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(54) **METHODS AND COMPOUNDS USEFUL IN THE SYNTHESIS OF OREXIN-2 RECEPTOR ANTAGONISTS**

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(51) **Int. Cl.**

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C07C 309/66	(2006.01)
C12P 7/22	(2006.01)
C07C 309/73	(2006.01)
C07D 401/12	(2006.01)
C07C 303/28	(2006.01)
C07C 29/147	(2006.01)

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USPC 549/75

See application file for complete search history.

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(57) **ABSTRACT**

The present disclosure provides compounds and methods that are useful for the preparation of compounds useful as orexin-2 receptor antagonists.

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Response to Office Action, Israeli Application No. 232949 (Hebrew) (3 pages), filed Mar. 20, 2016, and English translation thereof (3 pages); Annex A (1 page); Annex B (1 page); Annex C (1 page); Claims (13 pages); specification (69 pages).

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METHODS AND COMPOUNDS USEFUL IN THE SYNTHESIS OF OREXIN-2 RECEPTOR ANTAGONISTS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application No. 61/600,109, filed Feb. 17, 2012, which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

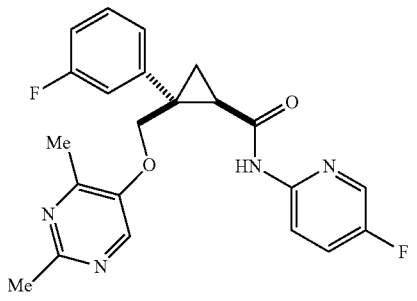
The present invention relates to compounds and methods that are useful for the preparation of compounds useful as orexin-2 receptor antagonists.

BACKGROUND OF THE INVENTION

Orexin receptors are G-protein coupled receptors found predominately in the brain. Their endogenous ligands, orexin-A and orexin-B, are expressed by neurons localized in the hypothalamus. Orexin-A is a 33 amino acid peptide; orexin-B consists of 28 amino acids. (Sakurai T. et al., Cell, 1998, 92, 573-585). There are two subtypes of orexin receptors, OX_1 and OX_2; OX_1 binds orexin-A preferentially, while OX_2 binds both orexin-A and -B. Orexins stimulate food consumption in rats, and it has been suggested that orexin signaling could play a role in a central feedback mechanism for regulating feeding behavior (Sakurai et al., supra). It has also been observed that orexins control wake-sleep conditions (Chemelli R. M. et al., Cell, 1999, 98, 437-451). Orexins may also play roles in brain changes associated with opioid and nicotine dependence (S. L. Borgland et al., Neuron, 2006, 49, 598-601; C. J. Winrow et al., Neuropharmacology, 2010, 58, 185-194), and ethanol dependence (J. R. Shoblock et al., Psychopharmacology, 2011, 215, 191-203). Orexins have additionally been suggested to play a role in some stress reactions (T. Ida et al., Biochem. Biophys. Res. Commun., 2000, 270, 318-323).

Compounds such as (1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide (Compound A, below) have been found to be potent orexin receptor antagonists, and may be useful in the treatment of sleep disorders such as insomnia, as well as for other therapeutic uses.

Compound A



There is thus a need for synthetic methods and intermediates useful in the preparation of Compound A and related

SUMMARY

Provided herein are compounds and methods that are useful for the preparation of compounds useful as orexin-2 receptor antagonists.

Provided is a process for making a compound of Formula I,

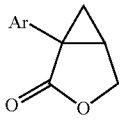
I

wherein Ar is an aryl such as phenyl, which aryl may be unsubstituted, or substituted 1-3 times, for example, with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl,

the method comprising one or more of the steps of:

i) providing a composition comprising a compound of Formula II:

II



wherein Ar is as given above, and an organic solvent, wherein said composition is at a temperature of from −30 to 40° C., or from −30 to 30° C., or from −30 to 10° C., or from −10 to 0° C., or from −10 to −5° C.; and

ii) adding to said composition a hydride reducing agent, wherein said agent reduces said compound of Formula II into said compound of Formula I,

to thereby make said compound of Formula I.

In some embodiments, Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

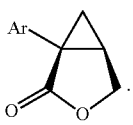
In some embodiments, the organic solvent is an aromatic hydrocarbon solvent, an aliphatic hydrocarbon solvent, a halogenated hydrocarbon solvent or an ether solvent.

In some embodiments, the process may further include the step of mixing (e.g., by stirring) the composition after said adding step for a time of 12 to 24 hours.

In some embodiments, the process may further include the step of quenching the reduction by adding to said composition a mild aqueous acid (e.g., citric acid, EDTA or tartaric acid).

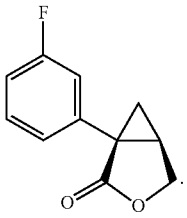
In some embodiments, the compound of Formula II has the absolute stereochemistry of Formula IIa:

IIa



In some embodiments, the compound of Formula II has an

In some embodiments, the compound of Formula II or Formula IIa is the compound:

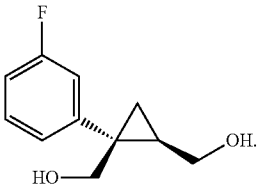


In some embodiments, the compound of Formula I has the absolute stereochemistry of Formula Ia:

Ia

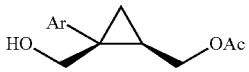
In some embodiments, the compound of Formula I has an enantiomeric excess (ee) of the Formula Ia stereoisomer of at least 75, 80, 85, 90, 95, 98, 99%, or greater.

