，１Ｈ），２．２５（ｓ，３Ｈ），２．５８（ｓ，３Ｈ），４．４５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．７５（ｔ，Ｊ＝８．８Ｈｚ，１Ｈ），６．９６－７．１２（ｍ，４Ｈ），７．４７－７．５３（ｍ，１Ｈ），７．６２（ｓ，１Ｈ），８．０１（ｓ，１Ｈ）．ＭＳ［Ｍ＋Ｈ］$^+$＝４４６

【０３１７】

【表３６】

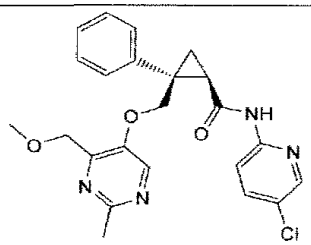
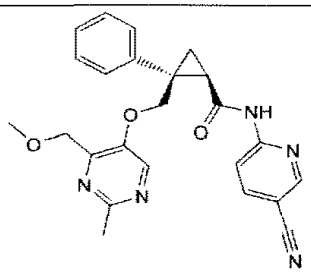
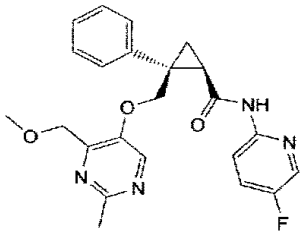
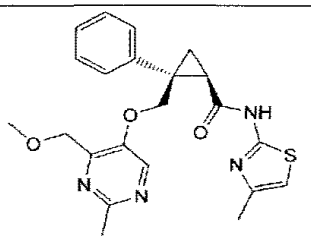
実施例	構造式	NMR及び／又はMS
１３５		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６３（ｄｄ，Ｊ＝５．６Ｈｚ、８．４Ｈｚ，１Ｈ），１．９３（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０９（ｄｄ，Ｊ＝５．６Ｈｚ，８．０Ｈｚ，１Ｈ），２．２６（ｓ，３Ｈ），２．５７（ｓ，３Ｈ），４．４４（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ）、４．５０（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．７４－７．０１（ｍ，５Ｈ），７．５９（ｂｒｄｓ，１Ｈ），８．００－８．０７（ｍ，２Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４４６
１３６		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６５（ｄｄ，Ｊ＝５．２Ｈｚ、８．４Ｈｚ，１Ｈ），１．９４（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１０（ｄｄ，Ｊ＝５．６Ｈｚ，８．０Ｈｚ，１Ｈ），２．２４（ｓ，３Ｈ），２．５７（ｓ，３Ｈ），４．４３（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ）、４．５１（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），６．７０－６．７９（ｍ，２Ｈ），６．９６－７．０８（ｍ，３Ｈ），７．７３（ｂｒｄｓ，１Ｈ），７．９６－８．０１（ｍ，２Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４４６
１３７		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６７（ｄｄ，Ｊ＝５．２Ｈｚ、８．４Ｈｚ，１Ｈ），１．９６（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．１５（ｂｒｄｔ，Ｊ＝７．２Ｈｚ，１Ｈ），２．２１（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），４．３９（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），４．４８（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），６．７７（ｔ，Ｊ＝８．４Ｈｚ，１Ｈ），６．８０－７．０２（ｍ，２Ｈ），７．８９（ｄｄ，Ｊ＝２．０Ｈｚ，８．８Ｈｚ，１Ｈ），７．９９（ｓ，１Ｈ），８．１８（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），８．５５－８．５８（ｍ，２Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４３６
１３８		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６３（ｄｄ，Ｊ＝５．８，８．０Ｈｚ，１Ｈ），１．９２（ｔ，Ｊ＝５．８Ｈｚ，１Ｈ），２．０８（ｄｄ，Ｊ＝５．８，８．０Ｈｚ，１Ｈ），２．２４（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），３．８７（ｓ，３Ｈ），４．４１（ｄ，Ｊ＝９．８Ｈｚ，１Ｈ），４．５０（ｄ，Ｊ＝９．８Ｈｚ，１Ｈ），６．７７（ｔｔ，Ｊ＝２．４，８．８Ｈ，１Ｈ），６．９７－７．０２（ｍ，２Ｈ），７．７８（ｄ，Ｊ＝６．８Ｈｚ，１Ｈ），７．９７（ｄ，Ｊ＝２．４Ｈｚ，１Ｈ），８．００（ｓ，１Ｈ），８．２８（ｂｒｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４５９

【０３１８】

＊実施例１３９－１４２は、カルボン酸Ｐｒｅｐ２３と任意のアミンを、実施例１と同様の手法により合成した。

【０３１９】

【表３７】

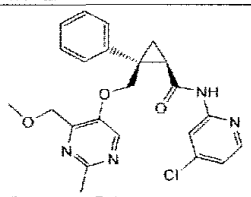
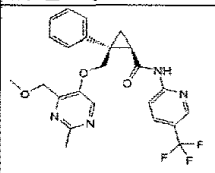
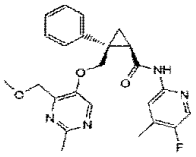
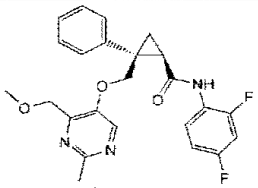
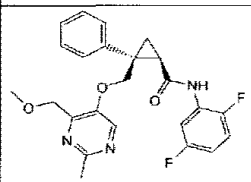
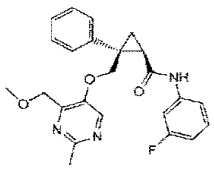
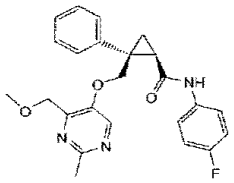
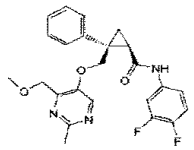
実施例	構造式	NMR及び／又はMS
１３９		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６４（ｄｄ，Ｊ＝８．０Ｈｚ，５．２Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１２（ｂｒｄｔ，Ｊ＝８．０Ｈｚ，１Ｈ），２．６２（ｓ，３Ｈ），３．２８（ｓ，３Ｈ），４．２７－４．５５（ｍ，４Ｈ），７．２６－７．４６（ｍ，６Ｈ），７．６２（ｄｄ，Ｊ＝２．４Ｈｚ，８．８Ｈｚ，１Ｈ），８．０５－８．０８（ｍ，２Ｈ），８．２３（ｄ，Ｊ＝２．４Ｈｚ，１Ｈ），８．２９（ｂｒｄｓ，１Ｈ）． ＭＳ［Ｍ＋Ｎａ］$^+$＝４６１
１４０		ＭＳ［Ｍ＋Ｎａ］$^+$＝４５２
１４１		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６２－１．６４（ｍ，１Ｈ），１．９０（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１２（ｂｒｄｔ，Ｊ＝７．６Ｈｚ，１Ｈ），２．６２（ｓ，３Ｈ），３．２７（ｓ，３Ｈ），４．２７－４．５５（ｍ，４Ｈ），７．３０－７．４６（ｍ，６Ｈ），８．０８－８．１２（ｍ，３Ｈ），８．３７（ｂｒｄｓ，１Ｈ）． ＭＳ［Ｍ＋］$^+$＝４２３
１４２		ＭＳ［Ｍ＋Ｈ］$^+$＝４２５

【０３２０】

＊実施例１４３－１５０は、カルボン酸Ｐｒｅｐ２３と任意のアミンを、実施例５１と同様の手法により合成した。

【０３２１】

【表３８】

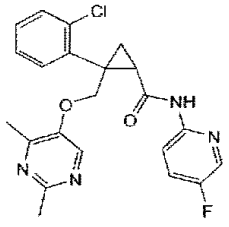
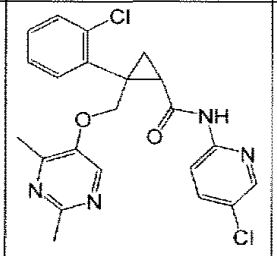
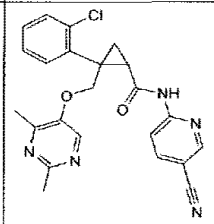
実施例	構造式、MS	実施例	構造式、MS	実施例	構造式、MS
143	 [M+H]$^+$=439	144	 [M+H]$^+$=473	145	 [M+H]$^+$=437
146	 [M+H]$^+$=440	147	 [M+H]$^+$=440	148	 [M+H]$^+$=422
149	 [M+H]$^+$=422	150	 [M+H]$^+$=440		

【０３２２】

＊実施例１５１－１５３は、カルボン酸Ｐｒｅｐ２４と任意のアミンとを、実施例１と同様の手法により合成した。

【０３２３】

【表３９】

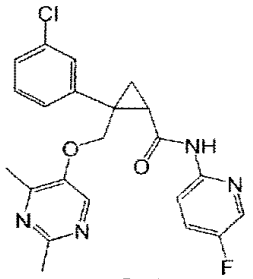
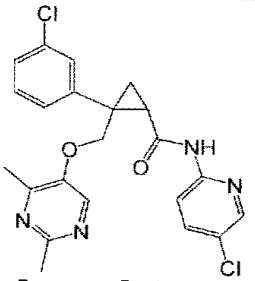
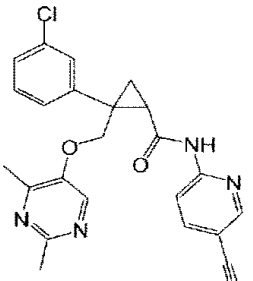
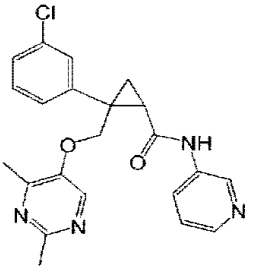
実施例	構造式、MS	実施例	構造式、MS	実施例	構造式、MS
151	 [M+H]$^+$=427	152	 [M+H]$^+$=443	153	 [M+H]$^+$=434

【０３２４】

＊実施例１５４－１５７は、カルボン酸Ｐｒｅｐ２５と任意のアミンとを、実施例１と同様の手法により合成した。

【０３２５】

【表４０】

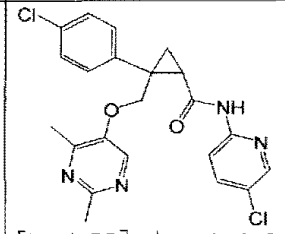
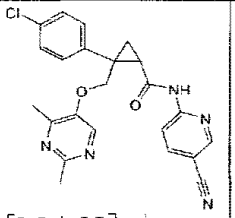
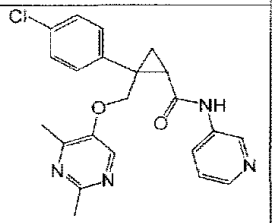
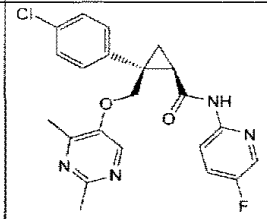
実施例	構造式、ＭＳ	実施例	構造式、ＭＳ
１５４	 [M+H]$^+$＝４２７	１５５	 [M+H]$^+$＝４３０
１５６	 [M+H]$^+$＝４３４	１５７	 [M+H]$^+$＝４０９

【０３２６】

＊実施例１５８－１６１は、カルボン酸Ｐｒｅｐ２６と任意のアミンを、実施例１と同様の手法で縮合することにより合成した。実施例１６１はラセミ生成物をキラル分取した（Ｃｈｉｒａｌｐａｋ－ＩＡ（ヘキサン：エタノール＝７０：３０、１５ｍＬ／ｍｉｎ、２５４ｎｍ、ｒｔ）１０．５ｍｉｎ（（＋）－体）、１３．０ｍｉｎ（（－）－体、標的化合物）。

【０３２７】

【表４１】

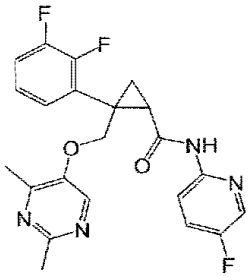
実施例	構造式、ＭＳ	実施例	構造式、ＭＳ	実施例	構造式、ＭＳ
１５８	 [Ｍ＋Ｈ]$^{+}$＝４４３	１５９	 [Ｍ＋Ｈ]$^{+}$＝４３４	１６０	 [Ｍ＋Ｈ]$^{+}$＝４０９
１６１		^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：１．５９（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０７（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．２１（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），４．４０（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４７（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．３４－７．７２（ｍ，５Ｈ），７．９７（ｓ，１Ｈ），８．０７（ｄｄ，Ｊ＝９．２，４．０Ｈｚ，１Ｈ），８．１２（ｄ，Ｊ＝２．８Ｈｚ，１Ｈ），８．３６（ｂｒｓ，１Ｈ）．		

【０３２８】

実施例１６２

２－（２，３－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド（１６２）の合成

【化６４】



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【０３２９】

カルボン酸Ｐｒｅｐ２７を、実施例５１と同様の手法でアミド化することにより合成した。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：１．５３（ｄｄ，Ｊ＝５．２Ｈｚ，８．０Ｈｚ，１Ｈ），１．９４（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１６－２．２２（ｍ，４Ｈ），２．５４（ｓ，３Ｈ），４．３４（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４２（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．０６－７．４２（ｍ，４Ｈ），７．９３（ｓ，１Ｈ），８．０９－８．１４（ｍ，２Ｈ），８．３４（ｂｒｄｓ，１Ｈ）．

ＭＳ［Ｍ＋Ｈ］$^{+}$＝４２９

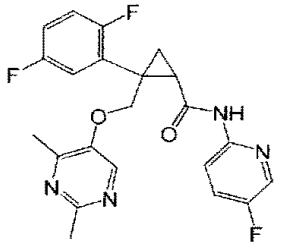
【０３３０】

実施例１６３

２－（２，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキ

シメチル］－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド（１６３）の合成

【化６５】



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【０３３１】

カルボン酸Ｐｒｅｐ２８を、実施例５１と同様の手法でアミド化することにより合成した。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：１．５３（ｄｄ，Ｊ＝５．２Ｈｚ、８．０Ｈｚ，１Ｈ），１．９４（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１７（ｂｒｄｔ，Ｊ＝７．６Ｈｚ，１Ｈ），２．２２（ｓ，３Ｈ），２．５４（ｓ，３Ｈ），４．３２（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４０（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．９７－７．４３（ｍ，４Ｈ），７．９３（ｓ，１Ｈ），８．１０－８．１４（ｍ，２Ｈ），８．３４（ｂｒｄｓ，１Ｈ）．

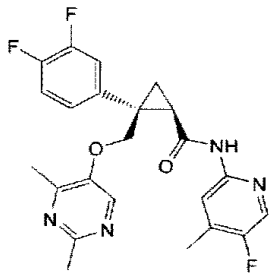
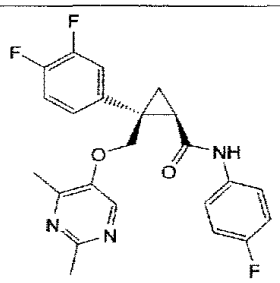
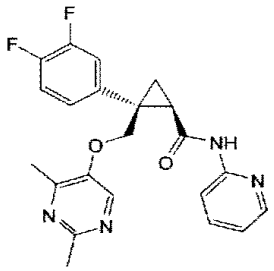
ＭＳ［Ｍ＋Ｈ］$^{+}$＝４２９

【０３３２】

＊実施例１６４－１７２は、カルボン酸（Ｐｒｅｐ２９）と任意のアミンを、実施例５２と同様の手法で縮合して合成した。

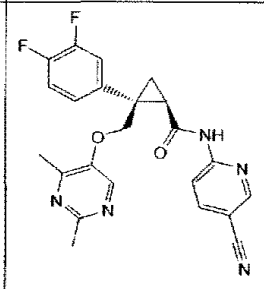
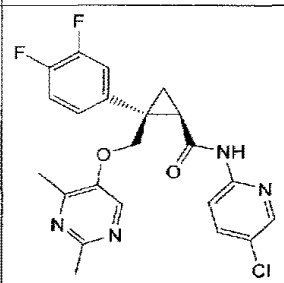
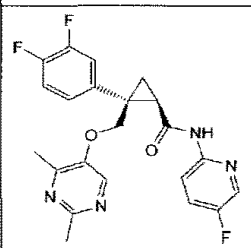
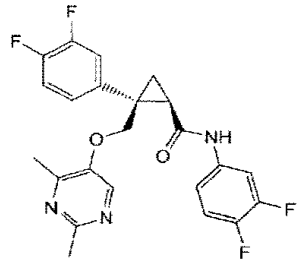
【０３３３】

【表４２】

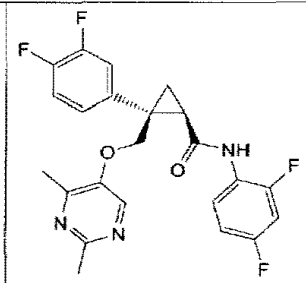
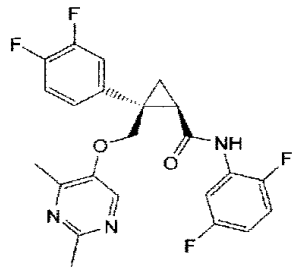
実施例	構造式	NMR及び／又はMS
１６４		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ppm）：１．５８（ｄｄ，Ｊ＝５．２Ｈｚ，８．４Ｈｚ、１Ｈ），１．９１（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０５（ｂｒｄｔ，Ｊ＝８．０Ｈｚ，１Ｈ），２．２１（ｓ，３Ｈ），２．２６（ｓ，３Ｈ），２．５５（ｓ，３Ｈ），４．４０（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），４．４６（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．１０－７．２３（ｍ，３Ｈ），７．９１（ｄ，Ｊ＝５．２Ｈｚ，１Ｈ），７．９６－７．９８（ｍ，２Ｈ），８．４９（ｂｒｄｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４４３
１６５		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ppm）：１．５７（ｄｄ，Ｊ＝５．２Ｈｚ，８．０Ｈｚ，１Ｈ），１．９０（ｔ，Ｊ＝４．８Ｈｚ，１Ｈ），２．００（ｂｒｄｔ，Ｊ＝８．０Ｈｚ，１Ｈ），２．２５（ｓ，３Ｈ），２．５７（ｓ，３Ｈ），４．４５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４８（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），６．９７－７．４１（ｍ，７Ｈ），７．５８（ｓ，１Ｈ），７．８０（ｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４２８
１６６		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ppm）：１．５８（ｄｄ，Ｊ＝５．２Ｈｚ，８．４Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０８（ｂｒｄｔ，１Ｈ），２．２１（ｓ，３Ｈ），２．５５（ｓ，３Ｈ），４．４０（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４６（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），７．０１－７．３２（ｍ，５Ｈ），７．６３－７．６７（ｍ，１Ｈ），７．９８（ｓ，１Ｈ），８．０３（ｄ，Ｊ＝８．４Ｈｚ，１Ｈ），８．２６（ｄ，Ｊ＝４．０Ｈｚ，１Ｈ），８．４４（ｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４１１

【０３３４】

【表４３－１】

実施例	構造式	NMR及び／又はMS
１６７		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６３－１．６８（ｍ，１Ｈ），１．９４（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１２（ｂｒｄｔ，Ｊ＝７．６Ｈｚ，１Ｈ），２．２１（ｓ，３Ｈ），２．５８（ｓ，３Ｈ），４．３８（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４４（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．１３－７．３２（ｍ，４Ｈ），７．９０（ｄｄ，Ｊ＝２．４Ｈｚ、９．２Ｈｚ，１Ｈ），７．９７（ｓ，１Ｈ），８．１９（ｓ，１Ｈ），８．５１（ｓ，１Ｈ），８．５６（ｄ，Ｊ＝２．０Ｈｚ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４３６
１６８		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．５８－１．６１（ｍ，１Ｈ），１．９１（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０７（ｂｒｄｔ，Ｊ＝６．０Ｈｚ，１Ｈ），２．２２（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），４．３８（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），４．４５（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），７．１２－７．３１（ｍ，３Ｈ），７．６２（ｄｄ，Ｊ＝２．４Ｈｚ，８．８Ｈｚ，１Ｈ），７．９７（ｓ，１Ｈ），８．０３（ｄ，Ｊ＝８．８Ｈｚ，１Ｈ），８．２２（ｄ，Ｊ＝２．８Ｈｚ，１Ｈ），８３３（ｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４４５
１６９		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．５８－１．６１（ｍ，１Ｈ），１．９１（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０７（ｂｒｄｔ，Ｊ＝８．０Ｈｚ，１Ｈ），２．２１（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），４．３９（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．１２－７．４１（ｍ，４Ｈ），７．９７（ｓ，１Ｈ），８．０４－８．０８（ｍ，１Ｈ），８．１２（ｄ，Ｊ＝２．４Ｈｚ，１Ｈ）８．３０（ｂｒｄｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４２９
１７０		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．５８－１．６１（ｍ，１Ｈ），１．９０（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），１．９１（ｄｄ，Ｊ＝６．０Ｈｚ，８．４Ｈｚ，１Ｈ），２．２５（ｓ，３Ｈ），２．５７（ｓ，３Ｈ），４．４４（ｄ，Ｊ＝１０Ｈｚ，１Ｈ），４．４７（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．０４－７．３１（ｍ，５Ｈ），７．４８－７．５３（ｍ，１Ｈ），７．５７（ｓ，１Ｈ），８．００（ｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４４６

【表４３－２】

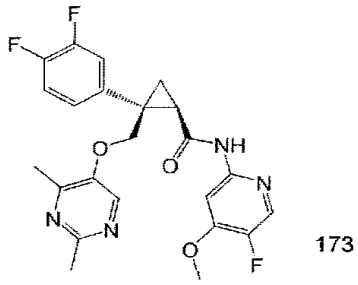
１７１		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．５８－１．６２（ｍ，１Ｈ），１．９１（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０６（ｄｄ，Ｊ＝６．０Ｈｚ，８．０Ｈｚ，１Ｈ），２．２６（ｓ，３Ｈ），２．５７（ｓ，３Ｈ），４．４３（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ）、４．４７（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），６．８１－６．９１（ｍ，２Ｈ），７．１１－７．３２（ｍ，３Ｈ），７．５９（ｂｒｄｓ，１Ｈ），７．９９－８．０８（ｍ，２Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４４６
１７２		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６２（ｄｄ，Ｊ＝５．６Ｈｚ、８．４Ｈｚ，１Ｈ），１．９２（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０８（ｄｄ，Ｊ＝５．６Ｈｚ，８．４Ｈｚ，１Ｈ），２．２４（ｓ，３Ｈ），２．５７（ｓ，３Ｈ），４．４２（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ）、４．４７（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），６．７１－６．７５（ｍ，１Ｈ），７．０２－７．３２（ｍ，４Ｈ），７．７３（ｂｒｄｓ，１Ｈ），７．９９（ｂｒｄｍ，２Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４４６

【０３３５】

実施例１７３

（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシピリジン－２－イル）シクロプロパンカルボキサミド（１７３）の合成

【化６６】



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【０３３６】

Ｐｒｅｐ２９から実施例７３に準じて合成した。

^{1}Ｈ－ＮＭＲ（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６０（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），１．９０（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０６（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），２．２４（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），３．８８（ｓ，３Ｈ），４．４０（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４６（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．１２－７．３２（ｍ，３Ｈ），７．７９（ｄ，Ｊ＝６．８Ｈｚ，１Ｈ），７．９８－７．９９（ｍ，２Ｈ），８．２５（ｂｒｓ，１Ｈ）．

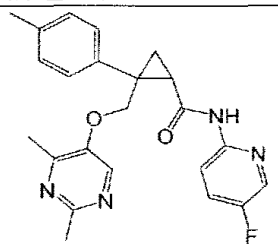
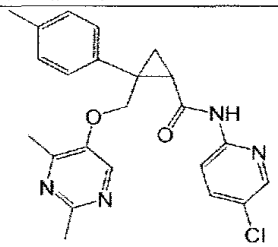
ＭＳ［Ｍ＋Ｈ］$^+$＝４５９

【０３３７】

＊実施例１７４－１７５は、カルボン酸Ｐｒｅｐ３０と任意のアミンを実施例４６の手法により縮合し合成した。

【０３３８】

【表４４】

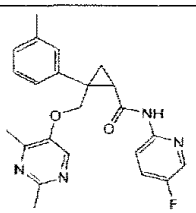
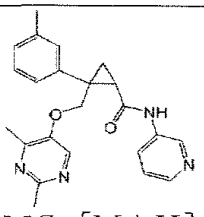
実施例	構造式、ＭＳ	実施例	構造式、ＭＳ
１７４	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４０７	１７５	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４２３

【０３３９】

＊実施例１７６－１７７は製造例３１のカルボン酸Ｐｒｅｐ３１と任意のアミンを実施例１の手法により縮合し合成した。

【０３４０】

【表４５】

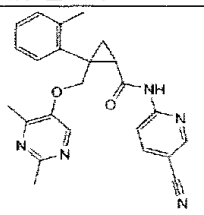
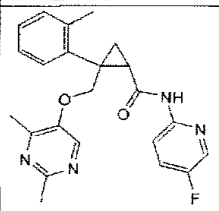
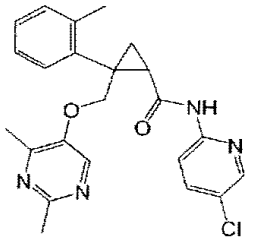
実施例	構造式、ＭＳ	実施例	構造式、ＭＳ
１７６	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４０７	１７７	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝３８９

【０３４１】

＊実施例１７８－１８０は製造例３２のカルボン酸Ｐｒｅｐ３２と任意のアミンを実施例１の手法により縮合し合成した。

【０３４２】

【表４６】

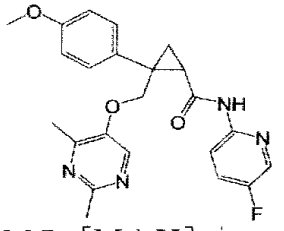
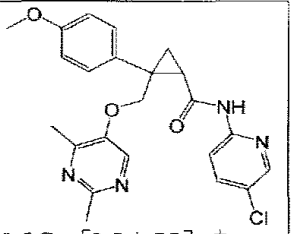
実施例	構造式、ＭＳ	実施例	構造式、ＭＳ
１７８	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４１４	１７９	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４０７
１８０		^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：１．４９－１．５５（ｍ，１Ｈ），１．９７（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１６（ｄｄ，Ｊ＝８．２，５．８Ｈｚ，１Ｈ），２．２１（ｓ，３Ｈ），２．５３（ｓ，３Ｈ），２．５５（ｓ，３Ｈ），４．４５（ｄｄ，Ｊ＝１１．０，９．４Ｈｚ，２Ｈ），７．１７－７．３１（ｍ，４Ｈ），７．４２－７．４８（ｍ，１Ｈ），７．８２（ｂｒｓ，１Ｈ），７．９３（ｓ，１Ｈ），８．１４（ｂｒｄ，Ｊ＝８．８Ｈｚ，１Ｈ），８．３６（ｄ，Ｊ＝３．６Ｈｚ，１Ｈ），８．５８（ｄ，Ｊ＝２．４Ｈｚ，１Ｈ）．		

【０３４３】

＊実施例１８１－１８２は製造例３３のカルボン酸Ｐｒｅｐ３３と任意のアミンを実施例４５の手法により縮合し合成した。

【０３４４】

【表４７】

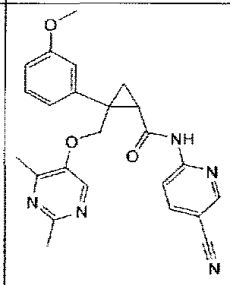
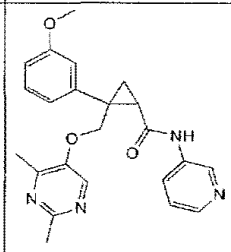
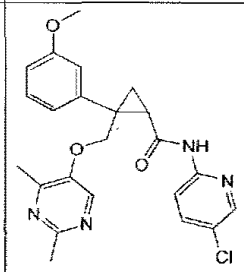
実施例	構造式、ＭＳ	実施例	構造式、ＭＳ
１８１	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４２３	１８２	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４３９

【０３４５】

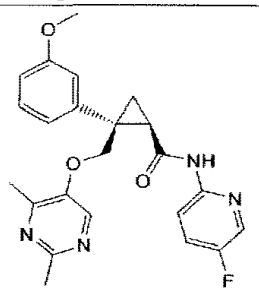
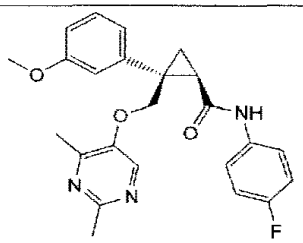
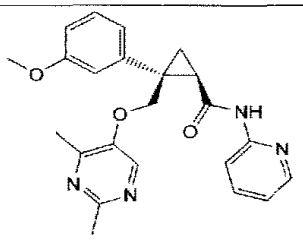
＊実施例１８３－１９０は製造例３４のカルボン酸Ｐｒｅｐ３４と任意のアミンを実施例１の手法により縮合し合成した。実施例１８６－１９０はキラル分取した。

【０３４６】

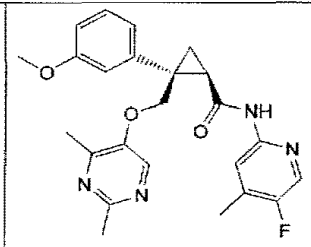
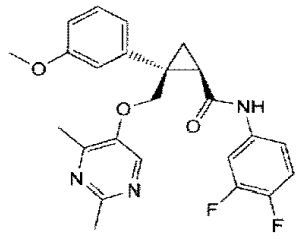
【表４８－１】

実施例	構造式	NMR及び／又はMS
１８３		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６８（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），１．９２（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．１６（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），２．２１（ｓ，３Ｈ），２．５５（ｓ，３Ｈ），３．８３（ｓ，３Ｈ），４．３７（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５０（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．８５（ｄｄｄ，Ｊ＝０．８，２．６，８．０Ｈｚ，１Ｈ），７．００－７．０５（ｍ，２Ｈ），７．２９（ｔ，Ｊ＝８．０Ｈｚ，１Ｈ），７．８９（ｄｄ，Ｊ＝２．２，８．８Ｈｚ，１Ｈ），７．９６（ｓ，１Ｈ），８．２１（ｄ，Ｊ＝８．８Ｈｚ，１Ｈ），８．４８（ｂｒｓ，１Ｈ），８．５６（ｄｄ，Ｊ＝０．８，２．２Ｈｚ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４３０
１８４		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６３（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），１．９０（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．１２（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），２．２４（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），３．８１（ｓ，３Ｈ），４．４５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５４（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．８３（ｄｄ，Ｊ＝２．０，８．４Ｈｚ，１Ｈ），７．０１－７．０４（ｍ，２Ｈ），７．２３－７．３０（ｍ，２Ｈ），７．８７（ｂｒｓ，１Ｈ），７．９９（ｓ，１Ｈ），８．１０（ｂｒｄ，１Ｈ），８．３４（ｄ，Ｊ＝４．４Ｈｚ，１Ｈ），８．５３（ｄ，Ｊ＝２．０Ｈｚ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４０５
１８５		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６３（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），１．８９（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．１３（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），２．２２（ｓ，３Ｈ），２．５５（ｓ，３Ｈ），３．８２（ｓ，３Ｈ），４．３８（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．８４（ｄｄｄ，Ｊ＝０．８，２．４，８．４Ｈｚ，１Ｈ），７．０１－７．０６（ｍ，２Ｈ），７．２６－７．３０（ｍ，１Ｈ），７．６１（ｄｄ，Ｊ＝２．４，８．８Ｈｚ，１Ｈ），７．９６（ｓ，１Ｈ），８．０４（ｄ，Ｊ＝８．８Ｈｚ，１Ｈ），８．２２（ｄｄ，Ｊ＝０．８，２．４Ｈｚ，１Ｈ），８．３２（ｂｒｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４３９

【表４８－２】

１８６		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６２（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），１．８９（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．１２（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），２．２２（ｓ，３Ｈ），２．５５（ｓ，３Ｈ），３．８２（ｓ，３Ｈ），４．３９（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．８４（ｄｄｄ，Ｊ＝０．８，２．６，８．０Ｈｚ，１Ｈ），７．０１－７．０６（ｍ，２Ｈ），７．２９（ｄ，Ｊ＝８．０Ｈｚ，１Ｈ），７．３８（ｄｄｄ，Ｊ＝２．８，７．６，９．２Ｈｚ，１Ｈ），７．９７（ｓ，１Ｈ），８．０７（ｄｄ，Ｊ＝４．０，９．２Ｈｚ，１Ｈ），８．１２（ｄ，Ｊ＝２．８Ｈｚ，１Ｈ），８．２８（ｂｒｓ，１Ｈ）．ＭＳ［Ｍ＋Ｈ］$^+$＝４２３
１８７		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．５６（ｄｄ，Ｊ＝８．２，５．２Ｈｚ，１Ｈ）１．８５（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０６（ｄｄ，Ｊ＝８．０，６．０Ｈｚ、１Ｈ），２．２５（ｓ，３Ｈ），２．５５（ｓ，３Ｈ），３．８０（ｓ，３Ｈ），４．４４（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．８０－６．８３（ｍ，１Ｈ），６．９３－７．０２（ｍ，４Ｈ），７．２３－７．２７（ｍ，１Ｈ），７．３５－７．４１（ｍ，２Ｈ）７．９９（ｓ，１Ｈ），７．９４－８．００（ｂｒｓ，１Ｈ）．
１８８		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６１（ｄｄ，Ｊ＝８．２，５．２Ｈｚ，１Ｈ）１．９０（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１２－２．１６（ｍ，１Ｈ），２．２１（ｓ，３Ｈ），２．５５（ｓ，３Ｈ），３．８１（ｓ，３Ｈ），４．４１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５４（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．８２－６．８５（ｍ，１Ｈ），６．９４－７．０５（ｍ，３Ｈ），７．２４－７．２９（ｍ，１Ｈ），７．６１－７．６５（ｍ，１Ｈ）７．９９（Ｓ，１Ｈ），８．０２－８．０５（ｍ，１Ｈ），８．１９－８．２１（ｍ，１Ｈ），８．８８（ｂｒｓ，１Ｈ）．

【表４８－３】

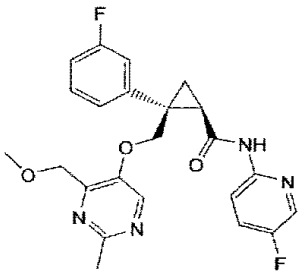
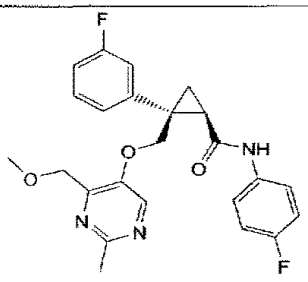
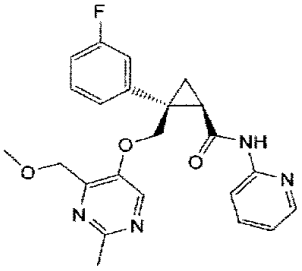
１８９		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６１（ｄｄ，Ｊ＝８．２，５．２Ｈｚ，１Ｈ）１．８８（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．１２（ｄｄ，Ｊ＝８．０，６．０Ｈｚ、１Ｈ），２．２２（ｓ，３Ｈ），２．２６（ｓ，３Ｈ），２．５５（ｓ，３Ｈ），３．８１（ｓ，３Ｈ），４．４１（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），４．５３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．８１－６．８５（ｍ，１Ｈ），６．９９－７．０４（ｍ，２Ｈ），７．２５－７．２９（ｍ，１Ｈ），７．９１－７．９５（ｍ，２Ｈ），７．９９（ｓ，１Ｈ），８．７０（ｂｒｓ，１Ｈ）．
１９０		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．５９－１．６２（ｍ，１Ｈ），１．８８（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０４（ｄｄ，Ｊ＝８．２，５．６Ｈｚ，１Ｈ），２．２４（ｓ，３Ｈ），２．５７（ｓ，３Ｈ），３．８２（ｓ，３Ｈ），４．４３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．８１－６．８５（ｍ，１Ｈ），６．９９－７．１２（ｍ，４Ｈ），７．２５－７．３０（ｍ，１Ｈ），７．４８－７．５４（ｍ，１Ｈ），７．６０（ｂｒ，１Ｈ），７．９９（ｓ，１Ｈ）．

【０３４７】

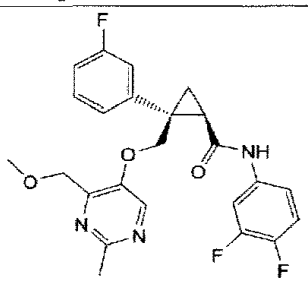
＊実施例１９１－２０１はカルボン酸Ｐｒｅｐ３５と任意のアミンを縮合し合成した。尚、縮合の手法は、実施例１９３－１９９は実施例５１の手法、実施例２００－２０１は実施例１の手法にそれぞれ準じて行った。

【０３４８】

【表４９－１】

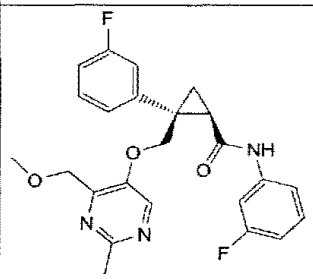
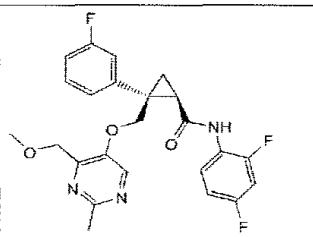
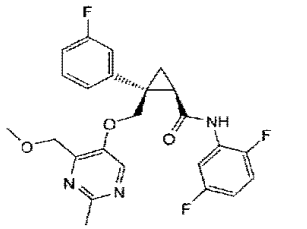
実施例	構造式	NMR及び／又はMS
１９１		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６３（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９２（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１２（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．６３（ｓ，３Ｈ），３．３０（ｓ，３Ｈ），４．２９（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），４．４４（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），４．４６（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．０１（ｔｄｄ，Ｊ＝８．０，２．４，１．２Ｈｚ，１Ｈ），７．１８－７．２４（ｍ，２Ｈ），７．３４（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），７．４０（ｄｄｄ，Ｊ＝１０．４，９．２，２．８Ｈｚ，１Ｈ），８．０８（ｄｄ，Ｊ＝９．２，４．０Ｈｚ，１Ｈ），８．１１（ｓ，１Ｈ），８．１３（ｄ，Ｊ＝２．４Ｈｚ，１Ｈ），８．３８（ｂｒｓ，１Ｈ）．
１９２		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．５９（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９０（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０６（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．６１（ｓ，３Ｈ），３．３０（ｓ，３Ｈ），４．３４（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４１（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４８（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５７（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．９７－７．０１（ｍ，３Ｈ），７．１８－７．２４（ｍ，２Ｈ），７．３１（ｔｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），７．３９－７．４３（ｍ，２Ｈ），７．６５（ｂｒｓ，１Ｈ），８．１２（ｓ，１Ｈ）．
１９３		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６３（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９３（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１４（ｂｒｓ，１Ｈ），２．６３（ｓ，３Ｈ），３．２６（ｓ，３Ｈ），４．２７（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），４．４３（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），４．４８（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５６（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．９８－７．０３（ｍ，２Ｈ），７．１９（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），７．２２（ｄ，Ｊ＝８．０Ｈｚ，１Ｈ），７．３３（ｔｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），７．６５（ｔｄ，Ｊ＝８．０，２．０Ｈｚ，１Ｈ），８．０５（ｄ，Ｊ＝８．０Ｈｚ，１Ｈ），８．１２（ｓ，１Ｈ），８．２２（ｄｄ，Ｊ＝４．８，１．２Ｈｚ，１Ｈ），８．８１（ｓ，１Ｈ）．

【表４９－２】

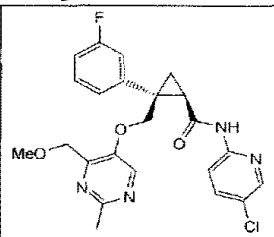
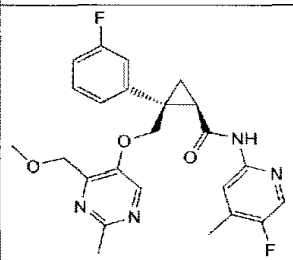
１９４		^{1}H－NMR（４００MHｚ，CDCｌ$_3$）δ（ｐｐｍ）：１．５９（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９０（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０６（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．６１（ｓ，３Ｈ），３．３１（ｓ，３Ｈ），４．３５（ｄ，Ｊ＝１２．８Ｈｚ，１Ｈ），４．４０（ｄ，Ｊ＝１２．８Ｈｚ，１Ｈ），４．４６（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５７（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．００（ｔｄ，Ｊ＝８．４，２．０Ｈｚ，１Ｈ），７．０４－７．１１（ｍ，２Ｈ），７．１８－７．２２（ｍ，２Ｈ），７．３２（ｔｄ，Ｊ＝８．４，６．０Ｈｚ，１Ｈ），７．５２（ｄｄ，Ｊ＝１０．８，６．８Ｈｚ，１Ｈ），７．８０（ｂｒｓ，１Ｈ），８．１２（ｓ，１Ｈ）．

【０３４９】

【表５０－１】

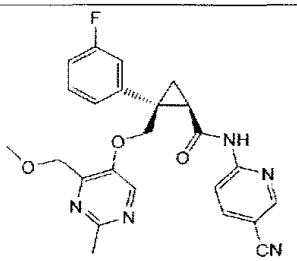
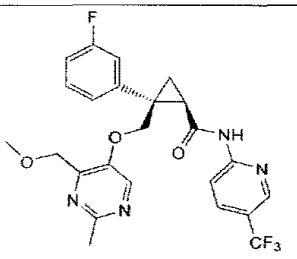
実施例	構造式	NMR及び／又はMS
１９５		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．５９（ｄｄ，Ｊ＝８．０，５．６Ｈｚ，１Ｈ），１．９５（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０９（ｄｄ，Ｊ＝８．０，５．６Ｈｚ，１Ｈ），２．６３（ｓ，３Ｈ），３．２９（ｓ，３Ｈ），４．３２（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４２（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４８（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），４．５８（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），６．８０（ｔ，Ｊ＝７．６Ｈｚ，１Ｈ），７．００（ｔｄｄ，Ｊ＝８．０，２．４，１．２Ｈｚ，１Ｈ），７．１３（ｄｔ，Ｊ＝９．６，２．４Ｈｚ，１Ｈ），７．１４－７．２７（ｍ，３Ｈ），７．３３（ｔｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），７．４１（ｔ，Ｊ＝１０．８Ｈｚ，１Ｈ），７．８５（ｂｒｓ，１Ｈ），８．１２（ｓ，１Ｈ）．
１９６		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６４（ｄｄ，Ｊ＝５．２Ｈｚ、８．０Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１１（ｄｄ，Ｊ＝６．０Ｈｚ，８．０Ｈｚ，１Ｈ），２．６３（ｓ，３Ｈ），３．３３（ｓ，３Ｈ），４．３２－４．５６（ｍ，４Ｈ），６．８１－６．９０（ｍ，２Ｈ），７．０１（ｔ，Ｊ＝８．８Ｈｚ，１Ｈ），７．２１－７．３６（ｍ，３Ｈ），７．６２（ｂｒｄｓ，１Ｈ），８．０５－８．１２（ｍ，２Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４５８
１９７		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６５（ｄｄ，Ｊ＝５．２Ｈｚ、８．０Ｈｚ，１Ｈ），１．９３（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１１（ｄｄ，Ｊ＝６．０Ｈｚ，８．４Ｈｚ，１Ｈ），２．６３（ｓ，３Ｈ），３．３１（ｓ，３Ｈ），４．２９－４．５７（ｍ，４Ｈ），６．７０－６．７６（ｍ，１Ｈ），６．９９－７．０８（ｍ，２Ｈ）、７．１７－７．３７（ｍ，３Ｈ），７．７７（ｂｒｄｓ，１Ｈ），８．０２－８．１２（ｍ，２Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４５８

【表５０－２】

１９８		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６１（ｄｄ，Ｊ＝８．２，５．２Ｈｚ，１Ｈ）１．８８（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．１２（ｄｄ，Ｊ＝８．０，６．０Ｈｚ、１Ｈ），２．２２（ｓ，３Ｈ），２．２６（ｓ，３Ｈ），２．５５（ｓ，３Ｈ），３．８１（ｓ，３Ｈ），４．４１（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），４．５３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．８１－６．８５（ｍ，１Ｈ），６．９９－７．０４（ｍ，２Ｈ），７．２５－７．２９（ｍ，１Ｈ），７．９１－７．９５（ｍ，２Ｈ），７．９９（ｓ，１Ｈ），８．７０（ｂｒｓ，１Ｈ）．
１９９		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６２（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９０（ｄ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１０（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．２７（ｓ，３Ｈ），２．６３（ｓ，３Ｈ），３．３１（ｓ，３Ｈ），４．２９（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４２（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．００（ｔｄｄ，Ｊ＝８．０，２．４，１．２Ｈｚ，１Ｈ），７．１９（ｄｔ，Ｊ＝１０．０，２．４Ｈｚ，１Ｈ），７．２２（ｄｔ，Ｊ＝８．０，１．２Ｈｚ，１Ｈ），７．３３（ｔｄ，Ｊ＝６．０，６．０Ｈｚ，１Ｈ），７．９５（ｂｒｓ，１Ｈ），８．０１（ｓ，１Ｈ），８．１０（ｓ，１Ｈ），８．２５（ｓ，１Ｈ）．

【０３５０】

【表５１】

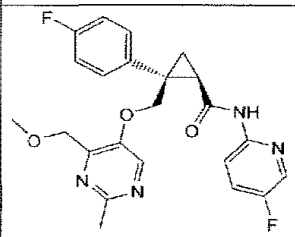
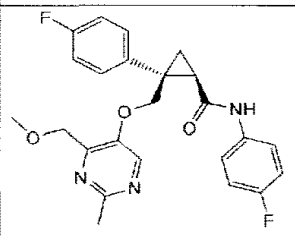
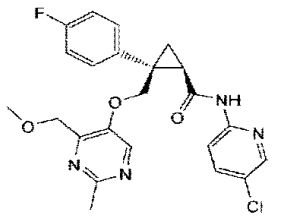
実施例	構造式	NMR（４００MHz，CDCl$_3$）
２００		^{1}H－NMR　δ（ｐｐｍ）：１．６９（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９５（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１６（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．６２（ｓ，３Ｈ），３．２９（ｓ，３Ｈ），４．３０（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．３８（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．０２（ｄｄ，Ｊ＝８．８，２．０Ｈｚ，１Ｈ），７．１９－７．２５（ｍ，２Ｈ），７．３５（ｔｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），７．９０（ｄｄ，Ｊ＝８．８，２．４Ｈｚ，１Ｈ），８．１１（ｓ，１Ｈ），８．２２（ｄｄ，Ｊ＝８．８，１．２Ｈｚ，１Ｈ），８．５５（ｂｒｓ，１Ｈ），８．５７（ｄｄ，Ｊ＝２．４，１．２Ｈｚ，１Ｈ）．
２０１		^{1}H－NMR　δ（ｐｐｍ）：１．６６（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９４（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１６（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．６１（ｓ，３Ｈ），３．２７（ｓ，３Ｈ），４．２９（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４０（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．０１（ｔｄｄ，Ｊ＝８．４，２．８，１．２Ｈｚ，１Ｈ），７．１９（ｄｔ，Ｊ＝１０．０，２．８Ｈｚ，１Ｈ），７．２３（ｄｔ，Ｊ＝８．４，１．２Ｈｚ，１Ｈ），７．３４（ｔｄ，Ｊ＝８．４，６．０Ｈｚ，１Ｈ），７．８８（ｄｄ，Ｊ＝８．８，２．４Ｈｚ，１Ｈ），８．１１（ｓ，１Ｈ），８．２１（ｄ，Ｊ＝８．８Ｈｚ，１Ｈ），８．５４（ｄ，Ｊ＝２．４Ｈｚ，１Ｈ），８．５７（ｂｒｓ，１Ｈ）．

【０３５１】

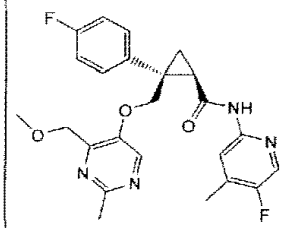
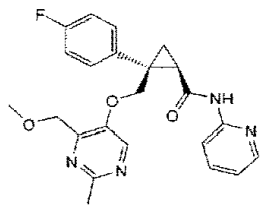
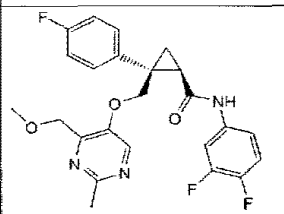
＊実施例２０２－２１０はカルボン酸Ｐｒｅｐ３６と任意のアミンを実施例５２の手法に準じて縮合し合成した。

【０３５２】

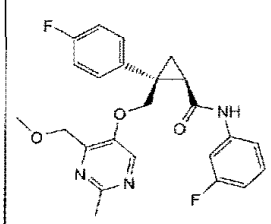
【表５２－１】

実施例	構造式	NMR（４００MHz，CDCl$_3$）及び／又はMS
２０２		^{1}H－NMR δ（ppm）：1．６０（ｄｄ，Ｊ＝8．０，５．２Ｈｚ，１Ｈ），１．９０（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０７（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．６２（ｓ，３Ｈ），３．２９（ｓ，３Ｈ），４．２９（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４０（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４４（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４９（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．０５（ｔｔ，Ｊ＝８．８，１．６Ｈｚ，２Ｈ），７．３７－７．４６（ｍ，３Ｈ），８．０９－８．１３（ｍ，３Ｈ），８．３２（ｂｒｓ，１Ｈ）．
２０３		^{1}H－NMR δ（ｐｐｍ）：１．５６（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．８８（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０５（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．６１（ｓ，３Ｈ），３．２９（ｓ，３Ｈ），４．３４（ｄ，Ｊ＝１２．８Ｈｚ，１Ｈ），４．３９（ｄ，Ｊ＝１２．８Ｈｚ，１Ｈ），４．４８（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．９９（ｔ，Ｊ＝８．４Ｈｚ，２Ｈ），７．０４（ｔ，Ｊ＝８．４Ｈｚ，２Ｈ），７．４０－７．４５（ｍ，４Ｈ），７．６３（ｂｒｓ，１Ｈ），８．１１（ｓ，１Ｈ）．
２０４		^{1}H－NMR δ（ｐｐｍ）：１．６０（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９０（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０８（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．６２（ｓ，３Ｈ），３．２８（ｓ，３Ｈ），４．２９（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），４．４０（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），４．４３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４９（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．０５（ｔ，Ｊ＝８．４Ｈｚ，２Ｈ），７．４４（ｄｄ，Ｊ＝８．４，４．８Ｈｚ，２Ｈ），７．６２（ｄｄ，Ｊ＝８．８，２．４Ｈｚ，１Ｈ），８．０６（ｄ，Ｊ＝８．８Ｈｚ，１Ｈ），８．０８（ｓ，１Ｈ），８．２３（ｄ，Ｊ＝２．４Ｈｚ，１Ｈ），８．３２（ｂｒｓ，１Ｈ）．

【表５２－２】

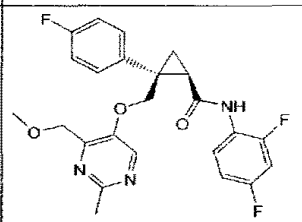
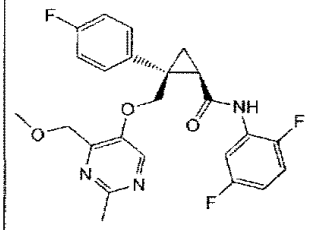
２０５		^{1}H－NMR δ（ｐｐｍ）：１．５９（ｄｄ，Ｊ＝８．０，５．６Ｈｚ，１Ｈ），１．８９（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０６（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．２８（ｓ，３Ｈ），２．６２（ｓ，３Ｈ），３．３０（ｓ，３Ｈ），４．２９（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），４．４１（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），４．４４（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），４．４９（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），７．０５（ｔ，Ｊ＝８．８Ｈｚ，２Ｈ），７．４３（ｄｄ，Ｊ＝８．８，４．８Ｈｚ，２Ｈ），７．９５（ｄ，Ｊ＝５．２Ｈｚ，１Ｈ），８．００（ｓ，１Ｈ），８．０９（ｓ，１Ｈ），８．２６（ｂｒｓ，１Ｈ）．
２０６		^{1}H－NMR δ（ｐｐｍ）：１．５９（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１０（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．６２（ｓ，３Ｈ），３．２６（ｓ，３Ｈ），４．２８（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），４．４４（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），４．４１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５０（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．０２－７．０８（ｍ，３Ｈ），７．４４（ｄｄ，Ｊ＝８．８，４．８Ｈｚ，２Ｈ），７．６６（ｔｄ，Ｊ＝７．２，２．０Ｈｚ，１Ｈ），８．０６（ｄ，Ｊ＝７．２Ｈｚ，１Ｈ），８．０９（ｓ，１Ｈ），８．２７（ｄｄ，Ｊ＝４．８，２．０Ｈｚ，１Ｈ），８．３６（ｂｒｓ，１Ｈ）．
２０７		^{1}H－NMR δ（ｐｐｍ）：１．５７（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．８８（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０２（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．６１（ｓ，３Ｈ），３．３０（ｓ，３Ｈ），４．３４（ｄ，Ｊ＝１２．８Ｈｚ，１Ｈ），４．３９（ｄ，Ｊ＝１２．８Ｈｚ，１Ｈ），４．４５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５２（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．０１－７．１１（ｍ，４Ｈ），７．４３（ｄｄ，Ｊ＝８．４，４．８Ｈｚ，２Ｈ），７．５２（ｄｄ，Ｊ＝１０．８，６．０Ｈｚ，１Ｈ），７．７４（ｂｒｓ，１Ｈ），８．１１（ｓ，１Ｈ）．

【表５２－３】

２０８		^{1}H－NMR δ（ｐｐｍ）：１．５６（ｄｄ，Ｊ＝８．０，５．６Ｈｚ，１Ｈ），１．８９（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０４（ｄｄ，Ｊ＝８．０，５．６Ｈｚ，１Ｈ），２．６１（ｓ，３Ｈ），３．２７（ｓ，３Ｈ），４．３２（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４０（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４６（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），４．５３（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），６．８０（ｔ，Ｊ＝８．０Ｈｚ，１Ｈ），７．０４（ｔ，Ｊ＝８．８Ｈｚ，２Ｈ），７．１２（ｄ，Ｊ＝８．０Ｈｚ，１Ｈ），７．２４（ｄｄ，Ｊ＝１４．４，８．０Ｈｚ，１Ｈ），７．４０－７．４４（ｍ，３Ｈ），７．７７（ｂｒｓ，１Ｈ），８．１０（ｓ，１Ｈ）．

【０３５３】

【表５３】

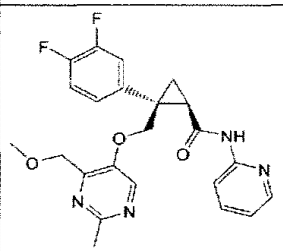
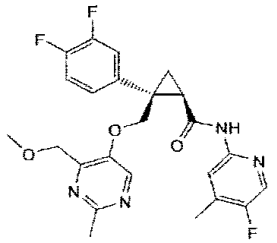
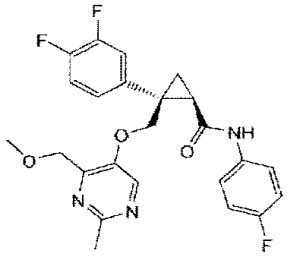
実施例	構造式	NMR（４００MHｚ，ＣＤＣｌ$_3$）及び／又はＭＳ
２０９		^{1}H－NMR δ（ｐｐｍ）：１．６０（ｄｄ，Ｊ＝５．２Ｈｚ、８．４Ｈｚ，１Ｈ），１．８９（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０８（ｄｄ，Ｊ＝５．６Ｈｚ，８．０Ｈｚ，１Ｈ），２．６３（ｓ，３Ｈ），３．３２（ｓ，３Ｈ），４．３１－４．５２（ｍ，４Ｈ），６．８２－６．９１（ｍ，２Ｈ），７．０５（ｔ，Ｊ＝８．８Ｈｚ，２Ｈ），７．４２－７．４５（ｍ，２Ｈ），７．６１（ｂｒｄｓ，１Ｈ），８．０８－８．１１（ｍ，２Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４５８
２１０		^{1}H－NMR δ（ｐｐｍ）：１．６２（ｄｄ，Ｊ＝５．２Ｈｚ、８．０Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０８（ｄｄ，Ｊ＝６．０Ｈｚ，８．４Ｈｚ，１Ｈ），２．６３（ｓ，３Ｈ），３．３０（ｓ，３Ｈ），４．２９－４．５２（ｍ，４Ｈ），６．７０－６．７６（ｍ，２Ｈ），７．０２－７．０８（ｍ，３Ｈ），７．４２－７．４５（ｍ，２Ｈ），７．５２（ｂｒｄｓ，１Ｈ），８．０３（ｂｒｄｓ，１Ｈ），８．１０（ｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４５８．

【０３５４】

＊実施例２１１－２１７はカルボン酸Ｐｒｅｐ３７と任意のアミンを実施例５１の手法に準じて縮合し合成した。

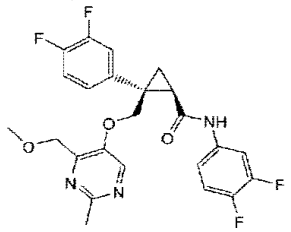
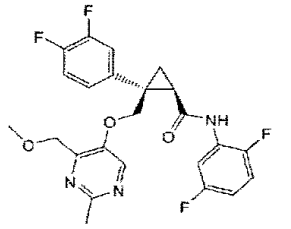
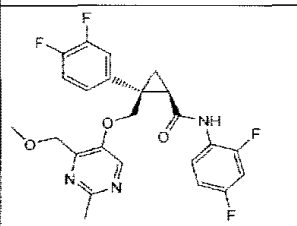
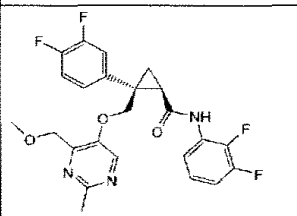
【０３５５】

【表５４】

実施例	構造式	NMR（４００MHz，CDCl$_3$）及び／又はMS
２１１		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ppm）：１．５７－１．６１（m，１H），１．９１（t，J＝５．６Hz，１H），２．０９（brdt，１H），２．６２（s，３H），３．２８（s，３H），４．２５－４．５０（m，４H），７．０３－７．３６（m，４H）、７．６６（t，J＝８．０Hz，１H），８．０３－８．０５（brdd，J＝８．０Hz，１H），８．１０（s，１H），８．２７（d，J＝３．６Hz，１H），８．３８（brds，１H）． MS［M+H］$^+$＝４４１
２１２		^{1}H－NMR δ（ppm）：１．５８－１．６１（m，１H），１．９０（t，J＝５．６Hz，１H），２．０６（brdt，J＝５．６Hz，１H），２．２７（s，３H），２．６３（s，３H），３．３２（s，３H），４．２７－４．５０（m，４H），７．１３－７．１９（m，２H）、７．３３（t，J＝９．２Hz，１H），７．９３（d，J＝５．６Hz，１H），８．００（s，１H），８．１０（s，１H），８．２９（s，１H）． MS［M+H］$^+$＝４７３
２１３		^{1}H－NMR δ（ppm）：１．５５－１．５７（m，１H），１．９０（t，J＝５．６Hz，１H），２．０２（dd，J＝６．０Hz，８．０Hz，１H），２．６２（s，３H），３．３２（s，３H），４．３２－４．５４（m，４H），６．９９（t，J＝８．８Hz，２H），７．１３－７．４２（m，５H）、７．６０（s，１H），８．１２（s，１H）． MS［M+H］$^+$＝４５８

【０３５６】

【表５５】

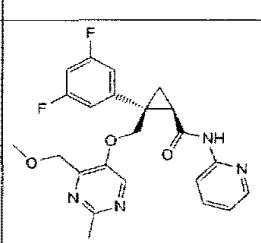
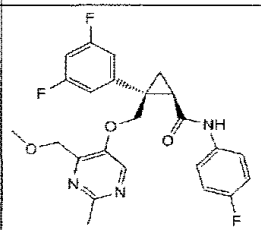
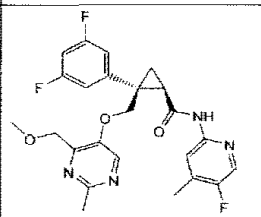
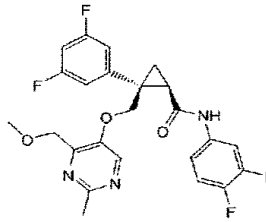
実施例	構造式	NMR（４００MHz，$CDCl_3$）及び／又はMS
２１４		^{1}H－NMR　δ（ｐｐｍ）：１．５５－１．５８（ｍ，１Ｈ），１．９０（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０２（ｄｄ，Ｊ＝６．０Ｈｚ，８．４Ｈｚ，１Ｈ），２．６１（ｓ，３Ｈ），３．３３（ｓ，３Ｈ），４．３４－４．５３（ｍ，４Ｈ），７．０５－７．１７（ｍ，４Ｈ），７．３５（ｔ，Ｊ＝９．２Ｈｚ，１Ｈ），７．５２（ｔ，Ｊ＝８．４Ｈｚ，１Ｈ），７．７３（ｓ，１Ｈ），８．１２（ｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４７６
２１５		^{1}H－NMR　δ（ｐｐｍ）：１．６２（ｄｄ，Ｊ＝５．６Ｈｚ、８．８Ｈｚ，１Ｈ），１．９２（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０８（ｄｄ，Ｊ＝６．０Ｈｚ，８．４Ｈｚ，１Ｈ），２．６３（ｓ，３Ｈ），３．３２（ｓ，３Ｈ），４．３０－４．５２（ｍ，４Ｈ），６．７１－６．７５（ｍ，１Ｈ），７．０２－７．３６（ｍ，４Ｈ），７．７９（ｂｒｄｓ，１Ｈ），８．００（ｍ，１Ｈ），８．１２（ｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４７６
２１６		^{1}H－NMR　δ（ｐｐｍ）：１．５８－１．６２（ｍ，１Ｈ），１．９０（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０７（ｄｄ，Ｊ＝６．０Ｈｚ，８．０Ｈｚ，１Ｈ），２．６３（ｓ，３Ｈ），３．３４（ｓ，３Ｈ），４．３２－４．５２（ｍ，４Ｈ），６．８１－６．９１（ｍ，２Ｈ），７．１２－７．１８（ｍ，２Ｈ），７．３４（ｔ，Ｊ＝８．８Ｈｚ，１Ｈ），７．６５（ｂｒｄｓ，１Ｈ），８．０３－８．１２（ｍ，２Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４７６
２１７		^{1}H－NMR　δ（ｐｐｍ）：１．６１（ｄｄ，Ｊ＝５．２Ｈｚ、８．４Ｈｚ，１Ｈ），１．９２（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．１０（ｄｄ，Ｊ＝６．０Ｈｚ，８．０Ｈｚ，１Ｈ），２．６２（ｓ，３Ｈ），３．３３（ｓ，３Ｈ），４．３０－４．５２（ｍ，４Ｈ），６．９０－７．３７（ｍ，５Ｈ），７．７７（ｂｒｄｓ，１Ｈ），７．９０（ｂｒｄｓ，１Ｈ），８．１２（ｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４７６

【０３５７】

＊実施例２１８－２２１はカルボン酸Ｐｒｅｐ３８と任意のアミンを実施例５１の手法に準じて縮合し合成した。

【０３５８】

【表５６】

実施例	構造式	NMR（４００MHz，$CDCl_3$）及び／又はMS
２１８		^{1}H－NMR　δ（ｐｐｍ）：１．６２（ｄｄ，Ｊ＝５．６Ｈｚ、８．０Ｈｚ，１Ｈ），１．９３（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１１（ｂｒｄｔ，１Ｈ），２．６２（ｓ，３Ｈ），３．２８（ｓ，３Ｈ），４．２５－４．５４（ｍ，４Ｈ），６．７６（ｔ，Ｊ＝７．２Ｈｚ，１Ｈ），７．００－７．０３（ｍ，３Ｈ），７．６５（ｔ，Ｊ＝８．０Ｈｚ，１Ｈ），８．０２（ｄ，Ｊ＝７．６Ｈｚ，１Ｈ），８．１２（ｓ，１Ｈ），８．２５（ｄ，Ｊ＝８．４Ｈｚ，１Ｈ），８．５９（ｓ，１Ｈ）． ＭＳ［Ｍ＋Ｎａ］$^+$＝４６４
２１９		^{1}H－NMR　δ（ｐｐｍ）：１．５８－１．６０（ｍ，１Ｈ），１．９２（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０５（ｄｄ，Ｊ＝５．６Ｈｚ、８．０Ｈｚ，１Ｈ），２．６１（ｓ，３Ｈ），３．３２（ｓ，３Ｈ），４．３３－４．５８（ｍ，４Ｈ），６．７６（ｔ，Ｊ＝８．８Ｈｚ，１Ｈ），６．９７－７．０２（ｍ，４Ｈ），７．３８－７．４２（ｍ，２Ｈ），７．６２（ｓ，１Ｈ），８．１４（ｓ，１Ｈ）． ＭＳ［Ｍ＋Ｎａ］$^+$＝４５９
２２０		^{1}H－NMR　δ（ｐｐｍ）：１．６０－１．６４（ｍ，１Ｈ），１．９２（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０８（ｂｒｄｔ，Ｊ＝８．０Ｈｚ，１Ｈ），２．２７（ｓ，３Ｈ），２．６３（ｓ，３Ｈ），３．３３（ｓ，３Ｈ），４．２７－４．５３（ｍ，４Ｈ），６．７６（ｔ，Ｊ＝８．８Ｈｚ，１Ｈ），６．９９－７．０２（ｍ，２Ｈ），７．９２（ｄ，Ｊ＝６．４Ｈｚ，１Ｈ），８．０１（ｓ，１Ｈ），８．１２（ｓ，１Ｈ），８．２７（ｓ，１Ｈ）． ＭＳ［Ｍ＋Ｎａ］$^+$＝４９６
２２１		^{1}H－NMR　δ（ｐｐｍ）：１．５７－１．６１（ｍ，１Ｈ），１．９２（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０５（ｄｄ，Ｊ＝５．６Ｈｚ，８．０Ｈｚ，１Ｈ），２．６１（ｓ，３Ｈ），３．３３（ｓ，３Ｈ），４．３３－４．５７（ｍ，４Ｈ），６．７６（ｔ，Ｊ＝８．８Ｈｚ，１Ｈ），７．００－７．０９（ｍ，４Ｈ），７．５２（ｂｒｄｔ，Ｊ＝７．２Ｈｚ，１Ｈ），７．７８（ｓ，１Ｈ），８．１３（ｓ，１Ｈ）． ＭＳ［Ｍ＋Ｎａ］$^+$＝４９８

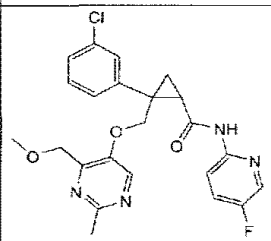
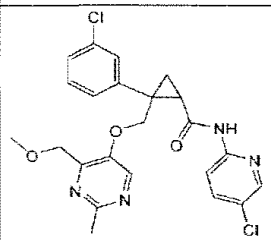
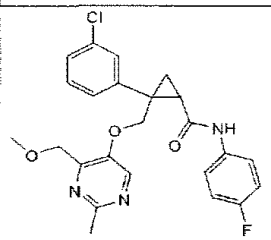
【０３５９】

＊実施例２２２－２２７はカルボン酸Ｐｒｅｐ３９と任意のアミンを縮合して合成した。縮合の手法は、実施例２２２－２２６は実施例５１の手法、実施例２２７は実施例１の手法に準じて行った。また、実施例２２５－２２６はラセミ生成物をキラル分取することに

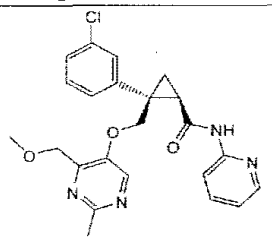
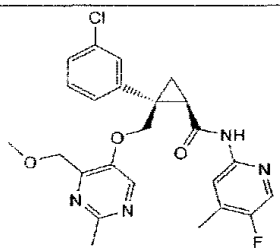
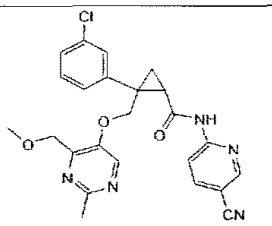
より得た。

【０３６０】

【表５７－１】

実施例	構造式	NMR（４００MHz，CDCl$_3$）及び／又はMS
２２２		^{1}H－NMR　δ（ｐｐｍ）：１．６１（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１１（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．６２（ｓ，３Ｈ），３．３１（ｓ，３Ｈ），４．３１（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４１（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４６（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４９（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．２８－７．４２（ｍ，４Ｈ），７．４８（ｓ，１Ｈ），８．０８（ｄｄ，Ｊ＝９．２，４．０Ｈｚ，１Ｈ），８．０９（ｓ，１Ｈ），８．１２（ｑ，Ｊ＝２．８Ｈｚ，１Ｈ），８．３９（ｂｒｓ，１Ｈ）．
２２３		^{1}H－NMR　δ（ｐｐｍ）：１．６２（ｄｄ，Ｊ＝８．０，５．６Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．１１（ｄｄ，Ｊ＝８．０，５．６Ｈｚ，１Ｈ），２．６２（ｓ，３Ｈ），３．３１（ｓ，３Ｈ），４．３０（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），４．４１（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），４．４４（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４９（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．２５－７．３５（ｍ，３Ｈ），７．４８（ｓ，１Ｈ），７．６２（ｄｄ，Ｊ＝８．８，２．８Ｈｚ，１Ｈ），８．０５（ｄ，Ｊ＝８．８Ｈｚ，１Ｈ），８．０９（ｓ，１Ｈ），８．２３（ｄ，Ｊ＝２．８Ｈｚ，１Ｈ），８．４２（ｂｒｓ，１Ｈ）．
２２４		^{1}H－NMR　δ（ｐｐｍ）：１．５９（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．８９（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０６（ｄｄ，Ｊ＝８．０，５．６Ｈｚ，１Ｈ），２．６２（ｓ，３Ｈ），３．２２（ｓ，３Ｈ），４．３５（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４２（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４８（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５４（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．９９（ｔ，Ｊ＝８．８Ｈｚ，２Ｈ），７．２４－７．３２（ｍ，３Ｈ），７．４２（ｄｄ，Ｊ＝８．８，４．８Ｈｚ，２Ｈ），７．４９（ｓ，１Ｈ），７．６６（ｂｒｓ，１Ｈ），８．１２（ｓ，１Ｈ）．

【表５７－２】

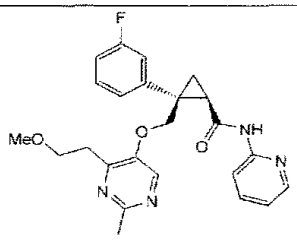
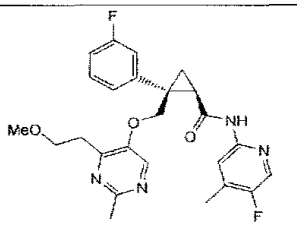
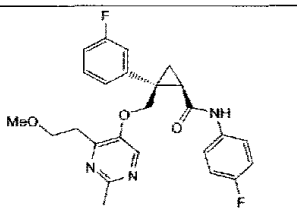
２２５		^{1}H－NMR δ（ｐｐｍ）：１．６１（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９２（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１２（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．６２（ｓ，３Ｈ），３．２９（ｓ，３Ｈ），４．２９（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），４．４３（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），４．４６（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．０３（ｄｄ，Ｊ＝７．２，４．８Ｈｚ，１Ｈ），７．２６－７．３５（ｍ，３Ｈ），７．４９（ｓ，１Ｈ），７．６６（ｔｄ，Ｊ＝７．２，２．０Ｈｚ，１Ｈ），８．０６（ｄ，Ｊ＝７．２Ｈｚ，１Ｈ），８．１０（ｓ，１Ｈ），８．２７（ｄ，Ｊ＝４．８Ｈｚ，１Ｈ），８．５０（ｂｒｓ，１Ｈ）．
２２６		^{1}H－NMR δ（ｐｐｍ）：１．６２（ｄｄ，Ｊ＝８．０，５．６Ｈｚ，１Ｈ），１．９０（ｄ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０９（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．２８（ｓ，３Ｈ），２．６３（ｓ，３Ｈ），３．３３（ｓ，３Ｈ），４．３１（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），４．４３（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），４．４６（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５０（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．２９－７．３５（ｍ，３Ｈ），７．４８（ｓ，１Ｈ），７．９５（ｄ，Ｊ＝５．６Ｈｚ，１Ｈ），８．０１（ｓ，１Ｈ），８．１０（ｓ，１Ｈ），８．３２（ｂｒｓ，１Ｈ）．
２２７		^{1}H－NMR δ（ｐｐｍ）：１．６７（ｄｄ，Ｊ＝８．０，５．６Ｈｚ，１Ｈ），１．９４（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．１５（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．６２（ｓ，３Ｈ），３．３１（ｓ，３Ｈ），４．３２（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．３８（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４４（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４９（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．３０－７．３５（ｍ，３Ｈ）７．４９（ｑ，Ｊ＝１．６Ｈｚ，１Ｈ），７．９１（ｄｄ，Ｊ＝８．４，１．６Ｈｚ，１Ｈ），８．１０（ｓ，１Ｈ），８．２２（ｑ，Ｊ＝８．４Ｈｚ，１Ｈ），８．５３（ｂｒｓ，１Ｈ），８．５７（ｑ，Ｊ＝１．６Ｈｚ，１Ｈ）．

【０３６１】

＊実施例２２８－２３０はカルボン酸Ｐｒｅｐ４０と任意のアミンを、実施例５２の手法に準じて縮合して合成した。

【０３６２】

【表５８】

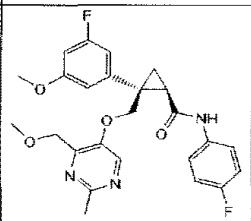
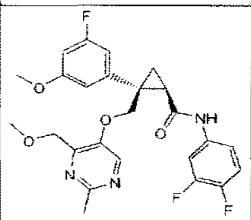
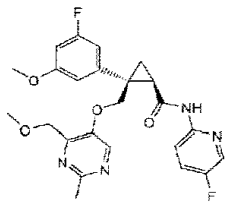
実施例	構造式	NMR（４００MHz，CDCl_3）及び／又はMS
２２８		^{1}H－NMR　δ（ｐｐｍ）：１．６０（ｄｄ，Ｊ＝８．０，５．６Ｈｚ，１Ｈ），１．９２（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．１４（ｄｄ，Ｊ＝８．０，５．６Ｈｚ，１Ｈ），２．５６（ｓ，３Ｈ），２．７７（ｑｕｉ，Ｊ＝６．８Ｈｚ，１Ｈ），２．９２（ｑｕｉ，Ｊ＝６．８Ｈｚ，１Ｈ），３．１８（ｓ，３Ｈ），３．４８－３．５７（ｍ，２Ｈ），４．４４（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．９７－７．０４（ｍ，２Ｈ），７．１９（ｄｔ，Ｊ＝８．０，１．２Ｈｚ，１Ｈ），７．２４（ｄｔ，Ｊ＝８．０，１．２Ｈｚ，１Ｈ），７．３２（ｄｔ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），７．６５（ｔｄ，Ｊ＝７．６，２．０Ｈｚ，１Ｈ），８．０２（ｓ，１Ｈ），８．０５（ｄ，Ｊ＝７．６Ｈｚ，１Ｈ），８．２６（ｄ，Ｊ＝４．８Ｈｚ，１Ｈ），８．５２（ｂｒｓ，１Ｈ）．
２２９		^{1}H－NMR　δ（ｐｐｍ）：１．６０（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９０（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１１（ｄｄ，Ｊ＝８．０，５．６Ｈｚ，１Ｈ），２．２７（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），２．７７（ｑｕｉ，Ｊ＝６．８Ｈｚ，１Ｈ），２．９３（ｑｕｉ，Ｊ＝６．８Ｈｚ，１Ｈ），３．２１（ｓ，３Ｈ），３．５１－３．５７（ｍ，２Ｈ），４．４３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．９９（ｔｄ，Ｊ＝８．０Ｈｚ，１Ｈ），７．１８（ｄｔ，Ｊ＝８．８，２．０Ｈｚ，１Ｈ），７．２３（ｄ，Ｊ＝８．０Ｈｚ，１Ｈ），７．３２（ｔｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），７．９４（ｄ，Ｊ＝６．０Ｈｚ，１Ｈ），８．００（ｓ，１Ｈ），８．０２（ｓ，１Ｈ），８．４３（ｂｒｓ，１Ｈ）．
２３０		^{1}H－NMR　δ（ｐｐｍ）：１．５６（ｄｄ，Ｊ＝８．０，５．６Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０８（ｄｄ，Ｊ＝８．０，５．６Ｈｚ，１Ｈ），２．５５（ｓ，３Ｈ），２．８２－２．９７（ｍ，２Ｈ），３．２３（ｓ，３Ｈ），３．５２－３．６１（ｍ，２Ｈ），４．４５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．９６－７．０１（ｍ，３Ｈ），７．１９－７．２４（ｍ，２Ｈ），７．３１（ｔｄ，Ｊ＝８．４，６．０Ｈｚ，１Ｈ），７．４０（ｄｄ，Ｊ＝８．８，４．８Ｈｚ，１Ｈ），７．７９（ｂｒｓ，１Ｈ），８．０３（ｓ，１Ｈ）．

【０３６３】

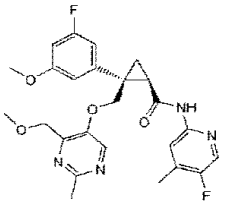
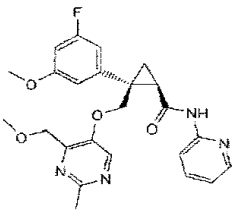
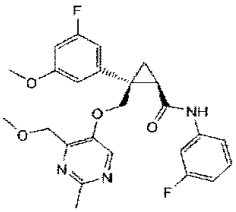
＊実施例２３１－２３６はカルボン酸Ｐｒｅｐ４１と任意のアミンを、実施例５１の手法に準じて縮合して合成した。

【０３６４】

【表５９－１】

実施例	構造式	NMR（４００MHz，CDCl$_3$）及び／又はMS
２３１		^{1}H－NMR δ（ppm）：1．５６（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．８７（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０７（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．６２（ｓ，３Ｈ），３．３０（ｓ，３Ｈ），３．８０（ｓ，３Ｈ），４．３５（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４４（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４６（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５６（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．５４（ｄｔ，Ｊ＝１０．８，２．０Ｈｚ，１Ｈ），６．７７－６．７９（ｍ，２Ｈ），６．９８（ｔ，Ｊ＝８．８Ｈｚ，２Ｈ），７．４１（ｄｄ，Ｊ＝８．８，４．８Ｈｚ，２Ｈ），７．８５（ｂｒｓ，１Ｈ），８．１２（ｓ，１Ｈ）．
２３２		^{1}H－NMR δ（ppm）：1．５６（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．８７（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０７（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．６１（ｓ，３Ｈ），３．３２（ｓ，３Ｈ），３．７９（ｓ，３Ｈ），４．３６（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４３（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４４（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．５４（ｄｔ，Ｊ＝１０．８，２．４Ｈｚ，１Ｈ），６．７６－６．７８（ｍ，２Ｈ），７．０２－７．１０（ｍ，２Ｈ），７．５３（ｄｄ，Ｊ＝１０．８，６．８Ｈｚ，１Ｈ），８．０３（ｂｒｓ，１Ｈ），８．１２（ｓ，１Ｈ）．
２３３		^{1}H－NMR δ（ppm）：1．６１（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．８９（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１１（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．６３（ｓ，３Ｈ），３．３０（ｓ，３Ｈ），３．８１（ｓ，３Ｈ），４．３０（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４３（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．５６（ｄｔ，Ｊ＝１０．８，２．４Ｈｚ，１Ｈ），６．７６－６．８０（ｍ，２Ｈ），７．３９（ｄｄｄ，Ｊ＝１０．４，９．２，２．８Ｈｚ，１Ｈ），８．０７（ｄｄ，Ｊ＝９．２，４．０Ｈｚ，１Ｈ），８．１０$_9$（ｓ，１Ｈ），８．１１$_2$（ｄ，Ｊ＝２．４Ｈｚ，１Ｈ），８．４９（ｂｒｓ，１Ｈ）．

【表５９－２】

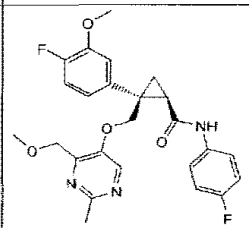
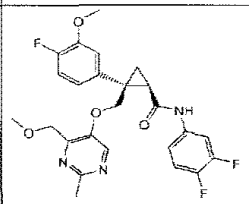
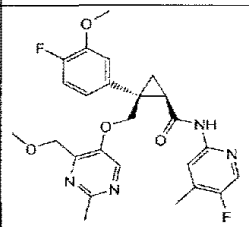
２３４		^{1}H－NMR δ（ｐｐｍ）：１．６１（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．８８（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０９（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．２７（ｓ，３Ｈ），２．６３（ｓ，３Ｈ），３．３１（ｓ，３Ｈ），３．８０（ｓ，３Ｈ），４．３０（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），４．４４$_5$（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），４．４４$_5$（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），４．５３（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），６．５６（ｄｔ，Ｊ＝１０．４，２．４Ｈｚ，１Ｈ），６．７５－６．７９（ｍ，２Ｈ），７．９４（ｄ，Ｊ＝５．６Ｈｚ，１Ｈ），７．９８（ｓ，１Ｈ），８．１１（ｓ，１Ｈ），８．４９（ｂｒｓ，１Ｈ）．
２３５		^{1}H－NMR δ（ｐｐｍ）：１．５９（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．８９（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１２（ｄｄ，Ｊ＝８．０，５．６Ｈｚ，１Ｈ），２．６２（ｓ，３Ｈ），３．２６（ｓ，３Ｈ），３．８０（ｓ，３Ｈ），４．２８（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），４．４３（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），４．４８（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．５５（ｄｔ，Ｊ＝１０．８，２．４Ｈｚ，１Ｈ），６．７６－６．７９（ｍ，２Ｈ），７．００（ｄｄ，Ｊ＝７．６，４．８Ｈｚ，１Ｈ），７．６５（ｔｄ，Ｊ＝７．６，２．０Ｈｚ，１Ｈ），８．０３（ｄ，Ｊ＝７．６Ｈｚ，１Ｈ），８．１０（ｓ，１Ｈ），８．２４（ｄ，Ｊ＝４．８Ｈｚ，１Ｈ），８．６７（ｂｒｓ，１Ｈ）．
２３６		^{1}H－NMR δ（ｐｐｍ）：１．５７（ｄｄ，Ｊ＝８．０，５．６Ｈｚ，１Ｈ），１．８８（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０７（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），２．６１（ｓ，３Ｈ），３．２９（ｓ，３Ｈ），３．８０（ｓ，３Ｈ），４．３３（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４３（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５６（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．５４（ｄｔ，Ｊ＝１０．４，２．４Ｈｚ，１Ｈ），６．７６－６．８１（ｍ，３Ｈ），７．１１（ｄｄ，Ｊ＝８．０，２．０Ｈｚ，１Ｈ），７．２３（ｄｄ，Ｊ＝１４．８，２．０Ｈｚ，１Ｈ），７．４０（ｄ，Ｊ＝１１．２Ｈｚ，１Ｈ），７．８２（ｂｒｓ，１Ｈ），８．１１（ｓ，１Ｈ）．

【０３６５】

＊実施例２３７－２３９はカルボン酸Ｐｒｅｐ４２と任意のアミンを、実施例５１の手法に準じて縮合して合成した。

【０３６６】

【表６０】

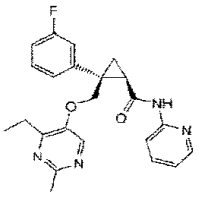
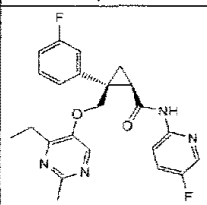
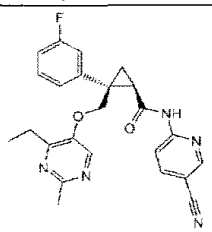
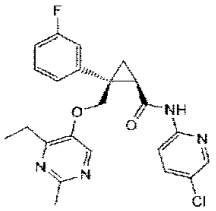
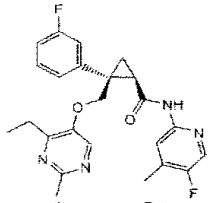
実施例	構造式	NMR（４００MHz，$CDCl_3$）及び／又はMS
２３７		^{1}H－NMR　δ（ｐｐｍ）：１．５９（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），１．８７（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０４（ｄｄ，Ｊ＝５．６，８．０Ｈｚ，１Ｈ），２．６３（ｓ，３Ｈ），３．２８（ｓ，３Ｈ），３．９２（ｓ，３Ｈ），４．３４（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４２（ｄ，Ｊ＝１３．２Ｈｚ，１Ｈ），４．４９（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），４．５５（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），６．９８－７．０８（ｍ，５Ｈ），７．３９－７．４３（ｍ，２Ｈ），７．５５（ｂｒｓ，１Ｈ），８．１３（ｓ，１Ｈ）． ＭＳ［Ｍ＋Ｎａ］$^+$＝４９２
２３８		^{1}H－NMR　δ（ｐｐｍ）：１．５９（ｄｄ，Ｊ＝５．６，８．２Ｈｚ，１Ｈ），１．８７（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０３（ｄｄ，Ｊ＝５．６，８．２Ｈｚ，１Ｈ），２．６３（ｓ，３Ｈ），３．３０（ｓ，３Ｈ），３．９１（ｓ，３Ｈ），４．３５（ｄ，Ｊ＝１３．０Ｈｚ，１Ｈ），４．４１（ｄ，Ｊ＝１３．０Ｈｚ，１Ｈ），４．４７（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．９７－７．１２（ｍ，５Ｈ），７．５０－７．５５（ｍ，１Ｈ），７．６７（ｂｒｓ，１Ｈ），８．１３（ｓ，１Ｈ）． ＭＳ［Ｍ＋Ｈ］$^+$＝４８８
２３９		^{1}H－NMR　δ（ｐｐｍ）：１．６０（ｄｄ，Ｊ＝５．２，８．０Ｈｚ，１Ｈ），１．８８（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０７（ｄｄ，Ｊ＝５．２，８．０Ｈｚ，１Ｈ），２．２８１－２．２８３（ｍ，３Ｈ），２．６３（ｓ，３Ｈ），３．２９（ｓ，３Ｈ），３．９２（ｓ，３Ｈ），４．２９（ｄ，Ｊ＝１３．４Ｈｚ，１Ｈ），４．４２（ｄ，Ｊ＝１３．４Ｈｚ，１Ｈ），４．４５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．９７－７．０９（ｍ，３Ｈ），７．９６（ｄ，Ｊ＝５．６Ｈｚ，１Ｈ），８．０２（ｄ，Ｊ＝１．２Ｈｚ，１Ｈ），８．１０（ｓ，１Ｈ），８．２１（ｂｒｓ，１Ｈ）． ＭＳ［Ｍ＋Ｎａ］$^+$＝５０７．

【０３６７】

＊実施例２４０－２４４はカルボン酸Ｐｒｅｐ４３と任意のアミンを、実施例１の手法に準じて縮合して合成した。

【０３６８】

【表６１】

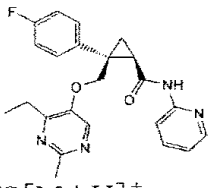
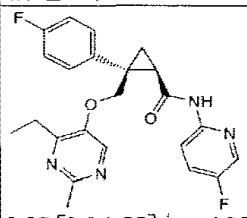
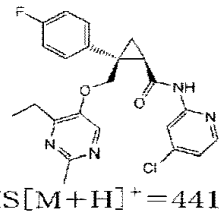
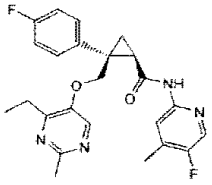
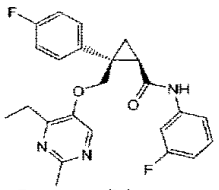
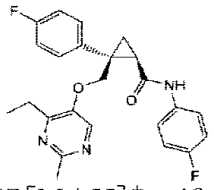
実施例	構造式、MS	実施例	構造式、MS	実施例	構造式、MS
240	 MS[M+H]$^+$＝407	241	 MS[M+H]$^+$＝425	242	 MS[M+H]$^+$＝432
243	 MS[M+H]$^+$＝441	244	 MS[M+H]$^+$＝439		

【０３６９】

＊実施例２４５－２５０はカルボン酸Ｐｒｅｐ４４と任意のアミンを、実施例１の手法に準じて縮合して合成した。

【０３７０】

【表６２】

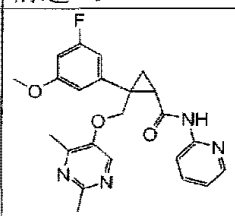
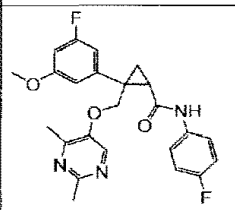
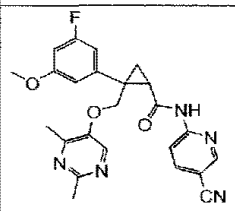
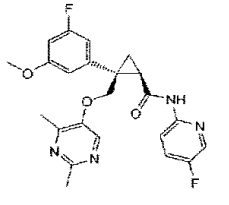
実施例	構造式、MS	実施例	構造式、MS	実施例	構造式、MS
245	 MS[M+H]$^+$＝407	246	 MS[M+H]$^+$＝425	247	 MS[M+H]$^+$＝441
248	 MS[M+H]$^+$＝439	249	 MS[M+H]$^+$＝424	250	 MS[M+H]$^+$＝424

【０３７１】

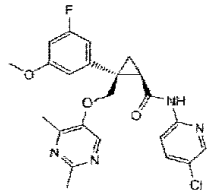
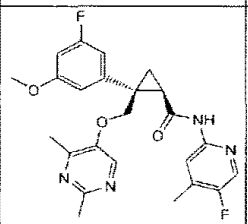
＊実施例２５１－２５６はカルボン酸Ｐｒｅｐ４５または対応するラセミ体と任意のアミンを縮合して合成した。実施例２５１－２５３は実施例５１の手法に準じて縮合し、実施例２５４－２５６は実施例１の方法に準じて縮合を行い、キラル分割を行った。

【０３７２】

【表６３－１】

実施例	構造式	NMR（４００MHz，$CDCl_3$）及び／又はMS
２５１		^{1}H－NMR δ（ppm）：1．５９（ｄｄ，Ｊ＝８．２，４．８Ｈｚ，１Ｈ），１．９１（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１２－２．１８（ｂｒ，１Ｈ），２．２１（ｓ，３Ｈ），２．５５（ｓ，３Ｈ），３．７９（ｓ，３Ｈ），４．４１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５２（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．５４（ｄｔ，Ｊ＝１０．４，２．０Ｈｚ、１Ｈ），６．７３－６．７９（ｍ，２Ｈ），６．９５－６．９９（ｍ，１Ｈ），７．６１－７．６７（ｍ，１Ｈ），８．００（ｓ，１Ｈ），７．９９－８．０５（ｍ，１Ｈ），８．１９－８．２１（ｍ，１Ｈ），９．２５（ｂｒｓ，１Ｈ）．
２５２		^{1}H－NMR δ（ppm）：1．５６（ｄｄ，Ｊ＝８．２，５．２Ｈｚ，１Ｈ），１．８７（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０３－２．０７（ｍ，１Ｈ），２．２６（ｓ，３Ｈ），２．５７（ｓ，３Ｈ），３．７９（ｓ，３Ｈ），４．４３（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．５３（ｄｔ，Ｊ＝１０．４，２．４Ｈｚ、１Ｈ），６．７４－６．７８（ｍ，２Ｈ），６．９５－７．００（ｍ，２Ｈ），７．３６－７．４１（ｍ，２Ｈ），７．９０（ｂｒｓ，１Ｈ）７．９９（ｓ，１Ｈ）．
２５３		^{1}H－NMR δ（ppm）：1．６６（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９２（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１６（ｔ，Ｊ＝９．０Ｈｚ，１Ｈ），２．２２（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），３．８１（ｓ，３Ｈ）４．３７（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４８（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．５０－６．５８（ｍ，１Ｈ）６．７５－６．８１（ｍ，２Ｈ），７．８７－７．９１（ｍ，１Ｈ），７．９８（ｓ，１Ｈ），８．１７－８．２１（ｍ，１Ｈ），８．５５－８．５７（ｍ，１Ｈ），８．６３（ｂｒｓ，１Ｈ）．
２５４		^{1}H－NMR δ（ppm）：1．５６（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．８８（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１０－２．１６（ｍ，１Ｈ），２．２０（ｓ，３Ｈ），２．５３（ｓ，３Ｈ），３．７７（ｓ，３Ｈ）４．３８（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４９（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．５２（ｄｔ，Ｊ＝１０．８，１．６Ｈｚ，１Ｈ）６．７３－６．７９（ｍ，２Ｈ），７．３２－７．３８（ｍ，１Ｈ），７．９７（ｓ，１Ｈ），８．００－８．０８（ｍ，２Ｈ），９．０２（ｂｒｓ，１Ｈ）．

