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WO 2006/105442 A3

(54) Title: SPIROCYCLIC HETEROCYCLIC DERIVATIVES AND METHODS OF THEIR USE

(57) Abstract: Spirocyclic heterocyclic derivatives, pharmaceutical compositions containing these compounds, and methods for their pharmaceutical use are disclosed. In certain embodiments, the spirocyclic heterocyclic derivatives are ligands of the δ opioid receptor and may be useful, inter alia, for treating and/or preventing pain, anxiety, gastrointestinal disorders, and other δ opioid receptor-mediated conditions.

SPIROCYCLIC HETEROCYCLIC DERIVATIVES AND METHODS OF THEIR USE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application Serial No. 60/667,177, filed March 31, 2005, and U.S. Application Serial No. 11/393,133 filed March 30, 2006, the disclosures of which are incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

[0002] The invention relates to spirocyclic heterocyclic derivatives (including derivatives of spiro(*2H*-1-benzopyran-2,4'-piperidines), pharmaceutical compositions containing these compounds, and methods for their pharmaceutical use. In certain embodiments, the spirocyclic heterocyclic derivatives are ligands of the δ opioid receptor and are useful, *inter alia*, for treating and/or preventing pain, anxiety, gastrointestinal disorders, and other δ opioid receptor-mediated conditions.

BACKGROUND OF THE INVENTION

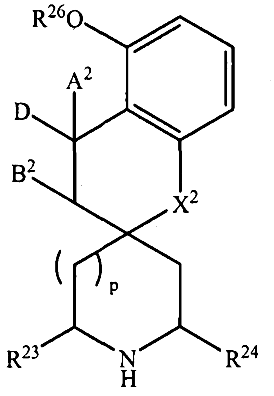
[0003] There are at least three different opioid receptors (μ, δ and κ) that are present in both central and peripheral nervous systems of many species, including humans. Lord, J.A.H., *et al.*, *Nature,* **1977**, 267, 495. Activation of the δ opioid receptors induces analgesia in various animal models. Moulin, *et al., Pain*, **1985**, 23, 213. Some work suggests that the analgesics working at δ opioid receptors do not have the attendant side effects associated with μ and κ opioid receptor activation. Galligan, *et al., J. Pharm. Exp. Ther.*, **1985**, 229, 641. The δ opioid receptor has also been identified as having a role in circulatory systems. Ligands for the δ receptor have also been shown to possess immunomodulatory activities. Dondio, *et al., Exp. Opin. Ther. Patents*, **1997**, 10, 1075. Further, selective δ opioid receptor agonists have been shown to promote organ and cell survival. Su, T-P, *Journal of Biomedical Science*, **2000**, 9(3), 195-199. Ligands for the δ opioid receptor may therefore find potential use as analgesics, as antihypertensive agents, as immunomodulatory agents, and/or agents for the treatment of cardiac disorders.

[0004] Numerous selective δ opioid ligands are peptidic in nature and thus are unsuitable for administration by systemic routes. Several non-peptidic δ opioid receptor ligands have been developed. See, for example, E. J. Bilsky, *et al.*, *Journal of Pharmacology and Experimental Therapeutics*, **1995**, 273(1), 359-366; WO 93/15062, WO 95/04734, WO 95/31464, WO 96/22276, WO 97/10216, WO 01/46192, WO 02/094794, WO 02/094810, WO 02/094811, WO 02/094812, WO 02/48122, WO 03/029215, WO 03/033486, JP-4275288, EP-A-0,864,559, US-A-5,354,863, US-B-6,200,978, US-B-6,436,959 and US 2003/0069241.

[0005] While there are a large number of non-peptidic δ opioid receptor modulators, there is still an unfulfilled need for compounds with selective δ opioid receptor activity that may be used in methods to provide beneficial pharmaceutical characteristics while minimizing undesirable side effects. The present invention is directed to these, as well as other important ends.

SUMMARY OF THE INVENTION

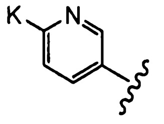
[0006] The invention, the subject of this application, is directed to a compound of formula XXVIII:



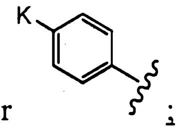
XXVIII ;

wherein:

D is :



or



;

K is carboxy (-COOH), $-C(=O)-O-C_1$ alkyl, heteroaryl having 5 members with 4 nitrogens; or N-alkylaminocarbonyl ($-C(=O)-NH(C_1$-C_4 alkyl));

R^{23} and R^{24} are each H;

R^{26} is C_1-C_6 alkyl or hydrogen;

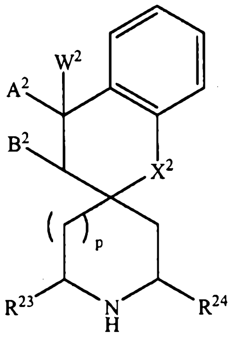
p is 1;

A^2 and B^2 are each H, or together form a double bond; and

X^2 is -O-;

or a stereoisomer or pharmaceutically acceptable salt thereof.

[0006a] In one embodiment, the invention is directed to compounds of formula XIV:



XIV ;

wherein:

W^2 is aryl or heteroaryl, wherein the aryl or heteroaryl is substituted with 0-3 groups selected independently from hydroxy, aminocarbonyl ($-C(=O)-NH_2$), N-alkylaminocarbonyl (-C(=O)-NH(alkyl)), and N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl));

R^{23} and R^{24} are each independently H or alkyl, provided that at least one of R^{23} and R^{24} is alkyl;

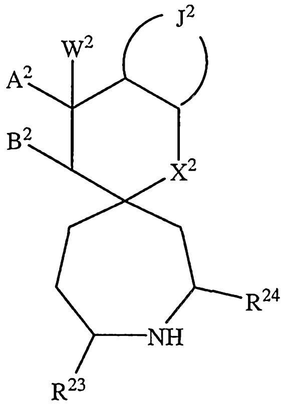
p is 1 or 2;

A^2 and B^2 are each H, or together form a double bond; and

X^2 is -CH_2- or -O-;

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof.

[0007] In another embodiment, the invention is directed to compounds of formula XVII:



XVII ;

wherein:

W^2 is aryl or heteroaryl, wherein the aryl or heteroaryl is substituted with 0-3 groups selected independently from hydroxy, aminocarbonyl (-C(=O)-NH_2), N-alkylaminocarbonyl (-C(=O)-NH(alkyl)), and N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl));

R^{23} and R^{24} are each independently H or alkyl;

A^2 and B^2 are each H, or together form a double bond;

X^2 is -CH_2- or -O-; and

J^2 when taken together with the carbon atoms to which it is attached forms a 6-membered aryl ring substituted with 0-3 groups selected independently from halo, hydroxy, and -S(=O)$_2$-alkyl;

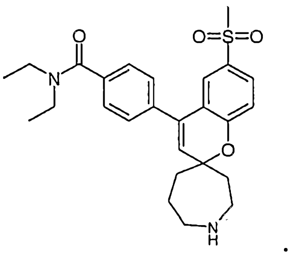
or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof;

provided that:

when W^2 is *para*-diethylaminocarbonylphenyl, X^2 is O, and A^2 and B^2 together form a double bond, then the aryl ring of J^2 is substituted with at least one group selected independently from halo and -S(=O)$_2$-alkyl in which the alkyl group is C_2-C_6 alkyl;

when W^2 is *para*-diethylaminocarbonylphenyl, X^2 is O, and A^2 and B^2 are each H, then the aryl ring of J^2 is substituted with 1-3 groups selected independently from halo, hydroxy, and -S(=O)$_2$-alkyl; and

the compound of formula XVII is other than:



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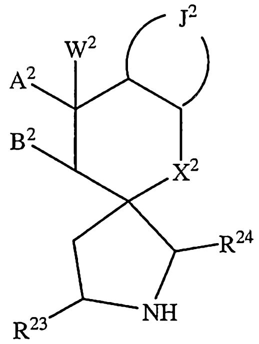
[0008] In yet another embodiment, the invention is directed to compounds of formula XX:



XX ;

wherein:

W^2 is aryl or heteroaryl, wherein the aryl or heteroaryl is substituted with 0-3 groups selected independently from hydroxy, aminocarbonyl (-C(=O)-NH$_2$), N-alkylaminocarbonyl (-C(=O)-NH(alkyl)), and N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl));

R^{23} and R^{24} are each independently H or alkyl;

A^2 and B^2 are each H, or together form a double bond;

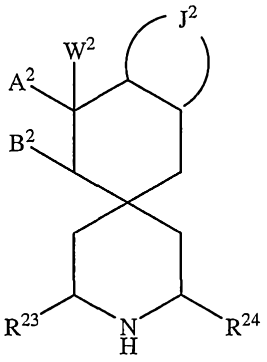
X^2 is -CH$_2$- or -O-; and

J^2 when taken together with the carbon atoms to which it is attached forms a 6-membered aryl ring substituted independently with 0-3 hydroxy or halo groups;

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof;

provided that the compound of formula XX is other than 4-[(4-*N*,*N*-diethylaminocarbonyl)phenyl]-spiro[2H,1-benzopyran-2,3'-pyrrolidine].

[0009] In still another embodiment, the invention is directed to compounds of formula XXII:



XXII

wherein:

W^2 is aryl or heteroaryl, wherein the aryl or heteroaryl is substituted with 0-3 groups selected independently from heteroaryl, hydroxy, carboxy (-COOH), -C(=O)-alkyl, -C(=O)-aryl, -C(=O)-O-alkyl, $-S(=O)_2-$N(alkyl)(alkyl); aminocarbonyl ($-C(=O)-NH_2$), N-alkylaminocarbonyl (-C(=O)-NH(alkyl)), and N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl));

R^{23} and R^{24} are each independently H or alkyl;

A^2 and B^2 are each H, or together form a double bond; and

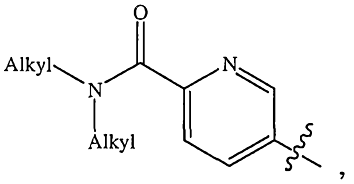
J^2 when taken together with the carbon atoms to which it is attached forms a 6-membered aryl ring substituted with 0-3 groups selected independently from halo, heterocycloalkyl, hydroxy, alkoxy, $-S(=O)_2$-alkyl, $-S(=O)_2-NH_2$, $-S(=O)_2$-NH(alkyl), $-S(=O)_2$-N(alkyl)(alkyl), carboxy (-COOH), -C(=O)-O-alkyl, and N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl));

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof;

provided that:

when W^2 is *para*-diethylaminocarbonylphenyl, *para*-prop-2-ylaminocarbonylphenyl, or *para*-pent-3-ylaminocarbonylphenyl, R^{23} and R^{24} are each H, and A and B are each H or together form a double bond, then J^2 is other than unsubstituted phenyl or anisyl; and

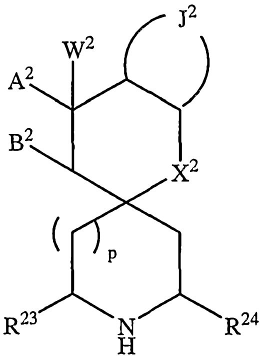
when W^2 is:



,

R^{23} and R^{24} are each H, and A and B together form a double bond; then J^2 is other than unsubstituted phenyl.

[0010] In another embodiment, the invention is directed to compounds of formula XXV:



XXV ;

wherein:

W^2 is aryl optionally substituted with -C(=O)-alkyl or -C(=O)-aryl;

R^{23} and R^{24} are each independently H or alkyl;

p is 1 or 2;

A^2 and B^2 are each H, or together form a double bond;

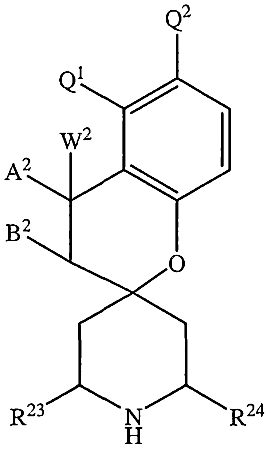
X^2 is $-CH_2-$ or -O-; and

J^2 when taken together with the carbon atoms to which it is attached forms a 6-membered aryl ring substituted with 0-3 groups selected independently from hydroxy, alkoxy, $-S(=O)_2$-alkyl, $-S(=O)_2-NH_2$, $-S(=O)_2$-NH(alkyl), $-S(=O)_2$-N(alkyl)(alkyl), -C(=O)-N(alkyl)(alkyl), carboxy (-COOH), and -C(=O)-O-alkyl;

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof;

provided that the compound of formula XXV is other than 4-phenyl-spiro[2H,1-benzopyran-2,4'-piperidine].

[0011] In yet another embodiment, the invention is directed to compounds of formula XXVII:



XXVII

wherein:

W^2 is *para*-dialkylaminocarbonylphenyl, the phenyl group of which is further optionally substituted with 1-2 groups independently selected from tetrazolyl, N-alkyltetrazolyl, hydroxy, carboxy (-COOH), and aminocarbonyl $(-C(=O)-NH_2)$;

R^{23} and R^{24} are each independently H or alkyl;

A^2 and B^2 are each H, or together form a double bond;

Q^1 and Q^2 are each independently H, hydroxy, alkoxy, haloalkoxy, halo, or heterocycloalkyl;

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof;

provided that :

when one of Q^1 and Q^2 is hydroxy and the other is H, or both Q^1 and Q^2 are hydroxy, then the phenyl group of W^2 is further substituted with 1-2 groups selected from tetrazolyl, N-alkyltetrazolyl, hydroxy, carboxy (-COOH), and aminocarbonyl ($-C(=O)-NH_2$);

when Q^1, Q^2, R^{23}, and R^{24} are each H and the phenyl group of W^2 is further substituted with one hydroxy, then A^2 and B^2 are each H;

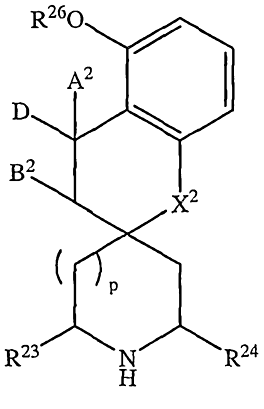
when W^2 is *para*-dialkylaminocarbonylphenyl, then at least one of Q^1, Q^2, R^{23}, and R^{24} is other than H;

when W^2 is *para*-dialkylaminocarbonylphenyl, R^{23} and R^{24} are each H, and Q^2 is halo, then Q^1 is other than H or hydroxy;

when W^2 is *para*-dialkylaminocarbonylphenyl, R^{23} and R^{24} are each H, Q^1 is methoxy, cyclopropylmethoxy, cyclobutoxy, or cyclopentoxy, and Q^2 is H, then A^2 and B^2 are each H; and

when W^2 is *para*-dialkylaminocarbonylphenyl, R^{23} and R^{24} are each H, and Q^1 is H or OH, then Q^2 is other than methoxy, cyclopropylmethoxy, cyclobutoxy, or cyclopentoxy.

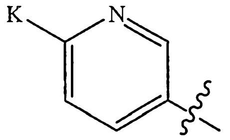
[0012] In still another embodiment, the invention is directed to compounds of formula XXVIII:



XXVIII ;

wherein:

D is:



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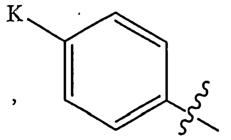
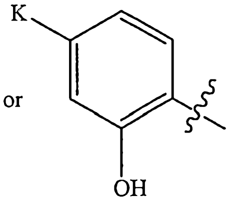


, or



;

K is carboxy (-COOH), -C(=O)-O-alkyl, $-S(=O)_2-N(alkyl)(alkyl)$, heteroaryl, alkylheteroaryl, aminocarbonyl $(-C(=O)-NH_2)$, or N-alkylaminocarbonyl (-C(=O)-NH(alkyl));

R^{23}, R^{24}, and R^{26} are each independently H or alkyl;

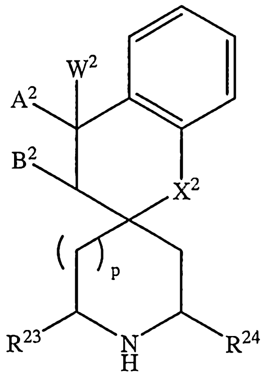
p is 1 or 2;

A^2 and B^2 are each H, or together form a double bond; and

X^2 is $-CH_2-$ or -O-;

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof.

[0013] In another embodiment, the invention is directed to compounds of formula XXIX:



XXIX

;

wherein:

W^2 is *para*-N(alkyl),N(alkyl-Z)aminocarbonylaryl or *para*-N(alkyl),N(alkyl-Z)aminocarbonylheteroaryl, wherein the aryl or heteroaryl ring of W^2 is substituted with 0-2 groups selected independently from hydroxy and alkoxy;

Z is alkoxy, alkylamino, or dialkylamino;

R^{23} and R^{24} are each independently H or alkyl;

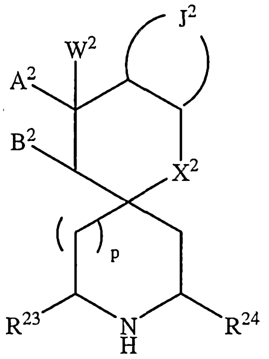
p is 1 or 2;

A^2 and B^2 are each H, or together form a double bond; and

X^2 is $-CH_2-$ or -O-;

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof.

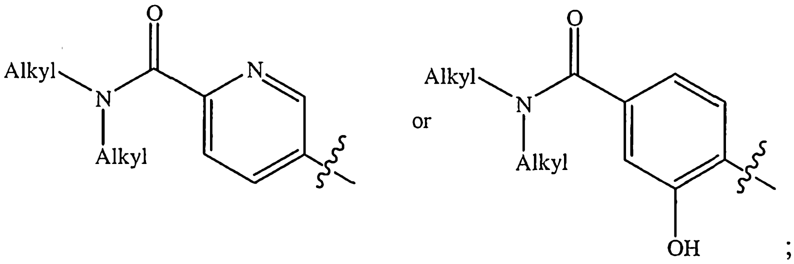
[0014] In yet another embodiment, the invention is directed to compounds of formula XXX:



XXX ;

wherein:

W^2 is:



;

R^{23} and R^{24} are each independently H or alkyl;

p is 1 or 2;

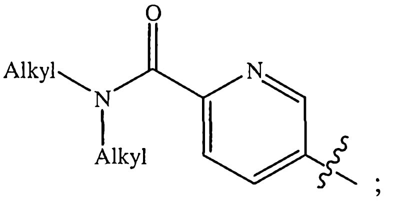
A^2 and B^2 are each H, or together form a double bond;

X^2 is $-CH_2-$ or -O-; and

J^2 when taken together with the carbon atoms to which it is attached forms a 6-membered aryl ring substituted with 1-3 groups selected independently from halo or haloalkoxy;

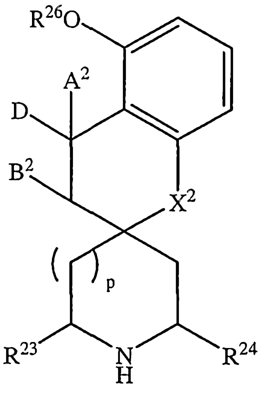
or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof;

provided that when W^2 is:



then the aryl ring of J^2 is substituted with at least one haloalkoxy.

[0015] In another embodiment, the invention is directed to compounds of formula XXXII:



XXXII

wherein:

D is N(alkyl),N(alkyl)aminocarbonylheteroaryl;

R^{23}, R^{24}, and R^{26} are each independently H or alkyl;

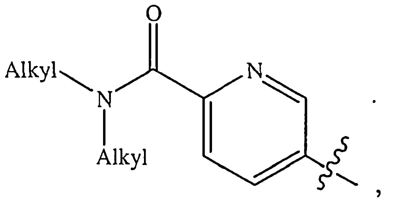
p is 1 or 2;

A^2 and B^2 are each H, or together form a double bond; and

X^2 is $-CH_2-$ or -O-;

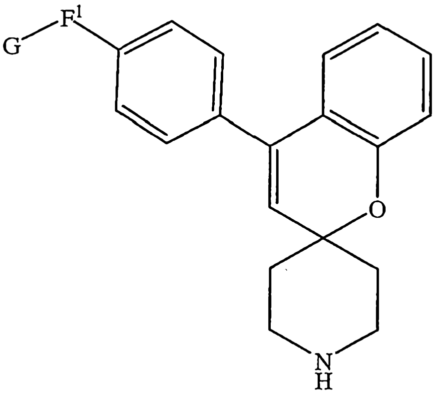
or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof;

provided that when D is:



and X^2 is –O-, then A^2 and B^2 are each H.

[0016] In one embodiment, the invention is directed to compounds of formula XXXIII:



XXXIII ;

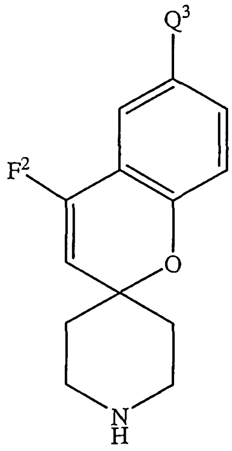
wherein:

F^1 is heteroaryl; and

G is C_{1-6}alkylene substituted with NH_2, NHC(=O)alkyl, NH(C(O)N(H)alkyl, or $NHS(=O)_2$alkyl;

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof.

[0017] In another embodiment, the invention is directed to compounds of formula XXXIV:



XXXIV ;

wherein:

F^2 is aryl or heteroaryl; and

Q^3 is hydroxy or alkoxy;

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof.

[0018] In still another embodiment, the invention is directed to pharmaceutical compositions, comprising:

a pharmaceutically acceptable carrier; and a compound as described herein including, for example, a compound of formula XIV, XVII, XX, XXII, XXV, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXII, XXXIII, and/or XXXIV.

[0019] In still another embodiment, the invention is directed to methods of binding opioid receptors in a patient in need thereof, comprising the step of:

administering to said patient an effective amount of a compound as described herein including, for example, a compound of formula XIV, XVII, XX, XXII, XXV, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXII, XXXIII, and/or XXXIV.

[0020] These and other embodiments of the invention will become more apparent from the following detailed description.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0021] The invention relates to spirocyclic heterocyclic derivatives, pharmaceutical compositions containing these compounds, and methods for their pharmaceutical use. This invention is related by subject matter to co-pending U.S. application Serial No. 10/957,554, filed October 1, 2004 and Provisional application Serial No. 60/507,864, filed October 1, 2003, the disclosures of which are hereby incorporated herein by reference, in their entireties.

[0022] In certain embodiments, the spirocyclic heterocyclic derivatives are ligands of the δ opioid receptor and may be useful, *inter alia*, in methods for treating and/or preventing diseases and conditions that may be mediated or modulated by the δ opioid receptor including, for example, pain, gastrointestinal disorders, urogenital tract disorders including incontinence and overactive bladder, immunomodulatory disorders, inflammatory disorders, respiratory function disorders, anxiety, mood disorders, stress-related disorders, attention deficit hyperactivity disorders, sympathetic nervous system disorders, depression, tussis, motor disorders, traumatic injuries, especially to the central nervous system, stroke, cardiac arrhythmias, glaucoma, sexual dysfunctions, shock, brain edema, cerebral ischemia, cerebral deficits subsequent to cardiac bypass surgery and grafting, systemic lupus erythematosus, Hodgkin's disease, Sjogren's disease, epilepsy, rejections in organ transplants and skin grafts, and substance addiction. In certain other embodiments, the spirocyclic heterocyclic derivatives are ligands of the δ opioid receptor and may be useful in, *inter alia*, methods for improving organ and cell survival, methods for providing cardioprotection following myocardial infarction, methods for reducing the need for anesthesia, methods for producing and/or maintaining an anaesthetic state, and methods of detecting, imaging or monitoring degeneration or dysfunction of opioid receptors in a patient.

[0023] As employed above and throughout the disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings.

[0024] "Alkyl" refers to an optionally substituted, saturated straight, or branched, hydrocarbon having from about 1 to about 20 carbon atoms (and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein), preferably from about 1 to about 8 carbon atoms, herein referred to as "lower alkyl," more preferably from about 1 to about 6, still more preferably from about 1 to about 4, with from about 2 to about 3 being most preferred. In certain alternative preferred embodiments, the alkyl group, more preferably, has one carbon atom. Alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, cyclopentyl, isopentyl, neopentyl, n-hexyl, isohexyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl.

[0025] As used herein, "alkylene" refers to an optionally substituted bivalent alkyl radical having the general formula $-(CH_2)_n-$, where n is 1 to 10, preferably 1 to 6, with 1 to 4 being most preferred. In alternative embodiments, n is preferably 4 to 6. Non-limiting examples include methylene, dimethylene, trimethylene, tetramethylene, pentamethylene, and hexamethylene.

[0026] "Cycloalkyl" refers to an optionally substituted alkyl group having one or more rings in their structures and having from about 3 to about 20 carbon atoms (and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein), with from about 3 to about 10 carbon atoms being preferred. Multi-ring structures may be bridged or fused ring structures. Cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, 2-[4-isopropyl-1-methyl-7-oxa-bicyclo[2.2.1]heptanyl], 2-[1,2,3,4-tetrahydro-naphthalenyl], and adamantyl.

[0027] "Alkylcycloalkyl" refers to an optionally substituted ring system comprising a cycloalkyl group having one or more alkyl substituents, wherein cycloalkyl and alkyl are each as previously defined. Exemplary alkylcycloalkyl groups include, for example, 2-methylcyclohexyl, 3,3-dimethylcyclopentyl, trans-2,3-dimethylcyclooctyl, and 4-methyldecahydronaphthalenyl.

[0028] "Heterocycloalkyl" refers to an optionally substituted ring system composed of a cycloalkyl radical wherein in at least one of the rings, one or more of the carbon atom ring members is independently replaced by a heteroatom group selected from the group consisting of O, S, N, and NH, wherein cycloalkyl is as previously defined. Heterocycloalkyl ring systems having a total of from about 5 to about 14 carbon atom ring members and heteroatom ring members (and all combinations and subcombinations of ranges and specific numbers of carbon and heteroatom ring members) are preferred. In other preferred embodiments, the heterocyclic groups may be fused to one or more aromatic rings. Exemplary heterocycloalkyl groups include, but are not limited to, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, isoxazolidinyl, isothiazolidinyl, pyrazolidinyl, oxazolidinyl, thiazolidinyl, piperazinyl, morpholinyl, piperadinyl, decahydroquinolyl, octahydrochromenyl, octahydro-cyclopenta[c]pyranyl, 1,2,3,4,-tetrahydroquinolyl, octahydro-[2]pyrindinyl, decahydro-cycloocta[c]furanyl, tetrahydroquinolyl, and imidazolidinyl.

[0029] "Alkylheterocycloalkyl" refers to an optionally substituted ring system comprising a heterocycloalkyl group having one or more alkyl substituents, wherein heterocycloalkyl and alkyl are each as previously defined. Exemplary alkylheterocycloalkyl groups include, for example, 2-methylpiperidinyl, 3,3-dimethylpyrrolidinyl, *trans*-2,3-dimethylmorpholinyl, and 4-methyldecahydroquinolinyl.

[0030] "Alkenyl" refers to an optionally substituted alkyl group having from about 2 to about 10 carbon atoms and one or more double bonds (and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein), wherein alkyl is as previously defined.

[0031] "Alkynyl" refers to an optionally substituted alkyl group having from about 2 to about 10 carbon atoms and one or more triple bonds (and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein), wherein alkyl is as previously defined.

[0032] "Aryl" refers to an optionally substituted, mono-, di-, tri-, or other multicyclic aromatic ring system having from about 5 to about 50 carbon atoms (and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein), with from about 6 to about 10 carbons being preferred. Non-limiting examples include, for example, phenyl, naphthyl, anthracenyl, and phenanthrenyl.

[0033] "Aralkyl" refers to an optionally substituted moiety composed of an alkyl radical bearing an aryl substituent and having from about 6 to about 50 carbon atoms (and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein), with from about 6 to about 10 carbon atoms being preferred. Non-limiting examples include, for example, benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl.

[0034] "Halo" refers to a fluoro, chloro, bromo, or iodo moiety, preferably fluoro..

[0035] "Heteroaryl" refers to an optionally substituted aryl ring system wherein in at least one of the rings, one or more of the carbon atom ring members is independently replaced by a heteroatom group selected from the group consisting of S, O, N, and NH, wherein aryl is as previously defined. Heteroaryl groups having a total of from about 5 to about 14 carbon atom ring members and heteroatom ring members (and all combinations and subcombinations of ranges and specific numbers of carbon and heteroatom ring members) are preferred. Exemplary heteroaryl groups include, but are not limited to, pyrryl, furyl, pyridyl, 1,2,4-thiadiazolyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, thiophenyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, purinyl, carbazolyl, benzimidazolyl, and isoxazolyl. Heteroaryl may be attached via a carbon or a heteroatom to the rest of the molecule.

[0036] "Heteroarylalkyl" and "heteroaralkyl" each refers to an optionally substituted, heteroaryl substituted alkyl radical where heteroaryl and alkyl are as previously defined Non-limiting examples include, for example, 2-(1H-pyrrol-3-yl)ethyl, 3-pyridylmethyl, 5-(*2H*-tetrazolyl)methyl, and 3-(pyrimidin-2-yl)-2-methylcyclopentanyl.

[0037] "Perhaloalkyl" refers to an alkyl group, wherein two or more hydrogen atoms are replaced by halo (F, Cl, Br, I) atoms, and alkyl is as previously defined. Exemplary perhaloalkyl groups include, for example, perhalomethyl, such as perfluoromethyl and difluoromethyl.

[0038] "Alkoxy" and "alkoxyl" refer to an optionally substituted alkyl-O- group wherein alkyl is as previously defined. Exemplary alkoxy and alkoxyl groups include, for example, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, and heptoxy.

[0039] "Alkenyloxy" refers to an optionally substituted alkenyl-O- group wherein alkenyl is as previously defined. Exemplary alkenyloxy and alkenyloxyl groups include, for example, allyloxy, butenyloxy, heptenyloxy, 2-methyl-3-buten-1-yloxy, and 2,2-dimethylallyloxy.

[0040] "Alkynyloxy" refers to an optionally substituted alkynyl-O- group wherein alkynyl is as previously defined. Exemplary alkynyloxy and alkynyloxyl groups include, for example, propargyloxy, butynyloxy, heptynyloxy, 2-methyl-3-butyn-1-yloxy, and 2,2-dimethylpropargyloxy.

[0041] "Aryloxy" and "aryloxyl" refer to an optionally substituted aryl-O- group wherein aryl is as previously defined. Exemplary aryloxy and aryloxyl groups include, for example, phenoxy and naphthoxy.

[0042] "Aralkoxy" and "aralkoxyl" refer to an optionally substituted aralkyl-O- group wherein aralkyl is as previously defined. Exemplary aralkoxy and aralkoxyl groups include, for example, benzyloxy, 1-phenylethoxy, 2-phenylethoxy, and 3-naphthylheptoxy.

[0043] "Cycloalkoxy" refers to an optionally substituted cycloalkyl-O- group wherein cycloalkyl is as previously defined. Exemplary cycloalkoxy groups include, for example, cyclopropanoxy, cyclobutanoxy, cyclopentanoxy, cyclohexanoxy, and cycloheptanoxy.

[0044] "Heteroaryloxy" refers to an optionally substituted heteroaryl-O- group wherein heteroaryl is as previously defined. Exemplary heteroaryloxy groups include, but are not limited to, pyrryloxy, furyloxyl, pyridyloxy, 1,2,4-thiadiazolyloxy, pyrimidyloxy, thienyloxy, isothiazolyloxy, imidazolyloxy, tetrazolyloxy, pyrazinyloxy, pyrimidyloxy, quinolyloxy, isoquinolyloxy, thiophenyloxy, benzothienyloxy, isobenzofuryloxy, pyrazolyloxy, indolyloxy, purinyloxy, carbazolyloxy, benzimidazolyloxy, and isoxazolyloxy.

[0045] "Heteroaralkoxy" refers to an optionally substituted heteroarylalkyl-O- group wherein heteroarylalkyl is as previously defined. Exemplary heteroaralkoxy groups include, but are not limited to, pyrrylethyloxy, furylethyloxy, pyridylmethyloxy, 1,2,4-thiadiazolylpropyloxy, pyrimidylmethyloxy, thienylethyloxy, isothiazolylbutyloxy, and imidazolyl-2-methylpropyloxy.

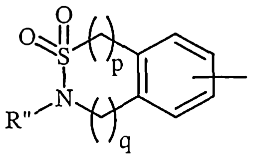
[0046] "Heterocycloalkylaryl" refers to an optionally substituted ring system composed of an aryl radical bearing a heterocycloalkyl substituent wherein heterocycloalkyl and aryl are as previously defined. Exemplary heterocycloalkylaryl groups include, but are not limited to, morpholinylphenyl, piperidinylnaphthyl, piperidinylphenyl, tetrahydrofuranylphenyl, and pyrrolidinylphenyl.

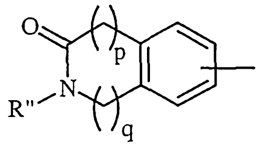
[0047] "Alkylheteroaryl" refers to an optionally substituted ring system composed of a heteroaryl radical bearing an alkyl substituent wherein heteroaryl and alkyl are as previously defined. Exemplary alkylheteroaryl groups include, but are not limited to, methylpyrryl, ethylfuryl, 2,3-dimethylpyridyl, N-methyl-1,2,4-thiadiazolyl, propylpyrimidyl, 2-butylthienyl, methylisothiazolyl, 2-ethylimidazolyl, butyltetrazolyl, 5-ethylbenzothienyl, and N-methylindolyl. Alkyheteroaryl groups may be attached via a carbon or a heteroatom to the rest of the molecule.

[0048] "Heteroarylaryl" refers to an optionally substituted ring system composed of an aryl radical bearing a heteroaryl substituent wherein heteroaryl and aryl are as previously defined. Exemplary heteroarylaryl groups include, but are not limited to, pyrrylphenyl, furylnaphthyl, pyridylphenyl, 1,2,4-thiadiazolylnaphthyl, pyrimidylphenyl, thienylphenyl, isothiazolylnaphthyl, imidazolylphenyl, tetrazolylphenyl, pyrazinylnaphthyl, pyrimidylphenyl, quinolylphenyl, isoquinolylnaphthyl, thiophenylphenyl, benzothienylphenyl, isobenzofurylnaphthyl, pyrazolylphenyl, indolylnaphthyl, purinylphenyl, carbazolylnaphthyl, benzimidazolylphenyl, and isoxazolylphenyl. Heteroarylaryl may be attached via a carbon or a heteroatom to the rest of the molecule.

[0049] "Alkylheteroarylaryl" refers to an optionally substituted ring system composed of an aryl radical bearing an alkylheteroaryl substituent and have from about 12 to about 50 carbon atoms (and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein), with from about 12 to about 30 carbon atoms being preferred wherein aryl and alkylheteroaryl are as previously defined. Exemplary heteroarylaryl groups include, but are not limited to, methylpyrrylphenyl, ethylfurylnaphthyl, methylethylpyridylphenyl, dimethylethylpyrimidylphenyl, and dimethylthienylphenyl.

[0050] Typically, substituted chemical moieties include one or more substituents that replace hydrogen. Exemplary substituents include, for example, halo (*e.g.*, F, Cl, Br, I), alkyl, cycloalkyl, alkylcycloalkyl, alkenyl, alkynyl, aralkyl, aryl, heteroaryl, heteroaralkyl, spiroalkyl, heterocycloalkyl, hydroxyl (-OH), oxo (=O), alkoxyl, aryloxyl, aralkoxyl, nitro ($-NO_2$), cyano (-CN), amino ($-NH_2$), -N-substituted amino (-NHR"), -N,N-disubstituted amino (-N(R")R"), carboxyl (-COOH), -C(=O)R", -OR", -C(=O)OR", $-C(=O)NHSO_2R''$, -NHC(=O)R", aminocarbonyl ($-C(=O)NH_2$), -N-substituted aminocarbonyl (-C(=O)NHR"), -N,N-disubstituted aminocarbonyl (-C(=O)N(R")R"), thiol, thiolato (SR"), sulfonic acid and its esters (SO_3R''), phosphonic acid and its mono-esters (P(=O)OR"OH) and di-esters (P(=O)OR"OR"), $S(=O)_2R''$, $S(=O)_2NH_2$, $S(=O)_2NHR''$, $S(=O)_2NR''R''$, $SO_2NHC(=O)R''$, $NHS(=O)_2R''$, $NR''S(=O)_2R''$, CF_3, CF_2CF_3, NHC(=O)NHR", NHC(=O)NR"R", NR"C(=O)NHR", NR"C(=O)NR"R", NR"C(=O)R", NR"C(=N-CN)NR"R", and the like. Aryl substituents may also include $(CH_2)_pSO_2NR''(CH_2)_q$ and $(CH_2)_pCO_2NR''(CH_2)_q$, where p and q are independently integers from 0 to 3, where the methylene units are attached in a 1,2 arrangement yielding substituted aryls of the type:



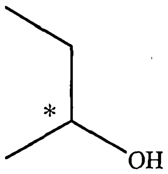


[0051] In relation to the aforementioned substituents, each moiety R" can be, independently, any of H, alkyl, cycloalkyl, alkenyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl, or when (R"(R")) is attached to a nitrogen atom, R" and R" can be taken together to form a 4- to 8-membered nitrogen heterocycloalkyl ring, wherein said heterocycloalkyl ring is optionally interrupted by one or more additional –O-, -S-, -SO, -SO_2-, -NH-, -N(alkyl)-, or –N(aryl)- groups, for example.

[0052] As used herein, an "*" denotes the presence of a non-racemic stereoisomeric center in a molecule, wherein one stereoisomeric form (R or S) predominates, but for which the absolute configuration at this center has not been conclusively established. This is equivalently expressed by saying that the molecule's configuration at the asterisked carbon atom is either greater than 50% R or greater than 50% S. More preferably the compound, or its stereoisomeric center, is "substantially enriched", and even more preferably is substantially enantiomerically pure.

[0053] As used herein, the term "substantially enriched", when referring to a stereoisomer or stereoisomeric center, denotes that at least about 60%, preferably about 705, more preferably about 805, still more preferably about 90% of one stereoisomer or one stereoisomeric center predominating in the mixture, with at least about 95% of one stereoisomer or one stereoisomeric center being even more preferred. In some preferred embodiments, the compound is "substantially enantiomerically pure", that is, at least about 97.5%, more preferably about 99%, even more preferably about 99.5% of one stereoisomeric forms predominates. For example, a compound having one stereoisomeric center may be represented by one of two stereoisomeric forms (R or S), differing only in the spatial arrangement of atoms about a single carbon atom. The "*" denotes non-equal amounts of the two isomers. When a compound has two or more stereoisomeric centers, each center denoted by an asterisk is evaluated individually. A predominance of one stereoisomeric form (R or S) occurring at at least one center is considered non-racemic within the definition herein provided. The range of possible non-racemic compounds extends from the point at which a stereoisomeric form predominates at a single chiral center and includes all combinations and subcombinations up to and including the compound wherein all stereoisomeric centers in the compound are each individually R or S.

[0054] Use of the "*" can be expressed, for example in a compound's identification number such as **4***, and indicates that the stereochemical configuration of at least one chiral center of the identified compound has not been established . The specific center is identified within a structure by placing the "*" adjacent the chiral center in question, such as, for example, in the structure below.



[0055] In some compounds, several chiral centers may be present. The presence of two asterisks "*" in a single structure indicates that two racemic pairs may be present, but that each pair is diastereomeric relative to the other pair. As such, the first pair of enantiomers having two chiral centers may have the configurations, for example, (R, R) and (S, S). The second pair then have configurations, for example, (R, S) and (S, R). Alternatively, where only two stereoisomers bearing an enantiomeric relationship to each other are initially provided, such as the (R, R) and (S,S) pair, the asterisks may indicate that the enantiomers have been enriched (partially resolved) or preferably fully resolved, into the individual enantiomers.

[0056] "Ligand" or "modulator" refers to a compound that binds to a receptor to form a complex, and includes, agonists, partial agonists, antagonists and inverse agonists.

[0057] "Agonist" refers to a compound that may bind to a receptor to form a complex that may elicit a full pharmacological response, which is typically peculiar to the nature of the receptor involved and which may alter the equilibrium between inactive and active receptor.

[0058] “Partial agonist” refers to a compound that may bind to a receptor to form a complex that may elicit only a proportion of the full pharmacological response, typically peculiar to the nature of the receptor involved, even if a high proportion of the receptors are occupied by the compound.

[0059] “Antagonist” refers to a compound that may bind to a receptor to form a complex that may not elicit any response, typically in the same manner as an unoccupied receptor, and which preferably does not alter the equilibrium between inactive and active receptor.

[0060] “Inverse agonist” refers to a compound that may bind to a receptor to form a complex that may preferentially stabilize the inactive conformation of the receptor.

[0061] “Prodrug” refers to compounds specifically designed to maximize the amount of active species that reaches the desired site of reaction that are themselves typically inactive or minimally active for the activity desired, but through biotransformation are converted into biologically active metabolites.

[0062] “Stereoisomers” refers to compounds that have identical chemical constitution, but differ as regards the arrangement of the atoms or groups in space.

[0063] “N-oxide” refers to compounds wherein the basic nitrogen atom of either a heteroaromatic ring or tertiary amine is oxidized to give a quaternary nitrogen bearing a positive formal charge and an attached oxygen atom bearing a negative formal charge.

[0064] "Hydrate" refers to a compound as described herein which is associated with water in the molecular form, i.e., in which the H-OH bond is not split, and may be represented, for example, by the formula $R \cdot H2O$, where R is a compound as described herein. A given compound may form more than one hydrate including, for example, monohydrates (R·H2O), dihydrates (R·2H2O), trihydrates (R·3H2O), and the like.

[0065] As used herein, "haloalkoxy" refers to an alkoxy group, wherein one, preferably two or more, hydrogen(s) of the alkyl moiety of said alkoxy are replaced by halo atoms, and alkoxy, alkyl, and halo are each as previously defined.

[0066] "Solvate" refers to a compound of the present invention which is associated with solvent in the molecular form, i.e., in which the solvent is coordinatively bound, and may be represented, for example, by the formula R·(solvent), where R is a compound of the invention. A given compound may form more than one solvate including, for example, monosolvates (R·(solvent)) or polysolvates (R·n(solvent)) wherein n is an integer > 1) including, for example, disolvates (R·2(solvent)), trisolvates (R·3(solvent)), and the like, or hemisolvates, such as, for example, R·n/2(solvent), R·n/3(solvent), R·n/4(solvent) and the like wherein n is an integer. Solvents herein include mixed solvents, for example, methanol/water, and as such, the solvates may incorporate one or more solvents within the solvate.

[0067] "Acid hydrate" refers to a complex that may be formed through association of a compound having one or more base moieties with at least one compound having one or more acid moieties or through association of a compound having one or more acid moieties with at least one compound having one or more base moieties, said complex being further associated with water molecules so as to form a hydrate, wherein said hydrate is as previously defined and R represents the complex herein described above.

[0068] "Pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like. These physiologically acceptable salts are prepared by methods known in the art, *e.g.*, by dissolving the free amine bases with an excess of the acid in aqueous alcohol, or neutralizing a free carboxylic acid with an alkali metal base such as a hydroxide, or with an amine.

[0069] Compounds described herein throughout can be used or prepared in alternate forms. For example, many amino-containing compounds can be used or prepared as an acid addition salt. Often such salts improve isolation and handling properties of the compound. For example, depending on the reagents, reaction conditions and the like, compounds as described herein can be used or prepared, for example, as their hydrochloride or tosylate salts. Isomorphic crystalline forms, all chiral and racemic forms, N-oxide, hydrates, solvates, and acid salt hydrates, are also contemplated to be within the scope of the present invention.

[0070] Certain acidic or basic compounds as described herein may exist as zwitterions. All forms of the compounds, including free acid, free base and zwitterions, are contemplated to be within the scope of the present invention. It is well known in the art that compounds containing both basic nitrogen atom and acidic groups often exist in equilibrium with their zwitterionic forms. Thus, any of the compounds described herein throughout that contain, for example, both basic nitrogen and acidic groups, also include reference to their corresponding zwitterions.

[0071] "Effective amount" refers to an amount of a compound as described herein that may be therapeutically effective to inhibit, prevent or treat the symptoms of particular disease, disorder, condition, or side effect. Such diseases, disorders, conditions, and side effects include, but are not limited to, those pathological conditions associated with the binding of δ opioid receptor (for example, in connection with the treatment and/or prevention of pain), wherein the treatment or prevention comprises, for example, agonizing the activity thereof by contacting cells, tissues or receptors with compounds as described herein. Thus, for example, the term "effective amount", when used in connection with compounds as described herein, opioids, or opioid replacements, for example, for the treatment of pain, refers to the treatment and/or prevention of the painful condition. The term "effective amount," when used in connection with compounds active against gastrointestinal dysfunction, refers to the treatment and/or prevention of symptoms, diseases, disorders, and conditions typically associated with gastrointestinal dysfunction. The term "effective amount," when used in connection with compounds useful in the treatment and/or prevention of urogenital tract disorders, refers to the treatment and/or prevention of symptoms, diseases, disorders, and conditions typically associated with urogenital tract disorders and other related conditions. The term "effective amount," when used in connection with compounds useful in the treatment and/or prevention of immunomodulatory disorders, refers to the treatment and/or prevention of symptoms, diseases, disorders, and conditions typically associated with immunomodulatory disorders and other related conditions. The term "effective amount," when used in connection with compounds useful in the treatment and/or prevention of inflammatory disorders, refers to the treatment and/or prevention of symptoms, diseases, disorders, and conditions typically associated with inflammatory disorders and other related conditions. The term "effective amount," when used in connection with compounds useful in the treatment and/or prevention of respiratory function disorders, refers to the treatment and/or prevention of symptoms, diseases, disorders, and conditions typically associated with respiratory function disorders and other related conditions. The term "effective amount," when used in connection with compounds useful in the treatment and/or prevention of anxiety, mood disorders, stress-related disorders, and attention deficit hyperactivity disorder, refers to the treatment and/or prevention of symptoms, diseases, disorders, and conditions typically associated with anxiety, mood disorders, stress-related disorders, attention deficit hyperactivity disorder and other related conditions. The term "effective amount," when used in connection with compounds useful in the treatment and/or prevention of sympathetic nervous system disorders, refers to the treatment and/or prevention of symptoms, diseases, disorders, and conditions typically associated with sympathetic nervous system disorders and other related conditions. The term “effective amount,” when used in connection with compounds useful in the treatment and/or prevention of tussis, refers to the treatment and/or prevention of symptoms, diseases, disorders, and conditions typically associated with tussis and other related conditions. The term “effective amount,” when used in connection with compounds useful in the treatment and/or prevention of motor disorders, refers to the treatment and/or prevention of symptoms, diseases, disorders, and conditions typically associated with motor disorders and other related conditions. The term “effective amount,” when used in connection with compounds useful in the treatment of traumatic injuries of the central nervous system, refers to the treatment and/or prevention of symptoms, diseases, disorders, and conditions typically associated with the central nervous system and other related conditions. The term “effective amount,” when used in connection with compounds useful in the treatment and/or prevention of stroke, cardiac arrhythmia or glaucoma, refers to the treatment and/or prevention of symptoms, diseases, disorders, and conditions typically associated with stroke, cardiac arrhythmia, glaucoma and other related conditions. The term “effective amount,” when used in connection with compounds useful in the treatment and/or prevention of sexual dysfunction, refers to the treatment and/or prevention of symptoms, diseases, disorders, and conditions typically associated with sexual dysfunction and other related conditions. The term “effective amount,” when used in connection with compounds useful in improving organ and cell survival, refers to refers to the maintenance and/or improvement of a minimally-acceptable level of organ or cell survival, including organ preservation. The term “effective amount,” when used in connection with compounds useful in the treatment and/or prevention of myocardial infarction, refers to the minimum level of compound necessary to provide cardioprotection after myocardial infarction. The term “effective amount,” when used in connection with compounds useful in the treatment and/or prevention of shock, brain edema, cerebral ischemia, cerebral deficits subsequent to cardiac bypass surgery and grafting, systemic lupus erythematosus, Hodgkin’s disease, Sjogren’s disease, epilepsy, and rejection in organ transplants and skin grafts, refers to the treatment and/or prevention of symptoms, diseases, disorders, and conditions typically associated with shock, brain edema, cerebral ischemia, cerebral deficits subsequent to cardiac bypass surgery and grafting, systemic lupus erythematosus, Hodgkin's disease, Sjogren's disease, epilepsy, and rejection in organ transplants and skin grafts and other related conditions. The term "effective amount," when used in connection with compounds useful in the treatment of substance addiction, refers to the treatment of symptoms, diseases, disorders, and conditions typically associated with substance addiction and other related conditions. The term "effective amount," when used in connection with compounds useful in reducing the need for anesthesia or producing and/or maintaining an anesthetic state, refers to the production and/or maintenance of a minimally-acceptable anesthetic state.

[0072] "Pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms that are, within the scope of sound medical judgment, suitable for contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio. The term specifically encompasses veterinary uses.

[0073] "In combination with," "combination therapy," and "combination products" refer, in certain embodiments, to the concurrent administration to a patient of a compound as described herein including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII, and/or XXXIV, and one or more additional agents including, for example, an opioid, an anaesthetic agent (such as for example, an inhaled anesthetic, hypnotic, anxiolytic, neuromuscular blocker and opioid), an anti-Parkinson's agent (for example, in the case of treating or preventing a motor disorder, particularly Parkinson's disease), an antidepressant (for example, in the case of treating or preventing a mood disorder, particularly depression), an agent for the treatment of incontinence (for example, in the case of treating or preventing a urogenital tract disorder), an agent for the treatment of pain, including neuralgias or neuropathic pain, and/or other optional ingredients (including, for example, antibiotics, antivirals, antifungals, anti-inflammatories, anesthetics and mixtures thereof). When administered in combination, each component may be administered at the same time or sequentially in any order at different points in time.

Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect.

[0074] "Dosage unit" refers to physically discrete units suited as unitary dosages for the particular individual to be treated. Each unit may contain a predetermined quantity of active compound(s) calculated to produce the desired therapeutic effect(s) in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention may be dictated by (a) the unique characteristics of the active compound(s) and the particular therapeutic effect(s) to be achieved, and (b) the limitations inherent in the art of compounding such active compound(s).

[0075] "Pain" refers to the perception or condition of unpleasant sensory or emotional experience, associated with actual or potential tissue damage or described in terms of such damage. "Pain" includes, but is not limited to, two broad categories of pain: acute and chronic pain (Buschmann, H.; Christoph, T; Friderichs, E.; Maul, C.; Sundermann, B; eds.; *Analgesics*, Wiley-VCH, Verlag GMbH & Co. KgaA, Weinheim; **2002**; Jain, K. K. "A Guide to Drug Evaluation for Chronic Pain"; *Emerging Drugs,* 5(2), 241-257(2000)). Non-limiting examples of pain include, for example, nociceptive pain, inflammatory pain, visceral pain, somatic pain, neuralgias, neuropathic pain, AIDS pain, cancer pain, phantom pain, and psychogenic pain, and pain resulting from hyperalgesia, pain caused by rheumatoid arthritis, migraine, allodynia and the like.

[0076] "Gastrointestinal dysfunction" refers collectively to maladies of the stomach, small and large intestine. Non-limiting examples of gastrointestinal dysfunction include, for example, diarrhea, nausea, emesis, post-operative emesis, opioid-induced emesis, irritable bowel syndrome, opioid-bowel dysfunction, inflammatory bowel disease, colitis, increased gastric motility, increased gastric emptying, stimulation of small intestinal propulsion, stimulation of large intestinal propulsion, decreased amplitude of non-propulsive segmental contractions, disorders associated with sphincter of Oddi, disorders associated with anal sphincter tone, impaired reflex relaxation with rectal distention, disorders associated with gastric, biliary, pancreatic or intestinal secretions, changes to the absorption of water from bowel contents, gastro-esophageal reflux, gastroparesis, cramping, bloating, distension, abdominal or epigastric pain and discomfort, non-ulcerogenic dyspepsia, gastritis, or changes to the absorption of orally administered medications or nutritive substances.

[0077] "Urogenital tract disorders" refers collectively to maladies of the urinary and genital apparati. Non-limiting examples of urogenital tract disorders include incontinence (i.e., involuntary loss of urine) such as stress urinary incontinence, urge urinary incontinence and benign prostatic hyperplasia, overactive bladder disorder, urinary retention, renal colic, glomerulonephritis, and interstitial cystitis.

[0078] "Overactive bladder disorder" refers to a condition with symptoms of urgency with or without incontinence, and is typically associated with increased urinary frequency and nocturia. Overactive bladder disorders are typically associated with urodynamic finding of involuntary bladder contractions, generally referred to as bladder instability.

[0079] "Immunomodulatory disorders" refers collectively to maladies characterized by a compromised or over-stimulated immune system. Non-limiting examples of immunomodulatory disorders include autoimmune diseases (such as arthritis, autoimmune disorders associated with skin grafts, autoimmune disorders associated with organ transplants, and autoimmune disorders associated with surgery), collagen diseases, allergies, side effects associated with the administration of an anti-tumor agent, side effects associated with the administration of an antiviral agent, multiple sclerosis and Guillain-Barre syndrome.

[0080] "Inflammatory disorders" refers collectively to maladies characterized by cellular events in injured tissues. Non-limiting examples of inflammatory diseases include arthritis, psoriasis, asthma, and inflammatory bowel disease.

[0081] "Respiratory function disorders" refers to conditions in which breathing and/or airflow into the lung is compromised. Non-limiting examples of respiratory function disorders include asthma, apnea, tussis,chronic obstruction pulmonary disease, and lung edema.

[0082] "Lung edema" refers to the presence of abnormally large amounts of fluid in the intercellular tissue spaces of the lungs.

[0083] "Anxiety" refers to the unpleasant emotional state consisting of psychophysiological responses to anticipation of real, unreal or imagined danger, ostensibly resulting from unrecognized intrapsychic conflict.

[0084] "Mood disorders" refers to disorders that have a disturbance in mood as their predominant feature, including depression, bipolar manic-depression, borderline personality disorder, and seasonal affective disorder.

[0085] "Depression" refers to a mental state of depressed mood characterized by feelings of sadness, despair and discouragement, including the blues, dysthymia, and major depression.

[0086] "Stress-related disorders" refer collectively to maladies characterized by a state of hyper- or hypo-arousal with hyper- and hypo-vigilance. Non-limiting examples of stress-related disorders include post-traumatic stress disorder, panic disorder, generalized anxiety disorder, social phobia, and obsessive-compulsive disorder.

[0087] "Attention deficit hyperactivity disorder" refers to a condition characterized by an inability to control behavior due to difficulty in processing neural stimuli.

[0088] "Sympathetic nervous system disorders" refer collectively to maladies characterized by disturbances of the autonomic nervous system. Non-limiting examples of sympathetic nervous system disorders include hypertension, and the like.

[0089] "Tussis" refers to a coughing condition, and "antitussive" agents refer to those materials that modulate the coughing response.

[0090] "Motor disorders" refers to involuntary manifestations of hyper or hypo muscle activity and coordination Non-limiting examples of motor disorders include tremors, Parkinson's disease, tourette syndrome, parasomnias (sleep disorders) including restless leg syndrome, postoperative shivering and dyskinesia.

[0091] "Traumatic injury of the central nervous system" refers to a physical wound or injury to the spinal cord or brain.

[0092] "Stroke" refers to a condition due to the lack of oxygen to the brain.

[0093] "Cardiac arrhythmia" refers to a condition characterized by a disturbance in the electrical activity of the heart that manifests as an abnormality in heart rate or heart rhythm. Patients with a cardiac arrhythmia may experience a wide variety of symptoms ranging from palpitations to fainting.

[0094] "Glaucoma" refers collectively to eye diseases characterized by an increase in intraocular pressure that causes pathological changes in the optic disk and typical defects in the field of vision.

[0095] "Sexual dysfunction" refers collectively to disturbances, impairments or abnormalities of the functioning of the male or female sexual organs, including, but not limited to premature ejaculation and erectile dysfunction.

[0096] "Cardioprotection" refers to conditions or agents that protect or restore the heart from dysfunction, heart failure and reperfusion injury.

[0097] “Myocardial infarction” refers to irreversible injury to heart muscle caused by a local lack of oxygen.

[0098] “Addiction” refers to a pattern of compulsive substance abuse (alcohol, nicotine, or drug) characterized by a continued craving for the substance and, in some cases, the need to use the substance for effects other than its prescribed or legal use.

[0099] “Anaesthetic state” refers to the state of the loss of feeling or sensation, including not only the loss of tactile sensibility or of any of the other senses, but also to the loss of sensation of pain, as it is induced to permit performance of surgery or other painful procedures, and specifically including amnesia, analgesia, muscle relaxation and sedation.

[0100] “Improving organ and cell survival” refers to the maintenance and/or improvement of a minimally-acceptable level of organ or cell survival.

[0101] “Patient” refers to animals, including mammals, preferably humans.

[0102] “Side effect” refers to a consequence other than the one(s) for which an agent or measure is used, as the adverse effects produced by a drug, especially on a tissue or organ system other then the one sought to be benefited by its administration. In the case, for example, of opioids, the term “side effect” may refer to such conditions as, for example, constipation, nausea, vomiting, dyspnea and pruritus.

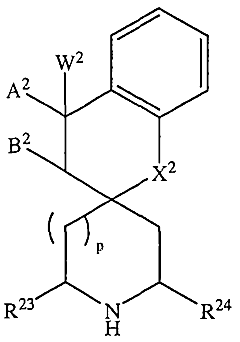
[0103] When any variable occurs more than one time in any constituent or in any formula, its definition in each occurrence is independent of its definition at every other occurrence. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[0104] It is believed the chemical formulas and names used herein correctly and accurately reflect the underlying chemical compounds. However, the nature and value of the present invention does not depend upon the theoretical correctness of these formulae, in whole or in part. Thus it is understood that the formulas used herein, as well as the chemical names attributed to the correspondingly indicated compounds, are not intended to limit the invention in any way, including restricting it to any specific tautomeric form or to any specific optical or geometric isomer, except where such stereochemistry is clearly defined.

[0105] In certain preferred embodiments, the compounds, pharmaceutical compositions and methods of the present invention may involve a peripheral δ opioid modulator compound. The term "peripheral" designates that the compound acts primarily on physiological systems and components external to the central nervous system. In preferred form, the peripheral δ opioid modulator compounds employed in the methods of the present invention exhibit high levels of activity with respect to peripheral tissue, such as, gastrointestinal tissue, while exhibiting reduced, and preferably substantially no, CNS activity. The phrase "substantially no CNS activity," as used herein, means that less than about 50% of the pharmacological activity of the compounds employed in the present methods is exhibited in the CNS, preferably less than about 25%, more preferably less than about 10%, even more preferably less than about 5% and most preferably 0% of the pharmacological activity of the compounds employed in the present methods is exhibited in the CNS.

[0106] Furthermore, it is preferred in certain embodiments of the invention that the δ opioid modulator compound does not substantially cross the blood-brain barrier. The phrase "does not substantially cross," as used herein, means that less than about 20% by weight of the compound employed in the present methods crosses the blood-brain barrier, preferably less than about 15% by weight, more preferably less than about 10% by weight, even more preferably less than about 5% by weight and most preferably 0% by weight of the compound crosses the blood-brain barrier. Selected compounds can be evaluated for CNS penetration, for example, by determining plasma and brain levels following i.v. administration.

[0107] Accordingly, in one embodiment, the invention is directed to compounds of formula XIV:



XIV ;

wherein:

W^2 is aryl or heteroaryl, wherein the aryl or heteroaryl is substituted with 0-3 groups selected independently from hydroxy, aminocarbonyl (-C(=O)-NH_2), N-alkylaminocarbonyl (-C(=O)-NH(alkyl)), and N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl));

R^{23} and R^{24} are each independently H or alkyl, provided that at least one of R^{23} and R^{24} is alkyl;

p is 1 or 2;

A^2 and B^2 are each H, or together form a double bond; and

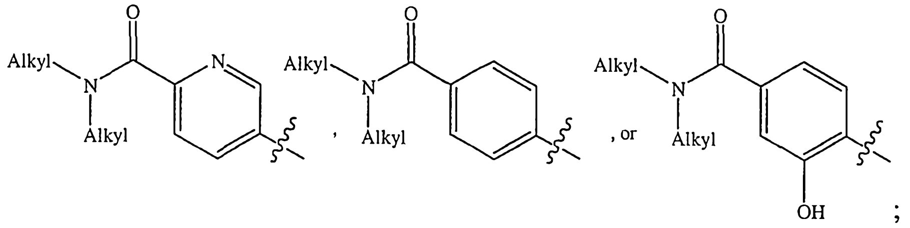
X^2 is -CH_2- or -O-;

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof.

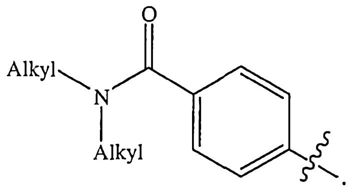
[0108] In preferred embodiments of formula XIV compounds, W^2 is aryl or heteroaryl. When W^2 is aryl, the aryl ring is preferably phenyl. When W^2 is heteroaryl, the heteroaryl ring is preferably pyridyl.

[0109] As set forth above, W^2 is substituted with 0-3 groups selected independently from hydroxy, aminocarbonyl (-C(=O)-NH_2), N-alkylaminocarbonyl (-C(=O)-NH(alkyl)), and N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl)). In preferred embodiments, W^2 is substituted with 1-2 groups, selected independently from hydroxy, aminocarbonyl (-C(=O)-NH_2), N-alkylaminocarbonyl (-C(=O)-NH(alkyl)), and N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl)). More preferably, W^2 is substituted with N,N-dialkylaminocarbonyl and/or hydroxyl.

[0110] In preferred embodiments of formula XIV compounds, W^2 is:



more preferably:



[0111] In embodiments in which W^2 is substituted with N-alkylaminocarbonyl (-C(=O)-NH(alkyl)) or N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl)), the alkyl group is preferably lower alkyl, with alkyl groups of 1 to 3 carbons being more preferred, and with alkyl groups of 2 carbons being still more preferred. In particularly preferred embodiments, the alkyl group is ethyl.

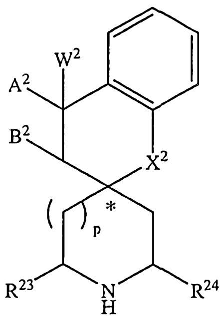
[0112] In preferred embodiments of formula XIV compounds, p is 1.

[0113] In preferred embodiments of formula XIV compounds, A^2 and B^2 together form a double bond.

[0114] In preferred embodiments of formula XIV compounds, X^2 is -O-.

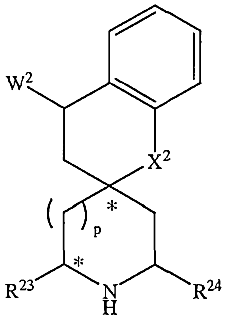
[0115] In preferred embodiments of formula XIV compounds, R^{23} and R^{24} are each independently H or alkyl, preferably H or C_1-C_3 alkyl, more preferably H or methyl. In certain preferred embodiments, one of R^{23} and R^{24} is H and the other is alkyl.

[0116] In preferred embodiments, the compounds of formula XIV have the following formula XV:



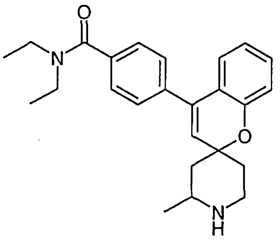
XV

with compounds of formula XVI being even more preferred:



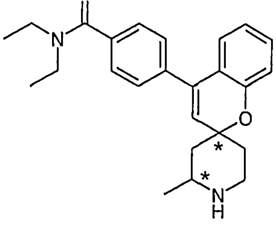
XVI .

[0117] In preferred embodiments, the compound of formula XIV is:



,

more preferably:



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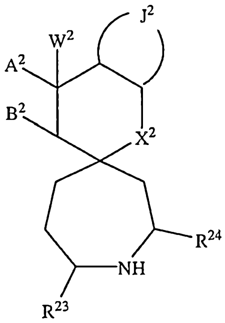
[0118] In an alternative embodiment, the invention is directed to compounds of formula XVII:



XVII ;

wherein:

W^2 is aryl or heteroaryl, wherein the aryl or heteroaryl is substituted with 0-3 groups selected independently from hydroxy, aminocarbonyl (-C(=O)-NH_2), N-alkylaminocarbonyl (-C(=O)-NH(alkyl)), and N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl));

R^{23} and R^{24} are each independently H or alkyl;

A^2 and B^2 are each H, or together form a double bond;

X^2 is -CH_2- or -O-; and

J^2 when taken together with the carbon atoms to which it is attached forms a 6-membered aryl ring substituted with 0-3 groups selected independently from halo, hydroxy, and -S(=O)$_2$-alkyl;

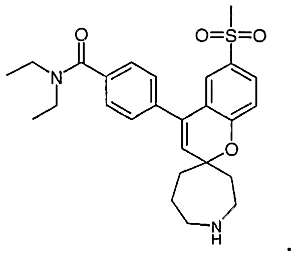
or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof;

provided that:

when W^2 is *para*-diethylaminocarbonylphenyl, X^2 is O, and A^2 and B^2 together form a double bond, then the aryl ring of J^2 is substituted with at least one group selected independently from halo, and -S(=O)$_2$-alkyl in which the alkyl group is C_2-C_6 alkyl;

when W^2 is *para*-diethylaminocarbonylphenyl, X^2 is O, and A^2 and B^2 are each H, then the aryl ring of J^2 is substituted with 1-3 groups selected independently from halo, hydroxy, and -S(=O)$_2$-alkyl; and

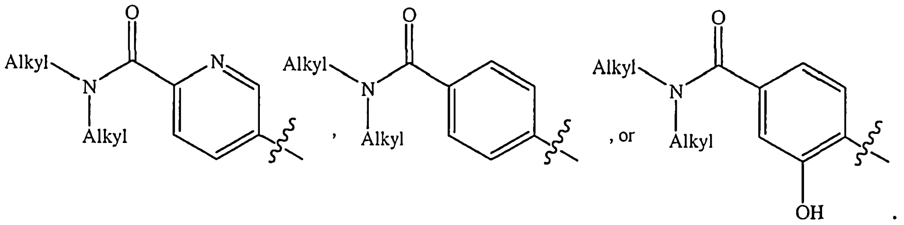
the compound of formula XVII is other than:



[0119] In preferred embodiments of formula XVII compounds, W^2 is aryl or heteroaryl. When W^2 is aryl, the aryl ring is preferably phenyl. When W^2 is heteroaryl, the heteroaryl ring is preferably pyridyl.

[0120] As set forth above, W^2 is substituted with 0-3 groups selected independently from hydroxy, aminocarbonyl ($-C(=O)-NH_2$), N-alkylaminocarbonyl (-C(=O)-NH(alkyl)), and N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl)). In preferred embodiments, W^2 is substituted with 1-2 groups, selected independently from hydroxy, aminocarbonyl ($-C(=O)-NH_2$), N-alkylaminocarbonyl (-C(=O)-NH(alkyl)), and N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl)). More preferably, W^2 is substituted with N,N-dialkylaminocarbonyl and/or hydroxyl.

[0121] In preferred embodiments of formula XVII compounds, W^2 is:



[0122] In embodiments in which W^2 is substituted with N-alkylaminocarbonyl (-C(=O)-NH(alkyl)) or N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl)), the alkyl group is preferably lower alkyl, with alkyl groups of 1 to 3 carbons being more preferred, and with alkyl groups of 2 carbons being still more preferred. In particularly preferred embodiments, the alkyl group is ethyl.

[0123] In preferred embodiments of formula XVII compounds, X^2 is -O-.

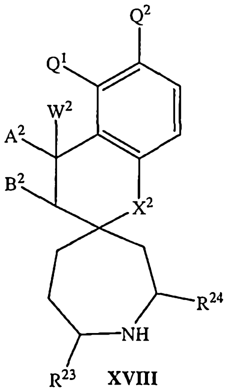
[0124] In preferred embodiments of formula XVII compounds, A^2 and B^2 together form a double bond.

[0125] In preferred embodiments of formula XVII compounds, R^{23} and R^{24} are each independently H or alkyl, preferably H or C_1-C_3 alkyl, more preferably H or methyl, yet more preferably H.

[0126] In preferred embodiments of formula XVII compounds, J^2 when taken together with the carbon atoms to which it is attached forms a 6-membered aryl ring, preferably phenyl.

[0127] As set forth above, J^2 is substituted with 0-3 groups, preferably 0-2, more preferably 0-1 groups, selected independently from halo, hydroxy, and -S(=O)$_2$-alkyl. In embodiments wherein J^2 is substituted with halo, the halo group is preferably fluoro. In embodiments wherein J^2 is substituted with -S(=O)$_2$-alkyl, the alkyl group is preferably lower alkyl, with alkyl groups of 1 to 3 carbons being more preferred, still more preferably alkyl groups of 1 to 2 carbons, yet more preferably methyl or ethyl.

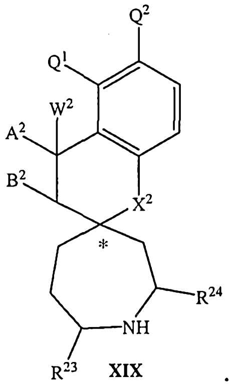
[0128] In preferred embodiments, the compounds of formula XVII have the following formula XVIII:



XVIII ;

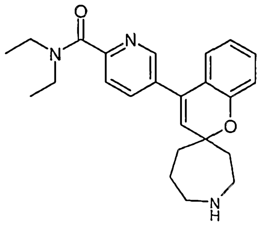
wherein:

Q^1 and Q^2 are each independently H, halo, hydroxy, or -S(=O)$_2$-alkyl. In embodiments wherein Q^1 or Q^2 is halo, the halo group is preferably fluoro. In embodiments wherein Q^1 or Q^2 is-S(=O)$_2$-alkyl, the alkyl group is preferably lower alkyl, with alkyl groups of 1 to 3 carbons being more preferred, still more preferably alkyl groups of 1 to 2 carbons, yet more preferably methyl or ethyl. Still more preferably, the compounds of formula XVIII have the following formula XIX:



XIX .

[0129] In preferred embodiments, the compounds of formula XVII have the following structures: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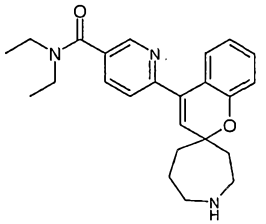
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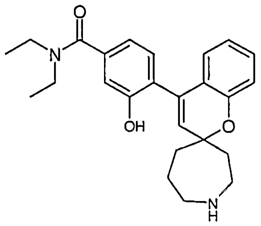
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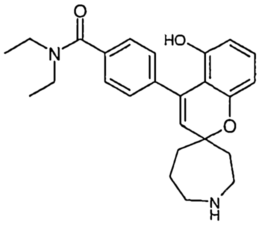
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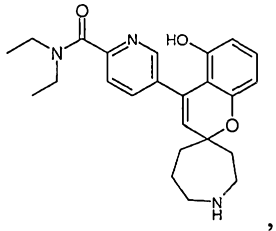
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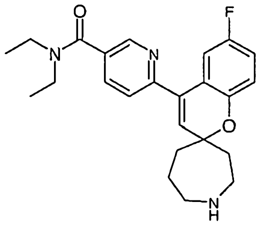
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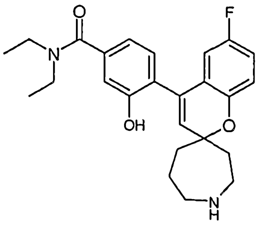
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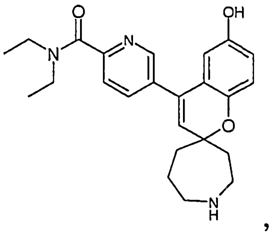
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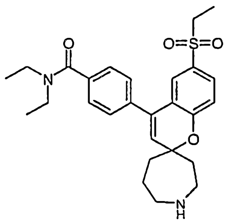
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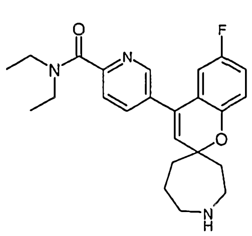
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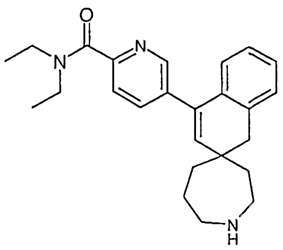
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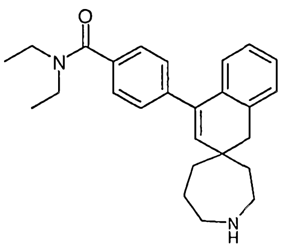
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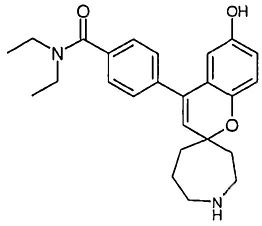
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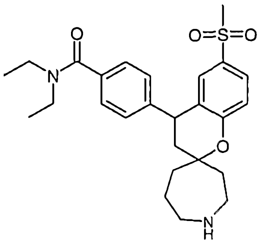
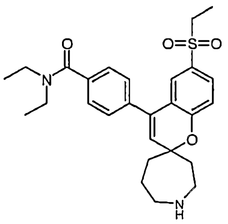

.

[0130] In certain embodiments, the above compounds may be resolved into any of their R and S, or (R,R), (S,S), (R,S), and (S,R) enantiomers, or partially resolved into any of their non-racemic mixtures.

[0131] More preferably, the compounds of formula XVII have the following structures: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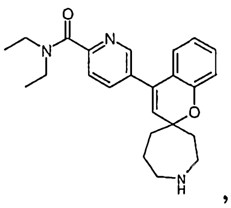
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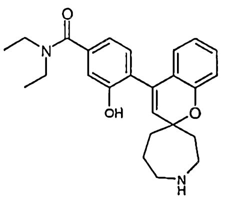
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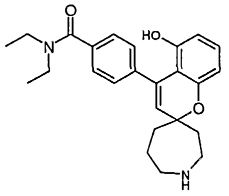

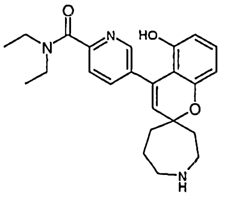
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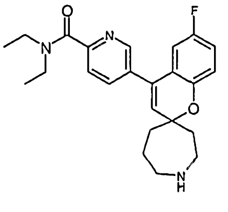
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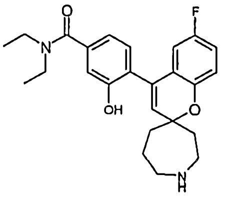
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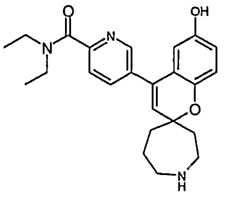
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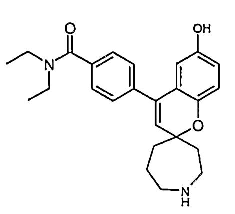
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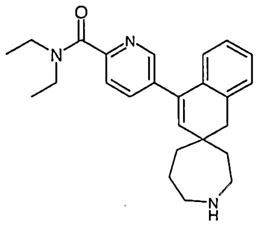
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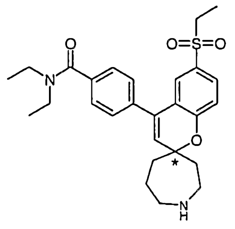
yet more preferably: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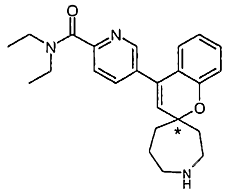
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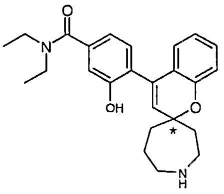
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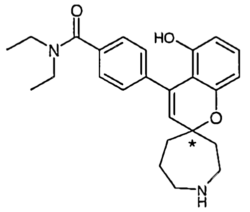

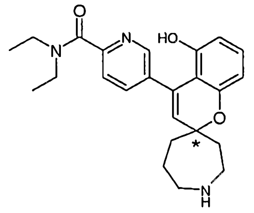
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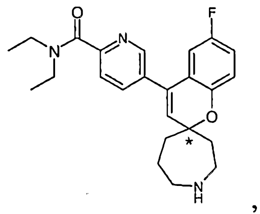
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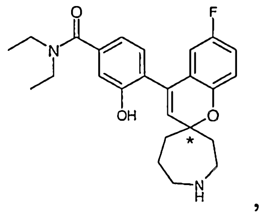
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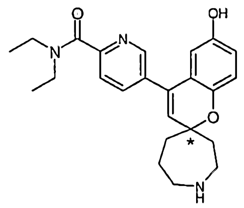
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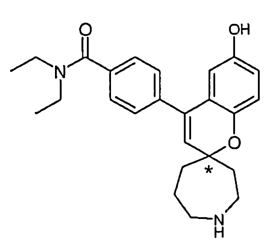
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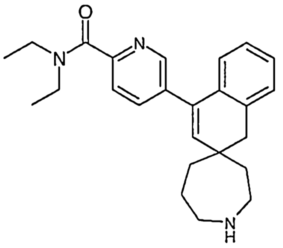
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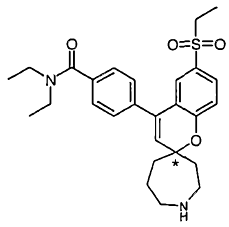
still more preferably: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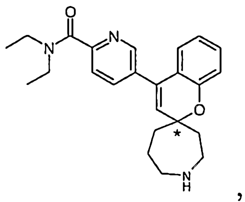
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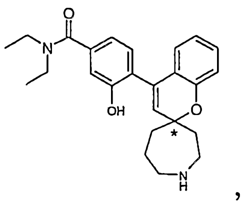
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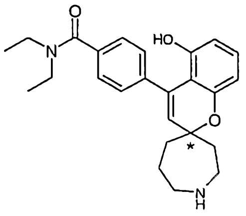
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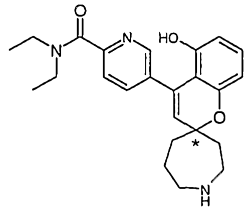
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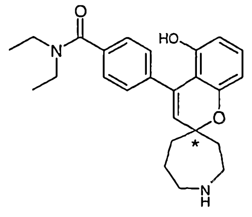
even more preferably: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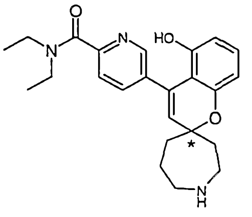
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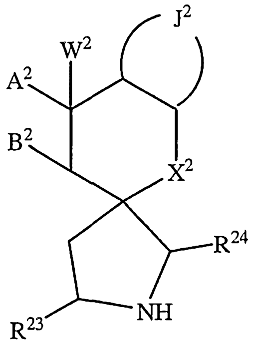
[0132] In certain embodiments, the invention is directed to compounds of formula XX:



XX ;

wherein:

W^2 is aryl or heteroaryl, wherein the aryl or heteroaryl is substituted with 0-3 groups selected independently from hydroxy, aminocarbonyl (-C(=O)-NH_2), N-alkylaminocarbonyl (-C(=O)-NH(alkyl)), and N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl));

R^{23} and R^{24} are each independently H or alkyl;

A^2 and B^2 are each H, or together form a double bond;

X^2 is -CH_2- or -O-; and

J^2 when taken together with the carbon atoms to which it is attached forms a 6-membered aryl ring substituted independently with 0-3 hydroxy or halo groups;

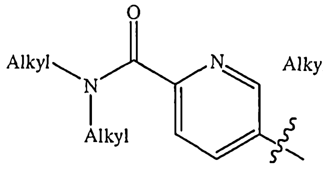
or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof;

provided that the compound of formula XX is other than 4-[(4-*N*,*N*-diethylaminocarbonyl)phenyl]-spiro[2H,1-benzopyran-2,3'-pyrrolidine].

[0133] In preferred embodiments of formula XX compounds, W^2 is aryl or heteroaryl. When W^2 is aryl, the aryl ring is preferably phenyl. When W^2 is heteroaryl, the heteroaryl ring is preferably pyridyl.

[0134] As set forth above, W^2 is substituted with 0-3 groups selected independently from hydroxy, aminocarbonyl (-C(=O)-NH_2), N-alkylaminocarbonyl (-C(=O)-NH(alkyl)), and N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl)). In preferred embodiments, W^2 is substituted with 1-2 groups, selected independently from hydroxy, aminocarbonyl (-C(=O)-NH_2), N-alkylaminocarbonyl (-C(=O)-NH(alkyl)), and N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl)). More preferably, W^2 is substituted with N,N-dialkylaminocarbonyl and/or hydroxyl.

[0135] In preferred embodiments of formula XX compounds, W^2 is:



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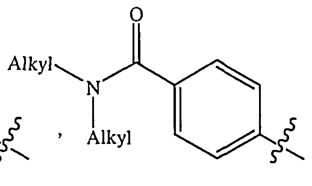

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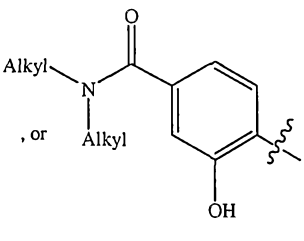


.

[0136] In embodiments in which W^2 is substituted with N-alkylaminocarbonyl (-C(=O)-NH(alkyl)) or N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl)), the alkyl group is preferably lower alkyl, with alkyl groups of 1 to 3 carbons being more preferred, and with alkyl groups of 2 carbons being still more preferred. In particularly preferred embodiments, the alkyl group is ethyl.

[0137] In preferred embodiments of formula XX compounds, A^2 and B^2 together form a double bond.

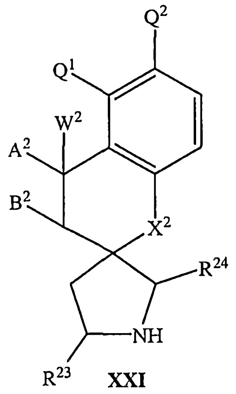
[0138] In preferred embodiments of formula XX compounds, X^2 is -O-.

[0139] In preferred embodiments of formula XX compounds, R^{23} and R^{24} are each independently H or alkyl, preferably H or C_1-C_3 alkyl, more preferably H or methyl, yet more preferably H.

[0140] In preferred embodiments of formula XX compounds, J^2 when taken together with the carbon atoms to which it is attached forms a 6-membered aryl ring, preferably phenyl.

[0141] As set forth above, J^2 is substituted independently with 0-3, preferably 0-2, more preferably 0-1, hydroxy or halo groups, more preferably still, 0-1 hydroxy groups.

[0142] In preferred embodiments, the compounds of formula XX have the following formula XXI:

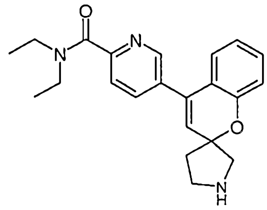


XXI ;

wherein:

Q^1 and Q^2 are each independently H, hydroxy, or halo. In embodiments wherein at least one of Q^1 and Q^2 is halo, the halo is preferably fluoro.

[0143] In preferred embodiments, the compounds of formula XX have the following structures: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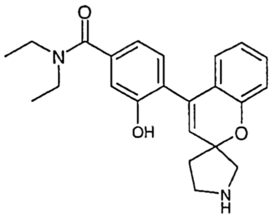
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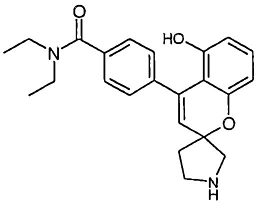
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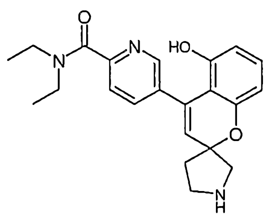
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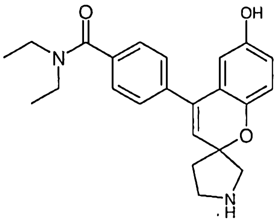
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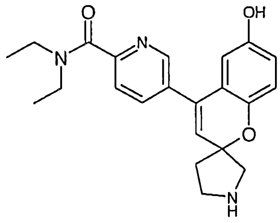
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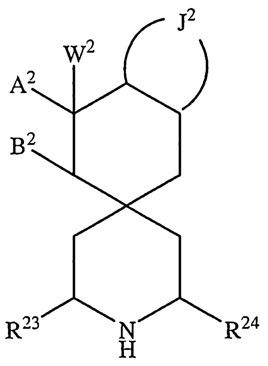
[0144] In an alternative embodiment, the invention is directed to compounds of formula XXII:



XXII

wherein:

W^2 is aryl or heteroaryl, wherein the aryl or heteroaryl is substituted with 0-3 groups selected independently from heteroaryl, hydroxy, carboxy (-COOH), -C(=O)-alkyl, -C(=O)-aryl, -C(=O)-O-alkyl, $-S(=O)_2-N(alkyl)(alkyl)$; aminocarbonyl ($-C(=O)-NH_2$), N-alkylaminocarbonyl (-C(=O)-NH(alkyl)), and N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl));

R^{23} and R^{24} are each independently H or alkyl;

A^2 and B^2 are each H, or together form a double bond; and

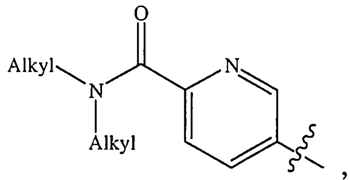
J^2 when taken together with the carbon atoms to which it is attached forms a 6-membered aryl ring substituted with 0-3 groups selected independently from halo, heterocycloalkyl, hydroxy, alkoxy, $-S(=O)_2$-alkyl, $-S(=O)_2-NH_2$, $-S(=O)_2$-NH(alkyl), $-S(=O)_2$-N(alkyl)(alkyl), carboxy (-COOH), -C(=O)-O-alkyl, and N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl));

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof;

provided that:

when W^2 is *para*-diethylaminocarbonylphenyl, *para*-prop-2-ylaminocarbonylphenyl, or *para*-pent-3-ylaminocarbonylphenyl, R^{23} and R^{24} are each H, and A and B are each H or together form a double bond, then J^2 is other than unsubstituted phenyl or anisyl; and

when W^2 is:



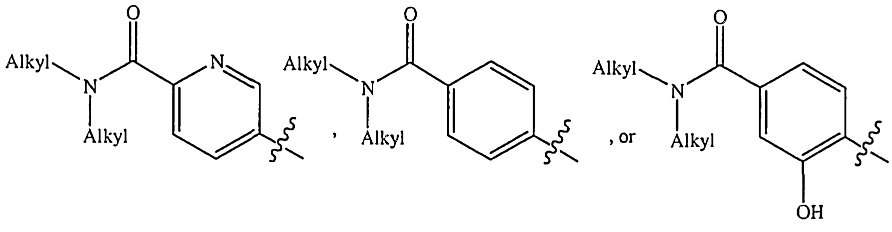
,

R^{23} and R^{24} are each H, and A and B together form a double bond; then J^2 is other than unsubstituted phenyl.

[0145] In preferred embodiments of formula XXII compounds, W^2 is aryl or heteroaryl. When W^2 is aryl, the aryl ring is preferably phenyl. When W^2 is heteroaryl, the heteroaryl ring is preferably pyridyl.

[0146] As set forth above, W^2 is substituted with 0-3 groups selected independently from hydroxy, aminocarbonyl (-C(=O)-NH_2), N-alkylaminocarbonyl (-C(=O)-NH(alkyl)), and N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl)). In preferred embodiments, W^2 is substituted with 1-2 groups, selected independently from hydroxy, aminocarbonyl (-C(=O)-NH_2), N-alkylaminocarbonyl (-C(=O)-NH(alkyl)), and N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl)). More preferably, W^2 is substituted with N,N-dialkylaminocarbonyl and/or hydroxyl.

[0147] In preferred embodiments of formula XXII compounds, W^2 is:



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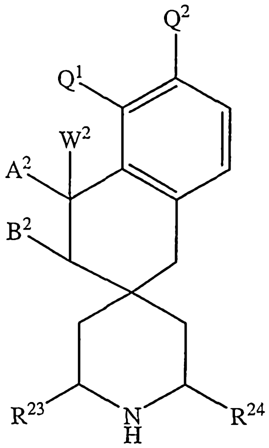
[0148] In embodiments in which W^2 is substituted with N-alkylaminocarbonyl (-C(=O)-NH(alkyl)) or N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl)), the alkyl group is preferably lower alkyl, with alkyl groups of 1 to 3 carbons being more preferred, and with alkyl groups of 2 carbons being still more preferred. In particularly preferred embodiments, the alkyl group is ethyl.

[0149] In preferred embodiments of formula XXII compounds, R^{23} and R^{24} are each independently H or alkyl, preferably H or C_1-C_3 alkyl, more preferably H or methyl, yet more preferably H.

[0150] In preferred embodiments of formula XXII compounds, J^2 when taken together with the carbon atoms to which it is attached forms a 6-membered aryl ring, preferably phenyl.

[0151] As set forth above, J^2 is substituted with 0-3 groups, preferably 0-2 groups, selected independently from halo, heterocycloalkyl, hydroxy, alkoxy, -$S(=O)_2$-alkyl, -$S(=O)_2$-NH_2, -$S(=O)_2$-NH(alkyl), -$S(=O)_2$-N(alkyl)(alkyl), carboxy (-COOH), -C(=O)-O-alkyl, and N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl)). In embodiments wherein J^2 is substituted with alkoxy, -$S(=O)_2$-alkyl, -$S(=O)_2$-NH(alkyl), -$S(=O)_2$-N(alkyl)(alkyl), -C(=O)-O-alkyl, or N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl)), the alkyl group is preferably lower alkyl, with alkyl groups of 1 to 3 carbons being more preferred, and with alkyl groups of 1 to 2 carbons being still more preferred. In particularly preferred embodiments, the alkyl group is methyl or ethyl. In embodiments wherein J^2 is substituted with halo, the halo group is preferably fluoro.

[0152] In preferred embodiments of formula XXII compounds, the compounds have the following formula XXIII:

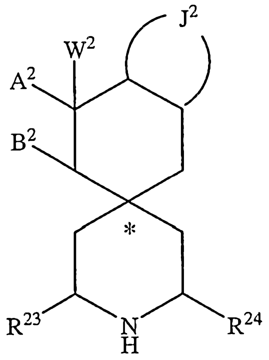


XXIII ;

wherein:

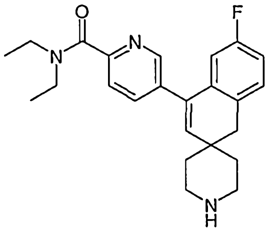
Q^1 and Q^2 are each independently H, halo, heterocycloalkyl, hydroxy, alkoxy, -S(=O)$_2$-alkyl, -S(=O)$_2$-NH$_2$, -S(=O)$_2$-NH(alkyl), -S(=O)$_2$-N(alkyl)(alkyl), carboxy (-COOH), -C(=O)-O-alkyl, or N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl)). In certain preferred embodiments, at least one of Q^1 or Q^2 is H, more preferably, one of Q^1 or Q^2 is H. In embodiments wherein Q^1 or Q^2 is alkoxy, -S(=O)$_2$-alkyl, -S(=O)$_2$-NH(alkyl), -S(=O)$_2$-N(alkyl)(alkyl), -C(=O)-O-alkyl, or N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl)), the alkyl group is preferably lower alkyl, with alkyl groups of 1 to 3 carbons being more preferred, and with alkyl groups of 1 to 2 carbons being still more preferred. In particularly preferred embodiments, the alkyl group is methyl or ethyl. In embodiments wherein Q^1 or Q^2 is halo, the halo group is preferably fluoro. In certain preferred embodiments, one of Q^1 or Q^2 is H.

[0153] In preferred embodiments, the compounds of formula XXII have the following formula XXIV:



XXIV .

[0154] In preferred embodiments, the compounds of formula XXII have the following structure:



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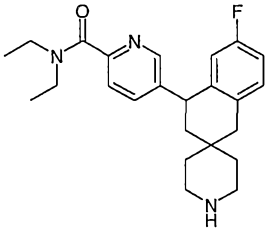

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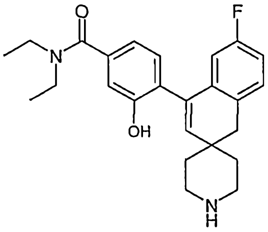

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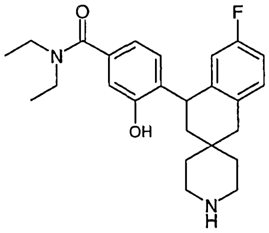

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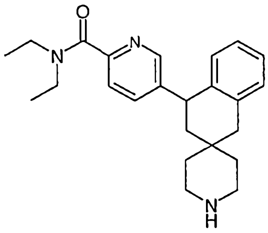

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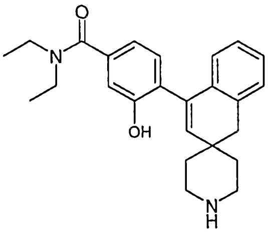

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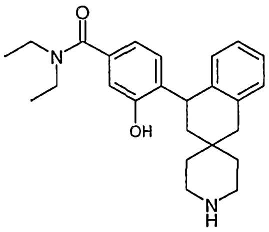

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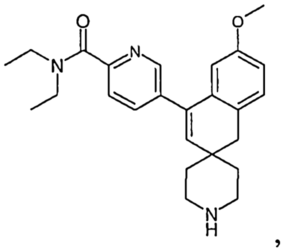

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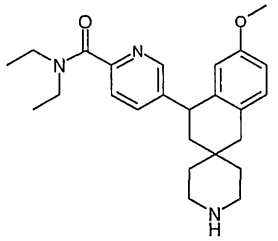

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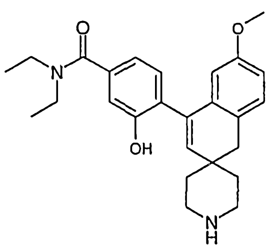

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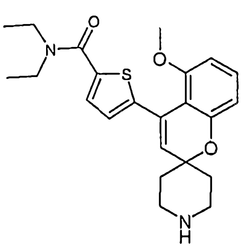

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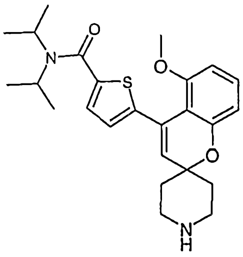

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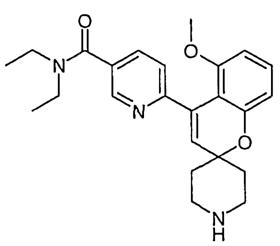
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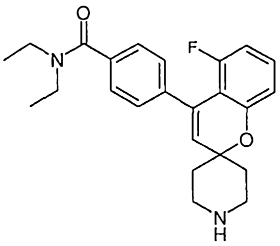
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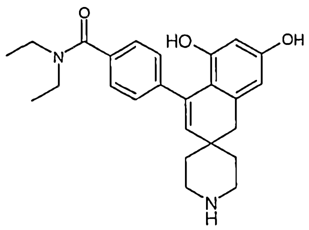
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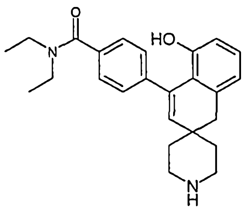
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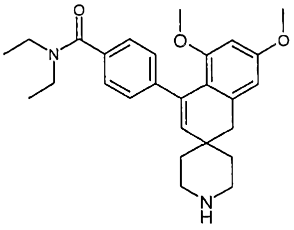
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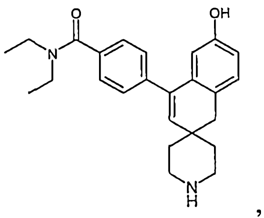
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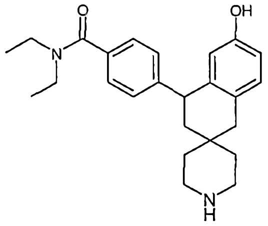
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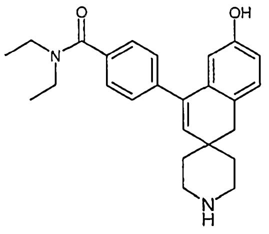
[0155] In preferred embodiments, the compounds of formula XXII have the following structure: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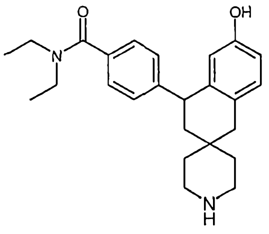
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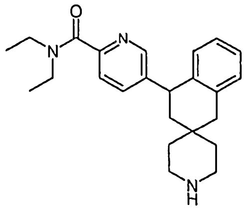
[0156] In certain embodiments, the above compounds may be resolved into any of their R and S, or (R,R), (S,S), (R,S), and (S,R) enantiomers, or partially resolved into any of their non-racemic mixtures.

[0157] More preferably, compounds of formula XXII have the following structures: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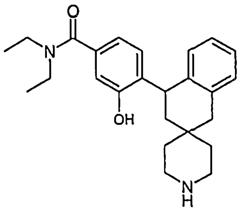
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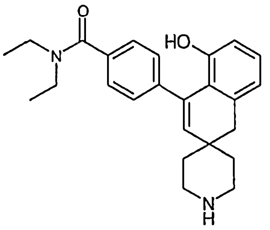
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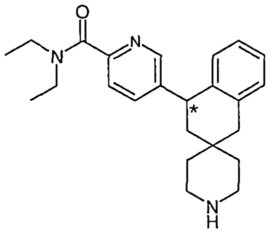
still more preferably



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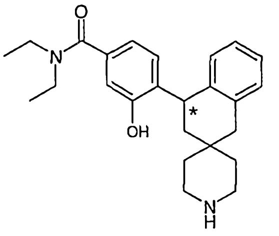

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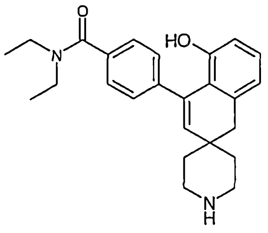

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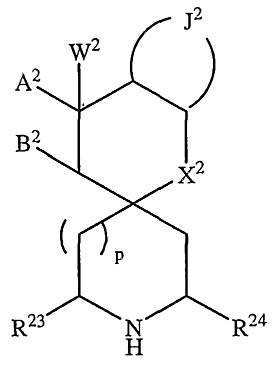
[0158] In an alternative embodiment, the invention is directed to compounds of formula XXV:



XXV ;

wherein:

W^2 is aryl optionally substituted with -C(=O)-alkyl or -C(=O)-aryl;

R^{23} and R^{24} are each independently H or alkyl;

p is 1 or 2;

A^2 and B^2 are each H, or together form a double bond;

X^2 is $-CH_2-$ or -O-; and

J^2 when taken together with the carbon atoms to which it is attached forms a 6-membered aryl ring substituted with 0-3 groups selected independently from hydroxy, alkoxy, $-S(=O)_2$-alkyl, $-S(=O)_2-NH_2$, $-S(=O)_2$-NH(alkyl), $-S(=O)_2$-N(alkyl)(alkyl), -C(=O)-N(alkyl)(alkyl), carboxy (-COOH), and -C(=O)-O-alkyl;

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof;

provided that the compound of formula XXV is other than 4-phenyl-spiro[2H,1-benzopyran-2,4'-piperidine].

[0159] In preferred embodiments of compounds of formula XXV, W^2 is aryl more preferably phenyl.

[0160] In embodiments wherein W^2 is substituted with -C(=O)-alkyl, the alkyl group is preferably lower alkyl, with alkyl groups of 1 to 3 carbons being more preferred, and with alkyl groups of 1 carbon being still more preferred. In particularly preferred embodiments, the alkyl group is methyl.

[0161] In embodiments wherein W^2 is substituted with or -C(=O)-aryl, preferably the aryl group is a 6-membered aryl ring, more preferably phenyl.

[0162] In preferred embodiments of formula XXV compounds, A^2 and B^2 together form a double bond.

[0163] In preferred embodiments of formula XXV compounds, X^2 is -O-.

[0164] In preferred embodiments of formula XXV compounds, p is 1.

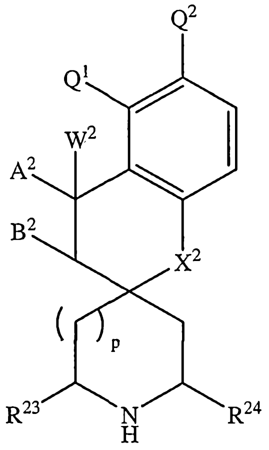
[0165] In preferred embodiments of formula XXV compounds, R^{23} and R^{24} are each independently H or alkyl, preferably H or C_1-C_3 alkyl, more preferably H or methyl, yet more preferably H.

[0166] In preferred embodiments of formula XXV compounds, J^2 when taken together with the carbon atoms to which it is attached forms a 6-membered aryl ring, preferably phenyl.

[0167] As set forth above, J^2 is substituted with 0-3 groups, preferably 0-2, yet more preferably 0-1 groups, selected independently from halo, heterocycloalkyl, hydroxy, alkoxy, $-S(=O)_2$-alkyl, $-S(=O)_2-NH_2$, $-S(=O)_2$-NH(alkyl), $-S(=O)_2$-N(alkyl)(alkyl), carboxy (-COOH), -C(=O)-O-alkyl, and N,N-dialkylaminocarbonyl (-

C(=O)-N(alkyl)(alkyl)). In embodiments wherein J^2 is substituted with alkoxy, -S(=O)$_2$-alkyl, -S(=O)$_2$-NH(alkyl), -S(=O)$_2$-N(alkyl)(alkyl), -C(=O)-O-alkyl, or N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl)), the alkyl group is preferably lower alkyl, with alkyl groups of 1 to 3 carbons being more preferred, and with alkyl groups of 1 to 2 carbons being still more preferred. In particularly preferred embodiments, the alkyl group is methyl or ethyl. In embodiments wherein J^2 is substituted with halo, the halo group is preferably fluoro.

[0168] In preferred embodiments, the compounds of formula XXV have the following formula XXVI:

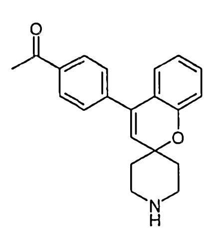


XXVI ;

wherein:

Q^1 and Q^2 are each independently H, hydroxy, alkoxy, -S(=O)$_2$-alkyl, -S(=O)$_2$-NH$_2$, -S(=O)$_2$-NH(alkyl), -S(=O)$_2$-N(alkyl)(alkyl), -C(=O)-N(alkyl)(alkyl), carboxy (-COOH), or -C(=O)-O-alkyl. In embodiments wherein Q^1 or Q^2 is alkoxy, -S(=O)$_2$-alkyl, -S(=O)$_2$-NH(alkyl), -S(=O)$_2$-N(alkyl)(alkyl), -C(=O)-O-alkyl, or N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl)), the alkyl group is preferably lower alkyl, with alkyl groups of 1 to 3 carbons being more preferred, and with alkyl groups of 1 to 2 carbons being still more preferred. **[0169]** In particularly preferred embodiments, the alkyl group is methyl or ethyl. In embodiments wherein Q^1 or Q^2 is halo, the halo group is preferably fluoro.

[0170] In preferred embodiments, the compounds of formula XXV have the following structure: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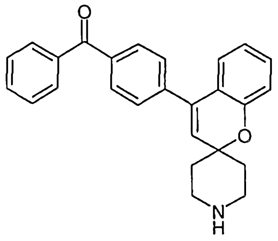
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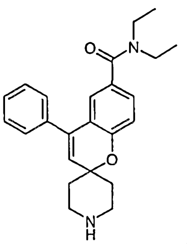
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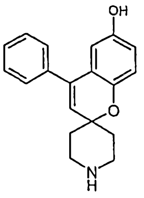
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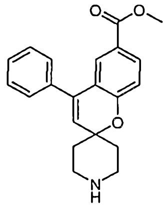
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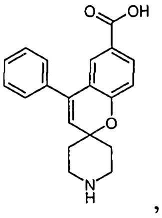
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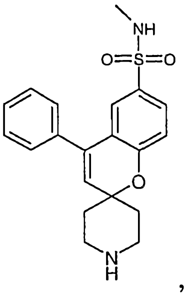
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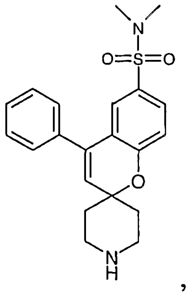
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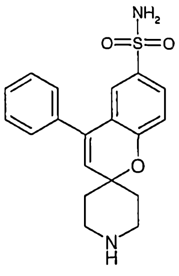
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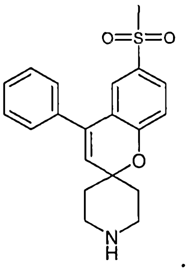
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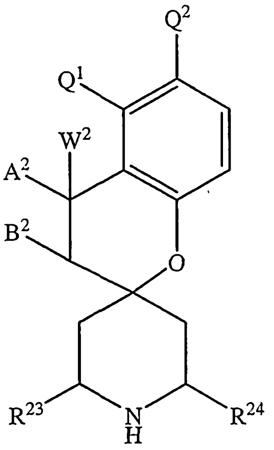
[0171] In an alternative embodiment, the invention is directed to compounds of formula XXVII:



XXVII

wherein:

W^2 is *para*-dialkylaminocarbonylphenyl, the phenyl group of which is further optionally substituted with 1-2 groups independently selected from tetrazolyl, N-alkyltetrazolyl, hydroxy, carboxy (-COOH), and aminocarbonyl (-C(=O)-NH_2);

R^{23} and R^{24} are each independently H or alkyl;

A^2 and B^2 are each H, or together form a double bond;

Q^1 and Q^2 are each independently H, hydroxy, alkoxy, haloalkoxy, halo, or heterocycloalkyl;

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof;

provided that :

when one of Q^1 and Q^2 is hydroxy and the other is H, or both Q^1 and Q^2 are hydroxy, then the phenyl group of W^2 is further substituted with 1-2 groups selected from tetrazolyl, N-alkyltetrazolyl, hydroxy, carboxy (-COOH), and aminocarbonyl (-C(=O)-NH_2);

when Q^1, Q^2, R^{23}, and R^{24} are each H and the phenyl group of W^2 is further substituted with one hydroxy, then A^2 and B^2 are each H;

when W^2 is *para*-dialkylaminocarbonylphenyl, then at least one of Q^1, Q^2, R^{23}, and R^{24} is other than H;

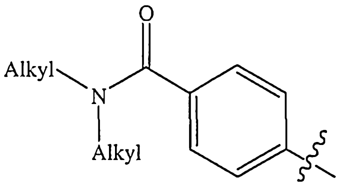
when W^2 is *para*-dialkylaminocarbonylphenyl, R^{23} and R^{24} are each H, and Q^2 is halo, then Q^1 is other than H or hydroxy;

when W^2 is *para*-dialkylaminocarbonylphenyl, R^{23} and R^{24} are each H, Q^1 is methoxy, cyclopropylmethoxy, cyclobutoxy, or cyclopentoxy, and Q^2 is H, then A^2 and B^2 are each H; and

when W^2 is *para*-dialkylaminocarbonylphenyl, R^{23} and R^{24} are each H, and Q^1 is H or OH, then Q^2 is other than methoxy, cyclopropylmethoxy, cyclobutoxy, or cyclopentoxy.

[0172] In preferred embodiments of formula XXVII compounds, W^2 is *para*-dialkylaminocarbonylphenyl. As set forth above, W^2 is further optionally substituted with 1-2 groups independently selected from tetrazolyl, N-alkyltetrazolyl, hydroxy, carboxy (-COOH), and aminocarbonyl (-C(=O)-NH_2). In preferred embodiments wherein W^2 is substituted with 1-2 groups, W^2 is preferably substituted with hydroxy.

[0173] In preferred embodiments of formula XXVII compounds, W^2 is:



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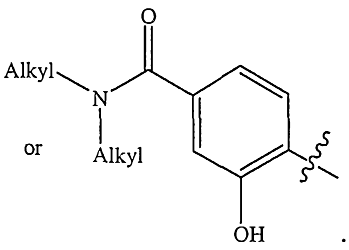

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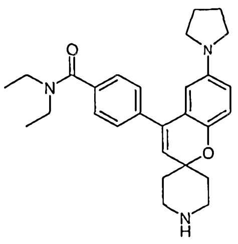
[0174] In embodiments in which W^2 is substituted with N,N-dialkylaminocarbonyl (-C(=O)-N(alkyl)(alkyl)), the alkyl group is preferably lower alkyl, with alkyl groups of 1 to 3 carbons being more preferred, and with alkyl groups of 2 carbons being still more preferred. In particularly preferred embodiments, the alkyl group is ethyl.

[0175] In preferred embodiments of formula XXVII compounds, R^{23} and R^{24} are each independently H or alkyl, preferably H or C_1-C_3 alkyl, more preferably H or methyl, yet more preferably H.

[0176] In preferred embodiments of formula XXVII compounds, Q^1 and Q^2 are each independently H, hydroxy, alkoxy, haloalkoxy, halo, or heterocycloalkyl. In embodiments where Q^1 or Q^2 is alkoxy, the alkoxy is preferably C_1-C_3 alkoxy, more preferably C_1 alkoxy, yet more preferably, methoxy. In embodiments where Q^1 or Q^2 is halo, the halo is preferably fluoro. In embodiments where Q^1 or Q^2 is heterocycloalkyl, the heterocycloalkyl is preferably a 5- or 6-membered ring heterocycloalkyl, more preferably pyrrolidinyl or morpholinyl. In embodiments where Q^1 or Q^2 is haloalkoxy, the alkoxy is substituted with one or more, preferably two or more, fluoro atoms.

[0177] In preferred embodiments, the compounds of formula XXVII, the compounds have the structures: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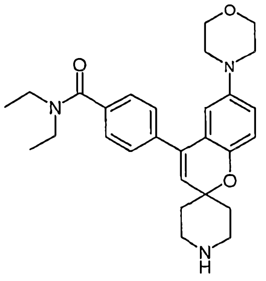
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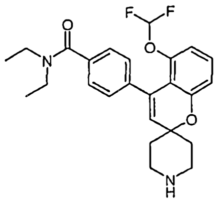
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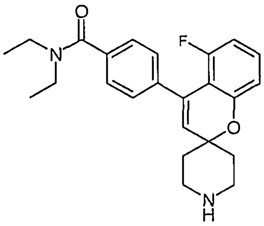
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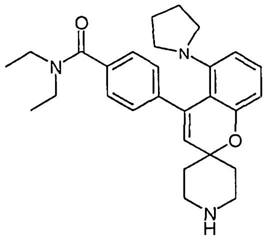
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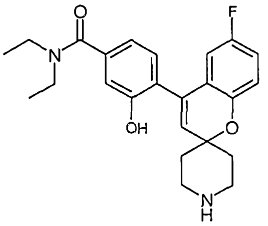
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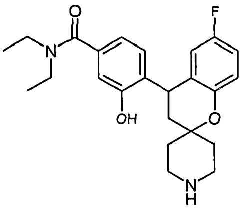
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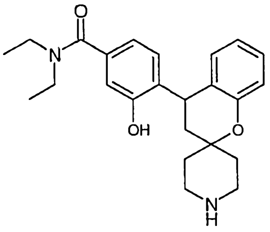
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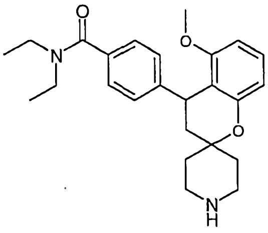
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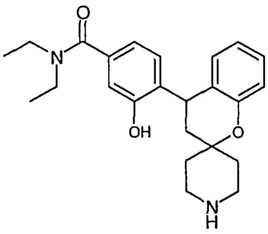
more preferably: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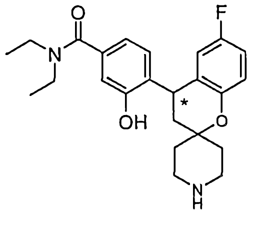
[0178] In some preferred embodiments, the compound of formula XXVII has the structure: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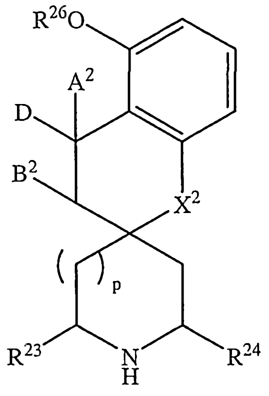
wherein denotes "*" a chiral center, as described herein above. In certain preferred embodiments, the compound is substantially enantiomerically pure.

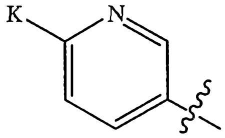
[0179] In an alternative embodiment, the invention is directed to compounds of formula XXVIII:



XXVIII ;

wherein:

D is:



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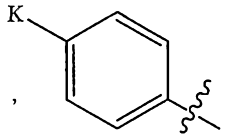

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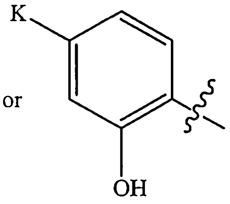


;

K is carboxy (-COOH), -C(=O)-O-alkyl, -S(=O)$_2$-N(alkyl)(alkyl), heteroaryl, alkylheteroaryl, aminocarbonyl (-C(=O)-NH$_2$), or N-alkylaminocarbonyl (-C(=O)-NH(alkyl));

R^{23}, R^{24}, and R^{26} are each independently H or alkyl;

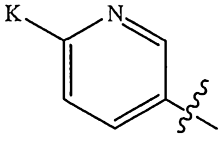
p is 1 or 2;

A^2 and B^2 are each H, or together form a double bond; and

X^2 is -CH$_2$- or -O-;

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof.

[0180] In preferred embodiments of formula XXVIII compounds, D is:



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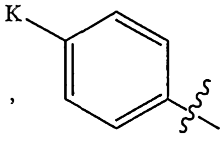

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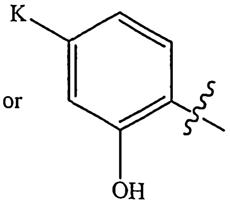

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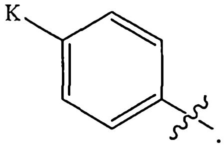
more preferably:



[0181] In preferred embodiments of formula XXVIII compounds wherein K is -S(=O)$_2$-N(alkyl)(alkyl), or N-alkylaminocarbonyl (-C(=O)-NH(alkyl)), the alkyl group independently is preferably lower alkyl, with alkyl groups of 1 to 3 carbons being more preferred, and with alkyl groups of 2 carbons being still more preferred. In particularly preferred embodiments, the alkyl group is ethyl.

[0182] In preferred embodiments of formula XXVIII compounds wherein K is -C(=O)-O-alkyl or alkyltetrazolyl, the alkyl group independently is preferably lower alkyl, with alkyl groups of 1 to 3 carbons being more preferred, and with alkyl groups of 1-2 carbon being still more preferred. In particularly preferred embodiments, the alkyl group is methyl or ethyl.

[0183] In preferred embodiments of formula XXVIII compounds wherein K is heteroaryl or alkylheteroaryl, the heteroaryl group is preferably a 5-membered ring heteroaryl, more preferably a tetrazolyl ring.

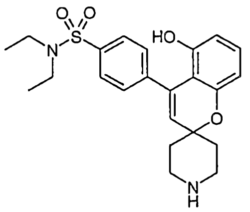
[0184] In preferred embodiments of formula XXVIII compounds, A^2 and B^2 together form a double bond.

[0185] In preferred embodiments of formula XXVIII compounds, p is 1.

[0186] In preferred embodiments of formula XXVIII compounds, X^2 is -O-.

[0187] In preferred embodiments of formula XXVIII compounds, R^{23}, R^{24}, and R^{26} are each independently H or alkyl, preferably H or C_1-C_3 alkyl, more preferably H or methyl, yet more preferably H. In certain preferred embodiments, one of R^{23} and R^{24} is H and the other is alkyl.

[0188] In preferred embodiments, the compounds of formula XXVIII, have the structures: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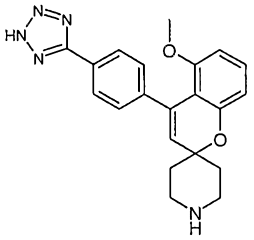
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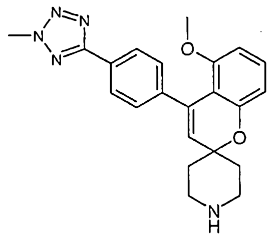
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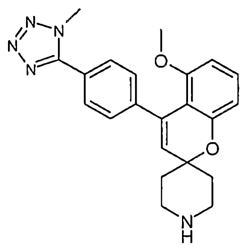
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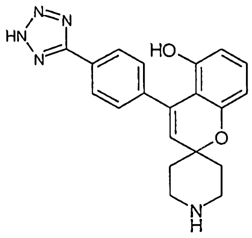
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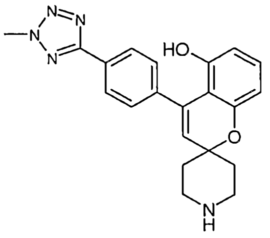
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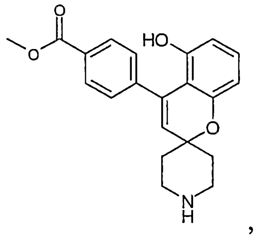
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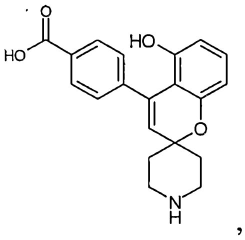
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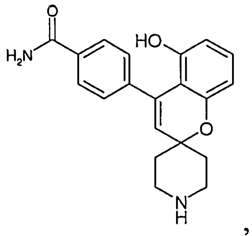
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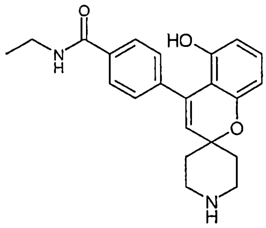
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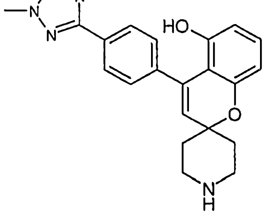
more preferably: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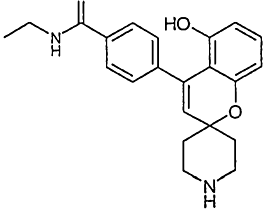
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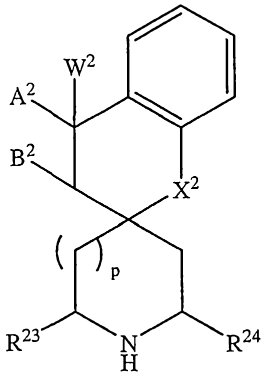
[0189] In an alternative embodiment, the invention is directed to compounds of formula XXIX:



XXIX ;

wherein:

W^2 is *para*-N(alkyl),N(alkyl-Z)aminocarbonylaryl or *para*-N(alkyl),N(alkyl-Z)aminocarbonylheteroaryl, wherein the aryl or heteroaryl ring of W^2 is substituted with 0-2 groups selected independently from hydroxy and alkoxy;

Z is alkoxy, alkylamino, or dialkylamino;

R^{23} and R^{24} are each independently H or alkyl;

p is 1 or 2;

A^2 and B^2 are each H, or together form a double bond; and

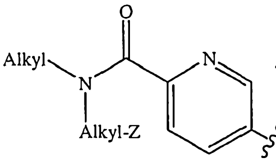
X^2 is $-CH_2-$ or -O-;

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof.

[0190] In preferred embodiments of formula XXIX compounds, W^2 is *para*-N(alkyl),N(alkyl-Z)-aminocarbonylaryl or *para*-N(alkyl),N(alkyl-Z)-aminocarbonylheteroaryl. When W^2 is *para*-N(alkyl),N(alkyl-Z)aminocarbonylaryl, the aryl ring is preferably phenyl. When *para*-N(alkyl),N(alkyl-Z)aminocarbonylheteroaryl, the heteroaryl ring is preferably pyridyl.

[0191] As set forth above, W^2 is substituted with 0-2 groups selected independently from selected independently from hydroxy and alkoxy. In preferred embodiments, W^2 is substituted with 0-1 groups, selected independently from hydroxy and alkoxy, more preferably hydroxy.

[0192] In preferred embodiments of formula XXIX compounds, W^2 is: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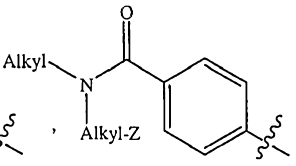
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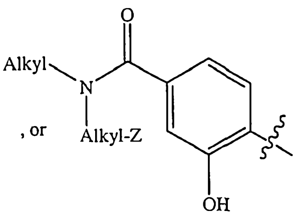
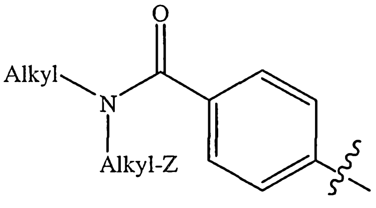

;

more preferably: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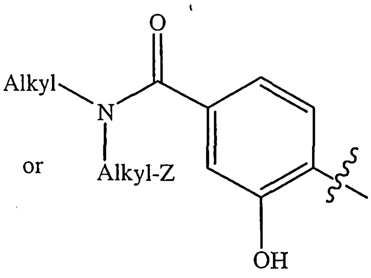
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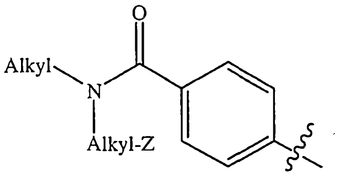
more preferably still:


.

[0193] In embodiments in which W^2 is *para*-N(alkyl),N(alkyl-Z)aminocarbonylaryl or *para*-N(alkyl),N(alkyl-Z)aminocarbonylheteroaryl, the alkyl group is preferably lower alkyl, with alkyl groups of 1 to 3 carbons being more preferred, and with alkyl groups of 2 carbons being still more preferred. In particularly preferred embodiments, the alkyl group is ethyl.

[0194] In preferred embodiments of formula XXIX compounds, p is 1.

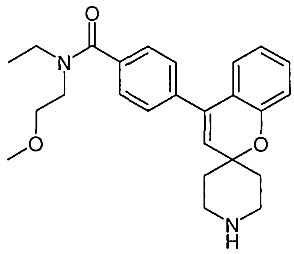
[0195] In preferred embodiments of formula XXIX compounds, A^2 and B^2 together form a double bond.

[0196] In preferred embodiments of formula XXIX compounds, X^2 is -O-.

[0197] In preferred embodiments of formula XXIX compounds, R^{23} and R^{24} are each independently H or alkyl, preferably H or C_1-C_3 alkyl, more preferably H or methyl. In certain preferred embodiments, one of R^{23} and R^{24} is H and the other is alkyl.

[0198] In preferred embodiments of formula XXIX compounds, Z is alkoxy, alkylamino, or dialkylamino, preferably alkoxy. In embodiments wherein Z is alkoxy, alkylamino, or dialkylamino the alkyl group is preferably lower alkyl, with alkyl groups of 1 to 3 carbons being more preferred, and with alkyl groups of 1 carbon being still more preferred. In particularly preferred embodiments, the alkyl group is methyl.

[0199] In certain embodiments, the compounds of formula XXIX have the structures:



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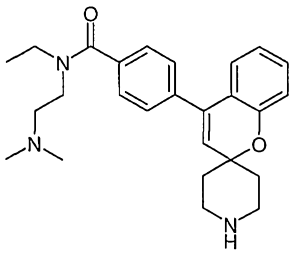

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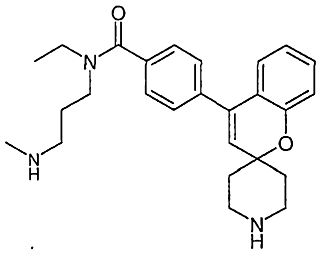

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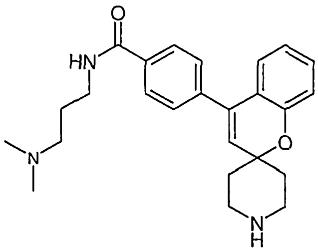

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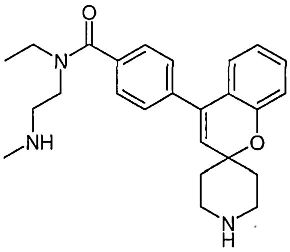
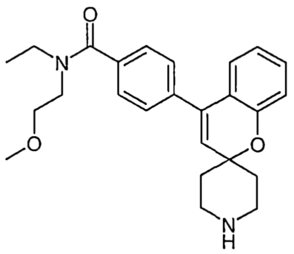


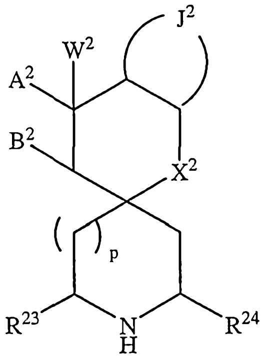
;

more preferably:



.

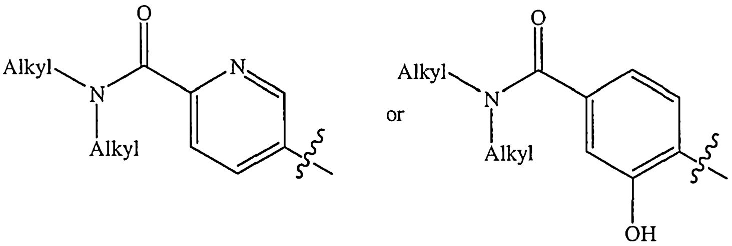
[0200] In an alternative embodiment, the invention is directed to compounds of formula XXX:



XXX ;

wherein:

W^2 is:



;

R^{23} and R^{24} are each independently H or alkyl;

p is 1 or 2;

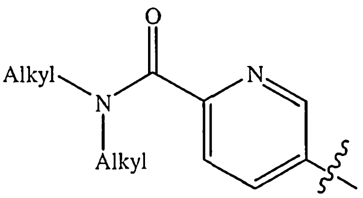
A^2 and B^2 are each H, or together form a double bond;

X^2 is $-CH_2-$ or -O-; and

J^2 when taken together with the carbon atoms to which it is attached forms a 6-membered aryl ring substituted with 1-3 groups selected independently from halo or haloalkoxy;

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof;

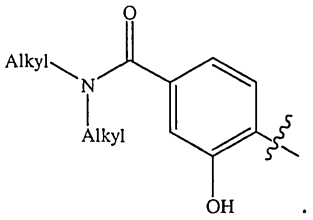
provided that when W^2 is:



;

then the aryl ring of J^2 is substituted with at least one haloalkoxy.

[0201] In preferred embodiments of compounds of formula XXX, W^2 is:

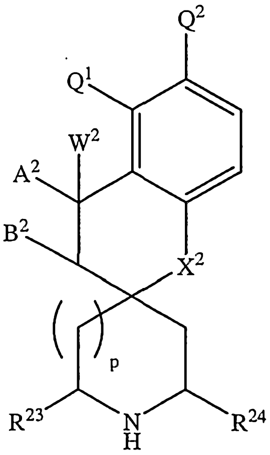


[0202] In preferred embodiments of formula XXX compounds, p is 1.

[0203] In preferred embodiments of formula XXX compounds, R^{23} and R^{24} are each independently H or alkyl, preferably H or C_1-C_3 alkyl, more preferably H or methyl, yet more preferably H. In certain preferred embodiments, one of R^{23} and R^{24} is H and the other is alkyl.

[0204] In preferred embodiments of formula XXX compounds, J^2 when taken together with the carbon atoms to which it is attached forms a 6-membered aryl ring, preferably a phenyl ring. In embodiments wherein J^2 is substituted with 1-3 groups selected independently from halo or haloalkoxy, the halo group of halo or haloalkoxy is preferably fluoro.

[0205] In preferred embodiments, the compounds of formula XXX have the following formula XXXI:

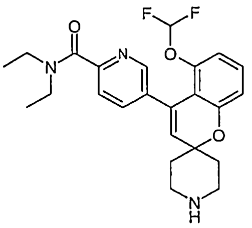


XXXI

wherein:

Q^1 and Q^2 are each independently H, halo, or haloalkoxy, provided that at least one of Q^1 and Q^2 is other than H. In embodiments wherein Q^1 or Q^2 is halo or haloalkoxy, the halo group of halo or haloalkoxy is preferably fluoro.

[0206] In preferred embodiments, the compounds of formula XXX have the structures:



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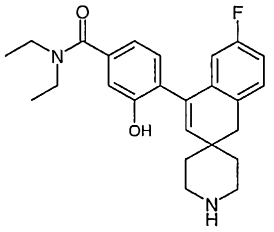

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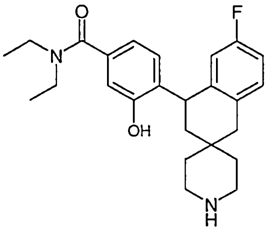

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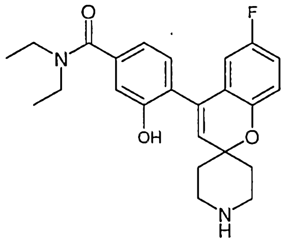

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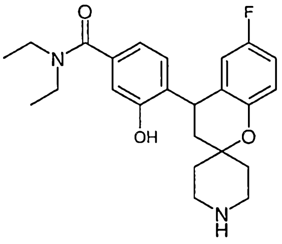

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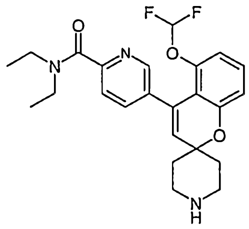
more preferably:



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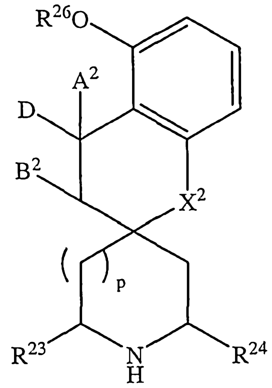
[0207] In an alternative embodiment, the invention is directed to compounds of formula XXXII:



XXXII

wherein:

D is N(alkyl),N(alkyl)aminocarbonylheteroaryl;

R^{23}, R^{24}, and R^{26} are each independently H or alkyl;

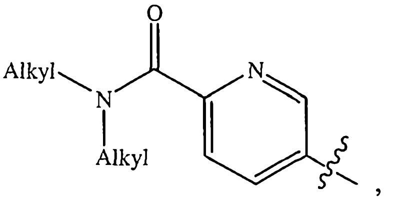
p is 1 or 2;

A^2 and B^2 are each H, or together form a double bond; and

X^2 is $-CH_2-$ or -O-;

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof;

provided that when D is:



and X^2 is –O-, then A^2 and B^2 are each H.

[0208] In embodiments of formula XXXII compounds wherein D is N(alkyl),N(alkyl)aminocarbonylheteroaryl, the heteroaryl group is preferably pyridyl or thienyl.

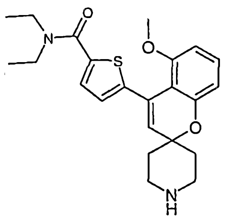
[0209] In embodiments of formula XXXII compounds wherein D is N(alkyl),N(alkyl)aminocarbonylheteroaryl, the alkyl group is preferably lower alkyl, with alkyl groups of 1 to 3 carbons being more preferred, and with alkyl groups of 2-3 carbons being still more preferred. In particularly preferred embodiments, the alkyl group is ethyl or isopropyl.

[0210] In preferred embodiments of formula XXXII compounds, A^2 and B^2 are each H.

[0211] In preferred embodiments of formula XXXII compounds, X^2 is -O-.

[0212] In preferred embodiments of formula XXXII compounds, R^{23} , R^{24} , and R^{26} are each independently H or alkyl, preferably H or C_1-C_3 alkyl, more preferably H or methyl, yet more preferably H. In certain preferred embodiments, one of R^{23} and R^{24} is H and the other is alkyl.

[0213] In certain embodiments, the compounds of formula XXXII, have the structures: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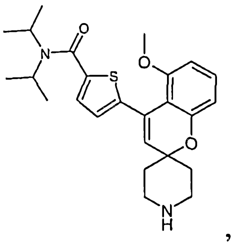
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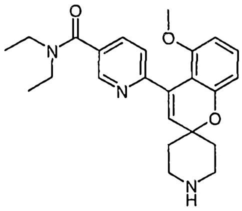
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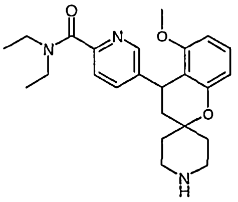
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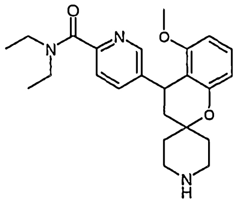
preferably: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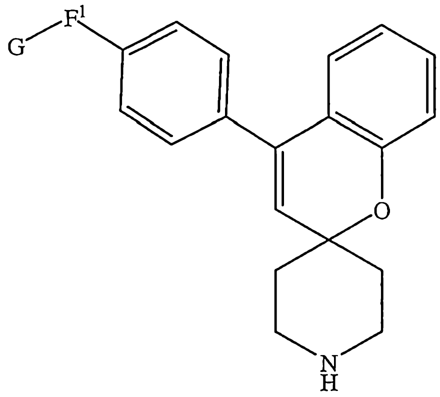
[0214] In another embodiment, the present invention is directed, in part, to compounds of formula XXXIII:



XXXIII ;

wherein:

F^1 is heteroaryl; and

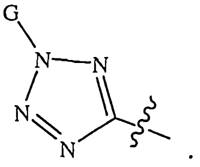
G is C_{1-6}alkylene substituted with NH_2, NHC(=O)alkyl, NH(C(O)N(H)alkyl, or $NHS(=O)_2$alkyl;

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof.

[0215] In formula XXXIII above, F^1 is heteroaryl, preferably a 5- or 6-membered heteroaryl having 1 to 4 heteroatoms, with 2 to 4 heteroaroms being more preferred. In certain more preferred embodiments, F^1 is a 5-membered heteroaryl, still more preferably a tetrazole.

[0216] Also in formula XXXIII above, G is C_{1-6}alkylene substituted with NH_2, NHC(=O)alkyl, NH(C(O)N(H)alkyl, or $NHS(=O)_2$alkyl. In preferred embodiments, G is C_{1-6}alkylene substituted with NH_2. In other preferred embodiments, G is C_{1-6}alkylene substituted with NHC(=O)alkyl. In still other preferred embodiments, G is C_{1-6}alkylene substituted with $NHS(=O)_2$alkyl. More preferably, G is C_{1-6}alkylene substituted with NH_2.

[0217] In some preferred embodiments of compounds of formula XXXIII, F^1-G is:



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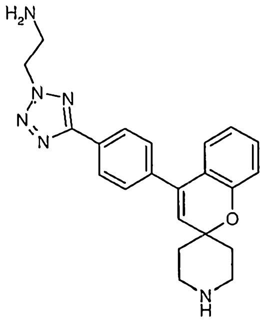
[0218] In certain preferred embodiments, the compounds of formula XXXIII are selected from the group consisting of:



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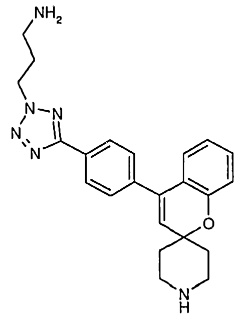

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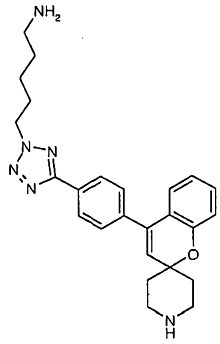

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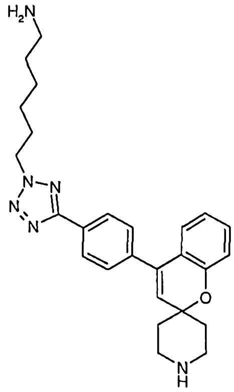

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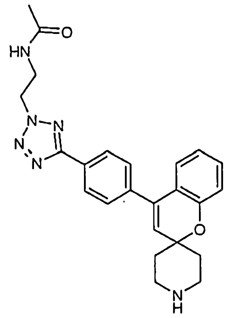
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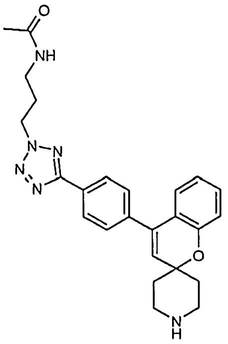
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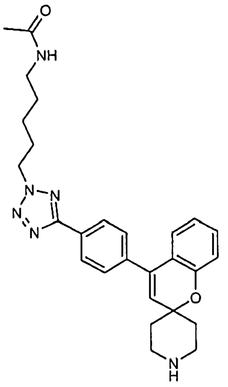
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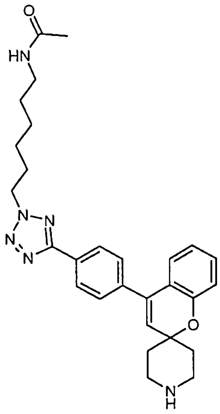
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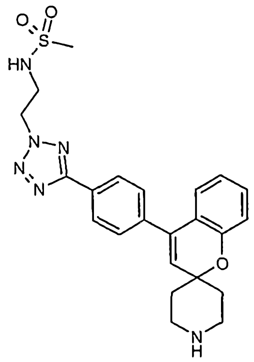
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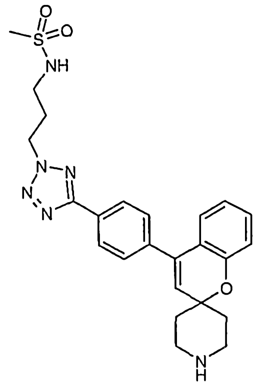
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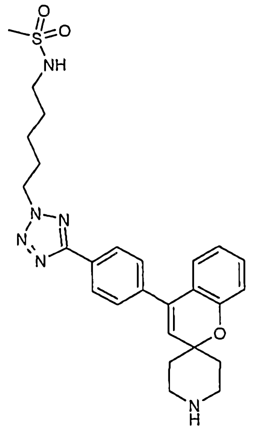
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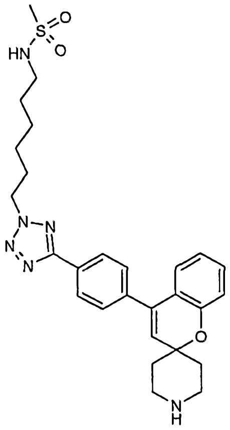
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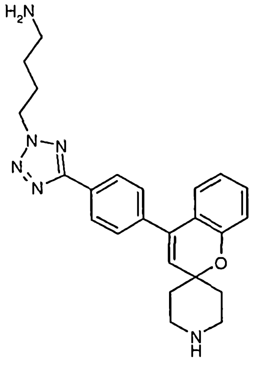
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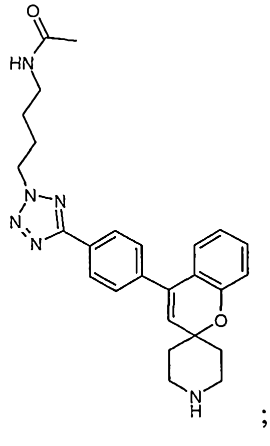
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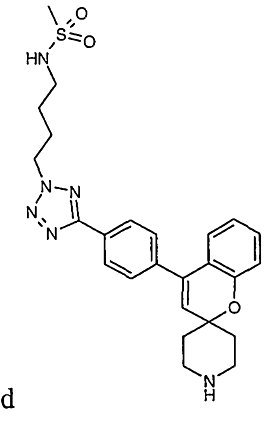
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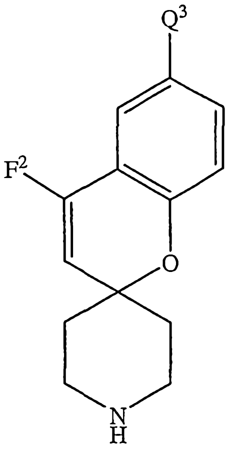
[0219] In one embodiment, the present invention is directed, in part, to compounds of formula XXXIV:



XXXIV ;

wherein:

F^2 is aryl or heteroaryl; and

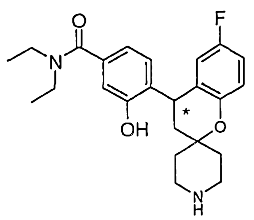
Q^3 is hydroxy or alkoxy;

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof.

[0220] In formula XXXIV above, F^2 is aryl or heteroaryl. When F^2 is aryl, preferably it is C_{6-10}aryl, more preferably C_6aryl, with phenyl being even more preferred. When F^2 is heteroaryl, preferably it is C_{6-10}heteroaryl, with pyridyl or benzothiophenyl being more preferred.

[0221] Also in formula XXXIV above, Q^3 is hydroxy or alkoxy, preferably hydroxy.

[0222] In another embodiment, the compound of the invention is selected from the group consisting of: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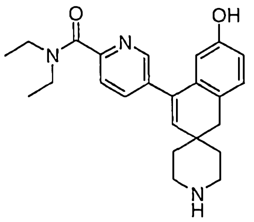
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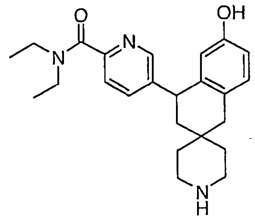
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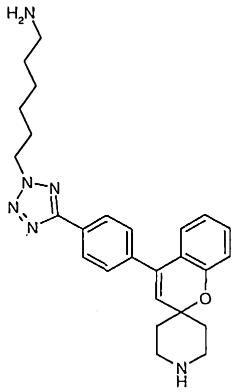
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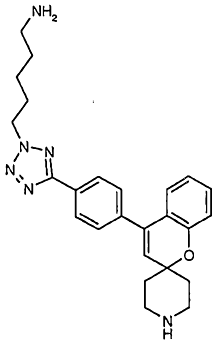
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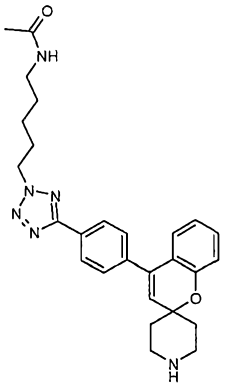
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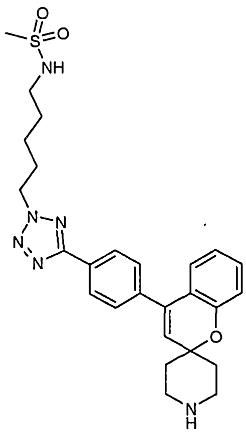
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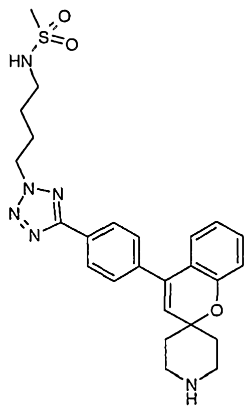
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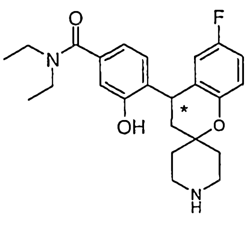
more preferably from the group consisting of: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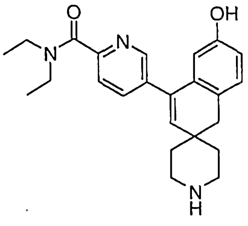
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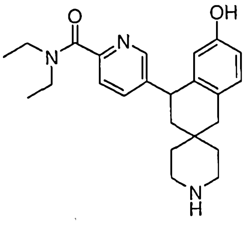
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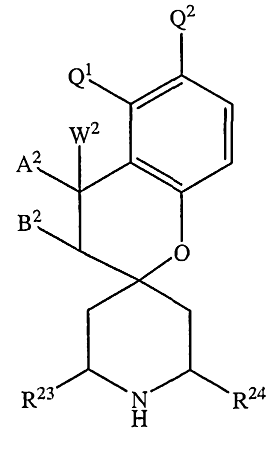
or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof.

[0223] The present invention is further directed to pharmaceutical compositions, comprising:

a pharmaceutically acceptable carrier; and an effective amount of a compound as described herein including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV. In certain embodiments, the pharmaceutical composition further comprises an effective amount of at least one opioid.

[0224] In a preferred embodiment, the invention is directed to pharmaceutical compositions, comprising:

a pharmaceutically acceptable carrier; and an effective amount of a compound of formula XXVIIA:



XXVIIA

wherein:

W^2 is *para*-dialkylaminocarbonylphenyl, the phenyl group of which is further optionally substituted with 1-2 groups independently selected from tetrazolyl, N-alkyltetrazolyl, hydroxy, carboxy (-COOH), and aminocarbonyl (-C(=O)-NH_2);

R^{23} and R^{24} are each independently H or alkyl;

A^2 and B^2 are each H, or together form a double bond;

Q^1 and Q^2 are each independently H, hydroxy, alkoxy, haloalkoxy, halo, or heterocycloalkyl;

or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, or N-oxide thereof;

provided that :

when one of Q^1 and Q^2 is hydroxy and the other is H, then the phenyl group of W^2 is further substituted with 1-2 groups selected from tetrazolyl, N-alkyltetrazolyl, hydroxy, carboxy (-COOH), and aminocarbonyl (-C(=O)-NH_2);

when Q^1, Q^2, R^{23}, and R^{24} are each H and the phenyl group of W^2 is further substituted with one hydroxy, then A^2 and B^2 are each H;

when W^2 is *para*-dialkylaminocarbonylphenyl, then at least one of Q^1, Q^2, R^{23}, and R^{24} is other than H;

when W^2 is *para*-dialkylaminocarbonylphenyl, R^{23} and R^{24} are each H, and Q^2 is halo, then Q^1 is other than H;

when W^2 is *para*-dialkylaminocarbonylphenyl, R^{23} and R^{24} are each H, Q^1 is methoxy, cyclopropylmethoxy, cyclobutoxy, or cyclopentoxy, and Q^2 is H, then A^2 and B^2 are each H; and

when W^2 is *para*-dialkylaminocarbonylphenyl, R^{23} and R^{24} are each H, and Q^1 is H, then Q^2 is other than methoxy, cyclopropylmethoxy, cyclobutoxy, or cyclopentoxy.

[0225] Compounds as described herein may be useful as analgesic agents for use during general anesthesia and monitored anesthesia care. Combinations of agents with different properties are often used to achieve a balance of effects needed to maintain the anaesthetic state (*e.g.*, amnesia, analgesia, muscle relaxation and sedation). Included in this combination are inhaled anesthetics, hypnotics, anxiolytics, neuromuscular blockers and opioids.

[0226] In any of the above teachings, a compound as described herein may be either a compound of one of the formulae herein described, or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, N-oxide or isomorphic crystalline form thereof.

[0227] The compounds employed in the methods and compositions of the present invention may exist in prodrug form. As used herein, "prodrug" is intended to include any covalently bonded carriers which release the active parent drug, for example, as according to formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV, or other formulas or compounds as described herein, such as for example, compounds of formula XXVIIA, *in vivo* when such prodrug is administered to a mammalian subject. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (*e.g.*, solubility, bioavailability, manufacturing, etc.), the compounds described herein may, if desired, be delivered in prodrug form. Thus, the present invention contemplates compositions and methods involving prodrugs. Prodrugs of the compounds employed in the present invention, for example formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV, may be prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound.

[0228] Accordingly, prodrugs include, for example, compounds described herein in which a hydroxy, amino, or carboxy group is bonded to any group that, when the prodrug is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or carboxylic acid, respectively. Examples include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups; and alkyl, carbocyclic, aryl, and alkylaryl esters such as methyl, ethyl, propyl, iso-propyl, butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, phenyl, benzyl, and phenethyl esters, and the like.

[0229] Compounds described herein may contain one or more asymmetrically substituted carbon atoms, and may be isolated in optically active or racemic forms. Thus, all chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. It is well known in the art how to prepare and isolate such optically active forms. For example, mixtures of stereoisomers may be separated by standard techniques including, but not limited to, resolution of racemic forms, normal, reverse-phase, and chiral chromatography, preferential salt formation, recrystallization, and the like, or by chiral synthesis either from chiral starting materials or by deliberate synthesis of target chiral centers.

[0230] The compounds as herein described may be prepared in a number of ways well known to those skilled in the art. The compounds can be synthesized, for example, by the methods described below, or variations thereon as appreciated by the skilled artisan. All processes disclosed in association with the present invention are contemplated to be practiced on any scale, including milligram, gram, multigram, kilogram, multikilogram or commercial industrial scale.

[0231] As will be readily understood, functional groups present may contain protecting groups during the course of synthesis. Protecting groups are known *per se* as chemical functional groups that can be selectively appended to and removed from functionalities, such as hydroxyl groups and carboxyl groups. These groups are present in a chemical compound to render such functionality inert to chemical reaction conditions to which the compound is exposed. Any of a variety of protecting groups may be employed with the present invention. Preferred protecting groups include the benzyloxycarbonyl group and the tert-butyloxycarbonyl group. Other preferred protecting groups that may be employed in accordance with the present invention may be described in Greene, T.W. and Wuts, P.G.M., *Protective Groups in Organic Synthesis* 2d. Ed., Wiley & Sons, 1991, the disclosures of which are hereby incorporated herein by reference, in their entirety.

[0232] The δ agonist compounds as described herein may be administered by any means that results in the contact of the active agent with the agent's site of action in the body of a patient. The compounds may be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. For example, they may be administered as the sole active agent in a pharmaceutical composition, or they can be used in combination with other therapeutically active ingredients including, for example, opioid analgesic agents. In such combinations, selected compounds as described herein may provide equivalent or even enhanced therapeutic activity such as, for example, pain ameliorization, while providing reduced adverse side effects associated with opioids, such as addiction or pruritus, by lowering the amount of opioid required to achieve a therapeutic effect.

[0233] The compounds are preferably combined with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice as described, for example, in *Remington's Pharmaceutical Sciences* (Mack Publishing Co., Easton, PA, 1980), the disclosures of which are hereby incorporated herein by reference, in their entirety.

[0234] In addition to the pharmaceutical carrier, the compounds of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV, may be co-administered with at least one opioid, preferably a μ opioid receptor modulator compound. In certain embodiments, the combination of the compounds of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV, with at least one opioid, preferably a μ opioid receptor modulator compound, provides a synergistic analgesic effect. The utility of the instant combination product may be determined by those skilled in the art using established animal models. Suitable opioids include, without limitation, alfentanil, allylprodine, alphaprodine, anileridine, benzyl-morphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioaphetylbutyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacylmorphan, lofentanil, loperamide, meperidine (pethidine), meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpinanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phanazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propiram, propoxyphene, sulfentanil, tilidine, tramadol, diastereoisomers thereof, pharmaceutically acceptable salts thereof, complexes thereof; and mixtures thereof.

[0235] The pain ameliorating and/or opioid combination products of the present compositions may further include one or more other active ingredients that may be conventionally employed in analgesic and/or cough-cold-antitussive combination products. Such conventional ingredients include, for example, aspirin, acetaminophen, phenylpropanolamine, phenylephrine, chlorpheniramine, caffeine, and/or guaifenesin. Typical or conventional ingredients that may be included in the opioid component are described, for example, in the *Physicians' Desk Reference*, 1999, the disclosure of which is hereby incorporated herein by reference, in its entirety.

[0236] In addition, the opioid component may further include one or more compounds that may be designed to enhance the analgesic potency of the opioid and/or to reduce analgesic tolerance development. Such compounds include, for example, dextromethorphan or other NMDA antagonists (Mao, M. J. *et al., Pain* **1996**, *67*, 361), L-364,718 and other CCK antagonists (Dourish, C.T. *et al., Eur J Pharmacol* **1988**, *147*, 469), NOS inhibitors (Bhargava, H.N. *et al., Neuropeptides* **1996**, *30*, 219), PKC inhibitors (Bilsky, E.J. *et al., J Pharmacol Exp Ther* **1996**, *277*, 484), and dynorphin antagonists or antisera (Nichols, M.L. *et al., Pain* **1997**, *69*, 317). The disclosures of each of the foregoing documents are hereby incorporated herein by reference, in their entireties.

[0237] Other opioids, optional conventional opioid components, and optional compounds for enhancing the analgesic potency of the opioid and/or for reducing analgesic tolerance development, that may be employed in the methods and compositions of the present invention, in addition to those exemplified above, would be readily apparent to one of ordinary skill in the art, once armed with the teachings of the present disclosure.

[0238] Compounds as described herein can be administered to a mammalian host in a variety of forms adapted to the chosen route of administration, *e.g.*, orally or parenterally. Parenteral administration in this respect includes administration by the following routes: intravenous, intramuscular, subcutaneous, rectal, intraocular, intrasynovial, transepithelial including transdermal, ophthalmic, sublingual and buccal; topically including ophthalmic, dermal, ocular, rectal, and nasal inhalation via insufflation aerosol.

[0239] The active compound may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compound may be incorporated with excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should preferably contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be, for example, from about 2 to about 6% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is preferably such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention may be prepared so that an oral dosage unit form contains from about 0.1 to about 1000 mg of active compound.

[0240] The tablets, troches, pills, capsules and the like may also contain one or more of the following: a binder, such as gum tragacanth, acacia, corn starch or gelatin; an excipient, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; or a flavoring agent, such as peppermint, oil of wintergreen or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring, such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form is preferably pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and formulations.

[0241] The active compound may also be administered parenterally or intraperitoneally. Solutions of the active compound as a free base or a pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. A dispersion can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

[0242] The pharmaceutical forms suitable for injectable use include, for example, sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form is preferably sterile and fluid to provide easy syringability. It is preferably stable under the conditions of manufacture and storage and is preferably preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier may be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, liquid polyethylene glycol and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of a dispersion, and by the use of surfactants. The prevention of the action of microorganisms may be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions may be achieved by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0243] Sterile injectable solutions may be prepared by incorporating the active compound in the required amount, in the appropriate solvent, with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions may be prepared by incorporating the sterilized active ingredient into a sterile vehicle that contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation may include vacuum drying and the freeze-drying technique that yield a powder of the active ingredient, plus any additional desired ingredient from the previously sterile-filtered solution thereof.

[0244] The therapeutic compounds of this invention may be administered to a patient alone or in combination with a pharmaceutically acceptable carrier. As noted above, the relative proportions of active ingredient and carrier may be determined, for example, by the solubility and chemical nature of the compound, chosen route of administration and standard pharmaceutical practice.

[0245] The dosage of the compounds as described herein that will be most suitable for prophylaxis or treatment will vary with the form of administration, the particular compound chosen and the physiological characteristics of the particular patient under treatment. Generally, small dosages may be used initially and, if necessary, increased by small increments until the desired effect under the circumstances is reached. The therapeutic human dosage, based on physiological studies using rats, may generally range from about 0.01 mg to about 100 mg/kg of body weight per day, and all combinations and subcombinations of ranges and specific dosages therein. Alternatively, the therapeutic human dosage may be from about 0.4 mg to about 10 g or higher, and may be administered in several different dosage units from once to several times a day. Generally speaking, oral administration may require higher dosages.

[0246] It will be further appreciated that the amount of the compound, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

[0247] The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, *e.g.,* into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

[0248] The dose may also be provided by controlled release of the compound, by techniques well known to those in the art.

[0249] The compounds as described herein may also be formulated with other optional active ingredients, in addition to or instead of the optional opioids, and in addition to the optional pharmaceutical-acceptable carriers. Other active ingredients include, but are not limited to, antibiotics, antivirals, antifungals, anti-inflammatories, including steroidal and non-steroidal anti-inflammatories, anesthetics and mixtures thereof. Such additional ingredients include any of the following:

a. Antibacterial agents

[0250] Aminoglycosides, such as Amikacin, Apramycin, Arbekacin, Bambermycins, Butirosin, Dibekacin, Dihydrostreptomycin, Fortimicin(s), Fradiomycin, Gentamicin, Ispamicin, Kanamycin, Micronomicin, Neomycin, Neomycin Undecylenate, Netilmicin, Paromomycin, Ribostamycin, Sisomicin, Spectinomycin, Streptomycin, Streptonicozid and Tobramycin;

Amphenicols, such as Azidamfenicol, Chloramphenicol, Chloramphenicol Palmirate, Chloramphenicol Pantothenate, Florfenicol, Thiamphenicol;

Ansamycins, such as Rifamide, Rifampin, Rifamycin and Rifaximin;

β-Lactams;

Carbapenems, such as Imipenem;

Cephalosporins, such as 1-Carba (dethia) Cephalosporin, Cefactor, Cefadroxil, Cefamandole, Cefatrizine, Cefazedone, Cefazolin, Cefixime, Cefmenoxime, Cefodizime, Cefonicid, Cefoperazone, Ceforanide, Cefotaxime, Cefotiam, Cefpimizole, Cefpirimide, Cefpodoxime Proxetil, Cefroxadine, Cefsulodin, Ceftazidime, Cefteram, Ceftezole, Ceftibuten, Ceftizoxime, Ceftriaxone, Cefuroxime, Cefuzonam, Cephacetrile Sodium, Cephalexin, Cephaloglycin, Cephaloridine, Cephalosporin, Cephalothin, Cephapirin Sodium, Cephradine and Pivcefalexin;

Cephamycins such as Cefbuperazone, Cefmetazole, Cefminox, Cefetan and Cefoxitin;

Monobactams such as Aztreonam, Carumonam and Tigemonan;

Oxacephems such as Flomoxef and Moxolactam;

Penicillins such as Amidinocillin, Amdinocillin, Pivoxil, Amoxicillin, Ampicillan, Apalcillin, Aspoxicillin, Azidocillan, Azlocillan, Bacampicillin, Benzylpenicillinic Acid, Benzylpenicillin, Carbenicillin, Carfecillin, Carindacillin, Clometocillin, Cloxacillin, Cyclacillin, Dicloxacillin, Diphenicillin, Epicillin, Fenbenicillin, Floxicillin, Hetacillin, Lenampicillin, Metampicillin, Methicillin, Mezlocillin, Nafcillin, Oxacillin, Penamecillin,, Penethamate Hydriodide, Penicillin G Benethamine, Penicillin G Benzathine, Penicillin G Benzhydrylamine, Penicillin G Calcium, Penicillin G Hydragamine, Penicillin G Potassium, Penicillin G. Procaine, Penicillin N, Penicillin O, Penicillin V, Penicillin V Benzathine, Penicillin V Hydrabamine, Penimepicycline, Phenethicillin, Piperacillin, Pivapicillin, Propicillin, Quinacillin, Sulbenicillin, Talampicillin, Temocillin and Ticarcillin;

Lincosumides such as Clindamycin and Lincomycin;

Macrolides such as Azithromycin, Carbomycin, Clarithromycin, Erythromycin(s) and Derivatives, Josamycin, Leucomycins, Midecamycins, Miokamycin, Oleandomycin, Primycin, Rokitamycin, Rosaramicin, Roxithromycin, Spiramycin and Troleandomycin;

Polypeptides such as Amphomycin, Bacitracin, Capreomycin, Colistin, Enduracidin, Enviomycin, Fusafungine, Gramicidin(s), Gramicidin S, Mikamycin, Polymyxin, Polymyxin β-Methanesulfonic Acid, Pristinamycin, Ristocetin, Teicoplanin, Thiostrepton, Tuberactinomycin, Tyrocidine, Tyrothricin, Vancomycin, Viomycin(s), Virginiamycin and Zinc Bacitracin;

Tetracyclines such as Spicycline, Chlortetracycline, Clomocycline, Demeclocycline, Doxycycline, Guamecycline, Lymecycline, Meclocycline, Methacycline, Minocycline, Oxytetracycline, Penimepicycline, Pipacycline, Rolitetracycline, Sancycline, Senociclin and Tetracycline; and

others such as Cycloserine, Mupirocin, Tuberin.

b. Synthetic Antibacterials

2,4-Diaminopyrimidines such as Brodimoprim, Tetroxoprim and Trimethoprim;

Nitrofurans such as Furaltadone, Furazolium, Nifuradene, Nifuratel, Nifurfoline, Nifurpirinol, Nifurprazine, Nifurtoinol and Nitrofurantoin;

Quinolones and analogs thereof, such as Amifloxacin, Cinoxacin, Ciprofloxacin, Difloxacin, Enoxacin, Fleroxacin, Flumequine, Lomefloxacin, Miloxacin, Nalidixic Acid, Norfloxacin, Ofloxacin, Oxolinic Acid, Perfloxacin, Pipemidic Acid, Piromidic Acid, Rosoxacin, Temafloxacin and Tosufloxacin;

Sulfonamides such as Acetyl Sulfamethoxypyrazine, Acetyl Sulfisoxazole, Azosulfamide, Benzylsulfamide, Chloramine-β, Chloramine-T, Dichloramine-T, Formosulfathiazole, N.sup.2 -Formyl-sulfisomidine, N.sup.4 -β-D-Glucosylsulfanilamide, Mafenide, 4'-(Methyl-sulfamoyl)sulfanilanilide, p-Nitrosulfathiazole, Noprylsulfamide, Phthalylsulfacetamide, Phthalylsulfathiazole, Salazosulfadimidine, Succinylsulfathiazole, Sulfabenzamide, Sulfacetamide, Sulfachlorpyridazine, Sulfachrysoidine, Sulfacytine, Sulfadiazine, Sulfadicramide, Sulfadimethoxine, Sulfadoxine, Sulfaethidole, Sulfaguanidine, Sulfaguanol, Sulfalene, Sulfaloxic Acid, Sulfamerazine, Sulfameter, Sulfamethazine, Sulfamethizole, Sulfamethomidine, Sulfamethoxazole, Sulfamethoxypyridazine, Sulfametrole, sulfamidochrysoidine, Sulfamoxole, Sulfanilamide, Sulfanilamidomethanesulfonic Acid Triethanolamine Salt, 4-Sulfanilamidosalicyclic Acid, N^4 -Sulfanilylsulfanilamide, Sulfanilylurea, N-Sulfanilyl-3,4-xylamide, Sulfanitran, Sulfaperine, Sulfaphenazole, Sulfaproxyline, Sulfapyrazine, Sulfapyridine, Sulfasomizole, Sulfasymazine, Sulfathiazole, Sulfathiourea, Sulfatolamide, Sulfisomidine and Sulfisoxazole;

Sulfones, such as Acedapsone, Acediasulfone, Acetosulfone, Dapsone, Diathymosulfone, Glucosulfone, Solasulfone, Succisulfone, Sulfanilic Acid, p-Sulfanilylbenzylamine, p,p'-sulfonyldianiline-N,N'-digalactoside, Sulfoxone and Thiazolsulfone;

Others such as Clofoctol, Hexedine, Magainins, Methenamine, Methenamine Anhydromethylene-citrate, Methenamine Hippurate, Methenamine Mandelate, Methenamine Sulfosalicylate, Nitroxoline, Squalamine and Xibomol.

c. Antifungal (antibiotics)

[0251] Polyenes such as Amphotericin-B, Candicidin, Dermostatin, Filipin, Fungichromin, Hachimycin, Hamycin, Lucensomycin, Mepartricin, Natamycin, Nystatin, Pecilocin, Perimycin; and others, such as Azaserine, Griseofulvin, Oligomycins, Pyrrolnitrin, Siccanin, Tubercidin and Viridin.

d. Antifungal (synthetic)

[0252] Allylamines such as Naftifine and terbinafine;

Imidazoles such as Bifonazole, Butoconazole, Chlordantoin, Chlormidazole, Cloconazole, Clotrimazole, Econazole, Enilconazole, Finticonazole, Isoconazole, Ketoconazole, Miconazole, Omoconazole, Oxiconazole Nitrate, Sulconazole and Tioconazole;

Triazoles such as Fluconazole, Itraconazole, Terconazole;

Others such as Acrisorcin, Amorolfine, Biphenamine, Bromosalicylchloranilide, Buclosamide, Chlophenesin, Ciclopirox, Cloxyquin, Coparaffinate, Diamthazole, Dihydrochloride, Exalamide, Flucytosine, Halethazole, Hexetidine, Loflucarban, Nifuratel, Potassium Iodide, Propionic Acid, Pyrithione, Salicylanilide, Sulbentine, Tenonitrozole, Tolciclate, Tolindate, Tolnaftate, Tricetin, Ujothion, and Undecylenic Acid.

e. Antiglaucoma agents

[0253] Antiglaucoma agents, such as Dapiprazoke, Dichlorphenamide, Dipivefrin and Pilocarpine.

f. Anti-inflammatory agents

[0254] Corticosteroids, aminoarylcarboxylic Acid Derivatives such as Etofenamate, Meclofenamic Acid, Mefanamic Acid, Niflumic Acid;

Arylacetic Acid Derivatives such as Acemetacin, Amfenac Cinmetacin, Clopirac, Diclofenac, Fenclofenac, Fenclorac, Fenclozic Acid, Fentiazac, Glucametacin, Isozepac, Lonazolac, Metiazinic Acid, Oxametacine, Proglumetacin, Sulindac, Tiaramide and Tolmetin;

Arylbutyric Acid Derivatives such as Butibufen and Fenbufen;

Arylcarboxylic Acids such as Clidanac, Ketorolac and Tinoridine;

Arylpropionic Acid Derivatives such as Bucloxic Acid, Carprofen, Fenoprofen, Flunoxaprofen, Ibuprofen, Ibuproxam, Oxaprozin, Piketoprofen, Pirprofen, Pranoprofen, Protizinic Acid and Tiaprofenic Add;

Pyrazoles such as Mepirizole;

Pyrazolones such as Clofezone, Feprazone, Mofebutazone, Oxyphenbutazone, Phenylbutazone, Phenyl Pyrazolidininones, Suxibuzone and Thiazolinobutazone;

Salicylic Acid Derivatives such as Bromosaligenin, Fendosal, Glycol Salicylate, Mesalamine, 1-Naphthyl Salicylate, Olsalazine and Sulfasalazine;

Thiazinecarboxamides such as Droxicam, Isoxicam and Piroxicam;

Others such as e-Acetamidocaproic Acid, S-Adenosylmethionine, 3-Amino-4-hydroxybutyric Acid, Amixetrine, Bendazac, Bucolome, Carbazones, Difenpiramide, Ditazol, Guaiazulene, Heterocyclic Aminoalkyl Esters of Mycophenolic Acid and Derivatives, Nabumetone, Nimesulide, Orgotein, Oxaceprol, Oxazole Derivatives, Paranyline, Pifoxime, 2-substituted-4,6-di-tertiary-butyl-s-hydroxy-1,3-pyrimidines, Proquazone and Tenidap.

g. Antiseptics

[0255] Guanidines such as Alexidine, Ambazone, Chlorhexidine and Picloxydine;

Halogens/Halogen Compounds such as Bomyl Chloride, Calcium Iodate, Iodine, Iodine Monochloride, Iodine Trichloride, Iodoform, Povidone-Iodine, Sodium Hypochlorite, Sodium Iodate, Symclosene, Thymol Iodide, Triclocarban, Triclosan and Troclosene Potassium;

Nitrofurans such as Furazolidone, 2-(Methoxymethyl)-5-Nitrofuran, Nidroxyzone, Nifuroxime, Nifurzide and Nitrofurazone;

Phenols such as Acetomeroctol, Chloroxylenol, Hexachlorophene, 1-Naphthyl Salicylate, 2,4,6-Tribromo-m-cresol and 3',4',5-Trichlorosalicylanilide;

Quinolines such as Aminoquinuride, Chloroxine, Chlorquinaldol, Cloxyquin, Ethylhydrocupreine, Halquinol, Hydrastine, 8-Hydroxyquinoline and Sulfate; and

others, such as Boric Acid, Chloroazodin, m-Cresyl Acetate, Cupric sulfate and Ichthammol.

h. Antivirals

[0256] Purines/Pyrimidinones, such as 2-Acetyl-Pyridine 5-((2-pyridylamino)thiocarbonyl) Thiocarbonohydrazone, Acyclovir, Dideoxyadenosine, Dideoxycytidine, Dideoxyinosine, Edoxudine, Floxuridine, Ganciclovir, Idoxuridine, MADU, Pyridinone, Trifluridine, Vidrarbine and Zidovudline;

others such as Acetylleucine Monoethanolamine, Acridinamine, Alkylisooxazoles, Amantadine, Amidinomycin, Cuminaldehyde Thiosemicarbzone, Foscamet Sodium, Kethoxal, Lysozyme, Methisazone, Moroxydine, Podophyllotoxin, Ribavirin, Rimantadine, Stallimycin, Statolon, Thymosins, Tromantadine and Xenazoic Acid.

i. Agents for Neuralgia/Neuropathic Pain

[0257] Mild OTC (over the counter) analgesics, such as aspirin, acetaminophen, and ibuprophen.