In some embodiments, the compound of Formula I or Formula Ia is:



Also provided is compound of Formula III:

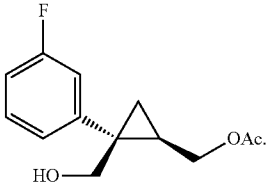
III



wherein Ar is an aryl such as phenyl, which aryl may be unsubstituted, or substituted 1-3 times, for example with substituents independently chosen from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl.

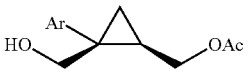
In some embodiments, Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

In some embodiments, the compound is:



Also provided is a process for making a compound of Formula III:

III



wherein Ar is aryl such as phenyl, which aryl may be unsubstituted, or substituted 1-3 times, for example with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl, comprising reacting a mixture of:

i) a compound of Formula Ia:

Ia

wherein Ar is as given above,

ii) vinyl acetate,

iii) a lipase, and

iv) an organic solvent

for a time of from 5 to 36 hours, or from 7 to 18 hours, to thereby make the compound of Formula III.

In some embodiments, Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

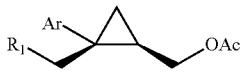
In some embodiments, the organic solvent is tetrahydrofuran, 2-methyltetrahydrofuran, an ether solvent, acetone, or acetonitrile.

In some embodiments, the lipase is a *Candida Antarctica* lipase, for example, a *Candida Antarctica* B lipase, which may be coupled to solid support such as an acrylic resin.

In some embodiments, the process may further include the step of filtering the mixture after said reacting to produce a filtrate, and may further include concentrating the filtrate to produce a concentrated filtrate. In some embodiments, the process may further include the step of washing the concentrated filtrate with water or water comprising a salt (e.g., a solution of 15-20% NaCl in water).

Also provided is a compound of Formula IV:

IV



wherein:

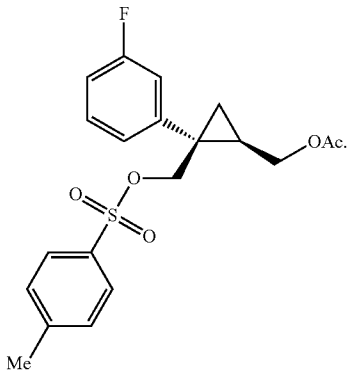
Ar is an aryl such as phenyl, which aryl may be unsubstituted, or substituted 1-3 times, for example with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl; and

R_1 is a leaving group.

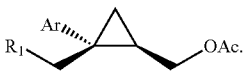
In some embodiments, Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

In some embodiments, the leaving group is a sulfonate ester leaving group selected from the group consisting of:

In some embodiments, the compound is:



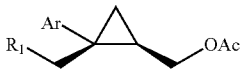
In some embodiments, the compound of Formula IV has the absolute stereochemistry of Formula IVa:



IVa

In some embodiments, the compound of Formula IV has an enantiomeric excess (ee) of the Formula IVa stereoisomer of at least 75, 80, 85, 90, 95, 98, 99%, or greater.

Further provided is a process for making a compound of Formula IV:



IV

wherein Ar is an aryl such as phenyl, which aryl may be unsubstituted, or substituted 1-3 times, for example with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl; and

R_1 is a sulfonate ester leaving group,

said process comprising reacting a compound of Formula III:

III

wherein Ar is as given above,

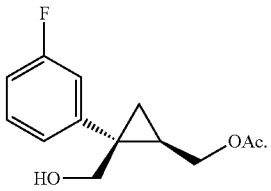
with a compound selected from the group consisting of: tosyl chloride, mesyl chloride, nosyl chloride, toluenesulfonyl chloride, toluenesulfonic anhydride and methanesulfonic anhydride, wherein said reacting is carried out in an organic solvent in the presence of a base,

to thereby make said compound of Formula IV.

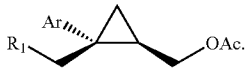
In some embodiments, Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

In some embodiments, the reacting is carried out for a time of from 10 minutes to 2 hours.

In some embodiments, the compound of Formula III is:



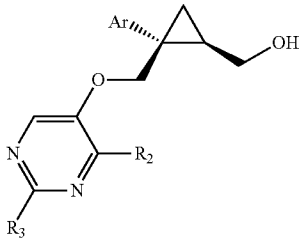
In some embodiments, the compound of Formula IV has the absolute stereochemistry of Formula IVa:



IVa

In some embodiments, the compound of Formula IV has an enantiomeric excess (ee) of the Formula IVa stereoisomer of at least 75, 80, 85, 90, 95, 98, 99%, or greater.

Also provided is a process for making a compound of Formula V,



V

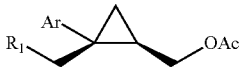
wherein Ar is an aryl such as phenyl, which aryl may be unsubstituted, or substituted 1-3 times, for example with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl; and

R_2 and R_3 are each independently selected from the group consisting of: hydrogen, C_{1-6}alkyl, haloC_{1-6} alkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl,

comprising the steps of:

a) stirring a mixture of:

i) a compound of Formula IV:

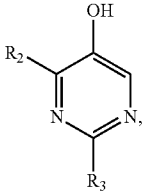


IV

wherein Ar is as given above; and

R_1 is a leaving group,

ii) a substituted pyrimidine of Formula VI:



VI

wherein R_2 and R_3 are as given above;

iii) a base; and

iv) an organic solvent,

at a temperature of from 65-70° C., for 1 to 12 hours; and then

b) reacting the mixture with an aqueous base for a time of

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