【表６３－２】

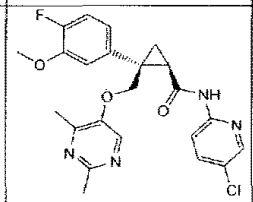
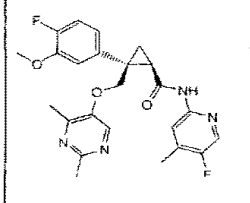
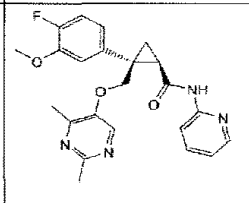
２５５		^{1}H－NMR　δ（ｐｐｍ）：１．６１（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９０（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１２（ｂｒ，１Ｈ），２．２３（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），３．８０（ｓ，３Ｈ）４．３８（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５０（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．５５（ｄｔ，Ｊ＝１０．８，１．６Ｈｚ，１Ｈ），６．７２－６．８２（ｍ，２Ｈ），７．５６－７．６４（ｍ，１Ｈ），７．９９（ｓ，１Ｈ），７．７８－８．０８（ｍ，１Ｈ），８．１６－８．２４（ｍ，１Ｈ），８．６２（ｂｒｓ，１Ｈ）．
２５６		^{1}H－NMR　δ（ｐｐｍ）：１．６０（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．８９（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．０９（ｄｄ，Ｊ＝７．８，６．４Ｈｚ，１Ｈ），２．２３（ｓ，３Ｈ），２．２６（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），３．７９（ｓ，３Ｈ），４．４０（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５２（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．５５（ｄｔ，Ｊ＝１０．４，２．０Ｈｚ，１Ｈ），６．７５（ｄｔ，Ｊ＝８．８，２．０Ｈｚ，１Ｈ），６．７７－６．７９（ｍ，１Ｈ），７．８９－７．９５（ｍ，２Ｈ），８．００（ｓ，１Ｈ），８．６８（ｂｒｓ，１Ｈ）．

【０３７３】

＊実施例２５７－２５９はカルボン酸Ｐｒｅｐ４６と任意のアミンを実施例５１の方法に準じて縮合して合成した。

【０３７４】

【表６４】

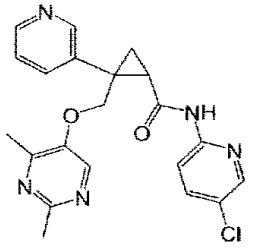
実施例	構造式	NMR（４００MHz，$CDCl_3$）及び／又はMS
２５７		^{1}H－NMR　δ（ｐｐｍ）：１．６１（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９０（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１２（ｔ，Ｊ＝６．０Ｈｚ，１Ｈ），２．２３（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），３．９１（ｓ，３Ｈ），４．３９（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４８（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．９６－７．１０（ｍ，３Ｈ），７．６０－７．６４（ｍ，１Ｈ），７．９８（ｓ，１Ｈ），８．０３－８．０６（ｍ，１Ｈ），８．２１－８．２２（ｍ，１Ｈ），８．４７（ｂｒｓ，１Ｈ）．
２５８		^{1}H－NMR　δ（ｐｐｍ）：１．５９（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．８９（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０４－２．１２（ｍ，１Ｈ），２．２３（ｓ，３Ｈ），２．２７（ｓ、３Ｈ），２．５６（ｓ，３Ｈ），３．９０（ｓ，３Ｈ），４．４１（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），４．４８（ｄ，Ｊ＝９．２Ｈｚ，１Ｈ），６．９５－７．２７（ｍ，３Ｈ），７．９３－８．０１（ｍ，２Ｈ）７．９９（ｓ，１Ｈ），８．６３（ｂｒｓ，１Ｈ）．
２５９		^{1}H－NMR　δ（ｐｐｍ）：１．５９（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），１．９０（ｔ，Ｊ＝４．８Ｈｚ，１Ｈ），２．１０－２．１４（ｍ，１Ｈ），２．２２（ｓ，３Ｈ），２．５５（ｓ、３Ｈ），３．９０（ｓ，３Ｈ）４．４１（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４８（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．９６－７．１０（ｍ，４Ｈ），７．６２－７．６８（ｍ，１Ｈ），７．９９（ｓ，１Ｈ），８．０２－８．０７（ｍ，１Ｈ），８．２２－８．２５（ｍ，１Ｈ），８．７２（ｂｒｓ，１Ｈ）．

【０３７５】

実施例２６０

Ｎ－（５－クロロピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－ピリジン－３－イルシクロプロパンカルボキサミド（２６０）の合成

【化６７】



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【０３７６】

カルボン酸Ｐｒｅｐ４７を実施例５１の方法に準じてアミド化することにより、合成した。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，$CDCl_3$）δ（ｐｐｍ）：１．６３（ｄｄ，Ｊ＝８．０

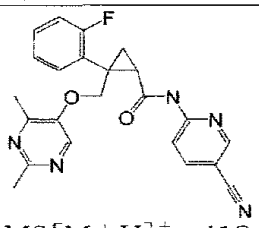
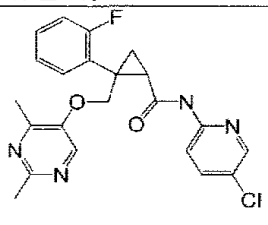
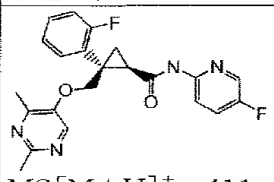
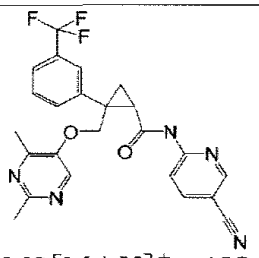
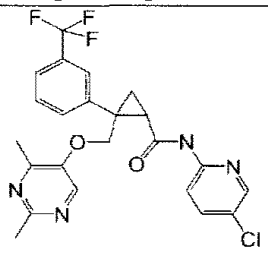
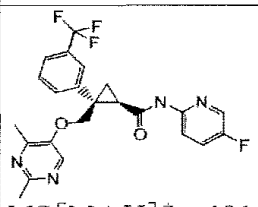
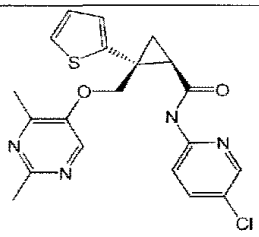
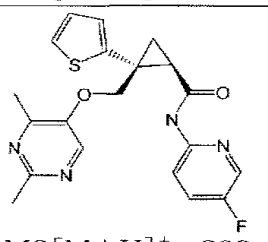
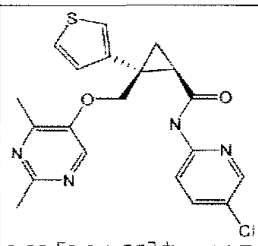
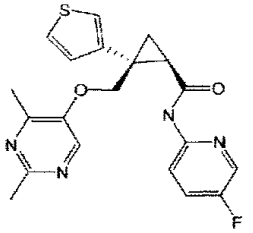
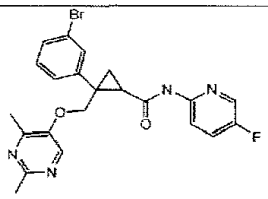
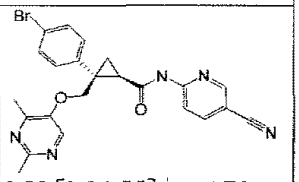
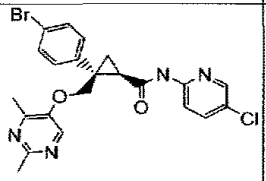
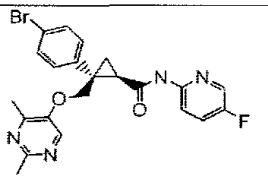
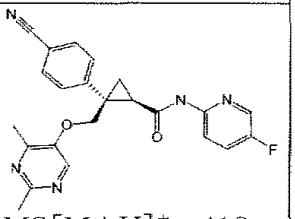
，５．２Ｈｚ，１Ｈ），１．９６（ｔ，Ｊ＝４．８Ｈｚ，１Ｈ），２．１４－２．２２（ｍ，１Ｈ），２．２２（ｓ，３Ｈ），２．５６（ｓ，３Ｈ），４．４４（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．４９（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．２９－７．３３（ｍ，１Ｈ），７．６１－７．６４（ｍ，１Ｈ），７．７９（ｄｔ，Ｊ＝７．６，１．９Ｈｚ，１Ｈ），７．９９（ｓ，１Ｈ），８．０４－８．０７（ｍ，１Ｈ），８．２０－８．２２（ｍ，１Ｈ），８．５６－８．５９（ｍ，１Ｈ），８．７７－８．７８（ｍ，１Ｈ），８．８９－８．９５（ｂｒｓ，１Ｈ）．

【０３７７】

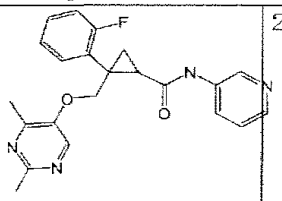
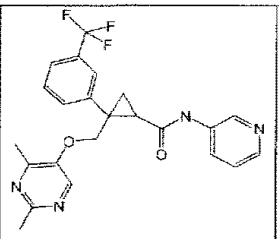
＊実施例２６１－２８１は製造例および実施例に記載の方法に準じて合成した。

【０３７８】

【表６５－１】

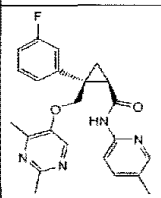
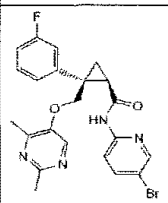
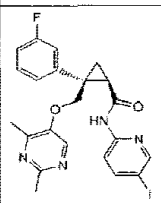
実施例	構造式、MS	実施例	構造式、MS	実施例	構造式、MS
261	 MS[M+H]$^+$=418	262	 MS[M+H]$^+$=427	263	 MS[M+H]$^+$=411
264	 MS[M+H]$^+$=468	265	 MS[M+H]$^+$=477	266	 MS[M+H]$^+$=461
267	 MS[M+H]$^+$=415	268	 MS[M+H]$^+$=399	269	 MS[M+H]$^+$=415
270	 MS[M+H]$^+$=399	271	 MS[M+H]$^+$=472	272	 MS[M+H]$^+$=478
273	 MS[M+H]$^+$=488	274	 MS[M+H]$^+$=472	275	 MS[M+H]$^+$=418

【表６５－２】

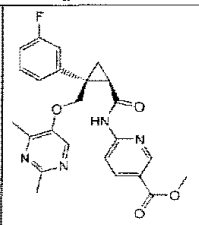
276	 MS[M+H]$^+$=393	277	 MS[M+H]$^+$=443		

【０３７９】

【表６６－１】

実施例	構造式	NMR（４００MHz，CDCl$_3$）及び／又はMS
２７８		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ppm）：１．５５－１．６５（m，１H），１．９１（t，J＝５．６Hz，１H），２．０７－２．１４（m，１H），２．２１（s，３H），２．２８（s，３H），２．５５（s，３H），４．４１（d，J＝９．６Hz，１H），４．５０（d，J＝９．６Hz，１H），６．９６－７．０４（m，１H），７．１４－７．２０（m，１H），７．２２－７．２８（m，１H），７．３３（td，J＝８．０，５．８Hz，１H），７．４４－７．４８（m，１H），７．９３（brd，J＝３．６Hz，１H），７．９７（s，１H），８．０６－８．１２（m，１H），８．３１（brs，１H）． MS［M＋H］$^+$＝４０７，MS［M＋Na］$^+$＝４２９
２７９		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ppm）：１．６０－１．６６（m，１H），１．９２（t，J＝５．６Hz，１H），２．０７－２．１５（m，１H），２．２１（s，３H），２．２６（s，３H），４．３９（d，J＝９．６Hz，１H），４．４９（d，J＝９．６Hz，１H），６．９７－７．０４（m，１H），７．１３－７．２０（m，１H），７．２２－７．２８（m，１H），７．３３（td，J＝８．０，６．０Hz，１H），７．７５（dd，J＝８．４，６．０Hz，１H），７．９６－８．０３（m，１H），７．９７（s，１H），８．２３（brs，１H），８．３１－８．３３（m，１H）． MS［M＋Na］$^+$＝４９３
２８０		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ppm）：１．５５－１．６５（m，１H），１．９１（t，J＝５．６Hz，１H），２．０５－２．１５（m，１H），２．２１（s，３H），２．５６（s，３H），４．３８（d，J＝９．２Hz，１H），４．４９（d，J＝９．６Hz，１H），６．９７－７．０４（m，１H），７．１４－７．２０（m，１H），７．２１－７．２８（m，１H），７．２９－７．３７（m，１H），７．８６－７．９４（m，２H），７．９７（s，１H），８．３５（brs，１H），８．４６（brs，１H）． MS［M＋Na］$^+$＝５４１

【表６６－２】

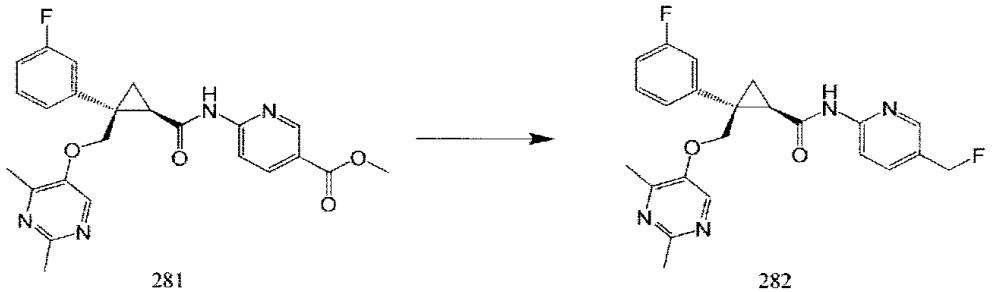
２８１		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ｐｐｍ）：１．６５（ｄｄ，Ｊ＝８．４Ｈｚ，５．２Ｈｚ，１Ｈ），１．９４（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．１２－２．１８（ｍ，１Ｈ），２．１９（ｓ，３Ｈ），２．５５（ｓ，３Ｈ），３．９３（ｓ，３Ｈ），４．３９（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），４．５０（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．９８－７．０４（ｍ，１Ｈ），７．１６－７．２０（ｍ，１Ｈ），７．２２－７．２８（ｍ，１Ｈ），７．３４（ｔｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），７．９８（ｓ，１Ｈ），８．１２（ｂｒｄ，Ｊ＝９．２Ｈｚ，１Ｈ），８．２３－８．２７（ｍ，１Ｈ），８．４９（ｂｒｓ，１Ｈ），８．９１（ｄｄ，Ｊ＝２．０Ｈｚ，０．８Ｈｚ，１Ｈ）． ＭＳ［Ｍ＋Ｎａ］$^+$＝４５１，ＭＳ［Ｍ＋Ｎａ］$^+$＝４７３

【０３８０】

実施例２８２

（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロメチルピリジン－２－イル）－２－（３－フルオロフェニル）シクロプロパンカルボキサミド（２８２）の合成

【化６８】



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【０３８１】

化合物２８１（５１．６ｍｇ）をＴＨＦ（５ｍｌ）に溶解し、氷水バス冷却下リチウムアルミニウムハイドライド（８．７３ｍｇ）を加えた。そのまま３０分撹拌した後、反応液を氷冷水に移した後、酢酸エチルを加えて分液を行った。有機層を飽和食塩水で洗浄した。硫酸マグネシウムで乾燥し、溶媒を減圧下濃縮した。残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ^{TM} ｃｏｌｕｍｎ，Ｓｉｚｅ：Ｍ，メタノール：酢酸エチル０％→１０％）で精製してアルコール中間体（２０ｍｇ）を得た。得られたアルコール中間体（２０ｍｇ）は塩化メチレン（３ｍｌ）に溶解し、氷水バス冷却下［ビス（２－メトキシエチル）アミノ］サルファトリフルオリド（０．０３４９ｍｌ）を加えた。そのまま０．５時間撹拌した後、室温で３時間撹拌した。反応液に飽和炭酸水素ナトリウム水溶液を加え、酢酸エチルにて分液した。有機層を水、飽和食塩水で順次洗浄した。硫酸マグネシウムで乾燥し、溶媒を減圧下濃縮した。残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ^{TM} ｃｏｌｕｍｎ，Ｓｉｚｅ：Ｓ，酢酸エチル：ヘプタン３０％→５０％）で精製して標記化合物（５．０ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．５５－１．６５（ｍ，１Ｈ），１．９３（ｔ，Ｊ＝５．６Ｈｚ，１Ｈ），２．１０－２．１８（ｍ，１Ｈ），２．

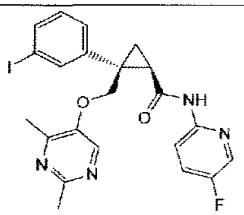
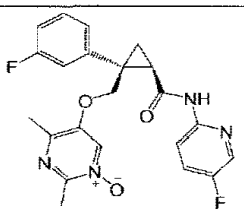
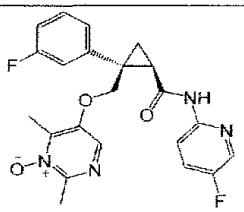
２１（ｓ，３Ｈ），２．，２．５５（ｓ，３Ｈ），４．４０（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），４．５０（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），５．３４（ｄ，Ｊ＝４８．０Ｈｚ，２Ｈ），６．９７－７．０４（ｍ，１Ｈ），７．１４－７．２１（ｍ，１Ｈ），７．２２－７．２８（ｍ，１Ｈ），７．３３（ｔｄ，Ｊ＝８．０Ｈｚ，６．０Ｈｚ，１Ｈ），７．７０（ｔｄ，Ｊ＝８．８Ｈｚ，２．０Ｈｚ，１Ｈ），８．０９（ｄ，Ｊ＝８．０Ｈｚ，１Ｈ），８．３０（ｄ，Ｊ＝２．０Ｈｚ，１Ｈ），８．３２（ｔ，Ｊ＝２．０Ｈｚ，１Ｈ），８．４０（ｂｒｓ，１Ｈ）．
ＭＳ［Ｍ＋Ｎａ］$^{+}$＝４４７

【０３８２】

実施例２８３は製造例５６で得られたカルボン酸Ｐれｐ５６を、実施例８２と同様の手法によって製造した。実施例２８４，２８５は実施例８１と同様の方法によって製造した。

【０３８３】

【表６７】

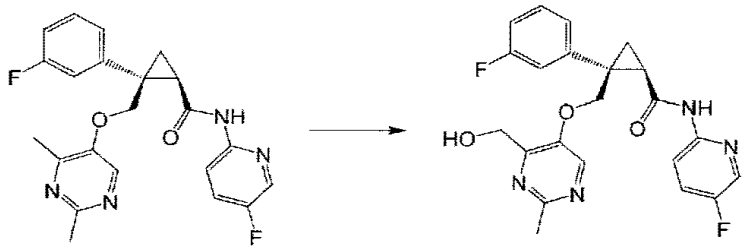
実施例	構造式	NMR及び／又はMS
２８３		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ppm）：１．５９－１．６２（m，１H），１．９０（t，J＝５．８Hz，１H），２．０３－２．１３（m，１H），２．２４（s，３H），２．５６（s，３H），４．４２（q，J＝１２．０Hz，２H），７．１０（t，J＝７．８Hz，１H），７．３６－７．４５（m，２H），７．６２－７．６７（m，１H），７．８５（s，１H），７．９７（s，１H），８．０４－８．１１（m，１H），８．１４（d，J＝２．４Hz，１H），８．２８（s，１H） MS［M＋H］$^+$＝５１９
２８４		^{1}H－NMR（６００MHz，CD$_3$OD）δ（ppm）：１．５８（t，J＝６．０Hz，１H），１．８８（t，J＝６．０Hz，１H），２．１９（s，３H），２．４９（s，３H），２．５２（t，J＝９．０Hz，１H），４．４２（d，J＝１２．０Hz，１H），４．６５（d，J＝１２．０Hz，１H），７．００－７．０４（m，１H），７．３３－７．３８（m，３H），７．４６－７．５０（m，１H），７．９６（dd，J＝６．０Hz，１H），８．１７（d，J＝０．３Hz，１H），８．１９（s，１H） MS［M＋H］$^+$＝４２７
２８５		^{1}H－NMR（４００MHz，CD$_3$OD）δ（ppm）：１．５８（dd，J＝８．０，５．２Hz，１H），１．８９（dd，J＝６．０，５．２Hz，１H），２．２１（s，３H），２．５０－２．５６（m，１H），２．５２（s，３H），４．５２（d，J＝１０．０Hz，１H），４．７６（d，J＝１０．０Hz，１H），６．９８－７．０６（m，１H），７．３２－７．４１（m，３H），７．４７（ddd，J＝９．２，８．０，３．２Hz，１H），７．９４（dd，J＝９．４，４．２Hz，１H），７．９８（s，１H），８．１８（d，J＝３．２Hz，１H） MS［M＋H］$^+$＝４２７

【０３８４】

実施例２８６

（１Ｒ，２Ｓ）－Ｎ－（５－フルオロピリジン－２－イル）－２－［（４－ヒドロキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）シクロプロパンカルボキサミド（２８６）の合成

【化６９】



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【０３８５】

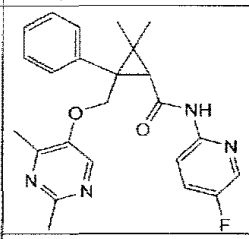
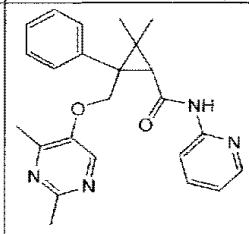
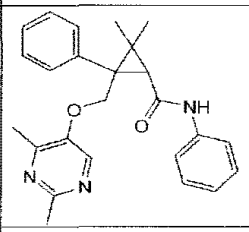
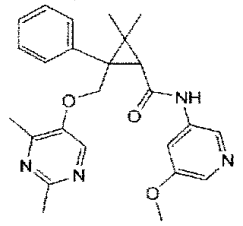
化合物９５（２００ｍｇ）のＴＨＦ（１０ｍｌ）溶液に、－７８℃撹拌下で、ｎ－ＢｕＬｉ（２．７６Ｍ　ｎ－ヘキサン溶液：０．３７１ｍｌ）を加え、一時間撹拌した。（２－ベンズスルフォニル－３－フェニルオキサジリジン）（Ｄａｖｉｓ，Ｆ．Ａ．，Ｊ．Ｏｒｇ．Ｃｈｅｍ．１９８８，５３，５００４－）（１３５ｍｇ）のＴＨＦ（３ｍｌ）溶液を－７８℃で加え、室温まで昇温させながら１４時間撹拌した。飽和塩化アンモニウム水溶液を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄した後、硫酸マグネシウムで乾燥し、減圧下濃縮した。得られた残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，ＨｉＦｌｕｓｈ™　ｃｏｌｕｍｎ，ヘプタン／酢酸エチル１０％＞＞１００％）で精製した後、再度ＨＰＬＣで精製し、標記化合物（１．１９ｍｇ）を得た。
^{1}Ｈ－ＮＭＲ（６００ＭＨｚ，CD_3OD）δ（ｐｐｍ）：１．５６（ｔ，Ｊ＝６．０Ｈｚ，１Ｈ），１．８５（ｔ，Ｊ＝６．０Ｈｚ，１Ｈ），２．４９（ｔ，Ｊ＝６．０Ｈｚ，１Ｈ），２．５３（ｓ，３Ｈ），４．４１（ｄ，Ｊ＝１２．０Ｈｚ，１Ｈ），４．４９（ｄ，Ｊ＝１２．０Ｈｚ，１Ｈ），４．５７（ｄ，Ｊ＝１２．０Ｈｚ，１Ｈ），４．６６（ｄ，Ｊ＝１２．０Ｈｚ，１Ｈ），６．９８－７．０４（ｍ，１Ｈ），７．３２－７．３６（ｍ，１Ｈ），７．３６－７．３９（ｍ，２Ｈ），７．４４－７．５０（ｍ，１Ｈ），７．９０－７．９５（ｍ，１Ｈ），８．１３（ｓ，１Ｈ），８．１７（ｄ，１Ｈ）．
ＭＳ［Ｍ＋Ｎａ］$^{+}$＝４４９

【０３８６】

実施例２８７から２９０の化合物はカルボン酸Ｐｒｅｐ４８－５から実施例に準じて合成した。

【０３８７】

【表６８】

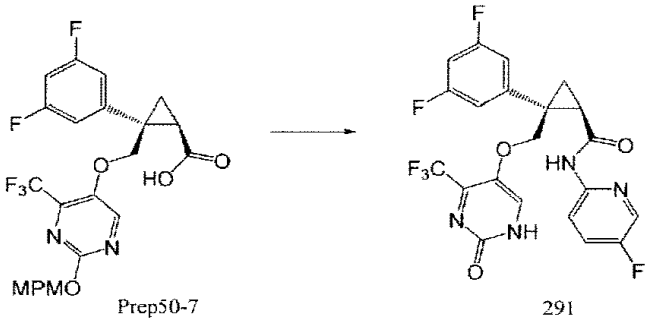
実施例	構造式	NMR（４００MHz，CDCl$_3$）及び／又はMS
２８７		MS［M+H］$^+$＝４２１
２８８		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ppm）：１．０６（s，３H），１．５６（s，３H），１．９４（s，１H），２．２６（s，３H），２．５７（s，３H），４．６７（d，J＝９．６Hz，１H），４．７４（d，J＝９．６Hz，１H），７．２３－７．４１（m，６H），７．８６－８．０６（m，２H），８．２０（brd，J＝８．８Hz，１H），８．３５（dd，J＝４．８，１．２Hz，１H），８．５４（d，J＝１．２Hz，１H）．
２８９		MS［M+H］$^+$＝４０２
２９０		MS［M+H］$^+$＝４３３

【０３８８】

実施例２９１

（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－Ｎ－（５－フルオロピリジン－２－イル）－２－［（２－オキソ－４－トリフルオロメチル－１，２－ジヒドロピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド（２９１）の合成

【化７０】



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【０３８９】

化合物Ｐｒｅｐ５０－７（１００ｍｇ）のＤＭＦ溶液（２ｍｌ）に２－アミノ－５－フルオロピリジン（２６．４ｍｇ）、ＨＡＴＵ（８９．４ｍｇ）、Ｎ，Ｎ－ジイソプロピルエチルアミン（４０．７μｌ）を加えた。室温で終夜攪拌した後、反応液に水を加え、ジエチルエーテルで抽出した。有機層を飽和食塩水で洗浄。無水硫酸マグネシウムで乾燥し濾過した。濾液を減圧濃縮し、残渣に４Ｎ塩酸／酢酸エチル（２ｍｌ）を加え室温で１時間撹拌させた。反応系を減圧濃縮した。残渣に飽和炭酸水素ナトリウム水溶液と酢酸エチルを加え分液抽出した。得られた有機層を硫酸マグネシウムで乾燥させた。減圧濃縮し、得られた残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ^{TM} ｃｏｌｕｍｎ，溶出溶媒：ｎ－ヘプタン：酢酸エチル＝２：１→酢酸エチル）で精製して標記化合物（３０ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：１．５９－１．６３（ｍ，１Ｈ），１．８６（ｔ，Ｊ＝６．０Ｈｚ，１Ｈ），２．１７（ｂｒｄｔ，Ｊ＝６．０Ｈｚ，１Ｈ），４．４１（ｔ，Ｊ＝１０．８Ｈｚ，２Ｈ），６．７０－６．７６（ｍ，１Ｈ），６．９７（ｄ，Ｊ＝６．０Ｈｚ，２Ｈ）７．３８－７．４３（ｍ，１Ｈ），７．９１（ｓ，１Ｈ），８．０６－８．０９（ｍ，２Ｈ），９．１３（ｓ，１Ｈ）．

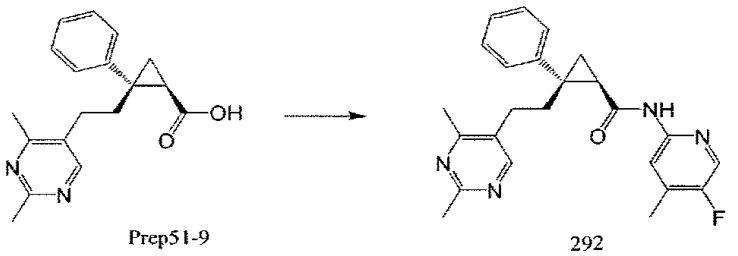
ＭＳ［Ｍ＋Ｎａ］$^{+}$＝４８５．

【０３９０】

実施例２９２

（１Ｒ，２Ｒ）－２－［２－（２，４－ジメチルピリミジン－５－イル）エチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド（２９２）の合成

【化７１】



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【０３９１】

化合物Ｐｒｅｐ５１－９から実施例２９１と同様にして標題化合物を得た。

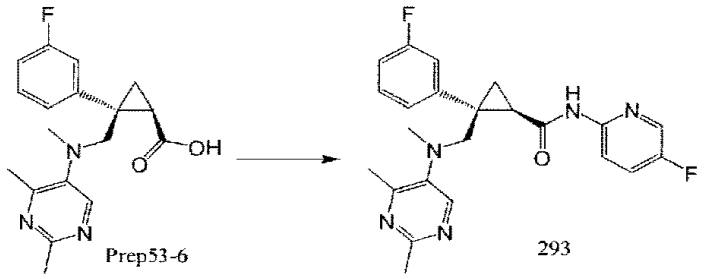
ＭＳ［Ｍ＋Ｈ］$^{+}$＝４０５

【０３９２】

実施例２９３

（１Ｒ，２Ｓ）－２－［Ｎ－（２，４－ジメチルピリミジン－５－イル）メチルアミノメチル］－Ｎ－（５－フルオロピリジン－２－イル）－２－（３－フルオロフェニル）シクロプロパンカルボキサミド（２９３）の合成

【化７２】



【０３９３】

化合物Ｐｒｅｐ５３－６（５０ｍｇ）をＤＭＦ（１５．６ｍｌ）に溶解させ、ＨＡＴＵ（１１６ｍｇ）、Ｎ，Ｎ－ジイソプロピルエチルアミン（７９．４μｌ）、２－アミノ－５－フルオロ－４－ピコリン（５７．５ｍｇ）を加え室温で１時間撹拌した。反応液に水を加えて、減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝７：３～３：７）で精製し、標記化合物（２６．８ｍｇ）を得た。

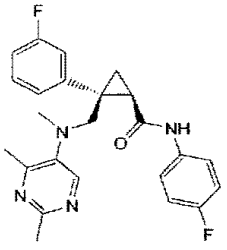
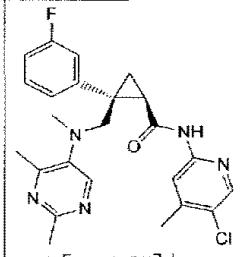
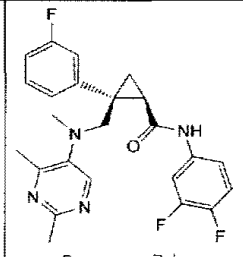
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：１．５４（ｄｄ，Ｊ＝９．６，４．８Ｈｚ），１．６９（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），１．８６－１．９０（ｍ，１Ｈ），２．０４（ｓ，３Ｈ），２，３２（ｓ，１Ｈ），２．５２（ｓ，３Ｈ），２．６３（ｓ，３Ｈ），３，５４（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），３．５９（ｄ，Ｊ＝１３．６Ｈｚ，１Ｈ），６．８９－７．０５（ｍ，３Ｈ），７．２０－７．２６（ｍ，２Ｈ），７．９７（ｓ，１Ｈ），８．０５－８．１０（ｍ，２Ｈ），８．１０（ｓ，１Ｈ），８．５５（ｂｒｓ，１Ｈ）．

【０３９４】

実施例２９４から２９６の化合物はカルボン酸Ｐｒｅｐ５３－６と任意のアミンから実施例２９３に準じて合成した。

【０３９５】

【表６９】

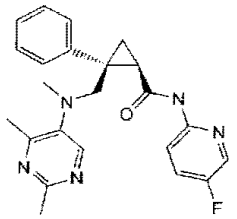
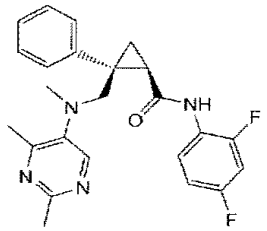
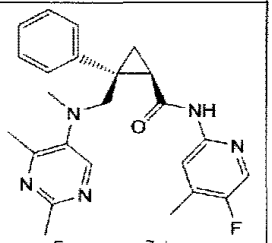
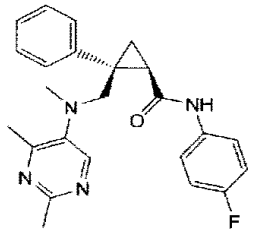
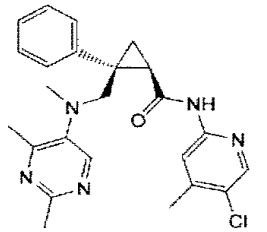
実施例	構造式、MS	実施例	構造式、MS	実施例	構造式、MS
294	 MS[M+H]$^{+}$＝423	295	 MS[M+H]$^{+}$＝454	296	 MS[M+H]$^{+}$＝441

【０３９６】

実施例２９７から３０１の化合物は化合物Ｐｒｅｐ５４を用いて実施例２９３に準じて合成した。

【０３９７】

【表７０】

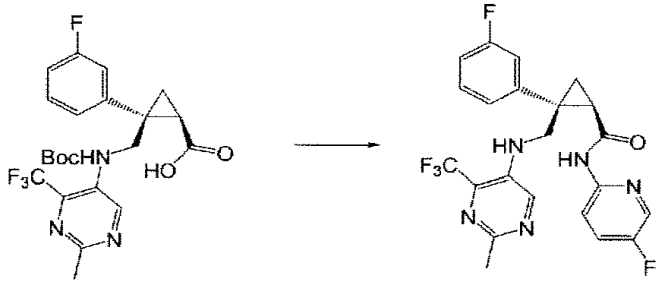
実施例	構造式、MS	実施例	構造式、MS	実施例	構造式、MS
297	 MS[M+H]$^+$=405	298	 MS[M+H]$^+$=423	299	 MS[M+H]$^+$=420
300	 MS[M+H]$^+$=405	301	 MS[M+H]$^+$=436		

【０３９８】

実施例３０２

（１Ｒ，２Ｓ）－２－（３－フルオロフェニル）－Ｎ－（５－フルオロピリジン－２－イル）－２－［Ｎ－（２－メチル－４－トリフルオロメチルピリミジン－５－イル）アミノメチル］シクロプロパンカルボキサミド（３０２）の合成

【化７３】



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【０３９９】

化合物Ｐｒｅｐ５５－６（３０ｍｇ）のＤＭＦ溶液（１ｍｌ）に２－アミノ－５－フルオロピリジン（８．６ｍｇ）、ＨＡＴＵ（２９．２ｍｇ）、Ｎ，Ｎ－ジイソプロピルエチルアミン（１３．３μｌ）を加えた。室温で終夜撹拌した後、反応液に水を加え、ジエチルエーテルで抽出した。有機層をブラインで洗浄。無水硫酸マグネシウムで乾燥し濾過した。濾液を減圧濃縮し、残渣に４Ｎ塩酸／酢酸エチル（３ｍｌ）を加え室温で１時間撹拌させた。反応系を減圧濃縮した。残渣に飽和炭酸水素ナトリウム水溶液と酢酸エチルを加え分液抽出した。得られた有機層を硫酸マグネシウムで乾燥させた。減圧濃縮し、得られた残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ^{TM} ｃｏｌｕｍｎ，溶出溶媒：ｎ－ヘプタン：酢酸エチル＝９：１→１：１）で精製して標記化合物（８．６ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_3$）δ（ｐｐｍ）：１．５３－１．５６（ｍ，１Ｈ），１．８１（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．０２（ｂｒｄｔ，１Ｈ），２．５７

（ｓ，３Ｈ），３．７７（ｄｄ，Ｊ＝５．６Ｈｚ，１４．０Ｈｚ，１Ｈ），３．８９（ｄｄ，Ｊ＝５．６Ｈｚ，１３．６Ｈｚ，１Ｈ），４．４５（ｂｒｄｓ，１Ｈ），６．９８－７．１５（ｍ，３Ｈ），７．３０－７．４７（ｍ，２Ｈ），８．１３－８．１７（ｍ，３Ｈ），８．３２（ｓ，１Ｈ）．

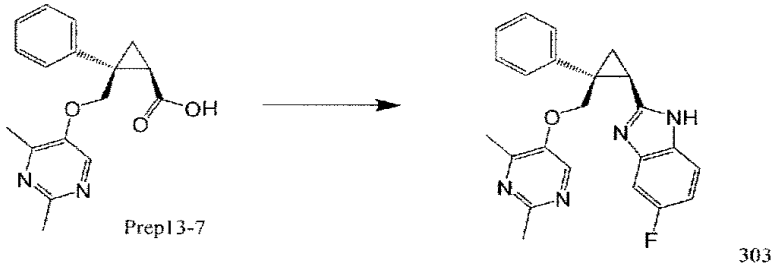
ＭＳ［Ｍ＋Ｎａ］$^{+}$＝４８６．

【０４００】

実施例３０３

２－｛（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロピル｝－５－フルオロ－１Ｈ－ベンズイミダゾール（３０３）の合成

【化７４】



【０４０１】

化合物Ｐｒｅｐ１３－７（１００ｍｇ）のＤＭＦ溶液（３ｍｌ）にＨＡＴＵ（１５３ｍｇ）、ＤＩＰＥＡ（１０４μｌ）、３，４－ジアミノ－１－フルオロベンゼン（４５．３ｍｇ）を加え室温で終夜撹拌させた。反応系に水を加え酢酸エチルで分液抽出した。得られた有機層を硫酸マグネシウムで乾燥させた。減圧濃縮し得られた残渣を酢酸（３ｍｌ）に溶解させ、９０℃にて５時間撹拌させた。反応系を減圧濃縮し、ＮＨ－シリカパッドにてろ過し、ろ液を減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ^{TM} ｃｏｌｕｍｎ，ｎ－ヘプタン：酢酸エチル＝５：１→酢酸エチル）で精製し標記化合物（１５ｍｇ）を得た。

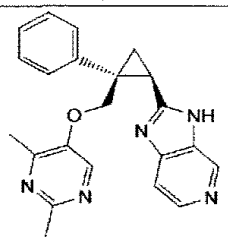
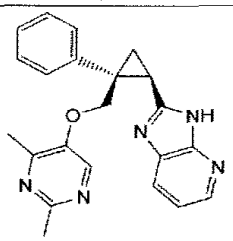
ＭＳ［Ｍ＋Ｈ］$^{+}$＝３８９．

【０４０２】

実施例３０４および３０５の化合物は実施例３０３と同様の手法で合成した。

【０４０３】

【表７１】

実施例	構造式、ＭＳ	実施例	構造式、ＭＳ
３０４	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝３７２	３０５	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝３７２

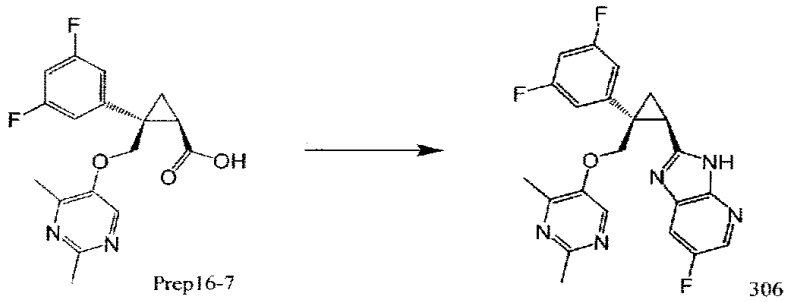
【０４０４】

実施例３０６

２－｛（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロピル｝－６－フルオロ－１Ｈ－イミ

ダゾ［４，５－ｂ］ピリジン（３０６）の合成

【化７５】



【０４０５】

化合物Ｐｒｅｐ１６－７（３０ｍｇ）のＤＭＦ溶液（９００μｌ）にＨＡＴＵ（４５．９ｍｇ）、ＤＩＰＥＡ（３１．２μｌ）、２，３－ジアミノ－５－フルオロベンゼン（１５．５ｍｇ）を加え室温で２時間撹拌させた。反応系に飽和炭酸水素ナトリウム水溶液を加え酢酸エチルで分液抽出した。得られた有機層を硫酸マグネシウムで乾燥させた。減圧濃縮し得られた残渣を酢酸（９００μｌ）に溶解させ、ＩＮＩＴＩＡＴＯＲ　ＭＡＩＣＲＯＷＡＶＥ　ＳＹＮＴＨＥＳＩＺＥＲ（Ｂｉｏｔａｇｅ）１５０℃にて１１時間撹拌させた。反応系を減圧濃縮し、残渣を酢酸エチル、炭酸水素ナトリウム水溶液を加え分液抽出した。得られた有機層を硫酸マグネシウムで乾燥させた。減圧濃縮し、得られた残渣をシリカゲルカラムクロマトグラフィー（ＹＡＭＡＺＥＮ，Ｈｉ－Ｆｌｕｓｈ™ ｃｏｌｕｍｎ，ｎ－ヘプタン：酢酸エチル＝５：１→酢酸エチル）で精製し標記化合物（９．３ｍｇ）を得た。

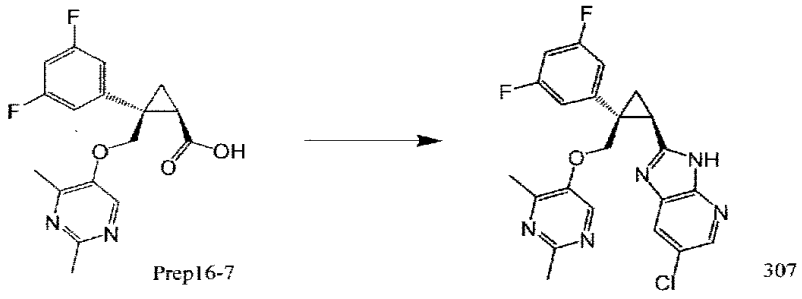
ＭＳ［Ｍ＋Ｈ］$^{+}$＝４２６．

【０４０６】

実施例３０７

６－クロロ－２－｛（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロピル｝－１Ｈ－イミダゾ［４，５－ｂ］ピリジン（３０７）の合成

【化７６】



【０４０７】

実施例３０６と同様の手法にて合成した。

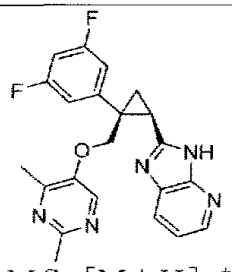
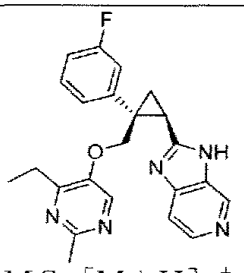
^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：１．８７（ｄｄ，Ｊ＝５．６Ｈｚ，８．８Ｈｚ，１Ｈ），２．１１（ｓ，３Ｈ），２．５０（ｓ，３Ｈ），２．２１（ｔ，Ｊ＝６．０Ｈｚ，１Ｈ），２．６８（ｄｄ，Ｊ＝６．４Ｈｚ，８．８Ｈｚ，１Ｈ），４．４１（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），４．４５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），６．７７－６．８２（ｍ，１Ｈ），６．９９－７．０９（ｍ，２Ｈ），７．８２（ｓ，１Ｈ），７．８８（ｄ，Ｊ＝２．４Ｈｚ，１Ｈ），８．２２（ｄ，Ｊ＝２．０Ｈｚ，１Ｈ），１１．５（ｓ，１Ｈ）．

【０４０８】

以下の化合物は実施例３０６と同様の手法で合成した。

【０４０９】

【表７２】

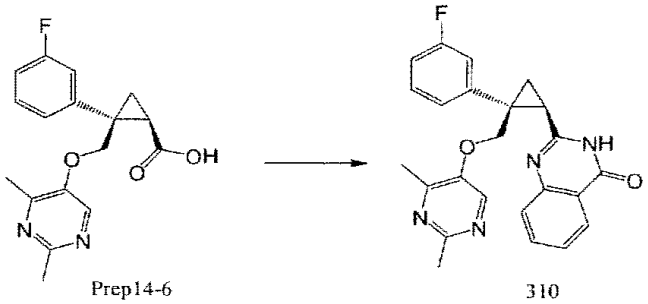
実施例	構造式、ＭＳ	実施例	構造式、ＭＳ
３０８	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４０８	３０９	 ＭＳ［Ｍ＋Ｈ］$^{+}$＝４０４

【０４１０】

実施例３１０

２－［（１Ｒ，２Ｓ）－２－｛［（２，４－ジメチルピリミジン－５－イル）オキシ］メチル｝－２－（３－フルオロフェニル）シクロプロピル］キナゾリン－４（１Ｈ）－オン（３１０）の合成

【化７７】



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【０４１１】

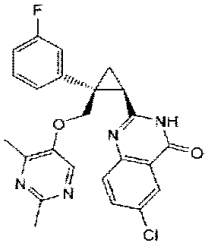
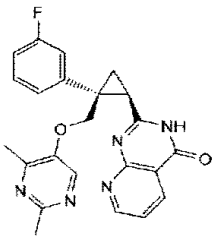
化合物Ｐｒｅｐ１４－６（５０ｍｇ）、２－アミノベンズアミド（２３．７ｍｇ）、ＨＡＴＵ（６６、１ｍｇ）をＤＭＦ（０．２４ｍｌ）に溶解させ、Ｎ，Ｎ－ジイソプロピルエチルアミン（２２．９μｌ）を加え室温で２４時間撹拌した。反応液に水を加え、酢酸エチル（ｘ３）で抽出した。有機層を水、飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥した。溶媒を減圧下留去し、残渣をＩＰＡ（３ｍｌ）に溶解させ、カリウムｔｅｒｔ－ブトキサイド（３５．５ｍｇ）を加え、１００℃で２時間加熱撹拌した。反応液を室温に冷却し、水を１滴滴下し、減圧濃縮した。残渣をＮＨ－シリカゲルカラムクロマトグラフィー（ｎ－ヘプタン：酢酸エチル＝９：１から０：１）で精製して標記化合物（２０．６ｍｇ）を得た。

^{1}Ｈ－ＮＭＲ（４００ＭＨｚ，ＣＤＣｌ$_{3}$）δ（ｐｐｍ）：１．６５（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），２．１４（ｓ，３Ｈ），２．３３（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．４４（ｓ，３Ｈ），２．７５－２．７９（ｍ，１Ｈ），４．４３（ｄ，Ｊ＝９．６，１Ｈ），４．４５（ｄ，Ｊ＝９．６Ｈｚ，１Ｈ），７．０７（ｔｄｄ，Ｊ＝８．０，２．０，１．２Ｈｚ，１Ｈ），７．３９（ｔｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），７．４６－７．５２（ｍ，２Ｈ），７．６２－７．６５（ｍ，２Ｈ），７．７５（ｔ，Ｊ＝６．８Ｈｚ，１Ｈ），７．７９（ｓ，１Ｈ），８．３３（ｄ，Ｊ＝８．０Ｈｚ，１Ｈ），１３．１（ｂｒｓ，１Ｈ）．

ＬＣ－ＭＳ（ＥＳ．Ｐｏｓ）：４１７［Ｍ＋Ｈ＋］／４１６

【０４１２】

【表７３】

実施例	構造式	NMR（４００MHz，CDCl$_3$）及び／又はMS
３１１		^{1}H－NMR（４００MHz，CDCl$_3$）δ（ppm）：１．６８（ｄｄ，Ｊ＝８．０，５．２Ｈｚ，１Ｈ），２．１１（ｓ，３Ｈ），２．３１（ｔ，Ｊ＝５．２Ｈｚ，１Ｈ），２．４５（ｓ，３Ｈ），２．７６（ｄｄ，Ｊ＝８．０，６．０Ｈｚ，１Ｈ），４．４０（ｄ，Ｊ＝１０．０，１Ｈ），４．４５（ｄ，Ｊ＝１０．０Ｈｚ，１Ｈ），７．１０（ｔｄ，Ｊ＝８．８，２．０Ｈｚ，１Ｈ），７．４３（ｔｄ，Ｊ＝８．８，６．０Ｈｚ，１Ｈ），７．５２（ｄ，Ｊ＝８．８Ｈｚ，１Ｈ），７．５６（ｄ，Ｊ＝８．８Ｈｚ，１Ｈ），７．６１（ｄ，Ｊ＝８．８Ｈｚ，１Ｈ），７．６８（ｄｄ，Ｊ＝８．８，２．４Ｈｚ，１Ｈ），７．７８（ｓ，１Ｈ），８．２７（ｄ，Ｊ＝２．４Ｈｚ，１Ｈ），１３．４（ｓ，１Ｈ）． ＬＣ－ＭＳ（ＥＳ．Ｐｏｓ）：４５１［Ｍ＋Ｈ＋］／４５０
３１２		ＬＣ－ＭＳ（ＥＳ．Ｐｏｓ）：４１８［Ｍ＋Ｈ＋］／４１７

【０４１３】

試験例

１．オレキシン受容体結合能測定

アッセイは９６ウェルのＷｈｅａｔ　Ｇｅｒｍ　Ａｇｇｌｕｔｉｎｉｎ　ＦｌａｓｈＰｌａｔｅ（Ｐｅｒｋｉｎ　Ｅｌｍｅｒ）を用いて行った。１アッセイのボリュームは１００μｌで、反応液の組成は以下の通りである：

２５ｍＭ　ＨＥＰＥＳ，ｐＨ７．５，１ｍＭ　ＣａＣｌ$_2$，５ｍＭ　ＭｇＣｌ$_2$，０．５％ＢＳＡ（牛血清アルブミン），０．１％アジ化ナトリウム，０．０５％Ｔｗｅｅｎ－２０，０．２％ＤＭＳＯ。

ＯＸ２ＲまたはＯＸ１Ｒを発現する組み換え型ＣＨＯ細胞から調製した細胞膜を５ｉｇ　ｐｒｏｔｅｉｎ／ａｓｓａｙ、様々な濃度の評価化合物、トレーサーとして［^{125}Ｉ］－オレキシン－Ａを０．２ｎＭ添加し、室温で３０分間反応を行った。反応後、反応溶液を全て除去し、２００μｌのｗａｓｈ　ｂｕｆｆｅｒ（２５ｍＭ　ＨＥＰＥＳ，ｐＨ７．５，１ｍＭ　ＣａＣｌ$_2$，５ｍＭ　ＭｇＣｌ$_2$，０．５％ＢＳＡ，０．１％アジ化ナトリウム，０．０５％Ｔｗｅｅｎ－２０および５００ｍＭ塩化ナトリウム）でウェルを１回洗浄した。最後にそれぞれのウェルの放射活性をシンチレーションカウンター（ＴｏｐＣｏｕｎｔ，Ｐｅｒｋｉｎ　Ｅｌｍｅｒ）で測定した。得られた結果を下の表に示した。

【０４１４】

【表７４】

実施例No.	OX1 RBA nM	OX2 RBA nM	実施例No.	OX1 RBA nM	OX2 RBA nM	実施例No.	OX1 RBA nM	OX2 RBA nM
1	139	7	2	296	19	3	1034	＞200
7	1235	71	15	213	41	16	40	1．9
17	294	38	18	344	33	20	1884	117
22	273	17	23	1697	67	26	20	3．7
29	459	55	37	41	8	38	518	29
44		26	45	13．9	6．2	48	1153	159
51	6．4	3．9	52	37	28	60	＞2000	105
61	874	16	62	＞2000	153	64	74	15
65	1034	81	66	398	50	67	1610	164
73	3．4	5．7	81	2592	63	82	2．4	3．7
84	6	3	87	43	10	88	267	13
95	13．4	5．2	96	32	5	98	18	10
100	40	7．5	105	195	18	109	12	5．8
113	22	179	114	40	1612	115		21
119	21	5．2	120	123	7	121	10	3．1
123	451	20	125	1045	84	127	1099	80
129	1	1．5	130	22	4	135	14	8
136		15	139	22	3．3	141	9	1．3
143		14	144		12	153	447	32
155	10	6	158	180	27	161	50	12
162	65	13	163	＜20	10	164	3	6
165	29	7	167	38	10	170		7
174	33	55	177	334	84	178	769	60
182	99	21	186	22	7	187		16
191	1	1	192	12	5	199	2	2
200	67	12	203	215	8	205	9	6
208		11	211	20	4	212	4	7
218	10	3	219	10	3	225	6	3
228		45	231		7	235		6
237		31	240	9	2．9	243	2	3．3
247	22	3	255		27	259		＞60
260	＞2000	70	263	82	17	266	30	2．7
267	118	64	270	264	58	275	188	132
278	76	10	279	24	3．2	280	24	21
282	21	2．4	283	172	9	284	112	6
285	77	16	286	＞200	4．5	290	226	＞200
291	＞200	49	295	5	6	300	495	34
302	8	3	303	75	3	308		31
309		10	311	23	3．1	312	136	62

【０４１５】

２．拮抗作用測定（ＰＬＡＰアッセイ）

天然ペプチドアゴニストであるオレキシンＡによるＯＸ２およびＯＸ１受容体の活性化を防止する、本発明化合物のアンタゴニスト機能を、細胞ベースレポーターアッセイを使用して測定した。発現ベクターとしてｐＢａｂｅＣＬＩＨ　を有し、遺伝子組換えヒトＯＸ２受容体を発現するＨＥＫ－２９３セルライン（受託番号：ＮＭ＿００１５２６．３）または遺伝子組換えヒトＯＸ１受容体を発現するＨＥＫ－２９３セルライン（受託番号：ＮＭ＿００１５２５．２）を使用した。細胞は、ダルベッコ修正イーグル培地（１０％ｖ／ｖ熱不活化ウシ胎児血清を含むＳｉｇｍａ　Ｃａｔ　Ｎｏ．Ｄ６０４６）中の非コート９６ウェルプレートに、１０，０００細胞／ｗｅｌｌで播種し、３７℃で一晩放置し、プレートに付着させた。翌日細胞を、ダルベッコ修正イーグル培地（０．１％ｗ／ｖ熱不活化ウシ胎児血清アルブミンＳｉｇｍａ　Ｃａｔ　Ｎｏ．Ａ８８０６を含む）に溶解させた本発明化合物でインキュベートし、最終濃度０．１％のメチルスルホキシドをセルプレートに追加した。

室温でのインキュベーション１時間後、ヒトオレキシン－Ａとフォルスコリンを、ウシ胎児血清アルブミンを含む同じ培地に溶解し、細胞に加えて、最終濃度３００　ｎｍｏｌ／Ｌのフォルスコリンを追加した。次いで細胞を３７℃で約１８－２４時間培養した。この間、オレキシン受容体の活性化および用量依存的な細胞内カルシウムの増加により、レポーター酵素である胎盤型アルカリホスファターゼ（ＰＬＡＰ）を、ｐＢａｂｅＣＬｃｒｅ４ｖＰｄＮＮベクター内のＣＲＥｘ４　＋　ＶＩＰプロモーターコントロール下の発現し分泌した。酵素活性の検出は、翌日に、細胞培地上清を、２０μｌ検出バッファー（炭酸水素ナトリウム１．３４ｇ／Ｌ、炭酸ナトリウム１．２７ｇ／Ｌおよび硫酸マグネシウム７水和物０．２ｇ／Ｌリットルを水中に含む）およびＬｕｍｉ－Ｐｈｏｓ５３０試薬２５μｌ（和光化学工業株式会社）と混合し、室温で２時間のインキュベーション後に、発光測定（ＡＲＶＯリーダー、パーキンエルマー）により、実施した。１ｎｍｏｌ／Ｌヒトオレキシン－Ａの活性に対する本発明化合物のＩＣ５０値を、ゼロから３００ｎｍｏｌ／Ｌの滴定によりそれぞれの受容体についてのオレキシン－ＡについてのＫｄ値を測定した後に、Ｃｈｅｎｇ－Ｐｒｕｓｏｆｆ式を用いて変換した。得られた結果を下の表に示した。

【０４１６】

【表７５】

実施例No.	OX1PLAP (Ki)	OX2PLAP (Ki)	実施例No.	OX1PLAP (Ki)	OX2PLAP (Ki)	実施例No.	OX1PLAP (Ki)	OX2PLAP (Ki)
1	157	10.2	16	80	5.4	26	27.3	0.4
45	19.4	0.44	51	29	1.2	61	>667	25.7
64	133.3	6.3	65	>667	60	66	>667	34.3
67	>667	57.1	82	0.96	0.085	95	9.9	0.69
100	146.7	9.4	114	47.3	285.7	119	21.3	0.6
120	273.3	5.7	121	26.7	0.3	129	0.97	0.059
139	113.3	1.7	161	32	2.9	164	0.93	0.124
186	86.7	3.4	240	17.8	0.89	263	193.3	8.6

【０４１７】

３．睡眠実験

本化合物の睡眠効果を測定する方法として、マウス（Ｃ５７ＢＬ／６ＮＣｒｌＣｒＬｊ）を用いて脳波測定（Ｅｌｅｃｔｒｏｅｎｃｅｐｈａｌｏｇｒａｍ：ＥＥＧ）を行なった。

脳波測定のために各マウスに電極埋め込み手術を行ない、個別ケージにて自由行動できる状態で１週間以上飼育した。その後、電極を脳波測定装置に接続した。

消灯直前に化合物を投与し、消灯から３時間の睡眠時間を計測した。化合物の睡眠効果

は、暗期、明期いずれの時間帯でも同様の作用を示すことが確認された。　化合物の投与は１０ｍｇ／ｋｇの経口もしくは腹腔内投与を行なった。

睡眠解析についてはキッセイコムテック株式会社の自動解析ソフト用いた後、周波数分析データを詳細に解析し、睡眠時間を算出した。

化合物の睡眠時間増加作用については、薬物無投与日の睡眠時間と薬物投与日の睡眠時間の変化によって評価を行なった。得られた結果を下の表に示した。

【０４１８】

【表７６】

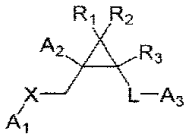
実施例No.	睡眠延長時間10mg／kg (min/3 hrs)	実施例No.	睡眠延長時間10mg／kg (min/3 hrs)	実施例No.	睡眠延長時間10mg／kg (min/3 hrs)
1	18. 3	16	19	45	15. 2
51	22. 2	73	22. 7	82	33. 5
95	39. 8	96	12. 1	100	23. 8
105	14. 3	119	16	120	11. 5
121	26. 7	129	30	130	24. 2
141	28. 7	161	10	164	48. 3
186	14. 7	191	41. 8	199	36. 2
240	7. 7	263	27. 3		

【産業上の利用可能性】

【０４１９】

以上に詳細に説明したように、本発明のシクロプロパン化合物又はその医薬上許容される塩は、極めて優れたオレキシン受容体阻害作用を有し、オレキシンに起因する、ナルコレプシーに代表される睡眠障害の予防剤または治療剤として極めて有用である。具体的には、不眠症、ナルコレプシー（発作性睡眠）および過剰の眠気、睡眠関連ジストニア、下肢静止不能症候群、睡眠時無呼吸、時差ぼけ症候群、交代勤務症候群、遅延睡眠相症候群又は睡眠相前進症候群のその他の疾患などの睡眠障害の予防または治療に有効である。更には、気分変調性障害、気分障害、精神及び不安障害；糖尿病及び食欲、味覚、摂食、又は摂飲障害；視床下部疾患；生物学的及び概日リズム障害；神経疾患、神経因性疼痛及び下肢静止不能症候群から選ばれる疾病に不随する睡眠障害；うつ病とうつ病に関連した不眠症；双極性障害と双極性障害に関連した不眠症；不安障害と不安障害に関連した不眠症；パーキンソン症に関連した不眠症；統合失調症に関連した不眠症；精神障害に関連した不眠症；睡眠時無呼吸；ナルコレプシー；特発性不眠症；睡眠時随伴症；麻薬依存症；ニコチン依存症；良性前立腺肥大症；健康な集団における並びに精神及び神経疾患における全認知症及び認知機能障害；並びに全身のオレキシン系機能不全に関連した他の疾病などの疾病の予防又は治療に有効である。

【書類名】特許請求の範囲
【請求項１】
式（Ｉ）：
【化１】



（Ｉ）

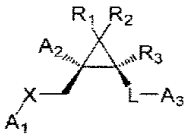
［式中、
A_1はそれぞれ置換基群αから選択される１乃至３個の置換基を有していてもよいピリミジニル基又はＮ－オキシドピリミジニル基であり、
A_2及びA_3は独立して置換基群αから選択される１乃至３個の置換基を有していてもよいグループ１から選択されるアリール基、又は置換基群βから選択される１乃至３個の置換基を有してもよいグループ３から選択される複素環基であり、
R_1、R_2及びR_3は独立して水素原子、ハロゲン原子、置換基群βから選択される１ないし３の置換基を有してもよいC_{1-6}アルキル基又は置換基群βから選択される１ないし３の置換基を有してもよいC_{3-8}シクロアルキル基であり、
Ｘは、酸素原子、C_{1-6}アルキレン基、式－NR_4－（式中、R_4は水素原子又はC_{1-6}アルキル基である。）、－Ｓ－、－ＳＯ－又は－SO_2－であり、
Ｌは、結合又は式－ＣＯNR_5－（R_5は水素原子、C_{1-6}アルキル基又はC_{3-8}シクロアルキル基である。）である。
置換基群α：シアノ基、ハロゲン原子、水酸基、オキソ基、式－NR_6R_7（式中、R_6およびR_7は独立して水素原子又はC_{1-6}アルキル基である。）、置換基群βから選択される１乃至３個の置換基を有していてもよいC_{1-6}アルキル基、置換基群βから選択される１乃至３個の置換基を有していてもよいC_{1-6}アルコキシ基、置換基群βから選択される１乃至３個の置換基を有していてもよいC_{1-6}アルキルカルボニル基、置換基群βから選択される１乃至３個の置換基を有していてもよいC_{1-6}アルキルスルホニル基、置換基群βから選択される１乃至３個の置換基を有していてもよいグループ１から選択されるアリール基及び置換基群βから選択される１乃至３個の置換基を有していてもよいグループ２から選択されるヘテロアリール基。
置換基群β：シアノ基、ハロゲン原子、水酸基、C_{3-8}シクロアルキル基及びC_{1-6}アルコキシ基。
グループ１：フェニル基、ナフチル基、アズレニル基、アントリル基及びフェナントリル基。
グループ２：フリル基、チエニル基、ピロリル基、イミダゾリル基、トリアゾリル基、テトラゾリル基、チアゾリル基、ピラゾリル基、オキサゾリル基、イソオキサゾリル基、イソチアゾリル基、フラザニル基、チアジアゾリル基、オキサジアゾリル基、ピリジル基、ピラジニル基、ピリダジニル基、トリアジニル基、インドリル基、イソインドリル基、インダゾリル基、ベンゾオキサゾリル基、ベンゾイソオキサジアゾリル基、ベンゾチアゾリル基、ベンゾイソチアゾリル基、キノリル基及びイソキノリル基。
グループ３：フリル基、チエニル基、ピロリル基、イミダゾリル基、トリアゾリル基、テトラゾリル基、チアゾリル基、ピラゾリル基、オキサゾリル基、イソオキサゾリル基、イソチアゾリル基、フラザニル基、チアジアゾリル基、オキサジアゾリル基、ピリジル基、ピラジニル基、ピリダジニル基、ピリミジニル基、トリアジニル基、２－ピリドニル基、４－ピリドニル基、ピリダジドニル基、ピリミジドニル基、プリニル基、プテリジニル基、キノリル基、イソキノリル基、ナフチリジル基、キノキサリル基、シンノリル基、キナゾリル基、フタラジル基、イミダゾピリジル基、イミダゾチアゾリル基、イミダゾオキサゾリル基、ベンゾイミダゾリル基、インドリル基、イソインドリル基、インダゾリル基、ピロロピリジル基、チエノピリジル基、フロピリジル基、ベンゾオキサゾリル基、ベン

ゾイソオキサジアゾリル基、ベンゾチアゾリル基、ベンゾイソチアゾリル基、ピリドピリミジニル基、オキソジヒドロピリドピリミジニル基、ベンゾフリル基、ベンゾチエニル基、ベンゾチアジアゾリル基、ベンゾ［１，３］ジオキソリル基、チエノフリル基、ジヒドロイソベンゾフラニル基、クロマニル基、イソクロマニル基、１，３－ジオキサインダニル基、１，４－ジオキサテトラリニル基及びジヒドロベンゾ［１，４］オキサジニル基。］で示される化合物又はその医薬上許容される塩。

【請求項２】

式（ＩＩ）：

【化２】



（ＩＩ）

［式中、A_1、A_2、A_3、R_1、R_2、R_3、Ｘ及びＬは請求項１に記載の定義と同義である。］

で示される請求項１記載の化合物又はその医薬上許容される塩。

【請求項３】

R_1、R_2及びR_3が水素原子である、請求項１又は２に記載の化合物又はその医薬上許容される塩。

【請求項４】

Ｌが式－ＣＯＮＨ－である、請求項３に記載の化合物又はその医薬上許容される塩。

【請求項５】

Ｘが酸素原子である、請求項４に記載の化合物又はその医薬上許容される塩。

【請求項６】

A_2及びA_3は独立して、それぞれシアノ基、ハロゲン原子、C_{1-6}アルキル基、ハロC_{1-6}アルキル基及びC_{1-6}アルコキシ基から選択される１乃至３個の置換基を有していてもよい、アリール基又はヘテロアリール基である、請求項５に記載の化合物又はその医薬上許容される塩。

【請求項７】

A_2及びA_3は独立して、それぞれシアノ基、ハロゲン原子、C_{1-6}アルキル基、ハロC_{1-6}アルキル基及びC_{1-6}アルコキシ基から選択される１乃至３個の置換基を有していてもよい、フェニル基、ナフチル基、ピリジル基、ピラジニル基、ピリダジニル基、ピリミジニル基、キノリル基又はイソキノリル基である、請求項６に記載の化合物又はその医薬上許容される塩。

【請求項８】

A_2がシアノ基、ハロゲン原子、C_{1-6}アルキル基、ハロC_{1-6}アルキル基及びC_{1-6}アルコキシ基から選択される１乃至３個の置換基を有していてもよいフェニル基である、請求項７に記載の化合物又はその医薬上許容される塩。

【請求項９】

A_3がシアノ基、ハロゲン原子、水酸基、C_{1-6}アルキル基、ハロC_{1-6}アルキル基及びC_{1-6}アルコキシ基から選択される１乃至３個の置換基を有していてもよいフェニル基又はピリジル基である、請求項８に記載の化合物又はその医薬上許容される塩。

【請求項１０】

A_1がハロゲン原子、C_{1-6}アルキル基、ハロC_{1-6}アルキル基、C_{1-6}アルコキシ基C_{1-6}アルキル基、C_{3-8}シクロアルキル基及びC_{1-6}アルコキシ基から選択される１乃至３個の置換基を有していてもよい５－ピリミジニル基である、請求項９に記載の化合物又はその医薬上許容される塩。

【請求項１１】

A_1がメチル基、ヒドロキシメチル基、メトキシメチル基及びメトキシエチル基から選

択される１乃至２個の置換基を有していてもよい５－ピリミジニル基である、請求項１０に記載の化合物又はその医薬上許容される塩。
【請求項１２】
以下の化合物から選ばれる、請求項１乃至１１の何れかに記載の化合物又はその医薬上許容される塩：
１）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド、
２）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド、
３）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロ－４－メチルピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
４）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド、
５）　（１Ｒ，２Ｓ）－Ｎ－（６－フルオロピリジン－３－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
６）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（６－フルオロ－５－メチルピリジン－３－イル）－２－フェニルシクロプロパンカルボキサミド、
７）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－メトキシピリジン－３－イル）－２－フェニルシクロプロパンカルボキサミド、
８）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ，２－ジフェニルシクロプロパンカルボキサミド、
９）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－メチルピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド、
１０）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－［５－フルオロ－４－（メトキシメチル）ピリジン－２－イル］－２－フェニルシクロプロパンカルボキサミド、
１１）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（２－メトキシピリジン－４－イル）－２－フェニルシクロプロパンカルボキサミド、
１２）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニル－Ｎ－［５－（トリフルオロメチル）ピリジン－２－イル］シクロプロパンカルボキサミド、
１３）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニル－Ｎ－［４－（トリフルオロメチル）ピリジン－２－イル］シクロプロパンカルボキサミド、
１４）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－［４－（メトキシメチル）ピリジン－２－イル］－２－フェニルシクロプロパンカルボキサミド、
１５）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
１６）　（１Ｒ，２Ｓ）－Ｎ－［３－（ジメチルアミノ）フェニル］－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
１７）　（１Ｒ，２Ｓ）－Ｎ－（３－クロロフェニル）－２－［（２，４－ジメチルピリ

ミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
１８）　（１Ｒ，２Ｓ）－Ｎ－（３－シアノ－４－フルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
１９）　（１Ｒ，２Ｓ）－Ｎ－（４－クロロ－３－シアノフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
２０）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－［３－（メチルスルフォニル）フェニル］－２－フェニルシクロプロパンカルボキサミド、
２１）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
２２）　（１Ｒ，２Ｓ）－Ｎ－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
２３）　（１Ｒ，２Ｓ）－Ｎ－（３－クロロ－４－フルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
２４）　（１Ｒ，２Ｓ）－Ｎ－（３－シアノ－５－フルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
２５）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（３－メトキシフェニル）－２－フェニルシクロプロパンカルボキサミド、
２６）　（１Ｒ，２Ｓ）－Ｎ－［３－（シアノメチル）フェニル］－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
２７）　（１Ｒ，２Ｓ）－Ｎ－（２－シアノピリジン－４－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
２８）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニル－Ｎ－［３－（トリフルオロメチル）フェニル］シクロプロパンカルボキサミド、
２９）　（１Ｒ，２Ｓ）－Ｎ－（４－シアノピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
３０）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（４－メトキシピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド、
３１）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
３２）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
３３）　（１Ｒ，２Ｓ）－Ｎ－（５－シアノピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
３４）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）シクロプロパンカルボキ

サミド、
３５）　（１Ｒ，２Ｓ）－Ｎ－（４－クロロピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
３６）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシメチルピリジン－２－イル）－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
３７）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシメチルピリジン－２－イル）－２－（３－フルオロフェニル）シクロプロパンカルボキサミド
３８）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）－Ｎ－（４－フルオロフェニル）シクロプロパンカルボキサミド、
３９）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）－Ｎ－フェニルシクロプロパンカルボキサミド、
４０）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシピリジン－２－イル）－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
４１）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（４－フルオロフェニル）－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
４２）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ，２－ビス（４－フルオフェニル）シクロプロパンカルボキサミド、
４３）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシメチルピリジン－２－イル）－２－（４－フルオロフェニル）シクロプロパンカルボキサミド、
４４）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（４－フルオロフェニル）シクロプロパンカルボキサミド、
４５）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシピリジン－２－イル）－２－（４－フルオロフェニル）シクロプロパンカルボキサミド、
４６）　（１Ｒ，２Ｓ）－２－（３－シアノフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（４－フルオロフェニル）シクロプロパンカルボキサミド、
４７）　（１Ｒ，２Ｓ）－２－（３－シアノフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
４８）　（１Ｒ，２Ｓ）－２－（３－シアノフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）シクロプロパンカルボキサミド、
４９）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニル－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド、
５０）　（１Ｒ，２Ｓ）－２－［（４エチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド、
５１）　（１Ｒ，２Ｓ）－Ｎ－（５－シアノピリジン－２－イル）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
５２）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
５３）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）－２－フェニルシクロプロパンカルボキサミド

、
５４）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－（４－フルオロフェニル）－２－フェニルシクロプロパンカルボキサミド、
５５）　（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）シクロプロパンカルボキサミド、
５６）　（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（４－フルオロフェニル）シクロプロパンカルボキサミド、
５７）　（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド
、
５８）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
５９）　（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
６０）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
６１）　（１Ｒ，２Ｓ）－Ｎ－（２，４－ジフルオロフェニル）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
６２）　（１Ｒ，２Ｓ）－Ｎ－（５－シアノピリジン－２－イル）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
６３）　（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシピリジン－２－イル）シクロプロパンカルボキサミド、
６４）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－｛［（４－（メトキシメチル）－２－メチルピリミジン－５－イル）オキシ］メチル｝－２－フェニルシクロプロパンカルボキサミド、
６５）　（１Ｒ，２Ｓ）－Ｎ－（５－シアノピリジン－２－イル）－２－｛［（４－（メトキシメチル）－２－メチルピリミジン－５－イル）オキシ］メチル｝－２－フェニルシクロプロパンカルボキサミド、
６６）　（１Ｒ，２Ｓ）－Ｎ－（５－フルオロピリジン－２－イル）－２－｛［（４－（メトキシメチル）－２－メチルピリミジン－５－イル）オキシ］メチル｝－２－フェニルシクロプロパンカルボキサミド、
６７）　（１Ｒ，２Ｓ）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニル－Ｎ－［５－（トリフルオロメチル）ピリジン－２－イル］シクロプロパンカルボキサミド、
６８）　（１Ｒ，２Ｓ）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
６９）　（１Ｒ，２Ｓ）－Ｎ－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパンカルボキサミド、
７０）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－２－フェニルシクロプロパ

ンカルボキサミド、
７１）　（１Ｒ，２Ｓ）－２－（４－クロロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
７２）　（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）シクロプロパンカルボキサミド、
７３）　（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（４－フルオロフェニル）シクロプロパンカルボキサミド、
７４）　（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド、
７５）　（１Ｒ，２Ｓ）－Ｎ－（５－シアノピリジン－２－イル）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
７６）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
７７）　（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
７８）　（１Ｒ，２Ｓ）－Ｎ，２－ビス（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
７９）　（１Ｒ，２Ｓ）－Ｎ－（２，４－ジフルオロフェニル）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
８０）　（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メトキシピリジン－２－イル）シクロプロパンカルボキサミド、
８１）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）－２－（３－メトキシフェニル）シクロプロパンカルボキサミド、
８２）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（４－フルオロフェニルル）－２－（３－メトキシフェニル）シクロプロパンカルボキサミド、
８３）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（３－メトキシフェニル）シクロプロパンカルボキサミド、
８４）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－メトキシフェニル）シクロプロパンカルボキサミド
８５）　（１Ｒ，２Ｓ）－２－（３－フルオロフェニル）－Ｎ－（５－フルオロピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
８６）　（１Ｒ，２Ｓ）－２－（３－フルオロフェニル）－Ｎ－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
８７）　（１Ｒ，２Ｓ）－２－（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－（ピリジン－２－イル）シクロプロパンカ

ルボキサミド、
８８）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
８９）　（１Ｒ，２Ｓ）－Ｎ，２－ビス（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９０）　（１Ｒ，２Ｓ）－Ｎ－（２，４－ジフルオロフェニル）－２－（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９１）　（１Ｒ，２Ｓ）－Ｎ－（２，５－ジフルオロフェニル）－２－（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９２）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９３）　（１Ｒ，２Ｓ）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９４）　（１Ｒ，２Ｓ）－Ｎ－（５－シアノピリジン－２－イル）－２－（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９５）　（１Ｒ，２Ｓ）－２－（３－フルオロフェニル）－２－（［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－［５－（トリフルオロメチル）ピリジン－２－イル］シクロプロパンカルボキサミド、
９６）　（１Ｒ，２Ｓ）－２－（４－フルオロフェニル）－Ｎ－（５－フルオロピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９７）　（１Ｒ，２Ｓ）－Ｎ，２－ビス（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９８）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
９９）　（１Ｒ，２Ｓ）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１００）　（１Ｒ，２Ｓ）－２－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド、
１０１）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１０２）　（１Ｒ，２Ｓ）－Ｎ－（３－フルオロフェニル）－２－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１０３）　（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－２－（［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－（ピリジン－２－イル）シクロプロパンカルボキサミド、
１０４）　（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、

１０５）　（１Ｒ，２Ｓ）－２－（３，４－ジフルオロフェニル）－Ｎ－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１０６）　（１Ｒ，２Ｓ）－Ｎ，２－ビス（３，４－ジフルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１０７）　（１Ｒ，２Ｓ）－Ｎ－（２，５－ジフルオロフェニル）－２－（３，４－ジフルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１０８）　（１Ｒ，２Ｓ）－Ｎ－（２，４－ジフルオロフェニル）－２－（３，４－ジフルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１０９）　（１Ｒ，２Ｓ）－Ｎ－（２，３－ジフルオロフェニル）－２－（３，４－ジフルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１１０）　（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド、
１１１）　（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－Ｎ－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１１２）　（１Ｒ，２Ｓ）－２－（３，５－ジフルオロフェニル）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１１３）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－（３，５－ジフルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１１４）　（１Ｒ，２Ｓ）－２－（３－クロロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド、
１１５）　（１Ｒ，２Ｓ）－２－（３－クロロフェニル）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１１６）　（１Ｒ，２Ｓ）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（３－フルオロフェニル）－２－（｛［４－（メトキシエチル）－２－メチルピリミジン－５－イル］オキシ｝メチル）シクロプロパンカルボキサミド、
１１７）　（１Ｒ，２Ｓ）－２－（３－フルオロ－５－メトキシフェニル）－Ｎ－（４－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１１８）　（１Ｒ，２Ｓ）－Ｎ－（３，４－ジフルオロフェニル）－２－（３－フルオロ－５－メトキシフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１１９）　（１Ｒ，２Ｓ）－２－（３－フルオロ－５－メトキシフェニル）－Ｎ－（５－フルオロピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１２０）　（１Ｒ，２Ｓ）－２－（３－フルオロ－５－メトキシフェニル）－Ｎ－（５－フルオロ－４－メトキシピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１２１）　（１Ｒ，２Ｓ）－２－（３－フルオロ－５－メトキシフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－ピリジン－２－イルシク

ロプロパンカルボキサミド、
１２２）　（１Ｒ，２Ｓ）－２－（３－フルオロ－５－メトキシフェニル）－Ｎ－（３－フルオロフェニル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１２３）　（１Ｒ，２Ｓ）－２－（４－フルオロ－３－メトキシフェニル）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－［（４－メトキシメチル－２－メチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１２４）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド、
１２５）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
１２６）　（１Ｒ，２Ｓ）－Ｎ－（５－シアノピリジン－２－イル）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
１２７）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
１２８）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
１２９）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（４－フルオロフェニル）－Ｎ－ピリジン－２－イルシクロプロパンカルボキサミド、
１３０）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（４－フルオロフェニル）－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
１３１）　（１Ｒ，２Ｓ）－Ｎ－（４－クロロピリジン－２－イル）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（４－フルオロフェニル）シクロプロパンカルボキサミド、
１３２）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（４－フルオロフェニル）シクロプロパンカルボキサミド、
１３３）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ－（３－フルオロフェニル）－２－（４－フルオロフェニル）シクロプロパンカルボキサミド、
１３４）　（１Ｒ，２Ｓ）－２－［（４－エチル－２－メチルピリミジン－５－イル）オキシメチル］－Ｎ，２－ビス（４－フルオロフェニル）シクロプロパンカルボキサミド、
１３５）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロ－５－メトキシフェニル）－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
１３６）　（１Ｒ，２Ｓ）－Ｎ－（５－クロロピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロ－５－メトキシフェニル）シクロプロパンカルボキサミド、
１３８）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロ－５－メトキシフェニル）－Ｎ－（５－フルオロ－４－メチルピリミジン－２－イル）シクロプロパンカルボキサミド、
１３９）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）－２－（３－トリフルオロメチルフェ

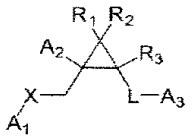
ニル）シクロプロパンカルボキサミド、
１４０）　（１Ｒ，２Ｒ）－２－（４－ブロモフェニル）－Ｎ－（５－クロロピリジン－２－イル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］シクロプロパンカルボキサミド、
１４１）　（１Ｒ，２Ｒ）－２－（４－ブロモフェニル）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）シクロプロパンカルボキサミド、
１４２）　（１Ｒ，２Ｓ）－２－（３－クロロフェニル）－Ｎ－（５－フルオロ－４－メチルピリジン－２－イル）－２－（｛［４－（メトキシメチル）－２－メチルピリミジン－５－イル］オキシ｝メチル）シクロプロパンカルボキサミド、
１４３）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロメチルピリジン－２－イル）－２－（３－フルオロフェニル）シクロプロパンカルボキサミド、
１４４）　（１Ｒ，２Ｓ）－２－［（２，４－ジメチルピリミジン－５－イル）オキシメチル］－Ｎ－（５－フルオロピリジン－２－イル）－２－（３－ヨードフェニル）シクロプロパンカルボキサミド、および
１４５）　（１Ｒ，２Ｓ）－Ｎ－（５－フルオロピリジン－２－イル）－２－［（４－ヒドロキシメチル－２－メチルピリミジン－５－イル）オキシメチル］－２－（３－フルオロフェニル）シクロプロパンカルボキサミド。
【請求項１３】
請求項１乃至１２の何れか一項に記載の化合物又はその医薬上許容される塩を有効成分として含有する医薬組成物。
【請求項１４】
不眠症、ナルコレプシー（発作性睡眠）および過剰の眠気、睡眠関連ジストニア、下肢静止不能症候群、睡眠時無呼吸、時差ぼけ症候群、交代勤務症候群、遅延睡眠相症候群又は睡眠相前進症候群のその他の疾患を含む睡眠障害の予防又は治療のための、請求項１３に記載の医薬組成物。
【請求項１５】
気分変調性障害、気分障害、精神及び不安障害；糖尿病及び食欲、味覚、摂食、又は摂飲障害；視床下部疾患；生物学的及び概日リズム障害；神経疾患、神経因性疼痛及び下肢静止不能症候群から選ばれる疾病に不随する睡眠障害；精神障害に関連した不眠症；うつ病とうつ病に関連した不眠症；双極性障害と双極性障害に関連した不眠症；不安障害と不安障害に関連した不眠症；パーキンソン症に関連した不眠症；統合失調症に関連した不眠症；睡眠時無呼吸；ナルコレプシー；特発性不眠症；睡眠時随伴症；麻薬依存症；ニコチン依存症；良性前立腺肥大症；健康な集団における並びに精神及び神経疾患における全認知症及び認知機能障害；並びに全身のオレキシン系機能不全に関連した他の疾病からなる群から選択される疾病の予防又は治療のための、請求項１３に記載の医薬組成物。

【書類名】要約書

【要約】

【課題】本発明の課題は、新規なシクロプロパン化合物又はその医薬上許容される塩およびそれらの医薬用途を提供することにある。

【解決手段】式（Ｉ）：



（Ｉ）

［式中、A_1はそれぞれピリミジニル基又はＮ－オキシドピリミジニル基等であり、A_2及びA_3は独立してアリール基又は複素環基等であり、R_1、R_2及びR_3は独立して水素原子又はC_{1-6}アルキル基等であり、Ｘは、酸素原子等であり、Ｌは、結合等である。）で表されるクロプロパン化合物又はその医薬上許容される塩は、オレキシン２受容体阻害作用を有し、オレキシンに起因する、不眠症に代表される睡眠障害の予防剤または治療剤として極めて有用である。

【選択図】なし

PTO/SB/14 (11-08)
Approved for use through 09/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	25724-0005P01
	Application Number	
Title of Invention	CYCLOPROPANE COMPOUNDS	

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Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Applicant Information:

Applicant 1 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Taro		Terauchi	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

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Citizenship under 37 CFR 1.41(b) [i] JP

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City	Ibaraki	State/Province	
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Applicant 2 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Ayumi		Takemura	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Tsukuba	Country Of Residence[i]	JP

Citizenship under 37 CFR 1.41(b) [i] JP

Mailing Address of Applicant:

Address 1	c/o Eisai Co., Ltd., Tsukuba Research Laboratories		
Address 2	1-3 Tokodai 5-chome, Tsukuba-shi		
City	Ibaraki	State/Province	
Postal Code		Country[i]	JP

Applicant 3 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Takashi		Doko	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Hatfield, Hertfordshire	Country Of Residence[i]	UK

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	25724-0005P01
	Application Number	
Title of Invention	CYCLOPROPANE COMPOUNDS	

Citizenship under 37 CFR 1.41(b) i	JP			
Mailing Address of Applicant:				
Address 1	c/o Eisai Co., Ltd., European Knowledge Centre			
Address 2	Mosquito Way, Hatfield			
City	Hertfordshire	**State/Province**		
Postal Code	AL10 9SN	**Country**i	UK	

Applicant 4 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Yu		Yoshida	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Tsukuba	**Country Of Residence**i	JP
Citizenship under 37 CFR 1.41(b) i	JP		

Mailing Address of Applicant:

Address 1	c/o Eisai Co., Ltd., Tsukuba Research Laboratories			
Address 2	1-3 Tokodai 5-chome, Tsukuba-shi			
City	Ibaraki	**State/Province**		
Postal Code		**Country**i	JP	

Applicant 5 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Toshiaki		Tanaka	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Tsukuba	**Country Of Residence**i	JP
Citizenship under 37 CFR 1.41(b) i	JP		

Mailing Address of Applicant:

Address 1	c/o Eisai Co., Ltd., Tsukuba Research Laboratories			
Address 2	1-3 Tokodai 5-chome, Tsukuba-shi			
City	Ibaraki	**State/Province**		
Postal Code		**Country**i	JP	

Applicant 6 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Keiichi		Sorimachi	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Tsukuba	**Country Of Residence**i	JP
Citizenship under 37 CFR 1.41(b) i	JP		

PTO/SB/14 (11-08)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	25724-0005P01
	Application Number	
Title of Invention	CYCLOPROPANE COMPOUNDS	

Mailing Address of Applicant:			
Address 1	c/o Eisai Co., Ltd., Tsukuba Research Laboratories		
Address 2	1-3 Tokodai 5-chome, Tsukuba-shi		
City	Ibaraki	State/Province	
Postal Code		Country[i]	JP

Applicant 7 — Remove

Applicant Authority	◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Yoshimitsu		Naoe	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Tsukuba	Country Of Residence[i]	JP
Citizenship under 37 CFR 1.41(b)[i]	JP		

Mailing Address of Applicant:			
Address 1	c/o Eisai Co., Ltd., Tsukuba Research Laboratories		
Address 2	1-3 Tokodai 5-chome, Tsukuba-shi		
City	Ibaraki	State/Province	
Postal Code		Country[i]	JP

Applicant 8 — Remove

Applicant Authority	◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Carsten		Beuckmann	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Tsukuba	Country Of Residence[i]	JP
Citizenship under 37 CFR 1.41(b)[i]	DE		

Mailing Address of Applicant:			
Address 1	c/o Eisai Co., Ltd., Tsukuba Research Laboratories		
Address 2	1-3 Tokodai 5-chome, Tsukuba-shi		
City	Ibaraki	State/Province	
Postal Code		Country[i]	JP

Applicant 9 — Remove

Applicant Authority	◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Yuji		Kazuta	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Tsukuba	Country Of Residence[i]	JP
Citizenship under 37 CFR 1.41(b)[i]	JP		

PTO/SB/14 (11-08)
Approved for use through 09/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	25724-0005P01
	Application Number	
Title of Invention	CYCLOPROPANE COMPOUNDS	

Mailing Address of Applicant:			
Address 1	c/o Eisai Co., Ltd., Tsukuba Research Laboratories		
Address 2	1-3 Tokodai 5-chome, Tsukuba-shi		
City	Ibaraki	State/Province	
Postal Code		Country[i]	JP

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	26211		
Email Address		Add Email	Remove Email

Application Information:

Title of the Invention	CYCLOPROPANE COMPOUNDS		
Attorney Docket Number	25724-0005P01	Small Entity Status Claimed	☐
Application Type	Provisional		
Subject Matter	Utility		
Suggested Class (if any)		Sub Class (if any)	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)	0	Suggested Figure for Publication (if any)	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S. C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Enter either Customer Number or complete the Representative Name section below. If both sections are completed the Customer Number will be used for the Representative Information during processing.

Please Select One:	○ Customer Number	◉ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	25724-0005P01
	Application Number	
Title of Invention	CYCLOPROPANE COMPOUNDS	

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix	Remove
	Jack		Brennan		
Registration Number	47443				

Additional Representative Information blocks may be generated within this form by selecting the **Add** button. Add

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

			Remove
Application Number	Country [i]	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			○ Yes ◉ No

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Assignee Information:

Providing this information in the application data sheet does not substitute for compliance with any requirement of part 3 of Title 37 of the CFR to have an assignment recorded in the Office.

Assignee 1			Remove
If the Assignee is an Organization check here. ☒			
Organization Name	Eisai R&D Management Co., Ltd.		
Mailing Address Information:			
Address 1	6-10 Koishikawa 4-Chome		
Address 2	Bunkyo-Ku		
City	Tokyo	**State/Province**	
Country [i] JP		Postal Code	112-8088
Phone Number		Fax Number	
Email Address			

Additional Assignee Data may be generated within this form by selecting the **Add** button. Add

PTO/SB/14 (11-08)
Approved for use through 09/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	25724-0005P01
	Application Number	
Title of Invention	CYCLOPROPANE COMPOUNDS	

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.					
Signature	/Jack Brennan/			Date (YYYY-MM-DD)	2010-09-22
First Name	Jack	Last Name	Brennan	Registration Number	47443

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	CYCLOPROPANE COMPOUNDS
First Named Inventor/Applicant Name:	Taro Terauchi
Filer:	Jack Brennan
Attorney Docket Number:	25724-0005P01

Filed as Large Entity

Provisional Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Provisional application filing	1005	1	220	220
Pages:				
Prov. Appl Size fee per 50 sheets >100	1085	1	270	270
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**490**

Electronic Acknowledgement Receipt	
EFS ID:	8474092
Application Number:	61385342
International Application Number:	
Confirmation Number:	3599
Title of Invention:	CYCLOPROPANE COMPOUNDS
First Named Inventor/Applicant Name:	Taro Terauchi
Customer Number:	26211
Filer:	Jack Brennan/Devon Weide
Filer Authorized By:	Jack Brennan
Attorney Docket Number:	25724-0005P01
Receipt Date:	22-SEP-2010
Filing Date:	
Time Stamp:	16:20:19
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$490
RAM confirmation Number	2519
Deposit Account	061050
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Transmittal of New Application	257240005P01PapTransmittal.pdf	51578 8b535af3912bd516730b062e1afdff9b8e290aff	no	1
Warnings:					
Information:					
2		257240005P01Application.pdf	9893730 d80771d91c058f3a38ae821b4646c12d78b980a7	yes	198

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification - Not in English	1	186
	Claims	187	197
	Abstract	198	198

Warnings:					
Information:					
3	Application Data Sheet	257240005PO1ADS.pdf	6213297 ac8552b59864a3693163252bfa98459f31db9101	no	7
Warnings:					
Information:					
4	Fee Worksheet (PTO-875)	fee-info.pdf	31210 4a70faeabed884c3132287d4b371ce93fe18a1cb	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	16189815		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
61/385,342	09/22/2010		490	25724-0005P01		

CONFIRMATION NO. 3599

26211
FISH & RICHARDSON P.C. (NY)
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

FILING RECEIPT

Date Mailed: 05/20/2011

Receipt is acknowledged of this provisional patent application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Taro Terauchi, Tsukuba, JAPAN;
Ayumi Takemura, Tsukuba, JAPAN;
Takashi Doko, Hatfield, UNITED KINGDOM;
Yu Yoshida, Tsukuba, JAPAN;
Toshiaki Tanaka, Tsukuba, JAPAN;
Keiichi Sorimachi, Tsukuba, JAPAN;
Yoshimitsu Naoe, Tsukuba, JAPAN;
Carsten Beuckmann, Tsukuba, JAPAN;
Yuji Kazuta, Tsukuba, JAPAN;

Power of Attorney:
John Brennan--47443

If Required, Foreign Filing License Granted: 05/17/2011

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 61/385,342**

Projected Publication Date: None, application is not eligible for pre-grant publication

Non-Publication Request: No

Early Publication Request: No

Title

CYCLOPROPANE COMPOUNDS

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The

date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

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NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
61/385,342	09/22/2010	Taro Terauchi	25724-0005P01

CONFIRMATION NO. 3599

IMPROPER PROVISIONAL LETTER

26211
FISH & RICHARDSON P.C. (NY)
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

OC000000047721150

Date Mailed: 05/20/2011

Letter re Non-English Language Application Papers in a Provisional Application

The above-identified provisional application was filed in a language other than English. An English-language translation of a non-English provisional application and a statement that the translation is accurate must be filed in the provisional application. See 37 CFR 1.78(a)(5)(iv). Applicants are strongly encouraged to file the English-language translation of the provisional application and the statement that the translation is accurate in the provisional application before a nonprovisional application claiming the benefit of the provisional application is filed, or, alternatively, when making a claim for the benefit of the provisional application in a nonprovisional application. If, however, an English translation and a statement that the translation is accurate have not been filed in the above-identified provisional application when a nonprovisional application is filed claiming the benefit of the filing date of the provisional application, the Office should mail a Notice requiring an English translation and the statement to be filed in the provisional application and a confirmation to be filed in the nonprovisional application.

In the event that the Office schedules a nonprovisional application that claims the benefit of a provisional application filed in a language other than English for publication without issuing a Notice requiring the applicant to file an English translation of the non-English provisional application, the applicant should file the English translation of the non-English provisional application and a statement that the translation is accurate as soon as possible in the provisional application.

/ltan/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Taro Terauchi et al.	Art Unit	:
Serial No.	: 61/385,342	Examiner	:
Filed	: September 22, 2010	Conf. No.	: 3599
Title	: CYCLOPROPANE COMPOUNDS		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUBMISSION OF VERIFIED ENGLISH TRANSLATION OF APPLICATION

This provisional patent application was originally filed in the Japanese language. Enclosed is a verified copy of an English translation of the originally filed provisional application. The attached Verification of Translation includes a statement from the translator that the English translation is accurate.

Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 25724-0005P01.

