



US006410550B1

(12) **United States Patent**
Coe et al.(10) **Patent No.:** US 6,410,550 B1
(45) **Date of Patent:** Jun. 25, 2002(54) **ARYL FUSED AZAPOLYCYCLIC COMPOUNDS**(75) Inventors: **Jotham Wadsworth Coe**, Niantic;
Paige Roanne Palmer Brooks, North
Stonington, both of CT (US)(73) Assignee: **Pfizer INC**, New York, NY (US)(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.(21) Appl. No.: **09/402,010**(22) PCT Filed: **Nov. 13, 1998**(86) PCT No.: **PCT/IB98/01813**

§ 371 (c)(1),

(2), (4) Date: **Sep. 28, 1999**(87) PCT Pub. No.: **WO99/35131**PCT Pub. Date: **Jul. 15, 1999****Related U.S. Application Data**(60) Provisional application No. 60/070,245, filed on Dec. 31,
1997.(51) **Int. Cl.**⁷ **A61K 31/44**; A61K 31/505;
C07D 221/22; C07D 413/00; A61P 1/00(52) **U.S. Cl.** **514/289**; 514/210.21; 514/228.2;
514/232.8; 514/253.02; 514/253.03; 514/256;
514/281; 514/295; 546/43; 546/74; 546/97;
544/58.2; 544/60; 544/125; 544/126; 544/242;
544/361(58) **Field of Search** 546/43, 74, 97;
544/58.2, 60, 125, 126, 242, 361; 514/210.21,
228.2, 232.8, 253.02, 253.03, 256, 281,
289, 295(56) **References Cited****U.S. PATENT DOCUMENTS**

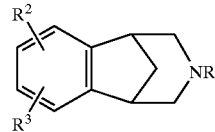
3,471,503 A * 10/1969 Carson 260/294.7

FOREIGN PATENT DOCUMENTSEP 0 955 301 * 11/1999
EP 1 078 637 * 2/2001
WO WO 99/55680 * 11/1999
WO WO 00/44755 * 8/2000
WO WO 00/45846 * 8/2000**OTHER PUBLICATIONS**Mazzocchi et al., Synthesis and Pharmacological Activity of
2,3,4,5-Tetrahydro1,5 methano-1H-3-benzazepines, Jour-
nal of Medicinal Chemistry, vol. 22, No. 4, pp. 455-457,
1979.*

* cited by examiner

Primary Examiner—Brenda Coleman(74) *Attorney, Agent, or Firm*—Peter C. Richardson; Paul
H. Ginsburg; Roy F. Waldron(57) **ABSTRACT**

Compounds of the formula



(I)

and their pharmaceutically acceptable salts, wherein R¹, R²,
and R³ are defined as in the specification, intermediates in
the synthesis of such compounds, pharmaceutical composi-
tions containing such compounds and methods of using such
compounds, in the treatment of neurological and psycho-
logical disorders.**15 Claims, No Drawings**

1

ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

This application is a national stage entry under 35 U.S.C. §371 of PCT/IB98/01813, filed Nov. 13, 1998 which claims the benefit of U.S. Provisional Application Ser. No. 60/070,245, filed Dec. 31, 1997.

BACKGROUND OF THE INVENTION

This invention relates to aryl fused azapolycyclic compounds, as defined more specifically by formula I below. Compounds of formula I bind to neuronal nicotinic acetylcholine specific receptor sites and are useful in modulating cholinergic function. Such compounds are useful in the treatment of inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac, arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder, psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome.