Narcotic analgesics, such as codeine.

Anti seizure medications, such as carbamazepine, gabapentin, lamotrigine and phenytoin.

Anti-depressants, such as amitryptiline.

j. Agents for the Treatment of Depression

[0258] Selective serotonin re-uptake inhibitors (SSRIs), such as Fluoxetine, Paroxetine, Fluvoxamine, Citaprolam, and Sertraline.

Tricyclics, such as Imipramine, Amitriptyline, Desipramine, Nortriptyline Protriptyline, Trimipramine, Doxepin, Amoxapine, and Clomipramine.

Monoamine Oxidase Inhibitors (MAOIs), such as Tranylcypromine, Phenelzine, and Isocarboxazid.

Heterocyclics, such as Amoxipine, Maprotiline and Trazodone.

others such as Venlafaxine, Nefazodone and Mirtazapine.

k. Agents for the treatment of Incontinence

[0259] Anticholinergic agents such as propantheline.
Antispasmodic medications such as oxybutynin, tolterodine, and flavoxate.
Tricyclic antidepressants such as imipramine, and doxepin.
Calcium channel blockers such as tolterodine.
Beta agonists such as terbutaline.

l. Anti-Parkinson's Agents

Deprenyl, Amantadine, Levodopa, and Carbidopa.

[0260] In yet another embodiment, the invention is directed to methods of binding opioid receptors, preferably δ opioid receptors, in a patient in need thereof, comprising the step of administering to said patient an effective amount of a compound as described herein including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV. The δ opioid receptors may be located in the central nervous system or located peripherally to the central nervous system. In certain preferred embodiments, the binding of the present compounds modulates the activity, preferably as an agonist, of said opioid receptors. In certain preferred embodiments, the compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV does not substantially cross the blood-brain barrier. Preferably, the compounds as described herein are peripherally selective.

[0261] The spirocyclic heterocyclic derivatives of the present invention and pharmaceutical compositions containing these compounds may be utilized in a number of ways. In certain embodiments, the spirocyclic heterocyclic derivatives are ligands of the δ opioid receptor and are useful, *inter alia*, in methods for treating and/or preventing pain, gastrointestinal disorders, urogenital tract disorders including incontinence, for example, stress urinary incontinence, urge urinary incontinence and benigh prostatic hyperplasia, and overactive bladder disorder (*see, e.g.,* R. B. Moreland et al., *Perspectives in Pharmacology*, Vol. 308(3), pp. 797-804 (2004) and M.O. Fraser, *Annual Reports in Medicinal Chemistry*, Chapter 6, pp. 51-60 (2003), the disclosures of which are hereby incorporated herein by reference, in their entireties), immunomodulatory disorders, inflammatory disorders, respiratory function disorders, depression, anxiety, mood disorders, stress-related disorders, sympathetic nervous system disorder, tussis, motor disorder, traumatic injury, stroke, cardiac arrhythmia, glaucoma, sexual dysfunction, shock, brain edema, cerebral ischemia, cerebral deficits subsequent to cardiac bypass surgery and grafting, systemic lupus erythematosus, Hodgkin's disease, Sjogren's disease, epilepsy, and rejection in organ transplants and skin grafts, and substance addiction. In certain other embodiments, the spirocyclic heterocyclic derivatives are ligands of the δ opioid receptor and are useful, *inter alia*, in methods for providing cardioprotection following myocardial infarction, in methods for providing and maintaining an anaesthetic state, and in methods of detecting, imaging or monitoring degeneration or dysfunction of opioid receptors in a patient.

[0262] Thus, in accordance with preferred embodiments of the invention, there are provided methods of preventing or treating pain, comprising the step of administering to said patient an effective amount of a compound as described herein including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV.

[0263] In certain preferred embodiments, the present methods of preventing or treating pain may further comprise the administration to a patient of an effective amount of an agent for the treatment of neuralgia and/or neuropathic pain.

[0264] In another embodiment, the invention is directed to methods for preventing or treating gastrointestinal dysfunction, comprising the step of administering to a patient in need of such treatment an effective amount of a compound as described herein including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV.

[0265] In another embodiment, the invention is directed to methods for preventing or treating a urogenital tract disorder, such as incontinence (including, for example, stress urinary incontinence and urge urinary incontinence, and overactive bladder), comprising the step of administering to a patient in need of such treatment an effective amount of a compound as described herein including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV.

[0266] In certain preferred embodiments, the present methods of preventing or treating a urogenital tract disorder may further comprise the administration to a patient of an effective amount of an agent for the treatment of incontinence.

[0267] In another embodiment, the invention is directed to methods of preventing or treating an immunomodulatory disorder, comprising the step of administering to a patient in need thereof an effective amount of a compound as described herein including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV. Immunomodulatory disorders include, but are not limited to, autoimmune diseases, collagen diseases, allergies, side effects associated with the administration of an anti-tumor agent, and side effects associated with the administration of an antiviral agent. Autoimmune diseases include, but are not limited to, arthritis, autoimmune disorders associated with skin grafts, autoimmune disorders associated with organ transplants, and autoimmune disorders associated with surgery.

[0268] In another embodiment, the invention is directed to methods of preventing or treating an inflammatory disorder, comprising the step of administering to a patient in need thereof an effective amount of a compound as described herein including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV. Inflammatory disorders include, but are not limited to, arthritis, psoriasis, asthma, or inflammatory bowel disease.

[0269] In another embodiment, the invention is directed to methods of preventing or treating a respiratory function disorder, comprising the step of administering to a patient in need thereof an effective amount of a compound as described herein including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV. Respiratory function disorders include but are not limited to asthma or lung edema.

[0270] In another embodiment, the invention is directed to methods for preventing or treating anxiety, comprising the step of administering to a patient in need of such treatment an effective amount of a compound as described hereiin including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV.

[0271] In another embodiment, the invention is directed to methods for preventing or treating a mood disorder, comprising the step of administering to a patient in need of such treatment an effective amount of a compound as described herein including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV.

[0272] In certain preferred embodiments, the present methods of preventing or treating a mood disorder may further comprise the administration to a patient of an effective amount of an agent for the treatment of depression.

[0273] In another embodiment, the invention is directed to methods for preventing or treating a stress-related disorder, comprising the step of administering to a patient in need of such treatment an effective amount of a compound as described herein including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV. Stress-related disorders include, but are not limited to, post-traumatic stress disorder, panic disorder, generalized anxiety disorder, social phobia, and obsessive compulsive disorder.

[0274] In another embodiment, the invention is directed to methods for preventing or treating attention deficit hyperactivity disorder, comprising the step of administering to a patient in need of such treatment an effective amount of a compound as described herein including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV.

[0275] In another embodiment, the invention is directed to methods for preventing or treating sympathetic nervous system disorders, including hypertension, comprising the step of administering to a patient in need of such treatment an effective amount of a compound as described herein including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV.

[0276] In another embodiment, the invention is directed to methods for preventing or treating tussis, comprising the step of administering to a patient in need of such treatment an effective amount of a compound as described herein including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV.

[0277] In another embodiment, the invention is directed to methods for preventing or treating a motor disorder, including tremors, Parkinson's disease, Tourette's syndrome and dyskenesia, comprising the step of administering to a patient in need of such treatment an effective amount of a compound as described herein including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV.

[0278] In certain preferred embodiments, the present methods of preventing or treating a motor disorder may further comprise the administration to a patient of an effective amount of an agent for the treatment of Parkinson's disease.

[0279] In another embodiment, the invention is directed to methods for treating a traumatic injury to the central nervous system, including the spinal cord or brain, comprising the step of administering to a patient in need of such treatment an effective amount of a compound as described herein including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV.

[0280] In another embodiment, the invention is directed to methods for preventing or treating stroke, comprising the step of administering to a patient in need of such treatment an effective amount of a compound as described herein including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV.

[0281] In another embodiment, the invention is directed to methods for preventing or treating cardiac arrhythmia, comprising the step of administering to a patient in need of such treatment an effective amount of a compound as described herein including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV.

[0282] In another embodiment, the invention is directed to methods for preventing or treating glaucoma, comprising the step of administering to a patient in need of such treatment an effective amount of a compound as described herein including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV.

[0283] In another embodiment, the invention is directed to methods for preventing or treating sexual dysfunction, including premature ejaculation, comprising the step of administering to a patient in need of such treatment an effective amount of a compound as described herein including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV.

[0284] In another embodiment, the invention is directed to methods for treating a condition selected from the group consisting of shock, brain edema, cerebral ischemia, cerebral deficits subsequent to cardiac bypass surgery and grafting, systemic lupus erythematosus, Hodgkin's disease, Sjogren's disease, epilepsy, and rejection in organ transplants and skin grafts, comprising the step of administering to a patient in need of such treatment an effective amount of a compound of the invention including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV.

[0285] In another embodiment, the invention is directed to methods for treating substance addiction, including addictions to alcohol, nicotine or drugs such as opioids, comprising the step of administering to a patient in need of such treatment an effective amount of a compound as described herein including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV.

[0286] In another embodiment, the invention is directed to methods for improving organ and cell survival, comprising the step of administering to a patient in need of such treatment an effective amount of a compound as described herein including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV.

[0287] Techniques for evaluating and/or employing the present compounds in methods for improving organ and cell survival and organ preservation are described, for example, in C.V. Borlongan et al., *Frontiers in Bioscience* (2004), 9(Suppl.), 3392-3398, Su, *Journal of Biomedical Science* (Basel) (2000), 7(3), 195-199, and U.S. Patent No. 5,656,420, the disclosures of each of which are hereby incorporated herein by reference in their entireties.

[0288] In another embodiment, the invention is directed to methods for providing cardioprotection following myocardial infarction, comprising the step of administering to a patient in need of such treatment an effective amount of a compound as described herein including, for example, a compound of formula XIV,

XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV.

[0289] In another embodiment, the invention is directed to methods for reducing the need for anesthesia, comprising the step of administering to a patient in need of such treatment an effective amount of a compound as described herein including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV.

[0290] In another embodiment, the invention is directed to methods of producing or maintaining an anesthetic state, comprising the step of administering to a patient in need of such treatment an effective amount of a compound as described herein including, for example, a compound of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV. The method may further comprise the step of administering to said patient an anesthetic agent, which may be co-administered with compound(s) of the invention. Suitable anesthetic agents include,, for example, an inhaled anaesthetic, a hypnotic, an anxiolytic, a neuromuscular blocker and an opioid. Thus, in the present embodiment, compounds of the invention may be useful as analgesic agents for use during general anesthesia and monitored anesthesia care. Combinations of agents with different properties may be used to achieve a balance of effects needed to maintain the anaesthetic state.

[0291] Additional diseases and/or disorders which may be treated and/or prevented with the compounds and pharmaceutical compositions of the present invention include those described, for example, in WO2004/062562 A2, WO 2004/063157 A1, WO 2004/063193 A1,
WO 2004/041801 A1, WO 2004/041784 A1, WO 2004/041800 A1, WO 2004/060321 A2,
WO 2004/035541 A1, WO 2004/035574 A2, WO 2004041802 A1, US 2004082612 A1,
WO 2004026819 A2, WO 2003057223 A1, WO 2003037342 A1, WO 2002094812

A1,
WO 2002094810 A1, WO 2002094794 A1, WO 2002094786 A1, WO 2002094785 A1,
WO 2002094784 A1, WO 2002094782 A1, WO 2002094783 A1, WO 2002094811 A1, the disclosures of each of which are hereby incorporated herein by reference in their entireties.

[0292] In certain embodiments, the present invention is directed to radiolabeled derivatives and isotopically labeled derivatives of compounds as described herein including, for example, compounds of formula XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIIA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII and/or XXXIV. Suitable labels include, for example, ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{13}N, ^{15}N, ^{15}O, ^{18}O, ^{18}F and ^{34}S. Such labeled derivatives may be useful for biological studies, for example, using positron emission tomography, for metabolite identification studies and the like. Such diagnostic imaging methods may comprise, for example, administering to a patient a radiolabeled derivative or isotopically labeled derivative of a compound of the invention, and imaging the patient, for example, by application of suitable energy, such as in positron emission tomography. Isotopically- and radio-labeled derivatives may be prepared utilizing techniques well known to the ordinarily skilled artisan.

[0293] The present invention will now be illustrated by reference to the following specific, non-limiting examples. Those skilled in the art of organic synthesis may be aware of still other synthetic routes to the invention compounds. The reagents and intermediates used herein are commercially available or may be prepared according to standard literature procedures.

Methods Of Preparation

[0294] The examples listed in Tables 1, 2, and 3 may be prepared according to Schemes 1-57. The synthesis of compounds **1A-1U** is outlined in Scheme 1. The 2'- hydroxyacetophenone derivatives **1.1a-1.1m** were condensed with 1-Boc-4-piperidone **1.2** in neat pyrrolidine (method 1A) at room temperature or in refluxing methanol in the presence of pyrrolidine (method 1B) to provide *N*-Boc-spiro[2*H*-1-

benzopyran-2,4'-piperidine]-4(3*H*)-one derivatives **1.3**. Conversion of the ketones **1.3** to the enol triflate derivatives **1.5** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivatives **1.5** with either 4-(*N*,*N*-diethylaminocarbonyl)phenyl boronic acid **1.6** (commercially available from Combi-Blocks Inc.) or 2-(*N*,*N*-diethylaminocarbonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)pyridine **1.7** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0) (method 1C) or palladium, 10 wt.% (dry basis) on activated carbon (method 1D), lithium chloride, and an aqueous solution of sodium carbonate afforded compounds **1.8** which were converted to the final products (compounds **1A-1T**) under acidic conditions (method 1E: anhydrous HCl, diethyl ether, room temperature or method 1F: neat trifluoroacetic acid, room temperature). Demethylation of compound **1G** using boron tribromide provided the corresponding phenolic derivative (compound **1U**). The boronate derivative **1.7** was prepared in 4 steps from 2,5-dibromopyridine **1.9**. Treatment of 2,5-dibromopyridine with *n*-butyllithium provided the corresponding lithiated derivative, which reacted with carbon dioxide to provide 5-bromopyridine-2-carboxylic acid **1.10**. Treatment of the carboxylic acid derivative **1.10** with oxalyl chloride furnished the acyl chloride **1.11**, which reacted with diethylamine **1.12** to provide 5-bromo-2-(*N*,*N*-diethylaminocarbonyl)-pyridine **1.13**. Conversion of the aryl bromide **1.13** to the corresponding boron derivative **1.7** was achieved using 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane **1.14** and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct, abbreviated as [Pd(dppf)Cl_2•CH_2Cl_2].

[0295] The synthesis of compounds **2A-2F** is outlined in Scheme 2. The 2'-5'-dihydroxyacetophenone derivative **2.1** was condensed with 1-Boc-4-piperidone **1.2** in refluxing methanol in the presence of pyrrolidine to provide *N*-Boc-spiro[2*H*-1-benzopyran-2,4'-piperidine]-4(3*H*)-one derivative **2.2** which was converted to the silyl ether derivative **2.4** using *tert*-butyldimethylsilyl chloride **2.3**. Conversion of the ketone **2.4** to the enol triflate derivative **2.5** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivative **2.5** with either 4-(*N*,*N*-diethylaminocarbonyl)-

phenyl boronic acid **1.6** or 2-(*N*,*N*-diethylaminocarbonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)pyridine **1.7** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0) (method 1C) or palladium, 10 wt.% (dry basis) on activated carbon (method 1D), lithium chloride, and an aqueous solution of sodium carbonate afforded compounds **2.6**. Removal of the silyl protecting group of **2.6** using a solution of tetrabutylammonium fluoride (TBAF) in tetrahydrofuran gave the phenolic derivatives **2.7** which were converted to the final products compounds **2A** and **2B** under acidic conditions. Preparation of each of the ether derivatives **2.9** from the phenols **2.7** was achieved by alkylation reaction using the appropriate alkyl bromide (**2.8a**, **2.8b**) (method 2A) or alkyl iodide (**2.8c**) reagent (method 2C). In some instances, the ether derivatives **2.9** were also obtained from the phenols **2.7** using the Mitsunobu conditions, i.e., condensation of the phenols **2.7** with the appropriate alcohol (**2.8d**, **2.8e**) in the presence of triphenylphosphine and diisopropyl azodicarboxylate (DIAD) (method 2B). Treatment of the Boc derivatives **2.9** with hydrochloric acid provided the final compounds **2C-F**.

[0296] The synthesis of compounds **3A-AC** is outlined in Scheme 3. Conversion of the phenols **2.7** to the triflate derivatives **3.1** was achieved using the triflating reagent *N*-phenylbis(trifluoromethanesulphonimide) **1.4**. Palladium catalyzed carbonylation of **3.1**, conducted in methanol or in a mixture dimethylsulfoxide/methanol using palladium (II) acetate, 1,1'-bis(diphenylphosphino)ferrocene (dppf) and carbon monoxide, provided the methyl esters **3.2** which were hydrolyzed under basic conditions to give the carboxylic acid derivatives **3.3**. Coupling of the carboxylic acids **3.3** with various amines (**3.4a-3.4q**) using *O*-benzotriazol-1-yl-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate (TBTU) as coupling agent afforded the primary, secondary, and tertiary amides **3.5**. Treatment of the Boc derivatives **3.2**, **3.3** and **3.5** with hydrochloric acid provided the final compounds **3A-3Y**. Suzuki type coupling of the triflate derivative **3.1a** (X = CH) with various organoboron reagents (**3.6a-3.6d**) in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), and/or dichloro[1,1'-bis(diphenylphosphino) ferrocene]palladium(II)dichloromethane, [Pd(dppf)Cl_2 CH_2Cl_2], lithium chloride, and an aqueous solution of sodium carbonate afforded compounds **3.7** which were converted to the final products (compounds **3Z-3AC**) under acidic conditions.

[0297] The synthesis of compounds **4A-4I** is outlined in Scheme 4. Treatment of compound **1A** with trifluoroacetic anhydride in tetrahydrofuran in the presence of triethylamine provided the trifluoroacetamide derivative **4.2** which was converted to the sulfonyl chloride **4.4** using sulfur trioxide *N,N*-dimethylformamide complex (**4.3**) as sulfating agent. Condensation of **4.4** with various primary and secondary amines (**3.4**, **4.5**) afforded the sulfonamide derivatives **4.6** which were converted to the compounds **4A-4G** under basic conditions. Treatment of the sulfonyl chloride **4.4** with ammonium hydroxide in acetonitrile provided the sulfonamide compound **4H**, which was further protected as its *tert*-butyloxycarbonyl (Boc) derivative **4.8** buy treatment with *tert*-butyloxycarbonyl anhydride (**4.7**). Acetylation of **4.8** using acetic anhydride (**4.9**) gave the acetylsulfonamide derivative **4.10** which was converted to compound **4I** by treatment with iodotrimethylsilane.

[0298] The synthesis of compound **5A** is described in Scheme 5. Condensation of hydrazine hydrate (**5.1**) with the sulfonyl chloride derivative **4.4** provided the sulfonyl hydrazide **5.2**, which was converted to the sulfone **5.3** by treatment with methyl iodide (**2.8c**) in the presence of sodium acetate. Deprotection of the trifluoroacetamide protecting group of **5.3** under basic conditions (potassium carbonate, methanol/tetrahydrofuran/water) provided the final compound **5A**.

[0299] The synthesis of compounds **6A-6E** is described in Scheme 6. Nitration of the trifluoroacetamide **4.2** using nitronium tetrafluoroborate complex (**6.1**) as nitrating reagent provided predominantly the *mono*-nitro isomer **6.2**. Reduction of the nitro functionality of **6.2** using tin(II) chloride dihydrate (**6.3**) gave the aniline derivative **6.4**, which reacted with the sulfonyl chloride derivatives **6.5** or with acetyl chloride (**6.7**) to provide the sulfonamides **6.6** or the acetamide **6.8**, respectively. Deprotection of the trifluoroacetamide protecting group of **6.2**, **6.4**, **6.6** and **6.8** under basic conditions (potassium carbonate, methanol/tetrahydrofuran/water) provided the final compounds (compounds **6A-6E**).

[0300] The synthesis of compounds **7A-7E** is described in Scheme 7. Buchwald type coupling of the triflate derivative **3.1a** with diphenylmethanimine (**7.1**) in toluene in the presence of tris(dibenzylideneacetone)dipalladium (0) [$Pd_2(dba)_3$], 1,1'-bis(diphenylphosphino)ferrocene (dppf) and sodium *tert*-butoxide afforded the benzophenone imine derivative **7.2,** which was converted to the aniline **7.3** by treatment with hydroxylamine hydrochloride in the presence of sodium acetate. Treatment of **7.3** with methanesulfonyl chloride (**7.4**) in dichloromethane in the presence of triethylamine provided the *bis*-methanesulfonamide **7.5**, which was hydrolyzed to the *mono* methanesulfonamide derivative **7.6** under basic conditions. Deprotection of the *tert*-butyloxycarbonyl protecting group of **7.6** under acidic conditions provided the final compound **7A**. Compound **7B** was obtained in two steps from **7.6**. Alkylation of **7.6** with methyl iodide (**2.8c**) in tetrahydrofuran in the presence of sodium hydride provided the *N*-methylsulfonamide **7.7**, which was converted to compound **7B** under acidic conditions. Treatment of the aniline derivative **6.4** with methanesulfonyl chloride (**7.4**) in dichloromethane in the presence of triethylamine provided the *bis*-methanesulfonamide **7.8**, which was hydrolyzed to the *mono*-methanesulfonamide derivative compound **7A** under basic conditions. During the course of this reaction, the *N*-methyl piperidine derivative compound **7C** was identified as a side product. The separation of the mixture containing compounds **7A** and **7C** was achieved by first treating the mixture of compounds **7A/7C** with *tert*-butyloxycarbonyl anhydride (**4.7**) which provided the Boc derivative **7.6** and unreacted compound **7C**, followed by purification of compound **7C** using flash colum chromatography. Buchwald type coupling of the triflate derivative **3.1a** with pyrrolidine (**3.4k**) or morpholine (**3.4p**) in ethylene glycol dimethyl ether in the presence of tris(dibenzylideneacetone)dipalladium (0) [$Pd_2(dba)_3$], the phosphine ligand 2-(di-*t*-butylphosphino)biphenyl **7.9** and potassium phosphate afforded the derivatives **7.10,** which were converted to compounds **7D,E** under acidic conditions.

[0301] The synthesis of compounds **8A-8F** is outlined in Scheme 8. The 2'-3'-dihydroxyacetophenone derivative **8.1** was condensed with 1-Boc-4-piperidone **1.2** in refluxing methanol in the presence of pyrrolidine to provide the *N*-Boc-spiro[2*H*-1-benzopyran-2,4'-piperidine]-4(3*H*)-one derivative **8.2** which was converted to the silyl ether derivative **8.3** using *tert*-butyldimethylsilyl chloride **2.3**. The ketone **8.3** was converted to the enol triflate derivative **8.4** using the triflating reagent

N-phenylbis(trifluoromethanesulphonimide) **1.4**. Suzuki type coupling of the enol triflate derivative **8.4** with either 4-(*N*,*N*-diethylaminocarbonyl)phenyl boronic acid **1.6** or 2-(*N*,*N*-diethylaminocarbonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)pyridine **1.7** in ethylene glycol dimethyl ether in the presence of palladium, 10 wt.% (dry basis) on activated carbon, lithium chloride, and an aqueous solution of sodium carbonate afforded compounds **8.5**. Removal of the silyl protecting group of **8.5** using a solution of tetrabutylammonium fluoride (TBAF) in tetrahydrofuran gave the phenolic derivatives **8.6** which were converted to the final products (compounds **8A** and **8B**) under acidic conditions. Preparation of the ether derivatives **8.7** from the phenols **8.6** was achieved by alkylation using the appropriate alkyl bromide (**2.8a**) or methyl iodide (**2.8c**) reagent. Treatment of the Boc derivatives **8.7** with hydrochloric acid provided the final compounds **8C-8F**.

[0302] The synthesis of compounds **9A-9B** is outlined in Scheme 9. The 2'-4'-dihydroxyacetophenone derivative **9.1** was condensed with 1-Boc-4-piperidone **1.2** in refluxing methanol in the presence of pyrrolidine to provide the *N*-Boc-spiro[2*H*-1-benzopyran-2,4'-piperidine]-4(3*H*)-one derivative **9.2** which was converted to the silyl ether derivative **9.3** using *tert*-butyldimethylsilyl chloride **2.3**. Conversion of the ketone **9.3** to the enol triflate derivative **9.4** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivative **9.4** with 4-(*N*,*N*-diethylaminocarbonyl)phenyl boronic acid **1.6** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded the phenolic derivative **9.5** (simultaneous removal of the silyl protecting group occurred under the Suzuki coupling conditions). Alkylation of the phenol **9.5** with (bromomethyl)cyclopropane (**2.8a**) in acetone in the presence of potassium carbonate provided the ether derivative **9.6** which was converted to compound **9A** under acidic conditions. Treatment of the phenol **9.5** with methyl chlorodifluoroacetate (**9.7**) in *N*,*N*-dimethylformamide in the presence of cesium carbonate provided the ether derivative **9.8** which was converted to compound **9B** under acidic conditions.

[0303] The synthesis of compounds **10A-10J** is outlined in Scheme 10. Conversion of the phenol **9.5** to the triflate derivative **10.1** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Palladium catalyzed carbonylation of **10.1**, conducted in a mixture *N*,*N*-dimethylformamide/methanol using palladium (II) acetate, 1,1'-bis(diphenylphosphino)ferrocene (dppf), and carbon monoxide, provided the methyl ester **10.2** which was hydrolyzed under basic conditions to give the carboxylic acid derivative **10.3**. Coupling of the carboxylic acid **10.3** with various amines (**3.4a,c,j,k,p**; **1.12**) using either *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate (HATU) (method 10B) or *O*-benzotriazol-1-yl-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate (TBTU) (method 10A) as coupling agents afforded the primary, secondary, and tertiary amides **10.4**. The dimethylamide derivative **10.4b** (R_1 = H, R_2 = CH_3) was obtained by heating a mixture of the ester **10.2** with methylamine (**3.4b**) in methanol in a sealed tube. Treatment of the Boc derivatives **10.2**, **10.3** and **10.4** with hydrochloric acid provided the final compounds **10A-10I**. Treatment of the ester **10.2** with lithium borohydride in tetrahydrofuran provided the primary alcohol **10.5** which was converted to the compound **10J** under acidic conditions.

[0304] The synthesis of compounds **11A-11I** is outlined in Scheme 11. The 2'-6'-dihydroxyacetophenone derivative **11.1** was condensed with 1-Boc-4-piperidone **1.2** in refluxing methanol in the presence of pyrrolidine to provide the *N*-Boc-spiro[2*H*-1-benzopyran-2,4'-piperidine]-4(3*H*)-one derivative **11.2** which was converted to the methoxymethyl (MOM) ether derivative **11.4** using chloro(methoxy)methane (**11.3**). Conversion of the ketone **11.4** to the enol triflate derivative **11.5** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivative **11.5** with either 4-(*N*,*N*-diethylaminocarbonyl)phenyl boronic acid **1.6** or 2-(*N*,*N*-diethylaminocarbonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)pyridine **1.7** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compounds **11.6**. Removal of the MOM and the Boc protecting groups of **11.6** in methanol at room temperature in the presence of hydrochloric acid (anhydrous solution in dioxane) afforded the phenolic compounds **11A** and **11B** which were converted to the corresponding Boc derivatives **11.7** by treatment with *tert*-butyloxycarbonyl anhydride (**4.7**). Preparation of the ether derivatives **11.9a** [X=CH; R = $CH_2c(C_3H_5)$], **11.9b** [X=N; R = $CH_2c(C_3H_5)$] and **11.9d** [X=N; R = $c(C_5H_9)$] from the corresponding phenols **11.7a** [X=CH] or **11.7b** [X=N] was achieved using the Mitsunobu conditions, i.e., condensation of the phenols **11.7a** or **11.7b** with cyclopropylmethanol (**2.8e**) or cyclopentanol (**11.10**) in dichloromethane in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD). The cyclobutyl ether **11.9c** [X=CH; R = $c(C_4H_7)$] was obtained by alkylation of the corresponding phenol **11.7a** [X=CH] with bromocyclobutane in acetone in the presence of potassium carbonate. Treatment of the Boc derivatives **11.9** with hydrochloric acid provided the final compounds **11C-11F**. Treatment of the phenol **11.2** with methyl chlorodifluoroacetate (**9.7**) in *N*,*N*-dimethylformamide in the presence of cesium carbonate provided the ether derivative **11.11**. Conversion of the ketone **11.11** to the enol triflate derivative **11.12** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivative **11.12** with either 4-(*N*,*N*-diethylaminocarbonyl)phenyl boronic acid **1.6** or 2-(*N*,*N*-diethylaminocarbonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)pyridine **1.7** in dioxane in the presence of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct, potassium phosphate, and potassium bromide, afforded compounds **11.13**. Removal of the Boc protecting group of **11.13** in dichloromethane at room temperature in the presence of hydrochloric acid (anhydrous solution in diethyl ether) afforded the compounds **11G** and **11H**. Conversion of the aryl bromide **32.2b** to the corresponding boron derivative **11.14** was achieved using 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane **1.14** and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct. Suzuki type coupling of the enol triflate derivative **11.5** with the boron derivative **11.14** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), potassium bromide and potassium phosphate afforded compound **11.15**. Removal of the Boc and the MOM protecting groups of **11.15** in methanol at room temperature in the presence of hydrochloric acid (anhydrous solution in diethyl ether) afforded the compound **11I**.

[0305] The synthesis of compounds **12A-12L** is outlined in Scheme 12. Conversion of the phenol **11.2** to the triflate derivative **12.1** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Palladium catalyzed Negishi-type coupling of **12.1** with methylzinc chloride (**12.2a**), propylzinc bromide (**12.2b**), or butylzinc bromide (**12.2c**), conducted in tetrahydrofuran using tetrakis triphenylphosphine palladium (0) as catalyst, provided the ketones **12.3**. Conversion of the ketones **12.3** to the enol triflate derivatives **12.4** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivative **12.4** with 4-(*N*,*N*-diethylaminocarbonyl)phenyl boronic acid **1.6** or 2-(*N*,*N*-diethylaminocarbonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)pyridine **1.7** using either method 1C (tetrakis triphenylphosphine palladium (0), lithium chloride, aqueous solution of sodium carbonate, ethylene glycol dimethyl ether) or method 12A (tetrakis triphenylphosphine palladium (0), potassium bromide, potassium phosphate, dioxane) afforded compounds **12.5**. Removal of the Boc protecting group of **12.5** in dichloromethane at room temperature in the presence of hydrochloric acid (anhydrous solution in diethyl ether) afforded compounds **12A** and **12H-12L**. Palladium catalyzed carbonylation of **12.1**, conducted in a mixture *N*,*N*-dimethylformamide/methanol using palladium (II) acetate, 1,3-bis(diphenylphosphino)propane (dppp) and carbon monoxide, provided the methyl ester **12.6** which was hydrolyzed under basic conditions (lithium hydroxide, methanol/tetrahydrofuran) to give the carboxylic acid derivative **12.7**. Coupling of the carboxylic acid **12.7** with dimethylamine (**3.4j**) using *O*-benzotriazol-1-yl-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate (TBTU) as coupling agent afforded the dimethylaminocarbonyl derivative **12.8**. Conversion of **12.8** to the enol triflate derivative **12.9** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivative **12.9** with 4-(*N*,*N*-diethylaminocarbonyl)phenyl boronic acid **1.6** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compound **12.10**. Removal of the Boc protecting group of **12.10** in dichloromethane at room temperature in the presence of hydrochloric acid (anhydrous solution in diethyl ether) afforded compound **12G** ($R_1 = R_2 = CH_3$). Conversion of **12.6** to the enol triflate derivative **12.11** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivative **12.11** with 4-(*N*,*N*-diethylaminocarbonyl)phenyl boronic acid **1.6** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded the ester **12.12** which was hydrolyzed under basic conditions (potassium *tert*-butoxide, diethyl ether, water) to give the carboxylic acid **12.13**. Coupling of the carboxylic acid **12.13** with various amines (**12.15** or **3.4b-3.4d**) using *O*-benzotriazol-1-yl-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate (TBTU) as coupling agent afforded the primary and secondary aminocarbonyl derivatives **12.14**. Treatment of the Boc derivatives **12.13** and **12.14** with hydrochloric acid provided the final compounds **12B-12F**.

[0306] The synthesis of compounds **13A-13S** is outlined in Scheme 13. The 2'-hydroxyacetophenone derivative **1.1a** was condensed with 1-Boc-4-piperidone **1.2** in refluxing methanol in the presence of pyrrolidine to provide *N*-Boc-spiro[2*H*-1-benzopyran-2,4'-piperidine]-4(3*H*)-one **1.3a**. Conversion of **1.3a** to the enol triflate derivative **1.5a** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivative **1.5a** with 4-(methoxycarbonyl)phenylboronic acid (**13.1**) in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded the ester **13.2** which was hydrolyzed under basic conditions (lithium hydroxide, methanol/tetrahydrofuran/water) to give the carboxylic acid **13.3**. Coupling of the carboxylic acid **13.3** with various amines (**3.4a-3.4c**, **3.4e**, **3.4j-3.4k**, **3.4o-3.4q**; **13.4a-13.4h**) using *O*-benzotriazol-1-yl-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate (TBTU) as coupling agent afforded the primary, secondary, and tertiary aminocarbonyl derivatives **13.5**. Treatment of the Boc derivatives **13.3** and **13.5** with hydrochloric acid provided the final compounds **13A-13R**. Hydrolysis of compound **13O** under basic conditions (sodium hydroxide, ethanol/tetrahydrofuran) provided the carboxylic acid compound **13S**.

[0307] The synthesis of compounds **14A-14C** is outlined in Scheme 14. Suzuki type coupling of the enol triflate derivative **1.5a** with 4-cyanophenylboronic acid (**14.1**) in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded the cyanide **14.2** which was converted to the tetrazole **14.4** using sodium azide (**14.3**) and zinc bromide in a solution isopropanol/water. Alkylation of **14.4** with methyl iodide (**2.8c**) in N,N-dimethylformamide in the presence of triethylamine afforded the two regioisomers **14.5** (major isomer) and **14.6** (minor isomer) separated by silica gel column chromatography. The Boc protecting group of **14.4**, **14.5**, and **14.6** was removed using hydrochloric acid to generate the compounds **14A-14C.** Alternatively, the Boc protecting group of **14.4** was also removed using trifluoroacetic acid to give **14A.**

[0308] The synthesis of compounds **15A-15N** is outlined in Scheme 15. Alkylation of **14.4** with the alkyl bromide derivatives **15.1a-15.1e** in *N,N*-dimethylformamide in the presence of triethylamine afforded the regioisomers **15.2** (major isomers) and **15.3** (minor isomers) separated by silica gel column chromatography. The Boc protecting group of **15.2** and **15.3** was removed using hydrochloric acid to generate the compounds **15A-15J.** Hydrolysis of compounds **15A** or **15C-15E** under basic conditions (sodium hydroxide, methanol (or ethanol) /tetrahydrofuran/water) provided the corresponding carboxylic acids compounds **15K-15N**, respectively. In some instances, compounds **15K-15N** were also obtained in two steps from **15.2**, i.e. by basic hydrolysis of the ester functionality of **15.2** followed by deprotection of the Boc derivatives **15.4** under acidic conditions.

[0309] The synthesis of compounds **16A-16C** is outlined in Scheme 16. Suzuki type coupling of the enol triflate derivative **1.5a** with 3-cyanophenylboronic acid (**16.1**) in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded the cyanide **16.2** which was converted to the tetrazole **16.3** using sodium azide (**14.3**) and zinc bromide in a solution isopropanol/water. Alkylation of **16.3** with methyl iodide (**2.8c**) in *N,N*-dimethylformamide in the presence of triethylamine afforded the two regioisomers **16.4** (major isomer) and **16.5**

(minor isomer) separated by silica gel column chromatography. The Boc protecting group of **16.3**, **16.4**, and **16.5** was removed using hydrochloric acid to generate the compounds **16A-16C.**

[0310] The synthesis of compounds **17A-17F** is outlined in Scheme 17. Alkylation of **16.3** with the alkyl bromide derivatives **15.1a** or **15.1c** in *N*,*N*-dimethylformamide in the presence of triethylamine afforded the regioisomers **17.1** (major isomers) and **17.2** (minor isomers) separated by silica gel column chromatography. Alkylation of **16.3** with 4-(2-bromoethyl)morpholine (**17.3**) in *N*,*N*-dimethylformamide in the presence of triethylamine afforded the isomer **17.4**. The Boc protecting group of **17.1**, **17.2**, and **17.4** was removed using hydrochloric acid to generate the compounds **17A-17D.** Hydrolysis of compounds **17A** and **17B** under basic conditions (sodium hydroxide, methanol/ tetrahydrofuran/water) provided the corresponding carboxylic acids compound **17E** and compound **17F**, respectively. In some instances compounds **17E** and **17F** could also be obtained in two steps from **17.1**, i.e. by basic hydrolysis of the ester functionality of **17.1** followed by deprotection of the Boc derivatives **17.5** under acidic conditions.

[0311] The synthesis of compounds **18A-18C** is outlined in Scheme 18. Coupling of the carboxylic acid **13.3** with ammonium chloride (**3.4a**) in acetonitrile in the presence of diisopropylethylamine using *O*-benzotriazol-1-yl-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate (TBTU) as coupling agent afforded the primary aminocarbonyl derivative **13.5a** which was converted to the thioamide **18.2** using the Lawesson's reagent (**18.1**) [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide]. Condensation of the thioamide **18.2** with 1-bromo-3,3-dimethylbutan-2-one (**18.3a**) or 2-bromo-1-phenylethanone (**18.3b**) afforded the thiazole derivatives **18.4** which were converted to the final compounds (compounds **18A** and **18B**) under acidic conditions. Condensation of the nitrile derivative **14.2** with hydroxylamine hydrochloride (**18.5**) in ethanol in the presence of triethylamine afforded the *N*-hydroxybenzamidine derivative **18.6** which reacted with acetyl chloride (**6.7**) in refluxing pyridine to give the 1,2,4-oxadiazole derivative **18.7**. Deprotection of the Boc functionality of **18.7** under acidic conditions afforded compound **18C**.

[0312] The synthesis of compound **19A-19D** is outlined in Scheme 19. The 2'-hydroxyacetophenone **1.1a** was condensed with benzyl 4-oxopiperidine-1-carboxylate (**19.1**) in refluxing methanol in the presence of pyrrolidine to provide *N*-Cbz-spiro[2*H*-1-benzopyran-2,4'-piperidine]-4(3*H*)-one (**19.2**). Conversion of the ketone **19.2** to the enol triflate derivative **19.3** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Conversion of the enol triflate **19.3** to the corresponding boron derivative **19.4** was achieved using 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane **1.14** and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct, abbreviated as [Pd(dppf)Cl_2•CH_2Cl_2]. Suzuki type coupling of the boronate derivative **19.4** with *tert*-butyl 4-bromophenylcarbamate **19.5** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded the *tert*-butyloxycarbonyl (Boc) protected aniline derivative **19.6**. Acidic hydrolysis of **19.6** provided the aniline derivative **19.7** which reacted with acyl chlorides **19.8a**, **19.8b**, *iso*propylsulfonyl chloride (**6.5b**) or ethyl isocyanate (**19.11**) to give the corresponding amide derivatives **19.9**, sulfonamide derivative **19.10** or urea derivative **19.12**, respectively. The derivatives **19.9**, **19.10** and **19.12** were converted to compounds **19A-19D** by treatment with iodotrimethylsilane.

[0313] The synthesis of compounds **20A-20R** is outlined in Scheme 20. The tertiary amine derivatives compounds **20A-20R** were obtained from the secondary amines of general formula **20I**, by reductive amination methods (methods 20A or 20B) using the aldehydes **20.1a-20.1d** and sodium cyanoborohydride as reducing agent or by alkylation method (method 20C) using the bromides **2.8a**, **20.2a-e** as the alkylating reagent.

[0314] The synthesis of compounds **21A-21F** is outlined in Scheme 21. Condensation of 1-Boc-4-piperidone **1.2** with ethyl diazoacetate (**21.1**) in the presence of boron trifluoride diethyl etherate provided 1-*tert*-butyl 4-ethyl 3-oxoazepane-1,4-dicarboxylate in equilibrium with its enol form (**21.2**). Ester hydrolysis followed by decarboxylation of **21.2** under acidic conditions provided the azepan-3-one (**21.3**), which was protected as its Boc derivative **21.4** by treatment with *tert*-

butyloxycarbonyl anhydride (**4.7**). The 2'-hydroxyacetophenone **1.1a** was condensed with **21.4** in refluxing methanol in the presence of pyrrolidine to provide the racemic ketone **21.5**. Conversion of **21.5** to the enol triflate derivative **21.6** was achieved using the triflating reagent *N*-phenylbis(trifluoromethanesulphonimide) **1.4**. Suzuki type coupling of the enol triflate derivative **21.6** with 4-(*N*,*N*-diethylaminocarbonyl)phenyl boronic acid (**1.6**) in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded the racemic derivative **21.7**, which was hydrolyzed under acidic conditions to give the compound **21A** (racemic mixture). The two enantiomers derived from **21.7**, i.e. compounds **21.7a** and **21.7b**, were separated by chiral HPLC. The pure enantiomers **21.7a** and **21.7b** were converted to compounds **21B** and **21C**, respectively under acidic conditions. Palladium catalyzed hydrogenation of compounds **21B** and **21C** afforded compounds **21D** (diastereoisomeric mixture) and **21E** (diastereoisomeric mixture), respectively. Treatment of compound **21A** with benzyl chloroformate (**21.8**) in dichloromethane in the presence of triethylamine provided the Cbz-protected derivative **21.9**, which was converted to the sulfonyl chloride **21.10** using sulfur trioxide *N*,*N*-dimethylformamide complex (**4.3**) as sulfating agent. Condensation of **21.10** with ethylamine (**3.4c**) in dichloromethane in the presence of triethylamine, afforded the ethyl sulfonamide derivative **21.11** which was converted to compound **21F** by treatment with iodotrimethylsilane.

[0315] The synthesis of compounds **22A-22F** is outlined in Scheme 22. Treatment of compound **21B** (most active enantiomer) with trifluoroacetic anhydride (**4.1**) in tetrahydrofuran in the presence of triethylamine provided the trifluoroacetamide derivative **22.1** which was converted to the sulfonyl chloride **22.2** using sulfur trioxide *N*,*N*-dimethylformamide complex (**4.3**) as sulfating agent. Condensation of **22.2** with various primary amines (**3.4b, 3.4c, 3.4d, 3.4g**) afforded the sulfonamide derivatives **22.3** which were converted to compounds **22A-22D** under basic conditions. Condensation of hydrazine hydrate (**5.1**) with the sulfonyl chloride derivative **22.2** provided the sulfonyl hydrazide **22.4**, which was converted to the sulfones **22.5** and **22.7** by treatment with methyl iodide (**2.8c**) and ethyl iodide (**22.6**), respectively, in the presence of sodium acetate. Deprotection of the trifluoroacetamide protecting group of **22.5** and **22.7** under basic conditions (potassium carbonate, methanol, water) provided the corresponding methyl sulfone (compound **22E**) and ethyl sulfone (compound **22F**) derivatives.

[0316] The synthesis of compounds **23A-23C** is outlined in Scheme 23. The 2'-hydroxyacetophenone **1.1a** was condensed with *tert*-butyl 3-oxopyrrolidine-1-carboxylate (**23.1a**) or *tert*-butyl 3-oxopiperidine-1-carboxylate (**23.1b**) in refluxing methanol in the presence of pyrrolidine to provide the racemic ketones **23.2a** (n=0) and **23.2b** (n=1), respectively. Conversion of the ketones **23.2** to the enol triflate derivatives **23.3** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivatives **23.3** with 4-(*N*,*N*-diethylaminocarbonyl)phenyl boronic acid **1.6** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded the Boc derivatives **23.4** which were converted to the final products compounds **23A** and **23B** (racemic mixtures) under acidic conditions. The 2'-hydroxyacetophenone **1.1a** was also condensed with 1-Boc-4-nortropinone (**23.5**) in refluxing methanol in the presence of pyrrolidine to provide the ketone **23.6**. Conversion of the ketone **23.6** to the enol triflate derivative **23.7** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivative **23.7** with 4-(*N*,*N*-diethylaminocarbonyl)phenyl boronic acid **1.6** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded the Boc derivative **23.8** which was converted to the final product compound **23C** under acidic conditions.

[0317] The synthesis of compounds **24A-24G** is outlined in Scheme 24. The 2'-hydroxyacetophenone **1.1a** was condensed with 1,4-cyclohexanedione *mono*-ethylene ketal (**24.1**) in refluxing methanol in the presence of pyrrolidine to provide the ketone **24.2**. Conversion of the ketone **24.2** to the enol triflate derivative **24.3** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivative **24.3** with 4-(*N*,*N*-diethylaminocarbonyl)phenyl boronic acid **1.6** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded the derivative **24.4** which was converted to the ketone compound **24A** under acidic conditions. The reduction of the ketone compound **24A**, conducted in tetrahydrofuran in the presence of sodium borohydride, provided the corresponding alcohol derivatives compounds **24B** and **24C**. Treatment of the ketone compound **24A** with propylamine (**3.4d**) or dimethylamine (**3.4j**) under reductive amination conditions using sodium cyanoborohydride as reducing agent, provided the amines compounds **24D-24G**.

[0318] The synthesis of compound **25A** is outlined in Scheme 25. The 2'-hydroxyacetophenone **1.1a** was also condensed with tetrahydropyran-4-one (**25.1**) in refluxing methanol in the presence of pyrrolidine to provide the ketone **25.2**. Conversion of the ketone **25.2** to the enol triflate derivative **25.3** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivative **25.3** with 4-(*N*,*N*-diethylaminocarbonyl)phenyl boronic acid **1.6** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compound **25A**.

[0319] The synthesis of compounds **26A-26B** is outlined in Scheme 26. Palladium catalyzed Negishi-type coupling of **1.5a** with 4-cyanobenzylzinc bromide (**26.1**) conducted in tetrahydrofuran using tetrakis triphenylphosphine palladium (0) as catalyst, provided the nitrile **26.2**. Acidic hydroysis of the nitrile **26.2** provided the carboxylic acid derivatives **26.3a** and **26.3b** (compounds **26.3a** and **26.3b** were separated by column chromatography; however, the following step was conducted using the mixture **26.3a / 26.3b**). Treatment of the mixture **26.3a / 26.3b** with methanol in the presence of hydrochloric acid afforded the piperidine esters **26.4a / 26.4b** which were converted to the corresponding Boc derivatives **26.5a / 26.5b** by treatment with *tert*-butyloxycarbonyl anhydride (**4.7**). Hydrolysis of the esters **26.5a / 26.5b** in basic conditions gave the carboxylic acid derivatives **26.6a / 26.6b**. Coupling of the carboxylic acid derivatives **26.6a / 26.6b** with diethylamine (**1.12**) using *O*-benzotriazol-1-yl-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate (TBTU) as coupling agent afforded the dimethylaminocarbonyl derivatives **26.7a / 26.7b**. Removal of the Boc protecting group of **26.7a / 26.7b** in dichloromethane at room temperature in the presence of hydrochloric acid (anhydrous solution in dioxane) afforded compounds **26A** and **26.8** which were separated by column chromatography. Palladium catalyzed hydrogenation of compound **26.8** afforded compound **26B.**

[0320] The synthesis of compounds **27A-27W** is outlined in Scheme 27. The saturated derivatives (compounds **27A, 27D, 27G, 27H, 27K, 27N,** and **27W**, as their racemic mixtures) were obtained by hydrogenation of the unsaturated analogs (compounds **1A, 1D, 2C, 1N, 1O, 1S,** and **1E**), respectively, in methanol in the presence of palladium, 10 wt.% (dry basis) on activated carbon (method 27A) or palladium hydroxide, 20 wt.% Pd (dry basis) on carbon (Pearlman's catalyst (method 27B)). Hydrogenation of **11.6a** in methanol in the presence of palladium hydroxide, 20 wt.% Pd (dry basis) on carbon (Pearlman's catalyst) provided the saturated derivative **27.1.** Acidic hydrolysis of **27.1** provided compound **27T**. Hydrolysis of **2.7a** in methanol in the presence of palladium, 10 wt.% (dry basis) on activated carbon, provided the saturated derivative **27.6**. Acidic hydrolysis of **27.6** provided the compound **27Q**. Chiral separation of the enantiomers derived from **27.1** provided compounds **27.4** and **27.5**. The enantiomers **27.4** and **27.5** were converted to compounds **27U** and **27V**, respectively under acidic conditions. Chiral separation of the enantiomers derived from each of the racemic compounds (compounds **27A, 27 D, 27G, 27H, 27K, 27N, 27Q** and **27W**) provided compounds **27B, 27E, 27I, 27L, 27O, 27R** (pure enantiomer) and compounds **27C, 27F, 27J, 27M, 27P, 27S** (pure enantiomer). Condensation of compound **27B** with (1*S*)-(+)-10-camphorsulfonyl chloride (**27.2**) (used as chiral resolving agent) in dichloromethane in the presence of triethylamine provided the chiral sulfonamide derivative **27.3**. The absolute configuration of **27.3** was determined by X-ray crystallography, therefore establishing the absolute configuration of compound **27B**, and therefore by inference, its enantiomer, compound **29C**.

[0321] The synthesis of compounds **28A-28E** is outlined in Scheme 28. Condensation of benzyl 4-oxopiperidine-1-carboxylate (**19.1**) with ethyl cyanoacetate (**28.1**) in the presence of acetic acid and ammonium acetate gave the unsaturated ester **28.2**. Compound **28.2** was subjected to conjugate addition by reaction with organo cuprate reagents derived from benzyl or methoxybenzyl magnesium chloride (**28.3a** and **28.3b**, respectively) and copper (I) cyanide to yield the cyano esters **28.4**. Treatment of the conjugate addition product **28.4a** (R^v =H) with concentrated sulfuric acid at 90 °C provided the amino ketone **28.5**. Treatment of **28.5** with benzyl chloroformate (**21.8**) in dichloromethane in the presence of triethylamine provided the corresponding Cbz-protected derivative **28.6a** (R^v =H). Decarboxylation of **28.4b** (R^v =OCH_3) by treatment with sodium chloride in dimethylsulfoxide containing small amount of water at 160°C afforded the nitrile **28.9**. Hydrolysis of the nitrile functionality of **28.9** to the methyl ester group by treatment with methanol in the presence of sulfuric acid provided the corresponding piperidine derivative (Cleavage of the Cbz protecting group of **28.9** occured during the course of the hydrolysis). Treatment of the piperidine derivative with benzyl chloroformate afforded the compound **28.10**. The ester **28.10** was hydrolyzed with lithium hydroxide to furnish the carboxylic acid **28.11**. Treatment of the acid **28.11** with oxalyl chloride followed by reaction of the resulting acyl chloride with aluminum chloride yielded the corresponding spiro piperidine derivative which was further protected as its CBz derivative **28.6b** (R^v =OCH_3) by treatment with benzylchloroformate. Conversion of the ketones **28.6** to the enol triflate derivatives **28.7** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivatives **28.7** with 4-(*N*,*N*-diethylaminocarbonyl)phenyl boronic acid **1.6** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded the derivatives **28.8** which were converted to the compounds **28A** and **28B** by treatment with iodotrimethylsilane. The compounds **28C** and **28D** (racemic mixtures) were obtained by hydrogenation of unsaturated derivatives **28.8** in methanol in the presence of palladium, 10 wt.% (dry basis) on activated carbon. Suzuki type coupling of the enol triflate derivative **28.7a** (R^v =H) with 2-(*N*,*N*-diethylaminocarbonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)pyridine **1.7** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded the derivative **28.12** which was converted to the compound **28E** by treatment with iodotrimethylsilane.

[0322] The synthesis of compounds **29A-29D** is outlined in Scheme 29. The Negishi coupling of the enol triflate **28.7a** with 4-(ethoxycarbonyl)phenylzinc iodide (**29.1**) in tetrahydrofuran in the presence of tetrakis triphenylphosphine palladium (0) gave the ester **29.2**, which was hydrolyzed with lithium hydroxide to afford the carboxylic acid **29.3**. Coupling of the carboxylic acid **29.3** with *iso*propylamine (**3.4h**) or

1-ethylpropylamine (**29.4**) using 2-chloro-1-methylpyridinium iodide (Mukaiyama acylating reagent) as coupling agent afforded the secondary aminocarbonyl derivatives **29.5**, which were converted to the compounds **29A** and **29B** by treatment with iodotrimethylsilane. Curtius rearrangement of the carboxylic acid **29.3** by reaction with diphenylphosphoryl azide (**29.6**) in the presence of *tert*-butyl alcohol provided the *tert*-butyloxycarbonyl (Boc) protected aniline derivative **29.7**. Acidic hydrolysis of **29.7** provided the aniline derivative **29.8** which reacted with propionyl chloride **29.9** or methanesulfonyl chloride (**7.4**) to give the corresponding amide derivative **29.10** or sulfonamide derivative **29.11**, respectively. The derivatives **29.10** and **29.11** were converted to compounds **29C** and **29D**, respectively, by treatment with iodotrimethylsilane.

[0323] The synthesis of compound **30A** is outlined in Scheme 30. Wittig type condensation of 1-benzoyl-4-piperidone (**30.1**) with methyl(triphenylphosphoranylidene)acetate (**30.2**) in toluene gave the unsaturated ester **30.3**. Compound **30.3** was subjected to conjugate addition by reaction with benzenethiol (**30.4**) to yield the thioether **30.5**. Treatment of the conjugate addition product **30.5** with concentrated sulfuric acid provided the cyclized product **30.6**, which was converted to the sulfone **30.7** by oxidation using a solution of hydrogen peroxide in glacial acetic acid. Acidic hydrolysis of **30.7** provided the amine **30.8**, which was treated with *tert*-butyloxycarbonyl anhydride (**4.7**) to give the Boc protected derivative **30.9**. Conversion of the ketone **30.9** to the enol triflate derivative **30.10** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivative **30.10** with 4-(*N*,*N*-diethylaminocarbonyl)phenyl boronic acid **1.6** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded the derivative **30.11** which was converted to compound **30A** under acidic conditions.

[0324] The synthesis of compounds **31A-31AA** is outlined in Scheme 31. Suzuki type coupling of the enol triflate derivative **1.5a** with the commercially available boronic acid derivatives **13.1**, **14.1**, **16.1** or **31.1a-31.1u** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compounds **13.2**, **14.2**, **16.2** and **31.2**, respectively. Compounds **13.2**, **14.2**, **16.2** and **31.2** were converted to the final products compounds **31A-31X** under acidic conditions (method 1E: anhydrous HCl, diethyl ether, room temperature or method 1F: neat trifluoroacetic acid (with optional dichloromethane), room temperature or method 31A: anhydrous HCl, methanol, dioxane, reflux). Treatment of the nitrile **16.2** with lithium aluminum hydride in tetrahydrofuran provided the diamine compound **31Y**, which reacted with acetyl chloride (**6.7**) or methanesulfonyl chloride (**7.4**) to give the corresponding amide derivative compounds **31Z** or the sulfonamide derivative compound **31AA**, respectively.

[0325] The synthesis of compounds **32A-32Z** is outlined in Scheme 32. Conversion of the enol triflate **1.5a** to the corresponding boron derivative **32.1** was achieved using 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane **1.14** and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct, abbreviated as [Pd(dppf)Cl_2•CH_2Cl_2]. Suzuki type coupling of the boronate derivative **32.1** with various aryl bromide derivatives **32.2** under different conditions [method 1C: ethylene glycol dimethyl ether, tetrakis triphenylphosphine palladium (0), lithium chloride, aqueous solution of sodium carbonate; method 1D: ethylene glycol dimethyl ether, palladium, 10 wt.% (dry basis) on activated carbon, lithium chloride, aqueous solution of sodium carbonate; method 12A: tetrakis triphenylphosphine palladium (0), potassium bromide, potassium phosphate, dioxane] afforded the derivatives **32.3**, which were converted to compounds **32A-32I** or **32K-32Z** under acidic conditions. The *tert*-butyl sulfonamide derivative compound **32.3b** was converted to the sulfonamide compound **32J** by treatment with trifluoroacetic acid. The derivatives

32.2 used in the Suzuki coupling step were prepared as follows. Coupling of the carboxylic acid **32.4** with diethylamine (**1.12**) using 2-chloro-1-methylpyridinium iodide (Mukaiyama acylating reagent) as coupling agent afforded 2-(4-bromophenyl)-*N*,*N*-diethylacetamide (**32.2a**). The sulfone derivatives **32.2j-32.2p** were obtained in two steps from 4-bromobenzenethiol (**32.7**). Alkylation of **32.7** with the alkyl bromide derivatives **20.2**, **2.8** or **32.8** in acetonitrile in the presence of triethylamine (method 32A) or in *N*,*N*-dimethylformamide in the presence of sodium hydride (method 32B) provided the thioether derivatives **32.9**, which were oxidized to the sulfone derivatives **32.2j-32.2p** in glacial acetic acid in the presence of an aqueous solution of hydrogen peroxide. Coupling of 4-bromobenzene-1-sulfonyl chloride (**32.5**) with various amines (**3.4**, **1.12**, **13.4** or **32.6**) in tetrahydrofuran in the presence of triethylamine provided the sulfonamides **32.2b-32.2i**. Acylation of *N*-methyl-4-bromoaniline (**32.10**) with various acyl chloride derivatives (**19.8**, **32.11** or **6.7**) in dichloromethane in the presence of triethylamine provided the amides **32.2q-32.2u**, **32.2x**, **32.2y**. The aryl bromides **32.2v** and **32.2w** are commercially available.

[0326] The synthesis of compounds **33A-33N** is outlined in Scheme 33. Suzuki type coupling of the boronate derivative **32.1** with various aryl bromide derivatives **33.1** under different conditions [method 1C: ethylene glycol dimethyl ether, tetrakis triphenylphosphine palladium (0), lithium chloride, aqueous solution of sodium carbonate; method 1D: ethylene glycol dimethyl ether, palladium, 10 wt.% (dry basis) on activated carbon, lithium chloride, aqueous solution of sodium carbonate; method 33A: ethylene glycol dimethyl ether, dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct, abbreviated as [Pd(dppf)Cl_2•CH_2Cl_2], lithium chloride, potassium phosphate; method 33B: dioxane, tetrakis triphenylphosphine palladium (0), potassium bromide, potassium phosphate] afforded the derivatives **33.2**, which were converted to compounds **33A-33K**, **33M** and **33N** under acidic conditions. The derivatives **33.1** used in the Suzuki coupling step were either obtained from commercial sources (**33.1 a-e,l,m**) or prepared as follows. Coupling of 5-bromopyridine-3-carboxylic acid (**33.3**) or 6-bromopyridine-2-carboxylic acid (**33.4**) with diethylamine (**1.12**) using *O*-benzotriazol-1-yl-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate (TBTU) as coupling agent afforded the diethylaminocarbonyl derivative derivatives **33.1f** and

33.1g, respectively. Treatment of 2,5-dibromopyridine (**1.9**) with *n*-butyllithium provided the corresponding lithiated derivative, which reacted with carbon dioxide to provide 5-bromopyridine-2-carboxylic acid **1.10**. The carboxylic acid **1.10** was also obtained by acidic hydrolysis of commercially available 5-bromopyridine-2-carbonitrile (**33.1e**). Treatment of the carboxylic acid derivative **1.10** with oxalyl chloride furnished the acyl chloride **1.11**, which reacted with dimethylamine (**3.4j**), ethylamine (**3.4c**) or methylamine (**3.4b**) to provide the corresponding aminocarbonyl derivatives **33.1h**, **33.1i** and **33.1j**, respectively. Treatment of commercially available 5-bromo-2-iodopyrimidine (**33.5**) with *n*-butyllithium provided the corresponding lithiated derivative, which reacted with carbon dioxide to provide 5-bromopyrimidine-2-carboxylic acid (**33.6**). Treatment of the carboxylic acid derivative **33.6** with oxalyl chloride furnished the acyl chloride **33.7**, which reacted with diethylamine **1.12** to provide 5-bromo-2-(*N*,*N*-diethylaminoarbonyl)-pyrimidine **33.1k**.

[0327] Hydrolysis of the nitrile derivative **33.2a** under acidic conditions provided the carboxylic acid derivative compound **33E** and compound **33L**. Compound **33E** and compound **33L** were readily separated by column chromatography.

[0328] The synthesis of compounds **34A-34P** is outlined in Scheme 34. Suzuki type coupling of the boronate derivative **32.1** with various aryl bromide derivatives **34.1** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compounds **34.2** which were converted to the final products compounds **34A-34P** under acidic conditions. The derivatives **34.1** used in the Suzuki coupling step were prepared as follow. Coupling of 6-bromopyridine-3-carboxylic acid (**34.3**), 5-bromothiophene-2-carboxylic acid (**34.4**), 4-bromothiophene-2-carboxylic acid (**34.7**) or 5-bromofuran-2-carboxylic acid (**34.6**) with diethylamine (**1.12**) or diisopropylamine (**3.4o**) using *O*-benzotriazol-1-yl-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate (TBTU) as coupling agent afforded the diethylaminocarbonyl derivatives **34.1 a-d**, **f-i**. Coupling of 5-bromothiophene-2-sulfonyl chloride (**34.5**) with diethylamine (**1.12**) in acetonitrile in the presence of triethylamine provided the sulfonamide **34.1e**. Coupling of the commercially available carboxylic acid derivatives **34.8a-34.8f** and **34.9** with diethylamine (**1.12**) using *O*-benzotriazol-1-yl-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate (TBTU) as coupling agent afforded the corresponding diethylaminocarbonyl derivatives **34.1j-34.1o** and **34.1p**.

[0329] The synthesis of compounds **35A** and **35B** is outlined in Scheme 35. Iodination of 3-hydroxybenzoic acid (**35.1**) afforded 3-hydroxy-4-iodobenzoic acid (**35.2**), which was converted to the methyl ester **35.3** under standard esterification conditions. Alkylation of the phenolic derivative **35.3** with methyl iodide (**2.8c**) in acetone in the presence of potassium carbonate afforded the methyl ether **35.4**, which was converted to the carboxylic acid **35.5** in the presence of lithium hydroxide. Coupling of the carboxylic acid derivatives **35.5** with diethylamine (**1.12**) using *O*-benzotriazol-1-yl-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate (TBTU) as coupling agent afforded the corresponding diethylaminocarbonyl derivative **35.6**. Demethylation of **35.6** using boron tribromide afforded the phenolic derivative **35.7** which was converted to the methyloxymethyl (MOM) ether derivative **35.8** using chloro(methoxy)methane **11.3**. Suzuki type coupling of the boronate derivative **32.1** with **35.6** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compound **35.9** which was converted to the final product compound **35A** under acidic conditions. Suzuki type coupling of the boronate derivative **32.1** with **35.8** in ethylene glycol dimethyl ether in the presence of palladium, 10 wt.% (dry basis) on activated carbon, lithium chloride, and an aqueous solution of sodium carbonate afforded compound **35.10** which was converted to the final product compound **35B** under acidic conditions.

[0330] The synthesis of compounds **36A** and **36B** is outlined in Scheme 36. Coupling of 4-bromo-2-hydroxybenzoic acid (**36.3**) [obtained from 4-amino-2-hydroxybenzoic acid (**36.1**) under Sandmeyer conditions] with diethylamine (**1.12**) using *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate (HATU) as coupling agent afforded the corresponding diethylaminocarbonyl derivative **36.4**. Suzuki type coupling of the boronate derivative **32.1** with **36.4** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compound **36.5** which was converted to the final product (compound **36A**) under acidic conditions. Compound **36B** was obtained in 7 steps from 2-(3-methoxyphenyl)ethanamine (**36.6**). Coupling of **36.6** with ethyl chloroformate (**36.7**) afforded the ethyl carbamate derivative **36.8** which was cyclized to 3,4-dihydro-6-methoxyisoquinolin-1-(2*H*)-one (**36.9**) in the presence of polyphosphoric acid. Alkylation of **36.9** with ethyl iodide (**36.10**) in tetrahydrofuran in the presence of sodium hydride, afforded the methyl ether **36.11**, which was converted to the phenolic derivative **36.12** by treatment with boron tribromide. Condensation of **36.12** with trifluoromethanesulfonic anhydride (**36.13**) in dichloromethane in the presence of pyridine afforded the triflate derivative **36.14**. Suzuki type coupling of the boronate derivative **32.1** with **36.14** in *N*,*N*-dimethylformamide in the presence of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct, abbreviated as [Pd(dppf)Cl_2•CH_2Cl_2], and potassium acetate afforded compound **36.15** which was converted to the final product (compound **36B**) under acidic conditions.

[0331] The synthesis of compounds **37A-37B** is outlined in Scheme 37. The 2'-hydroxyacetophenone **1.1a** was condensed with 1-benzyl-3-methylpiperidin-4-one (**37.1**) (racemic mixture) in refluxing methanol in the presence of pyrrolidine to provide the racemic ketones **37.2** and **37.3**. The diastereoisomers **37.2** and **37.3** were separated by column chromatography. Palladium catalyzed hydrogenation of **37.2** afforded the piperidine derivative **37.4**, which was converted to **37.5** by treatment with *tert*-butyloxycarbonyl anhydride (**4.7**). Conversion of the ketone **37.5** to the enol triflate derivative **37.6** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivative **37.6** with 4-(*N*,*N*-diethylaminocarbonyl)phenyl boronic acid **1.6** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded the Boc derivative **37.7**, which was converted to the final product compound **37A** (racemic mixture) under acidic conditions. Similarly, palladium catalyzed hydrogenation of **37.3** afforded the piperidine derivative **37.8**, which was converted to **37.9** by treatment with *tert*-butyloxycarbonyl anhydride (**4.7**). Conversion of the ketone **37.9** to the enol triflate derivative **37.10** was achieved using

N-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivative **37.10** with 4-(*N*,*N*-diethylaminocarbonyl)phenyl boronic acid **1.6** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded the Boc derivative **37.11,** which was converted to the final product compound **37B** (racemic mixture) under acidic conditions.

[0332] The synthesis of compounds **38A-38D** is outlined in Scheme 38. Condensation of benzyl 4-oxopiperidine-1-carboxylate (**19.1**) with 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid; **38.1**) in the presence of pyridine and piperidine gave the derivative **38.2**. Compound **38.2** was subjected to conjugate addition by reaction with organocuprate reagents derived from 4-fluorobenzyl magnesium chloride (**38.3**) and copper (I) iodide to yield, upon work-up, the sodium salt **38.4**. Hydrolysis and decarboxylation of the conjugate addition product **38.4** proceeded by heating a solution of **38.4** in *N*,*N*-dimethylformamide in the presence of water. Treatment of the corresponding carboxylic acid derivative **38.5** with oxalyl chloride followed by reaction of the resulting acyl chloride with aluminum chloride yielded the corresponding spiro piperidine derivative which was further protected as its *tert*-butyloxycarbonyl (Boc) derivative **38.6** by treatment with *tert*-butyloxycarbonyl anhydride (**4.7**). Conversion of the ketone **38.6** to the enol triflate derivative **38.7** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivative **38.7** with 2-(*N*,*N*-diethylaminocarbonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)pyridine **1.7** in dioxane in the presence of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct {[Pd(dppf)Cl_2•CH_2Cl_2]}, and an aqueous solution of potassium carbonate afforded the derivative **38.8** which was converted to the compound **38A** under acidic conditions. The compound **38B** (racemic mixture) was obtained by hydrogenation of the unsaturated derivative **38A** in methanol in the presence of palladium, 10 wt.% (dry basis) on activated carbon. Conversion of the enol triflate **38.7** to the corresponding boron derivative **38.9** was achieved using 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane **1.14** and dichloro[1,1'-

bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct {[Pd(dppf)Cl_2•CH_2Cl_2]}. Suzuki type coupling of the boron derivative **38.9** with the aryl iodide derivative **35.8** in dioxane in the presence of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct {[Pd(dppf)Cl_2•CH_2Cl_2]}, and an aqueous solution of potassium carbonate afforded the derivative **38.10** which was converted to the compound **38C** under acidic conditions. Hydrogenation of the unsaturated derivatives **38.10** in methanol in the presence of palladium, 10 wt.% (dry basis) on activated carbon provided the compound **38.11**, which was converted to the compound **38D** under acidic conditions.

[0333] The synthesis of compounds **39A-39G** is outlined in Scheme 39. Compound **38.2** was subjected to conjugate addition by reaction with organocuprate reagents derived from benzyl magnesium chloride (**28.3a**) and copper (I) iodide to yield, upon work-up, the sodium salt **39.1**. Hydrolysis and decarboxylation of the conjugate addition product **39.1** proceeded by heating a solution of **39.1** in *N*,*N*-dimethylformamide in the presence of water. Treatment of the corresponding carboxylic acid derivative **39.2** with oxalyl chloride followed by reaction of the resulting acyl chloride with aluminum chloride yielded the corresponding spiro piperidine derivative which was further protected as its CBz derivative **28.6a** (R^v =H) by treatment with benzylchloroformate. Conversion of the ketone **28.6a** to the enol triflate derivative **28.7a** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivatives **28.7a** 2-(*N*,*N*-diethylaminocarbonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)pyridine **1.7** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded the derivative **28.12** which was converted to the compound **39A** by hydrogenation in methanol in the presence of palladium, 10 wt.% (dry basis) on activated carbon. Treatment of compound **39A** with *tert*-butyloxycarbonyl anhydride (**4.7**) provided the Boc derivative **39.3**. Chiral separation of the enantiomers derived from **39.3** provided compounds **39.4** and **39.5**. The enantiomers **39.4** and **39.5** were converted to compounds **39B** and **39C**, respectively under acidic conditions. Suzuki type coupling of the enol triflate derivatives **28.7a** with *N*,*N*-diethyl-3-(methoxymethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-

dioxaborolan-2-yl)benzamide **39.6** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded the derivative **39.7** which was converted to the compound **39D** by treatment with iodotrimethylsilane followed by acidic cleavage of the MOM protecting group. Hydrogenation of **39.7** in methanol, in the presence of palladium, 10 wt.% (dry basis) on activated carbon, followed by acidic cleavage of the MOM protecting group, afforded compound **39E**. Treatment of compound **39E** with *tert*-butyloxycarbonyl anhydride (**4.7**) provided the Boc derivative **39.8**. Chiral separation of the enantiomers derived from **39.8** provided compounds **39.9** and **39.10**. The enantiomers **39.9** and **39.10** were converted to compounds **39F** and **39G**, respectively under acidic conditions.

[0334] The synthesis of compounds **40A-40C** is outlined in Scheme 40. Compound **38.2** was subjected to conjugate addition by reaction with organocuprate reagents derived from 4-methoxybenzyl magnesium chloride (**28.3b**) and copper (I) iodide to yield, upon work-up, the sodium salt **40.1**. Hydrolysis and decarboxylation of the conjugate addition product **40.1** proceeded by heating a solution of **40.1** in *N*,*N*-dimethylformamide in the presence of water. Treatment of the corresponding carboxylic acid derivative **28.11** with oxalyl chloride followed by reaction of the resulting acyl chloride with aluminum chloride yielded the corresponding spiro piperidine derivative which was further protected as its CBz derivative **28.6b** (R^v $=OCH_3$) by treatment with benzylchloroformate. Conversion of the ketone **28.6b** to the enol triflate derivative **28.7b** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivatives **28.7b** with 2-(*N*,*N*-diethylaminocarbonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)pyridine **1.7** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded the derivative **40.2** which was converted to the compound **40A** by treatment with iodotrimethylsilane. Hydrogenation of **40.2** in methanol in the presence of palladium, 10 wt.% (dry basis) on activated carbon afforded compound **40B** (racemic mixture). Suzuki type coupling of the enol triflate derivatives **28.7b** with *N*,*N*-diethyl-3-(methoxymethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide **39.6** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded the derivative **40.3** which was converted to the compound **40C** by treatment with iodotrimethylsilane.

[0335] The synthesis of compounds **41A-41E** is outlined in Scheme 41. Coupling of the carboxylic acid **13.3** with *N*-ethyl-2-methoxyethanamine (**41.1**) using *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) as coupling agent afforded the tertiary aminocarbonyl derivative **41.2**, which was converted to compound **41A** under acidic conditions. Coupling of the carboxylic acid **13.3** with *N*-ethyl-*N,N*-dimethylethane-1,2-diamine (**41.3**) using TBTU as coupling agent afforded the tertiary aminocarbonyl derivative **41.4**, which was converted to compound **41B** under acidic conditions. Coupling of the carboxylic acid **13.3** with *N*-(3-(ethylamino)propyl)-2,2,2-trifluoroacetamide (**41.7**) (obtained by treatment of *N*-ethylpropane-1,3-diamine **41.5** with ethyl 2,2,2-trifluoroacetate **41.6**) using TBTU as coupling agent afforded the tertiary aminocarbonyl derivative **41.8**, which was converted to **41.9** under basic conditions. Treatment of **41.9** with 2-nitrobenzene-1-sulfonyl chloride (**41.10**) afforded the sulfonamide derivative **41.11**, which was converted to **41.12** by treatment with methyl iodide. Thiophenol-mediated deprotection of **41.12** afforded the derivative **41.13**, which was converted to the final compound **41C** under acidic conditions. Coupling of the carboxylic acid **13.3** with *N,N*-dimethylpropane-1,3-diamine (**41.14**) using TBTU as coupling agent afforded the tertiary aminocarbonyl derivative **41.15**, which was converted to compound **41D** under acidic conditions. Coupling of the carboxylic acid **13.3** with *N*-(2-(ethylamino)ethyl)-2,2,2-trifluoroacetamide (**41.17**) (obtained by treatment of *N*-ethylethane-1,2-diamine **41.16** with ethyl 2,2,2-trifluoroacetate **41.6**) using TBTU as coupling agent afforded the tertiary aminocarbonyl derivative **41.18**, which was converted to **41.19** under basic conditions. Treatment of compound **41.19** with *tert*-butyloxycarbonyl anhydride (**4.7**) provided the bis-Boc derivative **41.20**. Treatment of **41.20** with methyl iodide in the presence of sodium hydride afforded the derivative **41.21**, which was converted to the compound **41E** under acidic conditions.

[0336] The synthesis of compounds **42A-42I** is outlined in Scheme 42. Suzuki type coupling of the enol triflate derivatives **21.6** with 2-(*N,N*-

diethylaminocarbonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)pyridine **1.7** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compound **42.1** (racemic mixture) which was converted to compound **42C** under acidic conditions. Chiral separation of the enantiomers derived from **42.1** provided compounds **42.2** and **42.3**. The enantiomers **42.2** and **42.3** were converted to compounds **42A** and **42B**, respectively under acidic conditions. Conversion of the enol triflate **21.6** to the corresponding boron derivative **42.4** was achieved using 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane **1.14** and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct {[Pd(dppf)Cl_2•CH_2Cl_2]}. Suzuki type coupling of the boron derivative **42.4** with the aryl bromide **34.1a** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compound **42.5** (racemic mixture), which was converted to compound **42F** under acidic conditions. Chiral separation of the enantiomers derived from **42.5** provided compounds **42.6** and **42.7**. The enantiomers **42.6** and **42.7** were converted to compounds **42D** and **42E**, respectively under acidic conditions. Suzuki type coupling of the boron derivative **42.4** with the aryl iodide **35.8** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compound **42.8** (racemic mixture), which was converted to compound **42I** under acidic conditions. Chiral separation of the enantiomers derived from **42.8** provided compounds **42.9** and **42.10**. The enantiomers **42.9** and **42.10** were converted to compounds **42G** and **42H**, respectively under acidic conditions.

[0337] The synthesis of compounds **43A-43F** is outlined in Scheme 43. The 2'-6'-dihydroxyacetophenone derivative **11.1** was condensed with *tert*-butyl 4-oxoazepane-1-carboxylate **21.4** in refluxing methanol in the presence of pyrrolidine to provide the derivative **43.1** which was converted to the methoxymethyl (MOM) ether derivative **43.2** using chloro(methoxy)methane (**11.3**). Conversion of the ketone **43.2** to the enol triflate derivative **43.3** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivative **43.3** with 4-(*N*,*N*-

diethylaminocarbonyl)phenyl boronic acid **1.6** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compound **43.4** (racemic mixture). Removal of the MOM and the Boc protecting groups of **43.4** in methanol at room temperature in the presence of hydrochloric acid (anhydrous solution in dichloromethane) afforded compound **43C** (racemic mixture). Chiral separation of the enantiomers derived from **43.4** provided compounds **43.5** and **43.6**. The enantiomers **43.5** and **43.6** were converted to compounds **43A** and **43B**, respectively under acidic conditions. Suzuki type coupling of the enol triflate derivative **43.3** with 2-(*N*,*N*-diethylaminocarbonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)pyridine **1.7** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compound **43.7** (racemic mixture). Removal of the MOM and the Boc protecting groups of **43.7** in methanol at room temperature in the presence of hydrochloric acid (anhydrous solution in dichloromethane) afforded compound **43F** (racemic mixture). Chiral separation of the enantiomers derived from **43.7** provided compounds **43.8** and **43.9**. The enantiomers **43.8** and **43.9** were converted to compounds **43D** and **43E**, respectively under acidic conditions.

[0338] The synthesis of compounds **44A-44F** is outlined in Scheme 44. The 5'-fluoro-2'-hydroxy-acetophenone derivative **1.1d** was condensed with *tert*-butyl 4-oxoazepane-1-carboxylate **21.4** in refluxing methanol in the presence of pyrrolidine to provide the derivative **44.1**. Conversion of the ketone **44.1** to the enol triflate derivative **44.2** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivative **44.2** with 2-(*N*,*N*-diethylaminocarbonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)pyridine **1.7** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compound **44.3** (racemic mixture) which was converted to compound **44C** under acidic conditions. Chiral separation of the enantiomers derived from **44.3** provided compounds **44.4** and **44.5**. The enantiomers **44.4** and **44.5** were converted to compounds **44A** and **44B**, respectively under acidic conditions. Conversion of the enol triflate **44.2** to the corresponding boron derivative **44.6** was achieved using

4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane **1.14** and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct{[Pd(dppf)Cl_2•CH_2Cl_2]}. Suzuki type coupling of the boron derivative **44.6** with the aryl bromide **34.1a** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compound **44.7** (racemic mixture), which was converted to compound **44F** under acidic conditions. Chiral separation of the enantiomers derived from **44.7** provided compounds **44.8** and **44.9**. The enantiomers **44.8** and **44.9** were converted to compounds **44D** and **44E**, respectively under acidic conditions.

[0339] The synthesis of compounds **45A-45F** is outlined in Scheme 45. Suzuki type coupling of the boron derivative **44.6** with the aryl iodide **35.8** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compound **45.1** (racemic mixture), which was converted to compound **45C** under acidic conditions. Chiral separation of the enantiomers derived from **45.1** provided compounds **45.2** and **45.3**. The enantiomers **45.2** and **45.3** were converted to compounds **45A** and **45B**, respectively under acidic conditions. The 2'-5'-dihydroxyacetophenone derivative **2.1** was condensed with *tert*-butyl 4-oxoazepane-1-carboxylate **21.4** in refluxing methanol in the presence of pyrrolidine to provide the derivative **45.4** which was converted to the silyl ether derivative **45.5** using *tert*-butyldimethylsilyl chloride **2.3**. Conversion of the ketone **45.5** to the enol triflate derivative **45.6** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivative **45.6** with 2-(*N*,*N*-diethylaminocarbonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)pyridine **1.7** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compound **45.7** (racemic mixture), which was converted to compound **45F** under acidic conditions. Chiral separation of the enantiomers derived from **45.7** provided compounds **45.8** and **45.9**. The enantiomers **45.8** and **45.9** were converted to compounds **45D** and **45E**, respectively under acidic conditions.

[0340] The synthesis of compounds **46A-46C** is outlined in Scheme 46. Suzuki type coupling of the enol triflate derivative **45.6** with 4-(*N*,*N*-diethylaminocarbonyl)phenyl boronic acid **1.6** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compound **46.1** (racemic mixture), which was converted to compound **46C** under acidic conditions. Treatment of **46.1** with chloro(methoxy)methane (**11.3**) provided the methoxymethyl (MOM) ether derivative **46.2** (racemic mixture). Chiral separation of the enantiomers derived from **46.2** provided compounds **46.3** and **46.4**. The enantiomers **46.3** and **46.4** were converted to compounds **46A** and **46B**, respectively under acidic conditions.

[0341] The synthesis of compounds **47A-47F** is outlined in Scheme 47. Suzuki type coupling of the enol triflate derivative **23.3a** with 2-(*N*,*N*-diethylaminocarbonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)pyridine **1.7** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compound **47.1** (racemic mixture) which was converted to compound **47A** under acidic conditions. Conversion of the enol triflate **23.3a** to the corresponding boron derivative **47.2** was achieved using 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane **1.14** and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct {[Pd(dppf)Cl_2•CH_2Cl_2]}. Suzuki type coupling of the boron derivative **47.2** with the aryl iodide **35.8** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compound **47.3** (racemic mixture), which was converted to compound **47B** under acidic conditions. The 2'-6'-dihydroxyacetophenone derivative **11.1** was condensed with *tert*-butyl 3-oxopyrrolidine-1-carboxylate **23.1a** in refluxing methanol in the presence of pyrrolidine to provide the derivative **47.4** which was converted to the methoxymethyl (MOM) ether derivative **47.5** using chloro(methoxy)methane (**11.3**). Conversion of the ketone **47.5** to the enol triflate derivative **47.6** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivative **47.6** with compound **1.6** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compound **47.7** (racemic mixture). Removal of the MOM and the Boc protecting groups of **47.7** in methanol at room temperature in the presence of hydrochloric acid afforded compound **47C** (racemic mixture). Suzuki type coupling of the enol triflate derivative **47.6** with 2-(*N*,*N*-diethylaminocarbonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)pyridine **1.7** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compound **47.8** (racemic mixture). Removal of the MOM and the Boc protecting groups of **47.8** in methanol at room temperature in the presence of hydrochloric acid afforded compound **47D** (racemic mixture). The 2'-5'-dihydroxyacetophenone derivative **2.1** was condensed with *tert*-butyl 3-oxopyrrolidine-1-carboxylate **23.1a** in refluxing methanol in the presence of pyrrolidine to provide the derivative **47.9** which was converted to the silyl ether derivative **47.10** using *tert*-butyldimethylsilyl chloride **2.3**. Conversion of the ketone **47.10** to the enol triflate derivative **47.11** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivative **47.11** with compound **1.6** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compound **47.12** (racemic mixture), which was converted to compound **47E** under acidic conditions. Suzuki type coupling of the enol triflate derivative **47.11** with 2-(*N*,*N*-diethylaminocarbonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)pyridine **1.7** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compound **47.13** (racemic mixture), which was converted to compound **47F** under acidic conditions.

[0342] The synthesis of compounds **48A-48F** is outlined in Scheme 48. Suzuki type coupling of the enol triflate derivative **1.5f** with 4-cyanophenylboronic acid (**14.1**) in dioxane in the presence of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct, and an aqueous solution of potassium carbonate afforded the cyanide **48.1** which was converted to the tetrazole **48.2** using sodium azide (**14.3**) and zinc bromide in a solution isopropanol/water. Alkylation of **48.2** with methyl iodide (**2.8c**) in *N*,*N*-dimethylformamide in the presence of triethylamine afforded the two regioisomers **48.3** (major isomer) and **48.4** (minor isomer) separated by silica gel column chromatography. The Boc protecting group of **48.2**, **48.3**, and **48.4** was removed using hydrochloric acid to generate the compounds **48A-48C**. Conversion of the enol triflate **1.5f** to the corresponding boron derivative **48.5** was achieved using 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane **1.14** and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct{[Pd(dppf)$Cl_2 \cdot CH_2Cl_2$]}. Suzuki type coupling of the boron derivative **48.5** with the aryl bromide **34.1a** in dioxane in the presence of tetrakis triphenylphosphine palladium (0), potassium bromide and potassium phosphate afforded compound **48.8** (racemic mixture), which was converted to compound **48F** under acidic conditions. Suzuki type coupling of the boron derivative **48.5** with the bromothiophene derivatives **34.1c** and **34.1d** in dioxane in the presence of and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct, and an aqueous solution o potassium carbonate afforded compound **48.6** and **48.7** respectively. Compounds **48.6** and **48.7** were converted to compound **48D** and **48E**, respectively, under acidic conditions.

[0343] The synthesis of compounds **49A-49D** is outlined in Scheme 49. The 6'-fluoro-2'-hydroxy-acetophenone derivative **49.1** was condensed with 1-Boc-4-piperidone **1.2** in methanol at 0°C in the presence of pyrrolidine to provide the derivative **49.2**. Conversion of the ketone **49.2** to the enol triflate derivative **49.3** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivative **49.3** with 4-(*N*,*N*-diethylaminocarbonyl)phenyl boronic acid **1.6** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compound **49.4** which was converted to compound **49A** under acidic conditions. Treatment of **49.2** with pyrrolidine afforded compound **49.5**. Conversion of the ketone **49.5** to the enol triflate derivative **49.6** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivative **49.6** with 4-(*N*,*N*-

diethylaminocarbonyl)phenyl boronic acid **1.6** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride, and an aqueous solution of sodium carbonate afforded compound **49.7** which was converted to compound **49B** under acidic conditions. Conversion of the enol triflate **1.5d** to the corresponding boron derivative **49.8** was achieved using 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane **1.14** and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct{[Pd(dppf)Cl_2•CH_2Cl_2]}. Suzuki type coupling of the boron derivative **49.8** with the aryl iodide **35.8** in dioxane in the presence of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct and an aqueous solution of potassium carbonate afforded compound **49.9**, which was converted to compound **49C** under acidic conditions. Hydrogenation of the unsaturated derivative **49C** in methanol in the presence of palladium, 10 wt.% (dry basis) on activated carbon provided the compound **49D** (racemic mixture).

[0344] The synthesis of compounds **50A-50D** is outlined in Scheme 50. Suzuki type coupling of the enol triflate derivative **2.5** with phenyl boronic acid **31.1g** in ethylene glycol dimethyl ether, in the presence of palladium, 10 wt.% (dry basis) on activated carbon, lithium chloride, and an aqueous solution of sodium carbonate afforded compound **50.1**. Conversion of the phenol **50.1** to the triflate derivative **50.2** was achieved using the triflating reagent *N*-phenylbis(trifluoromethanesulphonimide) **1.4**. Palladium catalyzed carbonylation of **50.2**, conducted in a mixture of dimethylsulfoxide/methanol using palladium (II) acetate, 1,1'-bis(diphenylphosphino)ferrocene (dppf) and carbon monoxide, provided the methyl ester **50.3** which was hydrolyzed under basic conditions to give the carboxylic acid derivatives **50.4**. Coupling of the carboxylic acid **50.4** with diethylamine (**1.12**) using TBTU as coupling agent afforded the tertiary amide **50.5**. Treatment of the Boc derivatives **50.3**, **50.4**, **50.5** and **50.1** with hydrochloric acid provided the final compounds **50A-50D**, respectively.

[0345] The synthesis of compounds **51A-51C** is outlined in Scheme 51. The 2'-hydroxyacetophenone **1.1a** was condensed with *tert*-butyl 2-methyl-4-oxopiperidine-1-carboxylate (**51.1**) (racemic mixture) in refluxing methanol in the presence of pyrrolidine to provide the racemic ketone **51.2**. Conversion of the ketone **51.2** to the enol triflate derivative **51.3** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivative **51.3** with 4-(*N*,*N*-diethylaminocarbonyl)phenyl boronic acid **1.6** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), potassium bromide, and potassium phosphate afforded the Boc derivative **51.4** (product eluted as a single peak), which was converted to compound **51C** under acidic conditions. Chiral separation of the intermediate **51.4** provided resolved products **51.5** and **51.6**. The resolved products **51.5** and **51.6** were converted to compounds **51A** and **51B**, respectively under acidic conditions.

[0346] The synthesis of compounds **52A-52F** is outlined in Scheme 52. Treatment of compound **21C** with trifluoroacetic anhydride (**4.1**) in tetrahydrofuran in the presence of triethylamine provided the trifluoroacetamide derivative **52.1** which was converted to the sulfonyl chloride **52.2** using sulfur trioxide *N*,*N*-dimethylformamide complex (**4.3**) as sulfating agent. Condensation of hydrazine hydrate (**5.1**) with the sulfonyl chloride derivative **52.2** provided the sulfonyl hydrazide **52.3**, which was converted to the sulfone **52.4** by treatment with methyl iodide (**2.8c**) in the presence of sodium acetate. Deprotection of the trifluoroacetamide protecting group of **52.4** under basic conditions (potassium carbonate, methanol, water) provided the methyl sulfonyl analog (compound **52A**) [Note: compound **52A** (derived from compound **21C**) and **22E** (derived from compound **21B**) are enantiomeric with respect to one another]. Palladium catalyzed hydrogenation of compound **22E** affords compounds **52B** and **52C**, respectively. Palladium catalyzed hydrogenation of compounds **35B**, **1Q**, and **1F** affords compounds **52D**, **52E**, and **52F**, respectively.

[0347] The synthesis of compounds **53A-53F** is outlined in Scheme 53. Treatment of compounds **48.2** and **48.3** with hydrobromic acid provided the phenolic derivatives **53A** and **53B**, respectively. Suzuki type coupling of the enol triflate derivative **11.5** with 4-(carboxy)phenylboronic acid (**53.1**) in dioxane in the presence of tetrakis triphenylphosphine palladium (0), and an aqueous solution of potassium carbonate afforded the carboxylic acid derivative **53.2** which was converted to **53D** under acidic conditions. The carboxylic acid derivative **53D** was converted to its methyl ester analog **53C** under classical esterification conditions, i.e. in the presence of concentrated hydrochloric acid and methanol. Coupling of the carboxylic acid **53.2** with ammonium chloride (**3.4a**) in acetonitrile, in the presence of *N*,*N*-diisopropylethylamine (Hunig's base), using *O*-benzotriazol-1-yl-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate (TBTU) as coupling agent affords the primary aminocarbonyl derivative **53.3**. Coupling of the carboxylic acid **53.2** with ethylamine (**3.4c**) in acetonitrile, in the presence of *N*,*N*-diisopropylethylamine (Hunig's base), using *O*-benzotriazol-1-yl-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate (TBTU) as coupling agent afforded the secondary aminocarbonyl derivative **53.4**. Treatment of the derivative **53.4** with hydrochloric acid provided the final compounds **53F**. Treatment of the derivative **53.3** with hydrochloric acid provides the final compound **53E**.

[0348] The synthesis of compounds **54A** and **54B** is outlined in Scheme 54. Condensation of benzyl 4-oxoazepane-1-carboxylate (**54.1**) (obtained by treatment of azepan-4-one **21.3** with benzylchloroformate) with 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid; **38.1**) in the presence of pyridine and piperidine gave the derivative **54.2**. The compound **54.2** was subjected to conjugate addition by reaction with organo cuprate reagents derived from benzyl magnesium chloride (**28.3a**) and copper (I) iodide to yield, upon work-up, the sodium salt **54.3**. Hydrolysis and decarboxylation of the conjugate addition product **54.3** proceeded by heating a solution of **54.3** in *N*,*N*-dimethylformamide in the presence of water. Treatment of the corresponding carboxylic acid derivative **54.4** with oxalyl chloride followed by reaction of the resulting acyl chloride with aluminum chloride yielded the corresponding spiro piperidine derivative which was further protected as its *tert*-butyloxycarbonyl (Boc) derivative **54.5** by treatment with *tert*-butyloxycarbonyl anhydride (**4.7**). Conversion of the ketone **54.5** to the enol triflate derivative **54.6** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivatives **54.6** with 4-(*N*,*N*-diethylaminocarbonyl)phenyl boronic acid **1.6** in dioxane in the presence of tetrakis triphenylphosphine palladium (0) and an aqueous solution of potassium carbonate afforded compound **54.7**, which was converted to compound **54A** under acidic conditions. Suzuki type coupling of the enol triflate derivative **54.6** with 2-(*N*,*N*-diethylaminocarbonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)pyridine **1.7** in dioxane in the presence of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct and an aqueous solution of potassium carbonate afforded compound **54.8**, which was converted to compound **54B** under acidic conditions.

[0349] The synthesis of compounds **55A-C** is outlined in Scheme 55. The compound **38.2** was subjected to conjugate addition by reaction with organo cuprate reagents derived from 3,5-dimethoxybenzyl magnesium bromide (**55.1**) and copper (I) iodide to yield, upon work-up, the sodium salt **55.2**. Hydrolysis and decarboxylation of the conjugate addition product **55.2** proceeded by heating a solution of **55.2** in *N*,*N*-dimethylformamide in the presence of water. Treatment of the corresponding carboxylic acid derivative **55.3** with oxalyl chloride followed by reaction of the resulting acyl chloride with aluminum chloride yielded the corresponding spiro piperidine derivative, which was further protected as its CBz derivative **55.4** by treatment with benzylchloroformate. Conversion of the ketone **55.4** to the enol triflate derivative **55.5** was achieved using *N*-phenylbis(trifluoromethanesulphonimide) **1.4** as triflating reagent. Suzuki type coupling of the enol triflate derivatives **55.5** with 4-(*N*,*N*-diethylaminocarbonyl)phenyl boronic acid **1.6** in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0), lithium chloride and an aqueous solution of sodium carbonate afforded compound **55.6** which was converted to either the compound **55C** by treatment with iodotrimethylsilane or the compound **55A** by treatment with boron tribromide. Treatment of **55A** with *tert*-butyloxycarbonyl anhydride (**4.7**) provided the corresponding Boc derivative **55.7**. Condensation of **55.7** with *N*-phenylbis(trifluoromethanesulphonimide) **1.4** provided the corresponding monotriflate derivative **55.8** which was converted to compound **55.9** by treatment with triethylsilane in the presence of 1,3-bis(diphenylphosphino)propane (dppp) and palladium (II) acetate. Acidic deprotection of the Boc-protecting group of **55.9** provided the compound **55B**.

[0350] The synthesis of compounds **56A** –**56D** is outlined in Scheme 56. Boron tribromide-mediated demethylation of **28.8b** provided the phenolic derivative **56A**, which was converted to **56B** under hydrogenation conditions. Similarly, boron tribromide-mediated demethylation of **40.3** provided the phenolic derivative **56C**, which was converted to **56D** under hydrogenation conditions.

[0351] The synthesis of compounds **57A-57D** is outlined in Scheme 57. Treatment of compound **31J** with trifluoroacetic anhydride (**4.1**) in tetrahydrofuran in the presence of triethylamine provided the trifluoroacetamide derivative **57.1** which was converted to the sulfonyl chloride **57.2** using sulfur trioxide *N*,*N*-dimethylformamide complex (**4.3**) as sulfonating agent. Condensation of **57.2** with methylamine (**3.4b**) and dimethylamine (**3.4j**) affords the corresponding sulfonamide derivatives **57.3** which are converted to compounds **57A**, **57B** under basic conditions. Condensation of **57.2** with ammonium hydroxide yields the compound **57C**. Condensation of hydrazine hydrate (**5.1**) with the sulfonyl chloride derivative **57.2** provided the sulfonyl hydrazide **57.4**, which was converted to the sulfone **57.5** by treatment with methyl iodide (**2.8c**) in the presence of sodium acetate. Deprotection of the trifluoroacetamide protecting group of **57.5** under basic conditions (potassium carbonate, methanol, water) provided the compound **57D**.

[0352] The synthesis of compounds **58A-58D** is outlined in Scheme 58. Suzuki type coupling of the enol triflate derivative **2.5** with either 3-(1,3,2-dioxaborinan-2-yl)pyridine (**3.6a**) or benzo[b]thiophen-2-ylboronic acid (**31.1n**) in dioxane in the presence of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (abbreviated as [Pd(dppf)Cl_2•CH_2Cl_2]) and an aqueous solution of potassium carbonate afforded compounds **58.1**. The derivatives **58.1a** and **58.1b** were then converted to the final products **58A** and **58B**, resepectively, under acidic conditions. Suzuki type coupling of the enol triflate derivative **2.5** with phenyl boronic acid (**31.1g**) in ethylene glycol dimethyl ether in the presence of tetrakis triphenylphosphine palladium (0) and an aqueous solution of potassium carbonate afforded compound **58.2**. Removal of the silyl protecting group of **58.2** using a solution of tetrabutylammonium fluoride (TBAF) in tetrahydrofuran gave the phenolic derivatives **58.3**. Preparation of each of the ether derivatives **58.5** from the phenol **58.3** was achieved by alkylation reaction using the appropriate alkyl iodide or alky chloride (**2.8c**, **58.4**) reagent. Treatment of the Boc derivatives **58.5** with hydrochloric acid provided the final compounds **58C-D**.

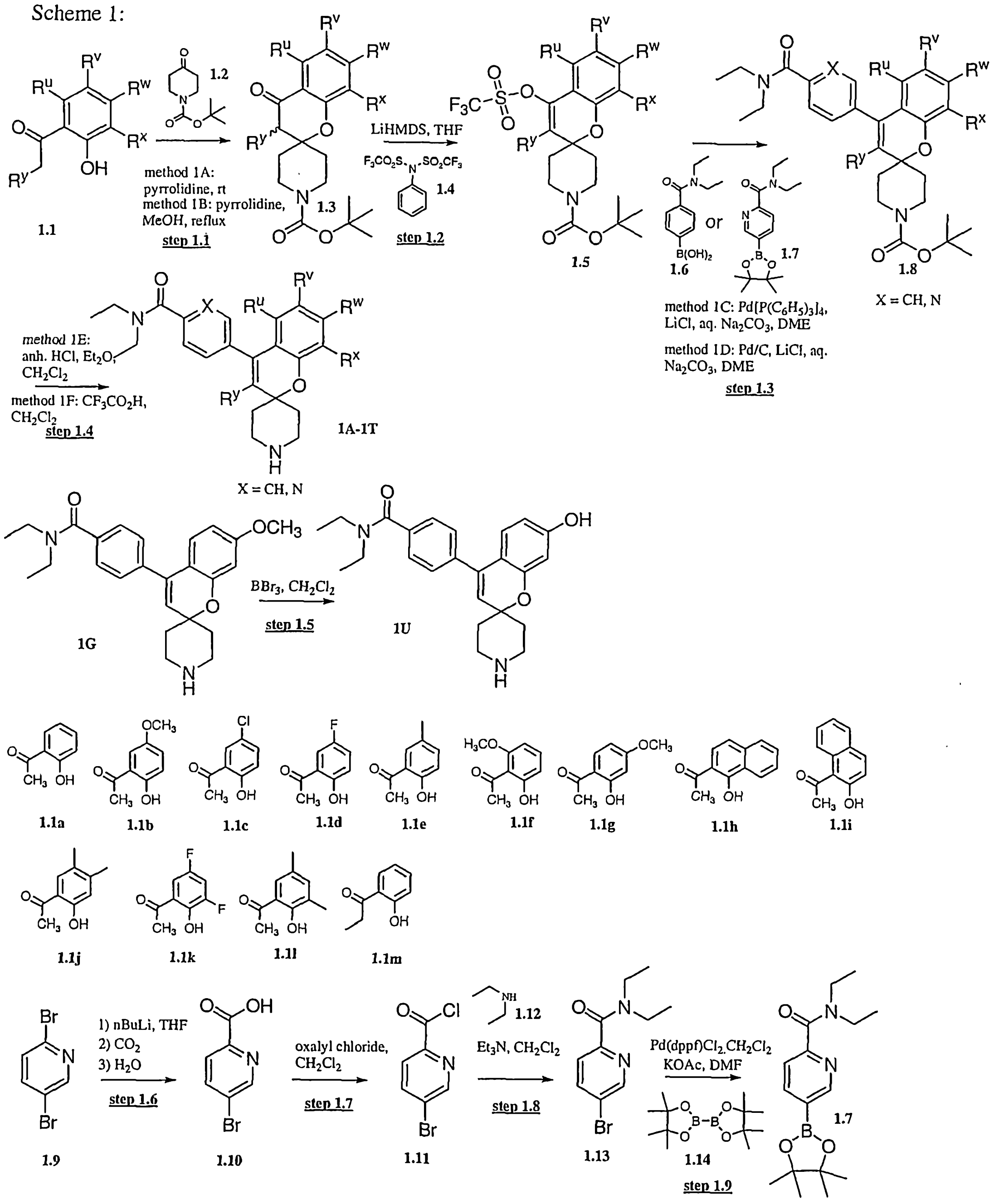
[0353] The synthesis of compounds **59A-59L** is outlined in Scheme 59. The alkyl bromide derivatives used as starting materials for the synthesis of compounds **59A-59L** were either commercially available (**59.2a**, **59.2b**) or prepared from the corresponding alcohols (preparation of **59.2c** and **59.2d**). Treatment of the amines **59.2** with ethyl 2,2,2-trifluoroacetate (**59.3**) in methanol in the presence of triethylamine provided the trifluoroacetamide derivatives **59.4**. Alkylation of 5-(4-bromophenyl)-2H-tetrazole (**59.6**) (obtained by treatment of 4-bromobenzonitrile (**59.5**) with sodium azide and ammonium chloride in *N*,*N*-dimethylformamide) with the alkyl bromide derivatives **59.4**, provided the derivatives **59.7**. Suzuki type coupling of the boronate derivative **32.1** with the aryl bromide derivatives **59.7** in dioxane in the presence of tetrakis triphenylphosphine palladium (0) and an aqueous solution of potassium carbonate afforded the compounds **59.8** which were converted to the derivatives **59.9** under basic conditions. The Boc protecting group of **59.9** was removed using hydrochloric acid to generate the compounds **59A-59D.** Treatment of the amines **59.9** with acetic anhydride in dichloromethane in the presence of triethylamine provided the acetamides **59.10**, which were converted to the final products **59E-59H** under acidic conditions. Treatment of the amines **59.9** with methane sulfonyl chloride in dichloromethane in the presence of triethylamine provided the sulfonamides **59.11**, which were converted to the final products **59I-59L** under acidic conditions.

[0354] The synthesis of compounds **60A-60C** is outlined in Scheme 60. Treatment of the amine **60.1** with ethyl 2,2,2-trifluoroacetate (**59.3**) in methanol in the presence of triethylamine provided the trifluoroacetamide derivative **60.2**. Treatment of the alcohol **60.2** with methane sulfonyl chloride in dichloromethane in the presence of triethylamine provided the mesylate derivative **60.3**. Alkylation of 5-(4-bromophenyl)-2H-tetrazole (**59.6**) with the mesylate derivative **60.3**, provided the derivative **60.4**. Suzuki type coupling of the boronate derivative **32.1** with the aryl bromide derivative **60.4** in dioxane in the presence of tetrakis triphenylphosphine palladium (0) and an aqueous solution of potassium carbonate afforded the compound **60.5** which was converted to the derivative **60.6** under basic conditions. The Boc protecting group of **60.6** was removed using hydrochloric acid to generate the compound **60A**. Treatment of the amine **60.6** with acetic anhydride in dichloromethane in the presence of triethylamine provided the acetamide **60.7**, which was converted to the final products **60B** under acidic conditions. Treatment of the amine **60.6** with methane sulfonyl chloride in dichloromethane in the presence of triethylamine provided the sulfonamide **60.8**, which was converted to the final products **60C** under acidic conditions.

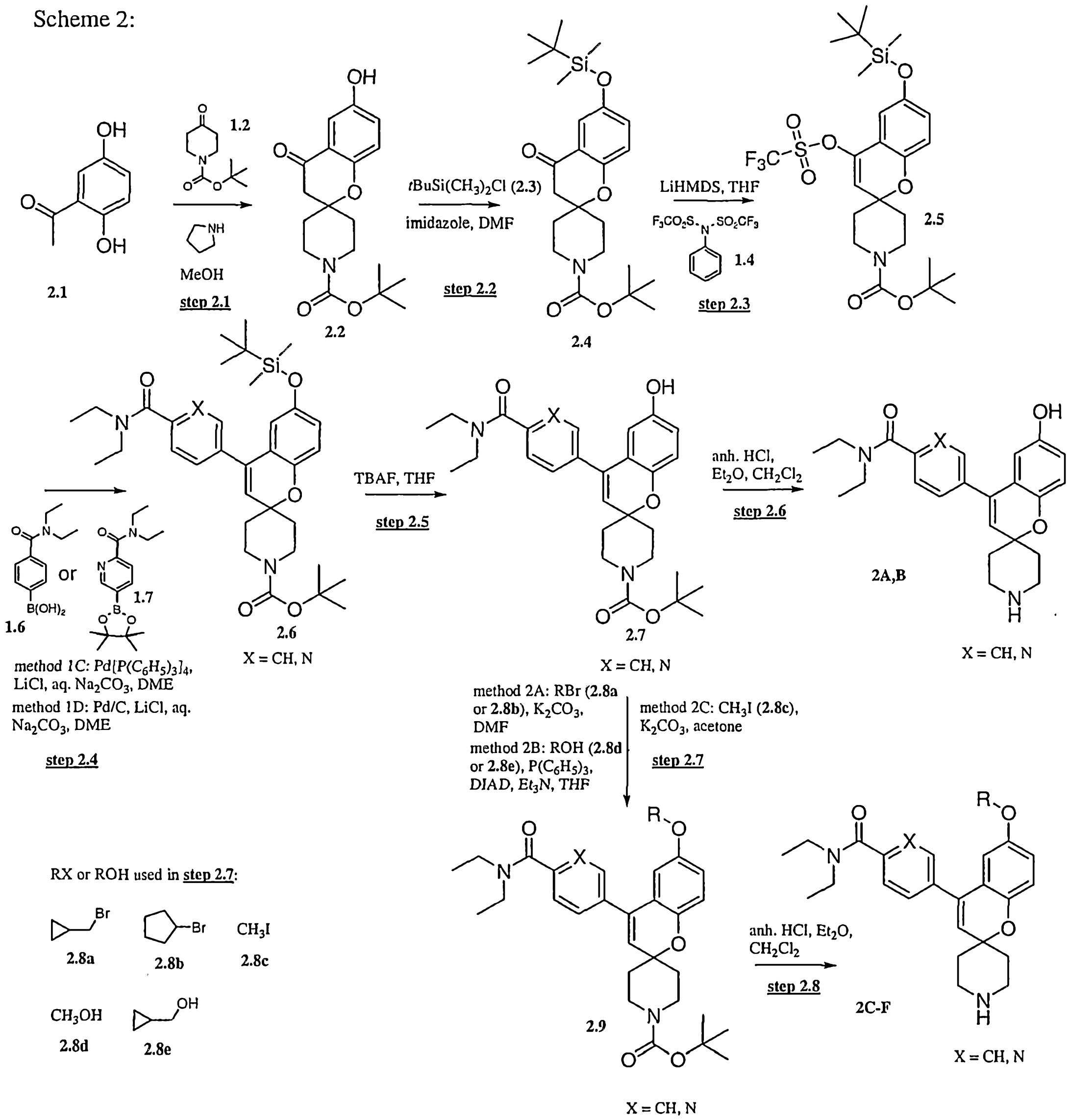
[0355] The synthesis of compounds **61A-61B** is outlined in Scheme 61. Chiral separation of the enantiomers derived from **61.1** (obtained by hydrogenation of **49.9**) provided compounds **61.2a** and **61.2b**, which were converted to the final products **61A** and **61B,** respectively, under acidic conditions. Condensation of compound **21C** with 6-bromo-2-naphthoic acid (**61.3**) (used as chiral resolving agent) in acetonitrile in the presence of TBTU and diisopropylethylamine (Hunig's base) provided the amide derivative **61.4**. The absolute configuration of **61.4** was determined by X-ray crystallography, therefore establishing the absolute configuration of compound **21C**, and therefore by inference, its enantiomer, compound **21B** (see also Scheme 21).

[0356] In some instances, the compounds of the invention have the potential for chirality but were prepared in racemic form. As one skilled in the art would readily recognize, the racemic mixtures of intermediates or final products initially prepared as their racemates may be partially or completely resolved into any, some, or all of the enantiomers contained in the racemate as described herein, for example in the separation of intermediates leading to **39F** and **39G**. As such, racemic mixtures, mixtures enriched in or or more stereoisomers, and pure enantiomers are considered to be within the ambit of the present invention.

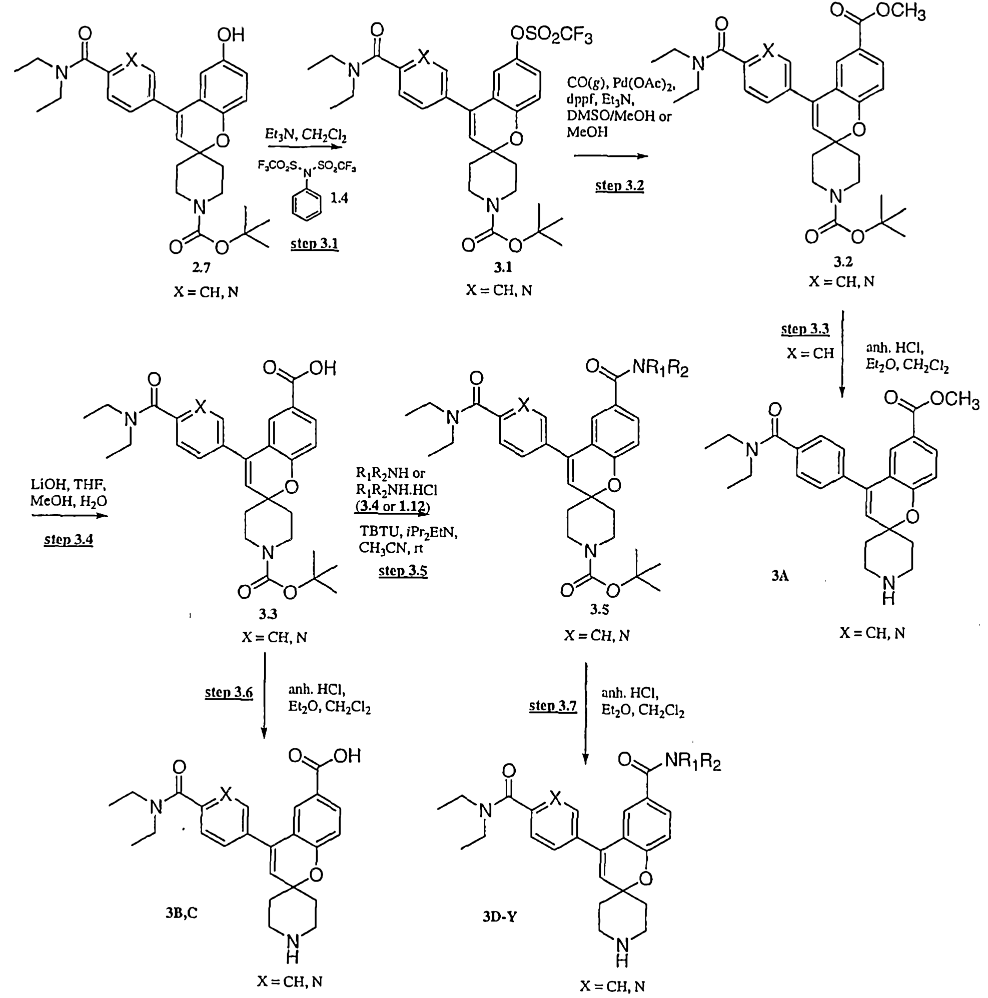
Scheme 1:


1.1
1.2
method 1A: pyrrolidine, rt
method 1B: pyrrolidine, MeOH, reflux
step 1.1
1.3
LiHMDS, THF
1.4
step 1.2
1.5
1.6
or
1.7
method 1C: Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
method 1D: Pd/C, LiCl, aq. Na2CO3, DME
step 1.3
1.8
X = CH, N
method 1E: anh. HCl, Et2O, CH2Cl2
method 1F: CF3CO2H, CH2Cl2
step 1.4
1A-1T
X = CH, N
1G
BBr3, CH2Cl2
step 1.5
1U
1.1a
1.1b
1.1c
1.1d
1.1e
1.1f
1.1g
1.1h
1.1i
1.1j
1.1k
1.1l
1.1m
1.9
1) nBuLi, THF
2) CO2
3) H2O
step 1.6
1.10
oxalyl chloride, CH2Cl2
step 1.7
1.11
1.12
Et3N, CH2Cl2
step 1.8
1.13
Pd(dppf)Cl2.CH2Cl2
KOAc, DMF
1.14
step 1.9
1.7

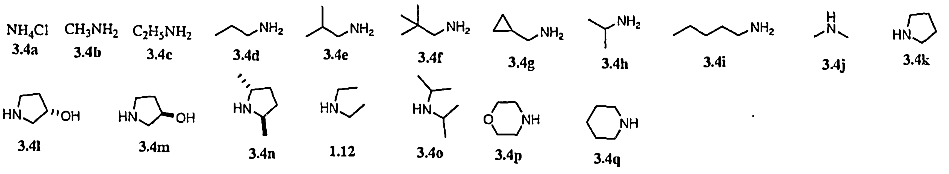
Scheme 2:

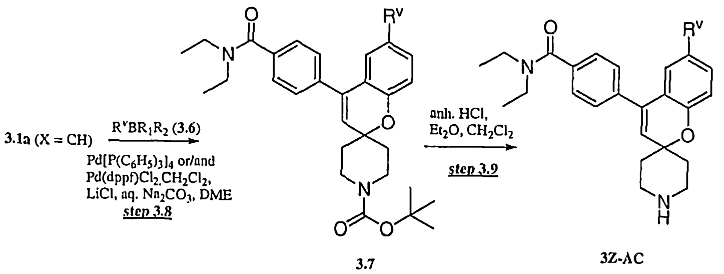

2.1
1.2
MeOH
step 2.1
2.2
tBuSi(CH$_3$)$_2$Cl (2.3)
imidazole, DMF
step 2.2
2.4
LiHMDS, THF
F$_3$CO$_2$S-N-SO$_2$CF$_3$
1.4
step 2.3
2.5
1.6
or
1.7
method 1C: Pd[P(C$_6$H$_5$)$_3$]$_4$, LiCl, aq. Na$_2$CO$_3$, DME
method 1D: Pd/C, LiCl, aq. Na$_2$CO$_3$, DME
step 2.4
2.6
X = CH, N
TBAF, THF
step 2.5
2.7
X = CH, N
anh. HCl, Et$_2$O, CH$_2$Cl$_2$
step 2.6
2A,B
X = CH, N
method 2A: RBr (2.8a or 2.8b), K$_2$CO$_3$, DMF
method 2B: ROH (2.8d or 2.8e), P(C$_6$H$_5$)$_3$, DIAD, Et$_3$N, THF
method 2C: CH$_3$I (2.8c), K$_2$CO$_3$, acetone
step 2.7
RX or ROH used in step 2.7:
2.8a
2.8b
CH$_3$I
2.8c
CH$_3$OH
2.8d
2.8e
2.9
X = CH, N
anh. HCl, Et$_2$O, CH$_2$Cl$_2$
step 2.8
2C-F
X = CH, N

Scheme 3:

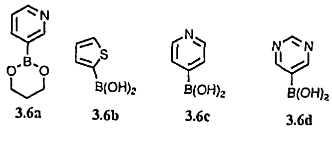


list of amines used in step 3.5:

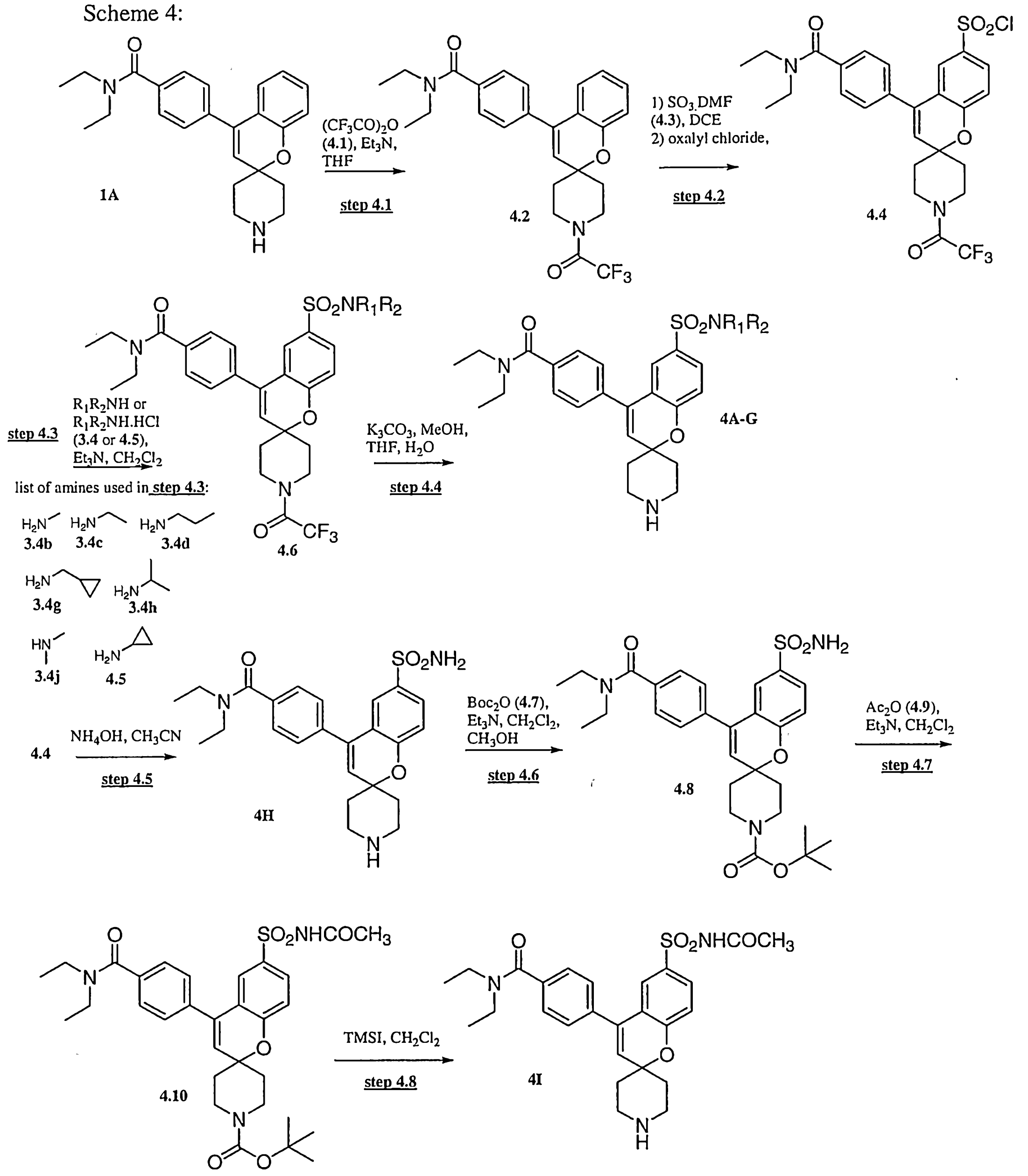




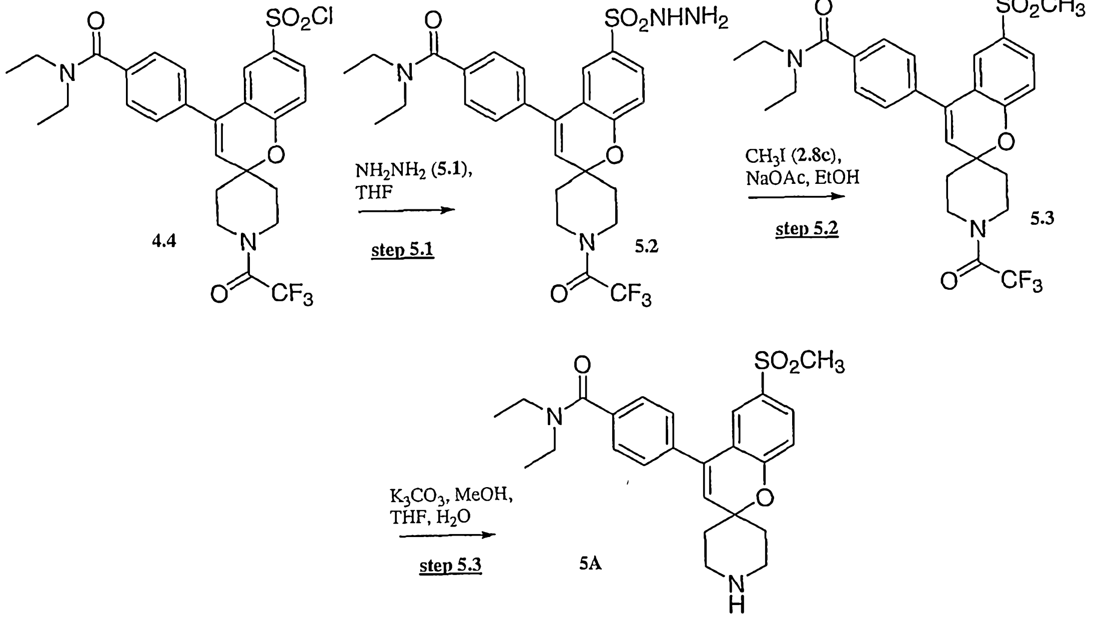
list of organoboron derivatives used in step 3.8:



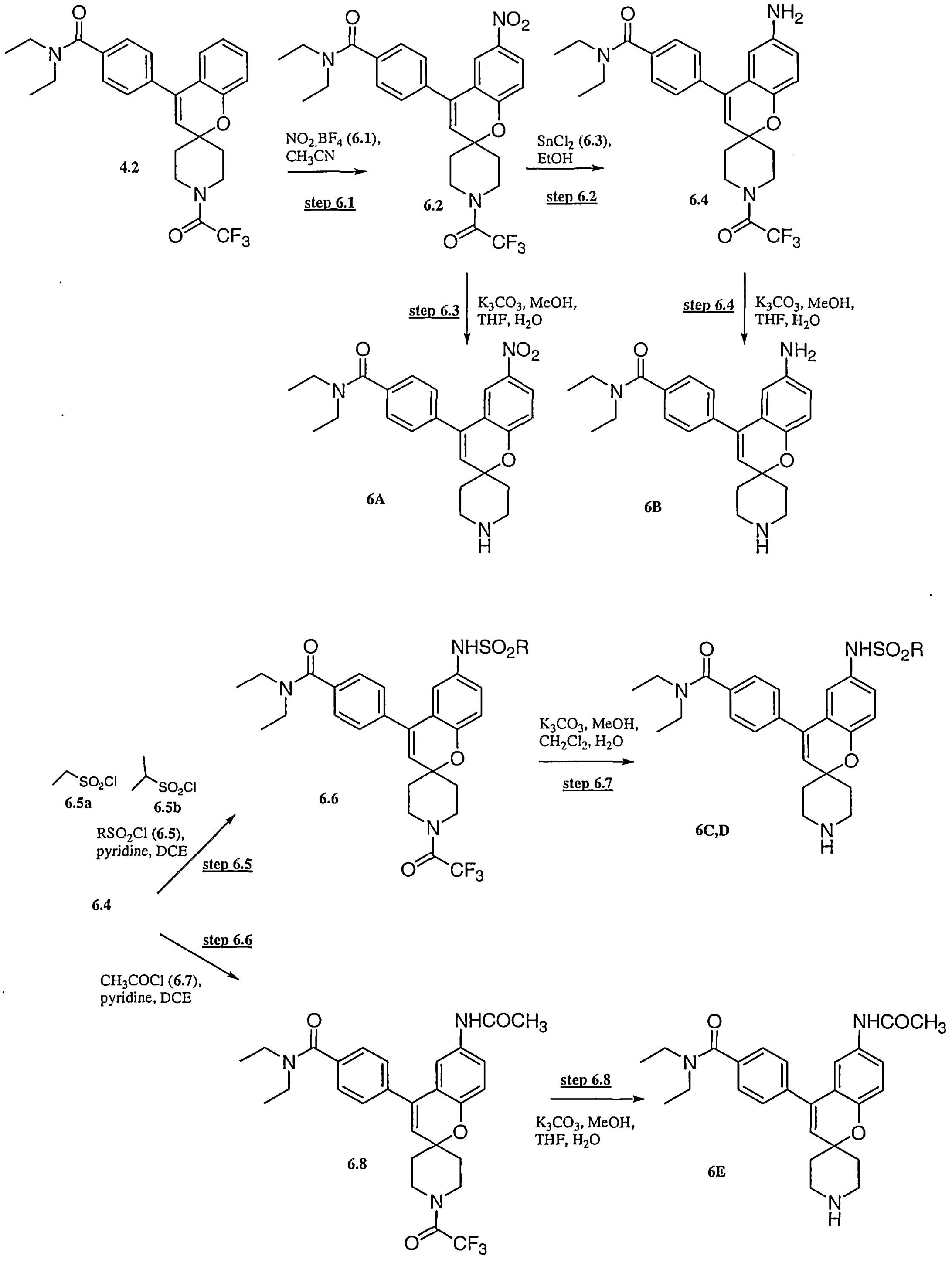
Scheme 4:


1A
(CF3CO)2O (4.1), Et3N, THF
step 4.1
4.2
1) SO3.DMF (4.3), DCE
2) oxalyl chloride,
step 4.2
SO2Cl
4.4
CF3
SO2NR1R2
step 4.3
R1R2NH or R1R2NH.HCl (3.4 or 4.5), Et3N, CH2Cl2
list of amines used in step 4.3:
3.4b
3.4c
3.4d
3.4g
3.4h
3.4j
4.5
4.6
K2CO3, MeOH, THF, H2O
step 4.4
4A-G
4.4
NH4OH, CH3CN
step 4.5
SO2NH2
4H
Boc2O (4.7), Et3N, CH2Cl2, CH3OH
step 4.6
4.8
Ac2O (4.9), Et3N, CH2Cl2
step 4.7
SO2NHCOCH3
4.10
TMSI, CH2Cl2
step 4.8
4I

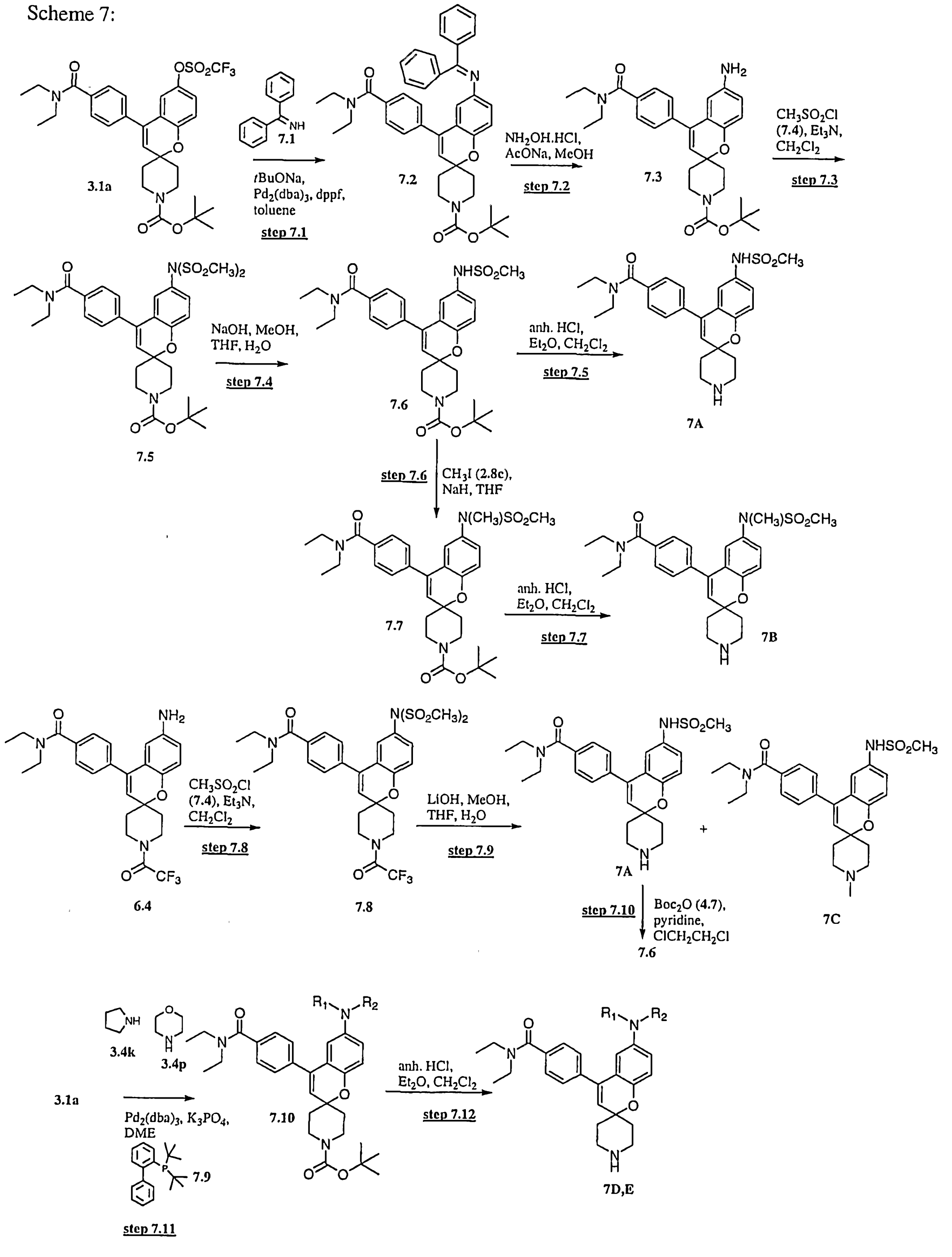
Scheme 5:


SO2Cl
O
N
4.4
O
CF3
NH2NH2 (5.1),
THF
step 5.1
SO2NHNH2
5.2
CH3I (2.8c),
NaOAc, EtOH
step 5.2
SO2CH3
5.3
K3CO3, MeOH,
THF, H2O
step 5.3
5A
NH

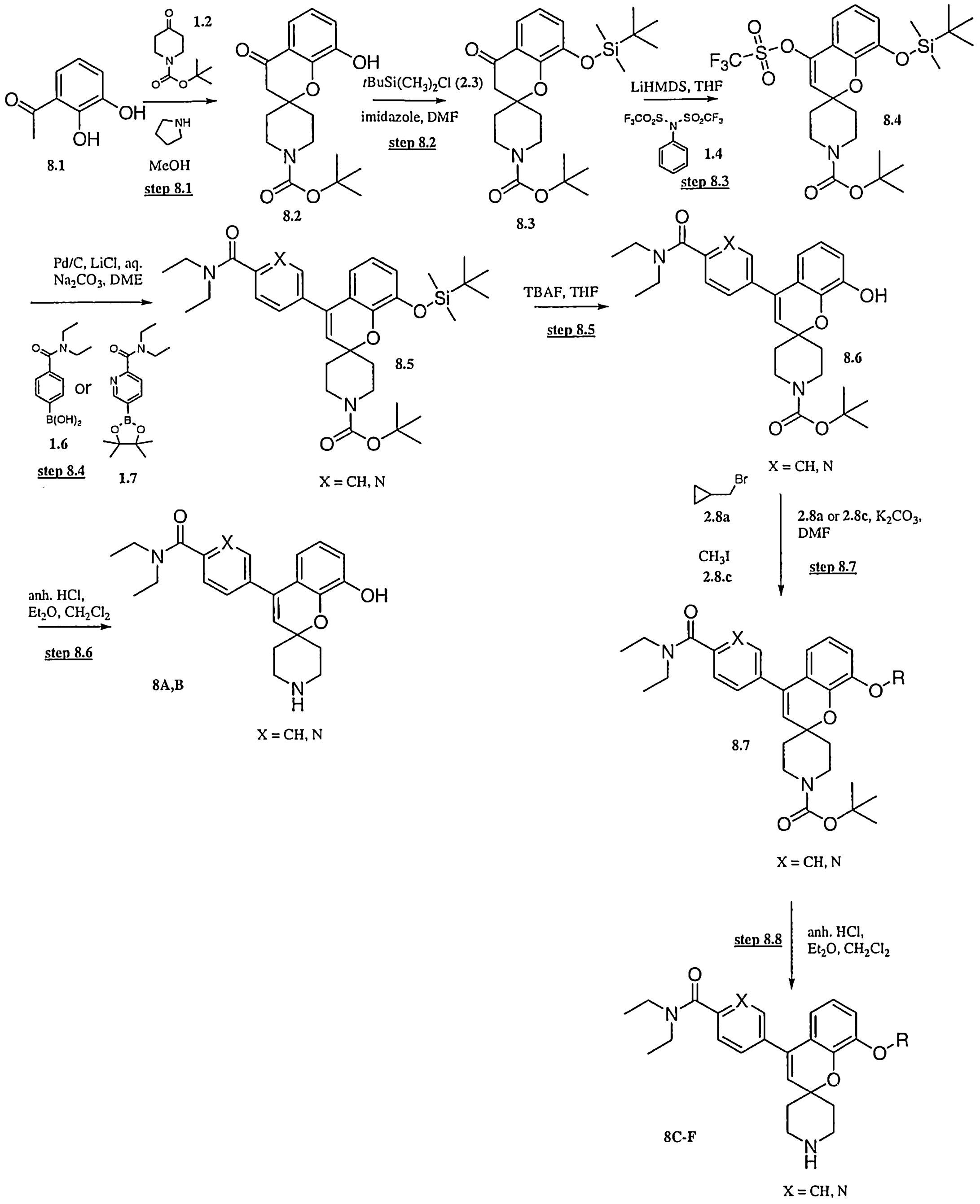
Scheme 6:


4.2
NO2.BF4 (6.1), CH3CN
step 6.1
6.2
NO2
SnCl2 (6.3), EtOH
step 6.2
6.4
NH2
step 6.3
K3CO3, MeOH, THF, H2O
step 6.4
K3CO3, MeOH, THF, H2O
6A
6B
6.5a
6.5b
SO2Cl
RSO2Cl (6.5), pyridine, DCE
step 6.5
6.4
step 6.6
CH3COCl (6.7), pyridine, DCE
6.6
NHSO2R
K3CO3, MeOH, CH2Cl2, H2O
step 6.7
6C,D
6.8
NHCOCH3
step 6.8
K3CO3, MeOH, THF, H2O
6E
CF3

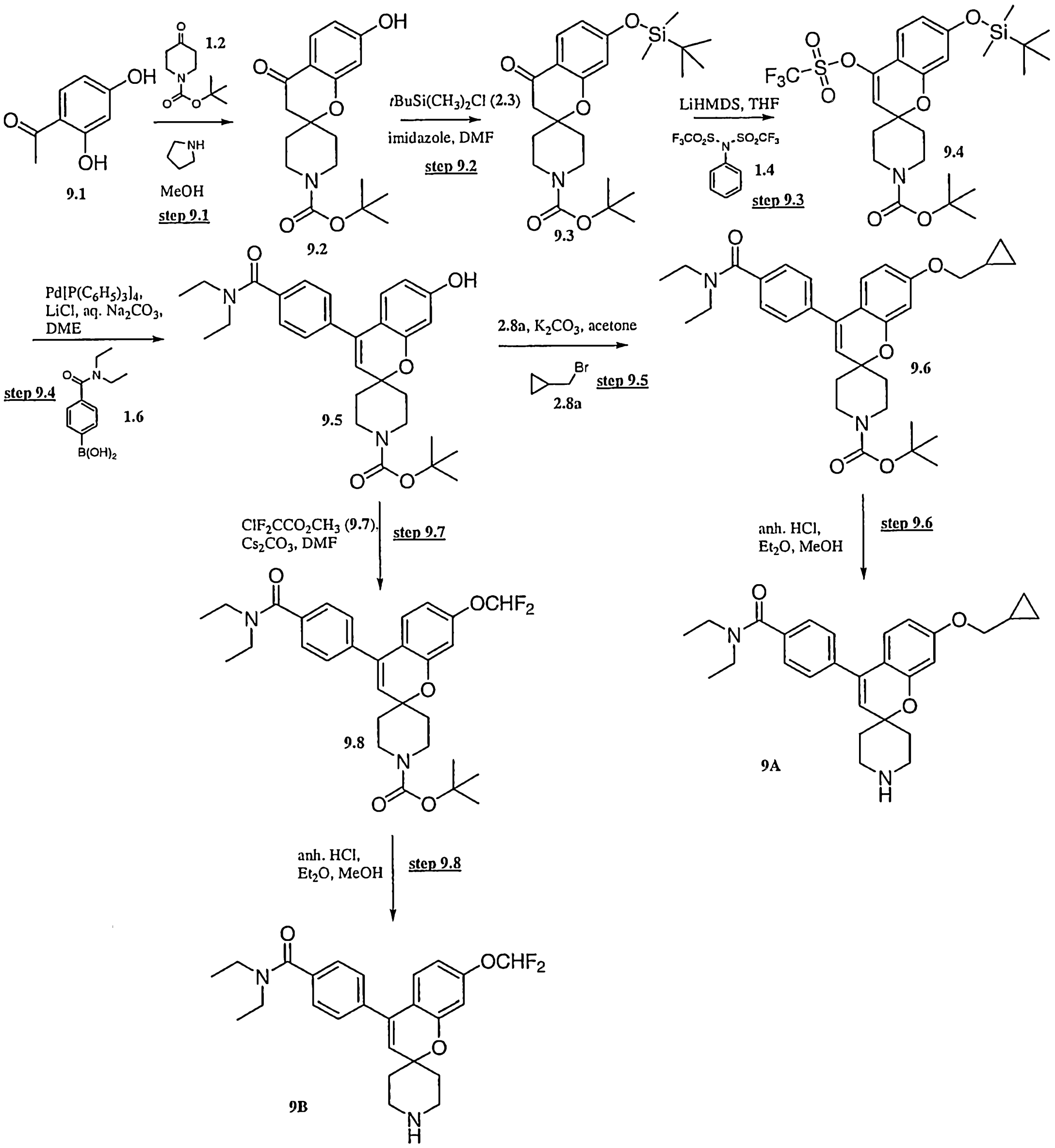
Scheme 7:


OSO2CF3
3.1a
7.1
NH
tBuONa, Pd2(dba)3, dppf, toluene
step 7.1
7.2
N
NH2OH.HCl, AcONa, MeOH
step 7.2
NH2
7.3
CH3SO2Cl (7.4), Et3N, CH2Cl2
step 7.3
N(SO2CH3)2
7.5
NaOH, MeOH, THF, H2O
step 7.4
NHSO2CH3
7.6
anh. HCl, Et2O, CH2Cl2
step 7.5
7A
step 7.6
CH3I (2.8e), NaH, THF
N(CH3)SO2CH3
7.7
anh. HCl, Et2O, CH2Cl2
step 7.7
7B
6.4
CF3
CH3SO2Cl (7.4), Et3N, CH2Cl2
step 7.8
7.8
LiOH, MeOH, THF, H2O
step 7.9
7A
+
7C
step 7.10
Boc2O (4.7), pyridine, ClCH2CH2Cl
7.6
3.4k
3.4p
3.1a
Pd2(dba)3, K3PO4, DME
7.9
step 7.11
R1
R2
7.10
anh. HCl, Et2O, CH2Cl2
step 7.12
7D,E

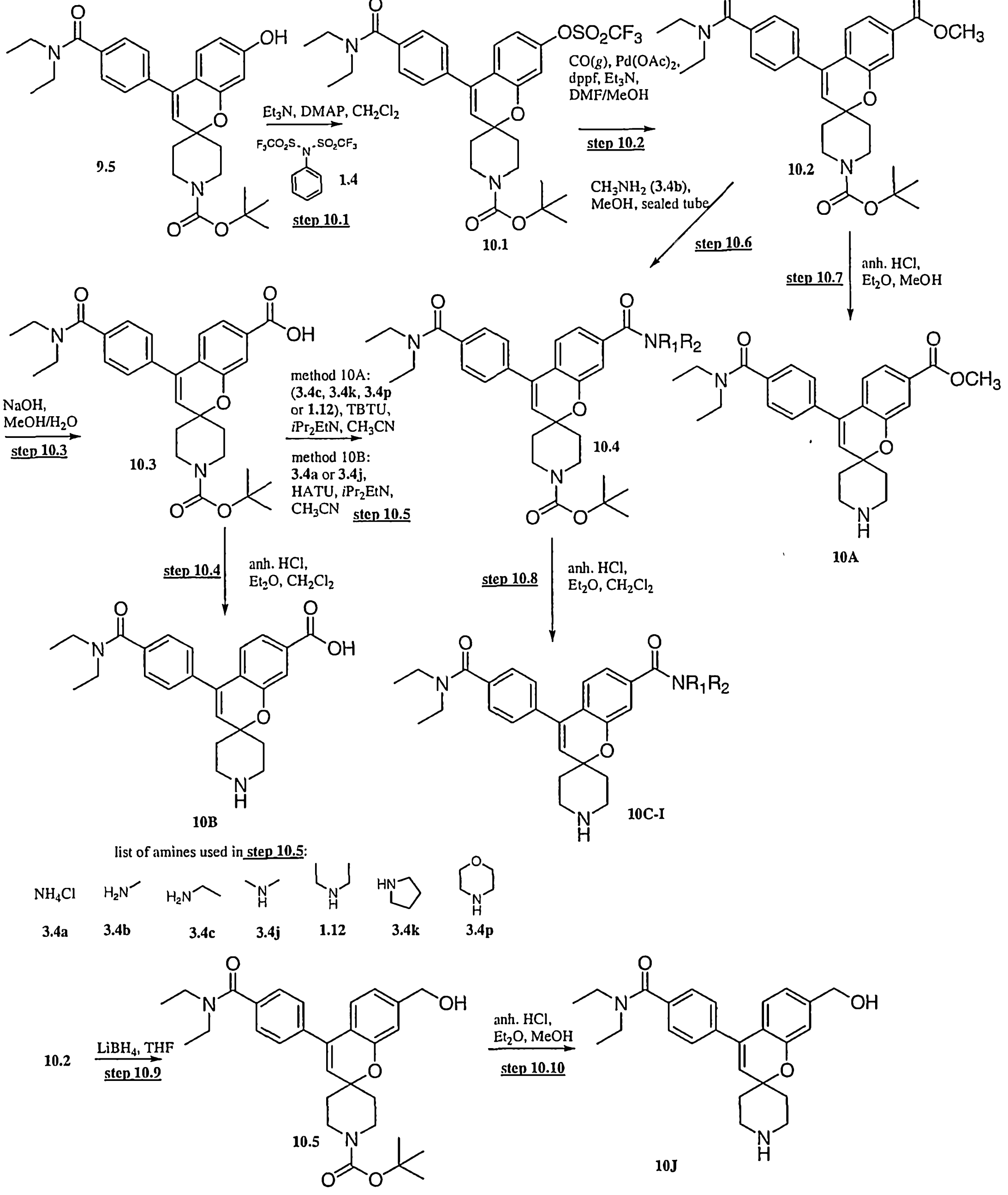
Scheme 8:


8.1
1.2
MeOH
step 8.1
8.2
tBuSi(CH3)2Cl (2.3)
imidazole, DMF
step 8.2
8.3
LiHMDS, THF
F3CO2S N SO2CF3
1.4
step 8.3
8.4
Pd/C, LiCl, aq.
Na2CO3, DME
B(OH)2
or
1.6
1.7
step 8.4
8.5
X = CH, N
TBAF, THF
step 8.5
8.6
X = CH, N
2.8a
CH3I
2.8.c
2.8a or 2.8c, K2CO3,
DMF
step 8.7
8.7
X = CH, N
anh. HCl,
Et2O, CH2Cl2
step 8.6
8A,B
X = CH, N
step 8.8
anh. HCl,
Et2O, CH2Cl2
8C-F
X = CH, N

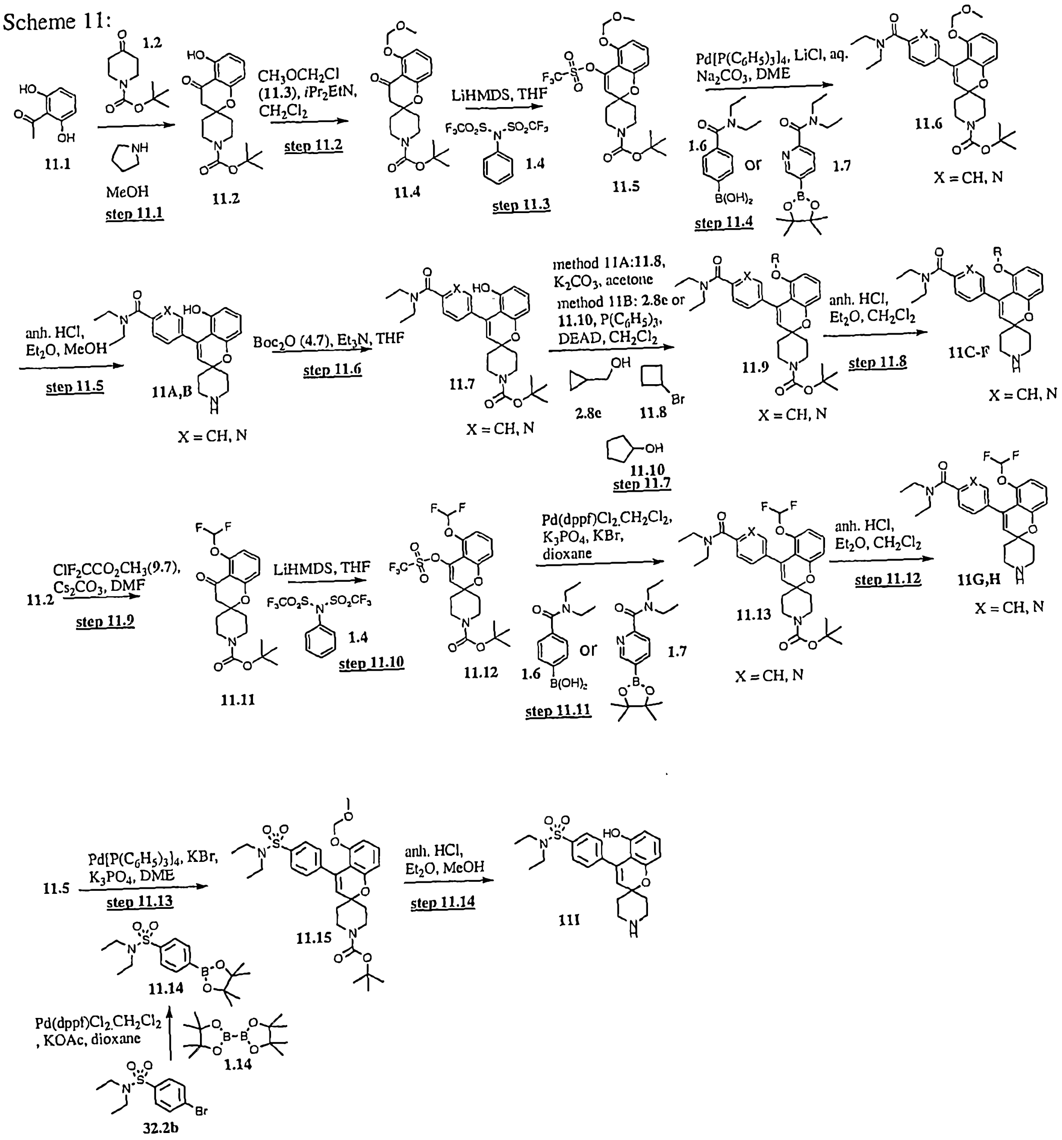
Scheme 9:


9.1
1.2
MeOH
step 9.1
9.2
tBuSi(CH3)2Cl (2.3)
imidazole, DMF
step 9.2
9.3
LiHMDS, THF
F3CO2S-N-SO2CF3
1.4
step 9.3
9.4
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
step 9.4
1.6
B(OH)2
9.5
2.8a, K2CO3, acetone
step 9.5
2.8a
9.6
ClF2CCO2CH3 (9.7), Cs2CO3, DMF
step 9.7
9.8
anh. HCl, Et2O, MeOH
step 9.8
9B
anh. HCl, Et2O, MeOH
step 9.6
9A
OH
O
N
O-Si
F3C-S-O
OCHF2
Br
H

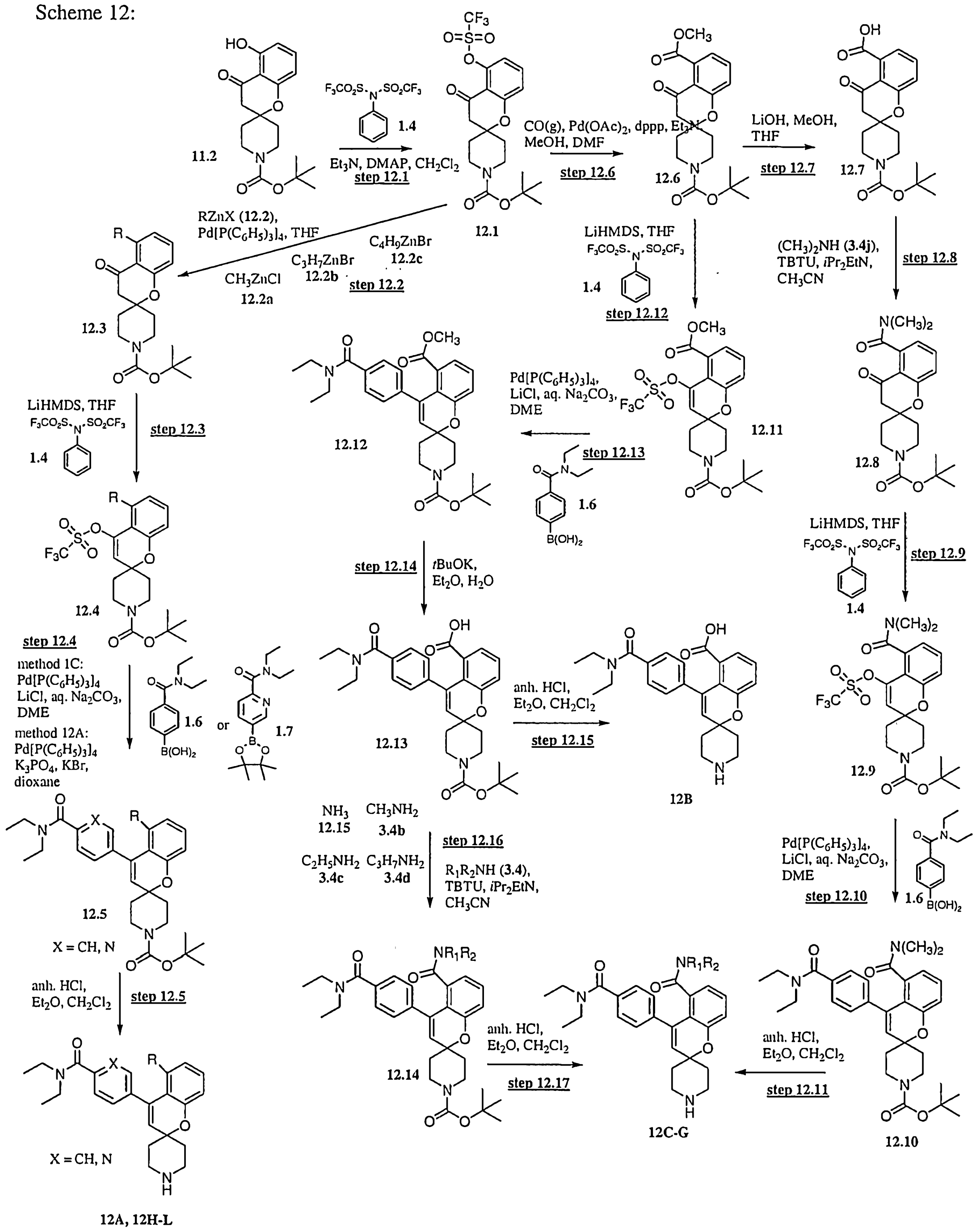
Scheme 10:


9.5
Et3N, DMAP, CH2Cl2
F3CO2S-N-SO2CF3
1.4
step 10.1
10.1
CO(g), Pd(OAc)2, dppf, Et3N, DMF/MeOH
step 10.2
10.2
CH3NH2 (3.4b), MeOH, sealed tube
step 10.6
step 10.7
anh. HCl, Et2O, MeOH
10A
NaOH, MeOH/H2O
step 10.3
10.3
method 10A: (3.4c, 3.4k, 3.4p or 1.12), TBTU, iPr2EtN, CH3CN
method 10B: 3.4a or 3.4j, HATU, iPr2EtN, CH3CN
step 10.5
10.4
NR1R2
step 10.4
anh. HCl, Et2O, CH2Cl2
10B
step 10.8
anh. HCl, Et2O, CH2Cl2
10C-I
list of amines used in step 10.5:
NH4Cl
3.4a
3.4b
3.4c
3.4j
1.12
3.4k
3.4p
10.2
LiBH4, THF
step 10.9
10.5
anh. HCl, Et2O, MeOH
step 10.10
10J

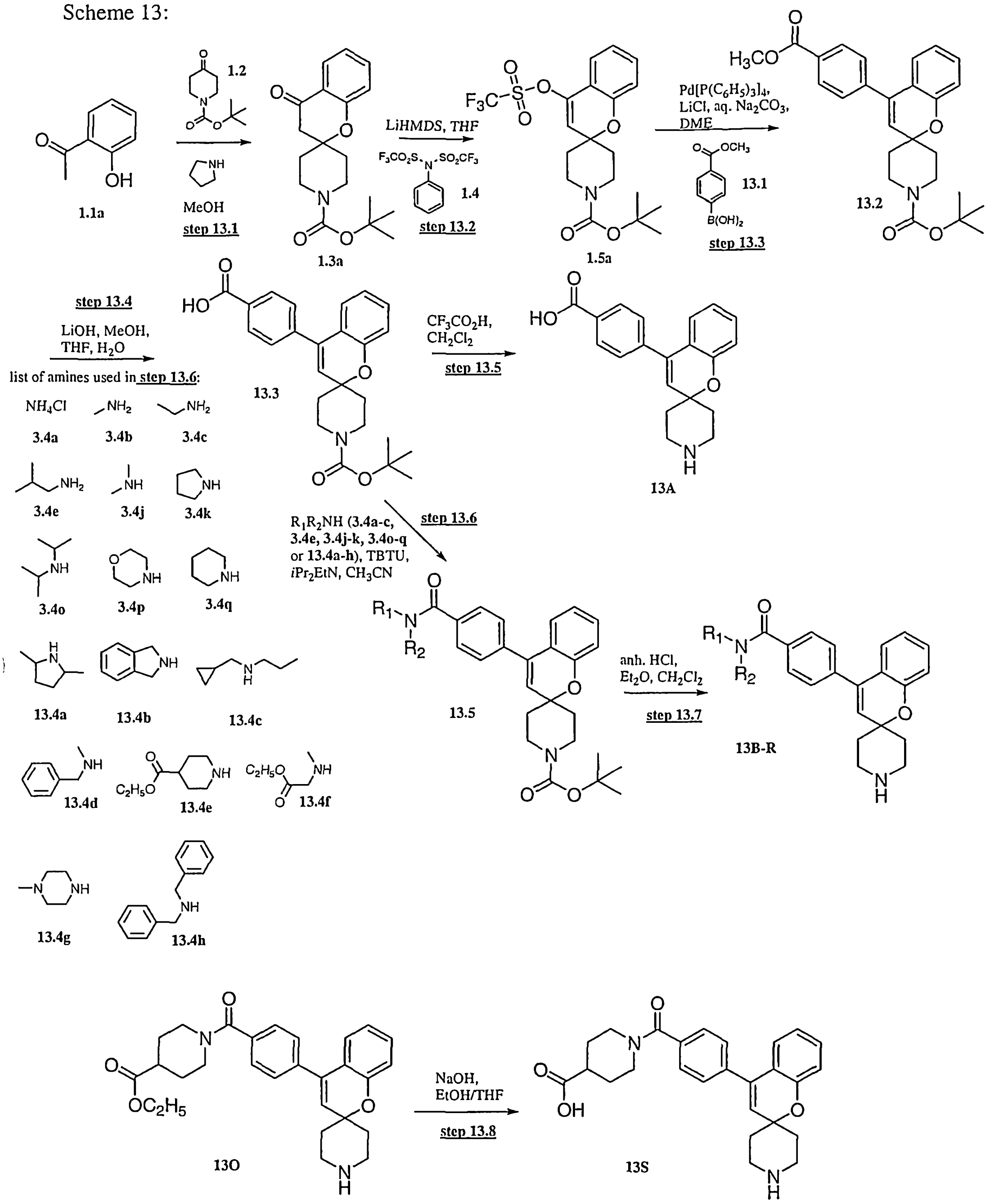
Scheme 11:


11.1
1.2
MeOH
step 11.1
11.2
CH3OCH2Cl (11.3), iPr2EtN, CH2Cl2
step 11.2
11.4
LiHMDS, THF
1.4
step 11.3
11.5
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
1.6
or
1.7
step 11.4
11.6
X = CH, N
anh. HCl, Et2O, MeOH
step 11.5
11A,B
X = CH, N
Boc2O (4.7), Et3N, THF
step 11.6
11.7
X = CH, N
method 11A: 11.8, K2CO3, acetone
method 11B: 2.8c or 11.10, P(C6H5)3, DEAD, CH2Cl2
2.8c
11.8
11.10
step 11.7
11.9
X = CH, N
anh. HCl, Et2O, CH2Cl2
step 11.8
11C-F
X = CH, N
ClF2CCO2CH3 (9.7), Cs2CO3, DMF
11.2
step 11.9
11.11
LiHMDS, THF
1.4
step 11.10
11.12
Pd(dppf)Cl2.CH2Cl2, K3PO4, KBr, dioxane
1.6
or
1.7
step 11.11
11.13
X = CH, N
anh. HCl, Et2O, CH2Cl2
step 11.12
11G,H
X = CH, N
11.5
Pd[P(C6H5)3]4, KBr, K3PO4, DME
step 11.13
11.14
Pd(dppf)Cl2.CH2Cl2, KOAc, dioxane
1.14
32.2b
11.15
anh. HCl, Et2O, MeOH
step 11.14
11I

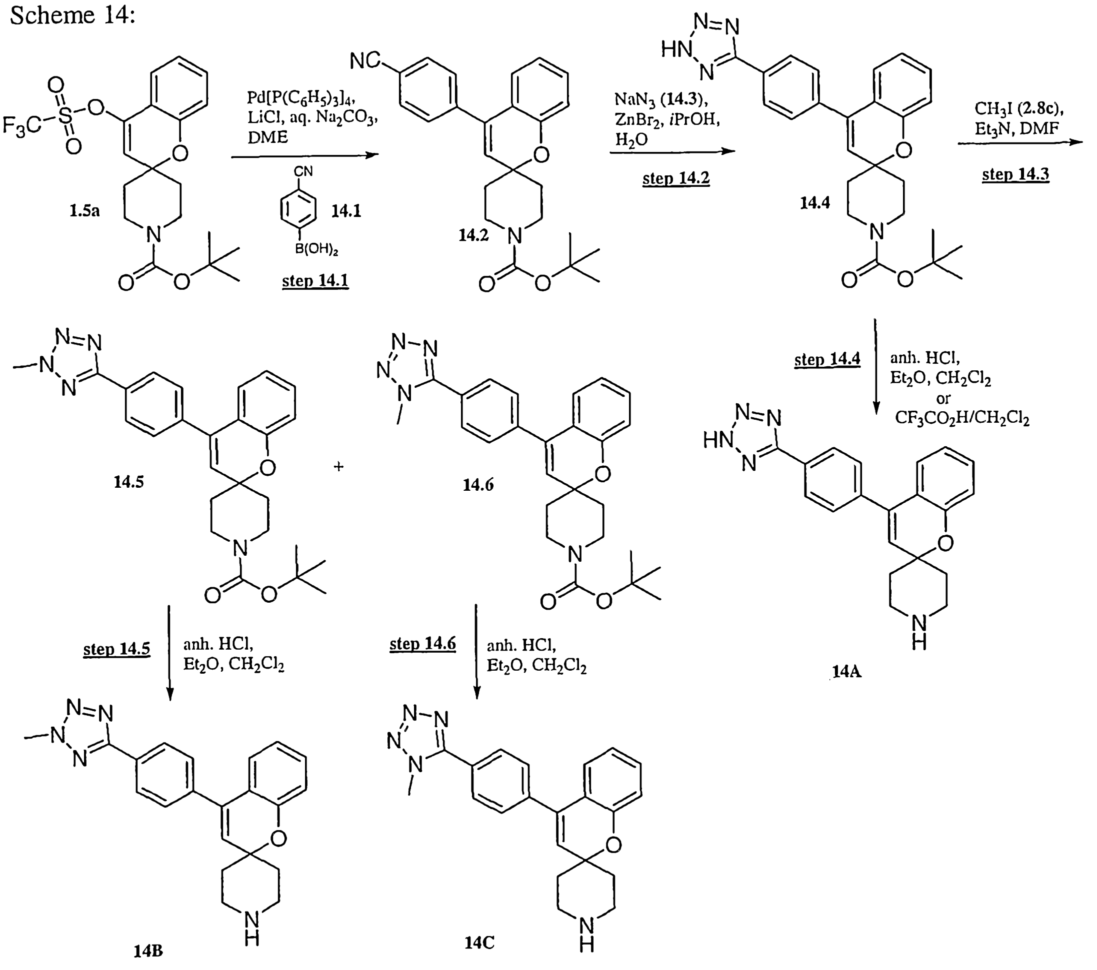
Scheme 12:


11.2
1.4
Et3N, DMAP, CH2Cl2
step 12.1
12.1
CO(g), Pd(OAc)2, dppp, Et3N
MeOH, DMF
step 12.6
12.6
LiOH, MeOH, THF
step 12.7
12.7
RZnX (12.2), Pd[P(C6H5)3]4, THF
CH3ZnCl 12.2a
C3H7ZnBr 12.2b
C4H9ZnBr 12.2c
step 12.2
12.3
LiHMDS, THF
1.4
step 12.3
12.4
step 12.4
method 1C: Pd[P(C6H5)3]4 LiCl, aq. Na2CO3, DME
method 12A: Pd[P(C6H5)3]4 K3PO4, KBr, dioxane
1.6
or
1.7
12.5
X = CH, N
anh. HCl, Et2O, CH2Cl2
step 12.5
X = CH, N
12A, 12H-L
LiHMDS, THF
1.4
step 12.12
12.11
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
step 12.13
1.6
12.12
step 12.14
tBuOK, Et2O, H2O
12.13
anh. HCl, Et2O, CH2Cl2
step 12.15
12B
NH3 12.15
CH3NH2 3.4b
C2H5NH2 3.4c
C3H7NH2 3.4d
step 12.16
R1R2NH (3.4), TBTU, iPr2EtN, CH3CN
12.14
anh. HCl, Et2O, CH2Cl2
step 12.17
12C-G
(CH3)2NH (3.4j), TBTU, iPr2EtN, CH3CN
step 12.8
12.8
LiHMDS, THF
1.4
step 12.9
12.9
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
step 12.10
1.6
12.10
anh. HCl, Et2O, CH2Cl2
step 12.11

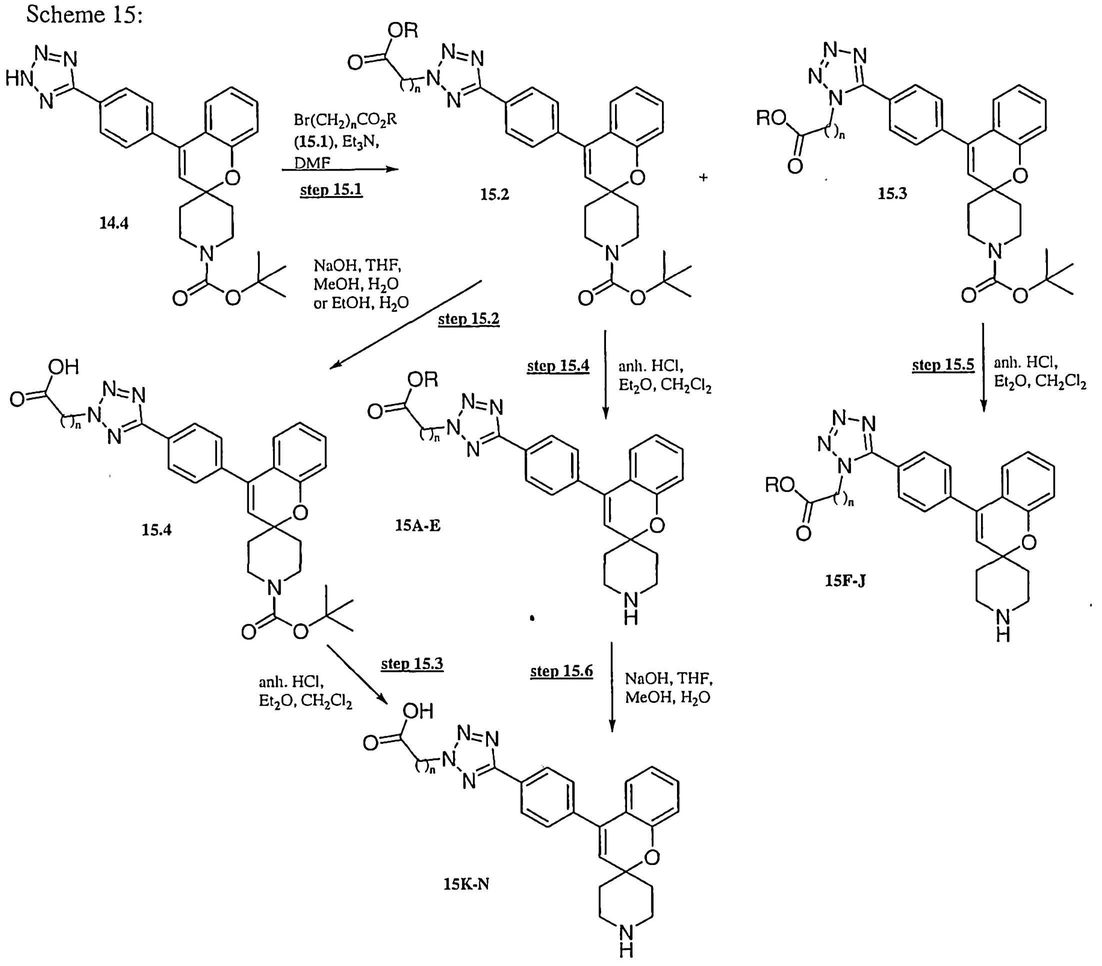
Scheme 13:


1.1a
1.2
MeOH
step 13.1
1.3a
LiHMDS, THF
1.4
step 13.2
1.5a
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
13.1
step 13.3
13.2
step 13.4
LiOH, MeOH, THF, H2O
13.3
CF3CO2H, CH2Cl2
step 13.5
13A
list of amines used in step 13.6:
NH4Cl
3.4a
3.4b
3.4c
3.4e
3.4j
3.4k
3.4o
3.4p
3.4q
13.4a
13.4b
13.4c
13.4d
13.4e
13.4f
13.4g
13.4h
R1R2NH (3.4a-c, 3.4e, 3.4j-k, 3.4o-q or 13.4a-h), TBTU, iPr2EtN, CH3CN
step 13.6
13.5
anh. HCl, Et2O, CH2Cl2
step 13.7
13B-R
13O
NaOH, EtOH/THF
step 13.8
13S

Scheme 14:


1.5a
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
14.1
step 14.1
14.2
NaN3 (14.3), ZnBr2, iPrOH, H2O
step 14.2
14.4
CH3I (2.8c), Et3N, DMF
step 14.3
step 14.4
anh. HCl, Et2O, CH2Cl2 or CF3CO2H/CH2Cl2
14A
14.5
+
14.6
step 14.5
anh. HCl, Et2O, CH2Cl2
step 14.6
anh. HCl, Et2O, CH2Cl2
14B
14C

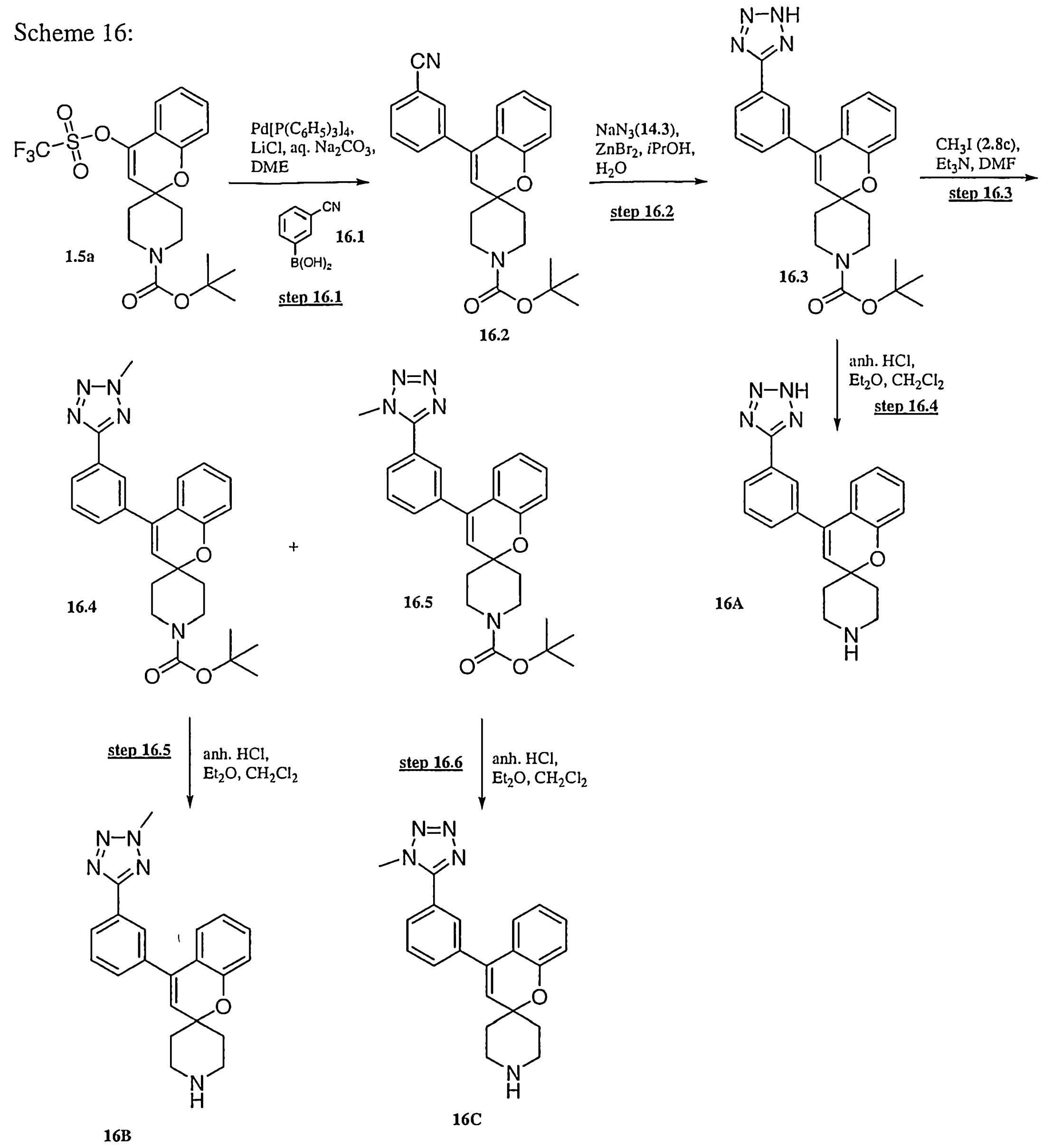
Scheme 15:



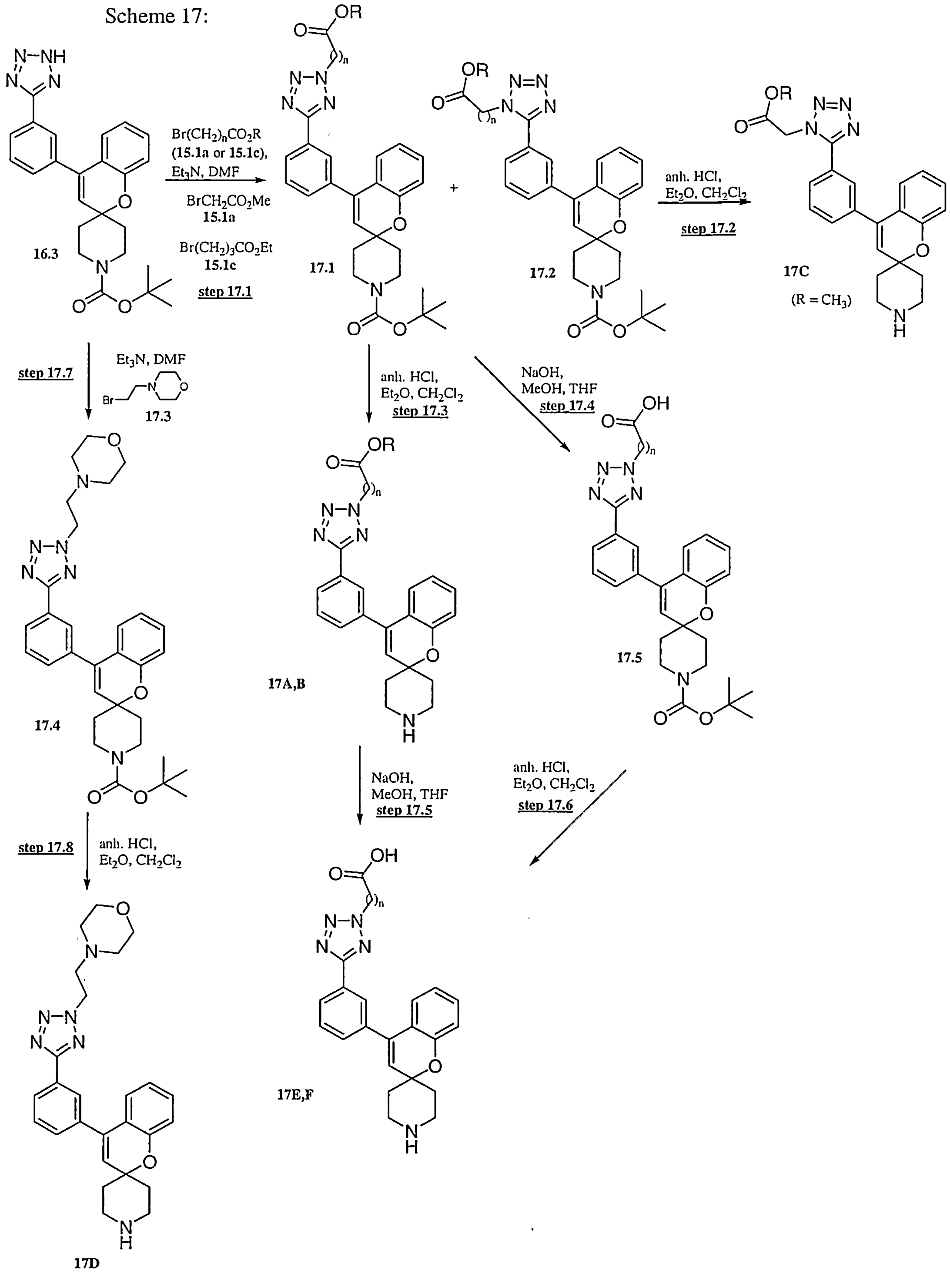
Br(CH$_2$)nCO$_2$R used in <u>step 15.1</u>:

$BrCH_2CO_2Me$	$Br(CH_2)_2CO_2Me$	$Br(CH_2)_3CO_2Et$	$Br(CH_2)_4CO_2Et$	$Br(CH_2)_5CO_2Et$
15.1a	**15.1b**	**15.1c**	**15.1d**	**15.1e**

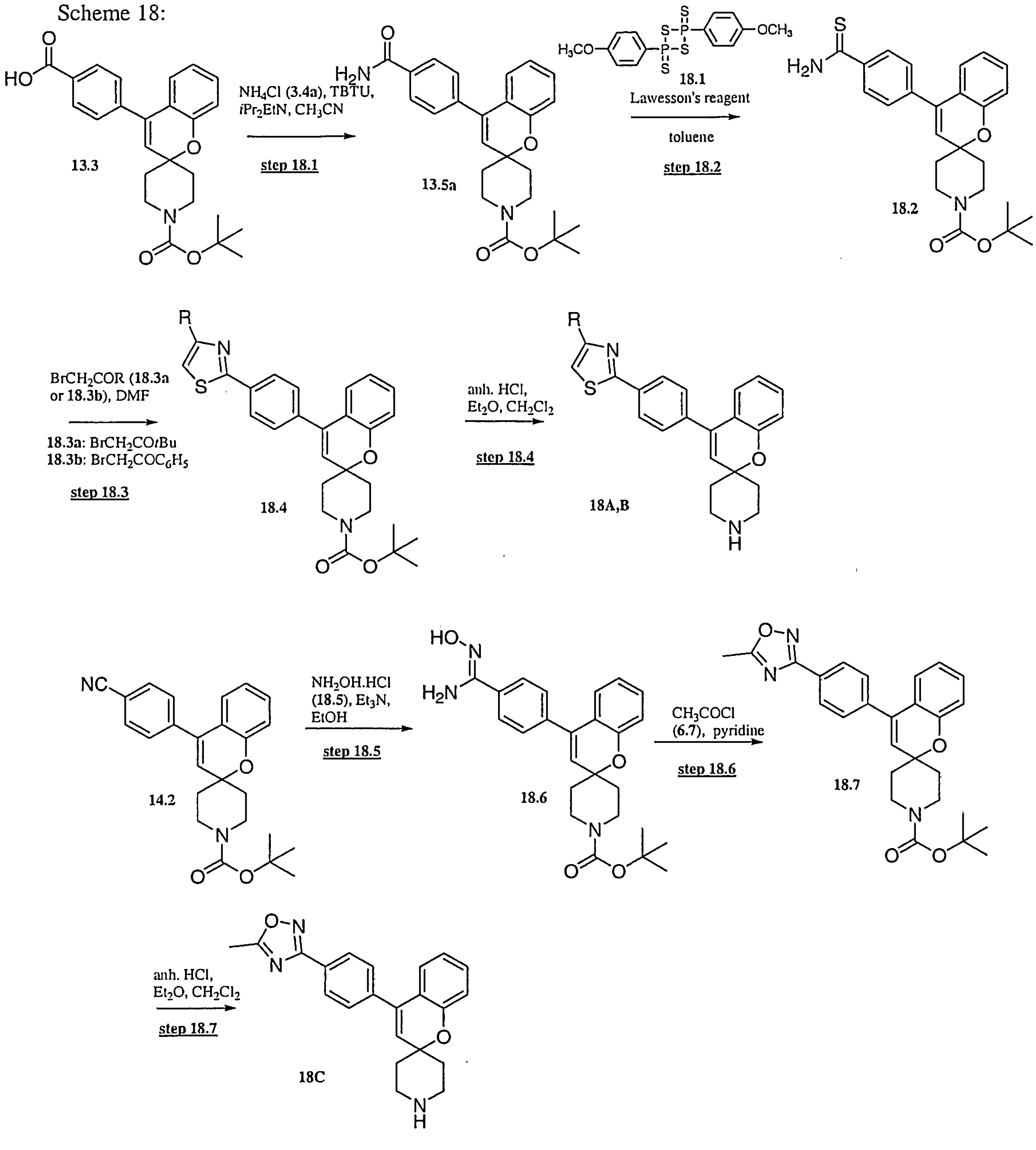
Scheme 16:


1.5a
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
16.1
step 16.1
16.2
NaN3(14.3), ZnBr2, iPrOH, H2O
step 16.2
16.3
CH3I (2.8c), Et3N, DMF
step 16.3
anh. HCl, Et2O, CH2Cl2
step 16.4
16A
16.4
+
16.5
step 16.5
anh. HCl, Et2O, CH2Cl2
step 16.6
anh. HCl, Et2O, CH2Cl2
16B
16C

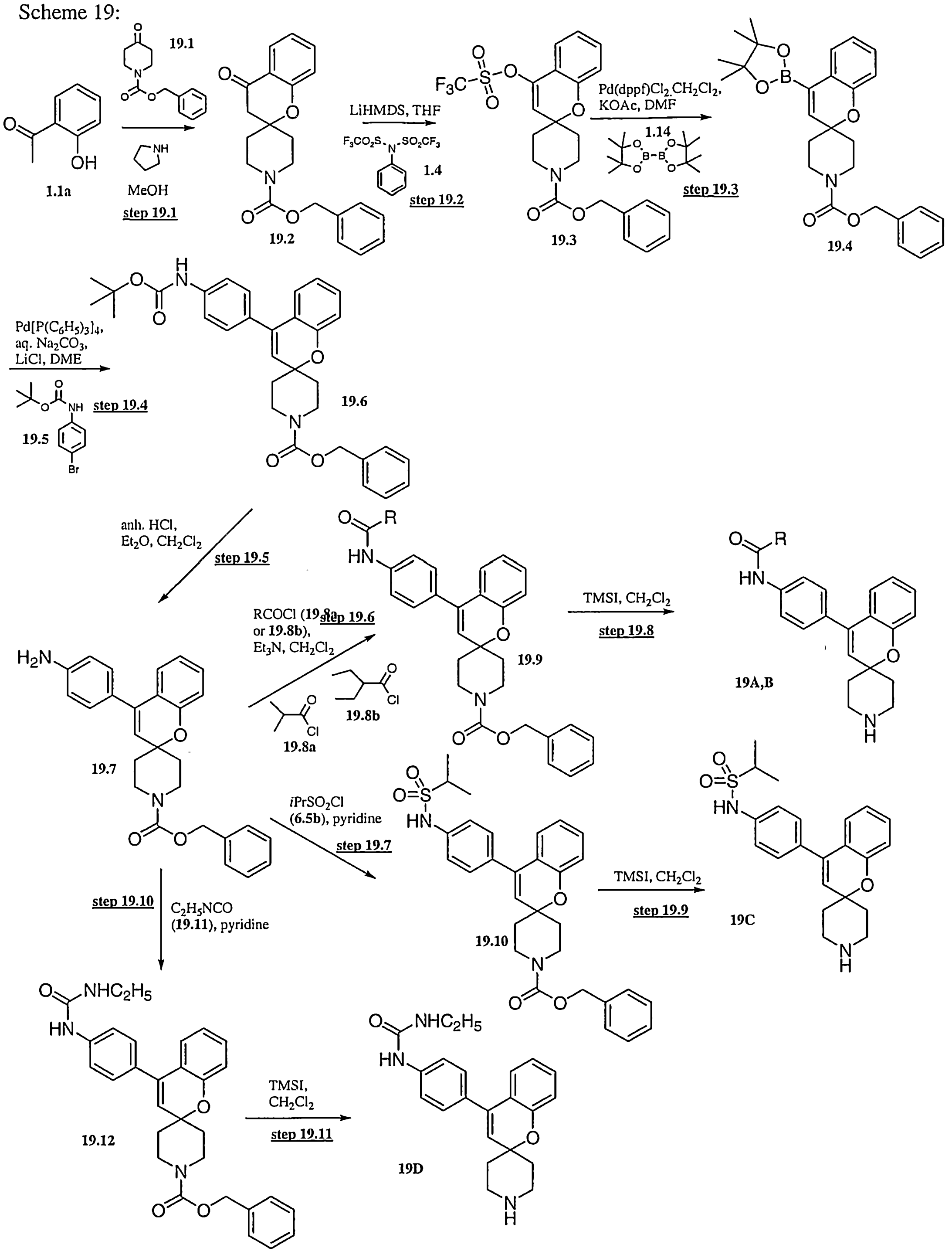
Scheme 17:


16.3
Br(CH2)nCO2R
(15.1a or 15.1c),
Et3N, DMF
BrCH2CO2Me
15.1a
Br(CH2)3CO2Et
15.1c
step 17.1
17.1
+
17.2
anh. HCl,
Et2O, CH2Cl2
step 17.2
17C
(R = CH3)
step 17.7
Et3N, DMF
17.3
anh. HCl,
Et2O, CH2Cl2
step 17.3
NaOH,
MeOH, THF
step 17.4
17.4
17A,B
17.5
NaOH,
MeOH, THF
step 17.5
anh. HCl,
Et2O, CH2Cl2
step 17.6
step 17.8
anh. HCl,
Et2O, CH2Cl2
17E,F
17D

Scheme 18:


13.3
NH4Cl (3.4a), TBTU, iPr2EtN, CH3CN
step 18.1
13.5a
18.1
Lawesson's reagent
toluene
step 18.2
18.2
BrCH2COR (18.3a or 18.3b), DMF
18.3a: BrCH2COtBu
18.3b: BrCH2COC6H5
step 18.3
18.4
anh. HCl, Et2O, CH2Cl2
step 18.4
18A,B
14.2
NH2OH.HCl (18.5), Et3N, EtOH
step 18.5
18.6
CH3COCl (6.7), pyridine
step 18.6
18.7
anh. HCl, Et2O, CH2Cl2
step 18.7
18C

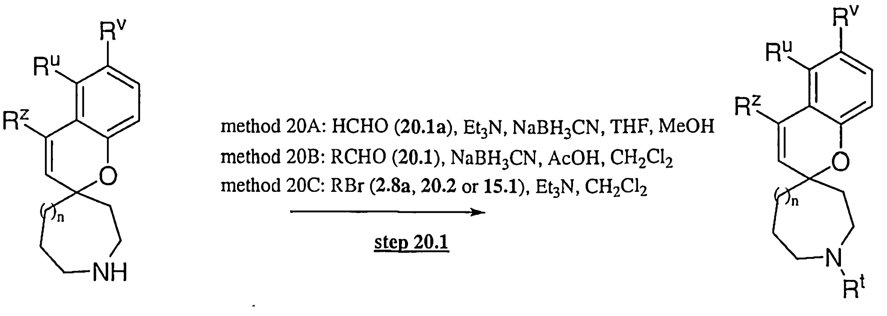
Scheme 19:


19.1
1.1a
MeOH
step 19.1
19.2
LiHMDS, THF
1.4
step 19.2
19.3
Pd(dppf)Cl2.CH2Cl2, KOAc, DMF
1.14
step 19.3
19.4
Pd[P(C6H5)3]4, aq. Na2CO3, LiCl, DME
step 19.4
19.5
19.6
anh. HCl, Et2O, CH2Cl2
step 19.5
19.7
RCOCl (19.8a or 19.8b), Et3N, CH2Cl2
step 19.6
19.8a
19.8b
19.9
TMSI, CH2Cl2
step 19.8
19A,B
iPrSO2Cl (6.5b), pyridine
step 19.7
19.10
TMSI, CH2Cl2
step 19.9
19C
step 19.10
C2H5NCO (19.11), pyridine
19.12
TMSI, CH2Cl2
step 19.11
19D

Scheme 20:

general formula **20I**

n = 0, 1



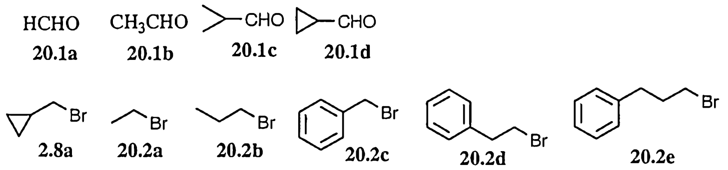
method 20A: HCHO (**20.1a**), Et_3N, $NaBH_3CN$, THF, MeOH
method 20B: RCHO (**20.1**), $NaBH_3CN$, AcOH, CH_2Cl_2
method 20C: RBr (**2.8a**, **20.2** or **15.1**), Et_3N, CH_2Cl_2

step 20.1

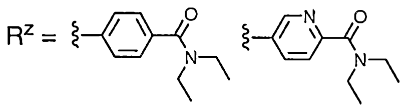
20 A-R

list of aldehydes and alkyl bromides used in step 20.1:

HCHO **20.1a** CH_3CHO **20.1b**



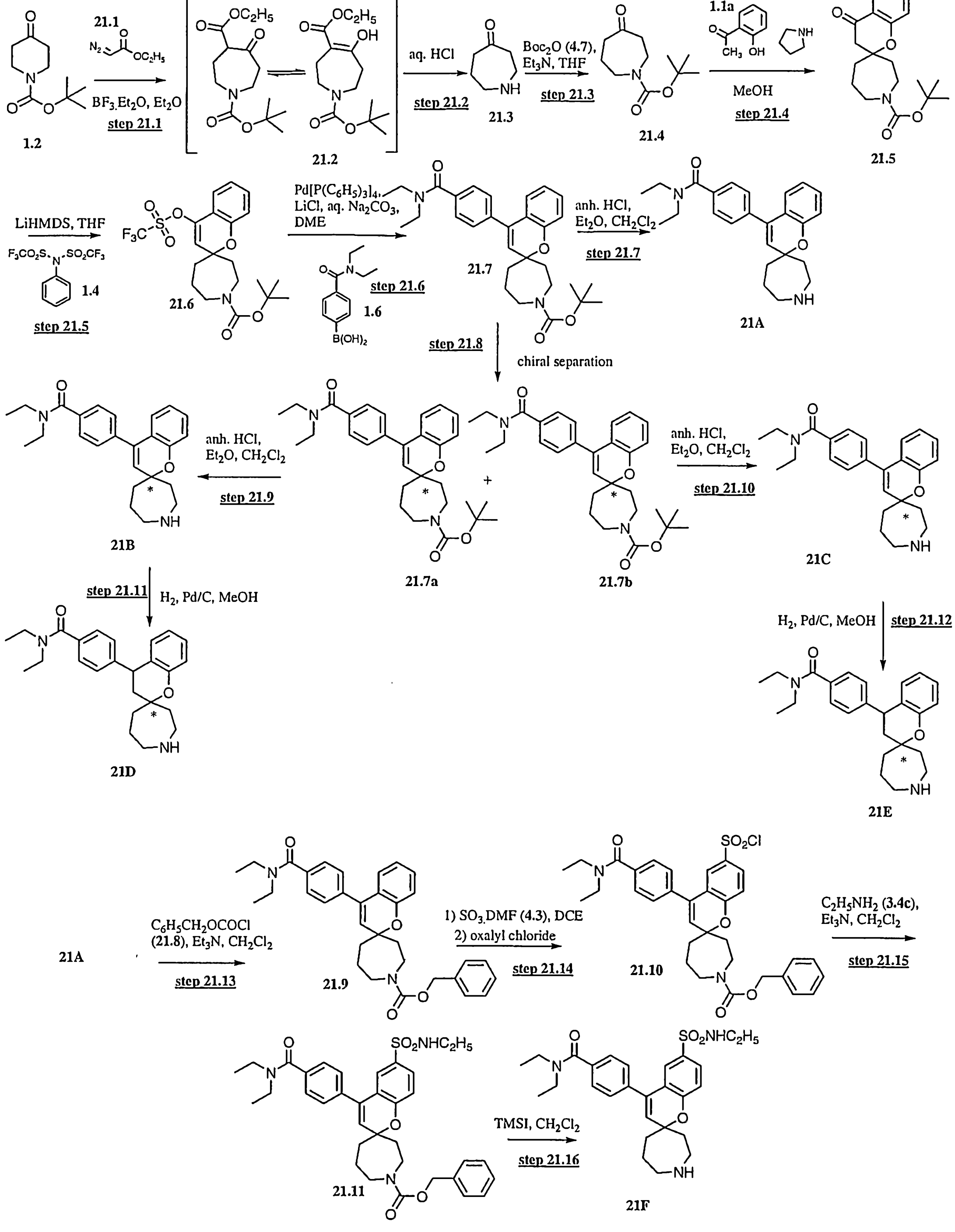
20.1c **20.1d** **2.8a** **20.2a** **20.2b** **20.2c** **20.2d** **20.2e**



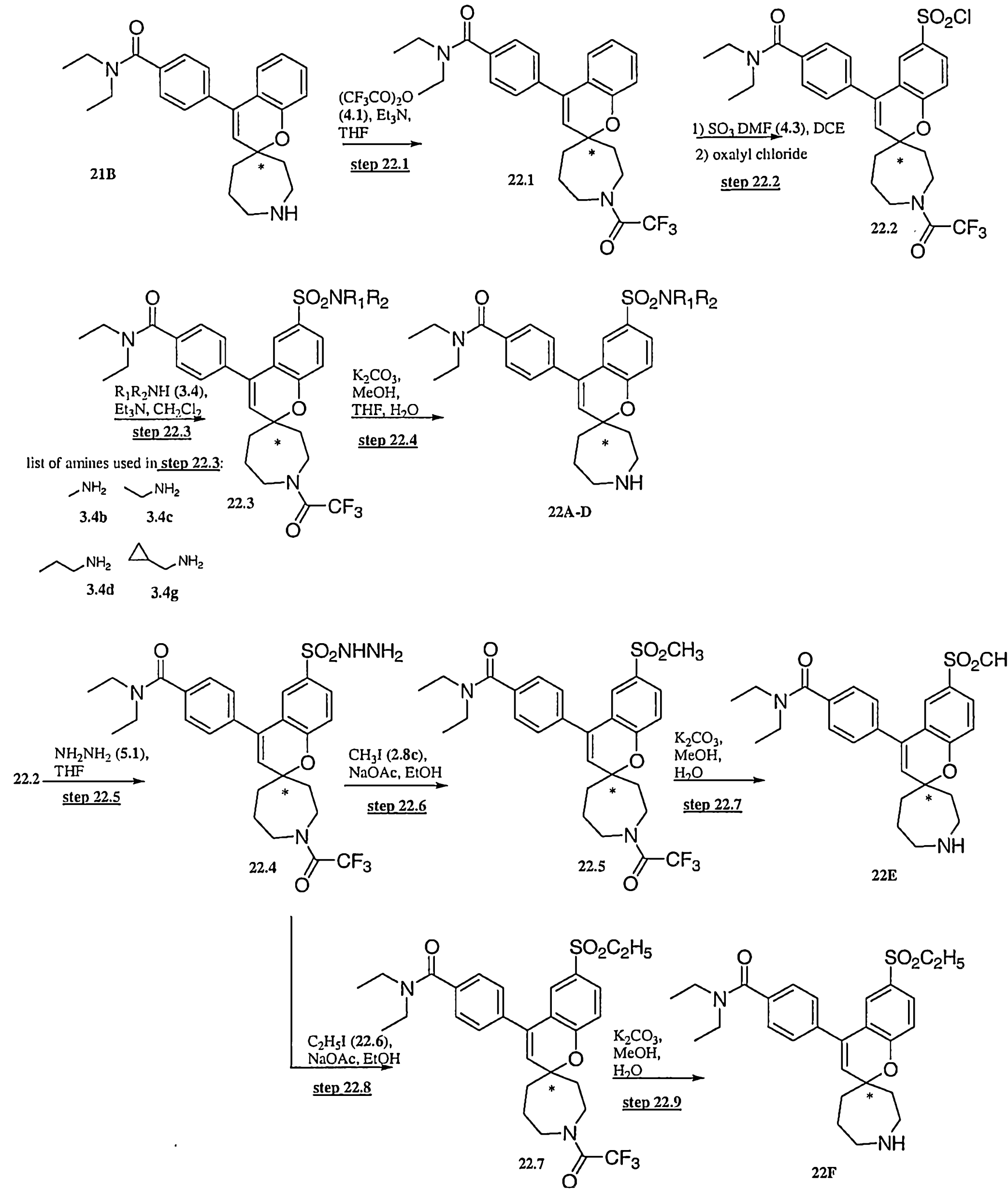
R^u = H, OH

R^v = H, OH, $CONH_2$, $CONHCH_3$, $CONHC_2H_5$, SO_2NH_2

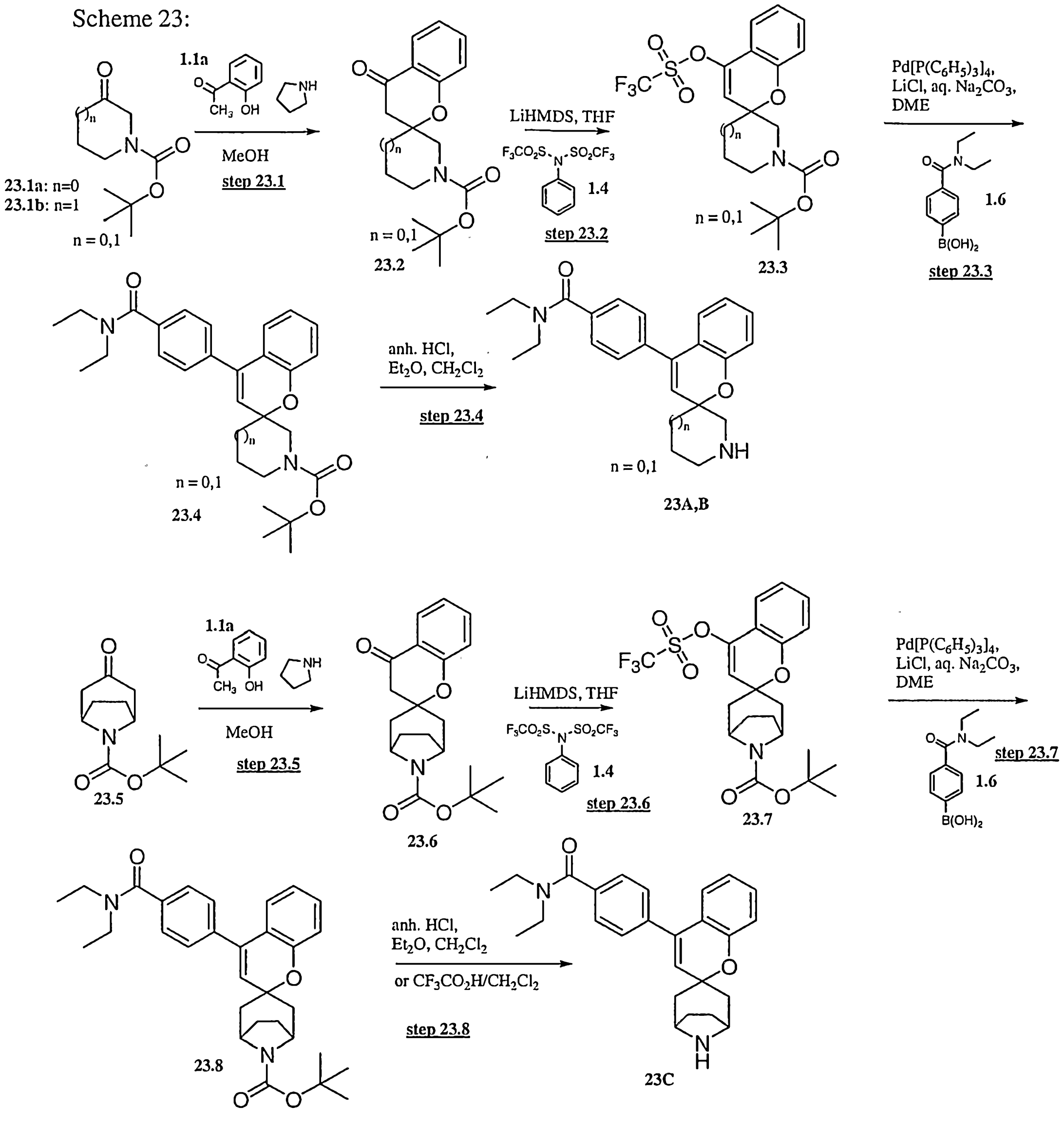
Scheme 21:


1.2
21.1
BF3.Et2O, Et2O
step 21.1
21.2
aq. HCl
step 21.2
21.3
Boc2O (4.7), Et3N, THF
step 21.3
21.4
1.1a
MeOH
step 21.4
21.5
LiHMDS, THF
1.4
step 21.5
21.6
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
1.6
step 21.6
21.7
anh. HCl, Et2O, CH2Cl2
step 21.7
21A
step 21.8
chiral separation
21.7a
21.7b
anh. HCl, Et2O, CH2Cl2
step 21.9
21B
anh. HCl, Et2O, CH2Cl2
step 21.10
21C
step 21.11
H2, Pd/C, MeOH
21D
H2, Pd/C, MeOH
step 21.12
21E
21A
C6H5CH2OCOCl (21.8), Et3N, CH2Cl2
step 21.13
21.9
1) SO3.DMF (4.3), DCE
2) oxalyl chloride
step 21.14
21.10
C2H5NH2 (3.4c), Et3N, CH2Cl2
step 21.15
21.11
TMSI, CH2Cl2
step 21.16
21F

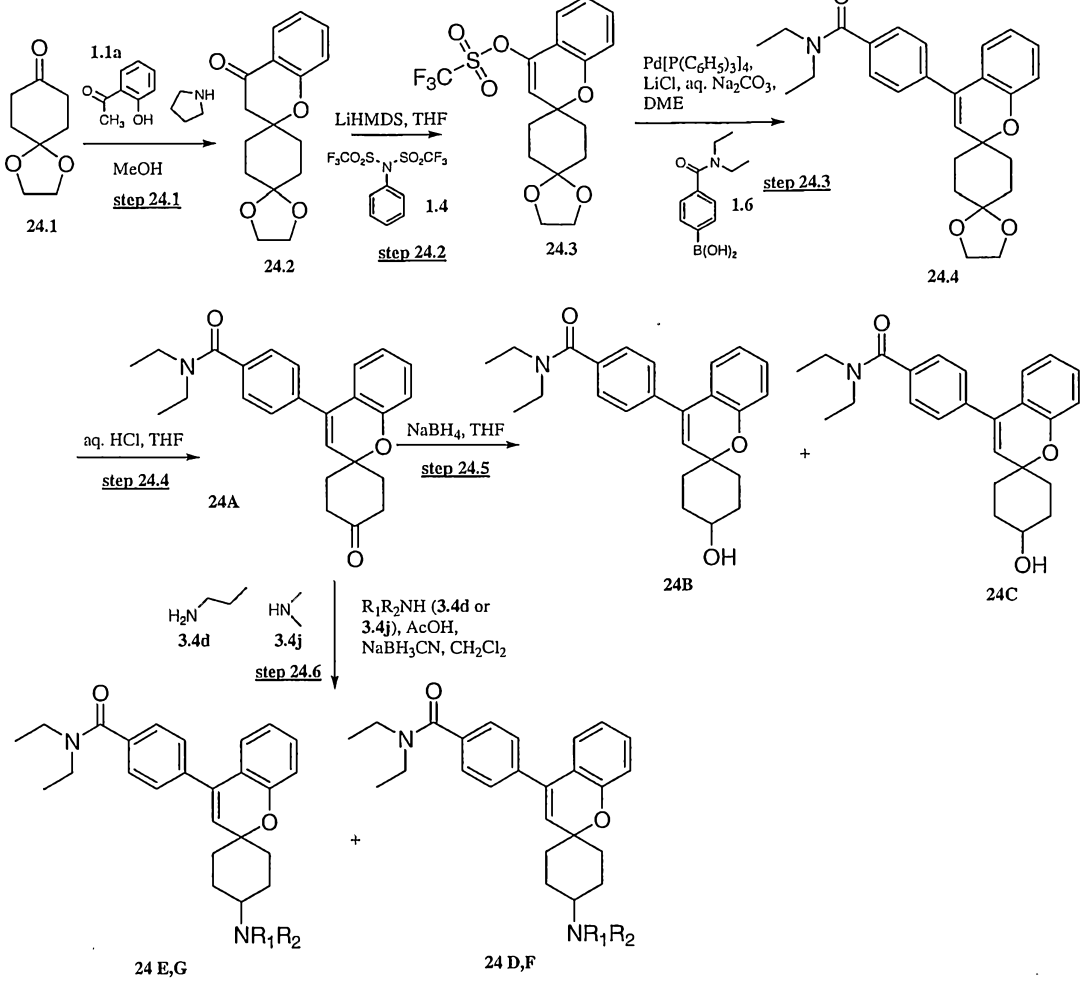
Scheme 22:


21B
(CF3CO)2O (4.1), Et3N, THF
step 22.1
22.1
1) SO3 DMF (4.3), DCE
2) oxalyl chloride
step 22.2
SO2Cl
22.2
CF3
R1R2NH (3.4), Et3N, CH2Cl2
step 22.3
SO2NR1R2
list of amines used in step 22.3:
3.4b
3.4c
3.4d
3.4g
22.3
K2CO3, MeOH, THF, H2O
step 22.4
22A-D
NH2NH2 (5.1), THF
step 22.5
SO2NHNH2
22.4
CH3I (2.8c), NaOAc, EtOH
step 22.6
SO2CH3
22.5
K2CO3, MeOH, H2O
step 22.7
22E
C2H5I (22.6), NaOAc, EtOH
step 22.8
SO2C2H5
22.7
K2CO3, MeOH, H2O
step 22.9
22F

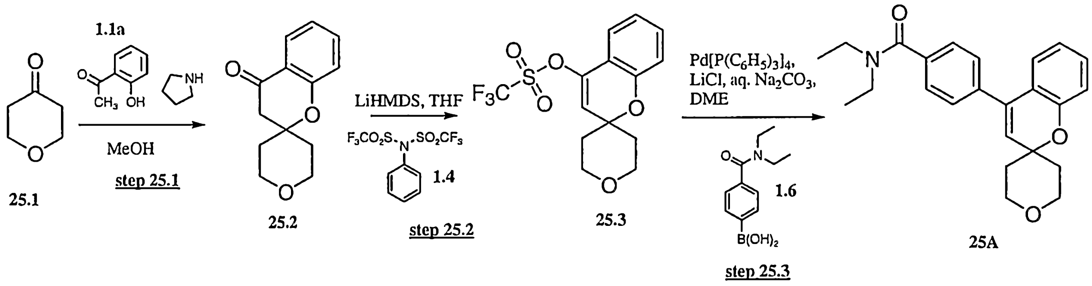
Scheme 23:


23.1a: n=0
23.1b: n=1
n = 0,1
1.1a
MeOH
step 23.1
n = 0,1
23.2
LiHMDS, THF
F3CO2S-N-SO2CF3
1.4
step 23.2
F3C
n = 0,1
23.3
Pd[P(C6H5)3]4,
LiCl, aq. Na2CO3,
DME
1.6
B(OH)2
step 23.3
n = 0,1
23.4
anh. HCl,
Et2O, CH2Cl2
step 23.4
n = 0,1
NH
23A,B
23.5
1.1a
MeOH
step 23.5
23.6
LiHMDS, THF
F3CO2S-N-SO2CF3
1.4
step 23.6
F3C
23.7
Pd[P(C6H5)3]4,
LiCl, aq. Na2CO3,
DME
step 23.7
1.6
B(OH)2
23.8
anh. HCl,
Et2O, CH2Cl2
or CF3CO2H/CH2Cl2
step 23.8
23C

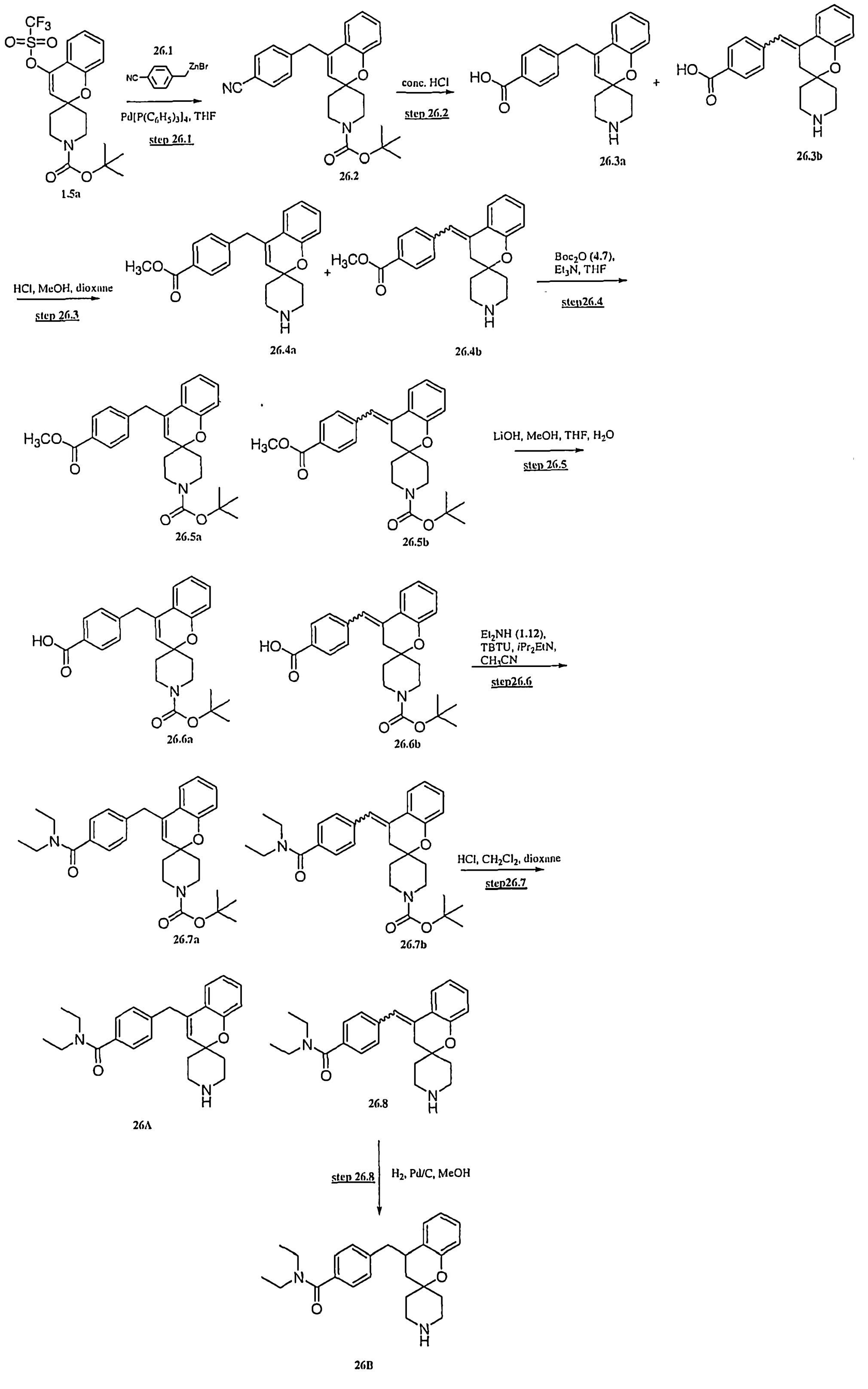
Scheme 24:



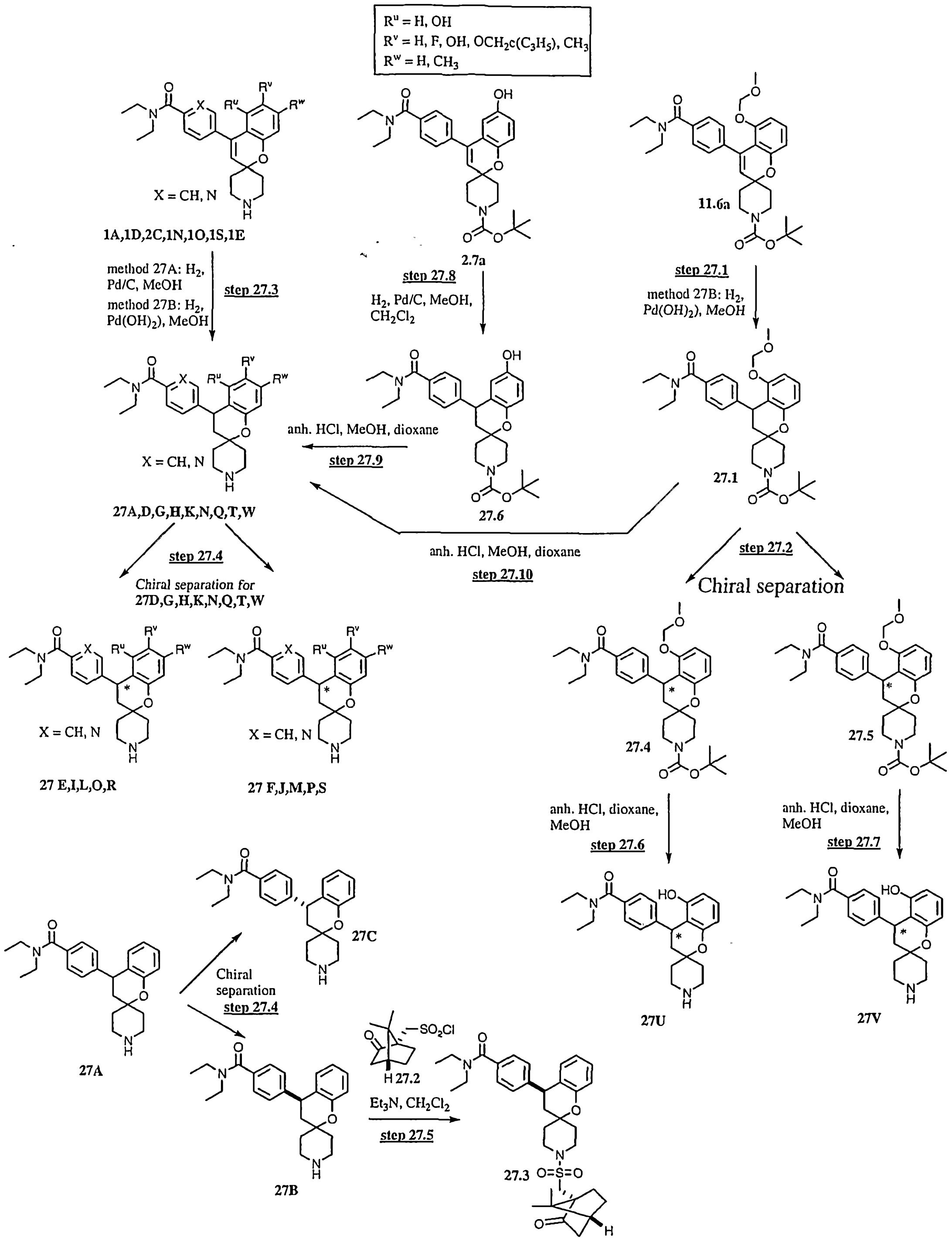
Scheme 25:



Scheme 26:

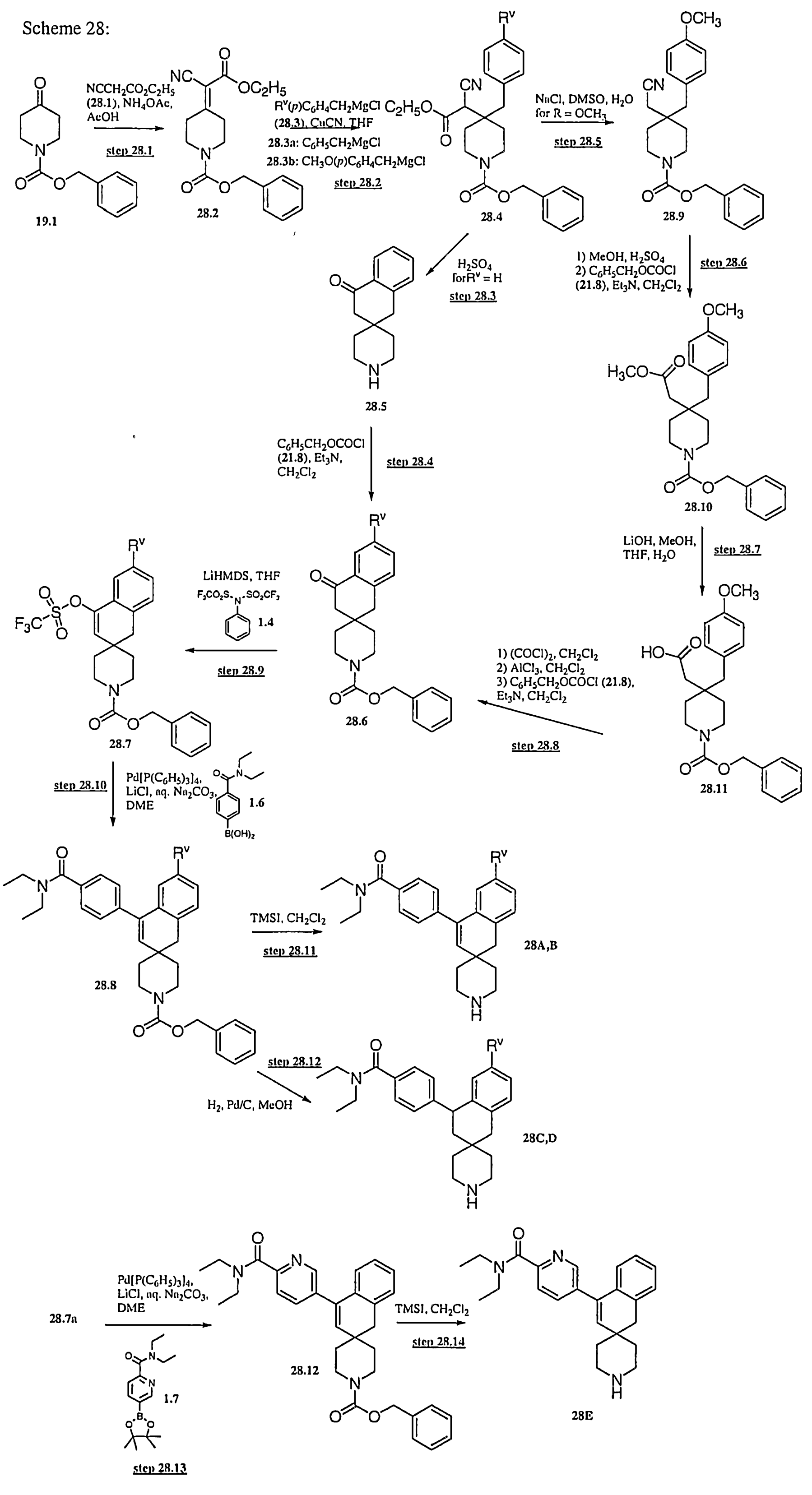

1.5a
26.1
Pd[P(C6H5)3]4, THF
step 26.1
26.2
conc. HCl
step 26.2
26.3a
26.3b
HCl, MeOH, dioxane
step 26.3
26.4a
26.4b
Boc2O (4.7), Et3N, THF
step26.4
26.5a
26.5b
LiOH, MeOH, THF, H2O
step 26.5
26.6a
26.6b
Et2NH (1.12), TBTU, iPr2EtN, CH3CN
step26.6
26.7a
26.7b
HCl, CH2Cl2, dioxane
step26.7
26A
26.8
step 26.8
H2, Pd/C, MeOH
26B

Scheme 27:

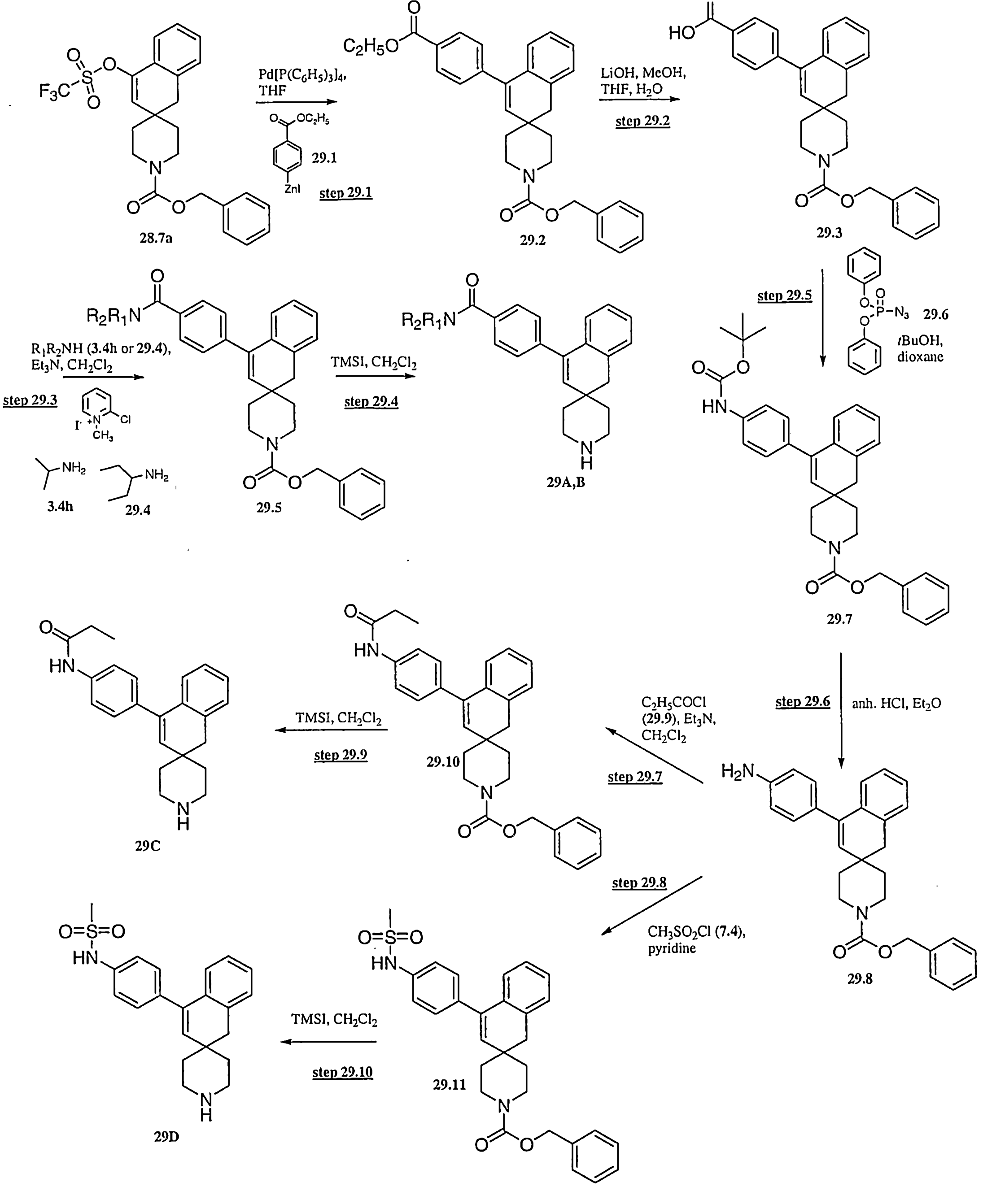

R^u = H, OH
R^v = H, F, OH, OCH2c(C3H5), CH3
R^w = H, CH3
X = CH, N
1A,1D,2C,1N,1O,1S,1E
2.7a
11.6a
method 27A: H2, Pd/C, MeOH
method 27B: H2, Pd(OH)2), MeOH
step 27.3
step 27.8
H2, Pd/C, MeOH, CH2Cl2
step 27.1
method 27B: H2, Pd(OH)2), MeOH
27A,D,G,H,K,N,Q,T,W
anh. HCl, MeOH, dioxane
step 27.9
27.6
27.1
anh. HCl, MeOH, dioxane
step 27.10
step 27.4
Chiral separation for 27D,G,H,K,N,Q,T,W
step 27.2
Chiral separation
27 E,I,L,O,R
27 F,J,M,P,S
27.4
27.5
anh. HCl, dioxane, MeOH
step 27.6
anh. HCl, dioxane, MeOH
step 27.7
27C
Chiral separation
step 27.4
27A
27U
27V
27.2
Et3N, CH2Cl2
step 27.5
27B
27.3

]

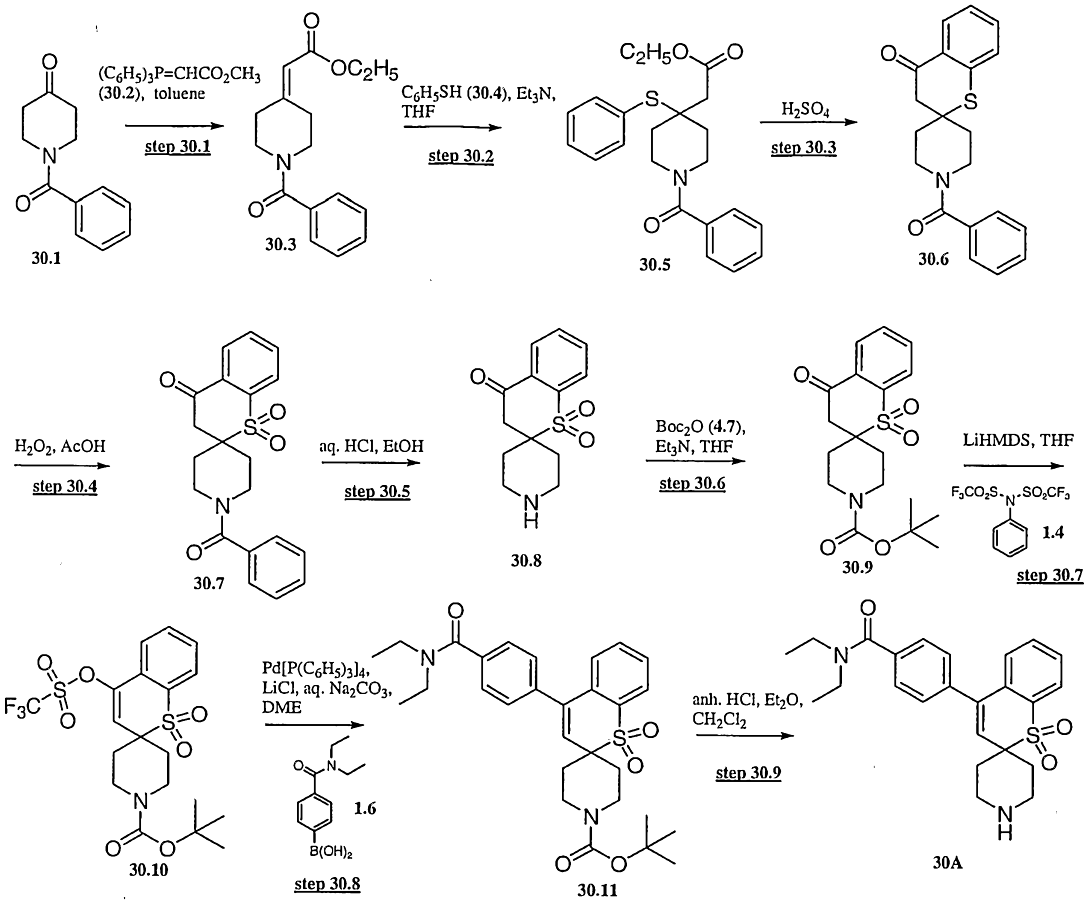
Scheme 28:


19.1
NCCH2CO2C2H5 (28.1), NH4OAc, AcOH
step 28.1
28.2
Rv(p)C6H4CH2MgCl (28.3), CuCN, THF
28.3a: C6H5CH2MgCl
28.3b: CH3O(p)C6H4CH2MgCl
step 28.2
28.4
NaCl, DMSO, H2O for R = OCH3
step 28.5
28.9
H2SO4 for Rv = H
step 28.3
28.5
1) MeOH, H2SO4
2) C6H5CH2OCOCl (21.8), Et3N, CH2Cl2
step 28.6
28.10
C6H5CH2OCOCl (21.8), Et3N, CH2Cl2
step 28.4
LiOH, MeOH, THF, H2O
step 28.7
LiHMDS, THF
1.4
step 28.9
28.6
1) (COCl)2, CH2Cl2
2) AlCl3, CH2Cl2
3) C6H5CH2OCOCl (21.8), Et3N, CH2Cl2
step 28.8
28.11
28.7
step 28.10
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
1.6
28.8
TMSI, CH2Cl2
step 28.11
28A,B
step 28.12
H2, Pd/C, MeOH
28C,D
28.7a
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
1.7
step 28.13
28.12
TMSI, CH2Cl2
step 28.14
28E

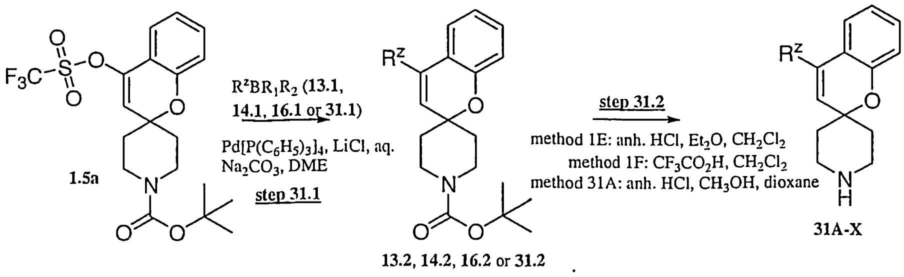
Scheme 29:


28.7a
Pd[P(C6H5)3]4, THF
29.1
step 29.1
29.2
LiOH, MeOH, THF, H2O
step 29.2
29.3
step 29.5
29.6
tBuOH, dioxane
R1R2NH (3.4h or 29.4), Et3N, CH2Cl2
step 29.3
3.4h
29.4
29.5
TMSI, CH2Cl2
step 29.4
29A,B
29.7
step 29.6
anh. HCl, Et2O
C2H5COCl (29.9), Et3N, CH2Cl2
step 29.7
29.8
29.10
TMSI, CH2Cl2
step 29.9
29C
step 29.8
CH3SO2Cl (7.4), pyridine
29.11
TMSI, CH2Cl2
step 29.10
29D

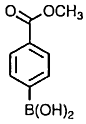
Scheme 30:


30.1
(C6H5)3P=CHCO2CH3 (30.2), toluene
step 30.1
30.3
C6H5SH (30.4), Et3N, THF
step 30.2
30.5
H2SO4
step 30.3
30.6
H2O2, AcOH
step 30.4
30.7
aq. HCl, EtOH
step 30.5
30.8
Boc2O (4.7), Et3N, THF
step 30.6
30.9
LiHMDS, THF
F3CO2S-N-SO2CF3
1.4
step 30.7
30.10
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
1.6
B(OH)2
step 30.8
30.11
anh. HCl, Et2O, CH2Cl2
step 30.9
30A

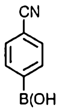
Scheme 31:



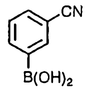
Commercially available boronic acid derivatives used in step **31.2**:



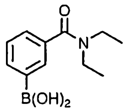
13.1



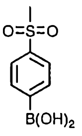
14.1



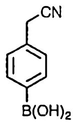
16.1



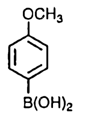
31.1a



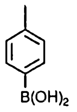
31.1b



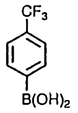
31.1c



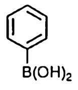
31.1d



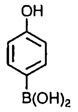
31.1e



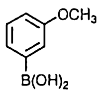
31.1f



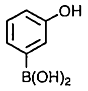
31.1g



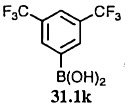
31.1h



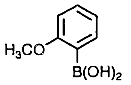
31.1i



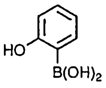
31.1j



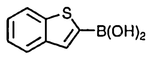
31.1k



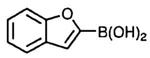
31.1l



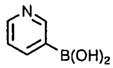
31.1m



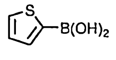
31.1n



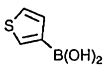
31.1o



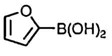
31.1p



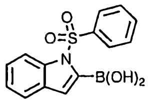
31.1q



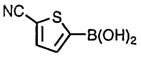
31.1r



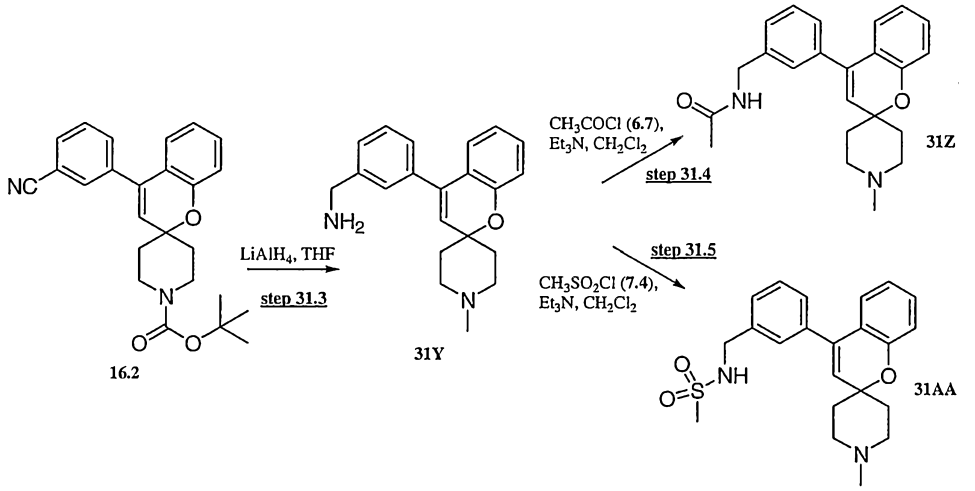
31.1s



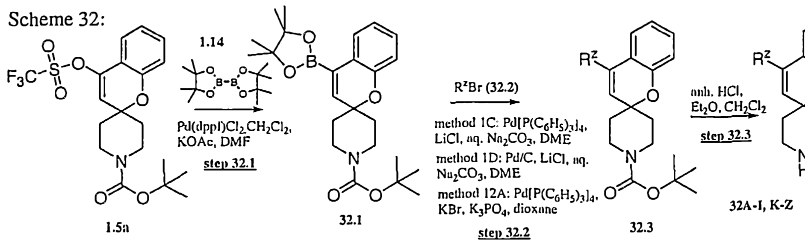
31.1t



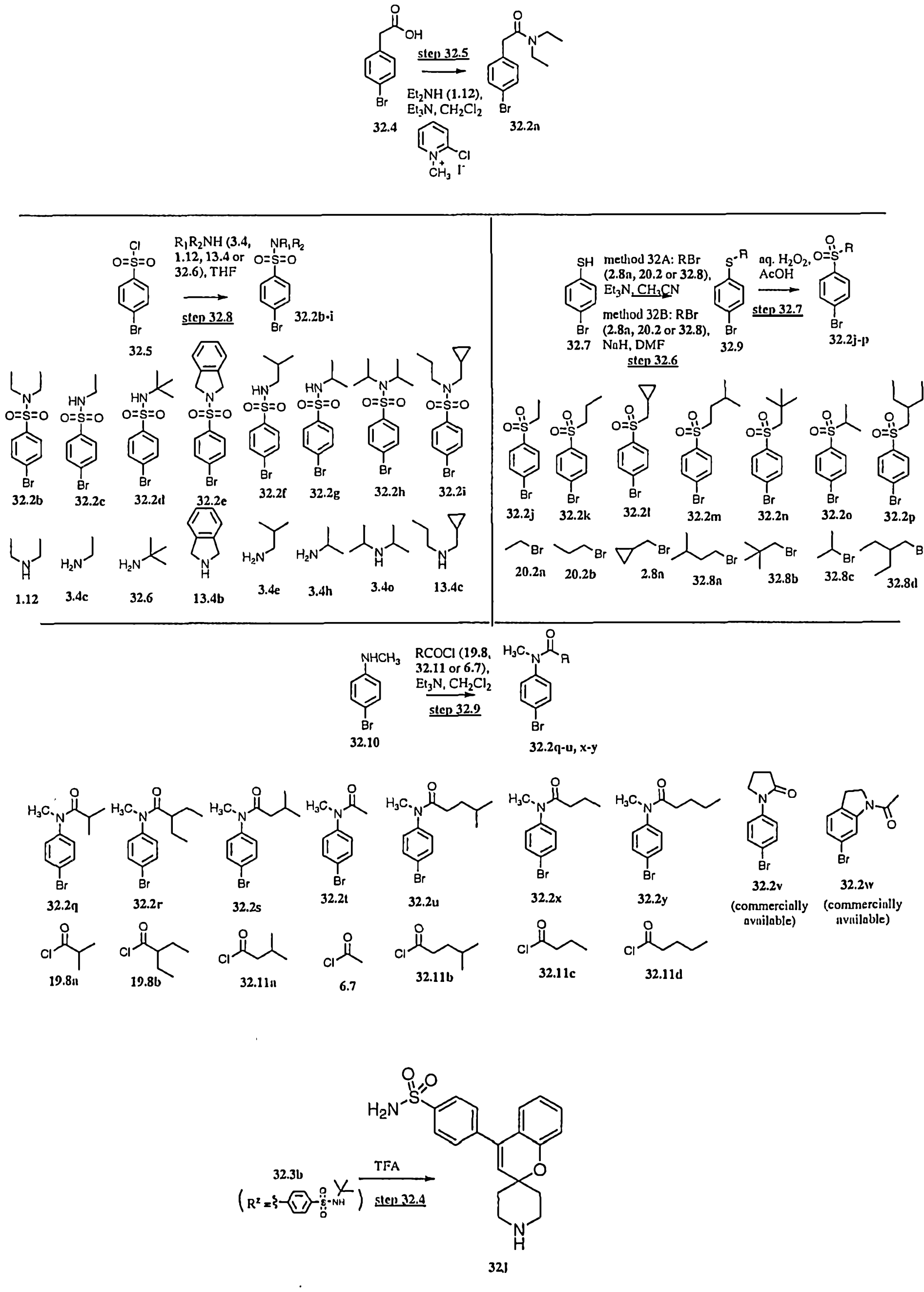
31.1u



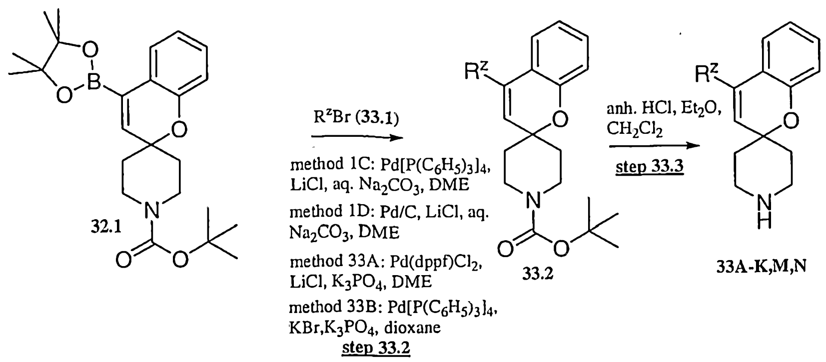
Scheme 32:



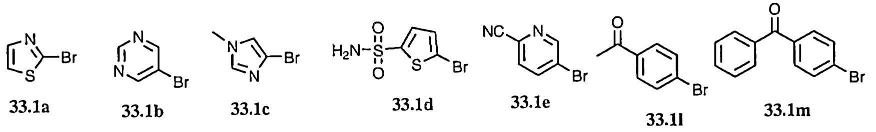
Description and preparation of aryl bromides (32.2) used in step 32.2:



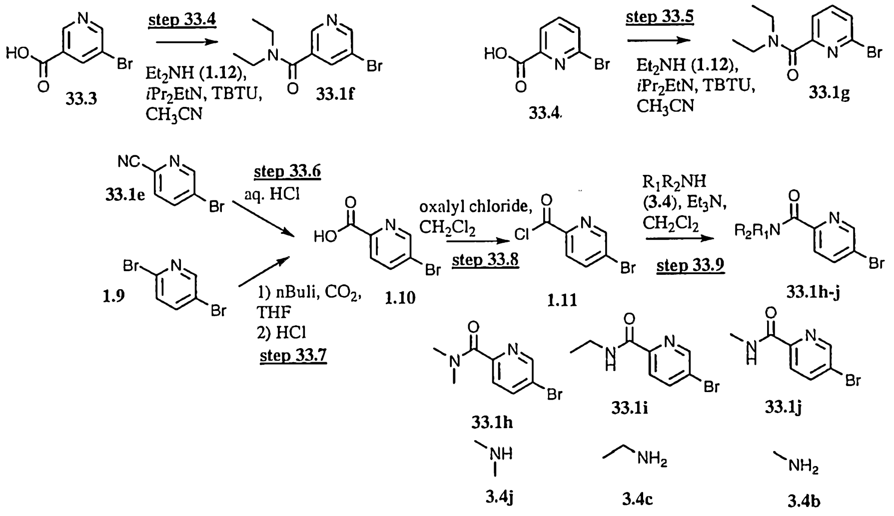
Scheme 33:

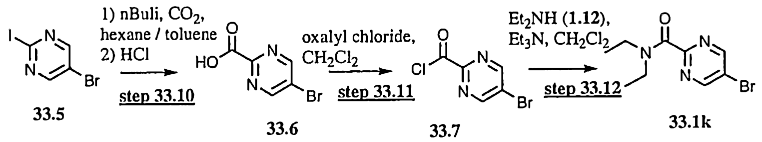


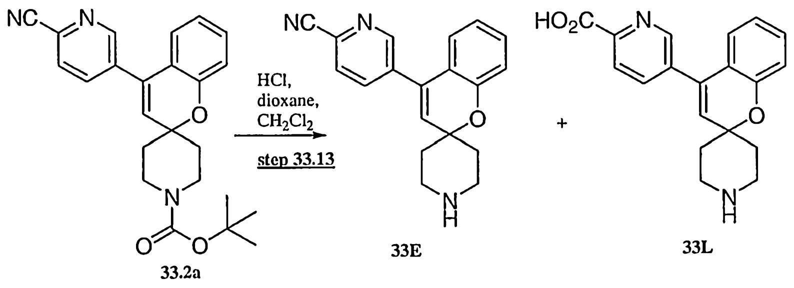
Commercially available R^{z}Br used in **step 33.2**:



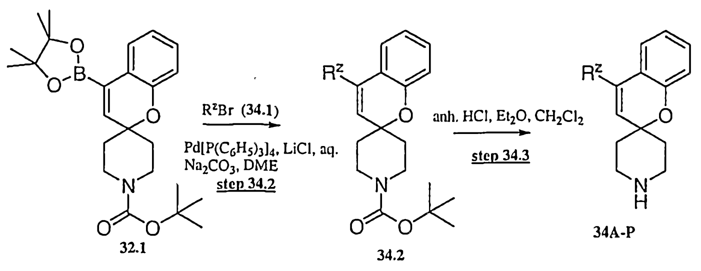
Preparation of R^{z}Br used in **step 33.2**:



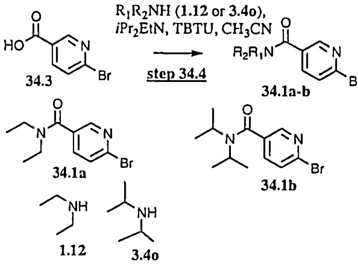


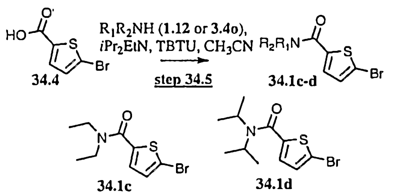


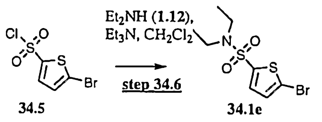
Scheme 34:

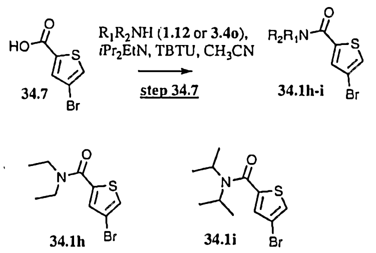


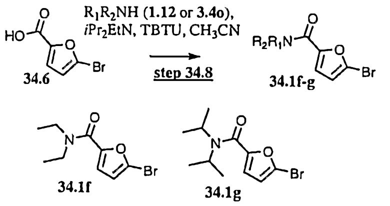
Preparation of R^zBr used in step 34.2:

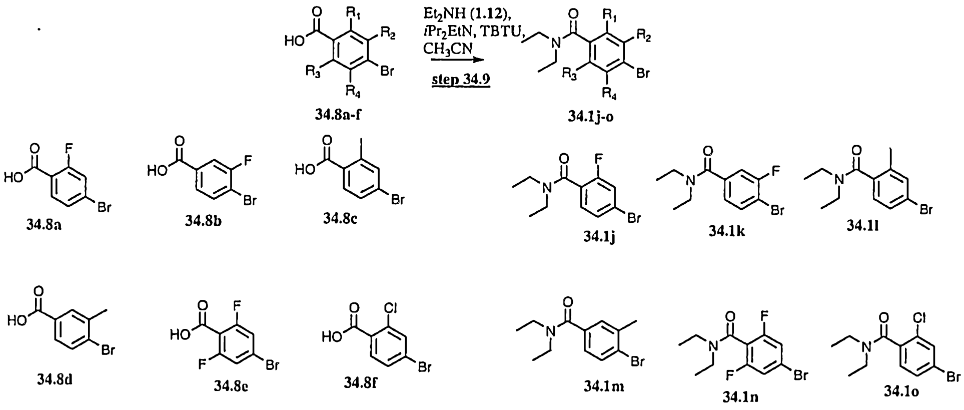


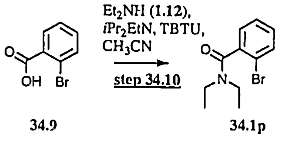




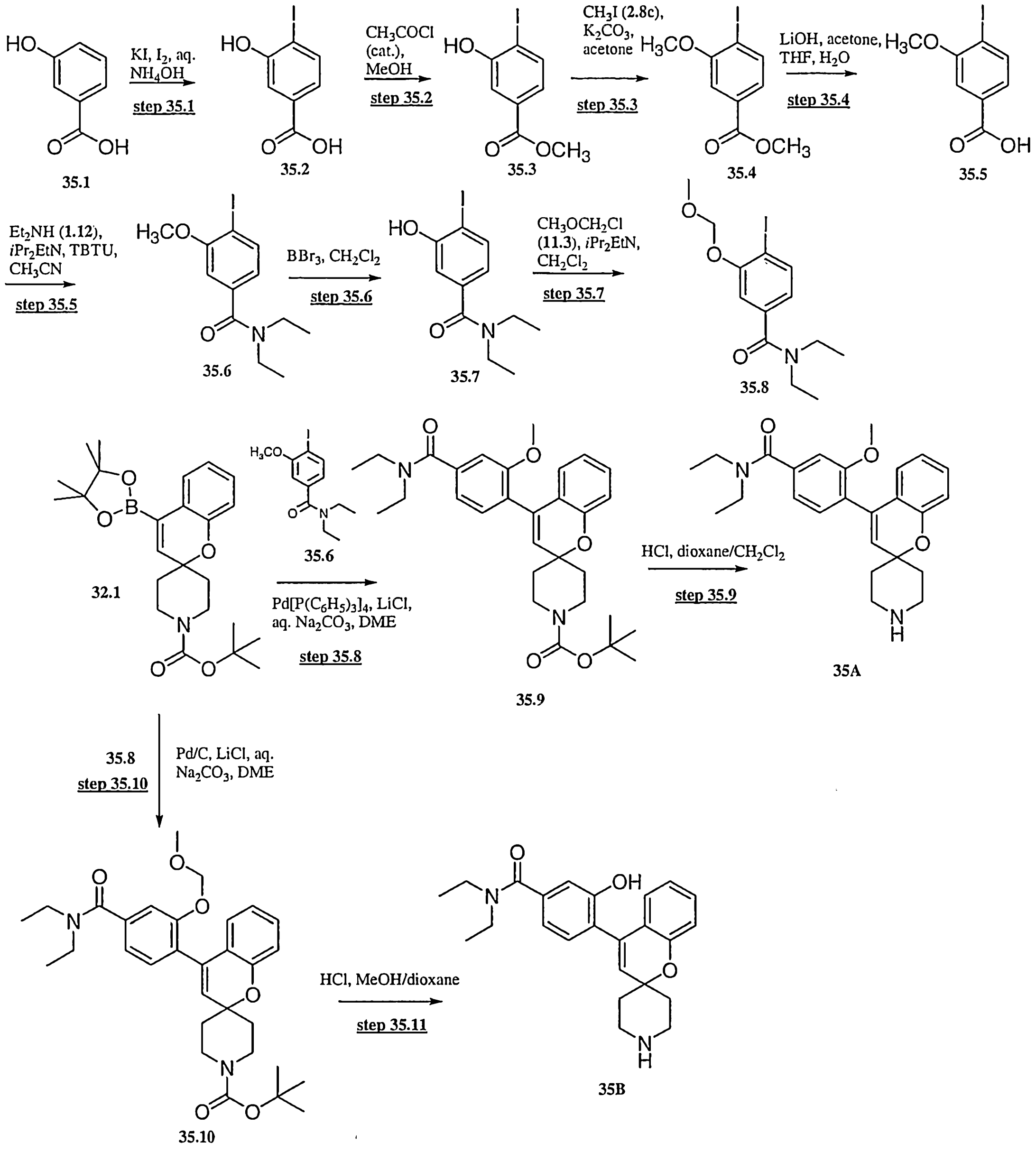




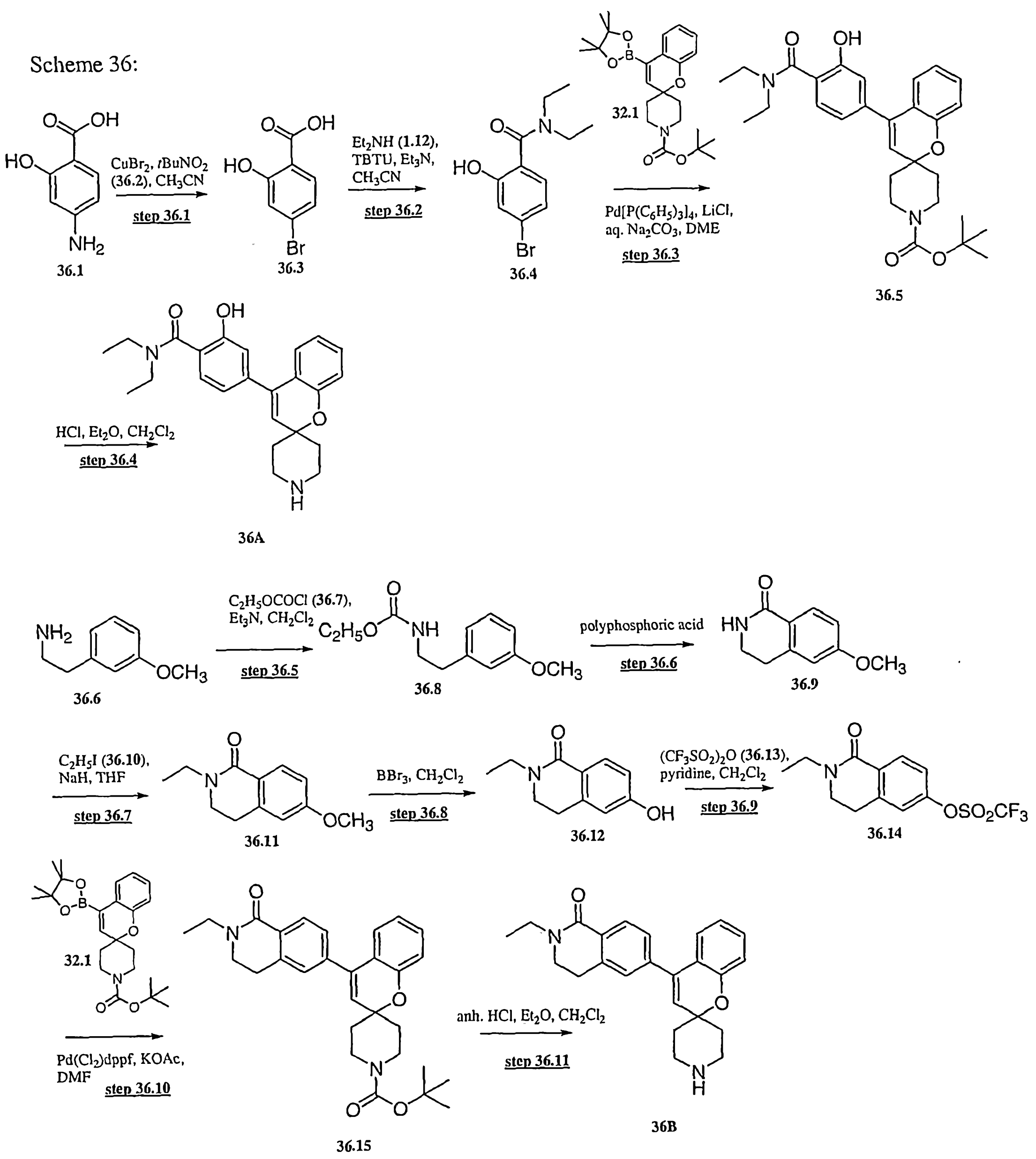




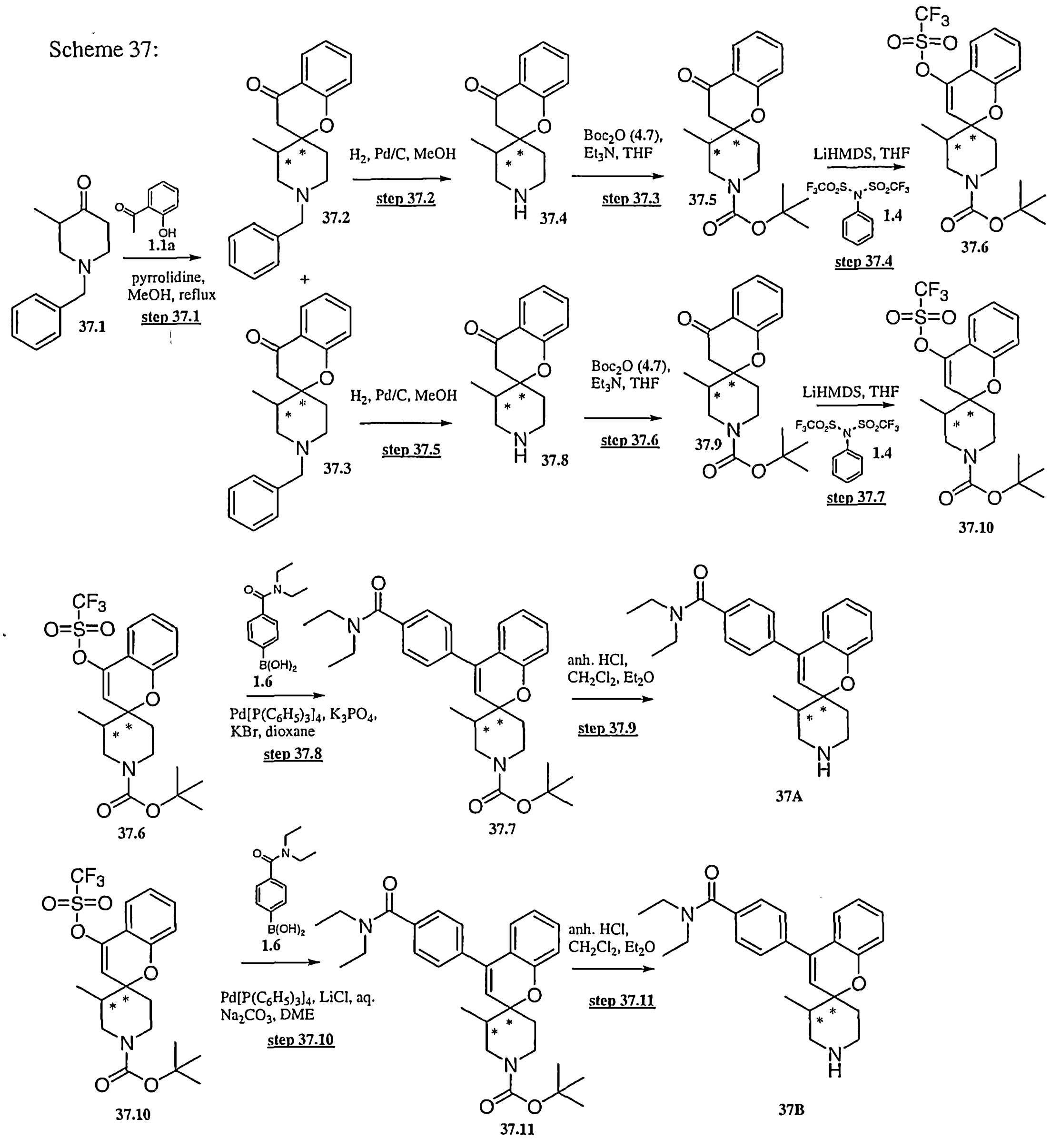
Scheme 35:


35.1
KI, I$_2$, aq. NH$_4$OH
step 35.1
35.2
CH$_3$COCl (cat.), MeOH
step 35.2
35.3
CH$_3$I (2.8c), K$_2$CO$_3$, acetone
step 35.3
35.4
LiOH, acetone, THF, H$_2$O
step 35.4
35.5
Et$_2$NH (1.12), iPr$_2$EtN, TBTU, CH$_3$CN
step 35.5
35.6
BBr$_3$, CH$_2$Cl$_2$
step 35.6
35.7
CH$_3$OCH$_2$Cl (11.3), iPr$_2$EtN, CH$_2$Cl$_2$
step 35.7
35.8
32.1
35.6
Pd[P(C$_6$H$_5$)$_3$]$_4$, LiCl, aq. Na$_2$CO$_3$, DME
step 35.8
35.9
HCl, dioxane/CH$_2$Cl$_2$
step 35.9
35A
35.8
step 35.10
Pd/C, LiCl, aq. Na$_2$CO$_3$, DME
35.10
HCl, MeOH/dioxane
step 35.11
35B

Scheme 36:

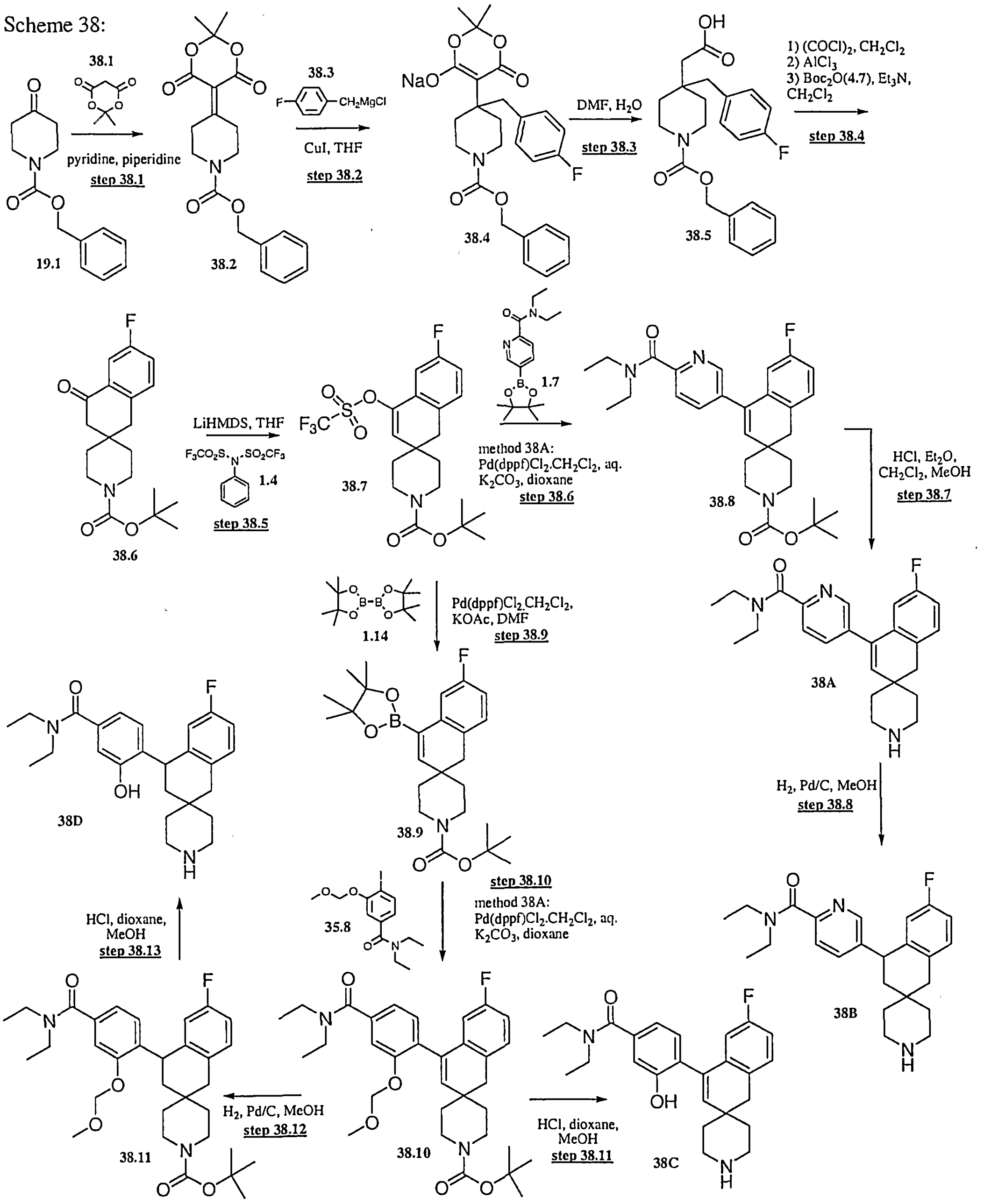

36.1
CuBr2, tBuNO2 (36.2), CH3CN
step 36.1
36.3
Et2NH (1.12), TBTU, Et3N, CH3CN
step 36.2
36.4
32.1
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
step 36.3
36.5
HCl, Et2O, CH2Cl2
step 36.4
36A
36.6
C2H5OCOCl (36.7), Et3N, CH2Cl2
step 36.5
36.8
polyphosphoric acid
step 36.6
36.9
C2H5I (36.10), NaH, THF
step 36.7
36.11
BBr3, CH2Cl2
step 36.8
36.12
(CF3SO2)2O (36.13), pyridine, CH2Cl2
step 36.9
36.14
32.1
Pd(Cl2)dppf, KOAc, DMF
step 36.10
36.15
anh. HCl, Et2O, CH2Cl2
step 36.11
36B

Scheme 37:

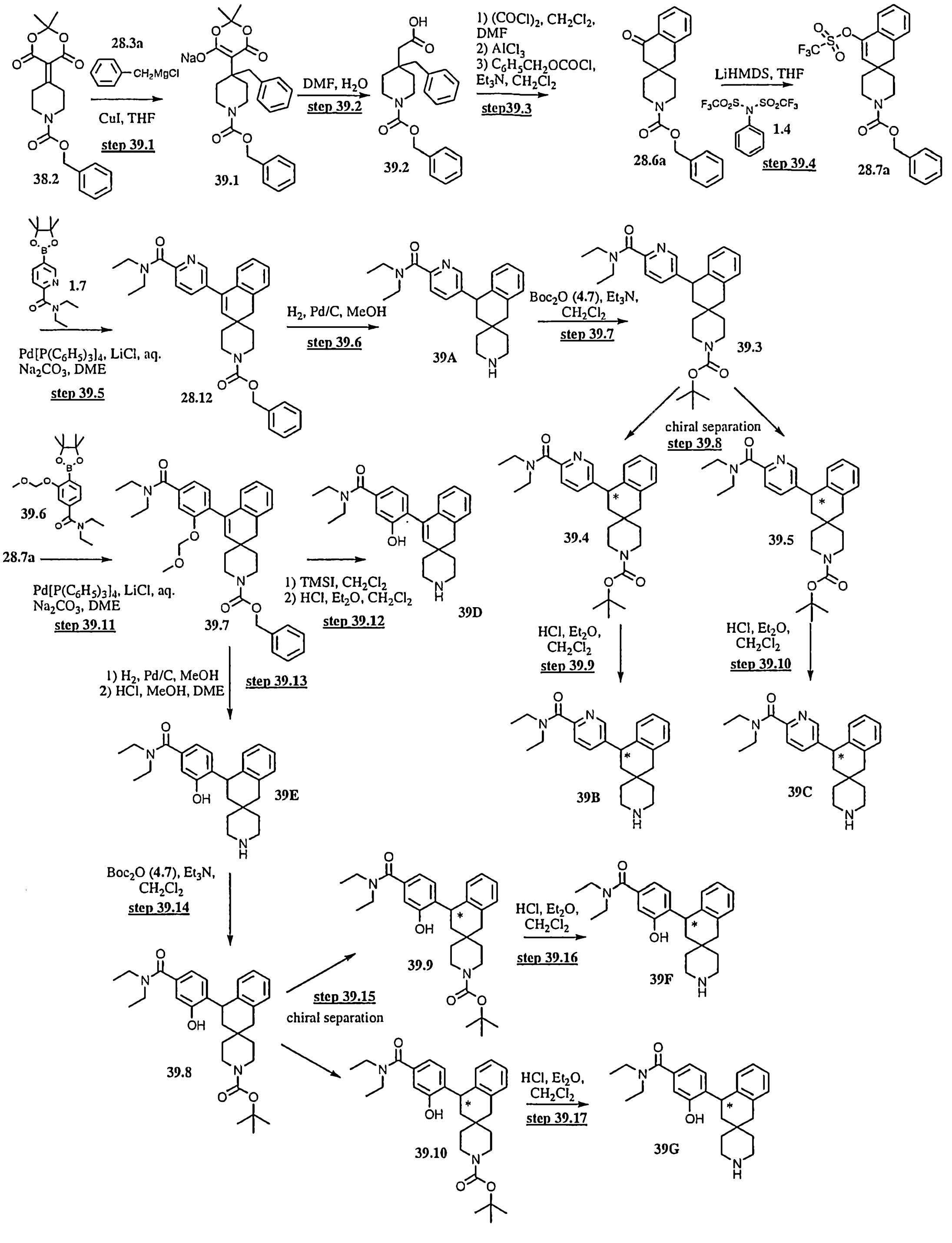


[0357] **37**A and **37B** are diastereomeric with respect to one another, but each is a racemic mixture of its two possible enantiomers. Their absolute stereochemistry has not been conclusively established.

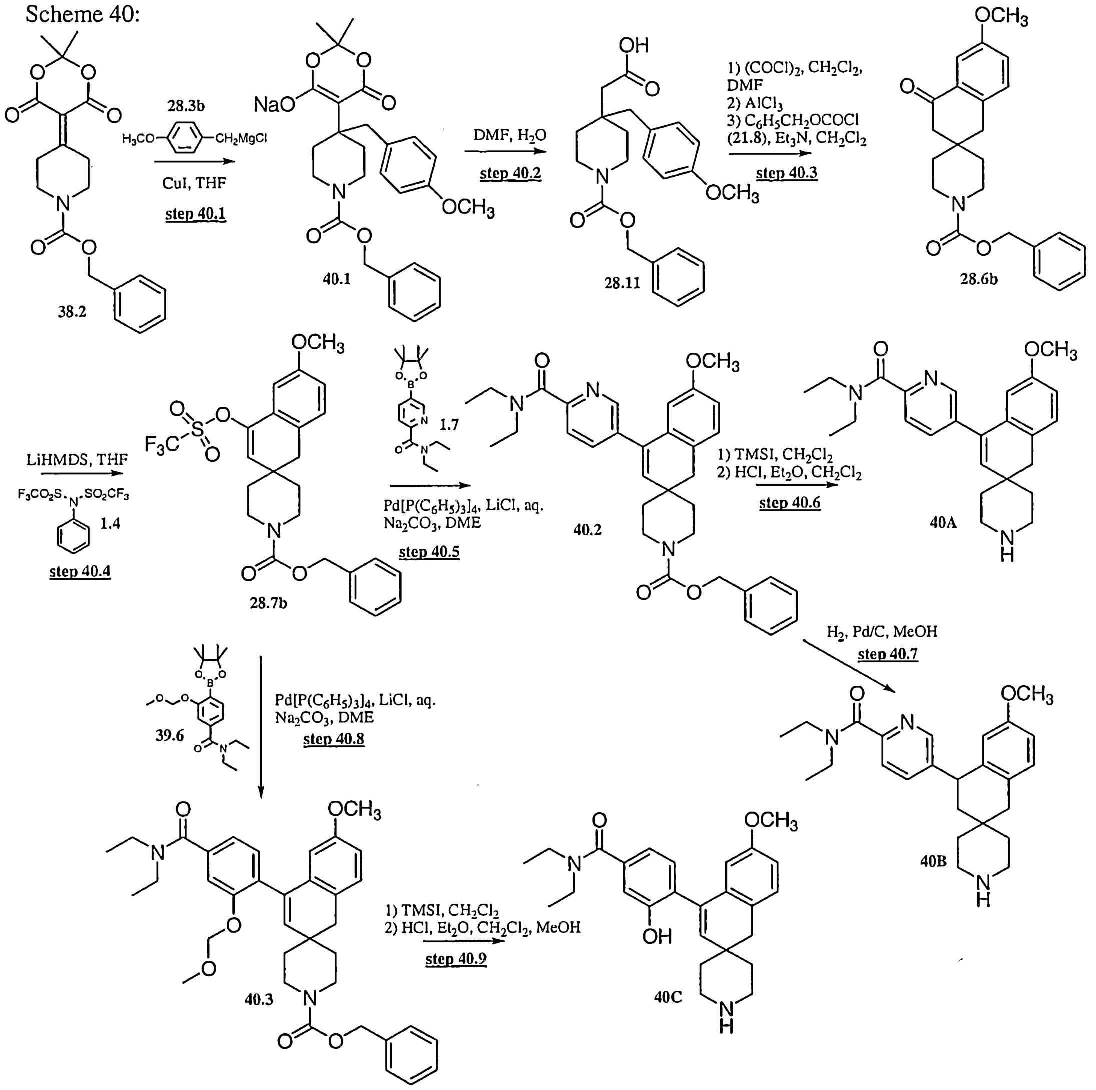
Scheme 38:


19.1
38.1
pyridine, piperidine
step 38.1
38.2
38.3
CuI, THF
step 38.2
NaO
38.4
DMF, H₂O
step 38.3
OH
38.5
1) (COCl)₂, CH₂Cl₂
2) AlCl₃
3) Boc₂O(4.7), Et₃N, CH₂Cl₂
step 38.4
38.6
LiHMDS, THF
1.4
step 38.5
38.7
1.7
method 38A:
Pd(dppf)Cl₂.CH₂Cl₂, aq. K₂CO₃, dioxane
step 38.6
38.8
HCl, Et₂O, CH₂Cl₂, MeOH
step 38.7
38A
1.14
Pd(dppf)Cl₂.CH₂Cl₂, KOAc, DMF
step 38.9
38.9
38D
H₂, Pd/C, MeOH
step 38.8
35.8
step 38.10
method 38A:
Pd(dppf)Cl₂.CH₂Cl₂, aq. K₂CO₃, dioxane
HCl, dioxane, MeOH
step 38.13
38B
38.11
H₂, Pd/C, MeOH
step 38.12
38.10
HCl, dioxane, MeOH
step 38.11
38C

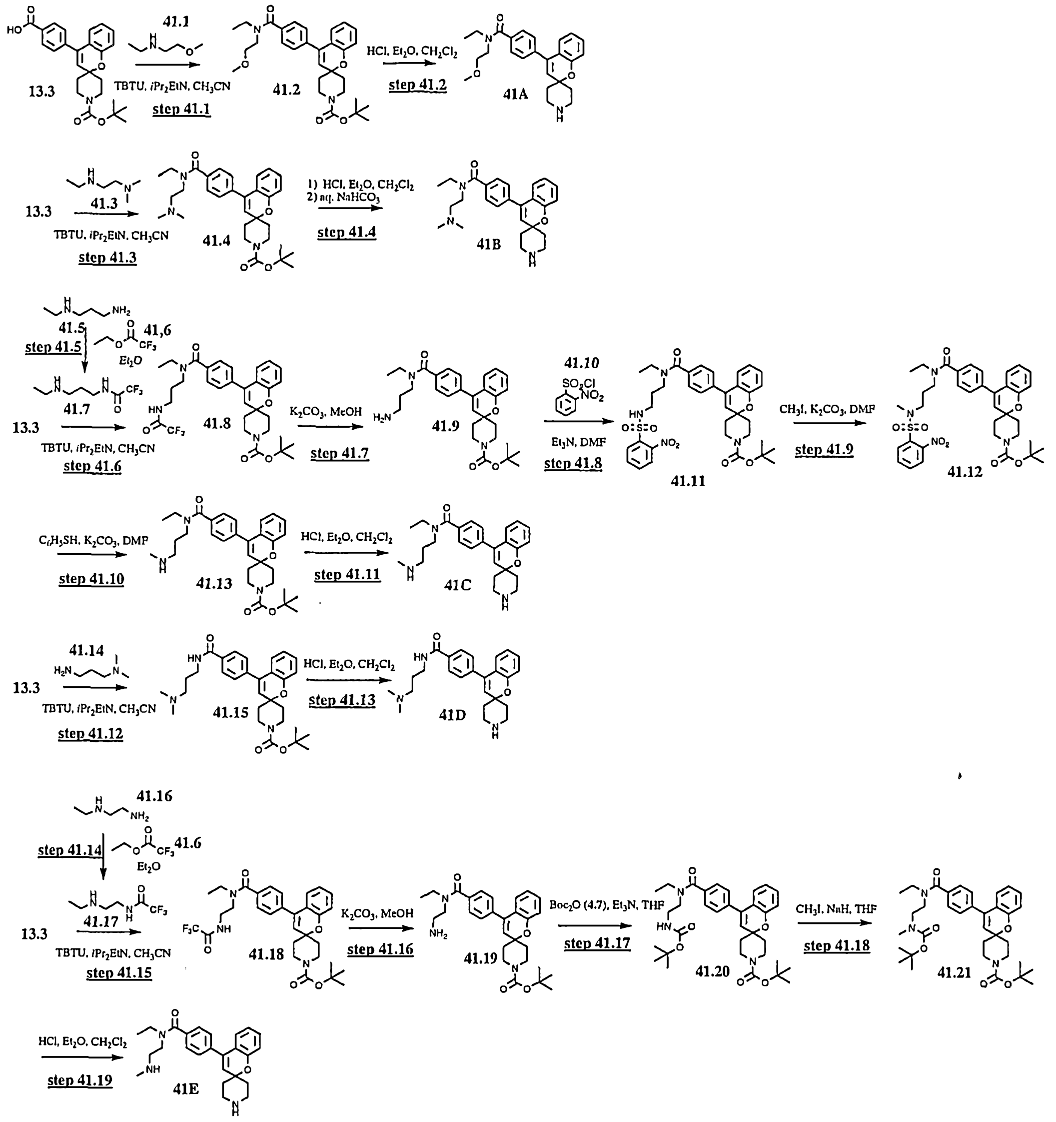
Scheme 39:


38.2
28.3a
CH2MgCl
CuI, THF
step 39.1
NaO
39.1
DMF, H2O
step 39.2
OH
39.2
1) (COCl)2, CH2Cl2, DMF
2) AlCl3
3) C6H5CH2OCOCl, Et3N, CH2Cl2
step39.3
28.6a
LiHMDS, THF
F3CO2S-N-SO2CF3
1.4
step 39.4
F3C
28.7a
1.7
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
step 39.5
28.12
H2, Pd/C, MeOH
step 39.6
39A
Boc2O (4.7), Et3N, CH2Cl2
step 39.7
39.3
chiral separation
step 39.8
39.4
39.5
HCl, Et2O, CH2Cl2
step 39.9
HCl, Et2O, CH2Cl2
step 39.10
39B
39C
39.6
28.7a
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
step 39.11
39.7
1) TMSI, CH2Cl2
2) HCl, Et2O, CH2Cl2
step 39.12
39D
1) H2, Pd/C, MeOH
2) HCl, MeOH, DME
step 39.13
39E
Boc2O (4.7), Et3N, CH2Cl2
step 39.14
39.8
step 39.15
chiral separation
39.9
HCl, Et2O, CH2Cl2
step 39.16
39F
39.10
HCl, Et2O, CH2Cl2
step 39.17
39G

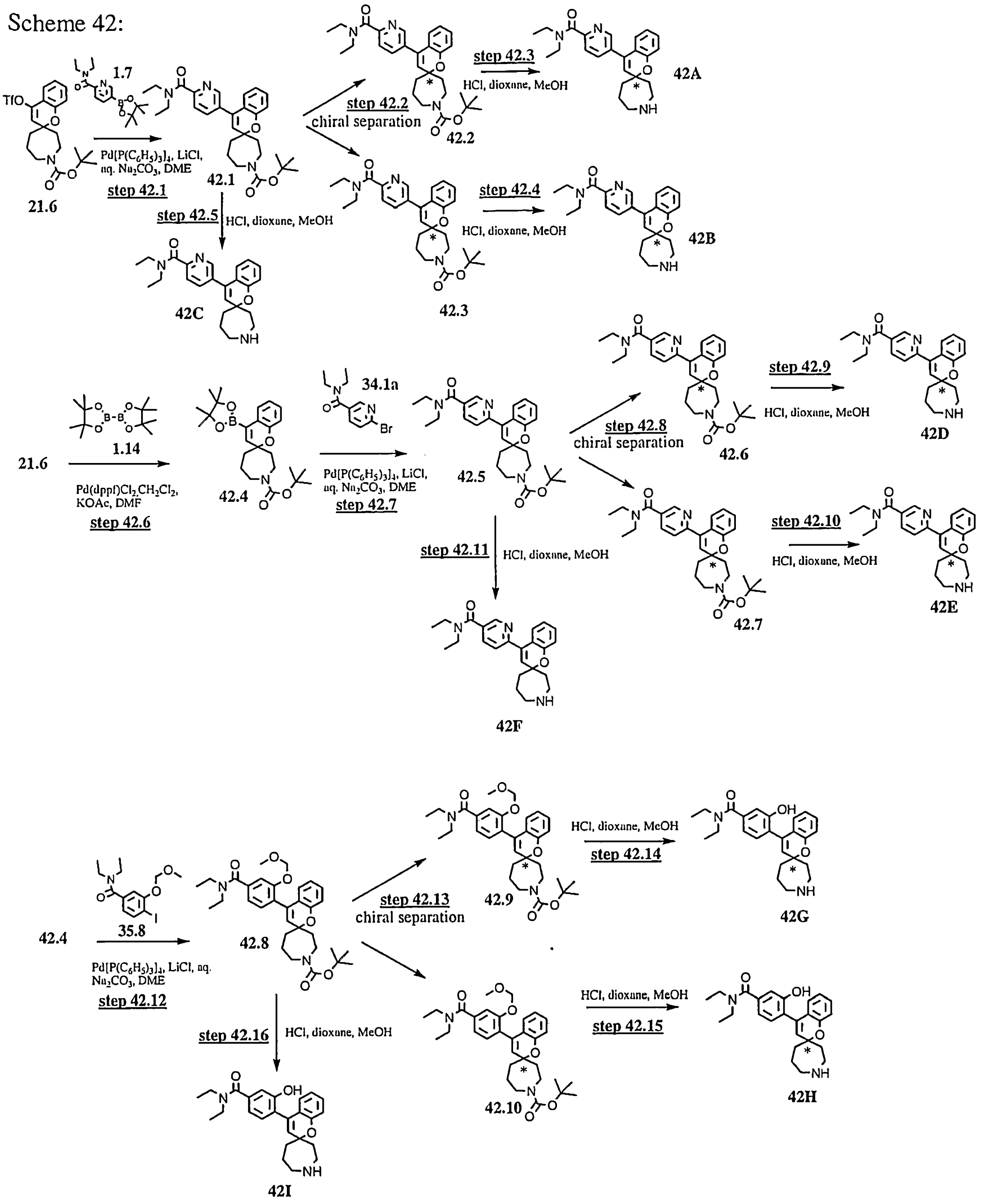
Scheme 40:


38.2
28.3b
H3CO—C6H4—CH2MgCl
CuI, THF
step 40.1
NaO
40.1
DMF, H2O
step 40.2
OH
28.11
1) (COCl)2, CH2Cl2, DMF
2) AlCl3
3) C6H5CH2OCOCl (21.8), Et3N, CH2Cl2
step 40.3
OCH3
28.6b
LiHMDS, THF
F3CO2S.N.SO2CF3
1.4
step 40.4
F3C
28.7b
1.7
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
step 40.5
40.2
1) TMSI, CH2Cl2
2) HCl, Et2O, CH2Cl2
step 40.6
40A
H2, Pd/C, MeOH
step 40.7
40B
39.6
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
step 40.8
40.3
1) TMSI, CH2Cl2
2) HCl, Et2O, CH2Cl2, MeOH
step 40.9
40C

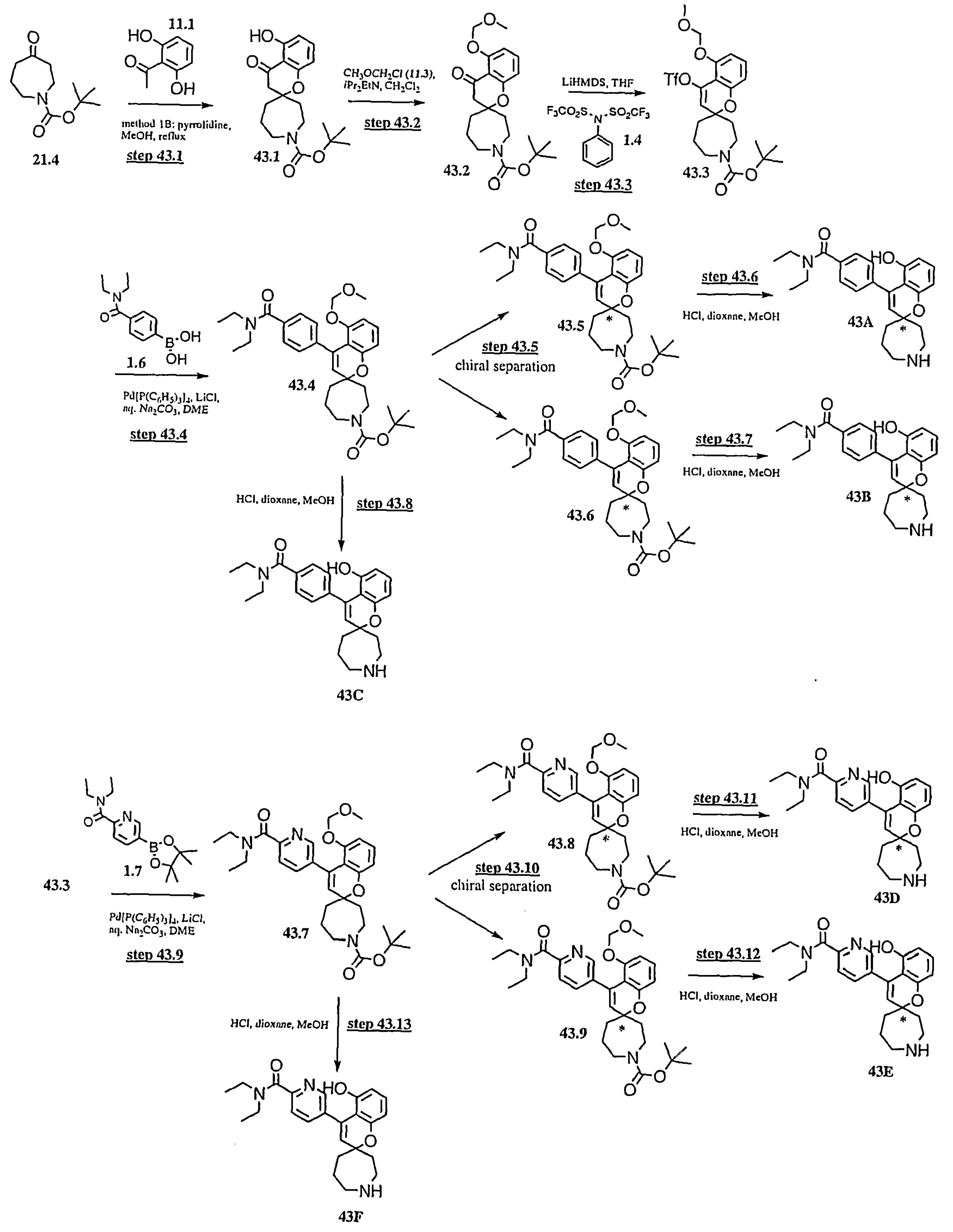
Scheme 41:


13.3
41.1
TBTU, iPr2EtN, CH3CN
step 41.1
41.2
HCl, Et2O, CH2Cl2
step 41.2
41A
13.3
41.3
TBTU, iPr2EtN, CH3CN
step 41.3
41.4
1) HCl, Et2O, CH2Cl2
2) aq. NaHCO3
step 41.4
41B
41.5
step 41.5
41.6
Et2O
41.7
13.3
TBTU, iPr2EtN, CH3CN
step 41.6
41.8
K2CO3, MeOH
step 41.7
41.9
41.10
Et3N, DMF
step 41.8
41.11
CH3I, K2CO3, DMF
step 41.9
41.12
C6H5SH, K2CO3, DMF
step 41.10
41.13
HCl, Et2O, CH2Cl2
step 41.11
41C
41.14
13.3
TBTU, iPr2EtN, CH3CN
step 41.12
41.15
HCl, Et2O, CH2Cl2
step 41.13
41D
41.16
step 41.14
41.6
Et2O
41.17
13.3
TBTU, iPr2EtN, CH3CN
step 41.15
41.18
K2CO3, MeOH
step 41.16
41.19
Boc2O (4.7), Et3N, THF
step 41.17
41.20
CH3I, NaH, THF
step 41.18
41.21
HCl, Et2O, CH2Cl2
step 41.19
41E

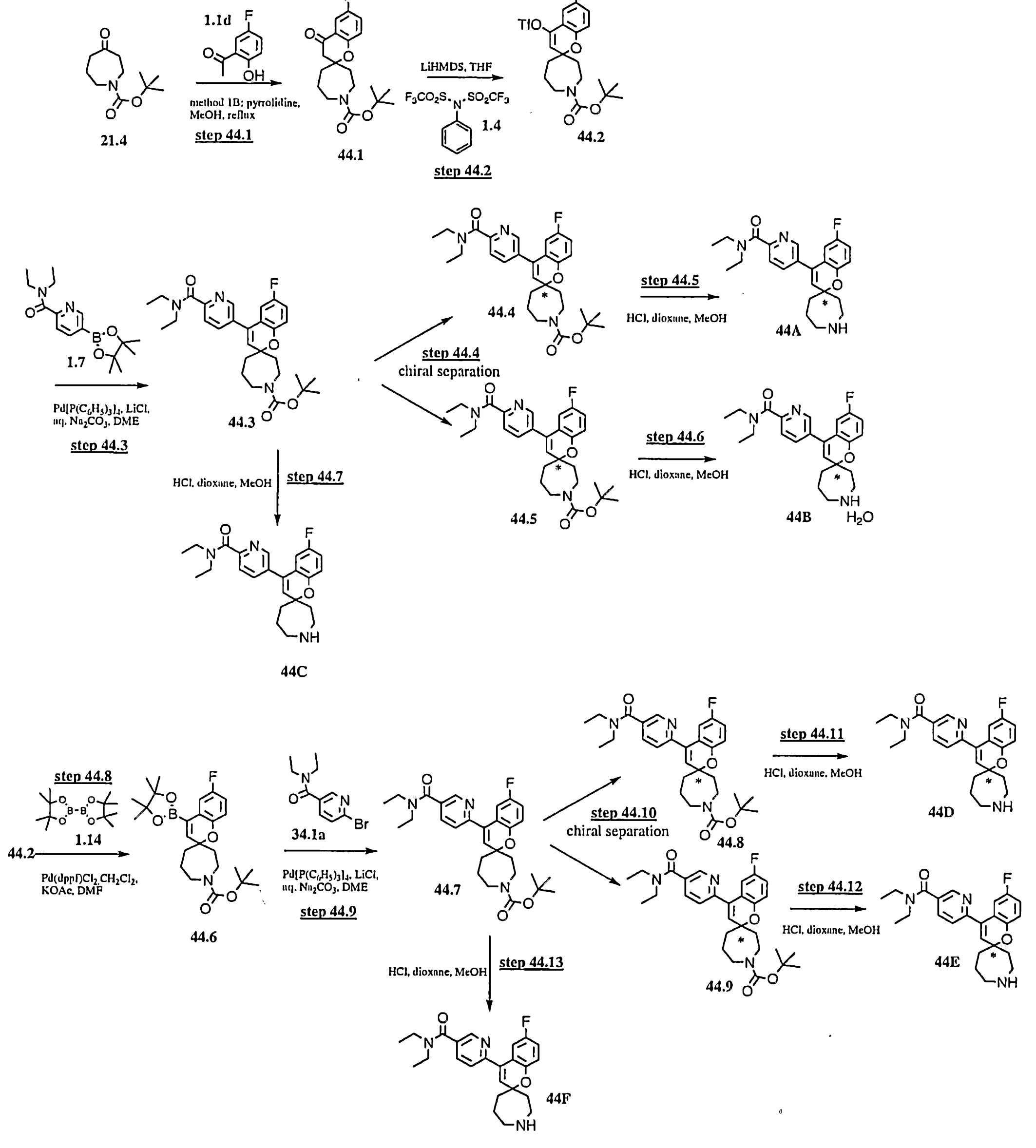
Scheme 42:


TfO
21.6
1.7
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
step 42.1
42.1
step 42.2
chiral separation
42.2
step 42.3
HCl, dioxane, MeOH
42A
42.3
step 42.4
HCl, dioxane, MeOH
42B
step 42.5
HCl, dioxane, MeOH
42C
21.6
1.14
Pd(dppf)Cl2CH2Cl2, KOAc, DMF
step 42.6
42.4
34.1a
Br
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
step 42.7
42.5
step 42.8
chiral separation
42.6
step 42.9
HCl, dioxane, MeOH
42D
42.7
step 42.10
HCl, dioxane, MeOH
42E
step 42.11
HCl, dioxane, MeOH
42F
42.4
35.8
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
step 42.12
42.8
step 42.13
chiral separation
42.9
HCl, dioxane, MeOH
step 42.14
42G
42.10
HCl, dioxane, MeOH
step 42.15
42H
step 42.16
HCl, dioxane, MeOH
42I

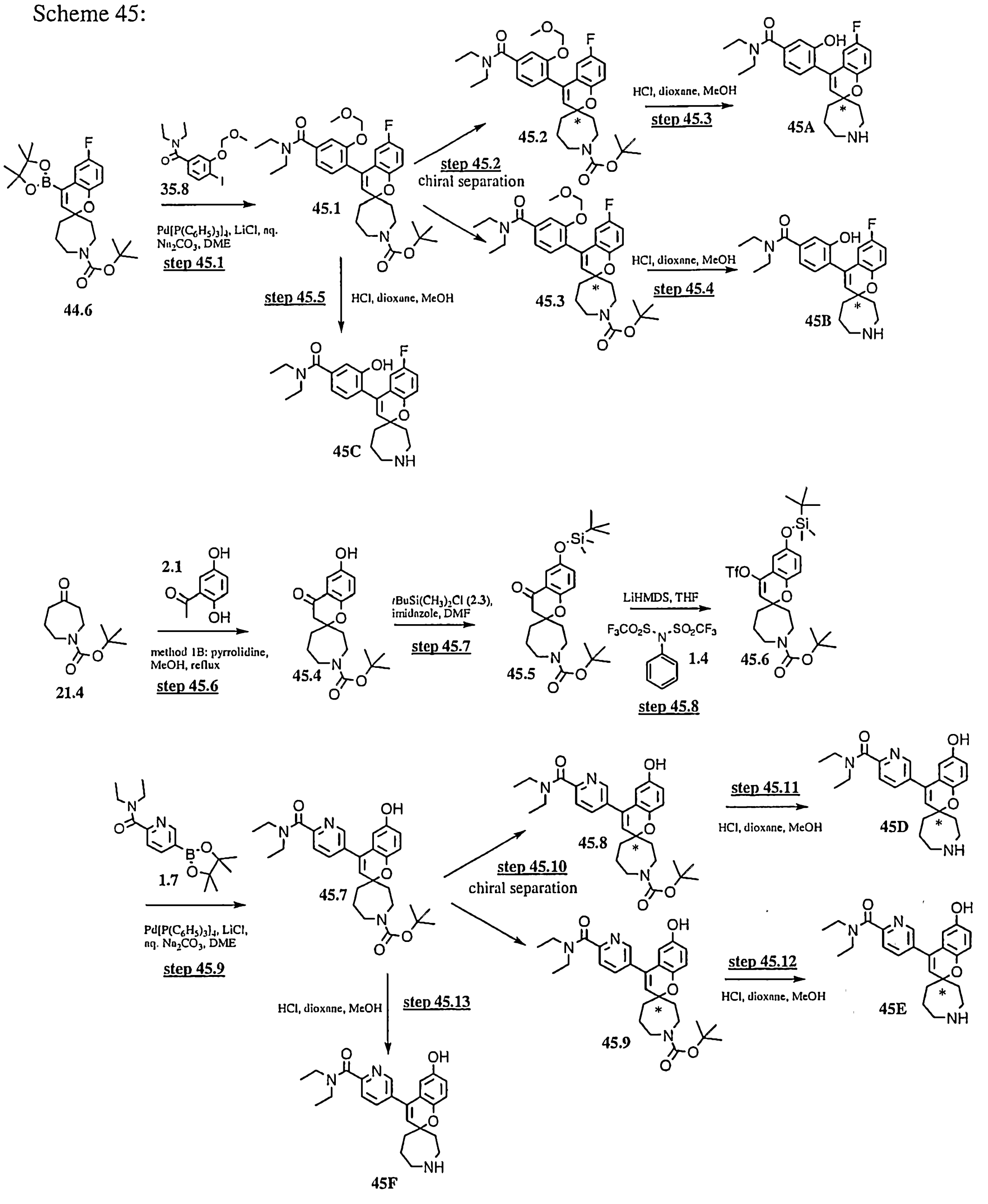
Scheme 43:


21.4
11.1
method 1B: pyrrolidine, MeOH, reflux
step 43.1
43.1
CH3OCH2Cl (11.3), iPr2EtN, CH2Cl2
step 43.2
43.2
LiHMDS, THF
F3CO2S-N-SO2CF3
1.4
step 43.3
TfO
43.3
1.6
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
step 43.4
43.4
step 43.5
chiral separation
43.5
43.6
step 43.6
HCl, dioxane, MeOH
43A
step 43.7
HCl, dioxane, MeOH
43B
HCl, dioxane, MeOH
step 43.8
43C
43.3
1.7
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
step 43.9
43.7
step 43.10
chiral separation
43.8
43.9
step 43.11
HCl, dioxane, MeOH
43D
step 43.12
HCl, dioxane, MeOH
43E
HCl, dioxane, MeOH
step 43.13
43F

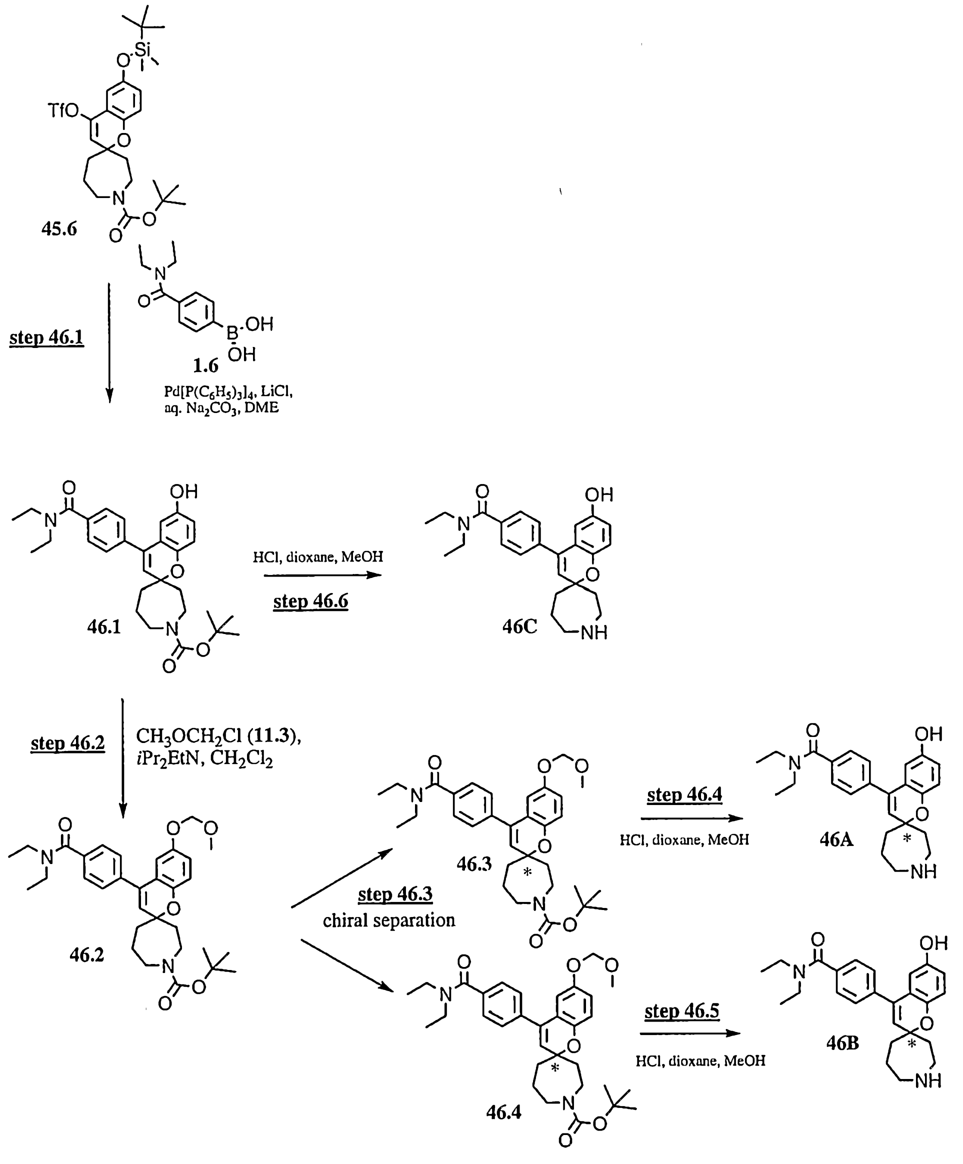
Scheme 44:


21.4
1.1d
method 1B: pyrrolidine, MeOH, reflux
step 44.1
44.1
LiHMDS, THF
F_3CO_2S-N-SO_2CF_3
1.4
step 44.2
44.2
1.7
$Pd[P(C_6H_5)_3]_4$, LiCl, aq. Na_2CO_3, DME
step 44.3
44.3
step 44.4
chiral separation
44.4
44.5
step 44.5
HCl, dioxane, MeOH
44A
step 44.6
HCl, dioxane, MeOH
44B
H_2O
HCl, dioxane, MeOH
step 44.7
44C
step 44.8
1.14
44.2
$Pd(dppf)Cl_2$ CH_2Cl_2, KOAc, DMF
44.6
34.1a
$Pd[P(C_6H_5)_3]_4$, LiCl, aq. Na_2CO_3, DME
step 44.9
44.7
step 44.10
chiral separation
44.8
44.9
step 44.11
HCl, dioxane, MeOH
44D
step 44.12
HCl, dioxane, MeOH
44E
HCl, dioxane, MeOH
step 44.13
44F

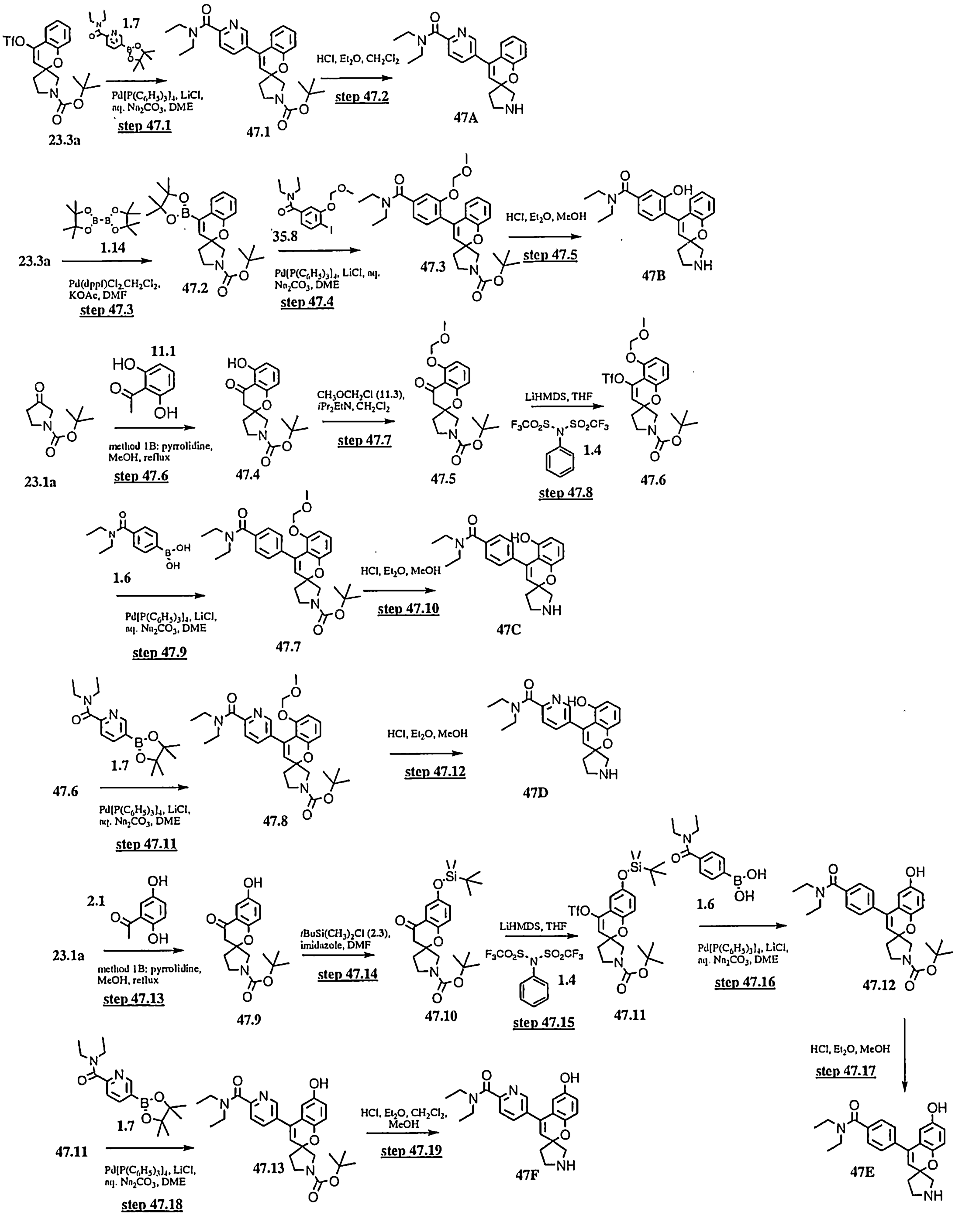
Scheme 45:


44.6
35.8
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
step 45.1
45.1
step 45.2
chiral separation
45.2
45.3
HCl, dioxane, MeOH
step 45.3
45A
HCl, dioxane, MeOH
step 45.4
45B
step 45.5
HCl, dioxane, MeOH
45C
21.4
2.1
method 1B: pyrrolidine, MeOH, reflux
step 45.6
45.4
tBuSi(CH3)2Cl (2.3), imidazole, DMF
step 45.7
45.5
LiHMDS, THF
F3CO2S-N-SO2CF3
1.4
step 45.8
45.6
TfO
1.7
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
step 45.9
45.7
step 45.10
chiral separation
45.8
45.9
step 45.11
HCl, dioxane, MeOH
45D
step 45.12
HCl, dioxane, MeOH
45E
HCl, dioxane, MeOH
step 45.13
45F

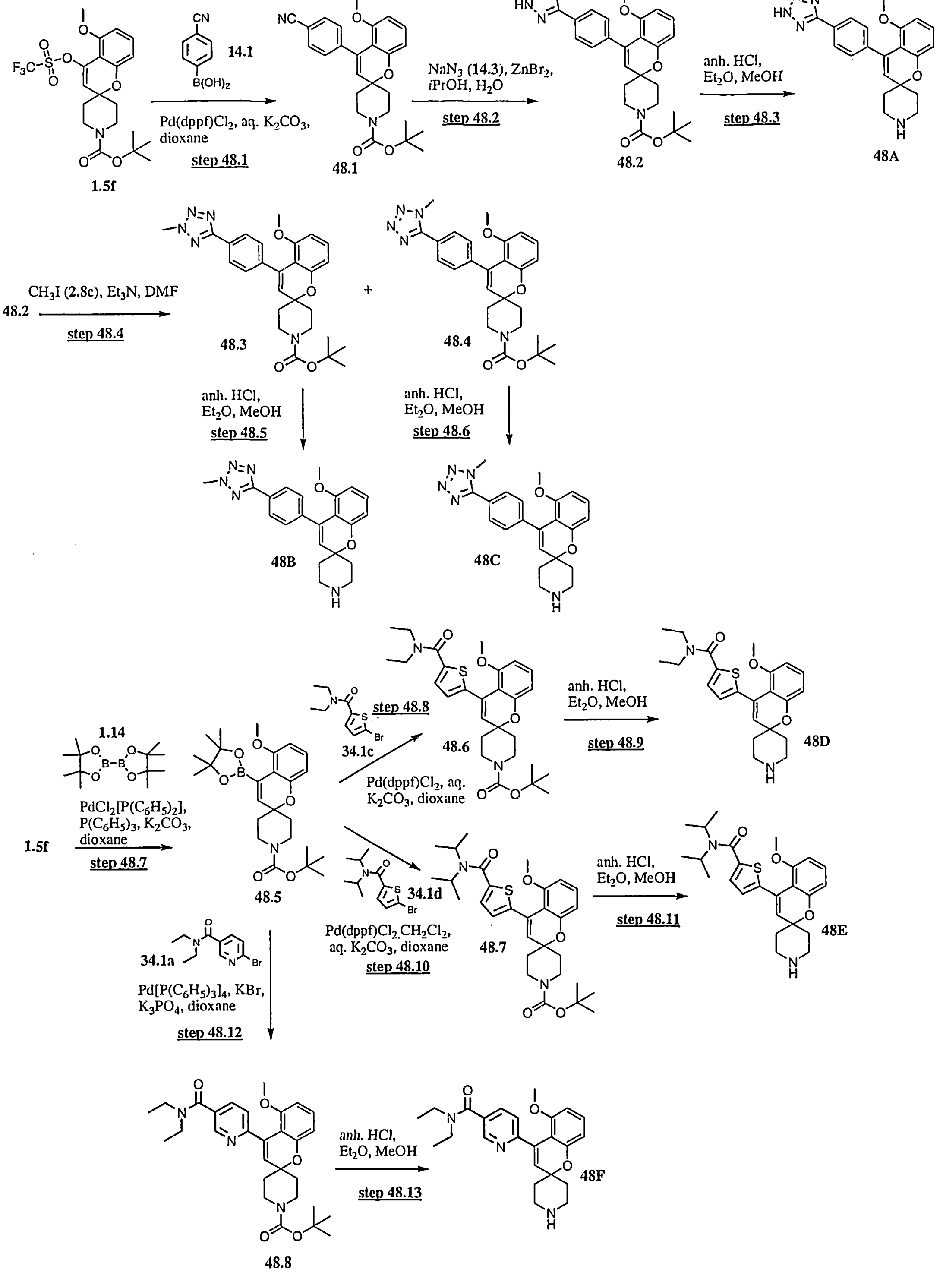
Scheme 46:


45.6
step 46.1
1.6
Pd[P(C6H5)3]4, LiCl,
aq. Na2CO3, DME
46.1
HCl, dioxane, MeOH
step 46.6
46C
step 46.2
CH3OCH2Cl (11.3),
iPr2EtN, CH2Cl2
46.2
step 46.3
chiral separation
46.3
46.4
step 46.4
HCl, dioxane, MeOH
46A
step 46.5
HCl, dioxane, MeOH
46B

Scheme 47:

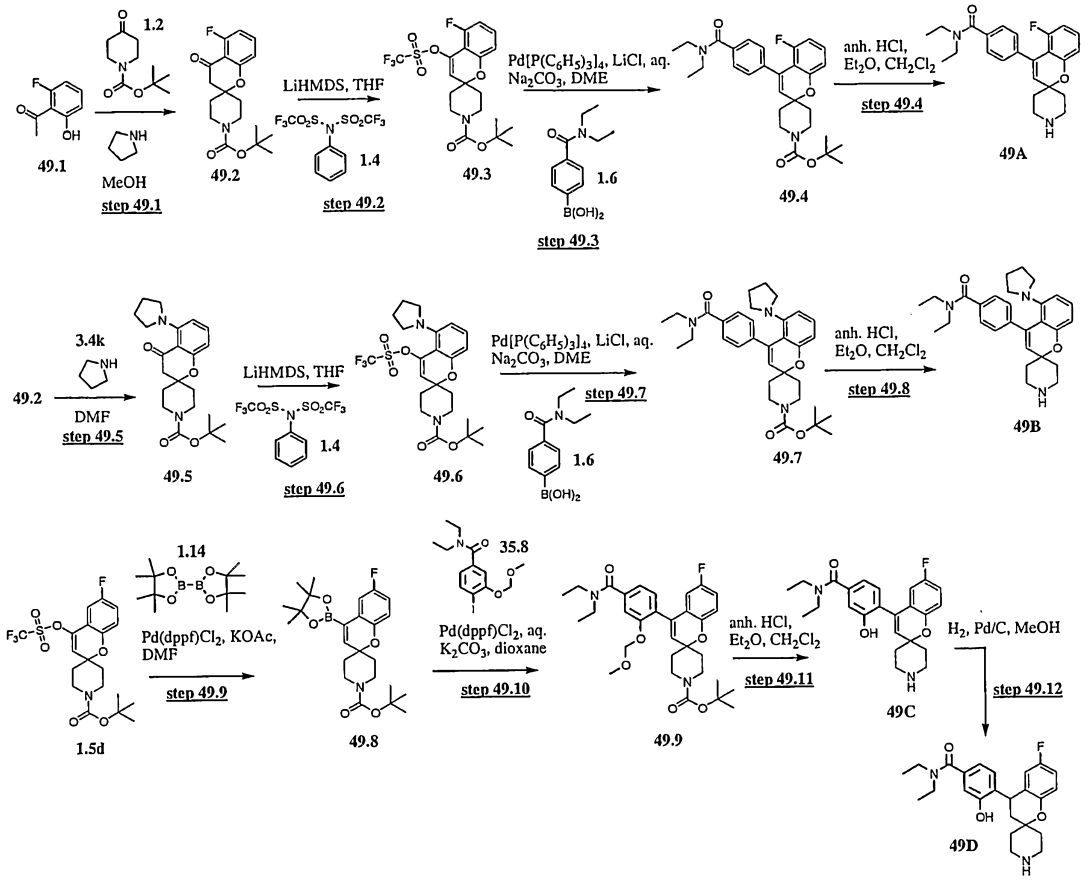

TfO
1.7
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
step 47.1
23.3a
47.1
HCl, Et2O, CH2Cl2
step 47.2
47A
NH
1.14
23.3a
Pd(dppf)Cl2CH2Cl2, KOAc, DMF
step 47.3
47.2
35.8
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
step 47.4
47.3
HCl, Et2O, MeOH
step 47.5
47B
11.1
HO
OH
method 1B: pyrrolidine, MeOH, reflux
step 47.6
23.1a
47.4
CH3OCH2Cl (11.3), iPr2EtN, CH2Cl2
step 47.7
47.5
LiHMDS, THF
F3CO2S.N.SO2CF3
1.4
step 47.8
47.6
1.6
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
step 47.9
47.7
HCl, Et2O, MeOH
step 47.10
47C
47.6
1.7
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
step 47.11
47.8
HCl, Et2O, MeOH
step 47.12
47D
2.1
23.1a
method 1B: pyrrolidine, MeOH, reflux
step 47.13
47.9
tBuSi(CH3)2Cl (2.3), imidazole, DMF
step 47.14
47.10
LiHMDS, THF
F3CO2S.N.SO2CF3
1.4
step 47.15
47.11
1.6
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
step 47.16
47.12
HCl, Et2O, MeOH
step 47.17
47E
47.11
1.7
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
step 47.18
47.13
HCl, Et2O, CH2Cl2, MeOH
step 47.19
47F

Scheme 48:

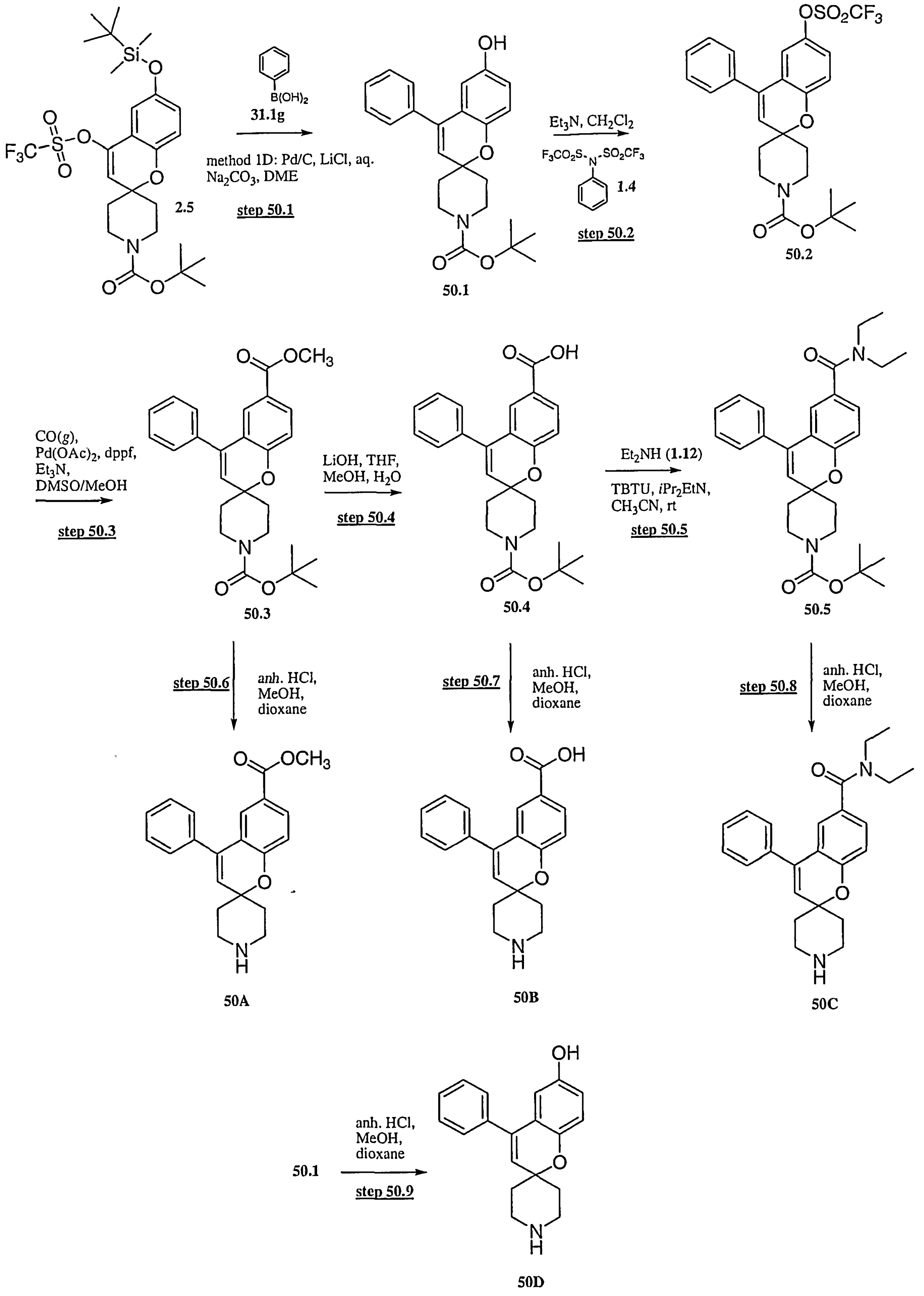


1.5f
14.1
Pd(dppf)Cl2, aq. K2CO3, dioxane
step 48.1
48.1
NaN3 (14.3), ZnBr2, iPrOH, H2O
step 48.2
48.2
anh. HCl, Et2O, MeOH
step 48.3
48A
CH3I (2.8c), Et3N, DMF
step 48.4
48.3
+
48.4
anh. HCl, Et2O, MeOH
step 48.5
anh. HCl, Et2O, MeOH
step 48.6
48B
48C
1.14
PdCl2[P(C6H5)2], P(C6H5)3, K2CO3, dioxane
step 48.7
48.5
34.1c
step 48.8
Pd(dppf)Cl2, aq. K2CO3, dioxane
48.6
anh. HCl, Et2O, MeOH
step 48.9
48D
34.1d
Pd(dppf)Cl2.CH2Cl2, aq. K2CO3, dioxane
step 48.10
48.7
anh. HCl, Et2O, MeOH
step 48.11
48E
34.1a
Pd[P(C6H5)3]4, KBr, K3PO4, dioxane
step 48.12
48.8
anh. HCl, Et2O, MeOH
step 48.13
48F

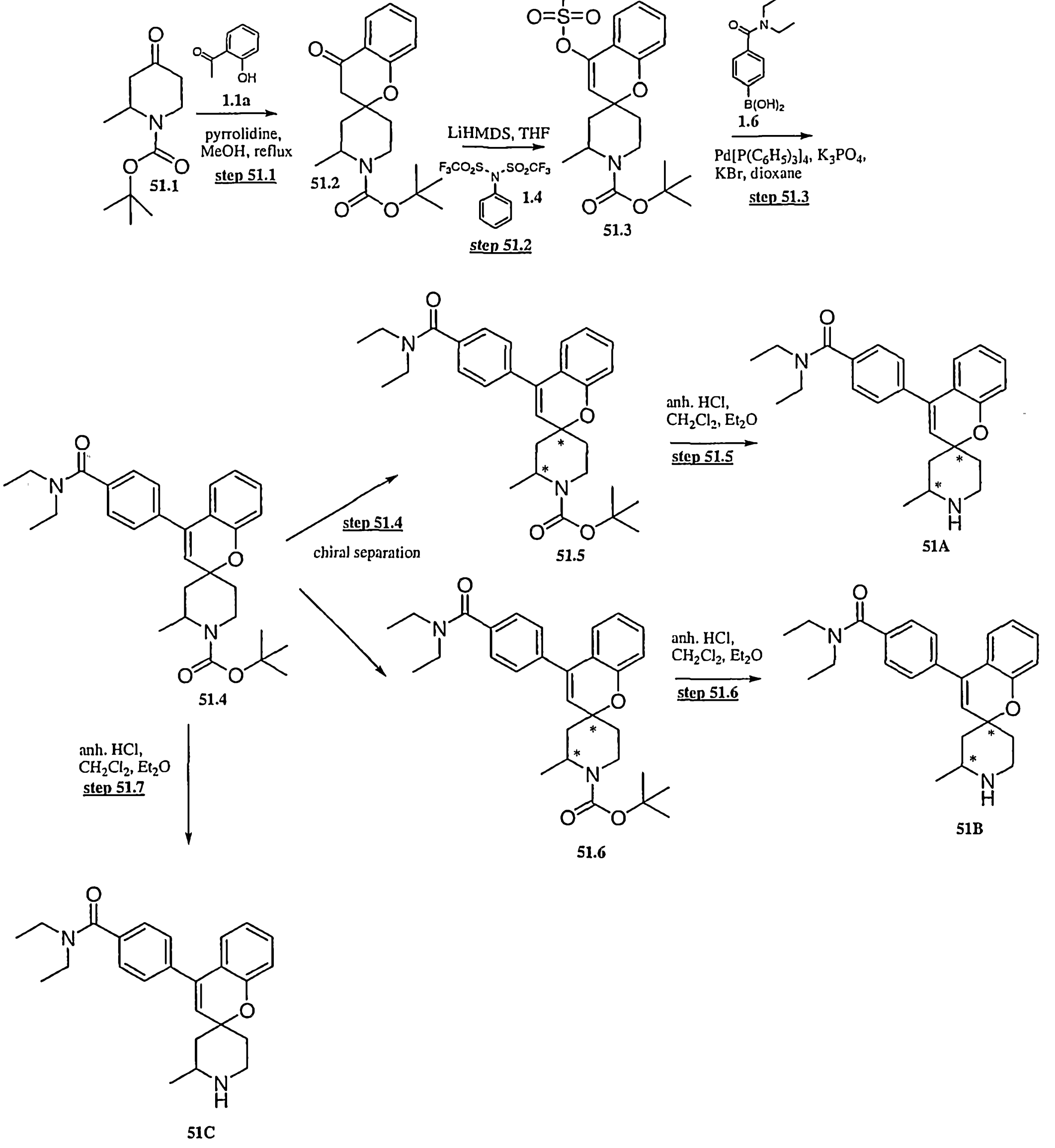
Scheme 49:


1.2
49.1
MeOH
step 49.1
49.2
LiHMDS, THF
1.4
step 49.2
49.3
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
1.6
B(OH)2
step 49.3
49.4
anh. HCl, Et2O, CH2Cl2
step 49.4
49A
3.4k
49.2
DMF
step 49.5
49.5
LiHMDS, THF
1.4
step 49.6
49.6
Pd[P(C6H5)3]4, LiCl, aq. Na2CO3, DME
step 49.7
1.6
B(OH)2
49.7
anh. HCl, Et2O, CH2Cl2
step 49.8
49B
1.14
Pd(dppf)Cl2, KOAc, DMF
step 49.9
1.5d
49.8
35.8
Pd(dppf)Cl2, aq. K2CO3, dioxane
step 49.10
49.9
anh. HCl, Et2O, CH2Cl2
step 49.11
49C
H2, Pd/C, MeOH
step 49.12
49D

Scheme 50:

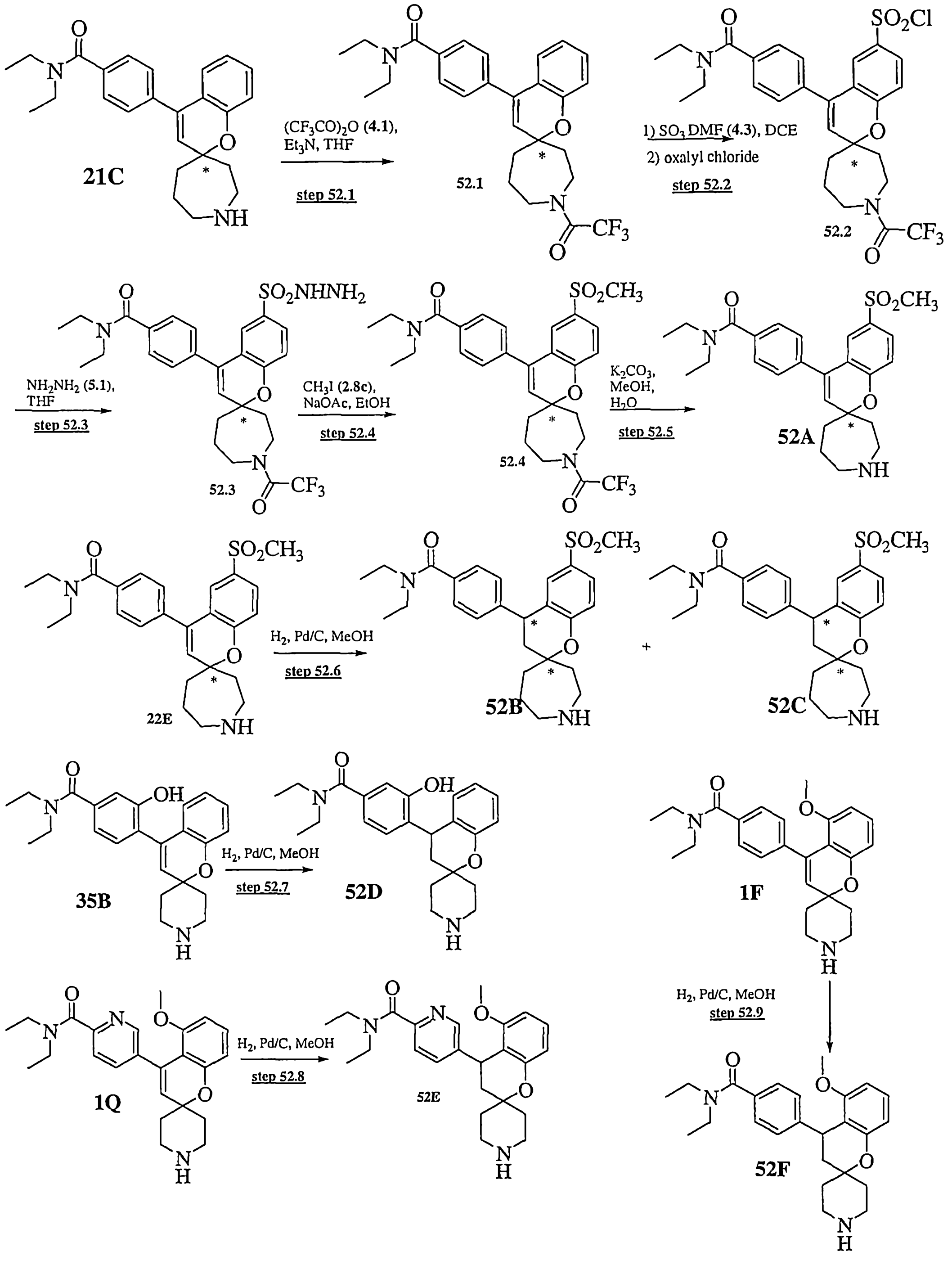

2.5
B(OH)₂
31.1g
method 1D: Pd/C, LiCl, aq. Na₂CO₃, DME
step 50.1
50.1
Et₃N, CH₂Cl₂
F₃CO₂S-N-SO₂CF₃
1.4
step 50.2
OSO₂CF₃
50.2
CO(g), Pd(OAc)₂, dppf, Et₃N, DMSO/MeOH
step 50.3
OCH₃
50.3
LiOH, THF, MeOH, H₂O
step 50.4
50.4
Et₂NH (1.12)
TBTU, iPr₂EtN, CH₃CN, rt
step 50.5
50.5
step 50.6
anh. HCl, MeOH, dioxane
step 50.7
anh. HCl, MeOH, dioxane
step 50.8
anh. HCl, MeOH, dioxane
50A
50B
50C
50.1
anh. HCl, MeOH, dioxane
step 50.9
50D

Scheme 51:



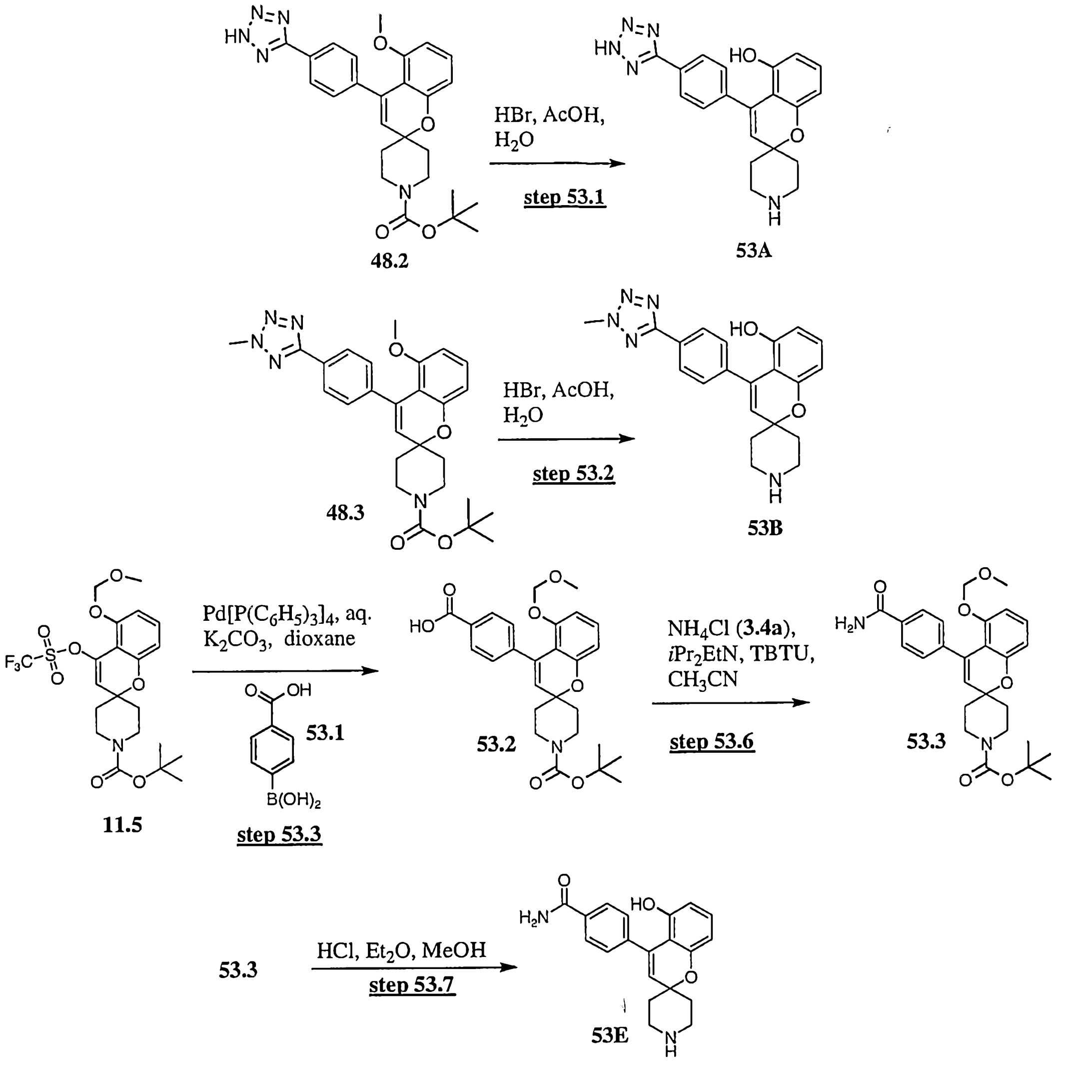
[0358] **51A** and **51B** are chirally resolved products derived from **51C**. Their absolute stereochemistries have not been conclusively established.