Respectfully submitted,

Date: December 29, 2011

/Jack Brennan/
Jack Brennan
Reg. No. 47,443

Customer Number 26211
Fish & Richardson P.C.
Telephone: (212) 765-5070
Facsimile: (877) 769-7945

30659538.doc

W5545

Declaration

I, Teruo NAGANUMA, a national of Japan, c/o Asamura Patent Office,p.c. of Tennoz Central Tower, 2-2-24, Higashi-Shinagawa, Shinagawa-ku, Tokyo, Japan do hereby solemnly and sincerely declare:

1) THAT I am well acquainted with the Japanese language and English language; and

2) THAT the attached is a full, true, accurate and faithful translation into the English language made by me of Japanese Text of the U.S. Serial No. 61/385342 filed on September 22, 2010.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001, of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date of Sign: November 21, 2011

Teruo NAGANUMA
Patent Attorney

[Kind of Document] Description

[Title of the Invention] Cyclopropane Compounds

[Technical Field]

[0001]

The present invention relates to a cyclopropane compound having orexin receptor antagonism or a pharmaceutically acceptable salt thereof, and a medicinal use thereof. More specifically, the present invention relates to a cyclopropane compound effective for the treatment of dyssomnia such as insomnia by orexin receptor antagonism, and a pharmaceutical composition comprising the same as an active ingredient.

[Background Art]

[0002]

Orexin A (OX-A, consisting of 33 amino acid peptides) and orexin B (OX-B, consisting of 28 amino acid peptides), which are two types of intracerebral neuropeptides localized at the hypothalamus in the brain, have been discovered (Patent Document No. 5 and Non-Patent Document No. 1) as endogenous ligands of, G protein-coupled receptors mainly existing in the brain, namely, orexin receptors (Patent Documents No. 1, 2, 3 and 4). It has been known that such orexin receptors include two subtypes, namely, an OX_1 receptor (OX1) as a type 1 subtype and an OX_2 receptor (OX2) as a type 2 subtype. OX1 is selective to OX-A, and OX2 is able to bind to OX-A as well as to OX-B. Orexin has been found to stimulate the food consumption of rats, and thus, it has been suggested that orexin would play a physiological role as a mediator of peptides in a central feedback mechanism for controlling feeding behavior (Non-Patent Document No. 1). On the other hand, it has been observed that orexin controls sleep-wake conditions. Thus, it is considered that orexin will potentially take an approach to a new therapy for narcolepsy, as well as for insomnia and other sleep disorders (Non-Patent Document No. 2). In addition, it has been suggested that orexin signals in the ventral tegmental area regarding neural plasticity associated with opioid dependence and nicotine dependence play an important role *in vivo* (Non-Patent Document No. 3 and Non-Patent Document No. 4). Moreover, it has been known that such orexin signals interact with CRF (corticotropin-releasing factor) signals involved in depression and anxiety disorder, and that the expression of orexin mRNA is increased by the effects of stress (Non-Patent Document No. 5).

Accordingly, orexin receptors are considered to have high pathological significance to: diseases such as dysthymia, mood, mental disease or anxiety disorder; diabetes,

anorexia, and disorder in taste, eating, alcohol drinking, etc.; hypothalamic disease; insomnia; biological and circadian rhythm disorder; sleep disorder related to diseases such as nervous disease, neurogenic pain and restless legs syndrome; insomnia related to mental disorder; sleep apnea; narcolepsy; idiopathic insomnia; parasomnia; opioid dependence; nicotine dependence; depression and bipolar disorder; anxiety disorder; prostatic hyperplasia; dementia and cognitive impairment in healthy people, patients with mental and nervous diseases, and patients with other diseases related to orexin dysfunction; and the like.

Recently, (2R)-2-{(1S)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-N-methyl-2-phenyl-acetamide, a compound that functions as an orexin receptor antagonist, has been clinically developed as a therapeutic agent for insomnia (Patent Document No. 6). This compound brings about a decrease in wakefulness to rats, which is characterized by decreased functions of awakening and walking, and it dose-dependently increases both REM sleep time and non-REM sleep time (Non-Patent Document No. 6). Furthermore, it has also been described that this compound improves the memory function of model rats (Patent Document No. 7), and that the compound is effective for posttraumatic stress disorder (Patent Document No. 8).

[Prior Art Documents]

[Patent Documents]

[0003]

[Patent Document No. 1] International Publication No. WO1996/34877

[Patent Document No. 2] JP 10-327888 A

[Patent Document No. 3] JP 10-327889 A

[Patent Document No. 4] JP 11-178588 A

[Patent Document No. 5] JP 10-229887 A

[Patent Document No. 6] International Publication No. WO2005/118548

[Patent Document No. 7] International Publication No. WO2007/105177

[Patent Document No. 8] International Publication No. WO2009/047723

[Non-Patent Documents]

[0004]

[Non-Patent Document No. 1] Sakurai T. et al., Cell, 1998, 92, 573-585

[Non-Patent Document No. 2] Chemelli R. M. et al., Cell, 1999, 98, 437-451)

[Non-Patent Document No. 3] S. L. Borgland et al., Neuron, 2006, 49, 589-601

[Non-Patent Document No. 4] C. J. Winrow et al., Neuropharmacology, 2010,

58, 185-194

[Non-Patent Document No. 5] T. Ida et al., Biochemical and Biophysical Research Communications, 2000, 270, 318-323

[Non-Patent Document No. 6] F. Jenck et al., Nature Medicine 2007, 13, 150-155

[Summary of the Invention]

[Problem to be Solved by the Invention]

[0005]

It is an object of the present invention to provide a cyclopropane compound, which has orexin receptor antagonism and is useful as a therapeutic agent for dyssomnia caused by an orexin receptor, including insomnia as a typical example, and a medicinal use thereof.

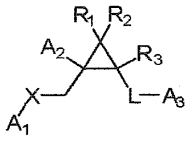
[Measures for Solving the Problem]

[0006]

The present invention relates to the following [1] to [15]:

[1] A compound represented by the following formula (I) or a pharmaceutically acceptable salt thereof:

[Formula 1]



(I)

wherein

A_1 represents a pyrimidinyl group or a N-oxide pyrimidinyl group, each of which may optionally have 1 to 3 substituents selected from Substituent group α,

A_2 and A_3 each independently represent an aryl group selected from Group 1, which may optionally have 1 to 3 substituents selected from Substituent group α, or a heterocyclic group selected from Group 3, which may optionally have 1 to 3 substituents selected from Substituent group β,

R_1, R_2 and R_3 each independently represent a hydrogen atom, a halogen atom, a C_{1-6} alkyl group which may optionally have 1 to 3 substituents selected from Substituent group β, or a C_{3-8} cycloalkyl group which may optionally have 1 to 3 substituents selected from Substituent group β,

X represents an oxygen atom, a C_{1-6} alkylene group, a formula $-NR_4-$ (wherein R_4 represents a hydrogen atom or a C_{1-6} alkyl group), -S-, -SO- or $-SO_2-$,

L represents a bond or a formula $-CONR_5-$ (wherein R_5 represents a hydrogen atom, a C_{1-6} alkyl group or a C_{3-8} cycloalkyl group), wherein

Substituent group α: a cyano group, a halogen atom, a hydroxyl group, an oxo group, a formula $-NR_6R_7$ (wherein R_6 and R_7 each independently represent a hydrogen atom or a C_{1-6} alkyl group), a C_{1-6} alkyl group which may optionally have 1 to 3 substituents selected from Substituent group β, a C_{1-6} alkoxy group which may optionally have 1 to 3 substituents selected from Substituent group β, a C_{1-6} alkylcarbonyl group which may optionally have 1 to 3 substituents selected from Substituent group β, a C_{1-6} alkylsulfonyl group which may optionally have 1 to 3 substituents selected from Substituent group β, an aryl group selected from Group 1, which may optionally have 1 to 3 substituents selected from Substituent group β, and a heteroaryl group selected from Group 2, which may optionally have 1 to 3 substituents selected from Substituent group β;

Substituent group β: a cyano group, a halogen atom, a hydroxyl group, a C_{3-8} cycloalkyl group, and a C_{1-6} alkoxy group;

Group 1: a phenyl group, a naphthyl group, an azulenyl group, an anthryl group, and a phenanthryl group;

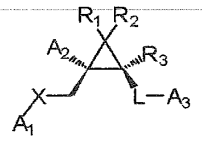
Group 2: a furyl group, a thienyl group, a pyrrolyl group, an imidazolyl group, a triazolyl group, a tetrazolyl group, a thiazolyl group, a pyrazolyl group, an oxazolyl group, an isoxazolyl group, an isothiazolyl group, a furazanyl group, a thiadiazolyl group, an oxadiazolyl group, a pyridyl group, a pyrazinyl group, a pyridazinyl group, a triazinyl group, an indolyl group, an isoindolyl group, an indazolyl group, a benzoxazolyl group, a benzisoxadiazolyl group, a benzothiazolyl group, a benzisothiazolyl group, a quinolyl group, and an isoquinolyl group; and

Group 3: a furyl group, a thienyl group, a pyrrolyl group, an imidazolyl group, a triazolyl group, a tetrazolyl group, a thiazolyl group, a pyrazolyl group, an oxazolyl group, an isoxazolyl group, an isothiazolyl group, a furazanyl group, a thiadiazolyl group, an oxadiazolyl group, a pyridyl group, a pyrazinyl group, a pyridazinyl group, a pyrimidinyl group, a triazinyl group, a 2-pyridonyl group, a 4-pyridonyl group, a pyridazidonyl group, a pyrimididonyl group, a purinyl group, a pteridinyl group, a quinolyl group, an isoquinolyl group, a naphthylidyl group, a quinoxalyl group, a cinnolyl group, a quinazolyl group, a phthalazyl group, an imidazopyridyl group, an imidazothiazolyl group, an imidazoxazolyl group, a benzimidazolyl group, an indolyl

group, an isoindolyl group, an indazolyl group, a pyrrolopyridyl group, a thienopyridyl group, a fluoropyridyl group, a benzoxazolyl group, a benzisoxadiazolyl group, a benzothiazolyl group, a benzisothiazolyl group, a pyridopyrimidinyl group, an oxodihydropyridopyrimidinyl group, a benzofuryl group, a benzothienyl group, a benzothiadiazolyl group, a benzo[1,3]dioxolyl group, a thienofuryl group, a dihydrousobenzofuranyl group, a chromanyl group, an isochromanyl group, a 1,3-dioxaindanyl group, a 1,4-dioxatetralinyl group, and a dihydrobenzo[1,4]oxazinyl group.

[2] The compound according to [1] above, which is represented by the following formula (II), or a pharmaceutically acceptable salt thereof:

[Formula 2]



(II)

wherein A_1, A_2, A_3, R_1, R_2, R_3, X and L have the same definitions as those according to [1] above.

[3] The compound according to [1] or [2] above, or a pharmaceutically acceptable salt thereof, wherein R_1, R_2 and R_3 each represent a hydrogen atom.

[4] The compound according to [3] above, or a pharmaceutically acceptable salt thereof, wherein L represents a formula -CONH-.

[5] The compound according to [4] above, or a pharmaceutically acceptable salt thereof, wherein X represents an oxygen atom.

[6] The compound according to [5] above, or a pharmaceutically acceptable salt thereof, wherein A_2 and A_3 each independently represent an aryl group or a heteroaryl group, which may optionally have 1 to 3 substituents selected from a cyano group, a halogen atom, a C_{1-6} alkyl group, a halo-C_{1-6} alkyl group and a C_{1-6} alkoxy group.

[7] The compound according to [6] above, or a pharmaceutically acceptable salt thereof, wherein A_2 and A_3 each independently represent a phenyl group, a naphthyl group, a pyridyl group, a pyrazinyl group, a pyridazinyl group, a pyrimidinyl group, a quinolyl group or an isoquinolyl group, which may optionally have 1 to 3 substituents selected from a cyano group, a halogen atom, a C_{1-6} alkyl group, a halo-C_{1-6} alkyl group and a C_{1-6} alkoxy group.

[8] The compound according to [7] above, or a pharmaceutically acceptable salt thereof, wherein A_2 represents a phenyl group which may optionally have 1 to 3 substituents selected from a cyano group, a halogen atom, a C_{1-6} alkyl group, a halo-C_{1-6} alkyl group and a C_{1-6} alkoxy group.

[9] The compound according to [8] above, or a pharmaceutically acceptable salt thereof, wherein A_3 represents a phenyl group or a pyridyl group which may optionally have 1 to 3 substituents selected from a cyano group, a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, a halo-C_{1-6} alkyl group and a C_{1-6} alkoxy group.

[10] The compound according to [9] above, or a pharmaceutically acceptable salt thereof, wherein A_1 represents a 5-pyrimidinyl group which may optionally have 1 to 3 substituents selected from a halogen atom, a C_{1-6} alkyl group, a halo-C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkyl group, a C_{3-8} cycloalkyl group and a C_{1-6} alkoxy group.

[11] The compound according to [10] above, or a pharmaceutically acceptable salt thereof, wherein A_1 represents a 5-pyrimidinyl group which may optionally have 1 or 2 substituents selected from a methyl group, a hydroxymethyl group, a methoxymethyl group and a methoxyethyl group.

[12] The compound according to any one of [1] to [11] above or a pharmaceutically acceptable salt thereof, which is selected from the following compounds:

(1) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)-2-phenylcyclopropanecarboxamide,

(2) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)-2-phenylcyclopropanecarboxamide,

(3) (1R,2S)-N-(5-chloro-4-methylpyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,

(4) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxypyridin-2-yl)-2-phenylcyclopropanecarboxamide,

(5) (1R,2S)-N-(6-fluoropyridin-3-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,

(6) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(6-fluoro-5-methylpyridin-3-yl)-2-phenylcyclopropanecarboxamide,

(7) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-methoxypyridin-3-yl)-2-phenylcyclopropanecarboxamide,

(8) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N,2-diphenylcyclopropanecarboxamide,

(9) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-methylpyridin-2-yl)-2-phenylcyclopropanecarboxamide,

(10) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-[5-fluoro-4-(methoxymethyl)pyridin-2-yl]-2-phenylcyclopropanecarboxamide,

(11) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(2-methoxypyridin-4-yl)-2-

phenylcyclopropanecarboxamide,
(12) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenyl-N-[5-(trifluoromethyl)pyridin-2-yl]cyclopropanecarboxamide,
(13) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenyl-N-[4-(trifluoromethyl)pyridin-2-yl]cyclopropanecarboxamide,
(14) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-[4-(methoxymethyl)pyridin-2-yl]-2-phenylcyclopropanecarboxamide,
(15) (1R,2S)-N-(5-chloropyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(16) (1R,2S)-N-[3-(dimethylamino)phenyl]-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(17) (1R,2S)-N-(3-chlorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(18) (1R,2S)-N-(3-cyano-4-fluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(19) (1R,2S)-N-(4-chloro-3-cyanophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(20) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-[3-(methylsulfonyl)phenyl]-2-phenylcyclopropanecarboxamide,
(21) (1R,2S)-N-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(22) (1R,2S)-N-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(23) (1R,2S)-N-(3-chloro-4-fluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(24) (1R,2S)-N-(3-cyano-5-fluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(25) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(3-methoxyphenyl)-2-phenylcyclopropanecarboxamide,
(26) (1R,2S)-N-[3-(cyanomethyl)phenyl]-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(27) (1R,2S)-N-(2-cyanopyridin-4-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(28) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenyl-N-[3-

(trifluoromethyl)phenyl]cyclopropanecarboxamide,
(29) (1R,2S)-N-(4-cyanopyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(30) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(4-methoxypyridin-2-yl)-2-phenylcyclopropanecarboxamide,
(31) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)-2-(3-fluorophenyl)cyclopropanecarboxamide,
(32) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(33) (1R,2S)-N-(5-cyanopyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)cyclopropanecarboxamide,
(34) (1R,2S)-N-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)cyclopropanecarboxamide,
(35) (1R,2S)-N-(4-chloropyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)cyclopropanecarboxamide,
(36) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxymethylpyridin-2-yl)-2-(3-fluorophenyl)cyclopropanecarboxamide,
(37) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxymethylpyridin-2-yl)-2-(3-fluorophenyl)cyclopropanecarboxamide
(38) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)-N-(4-fluorophenyl)cyclopropanecarboxamide,
(39) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)-N-phenylcyclopropanecarboxamide,
(40) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxypyridin-2-yl)-2-(3-fluorophenyl)cyclopropanecarboxamide,
(41) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(4-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(42) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N,2-bis(4-fluorophenyl)cyclopropanecarboxamide,
(43) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxymethylpyridin-2-yl)-2-(4-fluorophenyl)cyclopropanecarboxamide,
(44) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)-2-(4-fluorophenyl)cyclopropanecarboxamide,
(45) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxypyridin-2-yl)-2-

(4-fluorophenyl)cyclopropanecarboxamide,
(46) (1R,2S)-2-(3-cyanophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(4-fluorophenyl)cyclopropanecarboxamide,
(47) (1R,2S)-2-(3-cyanophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(48) (1R,2S)-2-(3-cyanophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)cyclopropanecarboxamide,
(49) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenyl-N-pyridin-2-ylcyclopropanecarboxamide,
(50) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)-2-phenylcyclopropanecarboxamide,
(51) (1R,2S)-N-(5-cyanopyridin-2-yl)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(52) (1R,2S)-N-(5-chloropyridin-2-yl)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(53) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)-2-phenylcyclopropanecarboxamide,
(54) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-(4-fluorophenyl)-2-phenylcyclopropanecarboxamide,
(55) (1R,2S)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)cyclopropanecarboxamide,
(56) (1R,2S)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(4-fluorophenyl)cyclopropanecarboxamide,
(57) (1R,2S)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-pyridin-2-ylcyclopropanecarboxamide,
(58) (1R,2S)-N-(5-chloropyridin-2-yl)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(59) (1R,2S)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(60) (1R,2S)-N-(3,4-difluorophenyl)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(61) (1R,2S)-N-(2,4-difluorophenyl)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(62) (1R,2S)-N-(5-cyanopyridin-2-yl)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-

yl)oxymethyl]cyclopropanecarboxamide,
(63) (1R,2S)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxypyridin-2-yl)cyclopropanecarboxamide,
(64) (1R,2S)-N-(5-chloropyridin-2-yl)-2-{[(4-(methoxymethyl)-2-methylpyrimidin-5-yl)oxy]methyl}-2-phenylcyclopropanecarboxamide,
(65) (1R,2S)-N-(5-cyanopyridin-2-yl)-2-{[(4-(methoxymethyl)-2-methylpyrimidin-5-yl)oxy]methyl}-2-phenylcyclopropanecarboxamide,
(66) (1R,2S)-N-(5-fluoropyridin-2-yl)-2-{[(4-(methoxymethyl)-2-methylpyrimidin-5-yl)oxy]methyl}-2-phenylcyclopropanecarboxamide,
(67) (1R,2S)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenyl-N-[5-(trifluoromethyl)pyridin-2-yl]cyclopropanecarboxamide,
(68) (1R,2S)-N-(5-fluoro-4-methylpyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(69) (1R,2S)-N-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(70) (1R,2S)-N-(3,4-difluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(71) (1R,2S)-2-(4-chlorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(72) (1R,2S)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)cyclopropanecarboxamide,
(73) (1R,2S)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(4-fluorophenyl)cyclopropanecarboxamide,
(74) (1R,2S)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-pyridin-2-ylcyclopropanecarboxamide,
(75) (1R,2S)-N-(5-cyanopyridin-2-yl)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(76) (1R,2S)-N-(5-chloropyridin-2-yl)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(77) (1R,2S)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(78) (1R,2S)-N,2-bis(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(79) (1R,2S)-N-(2,4-difluorophenyl)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-

yl)oxymethyl]cyclopropanecarboxamide,
(80) (1R,2S)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxypyridin-2-yl)cyclopropanecarboxamide,
(81) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)-2-(3-methoxyphenyl)cyclopropanecarboxamide,
(82) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(4-fluorophenyl)-2-(3-methoxyphenyl)cyclopropanecarboxamide,
(83) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)-2-(3-methoxyphenyl)cyclopropanecarboxamide,
(84) (1R,2S)-N-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-methoxyphenyl)cyclopropanecarboxamide
(85) (1R,2S)-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(86) (1R,2S)-2-(3-fluorophenyl)-N-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(87) (1R,2S)-2-(3-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-(pyridin-2-yl)cyclopropanecarboxamide,
(88) (1R,2S)-N-(3,4-difluorophenyl)-2-(3-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(89) (1R,2S)-N,2-bis(3-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(90) (1R,2S)-N-(2,4-difluorophenyl)-2-(3-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(91) (1R,2S)-N-(2,5-difluorophenyl)-2-(3-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(92) (1R,2S)-N-(5-chloropyridin-2-yl)-2-(3-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(93) (1R,2S)-N-(5-fluoro-4-methylpyridin-2-yl)-2-(3-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(94) (1R,2S)-N-(5-cyanopyridin-2-yl)-2-(3-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(95) (1R,2S)-2-(3-fluorophenyl)-2-([(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-[5-(trifluoromethyl)pyridin-2-yl]cyclopropanecarboxamide,
(96) (1R,2S)-2-(4-fluorophenyl)-N-(5-fluoropyridin-2-yl)-2-[(4-methoxymethyl-2-

methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(97) (1R,2S)-N,2-bis(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(98) (1R,2S)-N-(5-chloropyridin-2-yl)-2-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(99) (1R,2S)-N-(5-fluoro-4-methylpyridin-2-yl)-2-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(100) (1R,2S)-2-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-pyridin-2-ylcyclopropanecarboxamide,
(101) (1R,2S)-N-(3,4-difluorophenyl)-2-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(102) (1R,2S)-N-(3-fluorophenyl)-2-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(103) (1R,2S)-2-(3,4-difluorophenyl)-2-([(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-(pyridin-2-yl)cyclopropanecarboxamide,
(104) (1R,2S)-2-(3,4-difluorophenyl)-N-(5-fluoro-4-methylpyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(105) (1R,2S)-2-(3,4-difluorophenyl)-N-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(106) (1R,2S)-N,2-bis(3,4-difluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(107) (1R,2S)-N-(2,5-difluorophenyl)-2-(3,4-difluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(108) (1R,2S)-N-(2,4-difluorophenyl)-2-(3,4-difluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(109) (1R,2S)-N-(2,3-difluorophenyl)-2-(3,4-difluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(110) (1R,2S)-2-(3,5-difluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-pyridin-2-ylcyclopropanecarboxamide,
(111) (1R,2S)-2-(3,5-difluorophenyl)-N-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(112) (1R,2S)-2-(3,5-difluorophenyl)-N-(5-fluoro-4-methylpyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(113) (1R,2S)-N-(3,4-difluorophenyl)-2-(3,5-difluorophenyl)-2-[(4-methoxymethyl-2-

methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(114) (1R,2S)-2-(3-chlorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-pyridin-2-ylcyclopropanecarboxamide,
(115) (1R,2S)-2-(3-chlorophenyl)-N-(5-fluoro-4-methylpyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(116) (1R,2S)-N-(5-fluoro-4-methylpyridin-2-yl)-2-(3-fluorophenyl)-2-({[4-(methoxyethyl)-2-methylpyrimidin-5-yl]oxy}methyl)cyclopropanecarboxamide,
(117) (1R,2S)-2-(3-fluoro-5-methoxyphenyl)-N-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(118) (1R,2S)-N-(3,4-difluorophenyl)-2-(3-fluoro-5-methoxyphenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(119) (1R,2S)-2-(3-fluoro-5-methoxyphenyl)-N-(5-fluoropyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(120) (1R,2S)-2-(3-fluoro-5-methoxyphenyl)-N-(5-fluoro-4-methoxypyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(121) (1R,2S)-2-(3-fluoro-5-methoxyphenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-pyridin-2-ylcyclopropanecarboxamide,
(122) (1R,2S)-2-(3-fluoro-5-methoxyphenyl)-N-(3-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(123) (1R,2S)-2-(4-fluoro-3-methoxyphenyl)-N-(5-fluoro-4-methylpyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(124) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)-N-pyridin-2-ylcyclopropanecarboxamide,
(125) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(126) (1R,2S)-N-(5-cyanopyridin-2-yl)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)cyclopropanecarboxamide,
(127) (1R,2S)-N-(5-chloropyridin-2-yl)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)cyclopropanecarboxamide,
(128) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)-2-(3-fluorophenyl)cyclopropanecarboxamide,
(129) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(4-fluorophenyl)-N-pyridin-2-ylcyclopropanecarboxamide,
(130) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(4-fluorophenyl)-N-(5-

fluoropyridin-2-yl)cyclopropanecarboxamide,
(131) (1R,2S)-N-(4-chloropyridin-2-yl)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(4-fluorophenyl)cyclopropanecarboxamide,
(132) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)-2-(4-fluorophenyl)cyclopropanecarboxamide,
(133) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-(3-fluorophenyl)-2-(4-fluorophenyl)cyclopropanecarboxamide,
(134) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-N,2-bis(4-fluorophenyl)cyclopropanecarboxamide,
(135) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluoro-5-methoxyphenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(136) (1R,2S)-N-(5-chloropyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluoro-5-methoxyphenyl)cyclopropanecarboxamide,
(138) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluoro-5-methoxyphenyl)-N-(5-fluoro-4-methylpyrimidin-2-yl)cyclopropanecarboxamide,
(139) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)-2-(3-trifluoromethylphenyl)cyclopropanecarboxamide,
(140) (1R,2R)-2-(4-bromophenyl)-N-(5-chloropyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(141) (1R,2R)-2-(4-bromophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(142) (1R,2S)-2-(3-chlorophenyl)-N-(5-fluoro-4-methylpyridin-2-yl)-2-({[4-(methoxymethyl)-2-methylpyrimidin-5-yl]oxy}methyl)cyclopropanecarboxamide,
(143) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoromethylpyridin-2-yl)-2-(3-fluorophenyl)cyclopropanecarboxamide,
(144) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)-2-(3-iodophenyl)cyclopropanecarboxamide, and
(145) (1R,2S)-N-(5-fluoropyridin-2-yl)-2-[(4-hydroxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)cyclopropanecarboxamide.

[13] A pharmaceutical composition comprising, as an active ingredient, the compound according to any one of [1] to [12] above or a pharmaceutically acceptable salt thereof.

[14] The pharmaceutical composition according to [13] above, for the treatment of sleep disorder including insomnia, narcolepsy (paroxysmal sleep), and other diseases such as excessive sleepiness, sleep-related dystonia, restless legs syndrome, sleep apnea, jet lag

syndrome, shift work syndrome, delayed sleep phase syndrome or advanced sleep phase syndrome.

[15] The pharmaceutical composition according to [13] above, for the prevention or treatment of a disease selected from the group consisting of: dysthymic disorder, mood disorder, mental and anxiety disorder; diabetes, and appetite, taste, eating or drinking disorder; hypothalamic disease; biological and circadian rhythm disorder; sleep disorder associated with a disease selected from nervous disease, neurogenic pain and restless legs syndrome; insomnia related to mental disorder; depression and insomnia related to depression; bipolar disorder and insomnia related to bipolar disorder; anxiety disorder and insomnia related to anxiety disorder; insomnia related to Parkinson's disease; insomnia related to schizophrenia; sleep apnea; narcolepsy; idiopathic insomnia; parasomnia; benign prostatic hyperplasia; opioid dependence; nicotine dependence; pure dementia and cognitive impairment in a healthy group and in mental and nervous diseases; and other diseases related to systemic orexin dysfunction.

[Advantages of the Invention]

[0007]

According to the present invention, the cyclopropane compound represented by the formula (I) or a pharmaceutically acceptable salt thereof is useful for the treatment of dyssomnia such as narcolepsy by orexin receptor antagonism. More specifically, the cyclopropane compound represented by the formula (I) or a pharmaceutically acceptable salt thereof is useful for the treatment of sleep disorder including insomnia, narcolepsy (paroxysmal sleep), and other diseases such as excessive sleepiness, sleep-related dystonia, restless legs syndrome, sleep apnea, jet lag syndrome, shift work syndrome, delayed sleep phase syndrome or advanced sleep phase syndrome. Furthermore, the cyclopropane compound represented by the formula (I) or a pharmaceutically acceptable salt thereof is useful for the prevention or treatment of: dysthymic disorder, mood disorder, and mental and anxiety disorder; diabetes, and appetite, taste, eating or drinking disorder; hypothalamic disease; biological and circadian rhythm disorder; sleep disorder associated with a disease selected from nervous disease, neurogenic pain and restless legs syndrome; insomnia related to mental disorder; depression and insomnia related to depression; bipolar disorder and insomnia related to bipolar disorder; anxiety disorder and insomnia related to anxiety disorder; insomnia related to Parkinson's disease; insomnia related to schizophrenia; sleep apnea; narcolepsy; idiopathic insomnia; parasomnia; benign prostatic hyperplasia; opioid dependence; nicotine dependence; pure dementia and cognitive impairment in a healthy group and in mental and nervous diseases; and other diseases related to systemic

orexin dysfunction.

[Mode for Carrying out the Invention]

[0008]

Hereinafter, the meanings of symbols, terms and the like used in the specification of the present application will be explained, and thus, the present invention will be described in detail.

[0009]

In the specification of the present application, the structural formula of a compound may indicate a certain isomer for convenience sake. The present invention includes all isomers generated due to the structure of the compound, such as geometric isomers, optical isomers based on asymmetric carbon atoms, steric isomers or tautomers, and the isomeric mixtures thereof. Thus, the compound of the present invention is not limited to the descriptions of a formula given for convenience, and it may be either an isomer or a mixture. Accordingly, there may be a case in which the compound has asymmetric carbon atoms in a molecule thereof and an optically active form and a racemic form exist. However, the present invention is not limited thereto, but it includes all cases. Moreover, there may also be a case in which crystal polymorphisms exist. The present invention is not limited thereto, either, and it includes single crystals or the mixtures thereof. Other than anhydrides, hydrates may also be included. These substances are all included in the scope of claims in the specification of the present application.

The present invention includes a compound formed by isotopically labeling the compound of the formula (I). This compound is identical to the compound of the formula (I) with the exception that one or more atoms thereof are substituted with atom(s) having an atomic mass or mass number that are different from those generally found in the nature. Examples of an isotope that can be included in the compound of the present invention include the isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine, iodine and chloride. Specific examples include ^{2}H, ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{35}S, ^{123}I and ^{125}I.

The compound of the present invention and a pharmaceutically acceptable derivative thereof (e.g. a salt), which include the above described isotopes and/or other isotopes, are included in the scope of claims in the specification of the present application. The isotopically labeled compound of the present invention, for example, a compound, into which a radioisotope(s) such as ^{3}H and/or ^{14}C are incorporated, is useful for the tissue distribution assay of a pharmaceutical agent and/or a substrate. Isotopes ^{3}H and ^{14}C are considered useful because of the easiness of preparation and detection. Isotopes ^{11}C and ^{18}F are considered useful for PET

(positron-emission tomography), and isotope ^{125}I is considered useful for SPECT (single-photon-emission computed tomography). All of these isotopes are useful for brain imaging. Substitution with a heavy isotope such as ^{2}H is advantageous for a certain type of therapy, such as an increase in the *in vivo* half-life or a decrease in necessary dose due to its higher metabolic stability. Thus, such a heavy isotope is considered useful under certain circumstances. The isotopically labeled compound of the formula (I) of the present invention can be uniformly prepared by performing procedures disclosed in formulae and/or Examples as described below, using commonly used isotopically labeled reagents, instead of non-isotopically labeled reagents.

[0010]

In the present specification, the term "halogen atom" is used to mean a fluorine atom, a chlorine atom, a bromine atom, an iodine atom, etc. It is preferably a fluorine atom or a chloride atom.

[0011]

The term "C_{1-6} alkyl group" is used to mean an alkyl group containing 1 to 6 carbon atoms. Examples of a preferred C_{1-6} alkyl group include linear or branched alkyl groups such as a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, an isobutyl group, a t-butyl group, an n-pentyl group, an isopentyl group, a neopentyl group, an n-hexyl group, a 1-methylpropyl group, a 1,2-dimethylpropyl group, a 1-ethylpropyl group, a 1-methyl-2-ethylpropyl group, a 1-ethyl-2-methylpropyl group, a 1,1,2-trimethylpropyl group, a 1-methylbutyl group, a 2-methylbutyl group, a 1,1-dimethylbutyl group, a 2,2-dimethylbutyl group, a 2-ethylbutyl group, a 1,3-dimethylbutyl group, a 2-methylpentyl group and a 3-methylpentyl group. Of these, a methyl group, an ethyl group and an n-propyl group are more preferable.

[0012]

The term "C_{1-6} alkylene group" is used to mean an alkylene group containing 1 to 6 carbon atoms. Examples of a preferred C_{1-6} alkylene group include linear or branched alkylene groups such as a methylene group, an ethylene group, an n-propylene group, an isopropylene group, an n-butylene group, an isobutylene group, an n-pentylene group, an isopentylene group and a neopentylene group. Of these, a methylene group, an ethylene group and an n-propylene group are more preferable.

[0013]

The term "C_{1-6} alkoxy group" is used to mean an alkyl group containing 1 to 6 carbon atoms, in which one hydrogen atom is substituted with an oxygen atom. Examples of such a C_{1-6} alkoxy group include a methoxy group, an ethoxy group, an n-propoxy group, an

isopropoxy group, an n-butoxy group, an isobutoxy group, a sec-butoxy group, a t-butoxy group, an n-pentoxy group, an isopentoxy group, a sec-pentoxy group, a t-pentoxy group, an n-hexoxy group, an isohexoxy group, a 1,2-dimethylpropoxy group, a 2-ethylpropoxy group, a 1-methyl-2-ethylpropoxy group, a 1-ethyl-2-methylpropoxy group, a 1,1,2-trimethylpropoxy group, a 1,1-dimethylbutoxy group, a 2,2-dimethylbutoxy group, a 2-ethylbutoxy group, a 1,3-dimethylbutoxy group, a 2-methylpentoxy group, a 3-methylpentoxy group and a hexyloxy group.

[0014]

The term "C_{1-6} alkylcarbonyl group" is used to mean an alkyl group containing 1 to 6 carbon atoms, in which one hydrogen atom is substituted with a carbonyl group. Examples of a preferred C_{1-6} alkylcarbonyl group include an acetyl group, a propionyl group and a butyryl group.

[0015]

The term "C_{1-6} alkylsulfonyl group" is used to mean an alkyl group containing 1 to 6 carbon atoms, in which one hydrogen atom is substituted with a sulfonyl group. Examples of such a C_{1-6} alkylsulfonyl group include a methylsulfonyl group, an ethylsulfonyl group, an n-propylsulfonyl group, an isopropylsulfonyl group, an n-butylsulfonyl group, an isobutylsulfonyl group, a t-butylsulfonyl group, an n-pentylsulfonyl group, an isopentylsulfonyl group, a neopentylsulfonyl group, an n-hexylsulfonyl group and a 1-methylpropylsulfonyl group.

[0016]

The term "C_{3-8} cycloalkyl group" is used to mean a cyclic alkyl group containing 3 to 8 carbon atoms, Examples of a preferred C_{3-8} cycloalkyl group include a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group and a cyclooctyl group.

[0017]

The term "aryl group" is used to mean an aryl group selected from group 1. Group 1 consists of a phenyl group, a naphthyl group, an azulenyl group, an anthryl group and a phenanthryl group.

[0018]

The term "heteroaryl group" is used to mean a heteroaryl group selected from group 2. Group 2 consists of a furyl group, a thienyl group, a pyrrolyl group, an imidazolyl group, a triazolyl group, a tetrazolyl group, a thiazolyl group, a pyrazolyl group, an oxazolyl group, an isoxazolyl group, an isothiazolyl group, a furazanyl group, a thiadiazolyl group, an oxadiazolyl group, a pyridyl group, a pyrazinyl group, a pyridazinyl group, a triazinyl group, an

indolyl group, an isoindolyl group, an indazolyl group, a benzoxazolyl group, a benzisoxadiazolyl group, a benzothiazolyl group, a benzisothiazolyl group, a quinolyl group and an isoquinolyl group.

[0019]

The term "heterocyclic group" is used to mean an aryl group selected from group 3. Group 3 consists of a furyl group, a thienyl group, a pyrrolyl group, an imidazolyl group, a triazolyl group, a tetrazolyl group, a thiazolyl group, a pyrazolyl group, an oxazolyl group, an isoxazolyl group, an isothiazolyl group, a furazanyl group, a thiadiazolyl group, an oxadiazolyl group, a pyridyl group, a pyrazinyl group, a pyridazinyl group, a pyrimidinyl group, a triazinyl group, a 2-pyridonyl group, a 4-pyridonyl group, a pyridazidonyl group, a pyrimididonyl group, a purinyl group, a pteridinyl group, a quinolyl group, an isoquinolyl group, a naphthylidyl group, a quinoxalyl group, a cinnolyl group, a quinazolyl group, a phthalazyl group, an imidazopyridyl group, an imidazothiazolyl group, an imidazoxazolyl group, a benzimidazolyl group, an indolyl group, an isoindolyl group, an indazolyl group, a pyrrolopyridyl group, a thienopyridyl group, a fluoropyridyl group, a benzoxazolyl group, a benzisoxadiazolyl group, a benzothiazolyl group, a benzisothiazolyl group, a pyridopyrimidinyl group, an oxodihydropyridopyrimidinyl group, a benzofuryl group, a benzothienyl group, a benzothiadiazolyl group, a benzo[1,3]dioxolyl group, a thienofuryl group, a dihydroisobenzofuranyl group, a chromanyl group, an isochromanyl group, a 1,3-dioxaindanyl group, a 1,4-dioxatetralinyl group, and a dihydrobenzo[1,4]oxazinyl group.

[0020]

The term "Substituent group α" is used to consist of a cyano group, a halogen atom, a hydroxyl group, an oxo group, a formula $-NR_6R_7$ (wherein R_6 and R_7 each independently represent a hydrogen atom or a C_{1-6} alkyl group), a C_{1-6} alkyl group which may optionally have 1 to 3 substituents selected from Substituent group β, a C_{1-6} alkoxy group which may optionally have 1 to 3 substituents selected from substituent group β, a C_{1-6} alkylcarbonyl group which may optionally have 1 to 3 substituents selected from Substituent group β, a C_{1-6} alkylsulfonyl group which may optionally have 1 to 3 substituents selected from Substituent group β, an aryl group selected from Group 1, which may optionally have 1 to 3 substituents selected from Substituent group β, and a heteroaryl group selected from Group 2, which may optionally have 1 to 3 substituents selected from Substituent group β.

[0021]

The term "Substituent group β" is used to consist of a cyano group, a halogen

atom, a hydroxyl group, a C_{3-8} cycloalkyl group and a C_{1-6} alkoxy group.

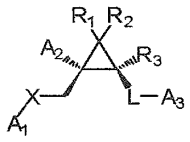
[0022]

The cyclopropane compound of the formula (I) of the present invention may also be a pharmaceutically acceptable salt. Specific examples of such a pharmaceutically acceptable salt include: inorganic acid salts (for example, a sulfate, a nitrate, a perchlorate, a phosphate, a carbonate, a bicarbonate, a hydrofluoride, a hydrochloride, a hydrobromide, a hydroiodide); organic carboxylates (for example, an acetate, an oxalate, a maleate, a tartrate, a fumarate, a citrate); organic sulfonates (for example, a methanesulfonate, a trifluoromethanesulfonate, an ethanesulfonate, a benzenesulfonate, a toluenesulfonate, a camphorsulfonate); amino acid salts (for example, an aspartate, a glutamate); quaternary amine salts; alkaline metal salts (for example, a sodium salt, a potassium salt); and alkaline-earth metal salts (for example, a magnesium salt, a calcium salt).

[0023]

The cyclopropane compound of the formula (I) of the present invention or a pharmaceutically acceptable salt thereof is preferably a cyclopropane compound represented by the following formula (II) or a pharmaceutically acceptable salt thereof:

[Formula 3]



(II)

wherein A_1, A_2, A_3, R_1, R_2, R_3, X and L have the same definitions as those described above.

[0024]

Moreover, the cyclopropane compound of the present invention or a pharmaceutically acceptable salt thereof is preferably a cyclopropane compound or a pharmaceutically acceptable salt thereof, wherein in the formula (I) or the formula (II), R_1, R_2 and R_3 each represent a hydrogen atom.

[0025]

Furthermore, a cyclopropane compound or a pharmaceutically acceptable salt thereof, wherein in the formula (I) or the formula (II), L represents a formula -CONH-, is more preferable; and a cyclopropane compound or a pharmaceutically acceptable salt thereof, wherein in the formula (I) or the formula (II), X represents an oxygen atom, is particularly preferable.

The cyclopropane compound of the present invention or a pharmaceutically acceptable salt thereof is preferably a cyclopropane compound or a pharmaceutically acceptable salt thereof, wherein, in the formula (I) or the formula (II), A_2 and A_3 each independently

represent an aryl group or a heteroaryl group, which may optionally have 1 to 3 substituents selected from a cyano group, a halogen atom, a C_{1-6} alkyl group, a halo-C_{1-6} alkyl group and a C_{1-6} alkoxy group.

[0026]

Further, a cyclopropane compound or a pharmaceutically acceptable salt thereof, wherein A_2 and A_3 each independently represent an aryl group or a heteroaryl group, which may optionally have 1 to 3 substituents selected from a cyano group, a halogen atom, a C_{1-6} alkyl group, a halo-C_{1-6} alkyl group and a C_{1-6} alkoxy group, is preferable; and a cyclopropane compound or a pharmaceutically acceptable salt thereof, wherein A_2 and A_3 each independently represent a phenyl group, a naphthyl group, a pyridyl group, a pyrazinyl group, a pyridazinyl group, a pyrimidinyl group, a quinolyl group or an isoquinolyl group, which may optionally have 1 to 3 substituents selected from a cyano group, a halogen atom, a C_{1-6} alkyl group, a halo-C_{1-6} alkyl group and a C_{1-6} alkoxy group, is particularly preferable.

Among others, a cyclopropane compound or a pharmaceutically acceptable salt thereof, wherein A_2 represents a phenyl group which may optionally have 1 to 3 substituents selected from a cyano group, a halogen atom, a C_{1-6} alkyl group, a halo-C_{1-6} alkyl group and a C_{1-6} alkoxy group; a cyclopropane compound or a pharmaceutically acceptable salt thereof, wherein A_3 represents a phenyl group or a pyridyl group which may optionally have 1 to 3 substituents selected from a cyano group, a halogen atom, a hydroxyl group, a C_{1-6} alkyl group, a halo-C_{1-6} alkyl group and a C_{1-6} alkoxy group; a cyclopropane compound or a pharmaceutically acceptable salt thereof, wherein A_1 represents a 5-pyrimidinyl group which may optionally have 1 to 3 substituents selected from a halogen atom, a C_{1-6} alkyl group, a halo-C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkyl group, a C_{3-8} cycloalkyl group and a C_{1-6} alkoxy group; and particularly, a cyclopropane compound or a pharmaceutically acceptable salt thereof, wherein A_1 represents a 5-pyrimidinyl group which may optionally have 1 or 2 substituents selected from a methyl group, a hydroxymethyl group, a methoxymethyl group and a methoxyethyl group, are preferable.

[0027]

Specifically, the cyclopropane compound of the present invention or a pharmaceutically acceptable salt thereof is preferably selected from the following compounds:

(1) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)-2-phenylcyclopropanecarboxamide,

(2) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)-2-phenylcyclopropanecarboxamide,

(3) (1R,2S)-N-(5-chloro-4-methylpyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(4) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxypyridin-2-yl)-2-phenylcyclopropanecarboxamide,
(5) (1R,2S)-N-(6-fluoropyridin-3-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(6) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(6-fluoro-5-methylpyridin-3-yl)-2-phenylcyclopropanecarboxamide,
(7) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-methoxypyridin-3-yl)-2-phenylcyclopropanecarboxamide,
(8) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N,2-diphenylcyclopropanecarboxamide,
(9) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-methylpyridin-2-yl)-2-phenylcyclopropanecarboxamide,
(10) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-[5-fluoro-4-(methoxymethyl)pyridin-2-yl]-2-phenylcyclopropanecarboxamide,
(11) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(2-methoxypyridin-4-yl)-2-phenylcyclopropanecarboxamide,
(12) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenyl-N-[5-(trifluoromethyl)pyridin-2-yl]cyclopropanecarboxamide,
(13) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenyl-N-[4-(trifluoromethyl)pyridin-2-yl]cyclopropanecarboxamide,
(14) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-[4-(methoxymethyl)pyridin-2-yl]-2-phenylcyclopropanecarboxamide,
(15) (1R,2S)-N-(5-chloropyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(16) (1R,2S)-N-[3-(dimethylamino)phenyl]-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(17) (1R,2S)-N-(3-chlorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(18) (1R,2S)-N-(3-cyano-4-fluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(19) (1R,2S)-N-(4-chloro-3-cyanophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(20) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-[3-(methylsulfonyl)phenyl]-2-

phenylcyclopropanecarboxamide,
(21) (1R,2S)-N-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(22) (1R,2S)-N-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(23) (1R,2S)-N-(3-chloro-4-fluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(24) (1R,2S)-N-(3-cyano-5-fluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(25) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(3-methoxyphenyl)-2-phenylcyclopropanecarboxamide,
(26) (1R,2S)-N-[3-(cyanomethyl)phenyl]-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(27) (1R,2S)-N-(2-cyanopyridin-4-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(28) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenyl-N-[3-(trifluoromethyl)phenyl]cyclopropanecarboxamide,
(29) (1R,2S)-N-(4-cyanopyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(30) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(4-methoxypyridin-2-yl)-2-phenylcyclopropanecarboxamide,
(31) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)-2-(3-fluorophenyl)cyclopropanecarboxamide,
(32) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(33) (1R,2S)-N-(5-cyanopyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)cyclopropanecarboxamide,
(34) (1R,2S)-N-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)cyclopropanecarboxamide,
(35) (1R,2S)-N-(4-chloropyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)cyclopropanecarboxamide,
(36) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxymethylpyridin-2-yl)-2-(3-fluorophenyl)cyclopropanecarboxamide,
(37) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxymethylpyridin-

2-yl)-2-(3-fluorophenyl)cyclopropanecarboxamide

(38) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)-N-(4-fluorophenyl)cyclopropanecarboxamide,

(39) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)-N-phenylcyclopropanecarboxamide,

(40) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxypyridin-2-yl)-2-(3-fluorophenyl)cyclopropanecarboxamide,

(41) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(4-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,

(42) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N,2-bis(4-fluorophenyl)cyclopropanecarboxamide,

(43) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxymethylpyridin-2-yl)-2-(4-fluorophenyl)cyclopropanecarboxamide,

(44) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)-2-(4-fluorophenyl)cyclopropanecarboxamide,

(45) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxypyridin-2-yl)-2-(4-fluorophenyl)cyclopropanecarboxamide,

(46) (1R,2S)-2-(3-cyanophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(4-fluorophenyl)cyclopropanecarboxamide,

(47) (1R,2S)-2-(3-cyanophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,

(48) (1R,2S)-2-(3-cyanophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)cyclopropanecarboxamide,

(49) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenyl-N-pyridin-2-ylcyclopropanecarboxamide,

(50) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)-2-phenylcyclopropanecarboxamide,

(51) (1R,2S)-N-(5-cyanopyridin-2-yl)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,

(52) (1R,2S)-N-(5-chloropyridin-2-yl)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,

(53) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)-2-phenylcyclopropanecarboxamide,

(54) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-(4-fluorophenyl)-2-

phenylcyclopropanecarboxamide,
(55) (1R,2S)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)cyclopropanecarboxamide,
(56) (1R,2S)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(4-fluorophenyl)cyclopropanecarboxamide,
(57) (1R,2S)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-pyridin-2-ylcyclopropanecarboxamide,
(58) (1R,2S)-N-(5-chloropyridin-2-yl)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(59) (1R,2S)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(60) (1R,2S)-N-(3,4-difluorophenyl)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(61) (1R,2S)-N-(2,4-difluorophenyl)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(62) (1R,2S)-N-(5-cyanopyridin-2-yl)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(63) (1R,2S)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxypyridin-2-yl)cyclopropanecarboxamide,
(64) (1R,2S)-N-(5-chloropyridin-2-yl)-2-{[(4-(methoxymethyl)-2-methylpyrimidin-5-yl)oxy]methyl}-2-phenylcyclopropanecarboxamide,
(65) (1R,2S)-N-(5-cyanopyridin-2-yl)-2-{[(4-(methoxymethyl)-2-methylpyrimidin-5-yl)oxy]methyl}-2-phenylcyclopropanecarboxamide,
(66) (1R,2S)-N-(5-fluoropyridin-2-yl)-2-{[(4-(methoxymethyl)-2-methylpyrimidin-5-yl)oxy]methyl}-2-phenylcyclopropanecarboxamide,
(67) (1R,2S)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenyl-N-[5-(trifluoromethyl)pyridin-2-yl]cyclopropanecarboxamide,
(68) (1R,2S)-N-(5-fluoro-4-methylpyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(69) (1R,2S)-N-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(70) (1R,2S)-N-(3,4-difluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(71) (1R,2S)-2-(4-chlorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-

fluoropyridin-2-yl)cyclopropanecarboxamide,
(72) (1R,2S)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)cyclopropanecarboxamide,
(73) (1R,2S)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(4-fluorophenyl)cyclopropanecarboxamide,
(74) (1R,2S)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-pyridin-2-ylcyclopropanecarboxamide,
(75) (1R,2S)-N-(5-cyanopyridin-2-yl)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(76) (1R,2S)-N-(5-chloropyridin-2-yl)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(77) (1R,2S)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(78) (1R,2S)-N,2-bis(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(79) (1R,2S)-N-(2,4-difluorophenyl)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(80) (1R,2S)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxypyridin-2-yl)cyclopropanecarboxamide,
(81) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)-2-(3-methoxyphenyl)cyclopropanecarboxamide,
(82) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(4-fluorophenyl)-2-(3-methoxyphenyl)cyclopropanecarboxamide,
(83) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)-2-(3-methoxyphenyl)cyclopropanecarboxamide,
(84) (1R,2S)-N-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-methoxyphenyl)cyclopropanecarboxamide
(85) (1R,2S)-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(86) (1R,2S)-2-(3-fluorophenyl)-N-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(87) (1R,2S)-2-(3-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-(pyridin-2-yl)cyclopropanecarboxamide,
(88) (1R,2S)-N-(3,4-difluorophenyl)-2-(3-fluorophenyl)-2-[(4-methoxymethyl-2-

methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(89) (1R,2S)-N,2-bis(3-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(90) (1R,2S)-N-(2,4-difluorophenyl)-2-(3-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(91) (1R,2S)-N-(2,5-difluorophenyl)-2-(3-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(92) (1R,2S)-N-(5-chloropyridin-2-yl)-2-(3-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(93) (1R,2S)-N-(5-fluoro-4-methylpyridin-2-yl)-2-(3-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(94) (1R,2S)-N-(5-cyanopyridin-2-yl)-2-(3-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(95) (1R,2S)-2-(3-fluorophenyl)-2-([(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-[5-(trifluoromethyl)pyridin-2-yl]cyclopropanecarboxamide,
(96) (1R,2S)-2-(4-fluorophenyl)-N-(5-fluoropyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(97) (1R,2S)-N,2-bis(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(98) (1R,2S)-N-(5-chloropyridin-2-yl)-2-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(99) (1R,2S)-N-(5-fluoro-4-methylpyridin-2-yl)-2-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(100) (1R,2S)-2-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-pyridin-2-ylcyclopropanecarboxamide,
(101) (1R,2S)-N-(3,4-difluorophenyl)-2-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(102) (1R,2S)-N-(3-fluorophenyl)-2-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(103) (1R,2S)-2-(3,4-difluorophenyl)-2-([(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-(pyridin-2-yl)cyclopropanecarboxamide,
(104) (1R,2S)-2-(3,4-difluorophenyl)-N-(5-fluoro-4-methylpyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(105) (1R,2S)-2-(3,4-difluorophenyl)-N-(4-fluorophenyl)-2-[(4-methoxymethyl-2-

methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(106) (1R,2S)-N,2-bis(3,4-difluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(107) (1R,2S)-N-(2,5-difluorophenyl)-2-(3,4-difluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(108) (1R,2S)-N-(2,4-difluorophenyl)-2-(3,4-difluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(109) (1R,2S)-N-(2,3-difluorophenyl)-2-(3,4-difluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(110) (1R,2S)-2-(3,5-difluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-pyridin-2-ylcyclopropanecarboxamide,
(111) (1R,2S)-2-(3,5-difluorophenyl)-N-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(112) (1R,2S)-2-(3,5-difluorophenyl)-N-(5-fluoro-4-methylpyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(113) (1R,2S)-N-(3,4-difluorophenyl)-2-(3,5-difluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(114) (1R,2S)-2-(3-chlorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-pyridin-2-ylcyclopropanecarboxamide,
(115) (1R,2S)-2-(3-chlorophenyl)-N-(5-fluoro-4-methylpyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(116) (1R,2S)-N-(5-fluoro-4-methylpyridin-2-yl)-2-(3-fluorophenyl)-2-({[4-(methoxyethyl)-2-methylpyrimidin-5-yl]oxy}methyl)cyclopropanecarboxamide,
(117) (1R,2S)-2-(3-fluoro-5-methoxyphenyl)-N-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(118) (1R,2S)-N-(3,4-difluorophenyl)-2-(3-fluoro-5-methoxyphenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(119) (1R,2S)-2-(3-fluoro-5-methoxyphenyl)-N-(5-fluoropyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(120) (1R,2S)-2-(3-fluoro-5-methoxyphenyl)-N-(5-fluoro-4-methoxypyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(121) (1R,2S)-2-(3-fluoro-5-methoxyphenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-pyridin-2-ylcyclopropanecarboxamide,
(122) (1R,2S)-2-(3-fluoro-5-methoxyphenyl)-N-(3-fluorophenyl)-2-[(4-methoxymethyl-2-

methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(123) (1R,2S)-2-(4-fluoro-3-methoxyphenyl)-N-(5-fluoro-4-methylpyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(124) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)-N-pyridin-2-ylcyclopropanecarboxamide,
(125) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(126) (1R,2S)-N-(5-cyanopyridin-2-yl)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)cyclopropanecarboxamide,
(127) (1R,2S)-N-(5-chloropyridin-2-yl)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)cyclopropanecarboxamide,
(128) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)-2-(3-fluorophenyl)cyclopropanecarboxamide,
(129) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(4-fluorophenyl)-N-pyridin-2-ylcyclopropanecarboxamide,
(130) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(4-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(131) (1R,2S)-N-(4-chloropyridin-2-yl)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(4-fluorophenyl)cyclopropanecarboxamide,
(132) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)-2-(4-fluorophenyl)cyclopropanecarboxamide,
(133) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-(3-fluorophenyl)-2-(4-fluorophenyl)cyclopropanecarboxamide,
(134) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-N,2-bis(4-fluorophenyl)cyclopropanecarboxamide,
(135) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluoro-5-methoxyphenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(136) (1R,2S)-N-(5-chloropyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluoro-5-methoxyphenyl)cyclopropanecarboxamide,
(138) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluoro-5-methoxyphenyl)-N-(5-fluoro-4-methylpyrimidin-2-yl)cyclopropanecarboxamide,
(139) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)-2-(3-trifluoromethylphenyl)cyclopropanecarboxamide,
(140) (1R,2R)-2-(4-bromophenyl)-N-(5-chloropyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-

yl)oxymethyl]cyclopropanecarboxamide,
(141) (1R,2R)-2-(4-bromophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(142) (1R,2S)-2-(3-chlorophenyl)-N-(5-fluoro-4-methylpyridin-2-yl)-2-({[4-(methoxymethyl)-2-methylpyrimidin-5-yl]oxy}methyl)cyclopropanecarboxamide,
(143) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoromethylpyridin-2-yl)-2-(3-fluorophenyl)cyclopropanecarboxamide,
(144) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)-2-(3-iodophenyl)cyclopropanecarboxamide, and
(145) (1R,2S)-N-(5-fluoropyridin-2-yl)-2-[(4-hydroxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)cyclopropanecarboxamide.

[0028]

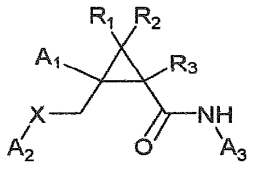
Next, a method for producing the compound of the formula (I) of the present invention [hereinafter referred to as a compound (I); compounds represented by other formulae will be referred to in the same manner] or a pharmaceutically acceptable salt thereof will be described.

In the formula (I), when L represents the formula -CONH-, the compound (I) or a pharmaceutically acceptable salt thereof can be produced by the following method.

The compound (I) represented by the following formula (I-1) and an intermediate thereof are synthesized, for example, by the following general production methods, and methods described in production examples and Examples, which will be described later.

Formula (I-1):

[Formula 4]



(I-1)

wherein A_1, A_2, A_3, R_1, R_2, R_3 and X have the same definitions as those described above.

[0029]

The "leaving group" in a raw material compound used in production of the compound (I) of the present invention is not particularly limited, as long as it can be used in a nucleophilic substitution reaction. Preferred examples of such a leaving group include a halogen atom, a C_{1-6} alkylsulfonyloxy group which may be substituted with the above described substituent group α, and an arylsulfonyloxy group which may be substituted with the above

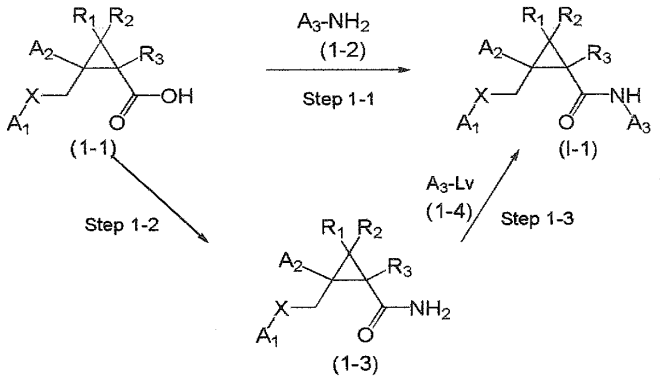
described substituent group α. Specific examples include a chlorine atom, a bromine atom, an iodine atom, a methanesulfonyloxy group, a trifluoromethanesulfonyloxy group and a p-toluenesulfonyloxy group.

[0030]

1. General production method 1:

[Formula 5]

Scheme 1



wherein R_1, R_2 and R_3 each represent hydrogen; Lv represents a leaving group including, for example, a halogen atom (a chlorine atom, a bromine atom, an iodine atom, etc.), and a sulfonyloxy group such as a methanesulfonyloxy group, a p-toluenesulfonyloxy group or a trifluoromethanesulfonyloxy group (which is represented by TfO in the formula); and A_1, A_2, A_3 and X have the same meanings as those described above.

[0031]

Step 1-1:

The present step is a step of directly condensing the compound (1-1) with the compound (1-2) (method 1), or inducing the compound (1-1) to an acid halide (method 2), a mixed acid anhydride (method 3), an active ester (method 4) or the like, and then condensing the obtained product with the compound (1-2), so as to obtain the compound (I-1).

[0032]

Method 1:

When the compound (1-1) is directly condensed with the compound (1-2), a condensing agent is used. Such a condensation reaction can be carried out under the same conditions as commonly used conditions described in publications as described below. Known methods are described, for example, in Rosowsky, A.; Forsch, R. A.; Moran, R. G.; Freisheim, J. H.; J. Med. Chem., 34(1), 227-234 (1991), Brzostwska, M.; Brossi, A.; Flippen-Anderson, J. L.;

Heterocycles, 32(10), 1968-1972 (1991), Romero, D. L.; Morge, R. A.; Biles, C.; Berrios-Pena, N.; May, P. D.; Palmer, J. R.; Johnson, P. D.; Smith, H. W.; Busso, M.; Tan, C.-K.; Voorman, R. L.; Reusser, F.; Althaus, I. W.; Downey, K. M.; So, A. G.; Resnick, L.; Tarpley, W. G., Aristoff, P. A.; J. Med. Chem., 37(7), 998-1014 (1994).

The compound (1-1) may be either a free form or a salt.

[0033]

The solvent used in the present invention is not particularly limited, as long as it does not inhibit the reaction. Examples of such a solvent include tetrahydrofuran, 1,4-dioxane, ethyl acetate, methyl acetate, dichloromethane, chloroform, N,N-dimethylformamide, toluene and xylene. Examples of a condensing agent include CDI (N,N'-carbonyldiimidazole), Bop (1H-1,2,3-benzotriazol-1-yloxy(tri(dimethylamino))phosphonium hexafluorophosphate), WSC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride), DCC (N,N-dicyclohexylcarbodiimide), diethylphosphorylcyanide, and PyBOP (benzotriazol-1-yloxytris(pyrrolidino)phosphoniumhexafluorophosphate). The compound (1-2) is used in an amount from 1 equivalent to a largely excessive amount with respect to the compound (1-1). In addition, an organic base such as triethylamine may be added in an amount from 1 equivalent to a largely excessive amount to the compound (1-1), as necessary.

The reaction time is not particularly limited. It is generally from 0.5 to 48 hours, and preferably from 0.5 to 24 hours. The reaction temperature depends on a raw material used, a solvent used, and the like, and thus, it is not particularly limited. It is preferably from an ice cooling temperature to a solvent reflux temperature.

[0034]

Method 2: (synthetic method using acid halide)

In the present reaction, the compound (1-1) is converted to the corresponding acid halide according to a method known to a person skilled in the art, and the acid halide is then allowed to react with the compound (1-2) to obtain the compound (I-1).

Examples of a base used in the reaction include triethylamine, pyridine, potassium carbonate and diisopropylethylamine. The reaction temperature is not particularly limited. It is generally from -78°C to a solvent reflux temperature, and preferably from -20°C to a room temperature. The solvent used in the reaction is not particularly limited, as long as it does not inhibit the reaction and is able to dissolve a starting substance to a certain extent. Preferred examples of such a solvent include tetrahydrofuran, ether, toluene and dichloromethane.

[0035]

Method 3: (synthetic method using acid anhydride)

After the compound (1-1) has been converted to a mixed acid anhydride, the mixed acid anhydride is allowed to react with the compound (1-2), so as to obtain the compound (I-1). The mixed acid anhydride can be synthesized by means known to a person skilled in the art. For example, it can be synthesized by reacting the compound (1-1) with a chloroformic acid ester such as ethyl chloroformate in the presence of a base such as triethylamine. Such a chloroformic acid ester and a base are used in an amount of 1 to 2 equivalents with respect to the compound (1-1). The reaction temperature is from -30°C to a room temperature, and preferably -20°C to a room temperature.

The step of condensing the mixed acid anhydride and the compound (1-2) is carried out, for example, by reacting the mixed acid anhydride with the compound (1-2) in a solvent such as dichloromethane, tetrahydrofuran or N,N-dimethylformamide. The compound (1-2) is used in an amount from 1 equivalent to a largely excessive amount with respect to the mixed acid anhydride

The reaction time is not particularly limited. It is generally from 0.5 to 48 hours, and preferably from 0.5 to 12 hours. The reaction temperature is from -20°C to 50°C, and preferably from -20°C to a room temperature.

[0036]

Method 4: (synthetic method using active ester)

After the compound (1-1) has been converted to an active ester, the active ester is allowed to react with the compound (1-2), so as to obtain the compound (I-1). The step of obtaining the active ester is carried out, for example, by reacting the compound (1-1) with an active ester-synthesizing reagent in a solvent such as 1,4-dioxane, tetrahydrofuran or N,N-dimethylformamide in the presence of a condensing agent such as DCC. An example of the active ester-synthesizing reagent is N-hydroxysuccinimide. Such an active ester-synthesizing reagent and a condensing agent are used in an amount of 1 to 1.5 equivalents with respect to the compound (1-1). The reaction time is not particularly limited. It is generally from 0.5 to 48 hours, and preferably from 0.5 to 24 hours.

The reaction temperature is from -20°C to -50°C, and preferably from -20°C to a room temperature.

The step of condensing the active ester and the compound (1-2) is carried out, for example, by reacting the active ester with the compound (1-2) in a solvent such as dichloromethane, tetrahydrofuran or N,N-dimethylformamide. The compound (1-2) is used in an amount from 1 equivalent to a largely excessive amount with respect to the active ester. The reaction time is not particularly limited. It is generally from 0.5 to 48 hours, and preferably

from 0.5 to 24 hours. The reaction temperature is from -20°C to -50°C, and preferably from -20°C to a room temperature.

[0037]

Step 1-2:

The present step is a step of obtaining the compound (1-3) from the compound (1-2).

The present step is a step of converting the compound (1-1) to the corresponding acid halide or acid anhydride by the methods described in Method 2 and Method 3 above and then reacting the acid halide or acid anhydride with ammonia, so as to obtain the compound (1-3). The ammonia used in the reaction may be either gas or an aqueous solution. It may also be an ammonia salt. The compound (1-3) can also be produced by reacting hexamethyl disilazane with an acid halide and then adding methanol to the reaction product, followed by an acid treatment (R. Pellegata et al., Synthesis, 1985, 517).

Moreover, the compound (1-3) can also be produced by heating the compound (1-1) and urea.

[0038]

Step 1-3:

The present step is a step of obtaining the compound (I-1) from the compound (1-3).

This is a step of subjecting the compound (1-3) and the compound (1-4) to a coupling reaction using a transition metal, so as to obtain the compound (I-1).

In the present step, the reaction can be carried out under conditions that are commonly applied to the coupling reaction between an aryl halide or arylboronic acid and an acid amide, in which a transition metal is used.

A coupling reaction using copper is described, for example, in publications such as Hanhui Xu, Christian Wolf, Chem. Commun, 2009, 1715; and Suribabu Jammi et al., Synlett. 2009 (20), 3323. The type of a copper reagent used in the present reaction is not particularly limited. Preferred examples of such a copper reagent include cuprous iodide, cuprous oxide, and copper(II) trifluoromethanesulfonate.

A coupling reaction using a palladium complex is described, for example, in publications such as Van den Hoogenband, A et al., Tetrahedron Lett. 2004, 45, 8535; and Ghosh, A et al., Org. Lett. 2003, 5, 2207. The type of a palladium reagent used in the present reaction is not particularly limited. Preferred examples of such a palladium reagent include tris(dibenzylideneacetone)dipalladium, palladium chloride, and palladium(II) acetate.

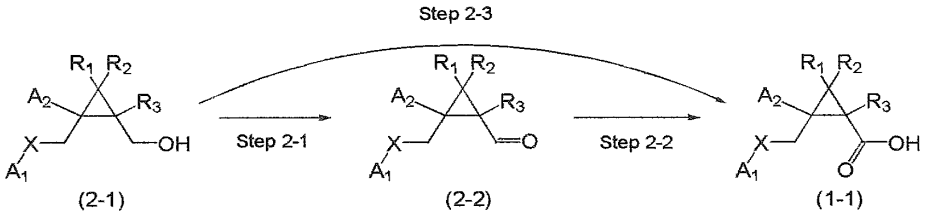
Examples of a ligand used in the present reaction include XantPhos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene), X-Phos (2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl), BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl), DPPF (1,1'-bis(diphenylphosphino)ferrocene), and tris(tert-butyloxy)phosphine. The transition metal reagent is used in an amount of approximately 0.001 to 0.1 equivalent with respect to the amount of a raw material. The type of a solvent used in the present reaction is not particularly limited, as long as it does not inhibit the reaction. Preferred examples of such a solvent include benzene, toluene, xylene, N,N-dimethylformamide, 1-methyl-2-pyrrolidone, tetrahydrofuran, 1,4-dioxane, acetonitrile, and propionitrile. The reaction temperature is not particularly limited. It is generally from an ice cooling temperature to a solvent reflux temperature, and preferably from a room temperature to a solvent reflux temperature, for example. The reaction time is not particularly limited. It is generally from 0.5 to 48 hours, and preferably from 0.5 to 24 hours.

[0039]

General production method 2:

[Formula 6]

Scheme 2



wherein A_1, A_2, R_1, R_2, R_3 and X have the same meanings as those described above.

[0040]

The general production method 2 is a method for producing the compound (1-1) that is a synthetic intermediate of the compound (I-1) according to the present invention, which uses the compound (2-1) as a raw material and involves [step 2-1] and [step 2-2] or [step 2-3].

The compound (2-1) can be produced from a commercially available product by a method known to a person skilled in the art. Further, it can also be produced by applying methods described in the production examples in the examples.

[0041]

Step 2-1:

The present step is a step of subjecting the compound (2-1) to an oxidation reaction to obtain the compound (2-2). An aldehyde compound can be obtained from an alcohol compound according to a method known to a person skilled in the art.

Examples of a known oxidation method used in the reaction include Swern oxidation, Corey-Kim oxidation, Moffatt oxidation, PCC oxidation, PDC oxidation, Dess-Martin oxidation, SO_3-pyridine oxidation, and TEMPO oxidation.

The solvent used in the reaction is not particularly limited, as long as it does not inhibit the reaction and dissolves a starting substance to a certain extent. Examples of such a solvent include dimethyl sulfoxide, tetrahydrofuran, toluene, dichloromethane and chloroform.

The reaction temperature is not particularly limited. It is generally from -78°C to a solvent reflux temperature, and preferably from -78°C to a room temperature. The reaction time is not particularly limited. It is generally from 5 minutes to 48 hours, and preferably from 5 minutes to 24 hours.

[0042]

Step 2-2:

The present step is a step of subjecting the compound (2-3) to an oxidation reaction to obtain the compound (1-1). A carboxylic acid compound can be obtained from an aldehyde compound according to a method known to a person skilled in the art.

As an oxidation method, a commonly used oxidation method can be applied. For example, methods described in the production examples in the Examples can be applied.

[0043]

Step 2-3:

The present step is a step of subjecting the compound (2-1) to an oxidation reaction to obtain the compound (1-1). As oxidation conditions, commonly used conditions can be applied. For example, oxidation can be carried out using TEMPO-bisacetyliodobenzene. The solvent used in the reaction is not particularly limited, as long as it does not inhibit the reaction and dissolves a starting substance to a certain extent. For example, dichloromethane, chloroform, acetonitrile, toluene or the like is mixed with water, and the mixed solvent can be used.

The reaction temperature is not particularly limited. It is generally from 0°C to a solvent reflux temperature. The reaction time is not particularly limited. It is generally from 5 minutes to 48 hours, and preferably from 5 minutes to 24 hours.

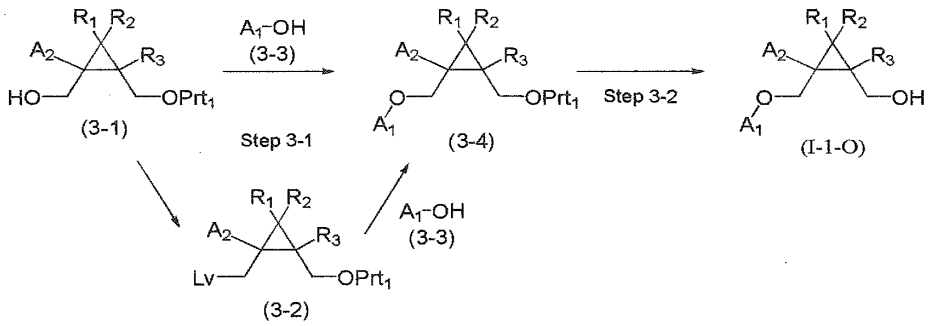
Moreover, methods described in the production examples in the Examples can be applied.

[0044]

General production method 3:

[Formula 7]

Scheme 3



wherein Lv represents a leaving group such as a halogen atom (a chlorine atom, a bromine atom, an iodine atom or the like), a sulfonyloxy group such as a methanesulfonyloxy group, a p-toluenesulfonyloxy group or a trifluoromethanesulfonyloxy group, or the like; Prt_1 represents a protecting group for a hydroxyl group; and A_1, A_2, R_1, R_2 and R_3 have the same meanings as those described above.

[0045]

The general production method 3 is a method for producing the compound (I-1-O) that is a synthetic intermediate of the compound (I) according to the present invention, which uses the compound (3-1) as a raw material and involves [step 3-1] and [step 3-2].

The compound (I-1-O) can also be produced from a commercially available product according to a method known to a person skilled in the art. Further, it can also be produced by applying methods described in the production examples in the Examples.

[0046]

Step 3-1:

The present step is a step of allowing the compound (3-1) to directly react with the compound (3-3), or of converting the compound (3-1) to the compound (3-2) and then allowing the compound (3-2) to react with the compound (3-3), so as to obtain the compound (3-4).

When the compound (3-1) is allowed to directly react with the compound (3-3), the present reaction can be carried out under conditions generally used in the Mitsunobu reaction (for example, conditions described in O. Mitsunobu, Synthesis, 1(1981), D. L. Hughes, Organic Reactions, 42, 335(1992), etc.).

The reaction is carried out using a phosphine derivative such as triphenylphosphine and an azodicarboxylic acid diester such as diethyl azodicarboxylate or diisopropyl azodicarboxylate. The solvent used in the reaction is not particularly limited, as

long as it does not inhibit the reaction and dissolves a starting substance to a certain extent. For example, tetrahydrofuran, benzene, toluene or N,N-dimethylformamide can be used. The reaction temperature is not particularly limited. It is generally from an ice cooling temperature to a room temperature.

Alternatively, the compound (3-4) can be produced by converting the compound (3-1) to the compound (3-2) having a leaving group and then performing a nucleophilic substitution reaction between the compound (3-2) and the compound (3-3). Specifically, a base is allowed to act on the compound (3-3) to form an anion, and the anion is then allowed to react with the compound (3-2), so as to obtain the compound (3-4), for example.

The solvent used in the reaction is not particularly limited, as long as it does not inhibit the reaction. The present reaction can be carried out by allowing a suitable base to act on the compound (3-3), in an amount of 1 equivalent to a largely excessive amount with respect to the compound, in an organic solvent such as diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide or dimethyl sulfoxide. Examples of the used base include sodium hydroxide, potassium hydroxide, sodium hydride, potassium hydride, sodium methoxide, sodium ethoxide, and potassium tert-butoxide.

The reaction temperature is not particularly limited. It is generally from -78°C to a solvent reflux temperature, and preferably from an ice cooling temperature to 100°C.

The compound (3-2) can be produced by converting the hydroxyl group of the compound (3-1) to a leaving group.

Examples of such a leaving group include a halogen atom (a chlorine atom, a bromine atom or an iodine atom), and a sulfonyloxy group such as a methanesulfonyloxy group, a p-toluenesulfonyloxy group or a trifluoromethanesulfonyloxy group.

The reaction can be carried out under the same conditions as those generally used in a reaction of converting the hydroxyl group to such a leaving group (for example, conditions described in R. K. Crossland and K. L. Servis, Journal of Organic Chemistry, 35, 3195 (1970), Y. Yoshida, Y. Sakakura, N. Aso, S. Okada, and Y. Tanabe, Tetrahedron, 55, 2183 (1999).

When the leaving group is a halogen atom for example, the compound (3-2) can be produced by allowing the compound (3-1) to react with thionyl chloride, thionyl bromide, phosphorus tribromide or tetrahalogenomethane triphenylphosphine. The solvent used in the reaction is not particularly limited, as long as it does not inhibit the reaction and dissolves a starting substance to a certain extent. Preferred examples of such a solvent include benzene, toluene, xylene, dichloromethane and chloroform. Further, there may be a case in which favorable results such as the improvement of a yield can be obtained by addition of a base. The

base used in the reaction is not particularly limited, as long as it does not inhibit the reaction. Preferred examples of such a base include sodium carbonate, potassium carbonate, triethylamine, pyridine and diisopropylethylamine. The reaction temperature is generally from -78°C to a solvent reflux temperature, and preferably from an ice cooling temperature to a solvent reflux temperature.

When the leaving group is a sulfonyloxy group, the compound (3-2) can be produced by allowing the compound (3-1) to react with methanesulfonyl chloride, p-toluenesulfonyl chloride, anhydrous trifluoromethanesulfonic acid, etc. The solvent used in the reaction is not particularly limited, as long as it does not inhibit the reaction and dissolves a starting substance to a certain extent. Preferred examples of such a solvent include tetrahydrofuran, toluene, xylene, dichloromethane, chloroform and N,N-dimethylformamide. The reaction temperature is generally from -78°C to a solvent reflux temperature, and preferably from an ice cooling temperature to a room temperature. Further, there may be a case in which favorable results such as the improvement of a yield can be obtained by addition of a base. The base used in the reaction is not particularly limited, as long as it does not inhibit the reaction. Preferred examples of such a base include sodium carbonate, potassium carbonate, triethylamine, pyridine and diisopropylethylamine.

[0047]

Step 3-2:

The present step is a step of deprotecting the compound (3-4) to obtain the compound (I-1-O).

When Prt_1 is a tert-butyldimethylsilyl group or a tert-butyldiphenylsilyl group, the reaction can be carried out under the same conditions as those generally used in the deprotection reaction of a silyl group (for example, conditions described in publications such as T. W. Green and P. G. M. Wuts, "Protective Groups in Organic Chemistry, Third Edition," John Wiley & Sons (1999), pp. 113-148). Specifically, tetra-n-butylammonium fluoride is allowed to act on the compound (3-4) in an organic solvent such as tetrahydrofuran, or hydrochloric acid is allowed to act on the compound (3-4) in ethanol, so as to obtain the compound (I-1-O). The solvent used in the present reaction is not particularly limited, as long as it does not inhibit the reaction. Preferred examples of such a solvent include dichloromethane, methanol, ethanol, propanol, ethyl acetate, tetrahydrofuran and 1,4-dioxane. Further, there may be a case in which favorable results such as the improvement of a yield can be obtained by addition of an acetic acid.

When Prt_1 is a benzyl group, the reaction can be carried out under the same conditions as those generally used in the deprotection reaction of a benzyl group (for example,

conditions described in publications such as T. W. Green and P. G. M. Wuts, "Protective Groups in Organic Chemistry, Third Edition," John Wiley & Sons (1999), pp. 76-86). Specifically, the reaction can be carried out, for example, by a catalytic reduction method, which uses palladium-carbon, palladium hydroxide-carbon or the like as a catalyst in an organic solvent such as ethanol in a hydrogen atmosphere.

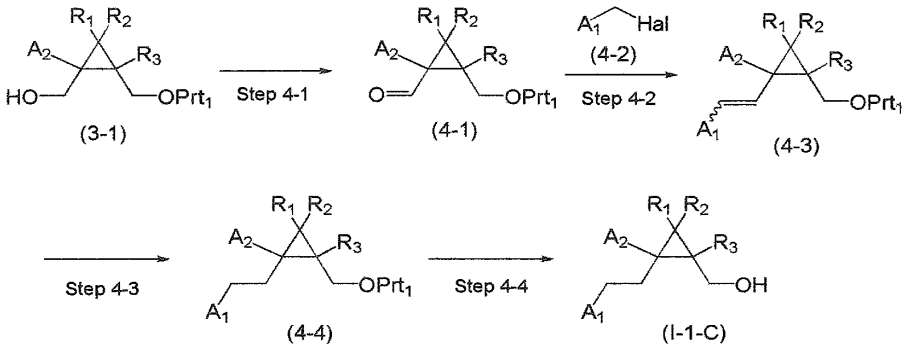
The solvent used in the present reaction is not particularly limited, as long as it does not inhibit the reaction. Examples of such a solvent include methanol, ethanol, propanol, ethyl acetate, tetrahydrofuran and 1,4-dioxane. The reaction conditions are not particularly limited. The reaction can be carried out at a temperature from a room temperature to a solvent reflux temperature at a normal atmospheric pressure to 150 atmospheric pressures, and preferably at a temperature from a room temperature to 60°C at a normal atmospheric pressure to 5 atmospheric pressures.

[0048]

General production method 4:

[Formula 8]

Scheme 4



wherein Prt_1, A_1, A_2, R_1, R_2 and R_3 have the same meanings as those described above.

The general production method 4 is a method for producing the compound (I-1-C) that is a synthetic intermediate of the compound (I) according to the present invention, which uses the compound (3-1) as a raw material and involves 4 steps from [step 4-1] to [step 4-4].

The compound (I-1-C) can also be produced from a commercially available product by a method known to a person skilled in the art. Further, it can also be produced by applying methods described in the production examples in the examples.

[0049]

Step 4-1

The present step is a step of oxidizing the alcohol of the compound (3-1) to obtain

an aldehyde body (4-1). The present reaction can be carried out under the same conditions as those in the step 2-1.

[0050]

Step 4-2

The present step is a step of obtaining the olefin (4-3) from the aldehyde (4-1). The present reaction can be carried out under commonly used conditions. Specifically, the compound (4-2) and a Wittig reagent synthesized from triphenylphosphine are used for example, and these are allowed to react with the compound (4-1) in the presence of a base, so as to obtain the compound (4-3).

[0051]

Step 4-3

The present step is a step of reducing olefin according to catalytic hydrogen reduction. The present reaction can be carried out under commonly used conditions.

[0052]

Step 4-4

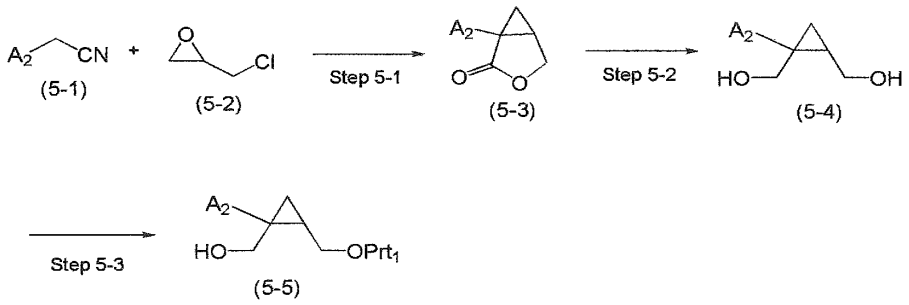
The present step is a step of deprotecting the compound (4-3) to obtain the compound (I-1-C). The present reaction can be carried out by the same method as that in the step 3-2.

[0053]

5. General production method 5:

[Formula 9]

Scheme 5



wherein Prt_1 and A_1 have the same meanings as those described above.

The general production method 5 is a method for producing the compound (5-5) that is a synthetic intermediate of the compound (I) according to the present invention, which uses the compound (5-1) as a raw material and involves [step 5-1] to [step 5-3].

The compound (5-5) can also be produced from a commercially available product

by a method known to a person skilled in the art. Further, it can also be produced by applying methods described in the production examples in the examples.

[0054]

Step 5-1

The present step is a step of reacting an acetonitrile derivative (5-1) with the epichlorohydrin (5-2) to obtain the compound (5-3). The compound (5-3) can be produced under commonly used reaction conditions (for example, conditions described in S, Shuto, Bioorganic & Medicinal Chemistry, 10 (2002), 3829), or by applying methods described in the production examples in the examples. Moreover, an optically active substance of the compound (5-3) can be obtained using an optically active epichlorohydrin.

[0055]

Step 5-2

The present step is a step of reducing the lactone (5-3) to obtain the compound (5-4). Examples of a reducing agent used in the reaction include sodium borohydride, lithium borohydride, and lithium aluminum hydride.

The solvent used in the present reaction is not particularly limited, as long as it does not inhibit the reaction and dissolves a starting substance to a certain extent. Examples of such a solvent include tetrahydrofuran and diethyl ether. In some cases, an alcoholic solvent such as methanol is mixed with such a solvent. The reaction temperature is not particularly limited. It is generally from -78°C to a solvent reflux temperature, and preferably from -78°C to a room temperature. The reaction time is not particularly limited. It is generally from 5 minutes to 48 hours, and preferably from 5 minutes to 24 hours.

[0056]

Step 5-3

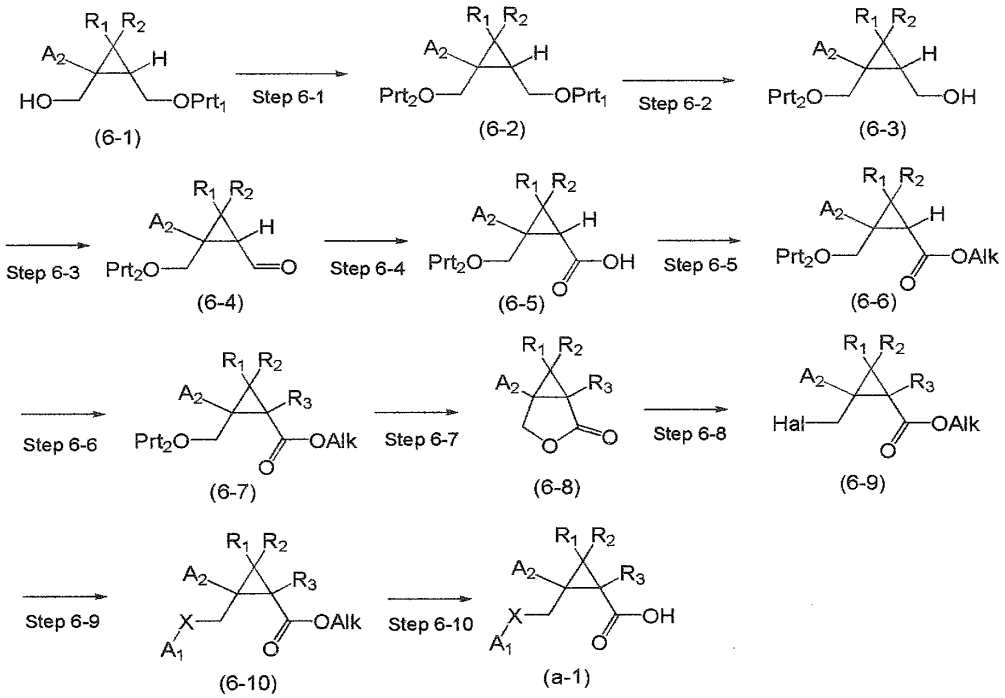
The present step is a step of protecting the hydroxyl group of the compound (5-4). Examples of a protecting group used herein include an acetyl group, a methoxymethyl group, a trityl group, a benzyl group, a t-butyldiphenylsilyl group, and a triisopropylsilyl group. The present reaction can be carried out under the same conditions as those commonly used in the introduction of a protecting group into a hydroxyl group (for example, conditions described in publications such as T. W. Green and P. G. M. Wuts, "Protective Groups in Organic Chemistry, Third Edition," John Wiley & Sons (1999), pp. 17-245). In addition, as in the case of Example 49, the present reaction can also be carried out by acetylation using enzyme.

[0057]

6. General production method 6:

[Formula 10]

Scheme 6



wherein Alk represents a C_{1-6} alkyl group; Hal represents a halogen atom; Prt_1 represents a silyl group such as a t-butyldimethylsilyl group, a t-butyldiphenylsilyl group or a triisopropylsilyl group; Prt_2 represents a protecting group for a hydroxyl group, other than a silyl group; and X, R_1, R_2, R_3, A_1 and A_2 have the same meanings as those described above.

The general production method 6 is a method for producing the compound (a-1) that is a synthetic intermediate of the compound (I) according to the present invention, which uses the compound (6-1) as a raw material and involves 10 steps from [step 6-1] to [step 6-10].

[0058]

Step 6-1

The present step is a step of protecting of the hydroxyl group of the compound (6-1). Examples of a protecting group used herein include a methoxymethyl group, a trityl group and a benzyl group. Such a protecting group can be introduced under commonly used conditions described in the step 5-3.

[0059]

Step 6-2

The present step is a step of selectively deprotecting the protecting group of the compound (6-2). The deprotection can be carried out under commonly used conditions.

[0060]

Steps 6-3, 6-4

The present steps are steps of obtaining the carboxylic acid (6-5) from the compound (6-3) by the same methods as those of the step 2-1 and step 2-2 of the general production method 2.

[0061]

Step 6-5

The present step is a step of esterifying the carboxylic acid (6-5) to obtain the compound (6-6). Esterification can be carried out under commonly used conditions.

[0062]

Step 6-6

The present step is a step of introducing the substituent (R3) into the carbonyl α carbon of the ester body (6-6). A preferred example of a base used herein is lithium diisopropylamide. As an alkylating agent, alkyl halide, aldehyde, ketone or the like is used. The solvent used in the reaction is not particularly limited, as long as it does not inhibit the reaction and dissolves a starting substance to a certain extent. Examples of such a solvent include tetrahydrofuran and diethyl ether. The reaction temperature is not particularly limited. It is generally from -78°C to a solvent reflux temperature, and preferably from -78°C to a room temperature. The reaction time is not particularly limited. It is generally from 5 minutes to 48 hours, and preferably from 5 minutes to 24 hours.

[0063]

Step 6-7

The present step is a step of selectively deprotecting the protecting group of the compound (6-7). In general, at the same time of deprotection, cyclization into lactone progresses in a molecule. The deprotection can be carried out under commonly used conditions.

[0064]

Step 6-8

The present step is a step of reacting the compound (6-8) with thionyl halide in an alcoholic solvent, so as to obtain the haloester (6-9). The thionyl halide used in the reaction is preferably thionyl bromide. As a solvent, methanol or ethanol is preferable. The reaction temperature is not particularly limited. It is generally from -78°C to a solvent reflux temperature, and preferably from -78°C to a room temperature. The reaction time is not particularly limited. It is generally from 5 minutes to 48 hours, and preferably from 5 minutes

to 48 hours.

[0065]

Step 6-9

The present step is a step of obtaining the compound (6-10) as a result of the nucleophilic substitution reaction between the compound (6-9) and the compound (3-3). The reaction conditions may be the same as those for the method for producing the compound (3-4) from the compound (3-2) in the general production method 3.

[0066]

Step 6-10

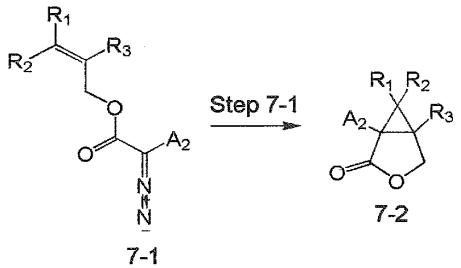
The present step is a step of obtaining the compound (a-1) as a result of the ester hydrolysis of the compound (6-10). As reaction conditions, a sodium hydroxide aqueous solution or a potassium hydroxide aqueous solution may be used, for example. Also, an organic solvent such as methanol or ethanol is used, as necessary. The reaction temperature is not particularly limited. It is generally from -78°C to a solvent reflux temperature, and preferably from a room temperature to a solvent reflux temperature. The reaction time is not particularly limited. It is generally from 5 minutes to 48 hours.

[0067]

General production method 7:

The general production method 7 is a method for producing a compound (7-2) that is a synthetic intermediate of the compound (I) according to the present invention, which uses a compound (7-1) as a raw material and involves [step 7-1]. The compound (7-1) can also be produced from a commercially available product by a method known to a person skilled in the art. Further, it can also be produced by applying methods described in the production examples in the Examples.

[Formula 11]



7-1 7-2

[0068]

Step 7-1

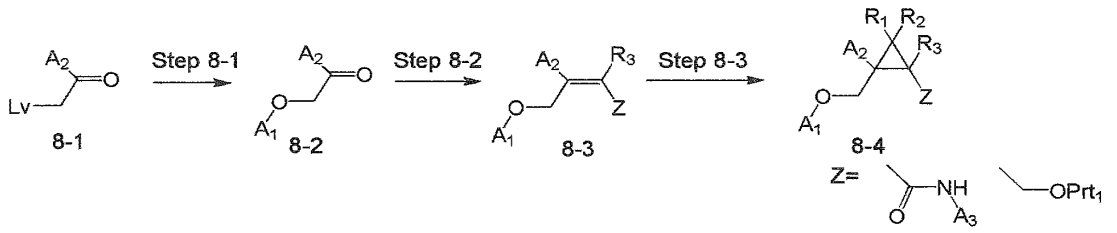
The present step is a step of obtaining the compound (7-2), which involves

intramolecular cyclization of the diazo compound (7-1). The reaction can be carried out under commonly used conditions for generating carbene from a diazo compound. The reaction can be carried out, for example, by the methods described in Doyle, M. P., Organic Letters 2(8)1145-; and Chen, C., Bioorganic & Medicinal Chemistry Letters, 18(2008) 3328-.

[0069]

General synthetic method 8:

[Formula 12]



The general production method 8 is a method for producing the compound (8-4) from the compound (8-1) via [step 8-1], [step 8-2] and [step 8-3]. The compound (8-1) can be produced from a commercially available product by a method known to a person skilled in the art.

[0070]

Step 8-1

The present step is a step of producing the compound (8-2) from the compound (8-1) by applying the method for producing the compound (3-4) from the compound (3-2) in the general production method 3.

[0071]

Step 8-2

The present step is a step of obtaining the olefin (8-3) from the ketone body (8-2) by the Wittig reaction or the Horner-Wadworth-Emmons reaction. The present reaction can be carried out under commonly used conditions.

[0072]

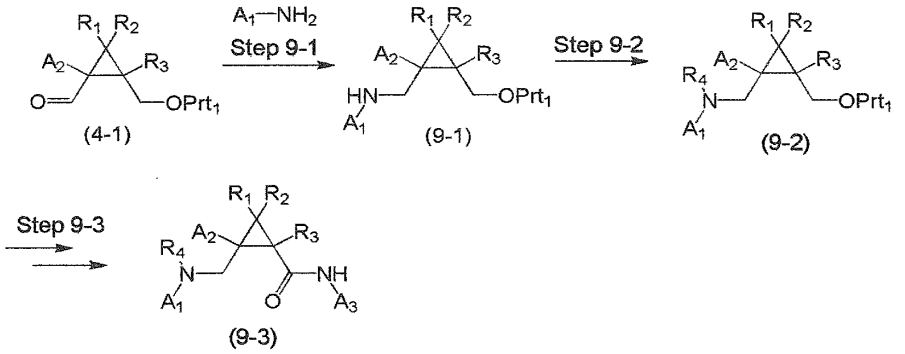
Step 8-3

The present step is a step of obtaining the compound (8-4) by cyclopropanation of the olefin (8-3). Such cyclopropanation can be carried out, for example, by the Simmons-Smith reaction, or under conditions in which a diazo compound is combined with a metal catalyst such as rhodium acetate.

[0073]

General production method 9:

[Formula 13]



[0074]

Step 9-1

The present step is a step of producing the compound (9-1) by reductive amination of the compound (4-1). As reaction conditions, ordinary conditions for reductive amination can be applied. Examples of a reducing agent include sodium borohydride and sodium triacetoxyborohydride.