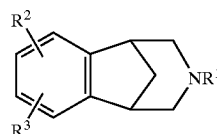
The compounds of this invention may also be used in combination with an antidepressant such as, for example, a tricyclic antidepressant or a serotonin reuptake inhibiting antidepressant (SRI), in order to treat both the cognitive decline and depression associated with AD, PD, stroke, Huntington's Chorea or traumatic brain injury (TBI): in combination with muscarinic agonists in order to stimulate both central muscarinic and nicotinic receptors for the treatment, for example, of ALS, cognitive dysfunction, age related cognitive decline, AD, PD, stroke, Huntington's Chorea and TBI; in combination with neurotrophic factors such as NGF in order to maximize cholinergic enhancement for the treatment, for example, of ALS, cognitive dysfunction, age related cognitive decline, AD, PD stroke, Huntington's Chorea and TBI; or in combination with agents that slow or arrest AD such as cognition enhancers, amyloid aggregation inhibitors, secretase inhibitors, tau kinase inhibitors, neuronal antiinflammatory agents and estrogen-like therapy.

Other compounds that bind to neuronal nicotinic receptor sites are referred to in U.S. patent application Ser. No. 08/963,852, which was filed on Nov. 4, 1997 now U.S. Pat. No. 6,020,335. The foregoing application is owned in common with the present application, and is incorporated herein by reference in its entirety.

2

SUMMARY OF THE INVENTION

This invention relates to aryl fused azapolycyclic compounds of the formula



R¹ is hydrogen, (C₁-C₆)alkyl, unconjugated (C₃-C₆) alkenyl, benzyl, XC(=O)R¹³ or -CH₂CH₂-O-(C₁-C₄)alkyl;

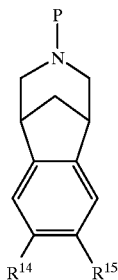
R² and R³ are selected, independently, from hydrogen, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, hydroxy, nitro, amino, halo, cyano, -SO_q(C₁-C₆)alkyl wherein q is zero, one or two, (C₁-C₆)alkylamino-, [(C₁-C₆)alkyl]₂amino-, -CO₂R⁴, -CONR⁵R⁶, -SO₂NR⁷R⁸, -C(=O)R¹³, -XC(=O)R¹³, aryl-(C₀-C₃)alkyl- or aryl-(C₀-C₃)alkyl-O-, wherein said aryl is selected from phenyl and naphthyl, heteroaryl-(C₀-C₃)alkyl- or heteroaryl-(C₀-C₃)alkyl-O-, wherein said heteroaryl is selected from five to seven membered aromatic rings containing from one to four heteroatoms selected from oxygen, nitrogen and sulfur, and X²(C₀-C₆)alkoxy-(C₀-C₆)alkyl-, wherein X² is absent or X² is (C₁-C₆)alkylamino- or [(C₁-C₆)alkyl]₂amino-, and wherein the (C₀-C₆)alkoxy-(C₀-C₆)alkyl- moiety of said X²(C₀-C₆)alkoxy-(C₀-C₆)alkyl- contains at least one carbon atom, and wherein from one to three of the carbon atoms of said (C₀-C₆)alkoxy-(C₀-C₆)alkyl- moiety may optionally be replaced by an oxygen, nitrogen or sulfur atom, with the proviso that any two such heteroatoms must be separated by at least two carbon atoms, and wherein any of the alkyl moieties of said (C₀-C₆)alkoxy-(C₀-C₆)alkyl- may be optionally substituted with from two to seven fluorine atoms, and wherein one of the carbon atoms of each of the alkyl moieties of said aryl-(C₀-C₃)alkyl- and said heteroaryl-(C₀-C₃)alkyl- may optionally be replaced by an oxygen, nitrogen or sulfur atom, and wherein each of the foregoing aryl and heteroaryl groups may optionally be substituted with one or more substituents, preferably from zero to two substituents, independently selected from (C₁-C₆)alkyl optionally substituted with from one to seven fluorine atoms, (C₁-C₆)alkoxy optionally substituted with from two to seven fluorine atoms, halo (e.g., chloro, fluoro, bromo or iodo), (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, hydroxy, nitro, cyano, amino, (C₁-C₆)-, [(C₁-C₆)alkyl]₂amino-, -CO₂R⁴, -CONR⁵R⁶, -SO₂NR⁷R⁸, -C(=O)R¹³ and -XC(=O)R¹³;