Scheme 52

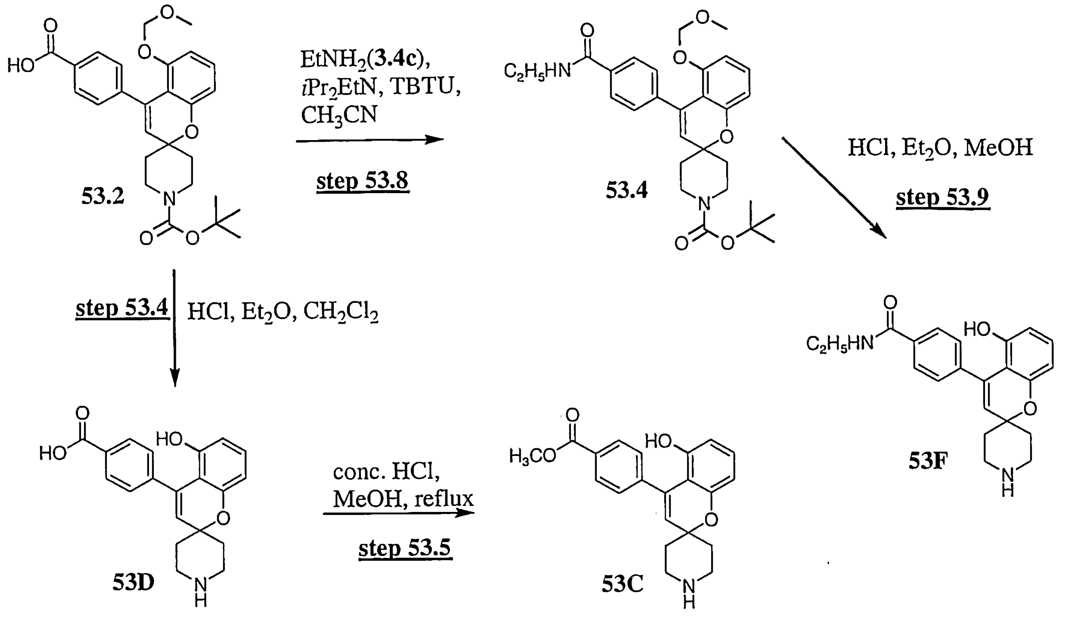


[0359] **52B** and **52C** are diastereomeric with respect to one another. **52B** and **52C** are chirally pure. Their absolute stereochemistry has not been conclusively established.

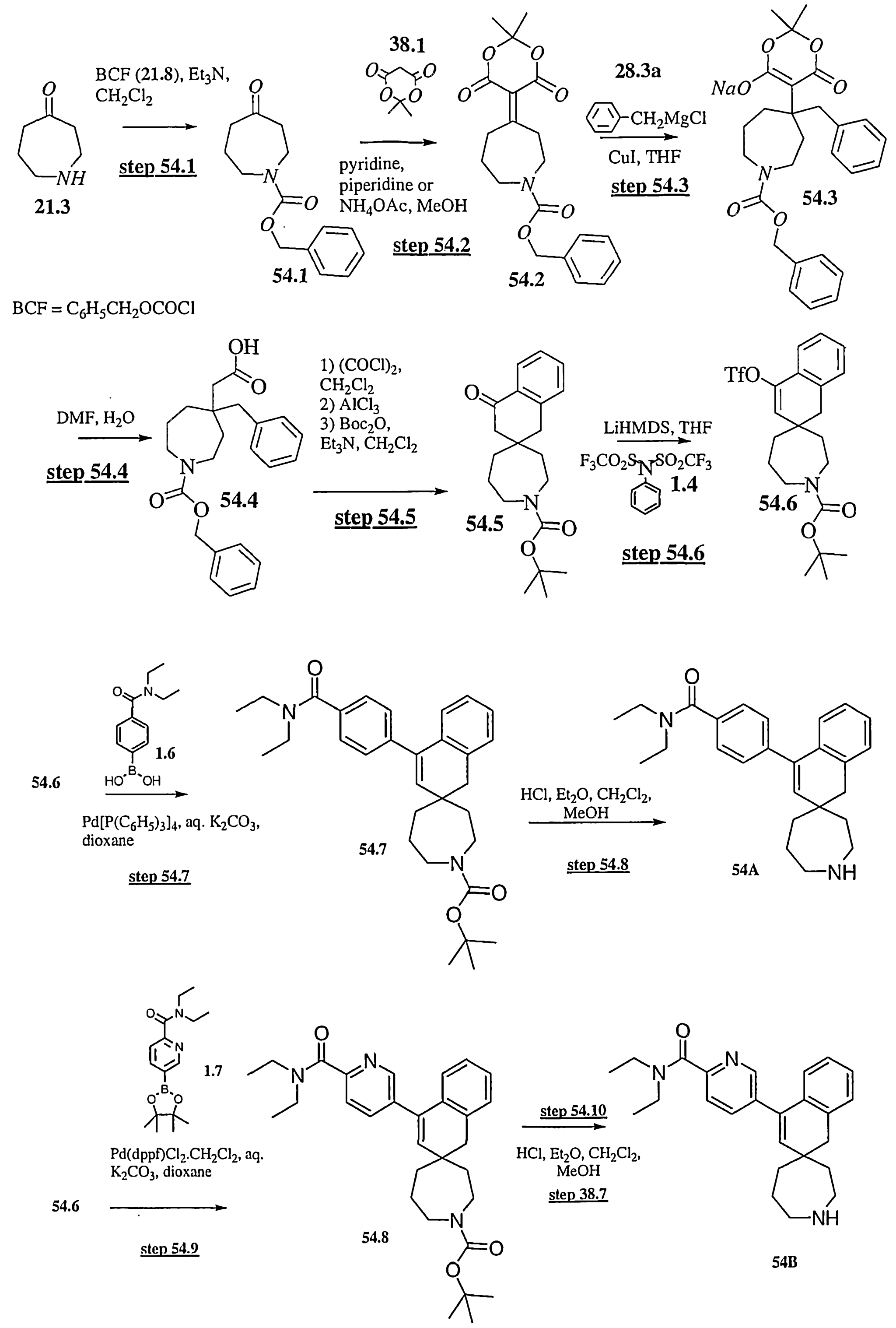
Scheme 53


48.2
HBr, AcOH, H_2O
step 53.1
53A
48.3
HBr, AcOH, H_2O
step 53.2
53B
11.5
$Pd[P(C_6H_5)_3]_4$, aq. K_2CO_3, dioxane
53.1
step 53.3
53.2
NH_4Cl (3.4a), $i$$Pr_2EtN$, TBTU, CH_3CN
step 53.6
53.3
53.3
HCl, Et_2O, MeOH
step 53.7
53E

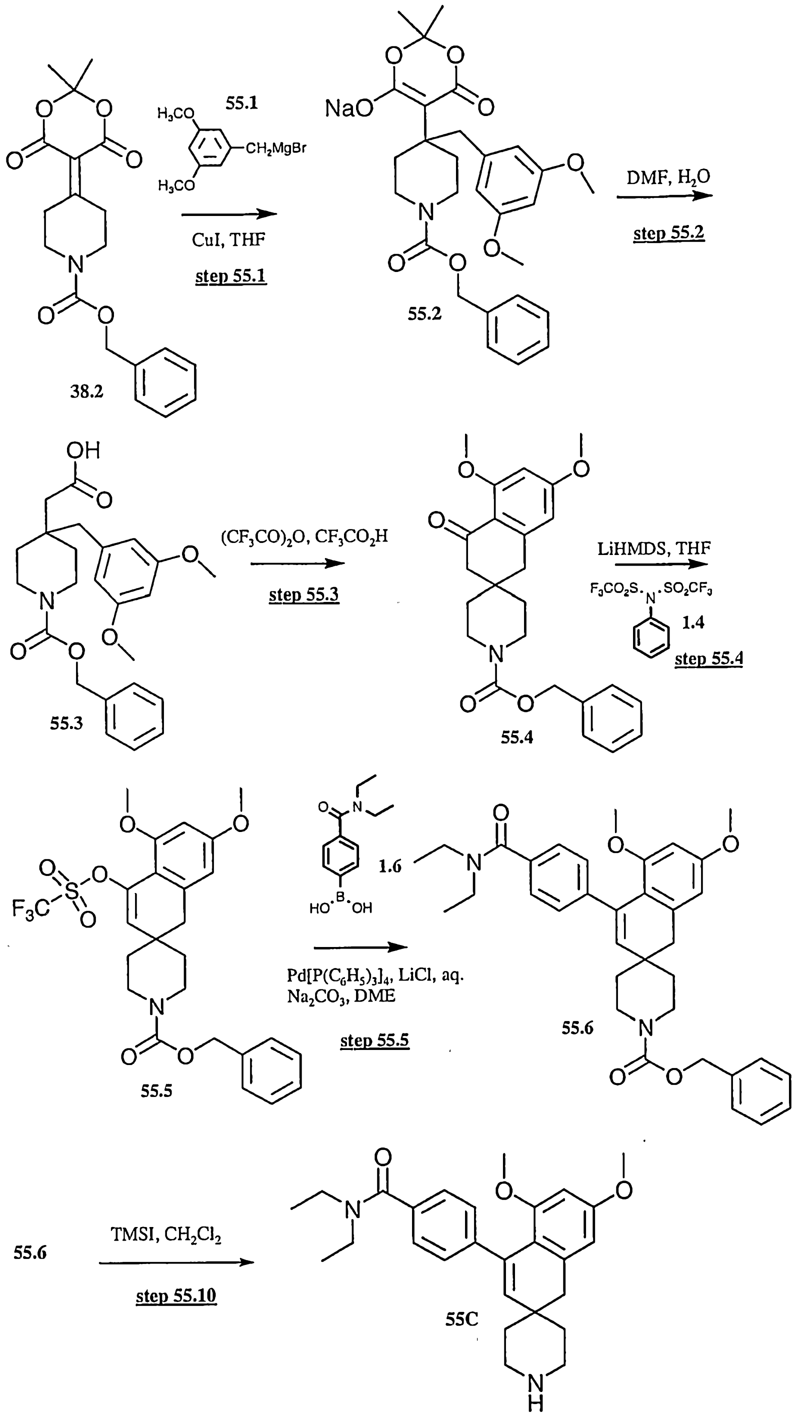
Scheme 53 (continued)



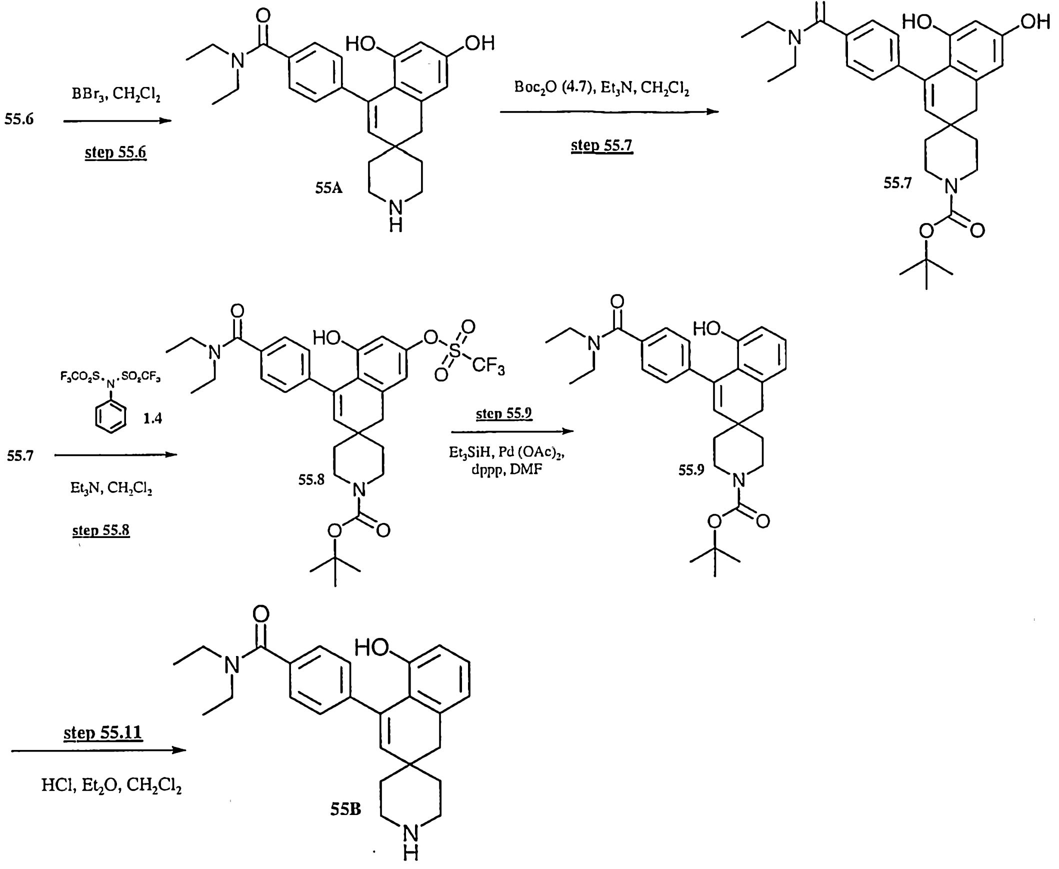
Scheme 54


21.3
BCF (21.8), Et$_3$N, CH$_2$Cl$_2$
step 54.1
54.1
38.1
pyridine, piperidine or NH$_4$OAc, MeOH
step 54.2
54.2
28.3a
CH$_2$MgCl
CuI, THF
step 54.3
NaO
54.3
BCF = C$_6$H$_5$CH$_2$OCOCl
DMF, H$_2$O
step 54.4
OH
54.4
1) (COCl)$_2$, CH$_2$Cl$_2$
2) AlCl$_3$
3) Boc$_2$O, Et$_3$N, CH$_2$Cl$_2$
step 54.5
54.5
LiHMDS, THF
F$_3$CO$_2$S-N-SO$_2$CF$_3$
1.4
step 54.6
TfO
54.6
54.6
1.6
HO B OH
Pd[P(C$_6$H$_5$)$_3$]$_4$, aq. K$_2$CO$_3$, dioxane
step 54.7
54.7
HCl, Et$_2$O, CH$_2$Cl$_2$, MeOH
step 54.8
54A
NH
1.7
Pd(dppf)Cl$_2$.CH$_2$Cl$_2$, aq. K$_2$CO$_3$, dioxane
54.6
step 54.9
54.8
step 54.10
HCl, Et$_2$O, CH$_2$Cl$_2$, MeOH
step 38.7
54B

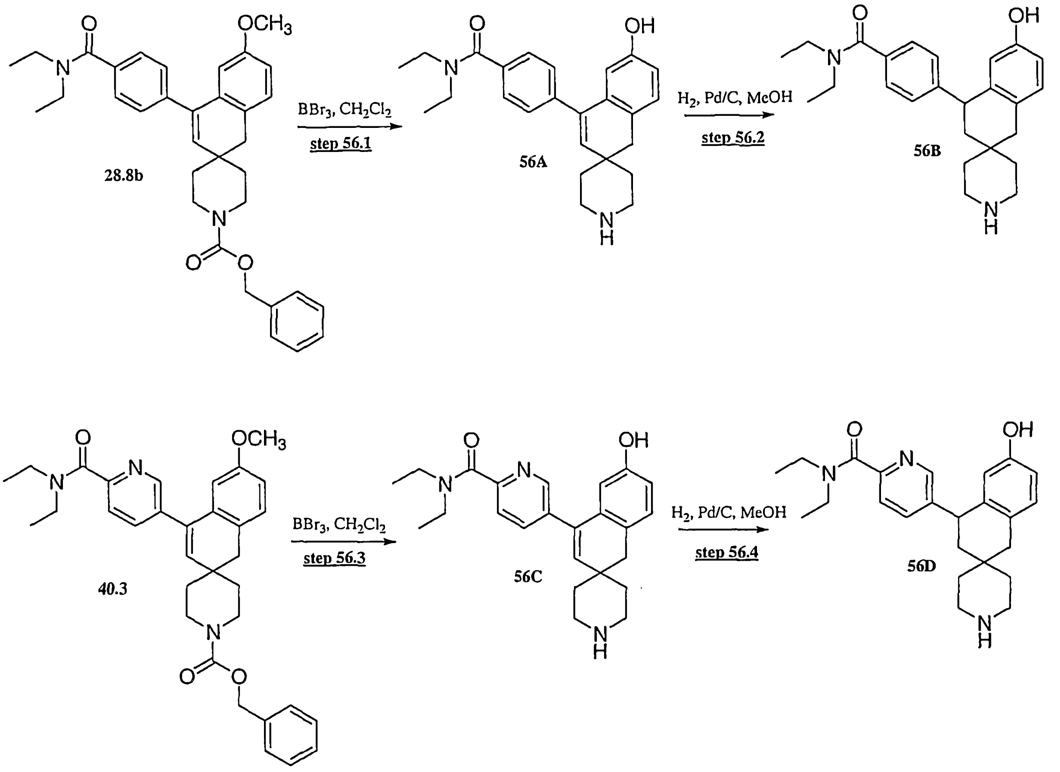
Scheme 55


38.2
55.1
H_3CO
CH_2MgBr
CuI, THF
step 55.1
NaO
55.2
DMF, H_2O
step 55.2
55.3
$(CF_3CO)_2O$, CF_3CO_2H
step 55.3
55.4
LiHMDS, THF
F_3CO_2S
SO_2CF_3
1.4
step 55.4
55.5
F_3C
1.6
HO B OH
$Pd[P(C_6H_5)_3]_4$, LiCl, aq. Na_2CO_3, DME
step 55.5
55.6
55.6
TMSI, CH_2Cl_2
step 55.10
55C

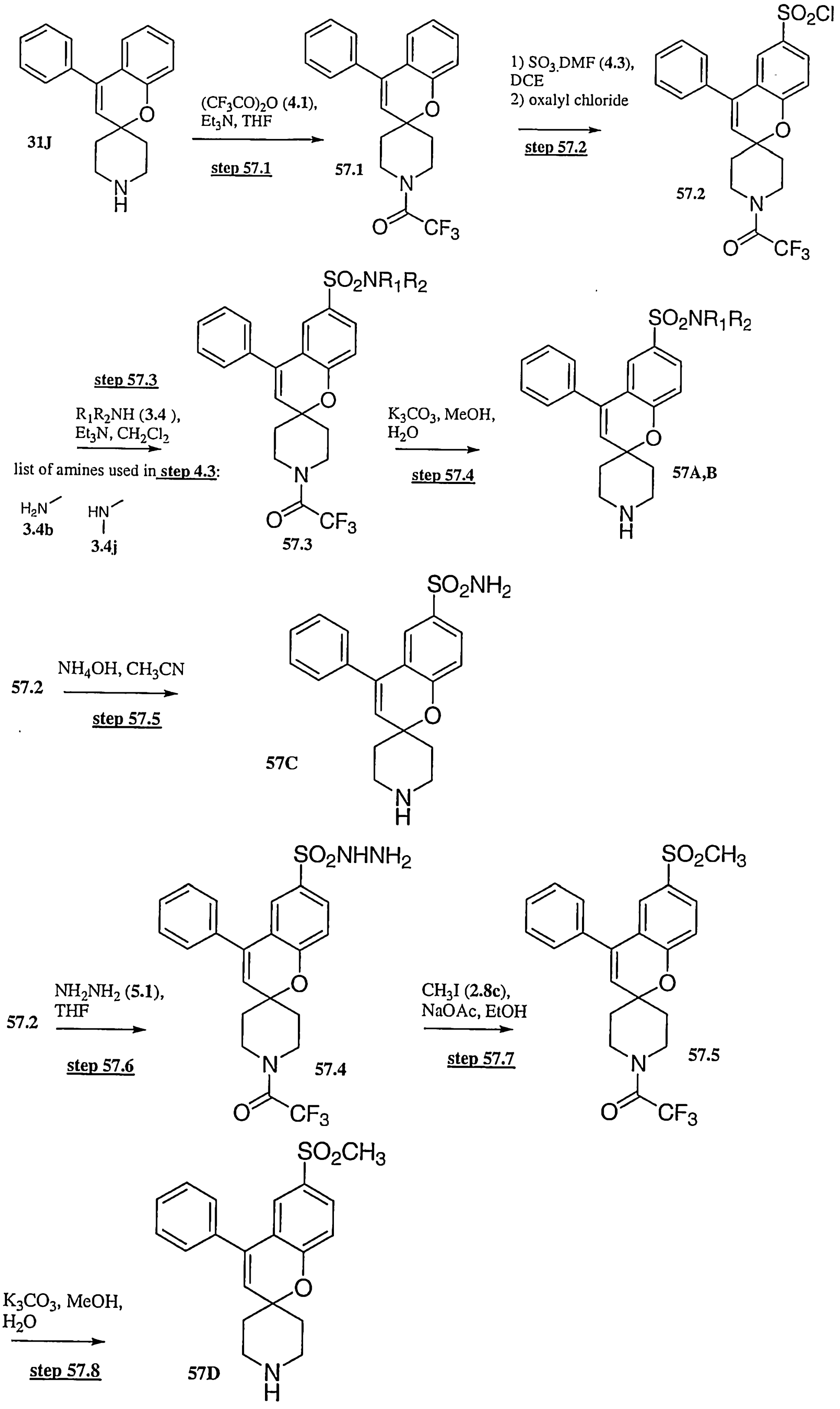
Scheme 55 (continued)



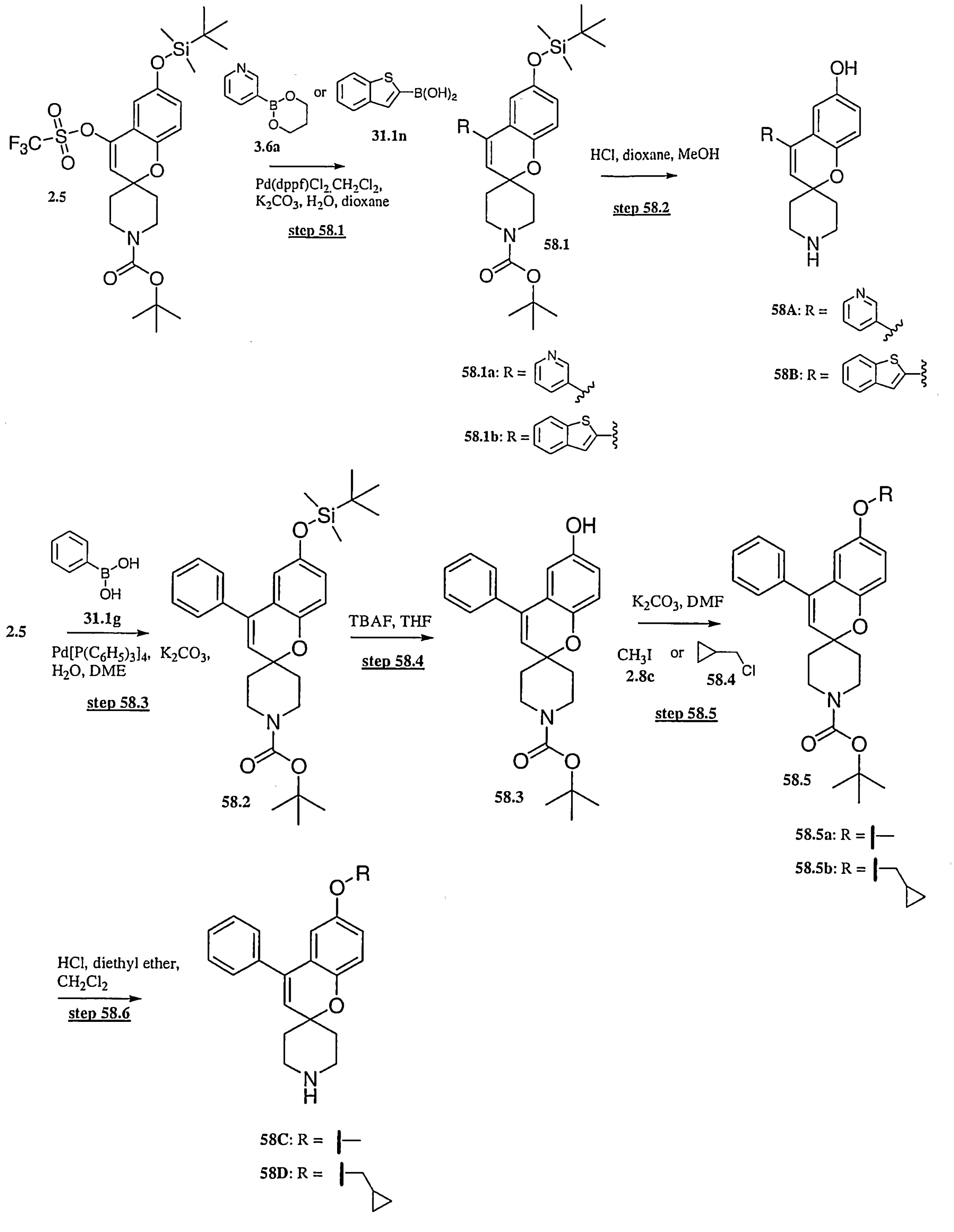
Scheme 56:


28.8b
BBr3, CH2Cl2
step 56.1
56A
H2, Pd/C, MeOH
step 56.2
56B
40.3
BBr3, CH2Cl2
step 56.3
56C
H2, Pd/C, MeOH
step 56.4
56D

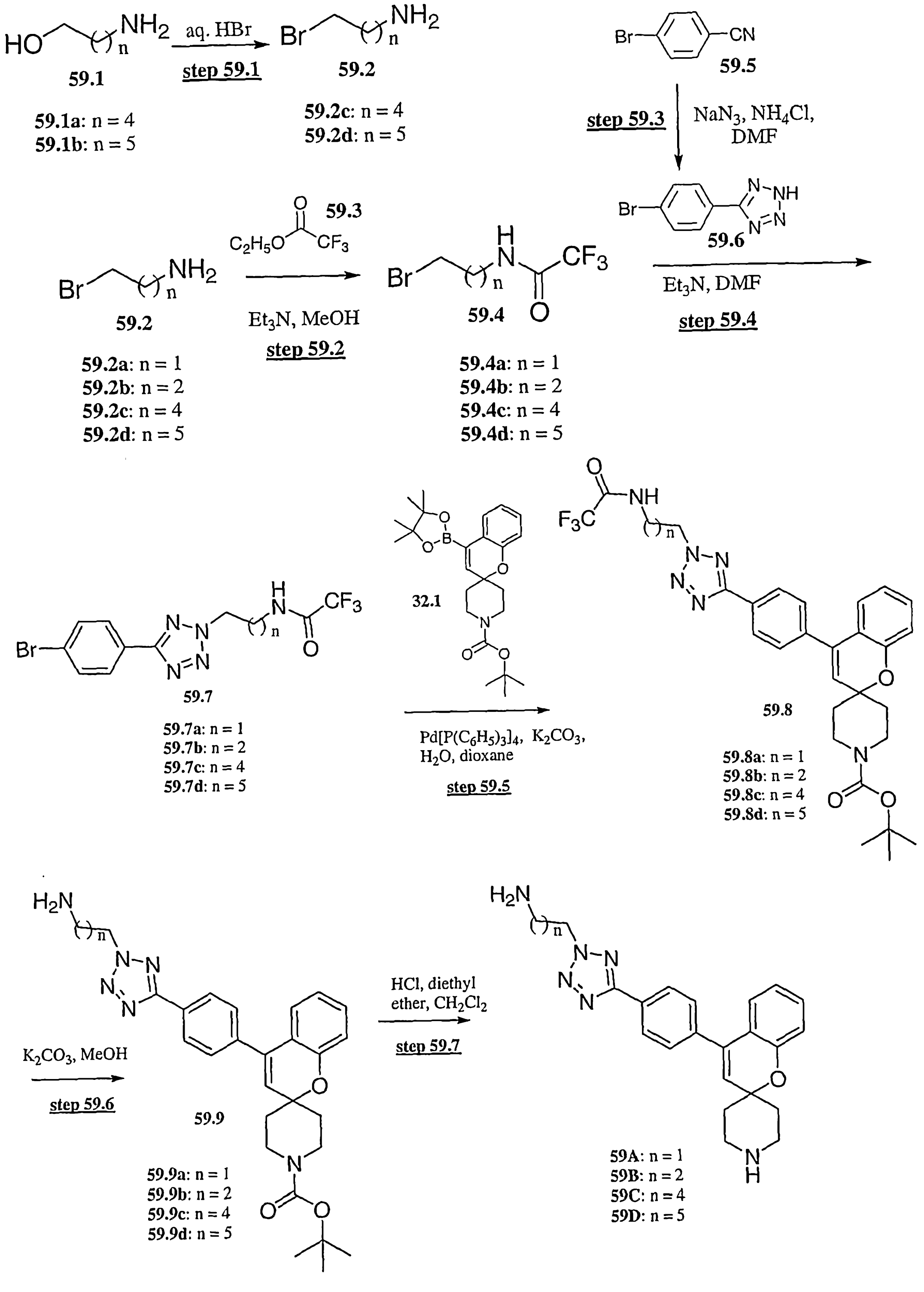
Scheme 57


31J
O
N
H
$(CF_3CO)_2O$ (4.1),
Et_3N, THF
step 57.1
57.1
O
N
O
CF_3
1) SO_3.DMF (4.3),
DCE
2) oxalyl chloride
step 57.2
SO_2Cl
O
57.2
N
O
CF_3
step 57.3
R_1R_2NH (3.4),
Et_3N, CH_2Cl_2
list of amines used in step 4.3:
H_2N
3.4b
HN
3.4j
$SO_2NR_1R_2$
O
N
O
CF_3
57.3
K_3CO_3, MeOH,
H_2O
step 57.4
$SO_2NR_1R_2$
O
N
H
57A,B
57.2
NH_4OH, CH_3CN
step 57.5
SO_2NH_2
O
57C
N
H
57.2
NH_2NH_2 (5.1),
THF
step 57.6
SO_2NHNH_2
O
N
57.4
O
CF_3
CH_3I (2.8c),
NaOAc, EtOH
step 57.7
SO_2CH_3
O
N
57.5
O
CF_3
K_3CO_3, MeOH,
H_2O
step 57.8
SO_2CH_3
O
57D
N
H

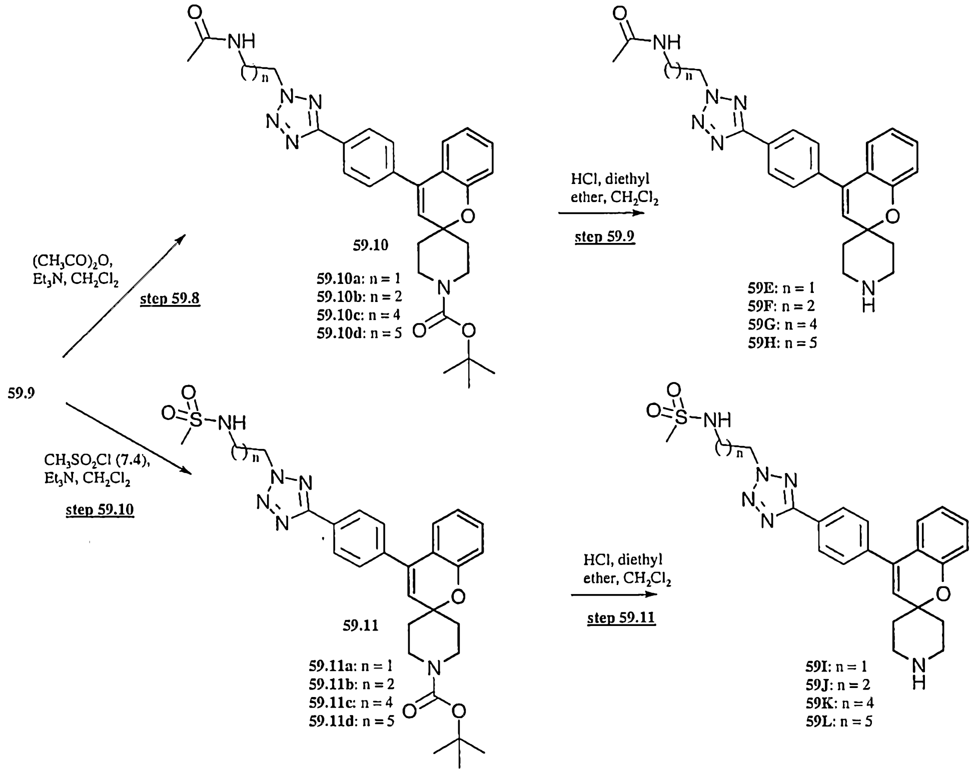
Scheme 58


2.5
3.6a
or
31.1n
Pd(dppf)Cl2.CH2Cl2, K2CO3, H2O, dioxane
step 58.1
58.1
HCl, dioxane, MeOH
step 58.2
58.1a: R =
58.1b: R =
58A: R =
58B: R =
2.5
31.1g
Pd[P(C6H5)3]4, K2CO3, H2O, DME
step 58.3
58.2
TBAF, THF
step 58.4
58.3
K2CO3, DMF
CH3I
2.8c
or
58.4
step 58.5
58.5
58.5a: R =
58.5b: R =
HCl, diethyl ether, CH2Cl2
step 58.6
58C: R =
58D: R =

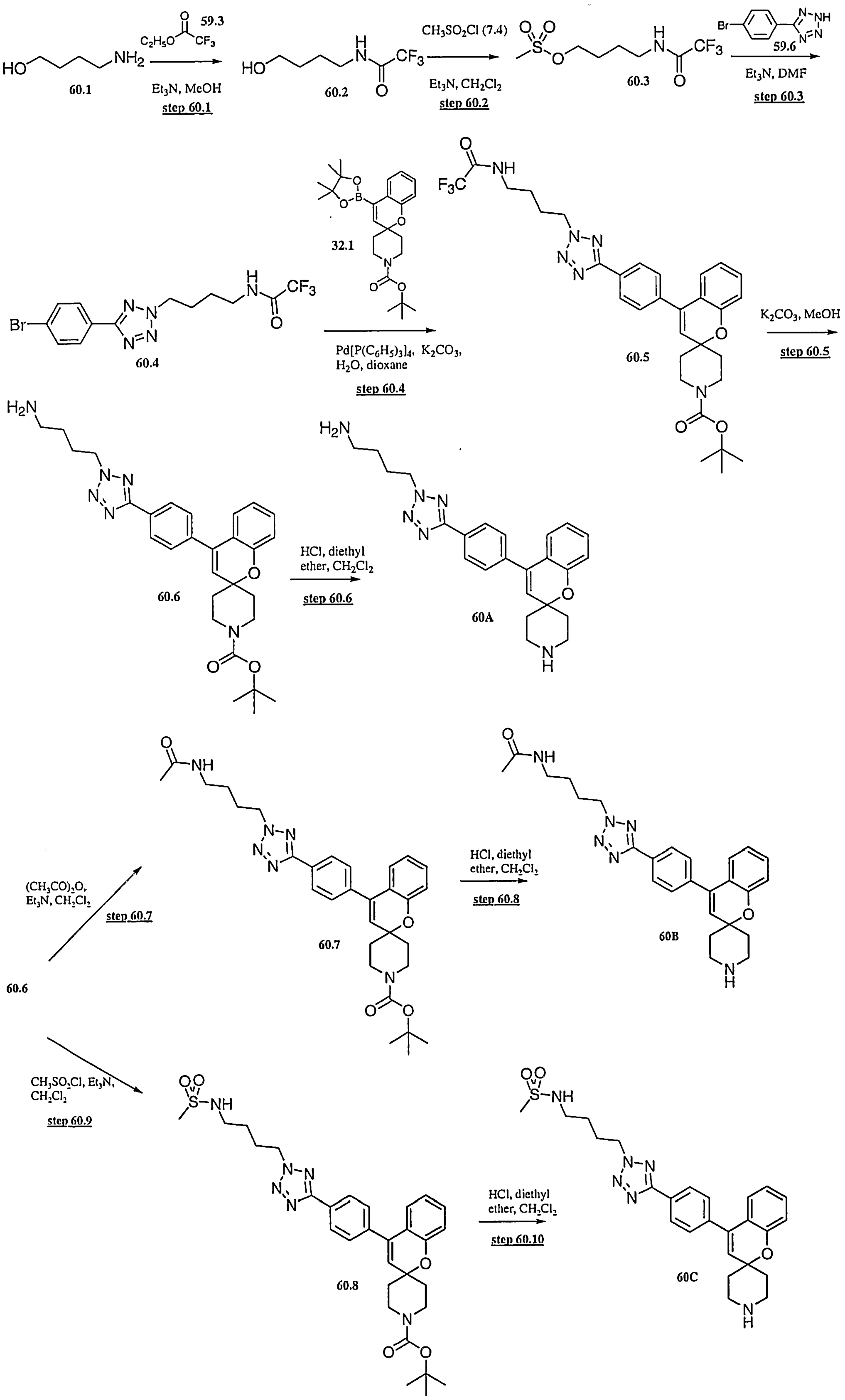
Scheme 59


HO
NH2
n
aq. HBr
step 59.1
Br
59.1
59.2
59.1a: n = 4
59.1b: n = 5
59.2c: n = 4
59.2d: n = 5
Br
CN
59.5
step 59.3
NaN3, NH4Cl, DMF
N-NH
N=N
59.6
59.3
C2H5O
CF3
O
Et3N, MeOH
step 59.2
59.2a: n = 1
59.2b: n = 2
59.2c: n = 4
59.2d: n = 5
H
N
CF3
59.4
59.4a: n = 1
59.4b: n = 2
59.4c: n = 4
59.4d: n = 5
Et3N, DMF
step 59.4
59.7
59.7a: n = 1
59.7b: n = 2
59.7c: n = 4
59.7d: n = 5
32.1
B
O
N
Pd[P(C6H5)3]4, K2CO3, H2O, dioxane
step 59.5
F3C
NH
59.8
59.8a: n = 1
59.8b: n = 2
59.8c: n = 4
59.8d: n = 5
H2N
K2CO3, MeOH
step 59.6
59.9
59.9a: n = 1
59.9b: n = 2
59.9c: n = 4
59.9d: n = 5
HCl, diethyl ether, CH2Cl2
step 59.7
59A: n = 1
59B: n = 2
59C: n = 4
59D: n = 5

Scheme 59 (continued)

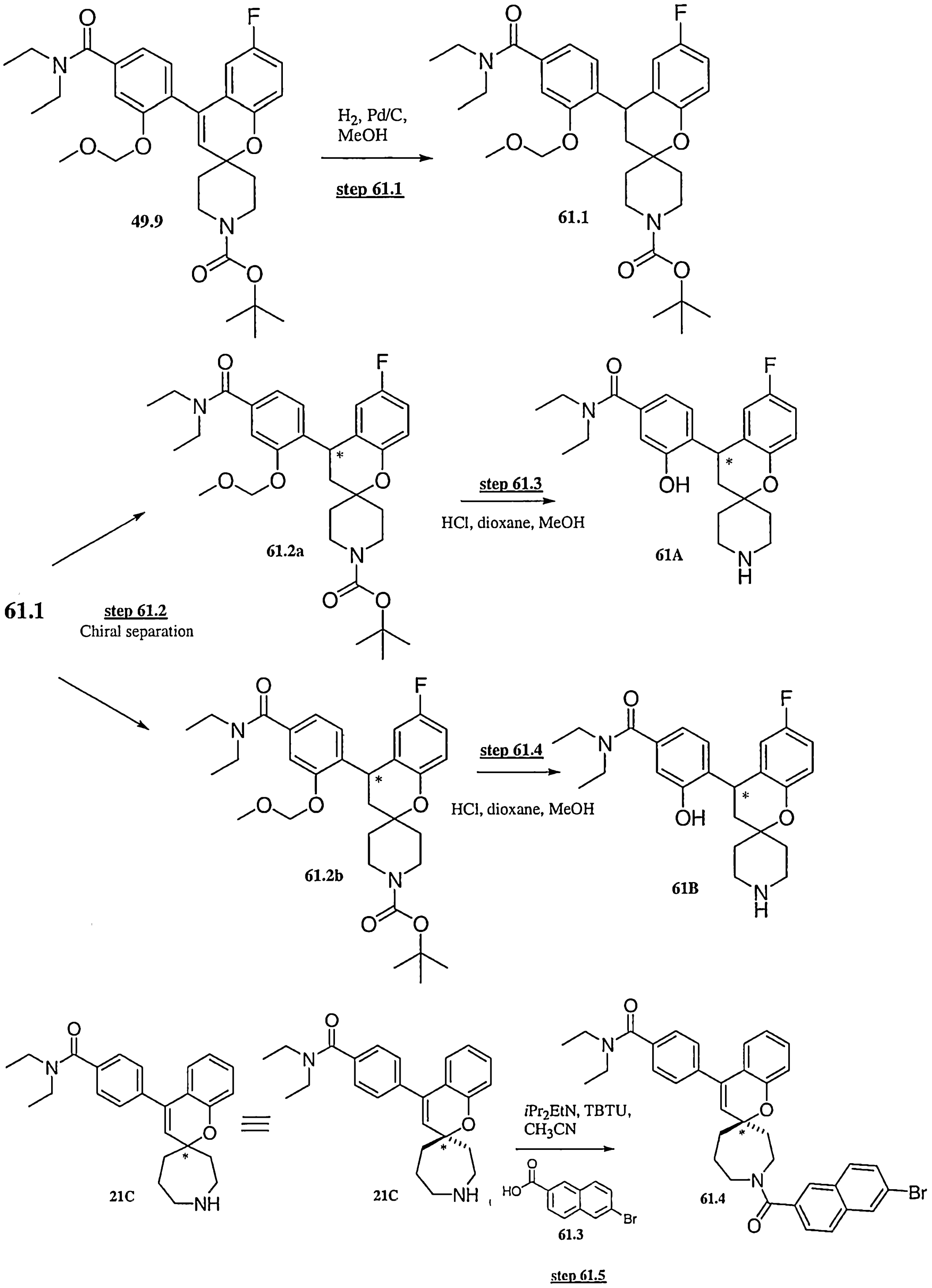


Scheme 60

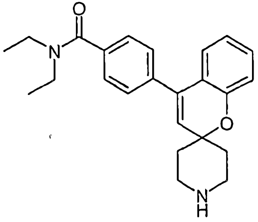
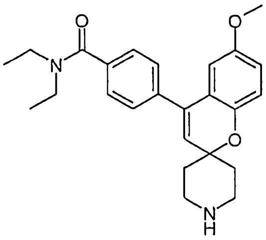
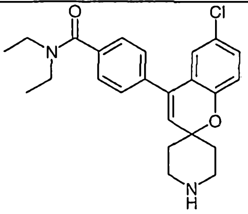
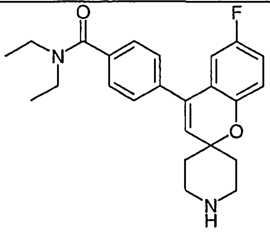
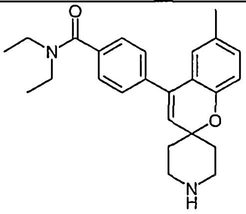
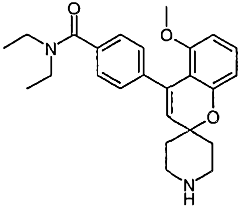


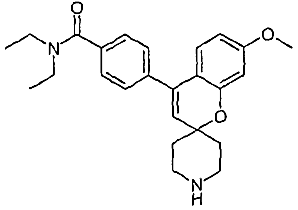
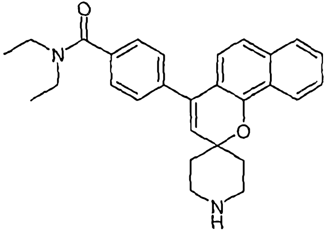
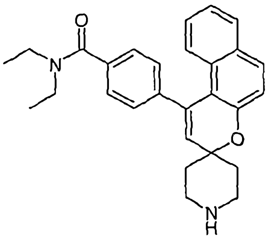
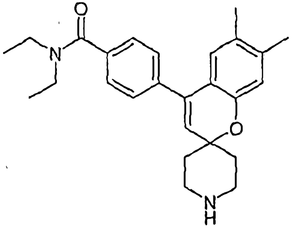
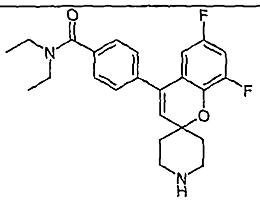
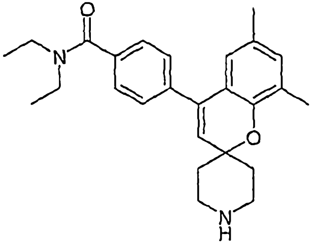
HO
NH2
60.1
59.3
C2H5O
CF3
Et3N, MeOH
step 60.1
60.2
CH3SO2Cl (7.4)
Et3N, CH2Cl2
step 60.2
60.3
Br
59.6
N-NH
Et3N, DMF
step 60.3
60.4
32.1
Pd[P(C6H5)3]4, K2CO3,
H2O, dioxane
step 60.4
60.5
F3C
NH
K2CO3, MeOH
step 60.5
H2N
60.6
HCl, diethyl ether, CH2Cl2
step 60.6
60A
(CH3CO)2O,
Et3N, CH2Cl2
step 60.7
60.6
60.7
HCl, diethyl ether, CH2Cl2
step 60.8
60B
CH3SO2Cl, Et3N,
CH2Cl2
step 60.9
60.8
HCl, diethyl ether, CH2Cl2
step 60.10
60C

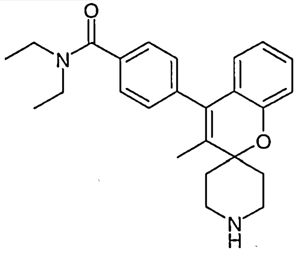
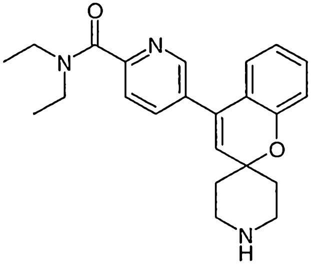
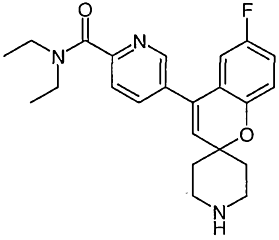
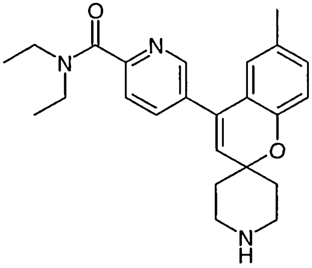
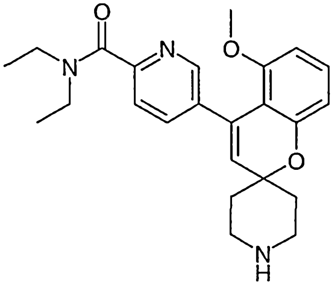
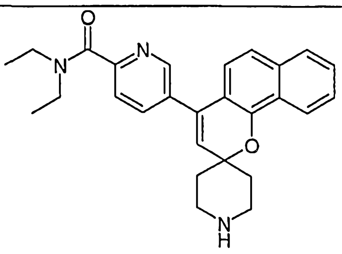
Scheme 61

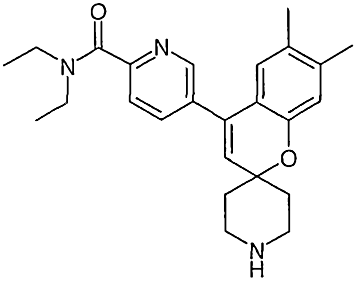
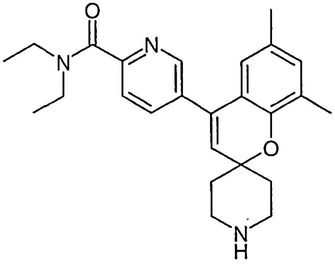
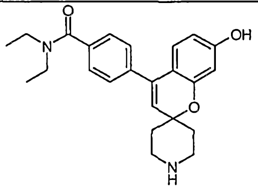
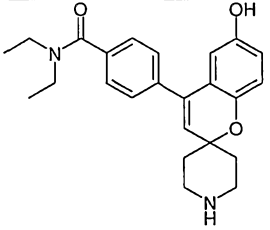
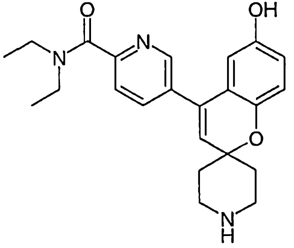
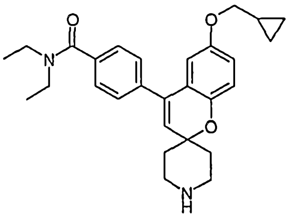

49.9
H_2, Pd/C, MeOH
step 61.1
61.1
61.1
step 61.2
Chiral separation
61.2a
step 61.3
HCl, dioxane, MeOH
61A
61.2b
step 61.4
HCl, dioxane, MeOH
61B
21C
21C
iPr$_2$EtN, TBTU, CH$_3$CN
61.3
step 61.5
61.4

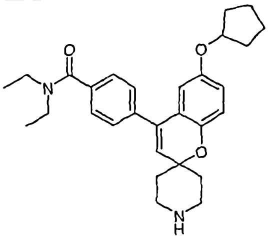
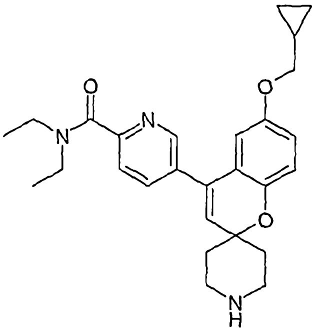
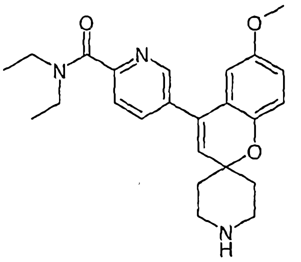
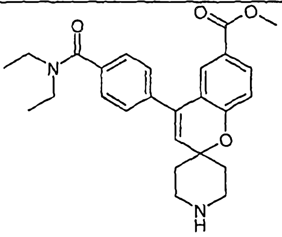
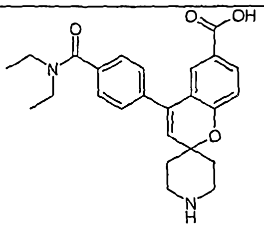
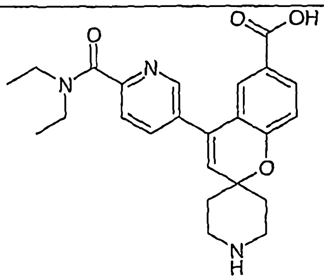
C. TABLE 1:

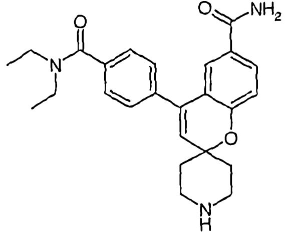
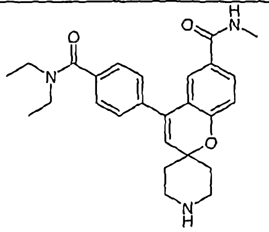
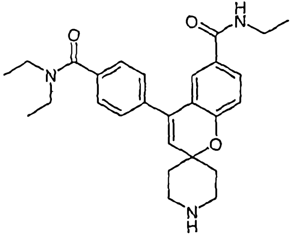
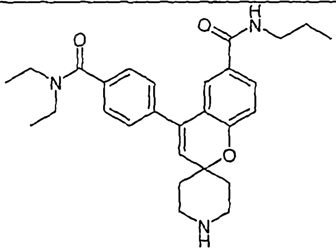
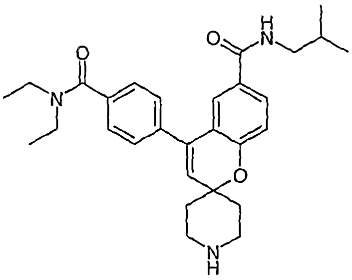
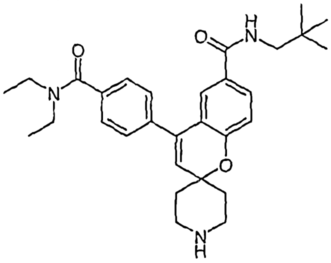
Example	*Structure*	[M+H]+
1A		377.4
1B		407.1
1C		411.2
1D		395.2
1E		391.3
1F		407.2

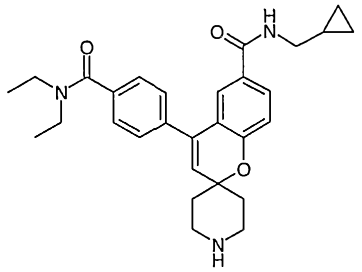
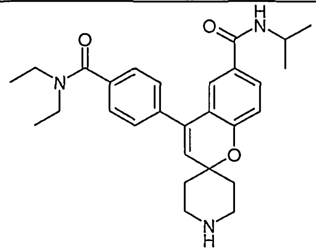
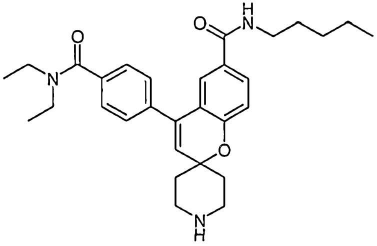
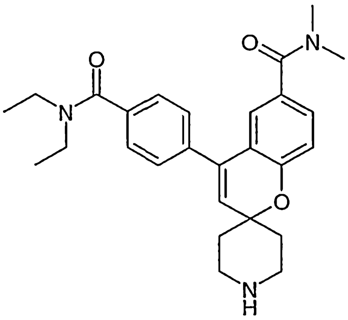
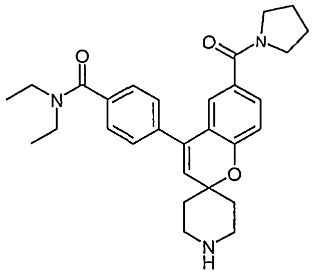
<u>*Example*</u>	<u>*Structure*</u>	$[M+H]^+$
1G		407.1
1H		427.4
1I		427.4
1J		405.4
1K		413.2
1L		405.4

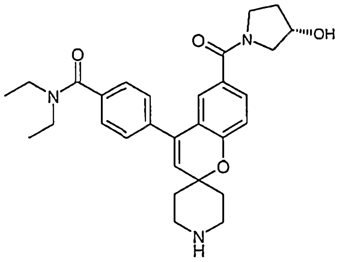
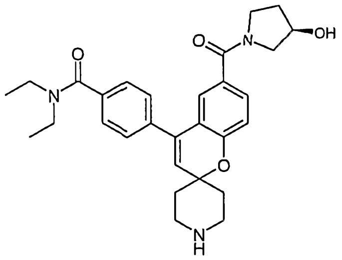
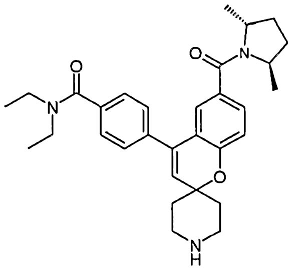
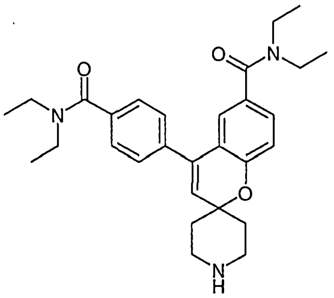
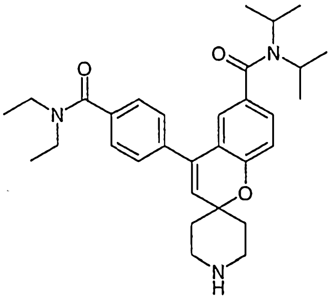
Example	*Structure*	[M+H]$^+$
1M		391.0
1N		378.4
1O		396.3
1P		392.3
1Q		408.3
1R		428.3

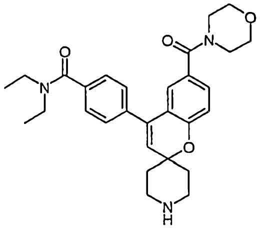
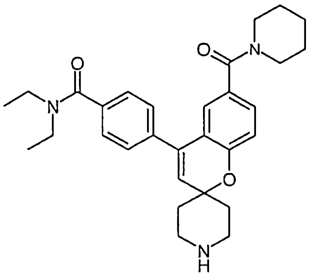
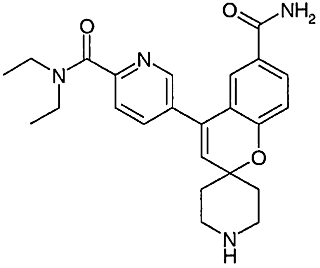
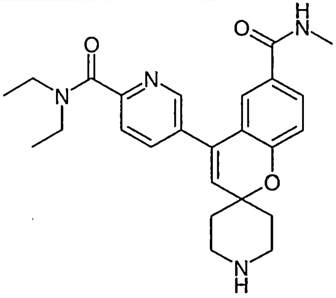
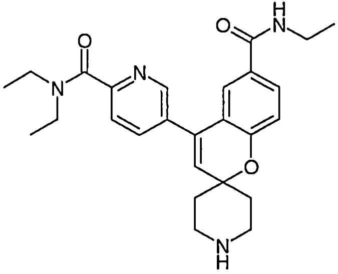
Example	*Structure*	[M+H]$^+$
1S		406.3
1T		406.4
1U		393.2
2A		393.3
2B		394
2C		447.1

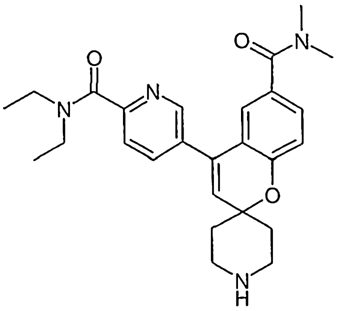
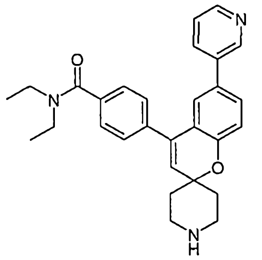
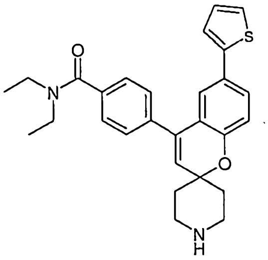
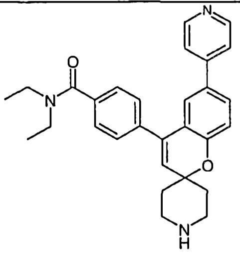
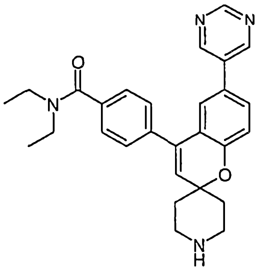
Example	*Structure*	[M+H]$^+$
2D		461.1
2E		448.3
2F		408.3
3A		435.0
3B		421.0
3C		422.2

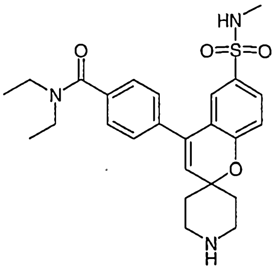
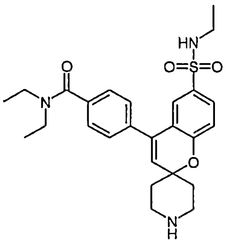
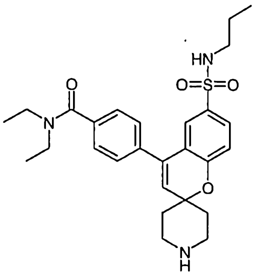
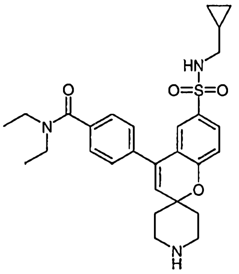
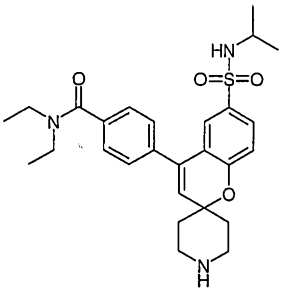
Example	*Structure*	$[M+H]^+$
3D		420.0
3E		434.3
3F		448.4
3G		462.4
3H		476.5
3I		490.6

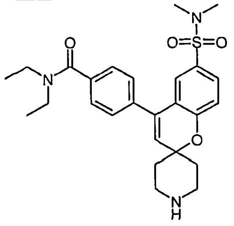
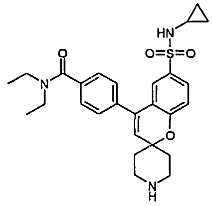
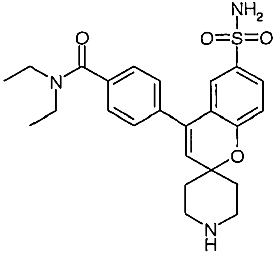
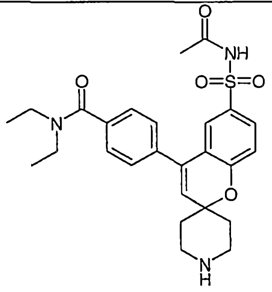
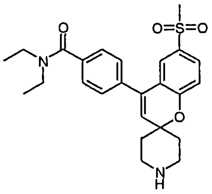
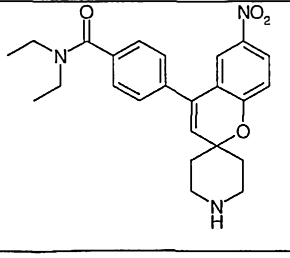
Example	Structure	[M+H]+
3J		474.4
3K		462.5
3L		490.5
3M		448.4
3N		474.5

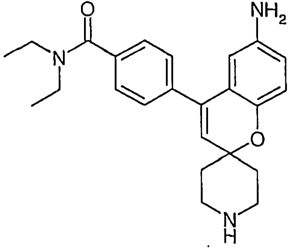
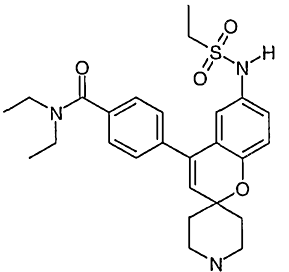
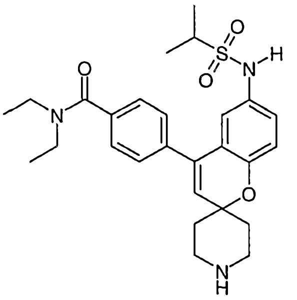
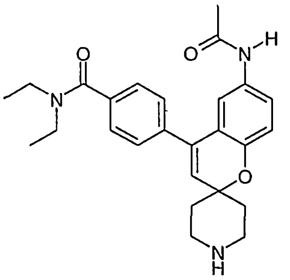
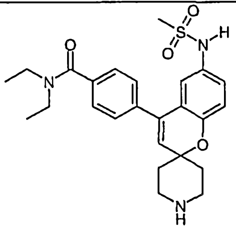
Example	*Structure*	[M+H]+
3O		490.3
3P		490.5
3Q		502.5
3R		476.5
3S		504.4

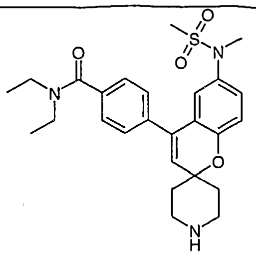
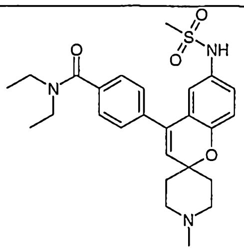
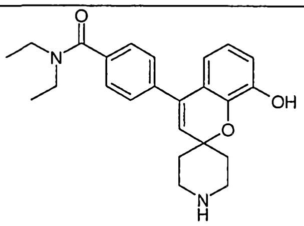
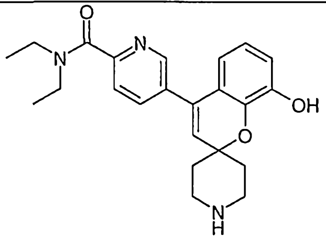
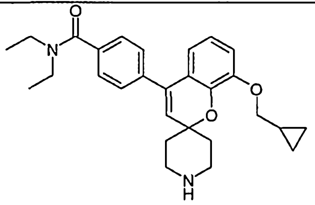
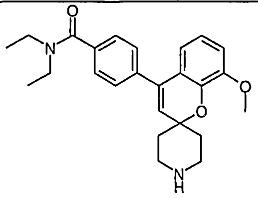
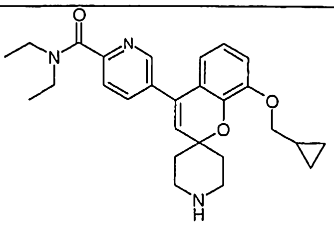
Example	*Structure*	[M+H]$^+$
3T		490.1
3U		488.4
3V		421.3
3W		435.3
3X		449.3

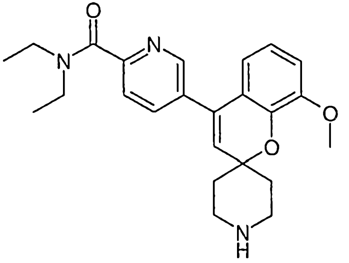
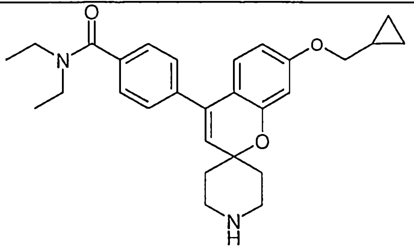
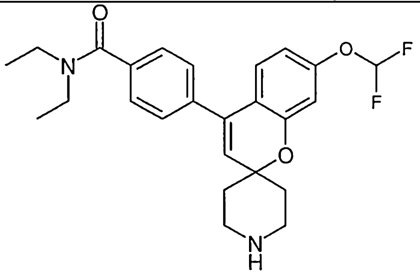
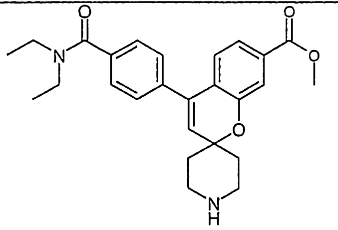
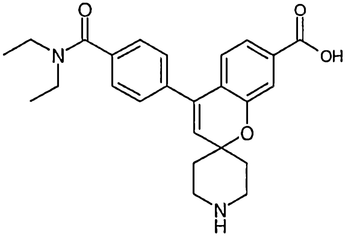
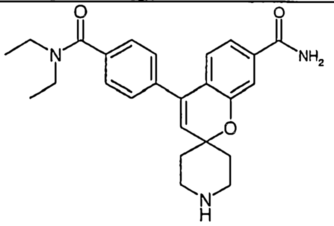
Example	*Structure*	[M+H]+
3Y		449.3
3Z		454.0
3AA		459.3
3AB		454.4
3AC		455.4

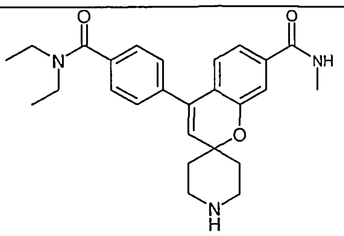
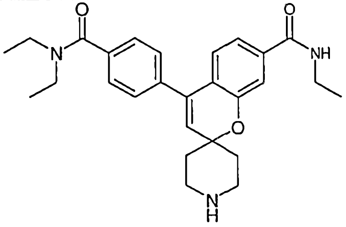
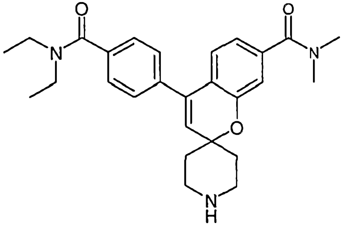
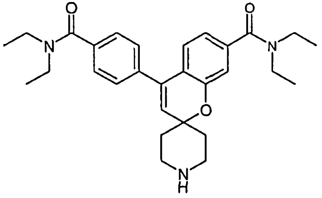
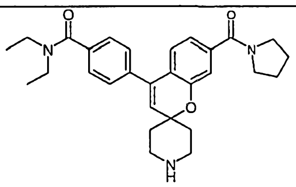
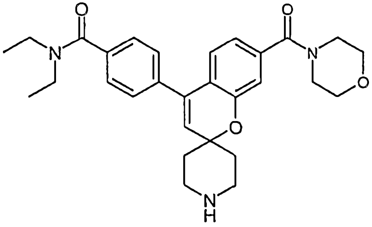
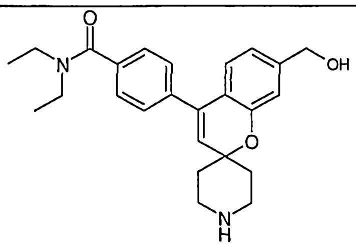
Example	*Structure*	$[M+H]^+$
4A		470.2
4B		484.3
4C		498.3
4D		510.3
4E		498.3

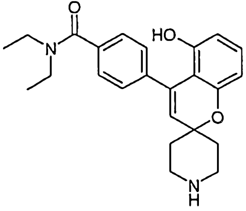
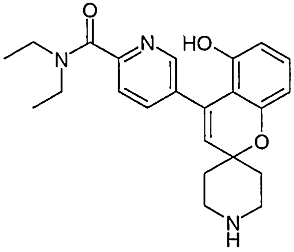
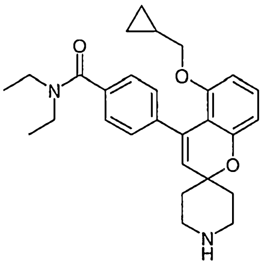
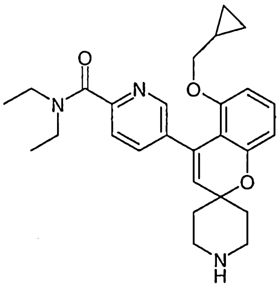
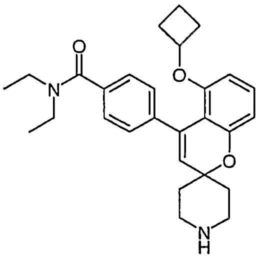
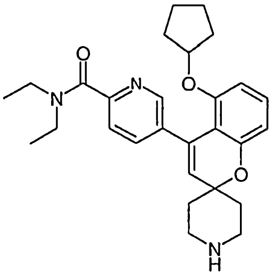
Example	*Structure*	$[M+H]^+$
4F		484.1
4G		496.2
4H		456.0
4I		498.3
5A		455.2
6A		422.3

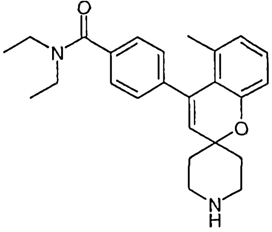
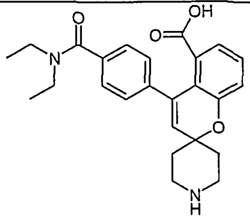
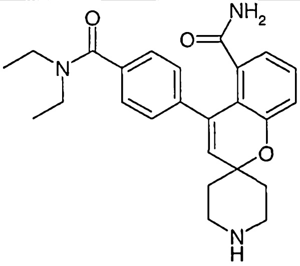
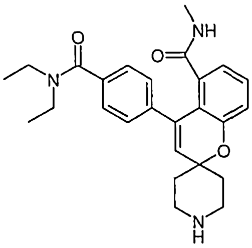
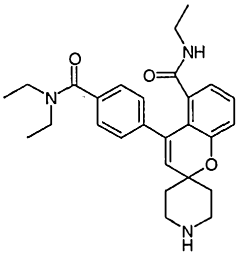
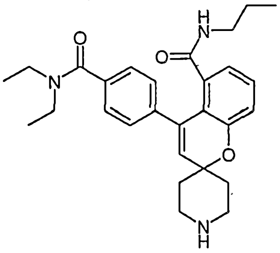
Example	*Structure*	[M+H]$^+$
6B		392.2
6C		484.2
6D		498.2
6E		434.2
7A		470.4

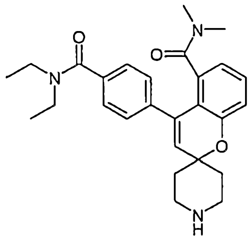
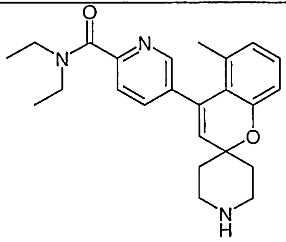
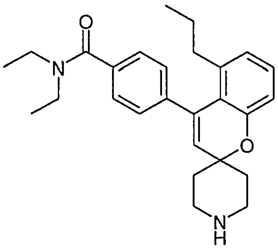
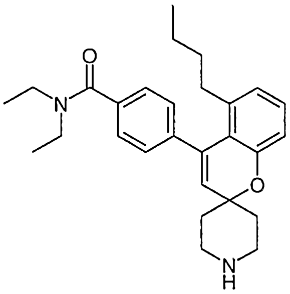
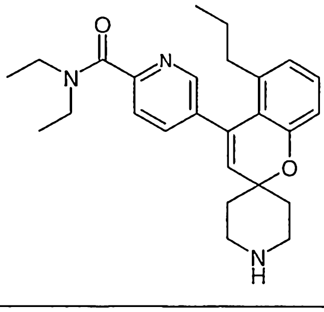
Example	*Structure*	[M+H]+
7B		484.2
7C		484.2
8A		393.4
8B		394.2
8C		447.3
8D		407.3
8E		448.3

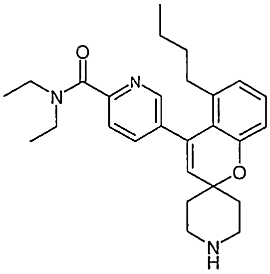
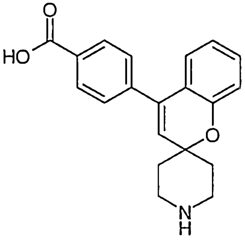
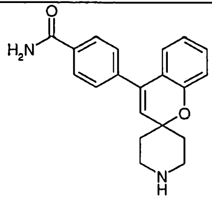
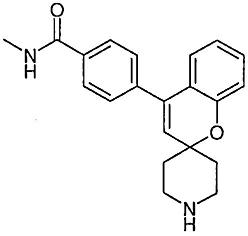
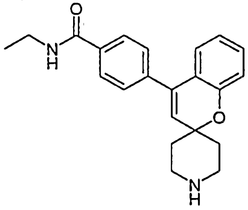
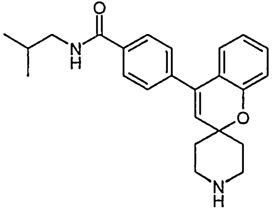
Example	*Structure*	[M+H]+
8F		408.4
9A		447.3
9B		443.4
10A		435.3
10B		421.3
10C		420.3

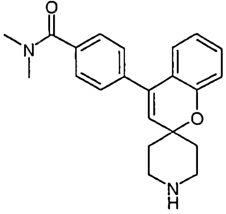
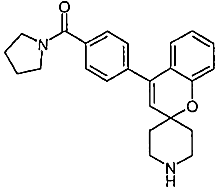
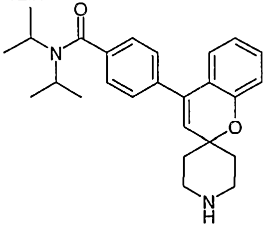
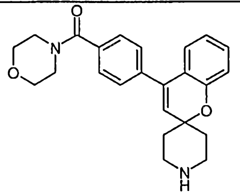
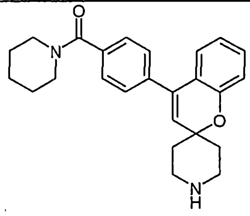
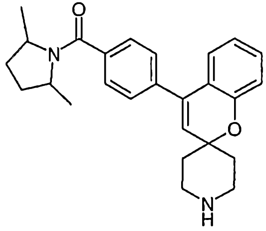
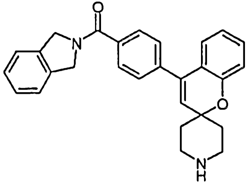
Example	*Structure*	[M+H]+
10D		434.3
10E		448.3
10F		448.3
10G		476.2
10H		474.3
10I		490.2
10J		407.4

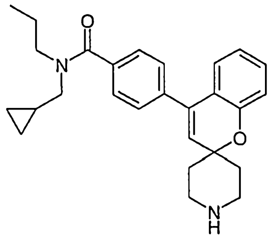
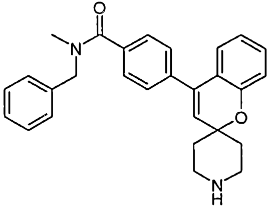
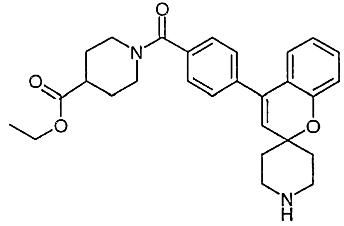
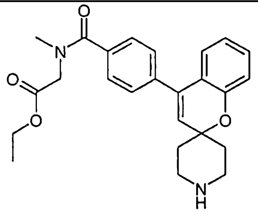
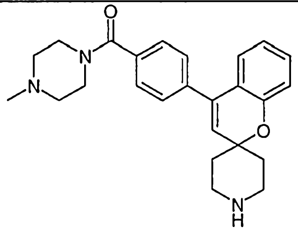
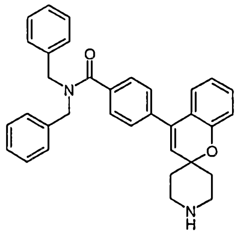
Example	*Structure*	[M+H]$^+$
11A		393.0
11B		394.3
11C		447.4
11D		448.4
11E		447.3
11F		462.4

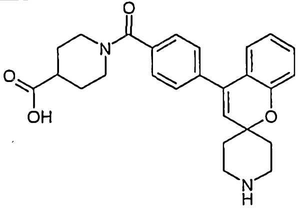
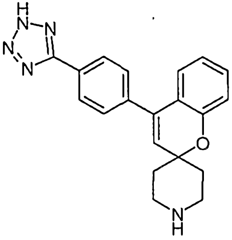
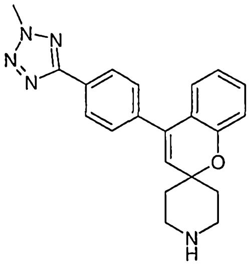
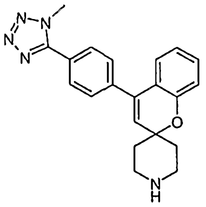
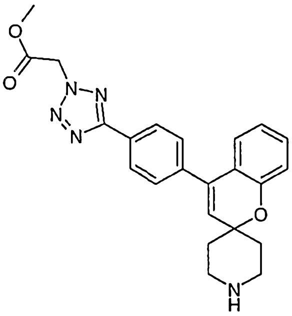
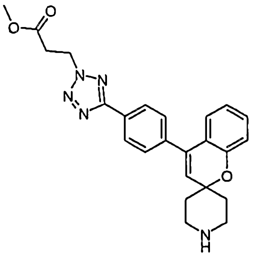
Example	*Structure*	$[M+H]^+$
12A		391.4
12B		421.3
12C		420.3
12D		434.3
12E		448.4
12F		462.4

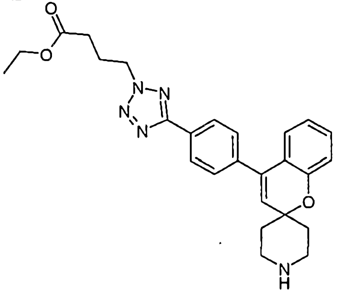
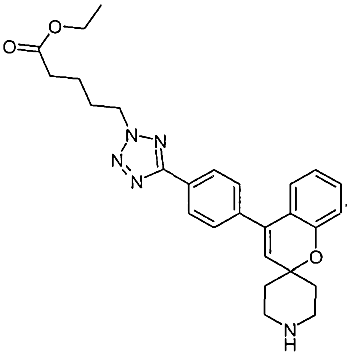
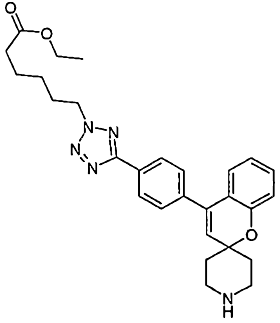
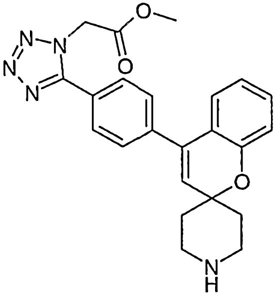
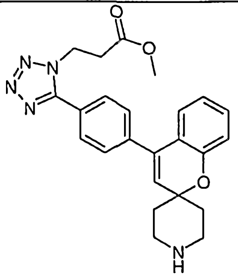
Example	*Structure*	$[M+H]^+$
12G		448.4
12H		392.4
12I		419.4
12J		433.4
12K		420.4

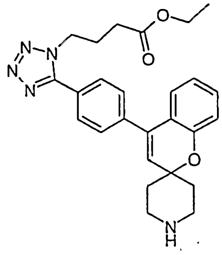
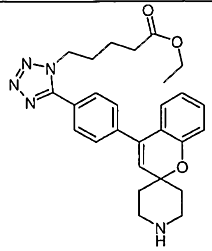
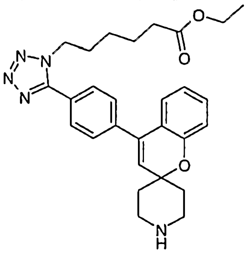
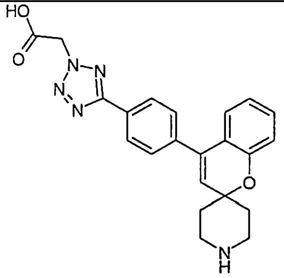
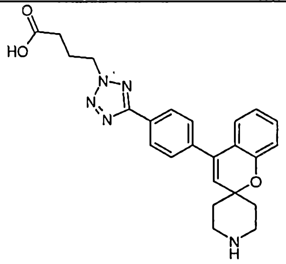
Example	***Structure***	[M+H]$^+$
12L		434.3
13A		322.1
13B		321.1
13C		335.2
13D		349.2
13E		377.2

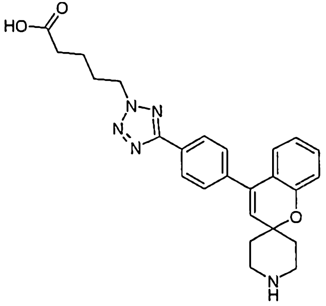
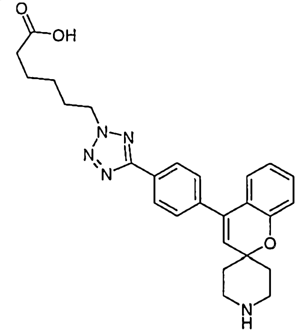
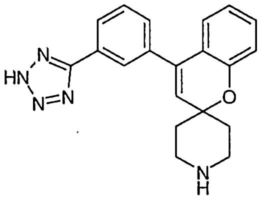
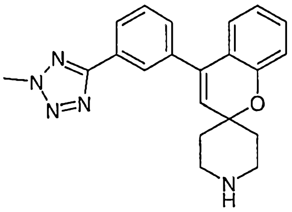
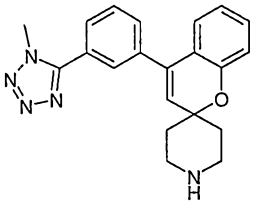
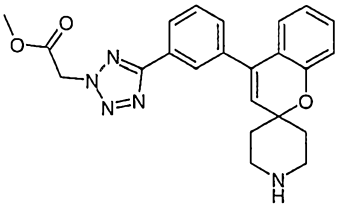
Example	*Structure*	[M+H]+
13F		349.1
13G		375.1
13H		405.3
13I		391.1
13J		389.1
13K		403.3
13L		423.1

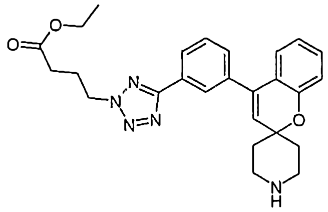
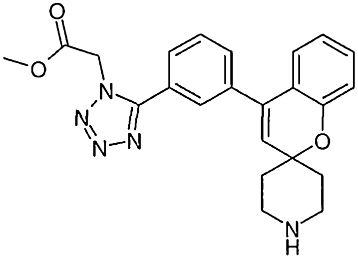
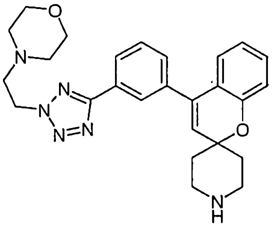
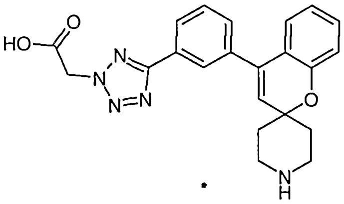
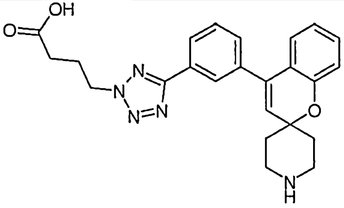
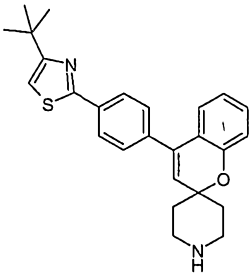
Example	*Structure*	[M+H]+
13M		417.2
13N		425.2
13O		461.2
13P		421.2
13Q		404.3
13R		501.2

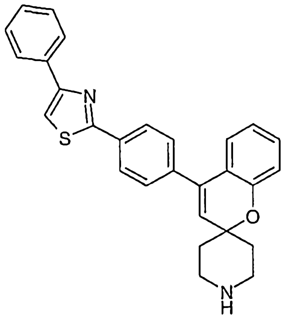
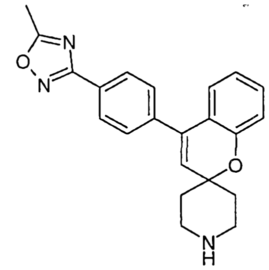
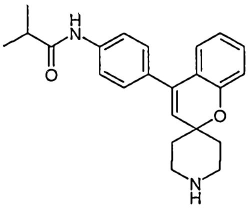
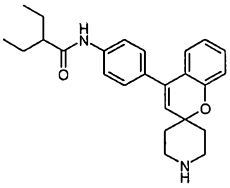
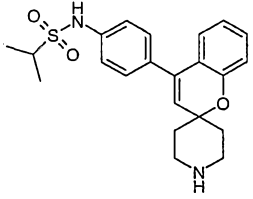
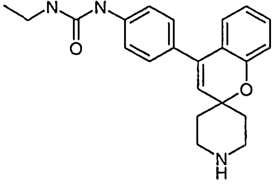
Example	*Structure*	[M+H]+
13S		433.1
14A		346.1
14B		360.1
14C		360.2
15A		418.1
15B		432.2

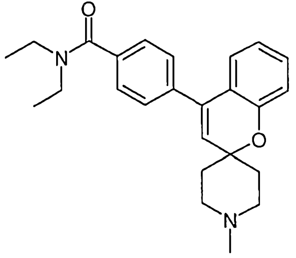
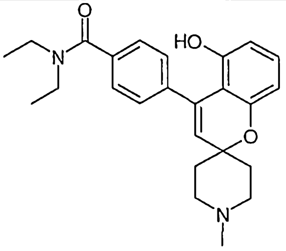
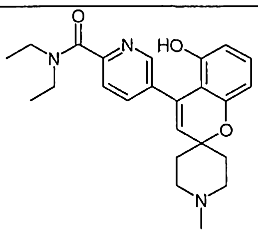
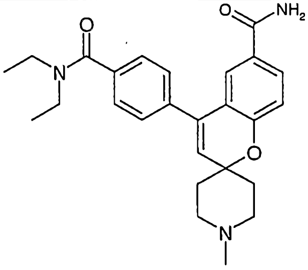
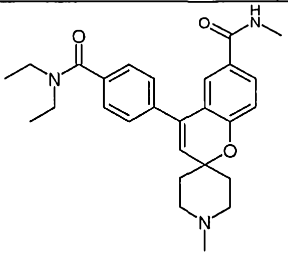
Example	*Structure*	$[M+H]^+$
15C		460.2
15D		474.2
15E		488.2
15F		418.2
15G		432.1

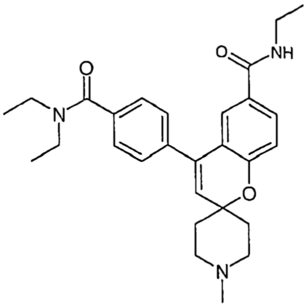
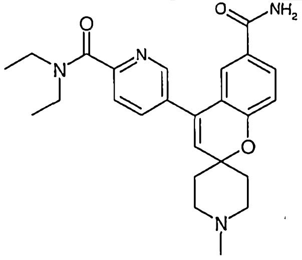
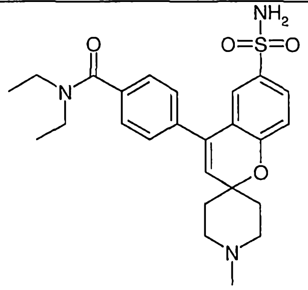
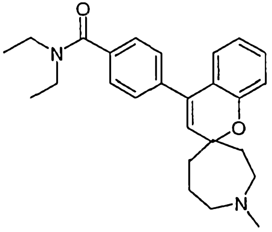
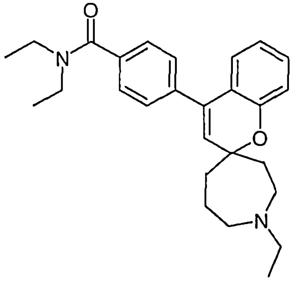
Example	*Structure*	[M+H]+
15H		460.2
15I		474.3
15J		488.3
15K		404.1
15L		432.1

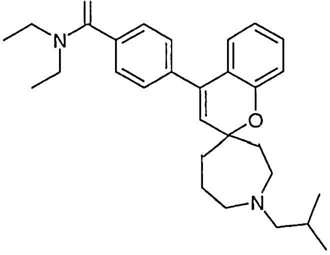
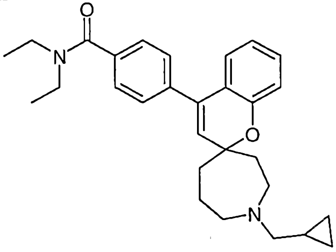
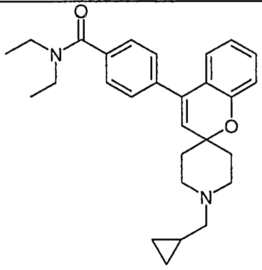
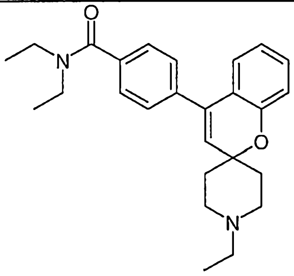
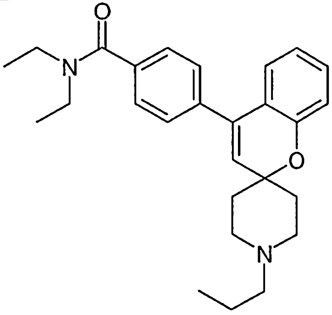
Example	*Structure*	[M+H]$^+$
15M		446.2
15N		460.2
16A		346.1
16B		360.1
16C		360.1
17A		418.1

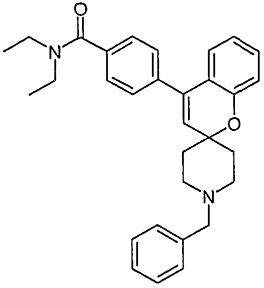
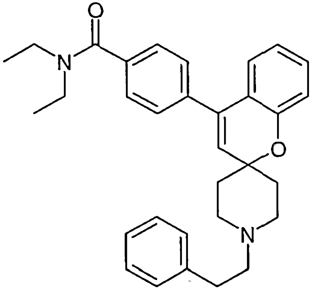
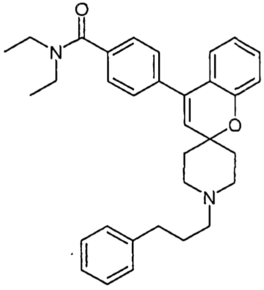
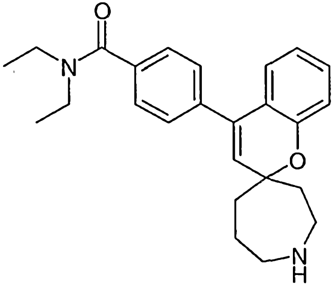
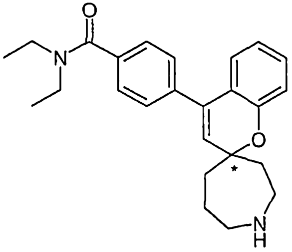
Example	*Structure*	[M+H]+
17B		460.2
17C		418.1
17D		459.2
17E		404.1
17F		432.1
18A		417.3

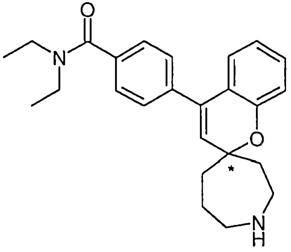
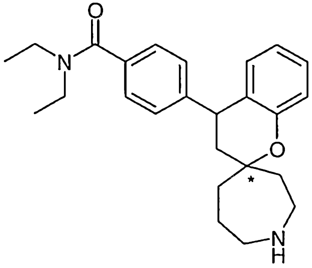
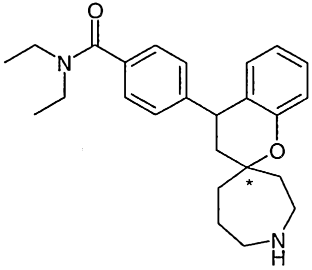
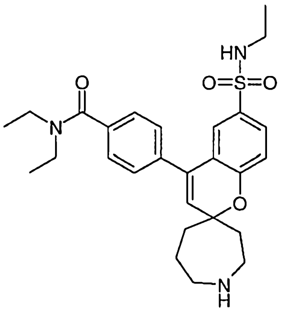
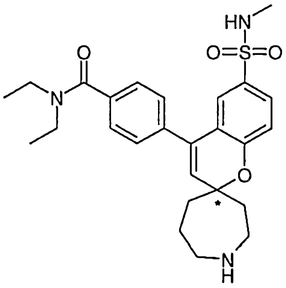
Example	*Structure*	[M+H]+
18B		437.1
18C		360.3
19A		363.4
19B		391.4
19C		399.3
19D		364.4

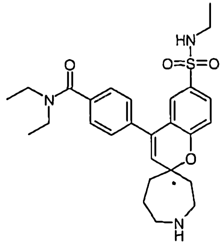
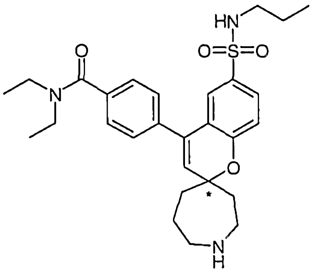
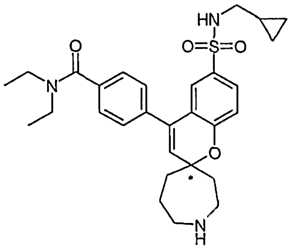
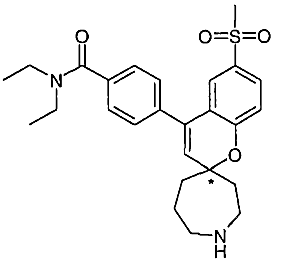
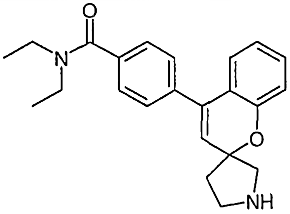
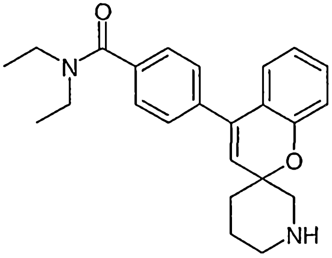
Example	*Structure*	$[M+H]^+$
20A		391.2
20B		407.3
20C		408.3
20D		434.4
20E		448.5

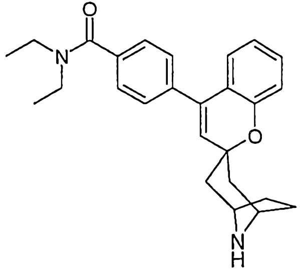
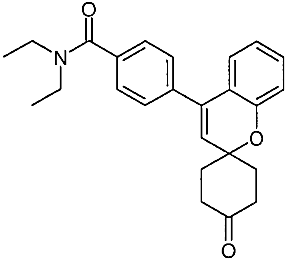
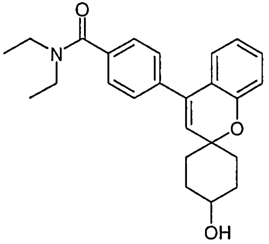
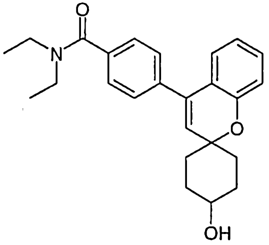
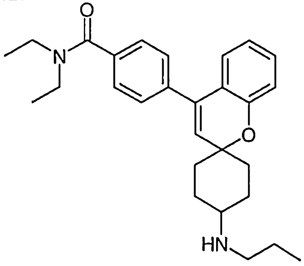
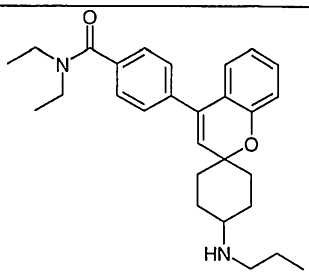
Example	***Structure***	[M+H]+
20F		462.5
20G		435.4
20H		470.3
20I		405.4
20J		419.4

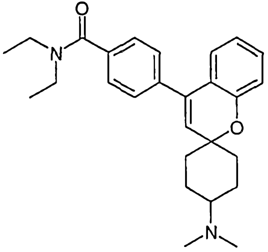
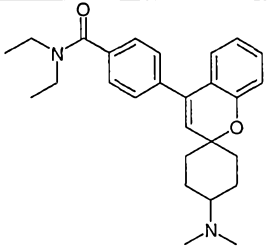
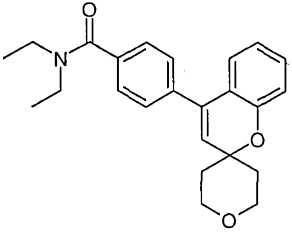
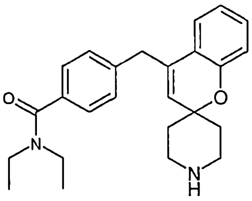
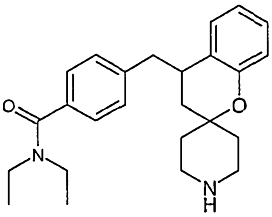
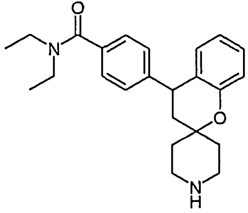
Example	*Structure*	[M+H]+
20K		447.5
20L		445.4
20M		431.0
20N		405.0
20O		419.1

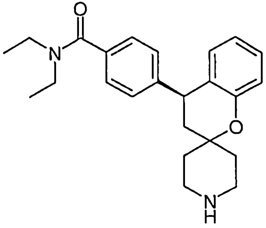
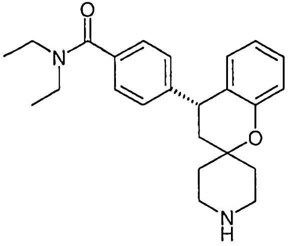
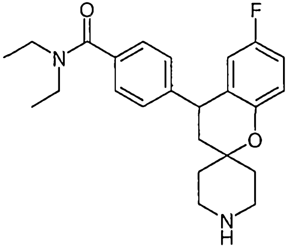
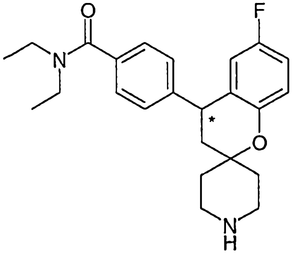
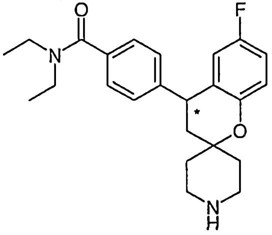
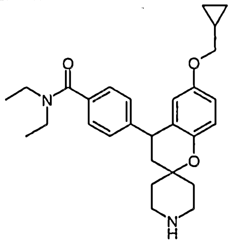
Example	*Structure*	[M+H]+
20P		467.3
20Q		481.3
20R		495.3
21A		391.2
21B		391.3

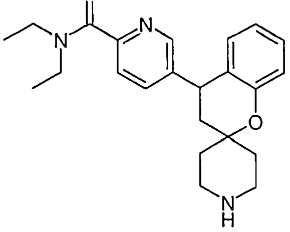
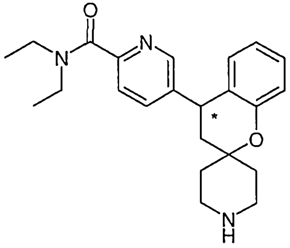
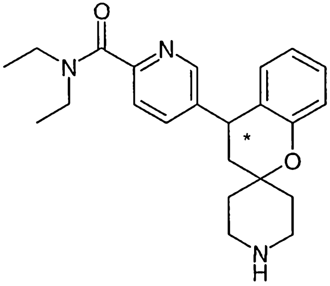
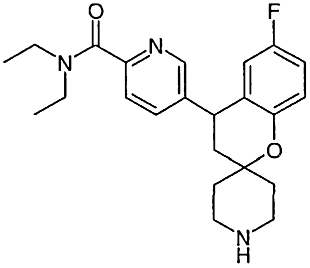
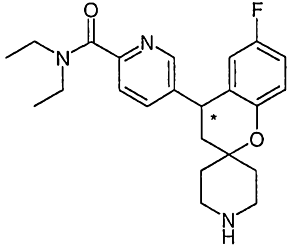
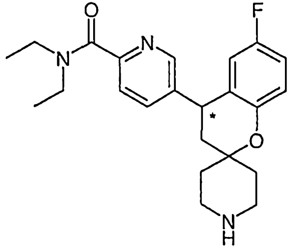
Example	*Structure*	[M+H]$^+$
21C		391.3
21D		393.3
21E		393.3
21F		498.5
22A		484.2

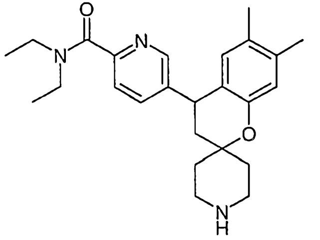
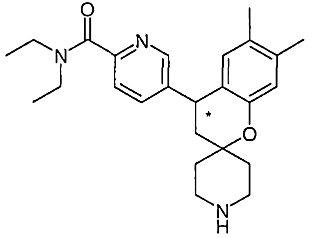
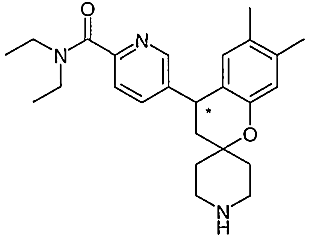
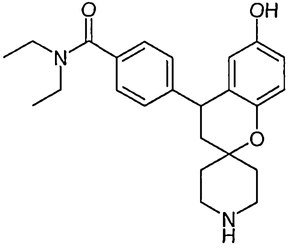
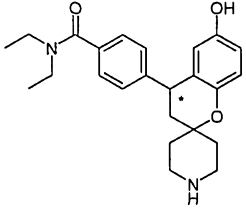
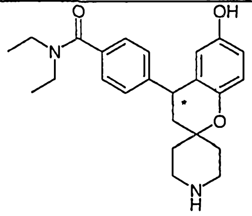
Example	Structure	[M+H]+
22B		498.3
22C		512.4
22D		524.3
22E		469.2
23A		363.2
23B		377.0

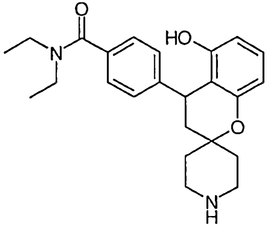
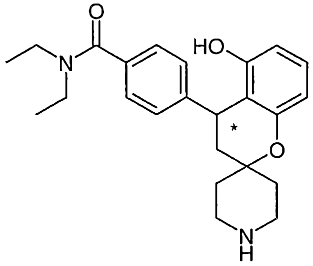
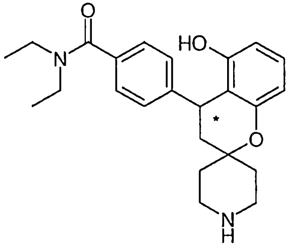
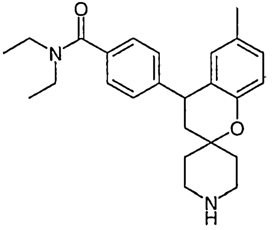
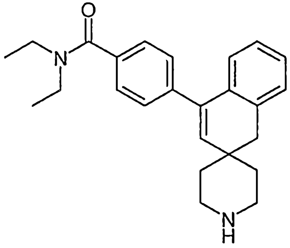
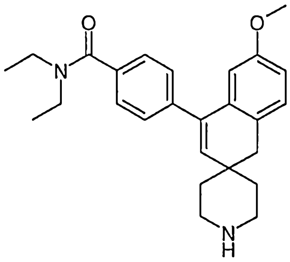
Example	*Structure*	[M+H]+
23C		403.2
24A		390.2
24B		392.2
24C		392.2
24D		433.2
24E		433.2

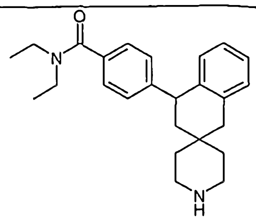
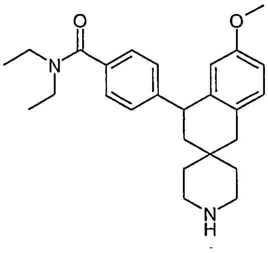
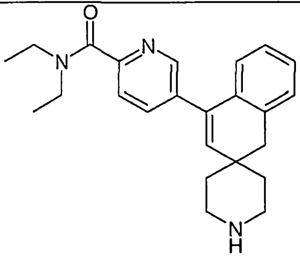
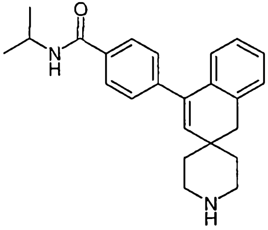
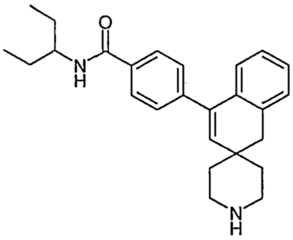
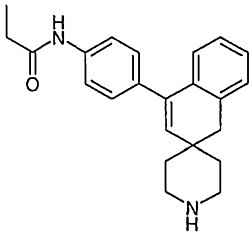
Example	*Structure*	$[M+H]^+$
24F		419.2
24G		419.2
25A		378.2
26A		391.0
26B		393.0
27A		379.1

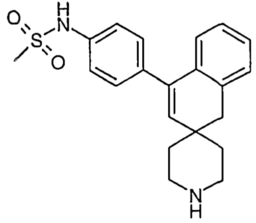
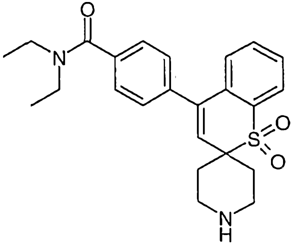
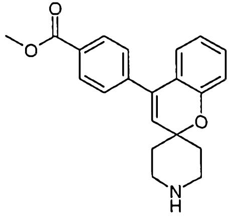
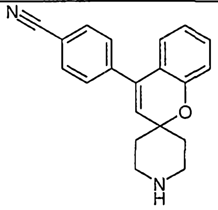
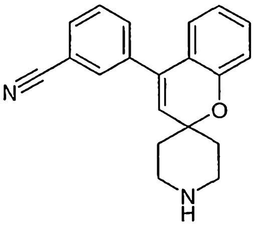
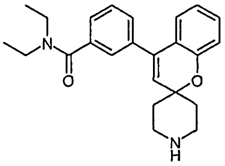
Example	*Structure*	[M+H]+
27B		379.4
27C		379.4
27D		397.3
27E		397.4
27F		397.3
27G		449.3

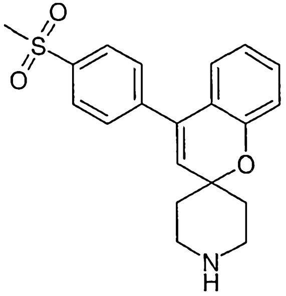
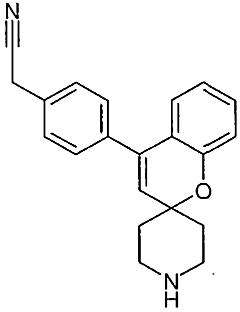
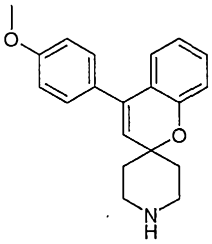
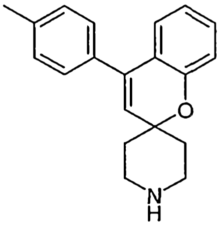
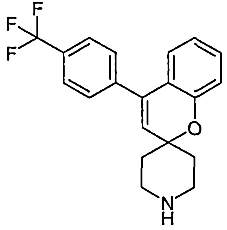
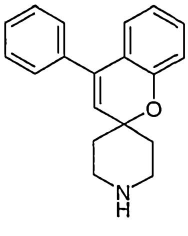
Example	*Structure*	[M+H]+
27H		380.2
27I		380.2
27J		380.2
27K		398.3
27L		398.3
27M		398.3

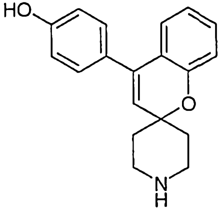
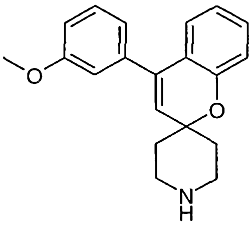
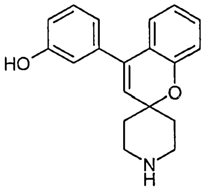
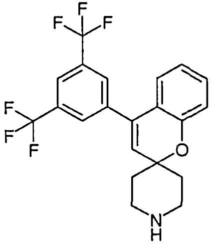
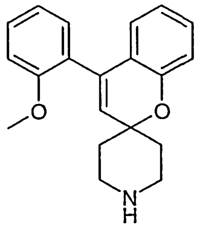
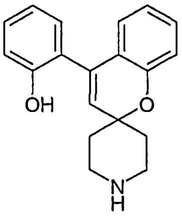
Example	*Structure*	[M+H]+
27N		408.3
27O		408.3
27P		408.3
27Q		395.4
27R'		395.1
27S		395.1

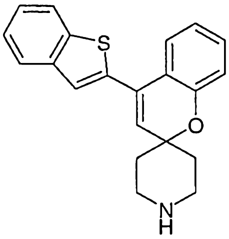
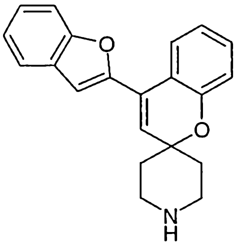
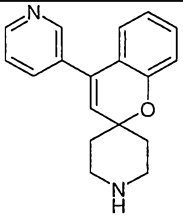
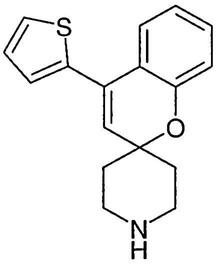
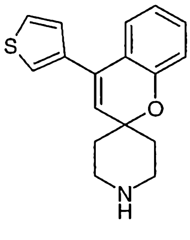
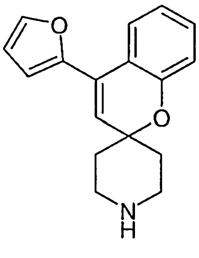
Example	*Structure*	[M+H]$^+$
27T		395.3
27U		395.1
27V		395.1
27W		393.4
28A		375.1
28B		405.1

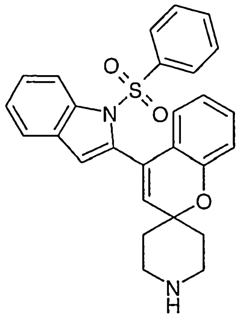
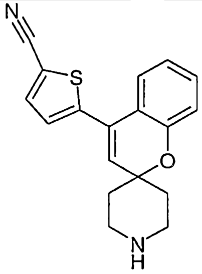
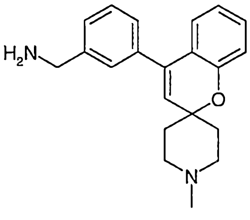
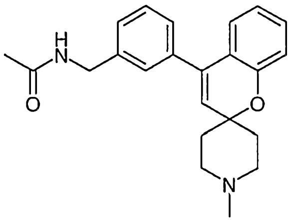
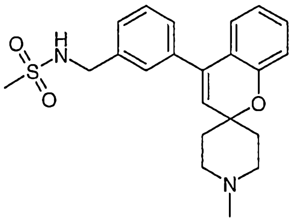
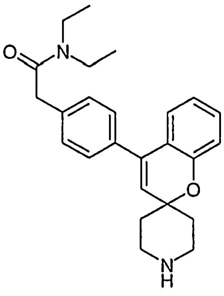
Example	Structure	[M+H]$^+$
28C		377.1
28D		407.3
28E		376.4
29A		361.0
29B		389.1
29C		347.0

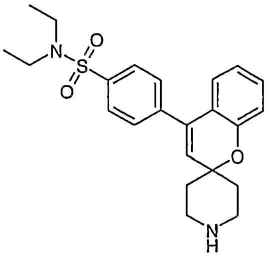
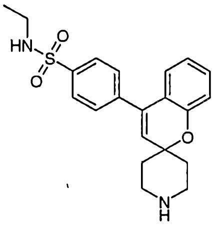
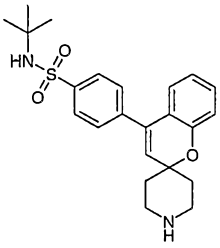
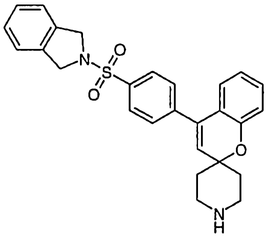
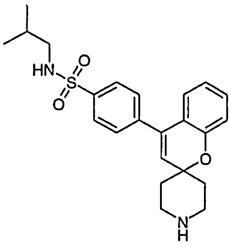
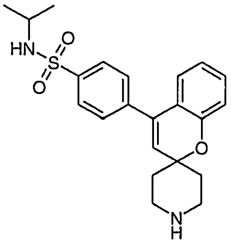
Example	Structure	[M+H]+
29D		368.9
30A		425.3
31A		336.0
31B		303.1
31C		303.1
31D		377.4

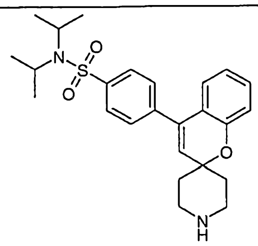
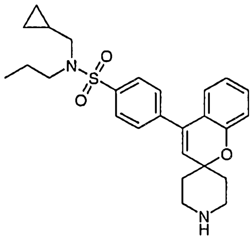
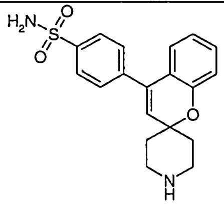
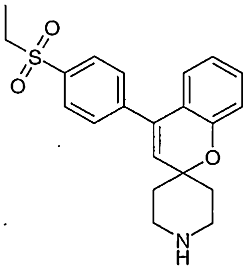
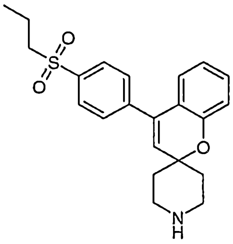
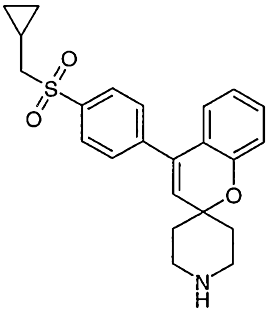
Example	*Structure*	[M+H]+
31E		356.1
31F		317.0
31G		308.0
31H		292.1
31I		346.1
31J		278.1

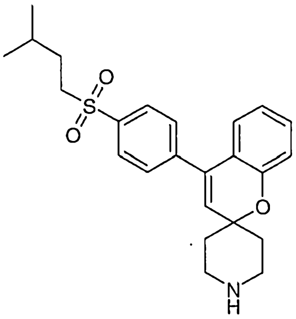
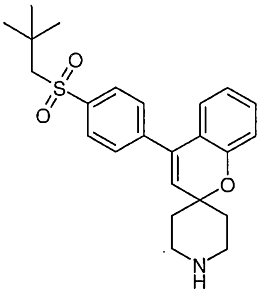
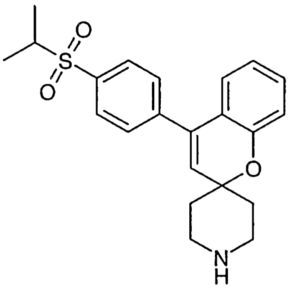
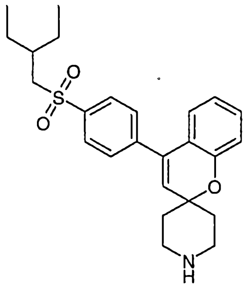
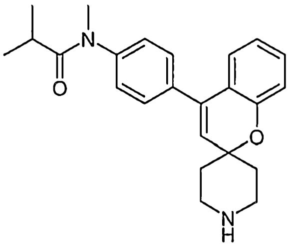
Example	*Structure*	[M+H]+
31K		294.0
31L		308.0
31M		294.0
31N		414.1
31O		308.0
31P		294.0

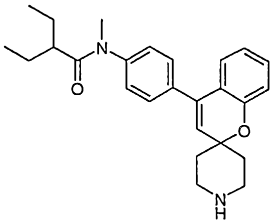
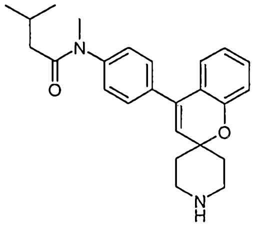
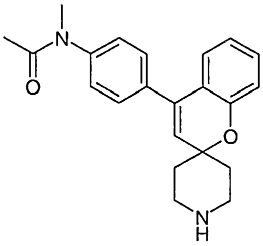
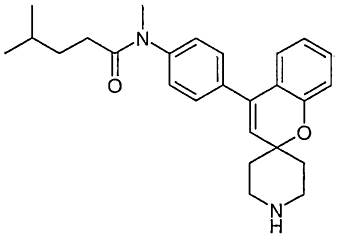
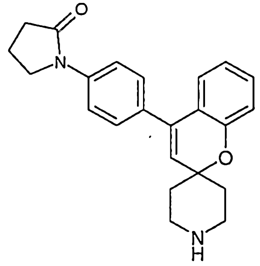
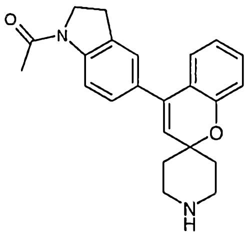
Example	*Structure*	[M+H]+
31Q		333.9
31R		318.1
31S		279.1
31T		283.9
31U		284.1
31V		268.1

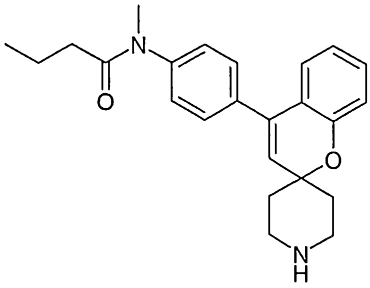
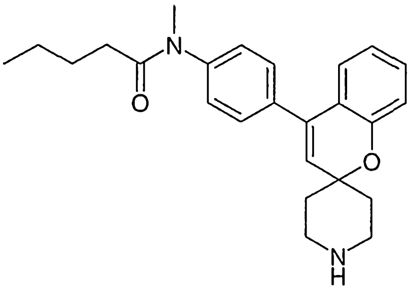
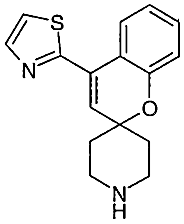
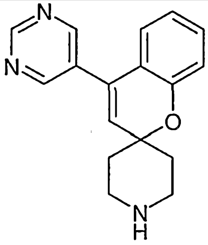
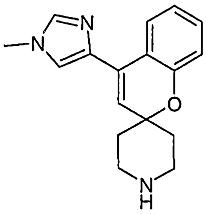
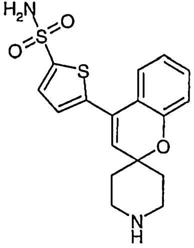
Example	*Structure*	[M+H]$^+$
31W		457.1
31X		308.8
31Y		321.1
31Z		363.1
31AA		399.1
32A		391.3

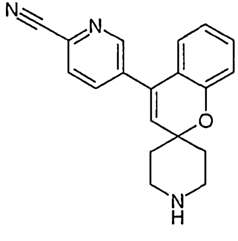
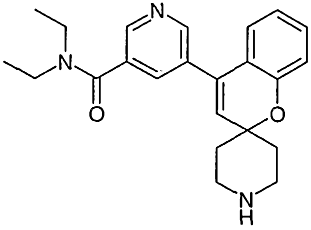
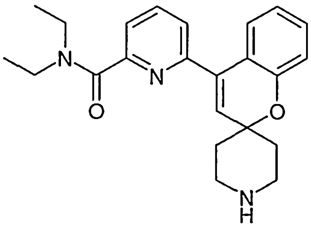
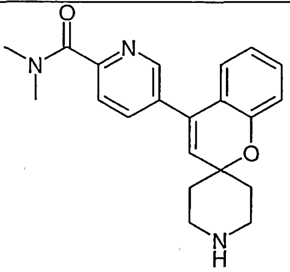
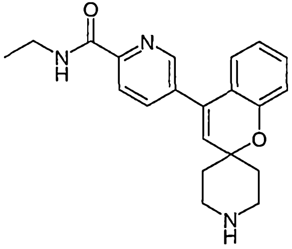
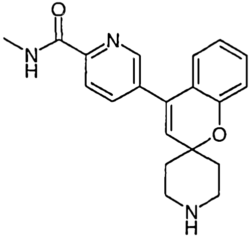
Example	*Structure*	[M+H]$^+$
32B		454.0
32C		385.3
32D		413.3
32E		459.3
32F		413.3
32G		399.4

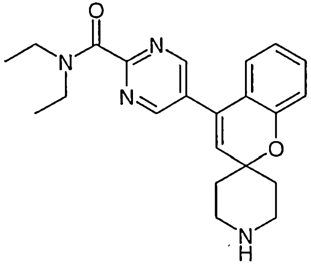
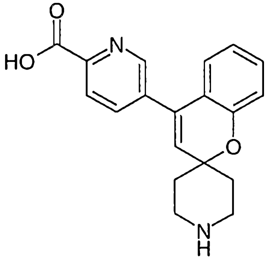
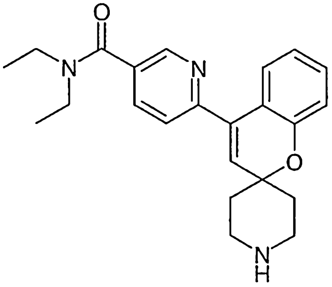
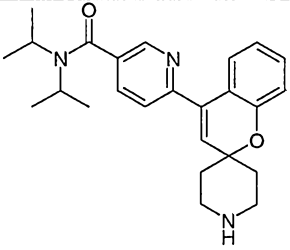
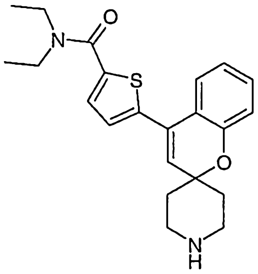
Example	Structure	[M+H]$^+$
32H		441.4
32I		453.3
32J		357.4
32K		370.2
32L		384.2
32M		396.2

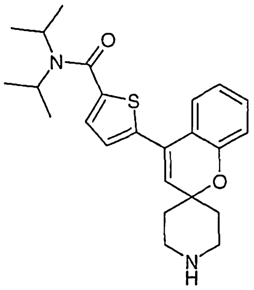
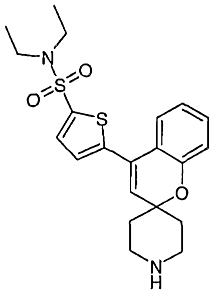
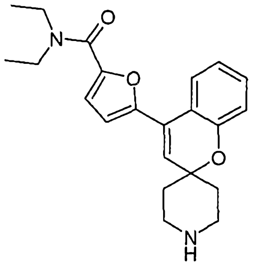
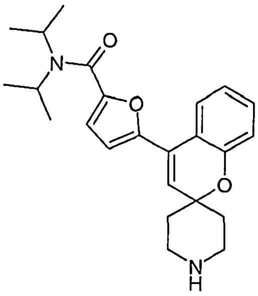
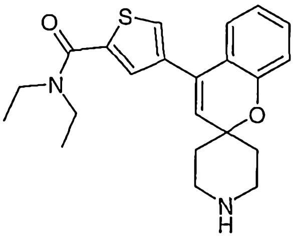
Example	Structure	[M+H]+
32N		412.2
32O		412.2
32P		384.2
32Q		426.2
32R		377.3

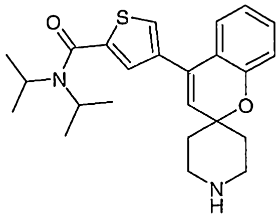
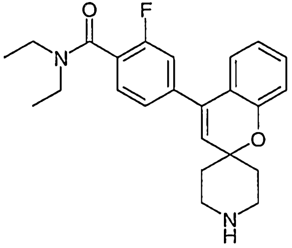
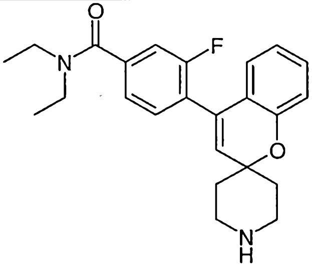
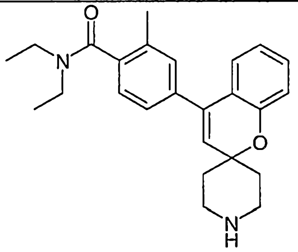
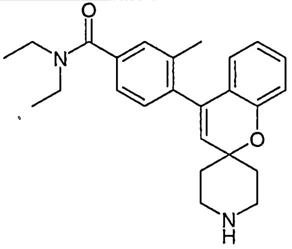
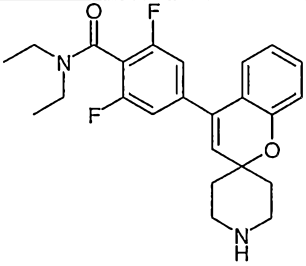
Example	*Structure*	[M+H]$^+$
32S		405.4
32T		391.3
32U		349.2
32V		405.3
32W		361.2
32X		361.3

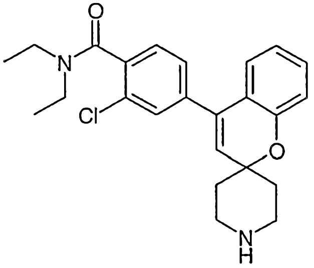
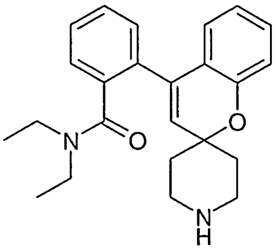
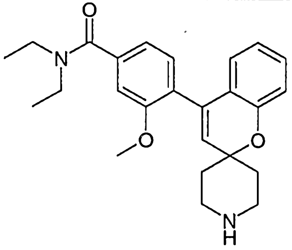
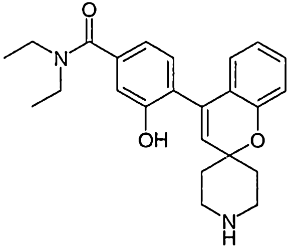
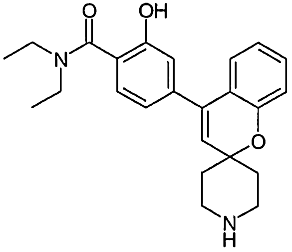
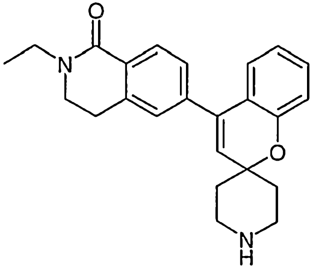
Example	*Structure*	[M+H]+
32Y		377.4
32Z		391.4
33A		284.9
33B		279.9
33C		282.0
33D		362.9

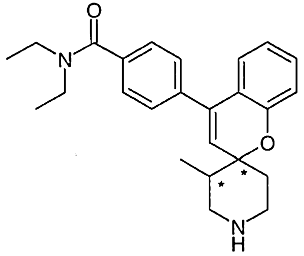
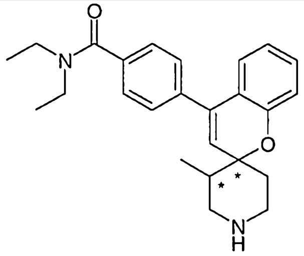
Example	*Structure*	[M+H]$^+$
33E		303.9
33F		378.3
33G		378.2
33H		350.2
33I		350.2
33J		336.2

Example	Structure	[M+H]$^+$
33K		379.3
33L		321.9
34A		378.4
34B		406.4
34C		383.3

Example	*Structure*	$[M+H]^+$
34D		411.4
34E		419.2
34F		367.3
34G		395.5
34H		383.4

Example	*Structure*	[M+H]+
34I		411.4
34J		395.0
34K		395.0
34L		391.0
34M		391.0
34N		413.0

Example	*Structure*	[M+H]$^+$
34O		411.0
34P		377.4
35A		407.0
35B		393.3
36A		393.4
36B		375.3

Example	Structure	[M+H]+
37A		391.3
37B		391.3

[0360] **21B** and **21C** are enantiomeric with respect to one another, but their absolute stereochemistry has not been conclusively established.

[0361] **21D** and **21E** are diastereomeric with respect to one another, but their absolute stereochemistry has not been conclusively established.

[0362] **24B** and **24C** are geometric isomers with respect to one another (wherein the hydroxyl is either equatorial or axial), but the conformation of each has not been conclusively established.

[0363] **24D** and **24E** are geometric isomers with respect to one another (wherein the hydroxyl is either equatorial or axial), but the conformation of each has not been conclusively established.

[0364] **24F** and **24G** are geometric isomers with respect to one another (wherein the hydroxyl is either equatorial or axial), but the conformation of each has not been conclusively established.

[0365] **27B** and **27C** are enantiomeric with respect to one another, and their absolute stereochemistry has been conclusively established using X-ray crystallography.

[0366] **27E** and **27F** are enantiomeric with respect to one another, but their absolute stereochemistry has not been conclusively established.

[0367] **27I** and **27J** are enantiomeric with respect to one another, but their absolute stereochemistry has not been conclusively established.

[0368] **27L** and **27M** are enantiomeric with respect to one another, but their absolute stereochemistry has not been conclusively established.

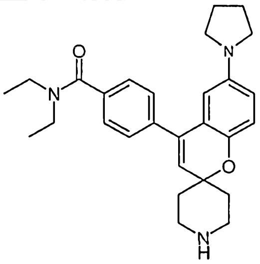
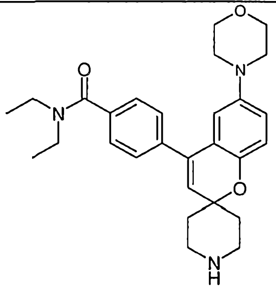
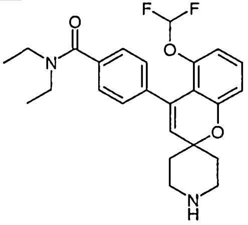
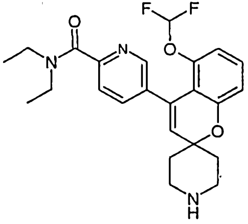
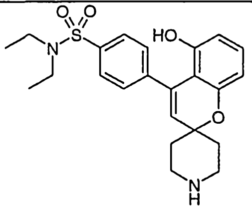
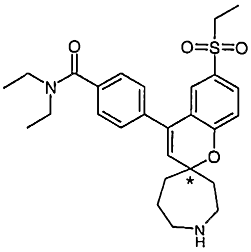
[0369] **27O** and **27P** are enantiomeric with respect to one another, but their absolute stereochemistry has not been conclusively established.

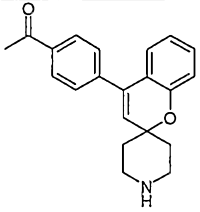
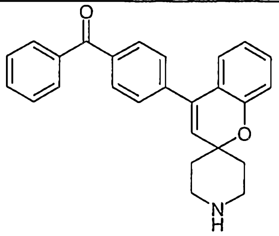
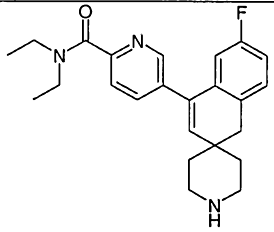
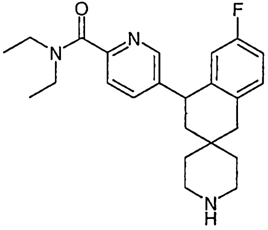
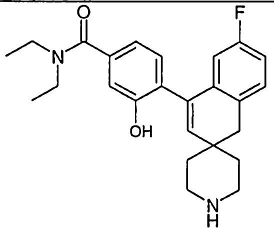
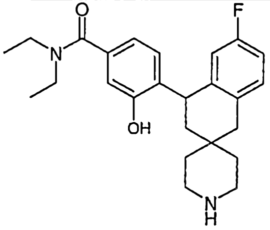
[0370] **27R** and **27S** are enantiomeric with respect to one another, but their absolute stereochemistry has not been conclusively established.

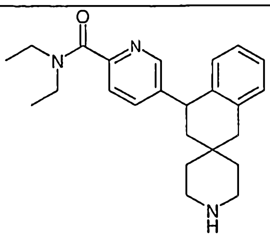
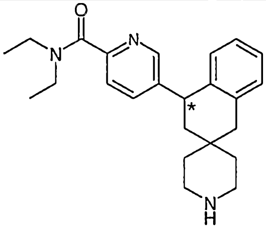
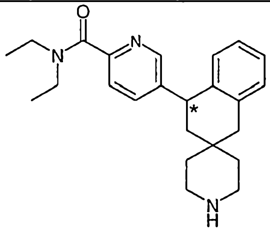
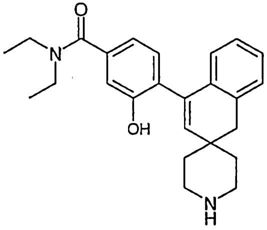
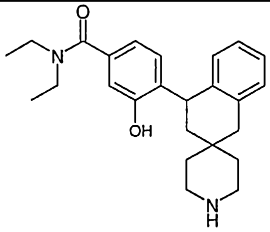
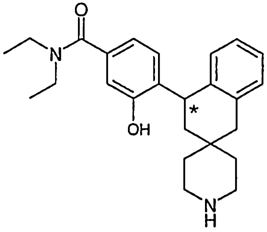
[0371] **27U** and **27V** are enantiomeric with respect to one another, but their absolute stereochemistry has not been conclusively established.

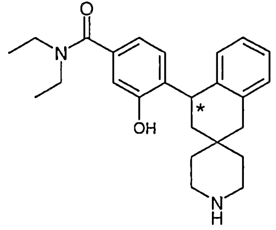
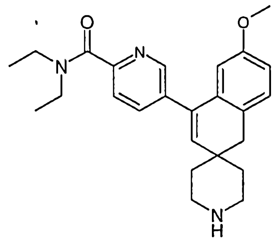
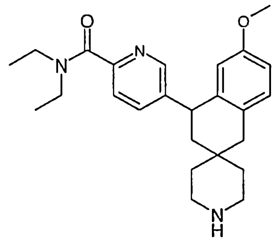
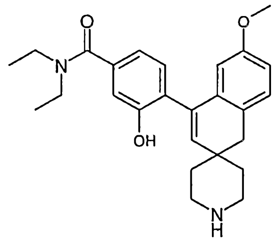
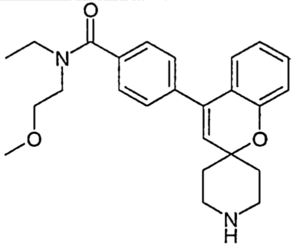
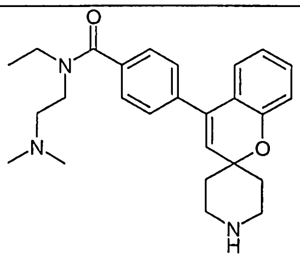
[0372] **37A** and **37B** are diastereomeric with respect to one another, but each is a racemic mixture of its two possible enantiomers. Their absolute stereochemistry has not been conclusively established.

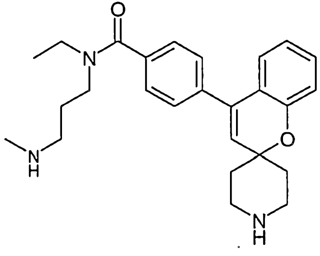
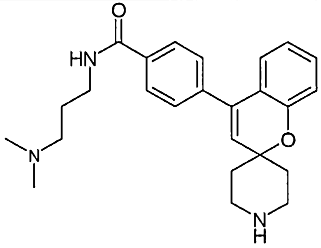
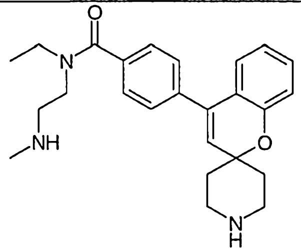
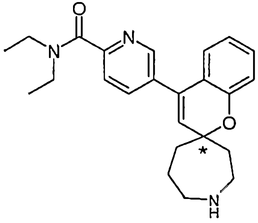
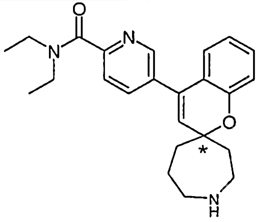
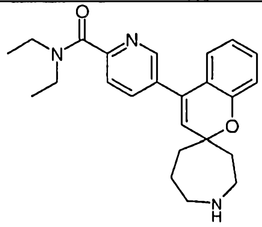
TABLE 2

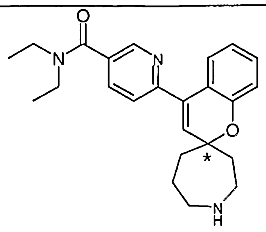
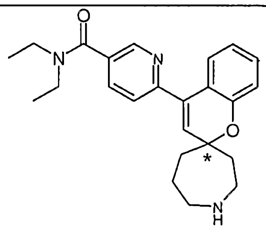
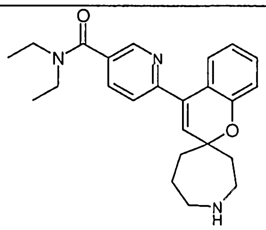
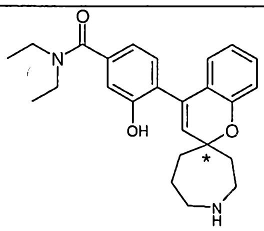
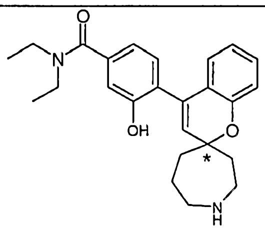
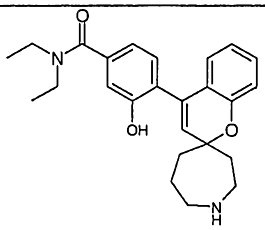
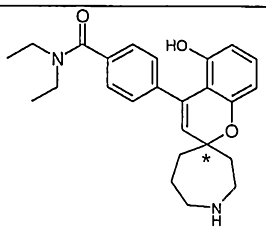
Example	*Structure*	$[M+H]^+$
7D		446.4
7E		462.4
11G		443.3
11H		444.3
11I		429.3
22F		483.2

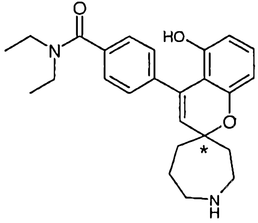
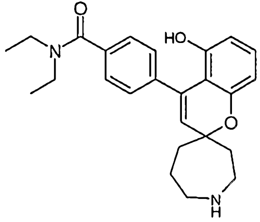
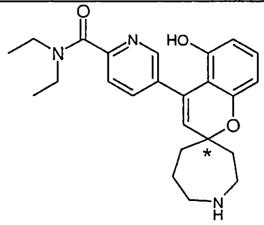
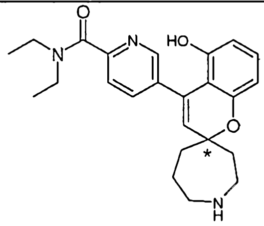
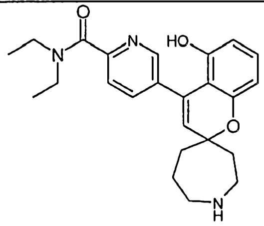
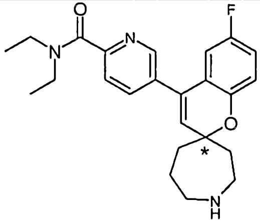
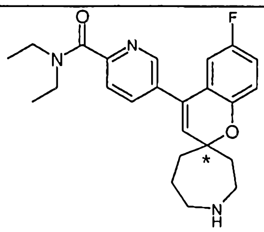
Example	*Structure*	[M+H]$^+$
33M		320.1
33N		382.4
38A		394.3
38B		396.4
38C		409.7
38D		411.7

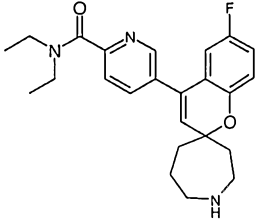
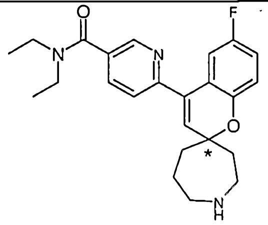
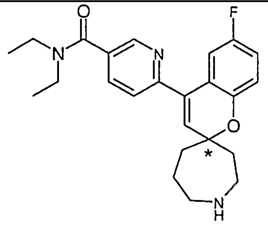
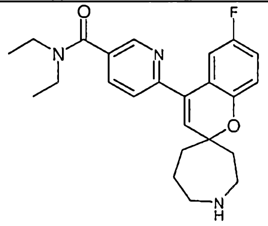
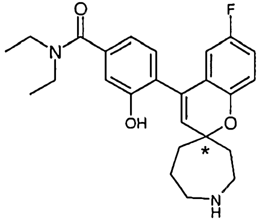
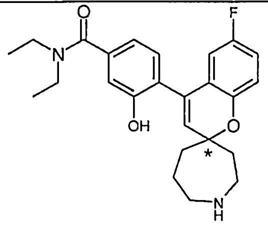
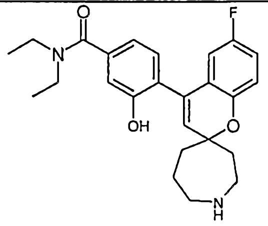
Example	*Structure*	[M+H]+
39A		378.3
39B		378.8
39C		378.8
39D		391.4
39E		393.4
39F		393.8

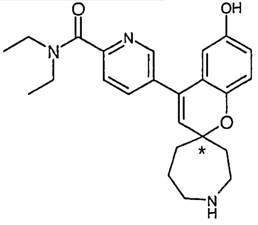
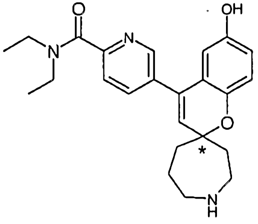
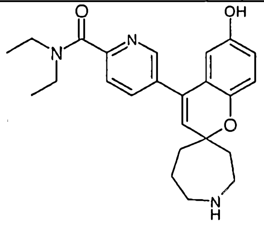
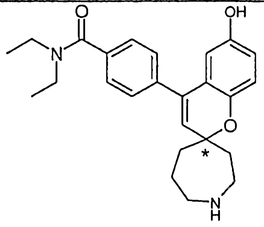
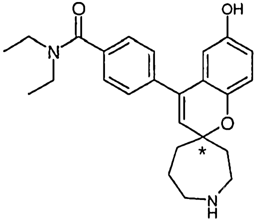
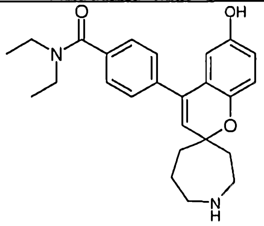
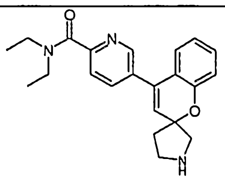
Example	*Structure*	[M+H]$^+$
39G		393.8
40A		406.3
40B		408.5
40C		421.3
41A		407.4
41B		420.3

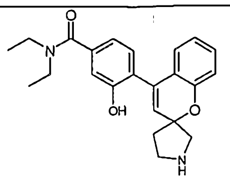
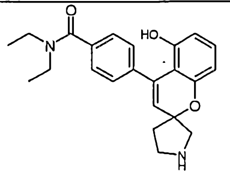
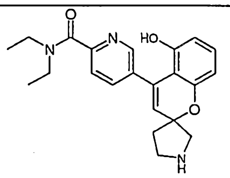
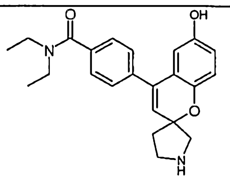
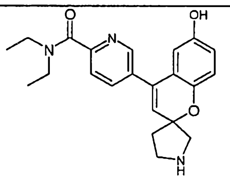
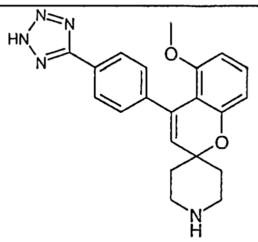
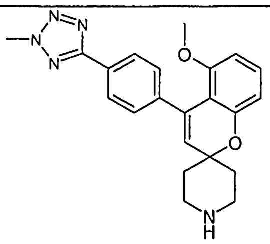
Example	*Structure*	[M+H]+
41C		420.3
41D		406.4
41E		406.8
42A		392.3
42B		392.3
42C		392.4

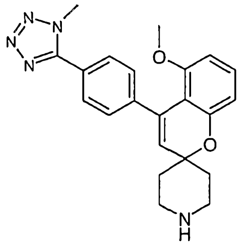
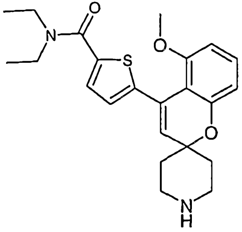
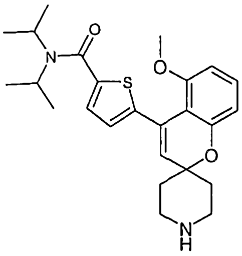
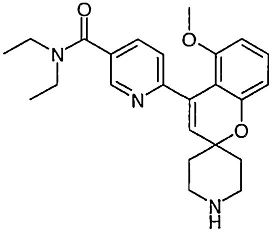
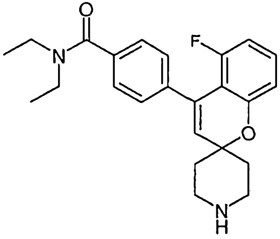
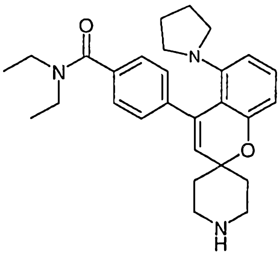
Example	*Structure*	[M+H]$^+$
42D		392.8
42E		392.8
42F		392.4
42G		407.7
42H		407.8
42I		407.4
43A		407.3

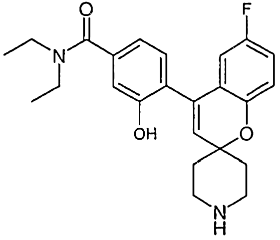
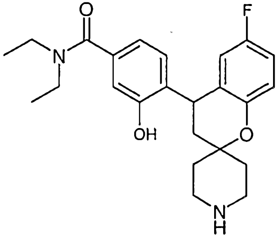
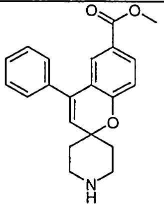
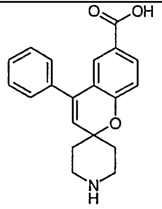
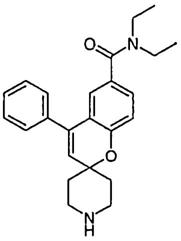
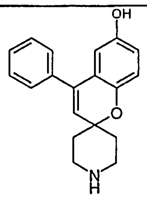
Example	*Structure*	$[M+H]^+$
43B		407.3
43C		407.4
43D		408.3
43E		408.3
43F		408.4
44A		410.3
44B		410.8

Example	*Structure*	[M+H]+
44C		410.4
44D		410.8
44E		410.8
44F		410.4
45A		425.8
45B		425.8
45C		425.4

Example	*Structure*	$[M+H]^+$
45D		408.3
45E		408.8
45F		408.4
46A		407.4
46B		407.4
46C		407.4
47A		364.7

Example	*Structure*	[M+H]+
47B		379.8
47C		379.3
47D		380.4
47E		379.8
47F		380.7
48A		376.3
48B		390.5

Example	*Structure*	[M+H]+
48C		390.4
48D		413.7
48E		441.4
48F		408.4
49A		395.3
49B		446.8

Example	*Structure*	[M+H]$^+$
49C		411.7
49D		413.7
50A		336.4
50B		322.1
50C		377.7
50D		294.1

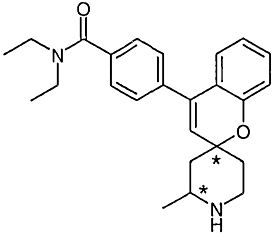
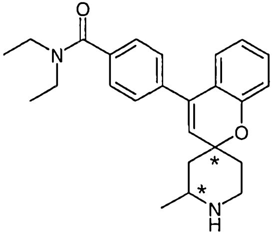
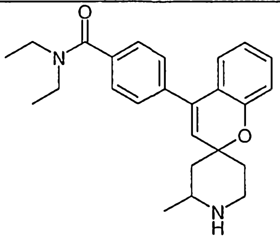
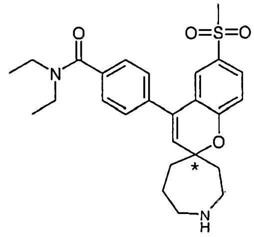
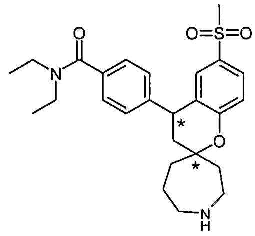
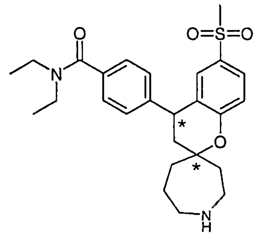
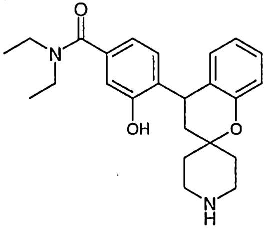
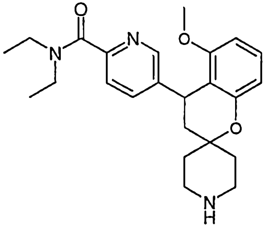
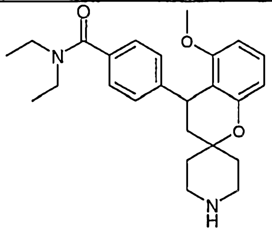
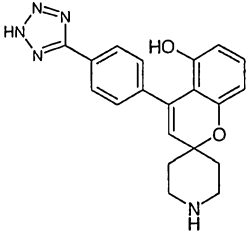
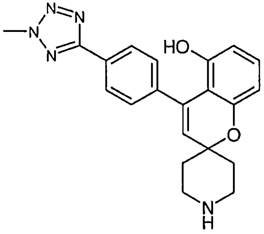
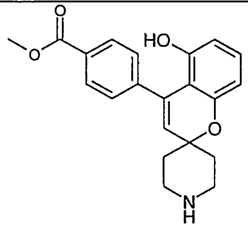
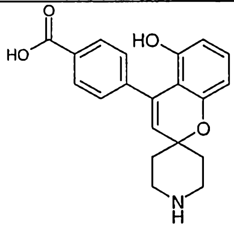
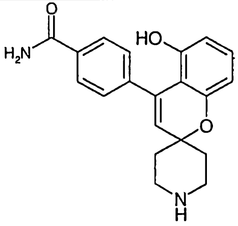
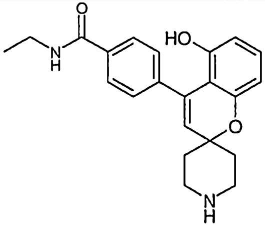
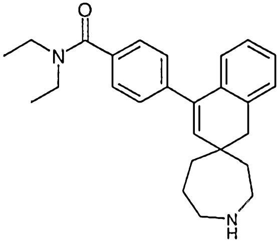
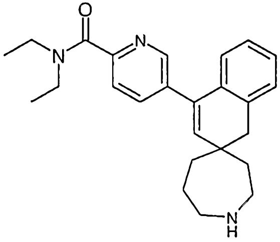
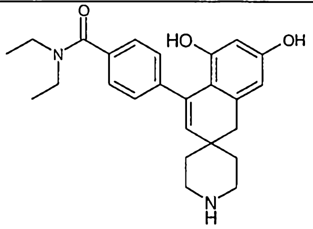
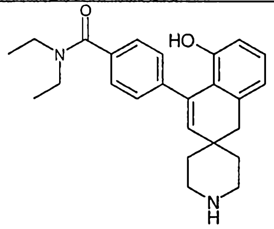
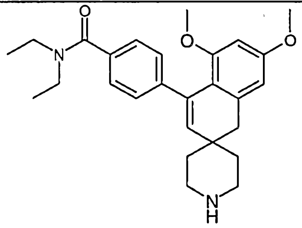
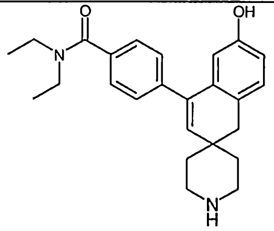
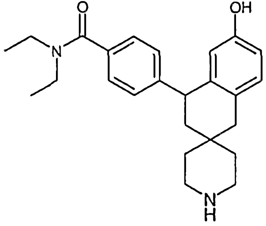
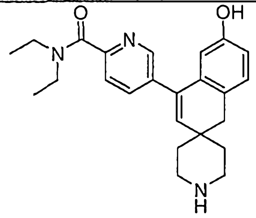
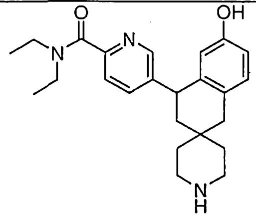
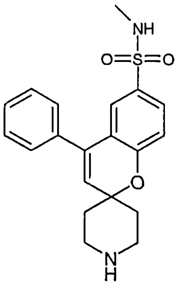
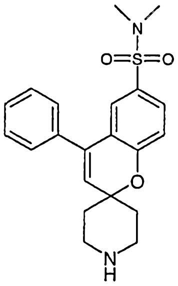
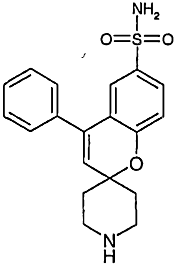
Example	*Structure*	[M+H]+
51A		391.4
51B		391.4
51C		391.4

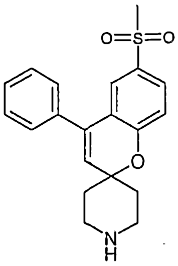
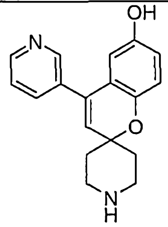
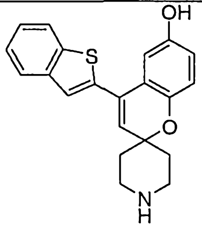
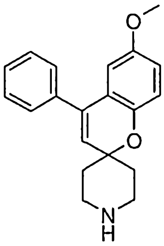
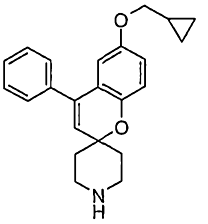
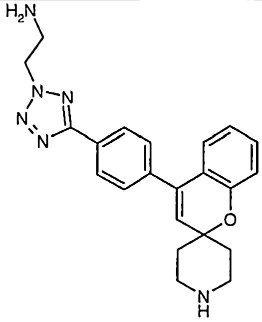
TABLE 3

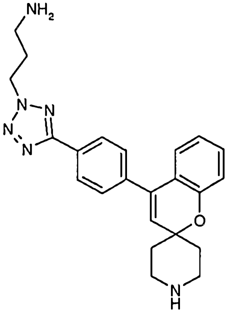
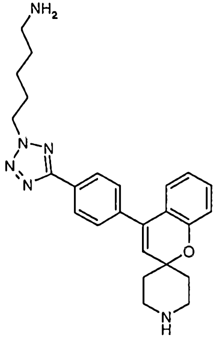
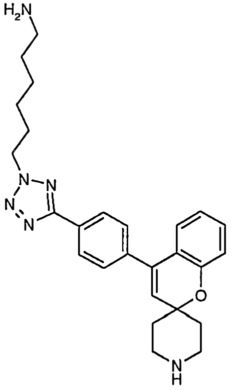
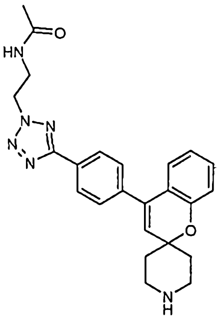
Example	Structure	[M+H]$^+$
52A		469.4
52B		
52C		
52D		
52E		
52F		

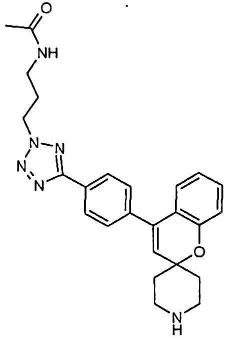
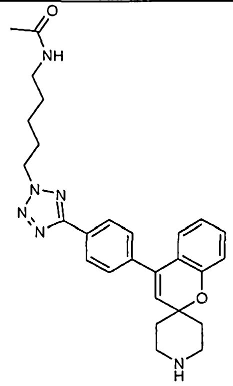
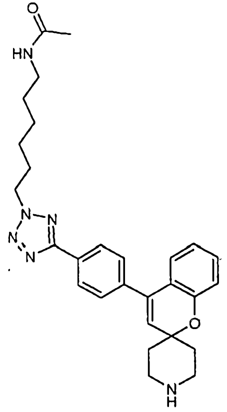
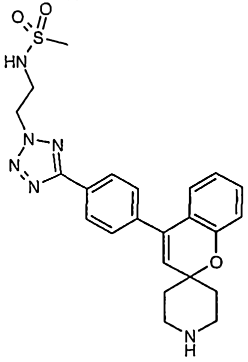
Example	*Structure*	[M+H]+
53A		360.8 (note: [M-H]-)
53B		376.8
53C		352.7
53D		338.7
53E		
53F		365.8

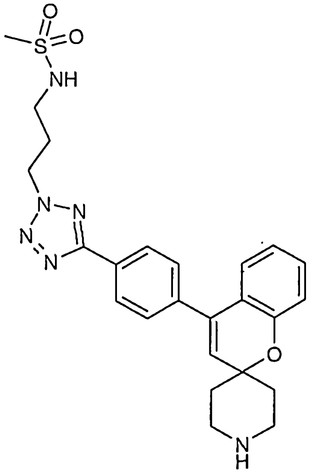
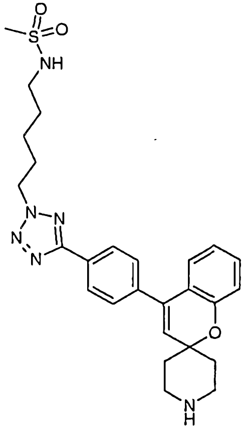
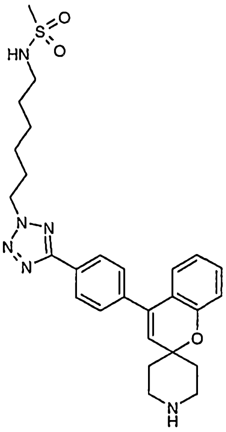
Example	*Structure*	[M+H]+
54A		389.9
54B		390.8
55A		407.5
55B		391.5
55C		435.7
56A		391.4

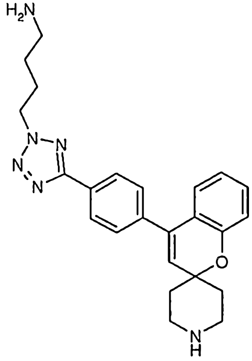
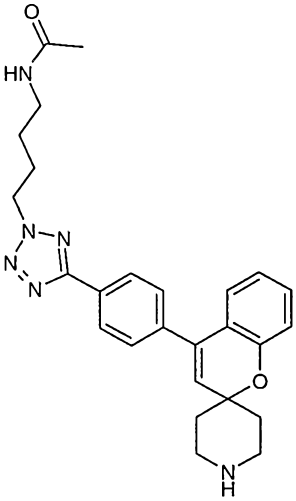
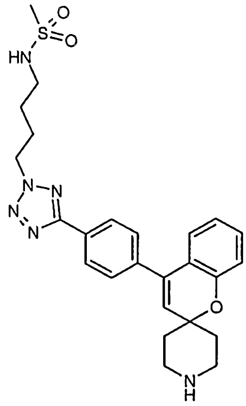
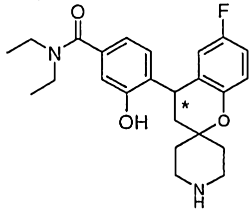
Example	*Structure*	[M+H]$^+$
56B		393.5
56C		392.4
56D		394.5
57A		
57B		
57C		

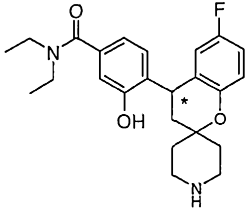
Example	*Structure*	[M+H]+
57D		356.3
58A		295.3
58B		350.3
58C		308.2
58D		348.2
59A		389.4

Example	*Structure*	[M+H]$^+$
59B		403.4
59C		431.5
59D		445.5
59E		431.5

Example	*Structure*	[M+H]$^+$
59F		445.5
59G		473.5
59H		487.5
59I		467.3

Example	*Structure*	[M+H]$^+$
59J		481.5
59K		509.5
59L		523.6

Example	*Structure*	[M+H]+
60A		417.5
60B		459.5
60C		495.5
61A		413.9

Example	*Structure*	[M+H]+
61B		413.8

[0373] **39B** and **39C** are enantiomeric with respect to one another, but their absolute stereochemistry has not been conclusively established.