The solvent used in the reaction is not particularly limited, as long as it does not inhibit the reaction and dissolves a starting substance to a certain extent. Examples of such a solvent include tetrahydrofuran and DMF. In some cases, an acid such as acetic acid may be mixed with such a solvent. The reaction temperature is not particularly limited. It is generally from -78°C to a solvent reflux temperature, and preferably from 0°C to a room temperature. The reaction time is not particularly limited. It is generally from 5 minutes to 48 hours, and preferably from 5 minutes to 24 hours.

[0075]

Step 9-2

The present step is a step of producing the compound (9-2) by reductive amination of the compound (9-1). The reaction conditions are the same as those applied in the step 9-1.

[0076]

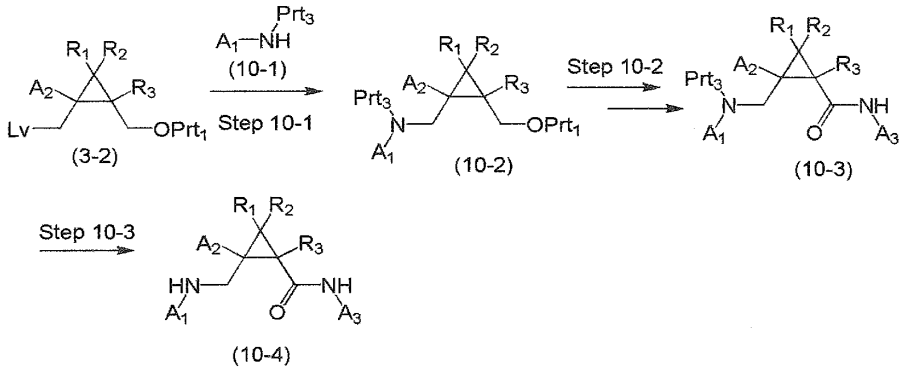
Step 9-3

The present step is a step of producing the compound (9-3) from the compound (9-2) according to the methods described in the step 3-2, step 2-1, step 2-2, and general production method 1.

[0077]

General production method 10:

[Formula 14]



[0078]

Step 10-1

The present step is a step of reacting the compound (3-2) with the amine (10-1) protected by amide or carbamate in the presence of a base, so as to produce the compound (10-2). Preferred examples of a base used herein include sodium hydride, cesium carbonate, and sodium hydroxide. The solvent used in the reaction is not particularly limited, as long as it does not inhibit the reaction and dissolves a starting substance to a certain extent. Examples of such a solvent include tetrahydrofuran, acetonitrile and DMF. The reaction temperature is not particularly limited. It is generally from 0°C to a solvent reflux temperature. The reaction time is not particularly limited. It is generally from 5 minutes to 48 hours, and preferably from 5 minutes to 24 hours. In addition, preferred examples of the protecting group Prt_3 include: amide protecting groups such as a trifluoroacetyl group; and carbamate protecting groups such as t-butyl carbamate.

[0079]

Step 10-2

The present step is a step of producing the compound (10-3) from the compound (10-2) according to the method described in the step 9-3.

[0080]

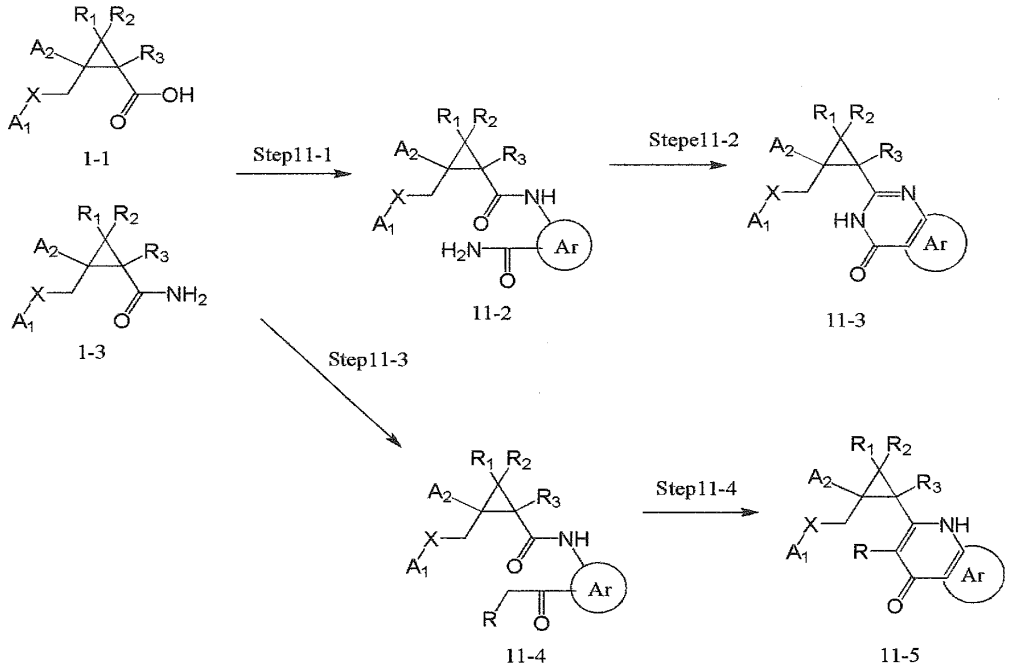
Step 10-3

The present step is a step of producing the compound (10-4) by deprotection of the compound (10-3). The deprotection can be carried out under commonly used conditions.

[0081]

General production method 11

[Formula 15]



[0082]

Step 11-1

The present step is a step of synthesizing the arylamide body (11-2) from the compound (1-1) or the compound (1-3) under the conditions described in the general production method 1.

[0083]

Step 11-2

The present step is a step of synthesizing the condensed pyrimidone derivative (11-3) from the compound (11-2) by an intramolecular cyclization reaction using a base. Preferred examples of a based used herein include potassium-tert-butoxide, sodium hydride, cesium carbonate, potassium carbonate, and sodium ethoxide. The solvent used in the reaction is not particularly limited, as long as it does not inhibit the reaction and dissolves a starting substance to a certain extent. Examples of such a solvent include tetrahydrofuran, 1,4-dioxane, DMF, MMP, acetonitrile, ethanol, and 2-propanol. The reaction temperature is not particularly limited. It is generally from 0°C to a solvent reflux temperature, and preferably from a room temperature to a solvent reflux temperature. The reaction time is not particularly limited. It is generally from 5 minutes to 48 hours, and preferably from 5 minutes to 24 hours.

[0084]

Step 11-3

The present step is a step of synthesizing the arylamide body (11-4) from the compound (1-1) or the compound (1-3) under the conditions described in the general production method 1.

[0085]

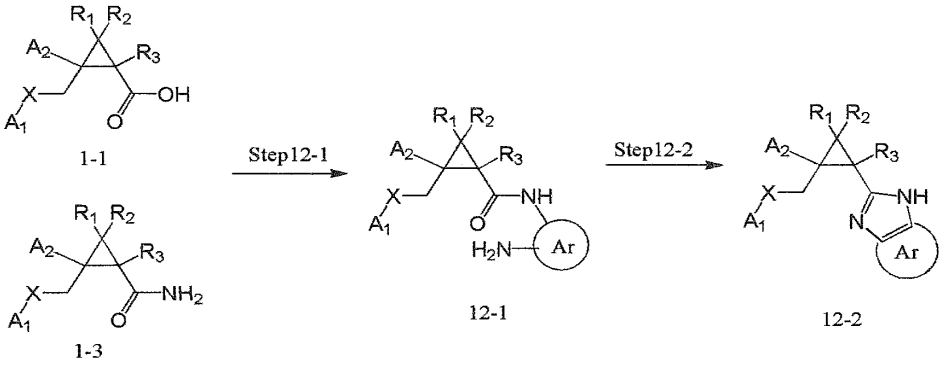
Step 11-4

The present step is a step of synthesizing the condensed pyridone derivative (11-5) from the compound (11-4) by an intramolecular cyclization reaction using a base. Preferred examples of a based used herein include potassium-tert-butoxide, sodium hydride, cesium carbonate, potassium carbonate, and sodium ethoxide. The solvent used in the reaction is not particularly limited, as long as it does not inhibit the reaction and dissolves a starting substance to a certain extent. Examples of such a solvent include tetrahydrofuran, 1,4-dioxane, DMF, NMP, acetonitrile, ethanol, and 2-propanol. The reaction temperature is not particularly limited. It is generally from 0°C to a solvent reflux temperature, and preferably from a room temperature to a solvent reflux temperature. The reaction time is not particularly limited. It is generally from 5 minutes to 48 hours, and preferably from 5 minutes to 24 hours.

[0086]

General production method 12:

[Formula 16]



[0087]

Step 12-1

The present step is a step of synthesizing the arylamide body (12-1) from the compound (1-1) or the compound (1-3) under the conditions described in the general production method 1.

[0088]

Step 12-2

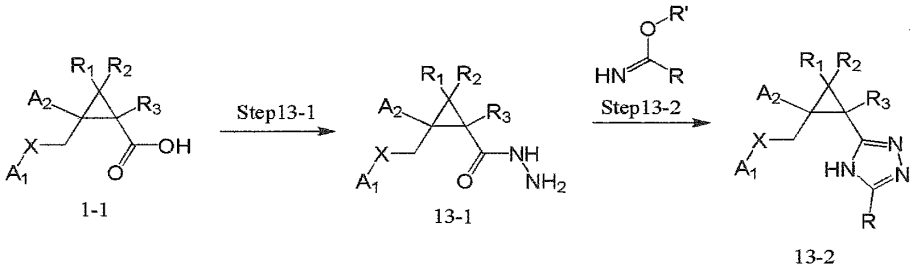
The present step is a step of synthesizing the condensed imidazole derivative (12-

2) from the compound (12-1) by an intramolecular cyclization reaction using an acid. Preferred examples of an acid used herein include acetic acid, trifluoroacetic acid, hydrochloric acid, and p-toluenesulfonic acid. The solvent used in the reaction is not particularly limited, as long as it does not inhibit the reaction and dissolves a starting substance to a certain extent. For example, acetic acid is used as a solvent. Other examples of a solvent include tetrahydrofuran, 1,4-dioxane, DMF, NMP, acetonitrile, ethanol, and 2-propanol. The reaction temperature is not particularly limited. It is generally from 0°C to a solvent reflux temperature, and preferably from a room temperature to a solvent reflux temperature. The reaction time is not particularly limited. It is generally from 5 minutes to 48 hours, and preferably from 5 minutes to 24 hours.

[0089]

General production method 13:

[Formula 17]



[0090]

Step 13-1

The present step is a step of synthesizing the hydrazide (13-1) from the compound (1-1). As synthetic conditions used herein, a generally known method can be applied. For example, mono-protected hydrazine and the compound (1-1) are subjected to amide condensation, and then deprotection is then carried out, so as to synthesize the aforementioned compound. The amidation can be carried out by the method described in the step (1-1). The protecting group of hydrazine is not particularly limited. Examples of such a protecting group include tert-butoxycarbonyl, benzyloxycarbonyl, and trifluoroacetyl.

[0091]

Step 13-2

The present step is a step of reacting the compound (13-1) with an imidate derivative to synthesize the triazole derivative (13-2). The reaction can be carried out under neutral conditions, or by adding an acid or a base. As an acid used herein, acetic acid, hydrochloric acid or the like is appropriate. As a base used herein, imidazole, triethylamine, potassium carbonate or the like is appropriate. The solvent used in the reaction is not

particularly limited, as long as it does not inhibit the reaction and dissolves a starting substance to a certain extent. For example, acetic acid is used as a solvent. Other examples of a solvent include tetrahydrofuran, 1,4-dioxane, DMF, NMP, acetonitrile, ethanol, and 2-propanol. The reaction temperature is not particularly limited. It is generally from 0°C to a solvent reflux temperature, and preferably from a room temperature to a solvent reflux temperature. The reaction time is not particularly limited. It is generally from 5 minutes to 48 hours, and preferably from 5 minutes to 24 hours.

[0092]

The thus obtained compound of the formula (I) of the present invention can be processed into a pharmaceutically acceptable salt according to an ordinary method, as necessary. Such a pharmaceutically acceptable salt can be produced by appropriately combining methods that are commonly used in the field of organic synthetic chemistry. Specifically, a free-type solution of the compound of the present invention is subjected to neutralization titration with an acid solution, for example. In addition, the compound of the formula (I) of the present invention is subjected to a well-known solvate formation reaction, as necessary, so that it can be converted to a solvate.

[0093]

The cyclopropane compound according to the present invention, a pharmaceutically acceptable salt thereof or a solvate thereof has extremely excellent orexin 2 receptor inhibitory action, and thus, is extremely useful as an agent for preventing or treating sleep disorder caused by orexin, including insomnia as a typical example. Specifically, it is useful for the prevention or treatment of sleep disorder including insomnia, narcolepsy (paroxysmal sleep), and other diseases such as excessive sleepiness, sleep-related dystonia, restless legs syndrome, sleep apnea, jet lag syndrome, shift work syndrome, delayed sleep phase syndrome or advanced sleep phase syndrome. Moreover, it is useful for the prevention or treatment of diseases including: dysthymic disorder, mood disorder, and mental and anxiety disorder; diabetes, and appetite, taste, eating or drinking disorder; hypothalamic disease; biological and circadian rhythm disorder; sleep disorder associated with a disease selected from nervous disease, neurogenic pain and restless legs syndrome; insomnia related to mental disorder; depression and insomnia related to depression; bipolar disorder and insomnia related to bipolar disorder; anxiety disorder and insomnia related to anxiety disorder; insomnia related to Parkinson's disease; insomnia related to schizophrenia; sleep apnea; opioid dependence; nicotine dependence; narcolepsy; idiopathic insomnia; parasomnia; benign prostatic hyperplasia; pure dementia and cognitive impairment in a healthy group and in mental and nervous diseases; and

other diseases related to systemic orexin dysfunction.

[0094]

The cyclopropane compound according to the present invention, a pharmaceutically acceptable salt thereof or a solvate thereof can be used to formulate a preparation according to an ordinary method. Examples of a preferred dosage form include a tablet, a coated tablet such as a film coated tablet or a sugar coated tablet, a fine granule, a granule, a powder, a capsule, a syrup, a troche, an inhalation, a suppository, an injection, an ointment, an ophthalmic preparation, a nasal preparation, an ear preparation, a cataplasm, and a lotion.

The aforementioned solid preparation such as a tablet, a capsule, a granule or a powder may comprise, as an active ingredient, the cyclopropane carboxylic acid derivative according to the present invention, a pharmaceutically acceptable salt thereof or a solvate thereof, in an amount of generally 0.01% to 100% by weight, and preferably 0.1% to 100% by weight.

[0095]

In order to formulate a preparation, ingredients that are generally used as raw materials for pharmaceutical preparations are mixed to the cyclopropane compound according to the present invention, a pharmaceutically acceptable salt thereof or a solvate thereof. For example, a diluent, a disintegrator, a binder, a lubricant, a coloring agent and a flavoring agent that are commonly used, and as necessary, a stabilizer, an emulsifier, a permeation enhancer, a surfactant, a pH adjuster, an antiseptic, an antioxidant, etc. are added to the cyclopropane compound according to the present invention, a pharmaceutically acceptable salt thereof or a solvate thereof, so as to formulate a preparation. Examples of these ingredients include: animal and vegetable oils such as soybean oil, tallow or synthetic glyceride; hydrocarbons such as liquid paraffin, squalane or solid paraffin; ester oils such as octyldodecyl myristate or isopropyl myristate; higher alcohols such as cetostearyl alcohol or behenyl alcohol; silicon resin; silicon oil; surfactants such as polyoxyethylene fatty acid ester, sorbitan fatty acid ester, glycerin fatty acid ester, polyoxyethylene sorbitan fatty acid ester, polyoxyethylene hydrogenated castor oil or a polyoxyethylene polyoxypropylene block copolymer; water-soluble polymers such as hydroxyethyl cellulose, polyacrylic acid, a carboxy vinyl polymer, polyethylene glycol, polyvinylpyrrolidone or methyl cellulose; lower alcohols such as ethanol or isopropanol; polyhydric alcohols such as glycerin, polypropylene glycol, dipropylene glycol or sorbitol; sugars such as glucose or sucrose; inorganic powders such as silicic acid anhydride, aluminum magnesium silicate or aluminum silicate; and purified water. Examples of a diluent used herein

include lactose, corn starch, saccharose, glucose, mannitol, sorbit, crystalline cellulose and silicon dioxide. Examples of a binder used herein include polyvinyl alcohol, polyvinyl ether, methyl cellulose, ethyl cellulose, gum arabic, gum tragacanth, gelatin, shellac, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, a polypropylene glycol-polyoxyethylene block copolymer and meglumine. Examples of a disintegrator used herein include starch, agar, gelatin powder, crystalline cellulose, calcium carbonate, sodium bicarbonate, calcium citrate, dextrin, pectin, and calcium carboxymethyl cellulose. Examples of a lubricant used herein include magnesium stearate, talc, polyethylene glycol, silica, and hydrogenated vegetable oil. Examples of a coloring agent used herein include those that are permitted to be added to pharmaceutical products. Examples of a flavoring agent used herein include cacao powder, menthol, aromatic powder, peppermint oil, borneol and cinnamon powder. However, needless to say, examples of excipient ingredients are not limited thereto.

[0096]

In the case of an oral preparation, for example, the cyclopropane compound according to the present invention, a pharmaceutically acceptable salt thereof or a solvate thereof, which is an active ingredient, is mixed with a diluent, and further, as necessary, with a binder, a disintegrator, a lubricant, a coloring agent, a flavoring agent and the like, and the obtained mixture is then processed into a powder, a fine granule, a granule, a tablet, a coated tablet, a capsule, etc. according to an ordinary method. In the case of production of a tablet or a granule, it may naturally be coated with sugar or the like, as necessary.

In the case of a syrup or an injection, for example, a pH adjuster, a dissolving agent, an isotonizing agent, etc., and as necessary, a solubilizer, a stabilizer, etc., are added to the cyclopropane compound according to the present invention, a pharmaceutically acceptable salt thereof or a solvate thereof, and the obtained mixture is then processed into such a syrup or an injection according to an ordinary method. In addition, such an injection may be previously dissolved. Alternatively, injection powder, or injection powder comprising suitable additives, may be dissolved when used. Such an injection solution may comprise an active ingredient in an amount of generally 0.01% to 100% by weight, and preferably 0.1% to 100% by weight. Further, a liquid for use in oral administration, such as a suspension or a syrup, may comprise an active ingredient in an amount of generally 0.01% to 100% by weight, and preferably 0.1% to 100% by weight.

In the case of an external preparation, for example, the production method thereof is not particularly limited. Such an external preparation can be produced by an ordinary method. As base materials used herein, various types of raw materials, which are generally

used in pharmaceutical products, quasi drugs, cosmetic products, and other products, can be used. Examples of such raw materials include animal and vegetable oil, mineral oil, ester oil, waxes, higher alcohols, fatty acids, silicon oil, surfactants, phospholipids, alcohols, polyhydric alcohols, water-soluble polymers, clay minerals, and purified water. As necessary, a pH adjuster, an antioxidant, a chelating agent, an antiseptic antifungal agent, a coloring agent, a fragrance, etc. may be added. Further, as necessary, ingredients such as an ingredient having differentiation-inducing action, a blood circulation promoter, a germicide, an anti-inflammatory agent, a cellular stimulant, vitamins, an amino acid, a moisturizing agent and a keratolytic drug may also be mixed.

[0097]

The dose of the cyclopropane compound according to the present invention, a pharmaceutically acceptable salt thereof or a solvate thereof is different depending on the degree of symptoms, age, sex, body weight, administration route/the type of a salt, the specific type of disease, and the like. In general, in the case of oral administration, the cyclopropane compound according to the present invention, a pharmaceutically acceptable salt thereof or a solvate thereof is administered at a dose of approximately 30 μg to 10 g, preferably 100 μg to 5 g, and more preferably 100 μg to 1 g per adult per day. In the case of administration via injection, it is administered at a dose of approximately 30 μg to 1 g, preferably 100 μg to 500 mg, and more preferably 100 μg to 300 mg per adult per day. In both cases, it is administered once or divided over several administrations.

[0098]

The compound of the present invention can be used as a chemical probe for capturing a target protein of a physiologically active low-molecular-weight compound. That is to say, the compound of the present invention can be converted to an affinity chromatography probe, a photoaffinity probe or the like, by introducing a labeling group, a linker or the like into a portion other than a structural portion essential for the expression of the activity of the compound according to the methods described in J. Mass Spectrum. Soc. Jpn. Vol. 51, No. 5, 2003, pp. 492-498; WO2007/139149; etc.

Examples of such a labeling group, a linker or the like used for such a chemical probe include groups described in the following groups (1) to (5).

(1) Protein labeling groups, such as photoaffinity labeling groups (for example, a benzoyl group, a benzophenone group, an azide group, a carbonyl azide group, a diaziridine group, an enone group, a diazo group, and a nitro group), and chemical affinity groups (for example, a ketone group in which the alpha carbon atom is replaced with a halogen atom, a carbamoyl group, an

ester group, an alkylthio group, a Michael acceptor such as α,β-unsaturated ketone or ester, and an oxirane group),

(2) Cleavable linkers such as -S-S-, -O-Si-O-, monosaccharide (a glucose group, a galactose group, etc.) or disaccharide (lactose, etc.), and oligopeptide linkers that can be cleaved by an enzyme reaction,

(3) Fishing tag groups such as biotin and a 3-(4,4-difluoro-5,7-dimethyl-4 H-3a,4a-diaza-4-bora-s-indacen-3-yl)propionyl group,

(4) Radioactive labeling groups such as ^{125}I, ^{32}P, ^{3}H and ^{14}C; fluorescent labeling groups such as fluorescein, rhodamine, dansyl, umbelliferone, 7-nitrofurazanyl, and 3-(4,4-difluoro-5,7-dimethyl-4H-3a,4a-diaza-4-bora-s-indacen-3-yl)propionyl group; chemiluminescent groups such as lumiferin and luminol; and detectable markers including heavy metal ions such as a lanthanoid metal ion and a radium ion, or

(5) Groups that are allowed to bind to solid-phase carriers, such as glass beads, a glass bed, a microtiter plate, agarose beads, an agarose bed, polystyrene beads, a polystyrene bed, nylon beads and a nylon bed.

A probe, which is prepared by introducing a labeling group or the like selected from the above described groups (1) to (5) into the compound of the present invention according to the methods described in the aforementioned publications and the like, can be used as a chemical probe for identifying a labeled protein useful for the search of a novel target of drug discovery.

[0099]

Hereinafter, the present invention will be described more in detail in the following examples, production examples and test examples. However, these examples are not intended to limit the scope of the present invention. Moreover, abbreviations used in the examples are commonly used abbreviations that are well known to a person skilled in the art. Several abbreviations are as follows.

THF: tetrahydrofuran

DMF: N,N-dimethylformamide

TFA: trifluoroacetic acid

EDC·HCl: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

HATU: O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

HBTU: O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate

pTLC: preparatory thin-layer chromatography

LC-MS: liquid chromatography-mass spectrometry

PyBOP: benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate

Pd_2DBA_3: tris(dibenzylideneacetone)dipalladium

$Pd(t\text{-}Bu_3P)_2$: bis(tri-t-butylphosphine)palladium

Chemical shifts in proton nuclear magnetic resonance spectrum are recorded by δ unit (ppm) with respect to tetramethylsilane. Coupling coefficients are recorded by hertz (Hz). With regard to pattern, s: singlet, d: doublet, t: triplet, q: quartette, and br: broad.

[0100]

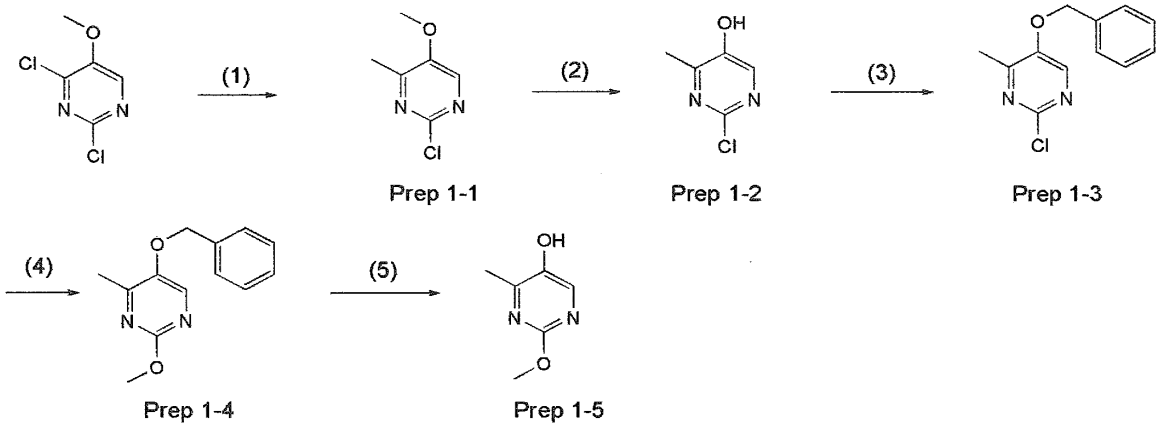
The term "room temperature" generally means approximately 10°C to approximately 35°C in the following examples and production examples. The symbol "%" means percent by weight, unless otherwise specified.

[0101]

Production Example 1

Synthesis of 2-methoxy-4-methylpyrimidin-5-ol (Prep 1-5)

[Formula 18]



[0102]

(1) 2-Chloro-5-methoxy-4-methylpyrimidine (Prep 1-1)

2,4-Dichloro-5-methoxypyrimidine (10 g) was dissolved in THF (100 ml), and while cooling, iron(III) acetylacetone (1.97 g), methyl magnesium chloride (Aldrich, 3.0 M: 22.4 ml) were then added to the solution. The obtained mixture was stirred at a room temperature overnight. Thereafter, iron(III) acetylacetone (1.97 g), and methyl magnesium chloride (Aldrich, 3.0 M: 22.4 ml) were added to the reaction solution further twice. Thereafter, a 1 N hydrochloric acid aqueous solution was added to the reaction system, and diethyl ether was then added to the reaction solution to carry out liquid separation and extraction. The organic layer was dried over magnesium sulfate, and the solvent was then concentrated under a reduced

pressure. The obtained residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, elution solvent: n-heptane : ethyl acetate), so as to obtain the above-captioned compound (6.6 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.46 (s, 3H), 3.92 (s, 3H), 8.06 (s, 1H).

[0103]

(2) 2-Chloro-4-methylpyrimidin-5-ol (Prep 1-2)

A dichloromethane solution (50 ml) of the compound Prep 1-1 (6.6 g) was added dropwise to a dichloromethane solution (Aldrich, 1.0 M: 100 ml) of boron tribromide, and the obtained mixture was then stirred at a room temperature for 4 days. Thereafter, methanol was added to the reaction system, and a 5 N sodium hydroxide aqueous solution was then added to the reaction solution for neutralization. Liquid separation and extraction were carried out successively using chloroform and ethyl acetate at a pH value of approximately pH 2 to 3. The organic layer was dried over magnesium sulfate, and the solvent was then concentrated under a reduced pressure. Diethyl ether was added to the obtained residue to solidify it, and the solidified product was collected by filtration and was then dried, so as to obtain the above-captioned compound.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.32 (s, 3H), 8.09 (s, 1H), 10.61 (s, 1H).

[0104]

(3) 5-Benzyloxy-2-chloro-4-methylpyrimidine (Prep 1-3)

NaH was added to a THF solution (4.0 ml) of the compound Prep 1-2 (200 mg), and the obtained mixture was then stirred at a room temperature for 10 minutes. Thereafter, benzyl bromide (197 μl) was added to the reaction solution. The obtained mixture was stirred at a room temperature for 2 hours. Thereafter, DMF (2.0 ml) was added to the reaction solution, and the obtained mixture was then stirred for 4 hours. Thereafter, a saturated ammonium chloride aqueous solution was added to the reaction system, and liquid separation and extraction were carried out with diethyl ether. The obtained organic layer was dried over magnesium sulfate, and the solvent was then concentrated under a reduced pressure. The obtained residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, elution solvent: n-heptane : ethyl acetate), so as to obtain the above-captioned compound (317 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.51 (s, 3H), 5.15 (s, 2H), 7.37-7.40 (m, 5H), 8.10 (s, 1H).

[0105]

(4) 5-Benzyloxy-2-methoxy-4-methylpyrimidine (Prep 1-4)

Sodium methoxide (143 mg) was added to a DMF solution (4.0 ml) of Prep 1-3

(310 mg), and the obtained mixture was then stirred at 70°C for 2 hours. Thereafter, the reaction system was cooled, a 1 N hydrochloric acid aqueous solution was then added thereto, and liquid separation and extraction were then carried out with diethyl ether. The obtained organic layer was dried over magnesium sulfate, and the solvent was then concentrated under a reduced pressure. The obtained residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, elution solvent: n-heptane : ethyl acetate), so as to obtain the above-captioned compound (220 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.44 (s, 3H), 3.93 (s, 1H), 5.07 (s, 2H), 7.35-7.41 (m, 5H), 7.99 (s, 1H).

[0106]

(5) 2-Methoxy-4-methylpyrimidin-5-ol (Prep 1-5)

Palladium hydroxide was added to a methanol solution (8.0 ml) of the compound Prep 1-4 (220 mg), and the obtained mixture was then stirred in a hydrogen atmosphere for 2.5 hours. Thereafter, the reaction mixture was filtered with Celite, and the obtained filtrate was then concentrated under a reduced pressure, so as to obtain the above-captioned crude compound (130 mg).

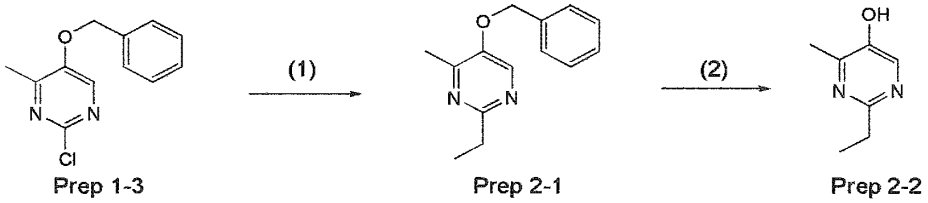
^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.26 (s, 3H), 3.77 (s, 1H), 7.95 (s, 1H).

[0107]

Production Example 2

Synthesis of 2-ethyl-4-methylpyrimidin-5-ol (Prep 2-2)

[Formula 19]



Prep 1-3 Prep 2-1 Prep 2-2

[0108]

(1) 5-Benzyloxy-2-ethyl-4-methylpyrimidine (Prep 2-1)

Potassium carbonate(1.4 g), 1,1-bis(diphenylphosphino)ferrocene palladium(II), and dichloromethane (276 mg) were added to a THF solution (10 ml) of the compound Prep 1-3 (793 mg), and diethylzinc (KANTO, 1 M: 3.72 ml) was then added thereto. The obtained mixture was stirred at 65°C overnight. Thereafter, water was added to the reaction system, and liquid separation and extraction were then carried out with ethyl acetate. The obtained organic layer was dried over magnesium sulfate, and the solvent was then concentrated under a reduced

pressure. The obtained residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, elution solvent: n-heptane : ethyl acetate), so as to obtain the above-captioned compound (400 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.32 (t, J=8.0 Hz, 1H), 2.49 (s, 3H), 2.86 (d, J=8.0 Hz, 1H), 2.90 (d, J=7.6 Hz, 1H), 5.13 (s, 2H), 7.33-7.43 (m, 5H), 8.16 (s, 1H).

[0109]

(2) 2-Ethyl-4-methylpyrimidin-5-ol (Prep 2-2)

Palladium hydroxide was added to a methanol solution (8.0 ml) of the compound Prep 2-1 (220 mg), and the obtained mixture was then stirred in a hydrogen atmosphere for 2.5 hours. Thereafter, the reaction mixture was filtered with Celite, and the obtained filtrate was then concentrated under a reduced pressure, so as to obtain the above-captioned crude compound (130 mg).

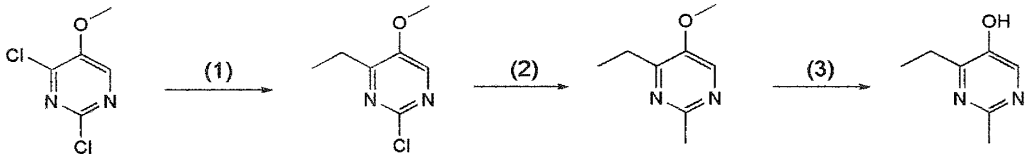
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.30 (t, J=8.0 Hz, 1H), 2.48 (s, 3H), 2.83 (d, J=8.0 Hz, 1H), 2.88 (d, J=8.0 Hz, 1H), 8.04 (s, 1H).

[0110]

Production Example 3

Synthesis of 4-ethyl-2-methylpyrimidin-5-ol (Prep 3-3)

[Formula 20]



Prep 3-1 Prep 3-2 Prep 3-3

[0111]

(1) 2-Chloro-4-ethyl-5-methoxypyrimidine (Prep 3-1)

2,4-Dichloro-5-methoxypyrimidine (5 g) was dissolved in THF (50 ml), and while cooling, iron(III) acetylacetone (985 mg) and ethyl magnesium chloride (KANTO, 0.91 M: 36.9 ml) were then added to the solution. The obtained mixture was stirred at a room temperature overnight. Thereafter, iron(III) acetylacetone (985 mg) and methyl magnesium chloride (KANTO, 0.91 M: 36.9 ml) were added to the reaction solution further twice. A 1 N hydrochloric acid aqueous solution was added to the reaction system, and liquid separation and extraction were then carried out with diethyl ether. The organic layer was dried over magnesium sulfate, and the solvent was then concentrated under a reduced pressure. The obtained residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™

column, elution solvent: n-heptane : ethyl acetate), so as to obtain the above-captioned compound (1 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.25 (t, J=8.0 Hz, 1H), 2.78 (d, J=7.6 Hz, 1H), 2.82 (d, J=8.0 Hz, 1H), 3.92 (s, 3H), 8.06 (s, 1H).

[0112]

(2) 4-Ethyl-5-methoxy-2-methylpyrimidine (Prep 3-2)

Trimethyl aluminum (ALDRICH, 2.0 M: 6.95 ml) and tetrakistriphenylphosphine palladium(0) (335 mg) were added to a THF solution (15.0 ml) of the compound Prep 3-1 (1.0 g), and the obtained mixture was then stirred at 70°C for 2 days. Thereafter, the reaction solution was added dropwise to ice water, and it was then converted to the neutral to mild acidic range by addition of 1 N hydrochloric acid. Subsequently, liquid separation and extraction were carried out with ethyl acetate. The organic layer was dried over magnesium sulfate, and the solvent was then concentrated under a reduced pressure. The obtained residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, elution solvent: :n-heptane : ethyl acetate), so as to obtain the above-captioned compound (736 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.24 (t, J=7.6 Hz, 1H), 2.64 (s, 3H), 2.76 (d, J=7.6 Hz, 1H), 2.80 (d, J=7.6 Hz, 1H), 3.89 (s, 1H), 8.10 (s, 1H).

[0113]

(3) 4-Ethyl-2-methylpyrimidin-5-ol (Prep 3-3)

Boron tribromide (TCI-JP; 1.0 M, 118 ml) was added dropwise to a dichloromethane solution (69.6 ml) of the compound Prep 3-2 (5.12 g). The obtained mixture was stirred at a room temperature for 4 days. Thereafter, ammonia/methanol was added to the reaction solution, followed by quenching. The reaction solution that had been converted to the neutral to mild acidic range was filtered, and the filtrate was then concentrated under a reduced pressure. The obtained residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, elution solvent: ethyl acetate → ethyl acetate : methanol), so as to obtain the above-captioned compound (4.0 g).

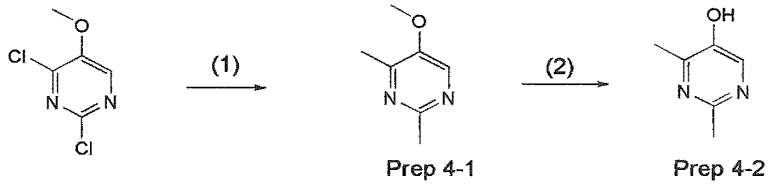
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.13 (t, J=8.0 Hz, 1H), 2.43 (s, 3H), 2.61 (d, J=8.0 Hz, 1H), 2.65 (d, J=7.6 Hz, 1H), 8.04 (s, 1H), 9.85 (s, 1H).

[0114]

Production Example 4

Synthesis of 2,4-dimethylpyrimidin-5-ol (Prep 4-2)

[Formula 21]



Prep 4-1 Prep 4-2

[0115]

(1) 5-Methoxy-2,4-dimethylpyrimidine (Prep 4-1)

2,4-Dichloro-5-methoxypyrimidine (5.3 g) was dissolved in THF (51.3 ml), and tetrakistriphenylphosphine palladium(0) (1.71 g) and trimethyl aluminum (Aldrich, 2.0 M: 51.8 ml) were then added to the solution. The temperature of the obtained mixture was increased to 75°C, and the obtained mixture was then stirred overnight. Thereafter, 1 equivalent of trimethyl aluminum was added to the reaction solution, and the obtained mixture was then stirred for 6 hours. Thereafter, saturated ammonium chloride was added dropwise to the reaction solution under cooling on ice, and liquid separation and extraction were carried out with chloroform. The organic layer was dried over magnesium sulfate, and the solvent was then concentrated under a reduced pressure. The obtained residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, elution solvent: n-heptane : ethyl acetate → ethyl acetate), so as to obtain the above-captioned compound (4.2 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.42 (s, 3H), 2.63 (s, 3H), 3.88 (s, 3H), 8.08 (s, 1H).

[0116]

(2) 2,4-Dimethylpyrimidin-5-ol (Prep 4-2)

A dichloromethane solution (100.0 ml) of the compound Prep 4-1 (15.5 g) was added dropwise to a boron tribromide (TCI-JP; 1.0 M, 400.0 ml) solution. The obtained mixture was stirred at a room temperature for 4 days, and the reaction solution was then quenched with methanol. The reaction solution that had been converted to the neutral to mild acidic range was filtered, and the filtrate was then concentrated under a reduced pressure. The obtained residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, elution solvent: ethyl acetate → ethanol), so as to obtain the above-captioned compound (10.1 g).

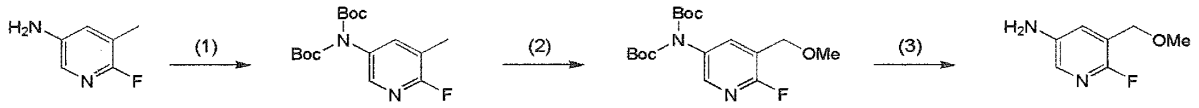
^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.26 (s, 3H), 2.41 (s, 3H), 8.02 (s, 1H).

[0117]

Production Example 5

Synthesis of 6-fluoro-5-methoxymethylpyridin-3-amine (Prep 5-3)

[Formula 22]



Prep 5-1 Prep 5-2 Prep 5-3

[0118]

(1) Di-tert-butyl(6-fluoro-5-methylpyridin-3-yl)-imide dicarbonate (Prep 5-1)

Di-tert-butyl carbonate (2.59 g) and a catalytic amount of 4-dimethylaminopyridine (0.01 g) were added to a THF solution (10 ml) of 5-amino-2-fluoro-3-picoline (0.5 g), and the obtained mixture was then stirred at a room temperature for 67 hours. Thereafter, water was added to the reaction solution, and the mixture was then extracted with ethyl acetate (× 3). The resultant extract was washed with water, and was then dried over anhydrous sodium sulfate. The solvent was distilled away under a reduced pressure, and the residue was then purified by silica gel column chromatography (chloroform), so as to obtain the above-captioned compound (1.14 g).

[0119]

(2) Di-tert-butyl[6-fluoro-5-methoxymethylpyridin-3-yl]-imide dicarbonate (Prep 5-2)

The compound Prep 5-1 (500 mg) and N-bromosuccinimide (272 mg) were dissolved in tetrachloromethane (5 ml), and 2,2'-azobis(isobutyl nitrate) (25.1 mg) was then added to the solution. The obtained mixture was stirred at 80°C for 5 hours. Thereafter, water was added to the reaction solution, and the mixture was then extracted with ethyl acetate (× 3). The resultant extract was washed with water, and was then dried over anhydrous sodium sulfate. The solvent was distilled away under a reduced pressure, and the residue was then dissolved in methanol (5 ml). Then, sodium methoxide (413 mg) was added to the solution, and the obtained mixture was then stirred at a room temperature for 1 hour. Thereafter, water was added to the reaction solution, and the mixture was then extracted with ethyl acetate (× 3). Thereafter, the resultant extract was washed with water, and was then dried over anhydrous sodium sulfate. The solvent was distilled away under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate = 20 : 1 to 2 : 1), so as to obtain the above-captioned compound.

[0120]

(3) 6-Fluoro-5-methoxymethylpyridin-3-amine (Prep 5-3)

Trifluoroacetic acid (1 ml) was added to a dichloromethane solution (5 ml) of the compound Prep 5-2, and the obtained mixture was then stirred at a room temperature for 1 hour. Thereafter, a saturated sodium bicarbonate aqueous solution was added to the reaction solution, and the mixture was then extracted with dichloromethane (× 3). The resultant extract was

washed with water, and was then dried over anhydrous sodium sulfate. The solvent was distilled away under a reduced pressure, so as to obtain the target compound (60 mg).

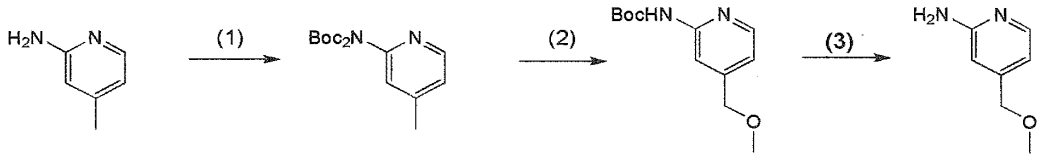
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.43 (s, 3H), 4.43 (s, 3H), 7.20 (ddt, J=8.0, 2.4, 0.8 Hz, 1H), 7.53 (t, J=2.4, Hz, 1H).

[0121]

Production Example 6

Synthesis of 4-methoxymethylpyridin-2-amine (Prep 6-3)

[Formula 23]



Prep 6-1 Prep 6-2 Prep 6-3

[0122]

(1) Di-tert-butyl(4-methylpyridin-2-yl)imide dicarbonate (Prep 6-1)

Di-tert-butyl carbonate (4.04 g), 4-dimethylaminopyridine (226 mg), and triethylamine (5.17 ml) were added to a dichloromethane solution (50 ml) of 2-amino-4-methylpyridine (1.0 g), and the obtained mixture was then stirred at a room temperature for 72 hours. Thereafter, water was added to the reaction solution, and the mixture was then extracted with ethyl acetate (× 1). The organic layer was successively washed with water and a saturated saline, and was then dried over anhydrous magnesium sulfate, followed by filtration. The filtrate was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate), so as to obtain the above-captioned compound (1.7 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.45 (s, 18H), 2.37 (s, 3H), 7.03 (dd, J=0.8, 5.2 Hz, 1H), 7.05 (d, J=0.8H, 1H), 8.34 (d, J=5.2 Hz, 1H).

MS $[M+H]^+$=309

[0123]

(2) Tert-butyl(4-methoxymethylpyridin-2-yl) carbamate (Prep 6-2)

Benzoyl peroxide (23.6 mg) was added to a tetrachloromethane solution (10 ml) of the compound Prep 6-1 (300 mg) and N-bromosuccinimide (173 mg), and the obtained mixture was then heated to reflux for 1 hour. Thereafter, 2,2'-azobis(isobutyl nitrate) (16.0 mg) was added to the reaction solution, and the obtained mixture was further heated to reflux for 5 hours. Thereafter, the reaction solution was cooled to a room temperature, and it was then

filtered with Celite. The filtrate was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate), so as to obtain the corresponding benzyl bromide body.

Sodium methoxide (Aldrich, 25% methanol solution: 1 ml) was added to a methanol solution (3 ml) of the obtained bromide body, and the obtained mixture was then stirred at a room temperature for 19 hours. Thereafter, the reaction solvent was distilled away under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate = 4 : 1 to 3 : 2), so as to obtain the above-captioned compound (62 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.53 (s, 9H), 3.42 (s, 3H), 4.46 (s, 2H), 6.96-6.97 (m, 1H), 7.91 (brs, 1H), 8.24-8.25 (m, 1H).

MS $[M+H]^+$=239

[0124]

(3) 4-Methoxymethylpyridin-2-amine (Prep 6-3)

Trifluoroacetic acid (1 ml) was added to a dichloromethane solution (3 ml) of the compound Prep 6-2 (62 mg), and the obtained mixture was then stirred at a room temperature for 3 hours. Thereafter, a 5 N sodium hydroxide aqueous solution was added to the reaction solution, and the mixture was then extracted with ethyl acetate (× 1). The organic layer was washed with a saturated saline, and was then dried over anhydrous magnesium sulfate, followed by filtration. The filtrate was concentrated under a reduced pressure, so as to obtain the target compound (35 mg).

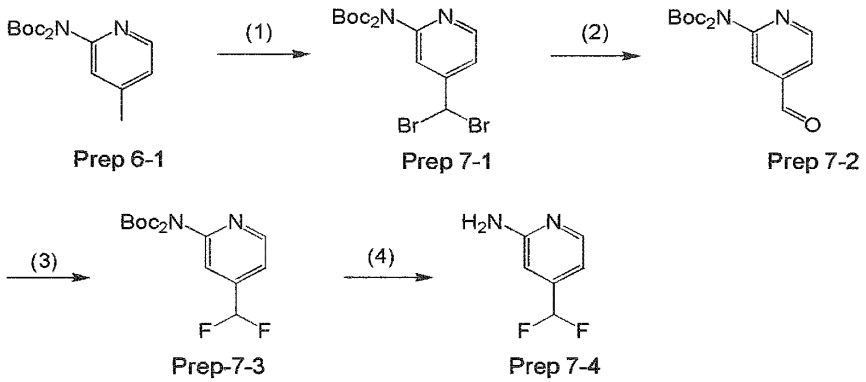
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.41 (s, 3H), 4.37 (s, 2H), 4.66 (brs, 2H), 6.51 (s, 1H), 6.59 (d, J=5.6 Hz, 1H), 7.99 (d, J=5.6 Hz, 1H).

[0125]

Production Example 7

Synthesis of 4-(difluoromethyl)pyridin-2-amine (Prep 7-4)

[Formula 24]



[0126]

(1) Di-tert-butyl[4-(dibromomethyl)pyridin-2-yl]imide dicarbonate (Prep 7-1)

2,2'-Azobis(isobutyl nitrate) (74.7 mg) was added to a tetrachloromethane solution (47 ml) of the compound Prep 6-1 (1.4 g) and N-bromosuccinimide (807 mg), and the obtained mixture was then heated to reflux for 4 hours. Thereafter, the reaction solution was cooled to a room temperature, and it was then filtered with Celite. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (n-heptane : ethyl acetate), so as to obtain the above-captioned compound (210 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.46 (s, 18H), 6.54 (s, 1H), 7.36 (dd, J=1.6, 5.2 Hz, 1H), 7.45 (d, J=1.6H, 1H), 8.48 (d, J=5.2 Hz, 1H).

MS $[M+H]^+$=467

[0127]

(2) Di-tert-butyl(4-formylpyridin-2-yl)imide dicarbonate (Prep 7-2)

Dimethyl sulfoxide (500 μl) and silver nitrite (692 mg) were added to a toluene solution (5 ml) of the compound Prep 7-1 (210 mg), and the obtained mixture was then stirred at 60°C for 2 hours. The temperature of the reaction solution was increased to 80°C, and the reaction solution was further stirred for 19 hours. Thereafter, the reaction solution was cooled to a room temperature, and was then filtered with silica gel. The filtrate was concentrated under a reduced pressure, so as to obtain the above-captioned compound (100 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.47 (s, 18H), 7.61 (dd, J=1.2, 5.2 Hz, 1H), 7.74 (d, J=1.2H, 1H), 8.70 (d, J=5.2 Hz, 1H), 10.08 (s, 1H).

[0128]

(3) Di-tert-butyl(4-difluoromethylpyridin-2-yl)imide dicarbonate (Prep 7-3)

Diethylaminosulfate trifluoride (122 μl) was added to a dichloromethane solution

(3 ml) of the compound Prep 7-2 (100 mg) at 0°C. The temperature of the reaction solution was increased to a room temperature, and the reaction solution was then stirred for 3.5 hours. Thereafter, a saturated sodium bicarbonate aqueous solution was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate (× 1). The organic layer was successively washed with water and a saturated saline, and was then dried over anhydrous magnesium sulfate, followed by filtration. The filtrate was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate), so as to obtain the above-captioned compound (78 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.46 (s, 18H), 6.65 (t, J=55.6 Hz, 1H), 7.32 (d, J=5.2 Hz, 1H), 7.43 (s, 1H), 8.58 (d, J=5.2 Hz, 1H).

MS $[2M+Na]^+$=711

[0129]

(4) 4-Difluoromethylpyridin-2-amine (Prep 7-4)

Trifluoroacetic acid (0.5 ml) was added to a dichloromethane solution (2 ml) of the compound Prep 7-3 (78 mg), and the obtained mixture was then stirred at a room temperature for 3 hours. Thereafter, a 5 N sodium hydroxide aqueous solution was added to the reaction solution, and the obtained mixture was then extracted with chloroform (× 3). The organic layer was washed with a saturated saline, and was then dried over anhydrous magnesium sulfate, followed by filtration. The filtrate was concentrated under a reduced pressure, so as to obtain the target compound (30 mg).

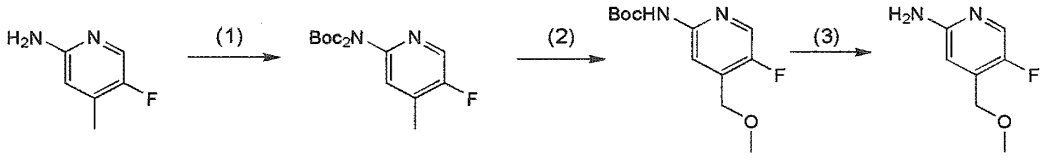
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.61 (brs, 2H), 6.51 (t, J=56.0 Hz, 1H), 6.60 (brs, 1H), 6.74-6.76 (m, 1H), 8.17 (d, J=5.2 Hz, 1H).

[0130]

Production Example 8

Synthesis of 5-fluoro-4-methoxymethylpyridin-2-amine (Prep 8-3)

[Formula 25]



Prep 8-1 Prep 8-2 Prep 8-3

[0131]

(1) Di-tert-butyl(5-fluoro-4-methylpyridin-2-yl)imide dicarbonate (Prep 8-1)

Di-tert-butyl carbonate (1.73 g), 4-dimethylaminopyridine (242 mg), and

triethylamine (1.66 ml) were added to a dichloromethane solution (50 ml) of 2-amino-5-fluoro-4-methylpyridine (500 mg), and the obtained mixture was then stirred at a room temperature for 6 days. Thereafter, water was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate (× 1). The organic layer was successively washed with water and a saturated saline, and was then dried over anhydrous magnesium sulfate, followed by filtration. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (n-heptane : ethyl acetate), so as to obtain the above-captioned compound (737 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.45 (s, 18H), 2.32-2.33 (m, 3H), 7.08 (brd, J=5.6 Hz, 1H), 8.23 (d, J=1.2 Hz, 1H).

MS $[2M+Na]^+$=675

[0132]

(2) Tert-butyl(5-fluoro-4-methoxymethylpyridin-2-yl) carbamate (Prep 8-2)

2,2'-azobis(isobutyl nitrate) (158 mg) was added to a tetrachloromethane solution (20 ml) of the compound Prep 8-1 (630 mg) and N-bromosuccinimide (377 mg), and the obtained mixture was then heated to reflux for 11 hours. Thereafter, the reaction solution was cooled to a room temperature, and it was then filtered with Celite. The filtrate was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate), so as to obtain the corresponding bromide body.

Sodium methoxide (104 mg) was added to a methanol solution (10 ml) of the obtained bromide body, and the obtained mixture was then stirred at a room temperature for 3 hours. Thereafter, water was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate (× 2). The organic layer was dried over anhydrous magnesium sulfate and was then filtered. The filtrate was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate), so as to obtain the above-captioned compound (180 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1·53 (s, 9H), 3.46 (s, 3H), 4.52 (brs, 2H), 7.21 (brs, 1H), 8.02-8.03 (m, 2H).

MS $[M-tBu+H]^+$=201

[0133]

(3) 5-Fluoro-4-methoxymethylpyridin-2-amine (Prep 8-3)

Trifluoroacetic acid (2 ml) was added to a dichloromethane solution (6 ml) of the compound Prep 8-2 (180 mg), and the obtained mixture was then stirred at a room temperature for 17 hours. Thereafter, a 5 N sodium hydroxide aqueous solution was added to the reaction

solution, and the obtained mixture was then extracted with chloroform (× 2). The organic layer was dried over anhydrous magnesium sulfate and was then filtered. The filtrate was concentrated under a reduced pressure, so as to obtain the target compound (90 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.45 (s, 3H), 4.32 (brs, 2H), 4.47 (s, 2H), 6.58 (d, J=4.8 Hz, 1H), 7.86 (d, J=1.6 Hz, 1H).

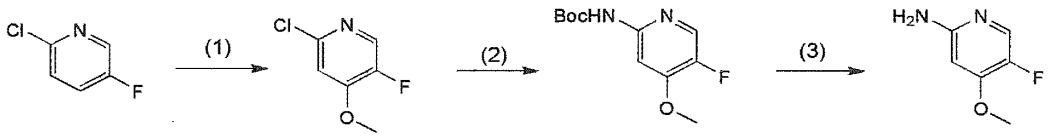
MS $[M+H]^+$=157

[0134]

Production Example 9

Synthesis of 5-fluoro-4-methoxypyridin-2-amine (Prep 9-3)

[Formula 26]



Prep 9-1 Prep 9-2 Prep 9-3

[0135]

(1) 2-Chloro-5-fluoro-4-methoxypyridine (Prep 9-1)

A THF solution (20 ml) of n-butyllithium (2.64 M n-hexane solution: 10.4 ml) was cooled to -78°C, and a THF solution (20 ml) of 2-chloro-5-fluoropyridine (3.0 g) and N,N-diisopropylethylamine (4.49 ml) was then added dropwise to the solution. The obtained mixture was stirred at the same temperature as described above for 2 hours. Thereafter, a THF solution (10 ml) of trimethyl borate (4.74 g) was added to the reaction solution, and the temperature was then increased to a room temperature, followed by stirring for 1.5 hours. Thereafter, the reaction solution was cooled to 0°C, and acetic acid (3.92 ml) was added thereto, followed by stirring for 20 minutes. Thereafter, hydrogen peroxide (30% aqueous solution; 7.05 ml) was added to the reaction solution, and the temperature was increased to a room temperature again, followed by stirring for 15 hours. Thereafter, the reaction solution was cooled to 0°C, and a saturated sodium thiosulfate aqueous solution was then added thereto, followed by stirring for 2 hours. Thereafter, 5 N hydrochloric acid was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate (× 2) and with chloroform (× 1). The organic layer was dried over magnesium sulfate and was then filtered. The solvent was concentrated under a reduced pressure, so as to obtain the corresponding alcohol.

Iodomethane (4.18 ml) was added to a chloroform solution (100 ml) of the

obtained alcohol and silver carbonate (16.4 g). The temperature of the obtained mixture was then increased to 40°C, and the mixture was then stirred for 4 hours. Thereafter, the reaction solution was cooled to a room temperature, and was then filtered with Celite-silica gel. The filtrate was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate), so as to obtain the above-captioned compound (1.9 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.95 (s, 3H), 6.91 (d, J=6.0 Hz, 1H), 8.11 (d, J=2.4 Hz, 1H).

MS $[M+H]^+$=162

[0136]

(2) Tert-butyl(5-fluoro-4-methoxypyridin-2-yl) carbamate (Prep 9-2)

The temperature of a 1,4-dioxane solution (50 ml) of the compound Prep 9-1 (1.0 g), tert-butyl carbamate (870 mg), xantphos (1.07 g), potassium triphosphate (1.97 g) and tris(dibenzylidene)dipalladium (567 mg) was increased to 100°C. Thereafter, the solution was then stirred for 3.5 hours. Subsequently, the reaction solution was cooled to a room temperature, and was then filtered with Celite. The filtrate was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate), so as to obtain the above-captioned compound (470 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.53 (s, 9H), 3.97 (s, 3H), 7.51 (brs, 1H), 7.69 (d, J=6.4 Hz, 1H), 7.96 (d, J=3.2 Hz, 1H).

MS $[M+H]^+$=243

[0137]

(3) 5-Fluoro-4-methoxypyridin-2-amine (Prep 9-3)

Trifluoroacetic acid (1 ml) was added to a dichloromethane solution (2 ml) of the compound Prep 9-2 (200 mg), and the obtained mixture was then stirred at a room temperature for 1.5 hours. Thereafter, a 5 N sodium hydroxide aqueous solution was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate (× 2). The organic layer was dried over anhydrous magnesium sulfate and was then filtered. The filtrate was concentrated under a reduced pressure, so as to obtain the target compound (110 mg).

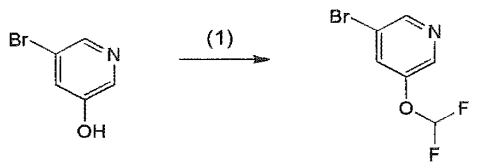
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.87 (s, 3H), 4.27 (brs, 2H), 6.06 (d, J=5.6 Hz, 1H), 7.80 (d, J=3.2 Hz, 1H).

[0138]

Production Example 10

Synthesis of 3-bromo-5-(difluoromethoxy)pyridine (Prep 10)

[Formula 27]



Prep 10

[0139]

(1) (3-Bromo-5-(difluoromethoxy)pyridine (Prep 10)

Potassium carbonate (7.13 g) and chlorodifluoroacetic acid (1.75 ml) were added to a DMF solution (40 ml) of 3-bromo-5-hydroxypyridine (3.0 g). The temperature of the obtained mixture was increased to 100°C, and the mixture was then stirred for 24 hours. Thereafter, water was added to the reaction solution, and the obtained mixture was then extracted with diethyl ether (× 1). The organic layer was successively washed with a saturated sodium bicarbonate aqueous solution and a saturated saline, and was then dried over magnesium sulfate, followed by filtration. The solvent was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-hexane : diethyl ether), so as to obtain the above-captioned compound (670 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.56 (t, J=72.0 Hz, 1H), 7.67-7.68 (m, 1H), 8.43 (d, J=2.4 Hz, 1H), 8.56 (d, J=2.0 Hz, 1H).

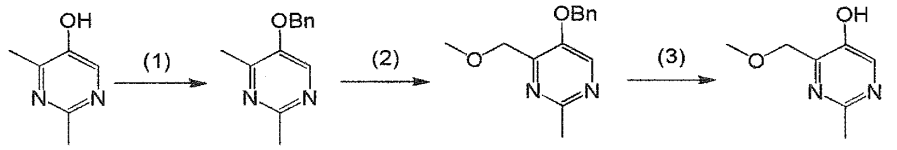
MS $[M+H]^+$=224

[0140]

Production Example 11

Synthesis of 4-methoxymethyl-2-methylpyrimidin-5-ol (Prep 11-3)

[Formula 28]



Prep 4-2 Prep 11-1 Prep 11-2 Prep 11-3

[0141]

(1) 5-Benzyloxy-2,4-dimethylpyrimidine (Prep 11-1)

A THF solution (80 ml) of Prep 4-2 (5.0 g) was cooled to 0°C, and potassium tert-butoxide (5.43 g) was then added to the solution. The obtained mixture was stirred at 0°C for 30 minutes. Thereafter, benzyl bromide (5.73 ml) was added to the reaction solution at the same temperature as described above, and the temperature of the mixture was then increased to a

room temperature, followed by stirring for 20 hours. Thereafter, water was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate (× 2). The organic layer was dried over anhydrous magnesium sulfate and was then filtered. The filtrate was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate, to ethyl acetate), so as to obtain the above-captioned compound (6.0 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.48 (s, 3H), 2.62 (s, 3H), 5.13 (s, 2H), 7.33-7.42 (m, 5H), 8.13 (s, 1H).

MS $[M+H]^+$=215

[0142]

(2) 5-Benzyloxy-4-methoxymethyl-2-methylpyrimidine (Prep 11-2)

A chloroform solution (200 ml) of the compound Prep 11-1 (13 g) was cooled to 0°C, and thereafter, bromine (3.11 ml) was slowly added dropwise thereto. The temperature of the reaction solution was increased to a room temperature, and the solution was then stirred for 18 hours. Thereafter, a saturated sodium bicarbonate aqueous solution was added to the reaction solution, and the obtained mixture was then extracted with chloroform (× 2). The organic layer was dried over anhydrous magnesium sulfate and was then filtered. The filtrate was concentrated under a reduced pressure, the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate to ethyl acetate), so as to obtain the corresponding bromide body.

Sodium methoxide (2.56 g) was added to a methanol solution (180 ml) of the obtained bromide body, and the obtained mixture was then heated to reflux for 21 hours. Thereafter, the reaction solution was concentrated under a reduced pressure, and ethyl acetate and water were then added to the concentrate. The obtained mixture was extracted with ethyl acetate (× 2). The organic layer was dried over anhydrous magnesium sulfate and was then filtered. The filtrate was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate), so as to obtain the above-captioned compound (9.0 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.70 (s, 3H), 3.52 (s, 3H), 4.63 (s, 2H), 5.16 (s, 2H), 7.34-7.41 (m, 5H), 8.24 (s, 1H).

MS $[M+H]^+$=245

[0143]

(3) (4-Methoxymethyl-2-methylpyrimidin-5-ol (Prep 11-3)

10% palladium-carbon (900 mg) was added to an ethyl acetate solution (300 ml)

of the compound Prep 11-2 (8.8 g), and the obtained mixture was then stirred in a hydrogen atmosphere at a room temperature for 2 hours. Thereafter, the reaction solution was filtered with Celite, and the filtrate was then concentrated under a reduced pressure, so as to obtain the above-captioned compound (5.3 g).

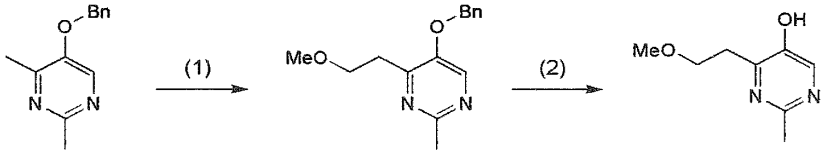
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.61 (s, 3H), 3.56 (s, 3H), 4.79 (s, 2H), 7.90 (brs, 1H), 8.25 (s, 1H).

[0144]

Production Example 12

Synthesis of 4-(2-methoxyethyl)-2-methylpyrimidin-5-ol (Prep 12-2)

[Formula 29]



Prep 12-1 Prep 12-2

[0145]

(1) 5-Benzyloxy-4-(2-methoxyethyl)-2-methylpyrimidine (Prep 12-1)

The compound Prep 11-1 (1.66 g) was dissolved in THF (130 ml), and the obtained solution was then cooled to 0°C. A THF solution (8.5 ml) of 1 N LDA was added dropwise to the solution, and the obtained mixture was then stirred for 30 minutes. Thereafter, chloromethyl methyl ether (0.88 ml) was added to the reaction solution. The obtained mixture was further stirred at a room temperature for 12 hours. Thereafter, water was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate (× 3). The resultant extract was washed with water, and was then dried over anhydrous sodium sulfate. The solvent was distilled away under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate), so as to obtain the above-captioned compound (0.65 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.63 (s, 3H), 3.11 (t, J=7.2 Hz, 2H), 3.35 (s, 3H), 3.79 (t, J=7.2 Hz, 2H), 5.13 (s, 2H), 7.33-7.42 (m, 5H), 8.16 (s, 1H).

[0146]

(2) 4-(2-Methoxyethyl)-2-methylpyrimidin-5-ol (Prep 12-2)

The compound Prep 12-1 (0.65 g) was dissolved in ethyl acetate (9 ml), and the obtained solution was then cooled to 0°C. Thereafter, 5% palladium carbon (0.31 g) was added to the solution, followed by hydrogen substitution. Then, the resultant product was stirred at a

room temperature for 2 hours. Thereafter, the reaction solution was filtered, and the solvent was then distilled away under a reduced pressure. The residue was purified by silica gel column chromatography (n-heptane : ethyl acetate-ethyl acetate:methanol), so as to obtain the above-captioned compound (0.36 g).

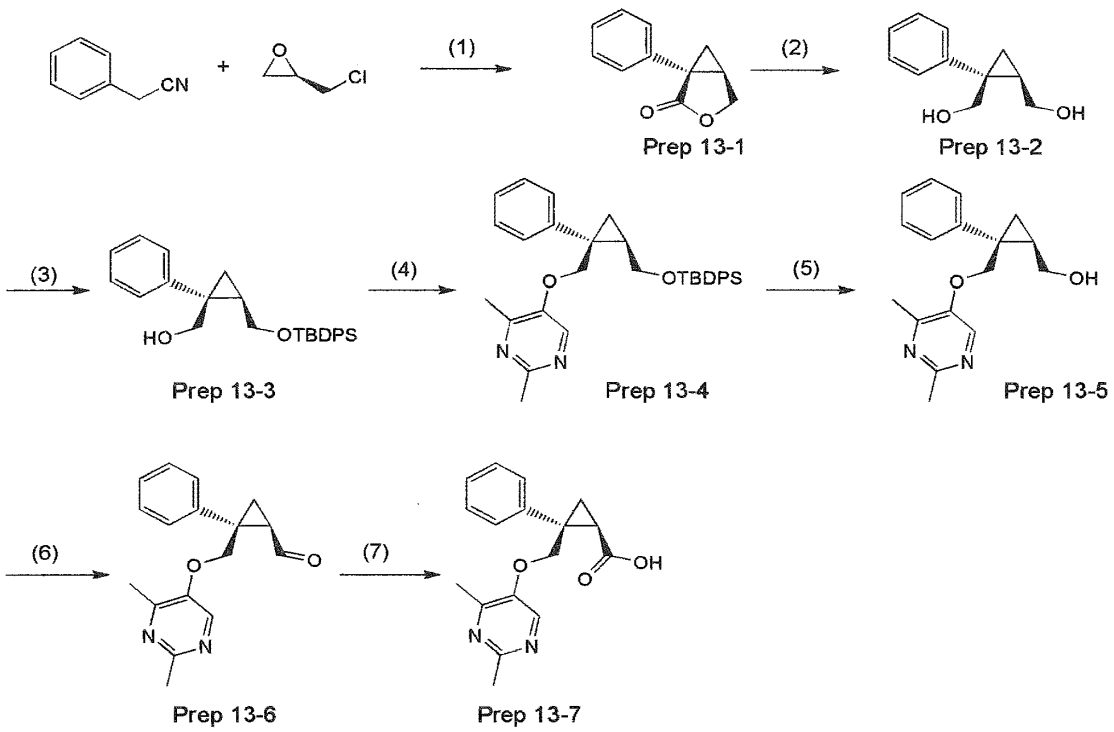
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.61 (s, 3H), 3.09 (t, J=5.6 Hz, 2H), 3.64 (s, 3H), 3.80 (t, J=5.6 Hz, 2H), 8.24 (s, 1H), 8.39 (brs, 1H).

[0147]

Production Example 13

Synthesis of (1R,2S)-2-(2,4-dimethylpyrimidin-5-yl)oxymethyl-2-phenylcyclopropanecarboxylate (Prep 13-7)

[Formula 30]



[0148]

(1) (1S,5R)-1-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (Prep 13-1)

Phenylacetonitrile (20 g) was dissolved in THF (500 ml), and NaHMDS (323 ml, 1.06 M) was then added dropwise to the solution under cooling in an ice-salt bath. The obtained mixture was stirred for 2 hours, and R-(-)-epichlorohydrin (15.8 g) was then added dropwise to the reaction solution (3 hours, 0°C). The obtained mixture was stirred for 2 hours (wherein the internal temperature was maintained around 0°C), and it was then stirred at a room

temperature overnight. Thereafter, the reaction solution was cooled on ice, and a small amount of water was added dropwise thereto. The reaction solution was concentrated under a reduced pressure, and thereafter, ethanol (200 ml) and a 1 N potassium hydroxide aqueous solution (200 ml) were added to the residue. The obtained mixture was heated to reflux for 8 hours. Thereafter, the temperature of the reaction solution was returned to a room temperature, and concentrated hydrochloric acid was then added to the solution, so that the pH value was adjusted to pH < 2. Thereafter, the mixture was stirred at 0°C for 2 hours. Thereafter, the reaction solution was stirred at a room temperature for 1 hour. Subsequently, the reaction solution was concentrated under a reduced pressure, and ethyl acetate and water were added to the concentrate to carry out liquid separation. The organic layer was successively washed with a saturated sodium bicarbonate aqueous solution and a saturated saline. The resultant organic layer was dried over magnesium sulfate, and the solvent was then concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, Size: 3L × 2, n-heptane : ethyl acetate), so as to obtain the above-captioned compound (24.7 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.37 (t, 1H, J= 4.8 Hz), 1.65 (dd, J=7.8, 4.4, 1H), 2.54-2.58 (m, 1H), 4.30 (d, J=9.2, 1H), 4.47 (dd, J=9.4, 4.4 Hz, 1H), 7.25-7.45 (m, 5H).

[0149]

(2) (1S,2R)-1-phenylcyclopropan-1,2-dimethanol (Prep 13-2)

Sodium borohydride (10.7 g) was added to a THF-methanol solution (200 ml-100 ml) of the compound Prep 13-1 (24.7 g) at 0°C, and the obtained mixture was then stirred at a room temperature for 1 hour. Under cooling on ice, water was added to the reaction solution, and the obtained mixture was concentrated under a reduced pressure and was then extracted with ethyl acetate. The organic layer was washed with a saturated saline, and was then dried over magnesium sulfate. The solvent was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, Size: 3L × 2, n-heptane : ethyl acetate), so as to obtain the above-captioned compound (20.5 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.78 (t, J= 5.2 Hz, 1H), 1.87 (dd, J=8.6, 5.2, 1H), 1.60-1.76 (m, 1H), 3.42 (t, J=11.6, 1H), 3.57 (dd, J=9.4, 4.4 Hz, 1H), 4.14-4.28 (m, 2H) 7.22-7.44 (m, 5H).

[0150]

(3) (1S,2R)-2-(tert-butyldiphenylsilyloxymethyl)-1-phenylcyclopropylmethanol (Prep 13-3)

The compound Prep 13-2 (10 g) and imidazole (4.01 g) were dissolved in DMF (90 ml), and the obtained mixture was cooled to -15°C. Thereafter, a DMF solution (20 ml) of

tert-butyldiphenylsilyl chloride was added dropwise to the reaction solution (for approximately 30 minutes; insoluble matters were precipitated almost at the same time after completion of dropping). After the mixture had been stirred for 1 hour, methanol was added to the reaction solution, and the obtained mixture was then stirred at a room temperature for 30 minutes. Thereafter, water was added to the organic layer, and the obtained mixture was then extracted with ethyl acetate. The resultant extract was successively washed with a saturated ammonium chloride aqueous solution, water and a saturated saline, and was then dried over anhydrous magnesium sulfate. The solvent was distilled away under a reduced pressure, and the residue was then purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, Size: 3L × 2, n-heptane : ethyl acetate), so as to obtain the above-captioned compound (10.5 g). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.71 (t, J=5.6 Hz, 1H), 1.04 (dd, J=9.6, 5.2 Hz, 1H), 1.5-1.58 (m, 1H), 3.50 (dd, J=12.4, 1.6 Hz, 1H), 3.53 (dd, J=11.6 Hz, 1H), 3.71 (dd, J=12.4, 1.6 Hz, 1H), 4.10 (t, J=12.0 Hz, 1H), 4.20 (dd, J=12.0, 5.6 Hz, 1H), 7.21-7.46 (m, 10H). 7.7-7.76 (m, 5H)

[0151]

(4) 5-[(1S,2R)-2-(tert-butyldiphenylsilyloxymethyl)-1-phenylcyclopropylmethoxy]-2,4-dimethylpyrimidine (Prep 13-4)

Diisopropyl azodicarboxylate (1.13 ml) was added dropwise to a THF solution (15 ml) of the compound Prep 13-3 (1.50 g), triphenylphosphine (1.42 g) and the 2,4-dimethyl-5-pyrimidinol (0.58 g) obtained in Production Example 4 at 0°C, and the obtained mixture was then stirred at a room temperature for 1 day. Thereafter, the reaction solution was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography ((YAMAZEN, Hi-Flush™ column, elution solvent: n-heptane : ethyl acetate), so as to obtain the above-captioned compound (1.76 g).

MS $[M+Na]^+$=545.

[0152]

(5) [(1R,2S)-2-(2,4-dimethylpyrimidin-5-yl)oxymethyl-2-phenylcyclopropyl]methanol (Prep 13-5)

Tetrabutylammonium fluoride (1 M THF solution: 4.24 ml) was added dropwise to a THF solution (21 ml) of the compound Prep 13-4 (1.76 g) at a room temperature, and the obtained mixture was then stirred at a room temperature for 17 hours. Thereafter, the reaction solution was concentrated under a reduced pressure, and the residue was then purified by NH-silica gel column chromatography (YAMAZEN, Hi-Flush™ column, elution solvent: n-heptane : ethyl acetate → ethyl acetate), so as to obtain the above-captioned compound (0.98 g).

MS $[M+H]^+$=285.

[0153]

(6) [(1R,2S)-2-(2,4-dimethylpyrimidin-5-yl)oxymethyl-2-phenyl]cyclopropanecarbaldehyde (Prep 13-6)

A dichloromethane solution (10 ml) of oxalyl chloride (593 μl) was cooled to -78°C, and a dichloromethane solution (2 ml) of dimethyl sulfoxide (981 μl) was added dropwise to the resultant solution. Fifteen minutes later, a dichloromethane solution (3 ml) of the compound Prep 13-5(981 mg) was added dropwise to the reaction solution at -78°C, and the obtained mixture was then stirred at the same temperature as described above for 75 minutes. Thereafter, triethylamine (3.83 ml) was added to the reaction solution, and the temperature of the obtained mixture was increased to 0°C. Water and a saturated ammonium chloride aqueous solution were added to the reaction solution, and the obtained mixture was then extracted with dichloromethane (× 2). The organic layer was dried over anhydrous magnesium sulfate and was then filtered. The filtrate was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, elution solvent: n-heptane : ethyl acetate → ethyl acetate), so as to obtain the above-captioned compound (753.4 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.69 (dd, J=4.8 Hz, 8.0 Hz, 1H), 1.97 (dd, J=5.2 Hz, 6.0 Hz, 1H), 2.35 (s, 3H), 2.50-2.53 (m, 1H), 2.59 (s, 3H), 4.19 (d, J=10.0 Hz, 1H), 4.45 (d, J=9.6 Hz, 1H), 7.25-7.52 (m, 5H), 7.94 (s, 1H), 9.86 (d, J=3.6 Hz, 1H).

[0154]

(7) (1R,2S)-2-(2,4-dimethylpyrimidin-5-yl)oxymethyl-2-phenylcyclopropanecarboxylate (Prep 13-7)

2-Methyl-2-butene (2.25 ml), anhydrous sodium dihydrogen phosphate (318 mg) and sodium chlorite (482 mg) were added to an acetone-water solution (12 ml) of the compound 13-6 at a room temperature, and the obtained mixture was then stirred for 100 minutes. The reaction solution was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, elution solvent: n-heptane : ethyl acetate = 1 : 1 to chloroform : methanol = 10 : 1), so as to obtain the above-captioned compound (639 mg).

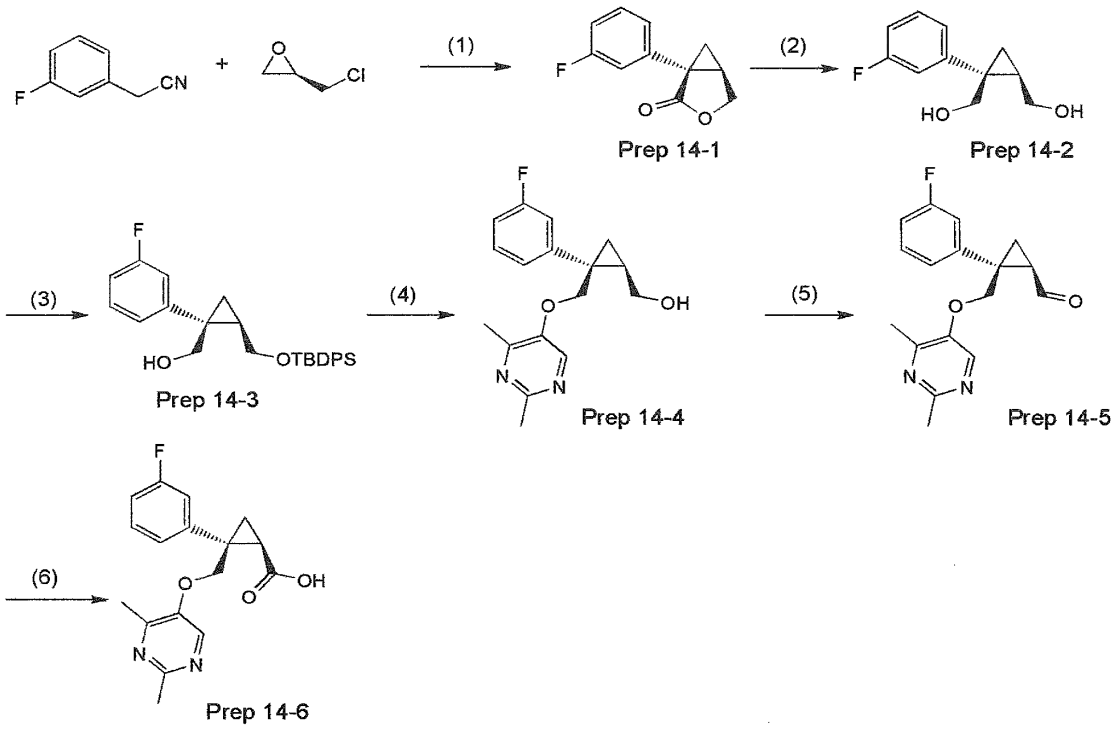
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.57 (dd, J=4.8 Hz, 8.0 Hz, 1H), 1.75 (t, J=4.8 Hz, 1H), 2.27 (dd, J=5.6 Hz, 8.0 Hz, 1H), 2.33 (s, 3H), 2.56 (s, 3H), 4.45 (d, J=9.6 Hz, 1H), 4.50 (d, J=9.2 Hz, 1H), 7.26-7.52 (m, 5H), 8.16 (s, 1H).

[0155]

Production Example 14

Synthesis of (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)cyclopropanecarboxylate (Prep 14-6)

[Formula 31]



[0156]

(1) (1S,5R)-1-(3-fluorophenyl)-3-oxabicyclo[3.1.0]hexan-2-one (Prep 14-1)

3-Fluoro phenyl acetonitrile (70 g) was dissolved in THF (500 ml), and NaHMDS (1000 ml, 1.06 M) was then added dropwise to the solution under cooling in an ice-salt bath. The obtained mixture was stirred for 1 hour, and R-(-)-epichlorohydrin (40.6 ml) was then added dropwise to the reaction solution (approximately 10 minutes, internal temperature < 10°C). The obtained mixture was stirred for 2 hours (wherein the internal temperature was maintained around 0°C), and it was then stirred at a room temperature for 14 hours. Thereafter, the reaction solution was cooled on ice, and a small amount of water was added dropwise thereto. The reaction solution was concentrated under a reduced pressure, and thereafter, ethanol (700 ml) and a 1 N potassium hydroxide aqueous solution (1000 ml) were added to the residue. The obtained mixture was heated to reflux for 5 hours. Thereafter, the temperature of the reaction solution was returned to a room temperature, and 5 N hydrochloric acid (400 ml) was then added

to the solution. The obtained mixture was stirred at 60°C for 1 hour. Thereafter, the reaction solution was concentrated under a reduced pressure, and ethyl acetate and water were added to the concentrate to carry out liquid separation. The organic layer was successively washed with a saturated sodium bicarbonate aqueous solution and a saturated saline. The resultant organic layer was dried over magnesium sulfate, and the solvent was then concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, n-heptane : ethyl acetate), so as to obtain the above-captioned compound (84.9 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.41 (t, J=5.2 Hz, 1H), 1.64 (dd, J=8.0, 5.2 Hz, 1H), 2.56-2.63 (m, 1H), 4.30 (d, J=9.2 Hz, 1H), 4.47 (dd, J=9.2, 4.8 Hz, 1H), 6.96-7.02 (m, 1H), 7.16-7.21 (m, 2H), 7.28-7.35 (m, 1H).

[0157]

(2) (1S,2R)-1-(3-fluorophenyl)cyclopropan-1,2-dimethanol (Prep 14-2)

Sodium borohydride (25 g) was added to a THF-methanol solution (440 ml-220 ml) of the compound Prep 14-1(72.7 g) at 0°C, and the obtained mixture was then stirred at a room temperature for 65 hours. Under cooling on ice, water and 5 N hydrochloric acid were added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate. The organic layer was washed with a saturated saline, and was then dried over magnesium sulfate. The solvent was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, n-heptane : ethyl acetate), so as to obtain the above-captioned compound (72.7 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.80 (t, J=5.0 Hz, 1H), 1.10 (dd, J=8.6, 5.0, 1H), 1.62-1.71 (m, 1H), 3.41 (t, J=11.4 Hz, 1H), 3.58 (d, J=12.0 Hz, 1H), 4.12-4.25 (m, 2H), 6.90-6.96 (m, 1H), 7.08-7.14 (m, 1H), 7.16-7.21 (m, 1H) 7.24-7.32 (m, 1H).

[0158]

(3) {(1S,2R)-[2-(tert-butyldiphenylsilyloxymethyl)-1-(3-fluorophenyl)cyclopropyl]}methanol (Prep 14-3)

The compound Prep 14-2 (42.4 g) and triethylamine (33.0 ml) were dissolved in dichloromethane (216 ml), and the obtained mixture was then cooled to -20°C. Thereafter, tert-butyldiphenylsilyl chloride (56.3 ml) was added dropwise to the reaction solution (approximately 30 minutes; insoluble matters were precipitated almost at the same time after completion of dropping). After the mixture had been stirred for 1 hour, the reaction solution was further stirred at a room temperature for 20 hours. Thereafter, water was added to the reaction solution, and the obtained mixture was then extracted with dichloromethane (× 3). The resultant extract was

washed with water, and was then dried over anhydrous magnesium sulfate. The solvent was distilled away under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate), so as to obtain the above-captioned compound (67.8 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.73 (t, J=5.2 Hz, 1H), 1.04 (dd, J=8.4, 5.2 Hz, 1H), 1.09 (s, 9H), 1.48-1.53 (m, 1H), 3.52 (t, J=12.0 Hz, 1H), 3.56 (dd, J=9.6, 1.6 Hz, 1H), 3.70 (dd, J=9.6, 1.6 Hz, 1H), 4.18 (t, J=12.0 Hz, 1H), 4.20 (dd, J=12.0, 5.2 Hz, 1H), 6.93 (tdd, J=8.0, 2.4, 1.2 Hz, 1H), 7.11 (dt, J=9.6, 2.4 Hz, 1H), 7.20 (dt, J=8.0, 1.2 Hz, 1H), 7.28 (td, J=8.0, 6.0 Hz, 1H), 7.37-7.49 (m, 6H), 7.69-7.74 (m, 4H).

[0159]

(4) {(1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)cyclopropyl}methanol (Prep 14-4)

Diisopropyl azodicarboxylate (0.316 ml) was added dropwise to a THF solution (10 ml) of the compound Prep 14-3 (581 mg), triphenylphosphine (1.3 g) and the 2,4-dimethyl-5-pyrimidinol (183 mg) obtained in Production Example 4 at 0°C, and the obtained mixture was then stirred at a room temperature for 2 days. Thereafter, the reaction solution was concentrated under a reduced pressure, and was then purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, Size: L, n-heptane : ethyl acetate 5% → 30%). The obtained (1S,2R)-2-(tert-butyldiphenylsilyloxymethyl)-1-(2,4-dimethylpyrimidin-5-yl)oxymethyl-1-(3-fluorophenyl)cyclopropane was dissolved in THF (15 ml), and tetrabutyl ammonium fluoride (1 M THF solution: 1.61 ml) was then added dropwise to the solution at a room temperature. The obtained mixture was stirred at a room temperature for 14 days. Thereafter, the reaction solution was concentrated under a reduced pressure, and was then purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, Size: M, n-heptane : ethyl acetate 10% → 100%), so as to obtain the above-captioned compound (238 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.00 (t, J=5.6 Hz, 1H), 1.25-1.33 (m, 1H), 1.78-1.88 (m, 1H), 2.39 (s, 3H), 2.61 (s, 3H), 3.58 (dd, J=12.0, 9.6 Hz, 1H), 4.02-4.11 (m, 1H), 4.12 (d, J=10.4 Hz, 1H), 4.43 (d, J=9.6 Hz, 1H), 6.92-6.98 (m, 1H), 7.10-7.16 (m, 1H), 7.18-7.23 (m, 1H), 7.29 (td, J=8.0, 6.0 Hz, 1H), 8.00 (s, 1H).

[0160]

(4 - Alternative Method)

{(1R,2S)-[2-(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)cyclopropyl}methanol (Prep 14-4) (Alternative Method)

Triethylamine (14.5 ml) was added to a dichloromethane solution (200 ml) of the

compound Prep 14-3 (41.3 g), and the obtained mixture was then cooled to 0°C. Methanesulfonyl chloride (7.34 ml) was added dropwise to the reaction solution, and the obtained mixture was then stirred for 1 hour. Thereafter, water was added to the reaction solution, and the obtained mixture was then extracted with dichloromethane (× 3). The resultant extract was dried over anhydrous sodium sulfate, and the solvent was then distilled away under a reduced pressure. The 2,4-dimethyl-5-pyrimidinol (14.1 g) obtained in Production Example 4-(2) and cesium carbonate (61.8 g) were added to an acetonitrile solution (200 ml) of the obtained residue, and the obtained mixture was then heated to 70°C. The reaction solution was stirred at 70°C for 4 hours, and it was then cooled to 0°C. Tetrabutyl ammonium fluoride (1 M THF solution: 190 ml) was added dropwise to the reaction solution, and the obtained mixture was then stirred at a room temperature for 1 hour. Thereafter, water was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate (× 3). The resultant extract was dried over anhydrous sodium sulfate, and the solvent was then distilled away under a reduced pressure. The residue was purified by NH-silica gel column chromatography (n-heptane : ethyl acetate = 9 : 1 to 1 : 1), so as to obtain the above-captioned compound (20.7 g).

[0161]

(5) (1R,2S)-[2-(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)cyclopropanecarbaldehyde (Prep 14-5)

A dichloromethane solution (7 ml) of oxalyl chloride (137 ul) was cooled to -78°C, and dimethyl sulfoxide (226 ul) was then added dropwise thereto (internal temperature: -60°C or lower). The obtained mixture was stirred at the same temperature as described above for 10 minutes. Thereafter, a dichloromethane solution (3 ml) of the compound Prep 14-4 (238 mg) was added dropwise to the reaction solution at -78°C, and the obtained mixture was then stirred at the same temperature as described above for 30 minutes. Thereafter, triethylamine (671 ul) was added to the reaction solution, and the obtained mixture was then stirred for 15 minutes. Thereafter, the temperature of the reaction solution was increased to a room temperature. A saturated saline was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and was then concentrated under a reduced pressure, so as to obtain a roughly purified product of the above-captioned compound (236 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.67 (dd, J=8.0, 4.8 Hz, 1H), 1.96-2.00 (m, 1H), 2.36 (s, 3H), 2.49-2.55 (m, 1H), 2.59 (s, 3H), 4.19 (d, J=9.6 Hz, 1H), 4.44 (d, J=10.0 Hz, 1H), 6.97-7.04

(m, 1H), 7.14-7.20 (m, 1H), 7.21-7.25 (m, 1H), 7.30-7.37 (m, 1H), 7.95 (s, 1H), 9.87 (d, J=3.2 Hz, 1H).

[0162]

(6) (1R,2S)-[2-(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)cyclopropanecarboxylate (Prep 14-6)

The compound Prep 14-5 (18.9 g), 2-methyl-2-butene (26.1 ml), and sodium dihydrogen phosphate (9.07 g) were dissolved in a mixed solvent of acetone and water (200 ml/40 ml), and sodium chlorite (6.26 g) was added, drop by drop, to the solution. The obtained mixture was stirred at a room temperature for 2 hours, and the reaction solution was then concentrated under a reduced pressure. The precipitated solid was collected by filtration, and was then washed with dichloromethane. Thereafter, the solvent was distilled away under a reduced pressure. The residue was purified by silica gel column chromatography (n-heptane : ethyl acetate = 1 : 1 to 0 : 1, and then, ethyl acetate : methanol = 10 : 1), so as to obtain the above-captioned compound (16.2 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.55 (dd, J=8.4, 5.6 Hz, 1H), 1.76 (t, J=5.6 Hz, 1H), 2.25 (dd, J=8.4, 6.4 Hz, 1H), 2.33 (s, 3H), 2.55 (s, 3H), 4.47 (t, J=9.6 Hz, 1H), 4.50 (d, J=9.6 Hz, 1H), 6.99 (tdd, J=8.0, 2.4, 1.2 Hz, 1H), 7.21 (dt, J=9.6, 2.4 Hz, 1H), 7.26 (td, J=8.0, 1.2 Hz, 1H), 7.32 (td, J=8.0, 6.0 Hz, 1H), 8.21 (s, 1H).

The compound Prep 14-6 can be directly produced from the compound Prep 14-4 by the following method.

The compound Prep 14-4 (300 mg) and TEMPO (5 mol%, 7.74 mg) were dissolved in an acetonitrile-phosphate (pH 6.4) buffer (5 ml, 5 ml), and 2 N HCl (150 μl) and sodium chlorite (180 mg) were then added to the solution. The obtained solution was heated to 40°C, and a 5w% hypochlorous acid aqueous solution (2 mol%, 26.5 μl) was then added to the reaction solution, followed by stirring for 2 hours. Thereafter, the reaction solution was cooled to a room temperature, and an excessive amount of 2-methyl-2-butene was then added to the reaction solution, followed by stirring for 5 minutes. Thereafter, the reaction solution was subjected to liquid separation and extraction with dichloromethane (× 3), and the solvent was then distilled away under a reduced pressure. The residue was purified by silica gel column chromatography (n-heptane : ethyl acetate = 1 : 1 to 0 : 1, and then, ethyl acetate: methanol = 9 : 1), so as to obtain the above-captioned compound (215 mg).

[0163]

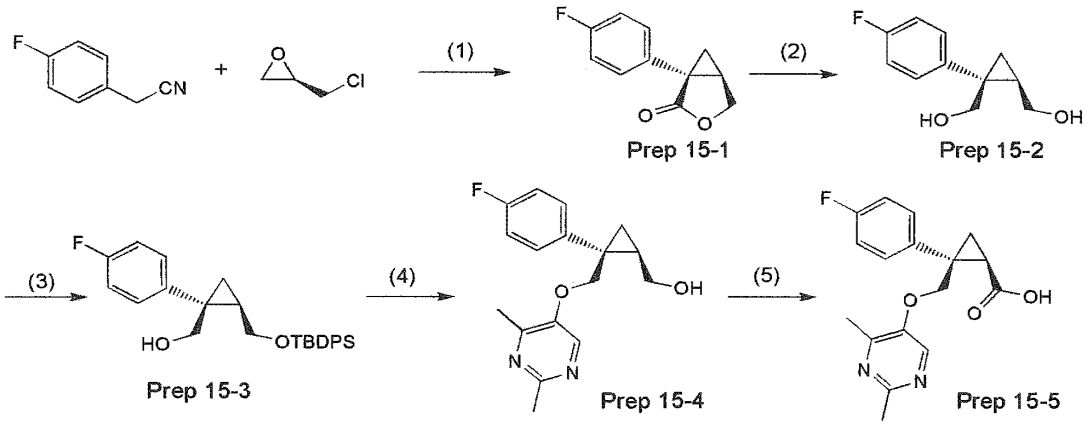
Production Example 15

Synthesis of (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl}-2-(4-

fluorophenyl)cyclopropanecarboxylate (Prep 15-5)

The above-captioned compound was synthesized from 4-fluoro phenyl acetonitrile by the same method as that of Production Example 13.

[Formula 32]



[0164]

[Table 1-1]

Compound No.	Compound name	Data (NMR and/or MS)
Prep 15-1	(1S,5R)-1-(4-fluorophenyl)-3-oxabicyclo[3.1.0]hexan-2-one	^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.37 (t, J=5.2 Hz, 1H), 1.60 (dd, J=4.8, 8.0 Hz, 1H), 2.50-2.60 (m, 1H), 4.30 (d, J=9.6 Hz, 1H), 4.48 (dd, J=4.8, 9.6 Hz, 1H), 6.96-7.18 (m, 2H), 7.30-7.46 (m, 2H).
Prep 15-2	(1S,2R)-1-(4-fluorophenyl)cyclopropan-1,2-dimethanol	^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.78 (t, J=5.2 Hz, 1H), 1.06 (dd, J=5.2, 8.8 Hz, 1H), 1.54-1.72 (m, 1H), 3.42 (dd, J=10.8, 11.6 Hz, 1H), 3.57 (d, J=12.0 Hz, 1H), 3.98-4.26 (m, 2H), 6.94-7.09 (m, 2H), 7.33-7.46 (m, 2H).
Prep 15-3	{(1S,2R)-2-[(tert-butyldiphenylsilyl)oxymethyl]-1-(4-fluorophenyl)cyclopropyl}methanol	^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.70 (t, J=5.6 Hz, 1H), 0.92-1.16 (m, 10H), 1.40-1.60 (m, 1H), 3.42-3.58 (m, 2H), 3.69 (dd, J=1.6, 12.4 Hz, 1H), 4.03 (t, J=11.6 Hz, 1H), 4.20 (dd, J=5.2, 11.6 Hz, 1H), 6.94-7.06 (m, 2H), 7.20-7.53 (m, 8H), 7.66-7.78 (m, 4H).
Prep 15-4	{(1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(4-fluorophenyl)cyclopropyl}methanol	^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.97 (t, J=5.6 Hz, 1H), 1.20-1.30 (m, 1H), 1.72-1.86 (m, 1H), 2.14-2.26 (m, 1H), 2.38 (s, 3H), 2.60 (s, 3H), 3.50-3.62 (m, 1H), 4.00-4.16 (m, 2H), 4.39 (d, J=10.0 Hz, 1H), 6.94-7.12 (m, 2H), 7.32-7.46 (m, 2H), 7.98 (s, 1H).