or R² and R³, together with the carbons to which they are attached, form a four to seven membered monocyclic, or a ten to fourteen membered bicyclic, carbocyclic ring that can be saturated or unsaturated, wherein from one to three of the nonfused carbon atoms of said monocyclic rings, and from one to five of the carbon atoms of said bicyclic rings that are not part of the benzo ring shown in formula I, may optionally and independently be replaced by a nitrogen, oxygen or sulfur, and wherein said monocyclic and bicyclic rings may optionally be substituted with one or more substituents, preferably from zero to two substituents for the monocyclic rings and from zero to three substituents for the bicyclic rings, that are selected, independently, from (C₀-C₆)alkoxy-(C₀-C₆)alkyl-, wherein the total number of carbon atoms does not

5

6-methyl-5,7-dioxo-6,13-diazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,8-triene hydrochloride;
 6-methyl-5-oxo-6,13-diazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,8-triene hydrochloride;
 5,7-dimethyl-6-oxo-5,7,13-triazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,8-triene hydrochloride;
 5,7-dioxo-6,13-diazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,8-triene hydrochloride;
 5-oxo-6,13-diazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,8-triene hydrochloride;
 6-oxo-5,7,13-triazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,8-triene hydrochloride;
 4,5-difluoro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene hydrochloride;
 5-fluoro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-4-carbonitrile hydrochloride;
 4-ethynyl-5-fluoro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene hydrochloride;
 5-ethynyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-4-carbonitrile hydrochloride;
 4-ethynyl-5-chloro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-4-carbonitrile hydrochloride;
 4-ethynyl-5-chloro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene hydrochloride.
 5-oxa-7-methyl-6-oxo-7,13-diazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,8-triene hydrochloride;
 4-fluoro-5-trifluoromethyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene hydrochloride;
 4-chloro-5-trifluoromethyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene hydrochloride;
 5-trifluoromethyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-4-carbonitrile hydrochloride;
 4-ethynyl-5-trifluoromethyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene hydrochloride.
 6-methyl-5-thia-5-dioxa-6,13-Diazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,8-triene hydrochloride;
 7-dimethylamino-5-thia-5-dioxa-6,13-Diazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,8-triene hydrochloride;
 6,7-dioxa-5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]hexadeca-2(11),3,9-triene hydrochloride; and
 5,8-dimethyl-6,7-dioxa-5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]hexadeca-2(11),3,9-triene hydrochloride.

This invention also relates to compounds of the formula



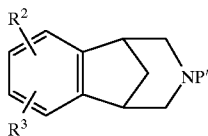
wherein P is hydrogen, methyl, COOR¹⁶ wherein R¹⁶ is (C₁-C₆)alkyl, allyl, 2^{2,2,2}-trichloroethyl or (C₁-C₆)alkyl; —C(=O)NR⁵R⁶ wherein R⁵ and R⁶ are defined as in formula I above; —C(=O)H, —C(=O)(C₁-C₆)alkyl wherein the alkyl moiety may optionally be substituted with from 1 to 3 halo atoms, preferably with from 1 to 3 fluoro or chloro atoms; benzyl or t-butoxycarbonyl (t-Boc); and R¹⁴ and R¹⁵ are selected independently from hydrogen

6

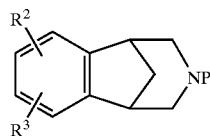
(C₁-C₆)alkyl optionally substituted with from one to seven fluorine atoms; —C(=O)(C₁-C₆)alkyl, cyano, hydroxy, nitro, amino, —O(C₁-C₆)alkyl or halo: with the proviso that R¹⁴ and R¹⁵ can not both be hydrogen when P is hydrogen or methyl. Such compounds are useful as intermediates in the synthesis of compounds of the formula I.