[0374] **39F** and **39G** are enantiomeric with respect to one another, but their absolute stereochemistry has not been conclusively established.

[0375] **42A** and **42B** are enantiomeric with respect to one another, but their absolute stereochemistry has not been conclusively established.

[0376] **42D** and **42E** are enantiomeric with respect to one another, but their absolute stereochemistry has not been conclusively established.

[0377] **42G** and **42H** are enantiomeric with respect to one another, but their absolute stereochemistry has not been conclusively established.

[0378] **43A** and **43B** are enantiomeric with respect to one another, but their absolute stereochemistry has not been conclusively established.

[0379] **43D** and **43E** are enantiomeric with respect to one another, but their absolute stereochemistry has not been conclusively established.

[0380] **44A** and **44B** are enantiomeric with respect to one another, but their absolute stereochemistry has not been conclusively established.

[0381] **44D** and **44E** are enantiomeric with respect to one another, but their absolute stereochemistry has not been conclusively established.

[0382] **45A** and **45B** are enantiomeric with respect to one another, but their absolute stereochemistry has not been conclusively established.

[0383] **45D** and **45E** are enantiomeric with respect to one another, but their absolute stereochemistry has not been conclusively established.

[0384] **46A** and **46B** are enantiomeric with respect to one another, but their absolute stereochemistry has not been conclusively established.

[0385] **51A** and **51B** are resolvable by chiral column chromatography as individual peaks with respect to one another, but their absolute stereochemistry has not been conclusively established.

[0386] **61A** and **61B** are enantiomeric with respect to one another, but their absolute stereochemistry has not been conclusively established.

Experimental Section

Introduction

[0387] **Materials**: All chemicals were reagent grade and used without further purification.

[0388] **Analytical**: Thin-layer chromatography (TLC) was performed on silica gel 60 flexible backed plates (250 microns) from Alltech and visualized by UV 254 irradiation and iodine. Flash chromatography was conducted using the ISCO CombiFlash with RediSep silica gel cartridges (4 g, 12 g, 40 g, 120 g). Flash chromatography was also conducted with silica gel (200-400 mesh, 60Å, Aldrich). Chromatographic elution solvent systems are reported as volume:volume ratios. All ^{1}H NMR spectra were recorded at ambient temperature on a Bruker-400 MHz spectrometer. They are reported in ppm on the δ scale, from TMS. LC-MS data were obtained using a Thermo-Finnigan Surveyor HPLC and a Thermo-Finnigan AQA MS using either positive or negative electrospray ionization. Program (positive) Solvent A: 10 mM ammonium acetate, pH 4.5, 1% acetonitrile; solvent B: acetonitrile; column: Michrom Bioresources Magic C18 Macro Bullet, detector: PDA $\lambda = 220\text{-}300$ nm. Gradient: 96%A-100%B in 3.2 minutes, hold 100%B for 0.4 minutes. Program (negative) Solvent A: 1 mM ammonium acetate, pH 4.5, 1% acetonitrile; solvent B: acetonitrile; column: Michrom Bioresources Magic C18 Macro Bullet, detector: PDA $\lambda = 220\text{-}300$ nm. Gradient: 96%A-100%B in 3.2 minutes, hold 100%B for 0.4 minutes.

[0389] The compounds set forth in Tables 1 and 2 are actual examples. The compounds set forth in Table 3 include actual and prophetic examples for which schemes and general procedure descriptions are set forth herein.

EXAMPLE 1A

Preparation of **1.3a**:

[0390] Method 1A: Pyrrolidine (6.12 mL, 73.38 mmol, 2.0 eq) was added at room temperature to **1.2** (7.31 g, 36.69 mmol, 1.0 eq) and **1.1a** (5.00 g, 36.69 mmol, 1.0 eq). The solution was stirred overnight at room temperature and then concentrated under reduced pressure. Diethyl ether (500 mL) was added. The organic mixture was washed with a 1N aqueous solution of hydrochloric acid, a 1N aqueous solution of sodium hydroxide, brine and dried over sodium sulfate. Hexane (300 mL) was added to the mixture. The resulting precipitate was collected by filtration, washed with hexane and used for the next step without further purification.

Yield: 68%

[0391] Method 1B: Pyrrolidine (42 mL, 73.38, 2.0 eq) was added drop wise at room temperature to a solution of **1.2** (49.8 g, 0.249 mol, 1.0 eq) and **1.1a** (34 g, 0.184 mol, 1.0 eq) in anhydrous methanol (400 mL). The solution was refluxed overnight and then concentrated under reduced pressure. Diethyl ether (500 mL) was added. The organic mixture was washed with a 1N aqueous solution of hydrochloric acid, a 1N aqueous solution of sodium hydroxide, brine and dried over sodium sulfate. Hexane (300 mL) was added to the mixture. The resulting precipitate was collected by filtration, washed with hexane, and used for the next step without further purification.

Yield: 72%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.86 (d, 1H), 7.50 (t, 1H), 7.00 (m, 2H), 3.87 (m, 2H), 3.22 (m, 2H), 2.72 (s, 2H), 2.05 (d, 2H), 1.61 (m, 2H), 1.46 (s, 9H)

Mass Spectral Analysis *m/z* = 318.0 $(M+H)^+$

Preparation of **1.5a**:

[0392] To a solution of **1.3a** (25 g, 0.078 mol, 1.0 eq) in tetrahydrofuran (250 mL) at -78°C under nitrogen was added drop wise a 1.0M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (94.5 mL, 0.095 mol, 1.2 eq). The mixture was stirred for 1h at -78°C. A solution of **1.4** (33.8 g, 0.095 mol, 1.2 eq) in tetrahydrofuran (150 mL) was added drop wise. The mixture was warmed slowly to room temperature and stirring was continued for a further 12h. The mixture was then poured into ice water and the two phases were separated. The organic phase was washed with a 1N aqueous solution of hydrochloric acid, a 1N aqueous solution of sodium hydroxide, brine and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 70%

^{1}H NMR (400MHz, DMSO d$_6$) □ 7.45-7.20 (m, 2H), 7.00 (m, 2H), 6.15 (s, 1H), 3.70 (m, 2H), 3.20 (m, 2H), 1.90 (m, 2H), 1.75 (m, 2H), 1.40 (s, 9H)
Mass Spectral Analysis *m/z* = 450.1 (M+H)$^+$

Preparation of **1.8a**:

[0393] Method 1C: To a solution of **1.5a** (15 g, 33.37 mmol, 1.0 eq) in dimethoxyethane (100 mL) was added sequentially a 2N aqueous solution of sodium carbonate (50.06 mL, 100.12 mmol, 3.0 eq), lithium chloride (4.24 g, 100.12 mmol, 3.0 eq), **1.6** (8.12 g, 36.71 mmol, 1.1 eq) and tetrakis(triphenylphosphine)palladium(0) (0.77 g, 0.67 mmol, 0.02 eq). The mixture was refluxed for 10h under nitrogen. The mixture was then cooled to room temperature and water (250 mL) was added. The mixture was extracted with ethyl acetate. The organic layer was further washed with brine and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 73%

[0394] Method 1D: To a solution of **1.5a** (10 g, 22.25 mmol, 1.0 eq) in dimethoxyethane (67 mL) was added sequentially a 2N aqueous solution of sodium carbonate (33.37 mL, 66.75 mmol, 3.0 eq), lithium chloride (2.83 g, 66.75 mmol, 3.0 eq), **1.6** (4.40 g, 24.47 mmol, 1.1 eq) and palladium, 10 weight % (dry basis) on activated carbon, wet, Degussa type E101 NE/W (0.24 g, 0.11 mmol, 0.005 eq). The mixture was refluxed for 2h under nitrogen. The mixture was then cooled to room temperature and diluted with dichloromethane (350 mL). The mixture was filtered through a celite plug and dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was triturated with diethyl ether. The precipitate was collected by filtration.

Yield: 60%

^{1}H NMR (400MHz, CDCl$_3$) δ 7.35 (m, 4H), 7.15 (t, 1H), 7.00-6.80 (m, 3H), 5.55 (s, 1H), 3.85 (m, 2H), 3.55 (m, 2H), 3.30 (m, 4H), 2.00 (m, 2H), 1.65 (m, 2H), 1.40 (s, 9H); 1.20 (m, 6H)

Mass Spectral Analysis *m/z* = 477.2 (M+H)$^+$

Preparation of **1A**:

[0395] Method 1E: A 2.0M solution of hydrochloric acid in diethyl ether (34.6 mL, 69.24 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **1.8a** (6.00 g, 12.59 mmol, 1.0 eq) in anhydrous dichloromethane (70 mL). The mixture was warmed to room temperature and stirring was continued for an additional 10h. Diethyl ether (100 mL) was added to the solution and the resulting precipitate was collected by filtration and washed with diethyl ether.

Yield: 99%

[0396] Method 1F: Trifluoroacetic acid (10.33 mL, 134.09 mmol, 5.5 eq) was added drop wise to a cold (0°C) solution of **1.8a** (11.62 g, 24.38 mmol, 1.0 eq) in anhydrous dichloromethane (50 mL). The mixture was warmed to room temperature and stirring was continued for an additional 10h. The mixture was then concentrated under reduced pressure. A saturated solution of sodium bicarbonate (100 mL) was added to the mixture, which was extracted with dichloromethane. The organic phase was separated, washed with brine, dried over sodium sulfate and concentrated under reduced pressure. To a cold (0°C) solution of the resulting oil in anhydrous dichloromethane was added drop wise a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (36.5 mL, 0.073 mol, 3.0 eq). The mixture was then stirred for 1h at room temperature and concentrated under reduced pressure. Diethyl ether was added. The resulting precipitate was collected by vacuum filtration and washed with diethyl ether.

Yield: 99%

^{1}H NMR (400MHz, DMSO d_6) δ 9.06 (m, 2H), 7.43 (s, 4H), 7.27 (t, 1H), 7.00 (m, 3H), 5.95 (s, 1H), 3.45 (m, 2H), 3.23 (m, 6H), 2.00 (m, 4H), 1.12 (m, 6H)

Mass Spectral Analysis *m/z* = 377.4 $(M+H)^+$

Elemental analysis:

$C_{24}H_{28}N_2O_2$, 1HCl

Theory: %C 69.80; %H 7.08; %N 6.78

Found: %C 69.73; %H 7.04; %N 6.81

EXAMPLE 1B

[0397] **1B** was obtained according to a procedure similar to the one described for **1A**, with the following exceptions:

Step 1.1: **1.1a** was replaced by **1.1b** and Method 1B was used.

Step 1.3: Method 1C was used.

Step 1.4: Method 1E was used.

^{1}H NMR (400MHz, DMSO d_6) δ 8.97 (m, 2H), 7.42 (m, 4H), 6.98 (m, 1H), 6.86 (m, 1H), 6.49 (m, 1H), 5.99 (s, 1H), 3.62 (m, 3H), 3.50 (m, 2H), 3.21 (m, 6H), 2.06 (m, 4H), 1.11 (m, 6H) Mass Spectral Analysis *m/z* = 407.1 $(M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_2O_3$, 1HCl, 1.25H_2O

Theory: %C 64.51; %H 7.25; %N 6.02

Found: %C 64.53; %H 7.11; %N 5.89

EXAMPLE 1C

[0398] **1C** was obtained according to a procedure similar to the one described for **1A**, with the following exceptions:

Step 1.1: **1.1a** was replaced by **1.1c** and Method 1A was used.

Step 1.3: Method 1C was used.

Step 1.4: Method 1E was used.

^{1}H NMR (400MHz, DMSO d_6) δ 9.05 (m, 1.5H), 7.45 (s, 4H), 7.30 (d, 1H), 7.10 (d, 1H), 6.90 (s, 1H), 6.00 (s, 1H), 3.1–3.55 (m, 8H), 2.05 (m, 4H), 1.10 (m, 6H)

Mass Spectral Analysis *m/z* = 411.2 $(M+H)^+$

EXAMPLE 1D

[0399] **1D** was obtained according to a procedure similar to the one described for **1A**, with the following exceptions:

Step 1.1: **1.1a** was replaced by **1.1d** and Method 1B was used.

Step 1.3: Method 1D was used.

Step 1.4: Method 1E was used.

^{1}H NMR (400MHz, DMSO d_6) δ 8.95 (m, 1H), 7.40 (s, 4H), 7.10 (m, 2H), 6.70 (m, 1H), 6.05 (s, 1H), 3.10-3.50 (m, 8H), 2.00 (m, 4H), 1.10 (m, 6H)

Mass Spectral Analysis *m/z* = 395.2 $(M+H)^+$

EXAMPLE 1E

[0400] **1E** was obtained according to a procedure similar to the one described for **1A**, with the following exceptions:

Step 1.1: **1.1a** was replaced by **1.1e** and Method 1A was used.

Step 1.3: Method 1D was used.

Step 1.4: Method 1E was used.

^{1}H NMR (400MHz, DMSO d$_6$) δ 8.92 (brm, 1H), 7.42 (s, 4H), 7.07 (dd, 1H), 6.94 (d, 1H), 6.79 (d, 1H), 5.92 (s, 1H), 3.45 (brs, 2H), 3.22 (brm, 6H), 2.18 (s, 3H), 2.08 (m, 2H), 1.97 (m, 2H), 1.12 (brd, 6H)

Mass Spectral Analysis *m/z* = 391.3 (M+H)$^+$

Elemental analysis:

$C_{25}H_{30}N_2O_2$, 1HCl, 1.5H_2O

Theory: %C 66.13; %H 7.55; %N 6.17

Found: %C 65.73; %H 7.38; %N 6.05

EXAMPLE 1F

[0401] **1F** was obtained according to a procedure similar to the one described for **1A**, with the following exceptions:

Step 1.1: **1.1a** was replaced by **1.1f** and Method 1B was used.

Step 1.3: Method 1C was used.

Step 1.4: Method 1F was used.

^{1}H NMR (400MHz, DMSO d$_6$) δ 8.90 (m, 2H), 7.25 (m, 5H), 6.71 (m, 1H), 6.64 (m, 1H), 5.81 (s, 1H), 3.45 (m, 2H), 3.39 (m, 3H), 3.20 (m, 6H), 2.00 (m, 4H), 1.09 (m, 6H)

Mass Spectral Analysis *m/z* = 407.2 (M+H)$^+$

Elemental analysis:

$C_{25}H_{30}N_2O_3$, 1HCl, 2H_2O

Theory: %C 62.69; %H 7.36; %N 5.85

Found: %C 62.78; %H 6.90; %N 5.61

EXAMPLE 1G

[0402] **1G** was obtained according to a procedure similar to the one described for **1A**, with the following exceptions:

Step 1.1: **1.1a** was replaced by **1.1g** and Method 1B was used.

Step 1.3: Method 1C was used.

Step 1.4: Method 1E was used.

^{1}H NMR (400MHz, DMSO d$_6$) δ 8.95 (m, 1H), 8.85 (m, 1H), 7.38 (m, 4H), 6.89 (m, 1H), 6.68 (m, 1H), 6.54 (m, 1H), 5.78 (s, 1H), 3.76 (m, 3H), 3.45 (m, 2H), 3.21 (m, 6H), 2.09 (m, 2H), 1.98 (m, 2H), 1.11 (m, 6H)

Mass Spectral Analysis *m/z* = 407.1 $(M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_2O_3$, 1HCl, 0.5H_2O

Theory: %C 66.43; %H 7.14; %N 6.20

Found: %C 66.25; %H 7.19; %N 6.11

EXAMPLE 1H

[0403] **1H** was obtained according to a procedure similar to the one described for **1A**, with the following exceptions:

Step 1.1: **1.1a** was replaced by **1.1h** and Method 1B was used.

Step 1.3: Method 1D was used.

Step 1.4: Method 1E was used.

^{1}H NMR (400MHz, DMSO d$_6$) δ 8.80 (brm, 1H), 8.33 (d, 1H), 7.90 (m, 1H), 7.58 (m, 2H), 7.51 (d, 1H), 7.46 (d, 4H), 7.16 (d, 1H), 5.97 (s, 1H), 3.46 (brs, 2H), 3.30 (brm, 6H), 2.25 (d, 2H), 2.05 (m, 2H), 1.13 (brd, 6H)

Mass Spectral Analysis *m/z* = 427.4 $(M+H)^+$

Elemental analysis:

$C_{28}H_{30}N_2O_2$, 1HCl, 1.5H_2O

Theory: %C 68.63; %H 6.99; %N 5.72

Found: %C 68.96; %H 6.82; %N 5.75

EXAMPLE 1I

[0404] **1I** was obtained according to a procedure similar to the one described for **1A**, with the following exceptions:

Step 1.1: **1.1a** was replaced by **1.1i** and Method 1B was used.

Step 1.3: Method 1D was used.

Step 1.4: Method 1E was used.

^{1}H NMR (400MHz, DMSO d_6) δ 8.90 (brm, 1H), 7.94 (d, 1H), 7.87 (d, 1H), 7.37 (m, 3H), 7.28 (t, 1H), 7.24 (d, 2H), 7.10 (t, 1H), 6.96 (d, 1H), 6.04 (s, 1H), 3.44 (brs, 2H), 3.23 (brs, 6H), 2.09 (brm, 4H), 1.12 (brd, 6H)

Mass Spectral Analysis *m/z* = 427.4 $(M+H)^+$

Elemental analysis:

$C_{28}H_{30}N_2O_2$, 1HCl, $0.67H_2O$

Theory: %C 70.80; %H 6.86; %N 5.90

Found: %C 70.57; %H 6.72; %N 5.83

EXAMPLE 1J

[0405] **1J** was obtained according to a procedure similar to the one described for **1A**, with the following exceptions:

Step 1.1: **1.1a** was replaced by **1.1j** and Method 1A was used.

Step 1.3: Method 1D was used.

Step 1.4: Method 1E was used.

^{1}H NMR (400MHz, DMSO d_6) δ 9.09 (brm, 1H), 7.41 (s, 4H), 6.87 (s, 1H), 6.75 (s, 1H), 5.84 (s, 1H), 3.45 (brs, 2H), 3.20 (brm, 6H), 2.19 (s, 3H), 2.08 (s, 3H), 2.05 (m, 2H), 1.97 (m, 2H), 1.12 (brd, 6H)

Mass Spectral Analysis *m/z* = 405.4 $(M+H)^+$

Elemental analysis:

$C_{26}H_{32}N_2O_2$, 1HCl, $0.5H_2O$

Theory: %C 69.39; %H 7.62; %N 6.22

Found: %C 69.22; %H 7.49; %N 6.24

EXAMPLE 1K

[0406] **1K** was obtained according to a procedure similar to the one described for **1A**, with the following exceptions:

Step 1.1: **1.1a** was replaced by **1.1k** and Method 1B was used.

Step 1.3: Method 1C was used.

Step 1.4: Method 1F was used.

^{1}H NMR (400MHz, DMSO d_6) δ 9.25 (m, 1H), 7.40 (m, 4H), 7.35 (m, 1H), 6.61 (s, 1H), 3.25 (m, 8H), 2.06 (m, 4H), 1.02 (m, 6H)

Mass Spectral Analysis *m/z* = 413.2 $(M+H)^+$

EXAMPLE 1L

[0407] **1L** was obtained according to a procedure similar to the one described for **1A**, with the following exceptions:

Step 1.1: **1.1a** was replaced by **1.1l** and Method 1B was used.

Step 1.3: Method 1D was used.

Step 1.4: Method 1E was used.

^{1}H NMR (400MHz, DMSO d$_6$) δ 8.84 (brs, 1H), 7.41 (d, 4H), 6.96 (s, 1H), 6.61 (s, 1H), 5.86 (s, 1H), 3.45 (brs, 2H), 3.20 (brm, 6H), 2.23 (s, 3H), 2.13 (s, 3H), 2.08 (m, 2H), 1.96 (m, 2H), 1.12 (brd, 6H)

Mass Spectral Analysis *m/z* = 405.4 $(M+H)^+$

Elemental analysis:

$C_{26}H_{32}N_2O_2$, 1HCl, $0.5H_2O$

Theory: %C 69.39; %H 7.62; %N 6.22

Found: %C 69.69; %H 7.56; %N 6.28

EXAMPLE 1M

[0408] **1M** was obtained according to a procedure similar to the one described for **1A**, with the following exceptions:

Step 1.1: **1.1a** was replaced by **1.1m** and Method 1B was used.

Step 1.3: Method 1C was used.

Step 1.4: Method 1E was used.

^{1}H NMR (400MHz, DMSO d$_6$) δ 9.05 (m, 2H), 7.46 (m, 2H), 7.20 (m, 3H), 7.01 (m, 1H), 6.82 (m, 1H), 6.48 (m, 1H), 3.45 (m, 2H), 3.28 (m, 6H), 2.24 (m, 2H), 2.06 (m, 2H), 1.60 (m, 3H), 1.12 (m, 6H)

Mass Spectral Analysis *m/z* = 391.0 $(M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_2O_2$, 1HCl, $0.25H_2O$

Theory: %C 69.59; %H 7.36; %N 6.49

Found: %C 69.25; %H 7.29; %N 6.58

EXAMPLE 1N

Preparation of **1.10**:

[0409] To an oven-dried 2-necked 500 mL flask charged with anhydrous toluene (90 mL) at -78°C was added *n*-butyl lithium (2.5 M solution in hexane, 40 mL, 0.1 mol, 1.0 eq). A solution of 2,5-dibromo-pyridine (**1.9**) (23.69 g, 0.1 mol, 1.0 eq) in anhydrous toluene (50 mL) was added dropwise. The reaction mixture was stirred at
-78°C for 2h and then poured onto freshly crushed dry-ice (~ 500 g). The dry-ice mixture was then left at room temperature for 10h. The volatiles were removed under reduced pressure and the residue was dissolved in water. The insoluble solids were filtered and the filtrate was acidified to pH 2, at which point a light brown solid precipitated out. The solids were collected by filtration and recrystallized from acetic acid (500 mL). This provided **1.10** isolated as its acetic acid salt.

Yield: 74%

^{1}H NMR (400MHz, DMSO d_6) δ 8.84 (d, 1H), 8.25 (dd, 1H), 7.98 (d, 1H)

Mass Spectral Analysis *m/z* = 202.06 $(M+H)^+$

Preparation of **1.11**:

[0410] To a suspension of 5-bromo-pyridine-2-carboxylic acid (**1.10**) (808 mg, 3.01 mmol, 1.0 eq) in dry dichloromethane (5 mL) was added oxalyl chloride (0.34 mL, 3.96 mmol, 1.3 eq) followed by 2 drops of *N,N*-dimethylformamide. The reaction mixture was heated under reflux for 1h. After cooling to room temperature, the mixture was concentrated under reduced pressure to provide the crude product **1.11,** which was used for the next step without purification.

Preparation of **1.13**:

[0411] To a suspension of **1.11** (crude, as of 3.01 mmol, 1.0 eq) in dry tetrahydrofuran (5 mL) was added *N,N*-diethylamine (**1.12**) (1.56 mL, 15.08 mmol, 5.0 eq) drop wise. The reaction mixture was stirred at room temperature for 2h. Ethyl acetate (20 mL) was added and the mixture was washed with water (20 mL), saturated aqueous sodium bicarbonate (30 mL), 1M aqueous hydrochloric acid (20 mL) and brine. The organics were dried over sodium sulfate, filtered and concentrated under reduced pressure to give a red/brown crystalline solid.

Yield: 88% over two steps

^{1}H NMR (400MHz, $CDCl_3$) δ 8.64 (d, 1H), 7.91 (dd, 1H), 7.53 (d, 1H), 3.56 (q, 2H), 3.39 (q, 2H), 1.27 (t, 3H), 1.17 (t, 3H)

Mass Spectral Analysis *m/z* = 257.15 $(M+H)^+$

Preparation of **1.7**:

[0412] To a solution of bis(pinacolato)diboron (**1.14**) (2.18 g, 8.6 mmol, 1.2 eq) in *N,N*-dimethylformamide (10 mL) at 0°C was added potassium acetate (2.3 g, 23.4 mmol, 3.0 eq), 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride complex with dichloromethane (171 mg, 0.23 mmol, 0.03 eq). The reaction mixture was heated at 80°C at which point a solution of **1.13** (2.0 g, 7.8 mmol, 1.0 eq) in *N,N*-dimethylformamide (10 mL) was added dropwise. The reaction mixture was stirred at 80°C for another 10h. Ethyl acetate (75 mL) and water (50 mL) were added and the two phases were separated. The organic phase was washed with brine (50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a dark brown oil, which solidified to needles. The crude product was triturated with hexane. The resulting solid was collected by filtration.

Yield: 52 %

^{1}H NMR (400MHz, $CDCl_3$) δ 8.92 (d, 1H), 8.14 (dd, 1H), 7.53 (d, 1H), 3.55 (q, 2H), 3.32 (q, 2H), 1.36 (s, 12H), 1.27 (t, 3H), 1.12 (t, 3H)

Preparation of **1.8b**:

[0413] To a solution of **1.5a** (1.48 g, 3.29 mmol, 1.0 eq) in dimethoxyethane (DME) (20 mL) under nitrogen was added sequentially a 2M aqueous solution of sodium carbonate (4.94 mL, 9.87 mmol, 3.0 eq), lithium chloride (0.42 g, 9.87 mmol, 3.0 eq), palladium (70 mg, 10 wt. % (dry basis) on activated carbon, 0.033 mmol, 0.01 eq), and **1.7** (1.0 g, 3.29 mmol, 1.0 eq). The mixture was heated under reflux for 10h. Dichloromethane (200 mL) was added to dilute the reaction mixture and palladium(0) on carbon was filtered off on a celite pad. The filtrate was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure.

The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 76%

^{1}H NMR (400MHz, $CDCl_3$) δ 8.56 (dd, 1H), 7.75 (dd, 1H), 7.64 (dd, 1H), 7.22 (m, 1H), 6.99–6.85 (m, 3H), 5.62 (s, 1H), 3.88 (m, 2H), 3.59 (q, 2H), 3.45 (q, 2H), 3.34 (m, 2H), 2.06 (m, 2H), 1.69 (m, 2H), 1.48 (s, 9H), 1.29 (t, 3H), 1.20 (t, 3H)

Mass Spectral Analysis *m/z* = 478.0 $(M+H)^+$

Preparation of **1N**:

[0414] To a cold (0°C) solution of **1.8b** (2 g, 4.18 mmol, 1.0 eq) in anhydrous dichloromethane (20 mL) was slowly added a 4.0 M solution of hydrogen chloride in dioxane (5.2 mL, 20.8 mmol, 5.0 eq). The reaction mixture was stirred at room temperature for 10h and then concentrated under reduced pressure. The resulting foamy solids were soaked in diethyl ether to give the fine powders, which were collected by filtration and washed sequentially with ethyl acetate and diethyl ether.

Yield: 95%

^{1}H NMR (400MHz, DMSO d_6) δ 8.99 (m, 2H), 8.60 (d, 1H), 7.90 (dd, 1H), 7.61 (d, 1H), 7.29 (m, 1H), 7.06 (d, 1H), 6.98 (m, 2H), 6.09 (s, 1H), 3.47 (q, 2H), 3.35–3.13 (m, 6H), 2.06 (m, 4H), 1.17 (t, 3H), 1.11 (t, 3H)

Mass Spectral Analysis *m/z* = 378.4 $(M+H)^+$

Elemental analysis:

$C_{23}H_{27}N_3O_2$, 2HCl, $0.5H_2O$

Theory: %C 60.13; %H 6.58; %N 9.15

Found: %C 60.34; %H 6.60; %N 9.10

EXAMPLE 1O

[0415] **1O** was obtained according to a procedure similar to the one described for **1N**, with the following exception:

Step 1.1: **1.1a** was replaced by **1.1d**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.96 (m, 1H), 8.62 (d, 1H), 7.92 (dd, 1H), 7.61 (d, 1H), 7.12 (m, 2H), 6.78 (dd, 1H), 6.20 (s, 1H), 3.47 (q, 2H), 3.30 (q, 2H), 3.24 (m, 4H), 2.05 (m, 4H), 1.17 (t, 3H), 1.11 (t, 3H)

Mass Spectral Analysis *m/z* = 396.3 $(M+H)^+$

Elemental analysis:

$C_{23}H_{26}FN_3O_2$, 1.05HCl, $1H_2O$

Theory: %C 61.15; %H 6.48; %N 9.30; %Cl 8.24

Found: %C 61.11; %H 6.44; %N 9.18; %Cl 8.28

EXAMPLE 1P

[0416] **1P** was obtained according to a procedure similar to the one described for **1N**, with the following exception:

Step 1.1: **1.1a** was replaced by **1.1e**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.93 (brm, 1H), 8.60 (d, 1H), 7.89 (dd, 1H), 7.61 (d, 1H), 7.09 (dd, 1H), 6.96 (d, 1H), 6.77 (s, 1H), 6.07 (s, 1H), 3.47 (q, 2H), 3.30 (q, 2H), 2.21 (brm, 4H), 2.18 (s, 3H), 2.04 (brm, 4H), 1.17 (t, 3H), 1.11 (t, 3H)

Mass Spectral Analysis *m/z* = 392.3 $(M+H)^+$

Elemental analysis:

$C_{24}H_{29}N_3O_2$, 2HCl

Theory: %C 62.07; %H 6.73; %N 9.05; %Cl 15.27

Found: %C 61.81; %H 6.69; %N 8.95; %Cl 15.42

EXAMPLE 1Q

[0417] **1Q** was obtained according to a procedure similar to the one described for **1N**, with the following exceptions:

Step 1.1: **1.1a** was replaced by **1.1f** and Method 1A was used.

^{1}H NMR (400MHz, DMSO d_6) δ 9.20 (m, 2H), 8.38 (m, 1H), 7.69 (m, 1H), 7.48 (m, 1H), 7.28 (m, 1H), 6.75 (m, 1H), 6.69 (m, 1H), 5.99 (s, 1H), 3.40 (m, 5H), 3.26 (m, 6H), 2.08 (m, 4H), 1.20 (m, 3H), 1.10 (m, 3H)

Mass Spectral Analysis *m/z* = 408.3 $(M+H)^+$

Elemental analysis:

$C_{24}H_{29}N_3O_3$, 1HCl, $0.25H_2O$

Theory: %C 64.28; %H 6.85; %N 9.37; %Cl 7.91

Found: %C 64.07; %H 6.84; %N 9.23; %Cl 8.18

EXAMPLE 1R

[0418] **1R** was obtained according to a procedure similar to the one described for **1N**, with the following exception:

Step 1.1: **1.1a** was replaced by **1.1h**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.06 (brs, 0.5H), 8.90 (brs, 0.5H), 8.65 (d, 1H), 8.33 (d, 1H), 7.95 (dd, 1H), 7.91 (m, 1H), 7.64 (d, 1H), 7.59 (m, 2H), 7.53 (d, 1H), 7.14 (d, 1H), 6.11 (s, 1H), 3.48 (q, 2H), 3.32 (brm, 6H), 2.26 (d, 2H), 2.10 (m, 2H), 1.18 (t, 3H), 1.12 (t, 3H)

Mass Spectral Analysis *m/z* = 428.3 $(M+H)^+$

Elemental analysis:

$C_{27}H_{29}N_3O_2$, 1.8HCl, $1H_2O$

Theory: %C 63.44; %H 6.47; %N 8.22; %Cl 12.48

Found: %C 63.36; %H 6.22; %N 8.14; %Cl 12.87

EXAMPLE 1S

[0419] **1S** was obtained according to a procedure similar to the one described for **1N**, with the following exception:

Step 1.1: **1.1a** was replaced by **1.1j**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.89 (brm, 2H), 8.59 (d, 1H), 7.88 (dd, 1H), 7.61 (d, 1H), 6.89 (s, 1H), 6.73 (s, 1H), 5.99 (s, 1H), 3.47 (q, 2H), 3.30 (q, 2H), 3.20 (brm, 4H), 2.20 (s, 3H), 2.09 (s, 3H), 2.06 (m, 2H), 1.97 (m, 2H), 1.17 (t, 3H), 1.11 (t, 3H)

Mass Spectral Analysis *m/z* = 406.3 $(M+H)^+$

Elemental analysis:

$C_{25}H_{31}N_3O_2$, 2HCl, $2H_2O$

Theory: %C 58.36; %H, 7.25; %N 8.17 %Cl 13.78

Found: %C 58.45; %H 7.16; %N 8.16; %Cl 13.68

EXAMPLE 1T

[0420] **1T** was obtained according to a procedure similar to the one described for **1N**, with the following exception:

Step 1.1: **1.1a** was replaced by **1.1l**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.02 (brm, 1H), 8.56 (d, 1H), 7.87 (dd, 1H), 7.61 (d, 1H), 6.98 (s, 1H), 6.59 (s, 1H), 6.01 (s, 1H), 3.47 (q, 2H), 3.30 (q, 2H), 3.25 (m, 2H), 3.14 (brs, 2H), 2.24 (s, 3H), 2.15 (s, 3H), 2.09 (m, 2H), 2.02 (m, 2H), 1.17 (t, 3H), 1.11 (t, 3H)
Mass Spectral Analysis *m/z* = 406.4 $(M+H)^+$
Elemental analysis:
$C_{25}H_{31}N_3O_2$, 1.9HCl, $0.5H_2O$
Theory: %C 62.06; %H 7.06; %N 8.69; %Cl 13.92
Found: %C 61.90; %H 7.03; %N 8.45; %Cl 13.85

EXAMPLE 1U

Preparation of **1U**:

[0421] A solution of **1G** (1.00 g, 2.46 mmol, 1.0 eq) in dichloromethane (12 mL) was added drop wise to a cold (-78°C) solution of boron tribromide, 1.0M, in anhydrous dichloromethane (13.53 mL, 13.53 mmol, 5.5 eq). The mixture was warmed to room temperature and stirring was continued for an additional 1h. Water (1.2 mL) was added drop wise to the cooled (0°C) reaction mixture and then a saturated solution of sodium bicarbonate (3.7 mL) was added. The resulting mixture was stirred for 1h at room temperature. A saturated solution of sodium bicarbonate was added to the mixture until the solution was basic when tested with pH paper. The phases were separated and the aqueous phase was extracted with dichloromethane. The organic phases were combined and washed with brine. A gummy residue stuck to the walls of the separatory funnel. It was dissolved in methanol and combined with the dichloromethane extracts. The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity).
Yield: 79%

^{1}H NMR (400MHz, DMSO d_6) δ 9.66 (m, 1H), 7.37 (m, 4H), 6.77 (m, 1H), 6.32 (m, 2H), 5.62 (s, 1H), 3.32 (m, 5H), 2.89 (m, 2H), 2.76 (m, 2H), 1.78 (m, 2H), 1.67 (m, 2H), 1.11 (m, 6H)
Mass Spectral Analysis *m/z* = 393.2 $(M+H)^+$

Elemental analysis:

$C_{24}H_{28}N_2O_3$, $0.5H_2O$

Theory: %C 71.80; %H 7.28; %N 6.98

Found: %C 71.79; %H 7.13; %N 6.94

EXAMPLE 2A

Preparation of **2.2**:

[0422] Pyrrolidine (104 mL, 1.256 mol, 2.0 eq) was added at room temperature to **1.2** (125.2 g, 0.628 mol, 1.0 eq) and **2.1** (95.6 g, 0.628 mol, 1.0 eq). The solution was stirred at 70°C for 30 min and then cooled to room temperature and stirred for 48h. The mixture was then concentrated under reduced pressure and ethyl acetate (800 mL) was added. The organic mixture was washed with a 1N aqueous solution of hydrochloric acid, water, brine and dried over sodium sulfate. Diethyl ether (500 mL) was added to the organics and the mixture was stirred overnight at room temperature. The resulting precipitate was collected by filtration, washed with hexane and used for the next step without further purification.

Yield: 75%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.31 (d, 1H), 7.08 (m, 1H), 6.87 (d, 1H), 6.06 (s, 1H), 3.86 (br s, 2H), 3.19 (br s, 2H), 2.69 (s, 2H), 2.02 (m, 2H), 1.58 (m, 2H), 1.47 (s, 9H)
Mass Spectral Analysis *m/z* = 332.4 $(M-H)^-$

Preparation of **2.4**:

[0423] To a solution of **2.3** (2.17 g, 14.4 mmol, 1.2 eq) and imidazole (2.04 g, 30.03 mmol, 2.5 eq) in dimethylformamide (20 mL) at room temperature under nitrogen was added drop wise a solution of **2.2** (4 g, 12.01 mmol, 1.0 eq) in dimethylformamide (15 mL). The mixture was stirred overnight at room temperature and then diluted with ethyl acetate. The organics were washed with water, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was triturated with methanol and then isolated using vacuum filtration and used without further purification.

Yield: 76%

^{1}H NMR (400MHz, DMSO d_6) δ 7.10 (m, 2H), 6.99 (d, 1H), 3.70 (m, 2H), 3.11 (brs, 2H), 2.81 (s, 2H), 1.84 (m, 2H), 1.60 (m, 2H), 1.40 (s, 9H), 0.94 (s, 9H), 0.17 (s, 6H)

Preparation of **2.5**:

[0424] To a solution of **2.4** (4 g, 8.94 mmol, 1.0 eq) in tetrahydrofuran (20 mL) at
-78°C under nitrogen was added drop wise a 1.0M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (6.2 mL, 10.72 mmol, 1.2 eq). The mixture was stirred for 1h at -78°C. A solution of **1.4** (3.83 g, 10.72 mmol, 1.2 eq) in tetrahydrofuran (20 mL) was added drop wise. The mixture was stirred and allowed to warm slowly to room temperature. The reaction was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 90.5%

^{1}H NMR (400MHz, $CDCl_3$) δ 6.76 (m, 3H), 5.56 (s, 1H), 3.85 (br s, 2H), 3.26 (m, 2H), 2.05 (m, 2H), 1.65 (m, 2H), 1.47 (s, 9H), 0.97 (s, 9H), 0.18 (s, 6H)

Preparation of **2.6a**:

[0425] To a solution of **2.5** (4.47 g, 7.71 mmol, 1.0 eq) in dimethoxyethane (35 mL) was added sequentially a 2N aqueous solution of sodium carbonate (11.6 mL, 23.13 mmol, 3.0 eq), lithium chloride (0.98 g, 23.13 mmol, 3.0 eq), **1.6** (1.87 g, 8.48 mmol, 1.1 eq) and tetrakis(triphenylphosphine)palladium(0) (0.18 g, 0.15 mmol, 0.02 eq). The mixture was refluxed for 4h under nitrogen. The mixture was then cooled to room temperature and water was added. The mixture was extracted with ethyl acetate. The organic layer was further washed with a 2N aqueous solution of sodium hydroxide, brine and dried over sodium sulfate. The crude product was triturated with hexanes and used without further purification.
Yield: 84%
^{1}H NMR (400MHz, DMSO d_6) δ 7.39 (m, 4H), 6.87 (d, 1H), 6.69 (m, 1H), 6.37 (d, 1H), 5.89 (s, 1H), 3.71 (m, 2H), 3.45 (brs, 2H), 3.23 (m, 4H), 1.85 (m, 2H), 1.70 (m, 2H), 1.41 (s, 9H); 1.10 (m, 6H), 0.87 (s, 9H), 0.08 (s, 6H)
Mass Spectral Analysis $m/z = 607.0\ (M+H)^+$

Preparation of **2.7a**:

[0426] To a solution of **2.6a** (0.50 g, 0.82 mmol, 1.0 eq) in tetrahydrofuran (10 mL) was added a 1N solution of tetrabutylammonium fluoride (2.5 mL, 2.47 mmol, 3.0 eq) in tetrahydrofuran at 0°C. The mixture was stirred for 1h at room temperature under nitrogen. The mixture was diluted with ethyl acetate. The organic layer was washed with a saturated solution of aqueous sodium bicarbonate, brine, a 1N solution of hydrochloric acid and brine. The solution was then dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was triturated with a diethyl ether/hexanes mixture (3:7) and used without further purification.

Yield: 74%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.34 (s, 4H), 6.80 (d, 1H), 6.67 (m, 1H), 6.49 (d, 1H), 5.87 (s, 1H), 5.57 (s, 1H), 3.84 (brs, 2H), 3.56 (brs, 2H), 3.30 (brs, 4H), 2.00 (m, 2H), 1.64 (m, 2H), 1.47 (s, 9H), 1.20 (m, 6H)

Mass Spectral Analysis *m/z* = 493.0 $(M+H)^+$

Preparation of **2A**:

[0427] A 2.0M solution of hydrochloric acid in diethyl ether (1.7 mL, 3.35 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **2.7a** (0.30 g, 0.61 mmol, 1.0 eq) in anhydrous dichloromethane (5 mL). The mixture was warmed to room temperature and stirring was continued for an additional 10h. Diethyl ether (100 mL) was added to the solution. The resulting precipitate was collected by filtration and washed with diethyl ether. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity).

Yield: 50%

^{1}H NMR (400MHz, DMSO d_6) δ 9.03 (m, 2H), 7.42 (s, 4H), 6.85 (d, 1H), 6.64 (m, 1H), 6.42 (d, 1H), 5.91 (s, 1H), 3.49 (m, 4H), 3.21 (m, 5H), 2.08 (m, 2H), 1.96 (m, 2H), 1.13 (m, 6H)

Mass Spectral Analysis *m/z* = 393.3 $(M+H)^+$

Elemental analysis:

$C_{24}H_{28}N_2O_2$, 1HCl, $1H_2O$

Theory: %C 64.49; %H 6.99; %N 6.27

Found: %C 64.59; %H 6.67; %N 6.26

EXAMPLE 2B

[0428] **2B** was obtained according to a procedure similar to the one described for **2A**, with the following exception:

Step 2.4: **1.6** was replaced by **1.7**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.94 (brm, 2H), 8.59 (s, 1H), 7.90 (dd, 1H), 7.62 (d, 1H), 6.88 (d, 1H), 6.67 (dd, 1H), 6.38 (d, 1H), 6.06 (s, 1H), 3.47 (q, 2H), 3.22 (m, 6H), 2.07 (m, 2H), 1.97 (m, 2H), 1.17 (t, 3H), 1.11 (t, 3H)

Mass Spectral Analysis *m/z* = 394 $(M+H)^+$

Elemental analysis:

$C_{23}H_{27}N_3O_3$, 2HCl, $1.25H_2O$

Theory: %C 56.50; %H 6.49; %N 8.59; %Cl 14.50

Found: %C 56.55; %H 6.46; %N 8.39; %Cl 14.49

EXAMPLE 2C

Preparation of **2.9a**

[0429] A mixture of **2.7a** (0.210g, 0.00042 mol, 1.0 eq), cyclopropylmethyl bromide (**2.8a**) (0.12 mL, 0.0012 mol, 2.95 eq) and potassium carbonate (0.350g, 0.0025 mole, 6.0 eq) in *N*,*N*-dimethylformamide (5mL) was stirred for 48h at 80°C. The mixture was cooled to room tempearture, poured into water (50 mL) and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 96%

Mass Spectral Analysis *m/z* = 547.12 $(M+H)^+$

Preparation of **2C**

[0430] To a cold (0°C) solution of **2.9a** (0.200g, 0.00036 mol, 1.0 eq) in anhydrous dichloromethane (10 mL) was added drop wise a 2.0 M solution of anhydrous hydrochloric acid in diethyl ether (1.8 mL, 0.0036 mole, 10.0 eq). The mixture was warmed slowly to room temperature and stirring was continued for 12h at room temperature. The mixture was concentrated under reduced pressure. Diethyl ether was then added to the mixture, which was stirred for 1h at room temperature. The precipitate was collected by filtration, washed with diethyl ether and dried under vacuum.

Yield: 63%

^{1}H NMR (400MHz, DMSO d_6) δ 8.85 (m, 1H), 7.40 (s, 4H), 6.97 (d, 1H), 6.80 (m, 1H), 6.45 (d, 1H), 5.95 (s, 1H), 3.65 (d, 2H), 3.10-3.50 (m, 8H), 2.00 (m, 4H), 1.10 (m, 7H), 0.50 (m, 2H), 0.20 (m, 2H)
Mass Spectral Analysis *m/z* = 447.1 $(M+H)^+$

EXAMPLE 2D

[0431] **2D** was obtained according to a procedure similar to the one described for **2C**, with the following exception:
Step 2.7: **2.8a** was replaced by **2.8b** (method 2A).
^{1}H NMR (400MHz, DMSO d_6) δ 9.00 (s, 1H), 7.45 (s, 4H), 7.00 (m, 1H), 6.80 (m, 1H), 6.45 (m, 1H), 6.00 (s, 1H), 4.55 (m, 1H), 3.10–3.55 (m, 8H), 2.00 (m, 4H), 1.80 (m, 2H), 1.60 (m, 4H), 1.50 (m, 2H), 1.10 (m, 6H)
Mass Spectral Analysis *m/z* = 461.1 $(M+H)^+$

EXAMPLE 2E

Preparation of **2.7b:**

[0432] Intermediate **2.7b** was obtained according to a procedure similar to the one described for **2.7a** (see **2A**), except **1.6** was replaced by **1.7** in Step 2.4.

Preparation of **2.9b**:

[0433] To a solution of **2.7b** (1.0 g, 2.03 mmol, 1.0 eq), **2.8e** (0.29 g, 4.06 mmol, 2.0 eq), triphenylphosphine (1.06 g, 4.06 mmol, 2.0 eq) and triethylamine (0.82 g, 8.12 mmol, 4.0 eq) in tetrahydrofuran (50 mL) at 0°C was added diisopropyl azodicarboxylate (DIAD) (0.82 g, 4.06 mmol, 2.0 eq). The mixture was warmed to room temperature and stirred for 48h at room tempearture. Methylene chloride was

added and the crude mixture was washed with water, concentrated under reduced pressure and purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 45%

^{1}H NMR (400MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.76 (dd, 1H), 7.64 (d, 1H), 6.89 (d, 1H), 6.78 (m, 1H), 6.50 (d, 1H), 5.65 (s, 1H), 3.86 (brm, 2H), 3.62 (m, 4H), 3.45 (q, 2H), 3.32 (brm, 2H), 2.05 (brm, 2H), 1.67 (brm, 2H), 1.48 (s, 9H), 1.30 (m, 4H), 1.21 (t, 3H), 0.60 (m, 2H), 0.30 (m, 2H)
Mass Spectral Analysis $m/z = 548.4\ (M+H)^+$

Preparation of **2E**:

[0434] To a solution of **2.9b** (0.50g, 0.913 mmol, 1.0 eq) in methylene chloride (3 mL) was slowly added an excess of a 1.0M solution of anhydrous hydrochloric acid in diethyl ether. The mixture was stirred for 16h at room tempearture and then concentrated under reduced pressure. This mixture (0.41 g) was purified by HPLC using a 20x150mm XTerra Reversed Phase-HPLC column (eluent: 95:5 A:B to 1:99 A:B where A is 0.1% ammonia in Milli-Q water and B is acetonitrile). After HPLC purification, the pure product (0.10 g, 0.22 mmol, 1.0 eq) was obtained as the free amine, which was dissolved in methanol (10 mL) at 0°C under nitrogen and treated with a 1.0M solution of anhydrous hydrochloric acid in diethyl ether (0.47 mL, 0.47 mmol, 2.1 eq). The mixture was stirred at 0°C for 30 min. The mixture was concentrated under reduced pressure and dried under vacuum.
Yield: 26%

^{1}H NMR (400MHz, $CDCl_3$) δ 9.75 (brs, 1H), 9.33 (brs, 1H), 9.18 (s, 1H), 8.45 (brd, 1H), 7.96 (brd, 1H), 6.94 (d, 1H), 6.80 (m, 1H), 6.42 (brm, 2H), 3.66 (brm, 4H), 3.46 (brm, 6H), 2.30 (brm, 4H), 1.35 (t, 3H), 1.22 (brm, 4H), 0.62 (m, 2H), 0.31 (m, 2H)

Mass Spectral Analysis $m/z = 448.3\ (M+H)^+$
Elemental analysis:
$C_{27}H_{33}N_3O_3$, 1.75HCl, $1.5H_2O$
Theory: %C 60.23; %H 7.07; %N 7.80; %Cl 11.52
Found: %C 60.50; %H 6.99; %N 7.77; %Cl 11.38

EXAMPLE 2F

[0435] **2F** was obtained according to a procedure similar to the one described for **2E**, with the following exception:

Step 2.7: **2.8e** was replaced by **2.8d**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.10 (brs, 2H), 8.62 (d, 1H), 7.93 (dd, 1H), 7.61 (d, 1H), 7.03 (d, 1H), 6.89 (dd, 1H), 6.47 (d, 1H), 6.13 (s, 1H), 3.64 (s, 3H), 3.47 (q, 2H), 3.24 (m, 6H), 2.05 (brm, 4H), 1.17 (t, 3H), 1.11 (t, 3H)

Mass Spectral Analysis *m/z* = 408.3 $(M+H)^+$

Elemental analysis:

$C_{24}H_{29}N_3O_3$, 1.25 HCl, 1.25 H_2O

Theory: %C 60.61; %H 6.94; %N 8.84 %Cl 9.32

Found: %C 60.69; %H 6.87; %N 8.66; %Cl 9.35

Note: **2F** was also obtained according to a procedure similar to the one descibed for **2C** with the following exceptions:

Step 2.7: **2.8a** was replaced by **2.8c** and method 2C was used (alkylation reaction conducted in acetone instead of *N,N*-dimethylformamide).

EXAMPLE 3A

Preparation of **3.1a**:

[0436] To a cold (0°C) solution of **2.7a** (2.5g, 0.0050 mol, 1.0eq) in anhydrous dichloromethane (100 mL), was added *N*-triphenyltrifluoromethane sulfonimide (**1.4**) (2 g, 0.0055 mol, 1.1 eq) followed by addition of triethylamine (0.85 mL, 0.060 mol, 1.2 eq). The mixture was allowed to warm slowly to room temperature and stirring was continued for 12h. The mixture was diluted with ethyl acetate and washed successively with water, aqueous 1N NaOH, water, and brine. The organic layer was dried over sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 78%

Mass Spectral Analysis *m/z* = 666.06 $(M+H+CH_3CN)^+$

Preparation of **3.2a**:

[0437] To a stirred solution of **3.1a** (2.5 g, 0.040 mol, 1.0 eq) in a mixture of methanol (30 mL) and dimethylsulfoxide (40 mL) was added triethylamine (1.23 mL, 0.088 mol, 2.2 eq). Carbon monoxide gas was bubbled through the mixture for 5 min. To the mixture was added palladium (II) acetate (0.090 g, 0.00040 mol, 0.1 eq) followed by 1,1'-bis(diphenylphosphino)ferrocene (0.443 g, 0.00080 mol, 0.2 eq). Carbon monoxide gas was bubbled through the mixture for 15 min and the mixture was then stirred under an atmosphere of carbon monoxide and heated at 65°C overnight. The mixture was cooled to room temperature and poured into water. The mixture was extracted with ethyl acetate. The combined organic extracts were washed with water, brine, dried over sodium sulfate and filtered. Evaporation of the solvent under reduced pressure afforded a dark oil. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 75%

Mass Spectral Analysis *m/z* = 576.08 $(M+H+CH_3CN)^+$

Preparation of **3A**:

[0438] To a cold (0°C) solution of **3.2a** (0.140g, 0.00026 mole, 1.0 eq) in anhydrous dichloromethane (10 mL) was added drop wise a 2.0 M solution of anhydrous hydrochloric acid in diethyl ether (2.6 mL, 0.0026 mole, 10 .0eq). The mixture was warmed slowly to room temperature and stirring was continued for 12h at room temperature. An additional 1.0 mL of a 2.0 M solution of anhydrous hydrochloric acid in diethyl ether was added to the reaction mixture, which was allowed to stir for an additional 12h at room temperature. The mixture was concentrated under reduced pressure. Diethyl ether was then added to the mixture, which was stirred for 2h at room temperature. The resulting precipitate was collected by filtration, washed with diethyl ether and dried under vacuum.

Yield: 53%

^{1}H NMR (400MHz, DMSO d_6) δ 9.08 (m, 2H), 7.90 (d, 1H), 7.60 (s, 1H), 7.40 (s, 4H), 7.15 (d, 1H), 6.00 (s, 1H), 3.70 (s, 3H), 3.10-3.50 (m, 8H), 2.1 (m, 4H), 1.10 (m, 6H) Mass Spectral Analysis *m/z* = 435.0 $(M+H)^+$

EXAMPLE 3B

Preparation of **3.3a**:

[0439] To a cold (0°C) solution of **3.2a** (1.41g, 0.0026 mol, 1.0eq) in tetrahydrofuran (20 mL), was added a solution of lithium hydroxide monohydrate (0.332g, 0.0079 mole, 3.0 eq) in water (3mL). Methanol (6mL) was then added to the reaction mixture, which was stirred at room temperature for 12h. A solution of lithium hydroxide monohydrate (0.165g, 0.0058 mole, 1.5 eq) in water (3mL) was added to the reaction mixture, which was stirred for an additional 12h at room temperature. The mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate. The organic solution was dried over sodium sulfate and filtered. Evaporation of the filtrate provided a solid, which was triturated in hexane. The precipitate was collected by filtration.

Yield: 85%

Mass Spectral Analysis *m/z* = 562.08 $(M+H+CH_3CN)^+$

Preparation of **3B**:

[0440] To a cold (0°C) solution of **3.3a** (0.200g, 0.00038 mole, 1.0 eq) in anhydrous dichloromethane (10 mL) was added drop wise a 2.0 M solution of anhydrous hydrochloric acid in diethyl ether (1.9 mL, 0.0038 mole, 10 eq). The mixture was warmed slowly to room temperature and stirring was continued for 12h at room temperature. The desired product precipitates from the reaction mixture. The precipitate was collected by filtration, washed with diethyl ether and dried under vacuum.

Yield: 60%

^{1}H NMR (400MHz, DMSO d_6) δ 9.10 (m, 1.5H), 7.85 (d, 1H), 7.60 (s, 1H), 7.40 (s, 4H), 7.10 (d, 1H), 6.00 (s, 1H), 3.10-3.55 (m, 8H), 2.10 (m, 4H), 1.10 (m, 6H)

Mass Spectral Analysis *m/z* = 421.0 $(M+H)^+$

EXAMPLE 3C

[0441] **3C** was obtained according to a procedure similar to the one described for **3B**, with the following exception:

Step 3.1: **2.7a** (X=H) was replaced by **2.7b** (X=N).

^{1}H NMR (400MHz, DMSO d_6) δ 9.02 (brm, 2H), 8.64 (d, 1H), 7.94 (dd, 1H), 7.87 (dd, 1H), 7.66 (d, 1H), 7.52 (d, 1H), 7.16 (d, 1H), 6.19 (s, 1H), 3.48 (q, 2H), 3.25 (brm, 6H), 2.10 (brm, 4H), 1.18 (t, 3H), 1.11 (t, 3H)

Mass Spectral Analysis *m/z* = 422.2 $(M+H)^+$

EXAMPLE 3D

[0442] **3D** was obtained according to a procedure similar to the one described for **3E**, with the following exception:

Step 3.5: **3.4b** was replaced by **3.4a**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.33 (m, 2H), 7.83 (m, 2H), 7.54 (m, 1H), 7.42 (m, 4H), 7.22 (m, 1H), 7.10 (m, 1H), 6.01 (s, 1H), 5.60 (m, 2H), 3.42 (m, 2H), 3.25 (m, 4H), 2.11 (m, 4H), 1.10 (m, 6H)

Mass Spectral Analysis *m/z* = 420.0 $(M+H)^+$

Elemental analysis:

$C_{25}H_{29}N_3O_3$, 1HCl, $3H_2O$

Theory: %C 58.87; %H 7.11; %N 8.24

Found: %C 58.85; %H 6.74; %N 8.03

EXAMPLE 3E

Preparation of **3.5a**:

[0443] *O*-Benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) (244.2 mg, 0.76 mmol, 1.1 eq) was added to a cooled (0°C) solution of **3.3a** (360.0 mg, 0.69 mmol, 1.0 eq), **3.4b** (256.8 mg, 3.80 mmol, 5.5 eq), and *N,N*-diisopropylethylamine (1.06 mL, 6.08 mmol, 7.7 eq) in acetonitrile (8 mL). The solution was stirred overnight at room temperature and then concentrated under reduced pressure. Ethyl acetate (10 mL) and a saturated aqueous solution of sodium bicarbonate (10 mL) were added to the crude product and the mixture was stirred for 20 min. The phases were separated and the organic phase was washed with an aqueous saturated solution of sodium bicarbonate and brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 68%

^{1}H NMR (400MHz, DMSO d$_6$) δ 8.28 (m, 1H), 7.70 (m, 1H), 7.50 (m, 1H), 7.42 (m, 4H), 7.04 (d, 1H), 5.94 (s, 1H), 3.72 (m, 2H), 3.45 (br s, 2H), 3.25 (m, 4H), 2.70 (d, 3H), 1.89 (m, 2H), 1.74 (m, 2H), 1.42 (s, 9H), 1.12 (m, 6H)
Mass Spectral Analysis *m/z* = 534.3 (M+H)$^+$

Preparation of **3E**:

[0444] A 2.0M solution of hydrochloric acid in diethyl ether (1.30 mL, 2.57 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **3.5a** (0.25 g, 0.47 mmol, 1.0 eq) in anhydrous dichloromethane (5 mL). The mixture was warmed to room temperature and stirring was continued for an additional 10h. Diethyl ether (100 mL) was added to the solution. The resulting precipitate was collected by filtration and washed with diethyl ether.
Yield: 99%
^{1}H NMR (400MHz, DMSO d$_6$) δ 9.14 (m, 2H), 8.34 (m, 1H), 7.77 (d, 1H), 7.54 (s, 1H), 7.44 (s, 4H), 7.12 (d, 1H), 6.01 (s, 1H), 3.63 (brs, 2H), 3.45 (brs, 2H), 3.24 (m, 4H), 2.69 (d, 3H), 2.09 (m, 4H), 1.11 (m, 6H)
Mass Spectral Analysis *m/z* = 434.3 (M+H)$^+$
Elemental analysis:
$C_{26}H_{31}N_3O_3$, 1HCl, 1.25H_2O
Theory: %C 63.40; %H 7.06; %N 8.53
Found: %C 63.13; %H 6.94; %N 8.39

EXAMPLE 3F

[0445] **3F** was obtained according to a procedure similar to the one described for **3E**, with the following exception:
Step 3.5: **3.4b** was replaced by **3.4c**.
^{1}H NMR (400MHz, DMSO d$_6$) δ 9.20 (m, 2H), 8.37 (m, 1H), 7.79 (m, 1H), 7.55 (m, 1H), 7.44 (m, 4H), 7.10 (m, 1H), 6.01 (s, 1H), 3.61 (m, 2H), 3.45 (m, 2H), 3.22 (m, 6H), 2.10 (m, 4H), 1.10 (m, 9H)

Mass Spectral Analysis m/z = 448.4 $(M+H)^+$

Elemental analysis:

$C_{27}H_{33}N_3O_3$, 1HCl, $1H_2O$

Theory: %C 64.59; %H 7.23; %N 8.37

Found: %C 64.70; %H 7.16; %N 8.30

EXAMPLE 3G

[0446] **3G** was obtained according to a procedure similar to the one described for **3E**, with the following exception:

Step 3.5: **3.4b** was replaced by **3.4d**.

^1H NMR (400MHz, DMSO d_6) δ 9.16 (m, 2H), 8.36 (m, 1H), 7.78 (m, 1H), 7.55 (m, 1H), 7.44 (m, 4H), 7.10 (m, 1H), 6.00 (s, 1H), 3.44 (m, 2H), 3.20 (m, 8H), 2.10 (m, 4H), 1.45 (m, 2H), 1.12 (m, 6H), 0.80 (m, 3H)

Mass Spectral Analysis m/z = 462.4 $(M+H)^+$

Elemental analysis:

$C_{28}H_{35}N_3O_3$, 1HCl, $1.5H_2O$

Theory: %C 64.05; %H 7.49; %N 8.00

Found: %C 63.76; %H 7.41; %N 7.76

EXAMPLE 3H

[0447] **3H** was obtained according to a procedure similar to the one described for **3E**, with the following exception:

Step 3.5: **3.4b** was replaced by **3.4e**.

^1H NMR (400MHz, DMSO d_6) δ 9.23 (m, 2H), 8.36 (m, 1H), 7.79 (m, 1H), 7.55 (m, 1H), 7.45 (m, 4H), 7.12 (m, 1H), 6.01 (s, 1H), 3.45 (m, 2H), 3.24 (m, 6H), 3.01 (m, 2H), 2.06 (m, 4H), 1.76 (m, 1H), 1.11 (m, 6H), 0.81 (m, 6H)

Mass Spectral Analysis m/z = 476.5 $(M+H)^+$

Elemental analysis:

$C_{29}H_{37}N_3O_3$, 1HCl, $1.5H_2O$

Theory: %C 64.61; %H 7.67; %N 7.79

Found: %C 64.94; %H 7.39; %N 7.77

EXAMPLE 3I

[0448] **3I** was obtained according to a procedure similar to the one described for **3E**, with the following exception:

Step 3.5: **3.4b** was replaced by **3.4f**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.14 (brs, 2H), 8.23 (m, 1H), 7.80 (m, 1H), 7.54 (m, 1H), 7.44 (m, 4H), 7.11 (m, 1H), 6.02 (s, 1H), 3.45 (m, 2H), 3.23 (m, 6H), 3.01 (m, 2H), 2.10 (m, 4H), 1.12 (m, 6H), 0.83 (m, 9H)

Mass Spectral Analysis *m/z* = 490.6 $(M+H)^+$

Elemental analysis:

$C_{30}H_{39}N_3O_3$, 1HCl, $0.75H_2O$

Theory: %C 66.77; %H 7.75; %N 7.79

Found: %C 66.63; %H 7.64; %N 7.77

EXAMPLE 3J

[0449] **3J** was obtained according to a procedure similar to the one described for **3E**, with the following exception:

Step 3.5: **3.4b** was replaced by **3.4g**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.21 (m, 2H), 8.45 (m, 1H), 7.80 (m, 1H), 7.54 (m, 1H), 7.44 (m, 4H), 7.11 (m, 1H), 6.01 (s, 1H), 3.45 (m, 2H), 3.24 (m, 6H), 3.09 (m, 2H), 2.11 (m, 4H), 1.12 (m, 6H), 0.96 (m, 1H), 0.36 (m, 2H), 0.16 (m, 2H)

Mass Spectral Analysis *m/z* = 474.4 $(M+H)^+$

Elemental analysis:

$C_{29}H_{35}N_3O_3$, 1HCl, $1.75H_2O$

Theory: %C 64.31; %H 7.35; %N 7.76

Found: %C 64.69; %H 7.17; %N 7.66

EXAMPLE 3K

[0450] **3K** was obtained according to a procedure similar to the one described for **3E**, with the following exception:

Step 3.5: **3.4b** was replaced by **3.4h**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.36 (m, 2H), 8.13 (m, 1H), 7.82 (m, 1H), 7.54 (m, 1H), 7.44 (m, 4H), 7.11 (m, 1H), 6.00 (s, 1H), 4.01 (m, 1H), 3.45 (m, 2H), 3.22 (m, 6H), 2.10 (m, 4H), 1.15 (m, 12H)

Mass Spectral Analysis *m/z* = 462.5 $(M+H)^+$

Elemental analysis:

$C_{28}H_{35}N_3O_3$, 1HCl, 2.25H_2O

Theory: %C 62.44; %H 7.58; %N 7.80

Found: %C 62.42; %H 7.58; %N 8.08

EXAMPLE 3L

[0451] **3L** was obtained according to a procedure similar to the one described for **3E**, with the following exception:

Step 3.5: **3.4b** was replaced by **3.4i**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.20 (m, 2H), 8.34 (m, 1H), 7.78 (m, 1H), 7.54 (m, 1H), 7.44 (m, 4H), 7.11 (m, 1H), 6.00 (s, 1H), 3.45 (m, 2H), 3.20 (m, 8H), 2.08 (m, 4H), 1.45 (m, 2H), 1.25 (m, 4H), 1.11 (m, 6H), 0.84 (m, 3H)

Mass Spectral Analysis *m/z* = 490.5 $(M+H)^+$

Elemental analysis:

$C_{30}H_{39}N_3O_3$, 1HCl, 1.5H_2O

Theory: %C 65.14; %H 7.84; %N 7.60

Found: %C 65.38; %H 7.60; %N 7.64

EXAMPLE 3M

[0452] **3M** was obtained according to a procedure similar to the one described for **3E**, with the following exception:

Step 3.5: **3.4b** was replaced by **3.4j**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.11 (m, 2H), 7.41 (m, 4H), 7.30 (m, 1H), 7.09 (m, 1H), 6.99 (m, 1H), 6.00 (s, 1H), 3.45 (m, 2H), 3.20 (m, 6H), 2.91 (m, 6H), 2.10 (m, 4H), 1.12 (m, 6H)

Mass Spectral Analysis *m/z* = 448.4 $(M+H)^+$

Elemental analysis:

$C_{27}H_{33}N_3O_3$, 1HCl, 1.25H_2O

Theory: %C 64.02; %H 7.26; %N 8.30

Found: %C 64.03; %H 7.21; %N 8.23

EXAMPLE 3N

[0453] **3N** was obtained according to a procedure similar to the one described for **3E**, with the following exception:

Step 3.5: **3.4b** was replaced by **3.4k**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.21 (m, 2H), 7.44 (m, 5H), 7.09 (m, 2H), 5.99 (s, 1H), 3.41 (m, 2H), 3.36 (m, 4H), 3.21 (m, 6H), 2.10 (m, 4H), 1.78 (m, 4H), 1.10 (m, 6H)

Mass Spectral Analysis *m/z* = 474.5 $(M+H)^+$

Elemental analysis:

$C_{29}H_{35}N_3O_3$, 1HCl, $1.25H_2O$

Theory: %C 65.40; %H 7.29; %N 7.89

Found: %C 65.48; %H 7.08; %N 7.90

EXAMPLE 3O

[0454] **3O** was obtained according to a procedure similar to the one described for **3E**, with the following exception:

Step 3.5: **3.4b** was replaced by **3.4l**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.03 (brs, 2H), 7.44 (m, 5H), 7.13 (m, 2H), 6.01 (s, 1H), 4.96 (m, 1H), 4.24 (m, 1H), 3.44 (m, 6H), 3.22 (m, 6H), 2.09 (m, 4H), 1.86 (m, 1H), 1.75 (m, 1H), 1.12 (m, 6H)

Mass Spectral Analysis *m/z* = 490.3 $(M+H)^+$

EXAMPLE 3P

[0455] **3P** was obtained according to a procedure similar to the one described for **3E**, with the following exception:

Step 3.5: **3.4b** was replaced by **3.4m**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.25 (m, 2H), 7.44 (m, 5H), 7.10 (m, 2H), 6.00 (s, 1H), 4.93 (m, 1H), 4.24 (m, 1H), 3.45 (m, 6H), 3.21 (m, 6H), 2.11 (m, 4H), 1.88 (m, 1H), 1.76 (m, 1H), 1.11 (m, 6H)

Mass Spectral Analysis *m/z* = 490.5 $(M+H)^+$

Elemental analysis:

$C_{29}H_{35}N_3O_4$, 1HCl, $1.5H_2O$

Theory: %C 62.98; %H 7.11; %N 7.60

Found: %C 62.79; %H 6.98; %N 7.58

EXAMPLE 3Q

[0456] **3Q** was obtained according to a procedure similar to the one described for **3E**, with the following exception:

Step 3.5: **3.4b** was replaced by **3.4n**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.25 (m, 2H), 7.40 (m, 5H), 7.09 (m, 1H), 6.99 (m, 1H), 6.01 (s, 1H), 4.10 (m, 2H), 3.45 (m, 2H), 3.25 (m, 6H), 2.11 (m, 6H), 2.51 (m, 2H), 1.19 (m, 9H), 0.80 (m, 3H)

Mass Spectral Analysis m/z = 502.5 $(M+H)^+$

Elemental analysis:

$C_{31}H_{39}N_3O_3$, 1HCl, $2H_2O$

Theory: %C 64.85; %H 7.72; %N 7.32

Found: %C 64.54; %H 7.37; %N 7.35

EXAMPLE 3R

[0457] **3R** was obtained according to a procedure similar to the one described for **3E**, with the following exception:

Step 3.5: **3.4b** was replaced by **1.12**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.21 (m, 2H), 7.41 (m, 4H), 7.29 (m, 1H), 7.08 (m, 1H), 6.89 (m, 1H), 5.98 (s, 1H), 3.41 (m, 2H), 3.22 (m, 10H), 2.10 (m, 4H), 1.02 (m, 12H)

Mass Spectral Analysis m/z = 476.5 $(M+H)^+$

Elemental analysis:

$C_{29}H_{37}N_3O_3$, 1HCl, $1.25H_2O$

Theory: %C 65.15; %H 7.64; %N 7.86

Found: %C64.85; %H 7.26; %N 7.79

EXAMPLE 3S

[0458] **3S** was obtained according to a procedure similar to the one described for **3E**, with the following exception:

Step 3.5: **3.4b** was replaced by **3.4o**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.67 (m, 1H), 8.55 (m, 1H), 7.43 (m, 4H), 7.22 (m, 1H), 7.09 (m, 1H), 6.82 (m, 1H), 6.01 (s, 1H), 3.66 (m, 2H), 3.44 (m, 2H), 3.23 (m, 6H), 2.10 (m, 2H), 1.98 (m, 2H), 1.16 (m, 18H)

Mass Spectral Analysis *m/z* = 504.4 $(M+H)^+$

EXAMPLE 3T

[0459] **3T** was obtained according to a procedure similar to the one described for **3E**, with the following exception:

Step 3.5: **3.4b** was replaced by **3.4p**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.00 (m, 1.3H), 7.45 (s, 4H), 7.32 (d, 1H), 7.10 (d, 1H), 7.00 (s, 1H), 6.00 (s, 1H), 4.10 (m, 4H), 3.35–3.60 (m, 8H), 3.20 (m, 4H), 2.10 (m, 4H), 1.10 (m, 6H)

Mass Spectral Analysis *m/z* = 490.1 $(M+H)^+$

EXAMPLE 3U

[0460] **3U** was obtained according to a procedure similar to the one described for **3E**, with the following exception:

Step 3.5: **3.4b** was replaced by **3.4q**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.23 (brs, 2H), 7.44 (m, 4H), 7.30 (m, 1H), 7.12 (m, 1H), 6.96 (m, 1H), 6.01 (s, 1H), 3.40 (m, 6H), 3.22 (m, 6H), 2.11 (m, 4H), 1.56 (m, 2H), 1.43 (m, 4H), 1.12 (m, 6H)

Mass Spectral Analysis *m/z* = 488.4 $(M+H)^+$

Elemental analysis:

$C_{30}H_{37}N_3O_3$, 1HCl, 1.75H_2O

Theory: %C 64.85; %H 7.53; %N 7.56

Found: %C 64.99; %H 7.37; %N 7.46

EXAMPLE 3V

[0461] **3V** was obtained according to a procedure similar to the one described for **3E**, with the following exceptions:

Step 3.5: **3.3a** (X=CH) was replaced by **3.3b** (X=N).

Step 3.5: **3.4b** was replaced by **3.4a**.

^{1}H NMR (400MHz, DMSO d$_6$) δ 9.20 (brm, 2H), 8.63 (d, 1H), 7.92 (m, 2H), 7.83 (dd, 1H), 7.64 (d, 1H), 7.53 (d, 1H), 7.25 (brs, 1H), 7.12 (d, 1H), 6.16 (s, 1H), 3.48 (q, 2H), 3.31 (q, 2H), 3.22 (brm, 4H), 2.10 (brm, 4H), 1.18 (t, 3H), 1.12 (t, 3H)

Mass Spectral Analysis *m/z* = 421.3 $(M+H)^+$

Elemental analysis:

$C_{24}H_{28}N_4O_3$, 1.6HCl, 1.4H_2O

Theory: %C 57.19; %H 6.48; %N 11.12; %Cl 11.25

Found: %C 57.14; %H 6.41; %N 10.98; %Cl 11.00

EXAMPLE 3W

[0462] **3W** was obtained according to a procedure similar to the one described for **3E**, with the following exception:

Step 3.5: **3.3a** was replaced by **3.3b**.

^{1}H NMR (400MHz, DMSO d$_6$) δ 9.21 (brm, 2H), 8.63 (d, 1H), 8.36 (m, 1H), 7.93 (dd, 1H), 7.79 (dd, 1H), 7.64 (d, 1H), 7.49 (d, 1H), 7.13 (d, 1H), 6.16 (s, 1H), 3.48 (q, 2H), 3.25 (brm, 6H), 2.71 (d, 3H), 2.10 (m, 4H), 1.18 (t, 3H), 1.12 (t, 3H)

Mass Spectral Analysis *m/z* = 435.3 $(M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_4O_3$, 1.8HCl, 2H_2O

Theory: %C 56.00; %H 6.73; %N 10.45; %Cl 11.90

Found: %C 56.16; %H 6.72; %N 10.47; %Cl 12.23

EXAMPLE 3X

[0463] **3X** was obtained according to a procedure similar to the one described for **3E**, with the following exceptions:

Step 3.5: **3.3a** was replaced by **3.3b**.

Step 3.5: **3.4b** was replaced by **3.4c**.

^{1}H NMR (400MHz, DMSO d$_6$) δ 9.23 (brm, 2H), 8.63 (d, 1H), 8.40 (t, 1H), 7.93 (dd, 1H), 7.81 (dd, 1H), 7.64 (d, 1H), 7.49 (d, 1H), 7.13 (d, 1H), 6.16 (s, 1H), 3.48 (q, 2H), 3.25 (brm, 8H), 2.10 (brm, 4H), 1.18 (t, 3H), 1.12 (t, 3H), 1.05 (t, 3H)

Mass Spectral Analysis *m/z* = 449.3 (M+H)$^+$

Elemental analysis:

$C_{26}H_{32}N_4O_3$, 2HCl, 1.5H_2O

Theory: %C 56.93; %H 6.80; %N 10.21; %Cl 12.93

Found: %C 56.64; %H 6.86; %N 10.13; %Cl 12.59

EXAMPLE 3Y

[0464] **3Y** was obtained according to a procedure similar to the one described for **3E**, with the following exceptions:

Step 3.5: **3.3a** was replaced by **3.3b**.

Step 3.5: **3.4b** was replaced by **3.4j**.

^{1}H NMR (400MHz, DMSO d$_6$) δ 9.06 (brs, 2H), 8.62 (d, 1H), 7.92 (dd, 1H), 7.63 (d, 1H), 7.36 (dd, 1H), 7.11 (d, 1H), 6.98 (d, 1H), 6.16 (s, 1H), 3.47 (q, 2H), 3.25 (brm, 6H), 2.91 (s, 6H), 2.10 (brm, 4H), 1.17 (t, 3H), 1.11 (t, 3H)

Mass Spectral Analysis *m/z* = 449.3 (M+H)$^+$

Elemental analysis:

$C_{26}H_{32}N_4O_3$, 1.75HCl, 1.25H_2O

Theory: %C 58.38; %H 6.83; %N 10.47; %Cl 11.60

Found: %C 58.37; %H 6.94; %N 10.21; %Cl 11.35

EXAMPLE 3Z

[0465] **3Z** was obtained according to a procedure similar to the one described for **3AC**, with the following exception:

Step 3.8: **3.6d** was replaced by **3.6a;** tetrakis(triphenylphosphine)palladium(0) was used.

^{1}H NMR (400MHz, DMSO d$_6$) δ 9.21 (brm, 2H), 9.01 (s, 1H), 8.73 (d, 1H), 8.47 (d, 1H), 7.87 (m, 1H), 7.76 (dd, 1H), 7.53 (d, 2H), 7.44 (d, 2H), 7.38 (d, 1H), 7.28 (d, 1H), 6.07 (s, 1H), 3.44 (m, 2H), 3.23 (brm, 6H), 2.11 (brm, 4H), 1.12 (brd, 6H)

Mass Spectral Analysis *m/z* = 454.0 (M+H)$^+$

EXAMPLE 3AA

[0466] **3AA** was obtained according to a procedure similar to the one described for **3AC**, with the following exception:

Step 3.8: **3.6d** was replaced by **3.6b**; tetrakis(triphenylphosphine)palladium(0) was used.

^{1}H NMR (400MHz, DMSO d_6) δ 8.84 (brm, 2H), 7.58 (dd, 1H), 7.46 (m, 5H), 7.27 (d, 1H), 7.18 (d, 1H), 7.12 (d, 1H), 7.06 (m, 1H), 6.04 (s, 1H), 3.46 (m, 2H), 3.23 (brm, 6H), 2.13 (m, 2H), 2.01 (m, 2H), 1.12 (brd, 6H)

Mass Spectral Analysis *m/z* = 459.3 $(M+H)^+$

Elemental analysis:

$C_{28}H_{30}N_2O_2S$, 1HCl, $0.5H_2O$

Theory: %C 66.71; %H 6.40; %N 5.56; % Cl 7.03

Found: %C 66.76; %H 6.27; %N 5.50; % Cl 7.34

EXAMPLE 3AB

[0467] **3AB** was obtained according to a procedure similar to the one described for **3AC**, with the following exception:

Step 3.8: **3.6d** was replaced by **3.6c**; tetrakis(triphenylphosphine)palladium(0) was used.

^{1}H NMR (400MHz, DMSO-d_6) δ 9.39 (b, 1H), 9.32 (b, 1H), 8.83 (d, 2H), 8.16 (d, 2H), 7.98 (d, 1H), 7.49 (m, 3H), 7.46 (d, 2H), 7.34 (d, 1H), 6.14 (s, 1H), 3.3-3.7 (m, 8H), 2.12 (m, 4H), 1.05-1.2 (b, 6H)

Mass Spectral Analysis *m/z* = 454.4 $(M+H)^+$

Elemental analysis:

$C_{29}H_{33}Cl_2N_3O_2$, 2HCl, $2.75H_2O$

Theory: %C 60.47; %H 6.74; %N 7.29

Found: %C 60.35; %H 6.46; %N 7.32

EXAMPLE 3AC

Preparation of **3.7a**:

[0468] To a solution of **3.1a** (1.50 g, 2.40 mmol, 1.0 eq) in dimethoxyethane (DME) (20 mL) was added sequentially a 2N aqueous solution of sodium carbonate (3.6 mL, 7.20 mmol, 3.0 eq), lithium chloride (0.305 g, 7.20 mmol, 3.0 eq), **3.6d** (0.357 g, 2.88 mmol, 1.2 eq) and tetrakis(triphenylphosphine)palladium(0) (0.277 g, 0.24 mmol, 0.10 eq). The mixture was heated at 120°C for 16h. After this time, only starting material **3.1a** was observed by LC/MS. Therefore, additional quantities of **3.6d** (0.10 g, 0.81 mmol, 0.34 eq), tetrakis(triphenylphosphine)palladium(0) (0.10 g, 0.087 mmol, 0.036 eq) and [1,1'-bis(diphenylphosphino)ferrocene palladium (II) chloride, dichloromethane complex] (0.50 g, 0.68 mmol, 0.28 eq) were added to the reaction mixture, which was heated at 120°C for 5h. The crude mixture was cooled to room temperature, dissolved in ethyl acetate and the mixture was washed with water. The organic extract was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity), and the product was used without further purification.

Yield: 20%

Mass Spectral Analysis *m/z* = 555.5 $(M+H)^+$

Preparation of **3AC**:

[0469] To a solution of **3.7a** (0.3 g, purity: 90%, 0.489 mmol, 1.0 eq) in methylene chloride (10 mL) was added an excess of a 1.0M solution of anhydrous hydrochloric acid in diethyl ether (10 mL). The mixture was stirred for 16h at room temperature, concentrated under reduced pressure and purified by column chromatography (eluent: methylene chloride/methanol mixtures of increasing polarity).

Yield: 90%

^{1}H NMR (400MHz, DMSO d_6) δ 9.26 (brs, 2H), 9.13 (s, 1H), 8.99 (s, 2H), 7.72 (d, 1H), 7.53 (d, 2H), 7.44 (d, 2H), 7.34 (s, 1H), 7.25 (d, 1H), 6.07 (s, 1H), 3.44 (brs, 2H), 3.23 (brm, 6H), 2.12 (brm, 4H), 1.12 (brd, 6H)

Mass Spectral Analysis *m/z* = 455.4 $(M+H)^+$

Elemental analysis:

$C_{28}H_{30}N_4O_2$, 2HCl, $2.75H_2O$

Theory: %C 58.28; %H 6.55; %N 9.71

Found: %C 58.53; %H 6.27; %N 9.74

EXAMPLE 4A

Preparation of **4.2**:

[0470] To a suspension of **1A** (21.9 g, 52.45 mmol, 1.0 eq) in tetrahydrofuran (200 mL) at 0°C was added triethylamine (18.3 mL, 131 mmol, 2.5 eq), followed by trifluoroacetic anhydride (**4.1**) (8.75 ml, 63 mmol, 1.2 eq) dropwise. The reaction mixture was slowly warmed up to and stirred at room temperature for 10h. Ethyl acetate (500 mL) was added and the organic layer was washed with a 1M aqueous solution of hydrochloric acid (5 x 100 mL) and brine, dried over sodium sulfate and filtered. The crude product was concentrated under reduced pressure and purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 93%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.42 (m, 2H), 7.36 (m, 2H), 7.22 (m, 1H), 7.02 (m, 1H), 6.96 (m, 1H), 6.90 (m, 1H), 5.54 (s, 1H), 4.39 (m, 1H), 3.87 (m, 1H), 3.71 (m, 1H), 3.58 (m, 2H), 3.35 (m, 3H), 2.22 (m, 2H), 1.74 (m, 2H), 1.22 (m, 6H)

Mass Spectral Analysis *m/z* = 473.3 $(M+H)^+$

Preparation of **4.4**:

[0471] To a solution of **4.2** (4.0 g, 8.47 mmol, 1.0 eq) in dry dichloroethane (100 mL) was added sulfur trioxide *N,N*-dimethylformamide complex (**4.3**) (1.98 g, 12.9 mmol, 1.5 eq) portionwise. The reaction mixture was heated under reflux for 10h and then cooled down to 0-10°C at which point oxalyl chloride (1.2 mL, 13.55 mmol, 1.6 eq) was added drop wise. The reaction mixture was then stirred at 70°C for another 3h. The reaction was quenched with ice/water (100 mL). Dichloromethane (100 mL) was added and the two phases were separated. The aqueous phase was extracted with dichloromethane (3 x 50 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 79%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.90 (dd, 1H), 7.72 (d, 1H), 7.49 (m, 2H), 7.36 (m, 2H), 7.13 (d, 1H), 5.68 (s, 1H), 4.44 (m, 1H), 3.92 (m, 1H), 3.70 (m, 1H), 3.58 (m, 2H), 3.35 (m, 3H), 2.25 (m, 2H), 1.83 (m, 2H), 1.22 (m, 6H)

Mass Spectral Analysis *m/z* = 571.2 $(M+H)^+$

Preparation of **4.6a**:

[0472] To a solution of **4.4** (0.7 g, 1.22 mmol, 1.0 eq) in dry dichloromethane (30 mL) at 0°C was added triethylamine (0.85 mL, 6.10 mmol, 5.0 eq) and methylamine (**3.4b**) hydrochloride salt (0.25 g, 3.66 mmol, 3.0 eq) in one portion. The reaction mixture was slowly warmed up to room temperature and stirred at room temperature for 10h. Water (50 mL) and chloroform (50 mL) were added and the two phases were separated. The aqueous phase was extracted with chloroform (3 x 50 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 86%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.73 (dd, 1H), 7.53 (d, 1H), 7.45 (m, 2H), 7.35 (m, 2H), 7.07 (d, 1H), 5.63 (s, 1H), 4.42 (m, 1H), 4.29 (q, 1H), 3.90 (m, 1H), 3.69 (m, 1H), 3.58 (m, 2H), 3.35 (m, 3H), 2.63 (d, 3H), 2.22 (m, 2H), 1.79 (m, 2H), 1.22 (m, 6H)

Mass Spectral Analysis *m/z* = 566.2 $(M+H)^+$

Preparation of **4A**:

[0473] To a solution of **4.6a** (0.63 g, 1.11 mmol, 1.0 eq) in a mixture of methanol (20mL) and water (5 mL) at 0°C was added potassium carbonate (0.92 g, 6.66 mmol, 6.0 eq) portionwise. The reaction mixture was warmed up to room temperature and stirred at room temperature for 10h. Brine (50 mL) and chloroform (50 mL) were added and the two phases were separated. The aqueous phase was extracted with chloroform (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity). The desired fractions were combined and concentrated under reduced pressure. To a cold (0°C) solution of the resulting oil in anhydrous dichloromethane was added a 2.0M solution of hydrogen chloride in diethyl ether (1.11 mL, 2.22 mmol, 2 eq) drop wise. The mixture was then stirred for 1h at room temperature, concentrated under reduced pressure, and dried under reduced pressure.

Yield: 85%

^{1}H NMR (400MHz, DMSO d_6) δ 8.99 (m, 2H), 7.66 (dd, 1H), 7.49–7.37 (m, 6H), 7.25 (d, 1H), 6.10 (s, 1H), 3.45 (m, 2H), 3.22 (m, 6H), 2.36 (d, 3H), 2.01 (m, 4H), 1.12 (m, 6H)

Mass Spectral Analysis *m/z* = 470.2 $(M+H)^+$

Elemental analysis:

$C_{25}H_{31}N_3O_4S$, 1HCl, 1.5H_2O

Theory: %C 56.33; %H 6.62; %N 7.88

Found: %C 56.06; %H 6.50; %N 8.18

EXAMPLE 4B

[0474] **4B** was obtained according to a procedure similar to the one described for **4A**, with the following exception:

Step 4.3: **3.4b** was replaced by **3.4c**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.88 (brs, 1H), 7.67 (dd, 1H), 7.46 (m, 4H), 7.39 (d, 1H), 7.23 (d, 1H), 6.10 (s, 1H), 3.52-3.15 (m, 9H), 2.71 (m, 2H), 2.08 (m, 4H), 1.42 (m, 6H), 0.94 (t, 3H)

Mass Spectral Analysis *m/z* = 484.3 $(M+H)^+$

Elemental analysis:

$C_{26}H_{33}N_3O_4S$, 1HCl, 1.25H_2O

Theory: %C 57.55; %H 6.78; %N 7.74

Found: %C 57.61; %H 6.75; %N 7.60

EXAMPLE 4C

[0475] **4C** was obtained according to a procedure similar to the one described for **4A**, with the following exception:

Step 4.3: **3.4b** was replaced by **3.4d**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.85 (m, 2H), 7.67 (dd, 1H), 7.51 (t, 1H), 7.45 (m, 3H), 7.39 (d, 1H), 7.23 (d, 1H), 6.10 (s, 1H), 3.45 (m, 2H), 3.24 (m, 7H), 2.63 (m, 2H), 2.08 (m, 4H), 1.34 (m, 2H), 1.12 (m, 6H), 0.77 (t, 3H)

Mass Spectral Analysis *m/z* = 498.3 $(M+H)^+$

Elemental analysis:

$C_{27}H_{35}N_3O_4S$, 1HCl, $1H_2O$

Theory: %C 58.74; %H 6.94; %N 7.61

Found: %C 58.82; %H 6.78; %N 7.56

EXAMPLE 4D

[0476] **4D** was obtained according to a procedure similar to the one described for **4A**, with the following exception:

Step 4.3: **3.4b** was replaced by **3.4g**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.90 (m, 2H), 7.68 (m, 2H), 7.45 (m, 3H), 7.40 (d, 1H), 7.22 (d, 1H), 6.09 (s, 1H), 3.45 (m, 2H), 3.24 (m, 7H), 2.59 (t, 2H), 2.07 (m, 4H), 1.12 (m, 6H), 0.75 (m, 1H), 0.32 (m, 2H), 0.04 (m, 2H)

Mass Spectral Analysis *m/z* = 510.3 $(M+H)^+$

Elemental analysis:

$C_{28}H_{33}N_3O_4S$, 1HCl, $1H_2O$

Theory: %C 59.61; %H 6.79; %N 7.45

Found: %C 59.55; %H 6.75; %N 7.40

EXAMPLE 4E

[0477] **4E** was obtained according to a procedure similar to the one described for **4A**, with the following exception:

Step 4.3: **3.4b** was replaced by **3.4h**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.79 (m, 2H), 7.69 (dd, 1H), 7.54 (d, 1H), 7.44 (m, 4H), 7.22 (d, 1H), 6.10 (s, 1H), 3.51-3.09 (m, 10H), 2.07 (m, 4H), 1.12 (m, 6H), 0.92 (d, 6H)

Mass Spectral Analysis *m/z* = 498.3 $(M+H)^+$

Elemental analysis:

$C_{27}H_{35}N_3O_4S$, 1HCl, $1.4H_2O$

Theory: %C 57.98; %H 6.99; %N 7.51 Found: %C 57.99; %H 7.04; %N 7.38

EXAMPLE 4F

[0478] **4F** was obtained according to a procedure similar to the one described for **4A**, with the following exception:

Step 4.3: **3.4b** was replaced by **3.4j**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.11 (m, 2H), 7.64 (dd, 1H), 7.46 (m, 4H), 7.29 (d, 1H), 7.24 (d, 1H), 6.13 (s, 1H), 3.45 (m, 2H), 3.23 (m, 6H), 2.56 (s, 6H), 2.11 (m, 4H), 1.12 (m, 6H)

Mass Spectral Analysis *m/z* = 484.1 $(M+H)^+$

Elemental analysis:

$C_{26}H_{33}N_3O_4S$, 1HCl, $2.75H_2O$

Theory: %C 54.82; %H 6.99; %N 7.38

Found: %C 54.66; %H 6.89; %N 7.30

EXAMPLE 4G

[0479] **4G** was obtained according to a procedure similar to the one described for **4A**, with the following exception:

Step 4.3: **3.4b** was replaced by **4.5**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.85 (m, 2H), 7.83 (d, 1H), 7.69 (dd, 1H), 7.45 (m, 3H), 7.41 (d, 1H), 7.25 (d, 1H), 6.11 (s, 1H), 3.45 (m, 2H), 3.25 (m, 7H), 2.09 (m 5H), 1.12 (m, 6H), 0.45 (m, 2H), 0.34 (m, 2H)

Mass Spectral Analysis *m/z* = 496.2 $(M+H)^+$

Elemental analysis:

$C_{27}H_{33}N_3O_4S$, 1HCl, $0.75H_2O$

Theory: %C 59.44; %H 6.56; %N 7.70

Found: %C 59.37; %H 6.46; %N 7.60

EXAMPLE 4H

Preparation of **4H**:

[0480] To a solution of **4.4** (1.5 g, 2.82 mmol) in acetonitrile (20 mL) was added a concentrated aqueous solution of ammonium hydroxide (28–35%, 20 mL). The reaction mixture was heated under reflux for 10h. Brine (100 mL) was added and the aqueous phase was adjusted to pH=10 with a 1M aqueous solution of sodium hydroxide. Chloroform (150 mL) was added and the two phases were separated. The aqueous phase was extracted with chloroform (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity). The desired fractions were combined and concentrated under reduced pressure. To a cold (0°C) solution of the resulting oil (0.32 g, 0.70 mmol, 1.0 eq) in dichloromethane/methanol was added drop wise a 2.0M solution of hydrogen chloride in diethyl ether (0.7 mL, 1.4 mmol, 2.0 eq). The mixture was then stirred for 1h at room temperature, concentrated under reduced pressure, and dried under vacuum.

Yield: 80%

^{1}H NMR (400MHz, DMSO d$_6$) δ 8.98 (m, 1.5H), 7.71 (dd, 1H), 7.45 (m, 5H), 7.27 (s, 2H), 7.22 (d, 1H), 6.09 (s, 1H), 3.46 (m, 2H), 3.23 (m, 6H), 2.07 (m, 4H), 1.12 (m, 6H)

Mass Spectral Analysis *m/z* = 456.0 $(M+H)^+$

Elemental analysis:

$C_{24}H_{29}N_3O_4S$, 1HCl, $2H_2O$

Theory: %C 54.59; %H 6.49; %N 7.96

Found: %C 54.50; %H 6.49; %N 7.82

EXAMPLE 4I

Preparation of **4.8**:

[0481] To a suspension of **4H** (1.12 g, 2.45 mmol, 1.0 eq) in a mixture of dichloromethane (50 mL) and methanol (5 mL) at 0°C was added sequentially triethylamine (0.85 mL, 6.12 mmol, 2.5 eq), and di-*tert*-butyl dicarbonate **4.7** (0.80 g, 3.67 mmol, 1.5 eq) portion wise. The reaction mixture was slowly warmed to room temperature and stirred at room temperature for 10h. The solvents were removed under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 92%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.75 (dd, 1H), 7.57 (d, 1H), 7.43 (m, 2H), 7.35 (m, 2H), 7.03 (d, 1H), 5.65 (s, 1H), 4.83 (s, 2H), 3.89 (m, 2H), 3.57 (m, 2H), 3.32 (m, 4H), 2.04 (m, 2H), 1.71 (m, 2H), 1.47 (s, 9H), 1.21 (m, 6H)
Mass Spectral Analysis $m/z = 556.3\ (M+H)^+$

Preparation of **4.10**:

[0482] To a solution of **4.8** (1.25 g, 2.25 mmol, 1.0 eq) in dichloromethane (40 mL) was added triethylamine (0.94 mL, 6.75 mmol, 3.0 eq), and acetic anhydride (**4.9**) (0.64 mL, 6.75 mmol, 3.0 eq) drop wise. The mixture was stirred at room temperature for 10h. Dichloromethane (100 mL) and water (100 mL) were added to the reaction mixture and the two phases were separated. The aqueous phase was extracted with dichloromethane (3 x 50 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 70%
Mass Spectral Analysis $m/z = 598.3\ (M+H)^+$

Preparation of **4I**:

[0483] To a solution of **4.10** (0.16 g, 0.27 mmol, 1.0 eq) in dichloromethane (5 mL) was added iodotrimethylsilane (0.06 mL, 0.43 mmol, 1.6 eq) dropwise. The mixture was stirred at room temperature for 30 min. The mixture was diluted in chloroform (100 mL) and methanol (5 mL), washed with a 20% aqueous solution of sodium thiosulfate (2 x 30 mL) and a 1M aqueous solution of sodium carbonate (2 x 30 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity).
Yield: 60%
^{1}H NMR (400MHz, DMSO d_6) δ 7.73 (dd, 1H), 7.51 (d, 1H), 7.45 (s, 4H), 7.17 (d, 1H), 6.01 (s, 1H), 3.45 (brs, 2H), 3.38-3.15 (m, 7H), 2.07 (m, 4H), 1.79 (s, 3H), 1.12 (m, 6H)
Mass Spectral Analysis $m/z = 498.3\ (M+H)^+$

EXAMPLE 5A

Preparation of **5.2**:

[0484] To a solution of **4.4** (1.4 g, 2.45 mmol, 1.0 eq) in a mixture tetrahydrofuran (5 mL) and dichloromethane (1 mL) at 0°C was added a 1.0 M solution of hydrazine (**5.1**) in tetrahydrofuran (24.5 mL, 24.5 mmol, 10.0 eq) in one portion. The reaction mixture was stirred at 0°C for 30 min. Water (50 mL) and chloroform (100 mL) were added and the two phases were separated. The aqueous phase was extracted with chloroform (3 x 50 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 70%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.78 (dd, 1H), 7.59 (d, 1H), 7.46 (d, 2H), 7.35 (d, 2H), 7.10 (d, 1H), 5.64 (s, 1H), 4.42 (m, 1H), 3.91 (m, 1H), 3.69 (m, 1H), 3.57 (m, 2H), 3.35 (m, 4H), 2.23 (m, 2H), 1.80 (m, 2H), 1.22 (m, 6H)

Mass Spectral Analysis $m/z = 567.4\ (M+H)^+$

Preparation of **5.3**:

[0485] To a suspension of **5.2** (0.9 g, 1.59 mmol, 1.0 eq) in ethanol (10 mL) was added sodium acetate (0.87 g, 10.8 mmol, 6.65 eq) and iodomethane (**2.8c**) (0.54 mL, 8.85 mmol, 5.45 eq). The mixture was heated under reflux for 10h. Water (100 mL) and dichloromethane (100 mL) were added and the two phases were separated. The aqueous phase was extracted with dichloromethane (3 x 50 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 74%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.81 (dd, 1H), 7.64 (d, 1H), 7.46 (d, 2H), 7.35 (d, 2H), 7.11 (d, 1H), 5.64 (s, 1H), 4.42 (m, 1H), 3.91 (m, 1H), 3.69 (m, 1H), 3.57 (m, 2H), 3.35 (m, 3H), 3.00 (s, 3H), 2.23 (m, 2H), 1.80 (m, 2H), 1.22 (m, 6H)

Mass Spectral Analysis $m/z = 551.2\ (M+H)^+$

Preparation of **5A**:

[0486] To a solution of **5.3** (0.65 g, 1.18 mmol, 1.0 eq) in a mixture of methanol (20 mL) and water (5 mL) at 0°C was added potassium carbonate (0.98 g, 7.08 mmol, 6.0 eq) portion wise. The mixture was warmed up to and stirred at room temperature for 10h. Brine (50 mL) and chloroform (50 mL) were added and the two phases were separated. The aqueous phase was extracted with chloroform (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity). The desired fractions were combined and concentrated under reduced pressure. To a cold (0°C) solution of the resulting oil in anhydrous dichloromethane was added dropwise a 2.0M solution of hydrogen chloride in diethyl ether (1.18 mL, 2.36 mmol, 2.0 eq). The mixture was then stirred at room temperature for 1h, concentrated under reduced pressure, and dried under vacuum.

Yield: 88%

^{1}H NMR (400MHz, DMSO d$_6$) δ 9.07 (m, 2H), 7.83 (dd, 1H), 7.47 (m, 5H), 7.30 (d, 1H), 6.12 (s, 1H), 3.63-3.10 (m, 11H), 2.10 (m, 4H), 1.12 (m, 6H)

Mass Spectral Analysis *m/z* = 455.2 $(M+H)^+$

Elemental analysis: $C_{25}H_{30}N_2O_4S$, 1HCl, $1.33H_2O$

Theory: %C 58.30; %H 6.59; %N 5.44 Found: %C 58.35; %H 6.56; %N 5.37

EXAMPLE 6A

Preparation of **6.2**:

[0487] To a cold (0°C) solution of **4.2** (0.23 g, 0.48 mmol, 1.0 eq) in dry acetonitrile (3 mL) under nitrogen was added nitronium tetrafluoroborate complex (**6.1**) (78.5 mg, 0.576 mmol, 1.2 eq) in one portion with rapid stirring. The reaction mixture was kept at 0°C for 1h and then quenched with ice/water (1:1) (15 mL). Dichloromethane (50 mL) was added and the two phases were separated. The aqueous phase was extracted with dichloromethane (3 x 30 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 38%

^{1}H NMR (400MHz, $CDCl_3$) δ 8.14 (dd, 1H), 7.97 (d, 1H), 7.48 (m, 2H), 7.36 (m, 2H), 7.06 (d, 1H), 5.66 (s, 1H), 4.43 (m, 1H), 3.92 (m, 1H), 3.70 (m, 1H), 3.58 (m, 2H), 3.36 (m, 3H), 2.23 (m, 2H), 1.82 (m, 2H), 1.23 (m, 6H)

Mass Spectral Analysis *m/z* = 518.3 $(M+H)^+$

Preparation of **6A**:

[0488] To a solution of **6.2** (0.2 g, 0.386 mmol, 1.0 eq) in a mixture of methanol (15 mL) and water (5 mL) at 0°C was added potassium carbonate (0.32 g, 2.32 mmol, 6.0 eq) portionwise. The mixture was warmed up to room temperature and stirred at room temperature for 10h. Brine (50 mL) and chloroform (50 mL) were added and the two phases were separated. The aqueous phase was extracted with chloroform (3 x 30 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparative liquid chromatography (mobile phase: acetonitrile/water/trifluoroacetic acid). The desired fractions were combined and concentrated under reduced pressure. The product was dissolved in chloroform (100 mL), washed with a 1M aqueous solution of sodium carbonate (2 x 30 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. To a cold (0°C) solution of the resulting oil in anhydrous dichloromethane was added dropwise a 1.0M solution of hydrogen chloride in diethyl ether (0.8 mL, 0.8 mmol, 2.0 eq). The mixture was then stirred for 1h at room temperature, concentrated under reduced pressure, and dried under vacuum.

Yield: 50%

^{1}H NMR (400MHz, DMSO d_6) δ 9.01 (m, 2H), 8.19 (dd, 1H), 7.79 (d, 1H), 7.49 (m, 4H), 7.29 (d, 1H), 6.19 (s, 1H), 3.56-3.14 (m, 8H), 2.11 (m, 4H), 1.13 (m, 6H)

Mass Spectral Analysis *m/z* = 422.3 $(M+H)^+$

EXAMPLE 6B

Preparation of **6.4**:

[0489] To a cold (0°C) solution of **6.2** (1.92 g, 3.71 mmol, 1.0 eq) in ethanol (50 mL) was added tin (II) chloride dihydrate (**6.3**) (2.51 g, 11.13 mmol, 3.0 eq) in one portion. The reaction mixture was heated under reflux for 10h and then concentrated

under reduced pressure to give the crude product, which was used for the next step without purification.
Mass Spectral Analysis *m/z* = 488.2 $(M+H)^+$

Preparation of **6B**:

[0490] To a suspension of **6.4** (1.3 g, crude, as of 0.91 mmol, 1.0 eq) in a mixture of methanol (30 mL) and water (10 mL) at 0°C was added potassium carbonate (0.75 g, 5.46 mmol, 6.0 eq) portion wise. The reaction mixture was warmed up to room temperature and stirred at room temperature for 10h. Brine (50 mL) and chloroform (50 mL) were added and the two phases were separated. The aqueous phase was extracted with chloroform (3 x 30 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparative liquid chromatography (mobile phase: acetonitrile/water/trifluoroacetic acid). The desired fractions were combined, concentrated under reduced pressure, and dried under vacuum.
Yield: 27% over two steps
^1H NMR (400MHz, DMSO d_6) δ 9.98 (brs, 2.5H), 9.11 (m, 2H), 7.44 (m, 4H), 7.23 (dd, 1H), 7.15 (d, 1H), 7.00 (d, 1H), 6.06 (s, 1H), 3.78-3.10 (m, 8H), 2.06 (m, 4H), 1.12 (m, 6H) Mass Spectral Analysis *m/z* = 392.2 $(M+H)^+$

EXAMPLE 6C

Preparation of **6.6a**:

[0491] To a suspension of **6.4** (1.5 g, crude, as of 1.05 mmol, 1.0 eq) in dichloroethane (50 mL) at 0°C was added pyridine (0.42 g, 5.25 mmol, 5 eq) followed by drop wise addition of ethylsulfonyl chloride (**6.5a**) (0.30 mL, 3.15 mmol, 3.0 eq) dropwise. The mixture was stirred at 0°C for another 2h. A 1M aqueous solution of hydrochloric acid (100 mL) and chloroform (100 mL) were added and the two phases were separated. The aqueous phase was extracted with chloroform (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 90%
Mass Spectral Analysis *m/z* = 580.3 $(M+H)^+$

Preparation of **6C**:

[0492] To a solution of **6.6a** (0.55 g, 0.9 mmol, 1.0 eq) in a mixture of methanol (20 mL) and water (5mL) at 0°C was added potassium carbonate (0.78 g, 5.4 mmol, 6.0 eq) portionwise. The mixture was warmed up to room temperature and stirred at room temperature for 10h. Brine (100 mL) and chloroform (100 mL) were added and the two phases were separated. The aqueous phase was extracted with chloroform (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixture of increasing polarity). The desired fractions were combined and concentrated under reduced pressure. To a cold (0°C) solution of the resulting oil in anhydrous dichloromethane was added drop wise a 1.0M solution of hydrogen chloride in diethyl ether (1.8 mL, 1.8 mmol, 2.0 eq). The mixture was then stirred for 1h at room temperature, concentrated under reduced pressure, and dried under vacuum.

Yield: 80%

^{1}H NMR (400MHz, DMSO d_6) δ 9.49 (s, 1H), 8.91 (m, 2H), 7.43 (m, 4H), 7.11 (dd, 1H), 7.02 (d, 1H), 6.93 (d, 1H), 6.00 (s, 1H), 3.45 (brs, 2H), 3.21 (m, 6H), 2.97 (q, 2H), 2.03 (m, 4H), 1.20-1.00 (m, 9H)

Mass Spectral Analysis *m/z* = 484.2 $(M+H)^+$

Elemental analysis:

$C_{26}H_{33}N_3O_4S$, 1HCl, 1.25H_2O

Theory: %C 57.55; %H 6.78; %N 7.74 Found: %C 57.52; %H 6.67; %N 7.73

EXAMPLE 6D

[0493] **6D** was obtained according to a procedure similar to the one described for **6C**, with the following exception:

Step 6.5: **6.5a** was replaced by **6.5b**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.48 (s, 1H), 8.66 (brm, 1H), 7.43 (s, 4H), 7.12 (dd, 1H), 7.01 (d, 1H), 6.95 (d, 1H), 6.00 (s, 1H), 3.46 (brs, 4H), 3.23 (brm, 4H), 3.12 (m, 1H), 2.06 (m, 2H), 1.95 (m, 2H), 1.20 (d, 6H), 1.12 (brd, 6H)

Mass Spectral Analysis *m/z* = 498.2 $(M+H)^+$

EXAMPLE 6E

Preparation of **6.8**:

[0494] To a suspension of **6.4** (1.0 g, crude, as of 0.58 mmol, 1.0 eq) in dichloroethane (30 mL) at 0°C was added pyridine (0.23 mL, 2.9 mmol, 5.0 eq) followed by a drop wise addition of acetyl chloride (**6.7**) (0.16 mL, 2.32 mmol, 4.0 eq). The reaction mixture was slowly warmed up to room tempearure and stirred at room temperature for 10h. A 1M aqueous solution of hydrochloric acid (50 mL) and chloroform (50 mL) were added and the two phases were separated. The aqueous phase was extracted with chloroform (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixture of increasing polarity).

Yield: 88%

Mass Spectral Analysis $m/z = 530.2\ (M+H)^+$

Preparation of **6E**:

[0495] To a solution of **6.8** (0.27 g, 0.5 mmol, 1.0 eq) in a mixture of methanol (20 mL) and water (5 mL) at 0°C was added potassium carbonate (0.42 g, 3.0 mmol, 6.0 eq) portion wise. The reaction mixture was warmed up to room temperature and stirred at room temperature for 10h. Brine (100 mL) and chloroform (100 mL) were added and the two phases were separated. The aqueous phase was extracted with chloroform (3 x 30 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was first purified by column chromatography (eluent: dichloromethane/methanol mixture of increasing polarity) and then repurified by preparative liquid chromatography (mobile phase: acetonitrile/water/trifluoroacetic acid). The desired fractions were combined and concentrated under reduced pressure. The product was dissolved in chloroform (100 mL) and washed with a 1M solution of sodium carbonate (2 x 30 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. To a cold (0°C) solution of the resulting oil in anhydrous dichloromethane was added dropwise 1.0M hydrogen chloride in diethyl ether (1.0 mL, 1.0 mmol, 2 eq). The mixture was then stirred for 1h at room temperature, concentrated under reduced pressure, and dried under reduced pressure.

Yield: 73%

^{1}H NMR (400MHz, DMSO d_6) δ 9.34 (s, 1H), 8.80 (brs, 2H), 7.68 (d, 1H), 7.42 (s, 4H), 6.90 (t, 1H), 6.77 (d, 1H), 5.95 (s, 1H), 3.45 (brs, 2H), 3.25 (m, 6H), 2.15 (s, 3H), 2.04 (m, 4H), 1.12 (m, 6H)

Mass Spectral Analysis *m/z* = 434.2 $(M+H)^+$

Elemental analysis:

$C_{26}H_{31}N_3O_3$, 1HCl, 1.7H_2O

Theory: %C 62.38; %H 7.13; %N 8.39

Found: %C 62.26; %H 6.81; %N 8.29

EXAMPLE 7A

Preparation of **7.2**:

[0496] To a solution of **3.1a** (3 g, 4.80 mmol, 1.0 eq), sodium *tert*-butoxide (0.55 g, 5.67 mmol, 1.18 eq), tris(dibenzylideneacetone)dipalladium(0) (0.22 g, 0.24 mmol, 0.05 eq) and 1,1'-bis(diphenylphosphino)ferrocene (dppf) (0.39 g, 0.70 mmol, 0.145 eq) in anhydrous toluene (48 mL) was added **7.1** (0.95 mL, 5.67 mmol, 1.18 eq) at room temperature. The solution was stirred at 80°C overnight and then cooled to room temperature. The mixture was diluted with ethyl acetate and vacuum filtered through a plug of celite. The filtrate was washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 33%

Mass Spectral Analysis *m/z* = 656.6 $(M+H)^+$

Preparation of **7.3**:

[0497] To a solution of **7.2** (1.00 g, 1.52 mmol, 1.0 eq) in anhydrous methanol (5 mL) at room temperature under nitrogen was added hydroxylamine hydrochloride (0.21 g, 2.97 mmol, 1.95 eq) and sodium acetate (0.64 g, 7.78 mmol, 5.1 eq). The mixture was stirred overnight at room temperature. The mixture was then diluted with ethyl acetate, washed with a saturated aqueous solution of sodium bicarbonate

and brine, dried over sodium sulfate and filtered. The organics were concentrated under reduced pressure and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 99%

Mass Spectral Analysis $m/z = 492.5\ (M+H)^+$

Preparation of **7.5**:

[0498] To a solution of **7.3** (0.75 g, 1.53 mmol, 1.0 eq) and triethylamine (1.06 mL, 7.63 mmol, 5.0 eq) in dichloromethane (10 mL) at 0°C under nitrogen was added drop wise **7.4** (0.35 mL, 4.58 mmol, 3.0 eq). The mixture was stirred overnight at room temperature. An aqueous solution of sodium bicarbonate was added and the mixture was stirred for 20 min. The phases were separated and the organic phase was washed with an aqueous solution of sodium bicarbonate, brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was used for the next step without further purification.
Yield: 83%

Mass Spectral Analysis $m/z = 648.5\ (M+H)^+$

Preparation of **7.6**:

[0499] To a solution of **7.5** (0.82 g, 1.27 mmol, 1.0 eq) in tetrahydrofuran (5 mL) and methanol (5 mL) was added a 1N aqueous solution of sodium hydroxide (5 mL, 5 mmol, 4.0 eq). The mixture was stirred at room temperature for 3h under nitrogen. The mixture was then neutralized with a 1N aqueous solution of hydrochloric acid (50 mL). The mixture was extracted with ethyl acetate and the organic layer was further washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 40%
^{1}H NMR (400MHz, DMSO d_6) δ 9.35 (m, 1H), 7.41 (s, 4H), 7.09 (m, 1H), 6.97 (d, 1H), 6.91 (d, 1H), 5.92 (s, 1H), 3.72 (m, 2H), 3.44 (m, 2H), 3.23 (m, 4H), 2.87 (s, 3H), 1.86 (m, 2H), 1.71 (m, 2H), 1.42 (s, 9H), 1.11 (m, 6H)
Mass Spectral Analysis $m/z = 570.4\ (M+H)^+$

Preparation of **7A**:

[0500] A 2.0M solution of hydrochloric acid in diethyl ether (1.4 mL, 2.78 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **7.6** (0.29 g, 0.51 mmol, 1.0 eq) in anhydrous dichloromethane (5 mL). The mixture was warmed to room temperature and stirring was continued for an additional 10h at room temperature. Diethyl ether (100 mL) was added to the solution and the resulting precipitate was collected by filtration and washed with diethyl ether. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity).

Yield: 25%

^{1}H NMR (400MHz, DMSO d_6) δ 9.42 (s, 1H), 8.85 (m, 2H), 7.43 (m, 4H), 7.12 (m, 1H), 7.05 (m, 1H), 6.93 (m, 1H), 6.00 (s, 1H), 3.45 (m, 2H), 3.37 (m, 2H), 3.24 (m, 4H), 2.88 (s, 3H), 2.07 (m, 2H), 1.98 (m, 2H), 1.11 (m, 6H)

Mass Spectral Analysis *m/z* = 470.4 $(M+H)^+$

Elemental analysis:

$C_{25}H_{31}N_3O_4S$, 1HCl, $2H_2O$

Theory: %C 55.39; %H 6.69; %N 7.75

Found: %C 55.03; %H 6.33; %N 7.36

EXAMPLE 7B

Preparation of **7.7**:

[0501] To a solution of **7.6** (0.5 g, 0.88 mmol, 1.0 eq) in dry tetrahydrofuran (20 mL) at 0°C was added sodium hydride (60% dispersion in mineral oil, 70 mg, 1.76 mmol, 2.0 eq) in one portion. The reaction mixture was kept at 0°C for 1h and methyliodide (**2.8c**) (0.08 mL, 1.1 mmol, 1.3 eq) was added drop wise. The mixture was kept at 0°C for another 30 min, warmed up to room temperature, and then heated at 80°C for 10h. Water (50 mL) and chloroform (100 mL) were added and the two phases were separated. The aqueous phase was extracted with chloroform (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 83%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.43 (m, 2H), 7.36 (m, 2H), 7.19 (dd, 1H), 7.01 (d, 1H), 6.95 (d, 1H), 5.61 (s, 1H), 3.87 (brs, 2H), 3.57 (brs, 2H), 3.32 (m, 4H), 3.21 (s, 3H), 2.81 (s 3H), 2.05 (m, 2H), 1.68 (m, 2H), 1.48 (s, 9H), 1.20 (m, 6H)

Mass Spectral Analysis *m/z* = 584.3 $(M+H)^+$

Preparation of **7B**

[0502] To a cold (0°C) solution of **7.7** (0.43 g, 0.73mmol, 1.0 eq) in anhydrous dichloromethane (20 mL) was added drop wise a 1.0 M solution of hydrogen chloride in diethyl ether (4.38 mL, 4.38 mmol, 6.0 eq). The reaction mixture was stirred at room temperature for 10h and then concentrated under reduced pressure. The crude product was purified by preparative liquid chromatography (mobile phase: acetonitrile/water/trifluoroacetic acid). The desired fractions were combined and concentrated under reduced pressure. The product was dissolved in chloroform (100 mL) and washed with a 1M solution of sodium carbonate (2 x 30 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. To a cold (0°C) solution of the resulting oil in anhydrous dichloromethane was added dropwise 1.0M hydrogen chloride in diethyl ether (1.46 mL, 1.46 mmol, 2.0 eq). The mixture was then stirred for 1h at room temperature, concentrated under reduced pressure, and dried under vacuum.

Yield: 60%

^{1}H NMR (400MHz, DMSO d_6) δ 8.79 (m, 2H), 7.44 (m, 4H), 7.34 (dd, 1H), 7.10 (d, 1H), 7.00 (d, 1H), 6.03 (s, 1H), 3.23 (m, 8H), 3.14 (s, 3H), 2.89 (s, 3H), 2.04 (m, 4H), 1.11 (m, 6H)

Mass Spectral Analysis *m/z* = 484.2 $(M+H)^+$

Elemental analysis:

$C_{26}H_{33}N_3O_4S$, 1HCl, $1.3H_2O$

Theory: %C 57.46; %H 6.79; %N 7.73

Found: %C 57.46; %H 6.86; %N 7.80

EXAMPLE 7C

Preparation of **7.8**:

[0503] To a suspension of **6.4** (2 g, crude, as of 1.4 mmol, 1.0 eq) in dichloromethane (50 mL) at 0°C was added triethylamine (0.98 mL, 7.0 mmol, 5 eq) followed by drop wise addition of methylsulfonyl chloride (**7.4**) (0.33 mL, 4.2 mmol, 3.0 eq). The reaction mixture was stirred at 0°C for 1h. A 1M aqueous solution of hydrochloric acid (100 mL) and chloroform (100 mL) were added and the two phases were separated. The aqueous phase was extracted with chloroform (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give the crude product, which was used for the next step without purification.

Mass Spectral Analysis *m/z* = 644.2 $(M+H)^+$

Preparation of the Mixture of **7A** & **7C**:

[0504] To a suspension of **7.8** (1.57 g, crude, as of 1.4 mmol, 1.0 eq) in a mixture of methanol (20 mL), tetrahydrofuran (20 mL) and water (20 mL) was added lithium hydroxide hydrate (0.98 mL, 7.0 mmol, 5.0 eq). The reaction mixture was stirred at room temperature for 10h and then concentrated under reduced pressure to give the crude product as a mixture of **7A** and **7C**, which was carried over for the next step without purification.

Mass Spectral Analysis *m/z* = 470.2 $(M+H)^+$ (**7A**)

Mass Spectral Analysis *m/z* = 484.2 $(M+H)^+$ (**7C**)

Preparation of **7C**

[0505] To a suspension of the mixture of **7A** and **7C** (2.2 g, crude, as of 1.4 mmol, 1.0 eq) in dry dichloroethane (50 mL) at 0°C was added pyridine (0.34 mL, 4.2 mmol, 3 eq) followed by di-*tert*-butyl dicarbonate (**4.7**) (0.46 g, 2.1 mmol, 1.5 eq) portion wise. The reaction mixture was slowly warmed up to room temperature and stirred at room temperature for 10h. Water (50 mL) and chloroform (100 mL) were added. The two phases were separated and the aqueous phase was further extracted with chloroform (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity to obtain **7.6** as pure compound; eluent: dichloromethane/methanol mixture of increasing polarity to obtain crude **7C**).

Yield: 62% for **7.6** over three steps

[0506] The crude **7C** (100 mg) was further purified by preparative liquid chromatography (mobile phase: acetonitrile/water/trifluoroacetic acid). The desired fractions were combined and concentrated under reduced pressure. The product was dissolved in chloroform (100 mL) and washed with a 1M aqueous solution of sodium carbonate (2 x 30 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. To a cold (0°C) solution of the resulting oil in anhydrous dichloromethane was added drop wise a 1.0M solution of hydrogen chloride in diethyl ether (0.41 mL, 0.41 mmol, 2.0 eq). The mixture was then stirred for 1h at room temperature, concentrated under reduced pressure, and dried under vacuum.

^{1}H NMR (400MHz, DMSO d_6) δ 10.47 (m, 1H), 9.435 & 9.422 (2s, 1H), 7.51-6.92 (m, 7H), 6.31 & 5.90 (2s, 1H,), 3.50-3.17 (m, 8H), 2.88 & 2.87 (2s, 3H,), 2.82 (d, 3H), 2.12 (m, 4H), 1.12 (m, 6H)

Mass Spectral Analysis *m/z* = 484.2 $(M+H)^+$

Elemental analysis:

$C_{26}H_{33}N_3O_4S$, 1HCl, $0.9H_2O$

Theory: %C 58.23; %H 6.73; %N 7.84

Found: %C 58.02; %H 6.68; %N 8.20

EXAMPLE 8A

[0507] **8A** was obtained according to a procedure similar to the one described for **2A**, with the following exception:

Step 2.1: **2.1** was replaced by **8.1** (see also step 8.1).

^{1}H NMR (400MHz, DMSO d_6) δ 9.16 (s, 1H), 8.92 (brs, 1H), 8.73 (brs, 1H), 7.40 (s, 4H), 6.78 (m, 2H), 6.43 (dd, 1H), 5.86 (s, 1H), 3.43 (brm, 4H), 3.20 (brm, 4H), 2.09 (m, 2H), 1.93 (m, 2H), 1.11 (brd, 6H)

Mass Spectral Analysis *m/z* = 393.4 $(M+H)^+$

Elemental analysis:

$C_{24}H_{28}N_2O_3$, 1HCl, $0.33H_2O$

Theory: %C 66.27; %H 6.87; %N 6.44

Found: %C 66.24; %H 6.77; %N 6.44

EXAMPLE 8B

[0508] **8B** was obtained according to a procedure similar to the one described for **2A**, with the following exceptions:

Step 2.1: **2.1** was replaced by **8.1** (see also step 8.1).

Step 2.4: **1.6** was replaced by **1.7** (see also step 8.4).

^{1}H NMR (400MHz, DMSO d_6) δ 9.12 (brm, 1H), 8.99 (brm, 1H), 8.57 (d, 1H), 7.88 (dd, 1H), 7.59 (d, 1H), 6.84 (m, 1H), 6.78 (t, 1H), 6.40 (dd, 1H), 6.00 (s, 1H), 3.47 (q, 2H), 3.40 (m, 2H), 3.29 (q, 2H), 3.19 (m, 2H), 2.10 (m, 2H), 1.97 (m, 2H), 1.17 (t, 3H), 1.10 (t, 3H)

Mass Spectral Analysis *m/z* = 394.2 $(M+H)^+$

Elemental analysis:

$C_{24}H_{27}N_3O_3$,, 2HCl, $0.67H_2O$

Theory: %C 57.74; %H 6.39; %N 8.78; %Cl 14.82

Found: %C 57.70; %H 6.28; %N 8.73; %Cl 14.47

EXAMPLE 8C

[0509] **8C** was obtained according to a procedure similar to the one described for **2C**, with the following exception:

Step 2.1: **2.1** was replaced by **8.1** (see also step 8.1).

^{1}H NMR (400MHz, DMSO d_6) δ 8.88 (brm, 2H), 7.42 (s, 4H), 7.00 (d, 1H), 6.86 (t, 1H), 6.58 (d, 1H), 5.97 (s, 1H), 3.90 (d, 2H), 3.44 (m, 2H), 3.23 (brm, 6H), 2.09 (m, 2H), 1.98 (m, 2H), 1.26 (m, 1H), 1.12 (brd, 6H), 0.59 (m, 2H), 0.37 (m, 2H)

Mass Spectral Analysis *m/z* = 447.3 $(M+H)^+$

Elemental analysis:

$C_{28}H_{34}N_2O_3$, 1HCl, $1.5H_2O$

Theory: %C 65.93; %H 7.51; %N 5.49

Found: %C 65.64; %H 7.29; %N 5.41

EXAMPLE 8D

[0510] **8D** was obtained according to a procedure similar to the one described for **2C**, with the following exceptions:

Step 2.1: **2.1** was replaced by **8.1** (see also step 8.1).

Step 2.7: **2.8a** was replaced by **2.8c** (method 2A was used) (see also step 8.7).

^{1}H NMR (400MHz, DMSO d_6) δ 8.78 (brs, 2H), 7.41 (s, 4H), 7.04 (d, 1H), 6.90 (t, 1H), 6.58 (d, 1H), 5.97 (s, 1H), 3.83 (s, 3H), 3.44 (brs, 2H), 3.20 (brm, 6H), 2.08 (m, 2H), 1.97 (m, 2H), 1.12 (brd, 6H)

Mass Spectral Analysis *m/z* = 407.3 $(M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_2O_3$, 1HCl, $1H_2O$

Theory: %C 65.14; %H 7.22; %N 6.08

Found: %C 65.22; %H 6.85; %N 6.02

EXAMPLE 8E

[0511] **8E** was obtained according to a procedure similar to the one described for **2C**, with the following exceptions:

Step 2.1: **2.1** was replaced by **8.1** (see also step 8.1).

Step 2.4: **1.6** was replaced by **1.7** (see also step 8.4).

^{1}H NMR (400MHz, DMSO d_6) δ 8.94 (brm, 2H), 8.59 (d, 1H), 7.88 (dd, 1H), 7.60 (d, 1H), 7.03 (d, 1H), 6.88 (t, 1H), 6.56 (d, 1H), 6.11 (s, 1H), 3.91 (d, 2H), 3.47 (q, 2H0, 3.29 (m, 4H), 3.17 (m, 2H), 2.10 (m, 2H), 2.01 (m, 2H), 1.26 (m, 1H), 1.17 (t, 3H), 1.11 (t, 3H), 0.59 (m, 2H), 0.37 (m, 2H)

Mass Spectral Analysis *m/z* = 448.3 $(M+H)^+$

Elemental analysis:

$C_{27}H_{33}N_3O_3$, 1.2HCl, $0.8H_2O$

Theory: %C 64.12, %H 7.14; %N 8.31; %Cl 8.41

Found: %C 64.09; %H 7.20; %N 8.18; %Cl 8.15

EXAMPLE 8F

[0512] **8F** was obtained according to a procedure similar to the one described for **2C**, with the following exceptions:

Step 2.1: **2.1** was replaced by **8.1** (see also step 8.1).

Step 2.4: **1.6** was replaced by **1.7** (see also step 8.4).

Step 2.7: **2.8a** was replaced by **2.8c** (see also step 8.7).

^{1}H NMR (400MHz, DMSO d_6) δ 8.96 (brm, 2H), 8.59 (d, 1H), 7.88 (dd, 1H), 7.60 (d, 1H), 7.06 (d, 1H), 6.92 (t, 1H), 6.56 (d, 1H), 6.12 (s, 1H), 3.84 (S, 3H), 3.47 (q, 2H), 3.28 (m, 4H), 3.14 (m, 2H), 2.09 (m, 2H), 2.02 (m, 2H), 1.17 (t, 3H), 1.11 (t, 3H)

Mass Spectral Analysis *m/z* = 408.4 $(M+H)^+$

Elemental analysis:

$C_{24}H_{29}N_3O_3$, 2HCl, 1.5H_2O

Theory: %C 56.81; %H 6.75; %N 8.28; %Cl 13.97

Found: %C 56.80; %H 6.48; %N 8.24; %Cl 13.89

EXAMPLE 9A

[0513] **9A** was obtained according to a procedure similar to the one described for **2C**, with the following exception:

Step 2.1: **2.1** was replaced by **9.1** (see also step 9.1).

^{1}H NMR (400MHz, DMSO d_6) δ 9.68 (brd, 2H), 7.41 (d, 2H), 7.35 (d, 2H), 6.92 (d, 1H), 6.43 (s, 1H), 6.37 (d, 1H), 5.44 (s, 1H), 3.80 (d, 2H), 3.56 (brs, 2H), 3.40 (brs, 4H), 3.30 (brs, 2H), 2.30 (m, 2H), 2.19 (m, 2H), 1.27 (m, 4H), 1.17 (brs, 3H), 0.66 (m, 2H), 0.36 (m, 2H)

Mass Spectral Analysis *m/z* = 447.3 $(M+H)^+$

Elemental analysis:

$C_{28}H_{34}N_2O_3$, 1.0HCl, 1.3H_2O

Theory: %C 66.40; %H 7.48; %N 5.53

Found: %C 66.28; %H 7.48; %N 5.48

EXAMPLE 9B

Preparation of **9.5**:

[0514] **9.5** was obtained according to a procedure similar to the one described for **2.7a** except **2.1** was replaced by **9.1** in step 2.1 (see also step 9.1).

Preparation of **9.8**:

[0515] To a solution of **9.5** (1.00 g, 2.02 mmol, 1.0 eq) in dimethylformamide (10 mL) was added sequentially cesium carbonate (3.30 g, 10.1 mmol, 5.0 eq) and methyl chlorodifluoroacetate (**9.7**) (1.47g, 10.1 mmol, 5.0 eq.). The reaction mixture was

heated at 90°C for 48h, poured into water (100 mL) and extracted with ethyl acetate. The organic extracts were washed with a 1N aqueous solution of sodium hydroxide and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane:ethyl acetate mixtures of increasing polarity).
Yield: 79%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.41 (d, 2H), 7.36 (d, 2H), 6.98 (d, 1H), 6.73 (d, 1H), 6.61 (dd, 1H), 6.52 (ts, 1H, J = 73.8 Hz), 5.54 (s, 1H), 3.86 (brs, 2H), 3.57 (brm, 2H), 3.32 (brm, 4H), 2.03 (d, 2H), 1.68 (m, 2H), 1.47 (s, 9H) 1.20 (brd, 6H)
Mass Spectral Analysis *m/z* = 543.4 $(M+H)^+$

Preparation of **9B**:

[0516] To a solution of **9.8** (860 mg, 1.58 mmol, 1.0 eq) in anhydrous methanol (15 mL) was added drop wise a 4.0M solution of hydrochloric acid in dioxane (4.0 mL, 15.8 mmol, 10.0 eq). The mixture was stirred at ambient temperature for 16h and the solvent was evaporated under vacuum. The crude oil was purified by reverse phase HPLC chromatography (eluent: acetonitrile/water (0.1% trifluoroacetic acid) mixtures of decreasing polarity). The solvent was evaporated under vacuum and a 1N solution of HCl in diethyl ether (25mL) was added. The resulting solid was filtered and washed with diethyl ether.
Yield: 23%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.42 (d, 2H), 7.35 (d, 2H), 7.02 (d, 1H), 6.75 (m, 1H), 6.66 (dd, 1H), 6.54 (ts, 1H, J = 73.4 Hz), 5.59 (s, 1H), 3.57 (brs, 2H), 3.41 (brd, 4H), 3.31 (brs, 2H), 2.26 (m, 4H), 1.21 (brd, 6H)
Mass Spectral Analysis *m/z* = 443.4 $(M+H)^+$
Elemental analysis:
$C_{28}H_{34}N_2O_3$, 1.0 HCl, 1.2 H_2O
Theory: %C 59.99; %H 6.32; %N 5.60
Found: %C 60.01; %H 6.25; %N 5.54

EXAMPLE 10A

[0517] **10A** was obtained from **9.5** according to a procedure similar to the one described for **3A**, with the following exception:

Step 3.1: **2.7a** was replaced by **9.5** (see also step 10.1).

^{1}H NMR (400MHz, DMSO d_6) δ 9.80 (brs, 1H), 7.60 (s, 1H), 7.58 (d, 1H), 7.42 (d, 2H), 7.36 (d, 2H), 7.09 (d, 1H), 5.75 (s, 1H), 3.91 (s, 3H), 3.61 (brs, 2H), 3.40 (m, 4H), 3.30 (brs, 2H), 2.27 (m, 4H), 1.20 (brd, 6H)

Mass Spectral Analysis *m/z* = 435.3 $(M+H)^+$

Elemental analysis:

$C_{26}H_{30}N_2O_4$, 1HCl, 1.1H_2O

Theory: %C 63.63; %H 6.82; %N 5.71

Found: %C 63.64; %H 6.75; %N 5.72

EXAMPLE 10B

[0518] **10B** was obtained according to a procedure similar to the one described for **3B**, with the following exception:

Step 3.1: **2.7a** was replaced by **9.5** (see also step 10.1).

^{1}H NMR (400MHz, DMSO-d_6) δ 13.10 (brs, 1H), 9.10 (brm, 2H), 7.57 (d, 1H), 7.52 (dd, 1H), 7.44 (s, 4H), 7.12 (d, 1H), 6.09 (s, 1H), 3.45 (brs, 2H), 3.35 (brm, 2H), 3.23 (brm, 4H), 2.08 (m, 4H), 1.10 (brd, 6H)

Mass Spectral Analysis *m/z* = 421.3 $(M+H)^+$

EXAMPLE 10C

[0519] **10C** was obtained according to a procedure similar to the one described for **3E**, with the following exceptions:

Step 3.5: **3.3a** was replaced by **10.3** and **3.4b** was replaced by **3.4a** (see also step 10.5).

^{1}H NMR (400MHz, $CDCl_3$) δ 9.50 (brd, 2H), 7.64 (brm, 2H), 7.32 (brm, 5H), 7.00 (brs, 2H), 5.68 (s, 1H), 3.50 (brm, 4H), 3.27 (brm, 4H), 2.62 (brs, 2H), 2.19 (brs, 2H), 1.17 (brd, 6H)

Mass Spectral Analysis *m/z* = 420.3 $(M+H)^+$

EXAMPLE 10D

Preparation of **10.2**:

[0520] Compound **10.2** was obtained according to a procedure similar to the one described for **3.2a** except **2.7a** was replaced by **9.5** in step 3.1 (see also step 10.1).

Preparation of **10.4**:

[0521] To a solution of a 2N solution of methylamine (**3.4b**) in methanol (10.0 mL, 20.0 mmol, 11.0 eq) was added portionwise at room temperature **10.2** (1.00g, 1.86 mmol) in a sealed tube. The mixture was heated at 60°C for 20h to form a homogeneous solution. The mixture was poured into water (25 mL), extracted with methylene chloride, washed with brine, dried over sodium sulfate, filtered and evaporated solvent to an off-white solid. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 80%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.47 (s, 1H), 7.45 (d, 2H), 7.23 (d, 1H), 7.04 (d, 1H), 6.20 (brs, 1H), 5.64 (s, 1H), 3.88 (brs, 2H), 3.57 (brm, 2H), 3.33 (brm, 4H), 3.00 (d, 3H), 2.03 (d, 2H), 1.68 (brm, 2H), 1.45 (s, 9H) 1.21 (brd, 6H)

Mass Spectral Analysis *m/z* = 534.4 $(M+H)^+$

Preparation of **10D**:

[0522] To a solution of **10.4a** (790mg, 1.48 mmol, 1.0 eq) in anhydrous methanol (20 mL) was added drop wise a 4M solution of hydrochloric acid in dioxane (3.7 mL, 14.8 mmol, 10.0 eq). The mixture was stirred at ambient temperature for 16h and the solvent evaporated under vacuum to a white solid. The white solid was triturated in diethyl ether (50mL). The resulting solid was collected by filtration and washed with diethyl ether.

Yield: 85%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.43 (m, 3H), 7.34 (m, 3H), 7.05 (d, 1H), 6.90 (brd, 1H), 5.69, (s, 1H), 3.57 (brm, 2H), 3.35 (brm, 6H), 3.00 (d, 3H), 2.20 (brs, 4H), 1.19 (brd, 6H)

Mass Spectral Analysis *m/z* = 434.3 $(M+H)^+$

Elemental analysis:

$C_{26}H_{31}N_3O_3$, 1.0 HCl, 1.5 H_2O

Theory: %C 62.83; %H 7.10; %N 8.45

Found: %C 62.74; %H 6.95; %N 8.29

EXAMPLE 10E

[0523] **10E** was obtained according to a procedure similar to the one described for **3E**, with the following exceptions:

Step 3.5: **3.3a** was replaced by **10.3** and **3.4b** was replaced by **3.4c** (see also step 10.5) (method 10A was used).

^{1}H NMR (400MHz, $CDCl_3$) δ 9.68 (brs, 2H), 7.43 (m, 3H), 7.34 (m, 3H), 7.06 (d, 1H), 6.61 (brs, 1H), 5.68 (s, 1H), 3.57 (brs, 2H), 3.50 (brm, 2H), 3.40 (brs, 2H), 3.32 (brs, 2H), 2.25 (brs, 4H), 1.28 (brm, 6H), 1.15 (brs, 3H)

Mass Spectral Analysis *m/z* = 448.3 $(M+H)^+$

EXAMPLE 10F

[0524] **10F** was obtained according to a procedure similar to the one described for **3E**, with the following exceptions:

Step 3.5: **3.3a** was replaced by **10.3** and **3.4b** was replaced by **3.4j** (see also step 10.5) and TBTU was replaced by HATU (method 10B was used).

^{1}H NMR (400MHz, DMSO d_6) δ 9.77 (brm, 2H), 7.42 (d, 2H), 7.36 (d, 2H), 7.08 (d, 1H), 7.03 (s, 1H), 6.97 (d, 1H), 5.66 (s, 1H), 3.59 (brs, 2H), 3.40 (brs, 4H), 3.32 (brs, 2H), 3.12 (s, 3H), 3.04 (s, 3H), 2.28 (m, 4H), 1.20 (brd, 6H)

Mass Spectral Analysis *m/z* = 448.3 $(M+H)^+$

Elemental analysis:

$C_{27}H_{33}N_3O_3$, 1HCl, 1.7H_2O

Theory: %C 63.01; %H 7.32; %N 8.16

Found: %C 63.06; %H 7.18; %N 8.09

EXAMPLE 10G

[0525] **10G** was obtained according to a procedure similar to the one described for **3E**, with the following exceptions:

Step 3.5: **3.3a** was replaced by **10.3** and **3.4b** was replaced by **1.12** (see also step 10.5) (method 10A was used).

^{1}H NMR (400MHz, DMSO d_6) δ 9.73 (brs, 2H), 7.43 (d, 2H), 7.36 (d, 2H), 7.07 (d, 1H), 6.98 (s, 1H), 6.92 (d, 1H), 5.67 (s, 1H), 3.56 (brs, 4H), 3.40 (brs, 4H), 3.31 (brs, 4H), 2.26 (brs, 4H), 1.22 (brd, 12H)

Mass Spectral Analysis *m/z* = 476.2 $(M+H)^+$

Elemental analysis:

$C_{29}H_{37}N_3O_3$, 1HCl, 1.7H_2O

Theory: %C 64.18; %H 7.69; %N 7.74

Found: %C 64.08; %H 7.45; %N 7.60

EXAMPLE 10H

[0526] **10H** was obtained according to a procedure similar to the one described for **3E**, with the following exception:

Step 3.5: **3.3a** was replaced by **10.3** and **3.4b** was replaced by **3.4k** (see also step 10.5) (method 10A was used).

^{1}H NMR (400MHz, DMSO d_6) δ 9.77 (brs, 2H), 7.43 (d, 2H), 7.37 (d, 2H), 7.12 (s, 1H), 7.09 (s, 2H), 5.68 (s, 1H), 3.64 (m, 2H), 3.60 (brm, 2H), 3.47 (m, 2H), 3.40 (brm, 4H), 3.30 (brs, 2H), 2.30 (brs, 4H), 2.00 (m, 2H), 1.93 (m, 2H), 1.24 (brd, 6H)

Mass Spectral Analysis *m/z* = 474.3 $(M+H)^+$

Elemental analysis:

$C_{29}H_{35}N_3O_3$, 1HCl, 0.7 H_2O

Theory: %C 66.64; %H 7.21; %N 8.04

Found: %C 66.56; %H 7.07; %N 7.91

EXAMPLE 10I

[0527] **10I** was obtained according to a procedure similar to the one described for **3E**, with the following exception:

Step 3.5: **3.3a** was replaced by **10.3** and **3.4b** was replaced by **3.4c** (see also step 10.5) (method 10A was used).

^{1}H NMR (400MHz, $CDCl_3$) δ 9.70 (brs, 2H), 7.44 (d, 2H), 7.35 (d, 2H), 7.09 (d, 1H), 7.02 (s, 1H), 6.96 (dd, 1H), 5.68 (s, 1H), 3.73 (brm, 6H), 3.58 (brs, 4H), 3.41 (brm, 4H), 3.31 (brs, 2H), 2.28 (m, 4H), 1.21 (m, 6H)

Mass Spectral Analysis *m/z* = 490.2 $(M+H)^+$

EXAMPLE 10J

Preparation of **10.5**:

[0528] To a slurry of $LiBH_4$ (82.0 mg, 3.75 mmol, 2.0 eq.) in tetrahydrofuran (20 mL) cooled to 0° C under a nitrogen atmosphere was added drop wise a solution of **10.2** (1.00g, 1.87 mmol, 1.0 eq) in tetrahydrofuran (10 mL). The reaction mixture was warmed to room temperature and stirred for 16h at room temperature. The reaction mixture was quenched with water (0.54 mL, 8 eq.), extracted with ethyl acetate, washed with brine, dried over sodium sulfate and filtered. The solvent was removed under vacuum and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 49%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.40 (d, 2H), 7.36 (d, 2H), 6.98 (m, 2H), 6.85 (d, 1H), 5.56 (s, 1H), 4.65 (s, 2H), 3.87 (brs, 2H), 3.57 (brs, 2H), 3.32 (brm, 4H), 2.05 (d, 2H), 1.91 (brt, 1H), 1.66 (m, 2H), 1.48 (s, 9H) 1.21 (brd, 6H)
Mass Spectral Analysis m/z = 507.3 $(M+H)^+$

Preparation of **10J**:

[0529] To a solution of **10.5** (460mg, 0.91 mmol, 1.0 eq) in anhydrous methanol (30 mL) was added drop wise a 4M solution of hydrochloric acid in dioxane (2.3 mL, 9.1 mmol, 10.0 eq). The mixture was stirred at room temperature for 16h and the solvent was evaporated under vacuum. The residue was triturated in ethyl ether (50mL); the solid was collected by filtration and washed with diethyl ether. The crude product was purified by column chromatography (eluent: methylene chloride/methanol mixtures of increasing polarity).
Yield: 46%

^{1}H NMR (400MHz, $CDCl_3$) δ 9.62 (brs, 2H), 7.38 (brd, 4H), 7.00 (m, 2H), 6.90 (brd, 1H), 5.60, (brs, 1H), 4.66 (brs, 2H), 3.58 (brm, 2H), 3.40 (brm, 4H), 3.31 (brm, 2H), 2.50 (brs, 1H), 2.25 (brs, 4H), 1.21 (brd, 6H)
Mass Spectral Analysis m/z = 407.4 $(M+H)^+$
Elemental analysis:
$C_{26}H_{31}N_3O_3$, 1HCl, $0.7H_2O$

Theory: %C 65.91; %H 7.17; %N 6.15

Found: %C 65.93; %H 6.99; %N 6.08

EXAMPLE 11A

Preparation of **11.2**:

[0530] 2',6'-hydroxyacetophenone (**11.1**) (200.0g g, 1.31 mol, 1.0 eq) was added portion wise at room temperature to pyrrolidine (220 mL, 2.0 eq) followed by portion wise addition of 1-Boc-4-piperidone (**1.2**) (262.0 g, 1.31 mo, 1.0 eq). Anhydrous methanol (100 mL) was then added and the red slurry heated to reflux to dissolve all solids. On dissolution the reaction was cooled to room temperature overnight with stirring to form a solid mass. This solid mass was dissolved in ethyl acetate, washed with a 1N aqueous solution of hydrochloric acid, a 1N aqueous solution of sodium hydroxide and brine, dried over sodium sulfate and filtered. The solvent was evaporated under vacuum. A mixture of hexane and diethyl ether (80:20) (400 mL) was added to the mixture and the resulting precipitate was collected by filtration, washed with hexane and used for the next step without further purification.

Yield: 74%.

^{1}H NMR (400MHz, CDCl$_3$) δ 11.61 (s, 1H), 7.37 (t, 1H), 6.49 (d, 1H), 6.44 (d, 1H), 3.89 (brs, 2H), 3.20 (brm, 2H), 2.73 (s, 2H), 2.02 (d, 2H), 1.64 (m, 2H), 1.46 (s, 9H)
Mass Spectral Analysis *m/z* = 334.0 $(M+H)^+$

Preparation of **11.4**:

[0531] To a solution of **11.2** (140.0 g, 0.420 mol, 1.0 eq) in dichloromethane (700 mL) at ambient temperature under nitrogen was added drop wise diisopropylethylamine (294.0 mL, 1.68 mol, 4.0 eq). To this solution was added drop wise chloro(methoxy)methane (**11.3**) (100.0 g, 1.26 mol, 3.0 eq). The mixture was heated to reflux for 16h, cooled to room temperature and the solvent was removed under vacuum to afford a brown oil. This oil was dissolved in ethyl acetate (700 mL) and washed with a 1N aqueous solution of hydrochloric acid, an aqueous saturated

solution of sodium bicarbonate and brine. The organic extracts were dried over sodium sulfate, filtered and the solvent was removed under vacuum to afford a brown oil. Diethyl ether (400 mL) was added and the resulting white precipitate was filtered and used for the next step without further purification.
Yield: 83%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.36 (t, 1H), 6.74 (d, 1H), 6.65 (d, 1H), 5.27 (s, 2H), 3.86 (brs, 2H), 3.52 (s, 3H), 3.22 (m, 2H), 2.69 (s, 2H), 2.02 (d, 2H), 1.60 (m, 2H), 1.46 (s, 9H)
Mass Spectral Analysis $m/z = 378.2\ (M+H)^+$

Preparation of **11.5**:

[0532] To a solution of **11.4** (131.2 g, 0.348 mol) in tetrahydrofuran (600 mL) at -78°C under nitrogen atmosphere was added drop wise a 1.0M solution of LiHMDS in tetrahydrofuran (420.0 mL, 1.2 eq). The mixture was stirred for 1h at -78°C. A solution of **1.4** (149.4 g, 0.418 mol, 1.2 eq) in tetrahydrofuran (200 mL) was added drop wise. The mixture was warmed slowly to room temperature and stirring was continued for a further 12h at room temperature. The mixture was then poured into ice water and the two phases were separated. The organic phase was washed with a 1N aqueous solution of hydrochloric acid, a 1N aqueous solution of sodium hydroxide and brine, dried over sodium sulfate and filtered. The solvent was removed under vacuum and the tan oily residue was used for the next step without further purification.
Yield: 100%

^{1}H NMR (400MHz, $CDCl_3$) δ 6.98 (t, 1H), 6.62 (d, 1H), 6.39 (d, 1H), 5.24 (s, 1H), 5.03 (s, 2H), 3.62 (brs, 2H), 3.30 (s, 3H), 3.07 (m, 2H), 1.84 (d, 2H), 1.46 (m, 2H), 1.26 (s, 9H)
Mass Spectral Analysis $m/z = 510.0\ (M+H)^+$

Preparation of **11.6a**:

[0533] To a solution of **11.5** (100 g, 196 mmol, 1.0 eq) in dimethoxyethane (DME) (600 mL) was added sequentially a 2N aqueous solution of sodium carbonate (294 mL, 588 mmol, 3.0 eq), lithium chloride (25.0 g, 588 mmol, 3.0 eq), 4-(*N*,*N*-

diethylaminocarbonyl)phenylboronic acid) (**1.6**) (36.9 g, 166 mmol, 1.1 eq) and tetrakis(triphenylphosphine)palladium(0) (4.54 g, 3.92 mmol, 0.02 eq). The mixture was refluxed for 10h under nitrogen. The mixture was then cooled to room temperature, filtered through a celite pad and the filtercake was washed with DME (100mL) and water (750 mL). The aqueous mixture was extracted with ethyl acetate. The organic layer was further washed with brine and dried over sodium sulfate. The crude product was purified by chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 62%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.21 (d, 2H), 7.17 (d, 2H), 7.05 (t, 1H), 6.60 (m, 2H), 5.45 (s, 1H), 4.58 (s, 2H), 3.71 (brs, 2H), 3.45 (brm, 2H), 3.22 (brm, 4H), 3.06 (s, 3H), 1.90 (d, 2H), 1.56 (m, 2H), 1.38 (s, 9H), 1.09 (brd, 6H)
Mass Spectral Analysis *m/z* = 537.4 $(M+H)^+$

Preparation of **11A**:

[0534] To a solution of **11.6a** (25.0 g, 46.6 mmol, 1.0 eq) in anhydrous methanol (250 mL) was added drop wise a 4M solution of hydrochloric acid in dioxane (58.2 mL, 233 mmol, 5.0 eq). The mixture was stirred at room temperature for 16h and the solvent was evaporated under vacuum to afford a brown oil. Methanol (20 mL) followed by diethyl ether (300 mL) was added to the brown oil and the resulting precipitate was collected by filtration and washed with diethyl ether. The solid was used for the next step without further purification.
Yield: 100%

^{1}H NMR (400MHz, DMSO d_6) δ 9.55 (s, 1H), 9.07 (brs, 2H), 7.27 (m, 4H), 7.06 (t, 1H), 6.52 (d, 1H), 6.47 (d, 1H), 5.76 (s, 1H), 3.42 (brm, 2H), 3.35 (s, 4H), 3.19, (brm, 6H), 2.03 (m, 4H), 1.11 (brm, 6H)
Mass Spectral Analysis *m/z* = 393.0 $(M+H)^+$
Elemental analysis:
$C_{24}H_{28}N_2O_3$, 1HCl, $0.67H_2O$
Theory: %C 65.37; %H 6.93; %N 6.35
Found: %C 65.41; %H 6.98; %N 6.31

EXAMPLE 11B

[0535] **11B** was obtained according to a procedure similar to the one described for **11A**, with the following exception:

Step 11.4: **1.6** was replaced by **1.7**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.67 (brs, 1H), 9.23 (brd, 2H), 8.50 (s, 1H), 7.79 (d, 1H), 7.52 (d, 1H), 7.09 (t, 1H), 6.57 (d, 1H), 6.50 (d, 1H), 5.93 (s, 1H), 3.43 (q, 2H), 3.26 (q, 2H), 3.21 (m, 2H), 3.14 (m, 2H), 2.05 (m, 4H), 1.18 (t, 3H), 1.11 (t, 3H)

Mass Spectral Analysis *m/z* = 394.3 $(M+H)^+$

Elemental analysis:

$C_{23}H_{27}N_3O_3$, 2HCl, $1.5H_2O$

Theory: %C 55.99; %H 6.54; %N 8.52

Found: %C 56.11; %H 6.54; %N 8.53

EXAMPLE 11C

Preparation of **11.7a**:

[0536] To a slurry of **11A** (10.0 g, 23.3 mmol, 1.0 eq) in tetrahydrofuran (200 mL) under a nitrogen atmosphere was added triethylamine (9.75 mL, 69.9 mmol, 3.0 eq). The reaction mixture was cooled to 0°C. A solution of di-*tert*-butyl dicarbonate (**4.7**) (4.58 g, 21.0 mmol, 0.9 eq) in tetrahydrofuran (50 mL) was added drop wise to the reaction mixture which was stirred for 3h at room temperature. The solvent was evaporated under vacuum and the residue was dissolved in ethyl acetate (500 mL), washed with water and brine, and dried over sodium sulfate and filtered. The solvent was evaporated under vacuum. The residue was sonicated and triturated in a mixture ethyl acetate/methanol 95:5 (75 mL). The solid was collected by filtration and washed with ethyl acetate.

Yield: 100%

^{1}H NMR (400MHz, DMSO d_6) δ 9.49 (s, 1H), 7.31 (s, 4H), 7.08 (t, 1H), 6.54 (d, 1H), 6.47 (d, 1H), 5.77 (s, 1H), 3.70 (m, 2H), 3.48 (brm, 2H), 3.30 (brm, 4H), 1.87 (d, 2H), 1.74 (m, 2H), 1.47 (s, 9H) 1.16 (brs, 6H)

Mass Spectral Analysis *m/z* = 493.4 $(M+H)^+$

Preparation of **11.9a**:

[0537] To a solution of **11.7a** (1.00 g, 2.02 mmol, 1.0 eq) in dichloromethane (4 mL) under a nitrogen atmosphere was added sequentially cyclopropylmethanol (**2.8e**) (189 mg, 2.63 mmol, 1.3 eq) and triphenylphosphine (690 mg, 2.63 mmol, 1.3 eq). The reaction mixture was stirred for 5 min at room temperature and a solution of diethylazodicarboxylate (460 mg, 2.63 mmol, 1.3 eq) was added drop wise. The reaction was stirred an additional 30 min at room temperature and the solvent was evaporated under vacuum. The crude product was purified by chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 42%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.31 (d, 2H), 7.27 (d, 2H), 7.13 (t, 1H), 6.64 (d, 1H), 6.42 (d, 1H), 5.50 (s, 1H), 3.78 (brd, 2H), 3.54 (brm, 2H), 3.49 (d, 2H), 3.35 (brt, 4H), 2.02 (d, 2H), 1.69 (m, 2H), 1.47 (s, 9H) 1.26 (brd, 6H), 0.53 (m, 1H), 0.29 (m, 2H), -0.07 (m, 2H)
Mass Spectral Analysis *m/z* = 547.5 $(M+H)^+$

Preparation of **11C**:

[0538] To a solution of **11.9a** (460 mg, 0.84 mmol, 1.0 eq) in anhydrous methanol (15 mL) was added dropwise a 4M solution of hydrochloric acid in dioxane (2.0 mL, 8.4 mmol, 10.0 eq). The mixture was stirred at room temperature for 16h and the solvent was evaporated under vacuum. The residue was triturated in diethyl ether (50mL). The resulting solid was collected by filtration and washed with diethyl ether.
Yield: 97%

^{1}H NMR (400MHz, $CDCl_3$) δ 9.67 (brs, 2H), 7.32 (d, 2H), 7.26 (d, 2H), 7.16 (t, 1H), 6.64 (d, 1H), 6.46 (d, 1H), 5.50 (s, 1H), 3.54 (brm, 2H), 3.49 (d, 2H), 3.36 (brm, 6H), 2.28 (d, 2H), 2.18 (m, 2H), 1.19 (brd, 6H), 0.53 (m, 1H), 0.30 (m, 2H), -0.07 (m, 2H)
Mass Spectral Analysis *m/z* = 447.4 $(M+H)^+$
Elemental analysis:

$C_{28}H_{34}N_2O_3$, 1.0 HCl, 0.7 H_2O

Theory: %C 67.73; %H 7.41; %N 5.64

Found: %C 67.73; %H 7.24; %N 5.59

EXAMPLE 11D

[0539] **11D** was obtained according to a procedure similar to the one described for **11C**, with the following exceptions:

Step 11.4: **1.6** was replaced by **1.7**.