[Table 1-2]

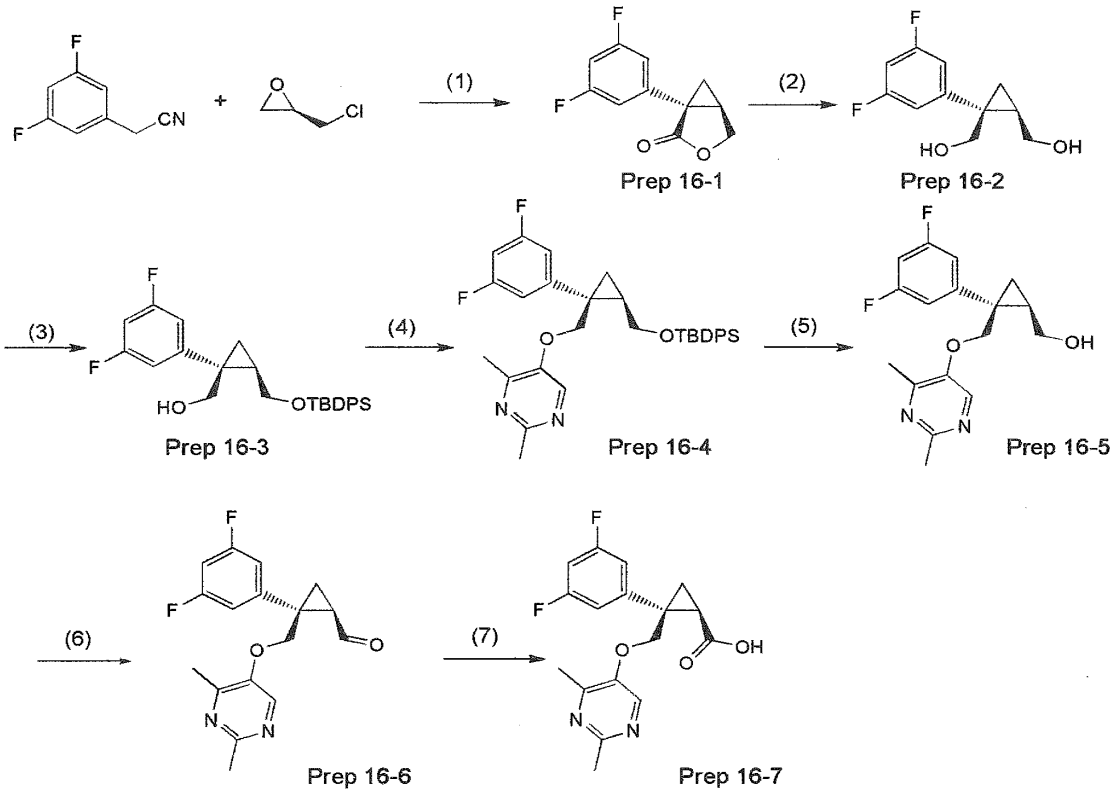
Prep 15-5	(1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(4-fluorophenyl)cyclopropanecarboxylate	^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.52 (dd, J=4.8, 8.0 Hz, 1H), 1.74 (dd, J=5.2, 5.6 Hz, 1H), 2.22 (dd, J=6.0, 8.4 Hz, 1H), 2.33 (s, 3H), 2.56 (s, 3H), 4.36-4.50 (m, 2H), 6.96-7.12 (m, 2H), 7.32-7.54 (m, 2H), 8.18 (s, 1H). MS $[M+H]^+$=317.

[0165]

Production Example 16

Synthesis of (1R,2S)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxylate (Prep 16-7)

[Formula 33]



[0166]

The above-captioned compound was synthesized from 3,5-difluoro phenyl acetonitrile by the same method as that of Production Example 13.

[0167]

[Table 2-1]

Compound No.	Compound name	Data (NMR and/or MS)
Prep 16-1	(1S,5R)-1-(3,5-difluorophenyl)-3-oxabicyclo[3.1.0]hexan-2-one	^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.45 (t, J=4.8 Hz, 1H), 1.63 (dd, J=5.2, 8.4 Hz, 1H), 2.58-2.63 (m, 1H), 4.30 (d, J=9.2 Hz, 1H), 4.46 (dd, J=4.4, 9.2 Hz, 1H), 6.71-6.77 (m, 1H), 6.97-7.02 (m, 2H).
Prep 16-2	(1S,2R)-1-(3,5-difluorophenyl)-1,2-cyclopropanedimethanol	MS $[M+Na]^+$=237.
Prep 16-3	(1S,2R)-2-(tert-butyldiphenylsilyloxymethyl)-1-(3,5-difluorophenyl)cyclopropylmethanol	^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.74 (t, J=5.2 Hz, 1H), 1.03 (dd, J=5.2, 8.4 Hz, 1H), 1.09 (s, 9H), 1.42-1.50 (m, 1H), 3.51 (t, J=11.6 Hz, 1H), 3.59-3.70 (m, 2H), 4.08-4.22 (m, 2H), 6.65-6.71 (m, 1H), 6.91-6.95 (m, 2H), 7.36-7.49 (m, 6H), 7.49-7.73 (m, 4H).
Prep16-4	5-[(1S,2R)-2-(tert-butyldiphenylsilyloxymethyl)-1-(3,5-difluorophenyl)cyclopropylmethyloxy]-2,4-dimethylpyrimidine	MS $[M+Na]^+$=559.
Prep16-5	(1R,2S)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropylmethanol	MS $[M+H]^+$=321.

[Table 2-2]

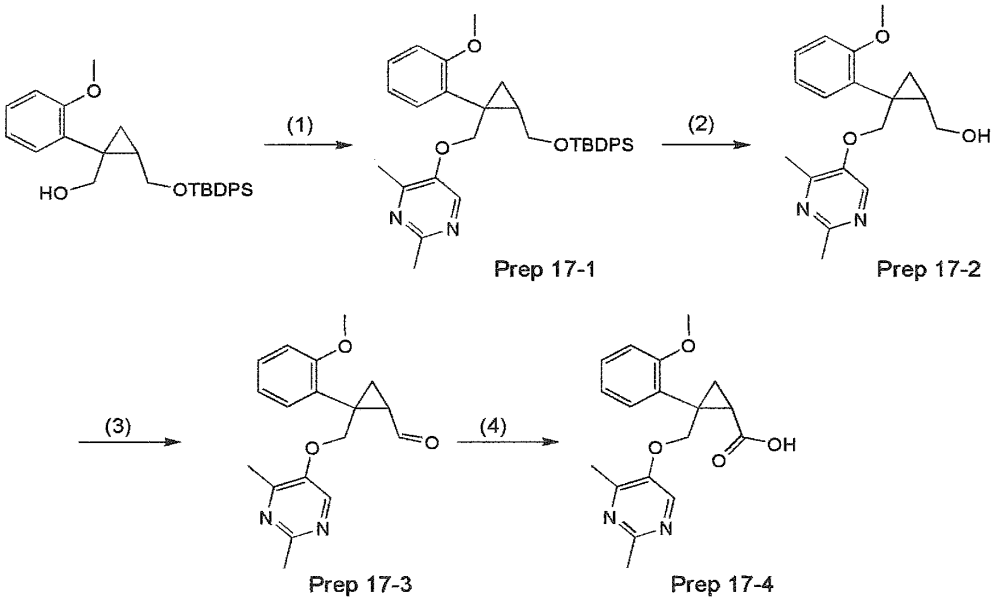
Prep 16-6	(1R,2S)-2-(3,5-difluorophenyl)-2-(2,4-dimethylpyrimidin-5-yl) oxymethylcyclopropanecarbaldehyde	^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.66 (dd, J=5.2, 8.4 Hz, 1H), 1.98 (t, J=5.2 Hz, 1H), 2.36 (s, 3H), 2.49-2.53 (m, 1H), 2.60 (s, 3H), 4.17 (d, J=9.6 Hz, 1H), 4.41 (d, J=9.6 Hz, 1H), 6.73-6.80 (m, 1H), 6.96-7.00 (m, 2H), 7.96 (s, 1H), 9.88 (d, J=3.2 Hz, 1H).
Prep 16-7	(1R,2S)-2-(3,5-difluorophenyl)-2-(2,4-dimethylpyrimidin-5-yl)oxymethylcyclopropanecarboxylate	^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.59 (dd, J=6.0 Hz, 8.4 Hz, 1H), 1.74 (t, J=6.0 Hz, 1H), 2.22 (dd, J=6.0 Hz, 8.0 Hz, 1H), 2.39 (s, 3H), 2.59 (s, 3H), 4.44 (d, J=9.6 Hz, 1H), 4.58 (d, J=9.6 Hz, 1H), 6.75 (t, J=9.2 Hz, 1H), 6.99-7.03 (m, 2H), 8.28 (s, 1H). MS $[M+H]^+$=335

[0168]

Production Example 17

Synthesis of 2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(2-methoxyphenyl)cyclopropanecarboxylate (Prep 17-4)

[Formula 34]



[0169]

(1) 5-{(1S,2R)-2-[tert-butyl(diphenyl)silyloxymethyl]-1-(2-methoxyphenyl)cyclopropyl}methoxy-2,4-dimethylpyrimidine (Prep 17-1)

Triphenylphosphine (610 mg) was added to a toluene solution (15 ml) of the [2-({[tert-butyl(diphenyl)silyl]oxy}methyl)-1-(2-methoxyphenyl)cyclopropyl]methanol (800 mg) synthesized from (2-methoxyphenyl)acetonitrile and epichlorohydrin according to the method of Production Example 13 and tetrabromomethane (772 mg) at a room temperature. The temperature of the obtained mixture was increased to 40°C, and the mixture was then stirred for 2 hours. Thereafter, a saturated sodium bicarbonate aqueous solution was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate (× 1). The organic layer was successively washed with water and a saturated saline, and was then anhydrous magnesium sulfate, followed by filtration. The filtrate was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate = 19 : 1 to 9 : 1), so as to obtain the corresponding bromide body.

The obtained bromide body and potassium carbonate (210 mg) were added to a DMF solution (10 ml) of the compound Prep 4-2 (113 mg) at a room temperature, and the temperature of the obtained mixture was increased to 50°C, followed by stirring for 2 hours. Thereafter, the temperature of the reaction solution was increased to 70°C, and the reaction solution was further stirred for 11 hours. Thereafter, water was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate (× 1). The organic layer was successively washed with water and a saturated saline, and was then dried over anhydrous magnesium sulfate, followed by filtration. The filtrate was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate = 9 : 1 to 1 : 4), so as to obtain the above-captioned compound (148 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.94 (dd, J=5.2, 6.2 Hz, 1H), 1.07 (s, 9H), 1.10 (dd, J=5.2, 8.8 Hz, 1H), 1.54-1.61 (m, 1H), 2.21 (s, 3H), 2.58 (s, 3H), 3.80 (s, 3H), 3.95 (d, J=6.8 Hz, 2H), 4.11 (d, J=9.8 Hz, 1H), 4.25 (d, J=9.8 Hz, 1H), 6.82-6.91 (m, 2H), 7.19-7.42 (m, 8H), 7.65-7.69 (m, 4H), 7.87 (s, 1H).

MS $[M+Na]^+$=575

[0170]

(2) {2-[(2,4-Dimethylpyrimidin-5-yl)oxymethyl]-2-(2-methoxyphenyl)cyclopropyl}methanol (Prep 17-2)

Tetrabutyl ammonium fluoride (1 M THF solution: 322 µl) was added dropwise to a THF solution (1.3 ml) of the compound Prep 17-1 (148 mg) at a room temperature, and the obtained mixture was then stirred at a room temperature for 23 hours. The reaction solution was concentrated under a reduced pressure, and the residue was then purified by silica gel

column chromatography (n-heptane : ethyl acetate = 1 : 1, to ethyl acetate, to ethyl acetate : methanol = 9 : 1), so as to obtain the above-captioned compound (75 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.99 (dd, J=5.2, 6.2 Hz, 1H), 1.21 (dd, J=5.2, 8.8 Hz, 1H), 1.68-1.76 (m, 1H), 2.32 (s, 3H), 2.45 (dd, J=2.4, 8.8 Hz, 1H), 2.58 (s, 3H), 3.48-3.54 (m, 1H), 3.88 (s, 3H), 4.13 (dt, 8.8, 6.4 Hz, 1H), 4.18 (d, J=10.0 Hz, 1H), 4.33 (d, J=10.0 Hz, 1H), 6.87 (dd, J=1.2, 8.0 Hz, 1H), 6.94 (dt, J=1.2, 8.0 Hz, 1H), 7.24-7.29 (m, 1H), 7.34 (dd, J=1.6, 8.0 Hz, 1H), 7.94 (s, 1H).

[0171]

(3) 2-[(2,4-Dimethylpyrimidin-5-yl)oxymethyl]-2-(2-methoxyphenyl)cyclopropanecarbaldehyde (Prep 17-3)

A dichloromethane solution (0.5 ml) of oxalyl chloride (82 μl) was cooled to -78°C, and thereafter, a dichloromethane solution (0.5 ml) of dimethyl sulfoxide (136 μl) was added dropwise thereto. Ten minutes later, a dichloromethane solution of the compound Prep - 2 (75 mg) was added dropwise to the reaction solution at -78°C, and the obtained mixture was then stirred at the same temperature as described above for 40 minutes. Thereafter, triethylamine (534 μl) was added to the reaction solution, and the temperature of the obtained mixture was then increased to 0°C, followed by stirring for 15 minutes. Thereafter, water was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate (× 1). The organic layer was successively washed with water and a saturated saline, and was then dried over anhydrous magnesium sulfate, followed by filtration. The filtrate was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate = 9 : 1 to ethyl acetate), so as to obtain the above-captioned compound (41 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.55 (dd, J=5.2, 8.4 Hz, 1H), 1.97 (dd, J=5.2, 6.2 Hz, 1H), 2.28 (s, 3H), 2.42 (ddd, J=4.0, 6.2, 8.4 Hz, 1H), 2.56 (s, 3H), 3.87 (s, 3H), 4.17 (d, J=9.6 Hz, 1H), 4.41 (d, J=9.6 Hz, 1H), 6.88 (dd, J=0.8, 8.0 Hz, 1H), 6.94 (dt, J=0.8, 8.0 Hz, 1H), 7.26-7.30 (m, 1H), 7.37 (dd, J=1.8, 8.0 Hz, 1H), 7.90 (s, 1H), 9.82 (d, J=4.0 Hz, 1H).

[0172]

(4) 2-[(2,4-Dimethylpyrimidin-5-yl)oxymethyl]-2-(2-methoxyphenyl)cyclopropanecarboxylate (Prep 17-4)

2-Methyl-2-butene (139 μl), anhydrous sodium dihydrogen phosphate (23.6 mg), and sodium chlorite (44.4 mg) were added to an acetone-water solution (1.3 ml) of the compound Prep 17-3 (41 mg) at a room temperature. The obtained mixture was stirred for 2.5

hours. Thereafter, the reaction solution was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate = 1 : 1 to chloroform : methanol = 9 : 1), so as to obtain the above-captioned compound (35 mg).

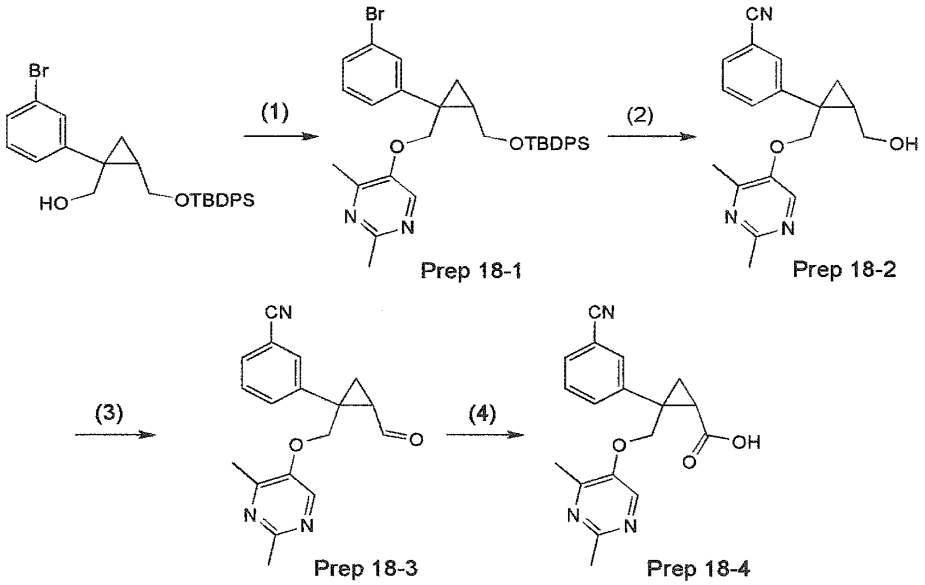
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.50 (dd, J=5.2, 8.0 Hz, 1H), 1.70 (dd, J=5.2, 6.4 Hz, 1H), 2.13 (dd, J=6.4, 8.0 Hz, 1H), 2.31 (s, 3H), 2.56 (s, 3H), 3.89 (s, 3H), 4.40 (d, J=9.2 Hz, 1H), 4.57 (d, J=9.2 Hz, 1H), 6.89 (dd, J=1.2, 8.0 Hz, 1H), 6.95 (dt, J=1.2, 8.0 Hz, 1H), 7.27-7.30 (m, 1H), 7.42 (dd, J=1.2, 8.0 Hz, 1H), 8.19 (s, 1H).

[0173]

Production Example 18

Synthesis of 2-(3-cyanophenyl)-2-(2,4-dimethylpyrimidin-5-yl)oxymethylcyclopropanecarboxylate (Prep 18-4)

[Formula 35]



[0174]

(1) 5-[1-(3-Bromophenyl)-2-(tert-butyldiphenylsilyloxymethyl)cyclopropylmethoxy-2,4-dimethylpyrimidine (Prep 18-1)

Diisopropyl azodicarboxylate (0.706 ml) was added dropwise to a THF solution (13 ml) of the [1-(3-bromophenyl)-2-(tert-butyldiphenylsilyloxymethyl)]cyclopropylmethanol (1.3 g) synthesized from (3-bromophenyl)acetonitrile and epichlorohydrin according to the same method as that of Production Example 13, triphenylphosphine (893 mg), and the 2,4-dimethyl-5-pyrimidinol (390 mg) synthesized in Production Example 4-(2) at 0°C. The obtained mixture was then stirred at a room temperature for 14 hours. Thereafter, water was added to the reaction

solution, and the obtained mixture was then extracted with ethyl acetate. The organic layer was washed with a saturated saline, was then dried over magnesium sulfate, and was then concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, Size: 2L, n-heptane : ethyl acetate 0% → 40%), so as to obtain the above-captioned compound (880 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.95 (t, J=5.8 Hz, 1H), 1.08 (s, 9H), 1.17-1.35 (m, 1H), 1.55-1.65 (m, 1H), 2.30 (s, 3H), 2.61 (s, 3H), 3.75 (dd, J=11.2, 8.0 Hz, 1H), 4.04 (dd, 1H, J=11.2, 5.4 Hz, 1H), 4.11 (d, J=9.6 Hz, 1H), 4.19 (d, J=9.6 Hz, 1H), 7.17 (t, J=7.8 Hz, 1H), 7.31-7.39 (m, 6H), 7.40-7.46 (m, 2H), 7.59 (t, J=2.0 Hz, 1H), 7.62-7.68 (m, 4H), 7.88 (s, 1H).

[0175]

(2) 3-{1-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-hydroxymethylcyclopropan-1-yl}benzonitrile (Prep 18-2)

Zinc cyanide (172 mg) and tetrakistriphenylphosphinepalladium (169 mg) were added to a DMF solution (20 ml) of the compound Prep 18-1 (880 mg), and the obtained mixture was then stirred in a nitrogen atmosphere at 90°C for 7 hours. Thereafter, the temperature of the reaction solution was returned to a room temperature, and a saturated sodium bicarbonate aqueous solution was added thereto. The obtained mixture was then extracted with ethyl acetate. The organic layer was washed with a saturated saline, was then dried over magnesium sulfate, and was then concentrated under a reduced pressure. The residue was dissolved in THF (10 ml), and tetrabutyl ammonium fluoride (Aldrich, 1 M THF solution: 2.19 ml) was then added dropwise to the solution at a room temperature. The obtained mixture was then stirred at a room temperature for 5 hours. Thereafter, the reaction solution was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, Size: L, n-heptane : ethyl acetate 0% → 100% → ethyl acetate : methanol 10%), so as to obtain the above-captioned compound (415 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.07 (t, J=6.0 Hz, 1H), 1.31 (dd, J=8.6, 5.4 Hz, 1H), 1.74-1.84 (m, 1H), 2.38 (s, 3H), 2.60 (s, 3H), 3.63 (dd, J=12.0, 9.2 Hz, 1H), 4.09 (dd, J=12.0, 5.4 Hz, 1H), 4.16 (d, J=10.0 Hz, 1H), 4.38 (d, J=10.0 Hz, 1H), 7.45 (t, J=7.6 Hz, 1H), 7.54-7.58 (m, 1H), 7.68-7.72 (m, 1H), 7.73-7.75 (m, 1H), 8.01 (s, 1H).

[0176]

(3) 3-{1-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-formylcyclopropan-1-yl}benzonitrile (Prep 18-3)

A dichloromethane solution (7 ml) of oxalyl chloride (239 ul) was cooled to -78°C, and dimethyl sulfoxide (394 ul) was then added dropwise thereto (internal temperature: -

60°C or lower). The obtained mixture was stirred at the same temperature as described above for 10 minutes. Thereafter, a dichloromethane solution (7 ml) of the compound Prep 18-2 (415 mg) was added dropwise to the reaction solution at -78°C, and the obtained mixture was then stirred at the same temperature as described above for 30 minutes. Thereafter, triethylamine (1.17 ml) was added to the reaction solution, and the mixture was then stirred for 15 minutes. Thereafter, the temperature of the reaction solution was increased to a room temperature. A saturated saline was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and was then concentrated under a reduced pressure, so as to obtain a roughly purified product of the above-captioned compound (236 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.41 (t, J=7.2 Hz, 1H), 1.69 (dd, J=8.4, 5.2 Hz, 1H), 2.03 (t, J=5.8 Hz, 1H), 2.35 (s, 3H), 2.59 (s, 3H), 4.22 (d, J=10.0 Hz, 1H), 4.42 (d, J=10.0 Hz, 1H), 7.50 (t, J=8.2 Hz, 1H), 7.59-7.65 (m, 1H), 7.70-7.75 (m, 1H), 7.76-7.79 (m, 1H), 7.96 (s, 1H), 9.92 (d, J=2.8 Hz, 1H).

[0177]

(4) 2-(3-Cyanophenyl)-2-{1-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]}cyclopropanecarboxylate (Prep 18-4)

The compound Prep 18-3 (415 mg), 2-methyl-2-butene (0.717 ml) and sodium dihydrogen phosphate (243 mg) were dissolved in a mixed solvent of acetone and water (10 ml/2 ml). Sodium chlorite (244 mg) was added, drop by drop, to the solution. The obtained mixture was then stirred at a room temperature for 14 hours, and the reaction solution was then concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, Size: M, ethyl acetate : methanol 0% → 15%), so as to obtain the above-captioned compound (265 mg).

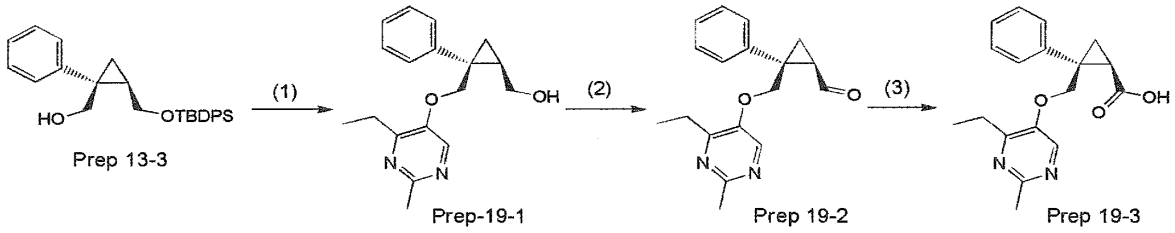
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.61 (dd, J=8.4, 5.6 Hz, 1H), 1.79 (t, J=5.6 Hz, 1H), 2.20-2.27 (m, 1H), 2.37 (s, 3H), 2.60 (s, 3H), 4.46 (d, J=9.6 Hz, 1H), 4.59 (d, J-9.6 Hz, 1H), 7.49 (t, J=7.8 Hz, 1H), 7.59-7.63 (m, 1H), 7.72-7.77 (m, 1H), 7.80 (t, J=1.8 Hz, 1H), 8.28 (s, 1H).

[0178]

Production Example 19

Synthesis of (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxylate (Prep 19-3)

[Formula 36]



[0179]

The above-captioned compound was synthesized from the compound Prep 13-3 by the same method as that of Production Example 13.

[0180]

[Table 3]

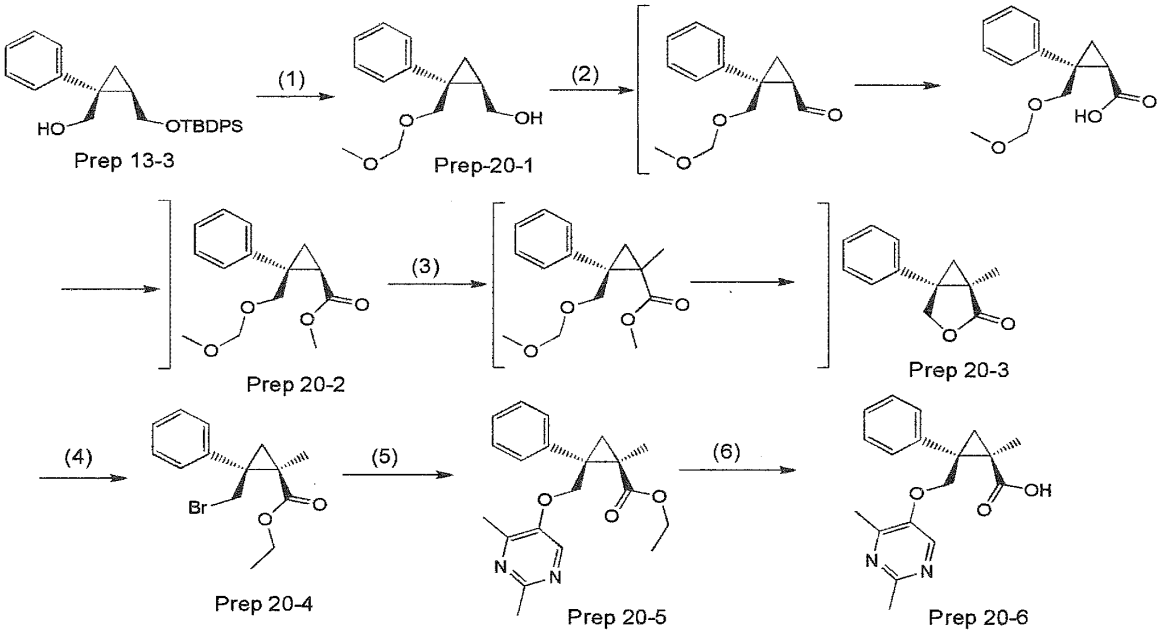
Compound No.	Compound name	Data (NMR and/or MS)
Prep 19-1	(1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropylmethanol	^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.97 (t, J=5.4 Hz, 1H), 1.15 (t, J=7.8 Hz, 3H), 1.27 (dd, J=8.8, 5.2 Hz, 1H), 1.80-1.90 (m, 1H), 2.19 (dd, J=9.6, 3.2 Hz, 1H), 2.60 (s, 3H), 2.70 (ddd, J=15.2, 7.6, 3.2 Hz, 2H), 3.54-3.63 (m, 1H), 4.03-4.15 (m, 1H), 4.11 (d, J=10.0 Hz, 1H), 4.44 (d, J=9.6 Hz, 1H), 7.21-7.29 (m, 1H), 7.29-7.36 (m, 2H), 7.42-7.46 (m, 2H), 7.99 (s, 1H).
Prep19-2	(1R,2S)-2-{[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropan-1-yl}carbaldehyde	^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.16 (t, J=7.6 Hz, 3H), 1.64-1.74 (m, 1H), 1.97 (t, J=5.6 Hz, 1H), 2.50-2.55 (m, 1H), 2.60 (s, 3H), 2.70 (q, J=7.6 Hz, 2H), 4.20 (d, J=10.0 Hz, 1H), 4.44 (d, J=9.6 Hz, 1H), 7.27-7.38 (m, 3H), 7.42-7.47 (m, 2H), 7.95 (s, 1H), 9.86 (d, J=3.6 Hz, 1H).
Prep19-3	(1R,2S)-2-{[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxylate	^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.08 (t, J=7.4 Hz, 3H), 1.53-1.58 (m, 1H), 1.76 (t, J=5.2 Hz, 1H), 2.24-2.29 (m, 1H), 2.57 (s, 3H), 2.60-2.71 (m, 2H), 4.49 (dd, J=13.2, 9.2 Hz, 2H), 7.25-7.32 (m, 1H), 7.32-7.39 (m, 2H), 7.46-7.52 (m, 2H), 8.23 (s, 1H).

[0181]

Production Example 20

Synthesis of (1R,2R)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxylate (Prep 20-6)

[Formula 37]



[0182]

(1) [(1R,2S)-2-(methoxymethoxymethyl)-2-phenylcyclopropyl]methanol (Prep 20-1)

N,N-diisopropylethylamine (4.35 ml) and chloromethyl methyl ether (1.52 ml) were added to a dichloromethane solution (40 ml) of the compound Prep 13-3 (4 g), while the solution was stirred under cooling on ice. The obtained mixture was stirred at a room temperature for 14 hours. Thereafter, water was added to the reaction solution, and the mixture was then extracted with dichloromethane. The organic layer was dried over magnesium sulfate, and the solvent was then distilled away under a reduced pressure. The obtained residue was dissolved in THF (40 ml), and tetrabutyl ammonium fluoride (1 M THF solution: 1.61 ml) was then added to the solution at a room temperature. The obtained mixture was stirred at a room temperature for 2 hours. Thereafter, the reaction solution was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, Size: 2L, n-heptane : ethyl acetate 10% → 50%), so as to obtain the above-captioned compound (1.93 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.79 (t, J=5.6 Hz, 1H), 1.11 (dd, J=8.8, 5.2 Hz, 1H), 1.70-1.80 (m, 1H), 3.19 (s, 3H), 3.35-3.45 (m, 1H), 3.57 (d, J=10.4 Hz, 1H), 4.04-4.16 (m, 2H), 4.52 (d, J=6.4 Hz, 1H), 4.59 (d, J=6.8 Hz, 1H), 7.18-7.24 (m, 1H), 7.25-7.34 (m, 2H), 7.35-7.42 (m, 2H).

[0183]

(2) Methyl (1R,2S)-2-methoxymethoxymethyl-2-phenylcyclopropanecarboxylate (Prep 20-2)

A dichloromethane solution (15 ml) of oxalyl chloride (1.5 ml) was cooled to -78°C, and a dichloromethane solution (5 ml) of dimethyl sulfoxide (2.49 ml) was then added dropwise thereto (internal temperature: -65°C or lower). The obtained mixture was stirred at the same temperature as described above for 5 minutes. Thereafter, a dichloromethane solution (20 ml) of the compound Prep 20-1 (1.93 g) was added dropwise to the reaction solution at -78°C, and the obtained mixture was then stirred at the same temperature as described above for 30 minutes. Thereafter, triethylamine (7.33 ml) was added to the reaction solution, and the obtained mixture was then stirred for 15 minutes. Thereafter, the temperature of the reaction solution was increased to a room temperature. A saturated saline was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and was then concentrated under a reduced pressure, so as to obtain an aldehyde body (1.93 g). The obtained aldehyde body (1.93 g), 2-methyl-2-butene (4.65 ml) and sodium dihydrogen phosphate were dissolved in a mixed solvent of acetone and water (60 ml/15 ml), and sodium chlorite (1.58 g) was then added, drop by drop, to the solution, while the solution was stirred under cooling on ice. The obtained mixture was stirred at a room temperature for 5 hours. Thereafter, water was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate (× 3). The organic layer was washed with a saturated saline, was then dried over magnesium sulfate, and was then concentrated under a reduced pressure. The residue was dissolved in a mixed solvent of methanol and THF (20 ml/20 ml), and while stirring at a room temperature, trimethylsilyldiazomethane (Aldrich, 2 M hexane solution: 8.76 ml) was added to the solution. The obtained mixture was stirred at a room temperature for 14 hours. Thereafter, a small amount of acetic acid was added to the reaction solution, and thereby excessive trimethylsilyldiazomethane was decomposed. The resultant product was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, Size: M, n-heptane : ethyl acetate 0% → 20%), so as to obtain the above-captioned compound (1.65 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.43 (dd, J=8.0, 4.8 Hz, 1H), 1.60 (dd, J=6.2, 4.8 Hz, 1H), 2.12 (dd, J=8.0, 6.2 Hz, 1H), 3.14 (s, 3H), 3.75 (s, 3H), 3.85 (d, J=10.0 Hz, 1H), 3.98 (d, J=9.6 Hz, 1H), 4.48 (s, 2H), 7.21-7.28 (m, 1H), 7.29-7.34 (m, 2H), 7.37-7.42 (m, 2H).

[0184]

(3) (1S,5R)-1-methyl-5-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (Prep 20-3)

While stirring at -78°C, n-butyllithium (2.69 M hexane solution: 3.3 ml) was added to a THF solution (22 ml) of diisopropylamine (1.25 ml). The obtained mixture was

stirred at -78°C for 30 minutes. Thereafter, a THF solution (11 ml) of the compound Prep 20-2 (1.11 g) was added to the reaction solution, and the obtained mixture was then stirred at -78°C for 1 hour. Thereafter, iodomethane (703 ul) was added to the reaction solution, and the obtained mixture was stirred for 3 hours, while the temperature was increased to a room temperature. Thereafter, a saturated ammonium chloride aqueous solution was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate. The obtained layer was washed with a saturated saline, was then dried over magnesium sulfate, and was then concentrated under a reduced pressure. The residue was dissolved in THF (10 ml), and while stirring at a room temperature, 7.5 N hydrochloric acid (10 ml) was added to the solution. The obtained mixture was stirred at a room temperature for 2 hours. Thereafter, water was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate. The obtained organic layer was successively washed with a saturated sodium bicarbonate aqueous solution and a saturated saline, and was then dried over magnesium sulfate. After completion of vacuum concentration, the residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, Size: M, n-heptane : ethyl acetate 0% → 20%), so as to obtain the above-captioned compound (314 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.15 (s, 3H), 1.36 (d, J=5.2 Hz, 1H), 1.51 (d, J=4.8 Hz, 1H), 4.38 (dd, J=12.4, 9.2 Hz, 2H), 7.20-7.44 (m, 5H).

[0185]

(4) Ethyl (1R,2R)-2-bromomethyl-1-methyl-2-phenylcyclopropanecarboxylate (Prep 20-4)

While stirring at -15°C, thionyl bromide (247 ul) was added dropwise to ethanol (2 ml). Thereafter, the compound Prep 20-3 (150 mg) was added to the solution, and the obtained mixture was then stirred at -15°C overnight. Thereafter, the reaction solution was concentrated under a reduced pressure, and was then purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, Size: M, n-heptane : ethyl acetate 0% → 85%), so as to obtain the above-captioned compound (131 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.02 (s, 3H), 1.31-1.37 (m, 1H), 1.34 (t, J=7.0 Hz, 3H), 1.91 (d, J=5.2 Hz, 1H), 3.79 (d, J=10.0 Hz, 1H), 3.87 (dd, J=10.0, 1.0 Hz, 1H), 4.24 (q, J=7.0 Hz, 2H), 7.26-7.43 (m, 5H).

[0186]

(5) Ethyl (1R,2R)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-1-methyl-2-phenylcyclopropanecarboxylate (Prep 20-5)

Potassium carbonate (91.4 mg), the 2,4-dimethyl-5-pyrimidinol (71.2 mg)

synthesized in Production Example 4-(2), and tetrabutyl ammonium iodide (81.4 mg) were added to a DMF solution (3 ml) of the compound Prep 20-4 (131 mg). The reaction solution was stirred at 70°C for 5 hours, and the temperature of the reaction solution was then returned to a room temperature. Water was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate. The organic layer was washed with a saturated saline, was then dried over magnesium sulfate, and was then concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, Size: M, n-heptane : ethyl acetate 5 % → 60%), so as to obtain the above-captioned compound (133 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.08 (s, 3H), 1.22 (t, J=7.0 Hz, 3H), 1.30 (d, J=4.8 Hz, 1H), 1.96 (d, J=4.8 Hz, 1H), 2.40 (s, 3H), 2.58 (s, 3H), 4.04-4.17 (m, 2H), 4.30 (dd, J=12.2, 5.4 Hz, 2H), 7.26-7.48 (m, 5H), 7.90 (s, 1H).

[0187]

(6) (1R,2R)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-1-methyl-2-phenylcyclopropanecarboxylate (Prep 20-6)

A 5 N sodium hydroxide aqueous solution (235 ul) was added to an ethanol solution (2 ml) of the compound Prep 20-5 (133 mg), and the obtained mixture was then stirred at 80°C for 5 hours. After the temperature of the reaction solution had been returned to a room temperature, the reaction solution was neutralized with 5 N hydrochloric acid, followed by vacuum concentration. The residue was fully washed with THF, and was then filtered. The filtrate was dried over magnesium sulfate, and was then concentrated under a reduced pressure, so as to obtain the above-captioned compound (144 mg).

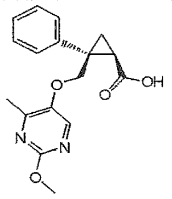
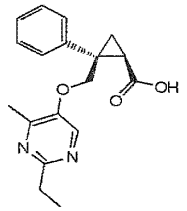
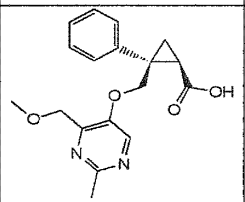
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.10 (s, 3H), 1.24-1.34 (m, 1H), 1.95 (brd, J=4.4 Hz, 1H), 2.34 (s, 3H), 2.51 (s, 3H), 4.36 (brd, J=9.2 Hz, 1H), 4.44 (brd, J=9.6 Hz, 1H), 7.26-7.47 (m, 5H), 8.04 (s, 1H).

[0188]

The carboxylic acids of Production Example 21-47 were synthesized by the same method as that of Production Example 13, with the exception that (±)-epichlorohydrin was used as a racemic body, instead of using R-(-)-epichlorohydrin.

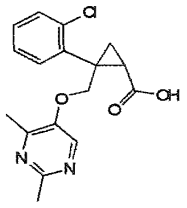
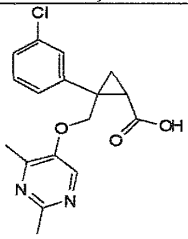
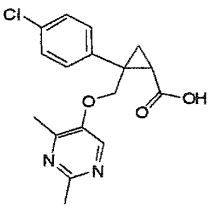
[0189]

[Table 4]

Production example	Structural formula	Compound name	Data (MS)
Prep 21		(1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxylate	MS $[M+H]^+$=315
Prep 22		(1R,2S)-2-[(2-ethyl-4-methylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxylate	MS $[M+H]^+$=313
Prep 23		(1R,2S)-2-(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl-2-phenylcyclopropanecarboxylate	MS $[M+H]^+$=329

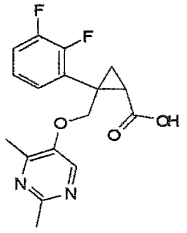
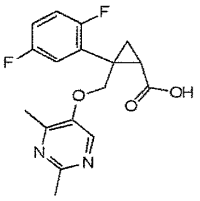
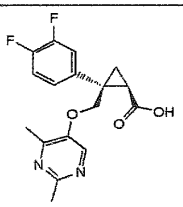
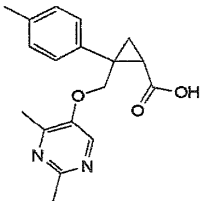
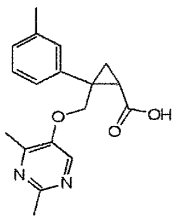
[0190]

[Table 5]

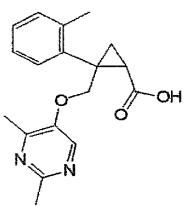
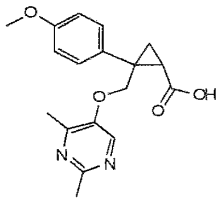
Production example	Structural formula, MS	Production example	Structural formula, MS	Production example	Structural formula, MS
Prep 24	 MS $[M+H]^+$= 333	Prep 25	 MS $[M+H]^+$= 333	Prep 26	 MS $[M+H]^+$= 333

[0191]

[Table 6-1]

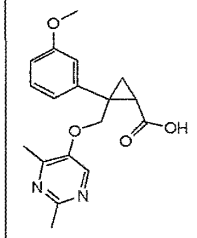
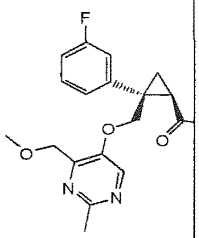
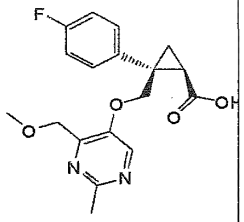
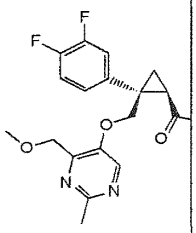
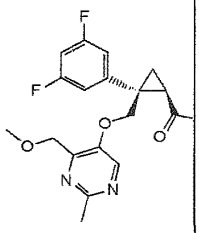
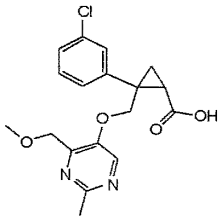
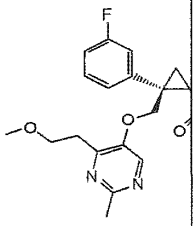
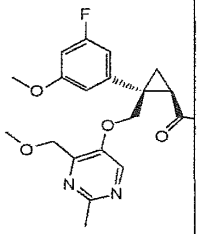
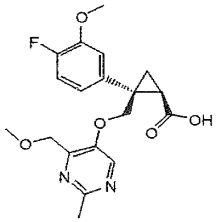
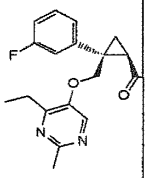
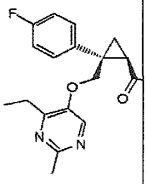
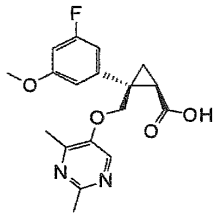
Production example	Structural formula	NMR and/or MS
Prep 27		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.59 (dd, J=5.2 Hz, 8.4 Hz, 1H), 1.77 (t, J=5.6 Hz, 1H), 2.20-2.25 (m, 1H), 2.33 (s, 3H), 2.59 (s, 3H), 4.43 (d, J=9.6 Hz, 1H), 4.61 (d, J=10.0 Hz, 1H), 7.01-7.30 (m, 3H), 8.26 (s, 1H). MS $[M+H]^+$=335
Prep 28		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.58 (dd, J=5.6 Hz, 8.4 Hz, 1H), 1.76 (t, J=6.0 Hz, 1H), 2.21 (dd, J=6.4 Hz, 8.4 Hz, 1H), 2.35 (s, 3H), 2.59 (s, 3H), 4.43 (d, J=9.6 Hz, 1H), 4.61 (d, J=10.0 Hz, 1H), 6.95-7.20 (m, 3H), 8.28 (s, 1H). MS $[M+H]^+$=335
Prep 29		^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 1.56 (dd, J=5.6 Hz, 8.0 Hz, 1H), 1.72 (t, J=5.6 Hz, 1H), 2.20 (dd, J=6.0 Hz, 8.4 Hz, 1H), 2.38 (s, 3H), 2.58 (s, 3H), 4.41 (d, J=9.2 Hz, 1H), 4.55 (d, J=9.6 Hz, 1H), 7.11-7.34 (m, 3H), 8.26 (s, 1H). MS $[M+H]^+$=335
Prep 30		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.48-1.60 (m, 1H), 1.70 (dd, J=5.2, 6.0 Hz, 1H), 2.22 (dd, J=6.0, 8.4 Hz, 1H), 2.28-2.44 (m, 6H), 2.57 (s, 3H), 4.32-4.62 (m, 2H), 7.10-7.44 (m, 4H), 8.20 (s, 1H). MS $[M+H]^+$=313
Prep 31		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.59 (dd, J=7.6, 5.2 Hz, 1H), 1.71 (dd, J=5.8, 5.0 Hz, 1H), 2.24 (dd, J=8.2, 6.2 Hz, 1H), 2.37 (s, 3H), 2.38 (s, 3H), 2.59 (s, 3H), 4.43 (d, J=9.2 Hz, 1H), 4.57 (d, J=9.6 Hz, 1H), 7.08-7.13 (m, 1H), 7.21-7.33 (m, 3H), 8.22 (s, 1H).

[Table 6-2]

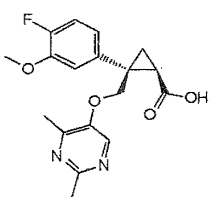
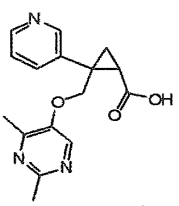
Prep 32		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.55 (dd, J=8.2, 4.6 Hz, 1H), 1.78 (dd, J=6.0, 5.2 Hz, 1H), 2.21 (dd, J=8.2, 6.2 Hz, 1H), 2.35 (s, 3H), 2.52 (s, 3H), 2.59 (s, 3H), 4.37 (d, J=9.6 Hz, 1H), 4.55 (d, J=9.2 Hz, 1H), 7.16-7.23 (m, 3H), 7.43-7.49 (m, 1H), 8.22 (s, 1H).
Prep 33		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.46-1.58 (m, 1H), 1.69 (t, J=4.8 Hz, 1H), 2.14-2.28 (m, 1H), 2.37 (s, 3H), 2.56 (s, 3H), 3.81 (s, 3H), 4.30-4.56 (m, 2H), 6.78-6.96 (m, 2H), 7.20-7.46 (m, 2H), 8.17 (s, 1H). MS $[M+H]^+$=329

[0192]

[Table 7-1]

Production example	Structural formula, MS	Production example	Structural formula, MS	Production example	Structural formula, MS
Prep 34	 MS $[M+H]^+$= 329	Prep 35	 LC-MS (ES.Pos): 347 [M+H+]/346	Prep 36	 LC-MS (ES.Pos): 347 [M+H+]/346
Prep 37	 MS $[M+H]^+$= 365	Prep 38	 MS $[M+H]^+$= 365	Prep 39	 LC-MS (ES.Pos): 363 [M+H+]/362
Prep 40	 LC-MS (ES.Pos): 361 [M+H+]/360	Prep 41	 LC-MS (ES.Pos): 377 [M+H+]/376	Prep 42	 MS $[M+H]^+$=377
Prep 43	 MS $[M+H]^+$= 331	Prep 44	 MS $[M+H]^+$= 331	Prep 45	 MS $[M+H]^+$= 347

[Table 7-2]

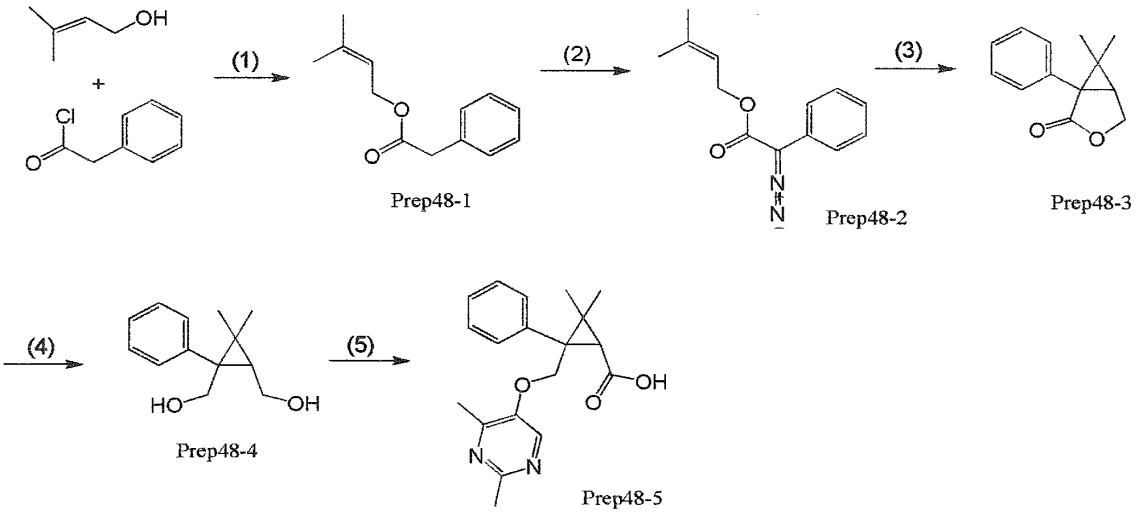
Prep 46	 MS $[M+H]^+$= 347	Prep 47	 MS $[M+H]^+$= 300		

[0193]

Production Example 48

Synthesis of 2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-3,3-dimethyl-2-phenylcyclopropanecarboxylate (Prep 48-5)

[Formula 38]



[0194]

(1) 3-Methyl-2-buten-1-yl phenylacetate (Prep 48-1)

Triethylamine (9.7 ml) and phenylacetyl chloride (7.67 ml) were added to a dichloromethane solution (50 ml) of 3-methyl-2-buten-1-ol (5 g), while the solution was stirred under cooling on ice. The obtained mixture was stirred under cooling on ice for 3 hours. Thereafter, water was added to the reaction solution, and the obtained mixture was then extracted with dichloromethane. The obtained organic layer was dried over magnesium sulfate, and was then concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, Size: 3L, n-heptane : ethyl acetate 0% →

5%), so as to obtain the above-captioned compound (11.5 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.69 (s, 3H), 1.75 (s, 3H), 3.63 (s, 2H), 4.59 (d, J=7.2 Hz, 2H), 5.30-5.37 (m, 1H), 7.23-7.36 (m, 5H).

[0195]

(2) 3-Methyl-2-buten-1-yl diazophenylacetate (Prep 48-2)

Prep 48-1

DBU (9.26 ml) and 4-acetamidebenzenesulfonyl azide (13.5 g) were added to an acetonitrile solution (100 ml) of the compound Prep 48-1 (11.5 g), while the solution was stirred under cooling on ice. The obtained mixture was stirred at a room temperature for 15 hours. The reaction solution was concentrated under a reduced pressure, and water was then added thereto. The obtained mixture was then extracted with ethyl acetate. The obtained organic layer was washed with a saturated saline, was then dried over magnesium sulfate, and was then concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush^{TM} column, Size: 3L, n-heptane : ethyl acetate 0% → 5%), so as to obtain the above-captioned compound (8.45 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.75 (s, 3H), 1.78 (s, 3H), 4.77 (d, J=7.6 Hz, 2H), 5.36-5.44 (m, 1H), 7.15-7.20 (m, 1H), 7.35-7.41 (m, 2H), 7.45-7.51 (m, 2H).

[0196]

(3) 6,6-Dimethyl-1-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (Prep 48-3)

While stirring at 50°C, a dichloromethane solution (180 ml) of Prep 48-2 (8.45 g) was added dropwise to a dichloromethane solution (360 ml) of rhodium(II) acetate dimer (324 mg) over 2 hours. Thereafter, the reaction solution was stirred at 50°C for 1 hour. Thereafter, the reaction solution was cooled to a room temperature, and was then concentrated under a reduced pressure, so as to obtain a roughly purified product of the above-captioned compound (8 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.88 (s, 3H), 1.32 (s, 3H), 2.39 (d, J=5.2 Hz, 1H), 4.25 (d, J=9.6 Hz, 1H), 4.53 (dd, J=9.6, 5.2 Hz, 1H), 7.27-7.39 (m, 5H).

[0197]

(4) (3,3-Dimethyl-1-phenylcyclopropan-1,2-diyl)dimethanol (Prep 48-4)

Lithium aluminum hydride (1.5 g) was added to a THF solution (100 ml) of Prep 48-3 (8 g), while the solution was stirred under cooling on ice. The obtained mixture was stirred for 1 hour. Thereafter, ice and a small amount of 27% ammonia aqueous solution were added to the reaction solution, and the obtained mixture was then stirred at a room temperature for 10 minutes. Thereafter, Celite and magnesium sulfate were added to the reaction solution, and the

obtained mixture was then stirred for 10 minutes. Thereafter, the reaction solution was filtered, and the filtrate was then concentrated under a reduced pressure, so as to obtain the above-captioned compound (6.52 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.78 (s, 3H), 1.25 (s, 3H), 1.49 (dd, J=7.0, 5.8 Hz, 1H), 3.72 (dd, J=12.2, 11.0 Hz, 1H), 3.89 (d, J=12.0 Hz, 1H), 4.03 (d, J=12.2 Hz, 1H), 4.10 (dd, J=11.8, 5.8 Hz, 1H), 7.21-7.37 (m, 5H).

[0198]

(5) 2-[(2,4-Dimethylpyrimidin-5-yl)oxymethyl]-3,3-dimethyl-2-phenylcyclopropanecarboxylate (Prep 48-5)

The above-captioned compound was synthesized from Prep 48-4 according to the method of Production Example 13-(7).

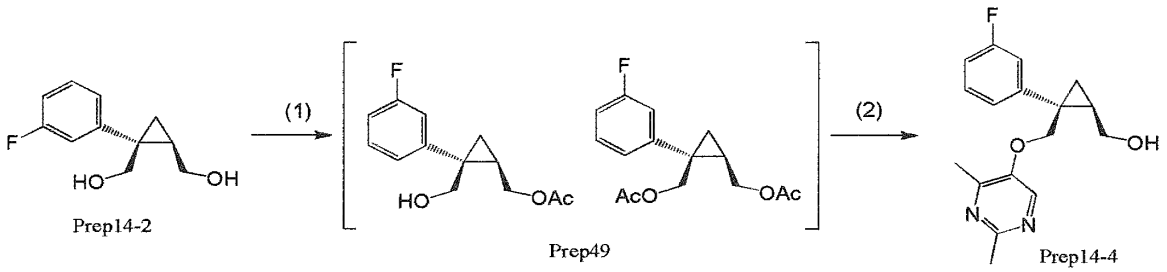
MS $[M+H]^+$=327

[0199]

Production Example 49

Synthesis of (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl}-2-(3-fluorophenylcyclopropyl)methanol (Prep 14-4)

[Formula 39]



Prep14-2 Prep49 Prep14-4

[0200]

(1) [(1R,2S)-2-(3-fluorophenyl)-2-(hydroxymethyl)cyclopropyl]methyl acetate, [(1S,2R)-1-(3-fluorophenyl)-1,2-diyl]bis(methylene) diacetate mixture (Prep 49)

NOVOZYME 435 (SIGMA, 1.78 g) was added to a THF (110 ml)-vinyl acetate (25 ml) solution of the compound Prep 14-2 (35.5 g) under cooling on ice. The obtained mixture was stirred at a room temperature for 17 hours. Thereafter, the reaction solution was subjected to Kiriyama filtration, and the obtained filtrate was then concentrated, so as to obtain the above-captioned compound (43.7 g).

MS $[M+H]^+$=239, 281

[0201]

(2) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl}-2-(3-fluorophenylcyclopropyl)methanol

(Prep 14-4)

Diisopropyl azodicarboxylate (45.8 ml) was added dropwise to a THF solution (400 ml) of the compound Prep 49 (43.7 g), triphenylphosphine (57 g) and 2,4-dimethyl-5-pyrimidinol (Prep 4-2, 24.7 g) at 0°C. The obtained mixture was stirred at a room temperature for 15 hours. Thereafter, a saturated sodium bicarbonate aqueous solution was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate. The organic layer was washed with a saturated saline, was then dried over magnesium sulfate, and was then concentrated. The obtained reaction product was dissolved in EtOH-1 N sodium hydroxide aqueous solution (200 ml-200 ml), and the obtained mixture was then stirred at a room temperature for 1 hour. Thereafter, a 5 N sodium hydroxide aqueous solution (100 ml) was added to the reaction solution, and the obtained mixture was then stirred at a room temperature for 1 hour. Subsequently, the reaction solution was concentrated under a reduced pressure at a room temperature, and the obtained residue was then extracted with ethyl acetate. The organic layer was washed with a saturated saline, and was then dried over magnesium sulfate. The solvent was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (heptane : ethyl acetate = 1 : 4, to ethyl acetate : methanol = 1 : 1). The obtained residue was filtered with NH-silica, followed by column purification, so as to obtain the above-captioned compound (39.3 g).

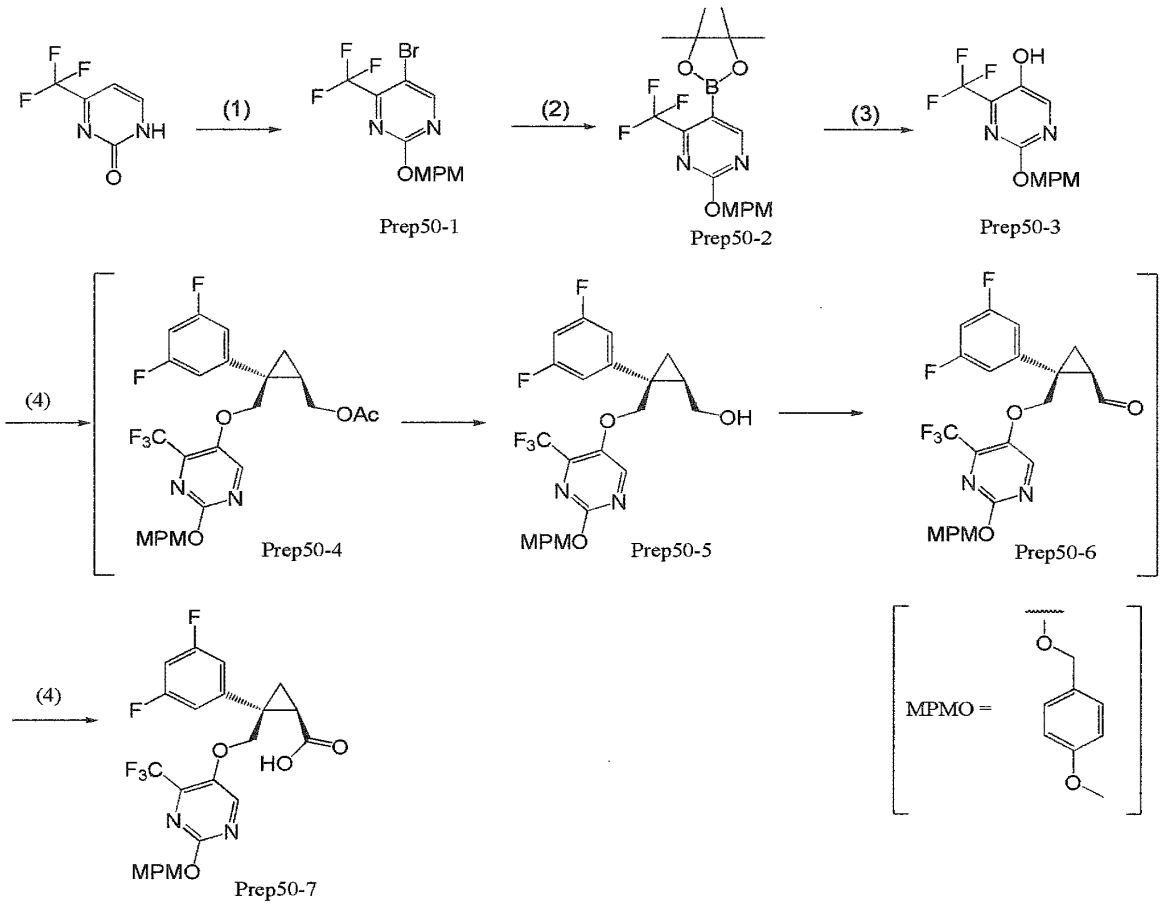
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.00 (t, J=5.2 Hz, 1H), 1.24-1.30 (m, 1H), 1.79-1.85 (m, 1H), 2.39 (s, 3H), 2.60 (s, 3H), 3.55-3.61 (m, 1H), 4.03-4.13 (m, 1H), 4.12 (d, J=9.6 Hz, 1H), 4.43 (d, J=9.6 Hz, 1H), 6.92-6.98 (m, 1H), 7.11-7.15 (m, 1H), 7.19-7.22 (m, 1H), 7.25-7.31 (m, 1H), 8.00 (s, 1H).

[0202]

Production Example 50

Synthesis of (1R,2S)-2-(3,5-difluorophenyl)-2-[2-(4-methoxybenzyloxy)-4-(trifluoromethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxylate (Prep 50-7)

[Formula 40]



[0203]

1) 5-Bromo-2-(4-methoxybenzyloxy)-4-trifluoromethylpyrimidine (Prep 50-1)

Potassium acetate (15.3 g) was added to an acetic acid solution (50 ml) of 4-(trifluoromethyl)pyrimidin-2(1H)-one (CAS No. 104048-92-2; 8.4 g), and thereafter, bromine (2.6 ml) was added dropwise to the solution at 40°C. The obtained mixture was stirred at 70°C for 1.5 hours. Thereafter, the reaction system was concentrated under a reduced pressure, and water and ethyl acetate were then added to the residue to carry out liquid separation and extraction. The obtained organic layer was dried over magnesium sulfate and was then concentrated under a reduced pressure. Phosphorous oxychloride (40 ml) was added to the obtained residue, and the thus obtained mixture was then stirred for 1.5 hours under heating to reflux. The reaction system was concentrated under a reduced pressure, and phosphorous oxychloride was then distilled away. Thereafter, ice was added to the residue, and liquid separation and extraction were then carried out with hexane. The obtained organic layer was dried over magnesium sulfate. The resultant organic layer was concentrated under a reduced pressure, so as to obtain a crude product.

NaH was added to a THF solution (150 ml) of 4-methoxybenzyl alcohol (7.07 g), and the obtained mixture was then stirred at a room temperature for 30 minutes. A THF solution of the above obtained crude product was added dropwise to the reaction system, and the obtained mixture was then stirred overnight. Thereafter, a saturated ammonium chloride aqueous solution was added to the reaction system, followed by quenching. THF was distilled away under a reduced pressure, and liquid separation and extraction were then carried out with ethyl acetate. The obtained organic layer was dried over magnesium sulfate and was then concentrated under a reduced pressure. The obtained residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, elution solvent: n-heptane : ethyl acetate = 19 : 1 → 3 : 1), so as to obtain the above-captioned compound (12.5 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.81 (s, 3H), 5.40 (s, 2H), 6.87-6.90 (m, 2H), 7.43 (brdd, J=7.6 Hz, 2H), 8.76 (s, 1H).

[0204]

(2) 2-(4-Methoxybenzyloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-trifluoromethylpyrimidine (Prep 50-2)

Potassium acetate (9.3 g) and bis(pinacolato)diboron (9.63 g) were added to a 1,4-dioxane solution (130 ml) of the compound Prep 50-1 (11.5 g), and deaeration and nitrogen substitution were then performed on the obtained solution. Thereafter, 1,1-bis(diphenylphosphino)ferrocene dichloropalladium(II) was added to the reaction solution, and the obtained mixture was heated to reflux at 110°C for 6 hours. Thereafter, the reaction system was moderately concentrated under a reduced pressure, and 1,4-dioxane was distilled away. Then, ethyl acetate was added to the resultant product, and the reaction solution was then subjected to Kiriyama filtration. The filtrate was concentrated under a reduced pressure, and the obtained residue was then purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, elution solvent: n-heptane : ethyl acetate = 19 : 1 → 1 : 2), so as to obtain the above-captioned compound (8.0 g).

MS $[M+H]^+$=433.

[0205]

(3) 2-(4-Methoxybenzyloxy)-4-trifluoromethylpyrimidin-5-ol (Prep 50-3)

A 30% hydrogen peroxide water (502 μl) and a 2 N sodium hydroxide aqueous solution (2.44 ml) were added to a THF solution (20 ml) of the compound Prep 50-2 (2 g) under cooling on ice, and the obtained mixture was then stirred for 15 minutes. Thereafter, the reaction solution was further stirred at a room temperature for 30 minutes. Thereafter, a 1 N hydrochloric acid aqueous solution was added to the reaction system, and the pH of the mixed

solution was adjusted around pH 5. Liquid separation and extraction were carried out on the reaction solution with diethyl ether. The obtained organic layer was dried over magnesium sulfate and was then concentrated under a reduced pressure. The obtained residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, n-heptane : ethyl acetate = 9 : 1 → 1 : 1), so as to obtain the above-captioned compound (980 mg).

MS $[M+Na]^+$=323.

[0206]

(4) (1R,2S)-2-(3,5-difluorophenyl)-2-[2-(4-methoxybenzyloxy)]-4-(trifluoromethylpyrimidin-5-yl)oxymethyl)cyclopropanecarboxylate (Prep 50-7)

The above-captioned compound was obtained from the compound Prep 49 and the compound Prep 50-3 according to the methods of Production Example 13-(4) to 13-(7).

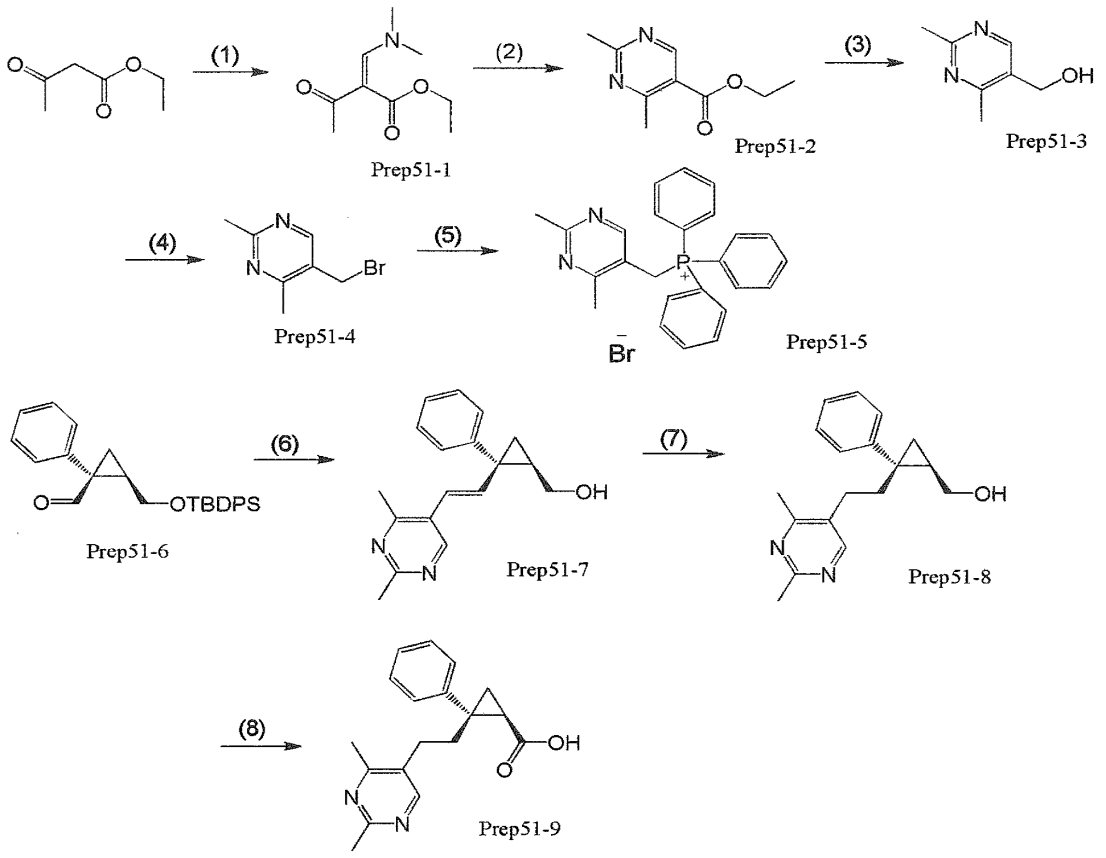
MS $[M+Na]^+$=533.

[0207]

Production Example 51

Synthesis of (1R,2S)-2-[2-(2,4-dimethylpyrimidin-5-yl)ethyl]-2-phenylcyclopropanecarboxylate (Prep 51-9)

[Formula 41]



[0208]

(1) Ethyl 2-[(dimethylamino)methylene]-3-oxobutanoate (Prep 51-1)

N,N-dimethylformamide dimethyl acetal (80.4 ml) was added dropwise to ethyl acetoacetate (63 g), and the obtained mixture was then stirred at a room temperature for 14 hours. Thereafter, the reaction solution was concentrated under a reduced pressure, and azeotropy with toluene was then performed three times, so as to obtain a roughly purified product of the above-captioned compound (89 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.33 (t, J=7.2 Hz, 3H), 2.33 (s, 3H), 3.07 (brs, 6H), 4.23 (q, J=7.2 Hz, 2H), 7.68 (s, 1H).

[0209]

(2) Ethyl 2,4-dimethylpyrimidin-5-carboxylate (Prep 51-2)

The compound Prep 51-1 (10 g), acetamidine hydrochloride (5.11 g) and sodium ethoxide (3.67 g) were dissolved in ethanol (100 ml), and the obtained mixture was then stirred at 100°C for 5 hours. Thereafter, the temperature of the reaction solution was returned to a room temperature, and the reaction solution was then concentrated under a reduced pressure.

Water was added to the residue, and the obtained mixture was then extracted with ethyl acetate. The organic layer was washed with a saturated saline and was then dried over magnesium sulfate, followed by vacuum concentration, so as to obtain a roughly purified product of the above-captioned compound (8.76 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.41 (t, J=7.0 Hz, 3H), 2.75 (s, 3H), 2.80 (s, 3H), 4.40 (q, J=7.0 Hz, 2H), 9.05 (s, 1H).

[0210]

(3) (2,4-Dimethylpyrimidin-5-yl)methanol (Prep 51-3)

A THF solution (30 ml) of the compound Prep 51-2 (8.76 g) was added dropwise to a THF suspension (50 ml) of lithium aluminum hydride (1.84 g), while the solution was stirred under cooling on ice. The obtained mixture was stirred at a room temperature for 3 hours. Thereafter, while the reaction solution was stirred under cooling on ice, a 27% ammonia aqueous solution and Celite were successively added thereto, and the obtained mixture was then stirred for 30 minutes. Thereafter, magnesium sulfate was added to the reaction solution, followed by filtration. The filtrate was then concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, Size: 2L, n-heptane : ethyl acetate 10% → 40% → ethyl acetate : methanol 10%) so as to obtain the above-captioned compound (670 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.52 (s, 3H), 2.68 (s, 3H), 4.71 (s, 2H), 8.50 (s, 1H).

[0211]

(4) 5-Bromomethyl-2,4-dimethylpyrimidine (Prep 51-4)

Phosphorus tribromide (0.912 ml) was added to a toluene dichloromethane solution (10 ml-5 ml) of the compound Prep 51-3 (670 mg), and the obtained mixture was then stirred at a room temperature for 3 hours. Thereafter, ice was added to the reaction solution, while the solution was stirred under cooling on ice, and a saturated sodium bicarbonate aqueous solution was then added to the reaction solution. The obtained mixture was extracted with ethyl acetate. The obtained organic layer was washed with a saturated saline and was dried over magnesium sulfate, followed by vacuum concentration, so as to obtain a roughly purified product of the above-captioned compound (354 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.58 (s, 3H), 2.70 (s, 3H), 4.44 (s, 2H), 8.48 (s, 1H).

[0212]

(5) [(2,4-Dimethylpyrimidin-5-yl)methyl]triphenylphosphoniumbromide (Prep 51-5)

Triphenylphosphine (462 mg) was added to a toluene solution (15 ml) of the compound Prep 51-4 (354 mg), and the obtained mixture was then stirred at 140°C for 5 hours.

The temperature of the reaction solution was returned to a room temperature, and a precipitated solid was then collected by filtration, followed by washing with tert-butyl methyl ether, so as to obtain the above-captioned compound (610 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.87 (d, J=1.2 Hz, 3H), 2.62 (d, J=1.6 Hz, 3H), 5.68 (d, J=14.4 Hz, 2H), 7.64-7.75 (m, 6H), 7.77-7.88 (m, 9H), 8.36 (d, J=2.4 Hz, 1H).

[0213]

(6) (1R,2S)-2-[(E,Z)-2-(2,4-dimethylpyrimidin-5-yl)vinyl]-2-phenylcyclopropylmethanol (Prep 51-7)

To a THF solution (7 ml) of the compound Prep 51-5 (610 mg), n-butyllithium (2.64 M n-hexane solution: 0.5 ml) was added, while stirring at -78°C. The obtained mixture was stirred at the same temperature as described above for 30 minutes. Thereafter, a THF solution (4 ml) of the (1S,2R)-2-(tert-butyldiphenylsilyloxymethyl)-1-phenylcyclopropanecarbaldehyde (Prep 51-6, 602 mg) that had been obtained from the compound Prep 13-3 according to the method of Production Example 53-(1) was added to the reaction solution, and the obtained mixture was then stirred at 0°C for 4 hours. Thereafter, water and a small amount of acetic acid were added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate. The obtained organic layer was washed with a saturated saline and was then dried over magnesium sulfate, followed by vacuum concentration. The residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, Size: L, n-heptane : ethyl acetate 0% → 20%). The obtained compound was dissolved in THF (10 ml), and tetrabutyl ammonium fluoride (1 M THF solution: 2.64 ml) was then added to the obtained solution. The obtained mixture was stirred at a room temperature for 12 hours. Thereafter, the reaction solution was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, Size: L, n-heptane : ethyl acetate 10% → 100% → ethyl acetate : methanol 5%), so as to obtain the above-captioned compound (113 mg).

MS $[M+H]^+$=281

[0214]

(7) (1R,2S)-2-[2-(2,4-dimethylpyrimidin-5-yl)ethyl]-2-phenylcyclopropylmethanol (Prep 51-8)

10% palladium-carbon (water content: 50%, 100 mg) was added to an ethyl acetate solution (20 ml) of the compound Prep 51-7 (113 mg), and catalytic hydrogen reduction was then carried out on the obtained solution at a room temperature at an ordinary pressure for 30 minutes. Thereafter, the reaction solution was filtered with Celite, and the filtrate was then concentrated under a reduced pressure, so as to obtain a roughly purified product of the above-

captioned compound (80 mg).

MS $[M+H]^+$=283

[0215]

(8) (1R,2S)-2-[2-(2,4-dimethylpyrimidin-5-yl)ethyl]-2-phenylcyclopropanecarboxylate (Prep 51-9)

The above-captioned compound was synthesized from the compound Prep 51-8 according to the method of Production Example 13-(7).

MS $[M+H]^+$=297

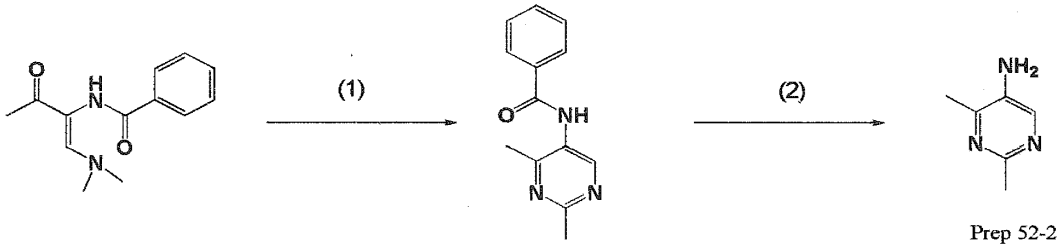
[0216]

Production Example 52

Synthesis of 2,4-dimethylpyrimidin-5-amine (Prep 52-2)

The starting substance was synthesized according to the method described in Heterocycles, 57(11), 2045-2064, 2002.

[Formula 42]



Prep 52-1 Prep 52-2

[0217]

(1) N-(2,4-dimethylpyrimidin-5-yl)benzamide (Prep 52-1)

Acetamidine hydrochloride (8.31 g) and potassium carbonate (6.06 g) were added to an ethanol solution (55.6 ml) of N-{(1Z)-1-[(dimethylamino)methylene]-2-oxopropyl}benzamide (6.8 g), and the temperature of the obtained mixture was then increased to 70°C, followed by stirring for 15 hours. Thereafter, the reaction solution was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate = 4 : 1 to 0 : 10), so as to obtain the above-captioned compound (4.1 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.53 (s, 3H), 2.72 (s, 3H), 7.44-7.64 (m, 3H), 7.89-7.92 (m, 2H), 8.01 (s, 1H).

[0218]

(2) 2,4-Dimethylpyrimidin-5-amine (Prep 52-2)

The compound Prep 52-1(4.1 g) was dissolved in an ethanol (55.6 ml)-1 N sodium hydroxide aqueous solution, and the obtained solution was then stirred at 70°C for 2 days. Thereafter, the reaction solution was extracted with ethyl acetate and chloroform, and the organic layer was then dried over magnesium sulfate, followed by filtration. The organic layer was concentrated under a reduced pressure, so as to obtain the above-captioned compound (2.1 g).

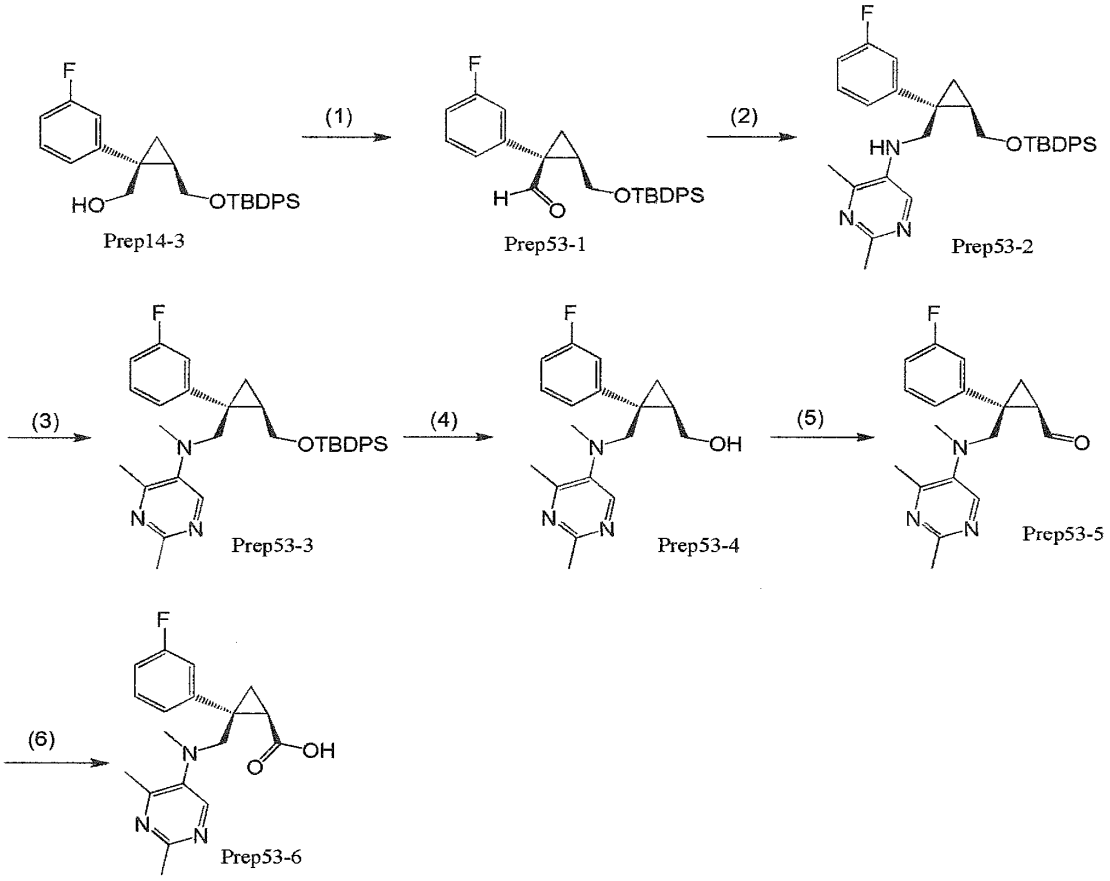
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.38 (s, 3H), 2.59 (s, 3H), 3.52 (brs, 2H), 8.01 (s, 1H).

[0219]

Production Example 53

Synthesis of (1R,2S)-2-{[(2,4-dimethylpyrimidin-5-yl)(methyl)amino]methyl}-2-(3-fluorophenyl)cyclopropanecarboxylate (Prep 53-6)

[Formula 43]



[0220]

(1) (1R,2S)-2-(tert-butyldiphenylsilyloxymethyl)-1-(3-fluorophenyl)cyclopropanecarbaldehyde

(Prep 53-1)

A dichloromethane solution (50 ml) of oxalyl chloride (1.26 ml) was cooled to -78°C, and a dichloromethane solution (10 ml) of dimethyl sulfoxide (2.04 ml) was then added dropwise to the reaction solution. Fifteen minutes later, a dichloromethane solution (12 ml) of the compound Prep 14-3 (3.0 g) was added dropwise to the reaction solution at -78°C, and the obtained mixture was then stirred at the same temperature as described above for 60 minutes. Thereafter, triethylamine (8.03 ml) was added to the reaction solution, and the temperature of the obtained mixture was then increased to 0°C, followed by stirring for 2 hours. Thereafter, a saturated ammonium chloride aqueous solution was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate. The organic layer was washed with a saturated sodium bicarbonate solution and a saturated sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and was then filtered. The filtrate was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate = 10 : 0 to 4 : 1), so as to obtain the above-captioned compound (3.7 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.53 (dd, 1H, J=8.2, 4.8 Hz), 1.76 (dd, J=7.2, 5.2 Hz), 1.90-2.10 (m, 1H), 3, 68 (dd, J=12.4, 9.6 Hz, 1H), 4.08 (dd, J=11.6, 9.6 Hz, 1H), 6.98-7.16 (m, 3H), 7.46-7.63 (m, 7H), 7.64-7.73 (m, 4H), 9.59 (s, 1H).

[0221]

(2) N-[(1S,2R)-2-(tert-butyldiphenylsilyloxymethyl)-1-(3-fluorophenyl)cyclopropylmethyl}-2,4-dimethylpyrimidin-5-amine (Prep 53-2)

Acetic acid (1.5 ml) was added to a chloroform solution (60 ml) of the compound Prep 53-1 (3.7 g) and the compound Prep 52-2 (1.37 g), and the obtained mixture was then stirred at a room temperature for 30 minutes. Thereafter, sodium triacetoxyborohydride (5.44 g) was added to the reaction solution, and the obtained mixture was then stirred for 15 hours. Thereafter, a saturated sodium bicarbonate aqueous solution was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate (× 2). The resultant extract was dried over anhydrous magnesium sulfate. The solvent was distilled away under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate = 9 : 1 to 0 : 10), so as to obtain the above-captioned compound (4.26 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.75 (t, J=5.2 Hz, 1H), 1.09-1.13 (m, 1H), 1.11 (s, 9H), 1.57 (m, 1H), 2.08 (s, 3H), 2.56 (s, 3H), 3, 32 (d, J=12.8 Hz, 1H), 3.50 (d, J=12.8 Hz, 1H), 3.59 (dd, J=11.6, 10.0 Hz, 1H), 4.16 (dd, J=11.6, 6.0 Hz, 1H), 6.90-6.96 (m, 1H), 7.04-7.08 (m, 1H), 7.13-7.16 (m, 1H), 7.25-7.47 (m, 7H), 7.63-7.69 (m, 4H),

7.79 (s, 1H).

[0222]

(3) N-{[(1S,2R)-2-(tert-butyldiphenylsilyloxymethyl)-1-(3-fluorophenyl)cyclopropylmethyl}-N,2,4-trimethylpyrimidin-5-amine (Prep 53-3)

Formaldehyde (1.59 ml) and sodium triacetoxyborohydride (3.71 g) were added to an acetonitrile solution (30 ml) of the compound Prep 53-2 (4.62 g), and the obtained mixture was then stirred for 1 hour. Thereafter, formaldehyde (1.59 ml) and sodium triacetoxyborohydride (3.71 g) were further added to the reaction solution, and the obtained mixture was then stirred for 30 minutes. Thereafter, a saturated sodium bicarbonate aqueous solution was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate (× 2). The resultant extract was dried over anhydrous magnesium sulfate. The solvent was distilled away under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate = 9 : 1 to 0 : 10), so as to obtain the above-captioned compound (4.26 g).

MS $[M+H]^+$=555

[0223]

(4) [(1R,2S)-2-{[(2,4-dimethylpyrimidin-5-yl)(methyl)amino]methyl}-2-(3-fluorophenyl)cyclopropyl]methanol (Prep 53-4)

Tetrabutylammonium fluoride (TCI-JP, 1 M THF solution: 17.5 ml) was added dropwise to a THF solution (30 ml) of the compound Prep 53-3 (3.23 g) at a room temperature, and the obtained mixture was then stirred at a room temperature for 17 hours. Thereafter, the reaction solution was concentrated under a reduced pressure, the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate = 1 : 1 to 0 : 10), so as to obtain the above-captioned compound (1.84 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.80 (t, J=5.2 Hz, 1H), 1.18 (dd, J=9.2, 5.2 Hz), 1.54-1.64 (m, 1H), 2.20 (s, 3H), 2.57 (s, 3H), 2.69 (s, 3H), 3, 35 (d, J=13.6 Hz, 1H), 3.47 (d, J=13.6 Hz, 1H), 3.60 (dd, J=11.6, 9.2 Hz, 1H), 4.03 (dd, J=11.6, 9.2 Hz, 1H), 6.82-6.87 (m, 1H), 6.92-6.96 (m, 1H), 7.01-7.04 (m, 1H), 7.13-7.19 (m, 1H), 8.10 (s, 1H).

[0224]

(5) [(1R,2S)-2-{[(2,4-dimethylpyrimidin-5-yl)(methyl)amino]methyl}-2-(3-fluorophenyl)cyclopropanecarbaldehyde (Prep 53-5)

A dichloromethane solution (40 ml) of oxalyl chloride (343 μl) was cooled to -78°C, and a dichloromethane solution (10 ml) of dimethyl sulfoxide (560 μl) was then added

dropwise thereto. Thirty minutes later, a dichloromethane solution (9.6 ml) of the compound Prep 53-4 (620 mg) was added dropwise to the reaction solution at -78°C, and the obtained mixture was then stirred at the same temperature as described above for 30 minutes. Thereafter, triethylamine (8.03 ml) was added to the reaction solution, and the obtained mixture was then stirred for 30 minutes. Thereafter, the temperature of the reaction solution was increased to 0°C, and the reaction solution was then stirred for 2 hours. Thereafter, a saturated sodium bicarbonate solution was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride. The organic layer was dried over anhydrous magnesium sulfate and was then filtered. The filtrate was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate = 2 : 3 to 0 : 10), so as to obtain the above-captioned compound (617 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.60-1.67 (m, 1H), 1.78 (t, J=5.6 Hz, 1H), 2.08 (s, 3H), 2, 26 (m, 1H), 2.58 (s, 3H), 2.66 (s, 3H), 3, 42 (d, J=14.0 Hz, 1H), 3.53 (d, J=14.0 Hz, 1H) 6.91-7.06 (m, 3H), 7.21-7.27 (m, 1H), 8.07 (s, 1H), 9.74 (d, J=4.0 Hz, 1H).

[0225]

(6) (1R,2S)-2-{[(2,4-dimethylpyrimidin-5-yl)(methyl)amino]methyl}-2-(3-fluorophenyl)cyclopropanecarboxylate (Prep 53-6)

2-Methyl-2-butene (1.08 ml), anhydrous sodium dihydrogen phosphate (731 mg) and sodium chlorite (367 mg) were added to an acetone-water solution (10 ml) of the compound Prep 53-5 (617 mg) at a room temperature, and the obtained mixture was then stirred for 2 hours. Thereafter, the reaction solution was extracted with ethyl acetate, and the organic layer was then washed with a saturated sodium chloride aqueous solution. The organic layer was dried over anhydrous magnesium sulfate and was then filtered. The filtrate was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate = 1 : 4 to ethyl acetate = 4 : 1), so as to obtain the above-captioned compound (632 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.60-1.63 (m, 2H), 2.03-2.08 (m, 1H), 2.08 (s, 3H), 2.60 (s, 3H), 2.66 (s, 3H), 3, 56 (d, J=12.8 Hz, 1H), 3.64 (d, J=12.8 Hz, 1H), 6.91-6.97 (m, 1H), 7.04-7.08 (m, 1H), 7.11-7.14 (m, 1H), 7.23-7.29 (m, 1H), 8.39 (s, 1H).

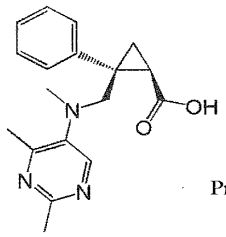
[0226]

Production Example 54

Synthesis of (1R,2S)-2-[(2,4-dimethoxypyrimidin-5-yl)(methyl)amino]methyl-2-phenylcyclopropanecarboxylate (Prep 54)

The above-captioned compound was synthesized in the same manner as that of Production Example 53.

[Formula 44]



Prep54

[0227]

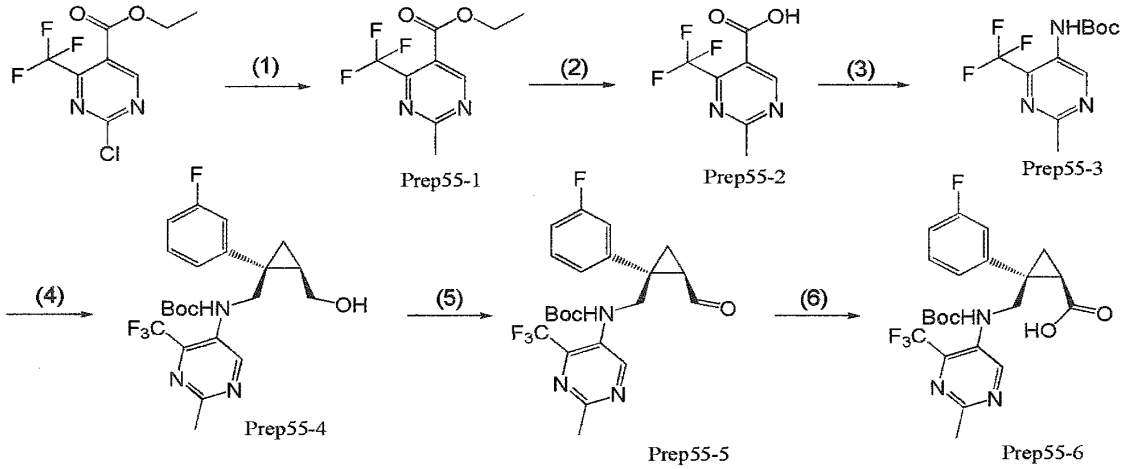
MS $[M+H]^+$=312

[0228]

Production Example 55

Synthesis of (1S,2R)-2-[(tert-butoxycarbonyl)(2-methyl-4-trifluoromethylpyrimidin-5-yl)amino]methyl-2-(3-fluorophenyl)cyclopentanecarboxylate (Prep 55-6)

[Formula 45]



Prep55-1 Prep55-2 Prep55-3 Prep55-4 Prep55-5 Prep55-6

[0229]

(1) Ethyl 2-methyl-4-trifluoromethylpyrimidinecarboxylate (Prep 55-1)

Ethyl 2-chloro-4-(trifluoromethyl)pyrimidin-5-carboxylate (9.7 g) was dissolved in THF (100 ml), and thereafter, trimethylaluminum (38.1 ml, 2 M) and tetrakis(triphenylphosphine)palladium(0) were added to the obtained solution. The obtained mixture was stirred at 70°C overnight. Thereafter, the reaction system was cooled to a room

temperature, and a saturated ammonium chloride aqueous solution and a 5 N hydrochloric acid aqueous solution were added dropwise to the reaction solution under cooling on ice. Thereafter, water was added to the reaction solution at a time point at which foaming was terminated, and liquid separation and extraction were then carried out with ethyl acetate. The organic layer was dried over magnesium sulfate, and the solvent was then concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, n-heptane : ethyl acetate = 19/1 → 2/1), so as to obtain the above-captioned compound (8.1 g).

MS $[M+H]^+$=235.

[0230]

(2) 2-Methyl-4-trifluoromethylpyrimidin-5-carboxylate (Prep 55-2)

A 2 N sodium hydroxide aqueous solution (26 ml) was added to a THF-ethanol solution (80 ml-20 ml) of the compound Prep 55-1 (8.1 g), and the obtained mixture was then stirred at a room temperature for 2 hours. Thereafter, termination of the reaction was confirmed by LC-MS, and a 1 N hydrochloric acid aqueous solution was then added to the reaction solution to neutralize it. Subsequently, the reaction solution was concentrated under a reduced pressure, and THF and ethanol were then distilled away. A 2 N hydrochloric acid aqueous solution was added to the residue to adjust the pH value thereof to pH 2 to 3, and liquid separation and extraction were then carried out with ethyl acetate. The organic layer was dried over magnesium sulfate. The solvent was concentrated under a reduced pressure, so as to obtain a crude product of the above-captioned compound (6.2 g).