The invention also relates to a compound of the formula

(I')



(I')



wherein R² and R³ are defined above; and P' is COOR¹⁶ wherein R¹⁶ is allyl, 2,2,2-trichloroethyl or (C₁-C₆)alkyl; —C(=O)NR⁵R⁶ wherein R⁵ and R⁶ are defined as in claim 2; —C(=O)H, —C(=O)(C₁-C₆)alkyl wherein the alkyl moiety may optionally be substituted with from 1 to 3 halo atoms, preferably with from 1 to 3 fluoro or chloro atoms; benzyl, or t-butoxycarbonyl (t-Boc).

Unless otherwise indicated, the term "halo", as used herein, includes fluoro, chloro, bromo and iodo.

Unless otherwise indicated, the term "alkyl", as used herein, includes straight, branched or cyclic, and may include straight and cyclic alkyl moieties as well as branched and cyclic moieties.

The term "alkoxy", as used herein, means "alkyl-O—", wherein "alkyl" is defined as above.

The term "alkylene, as used herein, means an alkyl radical having two available bonding sites (i.e., -alkyl-), wherein "alkyl" is defined as above.

Unless otherwise indicated, the term "one or more substituents", as used herein, refers to from one to the maximum number of substituents possible based on the number of available bonding sites.

The term "treatment", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such condition or disorder. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

The compounds of formula I may have optical centers and therefore may occur in different enantiomeric configurations. The invention includes all enantiomers, diastereomers, and other stereoisomers of such compounds of formula I, as well as racemic and other mixtures thereof.

The present invention also relates to all radiolabeled forms of the compounds of the formula I. Preferred radiolabeled compounds of formula I are those wherein the radiolabels are selected from as ³H, ¹¹C, ¹⁴C, ¹⁸F, ¹²³I and ¹²⁵I. Such radiolabeled compounds are useful as research and diagnostic tools in metabolism pharmacokinetics studies and in binding assays in both animals and man.

The present invention also relates to a pharmaceutical composition for use in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, including a human, comprising an amount of a compound of the formula I or a pharmaceutically acceptable salt thereof

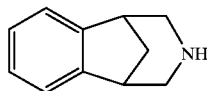
that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use and a pharmaceutically acceptable carrier.

The present invention also relates to a method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

The present invention also relates to a method of treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising administering to a mammal in need of such treatment an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition.

The present invention also relates to a pharmaceutical composition for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI) obsessive-compulsive disorder (OCD), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention also relates to a method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, comprising administering to said mammal an amount of a compound comprising an amount of a compound of the formula



5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

61

62

63

64

65

66

67

68

69

70

71

72

73

74

75

76

77

78

79

80

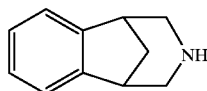
81

82

83

or a pharmaceutically acceptable salt thereof, that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

The present invention also relates to a method for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI) obsessive-compulsive disorder (OCD), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising administering to a mammal in need of such treatment an amount of a compound of the formula



35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

61

62

63

64

65

66

67

68

69

70

71

72

73

74

75

76

77

78

79

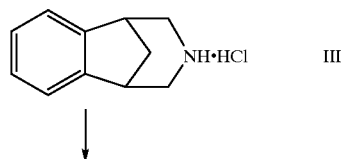
or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition.

This invention also relates to the pharmaceutically acceptable acid addition salts of the compounds of formula I. Examples of pharmaceutically acceptable acid addition salts of the compounds of formula I are the salts of hydrochloric acid, p-toluenesulfonic acid, fumaric acid, citric acid, succinic acid, salicylic acid, oxalic acid, hydrobromic acid, phosphoric acid, methanesulfonic acid, tartaric acid, malate, di-p-toluoyl tartaric acid, and mandelic acid.

DETAILED DESCRIPTION OF THE INVENTION

Except where otherwise stated, R¹ through R¹⁸, m and P, and structural formula I in the reaction schemes and discussion that follow are defined as above.

Scheme 1



60

61

62

63

64

65

66

67

68

69

70

71

72

73

74

75

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.