^{1}H NMR (400MHz, CDCl$_3$) δ 9.67 (brs, 1H), 8.44 (m, 1H), 7.61 (dd, 1H), 7.55 (d, 1H), 7.19 (t, 1H), 6.64 (d, 1H), 6.43 (d, 1H), 5.55 (s, 1H), 3.56 (q, 2H), 3.50 (d, 2H), 3.46 (q, 2H), 3.38 (m, 4H), 2.29 (m, 2H), 2.21 (m, 2H), 1.28 (t, 3H), 1.17 (t, 3H), 0.54 (m, 1H), 0.33 (m, 2H), -0.05 (m, 2H)

Mass Spectral Analysis m/z = 448.4 $(M+H)^+$

EXAMPLE 11E

Preparation of **11.9b**:

[0540] To a solution of **11.7a** (1.00 g, 2.02 mmol, 1.0 eq) in acetone (20mL) was added sequentially potassium carbonate (1.70 g, 12.1 mmol, 6.0 eq) and bromocyclobutane (**11.8**) (1.66 g, 12.1 mmol mmol, 6.0 eq). The reaction mixture was refluxed for 90h, poured into water (100 mL) and extracted with ethyl acetate. The organic extracts were washed with a 1N aqueous solution of sodium hydroxide and brine, dried over sodium sulfate and filtered. The solvent was evaporated and the crude product was first purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity) and then repurified by reverse phase HPLC chromatography (eluent: acetonitrile/water (0.1% trifluoroacetic acid) mixtures of decreasing polarity).

Yield: 18%

^{1}H NMR (400MHz, CDCl$_3$) δ 7.31 (d, 2H), 7.27 (d, 2H), 7.11 (t, 1H), 6.64 (d, 1H), 6.26 (d, 1H), 4.36 (m, 1H), 5.50 (s, 1H), 3.79 (brd, 2H), 3.54 (brm, 2H), 3.48 (d, 2H), 3.34 (brm, 4H), 2.12 (m, 2H), 2.02 (d, 2H), 1.67 (m, 2H), 1.55 (m, 2H), 1.47 (s, 9H) 1.19 (brd, 6H)

Mass Spectral Analysis m/z = 547.5 $(M+H)^+$

Preparation of **11E**:

[0541] To a solution of **11.9b** (200 mg, 0.37 mmol, 1.0 eq) in anhydrous methanol (25 mL) was added drop wise a 2M solution of hydrochloric acid in diethyl ether (0.73 mL, 1.44 mmol, 4.0 eq). The mixture was stirred at room temperature for 16h and the solvent was evaporated under vacuum. The residue was triturated in diethyl ether (50mL). The solid was collected by filtration and washed with diethyl ether.
Yield: 96%

^{1}H NMR (400MHz, DMSO d$_6$) δ 9.14 (brs, 2H), 7.29 (d, 2H), 7.24 (d, 2H), 7.19 (t, 1H), 6.68 (d, 1H), 6.42 (d, 1H), 5.79 (s, 1H), 4.43 (m, 1H), 3.40 (brm, 4H), 3.35 (brs, 4H), 3.17 (brm, 4H), 2.10 (m, 2H), 2.03 (m, 2H), 1.45 (m, 2H), 1.11 (m, 6H)
Mass Spectral Analysis *m/z* = 447.3 (M+H)$^+$

EXAMPLE 11F

[0542] **11F** was obtained according to a procedure similar to the one described for **11C**, with the following exceptions:
Step 11.4: **1.6** was replaced by **1.7**.
Step 11.7: **2.8e** was replaced by **11.10**.
^{1}H NMR (400MHz, CDCl$_3$) δ 9.71 (brd, 2H), 8.40 (s, 1H), 7.56 (m, 2H), 7.18 (t, 1H), 6.62 (d, 1H), 6.48 (d, 1H), 5.50 (s, 1H), 4.50 (m, 1H), 3.58 (m, 2H), 3.48 (m, 2H), 3.38 (brs, 4H), 2.30 (d, 2H), 2.22 (brs, 2H), 1.64 (m, 2H), 1.36 (m, 2H), 1.30 (m, 5H), 1.19 (m, 5H)
Mass Spectral Analysis *m/z* = 462.4 (M+H)$^+$

EXAMPLE 12A

Preparation of **12.1**:

[0543] To a solution of compound **11.2** (3.33 g, 10 mmol) in anhydrous methylene chloride (100 mL) was added sequentially triethylamine (3.48 mL, 25 mmol, 2.5 eq), 4-dimethylaminopyridine (122 mg, 1 mmol, 0.1 eq) and *N*-phenyltrifluoromethanesulfonimide (**1.4**) (4.48 g, 12.5 mmol, 1.25 eq). The reaction mixture was stirred at room temperature for 24 h, washed with a saturated aqueous

solution of sodium bicarbonate, dried over sodium sulfate and filtered. The solvent was evaporated under vacuum and the residue was purified by column chromatography (eluent: hexane/ethyl acetate, 3:1).
Yield: 92.5%

^{1}H NMR (400MHz, DMSO d_6) δ 7.52 (t, 1H), 7.09 (d, 1H), 6.88 (d, 1H), 3.90 (m, 2H), 3.21 (m, 2H), 2.80 (s, 2H), 2.03 (m, 2H), 1.63 (m, 2H), 1.48 (s, 9H)

Preparation of **12.3**:

[0544] To a solution of **12.1** (5.4 g, 11.6 mmol) in tetrahydrofuran (100 mL) at room temperature was added tetrakis(triphenylphosphine)palladium(0) (670 mg, 0.58 mmol, 0.05 eq) followed by drop wise addition of a 2.0 M solution of methylzinc chloride (**12.2a**) in tetrahydrofuran (10 mL, 20 mmol, 1.72 eq). The mixture was stirred at room temperature for 2 days. The reaction mixture was then quenched with a saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. The solvent was evaporated under vacuum and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate, 4:1).
Yield: 80.6%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.30 (t, 1H), 6.86 (d, 1H), 6.80 (d, 1H), 3.88 (m, 2H), 2.70 (s, 2H), 2.60 (s, 3H), 2.00 (m, 2H), 1.60 (m, 2H), 1.45 (s, 9H)

Preparation of **12.4**:

[0545] To a solution of **12.3** (2.8 g, 8.46 mmol) in anhydrous tetrahydrofuran (80 mL) at
-78°C under nitrogen was added drop wise a 1.0 M solution of LiHMDS in tetrahydrofuran (11 mL, 11 mmol, 1.1 eq). The reaction mixture was stirred for 45 min at -78°C. A solution of *N*-phenyltrifluoromethanesulfonimide (**1.4**) (3.95 g, 11 mmol, 1.1 eq) in tetrahydrofuran (15 mL) was added drop wise to the reaction mixture. The mixture was warmed slowly to room temperature and stirring was continued for a further 3 h at room temperature. The mixture was then poured into ice water and extracted with a mixture of hexane and diethyl ether (1:1). The organic layer was washed with water and brine, and dried over sodium sulfate and filtered.

The organics were concentrated under vacuum and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate, 6:1).
Yield: 61.3%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.11 (t, 1H), 6.80 (m, 2H), 3.82 (m, 2H), 3.29 (m, 2H), 2.50 (s, 3H), 2.03 (m, 2H), 1.68 (m, 2H), 1.48 (s, 9H)

Preparation of **12.5**:

[0546] To a solution of **12.4** (848 mg, 1.83 mmol) in dimethoxyethane (DME) (16 mL) was added sequentially a 2 N aqueous solution of sodium carbonate (3.1 mL, 6.2 mmol, 3.4 eq), lithium chloride (259 mg, 6.1 mmol, 3.3 eq), 4-(*N,N*-diethylaminocarbonyl)phenylboronic acid (**1.6**) (486 mg, 2.2 mmol, 1.2 eq) and tetrakis(triphenylphosphine)palladium(0) (64 mg, 0.055 mmol, 0.03 eq). The mixture was refluxed overnight under nitrogen. The mixture was then cooled to room temperature and water (20 mL) was added. The mixture was extracted with ethyl acetate. The organic layer was further washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate, 1:1).
Yield: 96.9%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.36 (d, 2H), 7.26 (d, 2H), 7.10 (t, 1H), 6.86 (d, 1H), 6.70 (d, 1H), 5.60 (s, 1H), 3.80 (m, 2H), 3.55 (m, 2H), 3.30 (m, 4H), 2.00 (m, 2H), 1.74 (s, 3H), 1.65 (m, 2H), 1.49 (s, 9H), 1.20 (m, 6H)

Preparation of **12A**:

[0547] To a solution of **12.5** (860 mg, 1.76 mmol) in methylene chloride (10 mL) was added a 2.0 M solution of anhydrous hydrochloric acid in diethyl ether (30 mL). The mixture was stirred at room temperature for 24 h and diethyl ether was added. The resulting precipitate was collected by filtration and washed with diethyl ether.
Yield: 97.8%

^{1}H NMR (400MHz, DMSO d_6) δ 8.99 (m, 2H), 7.38 (d, 2H), 7.29 (d, 2H), 7.18 (t, 1H), 6.93 (d, 1H), 6.80 (d, 1H), 5.95 (s, 1H), 3.45 (m, 2H), 3.20 (m, 6H), 2.00 (m, 4H), 1.70 (s, 3H), 1.10 (m, 6H)
Mass Spectral Analysis $m/z = 391.4$ $(M+H)^+$

Elemental analysis:
$C_{24}H_{28}N_2O_2$, 1HCl, 1/2H_2O
Theory: %C 68.87; %H 7.40; %N 6.43
Found: %C 68.99; %H 7.33; %N 6.39

EXAMPLE 12B

Preparation of **12.6**:

[0548] To a solution of **12.1** (14.4 g, 31 mmol) in *N*,*N*-dimethylformamide was added sequentially methanol (50 mL), triethylamine (7 mL, 50 mmol, 1.6 eq), 1,3-*bis*(diphenylphosphino)propane (dppp) (1.04 g, 2.5mmol, 0.08 eq) and palladium (II) acetate (565 mg, 2.5 mmol, 0.08 eq). The carbon monoxide was then bubbled through the reaction solution while the mixture was heated to 65-70°C for 3.5h. The reaction mixture was cooled to room temperature, diluted with diethyl ether and washed with water and brine. The organic layer was dried over sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate, 4:1).
Yield: 87.9%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.50 (t, 1H), 7.10 (d, 1H), 6.99 (d, 1H), 3.94 (s, 3H), 3.90 (m, 2H), 3.21 (m, 2H), 2.73 (s, 2H), 2.05 (m, 2H), 1.63 (m, 2H), 1.48 (s, 9H)

Preparation of **12.11**:

[0549] To a solution of **12.6** (13.2 g, 35.2 mmol) in anhydrous tetrahydrofuran (300 mL) at -78°C was added drop wise a 1.0 M solution of LiHMDS in tetrahydrofuran (42 mL, 42 mmol, 1.2 eq) under nitrogen. The reaction mixture was stirred for 45 min at -78°C. A solution of *N*-phenyltrifluoromethanesulfonimide (**1.4**) (15.1 g, 42 mmol, 1.2 eq) in tetrahydrofuran (60 mL) was added drop wise to the reaction mixture. The mixture was warmed slowly to room temperature and stirred for 3h. The mixture was then poured into ice water and extracted with a mixture of hexane and diethyl ether (1:1). The organic layer was washed with water and brine, dried over sodium sulfate and filtered. The organics were concentrated under vacuum and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate, 4:1).

Yield: 90.2%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.32 (d, 1H), 7.26 (t, 1H), 7.10 (d, 1H), 5.70 (s, 1H), 3.90 (s, 3H), 3.83 (m, 2H), 3.30 (m, 2H), 2.10 (m, 2H), 1.77 (m, 2H), 1.48 (s, 9H)

Preparation of **12.12**:

[0550] To a solution of **12.11** (16 g, 31.6 mmol) in dimethoxyethane (DME) (260 mL) was added sequentially a 2 N aqueous solution of sodium carbonate (53 mL, 106 mmol, 3.4 eq), lithium chloride (4.5 mg, 106 mmol, 3.4 eq.), 4-(*N,N*-diethylaminocarbonyl)phenylboronic acid (**1.6**) (8.4 g, 38 mmol, 1.2 eq) and tetrakis(triphenylphosphine)palladium(0) (1.1 g, 0.95 mmol, 0.03 eq). The mixture was refluxed overnight under nitrogen and then cooled to room temperature. Water (300 mL) was added to the mixture and the crude product was extracted with ethyl acetate. The organic layer was further washed with brine, dried over sodium sulfate and filtered. The organics were concentrated under vacuum and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate, 1:1).
Yield: 98.5%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.33 (d, 2H), 7.25 (m, 4H), 7.15 (d, 1H), 5.72 (s, 1H), 3.85 (m, 2H), 3.53 (m, 2H), 3.32 (m, 4H), 3.10 (s, 3H), 2.06 (m, 2H), 1.76 (m, 2H), 1.50 (s, 9H), 1.20 (m, 6H)

Preparation of **12.13**:

[0551] To a suspension of potassium *tert*-butoxide (9 g, 80 mmol, 8.0 eq) in diethyl ether (200 mL) was added drop wise water (0.72 mL, 40 mmol, 4.0 eq) at 0°C. The slurry was stirred for 30 min. To this mixture was added **12.12** (5.34 g, 10 mmol). The ice-bath was removed and the reaction mixture was stirred at room temperature overnight and quenched by addition of ice water. The aqueous layer was separated, acidified to pH 2-3 with a 1N aqueous solution of hydrochloric acid and extracted with methylene chloride. The organic layers were combined, dried over sodium sulfate and concentrated under vacuum. The crude product was used for the next step without further purification.
Yield: 86.9%

^{1}H NMR (400MHz, DMSO d_6) δ 12.55 (brs, 1H), 7.23 (m, 7H), 5.98 (s, 1H), 3.68 (m, 2H), 3.42-3.20 (m, 6H), 1.80 (m, 4H), 1.42 (s, 9H), 1.10 (m, 6H)

Preparation of **12B**:

[0552] To a solution of **12.13** (300 mg, 0.58 mmol) in methylene chloride (4 mL) was added a 2.0 M solution of anhydrous hydrochloric acid in diethyl ether (15 mL). The mixture was stirred at room temperature for 24 h and diluted with diethyl ether. The resulting precipitate was collected by filtration and washed with diethyl ether.
Yield: 95%

^{1}H NMR (400MHz, DMSO d_6) δ 12.61 (brs, 1H), 8.69 (m, 6H), 7.38-7.25 (m, 7H), 6.06 (s, 1H), 3.41 (m, 2H), 3.25 (m, 6H), 2.06 (m, 4H), 1.11 (m, 6H)

Mass Spectral Analysis *m/z* = 421.3 $(M+H)^+$

EXAMPLE 12C

Preparation of **12.14a**

[0553] To a solution of **12.13** (780 mg, 1.5 mmol) in acetonitrile (50 mL) was added sequentially diisopropylethylamine (1.75 mL, 10 mmol, 6.7 eq), a 0.5 M solution of ammonia (**12.15**) in dioxane (30 mL, 15mmol, 10 eq) and TBTU (580 mg, 1.8 mmol, 1.2 eq). The reaction mixture was stirred at room temperature for 3 days and then concentrated under vacuum. The residue was dissolved in ethyl acetate and washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by column chromatography (eluent: hexane/acetone, 1:1).
Yield: 60.4%

^{1}H NMR (400MHz, DMSO d_6) δ 7.51 (s, 1H), 7.29 (t, 1H), 7.22 (s, 4H), 7.10 (d, 1H), 7.05 (d, 1H), 6.97 (s, 1H), 5.90 (s, 1H), 3.63 (m, 2H), 3.41 (m, 2H), 3.32 (m, 2H), 3.20 (m, 2H), 1.80 (m, 4H), 1.42 (s, 9H), 1.10 (m, 6H)

Preparation of **12C**:

[0554] To a solution of **12.14a** (420 mg, 0.81 mmol) in methylene chloride (6 mL) was added a 2.0 M solution of anhydrous hydrochloric acid in diethyl ether (20 mL).

The mixture was stirred at room temperature for 2 days and diluted with diethyl ether. The resulting precipitate was collected by filtration and washed with diethyl ether.
Yield: 87.5%

^{1}H NMR (400MHz, DMSO d_6) δ 9.21 (m, 2H), 7.54 (s, 1H), 7.32-7.10 (m, 7H), 6.88 (s, 1H), 5.98 (s, 1H), 3.42 (m, 2H), 3.20 (m, 6H), 2.10 (m, 4H), 1.10 (m, 6H)
Mass Spectral Analysis $m/z = 420.3$ $(M+H)^+$

EXAMPLE 12D

[0555] **12D** was obtained according to a procedure similar to the one described for **12C**, with the following exception:
Step 12.16: **12.15** was replaced by **3.4b**.
^{1}H NMR (400MHz, DMSO d_6) δ 9.19 (m, 2H), 7.83 (m, 1H), 7.30-7.20 (m, 6H), 7.00 (d, 1H), 5.96 (s, 1H), 3.41 (m, 2H), 3.20 (m, 6H), 2.11 (m, 4H), 2.06 (d, 3H), 1.10 (m, 6H)
Mass Spectral Analysis $m/z = 434.3$ $(M+H)^+$

EXAMPLE 12E

[0556] **12E** was obtained according to a procedure similar to the one described for **12C**, with the following exception:
Step 12.16: **12.15** was replaced by **3.4c**.
^{1}H NMR (400MHz, DMSO d_6) δ 9.18 (m, 2H), 7.90 (t, 1H), 7.30-7.20 (m, 6H), 7.00 (d, 1H), 5.96 (s, 1H), 3.40 (m, 2H), 3.20 (m, 6H), 2.50 (m, 2H), 2.10 (m, 4H), 1.10 (m, 6H), 0.78 (t, 3H)
Mass Spectral Analysis $m/z = 448.4$ $(M+H)^+$
Elemental analysis:
$C_{27}H_{33}N_3O_3$, $5/4H_2O$
Theory: %C 68.99; %H 7.61; %N 8.94
Found: %C 69.27; %H 7.43; %N 8.93

EXAMPLE 12F

[0557] **12 F** was obtained according to a procedure similar to the one described for **12C**, with the following exception:
Step 12.16: **12.15** was replaced by **3.4d**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.98 (m, 2H), 7.91 (t, 1H), 7.31 (m, 1H), 7.20 (m, 5H), 7.00 (m, 1H), 5.96 (s, 1H), 3.45 (m, 4H), 3.20 (m, 6H), 2.40 (m, 2H), 2.08 (m, 4H), 1.10 (m, 6H), 0.70 (t, 3H)

Mass Spectral Analysis *m/z* = 462.4 $(M+H)^+$

Elemental analysis:

$C_{28}H_{35}N_3O_3$, 1HCl, 7/3H_2O

Theory: %C 62.27; %H 7.59; %N 7.78

Found: %C 62.37; %H 7.23; %N 7.74

EXAMPLE 12G

Preparation of **12.7**:

[0558] To a solution of **12.6** (2.25 g, 6 mmol) in a mixed solvent of methanol (40 mL), tetrahydrofuran (40 mL) and water (40 mL) was added lithium hydroxide (1.52 g, 36.2 mmol, 6.0 eq) in one portion. The reaction mixture was stirred at room temperature overnight. The mixture was concentrated under vacuum and extracted with diethyl ether. The aqueous phase was acidified to pH 2-3 using a 1 N aqueous solution of hydrochloric acid. The acidified solution was extracted with methylene chloride. The organics were combined, dried over sodium sulfate, filtered and concentrated under vacuum. The crude product was used in the next step without further purification.

Yield: 100%

^{1}H NMR (400MHz, DMSO d_6) δ 12.93 (brs, 1H), 7.59 (t, 1H), 7.15 (d, 1H), 6.97 (d, 1H), 3.71 (m, 2H), 3.12 (m, 2H), 1.90 (m, 2H), 1.65 (m, 2H), 1.40 (s, 9H)

Preparation of **12.8**:

[0559] To a solution of **12.7** (1.63 g, 4.5 mmol) in acetonitrile (100 mL) was added sequentially diisopropylethylamine (5.23, 30 mmol, 6.7 eq), dimethylamine (**3.4j**) hydrochloride (1.14 g, 14 mmol, 3.0 eq) and TBTU (1.74 g, 5.4 mmol, 1.2 eq). The reaction mixture was stirred at room temperature for 3 days and then concentrated under vacuum. The residue was dissolved in ethyl acetate and washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over sodium

sulfate, filtered and concentrated under vacuum. The crude product was purified by column chromatography (eluent: hexane/acetone, 2:1).
Yield: 60%

^{1}H NMR (400MHz, DMSO d_6) δ 7.50 (t, 1H), 7.00 (d, 1H), 6.85 (d, 1H), 3.89 (m, 2H), 3.22 (m, 2H), 3.14 (s, 3H), 2.74 (s, 3H), 2.03 (m, 2H), 1.62 (m, 2H), 1.48 (s, 6H)

Preparation of **12.9**:

[0560] To a solution of **12.8** (950 mg, 2.45 mmol) in anhydrous tetrahydrofuran (20 mL) at -78°C under nitrogen was added drop wise a 1.0 M solution of LiHMDS in tetrahydrofuran (3.2 mL, 3.2 mmol, 1.3 eq). The reaction mixture was stirred for 45 min at -78°C. A solution of *N*-phenyltrifluoromethanesulfonimide (**1.4**) (1.15 g, 3.2 mmol, 1.3 eq) in tetrahydrofuran (8 mL) was added drop wise to the reaction mixture. The mixture was warmed slowly to room temperature and stirring was continued for an additional 2.5 h at room temperature. The mixture was then poured into ice water and extracted with a mixture of hexane and diethyl ether (1:1). The organic layer was washed with water and brine, and dried over sodium sulfate and filtered. The organic extracts were concentrated under vacuum and the crude product was purified by column chromatography (eluent: methylene chloride/ethyl acetate, 3:1).
Yield: 78.6%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.28 (t, 1H), 6.96 (d, 1H), 6.83 (d, 1H), 5.65 (s, 1H), 3.80 (m, 2H), 3.38 (m, 1H), 3.20 (m, 1H), 3.10 (s, 3H), 2.92 (s, 3H), 2.09 (m, 2H), 1.70 (m, 2H), 1.48 (s, 9H)

Preparation of **12.10**:

[0561] To a solution of **12.9** (950 mg, 1.83 mmol) in dimethoxyethane (DME) (16 mL) was added sequentially a 2N aqueous solution of sodium carbonate (3.1 mL, 6.2 mmol, 3.4 eq), lithium chloride (259 mg, 6.1 mmol, 3.3 eq.), 4-(*N,N*-diethylaminocarbonyl)phenylboronic acid (**1.6**) (486 mg, 2.2 mmol, 1.2 eq) and tetrakis(triphenylphosphine)palladium(0) (64 mg, 0.055 mmol, 0.03 eq). The mixture was refluxed overnight under nitrogen and then cooled to room temperature. To this mixture was added water (20 mL) and the crude product was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and

filtered. The organics were concentrated under vacuum and the crude product was purified by column chromatography (eluent: hexane/acetone, 2:1).
Yield: 88%

^{1}H NMR (400MHz, CDCl$_3$) δ 7.35 (d, 2H), 7.25 (m, 3H), 7.05 (d, 1H), 6.91 (d, 1H), 5.62 (s, 1H), 3.86 (m, 2H), 3.55 (m, 2H), 3.30 (m, 4H), 2.69 (s, 3H), 2.30 (s, 3H), 2.10 (m, 1H), 1.98 (m, 1H), 1.70 (m, 2H), 1.49 (s, 6H), 1.20 (m, 6H)

Preparation of **12G**:

[0562] To a solution of **12.10** (840 mg, 1.54 mmol) in methylene chloride (10 mL) was added a 2.0 M solution of anhydrous hydrochloric acid in diethyl ether (30 mL). The mixture was stirred at room temperature for 2 days and diluted with diethyl ether. The resulting precipitate was collected by filtration and washed with diethyl ether.
Yield: 100%

^{1}H NMR (400MHz, DMSO d$_6$) δ 9.28 (m, 2H), 7.35-7.19 (m, 6H), 6.90 (d, 1H), 5.96 (s, 1H), 3.43 (m, 2H), 3.22 (m, 6H), 2.66 (s, 3H), 2.18 (s, 3H), 2.18 (s, 3H), 2.09 (m, 4H), 1.11 (m, 6H)
Mass Spectral Analysis *m/z* = 448.4 (M+H)$^+$

EXAMPLE 12H

[0563] **12H** was obtained according to a procedure similar to the one described for **12A**, with the following exception:
Step 12.4: **1.6** was replaced by **1.7**.
^{1}H NMR (400MHz, DMSO d$_6$) δ 9.20 (m, 2H), 8.48 (s, 1H), 7.73 (d, 1H), 7.58 (d, 1H), 7.20 (t, 1H), 6.98 (d, 1H), 6.82 (d, 1H), 6.10 (s, 1H), 3.42-3.12 (m, 8H), 2.02 (m, 4H), 1.70 (s, 3H), 1.18 (t, 3H), 1.10 (t, 3H)
Mass Spectral Analysis *m/z* = 392.4 (M+H)$^+$
Elemental analysis:
$C_{24}H_{29}N_3O_3$, 7/5HCl, 7/5H_2O
Theory: %C 61.60; %H 7.15; %N 8.98; %Cl 10.61
Found: %C 61.70; %H 6.78; %N 8.86; %Cl 10.73

EXAMPLE 12I

[0564] **12I** was obtained according to a procedure similar to the one described for **12A**, with the following exception:

Step 12.2: **12.2a** was replaced by **12.2b**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.89 (brs, 2H), 7.12 (d, 2H), 7.04 (d, 2H), 6.95 (t, 1H), 6.71 (d, 1H), 6.58 (d, 1H), 5.66 (s, 1H), 3.20 (brs, 2H), 2.92 (brm, 6H), 1.75 (brm, 6H), 0.86 (brm, 8H), 0.22 (t, 3H)

Mass Spectral Analysis *m/z* = 419.4 $(M+H)^+$

Elemental analysis:

$C_{27}H_{34}N_2O_2$, 1HCl, $1H_2O$

Theory: %C 68.55; %H 7.88; %N 5.92

Found: %C 68.42; %H 7.73; %N 5.92

EXAMPLE 12J

[0565] **12J** was obtained according to a procedure similar to the one described for **12A**, with the following exception:

Step 12.2: **12.2a** was replaced by **12.2c**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.12 (brs, 1.5H), 7.54 (d, 2H), 7.47 (d, 2H), 7.38 (t, 1H), 7.13 (d, 1H), 7.02 (d, 1H), 6.09 (s, 1H), 3.62 (brs, 2H), 3.36 (brm, 5H), 2.18 (brm, 6H), 1.30 (brm, 8H), 1.00 (m, 2H), 0.81 (t, 3H)

Mass Spectral Analysis *m/z* = 433.4 $(M+H)^+$

Elemental analysis:

$C_{28}H_{36}N_2O_2$, 1HCl, $2H_2O$

Theory: %C 66.58; %H 8.18; %N 5.55

Found: %C 66.82; %H 7.88; %N 5.59

EXAMPLE 12K

[0566] **12K** was obtained according to a procedure similar to the one described for **12A**, with the following exceptions:

Step 12.2: **12.2a** was replaced by **12.2b**.

Step 12.4: **1.6** was replaced by **1.7** and Method 12A was used.

^{1}H NMR (400MHz, DMSO d$_6$) δ 9.73 (brs, 1H), 9.61 (brs, 1H), 8.47 (s, 1H), 7.65 (m, 2H), 7.20 (m, 1H), 6.90 (d, 1H), 6.82 (d, 1H), 5.66 (s, 1H), 3.59 (q, 2H), 3.41 (brm, 6H), 2.24 (brs, 4H), 2.01 (brm, 2H), 1.25 (brm, 8H), 0.54 (t, 3H)
Mass Spectral Analysis *m/z* = 420.4 (M+H)$^+$

EXAMPLE 12L

[0567] **12L** was obtained according to a procedure similar to the one described for **12A**, with the following exceptions:
Step 12.2: **12.2a** was replaced by **12.2c**.
Step 12.4: **1.6** was replaced by **1.7** and Method 12A was used.
^{1}H NMR (400MHz, DMSO d$_6$) δ 8.86 (brd, 1.5H), 8.43 (d, 1H), 7.66 (dd, 1H), 7.48 (d, 1H), 7.16 (t, 1H), 6.91 (d, 1H), 6.79 (d, 1H), 5.98 (s, 1H), 3.40 (q, 2H), 3.12 (brm, 5H), 1.94 (brm, 6H), 1.10 (m, 5H), 1.01 (t, 3H), 0.76 (m, 2H), 0.56 (t, 3H)
Mass Spectral Analysis *m/z* = 434.3 (M+H)$^+$

EXAMPLE 13A

Preparation of **13.2**:

[0568] To a solution of **1.5a** (7.80 g, 17.35 mmol, 1.0 eq) in dimethoxyethane (75 mL) was added sequentially a 2N aqueous solution of sodium carbonate (26.03 mL, 52.06 mmol, 3.0 eq), lithium chloride (2.21 g, 52.06 mmol, 3.0 eq), **13.1** (3.44 g, 19.09 mmol, 1.1 eq) and tetrakis(triphenylphosphine)palladium(0) (0.40 g, 0.35 mmol, 0.02 eq). The mixture was refluxed overnight under nitrogen. The mixture was then cooled to room temperature and water (250 mL) was added. The mixture was extracted with ethyl acetate. The organic layer was further washed with brine and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 64%

^{1}H NMR (400MHz, DMSO d$_6$) δ 8.02 (d, 2H), 7.49 (d, 2H), 7.23 (m, 1H), 6.99 (d, 1H), 6.92 (m, 2H), 5.92 (s, 1H), 3.88 (s, 3H), 3.70 (m, 2H), 3.27 (m, 2H), 1.89 (m, 2H), 1.71 (m, 2H), 1.42 (s, 9H)
Mass Spectral Analysis *m/z* = 436.0 (M+H)$^+$

Preparation of **13.3**:

[0569] A solution of **13.2** (4.71 g, 10.81 mmol, 1.0 eq) in tetrahydrofuran (30 mL) at 0°C under nitrogen was added drop wise to a solution of lithium hydroxide monohydrate (0.54 g, 12.98 mmol, 1.2 eq) in water (30 mL). The mixture was stirred overnight at room temperature. The mixture was then concentrated under reduced pressure and redissolved in water. The mixture was then acidified to pH 2 using concentrated hydrochloric acid. The resulting precipitate was collected by filtration and the crude product was used for the next step without further purification.
Yield: 98%

^{1}H NMR (400MHz, DMSO d_6) δ 13.03 (br s, 1H), 8.01 (d, 2H), 7.47 (d, 2H), 7.23 (m, 1H), 6.98 (d, 1H), 6.92 (m, 2H), 5.91 (s, 1H), 3.70 (m, 2H), 3.28 (m, 2H), 1.86 (m, 2H), 1.72 (m, 2H), 1.42 (s, 9H)
Mass Spectral Analysis *m/z* = 420.1 $(M-H)^-$

Preparation of **13A**:

[0570] Trifluoroacetic acid (0.15 mL, 1.96 mmol, 5.5 eq) was added drop wise to a cold (0°C) solution of **13.3** (0.15 g, 0.36 mmol, 1.0 eq) in anhydrous dichloromethane (5 mL). The mixture was warmed to room temperature and stirred overnight at room temperature. The mixture was then concentrated under reduced pressure. The crude product was triturated with diethyl ether. The resulting precipitate was collected by filtration.
Yield: 87%

^{1}H NMR (400MHz, DMSO d_6) δ 13.05 (brs, 1H), 8.67 (m, 2H), 8.02 (d, 2H), 7.49 (d, 2H), 7.27 (m, 1H), 7.05 (d, 1H), 6.96 (m, 2H), 5.98 (s, 1H), 3.26 (m, 4H), 2.08 (m, 2H), 1.97 (m, 2H)
Mass Spectral Analysis *m/z* = 322.1 $(M+H)^+$
Elemental analysis:
$C_{20}H_{19}NO_3$, CF_3CO_2H, $0.2H_2O$
Theory: %C 60.19; %H 4.68; %N 3.19
Found: %C 60.18; %H 4.61; %N 3.24

EXAMPLE 13B

Preparation of **13.5a**:

[0571] *O*-Benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (150.8 mg, 0.47 mmol, 1.1 eq) was added to a cooled (0°C) solution of **13.3** (180.0 mg, 0.43 mmol, 1.0 eq), **3.4a** (50.3 mg, 0.94 mmol, 2.2 eq), and *N,N*-diisopropylethylamine (0.25 mL, 0.94 mmol, 2.2 eq) in acetonitrile (5 mL). The solution was stirred overnight at room temperature and then concentrated under reduced pressure. Ethyl acetate (10 mL) and a saturated aqueous solution of sodium bicarbonate (10 mL) were added to the crude product and the mixture was stirred for 20 min at room temperature. The phases were separated and the organic phase was washed with a saturated aqueous solution of sodium bicarbonate, brine, dried over sodium sulfate and filtered. The organics were concentrated under reduced pressure and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 10%

Mass Spectral Analysis *m/z* = 421.2 $(M+H)^+$

Preparation of **13B**:

[0572] A 2.0M solution of hydrochloric acid in diethyl ether (0.12 mL, 0.24 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **13.5a** (18 mg, 0.04 mmol, 1.0 eq) in anhydrous methanol (5 mL). The mixture was stirred overnight at room temperature and then concentrated under reduced pressure. The crude product was triturated with ethyl acetate. The resulting precipitate was collected by filtration.
Yield: 70%
^{1}H NMR (400MHz, DMSO d_6) δ 8.99 (m, 2H), 8.06 (m, 1H), 7.95 (m, 2H), 7.46 (m, 3H), 7.27 (m, 1H), 7.06 (m, 1H), 6.96 (m, 2H), 5.95 (s, 1H), 3.24 (m, 4H), 2.08 (m, 4H)
Mass Spectral Analysis *m/z* = 321.1 $(M+H)^+$

EXAMPLE 13C

[0573] **13C** was obtained according to a procedure similar to the one described for **13B**, with the following exception:

Step 13.6: **3.4a** was replaced by **3.4b**.

^{1}H NMR (400MHz, DMSO d$_6$) δ 9.05 (m, 2H), 8.55 (m, 1H), 7.92 (m, 2H), 7.41 (m, 2H), 7.26 (m, 1H), 7.06 (m, 1H), 6.95 (m, 2H), 5.95 (s, 1H), 3.20 (m, 4H), 2.81 (m, 3H), 2.08 (m, 4H)

Mass Spectral Analysis *m/z* = 335.2 $(M+H)^+$

EXAMPLE 13D

[0574] **13D** was obtained according to a procedure similar to the one described for **13B**, with the following exception:

Step 13.6: **3.4a** was replaced by **3.4c**.

^{1}H NMR (400MHz, DMSO d$_6$) δ 8.50 (m, 1H), 7.90 (d, 2H), 7.40 (d, 2H), 7.20 (m, 1H), 6.90 (m, 3H), 5.85 (s, 1H), 3.30 (m, 2H), 2.90 (m, 2H), 2.70 (m, 2H), 1.85-1.70 (m, 4H), 1.10 (t, 3H)

Mass Spectral Analysis *m/z* = 349.2 $(M+H)^+$

Elemental analysis:

$C_{22}H_{24}N_2O_2$, 0.25 $(CH_3)_2CO$, 0.25H_2O

Theory: %C 70.89; %H 7.32; %N 7.27

Found: %C 71.13; %H 7.04; %N 7.07

EXAMPLE 13E

[0575] **13E** was obtained according to a procedure similar to the one described for **13B**, with the following exception:

Step 13.6: **3.4a** was replaced by **3.4e**.

^{1}H NMR (400MHz, CDCl$_3$) δ 9.75 (brs, 1H), 9.31 (brs, 1H), 7.81 (d, 2H), 7.39 (d, 2H), 7.21 (m, 1H), 6.98 (m, 2H), 6.90 (m, 1H), 6.25 (m, 1H), 5.56 (s, 1H), 3.46 (m, 2H), 3.33 (m, 4H), 2.30 (m, 2H), 2.12 (m, 2H), 1.94 (m, 1H), 1.04 (d, 6H)

Mass Spectral Analysis *m/z* = 377.2 $(M+H)^+$

EXAMPLE 13F

[0576] **13F** was obtained according to a procedure similar to the one described for **13B**, with the following exception:

Step 13.6: **3.4a** was replaced by **3.4j**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.08 (m, 2H), 7.42 (m, 4H), 7.24 (m, 1H), 7.00 (m, 3H), 5.91 (s, 1H), 3.25 (m, 4H), 2.96 (m, 6H), 2.07 (m, 4H)

Mass Spectral Analysis *m/z* = 349.1 $(M+H)^+$

EXAMPLE 13G

[0577] **13G** was obtained according to a procedure similar to the one described for **13B**, with the following exception:

Step 13.6: **3.4a** was replaced by **3.4k**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.91 (m, 2H), 7.58 (d, 2H), 7.41 (d, 2H), 7.25 (m, 1H), 7.00 (m, 3H), 5.92 (s, 1H), 3.49 (m, 2H), 3.41 (m, 2H), 3.24 (m, 4H), 2.09 (m, 2H), 2.00 (m, 2H), 1.84 (m, 4H)

Mass Spectral Analysis *m/z* = 375.1 $(M+H)^+$

EXAMPLE 13H

[0578] **13H** was obtained according to a procedure similar to the one described for **13B**, with the following exception:

Step 13.6: **3.4a** was replaced by **3.4o**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.98 (m, 2H), 7.39 (dd, 4H), 7.24 (m, 1H), 6.95 (m, 3H), 5.91 (s, 1H), 3.66 (brs, 2H), 3.22 (m, 4H), 2.10 (m, 4H), 1.30 (m, 12H)

Mass Spectral Analysis *m/z* = 405.3 $(M+H)^+$

Elemental analysis:

$C_{26}H_{32}N_2O_2$, 1HCl, $0.5H_2O$

Theory: %C 69.39; %H 7.62; %N 6.22

Found: %C 69.31; %H 7.64; %N 6.19

EXAMPLE 13I

[0579] **13I** was obtained according to a procedure similar to the one described for **13B**, with the following exception:

Step 13.6: **3.4a** was replaced by **3.4p**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.91 (m, 2H), 7.46 (m, 4H), 7.26 (m, 1H), 7.01 (m, 3H), 5.94 (s, 1H), 3.61 (m, 6H), 3.35 (m, 2H), 3.21 (m, 4H), 2.09 (m, 2H), 1.98 (m, 2H)

Mass Spectral Analysis *m/z* = 391.1 $(M+H)^+$

EXAMPLE 13J

[0580] **13J** was obtained according to a procedure similar to the one described for **13B**, with the following exception:

Step 13.6: **3.4a** was replaced by **3.4q**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.90 (m, 2H), 7.44 (m, 4H), 7.26 (m, 1H), 7.00 (m, 3H), 5.91 (s, 1H), 3.59 (m, 2H), 3.21 (m, 6H), 2.09 (m, 2H), 1.99 (m, 2H), 1.55 (m, 6H)

Mass Spectral Analysis *m/z* = 389.1 $(M+H)^+$

EXAMPLE 13K

[0581] **13K** was obtained according to a procedure similar to the one described for **13B**, with the following exception:

Step 13.6: **3.4a** was replaced by **13.4a**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.75 (m, 2H), 7.49 (m, 2H), 7.41 (m, 2H), 7.26 (m, 1H), 7.05 (m, 1H), 6.97 (m, 2H), 5.95 (s, 1H), 4.00 (brm, 4H), 3.23 (m, 4H), 2.10 (m, 2H), 1.97 (m, 2H), 1.64 (m, 2H), 1.15 (brm, 6H)

Mass Spectral Analysis *m/z* = 403.3 $(M+H)^+$

Elemental analysis:

$C_{26}H_{30}N_2O_2$, 1HCl, 0.3H_2O

Theory: %C 70.27; %H 7.17; %N 6.30

Found: %C 70.02; %H 7.04; %N 6.27

EXAMPLE 13L

[0582] **13L** was obtained according to a procedure similar to the one described for **13B**, with the following exception:

Step 13.6: **3.4a** was replaced by **13.4b**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.90 (m, 2H), 7.70 (d, 2H), 7.50 (d, 2H), 7.40 (m, 1H), 7.30 (m, 4H), 7.00 (m, 3H), 5.95 (s, 1H), 4.90 (s, 2H), 4.80 (s, 2H), 3.30 (brm, 4H), 2.05 (m, 4H)

Mass Spectral Analysis *m/z* = 423.1 $(M+H)^+$

Elemental analysis:

$C_{28}H_{26}N_2O_2$, 1HCl, 1H_2O

Theory: %C 70.50; %H 6.13; %N 5.87

Found: %C 70.58; %H 5.95; %N 5.89

EXAMPLE 13M

[0583] **13M** was obtained according to a procedure similar to the one described for **13B**, with the following exception:

Step 13.6: **3.4a** was replaced by **13.4c**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.00 (m, 1H), 7.40 (m, 4H), 7.25 (m, 1H), 7.00 (m, 3H), 5.90 (s, 1H), 3.55-3.05 (m, 8H), 2.05 (m, 4H), 1.60 (m, 2H), 1.10 (m, 1H), 0.90 (m, 2H), 0.65 (m, 1H), 0.40 (m, 2H), 0.15 (m, 1H), 0.10 (m, 1H)

Mass Spectral Analysis *m/z* = 417.2 $(M+H)^+$

Elemental analysis:

$C_{27}H_{32}N_2O_2$, 1HCl, $0.4H_2O$

Theory: %C 70.46; %H 7.40; %N 6.09

Found: %C 70.54; %H 7.30; %N 6.15

EXAMPLE 13N

[0584] **13N** was obtained according to a procedure similar to the one described for **13B**, with the following exception:

Step 13.6: **3.4a** was replaced by **13.4d**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.88 (m, 2H), 7.40 (brm, 10H), 7.00 (m, 3H), 5.94 (s, 1H), 4.70 (m, 1H), 4.52 (m, 1H), 3.21 (m, 4H), 2.88 (m, 3H), 2.02 (m, 4H)

Mass Spectral Analysis *m/z* = 425.2 $(M+H)^+$

Elemental analysis:

$C_{28}H_{28}N_2O_2$, 1HCl, $0.6H_2O$

Theory: %C 71.28; %H 6.45; %N 5.94

Found: %C 71.13; %H 6.51; %N 5.97

EXAMPLE 13O

[0585] **13O** was obtained according to a procedure similar to the one described for **13B**, with the following exception:

Step 13.6: **3.4a** was replaced by **13.4e**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.65 (m, 2H), 7.45 (m, 4H), 7.26 (m, 1H), 7.00 (m, 3H), 5.95 (s, 1H), 4.36 (m, 2H), 4.11 (m, 2H), 3.88 (m, 2H), 3.60 (m, 2H), 3.00 (m, 2H), 2.65 (m, 1H), 2.09 (m, 2H), 1.99 (m, 4H), 1.52 (m, 2H), 1.19 (m, 3H)

Mass Spectral Analysis *m/z* = 461.2 $(M+H)^+$

EXAMPLE 13P

[0586] **13P** was obtained according to a procedure similar to the one described for **13B**, with the following exception:

Step 13.6: **3.4a** was replaced by **13.4f**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.60 (m, 2H), 7.47 (m, 4H), 7.25 (m, 1H), 7.00 (m, 3H), 5.95 (s, 1H), 4.18 (m, 2H), 3.80 (brs, 4H), 3.24 (m, 2H), 3.00 (s, 3H), 2.10 (m, 2H), 1.94 (m, 2H), 1.20 (m, 3H)

Mass Spectral Analysis *m/z* = 421.2 $(M+H)^+$

EXAMPLE 13Q

[0587] **13Q** was obtained according to a procedure similar to the one described for **13B**, with the following exception:

Step 13.6: **3.4a** was replaced by **13.4g**.

^{1}H NMR (400MHz, DMSO d_6) δ 10.32 (brs, 1H), 8.80 (m, 2H), 7.54 (m, 2H), 7.46 (m, 2H), 7.27 (m, 1H), 7.00 (m, 3H), 5.92 (s, 1H), 4.54 (brs, 2H), 3.84 (brs, 2H), 3.45 (m, 2H), 3.24 (m, 4H), 3.12 (m, 2H), 2.83 (s, 3H), 2.10 (m, 2H), 1.97 (m, 2H)

Mass Spectral Analysis *m/z* = 404.3 $(M+H)^+$

EXAMPLE 13R

[0588] **13R** was obtained according to a procedure similar to the one described for **13B**, with the following exception:

Step 13.6: **3.4a** was replaced by **13.4h**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.55 (m, 1H), 8.95 (m, 1H), 7.55 (m, 5H), 7.30 (brm, 10H), 7.04 (m, 1H), 6.95 (m, 2H), 5.93 (s, 1H), 4.62 (s, 2H), 4.46 (s, 2H), 3.20 (m, 4H), 2.02 (m, 4H)

Mass Spectral Analysis *m/z* = 501.2 $(M+H)^+$

EXAMPLE 13S

Preparation of **13S**:

[0589] A 2N aqueous solution of sodium hydroxide (1.0 mL, 2 mmol, 9.2 eq) was added to a solution of **13O** (0.10 g, 0.22 mmol, 1.0 eq) in tetrahydrofuran (5 mL) and anhydrous absolute ethanol (1 mL). The mixture was stirred for 10h at room temperature and acidified to pH 6 using a 2N aqueous solution of hydrochloric acid. The mixture was concentrated under reduced pressure. The crude product was dissolved in dichloromethane. The mixture was filtered and the filtrate was concentrated under reduced pressure.

Yield: 60%

^{1}H NMR (400MHz, DMSO d_6) δ 7.43 (m, 4H), 7.25 (m, 1H), 7.01 (m, 2H), 6.94 (m, 1H), 5.93 (s, 1H), 4.33 (br s, 2H), 3.65-2.90 (m, 9H), 1.91 (m, 6H), 1.52 (m, 2H)
Mass Spectral Analysis *m/z* = 433.1 $(M+H)^+$

EXAMPLE 14A

Preparation of **14.2**:

[0590] To a solution of **1.5a** (5.00 g, 11.12 mmol, 1.0 eq) in dimethoxyethane (17 mL) was added sequentially a 2N aqueous solution of sodium carbonate (16.69 mL, 33.37 mmol, 3.0 eq), lithium chloride (1.41 g, 33.37 mmol, 3.0 eq), **14.1** (1.80 g, 12.24 mmol, 1.1 eq) and tetrakis(triphenylphosphine)palladium(0) (0.26 g, 0.22 mmol, 0.02 eq). The mixture was refluxed for 10h under nitrogen. The mixture was then cooled to room temperature and a 1N aqueous solution of sodium hydroxide was added. The mixture was extracted with dichloromethane. The organic layer was further washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was triturated with diethyl ether. The resulting solid was collected bu filtration.

Yield: 78%

^{1}H NMR (400MHz, DMSO d_6) δ 7.90 (d, 2H), 7.50 (d, 2H), 7.20 (m, 1H), 7.00 (m, 1H), 6.90 (m, 2H), 5.95 (s, 1H), 3.70 (m, 2H), 3.25 (m, 2H), 1.85 (m, 2H), 1.70 (m, 2H), 1.40 (s, 9H)

Mass Spectral Analysis *m/z* = 403.1 $(M+H)^+$

Preparation of **14.4**:

[0591] A mixture of **14.2** (3.49 g, 8.67 mmol, 1.0 eq), **14.3** (1.13 g, 17.34 mmol, 2.0 eq) and zinc bromide (0.98 g, 4.34 mmol, 0.5 eq) in isopropanol (70 mL) and water (50 mL) was refluxed for 3 days. The reaction mixture was then cooled to 0°C and acidified to pH 1 using a 3N aqueous solution of hydrochloric acid. The mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Diethyl ether (30 mL) was added. The resulting precipitate was collected by filtration and washed with diethyl ether. The crude compound was used for the next step without further purification.

Yield: 89%

^{1}H NMR (400MHz, DMSO d_6) δ 8.10 (d, 2H), 7.55 (d, 2H), 7.20 (m, 1H), 7.00 (m, 2H), 6.90 (m, 1H), 5.90 (s, 1H), 3.70 (m, 2H), 3.30 (m, 2H), 1.90 (m, 2H), 1.70 (m, 2H), 1.40 (s, 9H)

Mass Spectral Analysis *m/z* = 446.0 $(M+H)^+$

Preparation of **14A**:

[0592] A 2.0M solution of hydrochloric acid in diethyl ether (21.3 mL, 42.58 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **14.4** (3.71 g, 7.74 mmol, 1.0 eq) in anhydrous dichloromethane (25 mL). The mixture was warmed to room temperature and stirring was continued for an additional 10h at room temperature. Diethyl ether (100 mL) was added to the solution. The resulting precipitate was collected by filtration and washed with diethyl ether. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity).

Yield: 20%

^{1}H NMR (400MHz, DMSO d_6) δ 9.08 (brs, 2H), 8.16 (d, 2H), 7.61 (d, 2H), 7.28 (m, 1H), 7.02 (m, 3H), 6.02 (s, 1H), 3.59 (brs, 1H), 3.24 (m, 4H), 2.06 (m, 4H)

Mass Spectral Analysis *m/z* = 346.1 $(M+H)^+$

Elemental analysis:

$C_{20}H_{19}N_5O$, 1HCl, $0.5H_2O$

Theory: %C 61.46; %H 5.42; %N 17.92

Found: %C 61.52; %H 5.23; %N 17.63

EXAMPLE 14B

Preparation of **14.5** and **14.6**

[0593] Methyl iodide (**2.8c**) (0.35 mL, 0.0056 mol, 5.0 eq) was added drop wise to a solution of **14.4** (0.500 g, 0.0011 mol, 1.0 eq) and triethylamine (0.80 mL, 0.0056 mol, 5.0 eq) in anhydrous dimethylformamide (5 mL) and the mixture was stirred at room temperature for 3 days. The mixture was poured into water (50 mL) and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield **14.5** (major regioisomer): 65%

Mass Spectral Analysis *m/z* = 460.1 $(M+H)^+$

Yield **14.6** (minor regioisomer): 17%

Mass Spectral Analysis *m/z* = 460.2 $(M+H)^+$

Preparation of **14B**

[0594] A 2.0M anhydrous solution of hydrochloric acid in diethyl ether (10 mL) was added drop wise to a cold (0°C) solution of **14.5** (0.330 g, 0.00071 mol, 1.0 eq) in anhydrous dichloromethane (10 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 h at room temperature. The mixture was concentrated under reduced pressure and diethyl ether was added to the residue. The resulting precipitate was collected by filtration and washed with diethyl ether.

Yield: 90%

^{1}H NMR (400MHz, DMSO d_6) δ 8.80 (m, 1H), 8.10 (d, 2H), 7.55 (d, 2H), 7.25 (t, 1H), 6.90-7.10 (m, 3H), 6.00 (s, 1H), 4.45 (s, 3H), 3.15-3.40 (m, 4H), 1.95-2.15 (m, 4H)

Mass Spectral Analysis *m/z* = 360.1 $(M+H)^+$

EXAMPLE 14C

Preparation of **14C**

[0595] A 2.0M anhydrous solution of hydrochloric acid in diethyl ether (5 mL) was added drop wise to a cold (0°C) solution of **14.6** (0.090 g, 0.00019 mol, 1.0 eq) in anhydrous dichloromethane (10 mL). The mixture was warmed to room temperature and stirring was continued for an additional 10h at room temperature. The mixture was concentrated under reduced pressure and diethyl ether was added to the reisdue. The resulting precipitate was collected by filtration and washed with diethyl ether. Yield: 88%

^{1}H NMR (400MHz, DMSO d_6) δ 8.80 (m, 1.5H), 7.90 (d, 2H), 7.60 (d, 2H), 7.25 (t, 1H), 6.90-7.10 (m, 3H), 6.00 (s, 1H), 4.20 (s, 3H), 3.20 (m, 4H), 1.95-2.15 (m, 4H)

Mass Spectral Analysis *m/z* = 360.2 $(M+H)^+$

EXAMPLE 15A

[0596] **15A** was obtained according to a procedure similar to the one described for **15C**, with the following exception:

Step 15.1: **15.1c** was replaced by **15.1a**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.87 (brm, 1H), 8.16 (d, 2H), 7.59 (d, 2H), 7.29 (m, 1H), 7.06 (m, 2H), 6.97 (m, 1H), 6.02 (s, 1H), 5.96 (s, 2H), 3.77 (s, 3H), 3.23 (brm, 4H), 2.11 (brm, 2H), 2.00 (brm, 2H)

Mass Spectral Analysis *m/z* = 418.1 $(M+H)^+$

EXAMPLE 15B

[0597] **15B** was obtained according to a procedure similar to the one described for **15C**, with the following exception:

Step 15.1: **15.1c** was replaced by **15.1b**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.75 (m, 1H), 8.15 (d, 2H), 7.57 (d, 2H), 7.25 (t, 1H), 7.00 (m, 3H), 6.00 (s, 1H), 5.00 (t, 2H), 3.60 (s, 3H), 3.10-3.40 (m, 6H), 1.95-2.18 (m, 4H)

Mass Spectral Analysis *m/z* = 432.2 $(M+H)^+$

EXAMPLE 15C

Preparation of **15.2a** and **15.3a**:

[0598] Ethyl bromobutyrate (**15.1c**) (0.40 mL, 0.0028 mol, 2.5 eq) was added drop wise to a solution of **14.4** (0.500 g, 0.0011 mol, 1.0 eq) and triethylamine (0.40 mL, 0.0028 mol, 2.5 eq) in anhydrous *N*,*N*-dimethylformamide and the mixture was stirred at room temperature for 3 days. The mixture was poured into water (50 mL) and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield **15.2a** (major regioisomer): 82%.

(15.2a) ^{1}H NMR (400MHz, DMSO d_6) δ 8.10 (d, 2H), 7.50 (d, 2H), 7.20 (m, 1H), 7.00 (m, 2H), 6.90 (m, 1H), 5.90 (s, 1H), 4.70 (t, 2H), 4.00 (q, 2H), 3.70 (m, 2H), 3.30 (m, 2H), 2.40 (m, 2H), 2.10 (m, 2H), 1.90 (m, 2H), 1.70 (m, 2H), 1.40 (s, 9H), 1.15 (t, 3H)

Mass Spectral Analysis *m/z* = 560.2 $(M+H)^+$

Yield **15.3a** (minor regioisomer): 6%.

(15.3a) ^{1}H NMR (400MHz, DMSO d_6) δ 7.90 (d, 2H), 7.60 (d, 2H), 7.20 (m, 1H), 7.00 (m, 2H), 6.90 (m, 1H), 5.95 (s, 1H), 4.55 (t, 2H), 4.00 (q, 2H), 3.70 (m, 2H), 3.30 (m, 2H), 2.40 (m, 2H), 2.10 (m, 2H), 1.90 (m, 2H), 1.70 (m, 2H), 1.40 (s, 9H), 1.10 (t, 3H)

Mass Spectral Analysis *m/z* = 560.2 $(M+H)^+$

Preparation of **15C**:

[0599] A 2.0M anhydrous solution of hydrochloric acid in diethyl ether (10 mL) was added drop wise to a cold (0°C) solution of **15.2a** (0.520 g, 0.00092 mol, 1.0 eq) in anhydrous dichloromethane (10 mL). The mixture was warmed to room temperature and stirring was continued for an additional 10h at room temperature. An additional amount of a 2.0M anhydrous solution of hydrochloric acid in diethyl ether (10 mL) was added to the mixture, which was stirred for an additional 6h at room temperature. The mixture was concentrated under reduced pressure and diethyl ether was added. The resulting precipitate was collected by filtration and washed with diethyl ether.

Yield: 70%

^{1}H NMR (400MHz, DMSO d_6) δ 8.80 (m, 1H), 8.15 (d, 2H), 7.60 (d, 2H), 7.25 (m, 1H), 7.00 (m, 3H), 6.00 (s, 1H), 4.80 (t, 2H), 4.00 (q, 2H), 3.35 (m, 2H), 3.20 (m, 2H), 2.40 (m, 2H), 2.20 (m, 2H), 2.10 (m, 2H), 1.95 (m, 2H), 1.15 (t, 3H)

Mass Spectral Analysis $m/z = 460.2\ (M+H)^+$

EXAMPLE 15D

[0600] **15D** was obtained according to a procedure similar to the one described for **15C**, with the following exception:

Step 15.1: **15.1c** was replaced by **15.1d**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.90 (brm, 1.5H), 8.14 (d, 2H), 7.57 (d, 2H), 7.28 (t, 1H), 7.04 (m, 2H), 6.96 (m, 1H), 6.00 (s, 1H), 4.78 (t, 2H), 4.04 (q, 2H), 3.22 (brm, 4H), 2.37 (t, 2H), 2.11 (brm, 2H), 2.01 (brm, 4H), 1.57 (m, 2H), 1.16 (t, 3H)

Mass Spectral Analysis $m/z = 474.2\ (M+H)^+$

EXAMPLE 15E

[0601] **15E** was obtained according to a procedure similar to the one described for **15C**, with the following exception:

Step 15.1: **15.1c** was replaced by **15.1e**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.88 (brm, 1.5H), 8.14 (d, 2H), 7.57 (d, 2H), 7.28 (t, 1H), 7.05 (m, 2H), 6.96 (m, 1H), 6.00 (s, 1H), 4.76 (t, 2H), 4.02 (q, 2H), 3.22 (brm, 4H), 2.29 (t, 2H), 2.10 (brm, 2H), 2.00 (brm, 4H), 1.57 (m, 2H), 1.30 (m, 2H), 1.14 (t, 3H)

Mass Spectral Analysis $m/z = 488.2\ (M+H)^+$

EXAMPLE 15F

[0602] **15F** was obtained according to a procedure similar to the one described for **15H**, with the following exception:

Step 15.1: **15.1c** was replaced by **15.1a**.

^{1}H NMR (400MHz, DMSO d$_6$) δ 8.86 (brm, 1H), 7.84 (d, 2H), 7.62 (d, 2H), 7.29 (m, 1H), 7.07 (d, 1H), 6.99 (m, 2H), 6.03 (s, 1H), 5.71 (s, 2H), 3.70 (s, 3H), 3.23 (m, 4H), 2.11 (brm, 2H), 2.00 (brm, 2H)

Mass Spectral Analysis *m/z* = 418.2 $(M+H)^+$

EXAMPLE 15G

[0603] **15G** was obtained according to a procedure similar to the one described for **15H**, with the following exception:

Step 15.1: **15.1c** was replaced by **15.1b**.

^{1}H NMR (400MHz, DMSO d$_6$) δ 8.78 (brm, 1H), 7.91 (d, 2H), 7.64 (d, 2H), 7.29 (m, 1H), 7.05 (m, 2H), 6.98 (m, 1H), 6.04 (s, 1H), 4.71 (t, 2H), 3.56 (s, 3H), 3.23 (m, 4H), 3.11 (t, 2H), 2.12 (brm, 2H), 2.00 (brm, 2H)

Mass Spectral Analysis *m/z* = 432.1 $(M+H)^+$

EXAMPLE 15H

Preparation of **15H**

[0604] A 2.0M anhydrous solution of hydrochloric acid in diethyl ether (10 mL) was added drop wise to a cold (0°C) solution of **15.3a** (0.030 g, 0.000053 mol, 1.0 eq) in anhydrous dichloromethane (10 mL). The mixture was warmed to room temperature and stirring was continued for an additional 10h at room temperature. An additional amount of a 2.0M anhydrous solution of hydrochloric acid in diethyl ether (10 mL) was added to the mixture, which was stirred for an additional 6h at room temperature. The mixture was concentrated under reduced pressure and diethyl ether was added. The resulting precipitate was collected by filtration and washed with diethyl ether.

Yield: 57%

^{1}H NMR (400MHz, DMSO d$_6$) δ 9.00 (m, 1.5H), 7.90 (d, 2H), 7.62 (d, 2H), 7.30 (m, 1H), 7.05 (m, 2H), 6.95 (m, 1H), 6.00 (s, 1H), 4.60 (t, 2H), 4.00 (q, 2H), 3.25 (m, 4H), 2.40 (m, 2H), 2.10 (m, 6H), 1.15 (t, 3H)

Mass Spectral Analysis *m/z* = 460.2 $(M+H)^+$

EXAMPLE 15I

[0605] **15I** was obtained according to a procedure similar to the one described for **15H**, with the following exception:

Step 15.1: **15.1c** was replaced by **15.1d**.

^{1}H NMR (400MHz, DMSO d$_6$) δ 8.96 (brm, 1.5H), 7.89 (d, 2H), 7.63 (d, 2H), 7.29 (t, 1H), 7.06 (m, 2H), 6.97 (m, 1H), 6.03 (s, 1H), 4.55 (t, 2H), 4.01 (q, 2H), 3.22 (brm, 4H), 2.29 (t, 2H), 2.12 (brm, 2H), 2.02 (brm, 2H), 1.85 (m, 2H), 1.49 (m, 2H), 1.13 (t, 3H)

Mass Spectral Analysis *m/z* = 474.3 $(M+H)^+$

EXAMPLE 15J

[0606] **15J** was obtained according to a procedure similar to the one described for **15H**, with the following exception:

Step 15.1: **15.1c** was replaced by **15.1e**.

^{1}H NMR (400MHz, DMSO d$_6$) δ 8.93 (brm, 1H), 7.87 (d, 2H), 7.62 (d, 2H), 7.29 (t, 1H), 7.05 (m, 2H), 6.97 (m, 1H), 6.03 (s, 1H), 4.52 (t, 2H), 4.01 (q, 2H), 3.23 (brm, 4H), 2.22 (t, 2H), 2.11 (brm, 2H), 2.02 (brm, 2H), 1.83 (m, 2H), 1.47 (m, 2H), 1.23 (m, 2H), 1.14 (t, 3H)

Mass Spectral Analysis *m/z* = 488.3 $(M+H)^+$

EXAMPLE 15K

[0607] **15K** was obtained according to a procedure similar to the one described for **15L**, with the following exception:

Step 15.6: **15C** was replaced by **15A**.

^{1}H NMR (400MHz, DMSO d$_6$) δ 8.18 (d, 2H), 7.60 (d, 2H), 7.29 (t, 1H), 7.06 (t, 2H), 6.97 (m, 1H), 6.02 (s, 1H), 5.80 (s, 2H), 3.27 (brm, 4H), 2.13 (brm, 2H), 2.00 (brm, 2H)

Mass Spectral Analysis *m/z* = 404.1 $(M+H)^+$

EXAMPLE 15L

[0608] Preparation of **15L**

A 2N aqueous solution of sodium hydroxide (1.8 mL, 0.0036 mol, 5.5 eq) was added to a solution of **15C** (0.300 g, 0.00060 mol, 1.0 eq) in tetrahydrofuran (10 mL) and absolute ethanol (1 mL). The mixture was stirred for 10h at room temperature and acidified to pH 6 using a 2N aqueous solution of hydrochloric acid. The mixture was concentrated under reduced pressure and diethyl ether was added. The mixture was then stirred for 1h at room temperature. The resulting precipitate was collected by filtration and washed several times with water and diethyl ether.

Yield: 98%

^{1}H NMR (400MHz, DMSO d_6 + CF_3CO_2D) δ 8.80 (m, 1H), 8.20 (m, 2H), 7.70 (m, 2H), 7.30 (m, 1H), 7.00 (m, 3H), 6.00 (s, 1H), 4.80 (m, 2H), 3.30 (m, 4H), 2.60-1.95 (m, 8H)

Mass Spectral Analysis *m/z* = 432.1 $(M+H)^+$

EXAMPLE 15M

[0609] **15M** was obtained according to a procedure similar to the one described for **15L**, with the following exception:

Step 15.6: **15C** was replaced by **15D**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.76 (brm 1H), 8.16 (d, 2H), 7.58 (d, 2H), 7.29 (t, 1H), 7.06 (t, 2H), 6.97 (m, 1H), 6.00 (s, 1H), 4.78 (t, 2H), 3.24 (m, 4H), 2.31 (t, 2H), 2.13 (brm, 2H), 2.01 (brm, 4H), 1.56 (m, 2H)

Mass Spectral Analysis *m/z* = 446.2 $(M+H)^+$

EXAMPLE 15N

[0610] **15N** was obtained according to a procedure similar to the one described for **15L**, with the following exception:

Step 15.6: **15C** was replaced by **15E**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.62 (brm, 1.5H), 8.15 (d, 2H), 7.57 (d, 2H), 7.28 (m, 1H), 7.05 (m, 2H), 6.97 (m, 1H), 6.00 (s, 1H), 4.76 (t, 2H), 3.25 (brm, 4H), 2.21 (t, 2H), 2.11 (brm, 2H), 1.98 (brm, 4H), 1.55 (m, 2H), 1.31 (m, 2H)

Mass Spectral Analysis *m/z* = 460.2 $(M+H)^+$

EXAMPLE 16A

[0611] **16A** was obtained according to a procedure similar to the one described for **14A**, with the following exception:

Step 14.1: **14.1** was replaced by **16.1** (see also step 16.1).

^{1}H NMR (400MHz, DMSO d$_6$) δ 9.00 (brs, 2H), 8.12 (t, 2H), 7.70 (t, 1H), 7.60 (t, 1H), 7.25 (t, 1H), 7.00 (m, 3H), 6.00 (s, 1H), 3.30 (m, 4H), 2.05 (m, 4H)

Mass Spectral Analysis *m/z* = 346.1 $(M+H)^+$

EXAMPLE 16B

[0612] **16B** was obtained according to a procedure similar to the one described for **14B**, with the following exception:

Step 14.1: **14.1** was replaced by **16.1** (see also step 16.1).

^{1}H NMR (400MHz, DMSO d$_6$) δ 8.66 (brm, 2H), 8.11 (m, 1H), 8.01 (m, 1H), 7.66 (t, 1H), 7.54 (m, 1H), 7.28 (m, 1H), 7.06 (d, 1H), 6.97 (m, 2H), 6.00 (s, 1H), 4.43 (s, 3H), 3.23 (brm, 4H), 2.12 (brm, 2H), 2.00 (brm, 2H)

Mass Spectral Analysis *m/z* = 360.1 $(M+H)^+$

EXAMPLE 16C

[0613] **16C** was obtained according to a procedure similar to the one described for **14C**, with the following exception:

Step 14.1: **14.1** was replaced by **16.1** (see also step 16.1).

^{1}H NMR (400MHz, DMSO d$_6$) δ 8.73 (brm, 2H), 7.91 (m, 1H), 7.83 (t, 1H), 7.72 (t, 1H), 7.03 (m, 1H), 7.28 (m, 1H), 7.05 (m, 2H), 6.96 (m, 1H), 6.02 (s, 1H), 4.20 (s, 3H), 3.23 (brm, 4H), 2.11 (brm, 2H), 1.99 (brm, 2H)

Mass Spectral Analysis *m/z* = 360.1 $(M+H)^+$

EXAMPLE 17A

[0614] **17A** was obtained according to a procedure similar to the one described for **15A**, with the following exception:

Step 15.1: **14.4** was replaced by **16.3** (see also step 17.1).

^{1}H NMR (400MHz, DMSO d_6) δ 8.93 (brs, 1.5H), 8.13 (m, 1H), 8.03 (t, 1H), 7.68 (t, 1H), 7.56 (m, 1H), 7.28 (m, 1H), 7.07 (m, 1H), 6.97 (m, 2H), 6.01 (s, 1H), 5.94 (s, 2H), 3.75 (s, 3H), 3.22 (brm, 4H), 2.12 (brm, 2H), 2.02 (brm, 2H)

Mass Spectral Analysis *m/z* = 418.1 $(M+H)^+$

EXAMPLE 17B

[0615] **17B** was obtained according to a procedure similar to the one described for **15C**, with the following exception:

Step 15.1: **14.4** was replaced by **16.3** (see also step 17.1).

^{1}H NMR (400MHz, DMSO d_6) δ 9.07 (brs, 2H), 8.11 (m, 1H), 8.01 (t, 1H), 7.66 (t, 1H), 7.54 (m, 1H), 7.28 (m, 1H), 7.07 (dd, 1H), 6.96 (m, 2H), 5.99 (s, 1H), 4.79 (t, 2H), 4.03 (q, 2H), 3.22 (brm, 4H), 2.42 (t, 2H), 2.21 (m, 2H), 2.09 (brm, 4H), 1.16 (t, 3H)

Mass Spectral Analysis *m/z* = 460.2 $(M+H)^+$

EXAMPLE 17C

[0616] **17C** was obtained according to a procedure similar to the one described for **15F**, with the following exceptions:

Step 15.1: **14.4** was replaced by **16.3** (see also step 17.1).

^{1}H NMR (400MHz, DMSO d_6) δ 8.95 (brs, 2H), 7.80 (m, 1H), 7.69 (m, 3H), 7.28 (m, 1H), 7.06 (d, 1H), 6.97 (m, 2H), 5.99 (s, 1H), 5.70 (s, 2H), 3.64 (s, 3H), 3.23 (brm, 4H), 2.10 (brm, 2H), 2.01 (brm, 2H)

Mass Spectral Analysis *m/z* = 418.1 $(M+H)^+$

EXAMPLE 17D

[0617] **17D** was obtained according to a procedure similar to the one described for **15C**, with the following exceptions:

Step 15.1: **14.4** was replaced by **16.3** (see also step 17.1).

^{1}H NMR (400MHz, DMSO d_6) δ 8.37 (dt, 1H), 8.30 (t, 1H), 7.81 (t, 1H), 7.71 (dt, 1H), 7.44 (m, 1H), 7.22 (m, 2H), 7.10 (m, 1H), 5.98 (s, 1H), 5.47 (t, 2H), 4.22 (brs, 2H), 4.15 (t, 2H), 4.02-3.46 (brm, 10H), 2.48 (brm, 2H), 2.22 (brm, 2H)

Mass Spectral Analysis *m/z* = 459.2 $(M+H)^+$

EXAMPLE 17E

[0618] **17E** was obtained according to a procedure similar to the one described for **15K**, with the following exceptions:

Step 15.1: **14.4** was replaced by **16.3** (see also step 17.1).

^{1}H NMR (400MHz, DMSO d_6) δ 8.87 (brm, 2H), 8.13 (dt, 1H), 8.03 (t, 1H), 7.68 (t, 1H), 7.56 (m, 1H), 7.28 (m, 1H), 7.07 (d, 1H), 6.98 (m, 2H), 6.01 (s, 1H), 5.77 (s, 2H), 3.24 (brm, 4H), 2.12 (brm, 2H), 2.02 (brm, 2H)

Mass Spectral Analysis *m/z* = 404.1 $(M+H)^+$

EXAMPLE 17F

[0619] **17F** was obtained according to a procedure similar to the one described for **15L**, with the following exception:

Step 15.1: **14.4** was replaced by **16.3** (see also step 17.1).

^{1}H NMR (400MHz, DMSO d_6) δ 8.11 (dt, 1H), 8.01 (m, 1H), 7.66 (t, 1H), 7.54 (dt, 1H), 7.28 (m, 1H), 7.07 (d, 1H), 6.97 (m, 2H), 5.99 (s, 1H), 4.78 (t, 2H), 3.21 (brm, 4H), 2.34 (t, 2H), 2.18 (m, 2H), 2.10 (brm, 4H)

Mass Spectral Analysis *m/z* = 432.1 $(M+H)^+$

EXAMPLE 18A

[0620] Preparation of **18.2**:

A mixture of **13.5a** (0.300g, 0.00071 mole, 1.0 eq), and the Lawesson's reagent (**18.1**) (0.288g, 0.00071 mole, 1 eq) in toluene (10 mL) was refluxed for 6h. The mixture was cooled to room temperature, poured onto a saturated aqueous solution of sodium bicarbonate (50 mL) and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Diethyl ether was added to the mixture, which was stirred at room temperature for 1h. The resulting precipitate was collected by filtration, washed with diethyl ether and used for the next step without further purification.

Yield: 64%

Mass Spectral Analysis *m/z* = 434.93 $(M-H)^-$

[0621] Preparation of **18.4a**:

A mixture of **18.2** (1g, 0.0022 mole, 1.0 eq) and 1-bromopinacolone (**18.3a**) (0.30 mL, 0.0022 mole, 1.0 eq) in *N,N*-dimethylformamide (5 mL) was stirred at room temperature for 48h. The mixture was poured into a saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 55%

^{1}H NMR (400MHz, DMSO d_6) δ 8.00 (d, 2H), 7.45 (d, 2H), 7.35 (s, 1H), 7.20 (t, 1H), 7.00 (d, 2H), 6.90 (t, 1H), 5.90 (s, 1H), 3.70 (m, 2H), 3.30 (m, 2H), 1.90 (m, 2H), 1.70 (m, 2H), 1.30 (s, 9H), 1.35 (s, 9H)

Mass Spectral Analysis *m/z* = 517.2 $(M+H)^+$

[0622] Preparation of **18A**:

To a cold (0°C) solution of **18.4a** (0.600g, 0.0011 mole, 1.0 eq) in anhydrous dichloromethane (20 mL) was added drop wise a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (5.8 mL, 0.0011 mole, 10.0 eq). The mixture was warmed slowly to room temperature and stirring was continued for 12h. The mixture was concentrated under reduced pressure. Diethyl ether was then added to the mixture, which was stirred for 1h at room temperature. The precipitate was collected by filtration, washed with diethyl ether and dried under vacuum.

Yield: 80%

^{1}H NMR (400MHz, DMSO d_6) δ 9.00 (s, 2H), 8.00 (d, 2H), 7.50 (d, 2H), 7.40 (s, 1H), 7.25 (t, 1H), 7.00 (m, 3H), 6.00 (s, 1H), 3.20 (m, 4H), 2.00 (m, 4H), 1.30 (s, 9H)

Mass Spectral Analysis *m/z* = 417.3 $(M+H)^+$

EXAMPLE 18B

[0623] **18B** was obtained according to a procedure similar to the one described for **18A**, with the following exception:

Step 18.3: **18.3a** was replaced by **18.3b**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.93 (brs, 2H), 8.24 (s, 1H), 8.10 (m, 4H), 7.52 (m, 4H), 7.40 (m, 1H), 7.29 (m, 1H), 7.06 (t, 2H), 6.97 (m, 1H), 6.00 (s, 1H), 3.22 (brm, 4H), 2.07 (brm, 4H)
Mass Spectral Analysis *m/z* = 437.1 $(M+H)^+$

EXAMPLE 18C

[0624] Preparation of **18.6**:

A mixture of **14.2** (1g, 0.00248 mole, 1.0 eq), hydroxylamine hydrochloride (**18.5**) (0.260g, 0.0037 mole, 1.5 eq.) and triethylamine (0.70 mL, 0.0049 mole, 2.0 eq) in absolute ethanol (15 mL) was refluxed for 6h. The mixture was cooled to room temperature and poured onto water. The resulting precipitate was collected by filtration, washed with water, dried under high vacuum and used for the next step without further purification.
Yield: 75%
Mass Spectral Analysis *m/z* = 436.2 $(M+H)^+$

[0625] Preparation of **18.7**

Acetyl chloride (**6.7**) (0.07 mL, 0.00097 mol, 2.0 eq) was added drop wise to a refluxing solution of **18.6** (0.212g, 0.00048 mole, 1.0 eq) in pyridine (2 mL). The mixture was heated to reflux for 3h. The mixture was cooled to room temperature, poured onto a saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate. The organic phase was washed with a 1N aqueous solution of hydrochloric acid and brine, dried over sodium sulfate and filtered. The organics were concentrated under reduced pressure and the crude product was purified by flash column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 35%
^{1}H NMR (400MHz, $CDCl_3$) δ 8.10 (d, 2H), 7.45 (d, 2H), 7.20 (m, 1H), 7.00 (m, 1H), 6.95 (m, 1H), 6.85 (m, 1H), 5.60 (s, 1H), 3.90 (m, 2H), 3.35 (m, 2H), 2.65 (s, 3H), 2.05 (d, 2H), 1.70 (m, 2H), 1.55 (s, 4H), 1.40 (s, 5H)
Mass Spectral Analysis *m/z* = 460.1 $(M+H)^+$

[0626] Preparation of **18C**

To a cold (0°C) solution of **18.7** (0.300g, 0.00065 mole, 1.0 eq) in anhydrous dichloromethane (20 mL) was added drop wise a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (3.2 mL, 0.0065 mole, 10.0 eq). The mixture was warmed slowly to room temperature and stirring was continued for 12h. The mixture was concentrated under reduced pressure. Diethyl ether was then added to the mixture, which was stirred for 1h at room temperature. The precipitate was collected by filtration, washed with diethyl ether and dried under vacuum.

Yield: 60%

^{1}H NMR (400MHz, DMSO d_6) δ 9.00 (m, 2H), 8.10 (m, 2H), 7.60 (m, 2H), 7.30 (m, 1H), 7.05 (m, 3H), 6.00 (s, 1H), 3.30 (m, 4H), 2.45-2.80 (m, 3H), 2.10 (m, 4H)
Mass Spectral Analysis *m/z* = 360.3 $(M+H)^+$

EXAMPLE 19A

[0627] Preparation of **19.2**:

To a solution of **19.1** (29.75 g, 127.5 mmol, 1.2 eq) in dry methanol (200 mL) was added pyrrolidine (17.6 mL, 212.6 mmol, 2.0 eq) followed by 2'-hydroxyacetophenone (**1.1a**) (12.8 mL, 106.3 mmol, 1.0 eq). The mixture was heated under reflux for 10h. The volatiles were removed under reduced pressure and the residue was dissolved in ethyl acetate (500 mL), washed with a 1M aqueous solution of hydrochloric acid (3 x 200 mL), a 1M aqueous solution of sodium hydroxide (3 x 200 mL) and brine. The organics were dried over sodium sulfate, filtered and concentrated under reduced pressure to give the crude product, which was used in the next step without further purification.
^{1}H NMR (400MHz, $CDCl_3$) δ 7.86 (dd, 1H), 7.50 (m, 1H), 7.42-7.29 (m, 5H), 7.00 (m, 2H), 5.14 (s, 2H), 3.97 (brs, 2H), 3.29 (brs, 2H), 2.71 (s, 2H), 2.04 (m, 2H), 1.61 (m, 2H)
Mass Spectral Analysis *m/z* = 352.1 $(M+H)^+$

[0628] Preparation of **19.3**:

Under nitrogen, to an oven-dried two-necked 1L flask charged with a solution of **19.2** (45.4 g, as of 106.3 mmol, 1.0 eq) in dry tetrahydrofuran (350 mL) at -78°C was added a solution of 1.0M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (127.6 mL, 127.6 mmol, 1.2 eq) over a 45 min time period. The reaction mixture was kept at -78°C for 1h and a solution of *N*-phenylbis(trifluoromethanesulfonamide) (**1.4**) (45.57 g, 127.6 mmol, 1.2 eq) in tetrahydrofuran (150 mL) was added over a 45 min time period. The reaction mixture was kept at -78°C for 1h, then slowly warmed up to room temperature and stirred for an additional 10h at room temperature. Ice water (300 mL) was added to quench the reaction and the product was extracted with diethyl ether (500 mL). The organic phase was then washed with a 1M aqueous solution of hydrochloric acid (3 x 150 mL), a 1M aqueous solution of sodium hydroxide (3 x 150 mL), and brine, dried over sodium sulfate and filtered. The organics were concentrated under reduced pressure to give the crude product, which was used for the next step without further purification.
Mass Spectral Analysis $m/z = 484.0\ (M+H)^+$

[0629] Preparation of **19.4**:

To a solution of **1.14** (53.58 g, 212.6 mmol, 2.0 eq) in *N,N*-dimethylformamide (200 mL) at 0°C was added potassium acetate (31.3 g, 318.9 mmol, 3.0 eq), 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride complex with dichloromethane (2.33 g, 3.19 mmol, 0.03 eq). The reaction mixture was heated to 80°C at which point a solution of **19.3** (60 g, crude, as of 106.3 mmol, 1.0 eq) in *N,N*-dimethylformamide (100 mL) was added to the reaction mixture over a 30 min time period. The reaction mixture was then stirred at 80°C for 10h. Diethyl ether (500 mL) and water (300 mL) were added and the two phases were separated. The organic phase was washed with a 1M aqueous solution of hydrochloric acid (2 x 150 mL) and brine, dried over sodium sulfate and filtered. The organics were concentrated under reduced pressure and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 75 % over three steps

^{1}H NMR (400MHz, $CDCl_3$) δ 7.71 (dd, 1H), 7.43-7.28 (m, 5H), 7.11 (m, 1H), 6.90 (m, 1H), 6.82 (dd, 1H), 6.27 (s, 1H), 5.14 (s, 2H), 3.94 (brs, 2H), 3.34 (brs, 2H), 1.96 (m, 2H), 1.61 (m, 2H), 1.33 (s, 12H)
Mass Spectral Analysis *m/z* = 462.2 $(M+H)^+$

[0630] Preparation of **19.6**:

To a solution of *tert*-butyl 4-bromophenylcarbamate (**19.5**) (20.7 g, 76 mmol, 1.04 eq) in dimethoxyethane (200 mL) was added sequentially a 2M aqueous solution of sodium carbonate (109.5 mL, 210 mmol, 3.0 eq), lithium chloride (9.28 g, 210 mmol, 3.0 eq), tetrakis(triphenylphosphine)palladium(0) (1.69 g, 1.46 mmol, 0.02 eq), and **19.4** (33.7 g, 73 mmol, 1.0 eq) under nitrogen. The reaction mixture was heated under reflux for 10h. Water (500 mL) and diethyl ether (300 mL) were added and the two phases were separated. The organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting foamy solids were soaked with hexane and the fine powders were collected by filtration.
Yield: 91%
^{1}H NMR (400MHz, $CDCl_3$) δ 7.43-7.30 (m, 7H), 7.28-7.23 (m, 2H), 7.17 (m, 1H), 7.02 (m, 1H), 6.92 (m, 1H), 6.85 (m, 1H), 6.53 (s, 1H), 5.50 (s, 1H), 5.15 (s, 2H), 3.96 (brs, 2H), 3.40 (brs, 2H), 2.06 (m, 2H), 1.67 (m, 2H), 1 53 (s, 9H)
Mass Spectral Analysis *m/z* = 527.4 $(M+H)^+$

[0631] Preparation of **19.7**:

To a cold (0°C) solution of **19.6** (35.5 g, 67 mmol, 1.0 eq) in anhydrous dichloromethane (150 mL) was slowly added a 2.0M solution of hydrogen chloride in diethyl ether (167.5 mL, 335 mmol, 5.0 eq). The reaction mixture was stirred at room temperature for 10h and then concentrated under reduced pressure. The resulting foamy solids were soaked in diethyl ether and the fine powders were collected by filtration. This crude product was used for the next steps without further purification.
Mass Spectral Analysis *m/z* = 427.3 $(M+H)^+$

[0632] Preparation of **19.9a**:

To a suspension of **19.7** (1.28 g, crude, as of 3 mmol, 1.0 eq) in dry dichloromethane (80 mL) at 0°C was slowly added triethylamine (2.1 mL, 15 mmol, 5.0 eq) followed by drop wise addition of isobutyryl chloride (**19.8a**) (0.48 mL, 4.5 mmol, 1.5 eq). The mixture was slowly warmed to room temperature and stirred for 10h at room temperature. Dichloromethane (100 mL) was added and the mixture was washed with a 1N aqueous solution of hydrochloric acid (3 x 50 mL), a saturated aqueous solution of sodium bicarbonate (2 x 50 mL) and brine, dried over sodium sulfate and filtered. The crude product was concentrated under reduced pressure and purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 81 % over two steps
^{1}H NMR (400MHz, $CDCl_3$) δ 7.57 (d, 2H), 7.40-7.27 (m, 8H), 7.17 (m, 1H), 7.01 (d, 1H), 6.93 (d, 1H), 6.85 (m, 1H), 5.50 (s, 1H), 5.15 (s, 2H), 3.96 (brs, 2H), 3.41 (brs, 2H), 2.53 (m, 1H), 2.06 (m, 2H), 1.67 (m, 2H), 1.28 (d, 6H)
Mass Spectral Analysis *m/z* = 467.3 $(M+H)^+$

[0633] Preparation of **19A**
To a stirred solution of **19.9a** (1.2 g, 2.44 mmol, 1.0 eq) in dry dichloromethane (20 mL) was added iodotrimethylsilane (0.66 mL, 4.89 mmol, 2.0 eq) drop wise. After stirring at room temperature for 1h, the mixture was concentrated to dryness under reduced pressure. A 1N aqueous solution of hydrochloric acid (300 mL) and diethyl ether (200 mL) were added to the residue. The resulting solid was collected by filtration, washed with diethyl ether, and dried under vacuum.
Yield: 92 %
^{1}H NMR (400MHz, DMSO d_6) δ 10.02 (s, 1H), 8.98 (brs, 2H), 7.70 (d, 2H), 7.36-7.22 (m, 3H), 7.02 (m, 2H), 6.94 (m, 1H), 5.82 (s, 1H), 3.21 (m, 4H), 2.63 (m, 1H), 2.03 (m, 4H), 1.11 (d, 6H)
Mass Spectral Analysis *m/z* = 363.4 $(M+H)^+$

EXAMPLE 19B

[0634] **19B** was obtained according to a procedure similar to the one described for **19A**, with the following exception:
Step 19.6: **19.8a** was replaced by **19.8b**.

^{1}H NMR (400MHz, DMSO d$_6$) δ 10.04 (s, 1H), 8.90 (m, 2H), 7.71 (m, 2H), 7.29 (m, 2H), 7.25 (m, 1H), 7.03 (m, 2H), 6.94 (m, 1H), 5.82 (s, 1H), 3.44-3.11 (m, 4H), 2.25 (m, 1H), 2.02 (m, 4H), 1.51 (m, 4H), 0.86 (t, 6H)
Mass Spectral Analysis *m/z* = 391.4 $(M+H)^+$

EXAMPLE 19C

[0635] Preparation of **19.10**:

To a solution of **19.7** (4.63 g, crude, as of 10 mmol, 1.0 eq) in dry pyridine (10 mL) at 0°C was slowly added isopropylsulfonyl chloride (**6.5b**) (1.68 mL, 15 mmol, 1.5 eq). The reaction mixture was stirred at room temperature for 10h. Pyridine was removed under reduced pressure and the residue was dissolved in ethyl acetate (200 mL). The solution was washed with a 1M aqueous solution of hydrochloric acid (5 x 50 mL) and brine, dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 55 % over two steps
^{1}H NMR (400MHz, CDCl$_3$) δ 7.43-7.16 (m, 10H), 6.99 (dd, 1H), 6.94 (dd, 1H), 6.86 (m, 1H), 6.60 (s, 1H), 5.51 (s, 1H), 5.15 (s, 2H), 3.96 (brs, 2H), 3.49-3.30 (m, 3H), 2.06 (m, 2H), 1.67 (m, 2H), 1.43 (d, 6H)
Mass Spectral Analysis *m/z* = 533.3 $(M+H)^+$

[0636] Preparation of **19C**:

To a stirred solution of **19.9a** (1.37 g, 2.57 mmol, 1.0 eq) in dry dichloromethane (20 mL) was added iodotrimethylsilane (0.70 mL, 5.14 mmol, 2.0 eq) dropwise. The mixture was stirred at room temperature for 1h and then concentrated under reduced pressure. To the residue was added a 1M aqueous solution of hydrochloric acid (300 mL) and diethyl ether (200 mL). The resulting solid was collected by filtration and washed with diethyl ether. The crude compound was further purified by preparative liquid chromatography (mobile phase: acetonitrile/water/trifluoroacetic acid). The desired fractions were combined, concentrated under reduced pressure, and dried unde vacuum.
Yield: 66%

^{1}H NMR (400MHz, DMSO d_6) δ 9.93 (brs, 1H), 8.67 (brs, 2H), 7.36-7.22 (m, 5H), 7.05-6.91 (m, 3H), 5.83 (s, 1H), 3.32-3.14 (m, 5H), 2.06 (m, 2H), 1.93 (m, 2H), 1.26 (d, 6H)

Mass Spectral Analysis *m/z* = 399.3 $(M+H)^+$

EXAMPLE 19D

[0637] Preparation of **19.12**:

To a solution of **19.7** (1.28 g, crude, as of 2.67 mmol, 1.0 eq) in dry pyridine (15 mL) at 0°C was slowly added ethyl isocyanate (**19.11**) (0.33mL, 4.15 mmol, 1.5 eq). The reaction mixture was stirred at room temperature for 10h. Pyridine was removed under reduced pressure and the residue was partitioned between water (100 mL) and dichlorometnane (200 mL). The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 78 % over two steps

^{1}H NMR (400MHz, $CDCl_3$) δ 7.44-7.12 (m, 10H), 7.05-6.79 (m, 4H), 5.45 (s, 1H), 5.16 (m, 3H), 3.95 (brs, 2H), 3.50-3.26 (m, 4H), 2.04 (m, 2H), 1.65 (m, 2H), 1.16 (t, 3H)

Mass Spectral Analysis *m/z* = 498.4 $(M+H)^+$

[0638] Preparation of **19D**:

To a stirred solution of **19.12** (1.03 g, 2.09 mmol, 1.0 eq) in dry dichloromethane (20 mL) was added iodotrimethylsilane (0.57 mL, 4.18 mmol, 2.0 eq) drop wise. The reaction mixture was stirred at room temperature for 1h and then concentrated under reduced pressure. The residue was suspended in methanol (50 mL) and stirred for another 1h at room temperature. The resulting solid was collected by filtration and washed with methanol. The solid was further washed with a 1M aqueous solution of sodium hydroxide (3 x 10 mL) and water (2 x 10mL), and then dried under vacuum.

Yield: 60%

^{1}H NMR (400MHz, DMSO d_6) δ 8.54 (s, 1H), 7.44 (d, 2H), 7.18 (m, 3H), 6.98 (m, 1H), 6.91 (m, 1H), 6.86 (m, 1H), 6.13 (t, 1H), 5.72 (s, 1H), 3.11 (m, 2H), 2.89 (m, 2H), 2.74 (m, 2H), 1.77 (m, 2H), 1.67 (m, 2H), 1.06 (t, 3H)

Mass Spectral Analysis *m/z* = 364.4 $(M+H)^+$

EXAMPLE 20A

[0639] Preparation of **20A**:

Triethylamine (0.37 mL, 2.66 mmol, 2.2 eq) was added to a solution of **1A** (0.50 g, 1.21 mmol, 1.0 eq) in anhydrous tetrahydrofuran (4 mL). Anhydrous methanol (4 mL) was then added followed by **20.1a** (0.20 mL, 2.42 mmol, 2.0 eq). Sodium cyanoborohydride (0.09 g, 1.45 mmol, 1.2 eq) was added to the reaction mixture which was stirred for 30 min at room temperature under nitrogen. The mixture was concentrated under reduced pressure. Dichloromethane (30 mL) and water (10 mL) were added and the suspension was stirred at room temperature for 10 min. The phases were separated. The organic phase was further washed with water and brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. To a cold (0°C) solution of the resulting oil in anhydrous dichloromethane was added drop wise a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (5 mL). The mixture was then stirred for 1h at room temperature and concentrated under reduced pressure. Diethyl ether was added. The resulting precipitate was collected by filtration and washed with diethyl ether.

Yield: 65%

^{1}H NMR (400MHz, DMSO d_6) δ 10.63 (brs, 0.25H), 10.50 (brs, 0.75H), 7.42 (m, 4H), 7.28 (m, 1H), 7.08 (d, 1H), 6.98 (m, 2H), 6.27 (s, 0.25H), 5.85 (s, 0.75H), 3.37 (brm, 8H), 2.82 (s, 3H), 2.11 (m, 4H), 1.12 (m, 6H)

Mass Spectral Analysis *m/z* = 391.2 $(M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_2O_2$, 1HCl, $0.9H_2O$

Theory: %C 67.75; %H 7.46; %N 6.32

Found: %C 67.89; %H 7.32; %N 6.26

EXAMPLE 20B

[0640] **20B** was obtained according to a procedure similar to the one described for **20A**, with the following exception:

Step 20.1: **1A** was replaced by **11A**.

^{1}H NMR (400MHz, DMSO d_6) δ 10.42 (brs, 1H), 9.47 (s, 1H), 7.30 (m, 4H), 7.08 (t, 1H), 6.60 (d, 1H), 6.46 (d, 1H), 5.68 (s, 1H), 3.40 (m, 4H), 3.30 (s, 3H), 3.20 (m, 2H), 2.81 (s, 2H), 2.15 (m, 2H), 2.05 (m, 2H), 1.10 (m, 6H)

Mass Spectral Analysis *m/z* = 407.3 $(M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_2O_3$, 1HCl, $0.5H_2O$

Theory: %C 66.43; %H 7.14; %N 6.20

Found: %C 66.53; %H 7.06; %N 6.24

EXAMPLE 20C

[0641] **20C** was obtained according to a procedure similar to the one described for **20A**, with the following exception:

Step 20.1: **1A** was replaced by **11B**.

^{1}H NMR (400MHz, DMSO d_6) δ 10.79 (brs, 1H), 9.74 (d, 1H), 8.41 (s, 1H), 7.69 (dd, 1H), 7.45 (d, 1H), 7.09 (t, 1H), 6.62 (d, 1H), 6.49 (d, 2H), 5.81 (s, 1H), 3.42 (m, 4H), 3.30 (m, 4H), 2.79 (d, 3H), 2.12 (m, 4H), 1.16 (m, 3H), 1.08 (m, 3H)

Mass Spectral Analysis *m/z* = 408.3 $(M+H)^+$

EXAMPLE 20D

[0642] **20D** was obtained according to a procedure similar to the one described for **20A**, with the following exception:

Step 20.1: **1A** was replaced by **3D**.

^{1}H NMR (400MHz, DMSO d_6) δ 11.00 (m, 0.25H), 10.85 (m, 0.75H), 7.80 (m, 2H), 7.54 (m, 1H), 7.40 (m, 4H), 7.22 (m, 1H), 7.10 (m, 0.75H), 7.02 (m, 0.25H), 6.32 (s, 0.25H), 5.91 (s, 0.75H), 3.33 (m, 10H), 2.80 (m, 2H), 2.20 (m, 3H), 1.11 (m, 6H)

Mass Spectral Analysis *m/z* = 434.4 $(M+H)^+$

Elemental analysis:

$C_{26}H_{31}N_3O_3$, 1HCl, $1H_2O$

Theory: %C 63.99; %H 7.02; %N 8.61

Found: %C 64.11; %H 6.70; %N 8.49

EXAMPLE 20E

[0643] **20E** was obtained according to a procedure similar to the one described for **20A**, with the following exception:

Step 20.1: **1A** was replaced by **3E**.

^{1}H NMR (400MHz, DMSO d_6) δ 10.84 (m, 1H), 8.31 (m, 1H), 7.78 (m, 1H), 7.52 (m, 1H), 7.42 (m, 3H), 7.10 (m, 1H), 5.90 (s, 1H), 3.46 (m, 2H), 3.31 (m, 10H), 2.82 (m, 2H), 2.72 (m, 2H), 2.12 (m, 3H), 1.16 (m, 6H)

Mass Spectral Analysis *m/z* = 448.5 $(M+H)^+$

Elemental analysis:

$C_{27}H_{33}N_3O_3$, 1HCl, 1H_2O

Theory: %C 64.59; %H 7.23; %N 8.37

Found: %C 64.77; %H 7.27; %N 8.40

EXAMPLE 20F

[0644] **20F** was obtained according to a procedure similar to the one described for **20A**, with the following exception:

Step 20.1: **1A** was replaced by **3F**.

^{1}H NMR (400MHz, DMSO d_6) δ 10.80 (brs, 1H), 8.35 (m, 1H), 7.78 (m, 1H), 7.50 (m, 1H), 7.40 (m, 3H), 7.09 (m, 1H), 5.93 (s, 1H), 3.41 (m, 2H), 3.20 (m, 10H), 2.72 (m, 2H), 2.10 (m, 3H), 1.10 (m, 9H)

Mass Spectral Analysis *m/z* = 462.5 $(M+H)^+$

Elemental analysis:

$C_{28}H_{35}N_3O_3$, 1HCl, 1H_2O

Theory: %C 65.17; %H 7.42; %N 8.14

Found: %C 65.28; %H 7.37; %N 8.21

EXAMPLE 20G

[0645] **20G** was obtained according to a procedure similar to the one described for **20A**, with the following exception:

Step 20.1: **1A** was replaced by **3V**.

^{1}H NMR (400MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.70 (m, 2H), 7.66 (d, 1H), 7.38 (s, 1H), 7.02 (d, 1H), 5.70 (s, 1H), 3.61 (m, 2H), 3.46 (m, 2H), 2.62 (m, 2H), 2.52 (m 2H), 2.12 (m, 2H), 2.78 (m, 2H), 1.30 (t, 3H), 1.23 (t, 3H)

Mass Spectral Analysis *m/z* = 435.4 $(M+H)^+$

EXAMPLE 20H

[0646] **20H** was obtained according to a procedure similar to the one described for **20L**, with the following exception:

Step 20.1: **21A** was replaced by **4H** and **20.1d** was replaced by **20.1a**.

^{1}H NMR (400MHz, DMSO d_6) δ 10.44-10.12 (m, 1H), 7.74 (dd, 0.7H), 7.67 (dd, 0.7H), 7.45 (m, 5H), 7.27 (m, 3H), 6.38 (s, 0.3H), 6.00 (s, 0.7H), 3.53-3.16 (m, 8H), 2.84 (m, 3H), 2.35-2.03 (m, 4H), 1.12 (brd, 6H)

Mass Spectral Analysis *m/z* = 470.3 $(M+H)^+$

Elemental analysis:

$C_{25}H_{31}N_3O_4S$, 1HCl, $1H_2O$

Theory: %C 57.30 %H 6.54 %N 8.02

Found: %C 57.46 %H 6.44 %N 7.96

EXAMPLE 20I

[0647] **20I** was obtained according to a procedure similar to the one described for **20L**, with the following exception:

Step 20.1: **20.1d** was replaced by **20.1a**.

^{1}H NMR (400MHz, DMSO d_6) δ 10.62 (brs, 1H), 7.41 (m, 4H), 7.24 (m, 1H), 6.97 (m, 2H), 6.93 (m, 1H), 5.92 & 5.86 (2s, 1H, rotamer), 3.55–2.92 (m, 8H), 2.80 & 2.77 (d, 3H), 2.56-1.76 (m, 6H), 1.12 (m, 6H)

Mass Spectral Analysis *m/z* = 405.4 $(M+H)^+$

EXAMPLE 20J

[0648] **20J** was obtained according to a procedure similar to the one described for **20L**, with the following exception:

Step 20.1: **20.1d** was replaced by **20.1b**.

^{1}H NMR (400MHz, DMSO d$_6$) δ 10.72 (m, 1H), 7.41 (m, 4H), 7.24 (m, 1H), 6.95 (m, 3H), 5.91 & 5.84 (2s, 1H, rotamer), 3.56-2.94 (m, 10H), 2.57-1.77 (m, 6H), 1.27 (m, 3H), 1.12 (m, 6H)
Mass Spectral Analysis *m/z* = 419.4 (M+H)$^+$

EXAMPLE 20K

[0649] **20K** was obtained according to a procedure similar to the one described for **20L**, with the following exception:
Step 20.1: **20.1d** was replaced by **20.1c**.
^{1}H NMR (400MHz, DMSO d$_6$) δ 9.99 (m, 1H), 7.41 (m, 4H), 7.25 (m, 1H), 6.95 (m, 3H), 5.88 & 5.86 (2s, 1H rotamer), 3.70-2.93 (m, 10H), 2.57-1.76 (m, 7H), 1.12 (m, 6H), 0.99 (m, 6H)
Mass Spectral Analysis *m/z* = 447.5 (M+H)$^+$

EXAMPLE 20L

[0650] Preparation of **20L**:

To a stirred solution of cyclopropanecarbaldehyde (**20.1d**) (0.22 mL, 3.0 mmol, 2.0 eq) in dry dichloromethane (25 mL) was added sequentially **21A** (0.64 g, 1.5 mmol, 1.0 eq), acetic acid (0.10 mL, 1.8 mmol, 1.2 eq), and sodium cyanoborohydride (0.14 g, 2.25 mmol, 1.5 eq). The reaction mixture was stirred at room temperature for 10h. Water (40 mL) was added and the aqueous layer was basified to pH=10 with a 1M aqueous solution of sodium hydroxide. The two phases were separated and the aqueous phase was saturated with sodium chloride and extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity). The desired fractions were combined and concentrated under reduced pressure. To a cold (0°C) solution of the resulting oil in dichloromethane was added dropwise a 2.0M solution of hydrogen chloride in diethyl ether (1.0 mL, 2.0 mmol, 2.0 eq). The mixture was then stirred for 1h at room temperature, concentrated under reduced pressure, and dried under vacuum.
Yield: 65%

^{1}H NMR (400MHz, DMSO d_6) δ 10.66 (brs, 1H), 7.41 (m, 4H), 7.25 (m, 1H), 7.03-6.89 (m, 3H), 5.91 & 5.86 (2s, 1H, rotomer), 3.80-2.95 (m, 10H), 2.44-1.78 (m, 6H), 1.12 (m, 7H), 0.64 (m, 2H), 0.42 (m, 2H)

Mass Spectral Analysis *m/z* = 445.4 $(M+H)^+$

EXAMPLE 20M

[0651] Preparation of **20M**:

Triethylamine (0.98 mL, 7.00 mmol, 3.3 eq) was added to a solution of **1A** (0.80 g, 2.12 mmol, 1.0 eq) in anhydrous dichloromethane (5 mL). Compound **2.8a** (0.68 mL, 7.00 mmol, 3.3 eq) was then added to the reaction mixture, which was stirred overnight at room temperature under nitrogen. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity). To a solution of the purified product in dichloromethane (5 mL) was added at 0°C a 2.0 M solution of hydrochloric acid in diethyl ether (3.2mL, 1.16 mmol, 5.5 eq). Diethyl ether was added to the mixture. The resulting precipitate was collected by filtration and washed with diethyl ether.

Yield: 46%

^{1}H NMR (400MHz, DMSO d_6) δ 10.83 (m, 0.25H), 10.71 (m, 0.75H), 7.45 (m, 4H), 7.28 (m, 1H), 7.08 (m, 1H), 7.00 (m, 2H), 6.24 (s, 0.25H), 5.85 (s, 0.75H), 3.47 (m, 5H), 3.25 (m, 4H), 3.06 (m, 2H), 2.18 (m, 4H), 1.12 (m, 6H), 0.65 (m, 2H), 0.43 (m, 2H)

Mass Spectral Analysis *m/z* = 431.0 $(M+H)^+$

EXAMPLE 20N

[0652] **20N** was obtained according to a procedure similar to the one described for **20M**, with the following exception:

Step 20.1: **2.8a** was replaced by **20.2a**.

^{1}H NMR (400MHz, DMSO d_6) δ 10.10 (m, 1H), 7.43 (m, 4H), 7.28 (m, 1H), 7.09 (m, 1H), 6.98 (m, 2H), 6.28 (s, 0.25H), 5.85 (s, 0.75H), 3.35 (brm, 10H), 2.15 (m, 4H), 1.28 (m, 3H), 1.11 (m, 6H)

Mass Spectral Analysis *m/z* = 405.0 $(M+H)^+$

EXAMPLE 20O

[0653] **20O** was obtained according to a procedure similar to the one described for **20M**, with the following exception:

Step 20.1: **2.8a** was replaced by **20.2b**.

^{1}H NMR (400MHz, DMSO d_6) δ 10.18 (m, 1H), 7.45 (m, 4H), 7.29 (m, 1H), 7.09 (m, 1H), 6.98 (m, 2H), 6.25 (m, 0.25H), 5.84 (m, 0.75H), 3.41 (m, 4H), 3.21 (m, 4H), 3.09 (m, 2H), 2.16 (m, 4H), 1.75 (m, 2H), 1.11 (m, 6H), 0.91 (m, 3H)

Mass Spectral Analysis *m/z* = 419.1 $(M+H)^+$

EXAMPLE 20P

[0654] **20P** was obtained according to a procedure similar to the one described for **20M**, with the following exception:

Step 20.1: **2.8a** was replaced by **20.2c**.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.35 (m, 9H), 7.17 (m, 1H), 6.98 (dd, 1H), 6.94 (dd, 1H), 6.84 (m, 1H), 5.61 (s, 1H), 3.58 (brs, 4H), 3.32 (brs, 2H), 2.60 (brm, 4H), 2.08 (brm, 2H), 1.81 (brm, 2H), 1.20 (brd, 6H)

Mass Spectral Analysis *m/z* = 467.3 $(M+H)^+$

EXAMPLE 20Q

[0655] **20Q** was obtained according to a procedure similar to the one described for **20M**, with the following exception:

Step 20.1: **2.8a** was replaced by **20.2d**.

^{1}H NMR (400MHz, DMSO d_6) δ 10.95 (brs, 0.5H) 7.44 (m, 4H), 7.33 (m, 6H), 7.04 (d, 1H), 6.99 (m, 2H), 6.24 (s, 0.3H), 5.87 (s, 0.7H), 3.40 (brm, 10H), 3.12 (m, 2H), 2.18 (brm, 4H), 1.13 (brd, 6H)

Mass Spectral Analysis *m/z* = 481.3 $(M+H)^+$

EXAMPLE 20R

[0656] **20R** was obtained according to a procedure similar to the one described for **20M**, with the following exception:

Step 20.1: **2.8a** was replaced by **20.2e**.

^{1}H NMR (400MHz, DMSO d_6) δ 10.70 (brm, 0.50H), 7.43 (m, 4H), 7.28 (m, 6H), 7.08 (d, 1H), 6.97 (m, 2H), 6.36 (s, 0.3H), 5.83 (s, 0.7H), 3.44 (m, 4H), 3.18 (brm, 6H), 2.67 (t, 2H), 2.12 (brm, 6H), 1.12 (brd, 6H)
Mass Spectral Analysis *m/z* = 495.3 $(M+H)^+$

EXAMPLE 21A

[0657] Preparation of **21.2**:

To a stirred solution of *N*-boc 4- piperidone (**1.2**) (2.0 g, 10 mmol, 1.0 eq) in dry diethyl ether (15 mL) at -25°C was simultaneously but independently added ethyl diazoacetate (**21.1**) (1.35 mL, 13 mmol, 1.3 eq) and boron trifluoride diethyl ether complex (1.33 mL, 10.5 mmol, 1.05 eq) under nitrogen atmosphere over a 20 min time period. The reaction mixture was stirred for another 1h at -25°C. A 1M aqueous solution of potassium carbonate was added drop wise to the stirred reaction mixture until gaseous evolution ceased. The two phases were separated and the organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was used for the next step without further purification.

[0658] Preparation of **21.3**:

A mixture of the crude **21.2** (3 g, as of 10 mmol) in a 4M aqueous hydrochloric acid solution (50 mL) was heated under reflux for 6h. Water was removed under reduced pressure and the resulting solid was washed with diethyl ether and dried under vacuum.
Yield: 90% over two steps
^{1}H NMR (400MHz, DMSO d_6) δ 9.41 (brs, 2H), 3.30 (m, 2H), 3.21 (m, 2H), 2.77 (m, 2H), 2.62 (m, 2H), 1.94 (m, 2H)

[0659] Preparation of **21.4**:

To a suspension of **21.3** (4.98 g, 33.3 mmol, 1.0 eq) in dry dichloromethane (100 mL) at 0°C was slowly added triethylamine (11 mL, 79.92 mmol, 2.4 eq) followed by a solution of di-*tert*-butyl-dicarbonate (**4.7**) (8.72 g, 39.96 mmol, 1.2 eq) in dichloromethane (30 mL) over a 20 min time period. The reaction mixture was stirred at room temperature for 10h and washed with a 1M aqueous solution of

hydrochloric acid (3 x 100 mL), brine, dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude product was used for next step without further purification.
^{1}H NMR (400MHz, $CDCl_3$) δ 3.58 (m, 4H), 2.65 (m, 4H), 1.78 (m, 2H), 1.45 (s, 9H)

[0660] Preparation of **21.5**:

To a solution of **21.4** (2.56 g, 12 mmol, 1.0 eq) in dry methanol (30 mL) was added pyrrolidine (2 mL, 24 mmol, 2.0 eq) followed by 2'-hydroxyacetophenone (**1.1a**) (1.44 mL, 12 mmol, 1.0 eq). The mixture was heated under reflux for 10h. The volatiles were removed under reduced pressure and the residue was dissolved in ethyl acetate (200 mL) and washed with a 1M aqueous solution of hydrochloric acid (3 x 50 mL), a 1M aqueous solution of sodium hydroxide (3 x 50 mL) and brine, dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 72% over two steps
^{1}H NMR (400MHz, $CDCl_3$) δ 7.85 (dd, 1H), 7.49 (m, 1H), 6.99 (m, 2H), 3.78-3.49 (m, 2H), 3.32 (m, 2H), 2.83-2.63 (m, 2H), 2.19 (m, 2H), 2.00-1.55 (m, 4H), 1.47 (s, 9H)
Mass Spectral Analysis *m/z* = 331.9 $(M+H)^+$

[0661] Preparation of **21.6**:

To an oven-dried two-neck 250 mL flask charged with a solution of **21.5** (2.86 g, 8.6 mmol, 1.0 eq) in dry tetrahydrofuran (40 mL) at -78°C under nitrogen was added a 1.0M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (10.3 mL, 10.3 mmol, 1.2 eq) over a 10 min time period. The mixture was kept at -78°C for 1h and a solution of *N*-phenylbis(trifluoromethanesulfonamide) (**1.4**) (3.68 g, 10.3 mmol, 1.2 eq) in tetrahydrofuran (20 mL) was added to the mixture over a 10 min time period. The mixture was kept at -78°C for another 1h, then slowly warmed to room temperature and stirred for an additional 10h at room temperature. Ice water (50 mL) was added to quench the reaction and the product was extracted with diethyl ether (200 mL). The organic phase was then washed with a 1N aqueous solution of hydrochloric acid (3 x 50 mL), a 1N aqueous solution of sodium hydroxide (3 x 50

mL) and brine, dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 85%
^{1}H NMR (400MHz, $CDCl_3$) δ 7.30-7.23 (m, 2H), 6.97 (m, 1H), 6.89 (m, 1H), 5.60 (s, 1H), 3.80-3.53 (m, 2H), 3.36-3.24 (m, 2H), 2.30-2.06 (m, 3H), 1.90-1.64 (m, 3H), 1.47 (s, 9H)

[0662] Preparation of **21.7**:

To a solution of **21.6** (3.38 g, 7.3 mmol, 1.0 eq) in dimethoxyethane (50 mL) was added sequentially a 2M aqueous solution of sodium carbonate (11 mL, 22 mmol, 3.0 eq), lithium chloride (0.93 g, 22 mmol, 3.0 eq), tetrakis(triphenylphosphine)palladium(0) (0.17 g, 0.15mmol, 0.02 eq), and 4-*N,N*-diethylphenylboronic acid (**1.6**) (1.77 g, 8.02 mmol, 1.1 eq) under a nitrogen athmosphere. The reaction mixture was heated under reflux for 10h and then cooled to room temperature. Water (200 mL) and diethyl ether (300 mL) were added and the two phases were separated. The organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 81%
^{1}H NMR (400MHz, $CDCl_3$) δ 7.39 (m, 4H), 7.18 (m, 1H), 6.99 (d, 1H), 6.92 (d, 1H), 6.85 (m, 1H), 5.60 (s, 1H), 3.86-3.50 (m, 4H), 3.42-3.24 (m, 4H), 2.27-1.68 (m, 6H), 1 48 (s, 9H), 1.21 (m, 6H)
Mass Spectral Analysis $m/z = 491.0\ (M+H)^+$

[0663] Preparation of **21A**:

To a cold (0°C) solution of **21.7** (1.15 g, 2.34 mmol, 1.0 eq) in anhydrous dichloromethane (20 mL) was added dropwise a 4.0M solution of hydrogen chloride in dioxane (3.51 mL, 14.04 mmol, 6.0 eq). The mixture was stirred at room temperature for 10h and concentrated under reduced pressure. The resulting foamy solids were soaked in diethyl ether. The resulting fine powder was collected by filtration and washed with diethyl ether.

Yield: 98%

^{1}H NMR (400MHz, $CDCl_3$) δ 9.76 (m, 2H), 7.41 (m, 2H), 7.36 (m, 2H), 7.20 (m, 1H), 7.00 (dd, 1H), 6.97 (dd, 1H), 6.88 (m, 1H), 5.63 (s, 1H), 3.68-3.23 (m, 8H), 2.50-2.23 (m, 4H), 2.02-1.82 (m, 2H), 1.35-1.07 (m, 6H)

Mass Spectral Analysis *m/z* = 391.2 $(M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_2O_2$, 1HCl

Theory: %C 70.32; %H 7.32; %N 6.56

Found: %C 70.14; %H 7.23; %N 6.55

EXAMPLE 21B

[0664] Preparation of **21.7a** & **21.7b**:

The racemic compound **21.7** (15 g) was resolved by chiral HPLC to provide **21.7a** (6.7 g) and **21.7b** (6.0 g) as pure enantiomers.

Chiral separation conditions:

Column: Chiralcel OJ, 4.6 x 250 mm
Flow: 1.0 mL / min
Temperature: room temperature
Detection: 335 nm
Mobile Phase: Methanol

21.7a:^{1}H NMR (400MHz, $CDCl_3$) δ 7.38 (m, 4H), 7.18 (m, 1H), 6.99 (dd, 1H), 6.92 (dd, 1H), 6.85 (m, 1H), 5.60 (s, 1H), 3.84-3.49 (m, 4H), 3.31 (m, 4H), 2.25-1.65 (m, 6H), 1.48 (s, 9H), 1.21 (m, 6H)

Mass Spectral Analysis *m/z* = 491.3 $(M+H)^+$

$[\alpha]_D^{25}$ = - 1.04 (c. 1.14 mg/mL, MeOH)

Chiral purity: ee= 99%; t_R = 4.6 min

21.7b:^{1}H NMR (400MHz, $CDCl_3$) δ 7.39 (m, 4H), 7.18 (m, 1H), 6.99 (dd, 1H), 6.92 (dd, 1H), 6.85 (m, 1H), 5.60 (s, 1H), 3.85-3.48 (m, 4H), 3.31 (m, 4H), 2.25-1.66 (m, 6H), 1.48 (s, 9H), 1.21 (m, 6H)

Mass Spectral Analysis *m/z* = 491.3 $(M+H)^+$

$[\alpha]_D^{25}$ = + 1.07 (c. 1.16 mg/mL, MeOH)

Chiral purity: ee= 99%; t_R = 5.2 min

[0665] Preparation of **21B**:

To a cold (0°C) solution of **21.7a** (1.3 g, 2.65 mmol, 1.0 eq) in anhydrous dichloromethane (20 mL) was added drop wise a 4.0M solution of hydrogen chloride in dioxane (3.31 mL, 13.25 mmol, 5.0 eq). The reaction mixture was stirred at room temperature for 10h and then concentrated under reduced pressure. The foamy solids were soaked in diethyl ether and the resulting fine powder was collected by filtration and washed with diethyl ether.

Yield: 87%

^{1}H NMR (400MHz, DMSO d_6) δ 8.97 (brs, 2H), 7.41 (m, 4H), 7.24 (m, 1H), 7.00-6.89 (m, 3H), 5.89 (s, 1H), 3.54-3.01 (m, 8H), 2.30-2.10 (m, 3H), 2.03-1.88 (m, 2H), 1.78 (m, 1H), 1.23-0.99 (m, 6H)

Mass Spectral Analysis *m/z* = 391.3 $(M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_2O_2$, 1HCl, 1/6 H_2O

Theory: %C 69.83; %H 7.35; %N 6.51

Found: %C 69.84; %H 7.27; %N 6.46

$[\alpha]_D^{25}$ = + 1.80 (c. 10.0 mg/mL, MeOH)

EXAMPLE 21C

[0666] Preparation of **21C**:

To a cold (0°C) solution of **21.7b** (1.3 g, 2.65 mmol, 1.0 eq) in anhydrous dichloromethane (20 mL) was added drop wise a 4.0 M solution of hydrogen chloride in dioxane (3.31 mL, 13.25 mmol, 5.0 eq). The reaction mixture was stirred at room temperature for 10h and then concentrated under reduced pressure. The foamy solids were soaked in diethyl ether and the resulting fine powder was collected by filtration and washed with diethyl ether.

Yield: 89%

^{1}H NMR (400MHz, DMSO d_6) δ 9.00 (brs, 2H), 7.41 (m, 4H), 7.24 (m, 1H), 7.02-6.89 (m, 3H), 5.89 (s, 1H), 3.52-3.02 (m, 8H), 2.35-2.10 (m, 3H), 2.04-1.88 (m, 2H), 1.78 (m, 1H), 1.23-0.99 (m, 6H)

Mass Spectral Analysis *m/z* = 391.3 $(M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_2O_2$, 1HCl, 1/6 H_2O

Theory: %C 69.83; %H 7.35; %N 6.51

Found: %C 69.84; %H 7.32; %N 6.47

$[\alpha]_D^{25}$ = - 1.81 (c. 10.25 mg/mL, MeOH)

EXAMPLE 21D

[0667] Preparation of **21D**:

To a stirred solution of **21B** (0.47 g, 1.1 mmol, 1.0 eq) in methanol (20 mL) was added palladium [90 mg, 10 wt.% (dry basis) on activated carbon, 20% wt. eq]. The reaction mixture was stirred under hydrogen atmosphere using a hydrogen balloon at room temperature for 10h. The palladium on activated carbon was filtered off on a celite pad and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol/ammonium hydroxide mixtures of increasing polarity). The desired fractions were combined and concentrated under reduced pressure. To a cold (0°C) solution of the resulting oil in dichloromethane was added dropwise a 2.0M solution of hydrogen chloride in diethyl ether (1.1 mL, 2.2 mmol, 2.0 eq). The mixture was then stirred for 1h at room temperature, concentrated under reduced pressure, and dried under vacuum.

Yield: 89%

^{1}H NMR (400MHz, DMSO d_6) δ 8.88 (brs, 2H), 7.30 (m, 4H), 7.12 (m, 1H), 6.86 (m, 1H), 6.78 (m, 1H), 6.62 (m, 1H), 4.20 (m, 1H), 3.50-2.96 (m, 8H), 2.29-1.66 (m, 8H), 1.10 (brm, 6H)

Mass Spectral Analysis *m/z* = 393.3 $(M+H)^+$

EXAMPLE 21E

[0668] Preparation of **21E**:

To a stirred solution of **21C** (0.49 g, 1.14 mmol, 1.0 eq) in methanol (20 mL) was added palladium [98 mg, 10 wt.% (dry basis) on activated carbon, 20% wt. eq]. The reaction mixture was stirred under hydrogen using a hydrogen balloon at room temperature for 10h. The palladium on activated carbon was filtered off on a celite pad and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol/ammonium hydroxide mixtures of increasing polarity). The desired fractions were combined and concentrated under reduced pressure. To a cold (0°C) solution of the resulting oil in dichloromethane was added dropwise a 2.0M solution of hydrogen chloride in diethyl ether (1.14 mL, 2.28 mmol, 2.0 eq). The mixture was then stirred for 1h at room temperature, concentrated under reduced pressure, and dried under vacuum.

Yield: 93%

^{1}H NMR (400MHz, DMSO d_6) δ 8.80 (brs, 2H), 7.29 (m, 4H), 7.12 (m, 1H), 6.85 (m, 1H), 6.77 (m, 1H), 6.62 (m, 1H), 4.20 (m, 1H), 3.52-2.96 (m, 8H), 2.22-1.66 (m, 8H), 1.10 (brm, 6H)

Mass Spectral Analysis *m/z* = 393.3 $(M+H)^+$

EXAMPLE 21F

[0669] Preparation of **21.9**:

To a stirred solution of **21A** (1.93 g, 4.52 mmol, 1.0 eq) in dry dichloromethane (30 mL) at 0°C was added triethylamine (1.51 mL, 10.85 mmol, 2.4 eq) followed by drop wise addition of benzyl chloroformate (**21.8**) (0.76 mL, 5.42 mmol, 1.2 eq). The reaction mixture was slowly warmed to room temperature and stirred for 10h at room temperature. The volatiles were removed under reduced pressure and the residue was partitioned between diethyl ether (200 mL) and water (100 mL). The organic layer was washed with a 1N aqueous solution of hydrochloric acid (3 x 50 mL) and brine, dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was used for the next step without further purification.

Mass Spectral Analysis *m/z* = 525.0 $(M+H)^+$

[0670] Preparation of **21.10**:

To a solution of **21.9** (0.9 g, crude, as of 1.71 mmol, 1.0 eq) in dry dichloroethane (10 mL) was added sulfur trioxide *N,N*-dimethylformamide complex (**4.3**) (315 mg, 2.06 mmol, 1.2 eq) portion wise. The reaction mixture was heated at 75°C for 10h and then cooled down to 0–10°C at which point oxalyl chloride (0.2 mL, 2.22 mmol, 1.3 eq) was added drop wise. The mixture was then stirred at 65°C for another 3h and then

quenched with ice water (50 mL) at room pemperature. Dichloromethane (100 mL) was added and the two phases were separated. The aqueous phase was extracted with dichloromethane (3 x 50 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give the crude product, which was used for next step without further purification.
Mass Spectral Analysis *m/z* = 622.9 $(M+H)^+$

[0671] Preparation of **21.11**:

To a solution of **21.10** (0.9 g, crude, as of 1.4 mmol, 1.0 eq) in dry dichloromethane (50 mL) at 0°C was slowly added triethylamine (0.4 mL, 2.8 mmol, 2.0 eq) and a 2.0M solution of ethylamine (**3.4c**) in tetrahydrofuran (7 mL, 14 mmol, 10.0 eq) drop wise. The mixture was slowly warmed to room temperature and stirred for 10h at room temperature. Water (50 mL) and chloroform (50 mL) were added and the two phases were separated. The aqueous phase was extracted with chloroform (3 x 50 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 34% over three steps
^{1}H NMR (400MHz, $CDCl_3$) δ 7.68 (m, 1H), 7.50 (m, 1H), 7.43 (m, 2H), 7.40-7.30 (m, 7H), 6.98 (d, 1H), 5.66 & 5.44 (2s, 1H), 5.18 & 5.16 (2s, 2H), 4.21 (t, 1H), 3.89-3.23 (m, 8H), 2.97 (m, 2H), 2.32-1.66 (m, 6H), 1.35-1.05 (m, 9H)
Mass Spectral Analysis *m/z* = 631.95 $(M+H)^+$

[0672] Preparation of **21F**:

To a solution of **21.11** (0.35 g, 0.55 mmol, 1.0 eq) in dichloromethane (10 mL) was added iodotrimethylsilane (0.15 mL, 1.1 mmol, 2.0 eq) drop wise. The mixture was stirred at room temperature for 2h. The mixture was diluted with chloroform 9100 mL) and methanol (5 mL). The solution was washed with a 20% aqueous solution of sodium thiosulfate (2 x 30 mL), with a 1M aqueous solution of sodium carbonate (2 x 30 mL), dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by preparative liquid chromatography (mobile phase: acetonitrile/water/trifluoroacetic acid). The desired fractions were combined and concentrated under reduced pressure. The product was dissolved in dichloromethane (50 mL); the organic phase was washed with a 1N aqueous solution of sodium hydroxide (2 x 20 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. To a cold (0°C) solution of the resulting oil in anhydrous dichloromethane was added dropwise a 1.0M solution of hydrogen chloride in diethyl ether (1.1 mL, 1.1 mmol, 2.0 eq). The mixture was then stirred for 1h at room temperature, concentrated under reduced pressure, and dried under vacuum.

Yield: 56%

^{1}H NMR (400MHz, DMSO d_6) δ 9.03 (brs, 2H), 7.65 (dd, 1H), 7.54-7.36 (m, 6H), 7.16 (d, 1H), 6.04 (s, 1H), 3.54-3.02 (m, 8H), 2.71 (m, 2H), 2.37-2.13 (m, 3H), 2.06-1.72 (m, 3H), 1.22-1.03 (m, 6H), 0.94 (t, 3H)

Mass Spectral Analysis *m/z* = 498.5 $(M+H)^+$

Elemental analysis:

$C_{27}H_{35}N_3O_4S$, 1HCl, $0.33H_2O$

Theory: %C 60.04; %H 6.84; %N 7.78

Found: %C 59.93; %H 6.81; %N 7.80

EXAMPLE 22A

[0673] Preparation of **22.1**:

To a suspension of **21B** (4.06 g, 9.5 mmol, 1.0 eq) in tetrahydrofuran (50 mL) at 0°C was added triethylamine (3.3 mL, 23.75 mmol, 2.5 eq) followed by drop wise addition of trifluoroacetic anhydride (**4.1**) (1.6ml, 11.4 mmol, 1.2 eq). The reaction mixture was slowly warmed to room temperature and stirred for 10h at room temperature. Ethyl acetate (200 mL) was added to the reaction mixture and the organic layer was washed with a 1M aqueous solution of hydrochloric acid (3 x 50 mL) and brine, dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was used for the next step without further purification.

Mass Spectral Analysis *m/z* = 487.2 $(M+H)^+$

[0674] Preparation of **22.2**:

To a solution of **22.1** (5.0 g, as of 9.5 mmol, 1.0 eq) in dry dichloroethane (100 mL) was added sulfur trioxide *N,N*-dimethylformamide complex (**4.3**) (2.18 g, 14.25 mmol, 1.5 eq) portion wise. The mixture was heated under reflux for 10h and then cooled to 0-10°C at which point oxalyl chloride (1.33 mL, 15.2 mmol, 1.6 eq) was added drop wise. The mixture was then stirred at 70°C for another 3h and quenched with ice water (1:1) (150 mL) at room temperature. Dichloromethane (100 mL) was added to the reaction mixture and the two phases were separated. The aqueous phase was further extracted with dichloromethane (3 x 50 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 84% over two steps

^{1}H NMR (400MHz, $CDCl_3$) δ 7.88 (m, 1H), 7.70 (m, 1H), 7.48 (m, 2H), 7.35 (m, 2H), 7.08 (d, 1H), 5.716 & 5.706 (2s, 1H), 4.03-3.26 (m, 8H), 2.49-2.21 (m, 3H), 2.03-1.72 (m, 3H), 1.33-1.11 (m, 6H)

Mass Spectral Analysis *m/z* = 585.2 $(M+H)^+$

[0675] Preparation of **22.3a**:

To a solution of **22.2** (0.6 g, 1.02 mmol, 1.0 eq) in dry dichloromethane (30 mL) at 0°C was added triethylamine (0.71 mL, 5.10 mmol, 5.0 eq) and methylamine (**3.4b**) hydrochloride salt (0.21 g, 3.06 mmol, 3.0 eq) in one portion. The reaction mixture was slowly warmed to room temperature and stirred for 10h at room temperature. Water (50 mL) and dichloromethane (50 mL) were added to the mixture and the two phases were separated. The aqueous phase was further extracted with dichloromethane (3 x 50 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 89%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.71 (dd, 1H), 7.51 (t, 1H), 7.45 (m, 2H), 7.34 (m, 2H), 7.02 (d, 1H), 5.665 & 5.657 (2s, 1H), 4.29 (m, 1H), 4.02-3.25 (m, 8H), 2.63 (d, 3H), 2.47-2.19 (m, 3H), 1.99-1.68 (m, 3H), 1.22 (m, 6H)

Mass Spectral Analysis *m/z* = 580.3 $(M+H)^+$

[0676] Preparation of **22A**:

To a solution of **22.3a** (0.53 g, 0.91 mmol, 1.0 eq) in a mixture of methanol (20 mL) and water (5 mL) at 0°C was added potassium carbonate (0.75 g, 5.46 mmol, 6.0 eq) portion wise. The reaction mixture was warmed to room temperature and stirred for 10h at room temperature. Brine (50 mL) and chloroform (50 mL) were added to the reaction mixture and the two phases were separated. The aqueous phase was extracted with chloroform (3 x 50 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity). The desired fractions were combined and concentrated under reduced pressure. To a cold (0°C) solution of the resulting oil in anhydrous dichloromethane was added drop wise a 2.0M solution of hydrogen chloride in diethyl ether (0.91 mL, 1.82 mmol, 2.0 eq). The mixture was stirred for 1h at room temperature, concentrated under reduced pressure, and dried under vacuum.
Yield: 82%
^{1}H NMR (400MHz, DMSO d_6) δ 9.04 (brs, 2H), 7.64 (dd, 1H), 7.49–7.34 (m, 6H), 7.17 (d, 1H), 6.04 (s, 1H), 3.45 (m, 2H), 3.31-3.15 (m, 5H), 3.09 (m, 1H), 2.35 (d, 3H), 2.28 (m, 2H), 2.18 (m, 1H), 1.99 (m, 2H), 1.80 (m, 1H), 1.12 (m, 6H)
Mass Spectral Analysis *m/z* = 484.2 $(M+H)^+$
Elemental analysis:
$C_{26}H_{33}N_3O_4S$, 1HCl, $1.2H_2O$
Theory: %C 57.65; %H 6.77; %N 7.76
Found: %C 57.69; %H 6.62; %N 7.71
$[\alpha]_D^{25}$ = - 4.18 (c. 9.4 mg/mL, MeOH)

EXAMPLE 22B

[0677] **22B** was obtained according to a procedure similar to the one described for **22A**, with the following exception:
Step 22.3: **3.4b** was replaced by **3.4c**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.98 (brs, 1H), 7.65 (dd, 1H), 7.44 (m, 5H), 7.37 (d, 1H), 7.16 (d, 1H), 6.04 (s, 1H), 3.45 (m, 2H), 3.32-3.05 (m, 6H), 2.71 (m, 2H), 2.35-1.75 (m, 6H), 1.12 (m, 6H), 0.94 (t, 3H)

Mass Spectral Analysis *m/z* = 498.3 $(M+H)^+$

Elemental analysis:

$C_{27}H_{35}N_3O_4S$, 1HCl, 1.1H_2O

Theory: %C 58.54; %H 6.95; %N 7.59

Found: %C 58.55; %H 6.82; %N 7.55

$[\alpha]_D^{25}$ = -5.10 (c = 9.25 mg/ml, MeOH)

EXAMPLE 22C

[0678] **22C** was obtained according to a procedure similar to the one described for **22A**, with the following exception:

Step 22.3: **3.4b** was replaced by **3.4d**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.05 (brs, 2H), 7.65 (dd, 1H), 7.56 (t, 1H), 7.43 (m, 4H), 7.37 (d, 1H), 7.16 (d, 1H), 6.04 (s, 1H), 3.53-3.04 (m, 8H), 2.63 (m, 2H), 2.35-1.75 (m, 6H), 1.33 (m, 2H), 1.12 (m, 6H), 0.77 (t, 3H)

Mass Spectral Analysis *m/z* = 512.4 $(M+H)^+$

Elemental analysis:

$C_{28}H_{37}N_3O_4S$, 1HCl, 0.5H_2O

Theory: %C 60.36; %H 7.06; %N 7.54

Found: %C 60.28; %H 7.10; %N 7.53

$[\alpha]_D^{25}$ = -5.95 (c = 9.55 mg/ml, MeOH)

EXAMPLE 22D

[0679] **22D** was obtained according to a procedure similar to the one described for **22A**, with the following exception:

Step 22.3: **3.4b** was replaced by **3.4g**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.0 (brs, 2H), 7.66 (m, 2H), 7.42 (m, 5H), 7.16 (d, 1H), 6.04 (s, 1H), 3.45 (m, 2H), 3.22 (m, 6H), 2.59 (m, 2H), 2.35-1.75 (m, 6H), 1.12 (m, 6H), 0.75 (m, 1H), 0.32 (m, 2H), 0.03 (m, 2H)

Mass Spectral Analysis *m/z* = 524.3 $(M+H)^+$

Elemental analysis:

$C_{29}H_{37}N_3O_4S$, 1HCl, $0.66H_2O$

Theory: %C 60.88; %H 6.93; %N 7.34

Found: %C 60.92; %H 6.96; %N 7.37

$[\alpha]_D^{25} = -5.89$ (c = 9.35 mg/ml, MeOH)

EXAMPLE 22E

[0680] Preparation of **22.4**:

To a solution of **22.2** (0.86 g, 1.47 mmol, 1.0 eq) in tetrahydrofuran (5 mL) at 0°C was added a 1.0M solution of hydrazine in tetrahydrofuran (**5.1**) (15 mL, 15 mmol, 15.0 eq) in one portion. The reaction mixture was stirred at 0°C for 30 min. Water (50 mL) and dichloromethane (100 mL) were added and the two phases were separated. The aqueous phase was extracted with dichloromethane (3 x 50 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 72%

Mass Spectral Analysis *m/z* = 581.2 $(M+H)^+$

[0681] Preparation of **22.5**:

To a suspension of **22.4** (0.62 g, 1.06 mmol, 1.0 eq) in ethanol (10 mL) was added sodium acetate (0.58 g, 7.1 mmol, 6.7 eq) and iodomethane (**2.8c**) (0.37 mL, 5.8 mmol, 5.5 eq). The reaction mixture was heated under reflux for 10h. Water (100 mL) and dichloromethane (100 mL) were added and the two phases were separated. The aqueous phase was extracted with dichloromethane (3 x 50 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 78%

^1H NMR (400MHz, $CDCl_3$) δ 7.78 (m, 1H), 7.61 (t, 1H), 7.45 (m, 2H), 7.35 (m, 2H), 7.06 (d, 1H), 5.685 & 5.675 (2s, 1H), 4.01-3.42 (m, 6H), 3.33 (brs, 2H), 3.00 (s, 3H), 2.46-2.22 (m, 3H), 2.00-1.69 (m, 3H), 1.22 (m, 6H)

Mass Spectral Analysis *m/z* = 565.3 $(M+H)^+$

[0682] Preparation of **22E**:

To a solution of **22.5** (0.45 g, 0.8 mmol, 1.0 eq) in a mixture of methanol (20 mL) and water (5 mL) at 0°C was added potassium carbonate (0.86 g, 4.8 mmol, 6.0 eq) portion wise. The reaction mixture was warmed to room temperature and stirred for 10h at room temperature. Brine (50 mL) and chloroform (50 mL) were added and the two phases were separated. The aqueous phase was extracted with chloroform (3 x 50 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity). The desired fractions were combined and concentrated under reduced pressure. To a cold (0°C) solution of the resulting oil in anhydrous dichloromethane was added dropwise a 2.0M solution of hydrogen chloride in diethyl ether (0.8 mL, 1.6 mmol, 2.0 eq). The mixture was then stirred for 1h at room temperature, concentrated under reduced pressure, and dried under vacuum.

Yield: 86%

^{1}H NMR (400MHz, DMSO d_6) δ 9.01 (brs, 2H), 7.80 (dd, 1H), 7.46 (m, 5H), 7.22 (d, 1H), 6.06 (s, 1H), 3.45 (m, 2H), 3.32-3.03 (m, 9H), 2.29 (m, 2H), 2.18 (m, 1H), 1.99 (m, 2H), 1.81 (m, 1H), 1.12 (m, 6H)

Mass Spectral Analysis *m/z* = 469.2 $(M+H)^+$

Elemental analysis:

$C_{26}H_{32}N_2O_4S$, 1HCl

Theory: %C 61.83; %H 6.59; %N 5.55

Found: %C 61.82; %H 6.60; %N 5.51

$[\alpha]_D^{25}$ = - 4.50 (c. 10.3 mg/mL, MeOH)

EXAMPLE 23A

[0683] **23A** was obtained according to a procedure similar to the one described for **1A**, with the following exceptions:

Step 1.1: Method 1B was used and **1.2** was replaced by **23.1a** (see also step 23.1).

Step 1.3: Method 1C was used (see also step 23.3).

Step 1.4: Method 1E was used (see also step 23.4).

^{1}H NMR (400MHz, $CDCl_3$) δ 10.20 (m, 2H), 7.40 (m, 4H), 7.22 (m, 1H), 7.04 (m, 2H), 6.91 (m, 1H), 5.66 (s, 1H), 3.85-3.50 (m, 5H), 3.31 (m, 3H), 2.60 (m, 1H), 2.13 (m, 1H), 1.27 (m, 3H), 1.16 (m, 3H)

Mass Spectral Analysis *m/z* = 363.2 $(M+H)^+$

EXAMPLE 23B

[0684] **23B** was obtained according to a procedure similar to the one described for **1A**, with the following exceptions:

Step 1.1: Method 1B was used and **1.2** was replaced by **23.1b** (see also step 23.1).

Step 1.3: Method 1C was used (see also step 23.3).

Step 1.4: Method 1E was used (see also step 23.4).

^{1}H NMR (400MHz, $CDCl_3$) δ 10.33 (m, 1H), 9.21 (m, 1H), 7.39 (m, 5H), 7.21 (m, 1H), 6.98 (m, 1H), 6.87 (m, 1H), 5.50 (s, 1H), 3.55 (m, 4H), 3.34 (m, 2H), 2.93 (m, 2H), 2.44 (m, 1H), 2.33 (m, 1H), 1.83 (m, 1H), 1.70 (m, 1H), 1.26 (m, 3H), 1.16 (m, 3H)

Mass Spectral Analysis *m/z* = 377.0 $(M+H)^+$

EXAMPLE 23C

[0685] **23C** was obtained according to a procedure similar to the one described for **1A**, with the following exceptions:

Step 1.1: Method 1B was used and **1.2** was replaced by **23.5** (see also step 23.5).

Step 1.3: Method 1C was used (see also step 23.7).

Step 1.4: Method 1E was used (see also step 23.8).

^{1}H NMR (400MHz, DMSO d_6) δ 9.28 (brm, 2H), 7.43 (d, 2H), 7.35 (d, 2H), 7.27 (m, 1H), 7.01 (d, 1H), 6.97 (m, 2H), 5.57 (s, 1H), 4.01 (brs, 2H), 3.44 (brs, 2H), 3.22 (brs, 2H), 2.36 (m, 2H), 2.27 (m, 4H), 2.04 (m, 2H), 1.12 (brd, 6H)

Mass Spectral Analysis *m/z* = 403.2 $(M+H)^+$

EXAMPLE 24A

[0686] Preparation of **24.2**:

To a solution of **24.1** (9.37 g, 60 mmol, 1.0 eq) in dry methanol (100 mL) was added pyrrolidine (10 mL, 120 mmol, 2.0 eq) followed by 2'-hydroxyacetophenone (**1.1a**) (7.22 mL, 60 mmol, 1.0 eq). The reaction mixture was heated under reflux for 10h.

The volatiles were removed under reduced pressure and the residue was dissolved in ethyl acetate (200 mL). The mixture was washed with a 1M aqueous solution of hydrochloric acid (3 x 50 mL), with a 1M aqueous solution of sodium hydroxide (3 x 50 mL) and brine. The organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 100%
^{1}H NMR (400MHz, $CDCl_3$) δ 7.86 (dd, 1H), 7.48 (m, 1H), 6.98 (m, 2H), 3.96 (m, 4H), 2.71 (s, 2H), 2.12 (m, 2H), 1.99 (m, 2H), 1.74 (m, 2H), 1.61 (m, 2H)

[0687] Preparation of **24.3**:

To an oven-dried two-neck 500 mL flask charged with a solution of **24.2** (16.46 g, 60 mmol, 1.0 eq) in dry tetrahydrofuran (100 mL) at -78°C under nitrogen was added a 1.0M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (72 mL, 72 mmol, 1.2 eq) over a 30 min time period. The mixture was kept at -78°C for 1h and a solution of *N*-phenylbis(trifluoromethanesulfonamide) (**1.4**) (25.72 g, 72 mmol, 1.2 eq) in tetrahydrofuran (100 mL) was added to the mixture over a 30 min time period. The reaction mixture was kept at -78°C for 1h, and was slowly warmed to room temperature and stirred for 10h at room temperature. Ice water (100 mL) was added to quench the reaction and the product was extracted with diethyl ether (200 mL). The organic phase was then washed with a 1M aqueous solution of hydrochloric acid (3 x 100 mL), with a 1M aqueous solution of sodium hydroxide (3 x 100 mL) and brine, dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 90%
^{1}H NMR (400MHz, $CDCl_3$) δ 7.34-7.19 (m, 2H), 6.97 (m, 1H), 6.89 (m, 1H), 5.60 (s, 1H), 4.03-3.91 (m, 4H), 2.20 (m, 2H), 2.09-1.97 (m, 2H), 1.81 (m, 2H), 1.62 (m, 2H)

[0688] Preparation of **24.4**:

To a solution of **24.3** (22 g, 54.14 mmol, 1.0 eq) in dimethoxyethane (200 mL) under nitrogen was added sequentially a 2M aqueous solution of sodium carbonate (81.2 mL, 162.42 mmol, 3.0 eq), lithium chloride (6.88 g, 162.42 mmol, 3.0 eq),

tetrakis(triphenylphosphine)palladium(0) (1.25 g, 1.08 mmol, 0.02 eq), and 4-*N,N*-diethylphenylboronic acid (**1.6**) (13.16 g, 59.55 mmol, 1.1 eq). The reaction mixture was heated under reflux for 10h. Water (200 mL) and diethyl ether (300 mL) were added and the two phases were separated. The aqueous phase was further extracted with diethyl ether (2 x 100 mL) and the combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 95%
^{1}H NMR (400MHz, $CDCl_3$) δ 7.38 (m, 4H), 7.18 (m, 1H), 6.99 (m, 1H), 6.93 (m, 1H), 6.85 (m, 1H), 5.62 (s, 1H), 3.99 (m, 4H), 3.57 (brs, 2H), 3.32 (brs, 2H), 2.24-2.02 (m, 4H), 1.80 (m, 2H), 1.65 (m, 2H), 1.21 (m, 6H)

[0689] Preparation of **24A**:

To a cold (0°C) solution of **24.4** (22.32 g, 51.48 mmol, 1.0 eq) in tetrahydrofuran (200 mL) was added a 1.0M aqueous solution of hydrochloric acid (155 mL, 155 mmol, 3.0 eq). The mixture was stirred at room temperature for 10h and then concentrated under reduced pressure. The resulting solid was collected by filtration, washed with hexane/ethyl acetate mixture (20:1), and dried under vacuum.
Yield: 85%
^{1}H NMR (400MHz, $CDCl_3$) δ 7.40 (m, 4H), 7.23 (m, 1H), 7.04 (d, 1H0, 7.00 (d, 1H), 6.91 (m, 1H), 5.62 (s, 1H), 3.57 (brs, 2H), 3.32 (brs, 2H), 2.87 (m, 2H), 2.50 (m, 2H), 2.33 (m, 2H), 1.94 (m, 2H), 1.21 (m, 6H)
Mass Spectral Analysis *m/z* = 390.2 $(M+H)^+$

EXAMPLE 24B / EXAMPLE 24C

[0690] Preparation of **24B / 24C**:

To a solution of **24A** (0.51 g, 1.3 mmol, 1.0 eq) in dry tetrafydrofuran (30 mL) at 0°C was added sodium borohydride (50 mg, 1.3 mmol, 1.0 eq) in one portion under a nitrogen athmosphere. The reaction mixture was stirred at room temperature for 1h. Water (50 mL) and diethyl ether (100 mL) were added and the two phases were separated. The aqueous phase was further extracted with diethyl ether (2 x 50 mL) and the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated to give the mixture of two isomers. The crude product was purified by preparative liquid chromatography affording **24B** and **24C**.

(24B) ^{1}H NMR (400MHz, $CDCl_3$) δ 7.39 (m, 4H), 7.18 (m, 1H), 6.97 (m, 2H), 6.85 (m, 1H), 5.55 (s, 1H), 3.73 (m, 1H), 3.58 (brs, 2H), 3.33 (brs, 2H), 2.51 (brs, 4H), 2.21 (m, 2H), 1.52 (m, 2H), 1.22 (brd, 6H)
Mass Spectral Analysis *m/z* = 392.2 $(M+H)^+$

(24C) ^{1}H NMR (400MHz, $CDCl_3$) δ 7.39 (m, 4H), 7.18 (m, 1H), 7.01-6.81 (m, 3H), 5.73 & 5.55 (2s, 1H), 4.07 & 3.74 (2m, 1H), 3.59 (brs, 2H), 3.34 (brs, 2H), 3.16 (brs, 4H), 2.31-1.89 (m, 2H), 1.68-1.46 (m, 2H), 1.22 (m, 6H)
Mass Spectral Analysis *m/z* = 392.2 $(M+H)^+$

EXAMPLE 24D / EXAMPLE 24E

[0691] Preparation of **24D / 24E**:

To a stirred solution of **24A** (0.63 mL, 1.62 mmol, 2.0 eq) in dry dichloromethane (20 mL) was added sequentially *n*-propylamine (**3.4d**) (0.16 g, 1.94 mmol, 1.2 eq), acetic acid (0.11 mL, 1.94 mmol, 1.2 eq), and sodium cyanoborohydride (0.153 g, 2.43 mmol, 1.5 eq). The reaction mixture was stirred at room temperature for 10h. Water (40 mL) was added and the aqueous layer was basified to pH=10 with a 1M aqueous solution of sodium hydroxide. The two phases were separated and the aqueous phase was saturated with sodium chloride and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give the crude mixture, which was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity).

(24D) ^{1}H NMR (400MHz, $CDCl_3$) δ 7.38 (m, 4H), 7.17 (m, 1H), 6.99 (dd, 1H), 6.90 (dd, 1H), 6.84 (m, 1H), 5.91 (s, 1H), 3.57 (brs, 2H), 3.31 (brs, 2H), 2.75 (brs, 1H), 2.65 (t, 2H), 2.11 (m, 2H), 1.98 (m, 2H), 1.82-1.46 (m, 7H), 1.21 (m, 6H), 0.95 (t, 3H)
Mass Spectral Analysis *m/z* = 433.2 $(M+H)^+$

(24E) ^{1}H NMR (400MHz, $CDCl_3$) δ 7.38 (m, 4H), 7.16 (m, 1H), 6.98 (dd, 1H), 6.93 (dd, 1H), 6.83 (m, 1H), 5.54 (s, 1H), 3.57 (brs, 2H), 3.31 (brs, 2H), 2.64 (t, 2H), 2.53 (m, 1H), 2.20 (m, 2H), 1.83-1.42 (m, 7H), 1.21 (m, 6H), 0.94 (t, 3H)
Mass Spectral Analysis *m/z* = 433.2 $(M+H)^+$

EXAMPLE 24F

[0692] **24F** was obtained according to a procedure similar to the one described for **24D**, with the following exception:
Step 24.6: **3.4d** was replaced by **3.4j**.
^{1}H NMR (400MHz, $CDCl_3$) δ 7.38 (m, 4H), 7.17 (m, 1H), 6.96 (m, 2H), 6.84 (m, 1H), 5.54 (s, 1H), 3.57 (m, 2H), 3.32 (m, 2H), 2.35 (s, 6H), 2.25 (m, 3H), 1.79 (m, 4H), 1.46 (m, 2H), 1.26 (m, 3H), 1.16 (m, 3H)
Mass Spectral Analysis *m/z* = 419.2 $(M+H)^+$

EXAMPLE 24G

[0693] **24G** was obtained according to a procedure similar to the one described for **24E**, with the following exception:
Step 24.6: **3.4d** was replaced by **3.4j**.
^{1}H NMR (400MHz, $CDCl_3$) δ 7.40 (m, 4H), 7.18 (m, 1H), 7.00 (m, 1H), 6.91 (m, 1H), 6.85 (m, 1H), 5.89 (s, 1H), 3.57 (m, 2H), 3.32 (m, 2H), 2.51 (m, 7H), 2.20 (m, 2H), 2.06 (m, 2H), 1.76 (m, 4H), 1.26 (m, 3H), 1.16 (m, 3H)
Mass Spectral Analysis *m/z* = 419.2 $(M+H)^+$

EXAMPLE 25A

[0694] **25A** was obtained according to a procedure similar to the one described for compound **1.8a** with the following exception:
Step 1.1: **1.2** was replaced by **25.1** (see also step 25.1).
^{1}H NMR (400MHz, DMSO d_6) δ 7.42 (d, 2H), 7.38 (d, 2H), 7.19 (m, 1H), 6.97 (m, 2H), 6.86 (m, 1H), 5.62 (s, 1H), 3.96 (m, 2H), 3.79 (m, 2H), 3.57 (brs, 2H), 3.32 (brs, 2H), 2.03 (d, 2H), 1.84 (m, 2H), 1.21 (brd, 6H)
Mass Spectral Analysis *m/z* = 378.2 $(M+H)^+$

EXAMPLE 26A

[0695] Preparation of **26.2**:

To a solution of **1.5a** (2.08 g, 4.63 mmol, 1 eq) in dry tetrahydrofuran (40 mL) was added *tetrakis*(triphenylphosphine)palladium(0) (0.535 g, 0.463 mmol, 0.1 eq), followed by 4-cyanobenzylzinc bromide (**26.1**) (0.5M solution in tetrahydrofuran, 23.16 mL, 11.58 mmol, 2.5 eq) drop wise under a nitrogen athmosphere. The reaction mixture was stirred at room temperature for 10h. A saturated aqueous solution of ammonium chloride (40 mL) was added to quench the reaction and diethyl ether (50 mL) was added to partition the two phases. The aqueous phase was extracted with diethyl ether (3 x 50 mL) and the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixture of increasing polarity).

Yield: 62 %

^{1}H NMR (400MHz, $CDCl_3$) δ 7.59 (d, 2H), 7.34 (d, 2H), 7.14 (m, 1H), 7.00 (dd, 1H), 6.88 (dd, 1H), 6.82 (m, 1H), 5.28 (s, 1H), 3.95-3.75 (m, 4H), 3.28 (m, 2H), 1.99 (m, 2H), 1.59 (m, 2H), 1.46 (s, 9H)

Mass Spectral Analysis *m/z* = 417 $(M+H)^+$

[0696] Preparation of **26.3a** & **26.3b**:

A mixture of **26.2** (1.2 g, 2.88 mmol) in concentrated hydrochloric acid (30 mL) was heated under reflux for 10h and then concentrated under reduced pressure to give the crude mixture of **26.3a** and **26.3b**. A 80 mg quantity of the mixture was purified by preparative liquid chromatography. The remaining mixture (**26.3a/26.3b**) was used for the next step without further purification.

26.3a: ^{1}H NMR (400MHz, DMSO-d_6) δ 12.87 (s,b, 1H), 8.58 (m, 2H), 7.86 (m, 2H), 7.41 (m, 2H), 7.21-7.12 (m, 2H), 6.92 (dd, 1H), 6.86 (m, 1H), 5.70 (s, 1H), 3.85 (s, 2H), 3.19 (m, 4H), 2.06 (m, 2H), 1.86 (m, 2H)

Mass Spectral Analysis *m/z* = 336.2 $(M+H)^+$

26.3b: ^{1}H NMR (400MHz, DMSO-d_6) δ 13.00 (s,b, 1H), 8.68 (m, 1H), 8.29 (m, 1H), 7.97 (m, 2H), 7.84 (dd, 1H), 7.50 (m, 2H), 7.41 (s, 1H), 7.27 (m, 1H), 7.03-6.94 (m, 2H), 3.19-3.00 (m, 4H), 2.82 (s, 2H), 1.91 (m, 2H), 1.63 (m, 2H)
Mass Spectral Analysis *m/z* = 336.2 $(M+H)^+$

[0697] [0698] Preparation of **26.4a** & **26.4b**:

To a solution of the mixture of **26.3a** and **26.3b** (1 g, 2.69 mmol) in methanol (50 mL) was slowly added a 4.0M solution of hydrogen chloride in dioxane (20 mL). The reaction mixture was stirred at room temperature for 10h and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (100 mL), washed with a 1M aqueous solution of sodium carbonate (4 x 50 mL), brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give the crude mixture of **26.4a** and **26.4b**. A small amount (150 mg) of the crude mixture was purified by column chromatography (eluent: hexane/ethyl acetate mixture of increasing polarity) and repurified preparative liquid chromatography. The remaining mixture (**26.4a/26.4b**) was used for the next step without further purification.
Yield: 90 %

26.4a: ^{1}H NMR (400MHz, $CDCl_3$) δ 9.05 (s,b, 1H), 8.72 (s,b, 1H), 7.98 (d, 2H), 7.29 (d, 2H), 7.17 (m, 1H), 7.11 (m, 1H), 6.93-6.85 (m, 2H), 5.29 (s, 1H), 3.91 (s, 3H), 3.80 (s, 2H), 3.37 (m, 4H), 2.24 (m, 2H), 1.95 (m, 2H)
Mass Spectral Analysis *m/z* = 350.2 $(M+H)^+$
26.4b: ^{1}H NMR (400MHz, $CDCl_3$) δ 9.42 (s,b, 1H), 8.95 (s,b, 1H), 8.05 (d, 2H), 7.66 (d, 1H), 7.40-7.22 (m, 4H), 7.00 (m, 1H), 6.92 (d, 1H), 3.94 (s, 3H), 3.25 (m, 4H), 2.78 (s, 2H), 2.04 (m, 2H), 1.75 (m, 2H)
Mass Spectral Analysis *m/z* = 350.2 $(M+H)^+$

[0699] Preparation of **26.5a** & **26.5b**:

To a solution of the mixture of **26.4a** and **26.4b** (0.5 g, 1.5 mmol, 1 eq) in dry dichloromethane (30 mL) at 0°C was slowly added triethylamine (0.42 mL, 3 mmol, 2 eq) and a solution of di-*tert*-butyl-dicarbonate **4.7** (0.38 g, 1.74 mmol, 1.2 eq) in dichloromethane (10 mL) drop wise. The reaction mixture was slowly warmed up to room temperature and stirred at room temperature for 10h. Dichloromethane (50 mL) was added and the mixture was washed with a 1N aqueous solution of hydrochloric acid (3 x 50 mL), brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give the crude mixture of **26.5a** and **26.5b**, which was used for the next step without purification.

[0700] Preparation of **26.6a** & **26.6b**:

To a solution of the mixture of **26.5a** and **26.5b** (0.57 g, 1.26 mmol, 1 eq) in a mixture methanol (15mL), tetrahydrofuran (15mL) and water (15 mL) was added lithium hydroxide monohydrate (0.21 g, 5 mmol, 4 eq) in one portion. The reaction mixture was stirred at room temperature for 10h. The volatiles were removed under reduced pressure and the remaining aqueous solution was acidified to pH = 3 with a 1N aqueous solution of hydrochloric acid while stirring. The mixture was stirred for 1h at room temperature and left at room temperature for 10h. The resulting solid was collected by filtration, washed with water, and dried under vacuum to give the mixture of **26.6a** and **26.6b**, which was used for the next step without further purification.

[0701] Preparation of **26.7a** & **26.7b**:

To a stirred solution of the mixture of **26.6a** and **26.6b** (0.49 g, 1.12 mmol, 1 eq) in acetonitrile (20 mL) was slowly added diisopropylethylamine (0.46 mL, 2.69 mmol, 2.4 eq), diethylamine **1.12** (0.24 g, 3.36 mmol, 3 eq) at room temperature. The mixture was stirred for 10 min at room temperature. The mixture was cooled to 0°C and *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) (0.43 g, 1.34 mmol, 1.2 eq) was added portion wise. The reaction mixture was slowly warmed up to room tempearture and stirred at room temperature for an additional 10h. The volatiles were removed under reduced pressure and the residue was partitioned between ethyl acetate (100 mL) and a 1M aqueous solution of sodium bicarbonate (100 mL). The organic phase was washed with a 1M aqueous solution of sodium bicarbonate (2 x 50 mL), a 1M aqueous solution of hydrochloric acid (3 x 50 mL), brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give the crude mixture of **26.7a** and **26.7b**. The crude mixture was purified by column chromatography (eluent: hexane/ethyl acetate mixture of increasing polarity). A small amount (85 mg) of the purified mixture was separated bypreparative liquid chromatography. The remaining mixture (**26.7a/26.7b**) was used for the next step without further purification.

Yield: 81% over three steps

26.7a: ^{1}H NMR (400MHz, $CDCl_3$) δ 7.33-7.24 (m, 4H), 7.15-7.07 (m, 2H), 6.89-6.80 (m, 2H), 5.25 (s, 1H), 3.84 (m, 2H), 3.74 (s, 2H), 3.55 (m, 2H), 3.28 (m, 4H), 1.98 (m, 2H), 1.57 (m, 2H), 1.46 (s, 9H), 1.18 (m, 6H)

Mass Spectral Analysis *m/z* = 491.1 $(M+H)^+$

26.7b: ^{1}H NMR (400MHz, $CDCl_3$) δ 7.63 (dd, 1H), 7.39 (m, 2H), 7.31 (m, 2H), 7.22 (m, 1H), 7.17 (s, 1H), 6.95 (m, 1H), 6.90 (dd, 1H), 3.81 (m, 2H), 3.58 (m, 2H), 3.34 (m, 2H), 3.17 (m, 2H), 2.71 (s, 2H), 1.82 (m, 2H), 1.43 (s, 9H), 1.38 (m, 2H), 1.22 (m, 6H)

Mass Spectral Analysis *m/z* = 491.1 $(M+H)^+$

[0702] Preparation of **26A**

To a cold (0°C) stirred solution of the mixture of **26.7a** and **26.7b** (0.36 g, 0.73 mmol, 1 eq) in dry dichloromethane (20 mL) was added dropwise a 4.0 M solution of hydrogen chloride in dioxane (1.8 mL, 7.2 mmol, 10 eq). The mixture was stirred at room temperature for 10h and concentrated under reduced pressure to give the crude mixture of **26A** and **26.8**. The crude mixture was purified by preparative liquid chromatography.

Yield: 85%

26A: ^{1}H NMR (400MHz, $CDCl_3$) δ 9.35 (s,b, 1H), 9.00 (s,b, 1H), 7.30 (m, 4H), 7.14 (m, 2H), 6.87 (m, 2H), 5.28 (s, 1H), 3.76 (s, 2H), 3.55 (m, 2H), 3.24 (m, 6H), 2.11 (m, 2H), 1.93 (m, 2H), 1.20 (m, 6H)

Mass Spectral Analysis *m/z* = 391.0 $(M+H)^+$

26.8: ^{1}H NMR (400MHz, $CDCl_3$) δ 9.12 (s,b, 1H), 8.71 (s,b, 1H), 7.65 (d, 1H), 7.39 (d, 2H), 7.31 (d, 2H), 7.28-7.19 (m, 2H), 7.00 (m, 1H), 6.92 (d, 1H), 3.59 (m, 2H), 3.29 (m, 6H), 2.78 (s, 2H), 2.05 (m, 2H), 1.78 (m, 2H), 1.23 (m, 6H)

Mass Spectral Analysis *m/z* = 391.0 $(M+H)^+$

EXAMPLE 26B

[0703] Preparation of **26B**:

To a stirred solution of **26.8** (0.12 g, 0.26 mmol, 1 eq) in methanol (10 mL) was added palladium [24 mg, 10 wt.% (dry basis) on activated carbon, 20% wt. eq]. The reaction mixture was stirred under hydrogen atmosphere using a hydrogen balloon at room temperature for 10h. The palladium on activated carbon was filtered off on a celite pad and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol/ammonium hydroxide mixture of increasing polarity). The desired fractions were combined and concentrated under reduced pressure. To a cold (0°C) solution of the resulting oil in dichloromethane was added dropwise a 2.0M solution of hydrogen chloride in diethyl ether (0.26 mL, 0.52 mmol, 2 eq). The mixture was then stirred for 1h at room temperature, concentrated under reduced pressure, and dried under vacuum.

Yield: 88%

^{1}H NMR (400MHz, $CDCl_3$) δ 9.41 (s,b, 1H), 8.95 (s,b, 1H), 7.40 (m, 1H), 7.33 (m, 2H), 7.25-7.14 (m, 3H), 6.97 (m, 1H), 6.86 (m, 1H), 3.62-3.04 (m, 10H), 2.63 (m, 1H), 2.03-1.49 (m, 6H), 1.20 (m, 6H)

Mass Spectral Analysis *m/z* = 393.0 $(M+H)^+$

EXAMPLE 27A

[0704] Preparation of **27A**:

A solution of **1A** (0.66 g, 1.75 mmol, 1.0 eq) in anhydrous methanol (13 mL) was hydrogenated at atmospheric pressure in the presence of palladium hydroxide [$Pd(OH)_2$: Pearlman's catalyst] (0.120 g, 0.09 mmol, 0.05 eq) for 10h. The mixture was then filtered through celite. The filtrate was concentrated and was hydrogenated at atmospheric pressure in the presence of palladium hydroxide (0.120 g) for an additional 10h. The mixture was filtered through celite and the filtrate was concentrated to dryness under reduced pressure. To a cold (0°C) solution of the resulting oil in anhydrous dichloromethane was added drop wise a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (5 mL). The mixture was then stirred for 1h at room temperature and concentrated under reduced pressure. Diethyl ether was added. The resulting precipitate was collected by filtration and washed with diethyl ether and ethyl acetate.