MS $[M+H]^+$=207.

[0231]

(3) Tert-butyl(2-methyl-4-trifluoromethylpyrimidin-5-yl)carbamate (Prep 55-3)

Triethylamine (10.3 ml) and diphenylphosphoryl azide (9.55 ml) were added to a toluene-tert-butanol solution (50 ml-50 ml) of the compound Prep 55-2 (6.2 g). The obtained mixture was stirred at 100°C overnight. Thereafter, the reaction system was cooled, and water was then added thereto, followed by vacuum concentration. A saturated sodium bicarbonate aqueous solution was added to the residue, and liquid separation and extraction were then carried out with ethyl acetate. The obtained organic layer was dried over magnesium sulfate and was then concentrated under a reduced pressure. The obtained residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, n-heptane : ethyl acetate = 19 : 1 → 3 : 1), so as to obtain the above-captioned compound (8.0 g).

MS $[M+H]^+$=278.

[0232]

(4) Tert-butyl{[(1S,2R)-1-(3-fluorophenyl)-2-hydroxymethylcyclopropyl]methyl}(2-methyl-4-trifluoromethylpyrimidin-5-yl)carbamate (Prep 55-4)

Triethylamine (322 μl) and methanesulfonyl chloride (171 μl) were added to a dichloromethane solution (6.0 ml) of the compound Prep 14-3 (500 mg) under cooling on ice, and the obtained mixture was then stirred at a room temperature for 1 hour. Thereafter, water was added to the reaction system, and liquid separation and extraction were then carried out with dichloromethane. The obtained organic layer was dried over magnesium sulfate and was then concentrated under a reduced pressure, so as to obtain a crude product. Thereafter, cesium carbonate and the compound Prep 55-3 (699 mg) were added to an acetonitrile solution (10 ml) of the crude product, and the obtained mixture was then stirred at 80°C overnight. Thereafter, the reaction system was cooled, and water was then added thereto. Subsequently, liquid separation and extraction were carried out with ethyl acetate. The obtained organic layer was dried over magnesium sulfate and was then concentrated under a reduced pressure. The obtained residue was dissolved in methanol (5 ml), and a 1 N sodium hydroxide aqueous solution (1.26 ml) was then added to the solution, followed by stirring at a room temperature for 30 minutes. Thereafter, water was added to the reaction system, and liquid separation and extraction were then carried out with ethyl acetate. The obtained organic layer was dried over magnesium sulfate and was then concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, elution solvent: n-heptane : ethyl acetate = 19 : 1 → 1 : 1), so as to obtain the above-captioned compound (200 mg).

MS $[M+Na]^+$=478.

[0233]

(5) Tert-butyl{[(1S,2R)-1-(3-fluorophenyl)-2-formylcyclopropyl]methyl}(2-methyl-4-trifluoromethylpyrimidin-5-yl)carbamate (Prep 55-5)

A Dess-Martin reagent was added to a dichloromethane solution (5 ml) of the compound Prep 55-4 (200 mg) under cooling on ice. The obtained mixture was stirred for 1 hour, and a mixed solution of a sodium bicarbonate aqueous solution and Na_2SO_3 was then added to the reaction system. The obtained mixture was stirred until it became transparent. The reaction system was subjected to liquid separation and extraction with dichloromethane. The obtained organic layer was dried over magnesium sulfate and was then concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (YAMAZEN,

Hi-Flush™ column, elution solvent: n-heptane : ethyl acetate = 4 : 1 → 1 : 1), so as to obtain the above-captioned compound (180 mg).

MS $[M+Na]^+$=476.

[0234]

(6) (1S,2R)-2-[(tert-butoxycarbonyl)(2-methyl-4-trifluoromethylpyrimidin-5-yl)amino]methyl-2-(3-fluorophenyl)cyclopropanecarboxylate (Prep 55-6)

2-Methyl-2-butene (210 μl), sodium dihydrogen phosphate (57.2 mg) and sodium chlorite (53.9 mg) were added to an acetone-water mixed solvent (4 ml-2 ml) of the compound Prep 55-5 (180 mg). The obtained mixture was stirred at a room temperature for 1 hour. Thereafter, water was added to the reaction solution, and liquid separation and extraction were then carried out with dichloromethane. The obtained organic layer was dried over magnesium sulfate. The organic layer was dried over anhydrous magnesium sulfate and was then filtered. The filtrate was concentrated under a reduced pressure, so as to obtain a crude product of the above-captioned compound (186 mg).

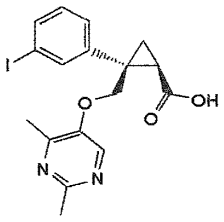
MS $[M+Na]^+$=492.

[0235]

The compound of Production Example 56 (Prep 56) was produced according to the method of Production Example 13. However, an alcohol body corresponding to Prep 13-5 was synthesized from a diol corresponding to Prep 13-2 according to the method of Production Example 49.

[0236]

[Table 8]

Production example	Structural formula	NMR (400MHz, $CDCl_3$) and/or MS
Prep 56		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.52-1.59 (m, 1H), 1.73-1.78 (m, 1H), 2.22-2.27 (m, 1H), 2.37 (s, 3H), 2.58 (s, 3H), 4.47 (s, 2H), 7.11 (t, J=7.8 Hz, 1H), 7.43-7.48 (m, 1H), 7.62-7.67 (m, 1H), 7.89 (t, J=1.6 Hz, 1H), 8.22 (s, 1H) MS $[M+H]^+$=425

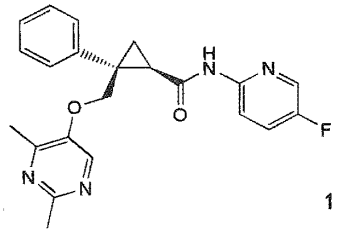
[0237]

Example 1

Synthesis of (1R,2S)-N-(5-fluoropyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-

phenylcyclopropanecarboxamide (1)

[Formula 46]



1

[0238]

The carboxylic acid Prep 13-7 (639 mg) was dissolved in dichloromethane (10 ml), and thereafter, oxalyl chloride (367 μl) and DMF (a catalytic amount) were added to the solution. The reaction solution was stirred at a room temperature for 1 hour. Thereafter, the reaction solution was concentrated under a reduced pressure to obtain a crude acid chloride. Subsequently, diisopropylethylamine (848 μl) was added to a THF solution (10.0 ml) of 2-amino-5-fluoropyridine (360 mg), and the temperature of the obtained mixture was then increased to 60°C. A THF solution (5.0 ml) of the crude acid chloride was added dropwise to the reaction solution, and the obtained mixture was then stirred at the same temperature as described above for 1 hour. Thereafter, the reaction system was cooled to a room temperature, and it was then stirred for 1 hour. Thereafter, the reaction solution was concentrated under a reduced pressure, and it was then distributed to ethyl acetate and water, so as to separate an organic layer. The organic layer was dried over anhydrous magnesium sulfate, and the filtrate was then concentrated under a reduced pressure. The residue was purified by NH-silica gel column chromatography (YAMAZEN, Hi-Flush™ column, elution solvent: n-heptane : ethyl acetate = 19 : 1 → 3 : 2). Then, diethyl ether was added to the obtained product of interest. The precipitated solid was collected by filtration and was then dried, so as to obtain the above-captioned compound (418 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.60-1.64 (m, 1H), 1.90 (t, J=5.2 Hz, 1H), 2.12 (brdt, 1H), 2.20 (s, 3H), 2.54 (s, 3H), 4.40 (d, J=9.2 Hz, 1H), 4.51 (d, J=9.2 Hz, 1H), 7.26-7.47 (m, 6H), 7.96 (s, 1H), 8, 06-8.12 (m, 2H), 8.33 (brds, 1H).

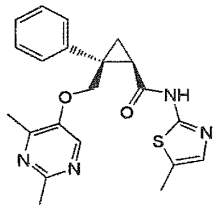
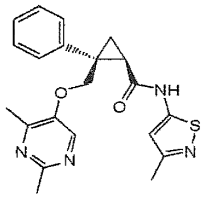
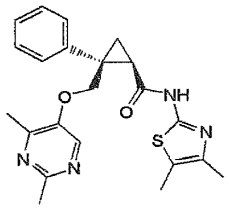
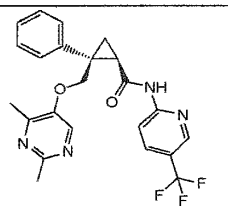
MS $[M+H]^+$=393

[0239]

* The compounds of Examples 2 to 45 were synthesized by reacting the carboxylic acid Prep 13-7 with any amine by the same method as that of Example 1.

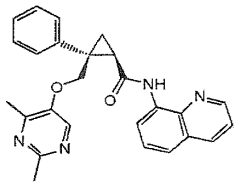
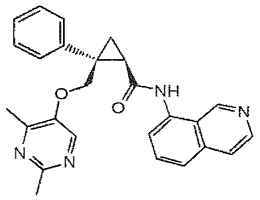
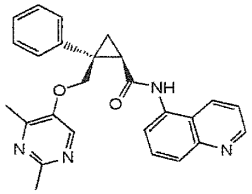
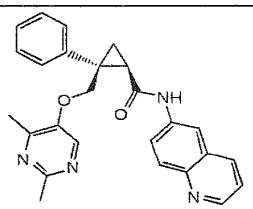
[240]

[Table 9]

Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
2		^{1}H-NMR δ (ppm): 1.78 (dd, J=5.6, 8.0 Hz, 1H), 2.01 (t, J=5.6 Hz, 1H), 2.17 (s, 3H), 2.18 (s, 3H), 2.25 (brt, 1H), 2.57 (s, 3H), 4.44 (d, J=9.6 Hz, 1H), 4.63 (d, J=9.6 Hz, 1H), 6.46 (brs, 1H), 7.32-7.41 (m, 3H), 7.44-7.47 (m, 2H), 8.02 (s, 1H). MS $[M+H]^+$=395
3		^{1}H-NMR δ (ppm): 1.72 (dd, J=5.6, 8.0 Hz, 1H), 1.98 (t, J=5.6 Hz, 1H), 2.16 (dd, J=5.6, 8.0 Hz, 1H), 2.20 (s, 3H), 2.41 (s, 3H), 2.56 (s, 3H), 4.43 (d, J=9.6 Hz, 1H), 4.52 (d, J=9.6 Hz, 1H), 6.59 (s, 1H), 7.30-7.38 (m, 3H), 7.42-7.45 (m, 2H), 7.98 (s, 1H), 8.91 (brs, 1H). MS $[M+H]^+$=395
4		^{1}H-NMR δ (ppm): 1.66 (dd, J=5.6, 8.0 Hz, 1H), 1.94 (t, J=5.6 Hz, 1H), 2.09 (dd, J=5.6, 8.0 Hz, 1H), 2.15 (brs, 3H), 2.21 (s, 3H), 2.23 (s, 3H), 2.55 (s, 3H), 4.40 (d, J=9.6 Hz, 1H), 4.50 (d, J=9.6 Hz, 1H), 7.29-7.42 (m, 5H), 7.97 (s, 1H). MS $[M+H]^+$=409
5		^{1}H-NMR δ (ppm): 1.67 (dd, J=5.6, 8.0 Hz, 1H), 1.94 (t, J=5.6 Hz, 1H), 2.16 (dd, J=5.6, 8.0 Hz, 1H), 2.22 (s, 3H), 2.55 (s, 3H), 4.41 (d, J=9.6 Hz, 1H), 4.51 (d, J=9.6 Hz, 1H), 7.36-7.40 (m, 3H), 7.46-7.48 (m, 2H), 7.88 (dd, J=2.4, 8.6 Hz, 1H), 7.97 (s, 1H), 8.21 (d, J=8.6 Hz, 1H), 8.41 (brs, 1H), 8.54-8.55 (m, 1H). MS $[M+H]^+$=443

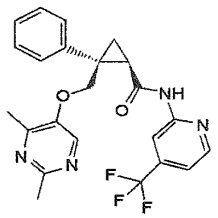
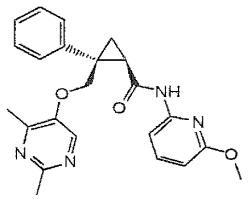
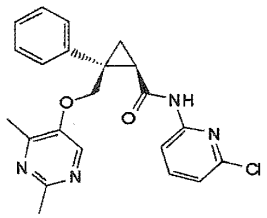
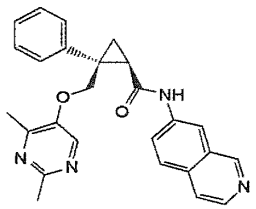
[0241]

[Table 10]

Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
6		^{1}H-NMR (δ (ppm): 1.66 (dd, J=5.0, 8.2 Hz, 1H), 1.97 (dd, J=5.0, 5.8 Hz, 1H), 2.08 (s, 3H), 2.40 (dd, J=5.8, 8.2 Hz, 1H), 2.51 (s, 3H), 4.51 (d, J=9.6 Hz, 1H), 4.59 (d, J=9.6 Hz, 1H), 7.29-7.34 (m, 1H), 7.37-7.42 (m, 2H), 7.47-7.55 (m, 5H), 7.99 (s, 1H), 8.18 (dd, J=1.8, 8.2 Hz, 1H), 8.62 (dd, J=2.6, 6.2 Hz, 1H), 8.84 (dd, J=1.8, 4.2 Hz, 1H), 10.21 (brs, 1H). MS $[M+Na]^+$=447
7		MS $[M+H]^+$=425
8		^{1}H-NMR (δ (ppm): 1.67 (dd, J=5.6, 8.0 Hz, 1H), 1.96 (t, J=5.6 Hz, 1H), 2.15 (dd, J=5.6, 8.0 Hz, 1H), 2.21 (s, 3H), 2.53 (s, 3H), 4.52 (d, J=9.6 Hz, 1H), 4.59 (d, J=9.6 Hz, 1H), 7.29-7.40 (m, 4H), 7.47-7.49 (m, 2H), 7.54 (dd, J=2.4, 8.8 Hz, 1H), 7.90 (brs, 1H), 8.02-8.08 (m, 3H), 8.27 (d, J=1.8 Hz, 1H), 8.83 (dd, J=1.8, 4.0 Hz, 1H). MS $[M+Na]^+$=447
9		MS $[M+H]^+$=425

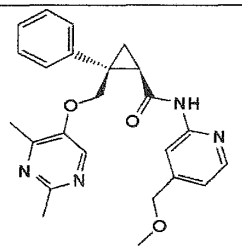
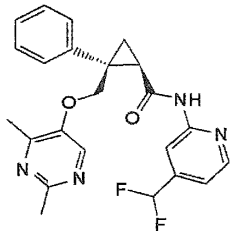
[0242]

[Table 11]

Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
10		^{1}H-NMR δ (ppm): 1.66 (dd, J=5.6, 8.0 Hz, 1H), 1.93 (t, J=5.6 Hz, 1H), 2.15 (dd, J=5.6, 8.0 Hz, 1H), 2.20 (s, 3H), 2.54 (s, 3H), 4.42 (d, J=9.6 Hz, 1H), 4.51 (d, J=9.6 Hz, 1H), 7.24-7.39 (m, 4H), 7.45-7.48 (m, 2H), 7.97 (s, 1H), 8.36 (brs, 1H), 8.43-8.44 (m, 2H).
11		^{1}H-NMR δ (ppm): 1.63 (dd, J=5.6, 8.0 Hz, 1H), 1.91 (t, J=5.6 Hz, 1H), 2.11-2.15 (m, 1H), 2.23 (s, 3H), 2.56 (s, 3H), 3.87 (s, 3H), 4.43 (d, J=9.6 Hz, 1H), 4.55 (d, J=9.6 Hz, 1H), 6.48 (d, J=8.8 Hz, 1H), 7.28-7.39 (m, 3H), 7.46-7.56 (m, 4H), 7.98-8.00 (m, 2H). MS $[M+H]^+$=405
12		^{1}H-NMR δ (ppm): 1.62 (dd, J=5.2, 8.0 Hz, 1H), 1.91 (t, J=5.2 Hz, 1H), 2.09 (brt, 1H), 2.22 (s, 3H), 2.55 (s, 3H), 4.38 (d, J=9.4 Hz, 1H), 4.47 (d, J=9.4 Hz, 1H), 7.06 (d, J=8.0 Hz, 1H), 7.30-7.38 (m, 3H), 7.45-7.46 (m, 2H), 7.62 (t, J=8.0 Hz, 1H), 7.95 (s, 1H), 7.99 (d, J=8.0 Hz, 1H), 8.25 (brs, 1H). MS $[M+H]^+$=409
13		^{1}H-NMR δ (ppm): 1.65 (t, J=6.0 Hz, 1H), 1.95 (t, J=6.0 Hz, 1H), 2.16 (t, J=6.0 Hz, 1H), 2.21 (s, 3H), 2.52 (s, 3H), 4.50 (d, J=9.4 Hz, 1H), 4.58 (d, J=9.4 Hz, 1H), 7.28-7.36 (m, 3H), 7.44-7.46 (m, 2H), 7.58 (d, J=5.8 Hz, 1H), 7.64-7.66 (m, 1H), 7.76 (d, J=8.8 Hz, 1H), 8.01 (s, 1H), 8.27 (brs, 1H), 8.45 (d, J=5.8 Hz, 1H), 9.14 (brs, 1H). MS $[M+H]^+$=425

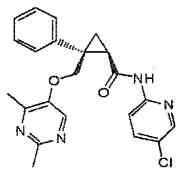
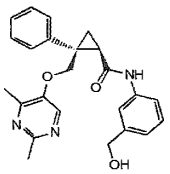
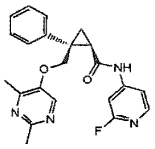
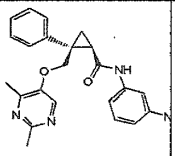
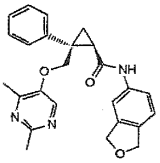
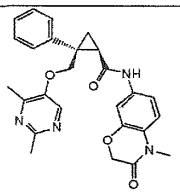
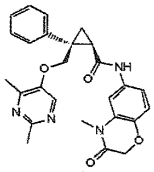
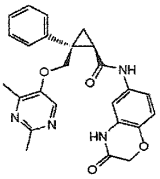
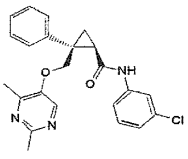
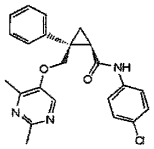
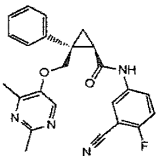
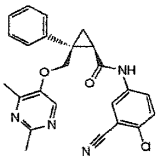
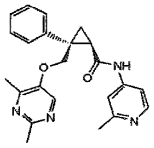
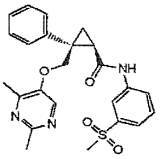
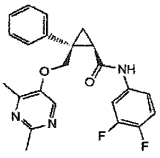
[0243]

[Table 12]

Example	Structural formula	NMR (400MHz, $CDCl_3$) and/or MS
14		^{1}H-NMR δ (ppm): 1.62 (dd, J=5.2, 8.0 Hz, 1H), 1.91 (t, J=5.2 Hz, 1H), 2.12-2.15 (m, 1H), 2.20 (s, 3H), 2.54 (s, 3H), 3.39 (s, 3H), 4.41-4.43 (m, 3H), 4.51 (d, J=9.2 Hz, 1H), 7.03-7.04 (m, 1H), 7.27-7.38 (m, 3H), 7.44-7.47 (m, 2H), 7.97 (s, 1H), 8.00 (brs, 1H), 8.22 (d, J=5.2 Hz, 1H), 8.48 (brs, 1H). MS $[M+H]^+$=419
15		^{1}H-NMR δ (ppm): 1.64 (dd, J=5.6, 8.0 Hz, 1H), 1.92 (t, J=5.6 Hz, 1H), 2.15 (dd, J=5.6, 8.0 Hz, 1H), 2.20 (s, 3H), 2.54 (s, 3H), 4.41 (d, J=9.6 Hz, 1H), 4.50 (d, J=9.6 Hz, 1H), 6.56 (t, J=56.0 Hz, 1H), 7.18-7.39 (m, 4H), 7.46-7.48 (m, 2H), 7.96 (s, 1H), 8.21 (brs, 1H), 8.38-8.40 (m, 1H). MS $[M+H]^+$=425

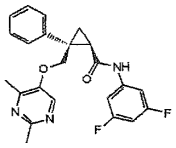
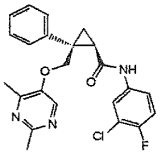
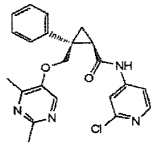
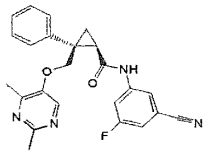
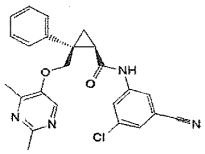
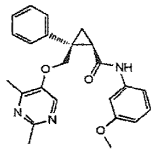
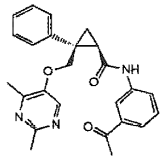
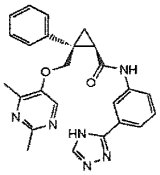
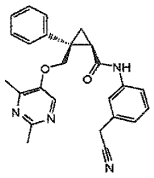
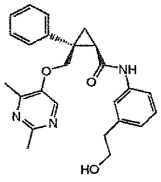
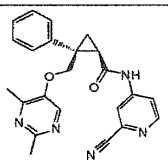
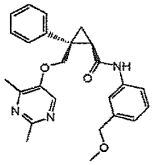
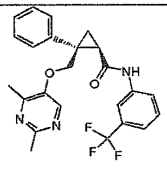
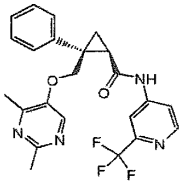
[0244]

[Table 13]

Example	Structural formula, MS	Example	Structural formula, MS	Example	Structural formula, MS
16	 MS $[M+H]^+$= 409	17	 MS $[M+H]^+$= 404	18	 MS $[M+H]^+$= 393
19	 MS $[M+H]^+$= 417	20	 MS $[M+H]^+$= 416	21	 MS $[M+H]^+$= 459
22	 MS $[M+H]^+$= 459	23	 MS $[M+H]^+$= 445	24	 MS $[M+H]^+$= 408
25	 MS $[M+H]^+$ =408	26	 MS $[M+H]^+$= 417	27	 MS $[M+H]^+$= 433
E28	 MS $[M+H]^+$=389	29	 MS $[M+H]^+$=452	30	 MS $[M+H]^+$=410

[0245]

[Table 14]

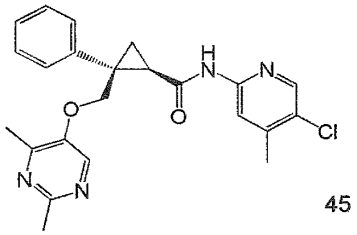
Example	Structural formula, MS	Example	Structural formula, MS	Example	Structural formula, MS
31	 MS $[M+H]^+$= 410	32	 MS $[M+H]^+$= 426	33	 MS $[M+H]^+$= 409
34	 MS $[M+H]^+$= 417	35	 MS $[M+H]^+$= 433	36	 MS $[M+H]^+$= 404
37	 MS $[M+H]^+$= 416	38	 MS $[M+H]^+$= 441	39	 MS $[M+H]^+$= 413
40	 MS $[M+H]^+$= 418	41	 MS $[M+H]^+$= 400	42	 MS $[M+H]^+$= 418
43	 MS $[M+H]^+$= 442	44	 MS $[M+H]^+$= 443		

[0246]

Example 45

Synthesis of (1R,2S)-N-(5-chloro-4-methylpyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide (45)

[Formula 47]



45

[0247]

The carboxylic acid Prep 13-7 (500 mg) was dissolved in dichloromethane(5 ml), and oxalyl chloride (288 μl) and DMF (several droplets) were then added to the obtained solution. The obtained mixture was stirred at a room temperature for 2 hours. Thereafter, the reaction solution was concentrated under a reduced pressure, so as to obtain a crude acid chloride. Thereafter, N,N-diisopropylethylamine (664 μl) was added to a 1,4-dioxane solution (4.5 ml) of 2-amino-5-chloro-4-methylpyridine (359 mg), and the temperature of the obtained mixture was then increased to 125°C. A 1,4-dioxane solution (3 ml) of the crude acid chloride was added dropwise to the reaction solution, and while maintaining the temperature, the obtained mixture was stirred for 1 hour. The reaction system was cooled to a room temperature, and the reaction solution was then stirred for 12 hours. Thereafter, several droplets of water were added to the reaction solution, followed by concentration under a reduced pressure. The residue was purified by NH-silica gel column chromatography (YAMAZEN, Hi-Flush™ column, Size: M + L, n-heptane : ethyl acetate). The obtained product of interest was washed with ether, was collected by filtration, and was then dried, so as to obtain the above-captioned compound (95.5 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.54-1.68 (m, 1H), 1.90 (t, J=5.6 Hz, 1H), 2.07-2.16 (m, 1H), 2.21 (s, 3H), 2.35 (s, 3H), 2.55 (s, 3H), 4.40 (d, J=9.6 Hz, 1H), 4.51 (d, J=9.6 Hz, 1H), 7.20-7.50 (m, 5H), 7.97 (s, 1H), 7.98 (s, 1H), 8.16 (s, 1H), 8.27 (s, 1H).

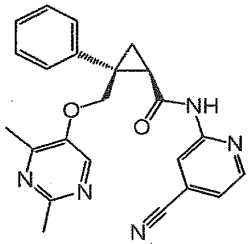
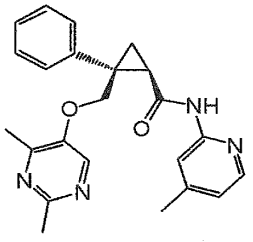
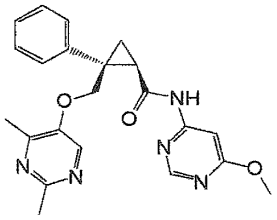
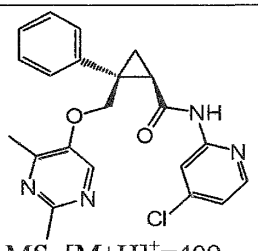
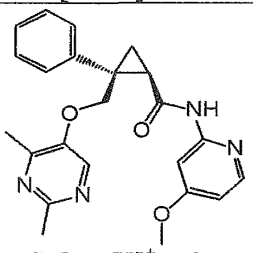
MS $[M+H]^+$=423

[0248]

* The compounds of Examples 46 to 50 were synthesized by reacting the carboxylic acid Prep 13-7 with any amine by the same method as that of Example 45. Purification was carried out by LC-MS.

[0249]

[Table 15]

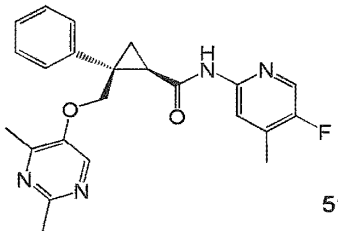
Example	Structural formula, MS	Example	Structural formula, MS	Example	Structural formula, MS
46	 MS $[M+H]^+$=400	47	 MS $[M+H]^+$=389	48	 MS $[M+H]^+$=406
49	 MS $[M+H]^+$=409	50	 MS $[M+H]^+$=405		

[0250]

Example 51

Synthesis of (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)-2-phenylcyclopropanecarboxamide (51)

[Formula 48]



51

[0251]

The carboxylic acid Prep 13-7 (2.86 g) was dissolved in N,N-dimethylformamide (57 ml), and 2-amino-5-fluoro-4-picoline (1.45 g) and N,N-diisopropylethylamine (2 ml) were then added to this solution. Thereafter, HATU (4.38 g) was added to the mixed solution under cooling on ice. The mixed solution was stirred in a nitrogen atmosphere at a room temperature for 3 hours. Thereafter, 2-amino-5-fluoro-4-picoline (242 mg) was added to the reaction solution, and the obtained mixture was further stirred for 15 hours. Thereafter, 2-amino-5-

fluoro-4-picoline (300 mg) was added to the reaction solution, and the obtained mixture was further stirred for 24.5 hours. Subsequently, water was added to the reaction solution, and the mixture was then extracted with ethyl acetate (× 3). The organic layer was washed with a saturated saline, and was then dried over anhydrous magnesium sulfate. The filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography {YAMAZEN, Hi-Flush™ column, Size: L (NH-inject column) + 3L, n-heptane : ethyl acetate}. The obtained product of interest was dissolved in ethyl acetate (2 ml) and hexane (24 ml) at 60°C, and while gradually cooling the obtained mixture to a room temperature, it was left overnight. Thereafter, the precipitated solid was collected by filtration and was then dried, so as to obtain the above-captioned compound (2.4 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.56-1.66 (m, 1H), 1.90 (t, J=4.8 Hz, 1H), 2.10 (dd, J=6.0, 8.0 Hz, 1H), 2.21 (s, 3H), 2.24-2.30 (m, 3H), 2.55 (s, 3H), 4.41 (d, J=9.6 Hz, 1H), 4.51 (d, J=9.6 Hz, 1H), 7.20-7.54 (m, 5H), 7.90-8.04 (m, 3H), 8.25 (s, 1H).

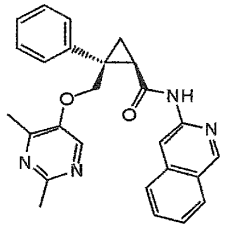
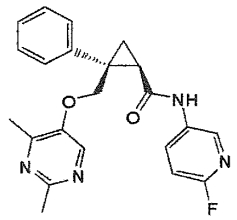
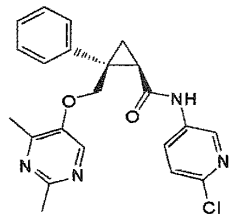
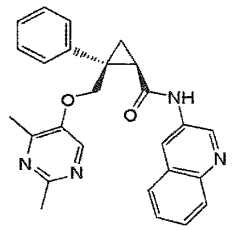
MS $[M+H]^+$=407

[0252]

* The compounds of Examples 52 to 72 were synthesized by reacting the carboxylic acid Prep 13-7 with any amine by the same method as that of Example 51.

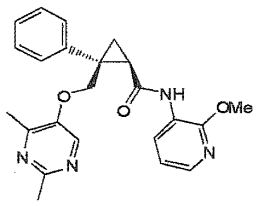
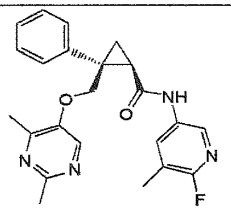
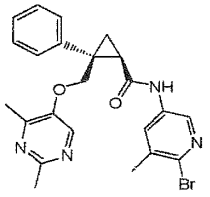
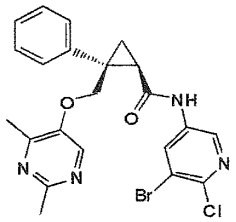
[0253]

[Table 16]

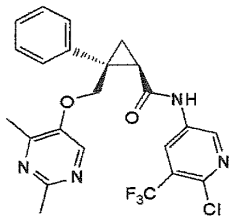
Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
52		^{1}H-NMR δ (ppm): 1.61 (dd, J=8.0, 4.8 Hz), 1.95 (t, J=5.2 Hz, 1H), 2.19-2.25 (m, 1H), 2.21 (s, 3H), 2.52 (s, 3H), 4.45 (d, J=9.6 Hz, 1H), 4.53 (d, J=9.6 Hz, 1H), 7.25-7.70 (m, 6H), 7.62-7.67 (m, 1H), 7.5-7.81 (m, 1H), 7.82-7.94 (m, 1H), 7.99 (s, 1H), 8.11-8.13 (m, 1H), 8.22-8.27 (m, 1H), 8.89-8.04 (brs, 1H).
53		^{1}H-NMR δ(ppm): 1.64 (dd, J=8.0, 5.2 Hz, 1H), 1.91 (t, J=5.2 Hz, 1H), 2.12 (dd, J=8.0, 6.0 Hz, 1H), 2.24 (s, 3H), 2.56 (s, 3H), 4.47 (d, J=9.6 Hz, 1H), 4.53 (d, J=9.6 Hz, 1H), 6.89 (dd, J=9.2, 2.8 Hz, 1H), 7.29 (t, J=7.2 Hz, 1H), 7.35 (t, J=7.2 Hz, 2H), 7.44 (d, J=7.2 Hz, 2H), 7.93 (brs, 1H), 7.99 (s, 1H), 8.12-8.17 (m, 2H).
54		^{1}H-NMR δ (ppm): 1.64 (dd, J=8.4, 5.2 Hz, 1H), 1.91 (t, J=5.2 Hz, 1H), 2.12 (dd, J=8.4, 6.0 Hz, 1H), 2.23 (s, 3H), 2.56 (s, 3H), 4.46 (d, J=9.6 Hz, 1H), 4.53 (d, J=9.6 Hz, 1H), 7.26 (t, J=8.8 Hz, 1H), 7.29 (t, J=7.2 Hz, 1H), 7.34 (d, J=7.2 Hz, 2H), 7.43 (d, J=7.2 Hz, 2H), 7.99 (s, 1H), 8.10 (dd ,J=8.8, 2.8 Hz, 1H), 8.11 (brs, 1H), 8.34 (d, J=2.8 Hz, 1H).
55		^{1}H-NMR δ (ppm): 1.67 (dd, J=8.0, 5.2 Hz, 1H), 1.96 (t, J=5.2 Hz, 1H), 2.19 (dd, J=8.0, 5.6 Hz, 1H), 2.20 (s, 3H), 2.52 (s, 3H), 4.52 (d, J=9.6 Hz, 1H), 4.58 (d, J=9.6 Hz, 1H), 7.29 (t, J=7.2 Hz, 1H), 7.36 (t, J=7.2 Hz, 2H), 7.47 (d, J=7.2 Hz, 2H), 7.53 (t, J=8.0 Hz, 1H), 7.63 (t, J=8.0 Hz, 1H), 7.75 (d, J=8.0 Hz, 1H), 8.02 (s, 1H), 8.04 (d, J=8.0 Hz, 1H), 8.17 (brs, 1H), 8.69 (d, J=2.0 Hz, 1H), 8.75 (d, J=2.0 Hz, 1H).

[0254]

[Table 17-1]

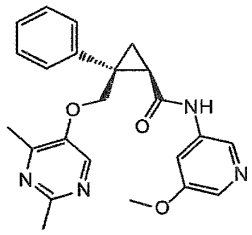
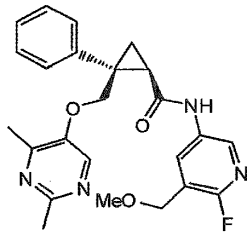
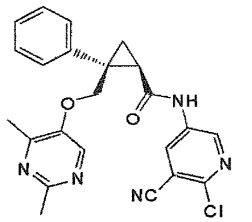
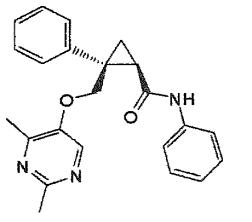
Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
56		^{1}H-NMR δ (ppm): 1.63 (dd, J=8.0, 5.2 Hz, 1H), 1.90 (t, J=5.2 Hz, 1H), 2.15 (dd, J=8.0, 5.6 Hz, 1H), 2.21 (s, 3H), 2.55 (s, 3H), 4.04 (s, 3H), 4.46 (d, J=9.2 Hz, 1H), 4.55 (d, J=9.2 Hz, 1H), 6.85 (dd, J=7.6, 4.8 Hz, 1H), 7.30 (t, J=7.6 Hz, 1H), 7.38 (t, J=7.6 Hz, 2H), 7.47 (d, J=7.6 Hz, 2H), 7.85 (d, J=4.8 Hz, 1H), 7.99 (s, 1H), 8.01 (brs, 1H), 8.43 (d, J=7.6 Hz, 1H).
57		^{1}H-NMR δ (ppm): 1.65 (dd, J=8.0, 5.2 Hz, 1H), 1.90 (t, J=5.2 Hz, 1H), 2.09 (dd, J=8.0, 6.0 Hz, 1H), 2.25 (s, 6H), 2.57 (s, 3H), 4.47 (d, J=9.6 Hz, 1H), 4.53 (d, J=9.6 Hz, 1H), 7.30 (t, J=7.2 Hz, 1H), 7.36 (t, J=7.2 Hz, 2H), 7.45 (d, J=7.2 Hz, 2H), 7.74 (brs, 1H), 7.93 (s, 1H), 7.97-7.99 (m, 2H).
58		^{1}H-NMR δ (ppm): 1.64 (dd, J=8.0, 5.2 Hz, 1H), 1.90 (t, J=5.2 Hz, 1H), 2.11 (dd, J=8.0, 5.6 Hz, 1H), 2.23 (s, 3H), 2.34 (s, 3H), 2.56 (s, 3H), 4.46 (d, J=9.6 Hz, 1H), 4.53 (d, J=9.6 Hz, 1H), 7.28 (t, J=7.2 Hz, 1H), 7.34 (t, J=7.2 Hz, 2H), 7.43 (d, J=7.2 Hz, 2H), 7.93-8.00 (m, 3H), 8.14 (d, J=2.8 Hz, 1H).
59		^{1}H-NMR δ (ppm): 1.66 (dd, J=8.0, 5.2 Hz, 1H), 1.91 (t, J=5.2 Hz, 1H), 2.10 (dd, J=8.0, 5.6 Hz, 1H), 2.24 (s, 3H), 2.57 (s, 3H), 4.45 (d, J=9.6 Hz, 1H), 4.52 (d, J=9.6 Hz, 1H), 7.29 (t, J=7.2 Hz, 1H), 7.35 (t, J=7.2 Hz, 2H), 7.42 (d, J=7.2 Hz, 2H), 7.99 (s, 1H), 8.04 (brs, 1H), 8.30 (d, J=2.4 Hz, 1H), 8.47 (d, J=2.4 Hz, 1H).

[Table 17-2]

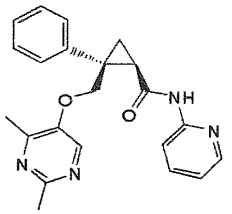
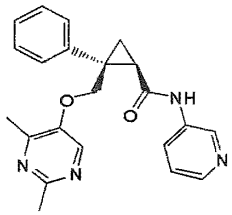
60		^{1}H-NMR δ (ppm): 1.68 (dd, J=8.0, 5.2 Hz, 1H), 1.93 (t, J=5.2 Hz, 1H), 2.12 (dd, J=8.0, 5.6 Hz, 1H), 2.24 (s, 3H), 2.56 (s, 3H), 4.46 (d, J=9.6 Hz, 1H), 4.52 (d, J=9.6 Hz, 1H), 7.30 (t, J=7.2 Hz, 1H), 7.36 (t, J=7.2 Hz, 2H), 7.44 (d, J=7.2 Hz, 2H), 7.99 (s, 1H), 8.01 (brs, 1H), 8.46 (d, J=2.8 Hz, 1H), 8.57 (d, J=2.8 Hz, 1H).

[0255]

[Table 18-1]

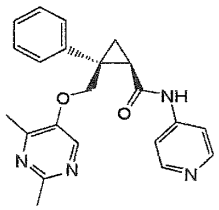
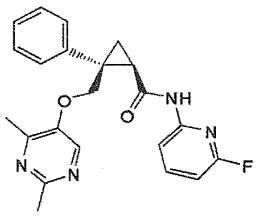
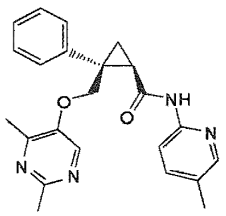
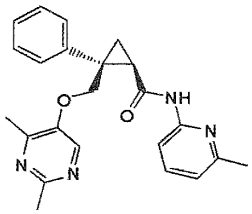
Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
61		^{1}H-NMR δ (ppm): 1.64 (dd, J=8.0, 5.2 Hz, 1H), 1.91 (t, J=5.2 Hz, 1H), 2.14 (dd, J=8.0, 6.0 Hz, 1H), 2.23 (s, 3H), 2.56 (s, 3H), 3.79 (s, 3H), 4.47 (d, J=9.6 Hz, 1H), 4.54 (d, J=9.6 Hz, 1H), 7.29 (t, J=7.6 Hz, 1H), 7.34 (t, J=7.6 Hz, 2H), 7.45 (d, J=7.6 Hz, 2H), 7.85 (brs, 1H), 8.00 (s, 1H), 8.04-8.07 (m, 3H).
62		^{1}H-NMR δ (ppm): 1.65 (dd, J=8.0, 5.2 Hz, 1H), 1.91 (t, J=5.2 Hz, 1H), 2.09 (dd, J=8.0, 5.6 Hz, 1H), 2.25 (s, 3H), 2.56 (s, 3H), 3.42 (s, 3H), 4.46 (s, 2H), 4.47 (d, J=9.6 Hz, 1H), 4.52 (d, J=9.6 Hz, 1H), 7.30 (t, J=7.2 Hz, 1H), 7.36 (t, J=7.2 Hz, 2H), 7.45 (d, J=7.2 Hz, 2H), 7.65 (brs, 1H), 7.99 (s, 1H), 8.11 (dd, J=8.4, 2.8 Hz, 1H), 8.15 (d, J=2.8 Hz, 1H).
63		^{1}H-NMR δ (ppm): 1.70 (dd, J=8.0, 5.2 Hz, 1H), 1.94 (t, J=5.2 Hz, 1H), 2.11 (dd, J=8.0, 5.6 Hz, 1H), 2.23 (s, 3H), 2.57 (s, 3H), 4.45 (d, J=9.2 Hz, 1H), 4.51 (d, J=9.2 Hz, 1H), 7.31 (t, J=7.2 Hz, 1H), 7.36 (t, J=7.2 Hz, 2H), 7.44 (d, J=7.2 Hz, 2H), 7.93 (brs, 1H), 7.99 (s, 1H), 8.52 (d, J=2.8 Hz, 1H), 8.55 (d, J=2.8 Hz, 1H).
64		^{1}H-NMR δ (ppm): 1.60 (dd, J=5.6, 8.0 Hz, 1H), 1.90 (t, J=5.6 Hz, 1H), 2.06 (dd, J=5.6, 8.0 Hz, 1H), 2.23 (s, 3H), 2.55 (s, 3H), 4.47 (d, J=9.4 Hz, 1H), 4.54 (d, J=9.4 Hz, 1H), 7.08-7.12 (m, 1H), 7.28-7.37 (m, 5H), 7.43-7.46 (m, 4H), 7.58 (brs, 1H), 7.99 (s, 1H). MS $[M+H]^+$=374

[Table 18-2]

65		^{1}H-NMR δ (ppm): 1.62 (dd, J=5.2, 8.0 Hz, 1H), 1.92 (t, J=5.2 Hz, 1H), 2.15 (brt, 1H), 2.19 (s, 3H), 2.55 (s, 3H), 4.43 (d, J=9.6 Hz, 1H), 4.54 (d, J=9.6 Hz, 1H), 6.94-6.98 (m, 1H), 7.27-7.38 (m, 3H), 7.44-7.46 (m, 2H), 7.99 (s, 1H), 8.04 (brd, 1H), 8.20 (brs, 1H), 8.81-8.93 (m, 1H). MS $[M+H]^+$=375
66		^{1}H-NMR δ (ppm): 1.62 (dd, J=5.6, 8.0 Hz, 1H), 1.91 (t, J=5.6 Hz, 1H), 2.14 (dd, J=5.6, 8.0 Hz, 1H), 2.22 (s, 3H), 2.55 (s, 3H), 4.48 (d, J=9.6 Hz, 1H), 4.54 (d, J=9.6 Hz, 1H), 7.21-7.43 (m, 6H), 7.99 (s, 1H), 8.12 (brd, 1H), 8.22-8.45 (m, 2H), 8.52 (d, J=2.0 Hz, 1H). MS $[M+H]^+$=375.

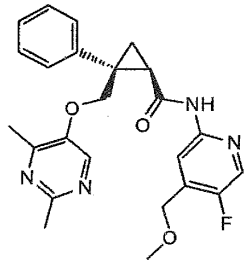
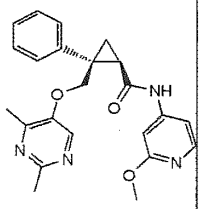
[0256]

[Table 19]

Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
67		^{1}H-NMR δ (ppm): 1.62-1.65 (m, 1H), 1.92 (t, J=5.4 Hz, 1H), 2.11-2.15 (m, 1H), 2.21 (s, 3H), 2.56 (s, 3H), 4.45 (d, J=9.6 Hz, 1H), 4.54 (d, J=9.6 Hz, 1H), 7.27-7.45 (m, 7H), 8.00 (s, 1H), 8.46 (brs, 2H). MS $[M+H]^+$=375
68		^{1}H-NMR δ (ppm): 1.63 (dd, J=5.2, 8.0 Hz, 1H), 1.91 (t, J=5.2 Hz, 1H), 2.11 (brt, 1H), 2.21 (s, 3H), 2.55 (s, 3H), 4.39 (d, J=9.4 Hz, 1H), 4.49 (d, J=9.4 Hz, 1H), 6.66 (dd, J=2.6, 8.0 Hz, 1H), 7.28-7.39 (m, 3H), 7.45-7.47 (m, 2H), 7.74 (q, J=8.0 Hz, 1H), 7.92 (brd, 1H), 7.96 (s, 1H), 8.17-8.19 (m, 1H). MS $[M+H]^+$=393
69		^{1}H-NMR δ (ppm): 1.60 (dd, J=5.2, 8.0 Hz, 1H), 1.90 (t, J=5.2 Hz, 1H), 2.11 (brt, 1H), 2.20 (s, 3H), 2.28 (s, 3H), 2.54 (s, 3H), 4.40 (d, J=9.4 Hz, 1H), 4.51 (d, J=9.4 Hz, 1H), 7.27-7.38 (m, 3H), 7.45-7.48 (m, 3H), 7.94 (brd, 1H), 7.96 (s, 1H), 8.08 (q, J=0.8 Hz, 1H), 8.27 (brs, 1H).
70		^{1}H-NMR δ (ppm): 1.60 (dd, J=5.2, 7.6 Hz, 1H), 1.90 (t, J=5.2 Hz, 1H), 2.13 (brt, 1H), 2.21 (s, 3H), 2.47 (s, 3H), 2.54 (s, 3H), 4.40 (d, J=9.6 Hz, 1H), 4.50 (d, J=9.6 Hz, 1H), 6.90 (d, J=7.2 Hz, 1H), 7.27-7.38 (m, 3H), 7.46-7.48 (m, 2H), 7.55 (brt, 1H), 7.86 (brd, 1H), 7.96 (s, 1H). MS $[M+H]^+$=389

[0257]

[Table 20]

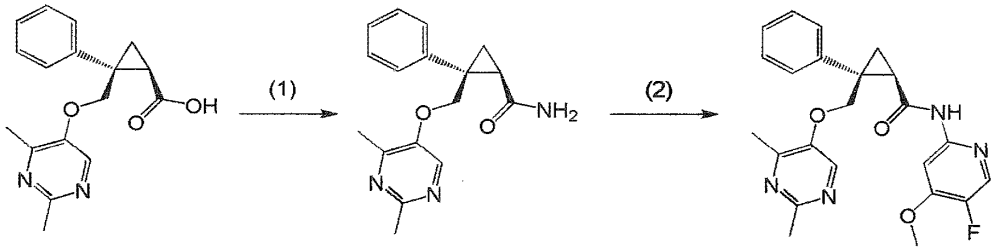
Example	Structural formula	NMR (400 MHz, $CDCl_3$ and/or MS
71		^{1}H-NMR δ (ppm): 1.62 (dd, J=5.2, 8.0 Hz, 1H), 1.91 (t, J=5.2 Hz, 1H), 2.12 (dd, J=5.2, 8.0 Hz, 1H), 2.21 (s, 3H), 2.55 (s, 3H), 3.41 (s, 3H), 4.41 (d, J=9.6 Hz, 1H), 4.45-4.54 (m, 3H), 7.30-7.39 (m, 3H), 7.45-7.48 (m, 2H), 7.96 (s, 1H), 8.07 (d, J=1.2 Hz, 1H), 8.17-8.18 (m, 1H), 8.25 (brs, 1H). MS $[M+H]^+$=437
72		MS $[M+H]^+$=405

[0258]

Example 73

Synthesis of (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxypyridin-2-yl)-2-phenylcyclopropanecarboxamide (73-2)

[Formula 49]



Prep 13-7 73-1 73-2

[0259]

(1) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide (73-1)

N,N-diisopropylethylamine was added to a DMF solution (15 ml) of the carboxylic acid Prep 13-7 (1.0 g), HOBt (679 mg), WSC (963 mg) and ammonium chloride (358 mg) at a room temperature, and the obtained mixture was then stirred for 7 days. Thereafter, a

saturated sodium bicarbonate aqueous solution was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate (× 2). The organic layer was dried over anhydrous magnesium sulfate and was then filtered. The filtrate was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate = 9 : 1 to 1 : 4). The obtained crude product was dissolved in ethyl acetate, and h-hexane was then added to the solution. The precipitated solid was collected by filtration and was then dried, so as to obtain compound 74-1 (606 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.53 (dd, J=4.8, 8.4 Hz, 1H), 1.79 (dd, J=4.8, 6.0 Hz, 1H), 1.99 (dd, J=6.0, 8.4 Hz, 1H), 2.35 (s, 3H), 2.58 (s, 3H), 4.45 (s, 2H), 5.40 (brs, 1H), 5.77 (brs, 1H), 7.27-7.36 (m, 3H), 7.42-7.45 (m, 2H), 7.98 (s, 1H).

MS $[M+H]^+$=298

[0260]

(2) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxypyridin-2-yl)-2-phenylcyclopropanecarboxamide (73-2)

The temperature of a 1,4-dioxane solution (20 ml) of the compound 73-1 (300 mg), the 2-chloro-5-fluoro-4-methoxypyridine (245 mg) obtained in Production Example 9-(1), xantphos (351 mg), potassium triphosphate (429 mg) and tris(dibenzylidene) dipalladium (185 mg) was increased to 95°C, and the solution was then stirred for 26 hours. Thereafter, water was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate (× 1). The organic layer was successively washed with water and a saturated saline, and was then dried over anhydrous magnesium sulfate, followed by filtration. The filtrate was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate = 7 : 3, to ethyl acetate), and then by NH-silica gel column chromatography (n-heptane : ethyl acetate = 4 : 1 to 2 : 3). The obtained crude product was dissolved in chloroform, and n-hexane was then added to the solution. The precipitated solid was collected by filtration and was then dried, so as to obtain compound 73-2 (304 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.63 (dd, J=5.6, 8.0 Hz, 1H), 1.89 (t, J=5.6 Hz, 1H), 2.11 (dd, J=5.6, 8.0 Hz, 1H), 2.23 (s, 3H), 2.55 (s, 3H), 3.88 (s, 3H), 4.41 (d, J=9.6 Hz, 1H), 4.51 (d, J=9.6 Hz, 1H), 7.28-7.39 (m, 3H), 7.45-7.48 (m, 2H), 7.82 (d, J=6.4 Hz, 1H), 7.97 (d, J=2.8 Hz, 1H), 7.98 (s, 1H), 8.30 (brs, 1H).

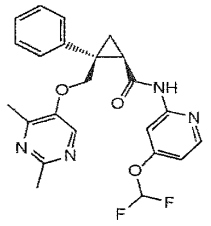
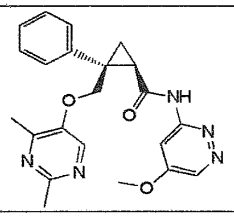
MS $[M+Na]^+$=445

[0261]

* The compounds of Examples 74 and 75 were synthesized from the carboxylic acid amide obtained in Example 74-1 by the same method as that of Example 73.

[0262]

[Table 21]

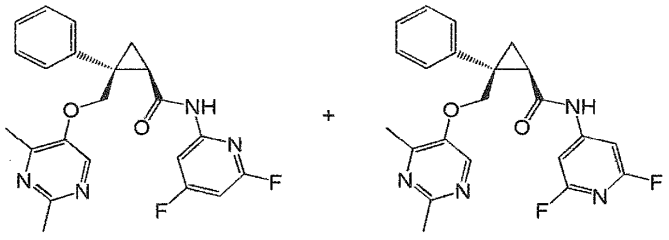
Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
74		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.67 (dd, J=5.6, 8.0 Hz, 1H), 1.93 (t, J=5.6 Hz, 1H), 2.11 (dd, J=5.6, 8.0 Hz, 1H), 2.23 (s, 3H), 2.56 (s, 3H), 4.46 (d, J=9.6 Hz, 1H), 4.53 (d, J=9.6 Hz, 1H), 6.53 (t, J=72.6 Hz, 1H), 7.28-7.39 (m, 3H), 7.44-7.46 (m, 2H), 7.79 (brs, 1H), 7.99 (s, 1H), 8.06 (brs, 1H), 8.23 (d, J=2.0 Hz, 1H), 8.37 (d, J=2.0 Hz, 1H). MS $[M+H]^+$=441
75		MS $[M+H]^+$=406

[0263]

Example 76

Synthesis of (1R,2S)-N-(4,6-difluoropyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide (76-1) and (1R,2S)-N-(2,6-difluoropyridin-4-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide (76-2)

[Formula 50]



76-1 76-2

[0264]

Sodium hydride (60%, 26.9 mg) was added to a NMP solution (5 ml) of the compound 73-1 (100 mg), and the obtained mixture was stirred at a room temperature for 10 minutes. Thereafter, 2,4,6-trifluoropyridine (89.4 mg) was added to the reaction solution. The temperature of the reaction solution was increased to 100°C, and it was then stirred for 4 days. Thereafter, water was added to the reaction solution, and the obtained mixture was then extracted

with ethyl acetate (× 1). The organic layer was successively washed with water and a saturated saline, and was then dried over anhydrous magnesium sulfate, followed by filtration. The filtrate was concentrated under a reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate = 4 : 1 to 1 : 9), so as to obtain the above-captioned compound 76-1 (11.1 mg) and compound 76-2 (23.4 mg).

[0265]

76-1

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.64 (dd, J=5.6, 8.0 Hz, 1H), 1.91 (t, J=5.6 Hz, 1H), 2.09 (dd, J=5.6, 8.0 Hz, 1H), 2.22 (s, 3H), 2.55 (s, 3H), 4.37 (d, J=9.8 Hz, 1H), 4.48 (d, J=9.8 Hz, 1H), 6.39 (dt, J=7.6, 1.6 Hz, 1H), 7.28-7.39 (m, 3H), 7.43-7.46 (m, 2H), 7.74 (dd, J=1.6, 10.0 Hz, 1H), 7.95 (s, 1H), 8.21 (brs, 1H).

MS $[M+H]^+$=411

[0266]

76-2

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.70 (dd, J=5.6, 8.0 Hz, 1H), 1.94 (t, J=5.6 Hz, 1H), 2.07 (dd, J=5.6, 8.0 Hz, 1H), 2.22 (s, 3H), 2.57 (s, 3H), 4.42 (d, J=9.6 Hz, 1H), 4.51 (d, J=9.6 Hz, 1H), 7.00 (s, 2H), 7.31-7.39 (m, 3H), 7.42-7.45 (m, 2H), 7.86 (brs, 1H), 7.98 (s, 1H).

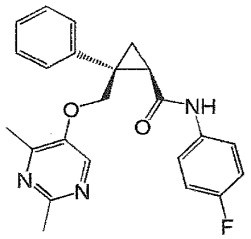
MS $[M+H]^+$=411

[0267]

Example 77

Synthesis of (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(4-fluorophenyl)-2-phenylcyclopropanecarboxamide (77)

[Formula 51]



77

[0268]

The carboxylic acid Prep 13-7 (30 mg) was dissolved in N,N-dimethylformamide (1 ml), and 4-fluoroaniline (33.7 mg), N,N-diisopropylethylamine (176 ul) and HOBt (40.9 mg) were then added to the obtained solution. Then, WSC (58.1 mg) was added thereto at a room temperature, and the obtained mixture was stirred for 21 hours. Thereafter, the reaction

solution was separated by purification using LC-MS (Waters, column: CAPCELL PAK, C18, ACR, S-5, 20 mm I.D. × 50 mm, AGEE01114, mobile phase: methanol-water-TFA), so as to obtain the above-captioned compound (10.34 mg).

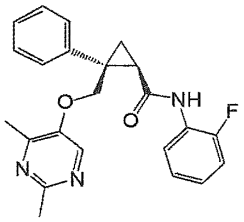
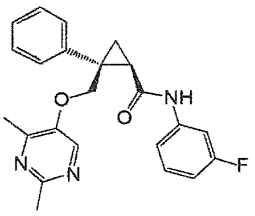
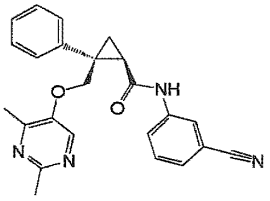
MS $[M+H]^+$=392

[0269]

* The compounds of Examples 78 to 80 were synthesized by reacting the carboxylic acid Prep 13-7 with any amine by the same method as that of Example 77. Purification was carried out by LC-MS.

[0270]

[Table 22]

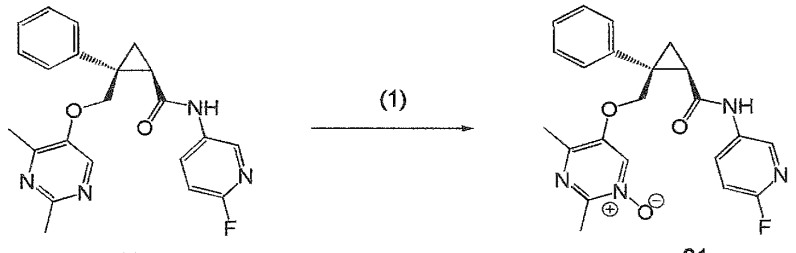
Example	Structural formula, MS	Example	Structural formula, MS	Example	Structural formula, MS
78	 MS $[M+H]^+$=392	79	 MS $[M+H]^+$=392	80	 MS $[M+H]^+$=399

[0271]

Example 81

Synthesis of (1R,2S)-2-[(2,4-dimethyl-1-oxopyrimidin-5-yl)oxymethyl]-N-(6-fluoropyridin-3-yl)-2-phenylcyclopropanecarboxamide (81)

[Formula 52]



54 81

[0272]

The compound 54 (40 mg) was dissolved in dichloromethane (5 ml), and 3-chloroperoxybenzoic acid (26.4 mg) was then added to the solution. The obtained mixture was stirred for 18 hours. Thereafter, potassium carbonate (50 mg) was added to the reaction

solution, and the obtained mixture was further stirred for 1 hour. After completion of filtration, the solvent was distilled away under reduced pressure, and the residue was then purified by silica gel column chromatography (n-heptane : ethyl acetate = 3 : 1 to 0 : 1, and then, ethyl acetate : methanol = 8 : 1), so as to obtain the above-captioned compound (25.0 mg).

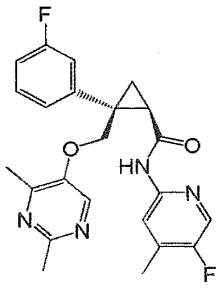
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.62 (dd, J=8.0, 5.2 Hz, 1H), 1.86 (t, J=5.2 Hz, 1H), 2.23 (dd, J=8.0, 6.0 Hz, 1H), 2.24 (s, 3H), 2.54 (s, 3H), 4.38 (d, J=9.6 Hz, 1H), 4.41 (d, J=9.6 Hz, 1H), 6.89 (dd, J=9.2, 2.8 Hz, 1H), 7.27 (t, J=7.2 Hz, 1H), 7.32 (t, J=7.2 Hz, 2H), 7.42 (d, J=7.2 Hz, 2H), 7.91 (s, 1H), 8.18-8.22 (m, 2H), 8.62 (brs, 1H).

[0273]

Example 82

Synthesis of (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)-2-(3-fluorophenyl)cyclopropanecarboxamide (82)

[Formula 53]



82

[0274]

N,N-diisopropylethylamine (278 ul) and HATU (604 mg) were added to a DMF solution (9.7 ml) of the carboxylic acid Prep 14-6 (388 mg) and 2-amino-5-fluoro-4-picoline (154 mg), while stirring at a room temperature. The obtained mixture was stirred at a room temperature for 6 hours. Thereafter, water was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, and was then concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, Size: L, n-heptane : ethyl acetate 10% → 60%). A solid was precipitated with THF-heptane and was then collected by filtration, so as to obtain the above-captioned compound (289 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.55-1.65 (m, 1H), 1.91 (t, J=5.6 Hz, 1H), 2.05-2.13 (m, 1H), 2.22 (s, 3H), 2.27 (s, 3H), 2.56 (s, 3H), 4.41 (d, J=10.0 Hz, 1H), 4.50 (d, J=9.2 Hz, 1H), 6.97-7.04 (m, 1H), 7.14-7.20 (m, 1H), 7.22-7.28 (m, 1H), 7.33 (td, J=8.0, 5.8 Hz, 1H), 7.93 (d, J=5.2 Hz, 1H), 7.99 (s, 1H), 8.00 (s, 1H), 8.24 (brs, 1H).

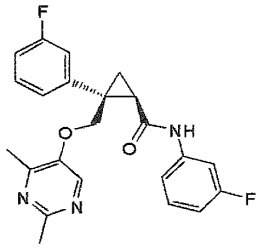
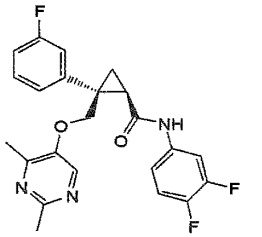
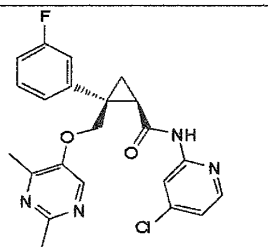
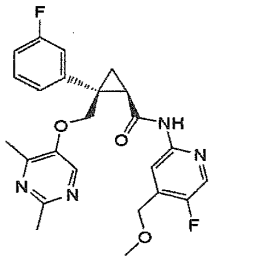
MS $[M+Na]^+$=447

[0275]

* The compounds of Examples 83 to 94 were synthesized by reacting the carboxylic acid Prep 14-6 with any amine by the same method as that of Example 82.

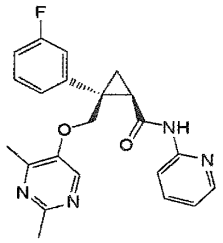
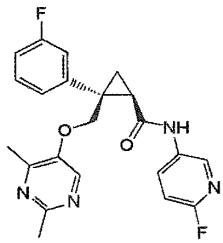
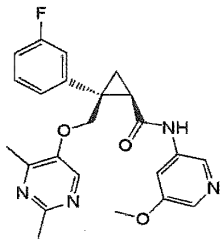
[0276]

[Table 23]

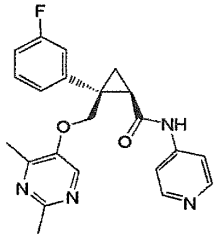
Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
83		^{1}H-NMR δ (ppm): 1.62 (dd, J=5.6, 8.0 Hz, 1H), 1.92 (t, J=5.6 Hz, 1H), 2.05 (dd, J=5.6, 8.0 Hz, 1H), 2.23 (s, 3H), 2.57 (s, 3H), 4.46 (d, J=9.6 Hz, 1H), 4.53 (d, J=9.6 Hz, 1H), 6.79-6.83 (m, 1H), 6.98-7.02 (m, 1H), 7.09-7.12 (m, 1H), 7.15-7.40 (m, 5H), 7.64 (brs, 1H), 8.01 (s, 1H). MS $[M+H]^+$=410
84		^{1}H-NMR δ (ppm): 1.63 (dd, J=5.6, 8.2 Hz, 1H), 1.92 (t, J=5.6 Hz, 1H), 2.03 (dd, J=5.6, 8.2 Hz, 1H), 2.24 (s, 3H), 2.58 (s, 3H), 4.45 (d, J=9.6 Hz, 1H), 4.52 (d, J=9.6 Hz, 1H), 6.98-7.36 (m, 6H), 7.49-7.54 (m, 2H), 8.01 (s, 1H). MS $[M+H]^+$=428
85		^{1}H-NMR δ (ppm): 1.63 (dd, J=5.6, 8.0 Hz, 1H), 1.93 (t, J=5.6 Hz, 1H), 2.13 (dd, J=5.6, 8.0 Hz, 1H), 2.22 (s, 3H), 2.56 (s, 3H), 4.40 (d, J=9.8 Hz, 1H), 4.50 (d, J=9.8 Hz, 1H), 6.98-7.06 (m, 2H), 7.16-7.20 (m, 1H), 7.23-7.36 (m, 2H), 7.98 (s, 1H), 8.13 (brs, 1H), 8.16 (d, J=5.6 Hz, 1H), 8.42 (brs, 1H). MS $[M+H]^+$=427
86		^{1}H-NMR δ (ppm): 1.62 (dd, J=5.2, 8.0 Hz, 1H), 1.92 (t, J=5.2 Hz, 1H), 2.09-2.13 (m, 1H), 2.22 (s, 3H), 2.55 (s, 3H), 3.41 (s, 3H), 4.41 (d, J=9.6 Hz, 1H), 4.45-4.54 (m, 3H), 6.98-7.03 (m, 1H), 7.16-7.19 (m, 1H), 7.23-7.36 (m, 2H), 7.98 (s, 1H), 8.07 (brs, 1H), 8.16-8.17 (m, 1H), 8.26 (brs, 1H). MS $[M+H]^+$=455

[0277]

[Table 24-1]

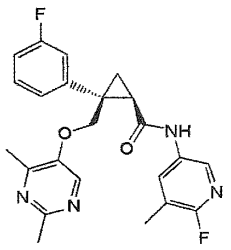
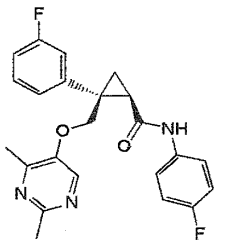
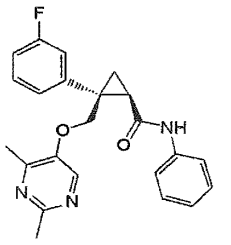
Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
87		^{1}H-NMR δ (ppm): 1.62 (dd, J=8.0, 5.2 Hz, 1H), 1.93 (t, J=5.2 Hz, 1H), 2.10-2.19 (m, 1H), 2.21 (s, 3H), 2.56 (s, 3H), 4.41 (d, J=9.6 Hz, 1H), 4.50 (d, J=9.6 Hz, 1H), 6.97-7.07 (m, 2H), 7.15-7.21 (m, 1H), 7.23-7.29 (m, 1H), 7.33 (td, J=8.0, 5.6 Hz, 1H), 7.65-7.71 (m, 1H), 7.98 (s, 1H), 8.06 (brd, J=8.4 Hz, 1H), 8.24-8.28 (m, 1H), 8.56 (brs, 1H).
88		^{1}H-NMR δ (ppm): 1.66 (dd, J=8.4, 5.2 Hz, 1H), 1.93 (t, J=5.4 Hz, 1H), 2.09 (dd, J=8.4, 5.6 Hz, 1H), 2.26 (s, 3H), 2.58 (s, 3H), 4.50 (dd, J=19.8, 9.4 Hz, 2H), 6.87-6.93 (m, 1H), 6.97-7.05 (m, 1H), 7.14-7.37 (m, 3H), 7.65 (brs, 1H), 8.01 (s, 1H), 8.10-8.18 (m, 2H). MS $[M+H]^+$=411
89		^{1}H-NMR δ (ppm): 1.62 (dd, J=7.8, 5.4 Hz, 1H), 1.92 (t, J=5.4 Hz, 1H), 2.14 (dd, J=8.2, 5.8 Hz, 1H), 2.24 (s, 3H), 2.57 (s, 3H), 3.78 (s, 3H), 4.47 (d, J=9.4 Hz, 1H), 4.53 (d, J=9.4 Hz, 1H), 6.96-7.02 (m, 1H), 7.12-7.19 (m, 1H), 7.20-7.24 (m, 1H), 7.31 (td, J=8.0, 6.0 Hz, 1H), 7.85 (brs, 1H), 8.00-8.05 (m, 2H), 8.08 (d, J=1.6 Hz, 1H), 8.33 (brs, 1H). MS $[M+H]^+$=423

[Table 24-2]

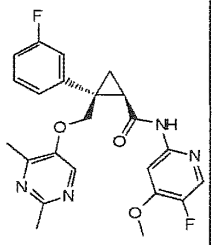
90		^{1}H-NMR δ (ppm): 1.64 (dd, J=8.2, 5.0 Hz, 1H), 1.94 (t, J=5.8 Hz, 1H), 2.13 (dd, J=8.2, 5.8 Hz, 1H), 2.22 (s, 3H), 2.56 (s, 3H), 4.44 (d, J=10.0 Hz, 1H), 4.52 (d, J=10.0 Hz, 1H), 6.95-7.02 (m, 1H), 7.11-7.16 (m, 1H), 7.18-7.23 (m, 1H), 7.27-7.34 (m, 1H), 7.43-7.47 (m, 2H), 8.01 (s, 1H), 8.39 (brs, 1H), 8.44-8.49 (m, 2H). MS $[M+H]^+$=393

[0278]

[Table 25-1]

Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
91		^{1}H-NMR δ (ppm): 1.63 (dd, J=8.2, 5.4 Hz, 1H), 1.92 (t, J=5.4 Hz, 1H), 2.11 (dd, J=8.2, 5.8 Hz, 1H), 2.24 (s, 3H), 2.26 (s, 3H), 2.58 (s, 3H), 4.47 (d, J=9.6 Hz, 1H), 4.52 (d, J=9.6 Hz, 1H), 6.96-7.03 (m, 1H), 7.14-7.20 (m, 1H), 7.20-7.25 (m, 1H), 7.32 (td, J=8.0, 6.0 Hz, 1H), 7.90-8.04 (m, 4H). MS $[M+H]^+$=425
92		^{1}H-NMR δ (ppm): 1.55-1.70 (m, 1H), 1.91 (t, J=5.6 Hz, 1H), 2.05 (dd, J=7.8, 6.2 Hz, 1H), 2.26 (s, 3H), 2.58 (s, 3H), 4.47 (d, J=9.6 Hz, 1H), 4.53 (d, J=9.6 Hz, 1H), 6.94-7.04 (m, 3H), 7.17 (dt, J=10.4, 2.0 Hz, 1H), 7.21-7.27 (m, 1H), 7.29-7.36 (m, 1H), 7.37-7.44 (m, 2H), 7.56 (brs, 1H), 8.01 (s, 1H). MS $[M+H]^+$=410
93		^{1}H-NMR δ (ppm): 1.55-1.69 (m, 1H), 1.92 (t, J=5.4 Hz, 1H), 2.06 (dd, J=8.2, 5.8 Hz, 1H), 2.25 (s, 3H), 2.57 (s, 3H), 4.48 (d, J=9.2 Hz, 1H), 4.54 (d, J=9.6 Hz, 1H), 6.96-7.03 (m, 1H), 7.08-7.14 (m, 1H), 7.14-7.20 (m, 1H), 7.20-7.37 (m, 4H), 7.44 (d, J=7.6 Hz, 2H), 7.56 (brs, 1H), 8.01 (s, 1H). MS $[M+H]^+$=392

[Table 25-2]

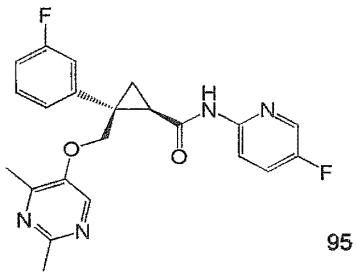
94		^{1}H-NMR δ (ppm): 1.63 (dd, J=5.6, 8.0 Hz, 1H), 1.91 (t, J=5.6 Hz, 1H), 2.10 (dd, J=5.6, 8.0 Hz, 1H), 2.23 (s, 3H), 2.56 (s, 3H), 3.87 (s, 3H), 4.41 (d, J=9.6 Hz, 1H), 4.51 (d, J=9.6 Hz, 1H), 6.99-7.03 (m, 1H), 7.16-7.26 (m, 2H), 7.31-7.36 (m, 1H), 7.80 (d, J=6.4 Hz, 1H), 7.98 (d, J=2.8 Hz, 1H), 7.99 (s, 1H), 8.28 (brs, 1H). MS $[M+Na]^+$=463

[0279]

Example 95

Synthesis of (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide (95)

[Formula 54]



95

[0280]

The carboxylic acid Prep 14-6 (226 mg) was dissolved in dichloromethane (10 ml), and oxalyl chloride (122 μl) and DMF (several droplets) were then added to the obtained solution. The obtained mixture was stirred at a room temperature for 1 hour. Thereafter, the reaction solution was concentrated under a reduced pressure, so as to obtain a crude acid chloride. N,N-diisopropylethylamine (283 μl) was added to a THF solution (10 ml) of 2-amino-5-fluoropyridine (96.1 mg), and the temperature of the solution was then increased to 60°C. A THF solution of the crude acid chloride was added dropwise to the reaction solution, and the obtained mixture was stirred for 1 hour while maintaining the temperature. Thereafter, the reaction system was cooled to a room temperature, and the reaction solution was then stirred for 1 hour. Thereafter, the reaction solution was concentrated under a reduced pressure, and was then distributed to ethyl acetate and water, so as to separate an organic layer. The organic layer was dried over anhydrous magnesium sulfate, and the filtrate was then concentrated under a reduced pressure. The residue was purified by NH-silica gel column chromatography (n-heptane : ethyl acetate = 2 : 1), and diethyl ether was then added to the obtained product of interest. The precipitated solid was collected by filtration and was then dried, so as to obtain the above-captioned compound (130 mg).

^{1}H-NMR (400 MHz, d-DMSO) δ (ppm): 1.46-1.50 (m, 1H), 1.68 (t, J=6.0 Hz, 1H), 2.01 (s, 3H), 2.36 (s, 3H), 2.59-2.63 (m, 1H), 4.27 (d, J=10.4 Hz, 1H), 4.66 (d, J=10.4 Hz, 1H), 7.06-7.11 (m, 1H), 7.37-7.44 (m, 3H), 7.60-7.65 (m, 1H), 7.85-7.89 (m, 1H), 8.11 (s, 1H), 8.30 (d, J=3.2 Hz, 1H), 11.20 (brds, 1H)

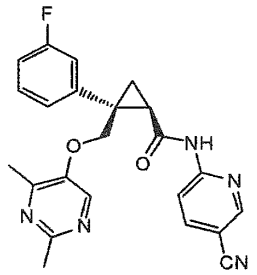
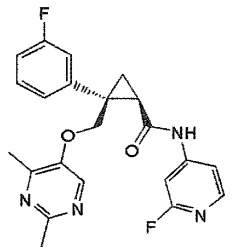
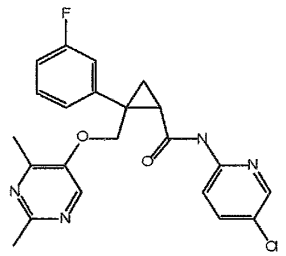
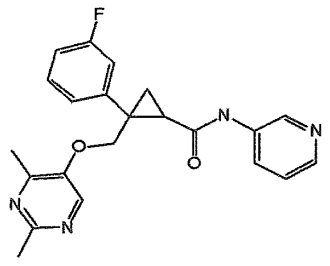
MS $[M+H]^+$=411

[0281]

* The compounds of Examples 96 to 99 were synthesized by reacting the carboxylic acid Prep 14-6 or a racemic body thereof with any amine by the same method as that of Example 95.

[0282]

[Table 26]

Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
96		^{1}H-NMR δ (ppm): 1.68 (dd, J=8.0, 5.6 Hz, 1H), 1.95 (t, J=5.6 Hz, 1H), 2.16 (dd, J=8.0, 6.0 Hz, 1H), 2.21 (s, 3H), 2.56 (s, 3H), 4.39 (d, J=9.6 Hz, 1H), 4.50 (d, J=9.6 Hz, 1H), 7.02 (tdd, J=8.0, 2.4, 1.2 Hz, 1H), 7.17 (dt, J=10.0, 2.4 Hz, 1H), 7.24 (dt, J=8.0, 1.2 Hz, 1H), 7.34 (td, J=8.0, 6.0 Hz, 1H), 7.90 (dd, J=8.8, 2.4 Hz, 1H), 7.98 (s, 1H), 8.20 (d, J=8.8 Hz, 1H), 8.48 (brs, 1H), 8.56 (dd, J=2.4, 0.8 Hz, 1H).
97		^{1}H-NMR δ (ppm): 1.69 (dd, J=8.2, 5.4 Hz, 1H), 1.95 (t, J=5.4 Hz, 1H), 2.07 (dd, J=7.8, 5.8 Hz, 1H), 2.23 (s, 3H), 2.57 (s, 3H), 4.44 (d, J=9.6 Hz, 1H), 4.52 (d, J=9.6 Hz, 1H), 6.98-7.05 (m, 1H), 7.14-7.20 (m, 2H), 7.20-7.31 (m, 2H), 7.31-7.38 (m, 1H), 7.78 (brs, 1H), 8.01 (s, 1H), 8.10 (d, J=5.2 Hz, 1H). MS $[M+H]^+$=411
98		MS $[M+H]^+$=428
99		MS $[M+H]^+$=393

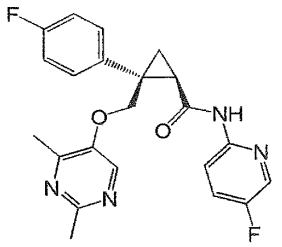
[0283]

Example 100

Synthesis of (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(4-fluorophenyl)-N-(5-

fluoropyridin-2-yl)cyclopropanecarboxamide (100)

[Formula 55]



100

[0284]

The carboxylic acid Prep 15-5 (200 mg) was dissolved in dichloromethane (10 ml), and oxalyl chloride (108 μl) and DMF (several droplets) were then added to the obtained solution. The obtained mixture was stirred at a room temperature for 1 hour. Thereafter, the reaction solution was concentrated under a reduced pressure, so as to obtain a crude acid chloride. N,N-diisopropylethylamine (250 μl) was added to a THF solution (10 ml) of 2-amino-5-fluoropyridine (85 mg), and the temperature of the solution was then increased to 60°C. A THF solution of the crude acid chloride was added dropwise to the reaction solution, and the obtained mixture was then stirred for 1 hour while maintaining the temperature. Thereafter, the reaction system was cooled to a room temperature, and the reaction solution was then stirred for 1 hour. Thereafter, the reaction solution was concentrated under a reduced pressure, and was then distributed to ethyl acetate and water, so as to separate an organic layer. The organic layer was dried over anhydrous magnesium sulfate, and the filtrate was concentrated under a reduced pressure. The residue was purified by NH-silica gel column chromatography (n-heptane : ethyl acetate = 2 : 1), and diethyl ether was then added to the obtained product of interest. The precipitated solid was collected by filtration and was then dried, so as to obtain the above-captioned compound (102 mg).

^{1}H-NMR (400 MHz, d-DMSO) δ (ppm): 1.43-1.45 (m, 1H), 1.66 (t, J=4.4 Hz, 1H), 2.02 (s, 3H), 2.36 (s, 3H), 2.55-2.58 (m, 1H), 4.26 (d, J=10.4 Hz, 1H), 4.59 (d, J=10.4 Hz, 1H), 7.15-7.20 (m, 2H), 7.57-7.65 (m, 3H), 7.86-7.89 (m, 1H), 8.09 (s, 1H), 8.30 (d, J=3.2 Hz, 1H), 11.18 (brds, 1H)
MS $[M+H]^+$=411

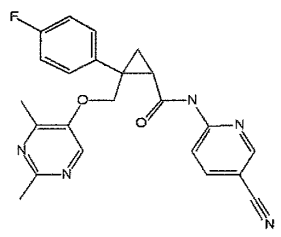
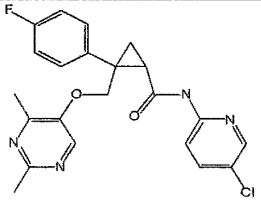
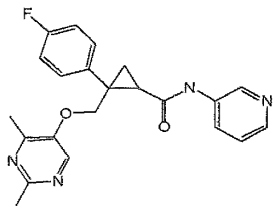
[0285]

* The compounds of Examples 101 to 104 were synthesized by the same method as that of Example 100, using 2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(4-fluorophenyl)cyclopropanecarboxylate, which can be synthesized using racemic epichlorohydrin in Production Example 15, or the carboxylic acid Prep 15-5 obtained in Production Example 15-

(5). Purification was carried out by LC-MS.

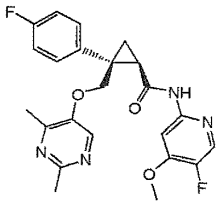
[0286]

[Table 27]

Example	Structural formula, MS	Example	Structural formula, MS	Example	Structural formula, MS
101	 MS $[M+H]^+$=418	102	 MS $[M+H]^+$=427	103	 MS $[M+H]^+$=393

[0287]

[Table 28]

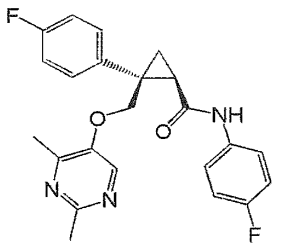
Example	Structural formula	NMR and/or MS
104		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.60 (dd, J=5.2, 8.0 Hz, 1H), 1.89 (t, J=5.2 Hz, 1H), 2.06 (dd, J=5.2, 8.0 Hz, 1H), 2.23 (s, 3H), 2.55 (s, 3H), 3.88 (s, 3H), 4.40 (d, J=9.4 Hz, 1H), 4.46 (d, J=9.4 Hz, 1H), 7.03-7.08 (m, 2H), 7.42-7.46 (m, 2H), 7.81 (d, J=6.8 Hz, 1H), 7.97-7.98 (m, 2H), 8.24 (brs, 1H). MS $[M+H]^+$=441

[0288]

Example 105

Synthesis of (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N,2-bis(4-fluorophenyl)cyclopropanecarboxamide (105)

[Formula 56]



105

[0289]

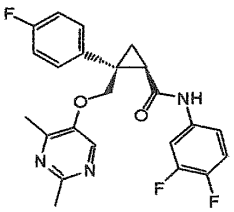
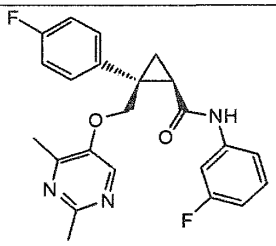
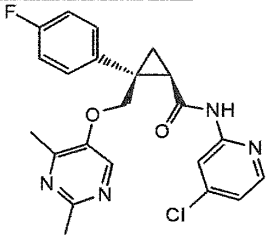
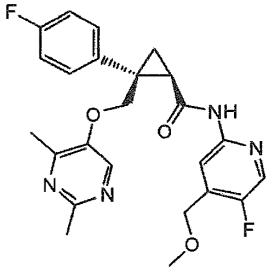
The carboxylic acid Prep 15-5 (33 mg) was dissolved in DMF (2 ml), and 4-fluoroaniline (15 mg), N,N-diisopropylethylamine(23.5 ul) and HATU (51.3 mg) were then added to the solution. The obtained mixture was stirred at a room temperature for 20 hours. Thereafter, water was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate. The organic layer was concentrated. The residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, Size: S (NH-inject column), n-heptane : ethyl acetate 10% → 60%), so as to obtain the above-captioned compound (22.1 mg). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.53-1.62 (m, 1H), 1.89 (t, J=5.4 Hz, 1H), 2.01 (dd, J=8.2, 5.8 Hz, 1H), 2.25 (s, 3H), 2.57 (s, 3H), 4.47 (dd, J=12.4, 9.6 Hz, 2H), 6.97-7.08 (m, 4H), 7.37-7.46 (m, 4H), 7.50 (brs, 1H), 7.99 (s, 1H).

[0290]

* The compounds of Examples 106 to 112 were synthesized by reacting the carboxylic acid Prep 15-5 with any amine by the same method as that of Example 105.

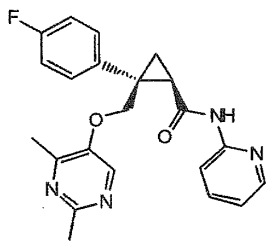
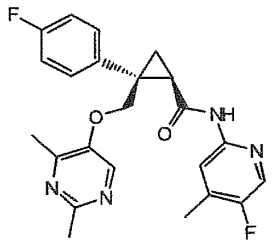
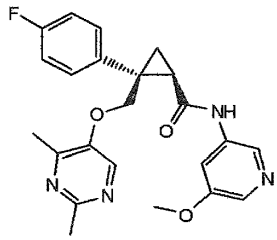
[0291]

[Table 29-1]

Example	Structural formula	NMR and/or MS
106		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.58 (dd, J=8.0, 5.2 Hz, 1H), 1.89 (t, J=5.2 Hz, 1H), 2.00 (dd, J=8.0, 6.0 Hz, 1H), 2.24 (s, 3H), 2.57 (s, 3H), 4.44 (d, J=9.6 Hz, 1H), 4.48 (d, J=9.6 Hz, 1H), 7.01-7.12 (m, 4H), 7.39-7.36 (m, 2H), 7.48-7.55 (m, 1H), 7.68 (br, 1H), 7.99 (s, 1H).
107		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.58 (dd, J=8.0, 5.2 Hz, 1H), 1.89 (t, J=5.2 Hz, 1H), 2.02 (dd, J=8.6, 6.0 Hz, 1H), 2.23 (s, 3H), 2.56 (s, 3H), 4.44 (d, J=9.6 Hz, 1H), 4.48 (d, J=9.6 Hz, 1H), 6.76-6.84 (m, 1H), 7.01-7.12 (m, 3H), 7.21-7.28 (m, 2H), 7.36-7.45 (m, 1H), 7.79 (br, 1H), 7.99 (s, 1H).
108		MS $[M+H]^+$=428
109		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.59 (dd, J=5.6, 8.0 Hz, 1H), 1.91 (t, J=5.6 Hz, 1H), 2.08 (dd, J=5.6, 8.0 Hz, 1H), 2.22 (s, 3H), 2.55 (s, 3H), 3.41 (s, 3H), 4.40 (d, J=9.6 Hz, 1H), 4.45 (d, J=9.6 Hz, 1H), 4.48 (d, J=13.6 Hz, 1H), 4.52 (d, J=13.6 Hz, 1H), 7.02-7.08 (m, 2H), 7.42-7.46 (m, 2H), 7.97 (s, 1H), 8.07 (d, J=1.2 Hz, 1H), 8.18 (brd, J=5.2 Hz, 1H), 8.26 (brs, 1H). MS $[M+H]^+$=455

[0292]

[Table 30]

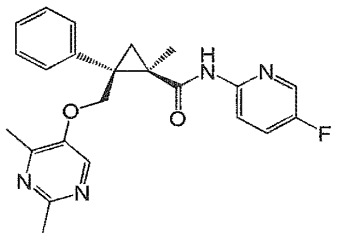
Example	Structural formula	NMR and/or MS
110		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.58 (dd, J=8.2, 5.0 Hz, 1H), 1.91 (t, J=5.4 Hz, 1H), 2.06-2.13 (m, 1H), 2.20 (s, 3H), 2.55 (s, 3H), 4.40 (d, J=9.2 Hz, 1H), 4.46 (d, J=9.6 Hz, 1H), 7.00-7.08 (m, 3H), 7.41-7.48 (m, 2H), 7.66 (td, J=7.8, 1.8 Hz, 1H), 7.97 (s, 1H), 8.05 (brd, J=10.4 Hz, 1H), 8.26 (dq, J=4.4, 0.8 Hz, 1H), 8.41 (brs, 1H)
111		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.58 (dd, J=7.6, 5.2 Hz, 1H), 1.89 (t, J=5.6 Hz, 1H), 2.03-2.09 (m, 1H), 2.22 (s, 3H), 2.28 (s, 3H), 2.56 (s, 3H), 4.40 (d, J=9.2 Hz, 1H), 4.46 (d, J=9.6 Hz, 1H), 7.01-7.12 (m, 2H), 7.40-7.47 (m, 2H), 7.94 (brd, J=6.0 Hz, 1H), 7.97 (s, 1H), 8.00 (d, J=1.2 Hz, 1H), 8.28 (brs, 1H)
112		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.62 (dd, J=8.4, 5.2 Hz, 1H), 1.90 (t, J=5.6 Hz, 1H), 2.06-2.14 (m, 1H), 2.24 (s, 3H), 2.56 (s, 3H), 3.79 (s, 3H), 4.47 (dd, J=13.6, 9.6 Hz, 2H), 7.01-7.08 (m, 2H), 7.41-7.48 (m, 2H), 7.86 (brs, 1H), 8.00 (s, 2H), 8.03-8.11 (m, 2H).

[0293]

Example 113

Synthesis of (1R, 2R)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)-1-methyl-2-phenylcyclopropanecarboxamide (113)

[Formula 57]



113

[0294]

Oxalyl chloride (22.8 ul) was added to a dichloromethane solution (1.5 ml) of the carboxylic acid Prep 20-6 (41.5 mg), while the solution was stirred under cooling on ice. The

obtained mixture was stirred at a room temperature for 2 hours, and the reaction solution was then concentrated under a reduced pressure. The residue was dissolved in dichloromethane (1 ml). Then, a dichloromethane solution (1 ml) of 2-amino-5-fluoropyridine (22.3 mg) and N,N-diisopropylethylamine (69.4 ul) were added to the obtained solution, while the solution was stirred under cooling on ice. The obtained mixture was stirred at a room temperature for 4 hours. Thereafter, water was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate. The organic layer was washed with a saturated saline, was dried over magnesium sulfate, and was then concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (first purification: YAMAZEN, Hi-Flush™ column, Size: M, n-heptane : ethyl acetate 0% → 100%) (second purification: YAMAZEN, Hi-Flush™ column amino, Size: S, n-heptane : ethyl acetate 0% → 50%), so as to obtain the above-captioned compound (8.0 mg).

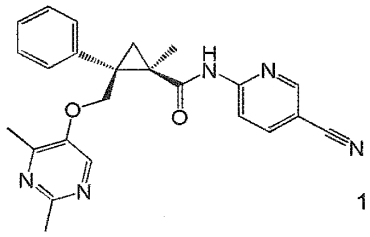
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.25 (s, 3H), 1.34 (d, J=5.6 Hz, 1H), 2.08 (d, J=5.2 Hz, 1H), 2.25 (s, 3H), 2.53 (s, 3H), 4.29 (dd, J=15.6, 9.6 Hz, 2H), 7.28-7.42 (m, 4H), 7.42-7.48 (m, 2H), 7.87 (s, 1H), 8.07-8.13 (m, 2H), 8.32 (brs, 1H).

[0295]

Example 114

Synthesis of (1R,2R)-N-(5-cyanopyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-1-methyl-2-phenylcyclopropanecarboxamide (114)

[Formula 58]



114

[0296]

Oxalyl chloride (24.7 ul) was added to a dichloromethane solution (1.5 ml) of the carboxylic acid Prep 20-6 (45 mg), while the solution was stirred under cooling on ice. The obtained mixture was stirred at a room temperature for 2 hours, and the reaction solution was then concentrated under a reduced pressure. The residue was dissolved in dichloromethane (1.5 ml), and thereafter, a THF solution (1 ml) of 2-amino-5-cyanopyridine (22.3 mg) and N,N-diisopropylethylamine (75.3 ul) were added to the solution, while the solution was stirred under cooling on ice. The obtained mixture was stirred at a room temperature for 3 hours.

Thereafter, water was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate. The organic layer was washed with a saturated saline, was then dried over magnesium sulfate, and was then concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (first purification: YAMAZEN, Hi-Flush™ column amino, Size: M, n-heptane : ethyl acetate 0% → 100%), so as to obtain the above-captioned compound (28.2 mg).

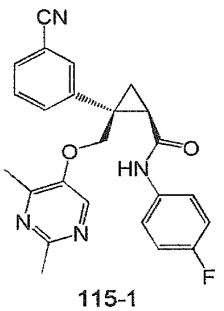
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.26 (s, 3H), 1.38 (d, J=5.2 Hz, 1H), 2.12 (d, J=5.2 Hz, 1H), 2.25 (s, 3H), 2.53 (s, 3H), 4.25 (d, J=9.6 Hz, 1H), 4.32 (d, J=9.6 Hz, 1H), 7.30-7.42 (m, 3H), 7.43-7.48 (m, 2H), 7.85-7.91 (m, 2H), 8.23 (dd, J=8.6, 1.0 Hz, 1H), 8.50 (brs, 1H), 8.53-8.56 (m, 1H).

[0297]

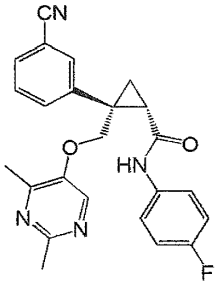
Example 115

Synthesis of (1R,2S)-2-(3-cyanophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(4-fluorophenyl)cyclopropanecarboxamide (115-1) and (1S,2R)-2-(3-cyanophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(4-fluorophenyl)cyclopropanecarboxamide (115-2)

[Formula 59]



115-1



115-2

[0298]

N,N-diisopropylethylamine (28.5 ul) and HATU (62.2 mg) were added to a DMF solution (1 ml) of the carboxylic acid Prep 18-4 (40 mg) and 4-fluoroaniline (18.2 mg), while the solution was stirred at a room temperature. The obtained mixture was stirred at a room temperature for 8 hours. Thereafter, water was added to the reaction solution, and the mixture was then extracted with ethyl acetate. The organic layer was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, Size: M, n-heptane : ethyl acetate 10% → 60%). Subsequently, the resultant product was subjected to chiral resolution using HPLC (Daicel Chiral pak IA column, n-hexane : ethanol 30%), so as to obtain the above-captioned compound (front peak: 13.1 mg, back peak: 12.4 mg).