Yield: 63%

^{1}H NMR (400MHz, DMSO d_6) δ 9.15 (m, 2H), 7.30 (m, 4H), 7.10 (m, 1H), 6.90 (m, 1H), 6.75 (m, 1H), 6.60 (m, 1H), 4.20 (m, 1H), 3.40 (m, 3H), 3.20 (m, 4H), 3.00 (m, 1H), 2.15 (m, 1H), 1.95 (m, 5H), 1.05 (m, 6H)

Mass Spectral Analysis *m/z* = 379.1 $(M+H)^+$

Elemental analysis:

$C_{24}H_{30}N_2O_2$, 1HCl, $0.75H_2O$

Theory: %C 67.28; %H 7.65; %N 6.54

Found: %C 67.32; %H 7.63; %N 6.37

EXAMPLE 27B

[0705] Preparation of **27B**:

27A (racemic mixture) (10 g, 24.10 mmol, 1.0 eq) was resolved using Chiral HPLC method:

Column: Chiralpak AD-H, 4.6 x 250mm, 5µ, Chiral Technologies PN# 19325

Column temperature: room temperature

Detection: UV photo diode array, 200 to 300nm, extract at 275nm

Injection volume: 40µL of 2 mg / mL sample in EtOH : MeOH (80 : 20)

Flow: 1 mL / minute

Mobile Phase: 85% Solution A, 15% Solution B

Solution A: 0.1% Di-isopropylethylamine in Hexane (HPLC Grade)

Solution B: 80% Ethanol, 20% Methanol (both HPLC Grade)

Note: Methanol is miscible in Hexane only if first dissolved in Ethanol. Solution B should be pre-mixed

Run time: 25 min.

HPLC: Waters Alliance 2695 (system dwell volume is ~350 µL)

Detector: Waters 996 (resolution: 4.8 nm, scan rate: 1 Hz)

Yield: 40%

^{1}H NMR (400MHz, DMSO d_6) δ 9.10 (m, 2H), 7.28 (m, 4H), 7.14 (m, 1H), 6.90 (d, 1H), 6.80 (m, 1H), 6.63 (d, 1H), 4.25 (m, 1H), 3.42 (m, 3H), 3.24 (m, 4H), 2.97 (m, 1H), 2.20 (m, 1H), 1.97 (m, 5H), 1.10 (m, 6H)

Mass Spectral Analysis m/z = 379.4 $(M+H)^+$

Chiral HPLC Method: t_R = 8.64 min. (*ee* = 97%)

Elemental analysis:

$C_{24}H_{30}N_2O_2$, 1HCl, $0.25H_2O$

Theory: %C 68.72; %H 7.57; %N 6.68

Found: %C 68.87; %H 7.52; %N 6.68

$[\alpha]_D^{25}$ = +58.40 (c. 0.01, MeOH)

DETERMINATION OF ABSOLUTE CONFIGURATION OF EXAMPLE 27B

[0706] Preparation of **27.3**:

Compound **27.2** (0.45g, 1.78 mmol, 1.1 eq) was added at 0°C to a solution of **27B** (0.67 g, 1.61 mmol, 1 eq) and triethylamine (0.74 mL, 5.33 mmol, 3.3 eq) in dichloromethane (6 mL). The reaction was warmed to room temperature and stirred overnight at room temperature. The mixture was washed with a saturated aqueous solution of sodium hydrogenocarbonate and brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 64%

^{1}H NMR (400MHz, DMSO d_6) δ 7.30 (m, 4H), 7.11 (t, 1H), 6.90 (d, 1H), 6.77 (t, 1H), 6.61 (d, 1H), 4.23 (m, 1H), 3.39 (br m, 9H), 2.93 (d, 1H), 2.37 (m, 2H), 2.24 (m, 1H), 2.06 (m, 2H), 1.93 (m, 6H), 1.53 (m, 1H), 1.41 (m, 1H), 1.10 (m, 6H), 1.03 (s, 3H), 0.83 (s, 3H)

Mass Spectral Analysis m/z = 593.4 $(M+H)^+$

Elemental analysis:

$C_{33}H_{44}N_2O_5S$, 0.25H2O

Theory: %C 68.37; %H 7.51; %N 4.69

Theory: %C 68.38; %H 7.50; %N 4.55

X-Ray Crystallography data:

[0707] Single crystals were grown as needles by dissolving **27.3** (10 mg, 0.017 mmol, 1 eq) in isopropanol (1 mL) and letting sit still at room temperature for 72 h.

Crystal data and structure refinement for **27.3**:

Identification code: ptut001

Empirical formula: $C_{34}H_{44}N_2O_5S$

Formula weight: 592.77

Temperature: 120(2) K

Wavelength: 0.71073 A

Crystal system, space group: Monoclinic, P2(1)

Unit cell dimensions:

a = 15.135(2) A, alpha = 90 deg

b = 6.1924(10) A, beta = 91.802(2) deg

c = 16.602(3) A, gamma = 90 deg

Volume: 1555.2(4) A^3

Z, Calculated density: 2, 1.266 Mg/m^3

Absorption coefficient: 0.148 mm^{-1}

F(000): 636

Crystal size: 0.30 x 0.08 x 0.04 mm

Theta range for data collection: 1.79 to 27.79 deg

Limiting indices: -18<=h<=19, -7<=k<=7, -20<=l<=21

Reflections collected/unique: 12166/6251 [R(int) = 0.0168]

Completeness to theta = 27.79: 91.9 %

Absorption correction: Semi-empirical from equivalents

Max. and min. transmission: 0.9941 and 0.9569

Refinement method: Full-matrix least-squares on F^2

Data/restraints/parameters: 6251/1/383

Goodness-of-fit on F^2: 1.040

Final R indices [I>2sigma(I)]: R1 = 0.0392, wR2 = 0.1030

R indices (all data): R1 = 0.0401, wR2 = 0.1041

Absolute structure parameter: -0.03(6)

Largest diff. peak and hole: 0.365 and -0.200 $e.A^{-3}$

EXAMPLE 27C

[0708] Preparation of **27C**:

27A (racemic mixture) (10 g, 24.10 mmol, 1 eq) was resolved using Chiral HPLC method:

Column: Chiralpak AD-H, 4.6 x 250mm, 5μ, Chiral Technologies PN# 19325
Column temperature: room temperature
Detection: UV photo diode array, 200 to 300nm, extract at 275nm
Injection volume: 40μL of 2 mg / mL sample in EtOH : MeOH (80 : 20)
Flow: 1 mL / minute
Mobile phase: 85% Solution A, 15% Solution B
Solution A: 0.1% Di-isopropylethylamine in Hexane (HPLC Grade)
Solution B: 80% Ethanol, 20% Methanol (both HPLC Grade)
Run time: 25 min
HPLC: Waters Alliance 2695 (system dwell volume is ~350 μL.)
Detector: Waters 996 (Resolution: 4.8 nm, Scan Rate: 1 Hz)
Yield: 40%

^{1}H NMR (400MHz, DMSO d_6) δ 9.12 (m, 2H), 7.28 (m, 4H), 7.14 (m, 1H), 6.90 (d, 1H), 6.79 (m, 1H), 6.63 (d, 1H), 4.25 (m, 1H), 3.44 (m, 3H), 3.24 (m, 4H), 2.96 (m, 1H), 2.18 (m, 1H), 1.97 (m, 5H), 1.10 (m, 6H)
Mass Spectral Analysis *m/z* = 379.4 $(M+H)^+$
Chiral HPLC Method: t_R = 11.914 min. (*ee* = 100%)
Elemental analysis:
$C_{24}H_{30}N_2O_2$, 1HCl, $0.25H_2O$
Theory: %C 68.72; %H 7.57; %N 6.68
Found: %C 68.79; %H 7.55; %N 6.68
$[\alpha]_D^{25}$ = -63.59 (c. 0.01, MeOH)

EXAMPLE 27D

[0709] **27D** was obtained according to a procedure similar to the one described for **27A**, with the following exception:

Step 27.3: Method 27A was used and **1A** was replaced by **1D**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.05 (m, 2H), 7.31 (q, 4H), 6.98 (m, 2H), 6.36 (dd, 1H), 6.47 (dd, 1H), 3.51-3.33 (m, 2H), 3.29-3.11 (m, 5H), 2.96 (m, 1H), 2.19 (m, 1H), 2.05-1.82 (m, 5H), 1.20-1.00 (m, 6H)

Mass Spectral Analysis *m/z* = 397.3 $(M+H)^+$

EXAMPLE 27E

[0710] **27E** was obtained from **27D** by chiral HPLC chromatography

^{1}H NMR (400MHz, DMSO d_6) δ 8.82 (m, 2H), 7.31 (m, 4H), 6.97 (m, 2H), 6.37 (m, 1H), 4.27 (m, 1H), 3.42 (m, 2H), 3.23 (m, 5H), 2.97 (m, 1H), 2.20 (m, 1H), 1.94 (m, 5H), 1.11 (m, 6H)

Mass Spectral Analysis *m/z* = 397.4 $(M+H)^+$

Elemental analysis:

$C_{24}H_{29}FN_2O_2$, 1HCl, $0.33H_2O$

Theory: %C 65.71; %H 7.09; %N 6.36

Found: %C 65.68; %H 7.07; %N 6.41

$[\alpha]_D^{25}$ = +65.32 (c = 9.85 mg/mL, MeOH)

EXAMPLE 27F

[0711] **27F** was obtained from **27D** by chiral HPLC chromatography

^{1}H NMR (400MHz, DMSO d_6) δ 8.92 (m, 2H), 7.32 (m, 4H), 6.98 (m, 2H), 6.37 (m, 1H), 4.27 (m, 1H), 3.42 (m, 2H), 3.24 (m, 5H), 2.97 (m, 1H), 2.20 (m, 1H), 1.95 (m, 5H), 1.11 (m, 6H)

Mass Spectral Analysis *m/z* = 397.3 $(M+H)^+$

Elemental analysis:

$C_{24}H_{29}FN_2O_2$, 1HCl, $0.2H_2O$

Theory: %C 66.03; %H 7.02; %N 6.42

Found: %C 66.07; %H 6.99; %N 6.34

$[\alpha]_D^{25}$ = -65.36 (c = 9.75 mg/mL, MeOH)

EXAMPLE 27G

[0712] **27G** was obtained according to a procedure similar to the one described for **27A**, with the following exception:

Step 27.3: Method 27A was used and **1A** was replaced by **2C**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.12 (brs, 1H), 8.97 (brs, 1H), 7.32 (d, 2H), 7.27 (d, 2H), 6.84 (d, 1H), 6.73 (dd, 1H), 6.12 (d, 1H), 4.21 (m, 1H), 3.55 (m, 3H), 3.42 (brs, 1H), 3.20 (brm, 5H), 2.94 (m, 1H), 2.16 (m, 1H), 1.92 (m, 5H), 1.09 (m, 7H), 0.46 (m, 2H), 0.18 (m, 2H)

Mass Spectral Analysis *m/z* = 449.3 $(M+H)^+$

Elemental analysis:

$C_{28}H_{36}N_2O_3$, 1HCl, 1H_2O

Theory: %C 66.85; %H 7.81; %N 5.57; %Cl 7.05

Found: %C 67.02; %H 7.51; %N 5.54; %Cl 7.25

EXAMPLE 27H

[0713] **27H** was obtained according to a procedure similar to the one described for **27A**, with the following exception:

Step 27.3: Method 27A was used and **1A** was replaced by **1N**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.07 (m, 1.5H), 8.53 (d, 1H), 7.70 (dd, 1H), 7.52 (d, 1H), 7.16 (m, 1H), 6.93 (dd, 1H), 6.82 (m, 1H), 6.63 (d, 1H), 4.36 (dd, 1H), 3.45 (q, 2H), 3.33-3.15 (m, 5H), 2.98 (m, 1H), 2.22 (m, 1H), 2.07-1.85 (m, 5H), 1.15 (t, 3H), 1.09 (t, 3H)

Mass Spectral Analysis *m/z* = 380.2 $(M+H)^+$

EXAMPLE 27I

[0714] **27I** was obtained from **27H** by chiral HPLC chromatography

^{1}H NMR (400MHz, DMSO d_6) δ 8.89 (m, 2H), 8.52 (d, 1H), 7.68 (dd, 1H), 7.51 (d, 1H), 7.16 (m, 1H), 6.94 (m, 1H), 6.82 (m, 1H), 6.62 (m, 1H), 4.35 (m, 1H), 3.44 (q, 2H), 3.26 (m, 5H), 2.98 (m, 1H), 2.23 (m, 1H), 1.95 (m, 5H), 1.15 (t, 3H), 1.09 (t, 3H)

Mass Spectral Analysis *m/z* = 380.2 $(M+H)^+$

Elemental analysis:

$C_{23}H_{29}N_3O_2$, 1.3HCl, 1.4H_2O

Theory: %C 61.10; %H 7.38; %N 9.29; %Cl 10.19

Found: %C 61.01; %H 7.35; %N 9.21; %Cl 10.41

$[\alpha]_D^{25}$ = +44.59 (c = 9.65 mg/mL, MeOH)

EXAMPLE 27J

27J was obtained from **27H** by chiral HPLC chromatography

^{1}H NMR (400MHz, DMSO d$_6$) δ 9.08 (m, 2H), 8.53 (d, 1H), 7.70 (dd, 1H), 7.52 (d, 1H), 7.16 (m, 1H), 6.93 (m, 1H), 6.82 (m, 1H), 6.63 (m, 1H), 4.36 (m, 1H), 3.45 (q, 2H), 3.25 (m, 5H), 2.97 (m, 1H), 2.22 (m, 1H), 1.97 (m, 5H), 1.15 (t, 3H), 1.09 (t, 3H)

Mass Spectral Analysis *m/z* = 380.2 $(M+H)^+$

Elemental analysis:

$C_{23}H_{29}N_3O_2$, 2HCl, 1.75H_2O

Theory: %C 57.08; %H 7.19; %N 8.68; %Cl 14.65

Found: %C 56.92; %H 7.15; %N 8.58; %Cl 15.02

$[\alpha]_D^{25}$ = -35.54 (c = 10.3 mg/ml, MeOH)

EXAMPLE 27K

[0715] **27K** was obtained according to a procedure similar to the one described for **27A**, with the following exception:

Step 27.3: Method 27A was used and **1A** was replaced by **1O**.

^{1}H NMR (400MHz, DMSO d$_6$) δ 9.17-8.85 (m, 2H), 8.53 (d, 1H), 7.70 (dd, 1H), 7.52 (d, 1H), 7.06-6.94 (m, 2H), 6.41 (dd, 1H), 4.37 (dd, 1H), 3.49-3.35 (m, 2H), 3.32-3.14 (m, 5H), 2.97 (m, 1H), 2.23 (m, 1H), 2.05-1.82 (m, 5H), 1.15 (t, 3H), 1.09 (t, 3H)

Mass Spectral Analysis *m/z* = 398.3 $(M+H)^+$

EXAMPLE 27L

[0716] **27L** was obtained from **27K** by chiral HPLC chromatography

^{1}H NMR (400MHz, DMSO d$_6$) δ 9.15 (m, 2H), 8.54 (d, 1H), 7.72 (dd, 1H), 7.54 (d, 1H), 7.00 (m, 2H), 6.42 (dd, 1H), 4.38 (m, 1H), 3.45 (q, 2H), 3.25 (m, 5H), 2.96 (m, 1H), 2.22 (m, 1H), 1.96 (m, 5H), 1.15 (t, 2H), 1.09 (t, 3H)

Mass Spectral Analysis *m/z* = 398.3 $(M+H)^+$

Elemental analysis:

$C_{23}H_{28}FN_3O_2$, 2HCl, 1.75H_2O

Theory: %C 55.04; %H 6.73; %Cl 14.13; %N 8.37

Found: %C 54.85; %H 6.53; %Cl 14.28; %N 8.45

$[\alpha]_D^{25}$ = +41.88 (c = 10.2 mg/mL, MeOH)

EXAMPLE 27M

[0717] **27M** was obtained from **27K** by chiral HPLC chromatography

^{1}H NMR (400MHz, DMSO d_6) δ 9.14 (m, 2H), 8.54 (d, 1H), 7.79 (dd, 1H), 7.54 (d, 1H), 7.00 (m, 2H), 6.42 (dd, 1H), 4.38 (m, 1H), 3.45 (q, 2H), 3.25 (m, 5H), 2.96 (m, 1H), 2.23 (m, 1H), 1.96 (m, 5H), 1.15 (t, 3H), 1.09 (t, 3H)

Mass Spectral Analysis *m/z* = 398.3 $(M+H)^+$

Elemental analysis:

$C_{23}H_{28}FN_3O_2$, 2HCl, $1.75H_2O$

Theory: %C 55.04; %H 6.73; %N 8.37; %Cl 14.13

Found: %C 54.85; %H 6.66; %N 8.37; %Cl 14.31

$[\alpha]_D^{25}$ = -40.91 (c = 10.25 mg/mL, MeOH)

EXAMPLE 27N

[0718] **27N** was obtained according to a procedure similar to the one described for **27A**, with the following exception:

Step 27.3: **1A** was replaced by **1S**.

Mass Spectral Analysis *m/z* = 408.3 $(M+H)^+$

EXAMPLE 27O

[0719] **27O** was obtained from **27N** by chiral HPLC chromatography

^{1}H NMR (400MHz, DMSO d_6) δ 8.93 (brs, 1H), 8.75 (brs, 1H), 8.50 (d, 1H), 7.65 (dd, 1H), 7.50 (d, 1H), 6.74 (s, 1H), 6.37 (s, 1H), 4.26 (m, 1H), 3.45 (q, 2H), 3.24 (m, 5H), 2.94 (m, 1H), 2.18 (m, 1H), 2.14 (s, 3H), 1.99 (s, 3H), 1.90 (m, 5H), 1.15 (t, 3H), 1.08 (t, 3H)

Mass Spectral Analysis *m/z* = 408.3 $(M+H)^+$

Elemental analysis:

$C_{25}H_{33}N_3O_2$, 1.25HCl, $1.63H_2O$

Theory: %C 62.25; %H 7.84; %N 8.70; %Cl 9.19

Found: %C 62.52; %H 7.64; %N 8.30; %Cl 8.80

EXAMPLE 27P

[0720] **27P** was obtained from **27N** by chiral HPLC chromatography

^1H NMR (400MHz, DMSO d_6) δ 9.00 (brs, 1H), 8.82 (brs, 1H), 8.50 (d, 1H), 7.65 (dd, 1H), 7.50 (d, 1H), 6.74 (s, 1H), 6.37 (s, 1H), 4.26 (m, 1H), 3.45 (q, 2H), 3.24 (m, 5H), 2.94 (m, 1H), 2.18 (m, 1H), 2.13 (s, 3H), 1.99 (s, 3H), 1.88 (m, 5H), 1.15 (t, 3H), 1.09 (t, 3H)

Mass Spectral Analysis m/z = 408.3 $(M+H)^+$

Elemental analysis:

$C_{25}H_{33}N_3O_2$, 1.2HCl, $1.6H_2O$

Theory: %C 62.54; %H 7.85; %N 8.75; %Cl 8.86

Found: %C 62.61; %H 7.73; %N 8.44; %Cl 8.52

EXAMPLE 27Q

[0721] Preparation of **27.6**:

A solution of **2.7a** (15.00 g, 30.45 mmol, 1 eq) in anhydrous dichloromethane (50 mL) and anhydrous methanol (100 mL) was hydrogenated at 1 atm, in the presence of palladium, 10 weight % (dry basis) on activated carbon, wet, Degussa type E101 NE/W (3.24 g, 1.52 mmol, 0.05 eq) for 10 h. The mixture was then filtered through celite and the filtrate was concentrated to dryness under reduced pressure. The product was used without further purification.

Yield: 99%

Mass Spectral Analysis m/z = 495.4 $(M+H)^+$

[0722] Preparation of **27Q**:

A 4.0M solution of hydrochloric acid in dioxane (41.9 mL, 167.46 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **27.6** (15.06 g, 30.45 mmol, 1 eq) in anhydrous methanol (50 mL). The mixture was warmed to room temperature and stirring was continued for an additional 10 h at room temperature. The mixture was concentrated under reduced pressure. Diethyl ether (100 mL) was added to the solution. The resulting precipitate was collected by filtration and washed with diethyl ether.

Yield: 85%

^{1}H NMR (400MHz, DMSO d_6) δ 9.03 (m, 1H), 8.90 (m, 1H), 8.80 (s, 1H), 7.28 (m, 4H), 6.71 (d, 1H), 6.53 (m, 1H), 6.05 (d, 1H), 4.16 (m, 1H), 3.43 (m, 3H), 3.21 (m, 5H), 2.92 (m, 1H), 2.11 (m, 1H), 1.98 (m, 1H), 1.90 (m, 4H), 1.11 (m, 6H)

Mass Spectral Analysis *m/z* = 395.4 $(M+H)^+$

Elemental analysis:

$C_{24}H_{30}N_2O_2$, 1HCl, 0.75H2O

Theory: %C 64.85, %H 7.37, %N 6.30

Found: %C 65.12, %H 7.43, %N 6.18

EXAMPLE 27R

[0723] Preparation of **27R**:

27R was obtained from **27Q** by chiral HPLC chromatography

27Q (racemic mixture) (10 g, 23.20 mmol, 1 eq) was resolved using Chiral HPLC method:

Column: Chiralpak AD-H, 4.4 x 250mm

Column temperature: 25°C

Detection: UV at 230nm

Flow: 2.0 mL/minute

Mobile phase: 80% carbon dioxide, 20% ethanol, 0.1% ethane sulfonic acid

Run time: 24 min.

The relevant fractions were combined and concentrated under reduced pressure. An aqueous 1N solution of sodium hydroxide was added to the resulting oil until the solution was basic using pH paper. The aqueous mixture was extracted with dichloromethane. The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. To a cold (0°C) solution of the resulting oil in anhydrous methanol was added drop wise a 4M solution of anhydrous hydrochloric acid in dioxane (5.5 eq). The mixture was then stirred for 1 hour at room temperature and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity).

Yield: 30%

^{1}H NMR (400MHz, DMSO d_6) δ 9.19 (m, 1H), 9.05 (m, 1H), 7.31 (m, 4H), 6.73 (d, 1H), 6.54 (m, 1H), 6.05 (d, 1H), 4.16 (m, 1H), 3.42 (br s, 2H), 3.17 (br m, 6H), 2.91 (m, 1H), 2.11 (m, 1H), 1.98 (m, 1H), 1.90 (m, 4H), 1.10 (m, 6H)
Mass Spectral Analysis *m/z* = 395.1 $(M+H)^+$
Chiral HPLC purity: t_R = 9.932 min. (*ee* = >99%)
$[\alpha]_D^{24.2}$ = +21.49 (c. 0.01, MeOH)

EXAMPLE 27S

[0724] Preparation of **27S**:

27S was obtained from **27Q** by chiral HPLC chromatography
27Q (racemic mixture) (10 g, 23.20 mmol, 1 eq) was resolved using Chiral HPLC method:
Column: Chiralpak AD-H, 4.4 x 250mm
Column Temperature: 25°C
Detection: UV at 230nm
Flow: 2.0 mL/minute
Mobile Phase: 80% carbon dioxide, 20% ethanol, 0.1% ethane sulfonic acid
Run Time: 24 min.

The relevant fractions were combined and concentrated under reduced pressure. An aqueous 1N solution of sodium hydroxide was added to the resulting oil until the solution was basic using pH paper. The aqueous mixture was extracted with dichloromethane. The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. To a cold (0°C) solution of the resulting oil in anhydrous methanol was added drop wise a 4M solution of anhydrous hydrochloric acid in dioxane (5.5 eq). The mixture was then stirred for 1 h at room temperature and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity).

Yield: 18%
^{1}H NMR (400MHz, DMSO d_6) δ 9.03 (m, 1H), 8.87 (m, 1H), 8.80 (s, 1H), 7.31 (m, 4H), 6.71 (d, 1H), 6.55 (d, 1H), 6.05 (m, 1H), 4.18 (m, 1H), 3.36 (m, 2H), 3.18 (m, 5H), 2.93 (m, 1H), 2.11 (m, 1H), 1.98 (m, 1H), 1.87 (m, 4H), 1.10 (m, 6H)
Mass Spectral Analysis *m/z* = 395.1 $(M+H)^+$

Chiral HPLC prity: t_R = 13.371 min. (*ee* = 98.1%)
$[\alpha]_D^{24.2}$ = -25.96 (c. 0.01, MeOH)

EXAMPLE 27T

[0725] Preparation of **27.1**:

A solution of **11.6a** (15.00 g, 27.95 mmol, 1 eq) in anhydrous methanol (100 mL) was hydrogenated at 70 psi in the presence of palladium hydroxide [$Pd(OH)_2$: Pearlman's catalyst] (1.96 g, 1.40 mmol, 0.05 eq) for 10 h. The mixture was filtered through celite. The filtrate was concentrated under reduced pressure and was hydrogenated at 70 psi in the presence of palladium hydroxide (1.96 g) for an additional 10 h. The mixture was filtered through celite and the filtrate was concentrated to dryness under reduced pressure. The crude product was used without further purification.
Yield: 84%
^{1}H NMR (400MHz, DMSO d_6) δ 7.23 (d, 2H), 7.11 (m, 3H), 6.60 (d, 1H), 6.52 (d, 1H), 4.85 (d, 1H), 4.74 (d, 1H), 4.16 (m, 1H), 3.61 (m, 2H), 3.30 (br m, 6H), 2.83 (s, 3H), 2.24 (m, 1H), 1.75 (m, 2H), 1.64 (m, 1H), 1.52 (m, 2H), 1.39 (s, 9H), 1.06 (m, 6H)
Mass Spectral Analysis *m/z* = 539.5 $(M+H)^+$

[0726] Preparation of **27T**:

To a cold (0°C) solution of **27.1** (2.00 g, 3.71 mmol, 1.0 eq) in anhydrous methanol (40 mL) was added drop wise a 4M solution of anhydrous hydrochloric acid in dioxane (9.3 mL, 37.20 mmol, 10.0 eq). The mixture was then stirred for 10 h at room temperature and concentrated under reduced pressure. Diethyl ether was added. The resulting precipitate was collected by filtration and washed with diethyl ether.
Yield: 99%
^{1}H NMR (400MHz, DMSO d_6) δ 9.30 (br s, 1H), 9.03 (br s, 1H), 8.96 (br s, 1H), 7.21 (d, 2H), 7.14 (d, 2H), 6.99 (t, 1H), 6.43 (d, 1H), 6.35 (d, 1H), 4.15 (m, 1H), 3.87 (br s, 3H), 3.39 (m, 2H), 3.15 (m, 5H), 2.90 (m, 1H), 2.25 (m, 1H), 1.83 (br m, 5H), 1.09 (m, 6H)
Mass Spectral Analysis *m/z* = 395.3 $(M+H)^+$

EXAMPLE 27U

[0727] Preparation of **27.4**:

Compound **27.1** (racemic mixture) (10 g, 18.56 mmol, 1 eq) was resolved using Chiral HPLC method:
Column: Chiralpak AD-H, 4.4 x 250mm
Column temperature: 25°C
Detection: UV at 280nm
Flow: 2.0 mL/minute
Mobile phase: 75% carbon dioxide, 25% isopropanol
Run time: 10 minutes.

The relevant fractions were combined and concentrated under reduced pressure. The crude product was used without further purification.

Yield: 79%

^{1}H NMR (400MHz, DMSO d_6) δ 7.21 (d, 2H), 7.11 (m, 3H), 6.60 (d, 1H), 6.55 (d, 1H), 4.83 (d, 1H), 4.74 (d, 1H), 4.16 (m, 1H), 3.62 (m, 2H), 3.15 (br m, 6H), 2.83 (s, 3H), 2.24 (m, 1H), 1.75 (m, 2H), 1.61 (m, 1H), 1.50 (m, 2H), 1.39 (s, 9H), 1.06 (m, 6H)

Mass Spectral Analysis *m/z* = 539.1 $(M+H)^+$

Chiral HPLC purity: t_R = 4.728 min. (*ee* = >99%)

$[\alpha]_D^{24.1}$ = -32.97 (c. 0.01, MeOH)

[0728] Preparation of **27U**:

To a cold (0°C) solution of **27.4** (1.00 g, 1.86 mmol , 1 eq) in anhydrous methanol was added drop wise a 4M solution of anhydrous hydrochloric acid in dioxane (2.5 mL, 10.21 mmol , 5.5 eq). The mixture was stirred for 10 hours at room temperature and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity).

Yield: 88%

^{1}H NMR (400MHz, DMSO d_6) δ 9.30 (s, 1H), 9.00 (m, 2H), 7.21 (d, 2H), 7.14 (d, 2H), 6.99 (t, 1H), 6.41 (d, 1H), 6.35 (d, 1H), 4.15 (m, 1H), 3.42 (br s, 5H), 3.12 (m, 2H), 2.90 (m, 1H), 2.24 (m, 1H), 1.83 (m, 4H), 1.72 (m, 1H), 1.09 (m, 6H)
Mass Spectral Analysis *m/z* = 395.1 $(M+H)^+$
$[\alpha]_D^{24.2}$ = +3.24 (c. 0.01, MeOH)

EXAMPLE 27V

[0729] Preparation of **27.5**:

27.1 (racemic mixture) (10 g, 18.56 mmol, 1 eq) was resolved using Chiral HPLC method:
Column: Chiralpak AD-H, 4.4 x 250mm
Column temperature: 25°C
Detection: UV at 280nm
Flow: 2.0 mL/minute
Mobile phase: 75% carbon dioxide, 25% isopropanol
Run time: 10 minutes.
The relevant fractions were combined and concentrated under reduced pressure. The crude product was used without further purification.
Yield: 83%
^{1}H NMR (400MHz, DMSO d_6) δ 7.23 (d, 2H), 7.11 (m, 3H), 6.58 (d, 1H), 6.54 (d, 1H), 4.85 (d, 1H), 4.73 (d, 1H), 4.16 (m, 1H), 3.63 (m, 2H), 3.16 (br m, 6H), 2.83 (s, 3H), 2.24 (m, 1H), 1.75 (m, 2H), 1.61 (m, 1H), 1.52 (m, 2H), 1.39 (s, 9H), 1.05 (m, 6H)
Mass Spectral Analysis *m/z* = 539.1 $(M+H)^+$
Chiral HPLC Method: t_R = 5.943 min. (*ee* = 98.7%)
$[\alpha]_D^{24.0}$ = +29.88 (c. 0.01, MeOH)

[0730] Preparation of **27V**:

To a cold (0°C) solution of **27.5** (1.00 g, 1.86 mmol, 1 eq) in anhydrous methanol was added drop wise a 4M solution of anhydrous hydrochloric acid in dioxane (2.5 mL, 10.21 mmol , 5.5 eq). The mixture was then stirred for 10 h at room temperature and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity).

Yield: 92%

^{1}H NMR (400MHz, DMSO d_6) δ 9.32 (s, 1H), 9.09 (br s, 2H), 7.21 (d, 2H), 7.12 (d, 2H), 6.99 (t, 1H), 6.41 (d, 1H), 6.38 (d, 1H), 4.16 (m, 1H), 3.36 (m, 5H), 3.13 (br m, 2H), 2.90 (m, 1H), 2.24 (m, 1H), 1.81 (br m, 5H), 1.09 (m, 6H)

Mass Spectral Analysis *m/z* = 395.1 $(M+H)^+$

$[\alpha]_D^{24.3}$ = -6.35 (c. 0.01, MeOH)

EXAMPLE 27W

[0731] **27W** was obtained according to a procedure similar to the one described for **27A**, with the following exception:

Step 27.3: **1A** was replaced by **1E**.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.34 (d, 2H), 7.18 (d, 2H), 6.96 (d, 1H), 6.78 (d, 1H), 6.54 (s, 1H), 4.06 (m, 1H), 3.72 (q, 1H), 3.55 (brm, 3H), 3.28 (brm, 3H), 3.17 (m, 1H), 3.03 (m, 1H), 2.14 (m, 5H), 1.97 (m, 2H), 1.49 (t, 1H), 1.20 (brd, 6H)

Mass Spectral Analysis *m/z* = 393.4 $(M+H)^+$

EXAMPLE 28A

[0732] Preparation of **28.2**:

To a solution of benzyl 4-oxopiperidine-1-carboxylate (**19.1**) (37.26 g, 160 mmol) in toluene (450 mL) were added ethyl cyanoacetate (**28.1**) (18.8 g , 166 mmol, 1.04 eq) , acetic acid (2 mL) and ammonium acetate (1.24 g, 16 mmol, 0.1 eq). The reaction mixture was refluxed for 2h with azeotropic removal of water formed during the reaction using a Dean-Stark trap. Additional ethyl cyanoacetate (10 g, 88.4 mmol, 0.55 eq), acetic acid (2 mL) and ammonium acetate (1.24 g, 6 mmol, 0.0375 eq) was added to the reaction mixture, which was then refluxed for 1.5h. Additional ethyl cyanoacetate (10 g, 88.4 mmol, 0.55 eq), acetic acid (2 mL) and ammonium acetate (1.24 g, 6 mmol, 0.0375 eq) were added, and refluxed for an additional 1h. The reaction mixture was cooled to room temperature and washed with a saturated aqueous solution of sodium bicarbonate, and dried over sodium sulfate. The mixture was filtered and the filtrate was concentrated under vacuum. To the residue was added hexane (300 mL) and ethyl acetate (20 mL). The mixture was kept at room

temperature overnight. The solid was collected by filtration, washed with hexane and dried under vacuum.
Yield: 87.7%

^{1}H NMR (400MHz, CDCl$_3$) δ 7.35 (m, 5H), 5.19 (s, 2H), 4.30 (q, 2H), 3.70 (m, 2H), 3.63 (m, 2H), 3.18 (m, 2H), 2.80 (m, 2H), 1.39 (t, 3H)

[0733] Preparation of **28.4a**:

To a suspension of copper (I) cyanide (17.3 g, 193.2 mmol, 2.0 eq) in anhydrous tetrahydrofuran (400 mL) was added drop wise a 2.0 M solution of benzylmagnesium chloride (**28.3a**) (192 mL, 384 mmol, 4.0 eq) in tetrahydrofuran under a nitrogen atmosphere at 0°C. After the reaction mixture was stirred at room temperature for 2h, a solution of compound **28.2** (31.5 g, 96 mmol) in tetrahydrofuran (100 mL) was added dropwise at -30°C. After the addition, the reaction mixture was stirred at room temperature overnight, and then quenched with a saturated aqueous solution of ammonium chloride, and filtered. The filtrate was extracted by diethyl ether and the combined organic extracts were dried over sodium sulfate. The organics were concentrated under reduced pressure and the residue was purified by column chromatography (eluent: hexane/methylene chloride/ethyl acetate, 4:1:1).
Yield: 100%

^{1}H NMR (400MHz, CDCl$_3$) δ 7.35-7.20 (m, 10H), 5.11 (s, 2H), 4.25 (q, 2H), 3.72-3.50 (m, 5H), 3.06 (d, 1H), 2.91 (d, 1H), 1.90-1.65 (m, 4H), 1.32 (t, 3H)

[0734] Preparation of **28.6a**:

Concentrated sulfuric acid (210 mL) was added slowly to **28.4a** (38 g, 90.5 mmol) at 0°C. The mixture was warmed to room temperature, stirred for 30 min at room temperature, and then heated at 90°C overnight. The reaction mixture was cooled in an ice bath and carefully basified to pH = 9-10 with a 6 N aqueous solution of sodium hydroxide. The mixture was extracted with methylene chloride, and the organic extracts were combined, dried over sodium sulfate and concentrated under vacuum. The residue was dissolved in methylene chloride (500 mL). To this solution was added triethylamine (30 mL, 215.6 mmol, 2.4 eq) followed by drop wise addition of benzyl chloroformate (**21.8**) (16 mL, 106.5 mmol, 1.2 eq) at 0°C. The reaction

mixture was stirred at 0°C for 1h and then washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over sodium sulfate and concentrated under vacuum. The residue was purified by column chromatography (eluent: hexane/methylene chloride/ethyl acetate, 4:1:1).
Yield: 41.2%

^{1}H NMR (400MHz, $CDCl_3$) δ 8.00 (d, 1H), 7.50 (t, 1H), 7.33-7.23 (m, 7H), 5.11 (s, 2H), 2.98 (s, 2H), 2.62 (s, 2H), 1.50 (m, 4H)

[0735] Preparation of **28.7a**:

A 1.0 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (3.6 mL, 3.6 mmol, 1.2 eq) was added at -78°C to a solution of **28.6a** (1.047 g, 3.0 mmol) in tetrahydrofuran (30mL). After 45 min, a solution of **1.4** (1.3 g, 3.6 mmol, 1.2 eq) in tetrahydrofuran (8 mL) was added drop wise to the reaction mixture. The reaction mixture was then warmed to room temperature and stirred for 2.5 h, quenched by addition of water (40 mL), and extracted with a mixture of hexane and diethyl ether (1:1). The organic extracts were combined and washed with water, brine and dried over sodium sulfate. Evaporation of the solvent gave the crude product, which was used for the next step without further purification.
Yield: 100%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.35-7.18 (m, 9H), 5.98 (s, 1H), 5.11 (s, 2H), 3.70 (m, 2H), 3.40 (m, 2H), 2.83 (s, 2H), 1.66-1.56 (m, 4H)

[0736] Preparation of **28.8a**:

To the solution of crude **28.7a** (3 mmol) in dimethoxyethane (25 mL) was added sequentially a 2 N aqueous solution of sodium carbonate (5 mL, 10 mmol, 3.3 eq), lithium chloride (424 mg, 10 mmol, 3.3 eq), 4-(*N*,*N*-diethylaminocarbonyl)phenylboronic acid (796 mg, 3.6 mmol, 1.2 eq) and tetrakis(triphenylphosphine)palladium(0) (104 mg, 0.09 mmol, 0.03 eq). The reaction mixture was refluxed overnight, cooled to room temperature, diluted with water (30 mL) and extracted with diethyl ether. The combined organic extracts were dried over sodium sulfate and concentrated under vacuum. The residue was purified by column chromatography (eluent: hexane/methylene chloride/ethyl acetate, 2:1:1).

Yield: 91.9%

^{1}H NMR (400MHz, CDCl$_3$) δ 7.36-7.12 (m, 12H), 7.00 (d, 1H), 6.00 (s, 1H), 5.13 (s, 2H), 3.70 (m, 2H), 3.58 (m, 2H), 3.45 (m, 2H), 3.30 (m, 2H), 2.82 (s, 2H), 1.65-1.52 (m, 4H), 1.21 (m, 6H)

[0737] Preparation of **28A**:

Iodotrimethylsilane (0.29 mL, 2 mmol, 2 eq) was added to a solution of **28.8a** (508 mg, 1mmol) in anhydrous methylene chloride (10 mL) under a nitrogen athmosphere. The reaction mixture was stirred at room temperature for 2h and quenched with a 1N aqueous solution of hydrochloric acid (30 mL) and extracted with diethyl ether. The aqueous phase was basified to pH = 9-10 with a 3N aqueous solution of sodium hydroxide, and extracted with methylene chloride. The organic extracts were combined, dried over sodium sulfate and concentrated under vacuum. The residue was dissolved in methylene chloride (3 mL) and diluted with diethyl ether (15 mL). To this solution was added a 2.0 M solution of anhydrous hydrochloric acid in diethyl ether (1.5 mL, 3 mmol, 3.0 eq) and the reaction was stirred at room temperature for 30 min. The solid was collected by filtration, washed with diethyl ether and dried under vacuum.

Yield: 92.7%

^{1}H NMR (400MHz, CDCl$_3$) δ 8.90 (m, 2H), 7.40-7.20 (m, 7H), 6.97 (d, 1H), 6.20 (s, 1H), 3.42 (m, 2H), 3.20 (m, 6H), 2.82 (s, 2H), 1.70 (m, 4H), 1.10 (m, 6H)
Mass Spectral Analysis $m/z = 375.1\ (M+H)^+$

EXAMPLE 28B

[0738] Preparation of **28.4b**:

Compound **28.4b** was prepared as described for **28.4a** except **28.3a** was replaced by **23.8b**.

[0739] Preparation of **28.9**:

To a solution of compound **28.4b** (29 g, 64.4 mmol) in dimethylsulfoxide (200 mL) was added sodium chloride (1.5 g, 25.6 mmol, 0.4 eq) and water (3.0 mL, 167 mmol, 2.6 eq). The reaction mixture was heated at 160°C for 2h and then cooled to room

temperature. Water (600 mL) was added to the mixture and the crude product was extracted with diethyl ether. The organic extracts were combined, washed with water and brine, dried over sodium sulfate, and concentrated under vacuum. The residue was purified by column chromatography (eluent: hexane/methylene chloride/ethyl acetate, 4:1:1).
Yield: 94.8%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.35 (m, 5H), 7.08 (d, 2H), 6.83 (d, 2H), 5.12 (s, 2H), 3.80 (s, 3H), 3.68 (m, 2H), 3.40 (m, 2H), 2.74 (s, 2H), 2.21 (s, 2H), 1.60-1.52 (m, 4H)

[0740] Preparation of **28.10**:

To a solution of compound **28.9** (7.56 g, 20 mmol) in methanol (200 mL) was added concentrated sulfuric acid (40 mL). The mixture was heated at reflux for 2 days. The reaction mixture was cooled to 0°C, basified to pH = 9 by slow addition of a 6 N aqueous solution of sodium hydroxide, and then concentrated under vacuum to remove the methanol. The mixture was extracted with methylene chloride. The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was dissolved in methylene chloride (80 mL) and cooled to 0°C. To this solution was added triethylamine (9.6 mL, 69 mmol, 3.5 eq) and followed by drop wise addition of benzyl chloroformate (**21.8**) (6.4 mL, 95%, 42.7 mmol, 2.1 eq). The reaction mixture was stirred at 0°C for 1h, washed with a saturated aqueous solution of sodium bicarbonate, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by column chromatography (eluent: hexane/methylene chloride/ethyl acetate, 4:1:1).
Yield: 94.8%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.38 (m, 5H), 7.10 (d, 2H), 6.80 (d, 2H), 5.12 (s, 2H), 3.80 (s, 3H), 3.75 (m, 2H), 3.70 (s, 3H), 3.32 (m, 2H), 2.73 (s, 2H), 2.30 (s, 2H), 1.50 (m, 4H)

[0741] Preparation of **28.11**:

Compound **28.10** (2.06 g, 5 mmol) was dissolved in mixture of methanol (40 mL), tetrahydrofuran (40 mL) and water (40 mL). To this solution was added lithium hydroxide (1.52 g, 36 mmol, 7.2 eq) in one portion. The reaction mixture was stirred

at room temperature overnight, concentrated under vacuum, acidified with a 3 N aqueous solution of hydrochloric acid and extracted with methylene chloride. The combined organic extracts were dried over sodium sulfate, filtered and concentrated under vacuum. The crude product was used fro the next step without further purification.
Yield: 100%

^{1}H NMR (400MHz, DMSO d_6) δ12.22 (brs, 1H), 7.33 (m, 5H), 7.10 (d, 2H), 6.86 (d, 2H), 5.06 (s, 2H), 3.73 (s, 3H), 3.60 (m, 2H), 3.32 (m, 2H), 2.69 (s, 2H), 2.17 (s, 2H), 1.45-1.35 (m, 4H)

[0742] Preparation of **28.6b**:

To a solution of **28.11** (1.98 g, 5 mmol) in anhydrous methylene chloride (10 mL) was added a 2.0 M solution of oxalyl chloride in methylene chloride (20 mL, 40 mmol, 8.0 eq) followed by 2 drops of anhydrous *N*,*N*-dimethylformamide. The reaction mixture was stirred at room temperature for 4h and then concentrated under vacuum. The resulting acyl chloride was dissolved in anhydrous methylene chloride (100 mL) and aluminum chloride (1.35 g, 10 mmol, 2.0 eq) was added in one portion. The reaction mixture was stirred at room temperature overnight and then quenched with water (60 mL) followed by addition of concentrated ammonium hydroxide to basify the aqueous layer. The organic layer was separated and the aqueous layer was further extracted with methylene chloride. The combined organic extracts were dried over sodium sulfate, filtered and concentrated under vacuum. The residue was then dissolved in methylene chloride (60 mL) and cooled to 0°C. To this solution was added triethylamine (3.0 mL, 21.6 mmol, 4.3 eq) followed by benzyl chloroformate (**21.8**) (2.0 mL, 13.3 mmol, 2.7 eq). The reaction mixture was stirred at 0°C for 1h and then washed with a saturated aqueous solution of sodium bicarbonate, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by column chromatography (eluent: hexane/methylene chloride/ethyl acetate, 4:1:1).
Yield: 89.7%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.48 (d, 1H), 7.35 (m, 5H), 7.16 (d, 1H), 7.10 (dd, 1H), 5.11 (s, 2H), 3.81 (s, 3H), 3.50 (m, 4H), 2.90 (s, 2H), 2.60 (s, 2H), 1.50 (m, 4H)

[0743] Preparation of **28B**:

28B was obtained from **28.6b** according to a procedure similar to the one described for **28A**.

^{1}H NMR (DMSO d_6) δ 8.90 (m, 2H), 7.48 (d, 2H), 7.40 (d, 2H), 7.26 (d, 1H), 6.85 (dd, 1H), 6.45 (d, 1H), 6.20 (s, 1H), 3.64 (s, 3H), 3.42 (m, 4H), 3.18 (m, 4H), 2.78 (s, 2H), 1.70 (m, 4H), 1.11 (m, 6H)
Mass Spectral Analysis *m/z* = 405.1 $(M+H)^+$

EXAMPLE 28C

[0744] Preparation of **28C**:

Compound **28.8a** (800 mg, 1.58 mmol) was dissolved in a mixture of methylene chloride (5 mL) and methanol (50 mL), and the reaction mixture was hydrogenated in the presence of 10% Pd/C (240 mg) using a hydrogen balloon. After 2 days at room temperature, the reaction mixture was filtered through celite and the filtrate was concentrated under vacuum. The residue was dissolved in methylene chloride (10 ml) and added 2.0 M solution of anhydrous hydrochloric acid in diethyl ether (2 mL, 4 mmol, 2.5 eq). The mixture was stirred for 1 h at room temperature and then concentrated under vacuum.
Yield: 100%

^{1}H NMR (400MHz, DMSO d_6) δ 9.12 (brs, 2H), 7.28-7.03 (m, 7H), 6.66 (d, 1H), 4.10 (m, 1H), 3.40 (m, 2H), 3.20-3.08 (m, 6H), 2.85 (d, 1H), 2.78 (d, 1H), 2.10 (m, 1H), 1.60 (m, 5H), 1.10 (m, 6H).
Mass Spectral Analysis *m/z* = 377.1 $(M+H)^+$

EXAMPLE 28D

[0745] **28D** was obtained according to a procedure similar to the one described for **28C**, with the following exception:
Step 28.12: **28.8a** was replaced by **28.8b**.
^{1}H NMR (400MHz, DMSO d_6) δ 8.77 (m, 2H), 7.28 (m, 4H), 7.89 (d, 1H), 6.75 (dd, 1H), 6.16 (d, 1H), 4.09 (m, 1H), 3.55 (s, 3H), 3.49-3.00 (m, 8H), 2.73 (m, 2H), 2.10 (m, 1H), 1.59 (m, 5H), 1.10 (m, 6H)

Mass Spectral Analysis $m/z = 407.3$ $(M+H)^+$

EXAMPLE 28E

[0746] **28E** was obtained according to a procedure similar to the one described for **28A**, with the following exception:

Step 28.10: **1.6** was replaced by **1.7** (see also step 28.13).

^{1}H NMR (400MHz, DMSO d_6) δ 8.91 (m, 2H), 8.61 (s, 1H), 7.89 (d, 1H), 760 (d, 1H), 7.31-7.20 (m, 3H), 6.90 (d, 1H), 6.33 (s, 1H), 3.45-3.15 (m, 8H), 2.83 (s, 2H), 1.70 (m, 4H), 1.12 (m, 6H)

Mass Spectral Analysis $m/z = 376.4$ $(M+H)^+$

Elemental analysis:

$C_{24}H_{29}N_{30}$, 4/3HCl, $1H_2O$

Theory: %C 65.20; %H 7.37; %N 9.50; %C 10.69

Found: %C 64.94; %H 7.06; %N 9.36; %Cl 10.56

EXAMPLE 29A

[0747] Preparation of **29.2**:

To a solution of crude compound **28.7a** (12 mmol) in anhydrous tetrahydrofuran (200 mL) at room temperature was added a 0.5 M solution of 4-(ethoxycarbonyl)phenylzinc iodide (**29.1**) in tetrahydrofuran (60 mL, 30 mmol, 2.5 eq) followed by tetrakis(triphenylphosphine)palladium(0) (833 mg, 0.72 mmol, 0.06 eq). The reaction mixture was heated at 40°C for 2 days and then cooled to room temperature. The reaction was quenched by addition of a saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The organic extracts were combined, dried over sodium sulfate and filtered. The organic extracts were concentrated under reduced pressure and the residue was purified by column chromatography (eluent: hexane/ethyl acetate, 5:1).

Yield: 86.6%

^{1}H NMR (400MHz, $CDCl_3$) δ 8.05 (d, 2H), 7.40-7.10 (m, 10H), 6.96 (d, 1H), 6.00 (s, 1H), 5.13 (s, 2H), 4.40 (q, 2H), 3.70 (m, 2H), 3.48 (m, 2H), 2.82 (s, 2H), 1.66-1.53 (m, 6H), 1.40 (t, 3H)

[0748] Preparation of **29.3**:

Lithium hydroxide (3.36 g, 80 mmol, 8.0 eq) was added to a solution of **29.2** (4.81 g, 10 mmol) in a mixture of methanol (100 mL), tetrahydrofuran (100 mL) and water (100 mL). The reaction mixture was stirred at room temperature overnight, concentrated under vacuum and acidified to pH = 1-2 with a 3N aqueous solution of hydrochloric acid. The acidified solution was extracted with methylene chloride and the organic extracts were combined, dried over sodium sulfate, filtered and concentrated under vacuum. The crude product was used for the next step without further purification.
Yield: 100%

^{1}H NMR (400MHz, DMSO d_6) δ 13.00 (brs, 1H), 7.99 (d, 2H), 7.48 (d, 2H), 7.38-7.15 (m, 8H), 6.91 (d, 1H), 6.18 (s, 1H), 5.10 (s, 2H), 3.60-3.46 (m, 4H), 2.82 (s, 2H), 1.53 (m, 2H), 1.42 (m, 2H)

[0749] Preparation of **29.5a**:

To a solution of **29.3** (680 mg, 1.5 mmol, 1.0 eq)) in methylene chloride (40 mL) was added *iso*propylamine (**3.4h**) (0.26 mL, 3 mmol, 2.0 eq) followed by triethylamine (0.84 ml, 6 mmol, 4.0 eq) and the Mukaiyama acylating reagent (2-chloro-1-methylpyridinium iodide) (461 mg, 1.8 mmol, 1.2 eq). The reaction mixture was stirred at room temperature overnight, washed with a saturated aqueous solution of sodium bicarbonate, dried over sodium sulfate, and filtered. The organic extracts were concentrated under reduced pressure and the residue was purified by column chromatography (eluent: hexane/methylene chloride/ethyl acetate, 2:1:1).
Yield: 95.8%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.78 (d, 2H), 7.40-7.10 (m, 10H), 6.94(d, 1H), 6.00 (s, 1H), 5.95 (d, 1H), 5.12 (s, 2H), 4.31 (m, 1H), 3.70 (m, 2H), 3.46 (m, 2H), 2.81 (s, 2H), 1.62-1.52 (m, 6H), 1.30 (d, 6H)

[0750] Preparation of **29A**:

Iodotrimethylsilane (0.37 mL, 2.6 mmol, 2.0 eq) was added to a solution **29.5** (620 mg, 1.26 mmol) in anhydrous methylene chloride (20 mL) under a nitrogen athmosphere. The reaction mixture was stirred at room temperature for 2h, quenched

with a 1N aqueous solution of hydrochloric acid (40 mL), and the mixture was extracted with diethyl ether. The aqueous phase was basified to pH = 9-10 with a 3N aqueous solution of sodium hydroxide and extracted with methylene chloride. The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was dissolved in methylene chloride (4 mL) and diluted with diethyl ether (20 mL). To this solution was added a 2.0 M solution of anhydrous hydrochloric acid in diethyl ether (2.0 mL, 4 mmol, 3.2 eq) and the mixture was stirred at room temperature for 30 min. The resulting precipitate was collected by filtration, washed with diethyl ether and dried under vacuum.
Yield: 100%

^{1}H NMR (400MHz, DMSO d_6) δ 8.90 (brd, 2H), 8.29 (d, 1H), 7.90 (d, 2H), 7.43 (d, 2H), 7.31-7.16 (m, 3H), 6.90 (d, 1H), 6.18 (s, 1H), 4.11 (m, 1H), 3.16 (m, 4H), 2.86 (s, 2H), 1.70 (m, 4H), 1.20 (d, 6H)
Mass Spectral Analysis *m/z* = 361.0 $(M+H)^+$

EXAMPLE 29B

[0751] **29B** was obtained according to a procedure similar to the one described for **29A**, with the following exception:
Step 29.3: **3.4h** was replaced by **29.4**.
^{1}H NMR (400MHz, DMSO d_6) δ 8.89 (m, 2H), 8.10 (d, 1H), 7.92 (d, 2H), 7.45 (d, 2H), 7.31 (d, 1H), 7.25 (t, 1H), 7.20 (t, 1H), 6.90 (d, 1H), 6.18 (s, 1H), 3.80 (m, 1H), 3.20 (m, 4H), 2.88 (s, 2H), 1.60 (m, 8H), 0.90 (t, 6H)
Mass Spectral Analysis *m/z* = 389.1 $(M+H)^+$

EXAMPLE 29C

[0752] Preparation of **29.7**:

To a solution of the carboxylic acid **29.3** (1.82 g, 4 mmol) in a mixture of dioxane (18 mL) and *tert*-butyl alcohol (18 mL) was added triethylamine (0.78 mL, 5.6 mmol, 1.4 eq) and diphenylphosphoryl azide (**29.6**) (1.12 mL, 5.2 mmol, 1.3 eq). The reaction mixture was refluxed overnight and concentrated under vacuum. The residue was purified by column chromatography (eluent: hexane/methylene chloride/ethyl acetate, 5:1:1) to afford the desired crude carbamate **29.7**, which was used for the next step without further purification.

Yield: 33.4%

[0753] Preparation of **29.8**:

To a solution of the crude carbamate **29.7** (700 mg) in methylene chloride (15 mL) was added a 2.0 M solution of anhydrous hydrochloric acid in diethyl ether (15 mL, 30 mmol). The reaction mixture was stirred at room temperature overnight and then diethyl ether was added to the reaction mixture, which was stirred for an additional 2h at room temperature. The resulting precipitate was collected by filtration and used for the next step without further purification.
Yield: 57%

^{1}H NMR (400MHz, DMSO d_6) δ 10.15 (brs, 3H), 7.40-7.15 (12H), 6.89 (d, 1H), 6.10 (s, 1H), 5.10 (s, 2H), 3.59 (m, 2H), 3.46 (m, 2H), 2.81 (s, 2H), 1.54 (m, 2H), 1.41 (m, 2H)

[0754] Preparation of **29.10**:

Triethylamine (0.42 mL, 3 mmol) was added to a suspension of **29.8** (300 mg, 0.65 mmol) in methylene chloride (20 mL) at 0°C followed by drop wise addition of propionyl chloride (**29.9**) (0.12 mL, 1.3 mmol, 2.0 eq). The reaction mixture was stirred at room temperature for 6h and washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by column chromatography (eluent: hexane/methylene chloride/ethyl acetate, 2:1:1).
Yield: 89.5%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.54 (d, 2H), 7.38-7.10 (m, 11H), 7.00 (d, 1H), 5.95 (s, 1H), 5.12 (s, 2H), 3.70 (m, 2H), 3.44 (m, 2H), 2.80 (s, 2H), 2.42 (q, 2H), 1.60 (m, 2H), 1.50 (m, 2H), 1.28 (t, 3H)

[0755] Preparation of **29C**:

Iodotrimethylsilane (0.21 mL, 1.47 mmol, 2.0 eq) was added to a solution of compound **29.10** (220 mg, 0.46 mmol) in anhydrous methylene chloride (8 mL) under a nitrogen athmosphere. The reaction mixture was stirred at room temperature for 2h

and quenched with a 1 N aqueous solution of hydrochloric acid (15 mL). The crude product was extracted with diethyl ether. The aqueous layer was basified to pH = 9-10 with a 3M aqueous solution of sodium hydroxide and the mixture was extracted with methylene chloride. The organic extracts were combined, dried over sodium sulfate and concentrated under vacuum. The residue was dissolved in methylene chloride (3 mL) and diluted with diethyl ether (10 mL). To this solution was added a 2.0 M solution of anhydrous hydrochloric acid in diethyl ether (0.7 mL, 1.4 mmol, 3.0 eq) and the mixture was stirred at room temperature for 30 min. The solid was collected by filtration, washed with diethyl ether and dried under vacuum.
Yield: 83.9%

^{1}H NMR (400 MHz, DMSO d_6) δ 10.05 (s, 1H), 8.94 (brd, 2H), 7.66 (d, 2H), 7.30-7.20 (m, 5H), 6.96 (d, 1H), 6.08 (s, 1H), 3.15 (m, 4H), 2.82 (s, 2H), 2.34 (q, 2H), 1.68 (m, 4H), 1.10 (t, 3H)
Mass Spectral Analysis *m/z* = 347.0 $(M+H)^+$

EXAMPLE 29D

[0756] Preparation of **29.11**:

Methanesulfonyl chloride (**7.4**) (0.051 mL, 0.66 mmol, 2.0 eq) was added to a solution of **29.8** (150 mg, 0.326 mmol) in pyridine (6 mL) at 0°C. The reaction mixture was stirred at room temperature overnight, diluted with methylene chloride (40 mL) and washed with a 1N aqueous solution of hydrochloric acid and brine. The organic layer was dried over sodium sulfate and concentrated under vacuum. The residue was purified by column chromatography (eluent: hexane/ethyl acetate, 1:1).
Yield: 97.7%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.38-7.13 (m, 12H), 6.99 (d, 1H), 6.50 (s, 1H), 5.96 (s, 1H), 5.12 (s, 2H), 3.70 (m, 2H), 3.46 (m, 2H), 3.08 (s, 3H), 2.81 (s, 2H), 1.62-1.52 (m, 4H)

[0757] Preparation of **29D**:

Iodotrimethylsilane (0.14 mL, 0.98 mmol, 3.5 eq) was added to a solution of **29.11** (140 mg, 0.28 mmol) in anhydrous methylene chloride (6 mL) under a nitrogen athmosphere. The reaction mixture was stirred at room temperature for 2h and quenched with a 1N aqueous solution of hydrochloric acid (10 mL). The crude product was extracted with diethyl ether. The aqueous layer was basified to pH = 9-10 with a 3N aqueous solution of sodium hydroxide and extracted with methylene chloride. The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was dissolved in methylene chloride (3 mL) and diluted with diethyl ether (10 mL). To this solution was added a 2.0 M solution of anhydrous hydrochloric acid in diethyl ether (0.42 mL, 0.84 mmol, 3.0 eq) and the mixture was stirred at room temperature for 30 min. The solid was collected by filtration, washed with diethyl ether and dried under vacuum.

Yield: 90.5%

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.91 (brd, 2H), 7.35-7.18 (m, 7H), 6.96 (d, 1H), 6.09 (s, 1H), 3.12 (m, 4H), 3.02 (s, 3H), 2.82 (s, 2H), 1.68 (m, 4H)

Mass Spectral Analysis *m/z* = 368.9 $(M+H)^+$

EXAMPLE 30A

[0758] Preparation of **30.3**:

A mixture of **30.1** (10.2 g, 0.050 mol, 1.0 eq) and **30.2** (25 g, 0.075 mol, 1.5 eq) in toluene (100 mL) under nitrogen was refluxed for 2h. The mixture was concentrated under reduced pressure and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate, 1:1).

Yield: 92%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.42 (s, 5H), 5.78 (brs, 1H), 3.83 (brs, 2H), 3.70 (s, 3H), 3.49 (brs, 2H), 3.02 (brm, 2H), 2.37 (brm, 2H)

Mass Spectral Analysis *m/z* = 259.9 $(M+H)^+$

[0759] Preparation of **30.5**:

A solution of **30.3** (5.0 g, 19.3 mmol, 1.0 eq), **30.4** (16.39 g, 149 mmol, 7.7 eq), and triethylamine (3.90 g, 38.6 mmol, 2.0 eq) in tetrahydrofuran (100 mL) was refluxed for 12h. The mixture was concentrated under reduced pressure and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate, 60:40).

Yield: 98%

^{1}H NMR (400MHz, CDCl$_3$) δ 7.56 (m, 2H), 7.37 (m, 8H), 4.40 (brs, 1H), 3.72(s, 3H), 3.58 (brm, 3H), 2.56 (s, 2H), 1.76 (brm, 4H)
Mass Spectral Analysis *m/z* = 369.9 (M+H)$^+$

[0760] Preparation of **30.6**:

A solution of **30.5** (10.0 g, 27.07 mmol, 1.0 eq) and concentrated sulfuric acid (50 mL) was stirred at room temperature for 18h. The mixture was poured onto ice water (1:1) (200 mL) and the crude product was extracted with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, concentrated under reduced pressure and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate, 70:30).
Yield: 22%

^{1}H NMR (400MHz, CDCl$_3$) δ 8.08 (dd, 1H), 7.40 (m, 7H), 7.20 (m, 1H), 4.47 (brs, 1H), 3.44 (brm, 3H), 2.97 (brd, 2H), 1.92 (brm, 4H)
Mass Spectral Analysis *m/z* = 337.9 (M+H)$^+$

[0761] Preparation of **30.7**:

To a solution of **30.6** (1.2 g, 3.56 mmol, 1.0 eq) in acetic acid (5 mL) was added at room temperature a 30% aqueous solution of hydrogen peroxide (2 mL). The solution was heated at 90°C for 2h and then cooled to room temperature. The mixture was concentrated to 1/3 of its volume under reduced pressure. Water was added and the crude product was extracted with methylene chloride. The combined organic extracts were then washed with a saturated sodium thiosulfate solution, brine, dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate, 1:1).
Yield: 84%

^{1}H NMR (400MHz, CDCl$_3$) δ 8.10 (m, 2H), 7.87 (m, 1H), 7.77 (m, 1H), 7.41 (m, 5H), 4.34 (brs, 1H), 3.90 (brm, 1H), 3.50 (brm, 4H), 2.36 (brs, 2H), 1.80 (brm, 2H)
Mass Spectral Analysis *m/z* = 369.8 (M+H)$^+$

[0762] Preparation of **30.8**:

A mixture of **30.7** (1.1 g, 2.98 mmol, 1.0 eq) and a 6N aqueous solution of hydrochloric acid (5 mL) in ethanol (20 mL) was heated at 90°C for 12h. The mixture was concentrated under reduced pressure and used for the next step without further purification.
Yield: 100%

Mass Spectral Analysis $m/z = 265.8\ (M+H)^+$

[0763] Preparation of **30.9**:

To a solution of **30.8** (0.9 g, 2.98 mmol, 1.0 eq) in tetrahydrofuran (10 mL) at 0°C was added triethylamine (1.2g, 11.92 mmol, 4.0 eq) and **4.7** (0.78 g, 3.58 mmol, 1.2 eq). The mixture was stirred at 0°C for 1h and at room temperature for 1h. Water (20 mL) was added and the crude mixture was extracted with ethyl acetate. The combined organics were washed with water, brine, dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: eluent: hexane/ethyl acetate, 1:1).
Yield: 79%

^{1}H NMR (400MHz, $CDCl_3$) δ 8.09 (m, 2H), 7.86 (m, 1H), 7.76 (m, 1H), 3.97 (brs, 2H), 3.39 (s, 2H), 3.20 (brm, 2H), 2.29 (m, 2H), 1.76 (brm, 2H), 1.46 (s, 9H)

[0764] Preparation of **30.10**:

To a solution of **30.9** (0.84 g, 2.30 mmol, 1.0 eq) in tetrahydrofuran (10 mL) at -78°C under a nitrogen athmosphere was added drop wise a 1.0M solution of LiHMDS in tetrahydrofuran (2.76 mL, 2.76 mmol, 1.2 eq). The mixture was stirred for 45 min at -78°C. A solution of **1.4** (0.986 g, 2.76 mmol, 1.2 eq) in tetrahydrofuran (3 mL) was added drop wise to the reaction mixture. The mixture was stirred for 3h at 0°C and at room temperature for 16h. The mixture was poured into ice water (20 mL) and the crude product was extracted with ethyl acetate. The combined organic extracts were washed with water, brine, dried over magnesium sulfate and filtered. The crude product was purified by column chromatography (eluent: 85/15 hexane/ethyl acetate mixture).
Yield: 52%

^{1}H NMR (400MHz, CDCl$_3$) δ 8.09 (dd, 1H), 7.76 (m, 1H), 7.69 (m, 1H), 7.61 (d, 1H), 6.36 (s, 1H), 4.17 (brs, 2H), 3.06 (brs, 2H), 2.24 (m, 2H), 1.82 (m, 2H), 1.47 (s, 9H)

[0765] Preparation of **30.11**:

To a solution of **30.10** (0.15 g, 0.30 mmol, 1.0 eq) in dimethoxyethane (DME) (30 mL) was added sequentially a 2N aqueous solution of sodium carbonate (0.45 mL, 0.90 mmol, 3.0 eq), lithium chloride (0.038 g, 0.90 mmol, 3.0 eq), **1.6** (0.106 g, 0.33 mmol, 1.1 eq) and tetrakis(triphenylphosphine)palladium(0) (0.007 g, 0.006 mmol, 0.02 eq). The mixture was refluxed for 16h under a nitrogen athmosphere. The mixture was then cooled to room temperature and ice water (20 mL) was added. The mixture was extracted with ethyl acetate. The combined organic extracts were further washed with water, brine, dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate, 70:30).
Yield: 86%

^{1}H NMR (400MHz, CDCl$_3$) δ 8.09 (m, 1H), 7.56 (m, 2H), 7.44 (d, 2H), 7.38 (d, 2H), 7.15 (m, 1H), 6.22 (s, 1H), 4.16 (brs, 2H), 3.58 (brs, 2H), 3.30 (brs, 2H), 3.14 (brs, 2H), 2.23 (m, 2H), 1.88 (m, 2H), 1.47 (s, 9H), 1.23 (brd, 6H)
Mass Spectral Analysis $m/z = 525.9$ $(M+H)^+$

[0766] Preparation of **30A**:

To a solution of **30.11** (0.440 g, 0.84 mmol, 1.0 eq) in anhydrous methylene chloride (20 mL) was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (8.0 mL, 16 mmol, 19 eq). The mixture was stirred for 48h at room temperature. The mixture was concentrated under reduced pressure and treated with diethyl ether. The resulting precipitate was collected by filtration.
Yield: 100%

^{1}H NMR (400MHz, DMSO d$_6$) δ 9.37 (brm, 1H), 8.80 (brm, 1H), 8.05 (d, 1H), 7.73 (m, 2H), 7.53 (d, 2H), 7.44 (d, 2H), 7.21 (d, 1H), 6.58 (s, 1H), 3.36 (brm, 8H), 2.26 (brm, 2H), 1.95 (brd, 2H), 1.13 (brd, 6H)
Mass Spectral Analysis $m/z = 425.3$ $(M+H)^+$

EXAMPLE 31A

[0767] Preparation of **13.2a**:

To a solution of **1.5a** (7.80 g, 17.35 mmol, 1.0 eq) in dimethoxyethane (75 mL) was added sequentially a 2N aqueous solution of sodium carbonate (26.03 mL, 52.06 mmol, 3.0 eq), lithium chloride (2.21 g, 52.06 mmol, 3.0 eq), **13.1** (3.44 g, 19.09 mmol, 1.1 eq) and tetrakis(triphenylphosphine)palladium(0) (0.40 g, 0.35 mmol, 0.02 eq). The mixture was refluxed overnight under nitrogen. The mixture was then cooled to room temperature and water (250 mL) was added. The mixture was extracted with ethyl acetate. The organic layer was further washed with brine and dried over sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 64%

^{1}H NMR (400MHz, DMSO d$_6$) δ 8.02 (d, 2H), 7.49 (d, 2H), 7.23 (m, 1H), 6.99 (d, 1H), 6.92 (m, 2H), 5.92 (s, 1H), 3.88 (s, 3H), 3.70 (m, 2H), 3.27 (m, 2H), 1.89 (m, 2H), 1.71 (m, 2H), 1.42 (s, 9H)
Mass Spectral Analysis *m/z* = 436.0 (M+H)$^+$

[0768] Preparation of **31A**:

31A was obtained according to a procedure similar to the one described for **1A**, with the following exceptions:
Step 1.4: method 1E was used; **1.8a** was replaced by **13.2a** (see also step 31.2).
^{1}H NMR (DMSO d$_6$) δ 8.81 (m, 2H), 8.00 (m, 2H), 7.45 (m, 2H), 7.24 (m, 1H), 7.03 (m, 1H), 6.91 (m, 2H), 5.99 (s, 1H), 3.90(s, 3H), 3.22 (m, 4H), 2.06 (m, 2H), 1.98 (m, 2H),
Mass Spectral Analysis *m/z* = 336.0 (M+H)$^+$
Elemental analysis:
$C_{21}H_{21}NO_3$, 1HCl, 0.2H_2O
Theory: %C 67.18; %H 6.01; %N 3.73
Found: %C 67.32; %H 5.98; %N 3.77

EXAMPLE 31B

[0769] **31B** was obtained according to a procedure similar to the one described for **31A**, with the following exceptions:

Step 31.1: **13.1** was replaced by **14.1**.

Step 31.2: Method 1F was used.

^{1}H NMR (400MHz, DMSO d_6) δ 8.92 (m, 2H), 7.94 (d, 2H), 7.59 (d, 2H), 7.29 (m, 1H), 7.06 (m, 1H), 6.94 (m, 2H), 6.02 (s, 1H), 3.22 (m, 4H), 2.05 (m, 4H)

Mass Spectral Analysis *m/z* = 303.1 $(M+H)^+$

Elemental analysis:

$C_{20}H_{18}N_2O$, 1HCl, $0.8H_2O$

Theory: %C 68.00; %H 5.88; %N 7.93

Found: %C 67.89; %H 5.59; %N 7.79

EXAMPLE 31C

[0770] **31C** was obtained according to a procedure similar to the one described for **31A**, with the following exceptions:

Step 31.1: **13.1** was replaced by **16.1**.

Step 31.2: Method 1F was used.

^{1}H NMR (400MHz, DMSO d_6) δ 9.10 (brs, 1H), 7.90 (s, 2H), 7.65 (m, 2H), 7.25 (t, 1H), 7.10 (d, 1H), 6.00 (s, 1H), 3.20 (m, 4H), 2.00 (m, 4H)

Mass Spectral Analysis *m/z* = 303.1 $(M+H)^+$

EXAMPLE 31D

[0771] **31D** was obtained according to a procedure similar to the one described for **31A**, with the following exceptions:

Step 31.1: **13.1** was replaced by **31.1a**.

Step 31.2: Method 1E was used.

^{1}H NMR (400MHz, DMSO d_6) δ 9.18 (m, 2H), 7.51 (m, 1H), 7.41 (m, 2H), 7.26 (m, 2H), 7.05 (m, 1H), 6.94 (m, 2H), 5.92 (s, 1H), 3.46 (m, 2H), 3.20 (m, 6H), 2.06 (m, 4H), 1.11 (m, 6H)

Mass Spectral Analysis *m/z* = 377.4 $(M+H)^+$

EXAMPLE 31E

[0772] **31E** was obtained according to a procedure similar to the one described for **31A**, with the following exceptions:

Step 31.1: **13.1** was replaced by **31.1b**.

Step 31.2: Method 1F was used.

^{1}H NMR (DMSO d_6) δ 8.95 (m, 2H), 8.00 (d, 2H), 7.65 (d, 2H), 7.25 (m, 1H), 7.05 (m, 2H), 6.95 (m, 1H), 6.00 (s, 1H), 3.30 (s, 3H), 3.20 (m, 4H), 2.10 (m, 4H); Mass Spectral Analysis *m/z* = 356.1 $(M+H)^+$ t_R = 1.54 minutes.

Mass Spectral Analysis *m/z* = 356.1 $(M+H)^+$

EXAMPLE 31F

[0773] **31F** was obtained according to a procedure similar to the one described for **31A**, with the following exceptions:

Step 31.1: **13.1** was replaced by **31.1c**.

Step 31.2: Method 1F was used.

^{1}H NMR (400MHz, DMSO d_6) δ 8.60 (m, 2H), 7.41 (m, 4H), 7.26 (m, 1H), 7.03 (m, 1H), 6.95 (m, 2H), 5.89 (s, 1H), 4.11 (s, 2H), 3.23 (m, 4H), 2.09 (m, 2H), 1.94 (m, 2H)

Mass Spectral Analysis *m/z* = 317.0 $(M+H)^+$

EXAMPLE 31G

[0774] **31G** was obtained according to a procedure similar to the one described for **31A**, with the following exceptions:

Step 31.1: **13.1** was replaced by **31.1d**.

Step 31.2: Method 31A was used.

^{1}H NMR (400MHz, DMSO d_6) δ 9.16 (brs, 2H), 7.30 (d, 2H), 7.24 (m, 1H), 7.02 (m, 4H), 6.93 (m, 1H), 5.80 (s, 1H), 3.80 (s, 3H), 3.20 (brm, 4H), 2.03 (brm, 4H)

Mass Spectral Analysis *m/z* = 308.0 $(M+H)^+$

EXAMPLE 31H

[0775] **31H** was obtained according to a procedure similar to the one described for **31A**, with the following exceptions:

Step 31.1: **13.1** was replaced by **31.1e**.

Step 31.2: Method 1F was used.

^{1}H NMR (400MHz, DMSO d_6) δ 9.07 (m, 2H), 7.26 (m, 5H), 6.98 (m, 3H), 5.82 (s, 1H), 3.21 (m, 4H), 2.35 (s, 3H), 2.03 (m, 4H)

Mass Spectral Analysis *m/z* = 292.1 $(M+H)^+$

EXAMPLE 31I

[0776] **31I** was obtained according to a procedure similar to the one described for **31A**, with the following exceptions:

Step 31.1: **13.1** was replaced by **31.1f**.

Step 31.2: Method 1F was used.

^{1}H NMR (400MHz, $CDCl_3$) δ 9.76 (m, 1H), 9.29 (m, 1H), 7.69 (m, 1H), 7.46 (m, 1H), 7.27 (brm, 4H), 6.96 (m, 2H), 5.64 (m, 1H), 3.44 (m, 2H), 3.30 (m, 2H), 2.29 (m, 2H), 2.11 (m, 2H)

Mass Spectral Analysis *m/z* = 346.1 $(M+H)^+$

EXAMPLE 31J

[0777] **31J** was obtained according to a procedure similar to the one described for **31A**, with the following exceptions:

Step 31.1: **13.1** was replaced by **31.1g**.

Step 31.2: Method 31A was used.

^{1}H NMR (400MHz, DMSO d_6) δ 8.92 (brs, 1.5H), 7.44 (m, 3H), 7.36 (m, 2H), 7.25 (m, 1H), 7.04 (d, 1H), 6.95 (m, 2H), 5.87 (s, 1H), 3.22 (brm, 4H), 2.09 (brm, 2H), 1.97 (brm, 2H)

Mass Spectral Analysis *m/z* = 278.1 $(M+H)^+$

EXAMPLE 31K

[0778] **31K** was obtained according to a procedure similar to the one described for **31A**, with the following exceptions:

Step 31.1: **13.1** was replaced by **31.1h**.

Step 31.2: Method 31A was used.

^{1}H NMR (400MHz, DMSO d_6) δ 9.66 (brs, 1H), 8.96 (brs, 2H), 7.50 (brm, 1H), 7.18 (brm, 3H), 6.97 (brm, 3H), 6.82 (brm, 1H), 5.67 (s, 1H), 3.18 (brm, 4H) 2.02 (brm, 4H) Mass Spectral Analysis *m/z* = 294.0 $(M+H)^+$

EXAMPLE 31L

[0779] **31L** was obtained according to a procedure similar to the one described for **31A**, with the following exceptions:

Step 31.1: **13.1** was replaced by **31.1i**.

Step 31.2: Method 31A was used.

^{1}H NMR (400MHz, DMSO d_6) δ 8.93 (brs, 2H), 7.37 (t, 1H), 7.25 (t, 1H), 6.97 (brm, 6H), 5.89 (s, 1H), 3.79 (s, 3H), 3.21 (brm, 4H), 2.03 (brm, 4H)

Mass Spectral Analysis *m/z* = 308.0 $(M+H)^+$

EXAMPLE 31M

[0780] **31M** was obtained according to a procedure similar to the one described for **31A**, with the following exceptions:

Step 31.1: **13.1** was replaced by **31.1j**.

Step 31.2: Method 31A was used.

^{1}H NMR (400MHz, DMSO d_6) δ 9.60 (s, 1H), 9.05 (brs, 2H), 7.24 (m, 2H), 7.02 (m, 2H), 6.94 (m, 1H), 6.82 (d, 1H), 6.76 (m, 2H), 5.82 (s, 1H), 3.20 (brm, 4H), 2.03 (brm, 4H)

Mass Spectral Analysis *m/z* = 294.0 $(M+H)^+$

EXAMPLE 31N

[0781] **31N** was obtained according to a procedure similar to the one described for **31A**, with the following exceptions:

Step 31.1: **13.1** was replaced by **31.1k**.

Step 31.2: Method 1F was used.

^{1}H NMR (400MHz, DMSO d_6) δ 9.10 (brm, 1.5H), 8.20 (s, 1H), 8.05 (s, 2H), 7.29 (m, 1H), 7.08 (d, 1H), 6.97 (t, 1H), 6.90 (dd, 1H), 6.16 (s, 1H), 3.23 (brm, 4H), 2.08 (brm, 4H)

Mass Spectral Analysis *m/z* = 414.1 $(M+H)^+$

EXAMPLE 31O

[0782] **31O** was obtained according to a procedure similar to the one described for **31A**, with the following exceptions:

Step 31.1: **13.1** was replaced by **31.1l**.

Step 31.2: Method 31A was used.

^{1}H NMR (400MHz, DMSO d_6) δ 8.88 (brs, 2H), 7.42 (m, 1H), 7.07 (brm, 5H), 6.83 (t, 1H), 6.60 (d, 1H), 5.73 (s, 1H), 3.65 (s, 3H), 3.18 (brm, 4H), 2.08 (brm, 2H), 1.96 (brm, 2H)

Mass Spectral Analysis *m/z* = 308.0 $(M+H)^+$

EXAMPLE 31P

[0783] **31P** was obtained according to a procedure similar to the one described for **31A**, with the following exceptions:

Step 31.1: **13.1** was replaced by **31.1m**.

Step 31.2: Method 31A was used.

^{1}H NMR (400MHz, DMSO d_6) δ 9.46 (s, 1H), 9.02 (brs, 2H), 7.22 (t, 1H), 7.16 (t, 1H), 7.10 (d, 1H), 6.93 (m, 2H), 6.84 (m, 2H), 6.70 (d, 1H), 5.71 (s, 1H), 3.20 (brm, 4H), 2.11 (brm, 2H), 1.97 (brm, 2H)

Mass Spectral Analysis *m/z* = 294.0 $(M+H)^+$

EXAMPLE 31Q

[0784] **31Q** was obtained according to a procedure similar to the one described for **31A**, with the following exceptions:

Step 31.1: **13.1** was replaced by **31.1n**.

Step 31.2: Method 1E was used.

^{1}H NMR (400MHz, $CDCl_3$) δ 9.75 (m, 2H), 7.85 (m, 1H), 7.78 (m, 1H), 7.49 (m, 1H), 7.37 (m, 3H), 7.28 (m, 1H), 6.99 (m, 2H), 5.88 (s, 1H), 3.42 (m, 4H), 2.27 (m, 4H)

Mass Spectral Analysis *m/z* = 333.9 $(M+H)^+$

EXAMPLE 31R

[0785] **31R** was obtained according to a procedure similar to the one described for **31A**, with the following exceptions:

Step 31.1: **13.1** was replaced by **31.1o**.

Step 31.2: Method 1F was used.

^{1}H NMR (400MHz, DMSO d_6) δ 9.04 (m, 2H), 7.66 (m, 3H), 7.34 (m, 4H), 7.10 (m, 2H), 6.48 (m, 1H), 3.23 (m, 4H), 2.09 (m, 4H)

Mass Spectral Analysis *m/z* = 318.1 $(M+H)^+$

EXAMPLE 31S

[0786] **31S** was obtained according to a procedure similar to the one described for **31A**, with the following exceptions:

Step 31.1: **13.1** was replaced by **31.1p**.

Step 31.2: Method 31A was used.

^{1}H NMR (400MHz, $CDCl_3$) δ 9.81 (brs, 1H), 9.40 (brs, 1H), 8.76 (brs, 2H), 7.98 (d, 1H), 7.67 (brs, 1H), 7.29 (m, 1H), 7.01 (d, 1H), 6.95 (t, 1H), 6.91 (d, 1H), 5.70 (s, 1H), 3.43 (m, 2H), 3.34 (m, 2H), 2.29 (m, 2H), 2.15 (m, 2H)

Mass Spectral Analysis *m/z* = 279.1 $(M+H)^+$

EXAMPLE 31T

[0787] **31T** was obtained according to a procedure similar to the one described for **31A**, with the following exceptions:

Step 31.1: **13.1** was replaced by **31.1q**.

Step 31.2: Method 1E was used.

^{1}HNMR (400MHz, $CDCl_3$) δ 9.71 (m, 2H), 7.44-7.21 (m, 3H), 7.11 (m, 2H), 6.96 (m, 2H), 5.75 (s, 1H), 3.39 (m, 4H), 2.24 (m, 4H)

Mass Spectral Analysis *m/z* = 283.9 $(M+H)^+$

EXAMPLE 31U

[0788] **31U** was obtained according to a procedure similar to the one described for **31A**, with the following exceptions:

Step 31.1: **13.1** was replaced by **31.1r**.

Step 31.2: Method 1F was used.

^{1}H NMR (400MHz, DMSO d_6) δ 9.04 (brm, 1.5H), 7.66 (m, 1H), 7.62 (m, 1H), 7.26 (m, 1H), 7.20 (m, 2H), 7.03 (d, 1H), 6.97 (t, 1H), 5.96 (s, 1H), 3.20 (brm, 4H), 2.07 (brm, 2H), 1.98 (brm, 2H)

Mass Spectral Analysis *m/z* = 284.1 $(M+H)^+$

EXAMPLE 31V

[0789] **31V** was obtained according to a procedure similar to the one described for **31A**, with the following exceptions:

Step 31.1: **13.1** was replaced by **31.1s**.

Step 31.2: Method 1F was used.

^{1}H NMR (400MHz, $CDCl_3$) δ 9.71 (brs, 1H), 9.29 (brs, 1H), 7.52 (m, 3H), 6.99 (m, 2H), 6.59 (m, 1H), 6.49 (m, 1H), 5.95 (s, 1H), 3.42 (m, 2H), 3.32 (m, 2H), 2.25 (m, 2H), 2.10 (m, 2H)

Mass Spectral Analysis *m/z* = 268.1 $(M+H)^+$

EXAMPLE 31W

[0790] **31W** was obtained according to a procedure similar to the one described for **31A**, with the following exceptions:

Step 31.1: **13.1** was replaced by **31.1t**.

Step 31.2: Method 1F was used.

^{1}H NMR (400MHz, DMSO d_6) δ 9.34 (brm, 1.5H), 8.12 (d, 1H), 7.60 (m, 6H), 7.42 (t, 1H), 7.32 (t, 1H), 7.22 (t, 1H), 7.02 (d, 1H), 6.89 (m, 2H), 6.81 (d, 1H), 5.98 (s, 1H), 3.41 (brs, 2H), 2.20 (brm, 6H)

Mass Spectral Analysis *m/z* = 457.1 $(M+H)^+$

EXAMPLE 31X

[0791] **31X** was obtained according to a procedure similar to the one described for **31A**, with the following exceptions:

Step 31.1: **13.1** was replaced by **31.1u**.

Step 31.2: Method 1E was used.

^{1}H NMR (400MHz, DMSO d_6) δ 8.93 (m, 2H), 8.03 (d, 1H), 7.42 (d, 1H), 7.32 (m, 2H), 7.05 (m, 2H), 6.25 (s, 1H), 3.22 (m, 4H), 2.03 (m, 4H)

Mass Spectral Analysis *m/z* = 308.8 $(M+H)^+$

EXAMPLE 31Y

[0792] Preparation of **31Y**:

A solution of **16.2** (0.200 g, 0.0046 mol, 1.0 eq) in tetrahydrofuran (50 mL) was added drop wise to a cold (0°C) suspension of lithium aluminum hydride (1.05 g, 0.027 mol, 6.0 eq) in tetrahydrofuran (50 mL). The mixture was allowed to warm to room temperature and was refluxed for 12h under a nitrogen athmosphere. The reaction was cooled to room temperature and quenched by careful addition of water (3 mL). The mixture was stirred for 1h at room temperature and filtered through celite. The celite was further rinsed with hot ethyl acetate. Evaporation of the filtrate afforded an oil which was dissolved in diethyl ether (20 mL). A 2.0M solution of hydrochloric acid in anhydrous diethyl ether (6.9 mL, 0.0138 mol, 3.0 eq) was added to the mixture. The resulting precipitate was collected by filtration and washed with diethyl ether.

Yield: 70%

^{1}H NMR (400MHz, DMSO d_6) δ 8.60 (m, 1H), 8.40 (m, 2H), 7.50 (m, 3H), 7.35 (m, 1H), 7.25 (m, 1H), 6.90-7.10 (m, 3H), 5.80 (s, 1H), 4.10 (m, 2H), 3.30 (m, 7H), 2.10 (m, 4H)

Mass Spectral Analysis *m/z* = 321.1 $(M+H)^+$

EXAMPLE 31Z

[0793] Preparation of **31Z**:

Acetyl chloride (0.14 mL, 0.0019 mol, 1.5 eq) was added drop wise to a cold solution of **31Y** (dihydrochloric acid salt) (0.500 g, 0.0012 mol, 1.0 eq) and triethylamine (0.90 mL, 0.006 mol, 5.0 eq) in dichloromethane (10 mL). The mixture was allowed to warm to room temperature and stirring was continued for 12h at room temperature. The mixture was poured into water and ethyl acetate (30 mL) was added. The organic layer was separated, washed with brine, dried over sodium sulfate, filtered and evaporated. The crude product was purified by column chromatography (eluent: dichloromethane/methanol, mixtures of increasing polarity). The purified compound was dissolved in diethyl ether (20 mL). A 2.0M solution of anhydrous hydrochloric acid in diethyl ether (1.8 mL, 0.0036 mol, 3.0 eq) was added to the mixture. The resulting precipitate was collected by filtration and washed with diethyl ether.

Yield: 31% Mass Spectral Analysis *m/z* = 363.1 $(M+H)^+$

^{1}H NMR (400MHz, DMSO d_6) δ 10.70 (m, 1H), 8.35 (m, 1H), 7.35 (m, 1H), 7.20-7.30 (m, 3H), 7.05 (m, 1H), 6.90 (m, 3H), 5.75 (s, 1H), 4.20 (s, 2H), 3.30 (m, 4H), 2.80 (s, 3H), 2.15 (m, 4H), 1.85 (s, 3H)

EXAMPLE 31AA

[0794] Preparation of **31AA**

Methane sulfonyl chloride (0.15 mL, 0.0019 mol, 1.5 eq) was added drop wise to a cold solution of **31Y** (dihydrochloric acid salt) (0.500 g, 0.0012 mol, 1.0 eq) and triethylamine (0.90 mL, 0.006 mol, 5.0 eq) in dichloromethane (10 mL). The mixture was allowed to warm to room temperature and stirring was continued for 12h at room temperature. The mixture was poured into water and ethyl acetate (30 mL) was added. The organic layer was separated, washed with brine, dried over sodium sulfate, filtered and evaporated. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity). The purified compound was dissolved in diethyl ether (20 mL). A 2.0M solution of anhydrous hydrochloric acid in diethyl ether (1.8 mL, 0.0036 mol, 3.0 eq) was added to the mixture. The resulting precipitate was collected by filtration and washed with diethyl ether.

Yield: 30%

^{1}H NMR (400MHz, DMSO d_6) δ 10.90 (m, 1H), 7.40 (m, 2H), 7.35 (m, 1H), 7.30 (m, 2H), 7.10 (m, 1H), 7.00 (m, 2H), 5.75 (s, 1H), 4.20 (d, 2H), 3.30 (m, 4H), 2.90 (s, 3H), 2.80 (s, 3H), 2.10 (m, 4H)

Mass Spectral Analysis *m/z* = 399.1 $(M+H)^+$

EXAMPLE 32A

[0795] Preparation of **32.1**:

To a solution of Bis(pinacolato)diboron **1.14** (14.7g, 57.8 mmol, 2.0 eq) in *N,N*-dimethylformamide (200 mL) at room temperature under a nitrogen atmosphere was added 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride complex with dichloromethane (710 mg, 0.867 mmol, 0.03 eq) followed by addition of potassium acetate (8.58g, 86.7mmol, 3.0eq.) The mixture was heated to 80°C followed by drop wise addition of a solution of the enol triflate **1.5a** (13.0g, 28.9 mmol, 1.0eq) in *N,N*-dimethylformamide (100 mL). After the addition was complete, the reaction mixture was heated at 80°C for an additional 16h. The solvent was evaporated under vacuum and the residue was added to a 1N aqueous solution of hydrochloric acid. The aqueous residue was extracted with ethyl acetate. The organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a brown semisolid. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

[0796] Yield: 96.0%
^{1}H NMR (400MHz, $CDCl_3$) δ 7.71 (d, 1H), 7.11 (t, 1H), 6.90 (t, 1H), 6.83 (d, 1H), 6.28 (s, 1H), 3.84 (brs, 2H), 3.27 (brm, 2H), 1.96 (d, 2H), 1.60 (m, 2H), 1.34 (s, 9H), 1.26 (s, 12H)
Mass Spectral Analysis *m/z* = 428.0 $(M+H)^+$

[0797] Preparation of **32.2a**:

To a solution of 4-bromophenylacetic acid (**32.4**) (3.21 g, 15 mmol) in methylene chloride (300 mL) was added diethylamine (**1.12**) (3.2 mL, 30 mmol, 2.0 eq) followed by triethylamine (8.4 ml, 60 mmol, 4.0 eq) and the Mukaiyama acylating reagent (2-chloro-1-methylpyridinium iodide) (4.61 mg, 18 mmol, 1.2 eq). The reaction mixture was stirred at room temperature overnight and the mixture was washed with a saturated aqueous solution of sodium bicarbonate, dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (eluent: hexane/methylene chloride/ethyl acetate, 2:1:1).
Yield: 89.2%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.43 (d, 2H), 7.15 (d, 2H), 3.63 (s, 2H), 3.40 (q, 2H), 3.30 (q, 2H), 1.10 (t, 3H)

[0798] Preparation of **32.3a**:

To a solution of **32.1** (2.14 g, 5 mmol) in dimethoxyethane (DME) (40 mL) was added sequentially a 2 N aqueous solution of sodium carbonate (8 mL, 16 mmol, 3.2

eq), lithium chloride (679 mg, 16 mmol, 3.2 eq.), **32.2a** (1.62 mg, 6 mmol, 1.2 eq) and tetrakis(triphenylphosphine)palladium(0) (174 mg, 0.15 mmol, 0.03 eq). The mixture was refluxed overnight under a nitrogen athmosphere. The mixture was then cooled to room temperature and water (50 mL) was added. The mixture was extracted with ethyl acetate. The organic layer was further washed with brine, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate, 1:1).
Yield: 61%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.29 (s, 4H), 7.18 (t, 1H), 7.03 (d, 1H), 6.95 (d, 1H), 5.86 (t, 1H), 5.53 (s, 1H), 3.86 (m, 2H), 3.72 (s, 2H), 3.39 (m, 6H), 2.05 (m, 2H), 1.68 (m, 2H), 1.49 (s, 9H), 1.16 (m, 6H)

[0799] Preparation of **32A**:

To a solution of **32.3a** (1.4 g, 3.38 mmol) in methylene chloride (15 mL) was added a 2.0 M solution of anhydrous hydrochloric acid in diethyl ether (50 mL). The mixture was stirred at room temperature for 24h and diluted by addition of diethyl ether was added. The resulting precipitate was collected by filtration and washed with diethyl ether.
Yield: 92%

^{1}H NMR (400MHz, DMSO d_6) δ 9.20 (m, 2H), 7.20 (s, 4H), 7.24 (m, 1H), 7.00 (m, 3H), 5.83 (s, 1H), 3.40-3.20 (m, 8H), 2.03 (m, 4H), 1.08 (m, 6H)
Mass Spectral Analysis *m/z* = 391.3 $(M+H)^+$

EXAMPLE 32B

[0800] **32B** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:
Step 32.2: **32.2a** was replaced by **32.2b** and Method 1C was used.
Note: **32.2b** was obtained according to a procedure similar to the one described for **32.2e** (see **32E**) except **13.4b** was replaced by **1.12** in step 32.8.
^{1}H NMR (400MHz, DMSO d_6) δ 9.02 (brs, 2H), 8.88 (s, 2H), 8.57 (s, 2H), 7.23 (s, 1H), 7.05 (s, 1H), 6.91 (s, 2H), 6.00 (s, 1H), 3.32 (s, 4H), 3.12 (brs, 4H), 2.08 (m, 4H), 1.02 (brd, 6H)

Mass Spectral Analysis *m/z* = 454.0 $(M+H)^+$

Elemental analysis:

$C_{23}H_{28}N_2O_3S$, 1HCl, $1/3H_2O$

Theory: %C 60.71; %H 6.57; %N 6.16

Found: %C 60.64; %H 6.36; %N 6.16

EXAMPLE 32C

[0801] **32C** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **32.2c** and Method 1D was used.

Note: **32.2c** was obtained according to a procedure similar to the one described for **32.2e** (see **32E**) except **13.4b** was replaced by **3.4c** in step 32.8.

^{1}H NMR (400MHz, DMSO d_6) δ 9.00 (brs, 2H), 7.86 (d, 2H), 7.68 (t, 1H), 7.60 (d, 2H), 7.28 (m, 1H), 7.06 (d, 1H), 6.96 (d, 2H), 6.01 (s, 1H), 3.21 (brm, 4H), 2.81 (m, 2H), 2.10 (brm, 2H), 2.01 (brm, 2H), 1.00 (t, 3H)

Mass Spectral Analysis *m/z* = 385.3 $(M+H)^+$

Elemental analysis:

$C_{21}H_{24}N_2O_3S$, 1HCl, $0.25H_2O$

Theory: %C 59.28; %H 6.04; %N 6.58

Found: %C 59.06; %H 5.92; %N 6.44

EXAMPLE 32D

[0802] **32D** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **32.2d**.

Note: **32.2d** was obtained according to a procedure similar to the one described for **32.2e** (see **32E**) except **13.4b** was replaced by **32.6** in step 32.8.

^{1}H NMR (400MHz, DMSO d_6) δ 9.13 (brs, 2H), 7.90 (d, 2H), 7.64 (s, 1H), 7.56 (d, 2H), 7.27 (m, 1H), 7.06 (d, 1H), 6.95 (m, 2H), 6.01 (s, 1H), 3.22 (brm, 4H), 2.07 (brm, 4H), 1.12 (s, 9H)

Mass Spectral Analysis *m/z* = 413.3 $(M+H)^+$

EXAMPLE 32E

[0803] Preparation of **32.2e**:

13.4b (7.33 mL, 64.58 mmol, 3.3 eq) was added at room temperature to a solution of **32.5** (5 g, 19.57 mmol, 1 eq) in tetrahydrofuran (20 mL). The reaction was stirred at room temperature overnight. The mixture was concentrated under reduced pressure and dichloromethane was added. The mixture was washed with water, a saturated aqueous solution of sodium bicarbonate and brine, and then dried over sodium sulfate and filtered. The organic extracts were concentrated under reduced pressure and the crude product was used for the next step without further purification.
Yield: 40%
^{1}H NMR (400MHz, DMSO d_6) δ 7.82 (s, 4H), 7.25 (s, 4H), 4.58 (s, 4H)
Mass Spectral Analysis *m/z* = 337.9 $(M+H)^+$

[0804] Preparation of **32E**:

32E was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:
Step 32.2: **32.2a** was replaced by **32.2e**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.06 (brs, 2H), 7.94 (d, 2H), 7.60 (d, 2H), 7.26 (m, 5H), 7.04 (d, 1H), 6.90 (m, 2H), 5.97 (s, 1H), 4.62 (s, 4H), 3.19 (brm, 4H), 2.03 (brm, 4H)
Mass Spectral Analysis *m/z* = 459.3 $(M+H)^+$

EXAMPLE 32F

[0805] **32F** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:
Step 32.2: **32.2a** was replaced by **32.2f**.
Note: **32.2f** was obtained according to a procedure similar to the one described for **32.2e** except **13.4b** was replaced by **3.4e** in step 32.8.
^{1}H NMR (400MHz, DMSO d_6) δ 9.04 (brs, 2H), 7.86 (d, 2H), 7.72 (t, 1H), 7.59 (d, 2H), 7.28 (m, 1H), 7.06 (d, 1H), 6.95 (d, 2H), 6.01 (s, 1H), 3.22 brm, 4H), 2.57 (t, 2H), 2.10 (brm, 2H), 2.02 (brm, 2H), 1.65 (m, 1H), 0.83 (d, 6H)
Mass Spectral Analysis *m/z* = 413.3 $(M+H)^+$

Elemental analysis:

$C_{23}H_{28}N_2O_3S$, 1HCl, $0.5H_2O$

Theory: %C 60.31; %H 6.60; %N 6.12

Found: %C 60.67; %H 6.33; %N 6.10

EXAMPLE 32G

[0806] **32G** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **32.2g** and Method 1D was used.

32.2g was obtained according to a procedure similar to the one described for **32.2e** except **13.4b** was replaced by **3.4h** in step 32.8.

^{1}H NMR (400MHz, DMSO d_6) δ 9.16 (brs, 2H), 7.87 (d, 2H), 7.70 (d, 1H), 7.59 (d, 2H), 7.28 (m, 1H), 7.06 (d, 1H), 6.95 (m, 2H), 6.01 (s, 1H), 3.24 (brm, 5H), 2.07 (brm, 4H), 0.98 (d, 6H)

Mass Spectral Analysis $m/z = 399.4$ $(M+H)^+$

Elemental analysis:

$C_{22}H_{26}N_2O_3S$, 1HCl

Theory: %C 60.75; %H 6.26; %N 6.44

Found: %C 60.58; %H 6.29; %N 6.36

EXAMPLE 32H

[0807] **32H** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **32.2h.**

32.2h was obtained according to a procedure similar to the one described for **32.2e** except **13.4b** was replaced by **3.4o** in step 32.8.

^{1}H NMR (400MHz, DMSO d_6) δ 9.09 (brs, 2H), 7.89 (d, 2H), 7.58 (d, 2H), 7.28 (m, 1H), 7.06 (d, 1H), 6.94 (m, 2H), 6.02 (s, 1H), 3.76 (m, 2H), 3.22 (brm, 4H), 2.05 (brm, 4H), 1.20 (d, 12H)

Mass Spectral Analysis $m/z = 441.4$ $(M+H)^+$

EXAMPLE 32I

[0808] **32I** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **32.2i**.

32.2i was obtained according to a procedure similar to the one described for **32.2e** except **13.4b** was replaced by **13.4c** in step 32.8.

^{1}H NMR (400MHz, DMSO d_6) δ 9.03 (brs, 2H), 7.66 (d, 2H), 7.38 (d, 2H), 7.08 (m, 1H), 6.86 (d, 1H), 6.74 (m, 2H), 5.81 (s, 1H), 3.00 (brm, 6H), 2.82 (d, 2H), 1.87 (brm, 4H), 1.37 (m, 2H), 0.71 (m, 1H), 0.65 (t, 3H), 0.27 (m, 2H), 0.01 (m, 2H)

Mass Spectral Analysis $m/z = 453.3\ (M+H)^+$

EXAMPLE 32J

[0809] Preparation of **32J**:

Trifluoroacetic acid (5 mL, 64.90 mmol, 10.0 eq) was added drop wise to **32.3b** (3.83 g, 7.47 mmol, 1.0 eq) at 0°C. The mixture was warmed to room temperature and stirring was continued for an additional 10h at room temperature. The mixture was concentrated under reduced pressure. A saturated solution of sodium bicarbonate (50 mL) was added to the mixture, which was then extracted with dichloromethane. The organic phase was separated, washed with brine, dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. To a cold (0°C) solution of the resulting oil in anhydrous dichloromethane (35 mL) was added drop wise a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (17 mL, 35.70 mmol, 5.5 eq). The mixture was then stirred for 1h at room temperature and concentrated under reduced pressure. Diethyl ether was added. The resulting precipitate was collected by filtration and washed with diethyl ether. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity).

Yield: 10%

^{1}H NMR (400MHz, DMSO d_6) δ 9.08 (m, 2H), 7.90 (m, 2H), 7.56 (m, 2H), 7.46 (m, 2H), 7.28 (m, 1H), 7.07 (m, 1H), 6.94 (m, 2H), 5.98 (s, 1H), 3.46 (m, 2H), 3.17 (m, 2H), 2.05 (m, 4H)

Mass Spectral Analysis $m/z = 357.4\ (M+H)^+$

Elemental analysis:
$C_{19}H_{20}N_2O_3S$, 1HCl, $1H_2O$
Theory: %C 55.54; %H 5.64; %N 6.82
Found: %C 55.30; %H 5.28; %N 6.55

EXAMPLE 32K

[0810] Preparation of **32.9a**:

Triethylamine (0.96 mL, 6.88 mmol, 1.3 eq) was added to a solution of **20.2a** (0.40 mL, 5.29 mmol, 1.0 eq) and **32.7** (1.0 g, 5.29 mmol, 1.0 eq) in acetonitrile (60 mL). The solution was refluxed for 1h and then concentrated under reduced pressure. Methylene chloride was added and the organic mixture was washed with water. The organic mixture was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was used for the next step without further purification.
Yield: 93%
^{1}HNMR (400MHz, $CDCl_3$) δ 7.40 (d, 2H), 7.18 (d, 2H), 2.92 (q, 2H), 1.31 (t, 3H)

[0811] Preparation of **32.2j**:

To a solution of **32.9a** (1.07 g, 4.93 mmol, 1.0 eq) in acetic acid (7 mL) was added a 30% aqueous solution of hydrogen peroxide (3 mL). The mixture was heated at 90°C for 2h. The mixture was cooled to room temperature. Water was added and the mixture was extracted with methylene chloride. The organic mixture was then washed with a saturated aqueous sodium thiosulfate solution and brine. The organic mixture was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was used for the next step without further purification.

Yield: 92%
^{1}HNMR (400MHz, $CDCl_3$) δ 7.78 (d, 2H), 7.72 (d, 2H), 3.11 (q, 2H), 1.28 (t, 3H)

[0812] Preparation of **32K**:

32K was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:
Step 32.2: **32.2a** was replaced by **32.2j** and Method 1D was used.

^{1}H NMR (400MHz, DMSO d$_6$) δ 8.86 (brs, 1H), 7.96 (d, 2H), 7.66 (d, 2H), 7.29 (m, 1H), 7.07 (d, 1H), 6.96 (d, 2H), 6.04 (s, 1H), 3.37 (m, 2H), 3.22 (m, 4H), 2.10 (m, 2H), 2.00 (m, 2H), 1.13 (t, 3H)
Mass Spectral Analysis *m/z* 370.2 (M+H)$^+$
Elemental analysis:
$C_{21}H_{23}NO_3S$, 1HCl, 0.33H_2O
Theory: %C 61.23; %H 6.04; %N 3.40; %S 7.78
Found: %C 61.15; %H 5.92; %N 3.39; %S 7.68

EXAMPLE 32L

[0813] **32L** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:
Step 32.2: **32.2a** was replaced by **32.2k** and Method 12A was used.
Note: **32.2k** was obtained according to a procedure similar to the one described for **32.2j** except **20.2a** was replaced by **20.2b** in step 32.6.
^{1}H NMR (400MHz, DMSO d$_6$) δ 8.92 (brs, 1H), 7.96 (d, 2H), 7.66 (d, 2H), 7.29 (m, 1H), 7.07 (d, 1H), 6.96 (d, 2H), 6.04 (s, 1H), 3.31 (m, 2H), 3.22 (m, 4H), 2.10 (m, 2H), 2.00 (m, 2H), 1.58 (m, 2H), 0.94 (t, 3H)
Mass Spectral Analysis *m/z* = 384.2 (M+H)$^+$
Elemental analysis:
$C_{22}H_{25}NO_3S$, lHCl, 0.5H_2O
Theory: %C 61.60; %H 6.34; %N 3.27; %S 7.47
Found: %C 61.88; %H 6.28; %N 3.36; %S 7.36

EXAMPLE 32M

[0814] **32M** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:
Step 32.2: **32.2a** was replaced by **32.2l** and Method 12A was used.

Note: **32.2l** was obtained according to a procedure similar to the one described for **32.2j** except **20.2a** was replaced by **2.8a** in step 32.6.

^{1}H NMR (400MHz, DMSO d_6) δ 8.93 (brs, 1H), 7.97 (d, 2H), 7.65 (d, 2H), 7.29 (m, 1H), 7.07 (d, 1H), 6.95 (m, 2H), 6.04 (s, 1H), 3.32 (m, 2H), 3.22 (m, 4H), 2.10 (m, 2H), 2.01 (m, 2H), 0.87 (m, 1H), 0.47 (m, 2H), 0.13 (m, 2H)

Mass Spectral Analysis *m/z* = 396.2 $(M+H)^+$

Elemental analysis:

$C_{23}H_{25}NO_3S$, 1HCl

Theory: %C 63.95; %H 6.07; %N 3.24; %S 7.42

Found: %C 63.94; %H 6.03; %N 3.32; %S 7.32

EXAMPLE 32N

[0815] **32N** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **32.2m** and Method 12A was used.

Note: **32.2m** was obtained according to a procedure similar to the one described for **32.2j** except **20.2a** was replaced by **32.8a** in step 32.6.

^{1}H NMR (400MHz, DMSO d_6) δ 8.91 (brs, 1H), 7.98 (d, 2H), 7.66 (d, 2H), 7.29 (m, 1H), 7.07 (d, 1H), 6.96 (m, 2H), 6.04 (s, 1H), 3.32 (m, 2H), 3.22 (m, 4H), 2.10 (m, 2H), 2.02 (m, 2H), 1.62 (m, 1H), 1.46 (m, 2H), 0.84 (d, 6H)

Mass Spectral Analysis *m/z* = 412.2 $(M+H)^+$

Elemental analysis:

$C_{24}H_{29}NO_3S$, 1HCl, $0.33H_2O$

Theory: %C 63.49; %H 6.81; %N 3.08

Found: %C 63.45; %H 6.71; %N 3.39

EXAMPLE 32O

[0816] **32O** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **32.2n** and Method 12A was used.

Note: **32.2n** was obtained according to a procedure similar to the one described for **32.2p** (see **32Q**) except **32.8d** was replaced by **32.8b** in step 32.6.

^{1}H NMR (400MHz, DMSO d_6) δ 8.93 (brm, 1H), 7.98 (d, 2H), 7.64 (d, 2H), 7.29 (m, 1H), 7.07 (d, 1H), 6.94 (m, 2H), 6.02 (s, 1H), 3.32 (m, 2H), 3.22 (m, 4H), 2.10 (m, 2H), 2.01 (m, 2H), 1.10 (s, 9H)

Mass Spectral Analysis m/z = 412.2 $(M+H)^+$

Elemental analysis:

$C_{24}H_{29}NO_3S$, 1HCl, $0.33H_2O$

Theory: %C 63.49; %H 6.81; %N 3.08; %S 7.06

Found: %C 63.49; %H 6.70; %N 3.25; %S 6.78

EXAMPLE 32P

[0817] **32P** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **32.2o** and Method 12A was used.

Note: **32.2o** was obtained according to a procedure similar to the one described for **32.2p** (see **32Q**) except **32.8d** was replaced by **32.8c** in step 32.6.

^{1}H NMR (400MHz, DMSO d_6) δ 8.82 (brs, 2H), 7.93 (d, 2H), 7.66 (d, 2H), 7.29 (m, 1H), 7.07 (d, 1H), 6.96 (m, 2H), 6.05 (s, 1H), 3.47 (m, 1H), 3.23 (m, 4H), 2.10 (m, 2H), 2.00 (m, 2H), 1.19 (d, 6H)

Mass Spectral Analysis m/z = 384.2 $(M+H)^+$

Elemental analysis:

$C_{22}H_{25}NO_3S$, 1HCl

Theory: %C 62.92; %H 6.24; %N 3.34; %S 7.63

Found: %C 63.18; %H 6.26; %N 3.46; %S 7.54

EXAMPLE 32Q

[0818] Preparation of **32.9b**:

To a suspension of sodium hydride (0.33 g, 13.75 mmol, 1.3 eq) in *N,N*-dimethylformamide (10 mL) at 0°C under nitrogen was added drop wise a solution of **32.7** (2.0 g, 10.58 mmol, 1.0 eq) in *N,N*-dimethylformamide (5 mL). The mixture was stirred for 10 min at 0°C and **32.8d** (1.48 mL, 10.58 mmol, 1.0 eq) was added drop wise. The mixture was allowed to warm to room temperature and stirring continued for a further 16h at room temperature. The reaction was carefully quenched with

water and the mixture was extracted with diethyl ether. The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was used for the next step without further purification.
Yield: 87%
^{1}HNMR (400MHz, $CDCl_3$) δ 7.38 (d, 2H), 7.18 (d, 2H), 2.87 (d, 2H), 1.45 (m, 5H), 0.88 (t, 6H)

[0819] Preparation of **32.2p**:

To a solution of **32.9b** (2.53 g, 9.26 mmol, 1.0 eq) in acetic acid (14 mL) was added a 30% aqueous solution of hydrogen peroxide (6 mL). The mixture was heated at 90°C for 2h. The mixture was cooled to room temperature. Water was added and the crude product was extracted with methylene chloride. The organic mixture was washed with a saturated aqueous sodium thiosulfate solution and brine. The mixture was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was used for the next step without further purification.

Yield: 80%
^{1}HNMR (400MHz, $CDCl_3$) δ 7.78 (d, 2H), 7.71 (d, 2H), 3.00 (d, 2H), 1.88 (m, 1H), 1.46 (m, 4H), 0.82 (t, 6H)

[0820] Preparation of **32Q**:

32Q was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:
Step 32.2: **32.2a** was replaced by **32.2p** and Method 12A was used.

(32Q) ^{1}H NMR (400MHz, DMSO d_6) δ 8.97 (brs, 2H), 7.99 (d, 2H), 7.65 (d, 2H), 7.29 (m, 1H), 7.07 (d, 1H), 6.94 (m, 2H), 6.03 (s, 1H), 3.23 (m, 6H), 2.10 (m, 2H), 2.02 (m, 2H), 1.73 (m, 1H), 1.40 (m, 4H), 0.77 (t, 6H)
Mass Spectral Analysis m/z = 426.2 $(M+H)^+$
Elemental analysis:
$C_{25}H_{31}NO_3S$, 1HCl, $0.33H_2O$
Theory: %C 64.15; %H 7.03; %N 2.99; %S 6.85
Found: %C 64.26; %H 6.91; %N 3.20; %S 6.35

EXAMPLE 32R

[0821] Preparation of **32.2q**:

To a solution 4-bromo-*N*-methylaniline of (**32.10**) (0.74 g, 4 mmol, 1.0 eq) in dry dichloromethane (50 mL) at 0°C was slowly added triethylamine (2.23 mL, 8 mmol, 2.0 eq). The mixture was stirred for 10 min at room temperature and **19.8a** (0.63 mL, 6 mmol, 1.5 eq) was added drop wise to the reaction mixture. The reaction mixture was slowly warmed to room temperature and was stirred for 10h at room temperature. Dichloromethane (100 mL) was added to the mixture which was washed with a 1M aqueous solution of hydrochloric acid (3 x 50 mL), a saturated aqueous sodium bicarbonate (2 x 50 mL) and brine. The organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give the crude product, which was used for next step without purification.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.56 (m, 2H), 7.08 (m, 2H), 3.23 (s, 3H), 2.49 (m, 1H), 1.02 (d, 6H)

Mass Spectral Analysis *m/z* = 256.15 $(M+H)^+$

[0822] Preparation of **32R**:

32R was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:
Step 32.2: **32.2a** was replaced by **32.2q** and Method 1D was used.

^{1}H NMR (400MHz, DMSO d_6) δ 8.91 (brs, 2H), 7.43 (m, 4H), 7.27 (m, 1H), 7.01 (m, 3H), 5.96 (s, 1H), 3.40-3.14 (m, 8H), 2.04 (m, 4H), 0.96 (m, 6H)
Mass Spectral Analysis *m/z* = 377.3 $(M+H)^+$
Elemental analysis:
$C_{24}H_{28}N_2O_3$, 1HCl, $2/3H_2O$
Theory: %C 67.83; %H 7.19; %N 6.59
Found: %C 67.78; %H 7.19; %N 6.50

EXAMPLE 32S

[0823] **32S** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:
Step 32.2: **32.2a** was replaced by **32.2r** and Method 1D was used.

Note: **32.2r** was obtained according to a procedure similar to the one described for **32.2q** except **19.8a** was replaced by **19.8b** in step 32.9.

^{1}H NMR (400MHz, DMSO d_6) δ 8.98 (brs, 2H), 7.47 (m, 2H), 7.33 (m, 2H), 7.27 (m, 1H), 7.00 (m, 3H), 5.96 (s, 1H), 3.40-3.12 (m, 7H), 2.25-1.94 (m, 5H), 1.48 (m, 2H), 1.30 (m, 2H), 0.76 (m, 6H)

Mass Spectral Analysis *m/z* = 405.4 $(M+H)^+$

Elemental analysis:

$C_{26}H_{32}N_2O_2$, 1HCl, 1/5H_2O

Theory: %C 70.24; %H 7.57; %N 6.30

Found: %C 70.20; %H 7.50; %N 6.19

EXAMPLE 32T

[0824] **32T** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **32.2s** and Method 1D was used.

Note: **32.2s** was obtained according to a procedure similar to the one described for **32.2q** except **19.8a** was replaced by **32.11a** in step 32.9.

^{1}H NMR (400MHz, DMSO d_6) δ 8.95 (brs, 2H), 7.44 (m, 2H), 7.37 (m, 2H), 7.27 (m, 1H), 7.00 (m, 3H), 5.96 (s, 1H), 3.21 (m, 7H), 2.03 (m, 7H), 0.81 (m, 6H)

Mass Spectral Analysis *m/z* = 391.3 $(M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_2O_2$, 1HCl, 0.1H_2O

Theory: %C 70.03; %H 7.33; %N 6.53

Found: %C 69.97; %H 7.33; %N 6.57

EXAMPLE 32U

[0825] **32U** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **32.2t** and Method 1D was used.

Note: **32.2t** was obtained according to a procedure similar to the one described for **32.2q** except **19.8a** was replaced by **6.7** in step 32.9.

^{1}H NMR (400MHz, DMSO d_6) δ 8.95 (m, 2H), 7.42 (m, 4H), 7.26 (m, 1H), 7.00 (m, 3H), 5.93 (s, 1H), 3.20 (m, 7H), 2.04 (m, 4H), 1.83 (s, 3H)

Mass Spectral Analysis *m/z* = 349.2 $(M+H)^+$

Elemental analysis:

$C_{22}H_{24}N_2O_2$, 1HCl, $1.4H_2O$

Theory: %C 64.43; %H 6.83; %N 6.83

Found: %C 64.49; %H 6.87; %N 6.89

EXAMPLE 32V

[0826] **32V** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **32.2u** and Method 1D was used.

Note: **32.2u** was obtained according to a procedure similar to the one described for **32.2q** except **19.8a** was replaced by **32.11b** in step 32.9.

^{1}H NMR (400MHz, DMSO d_6) δ 8.95 (m, 2H), 7.42 (m, 4H), 7.26 (m, 1H), 7.05 (m, 1H), 6.96 (m, 2H), 5.94 (s, 1H), 3.20 (m, 7H), 2.05 (m, 6H), 1.38 (m, 3H), 0.74 (m, 6H)

Mass Spectral Analysis *m/z* = 405.3 $(M+H)^+$

Elemental analysis:

$C_{26}H_{32}N_2O_2$, 1HCl, $1.5H_2O$

Theory: %C 66.72; %H 7.75; %N 5.99

Found: %C 66.57; %H 7.67; %N 5.93

[0827] EXAMPLE 32W

32W was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **32.2v** and Method 1D was used.

Note: **32.2v** is commercially available.

^{1}H NMR (400MHz, DMSO d_6) δ 8.91 (brs, 2H), 7.74 (m, 2H), 7.37 (m, 2H), 7.25 (m, 1H), 7.02 (m, 2H), 6.94 (m, 1H), 5.86 (s, 1H), 3.87 (t, 2H), 3.20 (m, 4H), 2.52 (t, 2H), 2.08 (m, 4H), 1.99 (m, 2H)

Mass Spectral Analysis *m/z* = 361.2 $(M+H)^+$

Elemental analysis:

$C_{23}H_{24}N_2O_2$, 1HCl, $0.5H_2O$

Theory: %C 68.06; %H 6.46; %N 6.90 Found: %C 68.10; %H 6.42; %N 6.96

EXAMPLE 32X

[0828] **32X** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **32.2w** and Method 1D was used.

Note: **32.2w** is commercially available.

^{1}H NMR (400MHz, DMSO d_6) δ 8.82 (brs, 2H), 8.07 (d, 1H), 7.24 (m, 2H), 7.14 (d, 1H), 7.02 (m, 2H), 6.94 (m, 1H), 5.82 (s, 1H), 4.13 (t, 2H), 3.19 (m, 6H), 2.18 (s, 3H), 2.06 (m, 2H), 1.96 (m, 2H)

Mass Spectral Analysis *m/z* = 361.3 $(M+H)^+$

Elemental analysis:

$C_{23}H_{24}N_2O_2$, 1HCl, $0.4H_2O$

Theory: %C 68.36 %H 6.44 %N 6.93

Found: %C 68.41 %H 6.23 %N 6.93

EXAMPLE 32Y

[0829] **32Y** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **32.2x** and Method 1D was used.

Note: **32.2x** was obtained according to a procedure similar to the one described for **32.2q** except **19.8a** was replaced by **32.11c** in step 32.9.

^{1}H NMR (400MHz, DMSO d_6) δ 9.04 (brs, 2H), 7.41 (m, 4H), 7.26 (m, 1H), 7.00 (m, 3H), 5.94 (s, 1H), 3.20 (m, 7H), 2.05 (m, 6H), 1.49 (m, 2H), 3.79 (m, 3H)

Mass Spectral Analysis *m/z* = 377.4 $(M+H)^+$

Elemental analysis:

$C_{24}H_{28}N_2O_2$, 1HCl, $1.1H_2O$

Theory: %C 66.61; %H 7.27; %N 6.47

Found: %C 66.51; %H 7.20; %N 6.39

EXAMPLE 32Z

[0830] **32Z** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **32.2y** and Method 1D was used.

Note: **32.2y** was obtained according to a procedure similar to the one described for **32.2q** except **19.8a** was replaced by **32.11d** in step 32.9.

^{1}H NMR (400MHz, DMSO d_6) δ 8.98 (brs, 2H), 7.41 (m, 4H), 7.26 (m, 1H), 7.00 (m, 3H), 5.94 (s, 1H), 3.20 (m, 7H), 2.05 (m, 6H), 1.46 (m, 2H), 1.18 (m, 2H), 3.79 (m, 3H)

Mass Spectral Analysis *m/z* = 391.4 $(M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_2O_2$, 1HCl, $0.9H_2O$

Theory: %C 67.75; %H 7.46; %N 6.32

Found: %C 67.71; %H 7.45; %N 6.30

EXAMPLE 33A

[0831] **33A** was obtained according to a procedure similar to the one described for **32A**, with the following exception:

Step 32.2: **32.2a** was replaced by **33.1a** (see also step 33.2).

Note: **33.1a** was commercially available.

^{1}H NMR (400MHz, DMSO d_6) δ 7.98 (d, 1H), 7.89 (dd, 1H), 7.84 (d, 1H), 7.29 (m, 1H), 7.01 (m, 2H), 6.42 (s, 1H), 3.07 (m, 4H), 1.95 (m, 4H)

Mass Spectral Analysis *m/z* = 284.9 $(M+H)^+$

EXAMPLE 33B

[0832] **33B** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **33.1b** and Method 33A was used (see also step 33.2).

Note: **33.1b** was commercially available.

^{1}H NMR (400MHz, DMSO d_6) δ 9.19 (m, 3H), 8.86 (m, 2H), 7.29 (m, 1H), 7.07 (m, 1H), 6.97 (m, 2H), 6.15 (s, 1H), 3.22 (m, 4H), 2.08 (m, 4H)

Mass Spectral Analysis *m/z* = 279.9 $(M+H)^+$

EXAMPLE 33C

[0833] **33C** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **33.1c** and Method 33A was used (see also step 33.2).

Note: **33.1c** is commercially available.

^{1}H NMR (400MHz, DMSO d_6) δ 7.73 (m, 1H), 7.21 (m, 1H), 6.90 (m, 5H), 5.94 & 5.88 (2s, 1H rotamer), 3.6-2.7 (m, 7H), 1.91 (m, 4H)

Mass Spectral Analysis *m/z* = 282.0 $(M+H)^+$

EXAMPLE 33D

[0834] **33D** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **33.1d** and Method 33A was used (see also step 33.2).

Note: **33.1d** is commercially available.

^{1}H NMR (400MHz, DMSO d_6) δ 8.87 (m, 2H), 7.80 (s, 2H), 7.56 (m, 1H), 7.32 (m, 2H), 7.26 (m, 1H), 7.15 (m, 2H), 6.18 (s, 1H), 3.30–3.07 (m, 4H), 2.03 (m, 4H)

Mass Spectral Analysis *m/z* = 362.9 $(M+H)^+$

EXAMPLE 33E

[0835] **33E** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **33.1e** and Method 33A was used (see also step 33.2).

Note: **33.1e** is commercially available.

^{1}H NMR (400MHz, DMSO d_6) δ 8.99 (brs, 2H), 8.80 (s, 1H), 8.15 (m, 1H), 8.08 (m, 1H), 7.30 (m, 1H), 7.07 (m, 1H), 6.96 (m, 2H), 6.17 (s, 1H), 3.23 (m, 4H), 2.08 (m, 4H)

Mass Spectral Analysis *m/z* = 303.9 $(M+H)^+$

EXAMPLE 33F

[0836] Preparation of **33.1f**:

To a stirred solution of **33.3** (3 g, 14.85 mmol, 1.0 eq) in acetonitrile (20 mL) was slowly added diisopropylethylamine (6.2 mL, 35.64 mmol, 2.4 eq) and diethylamine (**1.12**) (3.1 mL, 29.70 mmol, 2 eq) at room temperature. The mixture was stirred for 10 min at room temperature, cooled to 0°C and *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) (5.72 g, 17.82 mmol, 1.2 eq) was added portion wise. The reaction mixture was slowly warmed to room temperature and stirred for 10h at room temperature. The volatiles were removed under reduced pressure and the residue was partitioned between ethyl acetate (200 mL) and a 1M aqueous solution of sodium bicarbonate (100 mL). The organic phase was washed with a 1M aqueous solution of sodium bicarbonate (2 x 50 mL), a 1M aqueous solution of hydrochloric acid (3 x 50 mL) and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 100 %

^{1}H NMR (400MHz, $CDCl_3$) δ 8.72 (d, 1H), 8.55 (d, 1H), 7.87 (m, 1H), 3.56 (q, 2H), 3.27 (q, 2H), 1.26 (t, 3H), 1.16 (t, 3H)

Mass Spectral Analysis *m/z* = 256.81 $(M+H)^+$

[0837] Preparation of **33F**:

33F was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **33.1f** and Method 33A was used (see also step 33.2).

^{1}H NMR (400MHz, DMSO d_6) δ 9.07 (brs, 2H), 8.65 (m, 2H), 7.80 (m, 1H), 7.29 (m, 1H), 7.07 (m, 1H), 6.96 (m, 2H), 6.09 (s, 1H), 3.52-3.10 (m, 8H), 2.05 (m, 4H), 1.12 (m, 6H)

Mass Spectral Analysis *m/z* = 378.3 $(M+H)^+$

EXAMPLE 33G

[0838] Preparation of **33.1g**:

To a stirred solution of **33.4** (3 g, 14.85 mmol, 1.0 eq) in acetonitrile (20 mL) was slowly added diisopropylethylamine (6.2 mL, 35.64 mmol, 2.4 eq) and diethylamine (**1.12**) (3.1 mL, 29.70 mmol, 2 eq) at room temperature. The mixture was stirred for 10 min, cooled to 0°C and *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) (5.72 g, 17.82 mmol, 1.2 eq) was added portion wise. The reaction mixture was slowly warmed to room temperature and stirred for 10h at room temperature. The volatiles were removed under reduced pressure and the residue was partitioned between ethyl acetate (200 mL) and a 1M aqueous solution of sodium bicarbonate (100 mL). The organic phase was washed with a 1M aqueous solution of sodium bicarbonate (2 x 50 mL), a 1M aqueous solution of hydrochloric acid (3 x 50 mL) and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 100 %

^{1}H NMR (400MHz, $CDCl_3$) δ 7.64 (d, 1H), 7.59 (dd, 1H), 7.52 (dd, 1H), 3.54 (q, 2H), 3.38 (q, 2H), 1.25 (m, 6H)

Mass Spectral Analysis *m/z* = 256.7 $(M+H)^+$

[0839] Preparation of **33G**:

33G was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: 32.2a **was replaced by** 33.1g **and** Method 33A was used (see also step 33.2).

(33G) ^{1}H NMR (400MHz, DMSO d_6) δ 9.01 (m, 2H), 8.01 (m, 1H), 7.59 (m, 2H), 7.26 (m, 1H), 7.13 (m, 1H), 7.04 (m, 1H), 6.93 (m, 1H), 6.11 (s, 1H), 3.51–3.11 (m, 8H), 2.05 (m, 4H), 1.15 (t, 3H), 1.06 (t, 3H)

Mass Spectral Analysis *m/z* = 378.2 $(M+H)^+$

EXAMPLE 33H

[0840] **33H** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced with **33.1h** and Method 1D was used (see also step 33.2).

Note: **33.1h** was obtained according to a procedure similar to the one described for **1.13** (see **1N**) except **1.12** was replaced by **3.4j** in step 1.8 (see also step 33.9).

^{1}H NMR (400MHz, DMSO d_6) δ 8.99 (brs, 1H), 8.61 (d, 1H), 7.91 (dd, 1H), 7.64 (d, 1H), 7.29 (m, 1H), 7.06 (d, 1H), 6.97 (m, 2H), 6.09 (s, 1H), 3.23 (m, 4H), 3.04 (s, 3H), 2.99 (s, 3H), 2.11 (m, 2H), 2.02 (m, 2H)

Mass Spectral Analysis *m/z* = 350.2 $(M+H)^+$

Elemental analysis:

$C_{21}H_{23}N_3O_2$, 1.35HCl, $0.8H_2O$

Theory: %C 61.06; %H 6.33; %N 10.17; %Cl 11.59

Found: %C 60.72; %H 6.23; %N 10.05; %Cl 11.26

EXAMPLE 33I

[0841] **33I** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced with **33.1i** and Method 1D was used (see also step 33.2).

Note: **33.1i** was obtained according to a procedure similar to the one described for **1.13** (see **1N**) except **1.12** was replaced by **3.4c** in step 1.8 (see also step 33.9).

^{1}H NMR (400MHz, DMSO d_6) δ 8.87 (m, 2H), 8.62 (d, 1H), 8.11 (d, 1H), 7.99 (dd, 1H), 7.30 (m, 1H), 7.08 (d, 1H), 6.96 (m, 2H), 6.10 (s, 1H), 3.35 (m, 2H), 3.24 (m, 4H), 2.11 (m, 2H), 2.02 (m, 2H), 1.14 (t, 3H)

Mass Spectral Analysis *m/z* = 350.2 $(M+H)^+$

Elemental analysis:

$C_{21}H_{23}N_3O_2$, 1.4HCl, $1.8H_2O$

Theory: %C 58.26; %H 6.52; %N 9.71; %Cl 11.47

Found: %C 58.26; %H 6.23; %N 9.59; %Cl 11.83

EXAMPLE 33J

[0842] **33J** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced with **33.1j** and Method 1D was used (see also step 33.2).

Note: **33.1j** was obtained according to a procedure similar to the one described for **1.13** (see **1N**) except **1.12** was replaced by **3.4b** in step 1.8 (see also step 33.9).

^{1}H NMR (400MHz, DMSO d_6) δ 8.94 (brs, 1H), 8.83 (m, 1H), 8.62 (d, 1H), 8.11 (d, 1H), 7.98 (dd, 1H), 7.30 (m, 1H), 7.08 (d, 1H), 6.96 (m, 2H), 6.10 (s, 1H), 3.22 (m, 4H), 2.84 (d, 3H), 2.11 (m, 2H), 2.02 (m, 2H)

Mass Spectral Analysis *m/z* = 336.2 $(M+H)^+$

Elemental analysis:

$C_{20}H_{21}N_3O_2$, 1.1HCl, 0.8H_2O

Theory: %C 61.61; %H 6.13; %N 10.78; %Cl 10.00

Found: %C 61.84; %H 5.90; %N 10.75; %Cl 10.01

EXAMPLE 33K

[0843] Preparation of **33.6**:

To a mixture of a 2.5M solution of *n*-butyl lithium in hexanes (0.84 mL, 2.1 mmol, 1.05 eq) and toluene (4 mL) at –78°C was added a solution of **33.5** (0.57 g, 2.0 mmol, 1.0 eq) in toluene (2 mL). The reaction was stirred for 1h at –78°C. The reaction was quenched with freshly crushed dry ice. The mixture was warmed slowly to room temperature and was stirred for 2h at room temperature. The mixture was concentrated under reduced pressure and the resulting solid was treated with acetic acid. The solid was collected by filtration, dried under vacuum and used for the next step without further purification.

Yield: 62%

^{1}H NMR (400MHz, CD_3OD) δ 8.90 (s, 2H)

[0844] Preparation of **33.7**:

To a solution of **33.6** (0.055 g, 0.27 mmol, 1.0 eq) in methylene chloride (5 mL) was added oxalyl chloride (0.050 mL, 0.58 mmol, 2.1 eq). The mixture was refluxed for 1h and concentrated under reduced pressure. The crude acyl chloride was used for the next step without further purification.

[0845] Preparation of **33.1k**:

To a solution of **33.7** (0.060 g, 0.27 mmol, 1.0 eq) in tetrahydrofuran (2.5 mL) was added **1.12** (0.11 mL, 1.06 mmol, 4.0 eq). The mixture was stirred for 16h and then diluted with ethyl acetate. The organic mixture was washed with water, with a saturated aqueous solution of sodium bicarbonate, a 1N aqueous solution of hydrochloric acid and brine. The organic mixture was dried over sodium sulfate, filtered, concentrated under reduced pressure and the crude product was used for the next step without further purification. Note: the product was isolated with a 17% impurity corresponding to *N,N*-diethyl-2-iodopyrimidine-5-carboxamide.
Yield: 86%
^{1}H NMR (400MHz, $CDCl_3$) δ 8.82 (s, 2H), 3.56 (q, 2H), 3.20 (q, 2H), 1.28 (t, 3H), 1.18 (t, 3H)

[0846] Preparation of **33K**:

33K was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:
Step 32.2: **32.2a** was replaced by **33.1k** and Method 12A (see was used (see also step 33.2).

^{1}H NMR (400MHz, DMSO d_6) δ 8.81 (m, 2H), 7.18 (m, 1H), 6.92 (m, 2H), 6.85 (m, 1H), 6.06 (s, 0.8H), 6.04 (s, 0.2H), 3.41 (q, 2H), 3.06 (q, 2H), 2.86 (m, 2H), 2.76 (m, 2H), 1.73 (brm, 4H), 1.10 (t, 3H), 1.00 (t, 3H)
Mass Spectral Analysis *m/z* = 379.3 $(M+H)^+$

EXAMPLE 33L

[0847] Preparation of **33L**:

To a solution of **33.2a** (0.27 g, 0.67 mmol, 1 eq) in dry dichloromethane (15 mL) was added dropwise a 4.0M solution of hydrogen chloride in dioxane (1.34 mL, 5.35 mmol, 8 eq). The reaction mixture was stirred at room temperature for 10h and concentrated under reduced pressure. The crude mixture (containing a mixture of **33E** and **33L**) was purified by column chromatography (eluent:

dichloromethane/methanol/ammonium hydroxide mixture of increasing polarity), affording the **33L** in a pure form.

^{1}H NMR (400MHz, DMSO d_6) δ 8.59 (d, 1H), 8.17 (s, 1H), 8.09 (d, 1H), 7.95 (dd, 1H), 7.71 (s, 1H), 7.23 (m, 1H), 6.97 (d, 1H), 6.91 (m, 2H), 6.02 (s, 1H), 2.91 (m, 2H), 2.77 (m, 2H), 1.82 (m, 2H), 1.73 (m, 2H)
Mass Spectral Analysis *m/z* = 321.9

EXAMPLE 34A

[0848] Preparation of **34.1a**:

To a stirred solution of **34.3** (2.5 g, 12.38 mmol, 1.0 eq) in acetonitrile (20 mL) was slowly added diisopropylethylamine (4.74 mL, 27.24 mmol, 2.2 eq) and diethylamine (**1.12**) (2.56 mL, 24.76 mmol, 2.0 eq) at room temperature. The mixture was stirred for 10 min at room temperature, cooled to 0°C and *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) (4.37 g, 13.62 mmol, 1.1 eq) was added portion wise to the reaction mixture. The reaction mixture was slowly warmed to room temperature and stirred for 10h at room temperature. The volatiles were removed under reduced pressure and the residue was partitioned between ethyl acetate (200 mL) and 1M aqueous sodium bicarbonate (100 mL). The organic phase was washed with a 1M aqueous solution of sodium bicarbonate (2 x 50 mL), with a 1M aqueous solution of hydrochloric acid (3 x 50 mL) and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 78 %
^{1}H NMR (400MHz, $CDCl_3$) δ 8.41 (m, 1H), 7.59 (m, 1H), 7.55 (m, 1H), 3.55 (q, 2H), 3.27 (q, 2H), 1.25 (t, 3H), 1.15 (t, 3H)
Mass Spectral Analysis *m/z* = 257.04 $(M+H)^+$

[0849] Preparation of **34A**:

34A was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **34.1a** (see also step 34.2).

^{1}H NMR (400MHz, DMSO d_6) δ 8.94 (brm, 2H), 8.64 (s, 1H), 7.92 (dd, 1H), 7.65 (d, 1H), 7.29 (m, 2H), 7.05 (d, 1H), 6.96 (t, 1H), 6.22 (s, 1H), 3.48 (m, 2H), 3.24 (brm, 6H), 2.05 (brm, 4H), 1.14 (brd, 6H)

Mass Spectral Analysis *m/z* = 378.4 $(M+H)^+$

Elemental analysis:

$C_{23}H_{27}N_3O_2$, 1HCl, $1.3H_2O$

Theory: %C 63.16; %H 7.05; %N 9.61

Found: %C 63.05; %H 6.75; %N 9.50

EXAMPLE 34B

[0850] **34B** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **34.1b** (see also step 34.2).

Note: **34.1b** was obtained according to a procedure similar to the one described for **34.1a** except **1.12** was replaced by **3.4o** in step 34.4.

^{1}H NMR (400MHz, DMSO d_6) δ 9.04 (brs, 2H), 8.59 (d, 1H), 7.85 (dd, 1H), 7.64 (d, 1H), 7.28 (m, 2H), 7.05 (d, 1H), 6.96 (t, 1H), 6.21 (s, 1H), 3.67 (m, 2H), 3.22 (brm, 4H), 2.06 (brm, 4H), 1.45 (brs, 6H), 1.15 (brs, 6H)

Mass Spectral Analysis *m/z* = 406.4 $(M+H)^+$

Elemental analysis:

$C_{25}H_{31}N_3O_2$, 1.5HCl, $0.66H_2O$

Theory: %C 63.59; %H 7.22; %N 8.90; %Cl 11.26

Found: %C 63.68; %H 7.21; %N 8.99; %Cl 11.28

EXAMPLE 34C

[0851] Preparation of **34.1c**:

To a stirred solution of **34.4** (2.1 g, 10 mmol, 1.0 eq) in acetonitrile (20 mL) was slowly added diisopropylethylamine (4.2 mL, 24 mmol, 2.4 eq) and diethylamine (**1.12**) (2.1 mL, 20 mmol, 2 eq) at room temperature. The mixture was stirred for 10 min at room temperature, cooled to 0°C and *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) (3.85 g, 12 mmol, 1.2 eq) was added portion wise. The reaction mixture was slowly warmed to room temperature and stirred for 10h at room temperature. The volatiles were removed under reduced pressure and the residue was partitioned between ethyl acetate (200 mL) and a 1M aqueous solution of sodium bicarbonate (100 mL). The organic phase was washed with a 1M aqueous solution of sodium bicarbonate (2 x 50 mL), with a 1N aqueous solution of hydrochloric acid (3 x 50 mL) and brine, dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was used for next step without further purification.

Mass Spectral Analysis *m/z* = 262.1 $(M+H)^+$

Preparation of **34C**:
34C was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:
Step 32.2: **32.2a** was replaced by **34.1c** (see also step 34.2).

^{1}H NMR (400MHz, DMSO d_6) δ 9.07 (brs, 2H), 7.41 (d, 1H), 7.37 (d, 1H), 7.31 (t, 1H), 7.22 (d, 1H), 7.07 (d, 1H), 7.02 (t, 1H), 6.12 (s, 1H), 3.50 (brm, 4H), 3.21 (brm, 4H0, 2.03 (brm, 4H), 1.18 (brt, 6H)
Mass Spectral Analysis *m/z* = 383.3 $(M+H)^+$
Elemental analysis:
$C_{22}H_{26}N_2O_2S$, 1HCl
Theory: %C 63.07; %H 6.50; %N 6.69
Found: %C 63.03; %H 6.52; %N 6.61

EXAMPLE 34D

[0852] **34D** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:
Step 32.2: **32.2a** was replaced by **34.1d** (see also step 34.2).
Note: **34.1d** was obtained according to a procedure similar to the one described for **34.1c** except **1.12** was replaced by **3.4o** in step 34.5.
^{1}H NMR (400MHz, DMSO d_6) δ 8.93 (brs, 2H), 7.38 (d, 1H), 7.31 (t, 1H), 7.26 (d, 1H), 7.19 (d, 1H), 7.07 (d, 1H), 7.02 (t, 1H), 6.10 (s, 1H), 3.97 (brs, 2H), 3.21 (brm, 4H), 2.07 (brm, 2H), 1.97 (brm, 2H), 1.31 (brd, 12H)
Mass Spectral Analysis *m/z* = 411.4 $(M+H)^+$
Elemental analysis: $C_{24}H_{30}N_2O_2S$, 1HCl,

Theory: %C 64.48; %H 6.99; %N 6.27

Found: %C 64.25; %H 7.01; %N 6.22

EXAMPLE 34E

[0853] Preparation of **34.1e**:

To a stirred solution of **34.5** (4.58 g, 17.5 mmol, 1.0 eq) in dichloromethane (100 mL) at 0°C was slowly added triethylamine (7.32 mL, 52.5 mmol, 3 eq) followed by drop wise addition of diethylamine (**1.12**) (3.64 mL, 35.0 mmol, 2.0 eq). The reaction mixture was kept at 0°C for 30 min. and then stirred at room temperature for 3h. The mixture was washed with a 1N aqueous solution of hydrochloric acid (3 x 50 mL) and brine. The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure to give the crude product, which was used for the next step without further purification.

Yield: 100 %

^{1}H NMR (400MHz, $CDCl_3$) δ 7.30 (d, 1H), 7.05 (d, 1H), 3.24 (q, 4H), 1.19 (t, 6H)

Mass Spectral Analysis *m/z* = 297.92 $(M+H)^+$

[0854] Preparation of **34E**:

34E was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **34.1e** (see also step 34.2).

(34E) ^{1}H NMR (400MHz, DMSO d_6) δ 8.98 (brs, 2H), 7.68 (d, 1H), 7.34 (brm, 3H), 7.06 (m, 2H), 6.23 (s, 1H), 3.22 (brm, 8H), 2.03 (brm, 4H), 1.12 (m, 6H)

Mass Spectral Analysis *m/z* = 419.2 $(M+H)^+$

EXAMPLE 34F

[0855] Preparation of **34.1f**:

To a stirred solution of **34.6** (2 g, 10.47 mmol, 1.0 eq) in acetonitrile (20 mL) was slowly added diisopropylethylamine (4 mL, 23.03 mmol, 2.2 eq) and diethylamine (**1.12**) (2.1 mL, 20.94 mmol, 2.0eq) at room temperature. The mixture was stirred for 10 min at room temperature, cooled to 0°C and *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) (3.7 g, 11.52 mmol, 1.1 eq) was added portion wise. The reaction mixture was slowly warmed to room temperature and stirred for 10h at room temperature. The volatiles were removed under reduced pressure and the residue was partitioned between ethyl acetate (200 mL) and a 1M aqueous solution of sodium bicarbonate (100 mL). The organic phase was washed with a 1M aqueous solution of sodium bicarbonate (2 x 50 mL), a 1M aqueous solution of hydrochloric acid (3 x 50 mL) and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 91 %

^{1}H NMR (400MHz, $CDCl_3$) δ 6.99 (d, 1H), 6.41 (d, 1H), 3.54 (brs, 4H), 1.26 (brs, 6H)

Mass Spectral Analysis *m/z* = 246.0 $(M+H)^+$

[0856] Preparation of **34F**:

34F was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **34.1f** (see also step 34.2).

^{1}H NMR (400MHz, DMSO d_6) δ 9.05 (brs, 2H), 7.52 (d, 1H), 7.32 (t, 1H), 7.07 (brm, 3H), 6.91 (d, 1H), 6.26 (s, 1H), 3.50 (brs, 4H), 3.20 (brm, 4H), 2.05 (brm, 4H), 1.17 (brs, 6H)

Mass Spectral Analysis *m/z* = 367.3 $(M+H)^+$

EXAMPLE 34G

[0857] **34G** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **34.1g** (see also step 34.2).

Note: **34.1g** was obtained according to a procedure similar to the one described for **34.1f** except **1.12** was replaced by **3.4o** in step 34.8.

^{1}H NMR (400MHz, DMSO d_6) δ 8.89 (brs, 2H), 7.52 (d, 1H), 7.32 (t, 1H), 7.07 (m, 2H), 6.92 (d, 1H), 6.87 (d, 1H), 6.24 (s, 1H), 4.02 (brs, 2H), 3.20 (brm, 4H), 2.03 (brm, 4H), 1.31 (brs, 12H),

Mass Spectral Analysis *m/z* = 395.5 $(M+H)^+$

EXAMPLE 34H

[0858] Preparation of **34.1h**:

To a stirred solution of **34.7** (2.1 g, 10 mmol, 1.0 eq) in acetonitrile (20 mL) was slowly added diisopropylethylamine (4.2 mL, 24 mmol, 2.4 eq) and diethylamine (**1.12**) (2.1 mL, 20 mmol, 2 eq) at room temperature. The mixture was stirred for 10 min at room temperature, cooled to 0°C and O-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) (3.85 g, 12 mmol, 1.2 eq) was added portion wise. The reaction mixture was slowly warmed to room temperature and stirred for 10h at room temperature. The volatiles were removed under reduced pressure and the residue was partitioned between ethyl acetate (200 mL) and a 1M aqueous solution of sodium bicarbonate (100 mL). The organic phase was washed with a 1M aqueous solution of sodium bicarbonate (2 x 50 mL), a 1M aqueous solution of hydrochloric acid (3 x 50 mL) and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 87 %

Mass Spectral Analysis $m/z = 262.15$ $(M+H)^+$

[0859] Preparation of **34H**:

34H was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **34.1h** (see also step 34.2).

^{1}H NMR (400MHz, DMSO d_6) δ 9.01 (brs, 2H), 7.80 (s, 1H), 7.41 (s, 1H), 7.27 (t, 1H), 7.19 (d, 1H), 7.04 (d, 1H), 6.99 (t, 1H), 6.04 (s, 1H), 3.48 (brm, 4H), 3.21 (brm, 4H), 2.02 (brm, 4H), 1.16 (brt, 6H)

Mass Spectral Analysis $m/z = 383.4$ $(M+H)^+$

EXAMPLE 34I

[0860] **34I** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **34.1i** (see also step 34.2).

34.1i was obtained according to a procedure similar to the one described for **34.1h** except **1.12** was replaced by **3.4o** in step 34.7.

^{1}H NMR (400MHz, DMSO d_6) δ 8.99 (brs, 2H), 7.73 (d, 1H), 7.27 (m, 2H), 7.21 (dd, 1H), 7.04 (d, 1H), 6.99 (t, 1H), 6.04 (s, 1H), 3.90 (brs, 2H), 3.21 (brm, 4H), 2.07 (brm, 2H), 1.98 (brm, 2H), 1.30 (brd, 12H)

Mass Spectral Analysis *m/z* = 411.4 $(M+H)^+$

EXAMPLE 34J

[0861] **34J** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **34.1j** (see also step 34.2).

Note: **34.1j** was obtained according to a procedure similar to the one described for **34.1k** (see **34K**) except **34.8b** was replaced by **34.8a** in step 34.9.

^{1}H NMR (400MHz, DMSO d_6) δ 8.85 (brs, 2H), 7.43 (t, 1H), 7.35 (d, 1H), 7.27 (m, 2H), 7.04 (m, 2H), 6.97 (m, 1H), 6.03 (s, 1H), 3.48 (q, 2H), 3.22 (brm, 6H), 2.04 (brm, 4H), 1.16 (t, 3H), 1.04 (t, 3H)

Mass Spectral Analysis *m/z* = 395.0 $(M+H)^+$

Elemental analysis:

$C_{24}H_{27}FN_2O_2$, 1HCl, $0.25H_2O$

Theory: %C 66.20; %H 6.60; %N 6.43

Found: %C 65.97; %H 6.48; %N 6.21

EXAMPLE 34K

[0862] Preparation of **34.1k**:

To a stirred solution of **34.8b** (5.0 g, 22.83 mmol, 1.0 eq) in acetonitrile (50 mL) was added *N,N*-diisopropylethylamine (8.35 mL, 47.94 mmol, 2.1 eq), **1.12** (2.6 mL, 25.11 mmol, 1.1 eq) and *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) (8.06 g, 25.11 mmol, 1.1 eq). The reaction mixture was stirred at room temperature for 16h. The mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate. The mixture was washed with a saturated aqueous solution of sodium bicarbonate, dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 91 %

^{1}H NMR (400MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.03 (m, 1H), 3.53 (q, 2H), 3.24 (q, 2H), 1.27 (t, 3H), 1.13 (t, 3H)

[0863] Preparation of **34K**:

34K was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **34.1k** (see also step 34.2).

^{1}H NMR (400MHz, DMSO d_6) δ 8.92 (brs, 2H), 7.29 (m, 3H), 7.13 (s, 1H), 7.05 (d, 1H), 6.98 (m, 2H), 6.01 (s, 1H), 3.43 (brm, 2H), 3.23 (brm, 6H), 2.04 (brm, 4H), 1.10 (brd, 6H)

Mass Spectral Analysis *m/z* = 395.0 $(M+H)^+$

Elemental analysis:

$C_{24}H_{27}FN_2O_2$, 1HCl, $0.25H_2O$

Theory: %C 66.20; %H 6.60; %N 6.43

Found: %C 66.17; %H 6.57; %N 6.32

EXAMPLE 34L

[0864] **34L** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **34.1l** (see also step 34.2).

Note: **34.1l** was obtained according to a procedure similar to the one described for **34.1k** except **34.8b** was replaced by **34.8c** in step 34.9.

^{1}H NMR (400MHz, $CDCl_3$) δ 9.76 (brs, 1H), 9.63 (brs, 1H), 7.20 (m, 4H), 7.05 (dd, 1H), 6.93 (m, 2H), 5.60 (s, 1H), 3.76 (brs, 2H), 3.42 (brm, 4H), 3.18 (q, 2H), 2.32 (s, 3H), 2.21 (brm, 4H), 1.28 (t, 3H), 1.08 (t, 3H)

Mass Spectral Analysis *m/z* = 391.0 $(M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_2O_2$, 1HCl

Theory: %C 70.32; %H 7.32; %N 6.56 Found: %C 69.92; %H 7.27; %N 6.49

EXAMPLE 34M

[0865] **34M** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **34.1m** (see also step 34.2).

Note: **34.1m** was obtained according to a procedure similar to the one described for **34.1k** except **34.8b** was replaced by **34.8d** in step 34.9.

^{1}H NMR (400MHz, $CDCl_3$) δ 9.78 (brs, 1H), 9.62 (brs, 1H), 7.22 (m, 3H), 7.13 (d, 1H), 6.92 (d, 1H), 6.84 (t, 1H), 6.63 (dd, 1H), 5.48 (s, 1H), 3.42 (brm, 8H), 2.36 (brm, 2H), 2.21 (m, 2H), 2.13 (s, 3H), 1.21 (brd, 6H)

Mass Spectral Analysis *m/z* = 391.0 $(M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_2O_2$, 1HCl

Theory: %C 70.32; %H 7.32; %N 6.56

Found: %C 70.01; %H 7.30; %N 6.57

EXAMPLE 34N

[0866] **34N** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **34.1n** (see also step 34.2).

Note: **34.1n** was obtained according to a procedure similar to the one described for **34.1k** except **34.8b** was replaced by **34.8e** in step 34.9.

^{1}H NMR (400MHz, $CDCl_3$) δ 9.78 (brs, 1H), 9.68 (brs, 1H), 7.28 (m, 1H), 7.03 (dd, 1H), 6.95 (m, 4H), 5.64 (s, 1H), 3.62 (q, 2H), 3.41 (brm, 4H), 3.28 (q, 2H), 2.26 (brm, 4H), 1.28 (t, 3H), 1.05 (t, 3H)

Mass Spectral Analysis *m/z* = 413.0 $(M+H)^+$

Elemental analysis:

$C_{24}H_{26}F_2N_2O_2$, 1HCl, $0.25H_2O$

Theory: %C 63.57; %H 6.11; %N 6.18

Found: %C 63.54; %H 6.09; %N 6.20

EXAMPLE 34O

[0867] **34O** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **34.1o** (see also step 34.2).

Note: **34.1o** was obtained according to a procedure similar to the one described for **34.1k** except **34.8b** was replaced by **34.8f** in step 34.9.

^{1}H NMR (400MHz, $CDCl_3$) δ 9.78 (brs 1H), 9.66 (brs, 1h), 7.38 (s, 1H), 7.33 (d 1H), 7.25 (m, 2H), 7.02 (d, 1H), 6.95 (m, 2H), 5.63 (s, 1H), 3.81 (brs, 1H), 3.42 (brm 5H), 3.21 (brm, 2H), 2.26 (brm, 4H), 1.28 (t, 3H), 1.12 (t, 3H)

Mass Spectral Analysis *m/z* = 411.0 $(M+H)^+$

Elemental analysis:

$C_{24}H_{27}ClN_2O_2$, 1HCl

Theory: %C 64.43; %H 6.31; %N 6.26

Found: %C 64.34; %H 6.35; %N 6.28

EXAMPLE 34P

[0868] **34P** was obtained according to a procedure similar to the one described for **32A**, with the following exceptions:

Step 32.2: **32.2a** was replaced by **34.1p** (see also step 34.2).

Note: **34.1p** was obtained according to a procedure similar to the one described for **34.1k** except **34.8b** was replaced by **34.9** in step 34.9 (see also step 34.10).

^{1}H NMR (400MHz, DMSO d_6) δ 9.10 (brs, 2H), 7.47 (m, 2H), 7.34 (m, 1H), 7.27 (m, 1H), 7.20 (m, 1H), 6.98 (m, 1H), 6.87 (m, 1H), 6.76 (m, 1H), 5.69 (s, 1H), 3.29 (m, 2H), 3.18 (m, 4H), 3.01 (m, 2H), 2.04 (m, 2H), 1.93 (m, 2H), 0.96 (m, 6H)

Mass Spectral Analysis *m/z* = 377.4 $(M+H)^+$

EXAMPLE 35A

[0869] Preparation of **35.2**:

To a solution of **35.1** (41.44 g, 0.3 mol, 1.0 eq) in ammonium hydroxide (105 mL, 30% solution in H_2O) was added drop wise a solution of I_2 (61.23 g, 0.24 mol, 0.8 eq) and KI (47.71 g, 0.287 mol, 0.96 eq) in water (300 mL) over a 20 min period. The mixture was stirred at room temperature for1h, and the mixture was concentrated under reduced pressure to half of its volume. The pH was adjusted to 3-4 with a 6N aqueous solution of hydrochloric acid. The white solid was collected by filtration and washed by a small amount of water. The solid was re-crystallized from water/EtOH (2:1), and dried under high vacuum.

Yield: 22%

^{1}H NMR (400MHz, DMSO-d_6) δ 12.96 (b, 1H), 10.70 (s, 1H), 7.80 (d, 1H), 7.42 (s, 1H), 7.12 (d, 1H)

[0870] Preparation of **35.3**:

To an acidic methanolic solution, which was prepared by drop wise addition of acetyl chloride (0.5 mL) to anhydrous methanol (75 mL) was added **35.2** (20.0 g, 75.8 mmol). The mixture was heated to reflux for 18 h. The reaction mixture was allowed to cool to room temperature, and was concentrated under reduced pressure. The residue was diluted in ethyl acetate (100 mL), washed by water (100 mL), brine (100 mL), dried over Na_2SO_4. The solution was filtered and the filtrate was concentrated under reduced pressure. The crude product was dried under vacuum.

Yield: 92%

^{1}H NMR (400MHz, DMSO-d_6) δ10.79 (s, 1H), 7.85 (d, 1H), 7.46 (s, 1H), 7.15 (d, 1H), 3.84 (s, 3H)

[0871] Preparation of **35.4**:

A mixture of **35.3** (2.0 g, 7.19 mmol, 1.0 eq), **2.8c** (4.08 g, 28.8 mmol, 4.0 eq) and potassium carbonate (9.94 g, 71.9 mmol, 10.0 eq) in acetone (100 mL) was refluxed for 16h. The reaction was cooled to room temperature and the solid was collected by filtration. The volume of the filtrate was reduced to15 mL and this solution was taken on to the next step without further purification.

[0872] Preparation of **35.5**:

To a solution of **35.4** (2.10 g, 7.19 mmol, 1.0 eq) in acetone (15 mL) was added lithium hydroxide (1.2 g, 28.8 mmol, 4.0 eq) and a 1:1 tetrahydrofuran/water solution (30 mL). The mixture was stirred at room temperature for 16h. The mixture was reduced to half of its volume under reduced pressure and was acidified with a a 6N aqueous solution of hydrochloric acid (5 mL). The crude mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude product was used for the next step without further purification.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.91 (d, 1H), 7.49 (d, 1H), 7.45 (dd, 1H), 3.96 (s, 3H)

[0873] Preparation of **35.6**:

To a mixture of **35.5** (2.0g, 7.19 mmol, 1.0 eq) and *O*-Benzotriazol-1-yl-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate (TBTU) (2.54 g, 7.91 mmol, 1.1 eq) in acetonitrile (75 mL) at 0°C was added **1.12** (0.58 g, 7.91 mmol, 1.1 eq) and *N*,*N*-diisopropylethylamine (1.95 g, 15.1 mmol, 2.1 eq). The mixture was warmed to room temperature, stirred for 16h at room temperature and concentrated under reduced pressure. The crude mixture was dissolved in ethyl acetate. The mixture was washed with a saturated aqueous solution of sodium bicarbonate, dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixture, 60:40).

Yield: 96%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.78 (d, 1H), 6.84 (d, 1H), 6.70 (dd, 1H), 3.90 (s, 3H), 3.54 (brs, 2H), 3.26 (brs, 2H), 1.19 (brd, 6H)

Mass Spectral Analysis $m/z = 334.1$ $(M+H)^+$

[0874] Preparation of **35.9**

To a solution of **35.6** (1.34 g, 4.02 mmol, 1.0 eq) in dimethoxyethane (DME) (20 mL) was added sequentially a 2N aqueous solution of sodium carbonate (6.03 mL, 12.06 mmol, 3.0 eq), lithium chloride (0.511 g, 12.06 mmol, 3.0 eq), **32.1** (2.06 g, 4.83 mmol, 1.2 eq) and tetrakis(triphenylphosphine)palladium(0) (0.232 g, 0.20 mmol, 0.05 eq). The Suzuki coupling reaction was conducted under microwave conditions (A. 25°C to 170°C for 10 min; B. 170°C for 7 min). The crude mixture was dissolved in ethyl acetate, washed with water, dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 74%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.18 (d, 1H), 7.13 (m, 1H), 6.98 (m, 2H), 6.90 (d, 1H), 6.79 (m, 1H), 6.70 (dd, 1H), 5.53 (s, 1H), 3.84 (brs, 2H), 3.72 (s, 3H), 3.56 (brs, 2H), 3.33 (brs, 4H), 2.07 (brm, 2H), 1.67 (brm, 2H), 1.47 (s, 9H), 1.22 (brd, 6H)

Mass Spectral Analysis $m/z = 507.3\ (M+H)^+$

[0875] Preparation of **35A:**

Compound **35.9** (1.50 g, 2.96 mmol, 1.0 eq) was dissolved in a 4.0M anhydrous solution of hydrochloric acid in dioxane (15 mL, 60 mmol, 20 eq) and the mixture was stirred at room temperature for 16h. The mixture was concentrated under reduced pressure. The residue was dissolved in a minimum amount (until complete dissolution of the product) of methylene chloride, and ethyl acetate was added until the solution became cloudy. The mixture was stirred for 2h at room temperature. The resulting precipitate was collected by filtration.

Yield: 77%

^{1}H NMR (400MHz, $CDCl_3$) δ 9.75 (brs, 1H), 9.58 (brs, 1H), 7.16 (m, 2H), 6.98 (m, 2H), 6.90 (d, 1H), 6.83 (m, 1H), 6.72 (dd, 1H), 5.56 (s, 1H), 3.72 (s, 3H), 3.50 (brm, 8H), 2.35 (brm, 2H), 2.16 (brm, 2H), 1.23 (brd, 6H)

Mass Spectral Analysis $m/z = 407.0\ (M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_2O_3$, 1HCl, $0.5H_2O$

Theory: %C 66.43; %H 7.14; %N 6.20

Found: %C 66.28; %H 7.10; %N 5.94

EXAMPLE 35B

[0876] Preparation of **35.7**:

To a solution of **35.6** (1.10 g, 3.30 mmol, 1.0 eq) in methylene chloride (30 mL) at 0°C was added a 1.0M solution of boron tribromide in methylene chloride (5.0 mL, 5.0 mmol, 1.5 eq). The reaction was warmed to room temperature and stirred for 16h at room temperature. A saturated aqueous solution of sodium bicarbonate was added to the mixture and the crude product was extracted with methylene chloride. The combined organic extracts were dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The crude product was used for the next step without further purification.
Yield: 87%

^{1}H NMR (400MHz, $CDCl_3$) δ 8.28 (brs, 1H), 7.64 (d, 1H), 6.95 (d, 1H), 6.56 (dd, 1H), 3.54 (q, 2H), 3.25 (q, 2H), 1.24 (t, 3H), 1.10 (t, 3H)
Mass Spectral Analysis *m/z* = 320.0 $(M+H)^+$

[0877] Preparation of **35.8**:

To a solution of **35.7** (0.90 g, 2.82 mmol, 1.0 eq) and *N*,*N*-diisopropylethylamine (2.91 g, 22.6 mmol, 8.0 eq) in methylene chloride (25 mL) at 0°C under nitrogen was added drop wise **11.3** (0.86 mL, 11.3 mmol, 4.0 eq). The mixture was warmed to room temperature and stirred for 48h at room temperature. The mixture was concentrated under reduced pressure, dissolved in ethyl acetate and the solution was washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The crude product was used for the next step without further purification.
Mass Spectral Analysis *m/z* = 364.1 $(M+H)^+$

[0878] Preparation of **35.10**:

To a solution of **35.8** (1.02 g, 2.82 mmol, 1.0 eq) in dimethoxyethane (DME) (20 mL) was added sequentially a 2N aqueous solution of sodium carbonate (4.23 mL, 8.46 mmol, 3.0 eq), lithium chloride (0.359 g, 8.46 mmol, 3.0 eq), **32.1** (1.44 g, 3.38 mmol, 1.2 eq) and palladium on carbon (10%, 50% water) (0.038 g, 0.007 mmol, 0.0025 eq). The reaction was conducted under microwave conditions (A. 25°C to

170°C for 10 min; B. 170°C for 7 min). The mixture was dissolved in ethyl acetate, washed with water, dried over sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 50%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.21 (m, 2H), 7.13 (m, 1H), 7.06 (dd, 1H), 6.90 (d, 1H), 6.76 (m, 2H), 5.53 (s, 1H), 5.04 (s, 2H), 3.87 (brs, 2H), 3.55 (brs, 2H), 3.34 (brs, 4H), 3.30 (s, 3H), 2.08 (brm, 2H), 1.67 (brm, 2H), 1.48 (s, 9H), 1.24 (brm, 6H)

Mass Spectral Analysis *m/z* = 537.3 $(M+H)^+$

[0879] Preparation of **35B**:

To a solution of **35.10** (0.647 g, 1.21 mmole, 1 eq) in methanol (3 mL) was added an excess of a 4.0M solution of anhydrous hydrochloric acid in dioxane (20 mL). The mixture was stirred at room temperature for 16h. The mixture was concentrated under reduced pressure and treated with a mixture of methylene chloride (15 mL) and ethyl acetate (25 mL). The resulting precipitate was collected by filtration and dried under vacuum.