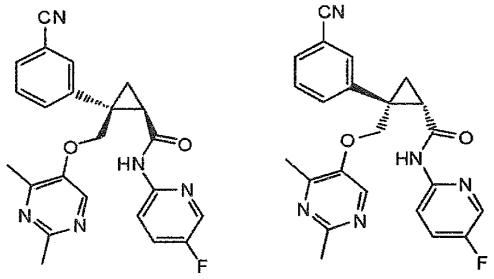
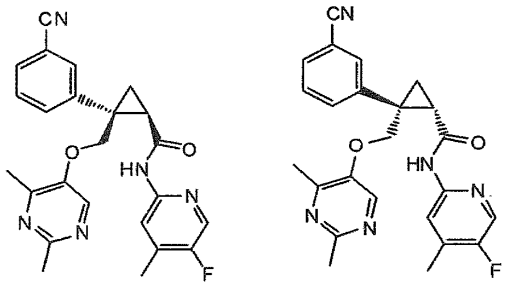
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.59 (dd, J=8.0, 5.2 Hz, 1H), 1.96 (t, J=5.4 Hz, 1H), 2.08 (dd, J=8.0, 6.0 Hz, 1H), 2.25 (s, 3H), 2.57 (s, 3H), 4.49 (s, 2H), 6.96-7.04 (m, 2H), 7.40-7.46 (m, 2H), 7.49 (t, J=7.8 Hz, 1H), 7.61 (brd, J=7.6 Hz, 1H), 7.72 (brd, J=7.6 Hz, 1H), 7.84 (brd, J=8.0 Hz, 2H), 8.00 (s, 1H).

[0299]

* The compounds of Examples 116 and 117 were synthesizing by condensing the carboxylic acid Prep 18-4 and any amine by the same method as that of Example 115.

[0300]

[Table 31]

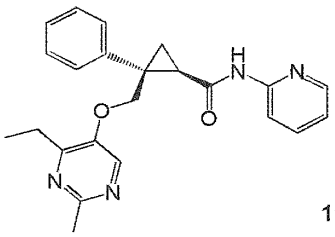
Example	Structural formula	NMR and/or MS
116		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.60-1.70 (m, 1H), 1.97 (t, J=5.5 Hz, 1H), 2.08-2.16 (m, 1H), 2.21 (s, 3H), 2.57 (s, 3H), 4.47 (dd, J=17.2, 9.8 Hz, 2H), 7.37-7.44 (m, 1H), 7.50 (t, J=7.8 Hz, 1H), 7.62 (dt, J=7.8, 1.6 Hz, 1H), 7.71-7.75 (m, 1H), 7.78 (brs, 1H), 7.99 (s, 1H), 8.04-8.11 (m, 1H), 8.13 (d, J=3.1 Hz, 1H), 8.43 (brs, 1H).
117		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.60-1.70 (m, 1H), 1.96 (t, J=7.4 Hz, 1H), 2.07-2.15 (m, 1H), 2.22 (s, 3H), 2.28 (s, 3H), 2.56 (s, 3H), 4.44 (d, J=9.2 Hz, 1H), 4.49 (d, J=10.0 Hz, 1H), 7.50 (t, J=8.0 Hz, 1H), 7.62 (dt, J=8.0, 1.2 Hz, 1H), 7.73 (dt, J=7.6, 1.6 Hz, 1H), 7.77 (brs, 1H), 7.93 (brd, J=4.8 Hz, 1H), 7.99 (s, 1H), 8.01 (brs, 1H), 8.36 (brs, 1H).

[0301]

Example 118

Synthesis of (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenyl-N-pyridin-2-ylcyclopropanecarboxamide (118)

[Formula 60]



118

[0302]

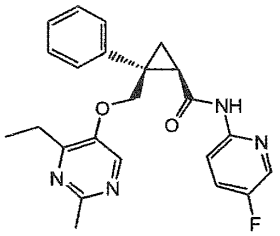
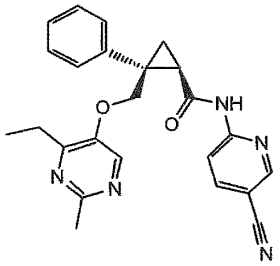
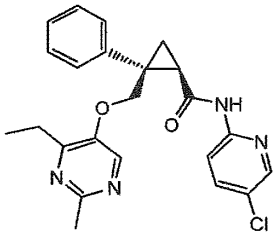
N,N-diisopropylethylamine (21.4 ul) and HATU (46.8 mg) were added to a DMF solution (0.75 ml) of the carboxylic acid Prep 19-3 (30 mg) and 2-aminopyridine (8.9 mg), while the solution was stirred at a room temperature. The obtained mixture was stirred at a room temperature for 3 hours. Thereafter, water was added to the reaction solution, and the mixture was then extracted with ethyl acetate. The organic layer was concentrated. The residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush^{TM} column, Size: S, n-heptane : ethyl acetate 10% → 60%), so as to obtain the above-captioned compound (32.1 mg). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.97 (t, J=7.6 Hz, 3H), 1.62 (dd, J=8.2, 5.0 Hz, 1H), 1.91 (t, J=5.4 Hz, 1H), 2.10-2.18 (m, 1H), 2.50-2.65 (m, 2H), 2.56 (s, 3H), 4.44 (d, J=9.2 Hz, 1H), 4.51 (d, J=9.2 Hz, 1H), 6.96-7.02 (m, 1H), 7.25-7.39 (m, 3H), 7.43-7.48 (m, 2H).7.62-7.68 (m, 1H), 7.99 (s, 1H), 8.07 (brd, J=8.8 Hz, 1H), 8.23 (dq, J=4.8, 0.8 Hz, 1H), 8.65 (brs, 1H).

[0303]

* The compounds of Examples 119 to 121 were synthesizing by condensing the carboxylic acid Prep 19-3 and any amine by the same method as that of Example 118.

[0304]

[Table 32]

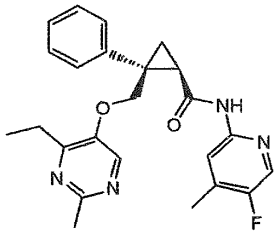
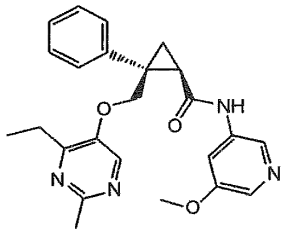
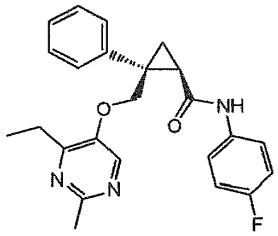
Example	Structural formula	NMR and/or MS
119		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.985 (t, J=7.6 Hz, 3H), 1.60-1.63 (m, 1H), 1.90 (t, J=5.2 Hz, 1H), 2.11 (brdt, 1H), 2.51-2.62 (m, 5H), 4.42 (d, J=9.2 Hz, 1H), 4.48 (d, J=9.2 Hz, 1H), 7.27-7.51 (m, 6H), 7.91 (s, 1H), 8.08 (m, 2H), 8.26 (brds, 1H). MS $[M+H]^+$=407
120		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.97 (t, J=8.0 Hz, 3H), 1.67 (dd, J=8.4 Hz, 5.2 Hz, 1H), 1.93 (t, J=5.2 Hz, 1H), 2.16 (dd, J=8.0 Hz, 5.6 Hz, 1H), 2.50-2.60 (m, 5H), 4.40 (d, J=9.6 Hz, 1H), 4.48 (d, J=9.6 Hz, 1H), 7.29-7.46 (m, 5H), 7.89 (dd, J=2.4 Hz, 8.8 Hz, 1H), 7.97 (s, 1H), 8.23 (d, J=8.8 Hz, 1H), 8.53-8.55 (m, 2H). MS $[M+H]^+$=414
121		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.99 (t, J=7.6 Hz, 3H), 1.63 (dd, J=8.0 Hz, 5.2 Hz, 1H), 1.93 (t, J=5.6 Hz, 1H), 2.12 (brdt, J=8.0 Hz, 1H), 2.51-2.60 (m, 5H), 4.41 (d, J=9.2 Hz, 1H), 4.48 (d, J=9.6 Hz, 1H), 7.26-7.47 (m, 5H), 7.61 (dd, J=2.8 Hz, 9.2 Hz, 1H), 7.97 (s, 1H), 8.06 (d, J=9.2 Hz, 1H), 8.22 (d, J=2.8 Hz, 1H) 8.29 (brds, 1H). MS $[M+H]^+$=423

[0305]

* The compounds of Examples 122 to 124 were synthesizing by reacting the carboxylic acid Prep 19-3 with any amine by the same method as that of Example 51.

[0306]

[Table 33]

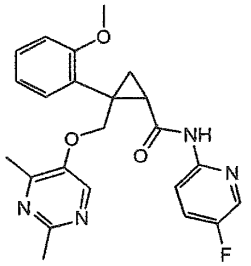
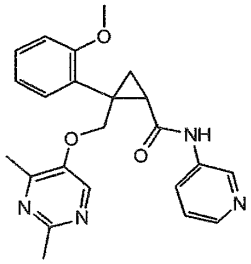
Example	Structural formula	NMR and/or MS
122		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.99 (t, J=7.4 Hz, 3H), 1.62 (dd, J=7.8, 5.0 Hz, 1H), 1.89 (t, J=5.6 Hz, 1H), 2.11 (dd, J=7.8, 5.8 Hz, 1H), 2.27 (s, 3H), 2.50-2.65 (m, 2H), 2.57 (s, 3H), 4.43 (d, J=9.2 Hz, 1H), 4.50 (d, J=9.2 Hz, 1H), 7.25-7.32 (m, 1H), 7.33-7.39 (m, 2H), 7.43-7.47 (m, 2H), 7.96 (brd, J=6.0 Hz, 1H), 7.97-8.01 (m, 2H), 8.40 (brs, 1H).
123		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.02 (t, J=7.2 Hz, 3H), 1.63 (dd, J=7.6, 5.2 Hz, 1H), 1.91 (t, J=5.4 Hz, 1H), 2.14 (dd, J=8.0, 6.0 Hz, 1H), 2.54-2.67 (m, 2H), 2.57 (s, 3H), 3.78 (s, 3H), 4.50 (dd, J=19.2, 9.6 Hz, 2H), 7.25-7.31 (m, 1H), 7.31-7.38 (m, 2H), 7.41-7.47 (m, 2H), 7.86 (t, J=2.2 Hz, 1H), 7.98-8.08 (m, 3H), 8.20 (brs, 1H).
124		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.04 (t, J=7.8 Hz, 3H), 1.58-1.67 (m, 1H), 1.89 (t, J=5.6 Hz, 1H), 2.03-2.09 (m, 1H), 2.55-2.66 (m, 2H), 2.58 (s, 3H), 4.50 (dd, J=14.6, 9.4 Hz, 2H), 6.95-7.03 (m, 2H), 7.26-7.32 (m, 1H), 7.33-7.48 (m, 6H), 7.57 (brs, 1H), 8.00 (s, 1H).

[0307]

* The compounds of Examples 125 and 126 were synthesizing by reacting the carboxylic acid Prep 17-4 with any amine by the same method as that of Example 1.

[0308]

[Table 34]

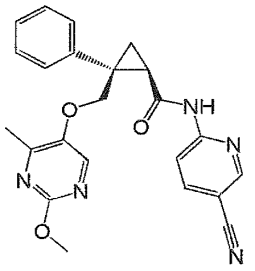
Example	Structural formula	NMR and/or MS
125		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.47 (dd, J=5.2, 8.0 Hz, 1H), 1.83 (dd, J=5.2, 6.4 Hz, 1H), 2.12 (dd, J=6.4, 8.0 Hz, 1H), 2.23 (s, 3H), 2.54 (s, 3H), 4.03 (s, 3H), 4.21 (d, J=9.4 Hz, 1H), 4.27 (d, J=9.4 Hz, 1H), 6.93-6.99 (m, 2H), 7.28-7.45 (m, 3H), 7.87 (s, 1H), 8.14 (d, J=3.2 Hz, 1H), 8.17 (dd, J=4.4, 9.6 Hz, 1H), 8.60 (brs, 1H).
126		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.49 (dd, J=5.6, 8.0 Hz, 1H), 1.85 (dd, J=5.6, 6.2 Hz, 1H), 2.12 (dd, J=6.2, 8.0 Hz, 1H), 2.22 (s, 3H), 2.54 (s, 3H), 3.98 (s, 3H), 4.27 (d, J=9.6 Hz, 1H), 4.32 (d, J=9.6 Hz, 1H), 6.93-7.00 (m, 2H), 7.29-7.33 (m, 2H), 7.38-7.40 (m, 1H), 7.89 (s, 1H), 7.96 (brs, 1H), 8.24 (brd, 1H), 8.36 (dd, J=1.4, 4.6 Hz, 1H), 8.57 (d, J=2.0 Hz, 1H). MS $[M+H]^+$=405

[0309]

Example 127

Synthesis of (1R,2S)-N-(5-cyanopyridin-2-yl)-2-[(2-methoxy-4-methylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide (127)

[Formula 61]



127

[0310]

The above-captioned compound was synthesized by amidating the carboxylic acid Prep 21 by the same method as that of Example 1.

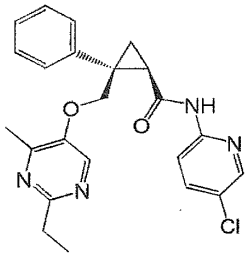
MS $[M+H]^+$=416

[0311]

Example 128

Synthesis of (1R,2S)-N-(5-chloropyridin-2-yl)-2-[(2-ethyl-4-methylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide (128)

[Formula 62]



128

[0312]

The above-captioned compound was synthesized by amidating the carboxylic acid Prep 22 of Production Example 22 by the same method as that of Example 1.

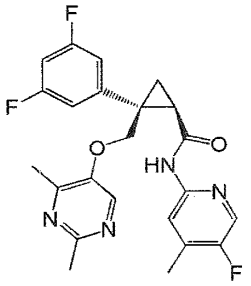
MS $[M+H]^+$=423

[0313]

Example 129

Synthesis of (1R,2S)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)cyclopropanecarboxamide (129)

[Formula 63]



129

[0314]

2-Amino-5-fluoro-4-picoline (415 mg), HATU (1.71 g) and N,N-diisopropylethylamine(1.56 ml) were added to a DMF solution (20 ml) of the carboxylic acid Prep 16-7 (1.0 g). The obtained mixture was stirred at a room temperature for 2 days. Thereafter, water was added to the reaction solution, and the obtained mixture was then extracted with diethyl ether. The organic layer was dried over anhydrous magnesium sulfate and was then filtered. The filtrate was concentrated under a reduced pressure, and the residue was then purified by NH-silica gel column chromatography (YAMAZEN, Hi-Flush™ column, elution solvent: n-heptane : ethyl acetate = 4 : 1 → 1 : 2) ×2, so as to obtain the above-captioned compound (880 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.60-1.63 (m, 1H), 1.92 (t, J=5.6 Hz, 1H), 2.07 (brdt, J=8.0 Hz, 1H), 2.22 (s, 3H), 2.27 (s, 3H), 2.56 (s, 3H), 4.41 (d, J=9.2 Hz, 1H), 4.49 (d, J=9.6 Hz,

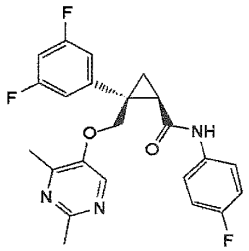
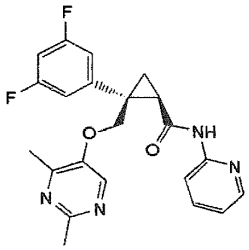
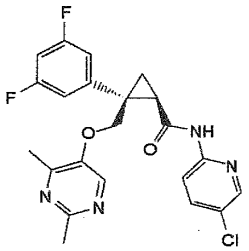
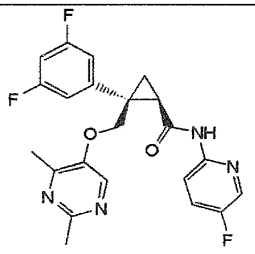
1H), 6.76 (t, J=8.8 Hz, 1H), 6.97-6.99 (brd, 2H), 7.90 (d, J=6.4 Hz, 1H), 7.99 (s, 2H), 8.27 (brds, 1H).

[0315]

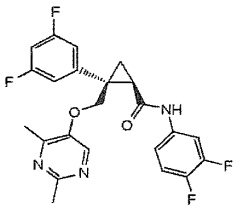
* The compounds of Examples 130 to 138 were synthesizing by reacting the carboxylic acid Prep 16-7 with any amine by the same method as that of Example 1.

[0316]

[Table 35-1]

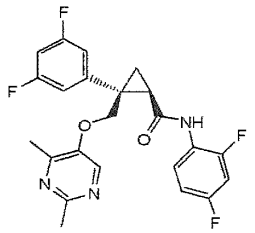
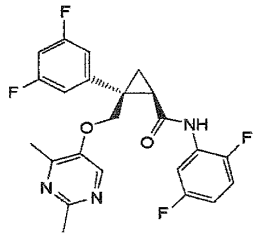
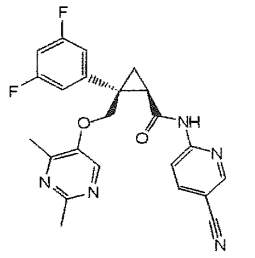
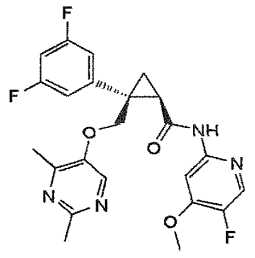
Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
130		^{1}H-NMR δ (ppm): 1.60 (dd, J=5.2 Hz, 8.0 Hz, 1H), 1.92 (t, J=5.6 Hz, 1H), 2.03 (brdt, J=7.6 Hz, 1H), 2.25 (s, 3H), 2.57 (s, 3H), 4.46 (d, J=9.6 Hz, 1H), 4.51 (d, J=10.0 Hz, 1H), 6.75 (t, J=6.8 Hz, 1H), 6.97-7.01 (m, 4H), 7.38-7.40 (m, 2H), 7.62 (s, 1H), 8.01 (s, 1H). MS $[M+H]^+$=428
131		^{1}H-NMR δ (ppm): 1.59-1.62 (m, 1H), 1.94 (t, J=5.2 Hz, 1H), 2.11 (brdt, J=8.0 Hz, 1H), 2.21 (s, 3H), 2.56 (s, 3H), 4.41 (d, J=9.6 Hz, 1H), 4.50 (d, J=9.6 Hz, 1H), 6.76 (t, J=6.8 Hz, 1H), 6.98-7.04 (m, 3H), 7.65 (t, J=7.6 Hz, 1H), 7.99-8.03 (m, 2H), 8.26 (d, J=4.0 Hz, 1H), 8.47 (s, 1H). MS $[M+H]^+$=411
132		^{1}H-NMR δ (ppm): 1.62 (dd, J=5.6 Hz, 8.4 Hz, 1H), 1.93 (t, J=5.2 Hz, 1H), 2.10 (brdt, J=7.6 Hz, 1H), 2.22 (s, 3H), 2.56 (s, 3H), 4.40 (d, J=10.0 Hz, 1H), 4.49 (d, J=9.2 Hz, 1H), 6.76 (t, J=8.8 Hz, 1H), 6.96-7.00 (m, 2H), 7.61 (dd, J=2.8 Hz, 9.2 Hz, 1H), 7.99-8.02 (m, 2H), 8.21 (d, J=2.0 Hz, 1H), 8.45 (s, 1H). MS $[M+H]^+$=445
133		^{1}H-NMR δ (ppm): 1.61-1.64 (m, 1H), 1.93 (t, J=5.2 Hz, 1H), 2.09 (brdt, J=8.0 Hz, 1H), 2.22 (s, 3H), 2.56 (s, 3H), 4.40 (d, J=9.6 Hz, 1H), 4.49 (d, J=9.6 Hz, 1H), 6.74-6.79 (m, 1H), 6.98 (d, J=6.0 Hz, 2H), 7.36-7.41 (m, 1H), 7.99 (s, 1H), 8.05 (dd, J=3.6 Hz, 9.2 Hz, 1H), 8.11 (d, J=2.8 Hz, 1H), 8.35 (brds, 1H). MS $[M+H]^+$=429

[Table 35-2]

134		^{1}H-NMR δ (ppm): 1.61-1.63 (m, 1H), 1.92 (t, J=5.6 Hz, 1H), 2.02 (dd, J=5.6 Hz, 8.4 Hz, 1H), 2.25 (s, 3H), 2.58 (s, 3H), 4.45 (d, J=9.6 Hz, 1H), 4.51 (d, J=9.6 Hz, 1H), 6.75 (t, J=8.8 Hz, 1H), 6.96-7.12 (m, 4H), 7.47-7.53 (m, 1H), 7.62 (s, 1H), 8.01 (s, 1H). MS $[M+H]^+$=446

[0317]

[Table 36]

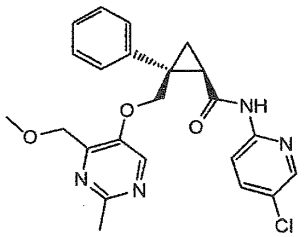
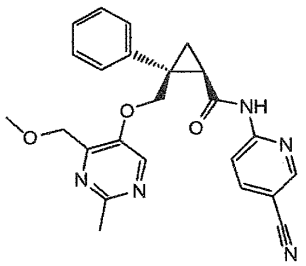
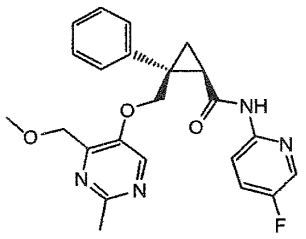
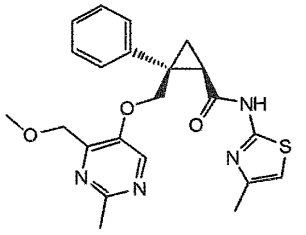
Example	Structural formula	NMR and/or MS
135		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.63 (dd, J=5.6 Hz, 8.4 Hz, 1H), 1.93 (t, J=5.2 Hz, 1H), 2.09 (dd, J=5.6 Hz, 8.0 Hz, 1H), 2.26 (s, 3H), 2.57 (s, 3H), 4.44 (d, J=9.2 Hz, 1H), 4.50 (d, J=9.6 Hz, 1H), 6.74-7.01 (m, 5H), 7.59 (brds, 1H), 8.00-8.07 (m, 2H). MS $[M+H]^+$=446
136		^{1}H-NMR (400 M Hz, $CDCl_3$) δ (ppm): 1.65 (dd, J=5.2 Hz, 8.4 Hz, 1H), 1.94 (t, J=5.2 Hz, 1H), 2.10 (dd, J=5.6 Hz, 8.0 Hz, 1H), 2.24 (s, 3H), 2.57 (s, 3H), 4.43 (d, J=10.0 Hz, 1H), 4.51 (d, J=10.0 Hz, 1H), 6.70-6.79 (m, 2H), 6.96-7.08 (m, 3H), 7.73 (brds, 1H), 7.96-8.01 (m, 2H). MS $[M+H]^+$=446
137		^{1}H-NMR (400 M Hz, $CDCl_3$) δ (ppm): 1.67 (dd, J=5.2 Hz, 8.4 Hz, 1H), 1.96 (t, J=5.6 Hz, 1H), 2.15 (brdt, J=7.2 Hz, 1H), 2.21 (s, 3H), 2.56 (s, 3H), 4.39 (d, J=10.0 Hz, 1H), 4.48 (d, J=10.0 Hz, 1H), 6.77 (t, J=8.4 Hz, 1H), 6.80-7.02 (m, 2H), 7.89 (dd, J=2.0 Hz, 8.8 Hz, 1H), 7.99 (s, 1H), 8.18 (d, J=9.2 Hz, 1H), 8.55-8.58 (m, 2H). MS $[M+H]^+$=436
138		^{1}H-NMR (400 M Hz, $CDCl_3$) δ (ppm): 1.63 (dd, J=5.8, 8.0 Hz, 1H), 1.92 (t, J=5.8 Hz, 1H), 2.08 (dd, J=5.8, 8.0 Hz, 1H), 2.24 (s, 3H), 2.56 (s, 3H), 3.87 (s, 3H), 4.41 (d, J=9.8 Hz, 1H), 4.50 (d, J=9.8 Hz, 1H), 6.77 (tt, J=2.4, 8.8H, 1H), 6.97-7.02 (m, 2H), 7.78 (d, J=6.8 Hz, 1H), 7.97 (d, J=2.4 Hz, 1H), 8.00 (s, 1H), 8.28 (brs, 1H). MS $[M+H]^+$=459

[0318]

* The compounds of Examples 139 to 142 were synthesized by reacting the carboxylic acid Prep 23 with any amine by the same method as that of Example 1.

[0319]

[Table 37]

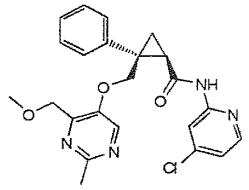
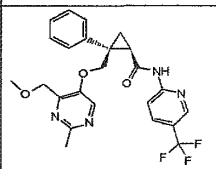
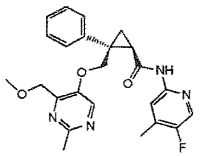
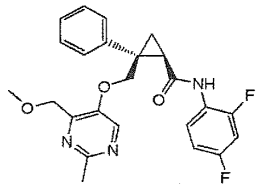
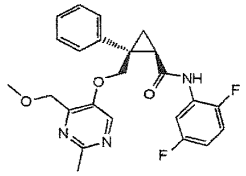
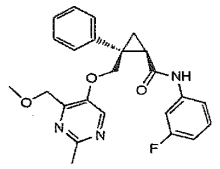
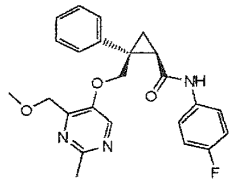
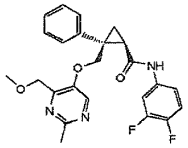
Example	Structural formula	NMR and/or MS
139		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.64 (dd, J=8.0 Hz, 5.2 Hz, 1H), 1.91 (t, J=5.2 Hz, 1H), 2.12 (brdt, J=8.0 Hz, 1H), 2.62 (s, 3H), 3.28 (s, 3H), 4.27-4.55 (m, 4H), 7.26-7.46 (m, 6H), 7.62 (dd, J=2.4 Hz, 8.8 Hz, 1H), 8.05-8.08 (m, 2H), 8.23 (d, J=2.4 Hz, 1H), 8.29 (brds, 1H). MS $[M+Na]^+$=461
140		MS $[M+Na]^+$=452
141		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.62-1.64 (m, 1H), 1.90 (t, J=5.2 Hz, 1H), 2.12 (brdt, J=7.6 Hz, 1H), 2.62 (s, 3H), 3.27 (s, 3H), 4.27-4.55 (m, 4H), 7.30-7.46 (m, 6H), 8.08-8.12 (m, 3H), 8.37 (brds, 1H). MS $[M+]^+$=423
142		MS $[M+H]^+$=425

[0320]

* The compounds of Examples 143 to 150 were synthesized by reacting the carboxylic acid Prep 23 with any amine by the same method as that of Example 51.

[0321]

[Table 38]

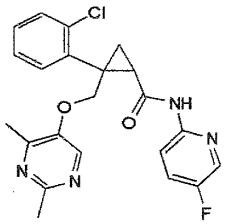
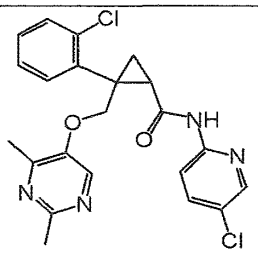
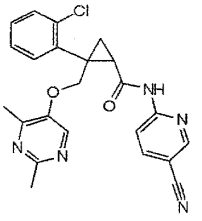
Example	Structural formula, MS	Example	Structural formula, MS	Example	Structural formula, MS
143	 [M+H]$^+$=439	144	 [M+H]$^+$=473	145	 [M+H]$^+$=437
146	 [M+H]$^+$=440	147	 [M+H]$^+$=440	148	 [M+H]$^+$=422
149	 [M+H]$^+$=422	150	 [M+H]$^+$=440		

[0322]

* The compounds of Examples 151 to 153 were synthesized by reacting the carboxylic acid Prep 24 with any amine by the same method as that of Example 1.

[0323]

[Table 39]

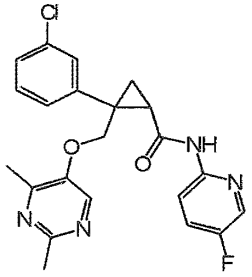
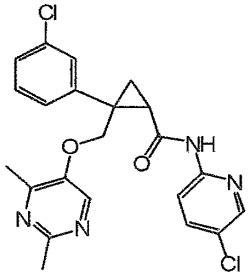
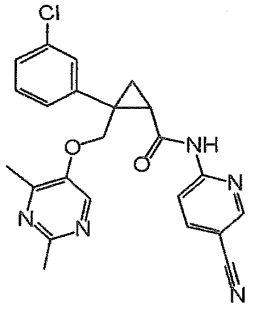
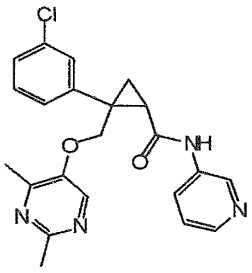
Example	Structural formula, MS	Example	Structural formula, MS	Example	Structural formula, MS
151	 [M+H]$^+$=427	152	 [M+H]$^+$=443	153	 [M+H]$^+$=434

[0324]

* The compounds of Examples 154 to 157 were synthesized by reacting the carboxylic acid Prep 25 with any amine by the same method as that of Example 1.

[0325]

[Table 40]

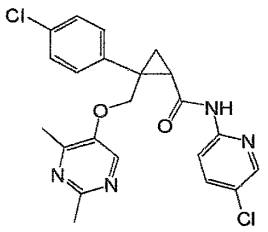
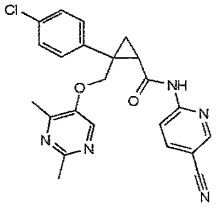
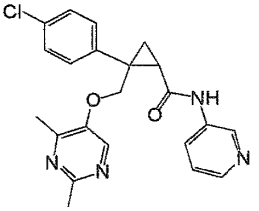
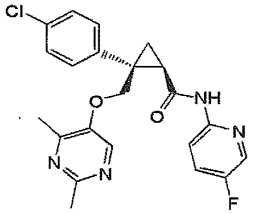
Example	Structural formula, MS	Example	Structural formula, MS
154	 [M+H]$^+$=427	155	 [M+H]$^+$=430
156	 [M+H]$^+$=434	157	 [M+H]$^+$=409

[0326]

* The compounds of Examples 158 to 161 were synthesized by condensing the carboxylic acid Prep 26 and any amine by the same method as that of Example 1. The compound of Example 161 was obtained by performing chiral resolution on racemic products (Chiral pak-IA (hexane : ethanol = 70 : 30, 15 mL/min, 254 nm, rt) 10.5 min ((+)- form), 13.0 min ((-)- form, target compound).

[0327]

[Table 41]

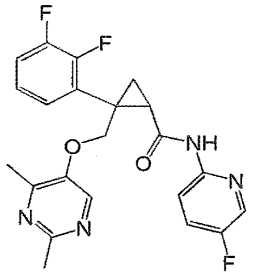
Example	Structural formula, MS	Example	Structural formula, MS	Example	Structural formula, MS
158	 $[M+H]^+$=443	159	 $[M+H]^+$= 434	160	 $[M+H]^+$=409
161		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.59 (dd, J=8.0, 5.2 Hz, 1H), 1.91 (t, J=5.2 Hz, 1H), 2.07 (dd, J=8.0, 6.0 Hz, 1H), 2.21 (s, 3H), 2.56 (s, 3H), 4.40 (d, J=9.6 Hz, 1H), 4.47 (d, J=9.6 Hz, 1H), 7.34-7.72 (m, 5H), 7.97 (s, 1H), 8.07 (dd, J=9.2, 4.0 Hz, 1H), 8.12 (d, J=2.8 Hz, 1H), 8.36 (brs, 1H).				

[0328]

Example 162

Synthesis of 2-(2,3-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide (162)

[Formula 64]



162

[0329]

The above-captioned compound was synthesized by amidating the carboxylic acid Prep 27 by the same method as that of Example 51.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.53 (dd, J=5.2 Hz, 8.0 Hz, 1H), 1.94 (t, J=5.2 Hz, 1H), 2.16-2.22 (m, 4H), 2.54 (s, 3H), 4.34 (d, J=9.6 Hz, 1H), 4.42 (d, J=9.6 Hz, 1H), 7.06-7.42 (m, 4H), 7.93 (s, 1H), 8.09-8.14 (m, 2H), 8.34 (brds, 1H).

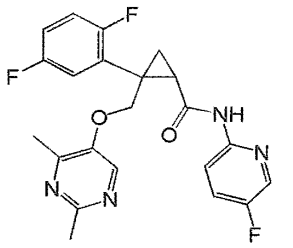
MS $[M+H]^+$=429

[0330]

Example 163

Synthesis of 2-(2,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide (163)

[Formula 65]



163

[0331]

The above-captioned compound was synthesized by amidating the carboxylic acid Prep 28 by the same method as that of Example 51.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.53 (dd, J=5.2 Hz, 8.0 Hz, 1H), 1.94 (t, J=5.2 Hz, 1H), 2.17 (brdt, J=7.6 Hz, 1H), 2.22 (s, 3H), 2.54 (s, 3H), 4.32 (d, J=9.6 Hz, 1H), 4.40 (d, J=9.6 Hz, 1H), 6.97-7.43 (m, 4H), 7.93 (s, 1H), 8.10-8.14 (m, 2H), 8.34 (brds, 1H).

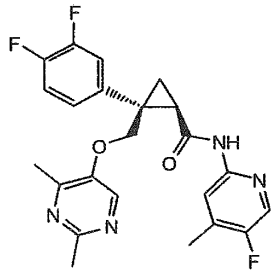
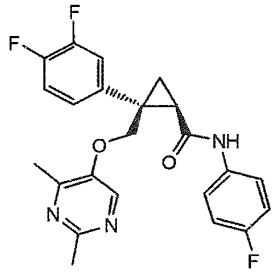
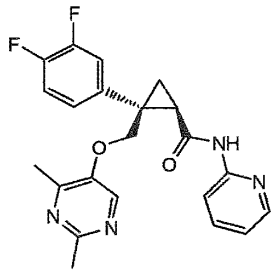
MS $[M+H]^+$=429

[0332]

* The compounds of Examples 164 to 172 were synthesized by condensing the carboxylic acid (Prep 29) and any amine by the same method as that of Example 52.

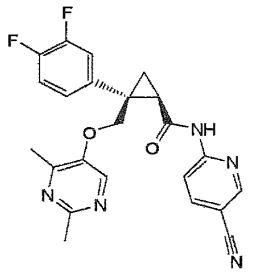
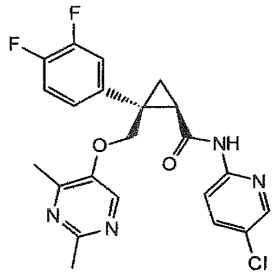
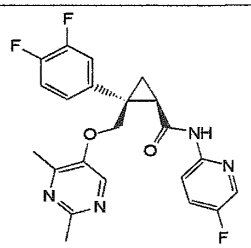
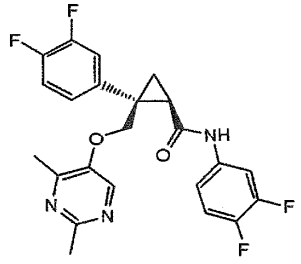
[0333]

[Table 42]

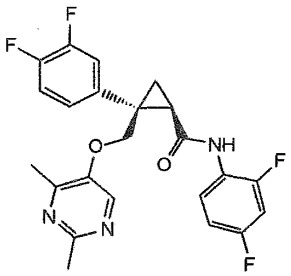
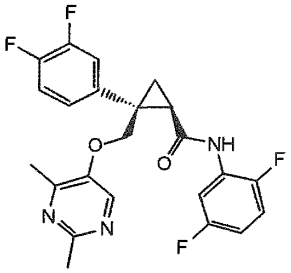
Example	Structural formula	NMR and/or MS
164		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.58 (dd, J=5.2 Hz, 8.4 Hz, 1H), 1.91 (t, J=5.2 Hz, 1H), 2.05 (brdt, J=8.0 Hz, 1H), 2.21 (s, 3H), 2.26 (s, 3H), 2.55 (s, 3H), 4.40 (d, J=10.0 Hz, 1H), 4.46 (d, J=9.6 Hz, 1H), 7.10-7.23 (m, 3H), 7.91 (d, J=5.2 Hz, 1H), 7.96-7.98 (m, 2H), 8.49 (brds, 1H). MS $[M+H]^+$=443
165		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.57 (dd, J=5.2 Hz, 8.0 Hz, 1H), 1.90 (t, J=4.8 Hz, 1H), 2.00 (brdt, J=8.0 Hz, 1H), 2.25 (s, 3H), 2.57 (s, 3H), 4.45 (d, J=9.6 Hz, 1H), 4.48 (d, J=10.0 Hz, 1H), 6.97-7.41 (m, 7H), 7.58 (s, 1H), 7.80 (s, 1H). MS $[M+H]^+$=428
166		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.58 (dd, J=5.2 Hz, 8.4 Hz, 1H), 1.91 (t, J=5.2 Hz, 1H), 2.08 (brdt, 1H), 2.21 (s, 3H), 2.55 (s, 3H), 4.40 (d, J=9.6 Hz, 1H), 4.46 (d, J=9.2 Hz, 1H), 7.01-7.32 (m, 5H), 7.63-7.67 (m, 1H), 7.98 (s, 1H), 8.03 (d, J=8.4 Hz, 1H), 8.26 (d, J=4.0 Hz, 1H), 8.44 (s, 1H). MS $[M+H]^+$=411

[0334]

[Table 43-1]

Example	Structural formula	NMR and/or MS
167		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.63-1.68 (m, 1H), 1.94 (t, J=5.2 Hz, 1H), 2.12 (brdt, J=7.6 Hz, 1H), 2.21 (s, 3H), 2.58 (s, 3H), 4.38 (d, J=9.6 Hz, 1H), 4.44 (d, J=9.6 Hz, 1H), 7.13-7.32 (m, 4H), 7.90 (dd, J=2.4 Hz, 9.2 Hz, 1H), 7.97 (s, 1H), 8.19 (s, 1H), 8.51 (s, 1H), 8.56 (d, J=2.0 Hz, 1H). MS $[M+H]^+$=436
168		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.58-1.61 (m, 1H), 1.91 (t, J=5.6 Hz, 1H), 2.07 (brdt, J=6.0 Hz, 1H), 2.22 (s, 3H), 2.56 (s, 3H), 4.38 (d, J=9.2 Hz, 1H), 4.45 (d, J=9.2 Hz, 1H), 7.12-7.31 (m, 3H), 7.62 (dd, J=2.4 Hz, 8.8 Hz, 1H), 7.97 (s, 1H), 8.03 (d, J=8.8 Hz, 1H), 8.22 (d, J=2.8 Hz, 1H), 833 (s, 1H). MS $[M+H]^+$=445
169		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.58-1.61 (m, 1H), 1.91 (t, J=5.2 Hz, 1H), 2.07 (brdt, J=8.0 Hz, 1H), 2.21 (s, 3H), 2.56 (s, 3H), 4.39 (d, J=9.6 Hz, 1H), 4.45 (d, J=9.6 Hz, 1H), 7.12-7.41 (m, 4H), 7.97 (s, 1H), 8.04-8.08 (m, 1H), 8.12 (d, J=2.4 Hz, 1H) 8.30 (brds, 1H). MS $[M+H]^+$=429
170		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.58-1.61 (m, 1H), 1.90 (t, J=5.6 Hz, 1H), 1.91 (dd, J=6.0 Hz, 8.4 Hz, 1H), 2.25 (s, 3H), 2.57 (s, 3H), 4.44 (d, J=10 Hz, 1H), 4.47 (d, J=9.6 Hz, 1H), 7.04-7.31 (m, 5H), 7.48-7.53 (m, 1H), 7.57 (s, 1H), 8.00 (s, 1H). MS $[M+H]^+$=446

[Table 43-2]

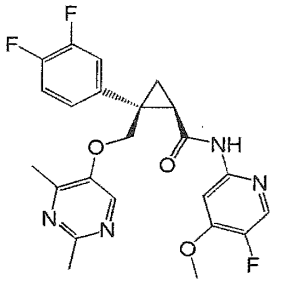
171		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.58-1.62 (m, 1H), 1.91 (t, J=5.6 Hz, 1H), 2.06 (dd, J=6.0 Hz, 8.0 Hz, 1H), 2.26 (s, 3H), 2.57 (s, 3H), 4.43 (d, J=9.2 Hz, 1H), 4.47 (d, J=9.2 Hz, 1H), 6.81-6.91 (m, 2H), 7.11-7.32 (m, 3H), 7.59 (brds, 1H), 7.99-8.08 (m, 2H). MS $[M+H]^+$=446
172		^{1}H-NMR (400 M Hz, $CDCl_3$) δ (ppm): 1.62 (dd, J=5.6 Hz, 8.4 Hz, 1H), 1.92 (t, J=5.6 Hz, 1H), 2.08 (dd, J=5.6 Hz, 8.4 Hz, 1H), 2.24 (s, 3H), 2.57 (s, 3H), 4.42 (d, J=9.6 Hz, 1H), 4.47 (d, J=10.0 Hz, 1H), 6.71-6.75 (m, 1H), 7.02-7.32 (m, 4H), 7.73 (brds, 1H), 7.99 (brdm, 2H). MS $[M+H]^+$=446

[0335]

Example 173

Synthesis of (1R,2S)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxypyridin-2-yl)cyclopropanecarboxamide (173)

[Formula 66]



173

[0336]

The above-captioned compound was synthesized from Prep 29 according to Example 73.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.60 (dd, J=5.6, 8.0 Hz, 1H), 1.90 (t, J=5.6 Hz, 1H), 2.06 (dd, J=5.6, 8.0 Hz, 1H), 2.24 (s, 3H), 2.56 (s, 3H), 3.88 (s, 3H), 4.40 (d, J=9.6 Hz, 1H), 4.46 (d, J=9.6 Hz, 1H), 7.12-7.32 (m, 3H), 7.79 (d, J=6.8 Hz, 1H), 7.98-7.99 (m, 2H), 8.25 (brs, 1H).

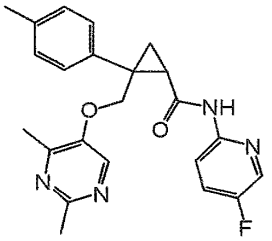
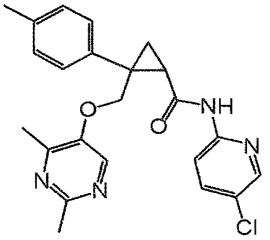
MS $[M+H]^+$=459

[0337]

* The compounds of Examples 174 and 175 were synthesized by condensing the carboxylic acid Prep 30 and any amine by the same method as that of Example 46.

[0338]

[Table 44]

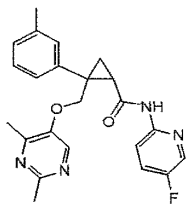
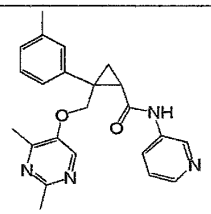
Example	Structural formula, MS	Example	Structural formula, MS
174	 MS $[M+H]^+$= 407	175	 MS $[M+H]^+$= 423

[0339]

* The compounds of Examples 176 and 177 were synthesized by condensing the carboxylic acid Prep 31 of Production Example 31 and any amine by the same method as that of Example 1.

[0340]

[Table 45]

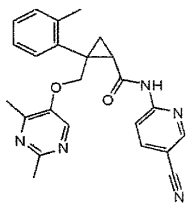
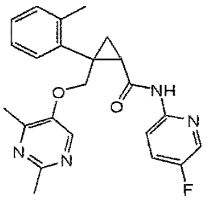
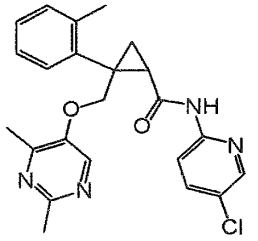
Example	Structural formula, MS	Example	Structural formula, MS
176	 MS $[M+H]^+$= 407	177	 MS $[M+H]^+$= 389

[0341]

* The compounds of Examples 178 to 180 were synthesized by condensing the carboxylic acid Prep 32 of Production Example 32 and any amine by the same method as that of Example 1.

[0342]

[Table 46]

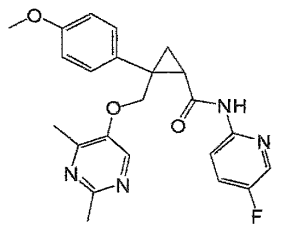
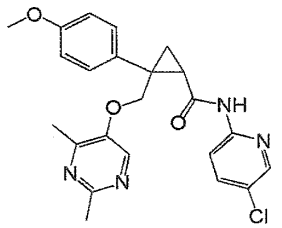
Example	Structural formula, MS	Example	Structural formula, MS
178	 MS $[M+H]^+$= 414	179	 MS $[M+H]^+$= 407
180		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.49-1.55 (m, 1H), 1.97 (t, J=5.2 Hz, 1H), 2.16 (dd, J=8.2, 5.8 Hz, 1H), 2.21 (s, 3H), 2.53 (s, 3H), 2.55 (s, 3H), 4.45 (dd, J=11.0, 9.4 Hz, 2H), 7.17-7.31 (m, 4H), 7.42-7.48 (m, 1H), 7.82 (brs, 1H), 7.93 (s, 1H), 8.14 (brd, J=8.8 Hz, 1H), 8.36 (d, J=3.6 Hz, 1H), 8.58 (d, J=2.4 Hz, 1H).		

[0343]

* The compounds of Examples 181 and 182 were synthesized by condensing the carboxylic acid Prep 33 of Production Example 33 and any amine by the same method as that of Example 45.

[0344]

[Table 47]

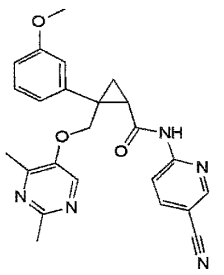
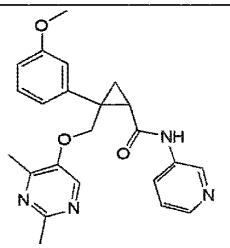
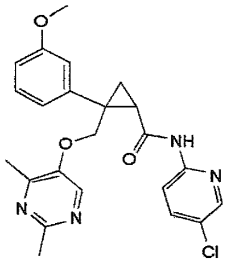
Example	Structural formula, MS	Example	Structural formula, MS
181	 MS $[M+H]^+$= 423	182	 MS $[M+H]^+$= 439

[0345]

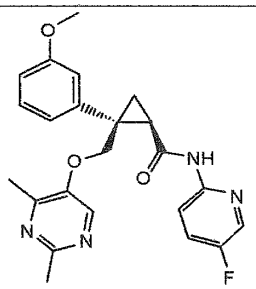
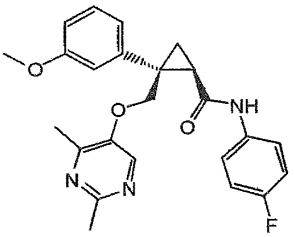
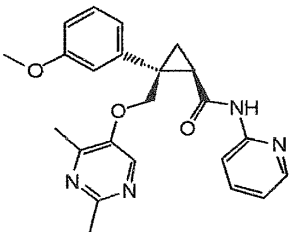
* The compounds of Examples 183 to 190 were synthesized by condensing the carboxylic acid Prep 34 of Production Example 34 and any amine by the same method as that of Example 1. The compounds of Examples 186 to 190 were obtained by performing chiral resolution.

[0346]

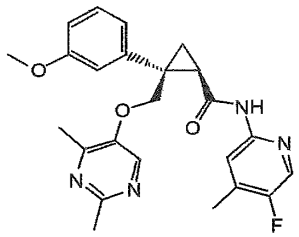
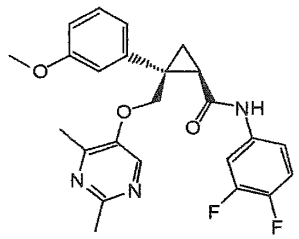
[Table 48-1]

Example	Structural formula	NMR and/or MS
183		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.68 (dd, J=5.6, 8.0 Hz, 1H), 1.92 (t, J=5.6 Hz, 1H), 2.16 (dd, J=5.6, 8.0 Hz, 1H), 2.21 (s, 3H), 2.55 (s, 3H), 3.83 (s, 3H), 4.37 (d, J=9.6 Hz, 1H), 4.50 (d, J=9.6 Hz, 1H), 6.85 (ddd, J=0.8, 2.6, 8.0 Hz, 1H), 7.00-7.05 (m, 2H), 7.29 (t, J=8.0 Hz, 1H), 7.89 (dd, J=2.2, 8.8 Hz, 1H), 7.96 (s, 1H), 8.21 (d, J=8.8 Hz, 1H), 8.48 (brs, 1H), 8.56 (dd, J=0.8, 2.2 Hz, 1H). MS $[M+H]^+$=430
184		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.63 (dd, J=5.6, 8.0 Hz, 1H), 1.90 (t, J=5.6 Hz, 1H), 2.12 (dd, J=5.6, 8.0 Hz, 1H), 2.24 (s, 3H), 2.56 (s, 3H), 3.81 (s, 3H), 4.45 (d, J=9.6 Hz, 1H), 4.54 (d, J=9.6 Hz, 1H), 6.83 (dd, J=2.0, 8.4 Hz, 1H), 7.01-7.04 (m, 2H), 7.23-7.30 (m, 2H), 7.87 (brs, 1H), 7.99 (s, 1H), 8.10 (brd, 1H), 8.34 (d, J=4.4 Hz, 1H), 8.53 (d, J=2.0 Hz, 1H). MS $[M+H]^+$=405
185		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.63 (dd, J=5.6, 8.0 Hz, 1H), 1.89 (t, J=5.6 Hz, 1H), 2.13 (dd, J=5.6, 8.0 Hz, 1H), 2.22 (s, 3H), 2.55 (s, 3H), 3.82 (s, 3H), 4.38 (d, J=9.6 Hz, 1H), 4.51 (d, J=9.6 Hz, 1H), 6.84 (ddd, J=0.8, 2.4, 8.4 Hz, 1H), 7.01-7.06 (m, 2H), 7.26-7.30 (m, 1H), 7.61 (dd, J=2.4, 8.8 Hz, 1H), 7.96 (s, 1H), 8.04 (d, J=8.8 Hz, 1H), 8.22 (dd, J=0.8, 2.4 Hz, 1H), 8.32 (brs, 1H). MS $[M+H]^+$=439

[Table 48-2]

186		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.62 (dd, J=5.6, 8.0 Hz, 1H), 1.89 (t, J=5.6 Hz, 1H), 2.12 (dd, J=5.6, 8.0 Hz, 1H), 2.22 (s, 3H), 2.55 (s, 3H), 3.82 (s, 3H), 4.39 (d, J=9.6 Hz, 1H), 4.51 (d, J=9.6 Hz, 1H), 6.84 (ddd, J=0.8, 2.6, 8.0 Hz, 1H), 7.01-7.06 (m, 2H), 7.29 (d, J=8.0 Hz, 1H), 7.38 (ddd, J=2.8, 7.6, 9.2 Hz, 1H), 7.97 (s, 1H), 8.07 (dd, J=4.0, 9.2 Hz, 1H), 8.12 (d, J=2.8 Hz, 1H), 8.28 (brs, 1H). MS $[M+H]^+$=423
187		^{1}H-NMR (400 M Hz, $CDCl_3$) δ (ppm): 1.56 (dd, J=8.2, 5.2 Hz, 1H) 1.85 (t, J=5.6 Hz, 1H), 2.06 (dd, J=8.0, 6.0 Hz, 1H), 2.25 (s, 3H), 2.55 (s, 3H), 3.80 (s, 3H), 4.44 (d, J=9.6 Hz, 1H), 4.53 (d, J=9.6 Hz, 1H), 6.80-6.83 (m, 1H), 6.93-7.02 (m, 4H), 7.23-7.27 (m, 1H), 7.35-7.41 (m, 2H) 7.99 (s, 1H), 7.94-8.00 (brs, 1H).
188		^{1}H-NMR (400 M Hz, $CDCl_3$) δ (ppm): 1.61 (dd, J=8.2, 5.2 Hz, 1H) 1.90 (t, J=5.2 Hz, 1H), 2.12-2.16 (m, 1H), 2.21 (s, 3H), 2.55 (s, 3H), 3.81 (s, 3H), 4.41 (d, J=9.6 Hz, 1H), 4.54 (d, J=9.6 Hz, 1H), 6.82-6.85 (m, 1H), 6.94-7.05 (m, 3H), 7.24-7.29 (m, 1H), 7.61-7.65 (m, 1H) 7.99 (S, 1H), 8.02-8.05 (m, 1H), 8.19-8.21 (m, 1H), 8.88 (brs, 1H).

[Table 48-3]

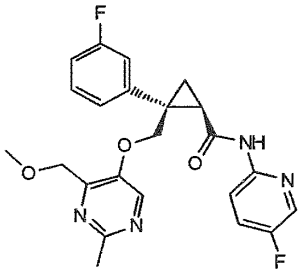
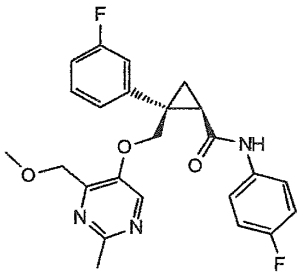
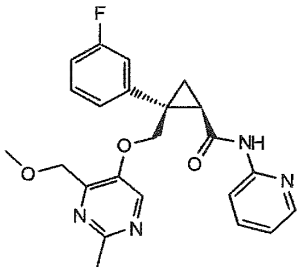
189		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.61 (dd, J=8.2, 5.2 Hz, 1H) 1.88 (t, J=5.6 Hz, 1H), 2.12 (dd, J=8.0, 6.0 Hz, 1H), 2.22 (s, 3H), 2.26 (s, 3H), 2.55 (s, 3H), 3.81 (s, 3H), 4.41 (d, J=9.2 Hz, 1H), 4.53 (d, J=9.6 Hz, 1H), 6.81-6.85 (m, 1H), 6.99-7.04 (m, 2H), 7.25-7.29 (m, 1H), 7.91-7.95 (m, 2H), 7.99 (s, 1H), 8.70 (brs, 1H).
190		^{1}H-NMR (400 M Hz, $CDCl_3$) δ (ppm): 1.59-1.62 (m, 1H), 1.88 (t, J=5.6 Hz, 1H), 2.04 (dd, J=8.2, 5.6 Hz, 1H), 2.24 (s, 3H), 2.57 (s, 3H), 3.82 (s, 3H), 4.43 (d, J=9.6 Hz, 1H), 4.53 (d, J=9.6 Hz, 1H), 6.81-6.85 (m, 1H), 6.99-7.12 (m, 4H), 7.25-7.30 (m, 1H), 7.48-7.54 (m, 1H), 7.60 (br, 1H), 7.99 (s, 1H).

[0347]

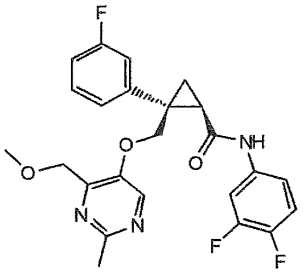
* The compounds of Examples 191 to 201 were synthesized by condensing the carboxylic acid Prep 35 and any amine. It is to be noted that, with regard to condensation methods, the compounds of Examples 193 to 199 were condensed according to the method of Example 51 and the compounds of Examples 200 and 201 were condensed by the method of Example 1.

[0348]

[Table 49-1]

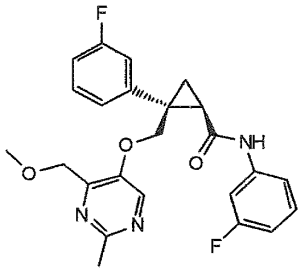
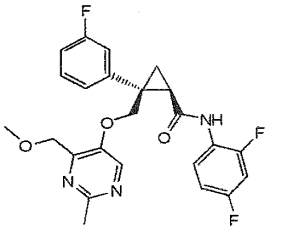
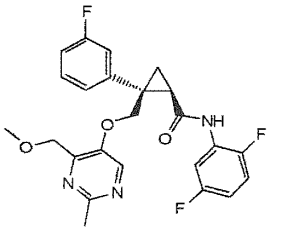
Example	Structural formula	NMR and/or MS
191		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.63 (dd, J=8.0, 5.2 Hz, 1H), 1.92 (t, J=5.2 Hz, 1H), 2.12 (dd, J=8.0, 6.0 Hz, 1H), 2.63 (s, 3H), 3.30 (s, 3H), 4.29 (d, J=13.6 Hz, 1H), 4.44 (d, J=13.6 Hz, 1H), 4.46 (d, J=9.6 Hz, 1H), 4.53 (d, J=9.6 Hz, 1H), 7.01 (tdd, J=8.0, 2.4, 1.2 Hz, 1H), 7.18-7.24 (m, 2H), 7.34 (dd, J=8.0, 6.0 Hz, 1H), 7.40 (ddd, J=10.4, 9.2, 2.8 Hz, 1H), 8.08 (dd, J=9.2, 4.0 Hz, 1H), 8.11 (s, 1H), 8.13 (d, J=2.4 Hz, 1H), 8.38 (brs, 1H).
192		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.59 (dd, J=8.0, 5.2 Hz, 1H), 1.90 (t, J=5.2 Hz, 1H), 2.06 (dd, J=8.0, 6.0 Hz, 1H), 2.61 (s, 3H), 3.30 (s, 3H), 4.34 (d, J=13.2 Hz, 1H), 4.41 (d, J=13.2 Hz, 1H), 4.48 (d, J=9.6 Hz, 1H), 4.57 (d, J=9.6 Hz, 1H), 6.97-7.01 (m, 3H), 7.18-7.24 (m, 2H), 7.31 (td, J=8.0, 6.0 Hz, 1H), 7.39-7.43 (m, 2H), 7.65 (brs, 1H), 8.12 (s, 1H).
193		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.63 (dd, J=8.0, 5.2 Hz, 1H), 1.93 (t, J=5.2 Hz, 1H), 2.14 (brs, 1H), 2.63 (s, 3H), 3.26 (s, 3H), 4.27 (d, J=13.6 Hz, 1H), 4.43 (d, J=13.6 Hz, 1H), 4.48 (d, J=9.6 Hz, 1H), 4.56 (d, J=9.6 Hz, 1H), 6.98-7.03 (m, 2H), 7.19 (d, J=10.0 Hz, 1H), 7.22 (d, J=8.0 Hz, 1H), 7.33 (td, J=8.0, 6.0 Hz, 1H), 7.65 (td, J=8.0, 2.0 Hz, 1H), 8.05 (d, J=8.0 Hz, 1H), 8.12 (s, 1H), 8.22 (dd, J=4.8, 1.2 Hz, 1H), 8.81 (s, 1H).

[Table 49-2]

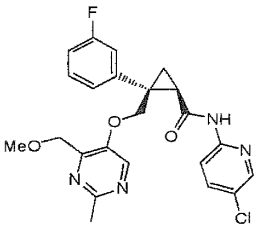
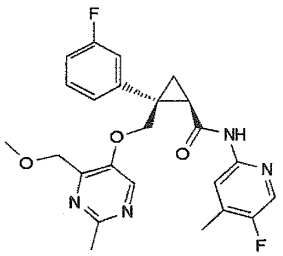
194		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.59 (dd, J=8.0, 5.2 Hz, 1H), 1.90 (t, J=5.2 Hz, 1H), 2.06 (dd, J=8.0, 6.0 Hz, 1H), 2.61 (s, 3H), 3.31 (s, 3H), 4.35 (d, J=12.8 Hz, 1H), 4.40 (d, J=12.8 Hz, 1H), 4.46 (d, J=9.6 Hz, 1H), 4.57 (d, J=9.6 Hz, 1H), 7.00 (td, J=8.4, 2.0 Hz, 1H), 7.04-7.11 (m, 2H), 7.18-7.22 (m, 2H), 7.32 (td, J=8.4, 6.0 Hz, 1H), 7.52 (dd, J=10.8, 6.8 Hz, 1H), 7.80 (brs, 1H), 8.12 (s, 1H).

[0349]

[Table 50-1]

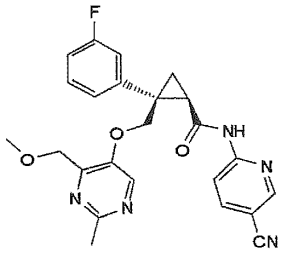
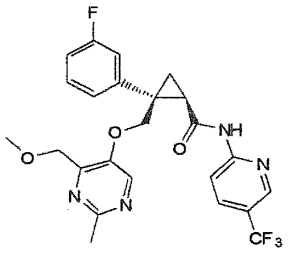
Example	Structural formula	NMR and/or MS
195		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.59 (dd, J=8.0, 5.6 Hz, 1H), 1.95 (t, J=5.6 Hz, 1H), 2.09 (dd, J=8.0, 5.6 Hz, 1H), 2.63 (s, 3H), 3.29 (s, 3H), 4.32 (d, J=13.2 Hz, 1H), 4.42 (d, J=13.2 Hz, 1H), 4.48 (d, J=10.0 Hz, 1H), 4.58 (d, J=10.0 Hz, 1H), 6.80 (t, J=7.6 Hz, 1H), 7.00 (tdd, J=8.0, 2.4, 1.2 Hz, 1H), 7.13 (dt, J=9.6, 2.4 Hz, 1H), 7.14-7.27 (m, 3H), 7.33 (td, J=8.0, 6.0 Hz, 1H), 7.41 (t, J=10.8 Hz, 1H), 7.85 (brs, 1H), 8.12 (s, 1H).
196		^{1}H-NMR (400 M Hz, $CDCl_3$) δ (ppm): 1.64 (dd, J=5.2 Hz, 8.0 Hz, 1H), 1.91 (t, J=5.2 Hz, 1H), 2.11 (dd, J=6.0 Hz, 8.0 Hz, 1H), 2.63 (s, 3H), 3.33 (s, 3H), 4.32-4.56 (m, 4H), 6.81-6.90 (m, 2H), 7.01 (t, J=8.8 Hz, 1H), 7.21-7.36 (m, 3H), 7.62 (brds, 1H), 8.05-8.12 (m, 2H). MS $[M+H]^+$=458
197		^{1}H-NMR (400 M Hz, $CDCl_3$) δ (ppm): 1.65 (dd, J=5.2 Hz, 8.0 Hz, 1H), 1.93 (t, J=5.2 Hz, 1H), 2.11 (dd, J=6.0 Hz, 8.4 Hz, 1H), 2.63 (s, 3H), 3.31 (s, 3H), 4.29-4.57 (m, 4H), 6.70-6.76 (m, 1H), 6.99-7.08 (m, 2H), 7.17-7.37 (m, 3H), 7.77 (brds, 1H), 8.02-8.12 (m, 2H). MS $[M+H]^+$=458

[Table 50-2]

198		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.61 (dd, J=8.2, 5.2 Hz, 1H) 1.88 (t, J=5.6 Hz, 1H), 2.12 (dd, J=8.0, 6.0 Hz, 1H), 2.22 (s, 3H), 2.26 (s, 3H), 2.55 (s, 3H), 3.81 (s, 3H), 4.41 (d, J=9.2 Hz, 1H), 4.53 (d, J=9.6 Hz, 1H), 6.81-6.85 (m, 1H), 6.99-7.04 (m, 2H), 7.25-7.29 (m, 1H), 7.91-7.95 (m, 2H), 7.99 (s, 1H), 8.70 (brs, 1H).
199		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.62 (dd, J=8.0, 5.2 Hz, 1H), 1.90 (d, J=5.2 Hz, 1H), 2.10 (dd, J=8.0, 6.0 Hz, 1H), 2.27 (s, 3H), 2.63 (s, 3H), 3.31 (s, 3H), 4.29 (d, J=13.2 Hz, 1H), 4.42 (d, J=13.2 Hz, 1H), 4.45 (d, J=9.6 Hz, 1H), 4.53 (d, J=9.6 Hz, 1H), 7.00 (tdd, J=8.0, 2.4, 1.2 Hz, 1H), 7.19 (dt, J=10.0, 2.4 Hz, 1H), 7.22 (dt, J=8.0, 1.2 Hz, 1H), 7.33 (td, J=6.0, 6.0 Hz, 1H), 7.95 (brs, 1H), 8.01 (s, 1H), 8.10 (s, 1H), 8.25 (s, 1H).

[0350]

[Table 51]

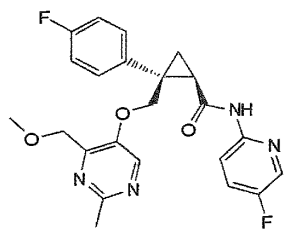
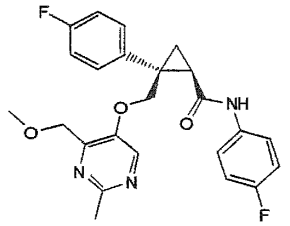
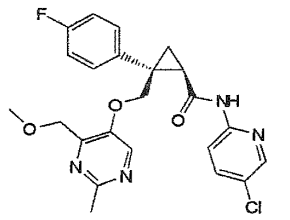
Example	Structural formula	NMR (400 MHz, $CDCl_3$)
200		^{1}H-NMR δ (ppm): 1.69 (dd, J=8.0, 5.2 Hz, 1H), 1.95 (t, J=5.2 Hz, 1H), 2.16 (dd, J=8.0, 6.0 Hz, 1H), 2.62 (s, 3H), 3.29 (s, 3H), 4.30 (d, J=13.2 Hz, 1H), 4.38 (d, J=13.2 Hz, 1H), 4.45 (d, J=9.6 Hz, 1H), 4.53 (d, J=9.6 Hz, 1H), 7.02 (dd, J=8.8, 2.0 Hz, 1H), 7.19-7.25 (m, 2H), 7.35 (td, J=8.0, 6.0 Hz, 1H), 7.90 (dd, J=8.8, 2.4 Hz, 1H), 8.11 (s, 1H), 8.22 (dd, J=8.8, 1.2 Hz, 1H), 8.55 (brs, 1H), 8.57 (dd, J=2.4, 1.2 Hz, 1H).
201		^{1}H-NMR δ (ppm): 1.66 (dd, J=8.0, 5.2 Hz, 1H), 1.94 (t, J=5.2 Hz, 1H), 2.16 (dd, J=8.0, 6.0 Hz, 1H), 2.61 (s, 3H), 3.27 (s, 3H), 4.29 (d, J=13.2 Hz, 1H), 4.40 (d, J=13.2 Hz, 1H), 4.45 (d, J=9.6 Hz, 1H), 4.53 (d, J=9.6 Hz, 1H), 7.01 (tdd, J=8.4, 2.8, 1.2 Hz, 1H), 7.19 (dt, J=10.0, 2.8 Hz, 1H), 7.23 (dt, J=8.4, 1.2 Hz, 1H), 7.34 (td, J=8.4, 6.0 Hz, 1H), 7.88 (dd, J=8.8, 2.4 Hz, 1H), 8.11 (s, 1H), 8.21 (d, J=8.8 Hz, 1H), 8.54 (d, J=2.4 Hz, 1H), 8.57 (brs, 1H).

[0351]

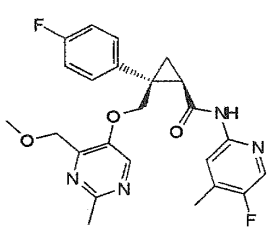
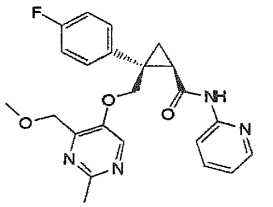
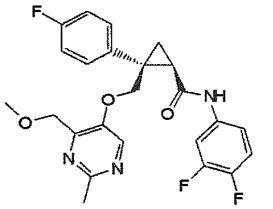
* The compounds of Examples 202 to 210 were synthesized by condensing the carboxylic acid Prep 36 and any amine by the same method as that of Example 52.

[0352]

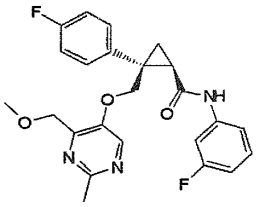
[Table 52-1]

Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
202		^{1}H-NMR δ (ppm): 1.60 (dd, J=8.0, 5.2 Hz, 1H), 1.90 (t, J=5.2 Hz, 1H), 2.07 (dd, J=8.0, 6.0 Hz, 1H), 2.62 (s, 3H), 3.29 (s, 3H), 4.29 (d, J=13.2 Hz, 1H), 4.40 (d, J=13.2 Hz, 1H), 4.44 (d, J=9.6 Hz, 1H), 4.49 (d, J=9.6 Hz, 1H), 7.05 (tt, J=8.8, 1.6 Hz, 2H), 7.37-7.46 (m, 3H), 8.09-8.13 (m, 3H), 8.32 (brs, 1H).
203		^{1}H-NMR δ (ppm): 1.56 (dd, J=8.0, 5.2 Hz, 1H), 1.88 (t, J=5.2 Hz, 1H), 2.05 (dd, J=8.0, 6.0 Hz, 1H), 2.61 (s, 3H), 3.29 (s, 3H), 4.34 (d, J=12.8 Hz, 1H), 4.39 (d, J=12.8 Hz, 1H), 4.48 (d, J=9.6 Hz, 1H), 4.53 (d, J=9.6 Hz, 1H), 6.99 (t, J=8.4 Hz, 2H), 7.04 (t, J=8.4 Hz, 2H), 7.40-7.45 (m, 4H), 7.63 (brs, 1H), 8.11 (s, 1H).
204		^{1}H-NMR δ (ppm): 1.60 (dd, J=8.0, 5.2 Hz, 1H), 1.90 (t, J=5.2 Hz, 1H), 2.08 (dd, J=8.0, 6.0 Hz, 1H), 2.62 (s, 3H), 3.28 (s, 3H), 4.29 (d, J=13.6 Hz, 1H), 4.40 (d, J=13.6 Hz, 1H), 4.43 (d, J=9.6 Hz, 1H), 4.49 (d, J=9.6 Hz, 1H), 7.05 (t, J=8.4 Hz, 2H), 7.44 (dd, J=8.4, 4.8 Hz, 2H), 7.62 (dd, J=8.8, 2.4 Hz, 1H), 8.06 (d, J=8.8 Hz, 1H), 8.08 (s, 1H), 8.23 (d, J=2.4 Hz, 1H), 8.32 (brs, 1H).

[Table 52-2]

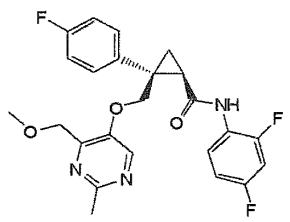
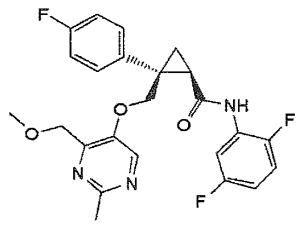
205		^{1}H-NMR δ (ppm): 1.59 (dd, J=8.0, 5.6 Hz, 1H), 1.89 (t, J=5.6 Hz, 1H), 2.06 (dd, J=8.0, 6.0 Hz, 1H), 2.28 (s, 3H), 2.62 (s, 3H), 3.30 (s, 3H), 4.29 (d, J=13.6 Hz, 1H), 4.41 (d, J=13.6 Hz, 1H), 4.44 (d, J=9.2 Hz, 1H), 4.49 (d, J=9.2 Hz, 1H), 7.05 (t, J=8.8 Hz, 2H), 7.43 (dd, J=8.8, 4.8 Hz, 2H), 7.95 (d, J=5.2 Hz, 1H), 8.00 (s, 1H), 8.09 (s, 1H), 8.26 (brs, 1H).
206		^{1}H-NMR δ (ppm): 1.59 (dd, J=8.0, 5.2 Hz, 1H), 1.91 (t, J=5.2 Hz, 1H), 2.10 (dd, J=8.0, 6.0 Hz, 1H), 2.62 (s, 3H), 3.26 (s, 3H), 4.28 (d, J=13.6 Hz, 1H), 4.44 (d, J=13.6 Hz, 1H), 4.41 (d, J=9.6 Hz, 1H), 4.50 (d, J=9.6 Hz, 1H), 7.02-7.08 (m, 3H), 7.44 (dd, J=8.8, 4.8 Hz, 2H), 7.66 (td, J=7.2, 2.0 Hz, 1H), 8.06 (d, J=7.2 Hz, 1H), 8.09 (s, 1H), 8.27 (dd, J=4.8, 2.0 Hz, 1H), 8.36 (brs, 1H).
207		^{1}H-NMR δ (ppm): 1.57 (dd, J=8.0, 5.2 Hz, 1H), 1.88 (t, J=5.2 Hz, 1H), 2.02 (dd, J=8.0, 6.0 Hz, 1H), 2.61 (s, 3H), 3.30 (s, 3H), 4.34 (d, J=12.8 Hz, 1H), 4.39 (d, J=12.8 Hz, 1H), 4.45 (d, J=9.6 Hz, 1H), 4.52 (d, J=9.6 Hz, 1H), 7.01-7.11 (m, 4H), 7.43 (dd, J=8.4, 4.8 Hz, 2H), 7.52 (dd, J=10.8, 6.0 Hz, 1H), 7.74 (brs, 1H), 8.11 (s, 1H).

[Table 52-3]

208		^{1}H-NMR δ (ppm): 1.56 (dd, J=8.0, 5.6 Hz, 1H), 1.89 (t, J=5.6 Hz, 1H), 2.04 (dd, J=8.0, 5.6 Hz, 1H), 2.61 (s, 3H), 3.27 (s, 3H), 4.32 (d, J=13.2 Hz, 1H), 4.40 (d, J=13.2 Hz, 1H), 4.46 (d, J=9.2 Hz, 1H), 4.53 (d, J=9.2 Hz, 1H), 6.80 (t, J=8.0 Hz, 1H), 7.04 (t, J=8.8 Hz, 2H), 7.12 (d, J=8.0 Hz, 1H), 7.24 (dd, J=14.4, 8.0 Hz, 1H), 7.40-7.44 (m, 3H), 7.77 (brs, 1H), 8.10 (s, 1H).

[0353]

[Table 53]

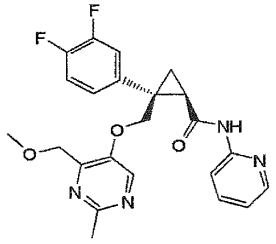
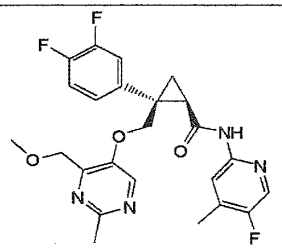
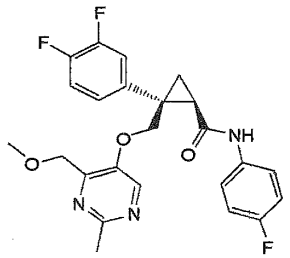
Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
209		^{1}H-NMR δ (ppm): 1.60 (dd, J=5.2 Hz, 8.4 Hz, 1H), 1.89 (t, J=5.2 Hz, 1H), 2.08 (dd, J=5.6 Hz, 8.0 Hz, 1H), 2.63 (s, 3H), 3.32 (s, 3H), 4.31-4.52 (m, 4H), 6.82-6.91 (m, 2H), 7.05 (t, J=8.8 Hz, 2H), 7.42-7.45 (m, 2H), 7.61 (brds, 1H), 8.08-8.11 (m, 2H). MS $[M+H]^+$=458
210		^{1}H-NMR δ (ppm): 1.62 (dd, J=5.2 Hz, 8.0 Hz, 1H), 1.91 (t, J=5.6 Hz, 1H), 2.08 (dd, J=6.0 Hz, 8.4 Hz, 1H), 2.63 (s, 3H), 3.30 (s, 3H), 4.29-4.52 (m, 4H), 6.70-6.76 (m, 2H), 7.02-7.08 (m, 3H), 7.42-7.45 (m, 2H), 7.52 (brds, 1H), 8.03 (brds, 1H), 8.10 (s, 1H). MS $[M+H]^+$=458.

[0354]

* The compounds of Examples 211 to 217 were synthesized by condensing the carboxylic acid Prep 37 and any amine by the same method as that of Example 51.

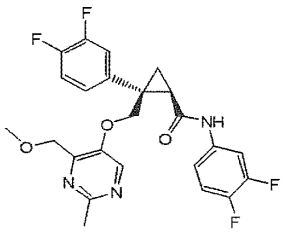
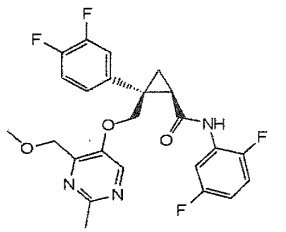
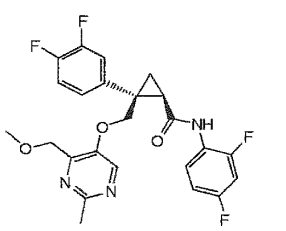
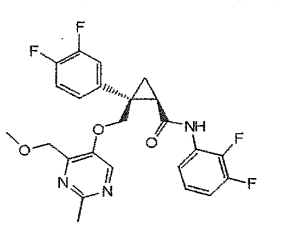
[0355]

[Table 54]

Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
211		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.57-1.61 (m, 1H), 1.91 (t, J=5.6 Hz, 1H), 2.09 (brdt, 1H), 2.62 (s, 3H), 3.28 (s, 3H), 4.25-4.50 (m, 4H), 7.03-7.36 (m, 4H), 7.66 (t, J=8.0 Hz, 1H), 8.03-8.05 (brdd, J=8.0 Hz, 1H), 8.10 (s, 1H), 8.27 (d, J=3.6 Hz, 1H), 8.38 (brds, 1H). MS $[M+H]^+$=441
212		^{1}H-NMR δ (ppm): 1.58-1.61 (m, 1H), 1.90 (t, J=5.6 Hz, 1H), 2.06 (brdt, J=5.6 Hz, 1H), 2.27 (s, 3H), 2.63 (s, 3H), 3.32 (s, 3H), 4.27-4.50 (m, 4H), 7.13-7.19 (m, 2H), 7.33 (t, J=9.2 Hz, 1H), 7.93 (d, J=5.6 Hz, 1H), 8.00 (s, 1H), 8.10 (s, 1H), 8.29 (s, 1H). MS $[M+H]^+$=473
213		^{1}H-NMR δ (ppm): 1.55-1.57 (m, 1H), 1.90 (t, J=5.6 Hz, 1H), 2.02 (dd, J=6.0 Hz, 8.0 Hz, 1H), 2.62 (s, 3H), 3.32 (s, 3H), 4.32-4.54 (m, 4H), 6.99 (t, J=8.8 Hz, 2H), 7.13-7.42 (m, 5H), 7.60 (s, 1H), 8.12 (s, 1H). MS $[M+H]^+$=458

[0356]

[Table 55]

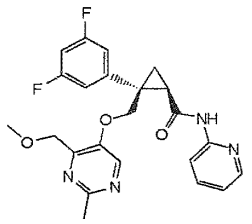
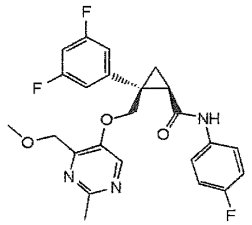
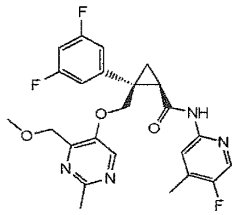
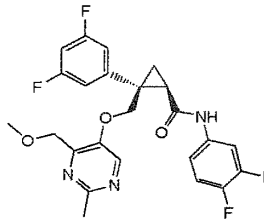
Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
214		^{1}H-NMR δ (ppm): 1.55-1.58 (m, 1H), 1.90 (t, J=5.2 Hz, 1H), 2.02 (dd, J=6.0 Hz, 8.4 Hz, 1H), 2.61 (s, 3H), 3.33 (s, 3H), 4.34-4.53 (m, 4H), 7.05-7.17 (m, 4H), 7.35 (t, J=9.2 Hz, 1H), 7.52 (t, J=8.4 Hz, 1H), 7.73 (s, 1H), 8.12 (s, 1H). MS $[M+H]^+$=476
215		^{1}H-NMR δ (ppm): 1.62 (dd, J=5.6 Hz, 8.8 Hz, 1H), 1.92 (t, J=5.2 Hz, 1H), 2.08 (dd, J=6.0 Hz, 8.4 Hz, 1H), 2.63 (s, 3H), 3.32 (s, 3H), 4.30-4.52 (m, 4H), 6.71-6.75 (m, 1H), 7.02-7.36 (m, 4H), 7.79 (brds, 1H), 8.00 (m, 1H), 8.12 (s, 1H). MS $[M+H]^+$=476
216		^{1}H-NMR δ (ppm): 1.58-1.62 (m, 1H), 1.90 (t, J=5.6 Hz, 1H), 2.07 (dd, J=6.0 Hz, 8.0 Hz, 1H), 2.63 (s, 3H), 3.34 (s, 3H), 4.32-4.52 (m, 4H), 6.81-6.91 (m, 2H), 7.12-7.18 (m, 2H), 7.34 (t, J=8.8 Hz, 1H), 7.65 (brds, 1H), 8.03-8.12 (m, 2H). MS $[M+H]^+$=476
217		^{1}H-NMR δ (ppm): 1.61 (dd, J=5.2 Hz, 8.4 Hz, 1H), 1.92 (t, J=5.6 Hz, 1H), 2.10 (dd, J=6.0 Hz, 8.0 Hz, 1H), 2.62 (s, 3H), 3.33 (s, 3H), 4.30-4.52 (m, 4H), 6.90-7.37 (m, 5H), 7.77 (brds, 1H), 7.90 (brds, 1H), 8.12 (s, 1H). MS $[M+H]^+$=476

[0357]

* The compounds of Examples 218 to 221 were synthesized by condensing the carboxylic acid Prep 38 and any amine by the same method as that of Example 51.

[0358]

[Table 56]

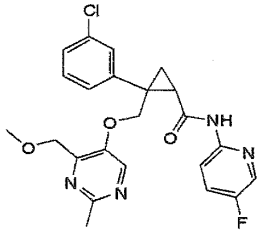
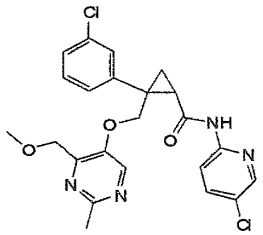
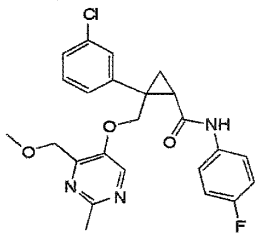
Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
218		^{1}H-NMR δ (ppm): 1.62 (dd, J=5.6 Hz, 8.0 Hz, 1H), 1.93 (t, J=5.2 Hz, 1H), 2.11 (brdt, 1H), 2.62 (s, 3H), 3.28 (s, 3H), 4.25-4.54 (m, 4H), 6.76 (t, J=7.2 Hz, 1H), 7.00-7.03 (m, 3H), 7.65 (t, J=8.0 Hz, 1H), 8.02 (d, J=7.6 Hz, 1H), 8.12 (s, 1H), 8.25 (d, J=8.4 Hz, 1H), 8.59 (s, 1H). MS $[M+Na]^+$=464
219		^{1}H-NMR δ (ppm): 1.58-1.60 (m, 1H), 1.92 (t, J=5.6 Hz, 1H), 2.05 (dd, J=5.6 Hz, 8.0 Hz, 1H), 2.61 (s, 3H), 3.32 (s, 3H), 4.33-4.58 (m, 4H), 6.76 (t, J=8.8 Hz, 1H), 6.97-7.02 (m, 4H), 7.38-7.42 (m, 2H), 7.62 (s, 1H), 8.14 (s, 1H). MS $[M+Na]^+$=459
220		^{1}H-NMR δ (ppm): 1.60-1.64 (m, 1H), 1.92 (t, J=5.6 Hz, 1H), 2.08 (brdt, J=8.0 Hz, 1H), 2.27 (s, 3H), 2.63 (s, 3H), 3.33 (s, 3H), 4.27-4.53 (m, 4H), 6.76 (t, J=8.8 Hz, 1H), 6.99-7.02 (m, 2H), 7.92 (d, J=6.4 Hz, 1H), 8.01 (s, 1H), 8.12 (s, 1H), 8.27 (s, 1H). MS $[M+Na]^+$=496
221		^{1}H-NMR δ (ppm): 1.57-1.61 (m, 1H), 1.92 (t, J=5.6 Hz, 1H), 2.05 (dd, J=5.6 Hz, 8.0 Hz, 1H), 2.61 (s, 3H), 3.33 (s, 3H), 4.33-4.57 (m, 4H), 6.76 (t, J=8.8 Hz, 1H), 7.00-7.09 (m, 4H), 7.52 (brdt, J=7.2 Hz, 1H), 7.78 (s, 1H), 8.13 (s, 1H). MS $[M+Na]^+$=498

[0359]

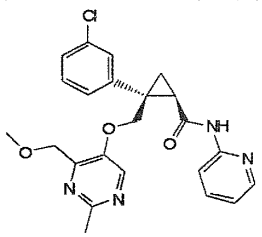
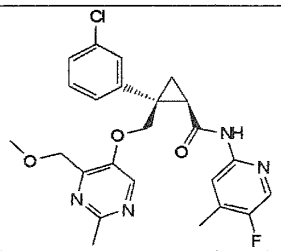
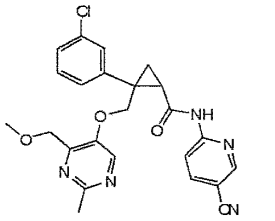
* The compounds of Examples 222 to 227 were synthesized by condensing the carboxylic acid Prep 39 and any amine. It is to be noted that, with regard to condensation methods, the compounds of Examples 222 to 226 were condensed according to the method of Example 51 and the compound of Example 227 was condensed by the method of Example 1. In addition, the compounds of Examples 225 and 226 were obtained by performing chiral resolution on racemic products.

[0360]

[Table 57-1]

Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
222		^{1}H-NMR δ (ppm): 1.61 (dd, J=8.0, 5.2 Hz, 1H), 1.91 (t, J=5.2 Hz, 1H), 2.11 (dd, J=8.0, 6.0 Hz, 1H), 2.62 (s, 3H), 3.31 (s, 3H), 4.31 (d, J=13.2 Hz, 1H), 4.41 (d, J=13.2 Hz, 1H), 4.46 (d, J=9.6 Hz, 1H), 4.49 (d, J=9.6 Hz, 1H), 7.28-7.42 (m, 4H), 7.48 (s, 1H), 8.08 (dd, J=9.2, 4.0 Hz, 1H), 8.09 (s, 1H), 8.12 (q, J=2.8 Hz, 1H), 8.39 (brs, 1H).
223		^{1}H-NMR δ (ppm): 1.62 (dd, J=8.0, 5.6 Hz, 1H), 1.91 (t, J=5.6 Hz, 1H), 2.11 (dd, J=8.0, 5.6 Hz, 1H), 2.62 (s, 3H), 3.31 (s, 3H), 4.30 (d, J=13.6 Hz, 1H), 4.41 (d, J=13.6 Hz, 1H), 4.44 (d, J=9.6 Hz, 1H), 4.49 (d, J=9.6 Hz, 1H), 7.25-7.35 (m, 3H), 7.48 (s, 1H), 7.62 (dd, J=8.8, 2.8 Hz, 1H), 8.05 (d, J=8.8 Hz, 1H), 8.09 (s, 1H), 8.23 (d, J=2.8 Hz, 1H), 8.42 (brs, 1H).
224		^{1}H-NMR δ (ppm): 1.59 (dd, J=8.0, 5.2 Hz, 1H), 1.89 (t, J=5.2 Hz, 1H), 2.06 (dd, J=8.0, 5.6 Hz, 1H), 2.62 (s, 3H), 3.22 (s, 3H), 4.35 (d, J=13.2 Hz, 1H), 4.42 (d, J=13.2 Hz, 1H), 4.48 (d, J=9.6 Hz, 1H), 4.54 (d, J=9.6 Hz, 1H), 6.99 (t, J=8.8 Hz, 2H), 7.24-7.32 (m, 3H), 7.42 (dd, J=8.8, 4.8 Hz, 2H), 7.49 (s, 1H), 7.66 (brs, 1H), 8.12 (s, 1H).

[Table 57-2]

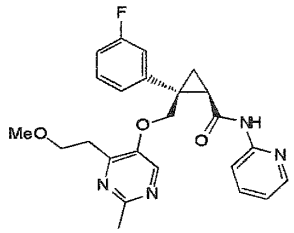
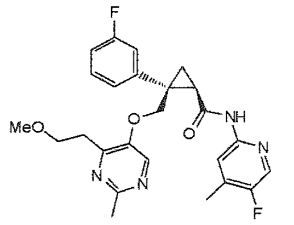
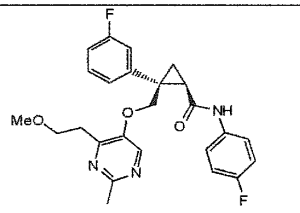
225		^{1}H-NMR δ (ppm): 1.61 (dd, J=8.0, 5.2 Hz, 1H), 1.92 (t, J=5.2 Hz, 1H), 2.12 (dd, J=8.0, 6.0 Hz, 1H), 2.62 (s, 3H), 3.29 (s, 3H), 4.29 (d, J=13.6 Hz, 1H), 4.43 (d, J=13.6 Hz, 1H), 4.46 (d, J=9.6 Hz, 1H), 4.51 (d, J=9.6 Hz, 1H), 7.03 (dd, J=7.2, 4.8 Hz, 1H), 7.26-7.35 (m, 3H), 7.49 (s, 1H), 7.66 (td, J=7.2, 2.0 Hz, 1H), 8.06 (d, J=7.2 Hz, 1H), 8.10 (s, 1H), 8.27 (d, J=4.8 Hz, 1H), 8.50 (brs, 1H).
226		^{1}H-NMR δ (ppm): 1.62 (dd, J=8.0, 5.6 Hz, 1H), 1.90 (d, J=5.6 Hz, 1H), 2.09 (dd, J=8.0, 6.0 Hz, 1H), 2.28 (s, 3H), 2.63 (s, 3H), 3.33 (s, 3H), 4.31 (d, J=13.6 Hz, 1H), 4.43 (d, J=13.6 Hz, 1H), 4.46 (d, J=9.6 Hz, 1H), 4.50 (d, J=9.6 Hz, 1H), 7.29-7.35 (m, 3H), 7.48 (s, 1H), 7.95 (d, J=5.6 Hz, 1H), 8.01 (s, 1H), 8.10 (s, 1H), 8.32 (brs, 1H).
227		^{1}H-NMR δ (ppm): 1.67 (dd, J=8.0, 5.6 Hz, 1H), 1.94 (t, J=5.6 Hz, 1H), 2.15 (dd, J=8.0, 6.0 Hz, 1H), 2.62 (s, 3H), 3.31 (s, 3H), 4.32 (d, J=13.2 Hz, 1H), 4.38 (d, J=13.2 Hz, 1H), 4.44 (d, J=9.6 Hz, 1H), 4.49 (d, J=9.6 Hz, 1H), 7.30-7.35 (m, 3H) 7.49 (q, J=1.6 Hz, 1H), 7.91 (dd, J=8.4, 1.6 Hz, 1H), 8.10 (s, 1H), 8.22 (q, J=8.4 Hz, 1H), 8.53 (brs, 1H), 8.57 (q, J=1.6 Hz, 1H).

[0361]

* The compounds of Examples 228 to 230 were synthesized by condensing the carboxylic acid Prep 40 and any amine by the same method as that of Example 52.

[0362]

[Table 58]

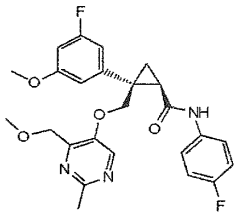
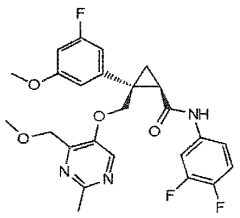
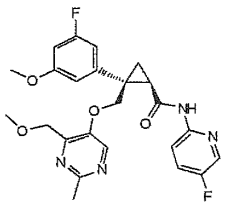
Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
228		^{1}H-NMR δ (ppm): 1.60 (dd, J=8.0, 5.6 Hz, 1H), 1.92 (t, J=5.6 Hz, 1H), 2.14 (dd, J=8.0, 5.6 Hz, 1H), 2.56 (s, 3H), 2.77 (qui, J=6.8 Hz, 1H), 2.92 (qui, J=6.8 Hz, 1H), 3.18 (s, 3H), 3.48-3.57 (m, 2H), 4.44 (d, J=9.6 Hz, 1H), 4.51 (d, J=9.6 Hz, 1H), 6.97-7.04 (m, 2H), 7.19 (dt, J=8.0, 1.2 Hz, 1H), 7.24 (dt, J=8.0, 1.2 Hz, 1H), 7.32 (dt, J=8.0, 6.0 Hz, 1H), 7.65 (td, J=7.6, 2.0 Hz, 1H), 8.02 (s, 1H), 8.05 (d, J=7.6 Hz, 1H), 8.26 (d, J=4.8 Hz, 1H), 8.52 (brs, 1H).
229		^{1}H-NMR δ (ppm): 1.60 (dd, J=8.0, 5.2 Hz, 1H), 1.90 (t, J=5.2 Hz, 1H), 2.11 (dd, J=8.0, 5.6 Hz, 1H), 2.27 (s, 3H), 2.56 (s, 3H), 2.77 (qui, J=6.8 Hz, 1H), 2.93 (qui, J=6.8 Hz, 1H), 3.21 (s, 3H), 3.51-3.57 (m, 2H), 4.43 (d, J=9.6 Hz, 1H), 4.51 (d, J=9.6 Hz, 1H), 6.99 (td, J=8.0 Hz, 1H), 7.18 (dt, J=8.8, 2.0 Hz, 1H), 7.23 (d, J=8.0 Hz, 1H), 7.32 (td, J=8.0, 6.0 Hz, 1H), 7.94 (d, J=6.0 Hz, 1H), 8.00 (s, 1H), 8.02 (s, 1H), 8.43 (brs, 1H).
230		^{1}H-NMR δ (ppm): 1.56 (dd, J=8.0, 5.6 Hz, 1H), 1.91 (t, J=5.6 Hz, 1H), 2.08 (dd, J=8.0, 5.6 Hz, 1H), 2.55 (s, 3H), 2.82-2.97 (m, 2H), 3.23 (s, 3H), 3.52-3.61 (m, 2H), 4.45 (d, J=9.6 Hz, 1H), 4.55 (d, J=9.6 Hz, 1H), 6.96-7.01 (m, 3H), 7.19-7.24 (m, 2H), 7.31 (td, J=8.4, 6.0 Hz, 1H), 7.40 (dd, J=8.8, 4.8 Hz, 1H), 7.79 (brs, 1H), 8.03 (s, 1H).

[0363]

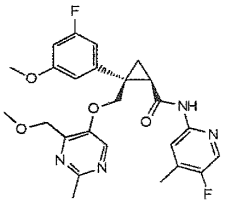
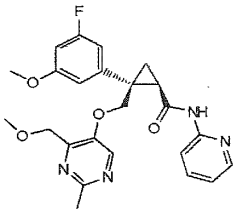
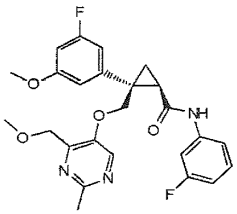
* The compounds of Examples 231 to 236 were synthesized by condensing the carboxylic acid Prep 41 and any amine by the same method as that of Example 51.

[0364]

[Table 59-1]

Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
231		^{1}H-NMR δ (ppm): 1.56 (dd, J=8.0, 5.2 Hz, 1H), 1.87 (t, J=5.2 Hz, 1H), 2.07 (dd, J=8.0, 6.0 Hz, 1H), 2.62 (s, 3H), 3.30 (s, 3H), 3.80 (s, 3H), 4.35 (d, J=13.2 Hz, 1H), 4.44 (d, J=13.2 Hz, 1H), 4.46 (d, J=9.6 Hz, 1H), 4.56 (d, J=9.6 Hz, 1H), 6.54 (dt, J=10.8, 2.0 Hz, 1H), 6.77-6.79 (m, 2H), 6.98 (t, J=8.8 Hz, 2H), 7.41 (dd, J=8.8, 4.8 Hz, 2H), 7.85 (brs, 1H), 8.12 (s, 1H).
232		^{1}H-NMR δ (ppm): 1.56 (dd, J=8.0, 5.2 Hz, 1H), 1.87 (t, J=5.2 Hz, 1H), 2.07 (dd, J=8.0, 6.0 Hz, 1H), 2.61 (s, 3H), 3.32 (s, 3H), 3.79 (s, 3H), 4.36 (d, J=13.2 Hz, 1H), 4.43 (d, J=13.2 Hz, 1H), 4.44 (d, J=9.6 Hz, 1H), 4.55 (d, J=9.6 Hz, 1H), 6.54 (dt, J=10.8, 2.4 Hz, 1H), 6.76-6.78 (m, 2H), 7.02-7.10 (m, 2H), 7.53 (dd, J=10.8, 6.8 Hz, 1H), 8.03 (brs, 1H), 8.12 (s, 1H).
233		^{1}H-NMR δ (ppm): 1.61 (dd, J=8.0, 5.2 Hz, 1H), 1.89 (t, J=5.2 Hz, 1H), 2.11 (dd, J=8.0, 6.0 Hz, 1H), 2.63 (s, 3H), 3.30 (s, 3H), 3.81 (s, 3H), 4.30 (d, J=13.2 Hz, 1H), 4.43 (d, J=13.2 Hz, 1H), 4.45 (d, J=9.6 Hz, 1H), 4.53 (d, J=9.6 Hz, 1H), 6.56 (dt, J=10.8, 2.4 Hz, 1H), 6.76-6.80 (m, 2H), 7.39 (ddd, J=10.4, 9.2, 2.8 Hz, 1H), 8.07 (dd, J=9.2, 4.0 Hz, 1H), 8.10_9 (s, 1H), 8.11_2 (d, J=2.4 Hz, 1H), 8.49 (brs, 1H).

[Table 59-2]

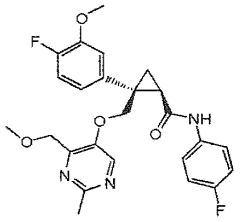
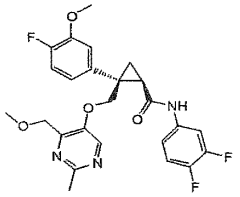
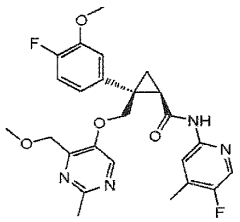
234		^{1}H-NMR δ (ppm): 1.61 (dd, J=8.0, 5.2 Hz, 1H), 1.88 (t, J=5.2 Hz, 1H), 2.09 (dd, J=8.0, 6.0 Hz, 1H), 2.27 (s, 3H), 2.63 (s, 3H), 3.31 (s, 3H), 3.80 (s, 3H), 4.30 (d, J=13.6 Hz, 1H), 4.44$_5$ (d, J=13.6 Hz, 1H), 4.44$_5$ (d, J=9.2 Hz, 1H), 4.53 (d, J=9.2 Hz, 1H), 6.56 (dt, J=10.4, 2.4 Hz, 1H), 6.75-6.79 (m, 2H), 7.94 (d, J=5.6 Hz, 1H), 7.98 (s, 1H), 8.11 (s, 1H), 8.49 (brs, 1H).
235		^{1}H-NMR δ (ppm): 1.59 (dd, J=8.0, 5.2 Hz, 1H), 1.89 (t, J=5.2 Hz, 1H), 2.12 (dd, J=8.0, 5.6 Hz, 1H), 2.62 (s, 3H), 3.26 (s, 3H), 3.80 (s, 3H), 4.28 (d, J=13.6 Hz, 1H), 4.43 (d, J=13.6 Hz, 1H), 4.48 (d, J=9.6 Hz, 1H), 4.53 (d, J=9.6 Hz, 1H), 6.55 (dt, J=10.8, 2.4 Hz, 1H), 6.76-6.79 (m, 2H), 7.00 (dd, J=7.6, 4.8 Hz, 1H), 7.65 (td, J=7.6, 2.0 Hz, 1H), 8.03 (d, J=7.6 Hz, 1H), 8.10 (s, 1H), 8.24 (d, J=4.8 Hz, 1H), 8.67 (brs, 1H).
236		^{1}H-NMR δ (ppm): 1.57 (dd, J=8.0, 5.6 Hz, 1H), 1.88 (t, J=5.6 Hz, 1H), 2.07 (dd, J=8.0, 6.0 Hz, 1H), 2.61 (s, 3H), 3.29 (s, 3H), 3.80 (s, 3H), 4.33 (d, J=13.2 Hz, 1H), 4.43 (d, J=13.2 Hz, 1H), 4.45 (d, J=9.6 Hz, 1H), 4.56 (d, J=9.6 Hz, 1H), 6.54 (dt, J=10.4, 2.4 Hz, 1H), 6.76-6.81 (m, 3H), 7.11 (dd, J=8.0, 2.0 Hz, 1H), 7.23 (dd, J=14.8, 2.0 Hz, 1H), 7.40 (d, J=11.2 Hz, 1H), 7.82 (brs, 1H), 8.11 (s, 1H).

[0365]

* The compounds of Examples 237 to 239 were synthesized by condensing the carboxylic acid Prep 42 and any amine by the same method as that of Example 51.

[0366]

[Table 60]

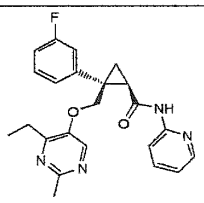
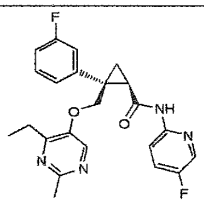
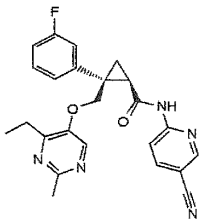
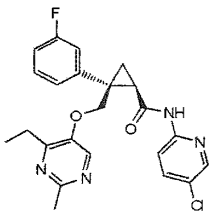
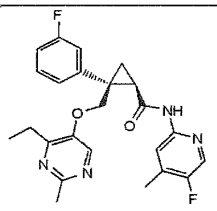
Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
237		^{1}H-NMR δ (ppm): 1.59 (dd, J=5.6, 8.0 Hz, 1H), 1.87 (t, J=5.6 Hz, 1H), 2.04 (dd, J=5.6, 8.0 Hz, 1H), 2.63 (s, 3H), 3.28 (s, 3H), 3.92 (s, 3H), 4.34 (d, J=13.2 Hz, 1H), 4.42 (d, J=13.2 Hz, 1H), 4.49 (d, J=9.2 Hz, 1H), 4.55 (d, J=9.2 Hz, 1H), 6.98-7.08 (m, 5H), 7.39-7.43 (m, 2H), 7.55 (brs, 1H), 8.13 (s, 1H). MS $[M+Na]^+$=492
238		^{1}H-NMR δ (ppm): 1.59 (dd, J=5.6, 8.2 Hz, 1H), 1.87 (t, J=5.6 Hz, 1H), 2.03 (dd, J=5.6, 8.2 Hz, 1H), 2.63 (s, 3H), 3.30 (s, 3H), 3.91 (s, 3H), 4.35 (d, J=13.0 Hz, 1H), 4.41 (d, J=13.0 Hz, 1H), 4.47 (d, J=9.6 Hz, 1H), 4.55 (d, J=9.6 Hz, 1H), 6.97-7.12 (m, 5H), 7.50-7.55 (m, 1H), 7.67 (brs, 1H), 8.13 (s, 1H). MS $[M+H]^+$=488
239		^{1}H-NMR δ (ppm): 1.60 (dd, J=5.2, 8.0 Hz, 1H), 1.88 (t, J=5.2 Hz, 1H), 2.07 (dd, J=5.2, 8.0 Hz, 1H), 2.281-2.283 (m, 3H), 2.63 (s, 3H), 3.29 (s, 3H), 3.92 (s, 3H), 4.29 (d, J=13.4 Hz, 1H), 4.42 (d, J=13.4 Hz, 1H), 4.45 (d, J=9.6 Hz, 1H), 4.51 (d, J=9.6 Hz, 1H), 6.97-7.09 (m, 3H), 7.96 (d, J=5.6 Hz, 1H), 8.02 (d, J=1.2 Hz, 1H), 8.10 (s, 1H), 8.21 (brs, 1H). MS $[M+Na]^+$=507.

[0367]

* The compounds of Examples 240 to 244 were synthesized by condensing the carboxylic acid Prep 43 and any amine by the same method as that of Example 1.

[0368]

[Table 61]

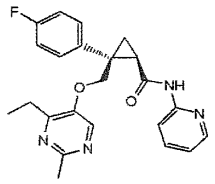
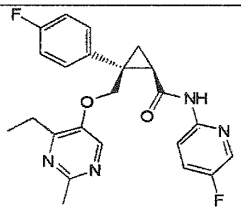
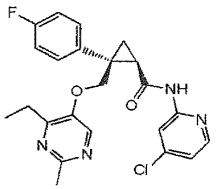
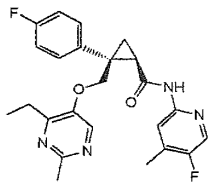
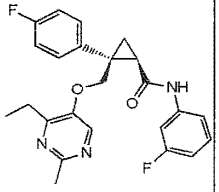
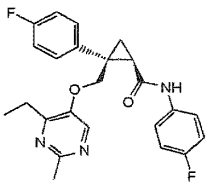
Example	Structural formula, MS	Example	Structural formula, MS	Example	Structural formula, MS
240	 MS $[M+H]^+$= 407	241	 MS $[M+H]^+$= 425	242	 MS $[M+H]^+$=432
243	 MS $[M+H]^+$= 441	244	 MS $[M+H]^+$= 439		

[0369]

* The compounds of Examples 245 to 250 were synthesized by condensing the carboxylic acid Prep 44 and any amine by the same method as that of Example 1.

[0370]

[Table 62]

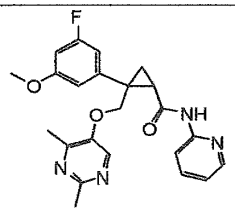
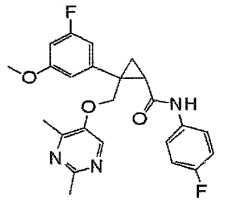
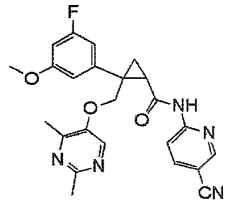
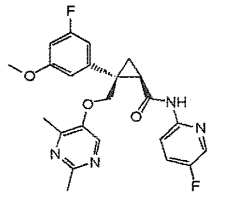
Example	Structural formula, MS	Example	Structural formula, MS	Example	Structural formula, MS
245	 MS $[M+H]^+$= 407	246	 MS $[M+H]^+$=425	247	 MS $[M+H]^+$=441
248	 MS $[M+H]^+$= 439	249	 MS $[M+H]^+$=424	250	 MS $[M+H]^+$=424

[0371]

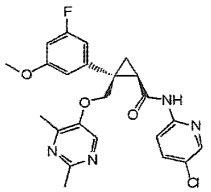
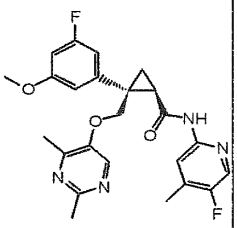
* The compounds of Examples 251 to 256 were synthesized by condensing the carboxylic acid Prep 45 or the corresponding racemic body and any amine. It is to be noted that the compounds of Examples 251 to 253 were condensed according to the method of Example 51, and that the compounds of Examples 254 to 256 were condensed by the method of Example 1, followed by chiral resolution.

[0372]

[Table 63-1]

Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
251		^{1}H-NMR δ (ppm): 1.59 (dd, J=8.2, 4.8 Hz, 1H), 1.91 (t, J=5.2 Hz, 1H), 2.12-2.18 (br, 1H), 2.21 (s, 3H), 2.55 (s, 3H), 3.79 (s, 3H), 4.41 (d, J=9.6 Hz, 1H), 4.52 (d, J=9.6 Hz, 1H), 6.54 (dt, J=10.4, 2.0 Hz, 1H), 6.73-6.79 (m, 2H), 6.95-6.99 (m, 1H), 7.61-7.67 (m, 1H), 8.00 (s, 1H), 7.99-8.05 (m, 1H), 8.19-8.21 (m, 1H), 9.25 (brs, 1H).
252		^{1}H-NMR δ (ppm): 1.56 (dd, J=8.2, 5.2 Hz, 1H), 1.87 (t, J=5.6 Hz, 1H), 2.03-2.07 (m, 1H), 2.26 (s, 3H), 2.57 (s, 3H), 3.79 (s, 3H), 4.43 (d, J=9.6 Hz, 1H), 4.51 (d, J=9.6 Hz, 1H), 6.53 (dt, J=10.4, 2.4 Hz, 1H), 6.74-6.78 (m, 2H), 6.95-7.00 (m, 2H), 7.36-7.41 (m, 2H), 7.90 (brs, 1H) 7.99 (s, 1H).
253		^{1}H-NMR δ (ppm): 1.66 (dd, J=8.0, 5.2 Hz, 1H), 1.92 (t, J=5.2 Hz, 1H), 2.16 (t, J=9.0 Hz, 1H), 2.22 (s, 3H), 2.56 (s, 3H), 3.81 (s, 3H) 4.37 (d, J=9.6 Hz, 1H), 4.48 (d, J=9.6 Hz, 1H), 6.50-6.58 (m, 1H) 6.75-6.81 (m, 2H), 7.87-7.91 (m, 1H), 7.98 (s, 1H), 8.17-8.21 (m, 1H), 8.55-8.57 (m, 1H), 8.63 (brs, 1H).
254		^{1}H-NMR δ (ppm): 1.56 (dd, J=8.0, 5.2 Hz, 1H), 1.88 (t, J=5.2 Hz, 1H), 2.10-2.16 (m, 1H), 2.20 (s, 3H), 2.53 (s, 3H), 3.77 (s, 3H) 4.38 (d, J=9.6 Hz, 1H), 4.49 (d, J=9.6 Hz, 1H), 6.52 (dt, J=10.8, 1.6 Hz, 1H) 6.73-6.79 (m, 2H), 7.32-7.38 (m, 1H), 7.97 (s, 1H), 8.00-8.08 (m, 2H), 9.02 (brs, 1H).

[Table 63-2]

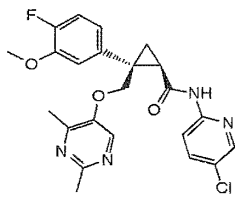
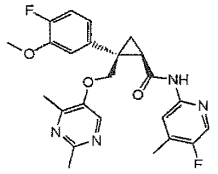
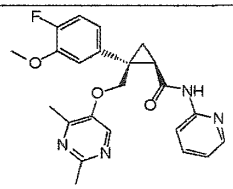
255		^{1}H-NMR δ (ppm): 1.61 (dd, J=8.0, 5.2 Hz, 1H), 1.90 (t, J=5.2 Hz, 1H), 2.12 (br, 1H), 2.23 (s, 3H), 2.56 (s, 3H), 3.80 (s, 3H) 4.38 (d, J=9.6 Hz, 1H), 4.50 (d, J=9.6 Hz, 1H), 6.55 (dt, J=10.8, 1.6 Hz, 1H), 6.72-6.82 (m, 2H), 7.56-7.64 (m, 1H), 7.99 (s, 1H), 7.78-8.08 (m, 1H), 8.16-8.24 (m, 1H), 8.62 (brs, 1H).
256		^{1}H-NMR δ (ppm): 1.60 (dd, J=8.0, 5.2 Hz, 1H), 1.89 (t, J=5.6 Hz, 1H), 2.09 (dd, J=7.8, 6.4 Hz, 1H), 2.23 (s, 3H), 2.26 (s, 3H), 2.56 (s, 3H), 3.79 (s, 3H), 4.40 (d, J=9.6 Hz, 1H), 4.52 (d, J=9.6 Hz, 1H), 6.55 (dt, J=10.4, 2.0 Hz, 1H), 6.75 (dt, J=8.8, 2.0 Hz, 1H), 6.77-6.79 (m, 1H), 7.89-7.95 (m, 2H), 8.00 (s, 1H), 8.68 (brs, 1H).

[0373]

* The compounds of Examples 257 to 259 were synthesized by condensing the carboxylic acid Prep 46 and any amine by the same method as that of Example 51.

[0374]

[Table 64]

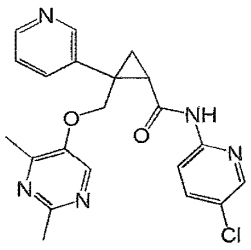
Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
257		^{1}H-NMR δ (ppm): 1.61 (dd, J=8.0, 5.2 Hz, 1H), 1.90 (t, J=5.2 Hz, 1H), 2.12 (t, J=6.0 Hz, 1H), 2.23 (s, 3H), 2.56 (s, 3H), 3.91 (s, 3H), 4.39 (d, J=9.6 Hz, 1H), 4.48 (d, J=9.6 Hz, 1H), 6.96-7.10 (m, 3H), 7.60-7.64 (m, 1H), 7.98 (s, 1H), 8.03-8.06 (m, 1H), 8.21-8.22 (m, 1H), 8.47 (brs, 1H).
258		^{1}H-NMR δ (ppm): 1.59 (dd, J=8.0, 5.2 Hz, 1H), 1.89 (t, J=5.2 Hz, 1H), 2.04-2.12 (m, 1H), 2.23 (s, 3H), 2.27 (s, 3H), 2.56 (s, 3H), 3.90 (s, 3H), 4.41 (d, J=9.2 Hz, 1H), 4.48 (d, J=9.2 Hz, 1H), 6.95-7.27 (m, 3H), 7.93-8.01 (m, 2H) 7.99 (s, 1H), 8.63 (brs, 1H).
259		^{1}H-NMR δ (ppm): 1.59 (dd, J=8.0, 5.2 Hz, 1H), 1.90 (t, J=4.8 Hz, 1H), 2.10-2.14 (m, 1H), 2.22 (s, 3H), 2.55 (s, 3H), 3.90 (s, 3H) 4.41 (d, J=9.6 Hz, 1H), 4.48 (d, J=9.6 Hz, 1H), 6.96-7.10 (m, 4H), 7.62-7.68 (m, 1H), 7.99 (s, 1H), 8.02-8.07 (m, 1H), 8.22-8.25 (m, 1H), 8.72 (brs, 1H).

[0375]

Example 260

Synthesis of N-(5-chloropyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-pyridin-3-ylcyclopropanecarboxamide (260)

[Formula 67]



260

[0376]

The above-captioned compound was synthesized by amidating the carboxylic acid Prep 47 according to the method of Example 51.

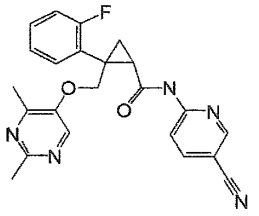
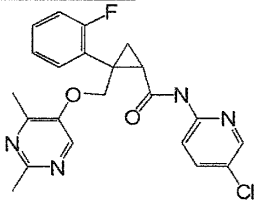
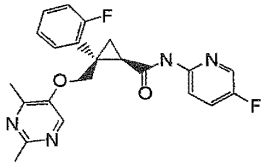
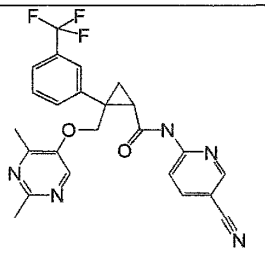
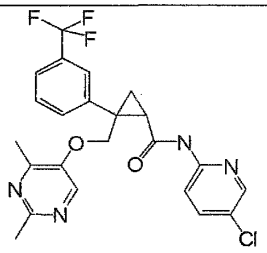
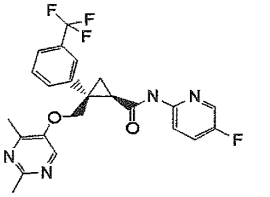
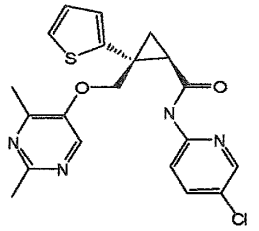
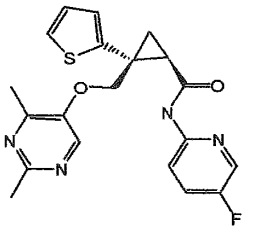
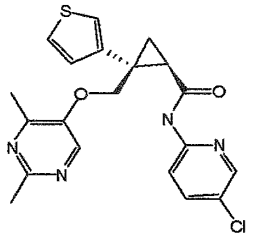
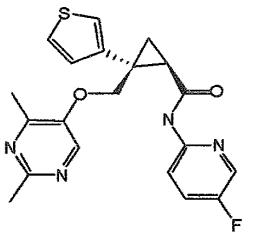
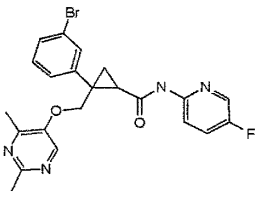
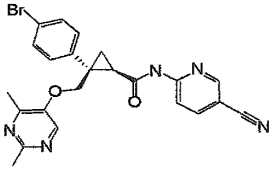
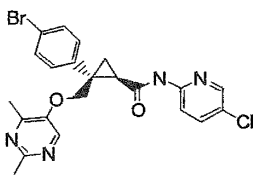
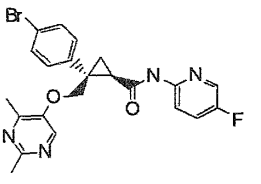
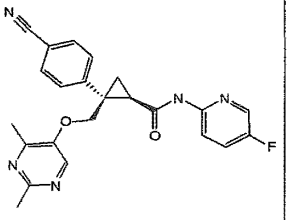
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.63 (dd, J=8.0, 5.2 Hz, 1H), 1.96 (t, J=4.8 Hz, 1H), 2.14-2.22 (m, 1H), 2.22 (s, 3H), 2.56 (s, 3H), 4.44 (d, J=9.6 Hz, 1H), 4.49 (d, J=9.6 Hz, 1H), 7.29-7.33 (m, 1H), 7.61-7.64 (m, 1H), 7.79 (dt, J=7.6, 1.9 Hz, 1H), 7.99 (s, 1H), 8.04-8.07 (m, 1H), 8.20-8.22 (m, 1H), 8.56-8.59 (m, 1H), 8.77-8.78 (m, 1H), 8.89-8.95 (brs, 1H).

[0377]

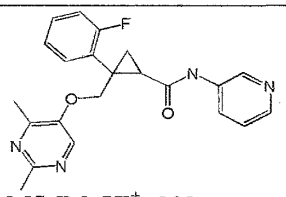
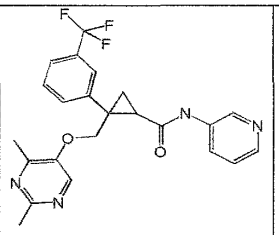
* The compounds of Examples 261 to 281 were synthesized according to the methods described in the production examples and the examples.

[0378]

[Table 65-1]

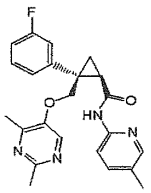
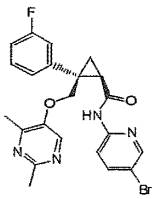
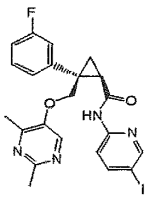
Example	Structural formula, MS	Example	Structural formula, MS	Example	Structural formula, MS
261	 MS $[M+H]^+$=418	262	 MS $[M+H]^+$=427	263	 MS $[M+H]^+$=411
264	 MS $[M+H]^+$=468	265	 MS $[M+H]^+$=477	266	 MS $[M+H]^+$=461
267	 MS $[M+H]^+$=415	268	 MS $[M+H]^+$=399	269	 MS $[M+H]^+$=415
270	 MS $[M+H]^+$=399	271	 MS $[M+H]^+$=472	272	 MS $[M+H]^+$=478
273	 MS $[M+H]^+$=488	274	 MS $[M+H]^+$=472	275	 MS $[M+H]^+$=418

[Table 65-2]

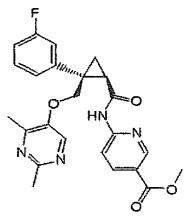
276	 MS $[M+H]^+$=393	277	 MS $[M+H]^+$=443		

[0379]

[Table 66-1]

Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
278		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.55-1.65 (m, 1H), 1.91 (t, J=5.6 Hz, 1H), 2.07-2.14 (m, 1H), 2.21 (s, 3H), 2.28 (s, 3H), 2.55 (s, 3H), 4.41 (d, J=9.6 Hz, 1H), 4.50 (d, J=9.6 Hz, 1H), 6.96-7.04 (m, 1H), 7.14-7.20 (m, 1H), 7.22-7.28 (m, 1H), 7.33 (td, J=8.0, 5.8 Hz, 1H), 7.44-7.48 (m, 1H), 7.93 (brd, J=3.6 Hz, 1H), 7.97 (s, 1H), 8.06-8.12 (m, 1H), 8.31 (brs, 1H). MS $[M+H]^+$=407, MS $[M+Na]^+$=429
279		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.60-1.66 (m, 1H), 1.92 (t, J=5.6 Hz, 1H), 2.07-2.15 (m, 1H), 2.21 (s, 3H), 2.26 (s, 3H), 4.39 (d, J=9.6 Hz, 1H), 4.49 (d, J=9.6 Hz, 1H), 6.97-7.04 (m, 1H), 7.13-7.20 (m, 1H), 7.22-7.28 (m, 1H), 7.33 (td, J=8.0, 6.0 Hz, 1H), 7.75 (dd, J=8.4, 6.0 Hz, 1H), 7.96-8.03 (m, 1H), 7.97 (s, 1H), 8.23 (brs, 1H), 8.31-8.33 (m, 1H). MS $[M+Na]^+$=493
280		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.55-1.65 (m, 1H), 1.91 (t, J=5.6 Hz, 1H), 2.05-2.15 (m, 1H), 2.21 (s, 3H), 2.56 (s, 3H), 4.38 (d, J=9.2 Hz, 1H), 4.49 (d, J=9.6 Hz, 1H), 6.97-7.04 (m, 1H), 7.14-7.20 (m, 1H), 7.21-7.28 (m, 1H), 7.29-7.37 (m, 1H), 7.86-7.94 (m, 2H), 7.97 (s, 1H), 8.35 (brs, 1H), 8.46 (brs, 1H). MS $[M+Na]^+$=541

[Table 66-2]

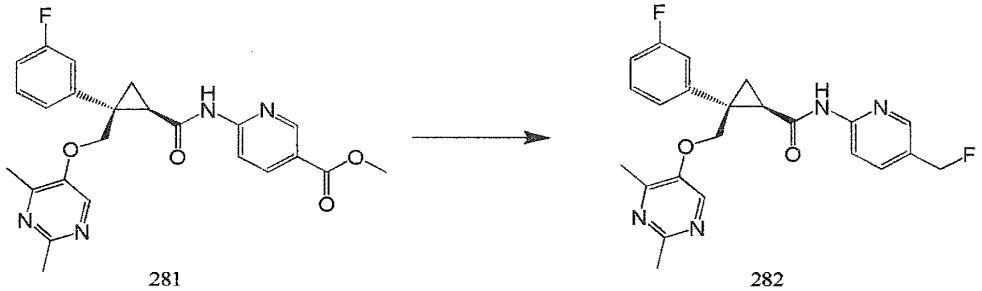
281		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.65 (dd, J=8.4 Hz, 5.2 Hz, 1H), 1.94 (t, J=5.2 Hz, 1H), 2.12-2.18 (m, 1H), 2.19 (s, 3H), 2.55 (s, 3H), 3.93 (s, 3H), 4.39 (d, J=10.0 Hz, 1H), 4.50 (d, J=9.6 Hz, 1H), 6.98-7.04 (m, 1H), 7.16-7.20 (m, 1H), 7.22-7.28 (m, 1H), 7.34 (td, J=8.0, 6.0 Hz, 1H), 7.98 (s, 1H), 8.12 (brd, J=9.2 Hz, 1H), 8.23-8.27 (m, 1H), 8.49 (brs, 1H), 8.91 (dd, J=2.0 Hz, 0.8 Hz, 1H). MS $[M+Na]^+$=451, MS $[M+Na]^+$=473

[0380]

Example 282

Synthesis of (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoromethylpyridin-2-yl)-2-(3-fluorophenyl)cyclopropanecarboxamide (282)

[Formula 68]



281 282

[0381]

The compound 281 (51.6 mg) was dissolved in THF (5 ml), and lithium aluminum hydride (8.73 mg) was then added to the obtained solution under cooling in an ice water bath. The obtained mixture was stirred for 30 minutes, and the reaction solution was then transferred into ice chilled water. Thereafter, ethyl acetate was added thereto to carry out liquid separation. The organic layer was washed with a saturated saline. The resultant organic layer was dried over magnesium sulfate, and the solvent was then concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, Size: M, methanol : ethyl acetate 0% → 10%), so as to obtain an alcohol intermediate (20 mg). The obtained alcohol intermediate (20 mg) was dissolved in methylene chloride (3 ml), and [bis(2-methoxyethyl)amino]sulfa trifluoride (0.0349 ml) was then added to the obtained solution under cooling in an ice water bath. The obtained mixture was stirred for 0.5 hours, and it was then stirred at a room temperature for 3 hours. Thereafter, a saturated

sodium bicarbonate aqueous solution was added to the reaction solution, and liquid separation was then carried out with ethyl acetate. The organic layer was successively washed with water and a saturated saline. The resultant organic layer was dried over magnesium sulfate, and the solvent was then concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, Size: S, ethyl acetate : heptane 30% → 50%), so as to obtain the above-captioned compound (5.0 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.55-1.65 (m, 1H), 1.93 (t, J=5.6 Hz, 1H), 2.10-2.18 (m, 1H), 2.21 (s, 3H), 2., 2.55 (s, 3H), 4.40 (d, J=9.6 Hz, 1H), 4.50 (d, J=9.6 Hz, 1H), 5.34 (d, J=48.0 Hz, 2H), 6.97-7.04 (m, 1H), 7.14-7.21 (m, 1H), 7.22-7.28 (m, 1H), 7.33 (td, J=8.0 Hz, 6.0 Hz, 1H), 7.70 (td, J=8.8 Hz, 2.0 Hz, 1H), 8.09 (d, J=8.0 Hz, 1H), 8.30 (d, J=2.0 Hz, 1H), 8.32 (t, J=2.0 Hz, 1H), 8.40 (brs, 1H).

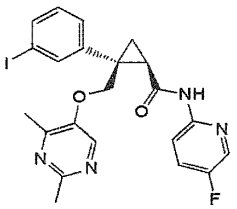
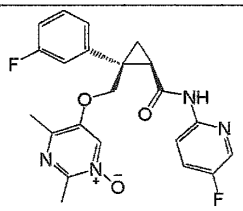
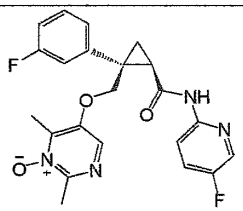
MS $[M+Na]^+$=447

[0382]

The compound of Example 283 was produced by treating the carboxylic acid Prep 56 obtained in Production Example 56 by the same method as that of Example 82. The compounds of Examples 284 and 285 were produced by the same method as that of Example 81.

[0383]

[Table 67]

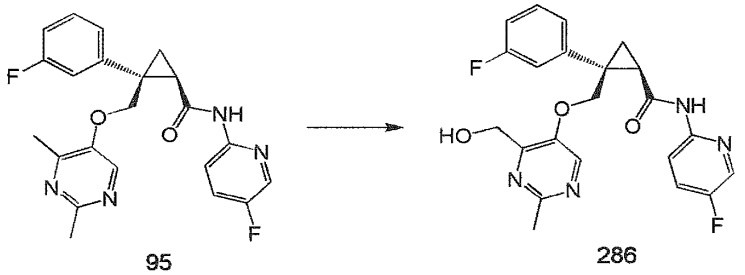
Example	Structural formula	NMR and/or MS
283		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.59-1.62 (m, 1H), 1.90 (t, J=5.8 Hz, 1H), 2.03-2.13 (m, 1H), 2.24 (s, 3H), 2.56 (s, 3H), 4.42 (q, J=12.0 Hz, 2H), 7.10 (t, J=7.8 Hz, 1H), 7.36-7.45 (m, 2H), 7.62-7.67 (m, 1H), 7.85 (s, 1H), 7.97 (s, 1H), 8.04-8.11 (m, 1H), 8.14 (d, J=2.4 Hz, 1H), 8.28 (s, 1H) MS $[M+H]^+$=519
284		^{1}H-NMR (600 MHz, CD_3OD) δ (ppm): 1.58 (t, J=6.0 Hz, 1H), 1.88 (t, J=6.0 Hz, 1H), 2.19 (s, 3H), 2.49 (s, 3H), 2.52 (t, J=9.0 Hz, 1H), 4.42 (d, J=12.0 Hz, 1H), 4.65 (d, J=12.0 Hz, 1H), 7.00-7.04 (m, 1H), 7.33-7.38 (m, 3H), 7.46-7.50 (m, 1H), 7.96 (dd, J=6.0 Hz, 1H), 8.17 (d, J=0.3 Hz, 1H), 8.19 (s, 1H) MS $[M+H]^+$=427
285		^{1}H-NMR (400 MHz, CD_3OD) δ (ppm): 1.58 (dd, J=8.0, 5.2 Hz, 1H), 1.89 (dd, J=6.0, 5.2 Hz, 1H), 2.21 (s, 3H), 2.50-2.56 (m, 1H), 2.52 (s, 3H), 4.52 (d, J=10.0 Hz, 1H), 4.76 (d, J=10.0 Hz, 1H), 6.98-7.06 (m, 1H), 7.32-7.41 (m, 3H), 7.47 (ddd, J=9.2, 8.0, 3.2 Hz, 1H), 7.94 (dd, J=9.4, 4.2 Hz, 1H), 7.98 (s, 1H), 8.18 (d, J=3.2 Hz, 1H) MS $[M+H]^+$=427

[0384]

Example 286

Synthesis of (1R,2S)-N-(5-fluoropyridin-2-yl)-2-[(4-hydroxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)cyclopropanecarboxamide (286)

[Formula 69]



95 286

[0385]

To a THF solution (10 ml) of the compound 95 (200 mg), n-BuLi (2.76 M n-hexane solution: 0.371 ml) was added while stirring at -78°C, and the obtained solution was then stirred for 1 hour. Thereafter, a THF solution (3 ml) of (2-benzsulfonyl-3-phenyloxaziridine) (Davis, F. A., J. Org. Chem. 1988, 53, 5004-) (135 mg) was added to the reaction solution at -78°C. While the temperature of the reaction solution was increased to a room temperature, it was stirred for 14 hours. Thereafter, a saturated ammonium chloride aqueous solution was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with a saturated saline, was then dried over magnesium sulfate, and was then concentrated under a reduced pressure. The obtained residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, heptane/ethyl acetate 10% >> 100%). The resultant product was purified by HPLC again, so as to obtain the above-captioned compound (1.19 mg).

^{1}H-NMR (600 MHz, CD_3OD) δ (ppm): 1.56 (t, J=6.0 Hz, 1H), 1.85 (t, J=6.0 Hz, 1H), 2.49 (t, J=6.0 Hz, 1H), 2.53 (s, 3H), 4.41 (d, J=12.0 Hz, 1H), 4.49 (d, J=12.0 Hz, 1H), 4.57 (d, J=12.0 Hz, 1H), 4.66 (d, J=12.0 Hz, 1H), 6.98-7.04 (m, 1H), 7.32-7.36 (m, 1H), 7.36-7.39 (m, 2H), 7.44-7.50 (m, 1H), 7.90-7.95 (m, 1H), 8.13 (s, 1H), 8.17 (d, 1H).

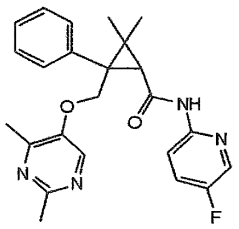
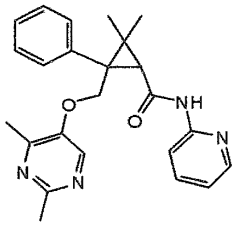
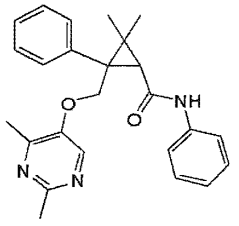
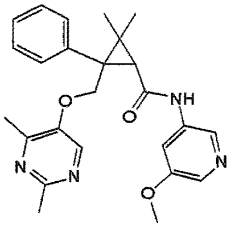
MS $[M+Na]^+$=449

[0386]

The compounds of Examples 287 to 290 were synthesized from the carboxylic acid Prep 48-5 according to the examples.

[0387]

[Table 68]

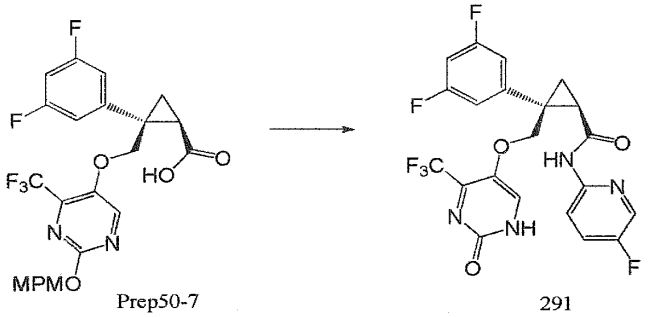
Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
287		MS $[M+H]^+$=421
288		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.06 (s, 3H), 1.56 (s, 3H), 1.94 (s, 1H), 2.26 (s, 3H), 2.57 (s, 3H), 4.67 (d, J=9.6 Hz, 1H), 4.74 (d, J=9.6 Hz, 1H), 7.23-7.41 (m, 6H), 7.86-8.06 (m, 2H), 8.20 (brd, J=8.8 Hz, 1H), 8.35 (dd, J=4.8, 1.2 Hz, 1H), 8.54 (d, J=1.2 Hz, 1H).
289		MS $[M+H]^+$=402
290		MS $[M+H]^+$=433

[0388]

Example 291

Synthesis of (1R,2S)-2-(3,5-difluorophenyl)-N-(5-fluoropyridin-2-yl)-2-[(2-oxo-4-trifluoromethyl-1,2-dihydropyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide (291)

[Formula 70]



Prep50-7 291

[0389]

2-Amino-5-fluoropyridine (26.4 mg), HATU (89.4 mg) and N,N-diisopropylethylamine (40.7 μl) were added to a DMF solution (2 ml) of the compound Prep 50-7 (100 mg). The obtained mixture was stirred at a room temperature overnight. Thereafter, water was added to the reaction solution, and the obtained mixture was then extracted with diethyl ether. The organic layer was washed with a saturated saline, was then dried over anhydrous magnesium sulfate, and was then filtered. The filtrate was concentrated under a reduced pressure. To the residue, 4 N hydrochloric acid/ethyl acetate (2 ml) was added, and the obtained mixture was then stirred at a room temperature for 1 hour. Thereafter, the reaction system was concentrated under a reduced pressure. To the residue, a saturated sodium bicarbonate aqueous solution and ethyl acetate were added, and the obtained mixture was then subjected to liquid separation and extraction. The obtained organic layer was dried over magnesium sulfate. The resultant organic layer was concentrated under a reduced pressure, and the obtained residue was then purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, elution solvent: n-heptane : ethyl acetate = 2 : 1 → ethyl acetate), so as to obtain the above-captioned compound (30 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.59-1.63 (m, 1H), 1.86 (t, J=6.0 Hz, 1H), 2.17 (brdt, J=6.0 Hz, 1H), 4.41 (t, J=10.8 Hz, 2H), 6.70-6.76 (m, 1H), 6.97 (d, J=6.0 Hz, 2H) 7.38-7.43 (m, 1H), 7.91 (s, 1H), 8.06-8.09 (m, 2H), 9.13 (s, 1H).

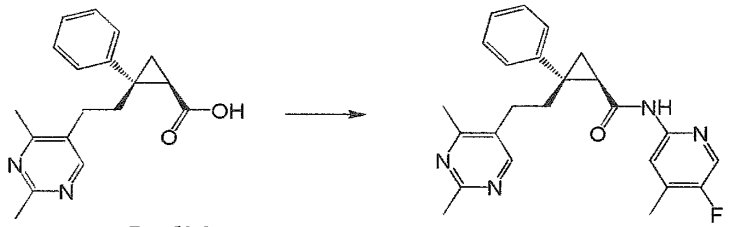
MS $[M+Na]^+$=485.

[0390]

Example 292

Synthesis of (1R,2R)-2-[2-(2,4-dimethylpyrimidin-5-yl)ethyl]-N-(5-fluoro-4-methylpyridin-2-yl)-2-phenylcyclopropanecarboxamide (292)

[Formula 71]



Prep51-9 292

[0391]

The compound Prep 51-9 was treated in the same manner as that of Example 291, so as to obtain the above-captioned compound.

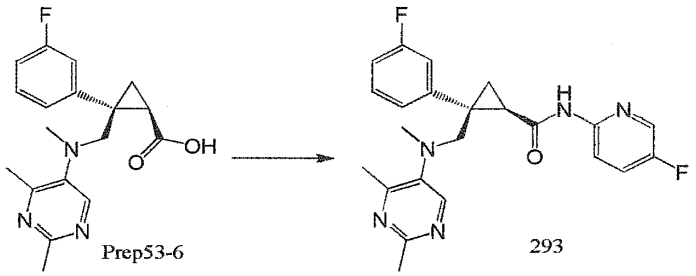
MS $[M+H]^+$=405

[0392]

Example 293

Synthesis of (1R,2S)-2-[N-(2,4-dimethylpyrimidin-5-yl)methylaminomethyl]-N-(5-fluoropyridin-2-yl)-2-(3-fluorophenyl)cyclopropanecarboxamide (293)

[Formula 72]



Prep53-6 293

[0393]

The compound Prep 53-6 (50 mg) was dissolved in DMF (15.6 ml), and thereafter, HATU (116 mg), N,N-diisopropylethylamine (79.4 μl) and 2-amino-5-fluoro-4-picoline (57.5 mg) were added to the solution. The obtained mixture was stirred at a room temperature for 1 hour. Thereafter, water was added to the reaction solution, and the reaction solution was then concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (n-heptane : ethyl acetate = 7 : 3 to 3 : 7), so as to obtain the above-captioned compound (26.8 mg).

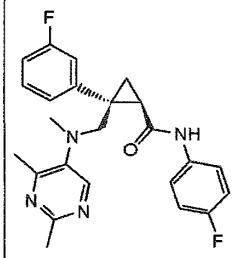
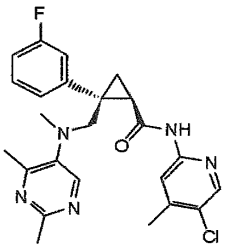
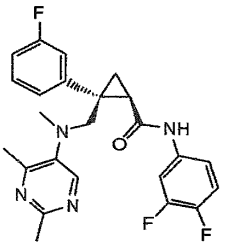
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.54 (dd, J=9.6, 4.8 Hz), 1.69 (t, J=5.2 Hz, 1H), 1.86-1.90 (m, 1H), 2.04 (s, 3H), 2, 32 (s, 1H), 2.52 (s, 3H), 2.63 (s, 3H), 3, 54 (d, J=13.6 Hz, 1H), 3.59 (d, J=13.6 Hz, 1H), 6.89-7.05 (m, 3H), 7.20-7.26 (m, 2H), 7.97 (s, 1H), 8.05-8.10 (m, 2H), 8.10 (s, 1H), 8.55 (brs, 1H).

[0394]

The compounds of Examples 294 to 296 were synthesized by reacting the carboxylic acid Prep 53-6 with any amine according to the method of Example 293.

[0395]

[Table 69]

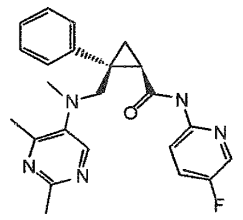
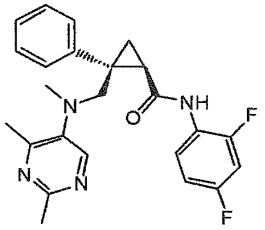
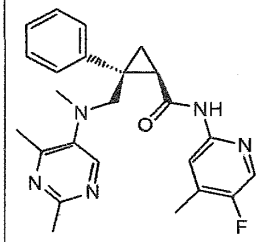
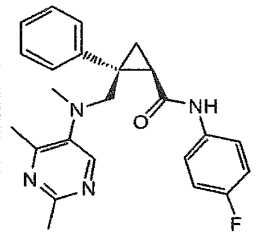
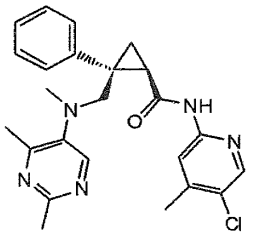
Example	Structural formula, MS	Example	Structural formula, MS	Example	Structural formula, MS
294	 MS $[M+H]^+$= 423	295	 MS $[M+H]^+$= 454	296	 MS $[M+H]^+$= 441

[0396]

The compounds of Examples 297 to 301 were synthesized from the carboxylic acid Prep 54 according to the method of Example 293.

[0397]

[Table 70]

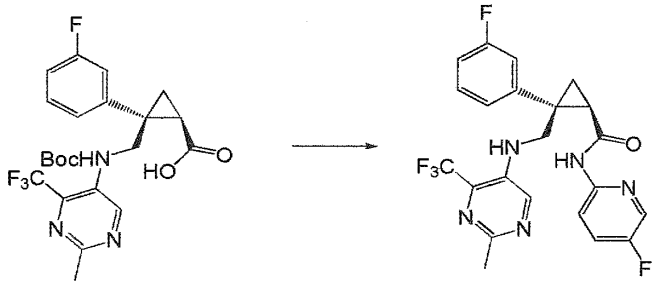
Example	Structural formula, MS	Example	Structural formula, MS	Example	Structural formula, MS
297	 MS $[M+H]^+$=405	298	 MS $[M+H]^+$=423	299	 MS $[M+H]^+$=420
300	 MS $[M+H]^+$=405	301	 MS $[M+H]^+$=436		

[0398]

Example 302

Synthesis of (1R,2S)-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)-2-[N-(2-methyl-4-trifluoromethylpyrimidin-5-yl)aminomethyl]cyclopropanecarboxamide (302)

[Formula 73]



Prep55-6 302

[0399]

2-Amino-5-fluoropyridine (8.6 mg), HATU (29.2 mg) and N,N-diisopropylethylamine (13.3 μl) were added to a DMF solution (1 ml) of the compound Prep 55-6 (30 mg). The obtained mixture was stirred at a room temperature overnight. Thereafter, water was added to the reaction solution, and the obtained mixture was then extracted with diethyl ether. The organic layer was washed with brine, was then dried over anhydrous magnesium sulfate, and was then filtered. The filtrate was concentrated under a reduced

pressure. To the residue, 4 N hydrochloric acid/ethyl acetate (3 ml) was added, and the obtained mixture was then stirred at a room temperature for 1 hour. Thereafter, the reaction system was concentrated under a reduced pressure. To the residue, a saturated sodium bicarbonate aqueous solution and ethyl acetate were added, and the obtained mixture was then subjected to liquid separation and extraction. The obtained organic layer was dried over magnesium sulfate. The resultant organic layer was concentrated under a reduced pressure, and the obtained residue was then purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, elution solvent: n-heptane : ethyl acetate = 9 : 1 → 1 : 1), so as to obtain the above-captioned compound (8.6 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.53-1.56 (m, 1H), 1.81 (t, J=5.2 Hz, 1H), 2.02 (brdt, 1H), 2.57 (s, 3H), 3.77 (dd, J=5.6 Hz, 14.0 Hz, 1H), 3.89 (dd, J=5.6 Hz, 13.6 Hz, 1H), 4.45 (brds, 1H), 6.98-7.15 (m, 3H), 7.30-7.47 (m, 2H), 8.13-8.17 (m, 3H), 8.32 (s, 1H).

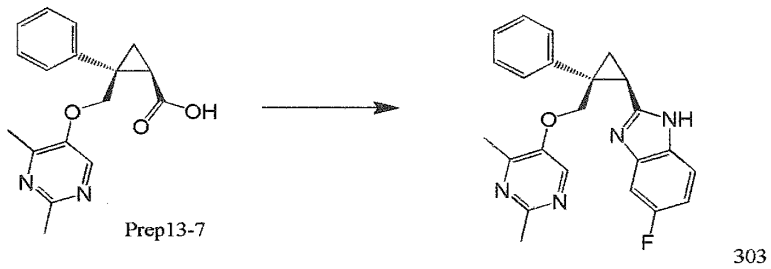
MS $[M+Na]^+$=486.

[0400]

Example 303

Synthesis of 2-{(1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropyl}-5-fluoro-1H-benzimidazole (303)

[Formula 74]



Prep13-7 303

[0401]

HATU (153 mg), DIPEA (104 μl) and 3,4-diami-1-fluorobenzene (45.3 mg) were added to a DMF solution (3 ml) of the compound Prep 13-7(100 mg), and the obtained mixture was then stirred at a room temperature overnight. Thereafter, water was added to the reaction system, and liquid separation and extraction were then carried out with ethyl acetate. The obtained organic layer was dried over magnesium sulfate, and the resultant organic layer was then concentrated under a reduced pressure. The obtained residue was dissolved in acetic acid (3 ml), and the obtained solution was then stirred at 90°C for 5 hours. Thereafter, the reaction system was concentrated under a reduced pressure, and the resultant product was filtered with a NH-silica pad. The filtrate was concentrated under a reduced pressure. The residue was

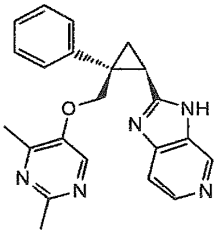
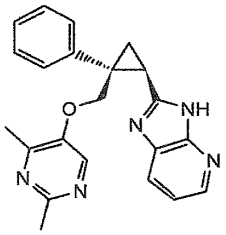
purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, n-heptane : ethyl acetate = 5 : 1 → ethyl acetate), so as to obtain the above-captioned compound (15 mg). MS $[M+H]^+$=389.

[0402]

The compounds of Examples 304 and 305 were synthesized by the same method as that of Example 303.

[0403]

[Table 71]

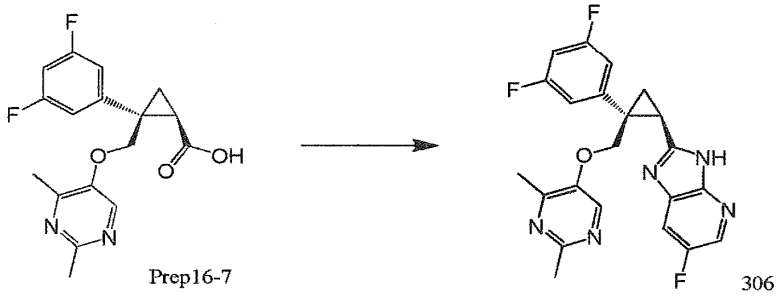
Example	Structural formula, MS	Example	Structural formula, MS
304	 MS $[M+H]^+$= 372	305	 MS $[M+H]^+$= 372

[0404]

Example 306

Synthesis of 2-{(1R,2S)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropyl}-6-fluoro-1H-imidazo[4,5-b]pyridine (306)

[Formula 75]



[0405]

HATU (45.9 mg), DIPEA (31.2 μl) and 2,3-diamino-5-fluorobenzene (15.5 mg) were added to a DMF solution (900 μl) of the compound Prep 16-7 (30 mg), and the obtained mixture was then stirred at a room temperature for 2 hours. Thereafter, a saturated sodium

bicarbonate aqueous solution was added to the reaction system, and liquid separation and extraction were then carried out with ethyl acetate. The obtained organic layer was dried over magnesium sulfate, and the resultant organic layer was then concentrated under a reduced pressure. The obtained residue was dissolved in acetic acid (900 μl), and the obtained solution was then stirred with INITIATOR MICROWAVE SYNTHESIZER (Biotage) at 150°C for 11 hours. Thereafter, the reaction system was concentrated under a reduced pressure, and ethyl acetate and a sodium bicarbonate aqueous solution were added to the residue to carry out liquid separation and extraction. The obtained organic layer was dried over magnesium sulfate, and the resultant organic layer was then concentrated under a reduced pressure. The obtained residue was purified by silica gel column chromatography (YAMAZEN, Hi-Flush™ column, n-heptane : ethyl acetate = 5 : 1 → ethyl acetate), so as to obtain the above-captioned compound (9.3 mg).

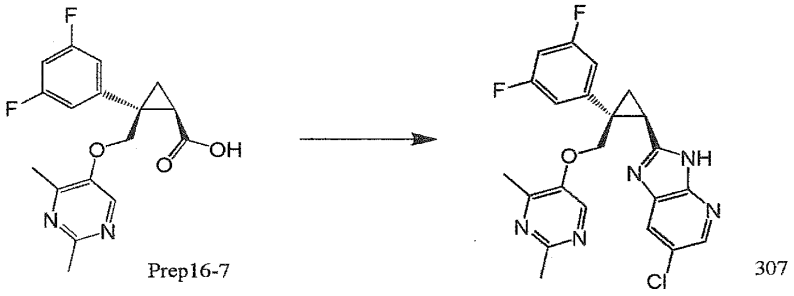
MS $[M+H]^+$=426.

[0406]

Example 307

Synthesis of 6-chloro-2-{(1R,2S)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropyl}-1H-imidazo[4,5-b]pyridine (307)

[Formula 76]



[0407]

The above-captioned compound was synthesized by the same method as that of Example 306.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.87 (dd, J=5.6 Hz, 8.8 Hz, 1H), 2.11 (s, 3H), 2.50 (s, 3H), 2.21 (t, J=6.0 Hz, 1H), 2.68 (dd, J=6.4 Hz, 8.8 Hz, 1H), 4.41 (d, J=10.0 Hz, 1H), 4.45 (d, J=9.6 Hz, 1H), 6.77-6.82 (m, 1H), 6.99-7.09 (m, 2H), 7.82 (s, 1H), 7.88 (d, J=2.4 Hz, 1H), 8.22 (d, J=2.0 Hz, 1H), 11.5 (s, 1H).

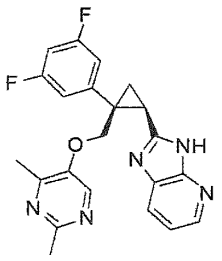
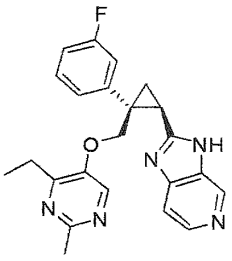
[0408]

The following compounds were synthesized by the same method as that of

Example 306.

[0409]

[Table 72]

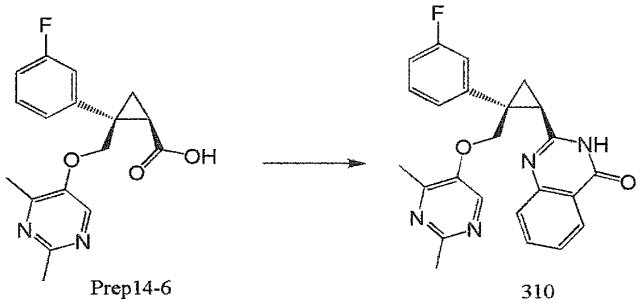
Example	Structural formula, MS	Example	Structural formula, MS
308	 MS $[M+H]^+$= 408	309	 MS $[M+H]^+$=404

[0410]

Example 310

Synthesis of 2-[(1R,2S)-2-{[(2,4-dimethylpyrimidin-5-yl)oxy]methyl}-2-(3-fluorophenyl)cyclopropyl]quinazolin-4(1H)-one (310)

[Formula 77]



Prep14-6 310

[0411]

The compound Prep 14-6 (50 mg), 2-aminobenzamide (23.7 mg) and HATU (66.1 mg) were dissolved in DMF (0.24 ml), and thereafter, N,N-diisopropylethylamine (22.9 μl) was added to the solution. The obtained mixture was stirred at a room temperature for 24 hours. Thereafter, water was added to the reaction solution, and the obtained mixture was then extracted with ethyl acetate (× 3). The organic layer was successively washed with water and a saturated saline, and was then dried over anhydrous sodium sulfate. The solvent was distilled away under a reduced pressure, and the residue was dissolved in IPA (3 ml). Potassium tert-butoxide

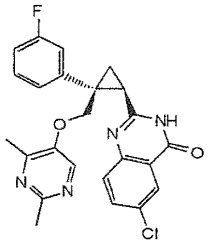
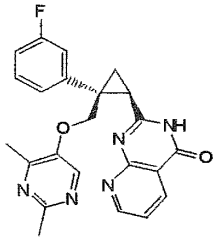
(35.5 mg) was added to the solution, and the obtained mixture was then stirred under heating at 100°C for 2 hours. Thereafter, the reaction solution was cooled to a room temperature. A droplet of water was added to the reaction solution, and the obtained mixture was then concentrated under a reduced pressure. The residue was purified by NH-silica gel column chromatography (n-heptane : ethyl acetate = 9 : 1 to 0 : 1), so as to obtain the above-captioned compound (20.6 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.65 (dd, J=8.0, 5.2 Hz, 1H), 2.14 (s, 3H), 2.33 (t, J=5.2 Hz, 1H), 2.44 (s, 3H), 2.75-2.79 (m, 1H), 4.43 (d, J=9.6, 1H), 4.45 (d, J=9.6 Hz, 1H), 7.07 (tdd, J=8.0, 2.0, 1.2 Hz, 1H), 7.39 (td, J=8.0, 6.0 Hz, 1H), 7.46-7.52 (m, 2H), 7.62-7.65 (m, 2H), 7.75 (t, J=6.8 Hz, 1H), 7.79 (s, 1H), 8.33 (d, J=8.0 Hz, 1H), 13.1 (brs, 1H).

LC-MS (ES.Pos): 417[M+H+]/416

[0412]

[Table 73]

Example	Structural formula	NMR (400 MHz, $CDCl_3$) and/or MS
311		^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.68 (dd, J=8.0, 5.2 Hz, 1H), 2.11 (s, 3H), 2.31 (t, J=5.2 Hz, 1H), 2.45 (s, 3H), 2.76 (dd, J=8.0, 6.0 Hz, 1H), 4.40 (d, J=10.0, 1H), 4.45 (d, J=10.0 Hz, 1H), 7.10 (td, J=8.8, 2.0 Hz, 1H), 7.43 (td, J=8.8, 6.0 Hz, 1H), 7.52 (d, J=8.8 Hz, 1H), 7.56 (d, J=8.8 Hz, 1H), 7.61 (d, J=8.8 Hz, 1H), 7.68 (dd, J=8.8, 2.4 Hz, 1H), 7.78 (s, 1H), 8.27 (d, J=2.4 Hz, 1H), 13.4 (s, 1H). LC-MS (ES.Pos): 451[M+H+]/450
312		LC-MS (ES.Pos): 418[M+H+]/417

[0413]

Test Example

1. Measurement of orexin receptor-binding ability

The assay was carried out using a 96-well Wheat Germ Agglutinin Flash Plate (PerkinElmer). The volume of a single assay was 100 μl, and the composition of a reaction

solution was as follows:

25 mM HEPES (pH 7.5), 1 mM $CaCl_2$, 5 mM $MgCl_2$, 0.5% BSA (bovine serum albumin), 0.1% sodium azide, 0.05% Tween-20, and 0.2% DMSO.

A cell membrane was prepared from recombinant CHO cells that expressed OX2R or OX1R. The cell membrane was used in an amount of 5 ig protein/assay. A compound to be evaluated, which had various concentrations, and 0.2 nM [^{125}I]-oxerin-A used as a tracer were added to the cell membrane, and the reaction was then carried out at a room temperature for 30 minutes. After completion of the reaction, the reaction solution as a whole was discarded, and the wells were then washed once with 200 μl of a wash buffer (25 mM HEPES (pH 7.5), 1 mM $CaCl_2$, 5 mM $MgCl_2$, 0.5% BSA, 0.1% sodium azide, 0.05% Tween-20, and 500 mM sodium chloride). Finally, the radioactivity of each well was measured using a scintillation counter (TopCount, PerkinElmer). The obtained results are shown in the following table.

[0414]

[Table 74]

Example No.	OX1 RBA nM	OX2 RBA nM	Example No.	OX1 RBA nM	OX2 RBA nM	Example No.	OX1 RBA nM	OX2 RBA nM
1	139	7	2	296	19	3	1034	>200
7	1235	71	15	213	41	16	40	1.9
17	294	38	18	344	33	20	1884	117
22	273	17	23	1697	67	26	20	3.7
29	459	55	37	41	8	38	518	29
44		26	45	13.9	6.2	48	1153	159
51	6.4	3.9	52	37	28	60	>2000	105
61	874	16	62	>2000	153	64	74	15
65	1034	81	66	398	50	67	1610	164
73	3.4	5.7	81	2592	63	82	2.4	3.7
84	6	3	87	43	10	88	267	13
95	13.4	5.2	96	32	5	98	18	10
100	40	7.5	105	195	18	109	12	5.8
113	22	179	114	40	1612	115		21
119	21	5.2	120	123	7	121	10	3.1
123	451	20	125	1045	84	127	1099	80
129	1	1.5	130	22	4	135	14	8
136		15	139	22	3.3	141	9	1.3
143		14	144		12	153	447	32
155	10	6	158	180	27	161	50	12
162	65	13	163	<20	10	164	3	6
165	29	7	167	38	10	170		7
174	33	55	177	334	84	178	769	60
182	99	21	186	22	7	187		16
191	1	1	192	12	5	199	2	2
200	67	12	203	215	8	205	9	6
208		11	211	20	4	212	4	7
218	10	3	219	10	3	225	6	3
228		45	231		7	235		6
237		31	240	9	2.9	243	2	3.3
247	22	3	255		27	259		>60
260	>2000	70	263	82	17	266	30	2.7
267	118	64	270	264	58	275	188	132
278	76	10	279	24	3.2	280	24	21
282	21	2.4	283	172	9	284	112	6
285	77	16	286	>200	4.5	290	226	>200
291	>200	49	295	5	6	300	495	34
302	8	3	303	75	3	308		31
309		10	311	23	3.1	312	136	62

[0415]

2. Measurement of antagonism (PLAP assay)

The antagonistic function of the compound of the present invention to prevent the activation of OX2 and OX1 receptors by orexin A that is a natural peptide agonist was measured by a cell-based reporter assay. A HEK-293 cell line expressing a genetically recombinant human OX2 receptor (accession No. NM_001526.3) or a HEK-293 cell line expressing a genetically recombinant human OX1 receptor (accession No. NM_001525.2), which had

pBabeCLIH as an expression vector, was used. The cells were plated at a cell density of 10,000 cells/well onto a non-coated 96-well plate in a Dulbecco's modified Eagle medium (Sigma Cat No. D6046 containing 10% v/v heat-inactivated fetal bovine serum). The cells were left at 37°C overnight, so that they were adhered to the plate. On the following day, the cells were incubated with the compound of the present invention dissolved in a Dulbecco's modified Eagle medium (which contained 0.1% w/v heat-inactivated fetal bovine serum albumin Sigma Cat No. A8806), and methyl sulfoxide having a final concentration of 0.1% was then added to the cell plate.

The thus obtained mixture was incubated at a room temperature for 1 hour. Thereafter, human orexin-A and forskolin were dissolved in the same medium as described above, which contained fetal bovine serum albumin, and the medium was then added to the cells. Then, forskolin having a final concentration of 300 nmol/L was further added thereto. Subsequently, the cells were cultured at 37°C for approximately 18 to 24 hours. During the culture, as a result of activation of the orexin receptor and a dose-dependent increase in intracellular calcium, placental alkaline phosphatase (PLAP) that was a reporter enzyme was expressed and secreted under the control of a CRE x4 + VIP promoter in a pBabeCLcre4vPdNN vector. On the following day, enzyme activity was detected by mixing the culture medium supernatant with 20 μl of detection buffer (containing 1.34 g/L sodium bicarbonate, 1.27 g/L sodium carbonate and 0.2 g/L magnesium sulfate heptahydrate in water) and 25 μl of Lumi-Phos530 reagent (Wako Pure Chemical Industries Ltd.), then incubating the obtained mixture at a room temperature for 2 hours, and then performing luminescence measurement (ARVO Reader, PerkinElmer). The Kd value of orexin-A with respect to each receptor was measured by titration from 0 to 300 nmol/L. Then, the IC50 value of the compound of the present invention with respect to the activity of 1 nmol/L human orexin-A was obtained by converting the obtained value using the Cheng-Prusoff equation. The obtained results are shown in the following table.

[0416]

[Table 75]

Example No.	OX1PLAP (Ki)	OX2PLAP (Ki)	Example No.	OX1PLAP (Ki)	OX2PLAP (Ki)	Example No.	OX1PLAP (Ki)	OX2PLAP (Ki)
1	157	10.2	16	80	5.4	26	27.3	0.4
45	19.4	0.44	51	29	1.2	61	>667	25.7
64	133.3	6.3	65	>667	60	66	>667	34.3
67	>667	57.1	82	0.96	0.085	95	9.9	0.69
100	146.7	9.4	114	47.3	285.7	119	21.3	0.6
120	273.3	5.7	121	26.7	0.3	129	0.97	0.059
139	113.3	1.7	161	32	2.9	164	0.93	0.124
186	86.7	3.4	240	17.8	0.89	263	193.3	8.6

[0417]

3. Sleep experiment

As a method for measuring the sleep effects of the present compound, electroencephalogram (EEG) was carried out using mice (C57BL/6NCrlCrLj).

In order to measure brain wave, electrode implantation was performed on individual mice, and the mice were then bled in a state in which they can freely move in individual cages for 1 week or longer. Thereafter, the electrode was connected with a brain wave measurement apparatus.

The mice were administered with the compound immediately before turning off the lights. Sleeping time for 3 hours after turning off the lights was measured. With regard to the sleep effects of the compound, it was confirmed that the compound exhibited the same action in both the dark period and the light period. The compound was administered at a dose of 10 mg/kg via oral or intraperitoneal administration.

With regard to sleep analysis, the automatic analysis software of Kissei Comtec Co., Ltd. was used, and the analysis data of frequency was analyzed in detail. Thereafter, sleeping time was calculated.

The action of the compound to increase the sleeping time was evaluated based on a change occurred between the sleeping time on the drug-non-administered day and the sleeping time on the drug-administered day. The obtained results are shown in the following table.

[0418]

[Table 76]

Example No.	Sleep extended time 10 mg/kg (min/3 hrs)	Example No.	Sleep extended time 10 mg/kg (min/3 hrs)	Example No.	Sleep extended time 10 mg/kg (min/3 hrs)
1	18.3	16	19	45	15.2
51	22.2	73	22.7	82	33.5
95	39.8	96	12.1	100	23.8
105	14.3	119	16	120	11.5
121	26.7	129	30	130	24.2
141	28.7	161	10	164	48.3
186	14.7	191	41.8	199	36.2
240	7.7	263	27.3		

[Industrial Applicability]

[0419]

As described in detail above, the cyclopropane compound of the present invention or a pharmaceutically acceptable salt thereof has extremely excellent orexin receptor inhibitory action, and is extremely useful as an agent for preventing or treating sleep disorder caused by orexin, including narcolepsy as a typical example. Specifically, the cyclopropane compound of the present invention or a pharmaceutically acceptable salt thereof is useful for the prevention or treatment of sleep disorder including insomnia, narcolepsy (paroxysmal sleep), and other diseases such as excessive sleepiness, sleep-related dystonia, restless legs syndrome, sleep apnea, jet lag syndrome, shift work syndrome, delayed sleep phase syndrome or advanced sleep phase syndrome. Furthermore, the cyclopropane compound of the present invention or a pharmaceutically acceptable salt thereof is useful for the prevention or treatment of diseases including: dysthymic disorder, mood disorder, and mental and anxiety disorder; diabetes, and appetite, taste, eating or drinking disorder; hypothalamic disease; biological and circadian rhythm disorder; sleep disorder associated with a disease selected from nervous disease, neurogenic pain and restless legs syndrome; depression and insomnia related to depression; bipolar disorder and insomnia related to bipolar disorder; anxiety disorder and insomnia related to anxiety disorder; insomnia related to Parkinson's disease; insomnia related to schizophrenia; insomnia related to mental disorder; sleep apnea; narcolepsy; idiopathic insomnia; parasomnia; opioid dependence; nicotine dependence; benign prostatic hyperplasia; pure dementia and

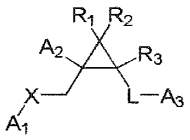
cognitive impairment in a healthy group and in mental and nervous diseases; and other diseases related to systemic orexin dysfunction.

[Kind of Document] CLAIMS

[Claim 1]

A compound represented by the following formula (I) or a pharmaceutically acceptable salt thereof:

[Formula 1]



(I)

wherein

A_1 represents a pyrimidinyl group or a N-oxide pyrimidinyl group, each of which may optionally have 1 to 3 substituents selected from Substituent group α,

A_2 and A_3 each independently represent an aryl group selected from Group 1, which may optionally have 1 to 3 substituents selected from Substituent group α, or a heterocyclic group selected from Group 3, which may optionally have 1 to 3 substituents selected from Substituent group β,

R_1, R_2 and R_3 each independently represent a hydrogen atom, a halogen atom, a $C_{1\text{-}6}$ alkyl group which may optionally have 1 to 3 substituents selected from Substituent group β, or a $C_{3\text{-}8}$ cycloalkyl group which may optionally have 1 to 3 substituents selected from Substituent group β,

X represents an oxygen atom, a $C_{1\text{-}6}$ alkylene group, a formula $-NR_4-$ (wherein R_4 represents a hydrogen atom or a $C_{1\text{-}6}$ alkyl group), -S-, -SO- or $-SO_2-$, and

L represents a bond or a formula $-CONR_5-$ (wherein R_5 represents a hydrogen atom, a $C_{1\text{-}6}$ alkyl group or a $C_{3\text{-}8}$ cycloalkyl group), wherein

Substituent group α: a cyano group, a halogen atom, a hydroxyl group, an oxo group, a formula $-NR_6R_7$ (wherein R_6 and R_7 each independently represent a hydrogen atom or a $C_{1\text{-}6}$ alkyl group), a $C_{1\text{-}6}$ alkyl group which may optionally have 1 to 3 substituents selected from Substituent group β, a $C_{1\text{-}6}$ alkoxy group which may optionally have 1 to 3 substituents selected from Substituent group β, a $C_{1\text{-}6}$ alkylcarbonyl group which may optionally have 1 to 3 substituents selected from Substituent group β, a $C_{1\text{-}6}$ alkylsulfonyl group which may optionally have 1 to 3 substituents selected from Substituent group β, an aryl group selected from Group 1, which may optionally have 1 to 3 substituents selected from Substituent group β, and a

heteroaryl group selected from Group 2, which may optionally have 1 to 3 substituents selected from Substituent group β;

Substituent group β: a cyano group, a halogen atom, a hydroxyl group, a C_{3-8} cycloalkyl group, and a C_{1-6} alkoxy group;

Group 1: a phenyl group, a naphthyl group, an azulenyl group, an anthryl group, and a phenanthryl group;

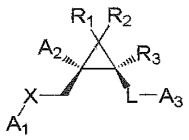
Group 2: a furyl group, a thienyl group, a pyrrolyl group, an imidazolyl group, a triazolyl group, a tetrazolyl group, a thiazolyl group, a pyrazolyl group, an oxazolyl group, an isoxazolyl group, an isothiazolyl group, a furazanyl group, a thiadiazolyl group, an oxadiazolyl group, a pyridyl group, a pyrazinyl group, a pyridazinyl group, a triazinyl group, an indolyl group, an isoindolyl group, an indazolyl group, a benzoxazolyl group, a benzisoxadiazolyl group, a benzothiazolyl group, a benzisothiazolyl group, a quinolyl group, and an isoquinolyl group; and

Group 3: a furyl group, a thienyl group, a pyrrolyl group, an imidazolyl group, a triazolyl group, a tetrazolyl group, a thiazolyl group, a pyrazolyl group, an oxazolyl group, an isoxazolyl group, an isothiazolyl group, a furazanyl group, a thiadiazolyl group, an oxadiazolyl group, a pyridyl group, a pyrazinyl group, a pyridazinyl group, a pyrimidinyl group, a triazinyl group, a 2-pyridonyl group, a 4-pyridonyl group, a pyridazidonyl group, a pyrimididonyl group, a purinyl group, a pteridinyl group, a quinolyl group, an isoquinolyl group, a naphthylidyl group, a quinoxalyl group, a cinnolyl group, a quinazolyl group, a phthalazyl group, an imidazopyridyl group, an imidazothiazolyl group, an imidazoxazolyl group, a benzimidazolyl group, an indolyl group, an isoindolyl group, an indazolyl group, a pyrrolopyridyl group, a thienopyridyl group, a fluoropyridyl group, a benzoxazolyl group, a benzisoxadiazolyl group, a benzothiazolyl group, a benzisothiazolyl group, a pyridopyrimidinyl group, an oxodihydropyridopyrimidinyl group, a benzofuryl group, a benzothienyl group, a benzothiadiazolyl group, a benzo[1,3]dioxolyl group, a thienofuryl group, a dihydroisobenzofuranyl group, a chromanyl group, an isochromanyl group, a 1,3-dioxaindanyl group, a 1,4-dioxatetralinyl group, and a dihydrobenzo[1,4]oxazinyl group.

[Claim 2]

The compound according to claim 1, which is represented by the following formula (II), or a pharmaceutically acceptable salt thereof:

[Formula 2]



(I I)

wherein A_1, A_2, A_3, R_1, R_2, R_3, X and L have the same definitions as those described in claim 1.

[Claim 3]

The compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R_1, R_2 and R_3 each represent a hydrogen atom.

[Claim 4]

The compound according to claim 3, or a pharmaceutically acceptable salt thereof, wherein L represents a formula -CONH-.

[Claim 5]

The compound according to claim 4, or a pharmaceutically acceptable salt thereof, wherein X represents an oxygen atom.

[Claim 6]

The compound according to claim 5, or a pharmaceutically acceptable salt thereof, wherein A_2 and A_3 each independently represent an aryl group or a heteroaryl group, which may optionally have 1 to 3 substituents selected from a cyano group, a halogen atom, a C_{1-6} alkyl group, a halo-C_{1-6} alkyl group and a C_{1-6} alkoxy group.

[Claim 7]

The compound according to claim 6, or a pharmaceutically acceptable salt thereof, wherein A_2 and A_3 each independently represent a phenyl group, a naphthyl group, a pyridyl group, a pyrazinyl group, a pyridazinyl group, a pyrimidinyl group, a quinolyl group or an isoquinolyl group, which may optionally have 1 to 3 substituents selected from a cyano group, a halogen atom, a C_{1-6} alkyl group, a halo-C_{1-6} alkyl group and a C_{1-6} alkoxy group.

[Claim 8]

The compound according to claim 7, or a pharmaceutically acceptable salt thereof, wherein A_2 represents a phenyl group which may optionally have 1 to 3 substituents selected from a cyano group, a halogen atom, a C_{1-6} alkyl group, a halo-C_{1-6} alkyl group and a C_{1-6} alkoxy group.

[Claim 9]

The compound according to claim 8, or a pharmaceutically acceptable salt thereof, wherein A_3 represents a phenyl group or a pyridyl group which may optionally have 1 to 3 substituents selected from a cyano group, a halogen atom, a hydroxyl group, a C_{1-6} alkyl group,

a halo-C_{1-6} alkyl group and a C_{1-6} alkoxy group.

[Claim 10]

The compound according to claim 9, or a pharmaceutically acceptable salt thereof, wherein A_1 represents a 5-pyrimidinyl group which may optionally have 1 to 3 substituents selected from a halogen atom, a C_{1-6} alkyl group, a halo-C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkyl group, a C_{3-8} cycloalkyl group and a C_{1-6} alkoxy group.

[Claim 11]

The compound according to claim 10, or a pharmaceutically acceptable salt thereof, wherein A_1 represents a 5-pyrimidinyl group which may optionally have 1 or 2 substituents selected from a methyl group, a hydroxymethyl group, a methoxymethyl group and a methoxyethyl group.

[Claim 12]

The compound according to any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof, which is selected from the following compounds:

(1) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)-2-phenylcyclopropanecarboxamide,

(2) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)-2-phenylcyclopropanecarboxamide,

(3) (1R,2S)-N-(5-chloro-4-methylpyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,

(4) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxypyridin-2-yl)-2-phenylcyclopropanecarboxamide,

(5) (1R,2S)-N-(6-fluoropyridin-3-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,

(6) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(6-fluoro-5-methylpyridin-3-yl)-2-phenylcyclopropanecarboxamide,

(7) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-methoxypyridin-3-yl)-2-phenylcyclopropanecarboxamide,

(8) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N,2-diphenylcyclopropanecarboxamide,

(9) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-methylpyridin-2-yl)-2-phenylcyclopropanecarboxamide,

(10) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-[5-fluoro-4-(methoxymethyl)pyridin-2-yl]-2-phenylcyclopropanecarboxamide,

(11) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(2-methoxypyridin-4-yl)-2-phenylcyclopropanecarboxamide,
(12) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenyl-N-[5-(trifluoromethyl)pyridin-2-yl]cyclopropanecarboxamide,
(13) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenyl-N-[4-(trifluoromethyl)pyridin-2-yl]cyclopropanecarboxamide,
(14) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-[4-(methoxymethyl)pyridin-2-yl]-2-phenylcyclopropanecarboxamide,
(15) (1R,2S)-N-(5-chloropyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(16) (1R,2S)-N-[3-(dimethylamino)phenyl]-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(17) (1R,2S)-N-(3-chlorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(18) (1R,2S)-N-(3-cyano-4-fluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(19) (1R,2S)-N-(4-chloro-3-cyanophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(20) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-[3-(methylsulfonyl)phenyl]-2-phenylcyclopropanecarboxamide,
(21) (1R,2S)-N-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(22) (1R,2S)-N-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(23) (1R,2S)-N-(3-chloro-4-fluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(24) (1R,2S)-N-(3-cyano-5-fluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(25) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(3-methoxyphenyl)-2-phenylcyclopropanecarboxamide,
(26) (1R,2S)-N-[3-(cyanomethyl)phenyl]-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(27) (1R,2S)-N-(2-cyanopyridin-4-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-

phenylcyclopropanecarboxamide,
(28) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenyl-N-[3-(trifluoromethyl)phenyl]cyclopropanecarboxamide,
(29) (1R,2S)-N-(4-cyanopyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(30) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(4-methoxypyridin-2-yl)-2-phenylcyclopropanecarboxamide,
(31) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)-2-(3-fluorophenyl)cyclopropanecarboxamide,
(32) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(33) (1R,2S)-N-(5-cyanopyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)cyclopropanecarboxamide,
(34) (1R,2S)-N-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)cyclopropanecarboxamide,
(35) (1R,2S)-N-(4-chloropyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)cyclopropanecarboxamide,
(36) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxymethylpyridin-2-yl)-2-(3-fluorophenyl)cyclopropanecarboxamide,
(37) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxymethylpyridin-2-yl)-2-(3-fluorophenyl)cyclopropanecarboxamide
(38) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)-N-(4-fluorophenyl)cyclopropanecarboxamide,
(39) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)-N-phenylcyclopropanecarboxamide,
(40) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxypyridin-2-yl)-2-(3-fluorophenyl)cyclopropanecarboxamide,
(41) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(4-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(42) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N,2-bis(4-fluorophenyl)cyclopropanecarboxamide,
(43) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxymethylpyridin-2-yl)-2-(4-fluorophenyl)cyclopropanecarboxamide,

(44) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)-2-(4-fluorophenyl)cyclopropanecarboxamide,
(45) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxypyridin-2-yl)-2-(4-fluorophenyl)cyclopropanecarboxamide,
(46) (1R,2S)-2-(3-cyanophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(4-fluorophenyl)cyclopropanecarboxamide,
(47) (1R,2S)-2-(3-cyanophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(48) (1R,2S)-2-(3-cyanophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)cyclopropanecarboxamide,
(49) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenyl-N-pyridin-2-ylcyclopropanecarboxamide,
(50) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)-2-phenylcyclopropanecarboxamide,
(51) (1R,2S)-N-(5-cyanopyridin-2-yl)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(52) (1R,2S)-N-(5-chloropyridin-2-yl)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(53) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)-2-phenylcyclopropanecarboxamide,
(54) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-(4-fluorophenyl)-2-phenylcyclopropanecarboxamide,
(55) (1R,2S)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)cyclopropanecarboxamide,
(56) (1R,2S)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(4-fluorophenyl)cyclopropanecarboxamide,
(57) (1R,2S)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-pyridin-2-ylcyclopropanecarboxamide,
(58) (1R,2S)-N-(5-chloropyridin-2-yl)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(59) (1R,2S)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(60) (1R,2S)-N-(3,4-difluorophenyl)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-

yl)oxymethyl]cyclopropanecarboxamide,
(61) (1R,2S)-N-(2,4-difluorophenyl)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(62) (1R,2S)-N-(5-cyanopyridin-2-yl)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(63) (1R,2S)-2-(3,5-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxypyridin-2-yl)cyclopropanecarboxamide,
(64) (1R,2S)-N-(5-chloropyridin-2-yl)-2-{[(4-(methoxymethyl)-2-methylpyrimidin-5-yl)oxy]methyl}-2-phenylcyclopropanecarboxamide,
(65) (1R,2S)-N-(5-cyanopyridin-2-yl)-2-{[(4-(methoxymethyl)-2-methylpyrimidin-5-yl)oxy]methyl}-2-phenylcyclopropanecarboxamide,
(66) (1R,2S)-N-(5-fluoropyridin-2-yl)-2-{[(4-(methoxymethyl)-2-methylpyrimidin-5-yl)oxy]methyl}-2-phenylcyclopropanecarboxamide,
(67) (1R,2S)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenyl-N-[5-(trifluoromethyl)pyridin-2-yl]cyclopropanecarboxamide,
(68) (1R,2S)-N-(5-fluoro-4-methylpyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(69) (1R,2S)-N-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(70) (1R,2S)-N-(3,4-difluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-phenylcyclopropanecarboxamide,
(71) (1R,2S)-2-(4-chlorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(72) (1R,2S)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)cyclopropanecarboxamide,
(73) (1R,2S)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(4-fluorophenyl)cyclopropanecarboxamide,
(74) (1R,2S)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-pyridin-2-ylcyclopropanecarboxamide,
(75) (1R,2S)-N-(5-cyanopyridin-2-yl)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(76) (1R,2S)-N-(5-chloropyridin-2-yl)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,

(77) (1R,2S)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(78) (1R,2S)-N,2-bis(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(79) (1R,2S)-N-(2,4-difluorophenyl)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(80) (1R,2S)-2-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methoxypyridin-2-yl)cyclopropanecarboxamide,
(81) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)-2-(3-methoxyphenyl)cyclopropanecarboxamide,
(82) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(4-fluorophenyl)-2-(3-methoxyphenyl)cyclopropanecarboxamide,
(83) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)-2-(3-methoxyphenyl)cyclopropanecarboxamide,
(84) (1R,2S)-N-(3,4-difluorophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-methoxyphenyl)cyclopropanecarboxamide
(85) (1R,2S)-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(86) (1R,2S)-2-(3-fluorophenyl)-N-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(87) (1R,2S)-2-(3-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-(pyridin-2-yl)cyclopropanecarboxamide,
(88) (1R,2S)-N-(3,4-difluorophenyl)-2-(3-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(89) (1R,2S)-N,2-bis(3-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(90) (1R,2S)-N-(2,4-difluorophenyl)-2-(3-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(91) (1R,2S)-N-(2,5-difluorophenyl)-2-(3-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(92) (1R,2S)-N-(5-chloropyridin-2-yl)-2-(3-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(93) (1R,2S)-N-(5-fluoro-4-methylpyridin-2-yl)-2-(3-fluorophenyl)-2-[(4-methoxymethyl-2-

methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(94) (1R,2S)-N-(5-cyanopyridin-2-yl)-2-(3-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(95) (1R,2S)-2-(3-fluorophenyl)-2-([(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-[5-(trifluoromethyl)pyridin-2-yl]cyclopropanecarboxamide,
(96) (1R,2S)-2-(4-fluorophenyl)-N-(5-fluoropyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(97) (1R,2S)-N,2-bis(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(98) (1R,2S)-N-(5-chloropyridin-2-yl)-2-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(99) (1R,2S)-N-(5-fluoro-4-methylpyridin-2-yl)-2-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(100) (1R,2S)-2-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-pyridin-2-ylcyclopropanecarboxamide,
(101) (1R,2S)-N-(3,4-difluorophenyl)-2-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(102) (1R,2S)-N-(3-fluorophenyl)-2-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(103) (1R,2S)-2-(3,4-difluorophenyl)-2-([(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-(pyridin-2-yl)cyclopropanecarboxamide,
(104) (1R,2S)-2-(3,4-difluorophenyl)-N-(5-fluoro-4-methylpyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(105) (1R,2S)-2-(3,4-difluorophenyl)-N-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(106) (1R,2S)-N,2-bis(3,4-difluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(107) (1R,2S)-N-(2,5-difluorophenyl)-2-(3,4-difluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(108) (1R,2S)-N-(2,4-difluorophenyl)-2-(3,4-difluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(109) (1R,2S)-N-(2,3-difluorophenyl)-2-(3,4-difluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,

(110) (1R,2S)-2-(3,5-difluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-pyridin-2-ylcyclopropanecarboxamide,
(111) (1R,2S)-2-(3,5-difluorophenyl)-N-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(112) (1R,2S)-2-(3,5-difluorophenyl)-N-(5-fluoro-4-methylpyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(113) (1R,2S)-N-(3,4-difluorophenyl)-2-(3,5-difluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(114) (1R,2S)-2-(3-chlorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-pyridin-2-ylcyclopropanecarboxamide,
(115) (1R,2S)-2-(3-chlorophenyl)-N-(5-fluoro-4-methylpyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(116) (1R,2S)-N-(5-fluoro-4-methylpyridin-2-yl)-2-(3-fluorophenyl)-2-({[4-(methoxyethyl)-2-methylpyrimidin-5-yl]oxy}methyl)cyclopropanecarboxamide,
(117) (1R,2S)-2-(3-fluoro-5-methoxyphenyl)-N-(4-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(118) (1R,2S)-N-(3,4-difluorophenyl)-2-(3-fluoro-5-methoxyphenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(119) (1R,2S)-2-(3-fluoro-5-methoxyphenyl)-N-(5-fluoropyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(120) (1R,2S)-2-(3-fluoro-5-methoxyphenyl)-N-(5-fluoro-4-methoxypyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(121) (1R,2S)-2-(3-fluoro-5-methoxyphenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-pyridin-2-ylcyclopropanecarboxamide,
(122) (1R,2S)-2-(3-fluoro-5-methoxyphenyl)-N-(3-fluorophenyl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(123) (1R,2S)-2-(4-fluoro-3-methoxyphenyl)-N-(5-fluoro-4-methylpyridin-2-yl)-2-[(4-methoxymethyl-2-methylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(124) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)-N-pyridin-2-ylcyclopropanecarboxamide,
(125) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(126) (1R,2S)-N-(5-cyanopyridin-2-yl)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(3-

fluorophenyl)cyclopropanecarboxamide,
(127) (1R,2S)-N-(5-chloropyridin-2-yl)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)cyclopropanecarboxamide,
(128) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)-2-(3-fluorophenyl)cyclopropanecarboxamide,
(129) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(4-fluorophenyl)-N-pyridin-2-ylcyclopropanecarboxamide,
(130) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(4-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(131) (1R,2S)-N-(4-chloropyridin-2-yl)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(4-fluorophenyl)cyclopropanecarboxamide,
(132) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-(5-fluoro-4-methylpyridin-2-yl)-2-(4-fluorophenyl)cyclopropanecarboxamide,
(133) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-N-(3-fluorophenyl)-2-(4-fluorophenyl)cyclopropanecarboxamide,
(134) (1R,2S)-2-[(4-ethyl-2-methylpyrimidin-5-yl)oxymethyl]-N,2-bis(4-fluorophenyl)cyclopropanecarboxamide,
(135) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluoro-5-methoxyphenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(136) (1R,2S)-N-(5-chloropyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluoro-5-methoxyphenyl)cyclopropanecarboxamide,
(138) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluoro-5-methoxyphenyl)-N-(5-fluoro-4-methylpyrimidin-2-yl)cyclopropanecarboxamide,
(139) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)-2-(3-trifluoromethylphenyl)cyclopropanecarboxamide,
(140) (1R,2R)-2-(4-bromophenyl)-N-(5-chloropyridin-2-yl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]cyclopropanecarboxamide,
(141) (1R,2R)-2-(4-bromophenyl)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide,
(142) (1R,2S)-2-(3-chlorophenyl)-N-(5-fluoro-4-methylpyridin-2-yl)-2-({[4-(methoxymethyl)-2-methylpyrimidin-5-yl]oxy}methyl)cyclopropanecarboxamide,
(143) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoromethylpyridin-2-yl)-2-(3-fluorophenyl)cyclopropanecarboxamide,

(144) (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-N-(5-fluoropyridin-2-yl)-2-(3-iodophenyl)cyclopropanecarboxamide, and
(145) (1R,2S)-N-(5-fluoropyridin-2-yl)-2-[(4-hydroxymethyl-2-methylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)cyclopropanecarboxamide.

[Claim 13]

A pharmaceutical composition comprising, as an active ingredient, a compound according to any one of claims 1 to 12 or a pharmaceutically acceptable salt thereof.

[Claim 14]

The pharmaceutical composition according to claim 13, for the prevention or treatment of sleep disorder including insomnia, narcolepsy (paroxysmal sleep), and other diseases such as excessive sleepiness, sleep-related dystonia, restless legs syndrome, sleep apnea, jet lag syndrome, shift work syndrome, delayed sleep phase syndrome or advanced sleep phase syndrome.

[Claim 15]

The pharmaceutical composition according to claim 13, for the prevention or treatment of a disease selected from the group consisting of: dysthymic disorder, mood disorder, mental and anxiety disorder; diabetes, and appetite, taste, eating or drinking disorder; hypothalamic disease; biological and circadian rhythm disorder; sleep disorder associated with a disease selected from nervous disease, neurogenic pain and restless legs syndrome; insomnia related to mental disorder; depression and insomnia related to depression; bipolar disorder and insomnia related to bipolar disorder; anxiety disorder and insomnia related to anxiety disorder; insomnia related to Parkinson's disease; insomnia related to schizophrenia; sleep apnea; narcolepsy; idiopathic insomnia; parasomnia; opioid dependence; nicotine dependence; benign prostatic hyperplasia; pure dementia and cognitive impairment in a healthy group and in mental and nervous diseases; and other diseases associated with systemic orexin dysfunction.

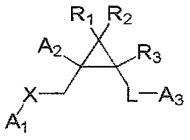
[Kind of Document] ABSTRACT

[Abstract]

[Problem] It is an object of the present invention to provide a novel cyclopropane compound or a pharmaceutically acceptable salt thereof, and a medicinal use thereof.

[Solution] A cyclopropane compound represented by the following formula (I) or a pharmaceutically acceptable salt thereof has orexin 2 receptor inhibitory action, and thus, is extremely useful as an agent for preventing or treating sleep disorder caused by orexin, including insomnia as a typical example:

[Formula I]



(I)

wherein A_1 represents a pyrimidinyl group, a N-oxide pyrimidinyl group or the like, A_2 and A_3 each independently represent an aryl group, a heterocyclic group or the like, R_1, R_2 and R_3 each independently represent a hydrogen atom, a $C_{1\text{-}6}$ alkyl group or the like, X represents an oxygen atom or the like, and L represents a bond or the like.

[Selected Drawing] None

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