Yield: 77%

^{1}H NMR (400MHz, DMSO d_6) δ 9.75 (s, 1H), 8.84 (brm, 2H), 7.16 (m, 2H), 6.96 (d, 1H), 6.84 (m, 3H), 6.72 (d, 1H), 5.78 (s, 1H), 3.42 (brs, 2H), 3.22 (brs, 6H), 2.10 (brm, 2H), 1.96 (brm, 2H), 1.12 (brs, 6H)

Mass Spectral Analysis *m/z* = 393.3 $(M+H)^+$

EXAMPLE 36A

[0880] Preparation of **36.3**:

To a mixture of copper (II) bromide (8.8 g, 39.4 mmol, 1.2 eq) in acetonitrile (50 mL) under a nitrogen athmosphere was added **36.2** (5.1 g, 49.5 mmol, 1.5 eq). The mixture was cooled to 0°C and **36.1** (5.0 g, 32.6 mmol, 1.0 eq) was added in small portions. Additional amount of acetonitrile (25 mL) was added to the mixture, which was stirred at 0°C for 2h. The mixture was poured onto a 20% aqueous solution of hydrochloric acid (200 mL) and extracted with diethyl ether. The combined organic extracts were washed with a 20% aqueous solution of hydrochloric acid, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was dissolved in diethyl ether. The mixtute was extracted with a 15% aqueous solution of sodium hydroxide. The aqueous portion was washed with diethyl ether, acidified to pH 1 with a 6N aqueous solution of hydrochloric acid and the mixture was extracted with diethyl ether. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was treated with chloroform and the resulting precipitate was collected by filtration. The product was used for the next step without further purification.

Mass Spectral Analysis *m/z* = 215.1 $(M-H)^-$

[0881] Preparation of **36.4**:

To a mixture of **1.12** (0.85 g, 11.58 mmol, 2.5 eq), *O*-Benzotriazol-1-yl-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate (TBTU) (1.93 g, 6.02 mmol, 1.3 eq) and *N*,*N*-diisopropylethylamine (1.25 g, 9.72 mmol, 2.1 eq) in acetonitrile (50 mL) at 0°C was added drop wise a solution of **36.3** (1.0 g, 4.63 mmol, 1.0 eq) in acetonitrile (10 mL). The mixture was warmed to room temperature and stirred for 48h at room temperature. An additional portion of TBTU (1.04 g, 3.24 mmol, 0.7 eq) was added to the mixture which was heated at 60°C for 5h. The mixture was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate. The mixture was washed by water, brine, dried over magnesium sulfate and filtrate. The solution was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity)

Yield: 63%

^{1}H NMR (400MHz, $CDCl_3$) δ 10.08 (s, 1H), 7.17 (d, 1H), 7.12 (d, 1H), 6.98 (dd, 1H), 3.50 (q, 4H), 1.27 (t, 6H)

Mass Spectral Analysis *m/z* = 270.1 $(M-H)^-$

[0882] Preparation of **36.5**:

To a solution of **36.4** (0.30 g, 1.11 mmol, 1.0 eq) in dimethoxyethane (DME) (10 mL) was added sequentially a 2N aqueous solution of sodium carbonate (1.66 mL, 3.32 mmol, 3.0 eq), lithium chloride (0.141 g, 3.32 mmol, 3.0 eq), **32.1** (0.57 g, 1.33 mmol, 1.2 eq) and tetrakis(triphenylphosphine)palladium(0) (0.128 g, 0.11 mmol, 0.1 eq). The reaction was conducted under microwave conditions (A. 25°C to 170°C for 10 min; B. 170°C for 10 min). The crude mixture was dissolved in ethyl acetate. The mixture was washed with a 0.5N aqueous solution of hydrochloric acid, brine, and dried over magnesium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 37%

^{1}H NMR (400MHz, $CDCl_3$) δ 9.94 (s, 1H), 7.29 (d, 1H), 7.18 (m, 1H), 7.06 (dd, 1H), 7.00 (d, 1H), 6.94 (d, 1H), 6.85 (m, 2H), 5.59 (s, 1H), 3.85 (brs, 2H), 3.55 (q, 4H), 3.34 (brs, 2H), 2.04 (brm, 2H), 1.66 (m, 2H), 1.48 (s, 9H), 1.30 (t, 6H)

Mass Spectral Analysis $m/z = 493.2$ $(M+H)^+$

[0883] Preparation of **36A**:

To a solution of **36.5** (0.20g, 0.406 mmol, 1.0 eq) in methylene chloride (2 mL) was added a 1.0M solution of anhydrous hydrochloric acid in diethyl ether (10 mL, 10 mmol, 25 eq). The mixture was stirred at room temperature for 16h. The mixture was concentrated under reduced pressure and treated with diethyl ether. The resulting precipitate was collected by filtration. By LC/MS some starting material remained; therefore, so the precipitate was treated with an excess of a 4.0M solution of anhydrous hydrochloric acid in dioxane. This mixture was stirred at room temperature for 16h. The mixture was concentrated under reduced pressure and the crude product was purified by column chromatography (eluent: methylene chloride/methanol mixtures of increasing polarity).

Yield: 66%

^{1}H NMR (400MHz, DMSO d_6) δ 9.91 (brs, 1H), 9.08 (brs, 2H), 7.26 (m, 1H), 7.13 (d, 1H), 7.04 (m, 2H), 6.95 (m, 1H), 6.84 (m, 2H), 5.87 (s, 1H), 3.66 (brs, 4H), 3.20 (brm, 4H), 2.05 (brm, 4H), 1.08 (brd, 6H)

Mass Spectral Analysis *m/z* = 393.4 $(M+H)^+$

Elemental analysis:
$C_{24}H_{28}N_2O_3$, 1HCl, $1.5H_2O$
Theory: %C 63.22; %H 7.07; %N 6.14
Found: %C 63.45; %H 6.88; %N 6.09

EXAMPLE 36B

[0884] Preparation of **36.8**:

To a solution of **36.6** (13.0 mL, 89.41 mmol, 1.0 eq) and triethylamine (13.71 mL, 98.35 mmol, 1.1 eq) in methylene chloride (100 mL) at 0°C under a nitrogen athmosphere was added drop wise ethyl chloroformate (9.40 mL, 98.35 mmol, 1.1 eq). The mixture was warmed to room temperature and stirred for 1h at room temperature. Water and methylene chloride were added to the reaction mixture and the layers were separated. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was used for the next step without further purification.

Yield: 100%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.22 (t, 1H), 6.76 (m, 3H), 4.66 (brs, 1H), 4.11 (q, 2H), 3.80 (s, 3H), 3.43 (m, 2H), 2.78 (m, 2H), 1.23 (t, 3H)
Mass Spectral Analysis *m/z* = 224.1 $(M+H)^+$

[0885] Preparation of **36.9**:

A mixture of **36.8** (20 g, 89.58 mmol, 1.0 eq) and polyphosphoric acid (90 g) was heated at 120°C under a nitrogen athmosphere for 1.5h. The mixture was cooled to room temperature. Water (200 mL) was added to the mixture which was extracted with ethyl acetate. The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: ethyl acetate). Polyphosphoric acid was still present

in the purified sample; therefore the residue was dissolved in ethyl acetate and the solution was washed with a saturated aqueous solution of sodium bicarbonate. The mixture was dried over sodium sulftate, filtered and concentrated under reduced pressure. Ethyl acetate (15 mL) was added to the mixture. The resulting precipitate was collected by filtration and was used for the next step without further purification.
Yield: 30%

^{1}H NMR (400MHz, $CDCl_3$) δ 8.02 (d, 1H), 6.86 (dd, 1H), 6.71 (d, 1H), 6.22 (brs, 1H), 3.85 (s, 3H), 3.55 (m, 2H), 2.97 (t, 2H)
Mass Spectral Analysis *m/z* = 178.1 $(M+H)^+$

Preparation of **36.11**:

[0886] To a suspension of NaH (0.81 g, 33.86 mmol, 6.0 eq) in tetrahydrofuran (30 mL) under a nitrogen athmosphere was added drop wise a solution of **36.9** (1.0 g, 5.64 mmol, 1.0 eq) in tetrahydrofuran (15 mL). To this mixture was added drop wise **36.10** (2.28 mL, 28.22 mmol, 5.0 eq) and stirring was continued for 16h at room temperature. A thick precipitate formed; therefore additional amount of tetrahydrofuran (15 mL) and **36.10** (1.0 mL, 12.39 mmol, 2.2 eq) were added and stirring was continued for an additional 24h at room temperature. The reaction was quenched by addition of a 1N aqueous solution of hydrochloric acid followed by ethyl acetate and water. The layers were separated. The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 83%.

^{1}H NMR (400MHz, $CDCl_3$) δ 8.03 (d, 1H), 6.84 (dd, 1H), 6.65 (d, 1H), 3.84 (s, 3H), 3.61 (q, 2H), 3.53 (t, 2H), 2.95 (t, 2H), 1.21 (t, 3H)
Mass Spectral Analysis *m/z* = 206.1 $(M+H)^+$

[0887] Preparation of **36.12**:

To a solution of **36.11** (0.96 g, 4.68 mmol, 1.0 eq) in anhydrous methylene chloride (30 mL) at -78°C under a nitrogen athmosphere was added drop wise a 1.0M solution of boron tribromide in methylene chloride (9.35 mL, 9.35 mmol, 2.0 eq). The

reaction was warmed to room temperature and stirred for 16h at room temperature. The mixture was cooled in an ice bath, quenched with methanol (10 mL) and concentrated under reduced pressure. The crude mixture was dissolved in ethyl acetate and the solution was washed with a 1N aqueous solution of hydrochloric acid and then brine. The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude solid was triturated in a ethyl acetate/hexane (1:1). The precipitate was collected by filtration.
Yield: 74%.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.89 (d, 1H), 6.82 (dd, 1H), 6.68 (d, 1H), 3.63 (q, 2H), 3.54 (t, 2H), 2.91 (t, 2H), 1.22 (t, 3H)
Mass Spectral Analysis *m/z* = 192.1 $(M+H)^+$

[0888] Preparation of **36.14**:

To a solution of **36.12** (0.38 g, 1.99 mmol, 1.0 eq) and pyridine (0.32 mL, 3.98 mmol, 2.0 eq) in methylene chloride (10 mL) at 0°C under a nitrogen athmosphere was added **36.13** (0.40 mL, 2.38 mmol, 1.2 eq). The reaction was warmed to room temperature and stirred for 2h at room temperature. Methylene chloride was added to the mixture which was washed with a 1N aqueous solution of hydrochloric acid, and with a 1N aqueous solution of sodium hydroxide. The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate, 1:1).
Yield: 45%.

^{1}H NMR (400MHz, $CDCl_3$) δ 8.18 (d, 1H), 7.23 (dd, 1H), 7.11 (d, 1H), 3.62 (m, 4H), 3.04 (t, 2H), 1.23 (t, 3H)
Mass Spectral Analysis *m/z* = 324.1 $(M+H)^+$

[0889] Preparation of **36.15**:

To a solution of **36.14** (0.100 g, 0.309 mmol, 1.0 eq) in *N*,*N*-dimethylformamide (5 mL) under a nitrogen athmosphere was added **32.1**(0.145 g, 0.340 mmol, 1.1 eq), potassium acetate (0.091 g, 0.928 mmol, 3.0 eq) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II), dichloromethane complex (0.005 g, 0.006 mmol, 0.02 eq). The reaction was stirred at 65°C for 16h. The mixture was

cooled to room temperature. Water was added and the mixture was extracted with ethyl acetate. The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 45%.

^{1}H NMR (400MHz, $CDCl_3$) δ 8.11 (d, 1H), 7.31 (dd, 1H), 7.19 (m, 1H), 7.15 (s, 1H), 6.96 (m, 2H), 6.86 (m, 1H), 5.58 (s, 1H), 3.86 (brm, 2H), 3.65 (q, 2H), 3.59 (t, 2H), 3.34 (m, 2H), 3.01 (t, 2H), 2.05 (m, 2H), 1.67 (m, 2H), 1.48 (s, 9H), 1.26 (t, 3H)
Mass Spectral Analysis $m/z = 475.3$ $(M+H)^+$

[0890] Preparation of **36B**:

To a solution of **36.15** (0.150 g, 0.316 mmol, 1.0 eq) in anhydrous methylene chloride (5 mL) at 0°C under a nitrogen athmosphere was added a 1.0M solution of anhydrous hydrochloric acid in diethyl ether (1.26 mL, 1.26 mmol, 4.0 eq). The reaction was warmed to room temperature and stirred for 4 days at room temperature. Diethyl ether was added (5 mL) and the resulting precipitate was collected by filtration.
Yield: 27%.

^{1}H NMR (400MHz, DMSO d_6) δ 8.80 (brs, 2H), 7.92 (d, 1H), 7.29 (m, 3H), 7.05 (d, 1H), 6.97 (m, 2H), 5.94 (s, 1H), 3.54 (m, 4H), 3.23 (brm, 4H), 3.00 (t, 2H), 2.08 (brm, 2H), 1.97 (brm, 2H), 1.13 (t, 3H)
Mass Spectral Analysis $m/z = 375.3$ $(M+H)^+$
Elemental analysis:
$C_{24}H_{26}N_2O_2$, 1HCl, $1H_2O$
Theory: %C 67.20; %H 6.81; %N 6.53
Found: %C 67.52; %H 6.46; %N 6.54

EXAMPLE 37A

[0891] Preparation of **37.2** and **37.3**:

To a solution of **37.1** (5.0 g, 24.60 mmol, 1.0 eq) and **1.1a** (2.56 mL, 24.60 mmol, 1.0 eq) in methanol (100 mL) was added pyrrolidine (5.53 mL, 66.90 mmol, 2.72 eq). The mixture was refluxed for 16h. The mixture was concentrated under reduced pressure, dissolved in ethyl acetate and the mixture was washed with a 1N aqueous

solution of sodium hydroxide and brine. The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity) to give a mixture of **37.2**/**37.3** (1/1.7).
Yield: 80%

(37.2) ^{1}H NMR (400MHz, CDCl$_3$) δ 7.82 (dd, 1H), 7.47 (m, 1H), 7.28 (m, 5H), 6.96 (m, 2H), 3.50 (q, 2H), 2.76 (q, 2H), 2.64 (brm, 1H), 2.40 (brm, 1H), 2.18 (brm, 2H), 2.00 (brm, 1H), 1.82 (brm, 1H), 1.70 (brm, 1H), 1.07 (brd, 3H)
Mass Spectral Analysis *m/z* = 322.3 (M+H)$^+$

(37.3) ^{1}H NMR (400MHz, CDCl$_3$) δ 7.84 (dd, 1H), 7.48 (m, 1H), 7.29 (m, 5H), 6.98 (m, 2H), 3.51 (m, 2H), 3.15 (d, 1H), 2.65 (m, 1H), 2.55 (m, 1H), 2.34 (m, 2H), 2.24 (m, 1H), 2.15 (m, 1H), 1.91 (m, 1H), 1.56 (m, 1H), 1.02 (d, 3H)
Mass Spectral Analysis *m/z* = 322.3 (M+H)$^+$

[0892] Preparation of **37.4**:

To a solution of **37.2** (2.30 g, 7.16 mmol, 1.0 eq) in methanol (25 mL) was added 10% Pd/C (0.50 g). The mixture was shaken for 6h under 55 psi of hydrogen. The mixture was filtered through celite, and concentrated under reduced pressure. The crude product was used for the next step without further purification.
Yield: 99%

^{1}H NMR (400MHz, CDCl$_3$) δ 7.83 (dd, 1H), 7.48 (m, 1H), 6.97 (m, 2H), 3.18 (dd, 1H), 3.02 (m, 1H), 2.77 (m, 2H), 2.55 (m, 1H), 2.06 (m, 1H), 1.80 (brm, 3H), 1.06 (d, 3H)
Mass Spectral Analysis *m/z* = 232.3 (M+H)$^+$

[0893] Preparation of **37.5**:

To a solution of **37.4** (1.65 g, 7.13 mmol, 1.0 eq) in tetrahydrofuran (50 mL) was added triethylamine (2.98 mL, 21.40 mmol, 3.0 eq) and **4.7** (1.87 g, 8.56 mmol, 1.2 eq). The mixture was stirred for 2h at room temperature. Water (100 mL) was added and the crude mixture was extracted with ethyl acetate and washed with brine. The

organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate, 70/30).
Yield: 100%

^{1}H NMR (400MHz, CDCl$_3$) δ 7.85 (dd, 1H), 7.50 (m, 1H), 6.99 (m, 2H), 3.80 (brs, 1H), 3.56 (brm, 2H), 3.30 (brs, 1H), 2.73 (m, 2H), 2.12 (brs, 1H), 1.82 (brm, 2H), 1.46 (s, 9H), 1.03 (d, 3H)
Mass Spectral Analysis *m/z* = 332.3 $(M+H)^+$

[0894] Preparation of **37.6**:

To a solution of **37.5** (2.70 g, 8.15 mmol, 1.0 eq) in tetrahydrofuran (20 mL) at -78°C under a nitrogen athmosphere was added drop wise a 1.0M solution of LiHMDS in tetrahydrofuran (9.78 mL, 9.78 mmol, 1.2 eq). The mixture was stirred for 45 min at -78°C. A solution of **1.4** (3.49 g, 9.78 mmol, 1.2 eq) in tetrahydrofuran (10 mL) was added drop wise to the mixture, which was warmed slowly to room temperature and stirred for 16h at room temperature. The mixture was then poured into ice water. A 1N aqueous solution of hydrochloric was added and the crude mixture was extracted with ethyl acetate. The organic extracts were washed with a 1N aqueous solution of sodium hydroxide, brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 62%

^{1}H NMR (400MHz, DMSO d$_6$) δ 7.31 (m, 1H), 7.15 (m, 1H), 6.95 (m, 1H), 6.85 (m, 1H), 6.25 (s, 0.6H), 5.83 (s, 0.4H), 3.54 (brs, 2H), 3.19 (brm, 2H), 1.96 (brm, 2H), 1.55 (brm, 1H), 1.33 (s, 9H), 0.83 (d, 3H)
Mass Spectral Analysis *m/z* = 464.2 $(M+H)^+$

[0895] Preparation of **37.7**:

To a solution of **37.6** (1.17 g, 2.52 mmol, 1.0 eq) in dioxane (20 mL) was added sequentially **1.6** (0.61 g, 2.78 mmol, 1.1 eq), potassium phosphate (0.80 g, 3.79 mmol, 1.5 eq) and potassium bromide (0.33 g, 2.78 mmol, 1.1 eq). The mixture was placed under vacuum, flushed with nitrogen and then the process was repeated.

Tetrakis(triphenylphosphine)palladium(0) (0.146 g, 0.13 mmol, 0.05 eq) was added and the mixture was heated at 100°C for 16h under a nitrogen athmosphere. The mixture was cooled to room temperature, dissolved in ethyl acetate and the mixture was washed with water. The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 53%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.42 (d, 2H), 7.37 (d, 2H), 7.18 (m, 1H), 6.99 (d, 1H), 6.92 (d, 1H), 6.84 (m, 1H), 5.70 (s, 1H), 3.65 (brm, 5H), 3.32 (brs, 3H), 2.15 (brs, 1H), 2.04 (m, 1H), 1.77 (brs, 1H), 1.48 (s, 9H), 1.22 (brd, 6H), 1.02 (d, 3H)
Mass Spectral Analysis *m/z* = 491.5 $(M+H)^+$

[0896] Preparation of **37 A**:

To a solution of **37.7** (0.65 g, 1.33 mmol, 1.0 eq) in anhydrous methylene chloride (10 mL) at 0°C under a nitrogen athmosphere was added a 1.0M solution of anhydrous hydrochloric acid in diethyl ether (5.31 mL, 5.31 mmol, 4.0 eq). The mixture was warmed to room temperature and stirred for 5 days at room temperature. The mixture was concentrated under reduced pressure and dissolved in methylene chloride (5 mL). Diethyl ether (10 mL) was added drop wise to the mixture which was stirred for1h at room temperature. The resulting precipitate was collected by filtration and dried under vacuum.
Yield: 82%

^{1}H NMR (400MHz, DMSO d_6) δ 9.46 (brm, 1.5H), 7.71 (d, 2H), 7.67 (d, 2H), 7.48 (m, 1H), 7.21 (m, 2H), 7.15 (m, 1H), 6.44 (s, 1H), 3.70 (brs, 2H), 3.42 (brm, 6H), 2.52 (brm, 1H), 2.44 (brm, 1H), 2.13 (brm, 1H), 1.36 (brd, 6H), 1.22 (d, 3H)
Mass Spectral Analysis *m/z* = 391.3 $(M+H)^+$
Elemental analysis:
$C_{25}H_{30}N_2O_2$, 1HCl, $0.25H_2O$
Theory: %C 69.59; %H 7.36; %N 6.49
Found: %C 69.29; %H 7.28; %N 6.40

EXAMPLE 37B

[0897] **37B** was obtained according to a procedure similar to the one described for **37A**, with the following exceptions:

Step 37.2: **37.2** was replaced by **37.3** (see also step 37.5).

^{1}H NMR (400MHz, DMSO d_6) δ 9.40 (brm, 1.5H), 7.66 (s, 4H) 7.48 (m, 1H), 7.27 (d, 1H), 7.21 (m, 1H), 7.15 (m, 1H), 6.03 (s, 1H), 3.69 (brs, 2H), 3.43 (brm, 4H), 3.24 (brm, 2H), 2.47 (brm, 1H), 2.35 (brm, 1H), 2.08 (brm, 1H), 1.37 (brd, 6H), 1.20 (d, 3H)

Mass Spectral Analysis *m/z* = 391.3 $(M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_2O_2$, 1HCl, $0.25H_2O$

Theory: %C 69.59; %H 7.36; %N 6.49

Found: %C 69.69; %H 7.18; %N 6.49

EXAMPLE 7D

[0898] Preparation of **7.10a**:

3.4k (0.10 mL, 1.20 mmol, 1.2 eq) was added drop wise at room temperature to a 1 neck 100 mL round bottom flask which was flame dried under N_2 and contained a solution of **3.1a** (625.0 mg, 1.00 mmol, 1 eq), tris(dibenzylideneacetone)dipalladium(0) (9.2 mg, 0.010 mmol, 0.01eq), **7.9** (6.0 mg, 0.020 mmol, 0.02 eq) and potassium phosphate (297.3 mg, 1.40 mmol, 1.4 eq) in ethylene glycol dimethyl ether (5 mL). The solution was heated to 80°C for 48 hours and then diluted with diethyl ether (90 mL) and filtered through a plug of celite. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 37%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.41 (m, 4H), 7.16 (d, 1H), 6.85 (d, 1H), 6.44 (m, 1H), 5.86 (s, 1H), 3.71 (m, 2H), 3.44 (m, 2H), 3.21 (m, 4H), 3.05 (m, 4H), 1.87 (m, 4H), 1.66 (m, 2H), 1.41 (s, 9H), 1.37 (m, 2H), 1.11 (m, 6H)

Mass Spectral Analysis *m/z* = 546.44 $(M+H)^+$

[0899] Preparation of **7D**:

A 2M solution of hydrochloric acid in diethyl ether (1.8 mL, 3.53 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **7.10a** (0.35 g, 0.64 mmol, 1 eq) in anhydrous dichloromethane (4 mL). The mixture was warmed to room temperature and stirring was continued for an additional 64 hours at room temperature. The solution was concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity).
Yield: 20%
^{1}H NMR (400MHz, DMSO d_6) δ 9.10 (m, 2H), 7.44 (M, 4H), 7.04 (m, 1H), 6.00 (s, 1H), 4.30 (br s, 5H), 3.44 (br s, 3H), 3.22 (m, 8H), 1.99 (m, 7H), 1.12 (m, 6H)
Mass Spectral Analysis *m/z* = 446.40 $(M+H)^+$

EXAMPLE 7E

[0900] Preparation of **7.10b**:

3.4p (167.4 mg, 1.92 mmol, 1.2 eq) was added drop wise at room temperature to a 1 neck 100 mL round bottom flask which was flame dried under N_2 and contained a solution of **3.1a** (1.00 g, 1.60 mmol, 1 eq), tris(dibenzylideneacetone)dipalladium(0) (14.7 mg, 0.016 mmol, 0.01eq), **7.9** (9.6 mg, 0.032 mmol, 0.02 eq) and potassium phosphate (475.7 mg, 2.24 mmol, 1.4 eq) in ethylene glycol dimethyl ether (10 mL). The solution was heated to 80°C for 72 hours and then diluted with diethyl ether (90 mL) and filtered through a 1 inch plug of celite. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 30%

Mass Spectral Analysis *m/z* = 561.76 $(M+H)^+$

[0901] Preparation of **7E**:

A 2M solution of hydrochloric acid in diethyl ether (1.3 mL, 2.55 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **7.10b** (0.26 g, 0.46 mmol, 1 eq) in anhydrous dichloromethane (4 mL). The mixture was warmed to room temperature and stirring was continued for an additional 20 hours at room temperature. The solution was concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity).

Yield: 10%

^{1}H NMR (400MHz, DMSO d_6) δ 9.00 (m, 2H), 7.45 (m, 4H), 7.04 (m, 2H), 6.74 (m, 1H), 5.98 (s, 1H), 4.00 (br s, 5H), 3.74 (br s, 4H), 3.45 (br s, 2H), 3.22 (m, 4H), 3.03 (m, 2H), 2.02 (m, 4H), 1.15 (m, 6H)

Mass Spectral Analysis *m/z* = 462.44 $(M+H)^+$

EXAMPLE 11G

[0902] Preparation of **11.11**:

To a suspension of **11.2** (5.0 g, 15.00 mmol, 1.0 eq) and cesium carbonate (24.4 g, 75.00 mmol, 5.0 eq) in *N*,*N*-dimethylformamide (50 mL) under nitrogen was added **9.7** (7.91 mL, 75.00 mmol, 5.0 eq). Evolution of white smoke was observed. The reaction was heated at 90°C for 16h and then cooled to room temperature. Water was added and the product was extracted three times with diethyl ether. The combined organics were then washed three times with a 1N aqueous solution of sodium hydroxide to remove any unreacted starting material. The organic layer was concentrated and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 26%

^{1}HNMR (400MHz, $CDCl_3$) δ 7.44 (t, 1H), 6.91 (m, 1H), 6.80 (m, 1H), 6.57 (t, 1H, J=75, CF_2H), 3.87 (brs, 2H), 3.21 (brt, 2H), 2.72 (s, 2H), 2.00 (brd, 2H), 1.62 (m, 2H), 1.46 (s, 9H)

Mass Spectral Analysis *m/z* = 384.4 $(M+H)^+$

[0903] Preparation of **11.12**:

To a solution of **11.11** (1.47 g, 3.83 mmol, 1.0 eq) in tetrahydrofuran (30 mL) at -78°C under nitrogen was added drop wise a 1.0M solution of LiHMDS in tetrahydrofuran (4.60 mL, 4.60 mmol, 1.2 eq). The mixture was stirred for 1h at -78°C. A solution of **1.4** (1.64 g, 4.60 mmol, 1.2 eq) in tetrahydrofuran (15 mL) was added drop wise to the mixture, which was warmed slowly to room temperature. Stirring was continued for a further 5h at room temperature. Ice was added to the reaction and the mixture was stirred for 15 min. Ethyl acetate and a 1N aqueous solution of sodium hydroxide were added and the layers were separated. The organics were washed again with a 1N aqueous solution of sodium hydroxide and concentrated. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 56%

^{1}HNMR (400MHz, $CDCl_3$) δ 7.24 (t, 1H), 6.82 (d, 2H), 6.57 (t, 1H, J=72, CF_2H), 5.59 (s, 1H), 3.84 (brs, 2H), 3.26 (brs, 2H), 2.06 (brd, 2H), 1.69 (m, 2H), 1.46 (s, 9H)

[0904] Preparation of **11.13a** (X=CH):

To a solution of **11.12** (0.50 g, 0.97 mmol, 1.0 eq) in dioxane (15 mL) was added **1.6** (0.24 g, 1.07 mmol, 1.1 eq), potassium phosphate (0.31 g, 1.46 mmol, 1.5 eq), potassium bromide (0.13 g, 1.07 mmol, 1.1 eq) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (0.040 g, 0.049 mmol, 0.05 eq). The mixture was heated at 100°C for 24h and then cooled to room temperature. Ethyl acetate and water were added and the layers were separated. The organics were washed with brine, concentrated and purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 67%

^{1}HNMR (400MHz, $CDCl_3$) δ 7.33 (d, 2H), 7.23 (m, 3H), 6.90 (d, 1H), 6.67 (d, 1H), 6.00 (t, 1H, J=74, CF_2H), 5.61 (s, 1H), 3.82 (brs, 2H), 3.55 (brs, 2H) 3.28 (brs, 4H), 2.01 (brd, 2H), 1.69 (m, 2H), 1.47 (s, 9H), 1.26 (brs, 3H), 1.11 (brs, 3H)

Mass Spectral Analysis *m/z* = 543.8 $(M+H)^+$

[0905] Preparation of **11G**:

To a solution of **11.13a (X=CH)** (0.35 g, 0.645 mmol, 1.0 eq) in anhydrous methylene chloride (7 mL) at 0°C under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (1.29 mL, 2.58 mmol, 4.0 eq). The reaction was warmed to room temperature and stirred for a further 16h at room temperature. The reaction was concentrated and the resulting foam was sonicated in diethyl ether (10 mL) for 5 min., stirred for 1h at room temperature, and the solids were collected by vacuum filtration.

Yield: 87%.

^{1}H NMR (400MHz, DMSO d_6) δ 8.97 (brs, 2H), 7.35 (t, 1H), 7.28 (m, 4H), 7.02 (d, 1H), 6.81 (t, 1H, J=74, CF_2H), 6.77 (d, 1H), 5.97 (s, 1H), 3.40 (brm, 2H), 3.20 (brm, 6H), 2.04 (brm, 4H), 1.14 (brs, 3H), 1.04 (brs, 3H)
Mass Spectral Analysis *m/z* = 443.3 $(M+H)^+$
Elemental analysis:
$C_{25}H_{28}F_2N_2O_3$, 1HCl
Theory: %C 62.69; %H 6.10; %N 5.85
Found: %C 62.39; %H 6.01; %N 5.77

EXAMPLE 11H

[0906] Preparation of **11.13b** (X=N):

To a solution of **11.12** (0.50 g, 0.97 mmol, 1.0 eq) in dioxane (15 mL) was added **1.7** (0.32 g, 1.07 mmol, 1.1 eq), potassium phosphate (0.31 g, 1.46 mmol, 1.5 eq), potassium bromide (0.13 g, 1.07 mmol, 1.1 eq) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (0.040 g, 0.049 mmol, 0.05 eq). The mixture was heated at 100°C for 24h and then cooled to room temperature. Ethyl acetate and water were added and the layers were separated. The organics were washed with brine, concentrated and purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 77%
^{1}HNMR (400MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.61 (dd, 1H), 7.54 (d, 1H), 7.22 (t, 1H), 6.91 (d, 1H), 6.67 (d, 1H), 6.06 (t, 1H, J=74, CF_2H), 5.64 (s, 1H), 3.85 (brs, 2H), 3.58 (q, 2H) 3.40 (q, 2H), 3.30 (brs, 2H), 2.03 (brd, 2H), 1.72 (m, 2H), 1.48 (s, 9H), 1.28 (t, 3H), 1.15 (t, 3H)
Mass Spectral Analysis *m/z* = 544.8 $(M+H)^+$

[0907] Preparation of **11H**:

To a solution of **11.13b** (X=N) (0.40 g, 0.736 mmol, 1.0 eq) in anhydrous methylene chloride (7 mL) at 0°C under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (2.21 mL, 4.41 mmol, 6.0 eq). The reaction was warmed to room temperature and stirred for a further 16h at room temperature. The reaction was concentrated and the resulting foam was sonicated in diethyl ether (10 mL) for 5 min., stirred for 1h at room temperature, and the solids were collected by vacuum filtration.

Yield: 84%.

^{1}H NMR (400MHz, DMSO d_6) δ 8.99 (brs, 2H), 8.45 (s, 1H), 7.75 (dd, 1H), 7.49 (d, 1H), 7.37 (t, 1H), 7.04 (d, 1H), 6.78 (d, 1H), 6.90 (t, 1H, J=74, CF_2H), 6.12 (s, 1H), 3.45 (m, 2H), 3.21 (brm, 6H), 2.06 (brm, 4H), 1.16 (t, 3H), 1.06 (t, 3H)

Mass Spectral Analysis *m/z* = 444.3 $(M+H)^+$

Elemental analysis:

$C_{24}H_{27}F_2N_3O_3$, 1.25HCl, $1H_2O$

Theory: %C 56.85; %H 6.01; %N 8.29; %Cl 8.74

Found: %C 56.93; %H 6.01; %N 8.23; %Cl 8.84

EXAMPLE 11I

[0908] Preparation of **11.14**:

To a solution of **32.2b** (2.05 g, 7.02 mmol, 1.0 eq) in dioxane (30 mL) under nitrogen was added **1.14** (2.14 g, 8.42 mmol, 1.2 eq), potassium acetate (2.07 g, 21.05 mmol, 3.0 eq) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (0.12 g, 0.14 mmol, 0.02 eq). The mixture was heated at 70°C for 16h and then cooled to room temperature. Ethyl acetate and water were added and the layers were separated. The aqueous phase was washed with ethyl acetate and the organics were combined and concentrated. The crude product was purified by column chromatography (eluent: ethyl acetate/hexane = 3:7).

Yield: 87%

^{1}HNMR (400MHz, $CDCl_3$) δ 7.92 (d, 2H), 7.79 (d, 2H), 3.24 (q, 4H), 1.36 (s, 12H), 1.11 (t, 6H)

Mass Spectral Analysis *m/z* = 340.3 $(M+H)^+$

[0909] Preparation of **11.15**:

To a solution of **11.5** (0.70 g, 1.37 mmol, 1.0 eq) in dioxane (15 mL) was added **11.14** (0.513 g, 1.51 mmol, 1.1 eq), potassium phosphate (0.437 g, 2.06 mmol, 1.5 eq), potassium bromide (0.18 g, 1.51 mmol, 1.1 eq) and tetrakis(triphenylphosphine) palladium(0) (0.079 g, 0.069 mmol, 0.05 eq). The mixture was heated at 100°C for 16h and then cooled to room temperature. Ethyl acetate and water were added and the layers were separated. The aqueous layer was washed with ethyl acetate and the organics were combined, concentrated and purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 47%

^{1}HNMR (400MHz, $CDCl_3$) δ 7.74 (d, 2H), 7.36 (d, 2H), 7.16 (t, 1H), 6.70 (m, 2H), 5.56 (s, 1H), 4.65 (s, 2H), 3.81 (brs, 2H), 3.32 (brs, 2H), 3.25 (q, 4H), 3.13 (s, 3H), 2.02 (brd, 2H), 1.68 (m, 2H), 1.48 (s, 9H), 1.15 (t, 6H)

Mass Spectral Analysis *m/z* = 573.4 $(M+H)^+$

[0910] Preparation of **11I**:

To a solution of **11.15** (0.365 g, 0.637 mmol, 1.0 eq) in methanol (20 mL) under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (3.20 mL, 6.37 mmol, 10.0 eq). The reaction was stirred for 16h at room temperature. The reaction was concentrated and the resulting solid was stirred in a methylene chloride (2 mL)/diethyl ether (15 mL) mixture for 30 min. at room temperature. The solids were then collected by vacuum filtration.

Yield: 79%

^{1}HNMR (400MHz, DMSO d_6) δ 9.60 (s, 1H), 8.83 (brs, 2H), 7.71 (d, 2H), 7.43 (d, 2H), 7.08 (t, 1H), 6.55 (d, 1H), 6.45 (d, 1H), 5.84 (s, 1H), 3.17 (brm, 8H), 2.00 (brm, 4H), 1.05 (t, 6H)

Mass Spectral Analysis *m/z* = 429.3 $(M+H)^+$

Elemental analysis:

$C_{23}H_{28}N_2O_4S$, 1HCl, $0.5H_2O$

Theory: %C 58.28; %H 6.38; %N 5.91

Found: %C 58.29; %H 6.20; %N 5.78

EXAMPLE 22F

[0911] Preparation of **22.7**:

To a suspension of **22.4** (0.8 g, 80% pure by LC, as of 1.37 mmol, 1 eq.) in ethanol (15 mL) was added sodium acetate (0.77 g, 9.38 mmol, 6.8 eq.) and iodoethane **22.6** (0.62 mL, 7.68 mmol, 5.6 eq.). The reaction mixture was heated under reflux for 10h.

Water (50 mL) was added to the reaction mixture and the organics were extracted with dichloromethane (3 x 75 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 89%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.75 (m, 1H), 7.57 (m, 1H), 7.45 (m, 2H), 7.34 (m, 2H), 7.06 (d, 1H), 5.67 (d, 1H), 4.02-3.25 (m, 8H), 3.05 (q, 2H), 2.47-2.25 (m, 3H), 2.00-1.69 (m, 3H), 1.32-1.12 (m, 9H)

Mass Spectral Analysis *m/z* = 579.26 $(M+H)^+$

[0912] Preparation of **22F**:

To a solution of **22.7** (0.57 g, 0.98 mmol, 1 eq.) in a mixture methanol (30 mL) and water (10 mL) at 0°C was added potassium carbonate (0.81 g, 5.88 mmol, 6 eq.) in one portion. The reaction mixture was slowly warmed up to room temperature and stirring was continued for 10h at room temperature. The methanol was removed under reduced pressure and the organics were extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was dissolved in anhydrous dichloromethane (10 mL). To this solution was added a 2M anhydrous solution of hydrogen chloride in diethyl ether (2 mL, 4 mmol, 4 eq.) dropwise at 0°C. The mixture was stirred for 1h at room temperature and then concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixture of increasing polarity).

Yield: 63%

^{1}H NMR (400MHz, DMSO-d_6) δ 9.19 (m, 2H), 7.75 (dd, 1H), 7.45 (m, 4H), 7.39 (d, 1H), 7.23 (d, 1H), 6.07 (s, 1H), 3.53-3.40 (m, 2H), 3.31-3.04 (m, 8H), 2.31 (m, 2H), 2.18 (m, 1H), 2.01 (m, 2H), 1.82 (m, 1H), 1.22-1.02 (m, 9H)

Mass Spectral Analysis *m/z* = 483.2 $(M+H)^+$

Elemental analysis:

$C_{27}H_{34}N_2O_4S$, 1HCl, 1.5 H_2O

Theory: %C 59.38; %H 7.01; %N 5.13

Found: %C 59.26; %H 6.64; %N 5.15

$[\alpha]_D^{25}$ = - 3.85 (c = 10.25 mg/mL, MeOH)

EXAMPLE 33M

[0913] To a solution of **32.1** (1.0 g, 2.34 mmol, 1.0 eq) in dioxane (40 mL) under nitrogen was added **33.11** (0.51 g, 2.57 mmol, 1.1 eq), potassium phosphate (0.75 g, 3.51 mmol, 1.5 eq), potassium bromide (0.31 g, 2.57 mmol, 1.1 eq) and tetrakis(triphenylphosphine) palladium(0) (0.14 g, 0.12 mmol, 0.05 eq). The mixture was heated at 100°C for 16h. Additional quantity of tetrakis(triphenylphosphine) palladium(0) (0.10 g, 0.087 mmol, 0.04 eq) was added to the reaction mixture, which was heated at 100°C for an additional 24h and then cooled to room temperature. Ethyl acetate and water were added and the layers were separated. The organics were concentrated and purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 65%

^{1}HNMR (400MHz, $CDCl_3$) δ 7.99 (d, 2H), 7.44 (d, 2H), 7.20 (m, 1H), 6.96 (m, 2H), 6.86 (m, 1H), 5.60 (s, 1H), 3.88 (brs, 2H), 3.34 (brs, 2H), 2.64 (s, 3H), 2.06 (brd, 2H), 1.68 (m, 2H), 1.48 (s, 9H)

Mass Spectral Analysis *m/z* = 420.2 $(M+H)^+$

[0914] Preparation of **33M**

To a solution of the Boc derivative, obtained previously, (0.63 g, 1.50 mmol, 1.0 eq) in methylene chloride (30 mL) at 0°C under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (3.00 mL, 6.00 mmol, 4.0 eq). The reaction mixture was stirred for 48h at room temperature and the resulting precipitate was collected by vacuum filtration. A saturated aqueous solution of sodium bicarbonate was added to a suspension of the resulting solid in ethyl acetate. The organic layer was separated and concentrated under vacuum. The crude product was further purified by column chromatography [eluent: methanol/(methylene chloride/ammonium hydroxide = 99:1) mixtures of increasing polarity].

Yield: 61%

^{1}HNMR (400MHz, DMSO d_6) δ 8.02 (d, 2H), 7.49 (d, 2H), 7.22 (m, 1H), 6.96 (d, 1H), 6.89 (m, 2H), 5.91 (s, 1H), 2.91 (m, 2H), 2.76 (m, 2H), 2.62 (s, 3H), 1.82 (m, 2H), 1.71 (m, 2H)

Mass Spectral Analysis *m/z* = 320.1 $(M+H)^+$
Elemental analysis:
$C_{21}H_{21}NO_2$, $0.6H_2O$
Theory: %C 76.38; %H 6.78; %N 4.24
Found: %C 76.33; %H 6.73; %N 4.33

EXAMPLE 33N

[0915] To a solution of **32.1** (1.0 g, 2.34 mmol, 1.0 eq) in dioxane (40 mL) under nitrogen was added **33.1m** (0.67 g, 2.57 mmol, 1.1 eq), potassium phosphate (0.75 g, 3.51 mmol, 1.5 eq), potassium bromide (0.31 g, 2.57 mmol, 1.1 eq) and tetrakis(triphenylphosphine) palladium(0) (0.14 g, 0.12 mmol, 0.05 eq). The mixture was heated at 100°C for 16h. Additional quantity of tetrakis(triphenylphosphine) palladium(0) (0.10 g, 0.087 mmol, 0.04 eq) was added and the reaction was heated at 100°C for an additional 24h and then cooled to room temperature. Ethyl acetate and water were added and the layers were separated. The organics were concentrated and purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 64%
^{1}HNMR (400MHz, $CDCl_3$) δ 7.84 (m, 4H), 7.61 (m, 1H), 7.49 (m, 4H), 7.21 (m, 1H), 7.02 (dd, 1H), 6.96 (dd, 1H), 6.88 (m, 1H), 5.64 (s, 1H), 3.88 (brs, 2H), 3.35 (brs, 2H), 2.08 (brd, 2H), 1.70 (m, 2H), 1.49 (s, 9H)
Mass Spectral Analysis *m/z* = 482.2 $(M+H)^+$

[0916] Preparation of **33N**

To a solution of the Boc derivative obtained previously (0.715 g, 1.48 mmol, 1.0 eq) in methylene chloride (30 mL) at 0°C under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (2.97 mL, 5.94 mmol, 4.0 eq). The reaction mixture was stirred for 48h at room temperature and diluted with diethyl ether (5 mL). The precipitate was sonicated and collected by vacuum filtration.
Yield: 95%

^{1}HNMR (400MHz, DMSO d_6) δ 8.75 (brs, 2H), 7.80 (m, 4H), 7.71 (m, 1H), 7.59 (m, 4H), 7.28 (m, 1H), 7.05 (m, 2H), 6.97 (m, 1H), 6.02 (s, 1H), 3.20 (brm, 4H), 2.06 (brm, 4H)
Mass Spectral Analysis *m/z* = 382.4 $(M+H)^+$
Elemental analysis:
$C_{26}H_{23}NO_2$, 1HCl, $0.5H_2O$
Theory: %C 73.14; %H 5.90; %N 3.28
Found: %C 72.95; %H 5.75; %N 3.32

EXAMPLES 38A, 38B, 38C, 38D

[0917] Preparation of **38.2**:

To a mixture of **19.1** (29.8 g, 127.7 mmol, 1 eq.) and **38.1** (18.4 g, 127.7 mmol, 1 eq.) was added pyridine (12.5 mL) followed by 10 drops of piperidine. The mixture was stirred at 45°C for 1h and then stood at room temperature for 10h. The resulting solids were washed with methanol and then dried *in vacuo.*
Yield: 82 %
^{1}H NMR (400MHz, $CDCl_3$) δ 7.41-7.30 (m, 5H), 5.17 (s, 2H), 3.70 (m, 4H), 3.18 (m, 4H), 1.75 (s, 6H)
Mass Spectral Analysis *m/z* = 360.22 $(M+H)^+$

[0918] Preparation of **38.4**:

To a suspension of copper(I) iodide (0.636 g, 3.34 mmol, 0.04 eq.) in dry tetrahydrofuran (200 mL) at –10°C was added **38.3** (500 mL, 0.25M in THF, 125 mmol, 1.5 eq.) over a 50 min time period. The mixture was kept at –10°C for another 15 min and then solid **38.2** (30 g, 83.48 mmol, 1 eq.) was added in 10 portions waiting for the exotherm subside between additions. The reaction mixture was kept at –10°C for another 2h and then slowly added to a mixture of 13% ammonium hydroxide/saturated ammonium chloride/water (1/1/1, 200 mL) and ethyl acetate (300 mL). The mixture was stirred for 15 min and then the two layers were separated. The organic layer was washed with 13% ammonium hydroxide/saturated ammonium chloride/water (1/1/1, 2 x 200 mL), brine (3 x 200 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. Diethyl ether (800 mL) was added to the crude mixture and the suspension was stirred at room temperature for 10h. The resulting fine powders were collected by filtration, washed with diethyl ether (3 x 50 mL) and dried *in vacuo*.

Yield: 100%

^{1}H NMR (400MHz, DMSO-d_6) δ 7.37-7.25 (m, 5H), 7.05-6.92 (m, 4H), 4.99 (s, 2H), 3.70 (m, 2H), 2.94 (m, 2H), 2.91-2.66 (m, 4H), 1.45 (s, 6H), 0.84 (m, 2H)

Mass Spectral Analysis *m/z* = 468.25 $(M-H)^-$

[0919] Preparation of **38.5**:

A mixture of **38.4** (41 g, 83.48 mmol, 1 eq.) in *N,N*-dimethylformamide/water (1:1, 400 mL) was stirred at 120°C for 10h. The reaction mixture was cooled to room temperature and was acidified with 1N aqueous hydrochloric acid until pH 1-2. The mixture was stirred at room temperature for 15min and the resulting solids were collected by filtration, washed with water (2 x 50 mL), and then dried in vacuum oven at 70°C.

Yield: 95%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.41-7.28 (m, 5H), 7.24 (m, 2H), 7.11 (m, 2H), 5.05 (s, 2H), 3.69-3.56 (m, 2H), 3.41-3.20 (m, 2H), 2.76 (s, 2H), 2.17 (s, 2H), 1.53-1.32 (m, 4H)

Mass Spectral Analysis *m/z* = 384.35 $(M-H)^-$

[0920] Preparation of **38.6**:

To a stirred solution of **38.5** (20 g, 51.9 mmol, 1 eq.) in dry dichloromethane (300 mL) was added oxalyl chloride (27.2 mL, 311.4 mmol, 6 eq.) in one portion followed by 5 drops of *N,N*-dimethylformamide. The reaction mixture was stirred at room temperature for 1h and then concentrated under reduced pressure. The crude mixture was further dried in vacuo for 4h and then dissolved in dry dichloromethane (600 mL), to which was added anhydrous aluminum chloride (13.84 g, 103.8 mmol, 2 eq.) in one portion. The reaction mixture was stirred at room temperature for 10h. The reaction was quenched with water at 0°C and the mixture was basified with concentrated ammonium hydroxide until pH 8-9. The two phases were separated and the aqueous phase was extracted with dichloromethane (3 x 100 mL). The combined organics were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was dissolved in dichloromethane (300 mL), to which were added triethylamine (21.7 mL, 155.7 mmol, 3 eq.) and **4.7** (13.6 g, 62.28 mmol, 1.2 eq.) portionwise at 0°C. The reaction mixture was slowly warmed up to and stirred at room temperature for 10h. Dichloromethane was removed under reduced pressure. The crude product was dissolved in ethyl acetate (500 mL) and washed with 0.5 N aqueous hydrochloric acid (2 x 100 mL), water (2 x 200 mL), brine (200 mL), and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixture of increasing polarity).

Yield: 62%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.67 (dd, 1H), 7.25-7.17 (M, 2H), 3.50-3.35 (m, 4H), 2.92 (s, 2H), 2.62 (s, 2H), 1.50 (m, 4H), 1.45 (s, 9H)

Mass Spectral Analysis *m/z* = 334.23 $(M+H)^+$

[0921] Preparation of **38.7**:

To a stirred solution of **38.6** (19.3 g, 57.88 mmol, 1 eq.) in dry tetrahydrofuran (250 mL) at –78°C under nitrogen was added as solution of lithium *bis*(trimethylsilyl)amide in tetrahydrofuran (1.0M, 69.46 mL, 69.46 mmol, 1.2 eq.) over a 20min time period. The mixture was kept at – 78°C for 1h and then *N*-phenylbis(trifluoromethanesulfonamide) **1.4** (24.81 g, 69.46 mmol, 1.2 eq.) in tetrahydrofuran (100 mL) was added to the mixture over a 20min time period. The mixture was kept at – 78°C for another hour, then slowly warmed up to and stirred room temperature for 10h. Tetrahydrofuran was removed under reduced pressure. The crude product was dissolved in diethyl ether (500 mL) and washed with water (2 x 150 mL), 0.5N aqueous hydrochloric acid (2 x 100 mL), 1N aqueous sodium hydroxide (3 x 100 mL), brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixture of increasing polarity).

Yield: 91%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.15 (dd, 1H), 7.07 (dd, 1H), 6.98 (m, 1H), 6.05 (s, 1H), 3.65-3.53 (m, 2H), 3.36-3.27 (m, 2H), 2.79 (s, 2H), 1.69-1.60 (m, 2H), 1.56-1.48 (m, 2H), 1.46 (s, 9H)

Mass Spectral Analysis *m/z* = 466.20 $(M+H)^+$

[0922] Preparation of **38.8**:

To a solution of aqueous potassium carbonate (2M solution, 6.7 mL, 13.4 mmol, 3 eq.) was added dioxane (45 mL), **1.7** (1.63 g, 5.36 mmol, 1.2 eq.), and **38.7** (2.08 g, 4.46 mmol, 1 eq.) successively. The reaction flask was purged with nitrogen and 1,1'-*bis*(diphenylphosphino)ferrocene palladium(II) chloride complex with dichloromethane (163 mg, 0.22 mmol, 0.05 eq.) was added to the mixture. The mixture was stirred at room temperature for 30min. Water (200 mL) and ethyl acetate (300 mL) were added and the two phases were separated. The aqueous phase was extracted with ethyl acetate (100 mL) and the combined organics were washed with brine (2 x 100 mL) and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 94%

^{1}H NMR (400MHz, $CDCl_3$) δ 8.54 (dd, 1H), 7.73 (m, 1H), 7.64 (dd, 1H), 7.17 (dd, 1H), 6.90 (m, 1H), 6.65 (dd, 1H), 6.10 (s, 1H), 3.60 (q, 4H), 3.51-3.35 (m, 4H), 2.80 (s, 2H), 1.68-1.49 (m, 4H), 1.47 (s, 9H), 1.33-1.18 (m, 6H)

Mass Spectral Analysis *m/z* = 494.46 $(M+H)^+$

[0923] Preparation of **38A**:

To a solution of **38.8** (4.5 g, 9 mmol, 1 eq.) in dichloromethane/methanol (5:1, 60 mL) was slowly added a 2M solution of hydrogen chloride in diethyl ether (2.0M, 22.5 mL, 45 mmol, 5 eq.). The mixture was stirred at room temperature for 10h. The organic solvents were removed under reduced pressure and the crude product was purified by column chromatography (eluent: dichloromethane/methanol mixture of increasing polarity).

Yield: 81%

^{1}H NMR (400MHz, DMSO-d_6) δ 9.15-8.92 (m, 2H), 8.64 (d, 1H), 7.91 (dd, 1H), 7.60 (dd, 1H), 7.38 (dd, 1H), 7.11 (m, 1H), 6.68 (dd, 1H), 6.44 (s, 1H), 3.47 (q, 2H), 3.32 (q, 2H), 3.27-3.08 (m, 4H), 2.83 (s, 2H), 1.79-1.62 (m, 4H), 1.17 (t, 3H), 1.12 (t, 3H)

Mass Spectral Analysis *m/z* = 394.3 $(M+H)^+$

Elemental analysis:

$C_{24}H_{28}FN_3O$, 1.4HCl, $0.8H_2O$

Theory: %C 62.81; %H 6.81; %Cl 10.81; %N 9.16
Found: %C 62.61; %H 6.67; %Cl 10.96; %N 9.04

[0924] Preparation of **38B**:

To a stirred solution of **38A** (150 mg, 0.35 mmol, 1 eq.) in methanol (10 mL) was added palladium [30 mg, 10 wt.% (dry basis) on activated carbon, 20% wt. eq.]. The reaction mixture was stirred under a hydrogen atmosphere using a hydrogen balloon at room temperature for 10h. The palladium on activated carbon was filtered off on a celite pad and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixture of increasing polarity).

Yield: 46%

^{1}H NMR (400MHz, DMSO-d_6) δ 8.88-8.78 (m, 2H), 8.51 (d, 1H), 7.67 (dd, 1H), 7.51 (d, 1H), 7.73 (m, 1H), 7.01 (m, 1H), 6.40 (dd, 1H), 4.22 (m, 1H), 3.44 (q, 2H), 3.28 (q, 2H), 3.18-3.02 (m, 4H), 2.85 (d, 1H), 2.75 (d, 1H), 2.16 (m, 1H), 1.75-1.46 (m, 5H), 1.15 (t, 3H), 1.09 (t, 3H)

Mass Spectral Analysis $m/z = 396.4\ (M+H)^+$

[0925] Preparation of **38.9**:

To a solution of **38.7** (11.88 g, 25.5 mmol, 1 eq.) in *N,N*-dimethylformamide (125 mL) at 0°C was added potassium acetate (7.51 g, 76.5 mmol, 3 eq.), *bis*(pinacolato)diboron **1.14** (7.77 g, 30.6 mmol, 1.2 eq.), 1,1'-*bis*(diphenylphosphino)ferrocene palladium(II) chloride complex with dichloromethane (560 mg, 0.76 mmol, 0.03 eq.) successively. The reaction mixture was stirred at 100°C for 10h. The reaction mixture was cooled to room temperature, diethyl ether (300 mL) and water (300 mL) were added and the mixture was stirred for another 30 minute at room temperature. The two phases were separated and the organic phase was washed with water (2 x 150 mL), brine (200 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 60 %

^{1}H NMR (400MHz, $CDCl_3$) δ 7.54 (dd, 1H), 7.01 (dd, 1H), 6.84-6.77 (m, 2H), 3.51-3.37 (m, 4H), 2.65 (s, 2H), 1.61-1.38 (m, 13H), 1.34 (s, 12H)
Mass Spectral Analysis *m/z* = 444.38 $(M+H)^+$

[0926] Preparation of **38.10**:

To a solution of an aqueous solution of potassium carbonate (2M solution, 16.2 mL, 48.6 mmol, 3 eq.) was added dioxane (110 mL), **35.8** (3.926 g, 10.8 mmol, 1 eq.), and **38.9** (5.6 g, 12.6 mmol, 1.17 eq.) successively. The reaction flask was purged with nitrogen and 1,1'-*bis*(diphenylphosphino)ferrocene palladium(II) chloride complex with dichloromethane (403 mg, 0.95 mmol, 0.05 eq.) was added to the mixture. The mixture was stirred at room temperature for 1h and then heated at 55°C for 10 h. Water (200 mL) and ethyl acetate (300 mL) were added and the mixture was stirred for another 10 min at room temperature. The two phases were separated and the organic phase was washed with brine (200 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 81%
^{1}H NMR (400MHz, $CDCl_3$) δ 7.22-7.16 (m, 2H), 7.13-7.07 (m, 2H), 6.82 (m, 1H), 6.48 (dd, 1H), 6.01 (s, 1H), 5.04 (s, 2H), 3.66-3.50 (m, 4H), 3.43-3.30 (m, 4H), 3.28 (s, 3H), 2.79 (s, 2H), 1.70-1.49 (m, 4H), 1.46 (s, 9H), 1.32-1.13 (m, 6H)
Mass Spectral Analysis *m/z* = 553.51 $(M+H)^+$

[0927] Preparation of **38C**:

To a stirred solution of **38.10** (1 g, 1.8 mmol, 1 eq.) in methanol (50 mL) was slowly added a 4M anhydrous solution of hydrogen chloride in dioxane (4.5 mL, 18 mmol, 10 eq.). The reaction mixture was stirred at room temperature for 10h. The organic solvents were removed under reduced pressure and the crude material was purified by column chromatography (eluent: dichloromethane/methanol mixture of increasing polarity).
Yield: 80%

^{1}H NMR (400MHz, DMSO-d_6) δ 9.68 (s, 1H), 8.85-8.66 (m, 2H), 7.29 (m, 1H), 7.19 (d, 1H), 7.01 (m, 1H), 6.87 (d, 1H), 6.83 (dd, 1H), 6.39 (dd, 1H), 6.12 (s, 1H), 3.51-3.07 (m, 8H), 2.82 (s, 2H), 1.79-1.57 (m, 4H), 1.20-1.04 (m, 6H)
Mass Spectral Analysis *m/z* = 409.7 $(M+H)^+$
Elemental analysis:
$C_{25}H_{29}FN_2O_2$, 1HCl, $1.2H_2O$
Theory: %C 64.35; %H 7.00; %N 6.00
Found: %C 64.34; %H 6.92; %N 6.04

[0928] Preparation of **38.11**:

To a stirred solution of **38.10** (1.8 g, 3.25 mmol, 1 eq.) in methanol (32 mL) was added palladium [360 mg, 10 wt.% (dry basis) on activated carbon, 20% wt. eq.]. The reaction mixture was stirred under a hydrogen atmosphere using a hydrogen balloon at room temperature for 10h. The palladium on activated carbon was filtered off on a celite pad and the filtrate was concentrated under reduced pressure and dried *in vacuo*.
Yield: 91%
^{1}H NMR (400MHz, $CDCl_3$) δ 7.14 (d, 1H), 7.04 (m, 2H), 6.96 (dd, 1H), 6.80 (m, 1H), 6.51 (m, 1H), 5.13 (s, 2H), 4.46 (m, 1H), 3.60-3.25 (m, 11H), 2.78 (d, 1H), 2.65 (d, 1H), 2.04 (m, 1H), 1.68-1.38 (m, 14H), 1.30-1.10 (m, 6H)
Mass Spectral Analysis *m/z* = 555.53 $(M+H)^+$

[0929] Preparation of **38D**:

To a solution of **38.11** (0.30 g, 0.54 mmol, 1 eq.) in methanol (20 mL) was slowly added a 4M anhydrous solution of hydrogen chloride in dioxane (1.35 mL, 5.4 mmol, 10 eq.). The reaction mixture was stirred at room temperature for 10h. The organic solvents were removed under reduced pressure and the crude material was purified by column chromatography (eluent: dichloromethane/methanol mixture of increasing polarity).
Yield: 79%

^{1}H NMR (400MHz, DMSO-d_6) δ 9.84 (s, 1H), 8.92-8.73 (m, 2H), 7.17 (m, 1H), 7.03-6.91 (m, 2H), 6.86 (d, 1H), 6.73 (dd, 1H), 6.41 (dd, 1H), 4.37 (m, 1H), 3.58-2.97 (m, 8H), 2.86 (d, 1H), 2.68 (d, 1H), 1.99 (m, 1H), 1.80-1.49 (m, 5H), 1.17-1.02 (m, 6H)
Mass Spectral Analysis *m/z* = 411.76 $(M+H)^+$

EXAMPLE 39A

[0930] Preparation of **39.1**:

To a suspension of copper (I) iodide (550 mg, 2.88 mmol, 0.036 eq) in anhydrous tetrahydrofuran (600 mL) was added dropwise a 2.0 M solution of benzylmagnesium chloride (**28.3a**) (100 mL, 200 mmol, 2,5 eq) in tetrahydrofuran under a nitrogen atmosphere at -10°C. After the reaction mixture was stirred at -10°C for 30 min, solid **38.2** (28.72 g, 80 mmol, 1.0 eq) was added in ten portions over a 1 h period. After the addition was complete, the reaction mixture was stirred between -10°C and -0°C for 3 h, and then quenched by a mixture of concentrated ammonium hydroxide/saturated aqueous ammonium chloride/water (1:2:3, 400 mL). The mixture was extracted with ethyl acetate, and the combined organic layers were washed with a mixture of concentrated ammonium hydroxide/saturated aqueous ammonium chloride/water (1:2:3) and brine, dried over sodium sulfate and concentrated *in vacuo*. To the residue was added diethyl ether and the mixture was stirred overnight at room temperature. The solid was collected by filtration, washed with diethyl ether and dried *in vacuo*.
Yield: 100%

^{1}H NMR (400MHz, DMSO d_6) δ 7.30–7.00 (m, 10H), 4.96 (s, 2H), 3.70 (m, 2H), 2.98 (m, 2H), 2.80 (s+m, 4H), 1.49 (s, 6H), 0.83 (m, 2H).
Mass Spectral Analysis *m/z* = 450.36 $(M-Na)^+$

[0931] Preparation of **39.2**:

Compound **39.1** (39 g, 82.5 mmol) was dissolved in a mixture of *N,N* dimethylformamide (200 mL) and water (200 mL) and heated at ~135°C for 2 days, then cooled to room temperature. To the reaction mixture was added a 1 N aqueous sodium hydroxide (125 mL) and water (500 mL), the resulting mixture was washed with diethyl ether, acidified with a 6 N aqueous solution of hydrochloric acid and

extracted with diethyl ether. The combined organic extracts were washed with water and brine, dried over sodium sulfate and concentrated *in vacuo*.
Yield: 92.9%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.25 (brs, 1H), 7.36-7.20 (m, 10H), 5.08 (s, 2H), 3.60 (m, 2H), 3.33 (m, 2H), 2.79 (s, 2H), 2.19 (s, 2H), 1.50-1.40 (m, 4H).

[0932] Preparation of **28.6a**:

To a solution of **39.2** (1.1 g, 3 mmol, 1 eq) in anhydrous methylene chloride (20 mL) was added oxalyl chloride (1.6 mL, 18.3 mmol, 6.1 eq) in one portion followed by 2 drops of anhydrous *N,N* dimethylformamide. The reaction mixture was stirred at room temperature for 4 h and then concentrated *in vacuo*. The resulting acyl chloride was dissolved in anhydrous methylene chloride (60 mL) and aluminum chloride (804 mg, 6 mmol, 2 eq) was added in one portion. The reaction mixture was stirred at room temperature overnight and then quenched by water (40 mL) followed by addition of concentrated ammonium hydroxide to basify the aqueous layer. The organic layer was separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue was then dissolved in methylene chloride (30 mL) and cooled to 0°C. To this solution was added triethylamine (1.3 mL, 9.34 mmol, 3.1 eq) followed by benzyl chloroformate (0.9 mL, 6.0 mmol, 2 eq). The reaction mixture was stirred at 0°C for 1 h and then washed with a saturated aqueous solution of sodium bicarbonate, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane-ethyl acetate-methylene chloride, 4:1:1), to yield the spiro ketone **28.6a**
Yield: 95.5%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.0 (d, 1H), 7.50 (t, 1H), 7.33-7.23 (m, 7H), 5.11 (s, 2H), 2.98 (s, 2H), 2.62 (s, 2H), 1.50 (m, 4H).

[0933] Preparation of **28.7a**:

A 1.0 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (3.6 mL, 3.6 mmol, 1.2 eq) was added at -78°C to a solution of compound **28.6a** (1.047 g, 3.0 mmol, 1 eq) in tetrahydrofuran (30mL). After 45 minutes, a solution of *N*-phenyltrifluoromethanesulfonimide (**1.4**) (1.3 g, 3.6 mmol, 1.2 eq) in tetrahydrofuran

(8 mL) was added dropwise to the reaction mixture. The reaction mixture was then warmed to room temperature and stirred for 2.5 h, quenched by addition of water (40 mL), and extracted with a mixture of hexane and diethyl ether (1:1). The organic extracts were combined and washed with water, brine and dried over sodium sulfate. Evaporation of the solvent provided **28.7a** used for the next step without further purification.
Yield: 100%

^{1}H NMR (400MHz, CDCl$_3$) δ 7.35-7.18 (m, 9H), 5.98 (s, 1H), 5.11 (s, 2H), 3.70 (m, 2H), 3.40 (m, 2H), 2.83 (s, 2H), 1.66-1.56 (m, 4H).

[0934] Preparation of **28.12**:

To the solution of the enol triflate **28.7a** (2.91 g, 6.04 mmol) in dimethoxyethane (60 mL) was added sequentially 2 N aqueous solution of sodium carbonate (10.4 mL, 20.8 mmol, 3.4 eq), lithium chloride (860 mg, 20.3 mmol, 3.4 eq), 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine-2-carboxylic acid diethylamide (**1.7**) (2.13 g, 7.0 mmol, 1.16 eq) and tetrakis(triphenylphosphine)palladium(0) (212 mg, 0.183 mmol, 0.03 eq). The reaction mixture was refluxed overnight, cooled to room temperature, diluted with water (60 mL) and extracted with diethyl ether. The combined organic extracts were dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography (eluent: hexane/ethyl acetate, 1:1).
Yield: 99%

^{1}H NMR (400MHz, CDCl$_3$) δ 8.53 (d, 1H), 7.76 (dd, 1H), 7.60 (d, 1H), 7.35-7.12 (m, 8H), 6.92 (d, 1H), 6.05 (s, 1H), 5.12 (s, 1H), 3.70 (m, 2H), 3.60 (m, 2H), 3.48 (m, 2H), 2.82 (s, 2H), 1.65-1.55 (m, 4H), 1.30 (t, 3H), 1.20 (t, 3H).

[0935] Preparation of **39A**:

Compound **28.12** (1.0 g, 2.7 mmol) was dissolved in methylene chloride (10 mL) and methanol (80 mL), and the mixture was hydrogenated in the presence of 10% Pd/C (300 mg) using a hydrogen balloon. After 2 days at room temperature, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue

was purified by column chromatography (eluent: methylene chloride/methanol/conc. ammonia hydroxide, 10:1:1).
Yield: 80%

^{1}H NMR (400MHz, $CDCl_3$) δ 8.42 (d, 1H), 7.52 (m, 2H), 7.12 (m, 2H), 7.05 (m, 1H), 6.70 (d, 1H), 4.10 (m, 1H), 3.56 (q, 2H), 3.42 (q, 2H), 3.10-2.50 (m, 6H), 2.10 (m, 1H), 1.60 (m, 5H), 1.28 (t, 3H), 1.20 (t, 3H).
Mass Spectral Analysis *m/z* = 378.3 $(M+H)^+$

EXAMPLES 39B, 39C

[0936] Preparation of **39.3**:

To the solution of compound **39A** (650 mg, 1.72 mmol) in methylene chloride (10 mL) was added triethylamine (0.34 mL, 2.4 mmol, 1.4 eq) followed by di-t-butyl dicarbonate (**4.7**) (450 mg, 2.06 mmol, 1.2 eq.). The reaction mixture was stirred at room temperature for 4 h and then concentrated in vacuo. The residue was purified by column chromatography (eluent: hexane/ethyl acetate, 1:1).
Yield: 91.2%

^{1}H NMR (400MHz, $CDCl_3$) δ 8.41 (d, 1H), 7.52 (m, 2H), 7.12 (m, 2H), 7.05 (m, 1H), 6.70 (d, 1H), 4.10 (m, 1H), 3.58-3.33 (m, 8H), 2.90 (d, 1H), 2.72 (d, 1H), 2.09 (m, 1H), 1.65-1.52 (m, 5H), 1.47 (s, 9H), 1.29 (t, 3H), 1.20 (t, 3H).

[0937] Preparation of **39.4 & 39.5**:

Chiral separation of **39.3** (680mg) gave the two enantiomers **39.4** and **39.5**.
Column: Chiralpak ADH, 21 x 250nm, 35°C; SFC
Eluent: 35% MeOH / 65% CO_2; 50mL/min, 200 bar
UV wavelength: 260 nm
Polarimeter: 670 nm

Sample: 80 mg/mL in MeOH, 2mL injected

Positive polarimeter peak elutes first at about 6.5 minutes and the negative polarimeter peak elutessecond at about 9 minutes in 35% MeOH/ CO_2

39.4: (-) enantiomer; ee >96% (268mg)

39.5: (+) enantiomer; ee >99% (295mg)

[0938] Preparation of **39B**:

To the solution of pure enantiomer **39.4** (268 mg, 0.56 mmol) in methylene chloride (5 mL) was added 2.0 M hydrochloric acid in diethyl ether (10 mL, 20 mmol, 35.7 eq.) The mixture was stirred at ambient temperature for 24 h and the solvent was evaporated *in vacuo*. The resulting solid was triturated in diethyl ether, filtered and washed with diethyl ether.

Yield: 86.2%.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.90 (brs, 2H), 8.50 (s, 1H), 7.65 (d, 1H), 7.50 (d, 1H), 7.14 (m, 2H), 7.05 (m, 1H), 6.62 (d, 1H), 4.20 (m, 1H), 3.42 (q, 2H), 3.28 (q, 2H), 3.09 (m, 4H), 2.85 (d, 1H), 2.78 (d, 1H), 2.15 (m, 1H), 1.70-1.50 (m, 5H), 1.12 (t, 3H), 1.08 (t, 3H).

Mass Spectral Analysis *m/z* = 378.83 $(M+H)^+$

Elemental analysis:

$C_{24}H_{31}N_3O$, 8/7 HCl, 6/7 H_2O

Theory: %C 66.32; %H 7.85; %N 9.67

Found: %C 66.33; %H 7.72; %N 9.53

$[\alpha]^{25}_D -69.1^\circ$ (c = 0.5, MeOH)

[0939] Preparation of **39C**:

To the solution of enantiomer **39.5** (295 mg, 0.62 mmol) in methylene chloride (5 mL) was added a 2.0 M solution of hydrochloric acid in diethyl ether (10 mL, 20 mmol, 32 eq.) The mixture was stirred at ambient temperature for 24 h and the solvent was evaporated *in vacuo*. The resulting solid was triturated in diethyl ether, filtered and washed with diethyl ether.

Yield: 88.2%

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.90 (brs, 2H), 8.50 (s, 1H), 7.65 (d, 1H), 7.50 (d, 1H), 7.14 (m, 2H), 7.05 (m, 1H), 6.62 (d, 1H), 4.20 (m, 1H), 3.42 (q, 2H), 3.28 (q, 2H), 3.09 (m, 4H), 2.85 (d, 1H), 2.78 (d, 1H), 2.15 (m, 1H), 1.70-1.50 (m, 5H), 1.12 (t, 3H), 1.08 (t, 3H).

Mass Spectral Analysis *m/z* = 378.83 $(M+H)^+$

Elemental analysis:

$C_{24}H_{31}N_3O$, 6/5 HCl, 6/5 H_2O

Theory: %C 65.09; %H 7.87; %N 9.49

Found: %C 65.03; %H 7.68; %N 9.34

$[\alpha]^{25}_{D}$ +70.2° (c = 0.7, MeOH)

EXAMPLES 39D, 39E

[0940] Preparation of **39.7**:

To the solution of the enol triflate **28.7a** (2.91 g, 6.04 mmol) in dimethoxyethane (60 mL) was added sequentially a 2 N aqueous solution of sodium carbonate (10.4 mL, 20.8 mmol, 3.4 eq), lithium chloride (860 mg, 20.3 mmol, 3.4 eq), **39.6** (2.792 g, 7.69 mmol, 1.27 eq) and tetrakis(triphenylphosphine)palladium(0) (212 mg, 0.183 mmol, 0.03 eq). The reaction mixture was refluxed overnight, cooled to room temperature, diluted with water (60 mL) and extracted with diethyl ether. The combined organic extracts were dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography (eluent: hexane/acetone, 2:1).
Yield: 98.4%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.38-7.05 (m, 11H), 6.72 (d, 1H), 5.95 (s, 1H), 5.12 (s, 2H), 5.00 (s, 2H), 3.69 (m, 2H), 3.53 (m, 2H), 3.45 (m, 2H), 3.32 (m, 2H), 3.25 (s, 3H), 2.80 (s, 2H), 1.66 (m, 2H), 1.55 (m, 2H), 1.26 (brs, 3H), 1.18 (brs, 3H).

[0941] Preparation of **39D**:

Iodotrimethylsilane (1.02 mL, 7.5 mmol, 2.84 eq) was added to the solution of compound **39.7** (1.5 g, 2.64 mmol) in anhydrous methylene chloride (30 mL) under nitrogen. The reaction mixture was stirred at room temperature for 2 h, quenched with a 1N aqueous solution of hydrochloric acid (40 mL) and washed with diethyl ether. The aqueous phase was basified to pH = 9-10 by addition of a 3N aqueous solution of sodium hydroxide, and extracted with methylene chloride. The organic extracts were combined, dried over sodium sulfate and concentrated *in vacuo*. The residue was dissolved in methylene chloride (10 mL) and methanol (20 mL). To this solution was added a 2.0 M anhydrous solution of hydrochloric acid in diethyl ether (30 mL, 60 mmol, 22.7 eq) and stirred at room temperature for 2 days. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography (eluent: methylene chloride/methanol, 5:1).

Yield: 100%

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.60 (s, 1H), 8.82 (brs, 2H), 7.24-7.10 (m, 4H), 6.86 (s, 1H), 6.80 (d, 1H), 6.70 (d, 1H), 6.00 (s, 1H), 3.40 (m, 2H), 3.23 (m, 2H), 3.12 (m, 4H), 2.82 (s, 2H), 1.66 (m, 4H), 1.10 (m, 6H).
Mass Spectral Analysis *m/z* = 391.4 $(M+H)^+$
Elemental analysis:
$C_{25}H_{30}N_2O_2$, 1 HCl, 4/5 H_2O
Theory: %C 68.03; %H 7.44; %N 6.35
Found: %C 67.94; %H 7.27; %N 6.34

[0942] Preparation of **39E**:

Compound **39.7** (1.7 g, 2.99 mmol) was dissolved in a mixed solvent of methylene chloride (15 mL) and methanol (120 mL), and the mixture was hydrogenated in the presence of 10% Pd/C (510 mg) using a hydrogen balloon. After 2 days of stirring at room temperature, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in methylene chloride (10 mL) and methanol (20 mL). To this solution was added a 2.0 M anhydrous solution of hydrochloric acid in diethyl ether (30 mL, 60 mmol, 22.7 eq) and the mixture was stirred at room temperature for 2 days. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in methylene chloride. The organic solution was washed with a saturated aqueous solution of sodium bicarbonate, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (eluent: methylene chloride/methanol, 5:1).
Yield: 90.4%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.10 (m, 2H), 7.03 (m, 1H), 6.94 (d, 1H), 6.82 (d, 1H), 6.76 (d, 1H), 6.70 (d, 1H), 4.70 (m, 1H), 3.50 (m, 2H), 3.32 (m, 2H), 2.98 (m, 5H), 2.62 (d, 1H), 2.11 (m, 1H), 1.78 (m, 1H), 1.55 (m, 2H), 1.40 (m, 2H), 1.21 (brs, 3H), 1.12 (brs, 3H).
Mass Spectral Analysis *m/z* = 393.4 $(M+H)^+$

EXAMPLES 39F, 39G

[0943] Preparation of **39.8**:

To the solution of compound **39E** (800 mg, 2.04 mmol) in methylene chloride (15 mL) was added triethylamine (0.42 mL, 3.0 mmol, 1.47 eq) followed by di-t-butyl dicarbonate (**4.7**) (446 mg, 2.04 mmol, 1.0 eq.). The reaction mixture was stirred at room temperature for 45 min and then concentrated *in vacuo*. The residue was purified by column chromatography (eluent: hexane/ethyl acetate, 1:2).

Yield: 81%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.98 (brs, 1H), 7.09 (m, 2H), 7.00 (m, 2H), 6.90 (d, 1H), 6.80 (d, 1H), 6.72 (d, 1H), 4.43 (m, 1H), 3.56 (m, 2H), 3.40 (m, 4H), 3.30 (m, 2H), 2.75 (d, 1H), 2.66 (d, 1H), 2.00 (m, 1H), 1.51-1.37 (m, 5H), 1.43 (s, 9H), 1.22 (m, 3H), 1.11 (m, 3H).

[0944] Preparation of **39.9** and **39.10**:

Chiral separation of **39.8** (800mg) gave the two enantiomers **39.9** and **39.10**.

Column: Chiralpak ADH, 21 x 250nm, 35°C; SFC

Eluent: 35% MeOH / 65% CO_2; 50mL/min, 200 bar

UV wavelength: 260 nm

Polarimeter: 670 nm

Sample: 40 mg/mL in MeOH, 1.5mL injected

Negative polarimeter peak elutes first at about 7.2 minutes and the positive polarimeter peak elutessecond at about 10.8 minutes in 35% MeOH/ CO_2

39.9: (-) enantiomer; ee >99% (363mg)

39.10: (+) enantiomer; ee >99% (304mg)

[0945] Preparation of **39F**:

To the solution of pure enantiomer **39.9** (305 mg, 0.62 mmol) in methylene chloride (5 mL) was added a 2.0 M anhydrous solution of hydrochloric acid in diethyl ether (10 mL, 20 mmol, 32.3 eq.) The mixture was stirred at ambient temperature for 24 h and the solvent was evaporated *in vacuo*. The resulting solid was triturated in diethyl ether, filtered and washed with diethyl ether.

Yield: 90.5%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.80 (s, 1H), 8.80 (brs, 2H), 7.10-6.93 (m, 4H), 6.83 (s, 1H), 6.70 (m, 2H), 4.40 (m, 1H), 3.35-3.03 (m, 8H), 2.86 (d, 1H), 2.72 (d, 1H), 2.00 (m, 1H), 1.60 (m, 5H), 1.10 (m, 6H).

Mass Spectral Analysis *m/z* = 393.8 $(M+H)^+$
Elemental analysis:
$C_{25}H_{32}N_2O_2$, 1 HCl, 3/5 H_2O
Theory: %C 68.27; %H 7.84; %N 6.37
Found: %C 68.17; %H 7.72; %N 6.41
$[\alpha]^{25}_D$ –59.6° (c = 0.55, MeOH)

[0946] Preparation of **39G**:
To the solution of pure enantiomer **39.10** (280 mg, 0.57 mmol) in methylene chloride (5 mL) was added a 2.0 M anhydrous solution of hydrochloric acid in diethyl ether (10 mL, 20 mmol, 35 eq.) The mixture was stirred at ambient temperature for 24 h and the solvent was evaporated *in vacuo*. The resulting solid was triturated in diethyl ether, filtered and washed with diethyl ether.
Yield: 90.3%

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.80 (s, 1H), 8.80 (brs, 2H), 7.10-6.93 (m, 4H), 6.83 (s, 1H), 6.70 (m, 2H), 4.40 (m, 1H), 3.35-3.03 (m, 8H), 2.86 (d, 1H), 2.72 (d, 1H), 2.00 (m, 1H), 1.60 (m, 5H), 1.10 (m, 6H).

Mass Spectral Analysis *m/z* = 393.8 $(M+H)^+$
Elemental analysis:
$C_{24}H_{31}N_3O$, 1 HCl, 3/5 H_2O
Theory: %C 68.27; %H 7.84; %N 6.37
Found: %C 68.02; %H 7.63; %N 6.33

$[\alpha]^{25}_D$ +52.6° (c = 0.85, MeOH)

EXAMPLE 40A

[0947] Preparation of **40.1**:

To a suspension of copper (I) iodide (553 mg, 2.90 mmol, 0.036 eq) in anhydrous tetrahydrofuran (50 mL) was added dropwise a 0.25 M solution of 4-methoxybenzylmagnesium chloride (**28.3b**) (640 mL, 160 mmol, 2,0 eq) in tetrahydrofuran under nitrogen atmosphere at -10°C. After the reaction mixture was stirred at -10°C for 30 min, solid **38.2** (28.8 g, 80 mmol, 1.0 eq) was added to the mixture in ten portions over a 1 h period. After the addition, the reaction mixture was stirred between -10°C and -0°C for 3 h, and then quenched by a mixture of concentrated ammonium hydroxide/aqueous saturated ammonium chloride/water (1:2:3, 400 mL) The mixture was extracted with ethyl acetate, and the combined organic layers were washed with concentrated ammonium hydroxide/aqueous saturated ammonium chloride/water (1:2:3) and brine, dried over sodium sulfate and concentrated *in vacuo*. To the residue was added diethyl ether and the mixture was stirred overnight at room temperature. The solid was collected by filtration, washed with diethyl ether and dried *in vacuo*.

Yield: 100%

^{1}H NMR (400MHz, DMSO d_6) δ 7.29 (m, 5H), 6.91 (δ, 2H), 6.73 (δ, 2H), 4.98 (s, 2H), 3.70 (s+m, 5H), 2.93 (m, 2H), 2.80 (m, 2H), 2.70 (s, 2H), 1.49 (s, 6H), 0.82 (m, 2H).

Mass Spectral Analysis *m/z* = 480.40 $(M\text{-}Na)^+$

[0948] Preparation of **28.11**:

Compound **40.1** (40.2 g, 79.92 mmol) was dissolved in a mixture of *N,N* dimethylformamide (200 mL) and water (200 mL) and the mixture was heated at ~135°C for 2 days, then cooled to room temperature. To the reaction mixture was added a 1N aqueous solution of sodium hydroxide (125 mL) and water (500 mL). The resulting mixture was washed with diethyl ether, acidified with a 6 N aqueous solution of hydrochloric acid and extracted with diethyl ether. The combined organic extracts were washed water and brine, dried over sodium sulfate and concentrated *in vacuo*.

Yield: 100%.

^{1}H NMR (400MHz, DMSO d_6) δ 12.22 (brs, 1H), 7.33 (m, 5H), 7.10 (d, 2H), 6.86 (d, 2H), 5.06 (s, 2H), 3.73 (s, 3H), 3.60 (m, 2H), 3.32 (m, 2H), 2.69 (s, 2H), 2.17 (s, 2H), 1.45-1.35 (m, 4H).

[0949] Preparation of **28.6b**:

To a solution of **28.11** (1.98 g, 5 mmol) in anhydrous methylene chloride (10 mL) was added a 2.0 M solution of oxalyl chloride in methylene chloride (20 mL, 40 mmol, 8 eq) followed by 2 drops of anhydrous *N*, *N*-dimethylformamide. The reaction mixture was stirred at room temperature for 4 h and then concentrated *in vacuo*. The resulting acyl chloride was dissolved in anhydrous methylene chloride (100 mL) and aluminum chloride (1.35 g, 10 mmol, 2 eq) was added in one portion. The reaction mixture was stirred at room temperature overnight and then quenched with water (60 mL) followed by addition of concentrated ammonium hydroxide to basify the aqueous layer. The organic layer was separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue was then dissolved in methylene chloride (60 mL) and cooled to 0°C. To this solution was added triethylamine (3.0 mL, 21.6 mmol, 4.3 eq) followed by benzyl chloroformate (2.0 mL, 13.3 mmol, 2.7 eq). The reaction mixture was stirred at 0°C for 1 h and then washed with saturated aqueous solution of sodium bicarbonate, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography (eluent: hexane/methylene chloride/ethyl acetate, 4:1:1).

Yield: 89.7%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.48 (d, 1H), 7.35 (m, 5H), 7.16 (d, 1H), 7.10 (dd, 1H), 5.11 (s, 2H), 3.81 (s, 3H), 3.50 (m, 4H), 2.90 (s, 2H), 2.60 (s, 2H), 1.50 (m, 4H).

[0950] Preparation of **28.7b**:

A 1.0 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (100 mL, 100 mmol, 1.22 eq) was added at -78°C to a solution of compound **28.6b** (31 g, 81.8 mmol, 1 eq) in tetrahydrofuran (600mL). After 45 minutes, a solution of *N*-phenyltrifluoromethanesulfonimide (**1.4**) (38 g, 106.4 mmol, 1.3 eq) in tetrahydrofuran (120 mL) was added dropwise. The reaction mixture was then warmed to room temperature, stirred for 4.5 h at room temperature, quenched by

addition of water (500 mL), and extracted with a mixture of hexane and diethyl ether (1:1). The organic extracts were combined and washed with water and brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (eluent: hexane/ethyl acetate, 1:4).
Yield: 98%.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.33 (m, 5H), 7.09 (d, 1H), 6.90 (d, 1H), 6.80 (dd, 1H), 5.98 (s, 1H), 5.12 (s, 2H), 3.80 (s, 3H), 3.68(m, 2H), 3.40 (m, 2H), 2.76 (s, 2H), 1.65 (m, 2H), 1.55 (m, 2H).

[0951] Preparation of **40.2**:

To the solution of the enol triflate **28.7b** (4.0 g, 7.83 mmol) in dimethoxyethane (80 mL) was added sequentially a 2 N aqueous solution of sodium carbonate (13.6 mL, 27.2 mmol, 3.47 eq), lithium chloride (1.12 g, 26.4 mmol, 3.37 eq), **1.7** (2.74 g, 9.0 mmol, 1.15 eq) and tetrakis(triphenylphosphine)palladium(0) (276 mg, 0.238 mmol, 0.03 eq). The reaction mixture was refluxed overnight, cooled to room temperature, diluted with water (120 mL) and extracted with diethyl ether. The combined organic extracts were dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography (eluent: hexane/ethyl acetate, 2:3).
Yield: 100%

^{1}H NMR (400MHz, $CDCl_3$) δ 8.57 (d, 1H), 7.73 (dd, 1H), 7.60 (d, 1H), 7.32 (m, 5H), 7.11 (d, 1H), 6.76 (dd, 1H), 6.50 (d, 1H), 6.05 (s, 1H), 5.12 (s, 1H), 3.70 (m, 2H), 3.68-3.43 (m, 8H), 2.78 (s, 2H), 1.66 (m, 2H), 1.55 (m, 2H), 1.30 (t, 3H), 1.22 (t, 3H).

[0952] Preparation of **40A**:

Iodotrimethylsilane (0.86 mL, 6 mmol, 3 eq) was added to a solution of compound **40.2** (1.08 g, 2 mmol) in anhydrous methylene chloride (15 mL) under nitrogen. The reaction mixture was stirred at room temperature for 1.5 h and quenched with a 1N aqueous solution of hydrochloric acid (40 mL). The aqueous phase was washed with diethyl ether. The aqueous was basified to pH = 9-10 by addition of a 3N aqueous solution of sodium hydroxide, and extracted with methylene chloride. The organic extracts were combined, dried over sodium sulfate and

concentrated *in vacuo*. The residue was dissolved in methylene chloride (10 mL) and diluted with diethyl ether (40 mL). To this solution was added a 2.0 M anhydrous solution of hydrochloric acid in diethyl ether (20 mL, 40 mmol, 20 eq) and the mixture was stirred at room temperature overnight. The precipitated solid was collected by filtration and washed with ether, dried *in vacuo*.
Yield: 87%

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (brs, 1H), 8.96 (brs, 1H), 8.66 (d, 1H), 7.91 (dd, 1H), 7.60 (d, 1H), 7.27 (d, 1H), 6.84 (dd, 1H), 6.40 (d, 1H), 6.35 (s, 1H), 3.65 (s, 3H), 3.47 (q, 2H), 3.30-3.10 (m, 6H), 2.78 (s, 2H), 1.70 (m, 4H), 1.12 (m, 6H).

Mass Spectral Analysis *m/z* = 406.3 $(M+H)^+$
Elemental analysis:
$C_{25}H_{31}N_3O_2$, 3/2 HCl, 3/4 H_2O
Theory: %C 63.38; %H 7.23; %N 8.87; %Cl 11.23
Found: %C 63.25; %H 7.24; %N 8.70; %Cl 11.24

EXAMPLE 40B

[0953] Preparation of **40B**:

Compound **40.2** (1.3 g, 2.41 mmol) was dissolved in methylene chloride (10 mL) and methanol (80 mL), and hydrogenated in the presence of 10% Pd/C (400 mg) using a hydrogen balloon. After 3 days at room temperature, the reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (eluent: methylene chloride/methanol/concentrated ammonium hydroxide, 10:1:1).
Yield: 92.7%

^{1}H NMR (400MHz, $CDCl_3$) δ 8.46 (d, 1H), 7.53 (m, 2H), 7.12 (m, 2H), 7.05 (d, 1H), 6.72 (dd, 1H), 6.23 (d, 1H), 4.10 (m, 1H), 3.63 (s, 3H), 3.58 (q, 2H), 3.44 (q, 2H), 2.90 (m, 5H), 2.60 (d, 1H), 2.08 (m, 1H), 1.52 (m, 5H), 1.28 (t, 3H), 1.20 (t, 3H).
Mass Spectral Analysis *m/z* = 408.5 $(M+H)^+$

EXAMPLE 40C

[0954] Preparation of **40.3**:

To a solution of the enol triflate **28.7b** (2.05 g, 4 mmol) in dimethoxyethane (40 mL) was added sequentially 2 N aqueous solution of sodium carbonate (7.0 mL, 14 mmol, 3.5 eq), lithium chloride (580 mg, 13.7 mmol, 3.43 eq), **39.6** (1.96 g, 5.4 mmol, 1.35 eq) and tetrakis(triphenylphosphine)palladium(0) (142 mg, 0.123 mmol, 0.03 eq). The reaction mixture was refluxed overnight, cooled to room temperature, diluted with water (50 mL) and extracted with diethyl ether. The combined organic extracts were dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography (eluent: hexane/acetone, 2:1).
Yield: 96.6%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.35 (m, 5H), 7.20 (m, 2H), 7.08 (m, 2H), 6.69 (dd, 1H), 6.35 (d, 1H), 5.95 (s, 1H), 5.12 (s, 2H), 5.00 (s, 2H), 3.70 (m, 2H), 3.68 (s, 3H), 3.54 (m, 2H), 3.44 (m, 2H), 3.30 (m, 2H), 3.27 (s, 3H), 2.79 (s, 2H), 1.68 (m, 2H), 1.52 (m, 2H), 1.28 (brs, 3H), 1.20 (brs, 3H).

[0955] Preparation of **40C**:

Iodotrimethylsilane (1.02 mL, 7.5 mmol, 2.84 eq) was added to a solution of compound **40.3** (1.5 g, 2.64 mmol) in anhydrous methylene chloride (30 mL) under nitrogen. The reaction mixture was stirred at room temperature for 2 h, quenched with 1N aqueous solution of hydrochloric acid (40 mL). The queous phase was washed with diethyl ether. The aqueous phase was basified o pH = 9-10 by addition of a 3 N aqueous solution of sodium hydroxide, and extracted with methylene chloride. The organic extracts were combined, dried over sodium sulfate and concentrated *in vacuo*. The residue was dissolved in methylene chloride (10 mL) and methanol (20 mL). To this solution was added a 2.0 M solution of anhydrous hydrochloric acid in diethyl ether (30 mL, 60 mmol, 22.7 eq) and stirred atroom temperature for 2 days. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography (eluent: methylene chloride/methanol, 5:1).
Yield: 94%

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.63 (brs, 1H), 8.98 (brd, 2H), 7.14 (m, 2H), 6.89 (s, 1H), 6.80 (d, 1H), 6.73 (dd,. 1H), 6.21 (d, 1H), 6.00 (s, 1H), 3.60 (s, 3H), 3.40 (m, 2H), 3.23 (m, 2H), 3.12 (m, 4H), 2.75 (s, 2H), 1.69 (m, 4H), 1.12 (m, 6H).
Mass Spectral Analysis $m/z = 421.3$ $(M+H)^+$

Elemental analysis:

$C_{26}H_{32}N_2O_3$, 1 HCl, 1 H_2O

Theory: %C 65.74; %H 7.43; %N 5.90

Found: %C 66.02; %H 7.32; %N 5.89

EXAMPLE 41A

[0956] Preparation of **41.2**:

To a solution of **13.3** (0.50 g, 1.19 mmol, 1.0 eq) in acetonitrile (15 mL) under nitrogen was added *N,N*-diisopropylethylamine (0.50 mL, 2.85 mmol, 2.4 eq) and **41.1** (0.30 mL, 2.37 mmol, 2.0 eq). The mixture was stirred for 10 min. at room temperature, cooled to 0°C and *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) (0.46 g, 1.42 mmol, 1.2 eq) was slowly added to the reaction mixture which was warmed to room temperature and stirring was continued for 16h at room temperature. The reaction mixture was concentrated, dissolved in ethyl acetate and washed three times with a saturated aqueous solution of sodium bicarbonate, then brine. The organics were concentrated and purified by column chromatography (eluent: 50% hexane/ethyl acetate).

Yield: 75%

^{1}HNMR (400MHz, $CDCl_3$) δ 7.43 (d, 2H), 7.37 (d, 2H), 7.19 (m, 1H), 7.00 (dd, 1H), 6.94 (dd, 1H), 6.86 (m, 1H), 5.57 (s, 1H), 3.86 (brs, 2H), 3.69 (brs, 3H), 3.46-3.30 (brm, 8H), 2.05 (brd, 2H), 1.67 (m, 2H), 1.48 (s, 9H), 1.14 (brs, 3H)

Mass Spectral Analysis *m/z* = 507.5 $(M+H)^+$

[0957] Preparation of **41A**

To a solution of **41.2** (0.45 g, 0.888 mmol, 1.0 eq) in methylene chloride (10 mL) at 0°C under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (1.78 mL, 3.55 mmol, 4.0 eq). The reaction was warmed to room temperature, stirred for 48h and concentrated to a foam, which was sonicated in 25 mL of a 4:1 hexane/diethyl ether solution. The resulting solid was collected by vacuum filtration.

Yield: 71%

^{1}HNMR (400MHz, DMSO d_6) δ 8.96 (brs, 2H), 7.35 (s, 4H), 7.18 (m, 1H), 6.97 (d, 1H), 6.88 (m, 2H), 5.86 (s, 1H), 3.52-3.10 (brm, 13H), 1.96 (brm, 4H), 1.02 (brd, 3H)

Mass Spectral Analysis m/z = 407.4 $(M+H)^+$
Elemental analysis:
$C_{25}H_{30}N_2O_3$, 1HCl, $0.50H_2O$
Theory: %C 66.43; %H 7.14; %N 6.20
Found: %C 66.43; %H 7.00; %N 6.10

EXAMPLE 41B

[0958] Preparation of **41.4**:

To a solution of **13.3** (0.50 g, 1.19 mmol, 1.0 eq) in acetonitrile (15 mL) under nitrogen was added *N,N*-diisopropylethylamine (0.50 mL, 2.85 mmol, 2.4 eq) and **41.3** (0.37 mL, 2.37 mmol, 2.0 eq). The mixture was stirred for 10 min at room temperature, cooled to 0°C and *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) (0.46 g, 1.42 mmol, 1.2 eq) was slowly added to the reaction mixture, which was warmed to room temperature and stirred for 16h at room temperature. The reaction was concentrated, dissolved in ethyl acetate and washed three times with a saturated aqueous solution of sodium bicarbonate, then brine. The organics were concentrated and purified by column chromatography (eluent: methanol/methylene chloride, 5:95).
Yield: 77%

^{1}HNMR (400MHz, $CDCl_3$) δ 7.42 (d, 2H), 7.37 (d, 2H), 7.19 (m, 1H), 6.99 (brs, 1H), 6.94 (dd, 1H), 6.85 (m, 1H), 5.57 (s, 1H), 3.86 (brs, 2H), 3.61 (brs, 2H), 3.35 (brs, 4H), 2.62 (brs, 1H), 2.34 (brs, 4H), 2.06 (brm, 5H), 1.68 (m, 2H), 1.48 (s, 9H), 1.15 (brs, 3H)
Mass Spectral Analysis m/z = 520.5 $(M+H)^+$

[0959] Preparation of **41B**

To a solution of **41.4** (0.47 g, 0.904 mmol, 1.0 eq) in methylene chloride (10 mL) at 0°C under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (2.71 mL, 5.43 mmol, 6.0 eq). The reaction was warmed to room temperature, stirred for 48h at room temperature and diluted with diethyl ether (10 mL). The precipitate was filtered and partitioned in a saturated aqueous solution of sodium bicarbonate and ethyl acetate. The organic layer was separated. The aqueous phase was further extracted with methylene chloride and all organics were combined and concentrated.

Yield: 72%

^{1}HNMR (400MHz, $CDCl_3$) δ 7.39 (m, 4H), 7.19 (m, 1H), 6.97 (m, 2H), 6.85 (t, 1H), 5.63 (s, 1H), 3.62 (brs, 2H), 3.36 (brs, 2H), 3.19 (m, 2H), 2.98 (m, 2H), 2.60 (brs, 3H), 2.33 (brs, 3H), 2.09 (brm, 4H), 1.81 (brm, 2H), 1.22 (brd, 3H)
Mass Spectral Analysis *m/z* = 420.3 $(M+H)^+$
Elemental analysis:
$C_{26}H_{33}N_3O_2$, $0.67H_2O$
Theory: %C 72.36; %H 8.02; %N 9.74
Found: %C 72.02; %H 7.80; %N 9.55

EXAMPLE 41C

[0960] Preparation of **41.7**:

To a solution of **41.6** (5.82 mL, 48.93 mmol, 1.0 eq) in diethyl ether (15 mL) at 0°C under nitrogen was added drop wise a solution of **41.5** (5.0 g, 48.93 mmol, 1.0 eq) in diethyl ether (10 mL). The reaction was stirred at 0°C for 30 min. and then at room temperature for 2h. The reaction was concentrated. The crude product was used for the next step without further purification.
Yield: 99%

^{1}HNMR (400MHz, $CDCl_3$) δ 9.91 (brs, 1H), 3.48 (t, 2H), 2.87 (t, 2H), 2.64 (q, 2H), 1.70 (m, 2H), 1.11 (t, 3H)

[0961] Preparation of **41.8**:

To a solution of **13.3** (3.0 g, 7.12 mmol, 1.0 eq) in acetonitrile (60 mL) under nitrogen was added *N*,*N*-diisopropylethylamine (2.98 mL, 17.08 mmol, 2.4 eq) and **41.7** (2.82 g, 14.23 mmol, 2.0 eq). The mixture was stirred for 10 min at room temperature, cooled to 0°C and *O*-benzotriazol-1-yl-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate (TBTU) (2.74 g, 8.54 mmol, 1.2 eq) was slowly added. The reaction mixture was warmed to room temperature and stirred for 16h at room temperature. The reaction was concentrated, dissolved in ethyl acetate and the solution was washed with a saturated aqueous solution of sodium bicarbonate, then brine. The organics were concentrated to a solid, which was triturated in a ethyl acetate/hexane solution (1:9, 50 mL). The reuslting precipitate was collected by vacuum filtration.

Yield: 74%

^{1}HNMR (400MHz, $CDCl_3$) δ 8.42 (brs, 1H), 7.41 (s, 4H), 7.20 (m, 1H), 6.96 (m, 2H), 6.86 (m, 1H), 5.57 (s, 1H), 3.87 (brs, 2H), 3.65 (brt, 2H), 3.46-3.30 (brm, 6H), 2.06 (brd, 2H), 1.87 (brm, 2H), 1.67 (m, 2H), 1.48 (s, 9H), 1.19 (t, 3H)
Mass Spectral Analysis *m/z* = 602.4 $(M+H)^+$

[0962] Preparation of **41.9**:

To a suspension of **41.8** (1.0 g, 1.66 mmol, 1.0 eq) in methanol (30 mL) was added potassium carbonate (0.69 g, 4.99 mmol, 3.0 eq). The reaction was stirred for 48h at room temperature and concentrated. Water was added and the product was extracted three times with ethyl acetate. The organics were combined and concentrated to a solid, which was triturated in hexane and collected by vacuum filtration.
Yield: 75%

^{1}HNMR (400MHz, DMSO d_6) δ 7.47 (s, 4H), 7.29 (m, 1H), 7.05 (m, 2H), 6.97 (m, 1H), 5.95 (s, 1H), 3.79 (brd, 2H), 3.58-3.25 (brm, 8H), 1.94 (m, 2H), 1.78 (brm, 4H), 1.49 (s, 9H), 1.17 (brd, 3H)
Mass Spectral Analysis *m/z* = 506.5 $(M+H)^+$

[0963] Preparation of **41.11**:

To a solution of **41.9** (0.466 g, 0.922 mmol, 1.0 eq) in *N,N* dimethylformamide (10 mL) was added triethylamine (0.19 mL, 1.38 mmol, 1.5 eq) and **41.10** (0.22 g, 0.968 mmol, 1.05 eq). The reaction was stirred for 3.5h at room teperature. Ethyl acetate and a saturated aqueous solution of sodium bicarbonate were added to the mixture. The layers were separated and the aqueous phase was further extracted with ethyl acetate. The organics were combined, concentrated and used for the next step without further purification.
Yield: 100% (crude)
Mass Spectral Analysis *m/z* = 691.8 $(M+H)^+$

[0964] Preparation of **41.12**:

To a solution of **41.11** (0.64 g, 0.926 mmol, 1.0 eq) in *N,N* dimethylformamide (10 mL) was added potassium carbonate (0.196 g, 1.42 mmol, 1.5 eq) and methyl iodide (0.12 mL, 1.85 mmol, 2.0 eq). The reaction was stirred at room temperature for 16h. Ethyl acetate and water were added to the mixture. The layers were separated and the organics were concentrated. The crude product was used for the next step without further purification.
Yield: 96%
Mass Spectral Analysis *m/z* = 705.7 $(M+H)^+$

[0965] Preparation of **41.13**:

To a solution of **41.12** (0.626 g, 0.888 mmol, 1.0 eq) in *N,N* dimethylformamide (10 mL) under nitrogen was added potassium carbonate (0.307 g, 2.22 mmol, 2.5 eq) and benzenethiol (0.14 mL, 1.33 mmol, 1.5 eq). The reaction was stirred for 2h at room temperature. Ethyl acetate and a saturated aqueous solution of sodium bicarbonate were added to the mixture. The layers were separated. The organics were concentrated and the crude product was purified by column chromatography [eluent: methanol/(methylene chloride/ammonium hydroxide, 99:1) mixtures of increasing polarity].
Yield: 68%

^{1}HNMR (400MHz, $CDCl_3$) δ 7.39 (m, 4H), 7.19 (m, 1H), 6.96 (m, 2H), 6.87 (m, 1H), 5.57 (s, 1H), 3.87 (brs, 2H), 3.60 (brs, 2H), 3.34 (brs, 4H), 2.70 (brs, 1H), 2.50 (brs, 2H), 2.35 (brs, 1H), 2.06 (brd, 2H), 1.91 (brs, 1H), 1.68 (m, 4H), 1.48 (s, 9H), 1.21 (brd, 3H)
Mass Spectral Analysis *m/z* = 520.5 $(M+H)^+$

[0966] Preparation of **41C**

To a solution of **41.13** (0.31 g, 0.60 mmol, 1.0 eq) in methylene chloride (10 mL) at 0°C under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (1.80 mL, 3.58 mmol, 6.0 eq). The reaction mixture was warmed to room temperature, stirred for 48h at room temperature and concentrated to a foam, which was triturated in diethyl ether (7 mL). The resulting solid was collected by vacuum filtration.

Yield: 82%

^{1}HNMR (400MHz, DMSO d_6) δ 9.22 (brs, 2H), 8.93 (brs, 2H), 7.52 (m, 4H), 7.33 (m, 1H), 7.12 (d, 1H), 7.06 (m, 2H), 6.00 (s, 1H), 3.57 (brs, 2H), 3.26 (brm, 6H), 3.00 (brs, 2H), 2.62 (brs, 2H), 2.18-1.92 (brm, 7H), 1.15 (brm, 3H)

Mass Spectral Analysis *m/z* = 420.3 $(M+H)^+$

Elemental analysis:

$C_{26}H_{33}N_3O_2$, 2HCl, $0.50H_2O$

Theory: %C 62.27; %H 7.24; %N 8.38; %Cl 14.14

Found: %C 62.15; %H 7.05; %N 8.31; %Cl 14.19

EXAMPLE 41D

[0967] Preparation of **41.15**:

To a solution of **13.3** (1.00 g, 2.37 mmol, 1.0 eq) in acetonitrile (15 mL) under nitrogen was added *N,N*-diisopropylethylamine (1.45 mL, 8.30 mmol, 3.5 eq) and **41.14** (0.60 mL, 4.74 mmol, 2.0 eq). The mixture was stirred for 10 min at room temperature, cooled to 0°C and *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) (0.91 g, 2.85 mmol, 1.2 eq) was slowly added to the reaction mixture, which was warmed to room temperature and stirred for 40h at room temperature. Water was added and the product was extracted two times with ethyl acetate. The organics were concentrated and the crude product was purified by column chromatography (eluent: methanol/methylene chloride mixtures of increasing polarity).

Yield: 51%

^{1}HNMR (400MHz, $CDCl_3$) δ 8.32 (brt, 1H), 7.85 (d, 2H), 7.41 (d, 2H), 7.19 (m, 1H), 6.96 (m, 2H), 6.85 (m, 1H), 5.58 (s, 1H), 3.86 (brs, 2H), 3.61 (q, 2H), 3.34 (brs, 2H), 2.77 (t, 2H), 2.53 (s, 6H), 2.04 (brd, 2H), 1.94 (m, 2H), 1.67 (m, 2H), 1.47 (s, 9H)

Mass Spectral Analysis *m/z* = 506.5 $(M+H)^+$

[0968] Preparation of **41D**

To a solution of **41.15** (0.090 g, 0.18 mmol, 1.0 eq) in methylene chloride (5 mL) at 0°C under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid

in diethyl ether (0.53 mL, 1.07 mmol, 6.0 eq). The reaction was warmed to room temperature and stirred for 16h at room temperature. Additional amount of an anhydrous solution of hydrochloric acid in diethyl ether (0.50 mL) was added to the reaction which was stirred for an additional 16h at room temperature. The precipitate was collected by vacuum filtration.
Yield: 65%

^{1}HNMR (400MHz, DMSO d_6) δ 9.98 (brs, 1H), 8.94 (brs, 2H), 8.77 (t, 1H), 7.96 (d, 2H), 7.47 (d, 2H), 7.27 (m, 1H), 7.06 (d, 1H), 6.95 (d, 2H), 5.94 (s, 1H), 3.36 (m, 2H), 3.22 (brm, 4H), 3.09 (m, 2H), 2.76 (s, 6H), 2.12-1.89 (brm, 6H)
Mass Spectral Analysis *m/z* = 406.4 $(M+H)^+$

EXAMPLE 41E

[0969] Preparation of **41.17**:

To a solution of **41.6** (6.75 mL g, 56.72 mmol, 1.0 eq) in diethyl ether (15 mL) at 0°C under nitrogen was added drop wise **41.16** (5.97 mL, 56.72 mmol, 1.0 eq). The reaction was stirred at 0°C for 30 min and then at room temperature for 2h. The reaction mixture was concentrated to a solid, which was triturated in hexanes. The suspension was stirred overnight at room temperature and the precipitate was collected by vacuum filtration.
Yield: 90%

^{1}HNMR (400MHz, $CDCl_3$) δ 7.15 (brs, 1H), 3.41 (t, 2H), 2.83 (t, 2H), 2.66 (q, 2H), 1.11 (t, 3H)

[0970] Preparation of **41.18**:

To a solution of **13.3** (2.0 g, 4.74 mmol, 1.0 eq) in acetonitrile (50 mL) under nitrogen was added *N,N*-diisopropylethylamine (1.98 mL, 11.39 mmol, 2.4 eq) and **41.17** (1.75 g, 9.48 mmol, 2.0 eq). The mixture was stirred for 10 min at room temperature, cooled to 0°C and *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) (1.83 g, 5.69 mmol, 1.2 eq) was slowly added to the reaction mixture, which was warmed to room temperature and stirred for 16h at room temperature. The reaction mixture was concentrated, dissolved in ethyl acetate and washed with a saturated aqueous solution of sodium bicarbonate, then brine. The

organics were concentrated to a solid, which was triturated in a ethyl acetate/hexane solution (1:9; 50 mL). The precipitate was collected by vacuum filtration.
Yield: 72%

^{1}HNMR (400MHz, $CDCl_3$) δ 8.23 (brs, 1H), 7.41 (s, 4H), 7.20 (m, 1H), 6.96 (m, 2H), 6.86 (m, 1H), 5.58 (s, 1H), 3.97 (brs, 2H), 3.79 (brs, 2H), 3.66 (brs, 2H), 3.38 (brm, 4H), 2.05 (m, 2H), 1.68 (m, 2H), 1.48 (s, 9H), 1.22 (t, 3H)
Mass Spectral Analysis *m/z* = 588.5 $(M+H)^+$

[0971] Preparation of **41.19**:

To a suspension of **41.18** (1.0 g, 1.70 mmol, 1.0 eq) in methanol (30 mL) was added potassium carbonate (0.71 g, 5.11 mmol, 3.0 eq). The reaction was stirred for 48h at room temperature and concentrated. Water was added to the mixture and the product was extracted with ethyl acetate. The organics were combined and concentrated to a solid, which was triturated in hexane and collected by vacuum filtration.
Yield: 72%

^{1}HNMR (400MHz, $CDCl_3$) δ 7.82 (d, 1H), 7.40 (m, 2H), 7.19 (m, 1H), 6.95 (m, 2H), 6.85 (m, 2H), 5.58 (s, 1H), 3.86 (brs, 2H), 3.56 (q, 2H), 3.34 (brs, 2H), 2.89 (t, 1H), 2.70 (q, 1H), 2.05 (m, 2H), 1.68 (m, 2H), 1.48 (s, 11H), 1.13 (t, 3H)
Mass Spectral Analysis *m/z* = 492.5 $(M+H)^+$

[0972] Preparation of **41.20**:

To a solution of **41.19** (0.90 g, 1.83 mmol, 1.0 eq) and triethylamine (0.77 mL, 5.49 mmol, 3.0 eq) in tetrahydrofuran (20 mL) at 0°C under nitrogen was added **4.7** (0.44 g, 2.01 mmol, 1.1 eq). The ice bath was removed and the reaction was stirred at room temperature for 30 min. Water was added and the product was extracted with ethyl acetate. The organics were combined, concentrated and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 67%

^{1}HNMR (400MHz, $CDCl_3$) δ 7.86 (d, 2H), 7.67 (s, 1H), 7.38 (d, 2H), 7.19 (m, 1H), 6.94 (d, 2H), 6.85 (m, 1H), 5.58 (s, 1H), 3.86 (brs, 2H), 3.61 (m, 2H), 3.53 (s, 2H), 3.30 (brm, 4H), 2.05 (m, 2H), 1.68 (m, 2H), 1.48 (s, 9H), 1.46 (s, 9H), 1.14 (t, 3H)
Mass Spectral Analysis *m/z* = 592.6 $(M+H)^+$

[0973] Preparation of **41.21**:

To a solution of **41.20** (0.70 g, 1.18 mmol, 1.0 eq) in tetrahydrofuran (30 mL) under nitrogen was added sodium hydride (0.085 g, 3.55 mmol, 3.0 eq) and the mixture was stirred for 10 min at room temperature. Methyl iodide (0.22 mL, 3.55 mmol, 3.0 eq) was added to the reaction mixture, which was stirred for 16h at room temperature. The reaction mixture was carefully quenched with water and the product was extracted with ethyl acetate. The organics were concentrated and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 96%

^{1}HNMR (400MHz, $CDCl_3$) δ 7.40 (brm, 4H), 7.19 (m, 1H), 6.96 (m, 2H), 6.85 (m, 1H), 5.54 (s, 1H), 3.86 (brs, 2H), 3.70 (brs, 2H), 3.48 (m, 1H), 3.32 (brs, 4H), 3.15 (brs, 2H), 3.07 (brs, 2H), 2.05 (m, 2H), 1.67 (m, 2H), 1.48 (s, 9H), 1.41 (s, 9H), 1.14 (brt, 3H)
Mass Spectral Analysis *m/z* = 606.7 $(M+H)^+$

[0974] Preparation of **41E**

To a solution of **41.21** (0.68 g, 1.12 mmol, 1.0 eq) in methylene chloride (10 mL) at 0°C under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (6.74 mL, 13.47 mmol, 12.0 eq). The reaction mixturewas warmed to room temperature and stirred for 16h at room temperature. The precipitate was collected by vacuum filtration.
Yield: 90%

^{1}HNMR (400MHz, DMSO d_6) δ 9.16 (brs, 2H), 8.97 (brs, 2H), 7.62 (m, 2H), 7.44 (d, 2H), 7.27 (m, 1H), 7.06 (d, 1H), 6.97 (m, 2H), 5.94 (s, 1H), 3.77 (brs, 2H), 3.34 (s, 3H), 3.20 (brm, 4H), 3.00 (brs, 4H), 2.06 (brm, 4H), 1.24 (brt, 3H)
Mass Spectral Analysis *m/z* = 406.8 $(M+H)^+$

Elemental analysis:
$C_{25}H_{31}N_3O_2$, 2HCl, $0.50H_2O$
Theory: %C 61.60; %H 7.03; %N 8.62; %Cl 14.55
Found: %C 61.45; %H 6.78; %N 8.64; %Cl 14.78

EXAMPLE 42A

[0975] Preparation of **42.1:**

To a solution of **21.6** (6.03 g , 13.0 mmol) and **1.7** (3.95 g, 13.0 mmol, 1 eq) in dimethoxyethane (DME) (125 mL) was added sequentially a 2N aqueous solution of sodium carbonate (19.5 mL, 39.0 mmol, 3 eq), lithium chloride (1.65 g, 39.0 mmol, 3 eq) and tetrakis(triphenylphosphine)palladium(0) (0.45 g, 0.39 mmol, 0.03 eq). The reaction mixture was evacuated for 2 min and then purged with argon and heated under reflux for 23h. The mixture was then cooled to room temperature and diluted with ethyl acetate (100 mL) and filtered through a 1 inch plug of celite. The cake was further washed with ethyl acetate, the organic layer was washed with water followed by brine and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 65%

^{1}H NMR (400MHz, $CDCl_3$) δ 8.50 (br.s, 1H), 7.71 (dd, 1H), 7.58 (dd, 1H), 7.15 (dt, 1H),
6.87-6.80 (m, 3H), 5.62 (br.s, 1H), 3.85-3.51 (m, 4H), 3.50-3.20 (m, 4H), 2.29-2.04 (m, 2H), 2.00-1.80 (m, 2H), 1.47 (s, 9H),1.29-1.14 (m, 6H)
Mass Spectral Analysis *m/z* = 492.39 $(M+H)^+$

[0976] Preparation of **42.2**:

42.1 (1 g, 2.03 mmol, 1 eq) was resolved using Chiral HPLC method:
Column: Chiral Technologies Chiralcel OD-H, 4.6 x 250mm
Mobile Phase: 90% Hexane / 0.2% Diisopropylethylamine 10% Ethanol
Flow: 1.0 mL min
Detector: UV 275 nm
Yield: 40%
Mass Spectral Analysis *m/z* = 492.36 $(M+H)^+$
Chiral HPLC Method: t_R = 6.611 min. (*ee* > 99%)

[0977] Preparation of **42A**:

Hydrochloric acid, 4M, in 1,4-dioxane (1.1 mL, 4.26 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **42.2** (0.38 g, 0.77 mmol, 1 eq) in anhydrous methanol (4 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.

Yield: 90%

^{1}H NMR (400MHz, DMSO d_6) δ 9.23 (br s, 2H), 8.56 (d, 1H), 7.89 (dd, 1H), 7.62 (d, 1H), 7.26 (m, 1H), 6.99 (d, 1H), 6.95 (m, 2H), 6.03 (s, 1H), 3.79 (br s, 2H), 3.46 (q, 2H), 3.29 (q, 2H), 3.21 (brs, 2H), 3.10 (br s, 1H), 2.26 (m, 2H), 2.17 (m, 1H), 1.95 (m, 2H), 1.79 (m, 1H), 1.17 (t, 3H), 1.11 (t, 3H)

Mass Spectral Analysis *m/z* = 392.3 $(M+H)^+$

Elemental analysis:

$C_{24}H_{29}N_3O_2$, 1.25HCl, 0.75 H_2O

Theory: %C 63.97; %H 7.10; %N 9.33, %Cl 9.83

Found: %C 63.78; %H 7.04; %N 9.17, %Cl 9.81

$[\alpha]_D^{25}$ = -1.93 (c. 0.01, MeOH)

EXAMPLE 42B

[0978] Preparation of **42.3**:

42.1 (1 g, 2.03 mmol, 1 eq) was resolved using Chiral HPLC method:

Column: Chiral Technologies Chiralcel OD-H, 4.6 x 250mm

Mobile Phase: 90% Hexane / 0.2% Diisopropylethylamine 10% Ethanol

Flow: 1.0 mL min

Detector: UV 275 nm

Yield: 40%

Mass Spectral Analysis *m/z* = 492.29 $(M+H)^+$

Chiral HPLC Method: t_R = 8.399 min. (*ee* > 99%)

[0979] Preparation of **42B**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (1.1 mL, 4.35 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **42.3** (0.39 g, 0.79 mmol, 1 eq) in anhydrous methanol (4 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.

Yield: 90%

^{1}H NMR (400MHz, DMSO d_6) δ 9.18 (br s, 2H), 8.56 (d, 1H), 7.87 (dd, 1H), 7.62 (d, 1H), 7.26 (m, 1H), 7.01 (d, 1H), 6.95 (m, 2H), 6.03 (s, 1H), 3.61 (br s, 2H), 3.46 (q, 2H), 3.29 (q, 2H), 3.22 (br s, 2H), 3.10 (br s, 1H), 2.56 (m, 2H), 2.17 (m, 1H), 1.95 (m, 2H), 1.79 (m, 1H), 1.17 (t, 3H), 1.11 (t, 3H)

Mass Spectral Analysis *m/z* = 392.30 $(M+H)^+$

Elemental analysis:

$C_{24}H_{29}N_3O_2$, 1.25HCl, 0.75 H_2O

Theory: %C 63.97; %H 7.10; %N 9.33, %Cl 9.83

Found: %C 64.04; %H 7.03; %N 9.18, %Cl 9.43

$[\alpha]_D^{25}$ = +0.57 (c. 0.01, MeOH)

EXAMPLE 42C

[0980] Preparation of **42C**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (1.38 mL, 5.50 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **42.1** (0.49 g, 1.00 mmol, 1 eq) in anhydrous methanol (5 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the suspension was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.

Yield: 90%

^{1}HNMR (400MHz, DMSO d_6) δ 9.44 (brs, 2H), 8.58 (d, 1H), 7.90 (dd, 1H), 7.62 (d, 1H), 7.26 (m, 1H), 7.01 (d, 1H), 6.93 (m, 2H), 6.04 (s, 1H), 3.48 (q, 2H), 3.30 (q, 2H),

3.15 (brm, 4H), 2.28 (brm, 2H), 2.16 (m, 1H), 1.97 (m, 2H), 1.81 (brm, 1H), 1.18 (t, 3H), 1.11 (t, 3H)
Mass Spectral Analysis *m/z* = 392.4 $(M+H)^+$

EXAMPLE 42D

[0981] Preparation of **42.4**:

A solution of **1.14** (5.58 g, 22.0 mmol), potassium acetate (5.89g, 60.0 mmol, 3 eq) and [1,1'bis(diphenylphosphino)ferrocene]palladium(II) chloride $Pd(dppf)Cl_2$ (0.44 g, 0.60 mmol, 0.03 eq) in anhydrous *N,N*-dimethylformamide (30 mL) was evacuated for 2 min and then purged with argon and heated to 85°C. A solution of **21.6** (9.27 g, 20.0 mmol) in anhydrous *N,N*-dimethylformamide (20 mL) was added to this reaction mixture and the resultant mixture was stirred at 85°C under argon for 22h. The mixture was then cooled to room temperature, *N,N*-dimethylformamide was removed under reduced pressure and o solution of the resultant residue in ethyl acetate (150 mL) was filtered through a plug of celite. The cake was further washed with ethyl acetate (50 mL), the organic layer was then washed with water (2 x 250 mL), brine and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 80%

^1H NMR (400MHz, $CDCl_3$):.δ 7.69 (dd, 1H), 7.10 (dt, 1H), 6.88 (dt,1H), 6.80 (d, 1H), 6.31 (s, 1H), 3.77-3.52 (m, 2H), 3.36-3.23 (m, 2H), 2.17-2.05 (m, 3H), 2.00 (m, 2H), 1.81-1.53 (m, 3H), 1.46 (s, 9H); 1.32 (s, 12H)

[0982] Preparation of **42.5**:

To a solution of **42.4** (7.94 g, 18.0 mmol, 1 eq) and **34.1a** (4.62 g, 18.0 mmol) in dimethoxyethane (DME) (130 mL) was added sequentially a 2N aqueous solution of sodium carbonate (27 mL, 54.0 mmol, 3 eq), lithium chloride (2.29 g, 54.0 mmol, 3 eq), and tetrakis(triphenylphosphine)palladium(0) (0.62 g, 0.54 mmol, 0.03 eq). The mixture was evacuated and then purged with argon and heated under reflux for 17h. The mixture was then cooled to room temperature and diluted with ethyl acetate (125 mL) and filtered through a 1 inch plug of celite. The cake was further washed with ethyl acetate, the organic layer was washed with water followed by brine and dried

over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 75%

^{1}H NMR (400MHz, $CDCl_3$) δ 8.65 (m, 1H), 7.70 (d, 1H), 7.41 (dd, 1H), 7.20-7.10 (m, 2H), 6.90-6.80 (m, 2H), 5.91 and 5.89 (s, 1H), 3.78-3.62 (m, 1H), 3.60-3.47 (m, 4H), 3.35-3.20 (m, 4H), 2.21-2.13 (m, 2H), 1.92-1.75 (m, 1H), 1.73-1.62 (m, 2H), 1.43 and 1.41 (s, 9H),1.27-1.15 (m, 6H)
Mass Spectral Analysis *m/z* = 492.37 $(M+H)^+$

[0983] Preparation of **42.6**:

42.5 (1 g, 2.03 mmol, 1 eq) was resolved using Chiral HPLC method:
Column: Chiral Technologies Chiralcel OD-H, 4.6 x 250mm
Mobile Phase: 90% Hexane / 0.2% Diisopropylethylamine 10% Ethanol
Flow: 1.0 mL min
Detector: UV 275 nm
Yield: 50%
Mass Spectral Analysis *m/z* = 492.84 $(M+H)^+$
Chiral HPLC Method: t_R = 9.178 min. (*ee* = 97.62%)

[0984] Preparation of **42D**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (1.40 mL, 5.59 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **42.6** (0.50 g, 1.02 mmol, 1 eq) in anhydrous methanol (5 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the suspension was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.
Yield: 99%
^{1}H NMR (400MHz, DMSO d_6) δ 9.21 (br s, 2H), 8.65 (d, 1H), 7.91 (dd, 1H), 7.60 (d, 1H), 7.29 (d, 1H), 7.25 (t, 1H), 6.98 (d, 1H), 6.92 (t, 1H), 6.18 (s, 1H), 4.23 (br s, 2H), 3.47 (m, 2H), 3.24 (m, 4H), 3.10 (m, 1H), 2.26 (m, 2H), 2.15 (m, 1H), 1.99 (m, 2H), 1.78 (m, 1H), 1.18 (br s, 3H), 1.10 (br s, 3H)

Mass Spectral Analysis m/z = 392.81 $(M+H)^+$

Elemental analysis:

$C_{24}H_{29}N_3O_2$, 1HCl, $1.25H_2O$

Theory: %C 63.99; %H 7.27; %N 9.33

Found: %C 63.90; %H 6.98; %N 9.14

$[\alpha]_D^{25}$ = -1.48 (c. 0.01, MeOH)

EXAMPLE 42E

[0985] Preparation of **42.7**:

42.5 (1 g, 2.03 mmol, 1 eq) was resolved using Chiral HPLC method:

Column: Chiral Technologies Chiralcel OD-H, 4.6 x 250mm

Mobile Phase: 90% Hexane / 0.2% Diisopropylethylamine 10% Ethanol

Flow: 1.0 mL min

Detector: UV 275 nm

Yield: 50%

Mass Spectral Analysis m/z = 492.84 $(M+H)^+$

Chiral HPLC Method: t_R = 12.364 min. (*ee* = 96.90%)

[0986] Preparation of **42E**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (1.40 mL, 5.59 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **42.7** (0.50 g, 1.02 mmol, 1 eq) in anhydrous methanol (5 mL). The reaction mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.

Yield: 99%

^{1}H NMR (400MHz, DMSO d_6) δ 9.27 (br s, 2H), 8.65 (d, 1H), 7.93 (dd, 1H), 7.61 (d, 1H), 7.28 (d, 1H), 7.25 (t, 1H), 6.98 (d, 1H), 6.92 (t, 1H), 6.18 (s, 1H), 4.40 (br s, 2H), 3.47 (m, 2H), 3.24 (m, 4H), 3.10 (m, 1H), 2.27 (m, 2H), 2.15 (m, 1H), 1.99 (m, 2H), 1.79 (m, 1H), 1.17 (br s, 3H), 1.10 (br s, 3H)

Mass Spectral Analysis m/z = 392.80 $(M+H)^+$

Elemental analysis:

$C_{24}H_{29}N_3O_2$, 1HCl, $1.25H_2O$

Theory: %C 63.99; %H 7.27; %N 9.33

Found: %C 64.02; %H 7.08; %N 9.11

$[\alpha]_D^{25} = -2.83$ (c. 0.01, MeOH)

EXAMPLE 42F

[0987] Preparation of **42F**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (1.38 mL, 5.50 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **42.5** (0.49 g, 1.00 mmol, 1 eq) in anhydrous methanol (5 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.

Yield: 99%

^{1}HNMR (400MHz, DMSO d_6) δ 9.42 (brs, 2H), 8.69 (d, 1H), 7.99 (dd, 1H), 7.67 (d, 1H), 7.26 (m, 2H), 7.00 (d, 1H), 6.93 (t, 1H), 6.21 (s, 1H), 3.48 (brs, 2H), 3.18 (brm, 6H), 2.28 (brm, 2H), 2.16 (m, 1H), 1.98 (m, 2H), 1.78 (brm, 1H), 1.14 (brd, 6H)

Mass Spectral Analysis $m/z = 392.4$ $(M+H)^+$

EXAMPLE 42G

[0988] Preparation of **42.8**:

To a solution of **42.4** (4.41 g, 10.0 mmol) and **35.8** (3.45 g, 9.50 mmol, 0.95 eq) in dimethoxyethane (DME) (60 mL) was added sequentially a 2N aqueous solution of sodium carbonate (15 mL, 30.0 mmol, 3 eq), lithium chloride (1.27 g, 30.0 mmol, 3 eq), and tetrakis(triphenylphosphine)palladium(0) (0.58 g, 0.50 mmol, 0.03 eq). The mixture was evacuated and then purged with argon and heated under reflux for 20h. The mixture was then cooled to room temperature and diluted with ethyl acetate (50 mL) and filtered through a 1 inch plug of celite. The cake was further washed with ethyl acetate; the organic layer was washed with brine, dried over sodium sulfate and concentrated. The crude product was triturated with a 10:1

hexane/ether mixture and the resultant colorless crystalline precipitate was collected by vacuum filtration. The filtrate was collected, concentrated and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 42%

^{1}H NMR (300MHz, $CDCl_3$) δ 7.22-7.16 (m, 2H), 7.13-7.07 (m, 1H), 7.03 (dd, 1H), 6.89-6.85 (m, 1H), 6.79-6.69 (m, 2H), 5.58 (s, 1H), 5.05 (s, 2H), 3.74-3.48 (m, 4H), 3.40-3.25 (m, 4H), 3.32 (s, 3H), 2.29-2.08 (m, 2H), 1.97-1.67 (m, 4H), 1.48 (s, 9H),1.32-1.12 (m, 6H)
Mass Spectral Analysis *m/z* = 551.45 $(M+H)^+$

[0989] Preparation of **42.9**:

42.8 (1 g, 1.82 mmol, 1 eq) was resolved using Chiral HPLC method:
Column: Chiral Technologies Chiralcel OD-H, 4.6 x 250mm
Mobile Phase: 90% Hexane / 0.2% Diisopropylethylamine 10% Isopropanol
Flow: 1.0 mL min
Detector: UV 275 nm
Yield: 30%
Mass Spectral Analysis *m/z* = 551.84 $(M+H)^+$
Chiral HPLC Method: t_R = 9.796 min. (*ee* = 97.60%)

[0990] Preparation of **42G**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (0.83 mL, 3.30 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **42.9** (0.33 g, 0.60 mmol, 1 eq) in anhydrous methanol (5 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.
Yield: 99%

^{1}H NMR (400MHz, DMSO d_6) δ 9.78 (s, 1H), 9.12 (br s, 2H), 7.13 (m, 2H), 6.89 (m, 2H), 6.83 (m, 2H), 6.69 (m, 1H), 5.73 (s, 1H), 3.42 (br s, 2H), 3.25 (br s, 5H), 3.09 (br s, 1H), 2.20 (m, 3H), 1.95 (m, 2H), 1.77 (m, 1H), 1.12 (br s, 6H)

Mass Spectral Analysis *m/z* = 407.7 $(M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_2O_3$, 1HCl

Theory: %C 67.78; %H 7.05; %N 6.32

Found: %C 67.50; %H 6.93; %N 6.18

$[\alpha]_D^{25}$ = +1.11 (c. 0.01, MeOH)

EXAMPLE 42H

[0991] Preparation of **42.10**:

42.8 (1 g, 1.82 mmol, 1 eq) was resolved using Chiral HPLC method:

Column: Chiral Technologies Chiralcel OD-H, 4.6 x 250mm

Mobile Phase: 90% Hexane / 0.2% Diisopropylethylamine 10% Isopropanol

Flow: 1.0 mL min

Detector: UV 275 nm

Yield: 30%

Mass Spectral Analysis *m/z* = 551.97 $(M+H)^+$

Chiral HPLC Method: t_R = 15.281 min. (*ee* = 98.30%)

[0992] Preparation of **42H**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (0.83 mL, 3.30 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **42.10** (0.33 g, 0.60 mmol, 1 eq) in anhydrous methanol (5 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.

Yield: 99%

^{1}H NMR (400MHz, DMSO d_6) δ 9.78 (s, 1H), 9.10 (br s, 2H), 7.13 (m, 2H), 6.89 (m, 2H), 6.83 (m, 2H), 6.69 (m, 1H), 5.73 (s, 1H), 3.42 (br s, 2H), 3.25 (br s, 5H), 3.09 (br s, 1H), 2.20 (m, 3H), 1.95 (m, 2H), 1.77 (m, 1H), 1.12 (br s, 6H)
Mass Spectral Analysis *m/z* = 407.8 $(M+H)^+$
Elemental analysis:
$C_{25}H_{30}N_2O_3$, 1HCl, $0.25H_2O$
Theory: %C 67.10; %H 7.10; %N 6.26
Found: %C 67.13; %H 7.04; %N 6.19
$[\alpha]_D^{25}$ = -5.36 (c. 0.01, MeOH)

EXAMPLE 42I

[0993] Preparation of **42I**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (1.38 mL, 5.50 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **42.8** (0.55 g, 1.00 mmol, 1 eq) in anhydrous methanol (5 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.
Yield: 99%
^{1}HNMR (400MHz, DMSO d_6) δ 9.81 (brs, 1H), 9.22 (brs, 2H), 7.14 (m, 2H), 6.90 (m, 2H), 6.82 (m, 2H), 6.69 (dd, 1H), 5.72 (s, 1H), 3.77 (brs, 3H), 3.42 (brs, 2H), 3.16 (brm, 3H), 2.20 (m, 3H), 1.95 (m, 2H), 1.76 (brm, 1H), 1.12 (brs, 6H)
Mass Spectral Analysis *m/z* = 407.4 $(M+H)^+$

EXAMPLE 43A

[0994] Preparation of **43.1**:

To a round bottomed flask was added successively **11.1** (7.60 g, 50.0 mmol) followed by pyrrolidine (8.3 mL, 100.0 mmol, 2 eq), **21.4** (10.66 g, 50.0 mmol) and a minimum amount of methanol used to wash any remaining material. The resultant reaction was heated to 80°C for 30 min to dissolve all solids. The mixture was then cooled to room temperature and diluted with ethyl acetate (50 mL). The mixture was

washed with a 1N aqueous solution of hydrochloric acid, water, brine and dried over sodium sulfate. The crude material was triturated with hexanes and then left to stand at room temperature over 2 days. A pale yellow solid was formed which was filtered, washed with hexanes and collected.
Yield: 65%

^{1}H NMR (400MHz, $CDCl_3$) δ 11.61 and 11.60 (s, 1H), 7.34 (t, 1H), 6.50-6.40 (m, 2H), 3.80-3.49 (m, 2H), 3.38-3.21 (m, 2H), 2.27-2.10 (m, 2H), 2.08-1.57 (m, 4H), 1.46 (s, 9H)

[0995] Preparation of **43.2**:

To a solution of **43.1** (41.69 g, 0.12 mol) and *N,N*-diisopropylethylamine (62.7 mL, 0.36 mol, 3 eq) in dichloromethane (200 mL) was added dropwise, **11.3** (27.5 mL, 0.36 mol, 3 eq) under argon. The resultant reaction mixture was heated under reflux for 16h then allowed to cool to room temperature. The mixture was concentrated to remove the majority of dichloromethane then diluted with ethyl acetate (200 mL) and washed with a 2N aqueous solution of hydrochloric acid until the aqueous layer was acidic. The organic layer was washed with brine and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 68%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.34 (t, 1H), 6.70 (d, 1H), 6.60 (d, 1H), 5.27 (s, 2H), 3.67-3.44 (m, 2H), 3.52 (s, 3H), 3.37-3.23 (m, 2H), 2.80-2.58 (m, 2H), 2.13-2.09 (m, 2H), 2.05-1.54 (m, 4H), 1.45 (s, 9H)

[0996] Preparation of **43.3**:

To a solution of **43.2** (32.11 g, 82.0 mmol) in tetrahydrofuran (275 mL) at -78°C under argon was added drop wise, a 1.0M solution of LiHMDS in tetrahydrofuran (95 mL). The mixture was stirred for 1h at -78°C. A solution of **1.4** (33.94 g, 1.16 eq) in tetrahydrofuran (175 mL) was added drop wise to the reaction mixture. The mixture was warmed slowly to room temperature and stirring was continued for a further 12h at room temperature. The mixture was then poured into ice water and the two phases were separated. The organic phase was washed with a

1N aqueous solution of hydrochloric acid, a 1N aqueous solution of sodium hydroxide, brine and dried over sodium sulfate. The crude product was used for the next step without further purification.
Yield: 87%.
^{1}H NMR (300MHz, CDCl$_3$) δ 7.14 (t, 1H), 6.77 (d, 1H), 6.55 (d, 1H), 5.48 (s, 1H), 5.21 (s, 2H), 3.78-3.43 (m, 2H), 3.49 (s, 3H), 3.33-3.20 (m, 2H), 2.27-2.13 (m, 2H), 2.11-1.95 (m, 1H), 1.88-1.57 (m, 3H), 1.48 (s, 9H)

[0997] Preparation of **43.4:**

To a solution of **43.3** (10.47 g , 20.0 mmol) in dimethoxyethane (DME) (175 mL) was added sequentially a 2N aqueous solution of sodium carbonate (30.0 mL, 60.0 mmol, 3 eq), lithium chloride (2.54 g, 60.0 mmol, 3 eq), **1.6** (4.20 g, 19.0 mmol, 0.95 eq) and tetrakis(triphenylphosphine)palladium(0) (0.69 g, 0.6 mmol, 0.03 eq). The reaction mixture was evacuated for 2 min and then purged with argon and heated under reflux for 18h. The mixture was then cooled to room temperature, diluted with ethyl acetate (120 mL) and filtered through a 1 inch plug of celite. The cake was further washed with ethyl acetate; the organic layer was washed with water followed by brine and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 60%

^{1}H NMR (300MHz, CDCl$_3$) δ 7.35-7.24 (m, 4H), 7.13 (t, 1H), 6.65 (d, 2H), 5.55 (s, 1H), 4.67 (s, 2H), 3.81-3.45 (m, 4H), 3.37-3.20 (m, 4H), 3.18 (s, 3H), 2.22-2.10 (m, 2H), 1.97-1.64 (m, 4H), 1.49 and 1.48 (s, 9H),1.30-1.04 (m, 6H)
Mass Spectral Analysis *m/z* = 551.50 $(M+H)^+$

[0998] Preparation of **43.5**:

43.4 (1 g, 1.81 mmol, 1 eq) was resolved using Chiral HPLC method:
Column: Chiral Technologies Chiralcel OD-H, 4.6 x 250mm
Mobile Phase: 90% Hexane / 0.2% Diisopropylethylamine 10% Ethanol
Flow: 1.0 mL min
Detector: UV 275 nm
Yield: 40%

Mass Spectral Analysis *m/z* = 551.49 $(M+H)^+$

Chiral HPLC Method: t_R = 5.305 min. (*ee* > 99%)

[0999] Preparation of **43A**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (1.0 mL, 4.09 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **43.5** (0.41 g, 0.74 mmol, 1 eq) in anhydrous methanol (4 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the reaction mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.

Yield: 99%

^{1}H NMR (400MHz, DMSO d_6) δ 9.49 (s, 1H), 9.14 (br s, 2H), 7.25 (s, 4H), 7.04 (t, 1H), 6.49 (d, 1H), 6.42 (d, 1H), 5.70 (s, 1H), 3.39 (s, 2H), 3.21 (br s, 4H), 3.11 (br s, 2H), 2.18 (m, 2H), 2.10 (m, 1H), 1.92 (m, 2H), 1.75 (m, 1H), 1.10 (br s, 6H)

Mass Spectral Analysis *m/z* = 407.3 $(M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_2O_3$, 1HCl, 1.75 H_2O

Theory: %C 63.28; %H 7.33; %N 5.90

Found: %C 63.36; %H 7.07; %N 5.71

$[\alpha]_D^{25}$ = +0.53 (c. 0.01, MeOH)

EXAMPLE 43B

[1000] Preparation of **43.6**:

43.4 (1 g, 1.81 mmol, 1 eq) was resolved using Chiral HPLC method:

Column: Chiral Technologies Chiralcel OD-H, 4.6 x 250mm

Mobile Phase: 90% Hexane / 0.2% Diisopropylethylamine 10% Ethanol

Flow: 1.0 mL min

Detector: UV 275 nm

Yield: 40%

Mass Spectral Analysis *m/z* = 551.43 $(M+H)^+$

Chiral HPLC Method: t_R = 6.361 min. (*ee* = 98.52%)

[1001] Preparation of **43B**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (1.1 mL, 4.59 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **43.6** (0.46 g, 0.83 mmol, 1 eq) in anhydrous methanol (5 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.

Yield: 99%

^{1}H NMR (400MHz, DMSO d$_6$) δ 9.49 (s, 1H), 9.13 (br s, 2H), 7.25 (s, 4H), 7.04 (t, 1H), 6.49 (d, 1H), 6.42 (d, 1H), 5.70 (s, 1H), 3.39 (br s, 2H), 3.22 (br s, 4H), 3.11 (br s, 2H), 2.18 (m, 2H), 2.11 (m, 1H), 1.92 (m, 2H), 1.75 (m, 1H), 1.11 (br s, 6H)

Mass Spectral Analysis *m/z* = 407.3 $(M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_2O_3$, 1HCl, 1.75 H_2O

Theory: %C 63.28; %H 7.33; %N 5.90

Found: %C 63.13; %H 7.14; %N 5.81

$[\alpha]_D^{25}$ = -1.43 (c. 0.01, MeOH)

EXAMPLE 43C

[1002] Preparation of **43C**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (1.38 mL, 5.50 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **43.4** (0.55 g, 1.00 mmol, 1 eq) in anhydrous methanol (5 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.

Yield: 99%

^{1}HNMR (400MHz, DMSO d$_6$) δ 9.49 (s, 1H), 9.13 (brs, 2H), 7.25 (s, 4H), 7.04 (t, 1H), 6.48 (d, 1H), 6.42 (d, 1H), 5.70 (s, 1H), 3.40 (brs, 2H), 3.16 (brm, 6H), 2.18 (brm, 2H), 2.10 (m, 1H), 1.90 (m, 2H), 1.75 (brm, 1H), 1.11 (brs, 6H)

Mass Spectral Analysis *m/z* = 407.4 $(M+H)^+$

EXAMPLE 43D

[1003] Preparation of **43.7:**

To a solution of **43.3** (6.81 g , 13.0 mmol) and **1.7** (3.95 g, 13.0 mmol, 1 eq) in dimethoxyethane (DME) (125 mL) was added sequentially a 2N aqueous solution of sodium carbonate (19.5 mL, 39.0 mmol, 3 eq), lithium chloride (1.65 g, 39.0 mmol, 3 eq) and tetrakis(triphenylphosphine)palladium(0) (0.45 g, 0.39 mmol, 0.03 eq). The reaction mixture was evacuated for 2 min and then purged with argon and heated under reflux for 20h. The mixture was then cooled to room temperature, diluted with ethyl acetate (100 mL) and filtered through a 1 inch plug of celite. The cake was further washed with ethyl acetate, the organic layer was washed with water followed by brine and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 59%

^{1}H NMR (300MHz, $CDCl_3$) δ 8.41 (br.s, 1H), 7.62 (dd, 1H), 7.57 (dd, 1H), 7.13 (t, 1H), 6.69 (d, 2H), 5.56 (br.s, 1H), 4.70 (s, 2H), 3.82-3.60 (m, 1H), 3.55 (q, 2H), 3.40 (q, 2H), 3.37-3.22 (m, 3H), 3.17 (s, 3H), 2.25-2.10 (m, 2H), 2.10-1.82 (m, 1H), 1.80-1.63 (m, 3H), 1.45 (s, 9H),1.29 (t, 3H), 1.16 (t, 3H)
Mass Spectral Analysis *m/z* = 552.50 $(M+H)^+$

[1004] Preparation of **43.8**:

43.7 (1 g, 1.81 mmol, 1 eq) was resolved using Chiral HPLC method:
Column: Chiral Technologies Chiralcel OD-H, 4.6 x 250mm
Mobile Phase: 90% Hexane / 0.2% Diisopropylethylamine 10% Ethanol
Flow: 1.0 mL min
Detector: UV 275 nm
Yield: 40%
Mass Spectral Analysis *m/z* = 552.47 $(M+H)^+$
Chiral HPLC Method: t_R = 6.387 min. (*ee* > 99%)

[1005] Preparation of **43D**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (0.9 mL, 3.48 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **43.8** (0.35 g, 0.63 mmol, 1 eq) in anhydrous methanol (4 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.

Yield: 80%

^{1}HNMR (400MHz, DMSO d_6) δ 9.75 (brs, 1H), 9.37 (brs, 2H), 8.45 (d, 1H), 7.77 (dd, 1H), 7.53 (d, 1H), 7.06 (t, 1H), 6.49 (m, 2H), 5.87 (s, 1H), 3.46 (q, 2H), 3.29 (q, 2H), 3.15 (brm, 4H), 2.22 (brm, 2H), 2.11 (m, 1H), 1.94 (brm, 2H), 1.78 (brm, 1H), 1.17 (t, 3H), 1.09 (t, 3H)

Mass Spectral Analysis *m/z* = 408.3 $(M+H)^+$

Elemental analysis:

$C_{24}H_{29}N_3O_3$, 2HCl, 1.75 H_2O

Theory: %C 56.31; %H 6.79; %N 8.21, %Cl 13.85

Found: %C 56.36; %H 6.73; %N 7.94, %Cl 13.59

$[\alpha]_D^{25}$ = +1.76 (c. 0.01, MeOH)

EXAMPLE 43E

[1006] Preparation of **43.9**:

43.7 (1 g, 1.81 mmol, 1 eq) was resolved using Chiral HPLC method:

Column: Chiral Technologies Chiralcel OD-H, 4.6 x 250mm

Mobile Phase: 90% Hexane / 0.2% Diisopropylethylamine 10% Ethanol

Flow: 1.0 mL min

Detector: UV 275 nm

Yield: 40%

Mass Spectral Analysis *m/z* = 552.42 $(M+H)^+$

Chiral HPLC Method: t_R = 7.915 min. (*ee* = 98.36%)

[1007] Preparation of **43E**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (0.9 mL, 3.69 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **43.9** (0.37 g, 0.67 mmol, 1 eq) in anhydrous methanol (4 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.

Yield: 74%

^{1}HNMR (400MHz, DMSO d_6) δ 9.72 (brs, 1H), 9.32 (brs, 2H), 8.44 (d, 1H), 7.75 (dd, 1H), 7.51 (d, 1H), 7.06 (t, 1H), 6.48 (m, 2H), 5.86 (s, 1H), 3.46 (q, 2H), 3.29 (q, 2H), 3.15 (brm, 4H), 2.22 (brm, 2H), 2.12 (m, 1H), 1.93 (brm, 2H), 1.78 (brm, 1H), 1.16 (t, 3H), 1.09 (t, 3H)

Mass Spectral Analysis *m/z* = 408.3 $(M+H)^+$

Elemental analysis:

$C_{24}H_{29}N_3O_3$, 2HCl, $2H_2O$

Theory: %C 55.82; %H 6.83; %N 8.14, %Cl 13.73

Found: %C 55.56; %H 6.71; %N 7.84, %Cl 13.38

$[\alpha]_D^{25}$ = -1.42 (c. 0.01, MeOH)

EXAMPLE 43F

[1008] Preparation of **43F**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (1.38 mL, 5.50 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **43.7** (0.55 g, 1.00 mmol, 1 eq) in anhydrous methanol (5 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.

Yield: 99%

^{1}HNMR (400MHz, DMSO d_6) δ 9.71 (brs, 1H), 9.31 (brs, 2H), 8.44 (d, 1H), 7.74 (dd, 1H), 7.51 (d, 1H), 7.06 (t, 1H), 6.48 (m, 2H), 5.86 (s, 1H), 3.46 (q, 2H), 3.29 (q, 2H), 3.15 (brm, 4H), 2.22 (brm, 2H), 2.11 (m, 1H), 1.93 (m, 2H), 1.78 (brm, 1H), 1.16 (t, 3H), 1.09 (t, 3H)

Mass Spectral Analysis $m/z = 408.4\ (M+H)^+$

EXAMPLE 44A

[1009] Preparation of **44.1**:

To a roud bottomed flas was added successively **1.1d** (13.87 g, 0.09 mol, 0.90 eq) followed by pyrrolidine (20.7 mL, 0.25 mol, 2.5 eq), **21.4** (21.33 g, 0.10 mol) and a minimum amount of methanol used to wash any remaining material. The resultant reaction mixture was heated to 80°C for 30 min to dissolve all solids. The mixture was then cooled to room temperature and diluted with ethyl acetate (100 mL). The mixture was washed with a 1N aqueous solution of hydrochloric acid, a 1N aqueous solution of sodium hydroxide, brine and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 64%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.47 (dd, 1H), 7.24-7.15 (m, 1H), 6.92 (dd, 1H), 3.77-3.48 (m, 2H), 3.37-3.23 (m, 2H), 2.82-2.62 (m, 2H), 2.22-2.11 (m, 2H), 2.02-1.57 (m, 4H), 1.47 (s, 9H)

[1010] Preparation of **44.2**:

To a solution of **44.1** (14.91 g, 42.7 mmol) in tetrahydrofuran (175 mL) at -78°C under argon was added drop wise, a 1.0M solution of LiHMDS in tetrahydrofuran (49 mL). The mixture was stirred for 1h at -78°C. A solution of **1.4** (17.51 g, 49.0 mmol, 1.15 eq) in tetrahydrofuran (100 mL) was added drop wise to the reacgtion mixture. The mixture was warmed slowly to room temperature and stirring was continued for a further 15h at room temperature. The mixture was then poured into ice water and the two phases were separated. The organic phase was washed with a 1N aqueous solution of hydrochloric acid, a 1N aqueous solution of sodium hydroxide, brine and dried over sodium sulfate. The crude product was used for the next step without further purification.

Yield: 100% (crude).

[1011] Preparation of **44.3:**

To a solution of **44.2** (6.50 g , 13.5 mmol) and **1.7** (3.95 g, 13.0 mmol, 1 eq) in dimethoxyethane (DME) (125 mL) was added sequentially a 2N aqueous solution of sodium carbonate (20.5 mL, 41.0 mmol, 3 eq), lithium chloride (1.72 g, 40.6 mmol, 3 eq) and tetrakis(triphenylphosphine)palladium(0) (0.47 g, 0.41 mmol, 0.03 eq). The reaction mixture was evacuated for 2 min, purged with argon and heated under reflux for 17h. The mixture was then cooled to room temperature, diluted with ethyl acetate (100 mL) and filtered through a 1 inch plug of celite. The cake was further washed with ethyl acetate, the organic layer was washed with water followed by brine and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 64%

^{1}H NMR (300MHz, $CDCl_3$) δ 8.52 (br.s, 1H), 7.72 (dd, 1H), 7.63 (dd, 1H), 6.61 (d, 1H), 5.69 (br.s, 1H), 3.84-3.52 (m, 4H), 3.43 (q, 2H), 3.38-3.25 (m, 2H), 2.24-2.00 (m, 2H), 1.82-1.65 (m, 4H), 1.47 (s, 9H),1.29 (t, 3H), 1.19 (t, 3H)
Mass Spectral Analysis *m/z* = 510.44 $(M+H)^+$

[1012] Preparation of **44.4**:

44.3 (1 g, 1.96 mmol, 1 eq) was resolved using Chiral HPLC method:
Column: Chiral Technologies Chiralcel OD-H, 4.6 x 250mm
Mobile Phase: 90% Hexane / 0.2% Diisopropylethylamine 10% Ethanol
Flow: 1.0 mL min
Detector: UV 275 nm
Yield: 40%
Mass Spectral Analysis *m/z* = 510.37 $(M+H)^+$
Chiral HPLC Method: t_R = 7.430 min. (*ee* > 99%)

[1013] Preparation of **44A**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (1.1 mL, 4.32 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **44.4** (0.40 g, 0.78

mmol, 1 eq) in anhydrous methanol (4 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.

Yield: 99%

^{1}HNMR (400MHz, DMSO d_6) δ 9.32 (brs, 2H), 8.59 (d, 1H), 7.92 (dd, 1H), 7.62 (d, 1H), 7.11 (m, 1H), 7.05 (m, 1H), 6.74 (dd, 1H), 6.13 (s, 1H), 3.47 (q, 2H), 3.30 (q, 2H), 3.15 (brm, 4H), 2.27 (brm, 2H), 2.15 (m, 1H), 1.96 (brm, 2H), 1.80 (brm, 1H), 1.18 (t, 3H), 1.11 (t, 3H)

Mass Spectral Analysis m/z = 410.80 $(M+H)^+$

Elemental analysis:

$C_{24}H_{28}FN_3O_2$, 1HCl, $1.5H_2O$

Theory: %C 60.95; %H 6.82; %N 8.88

Found: %C 60.93; %H 6.68; %N 8.73

$[\alpha]_D^{25}$ = -2.77 (c. 0.01, MeOH)

EXAMPLE 44B

[1014] Preparation of **44.5**:

44.3 (1 g, 1.96 mmol, 1 eq) was resolved using Chiral HPLC method:

Column: Chiral Technologies Chiralcel OD-H, 4.6 x 250mm

Mobile Phase: 90% Hexane / 0.2% Diisopropylethylamine 10% Ethanol

Flow: 1.0 mL min

Detector: UV 275 nm

Yield: 40%

Mass Spectral Analysis m/z = 510.97 $(M+H)^+$

Chiral HPLC Method: t_R = 11.689 min. (*ee* = 98.2%)

[1015] Preparation of **44B**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (1.1 mL, 4.32 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **44.5** (0.40 g, 0.78 mmol, 1 eq) in anhydrous methanol (4 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.

Yield: 80%

^{1}HNMR (400MHz, DMSO d_6) δ 9.30 (brs, 2H), 8.59 (d, 1H), 7.92 (dd, 1H), 7.62 (d, 1H), 7.12 (m, 1H), 7.05 (m, 1H), 6.74 (dd, 1H), 6.13 (s, 1H), 3.47 (q, 2H), 3.30 (q, 2H), 3.15 (brm, 4H), 2.27 (brm, 2H), 2.15 (m, 1H), 1.96 (brm, 2H), 1.80 (brm, 1H), 1.17 (t, 3H), 1.11 (t, 3H)

Mass Spectral Analysis m/z = 410.7 $(M+H)^+$

Elemental analysis:

$C_{24}H_{28}FN_3O_2$, 2HCl, $1H_2O$

Theory: %C 57.60; %H 6.45; %N 8.40

Found: %C 57.68; %H 6.32; %N 8.17

$[\alpha]_D^{25}$ = -1.50 (c. 0.01, MeOH)

EXAMPLE 44C

[1016] Preparation of **44C**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (1.38 mL, 5.50 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **44.3** (0.51 g, 1.00 mmol, 1 eq) in anhydrous methanol (5 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.

Yield: 99%

^{1}HNMR (400MHz, DMSO d_6) δ 9.36 (brs, 2H), 8.59 (d, 1H), 7.92 (dd, 1H), 7.62 (d, 1H), 7.12 (m, 1H), 7.05 (m, 1H), 6.74 (dd, 1H), 6.13 (s, 1H), 3.48 (q, 2H), 3.30 (q, 2H), 3.16 (brm, 4H), 2.27 (brm, 2H), 2.12 (m, 1H), 1.96 (m, 2H), 1.80 (brm, 1H), 1.18 (t, 3H), 1.12 (t, 3H)

Mass Spectral Analysis m/z = 410.41 $(M+H)^+$

EXAMPLE 44D

[1017] Preparation of **44.6**:

A solution of **1.14** (3.56 g, 14.0 mmol), potassium acetate (4.42 g, 45.0 mmol, 3 eq) and Pd(dppf)Cl_2 (0.33 g, 0.45 mmol, 0.03 eq) in anhydrous *N,N* dimethylformamide (25 mL) was evacuated for 2 min, purged with argon and heated to 85°C. A solution of **44.2** (7.22 g, 15.0 mmol) in anhydrous *N,N* dimethylformamide (15 mL) was added to this reaction mixture, which was stirred at 85°C under argon for 18h. The mixture was then cooled to room temperature. The *N,N* dimethylformamide was removed under reduced pressure. The resultant residue was dissolved in ethyl acetate (120 mL) and filtered through a plug of celite. The cake was further washed with ethyl acetate (35 mL), the organic layer was then washed with water, brine and dried over sodium sulfate. The crude product was used for the next step without further purification.

Yield: 64% (crude)

^{1}H NMR (400MHz, $CDCl_3$),. δ 7.13-7.05 (m, 1H), 6.90-6.76 (m, 2H), 6.25 (br.s,1H), 3.78-3.49 (m, 2H), 3.35-3.2 (m, 2H), 2.08-2.03 (m, 3H), 1.83-1.51 (m, 3H), 1.45 (s, 9H); 1.32 (s, 12H)

[1018] Preparation of **44.7:**

To a solution of **44.6** (4.37 g, 9.5 mmol, 1 eq) and **34.1a** (2.44 g, 9.5 mmol) in dimethoxyethane (DME) (75 mL) was added sequentially a 2N aqueous solution of sodium carbonate (14.25 mL, 28.5 mmol, 3 eq), lithium chloride (1.21 g, 28.5 mmol, 3 eq), and tetrakis(triphenylphosphine)palladium(0) (0.35 g, 0.54 mmol, 0.03 eq). The mixture was evacuated, purged with argon and heated under reflux for 22h. The mixture was then cooled to room temperature and diluted with ethyl acetate (80 mL) and filtered through a 1 inch plug of celite. The cake was further washed with ethyl acetate, the organic layer was washed with water followed by brine and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 70%

^{1}H NMR (400MHz, $CDCl_3$) δ 8.69 (br.s, 1H), 7.78 (dd, 1H), 7.45 (dd, 1H), 6.96 (dd, 1H), 6.92-6.85 (m, 2H), 5.98 and 5.97 (s, 1H), 3.82-3.53 (m, 4H), 3.38-3.25 (m, 4H), 2.25-2.03 (m, 2H), 1.96-1.65 (m, 4H), 1.47 and 1.45 (s, 9H),1.30-1.15 (m, 6H)
Mass Spectral Analysis *m/z* = 510.35 $(M+H)^+$

[1019] Preparation of **44.8**:

44.7 (1 g, 1.96 mmol, 1 eq) was resolved using Chiral HPLC method:
Column: Chiral Technologies Chiralcel OD-H, 4.6 x 250mm
Mobile Phase: 90% Hexane / 0.2% Diisopropylethylamine 10% Ethanol
Flow: 1.0 mL min
Detector: UV 275 nm
Yield: 30%
Mass Spectral Analysis *m/z* = 510.89 $(M+H)^+$
Chiral HPLC Method: t_R = 8.818 min. (*ee* = 98.98%)

[1020] Preparation of **44D**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (0.8 mL, 3.24 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **44.8** (0.30 g, 0.59 mmol, 1 eq) in anhydrous methanol (4 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.
Yield: 95%
^{1}HNMR (400MHz, DMSO d_6) δ 9.35 (brd, 2H), 8.67 (d, 1H), 7.95 (dd, 1H), 7.69 (d, 1H), 7.21 (dd, 1H), 7.10 (m, 1H), 7.03 (m, 1H), 6.31 (s, 1H), 3.49 (brm, 2H), 3.24 (brm, 5H), 3.09 (brs, 1H), 2.28 (brm, 2H), 2.15 (m, 1H), 1.98 (m, 2H), 1.79 (brm, 1H), 1.14 (brd, 6H)
Mass Spectral Analysis *m/z* = 410.8 $(M+H)^+$
Elemental analysis:
$C_{24}H_{28}FN_3O_2$, 1HCl, $1.75H_2O$
Theory: %C 60.37; %H 6.86; %N 8.80

Found: %C 60.32; %H 6.61; %N 8.56
$[\alpha]_D^{25}$ = -3.34 (c. 0.01, MeOH)

EXAMPLE 44E

[1021] Preparation of **44.9**:

44.7 (1 g, 1.96 mmol, 1 eq) was resolved using Chiral HPLC method:
Column: Chiral Technologies Chiralcel OD-H, 4.6 x 250mm
Mobile Phase: 90% Hexane / 0.2% Diisopropylethylamine 10% Ethanol
Flow: 1.0 mL min
Detector: UV 275 nm
Yield: 36%
Mass Spectral Analysis *m/z* = 510.87 $(M+H)^+$
^{1}HNMR (400MHz, DMSO d_6) δ 8.64 (m, 1H), 7.90 (m, 1H), 7.65 (d, 1H), 7.19 (m, 1H), 7.06 (m, 1H), 6.96 (m, 1H), 6.28 (s, 0.5H), 6.25 (s, 0.5H), 3.48 (brm, 4H), 3.28 (brm, 4H), 2.12-1.87 (brm, 4H), 1.72 (brm, 2H), 1.43 (s, 4.5H), 1.41 (s, 4.5H), 1.14 (brd, 6H)
Chiral HPLC Method: t_R = 11.120 min. (*ee* = 98.17%)

[1022] Preparation of **44E**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (1.0 mL, 3.89 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **44.9** (0.36 g, 0.71 mmol, 1 eq) in anhydrous methanol (4 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.
Yield: 99%
^{1}HNMR (400MHz, DMSO d_6) δ 9.46 (brd, 2H), 8.70 (d, 1H), 8.00 (dd, 1H), 7.72 (d, 1H), 7.21 (dd, 1H), 7.11 (m, 1H), 7.04 (m, 1H), 6.34 (s, 1H), 3.57 (s, 2H), 3.48 (m, 2H), 3.25 (m, 4H), 3.10 (m, 1H), 2.28 (m, 2H), 2.15 (m, 1H), 1.98 (m, 2H), 1.79 (m, 1H), 1.18 (m, 3H), 1.11 (m, 3H)
Mass Spectral Analysis *m/z* = 410.8 $(M+H)^+$
$[\alpha]_D^{25}$ = +1.87 (c. 0.01, MeOH)

EXAMPLE 44F

[1023] Preparation of **44F**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (1.38 mL, 5.50 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **44.7** (0.51 g, 1.00 mmol, 1 eq) in anhydrous methanol (5 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.

Yield: 99%

^{1}HNMR (400MHz, DMSO d_6) δ 9.39 (brd, 2H), 8.68 (d, 1H), 7.96 (dd, 1H), 7.69 (d, 1H), 7.21 (dd, 1H), 7.10 (m, 1H), 7.03 (m, 1H), 6.32 (s, 1H), 3.48 (brs, 2H), 3.18 (brm, 6H), 2.28 (brm, 2H), 2.15 (m, 1H), 1.97 (m, 2H), 1.80 (brm, 1H), 1.14 (brd, 6H)

Mass Spectral Analysis *m/z* = 410.4 $(M+H)^+$

EXAMPLE 45A

[1024] Preparation of **45.1**:

To a solution of **44.6** (4.44 g, 9.70 mmol) and **35.8** (3.45 g, 9.50 mmol, 0.98 eq) in dimethoxyethane (DME) (60 mL) was added sequentially a 2N aqueous solution of sodium carbonate (15 mL, 30.0 mmol, 3 eq), lithium chloride (1.27 g, 30.0 mmol, 3 eq), and tetrakis(triphenylphosphine)palladium(0) (0.56 g, 0.48 mmol, 0.03 eq). The mixture was evacuated, purged with argon and heated under reflux for 20h. The mixture was then cooled to room temperature, diluted with ethyl acetate (50 mL) and filtered through a 1 inch plug of celite. The cake was further washed with ethyl acetate; the organic layer was washed with brine and dried over sodium sulfate and concentrated. The crude product was triturated with a 10:1 hexane/ether mixture and the resultant colorless crystalline precipitate was filtered. The filtrate was collected, concentrated and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 64%

^{1}HNMR (400MHz, DMSO d_6) δ 7.26 (dd, 1H), 7.12 (s, 1H), 7.00 (m, 2H), 6.90 (m, 1H), 6.36 (dd, 1H), 5.85 (s, 0.5H), 5.83 (s, 0.5H), 5.14 (s, 1H), 5.13 (s, 1H), 3.44

(brm, 4H), 3.32-3.20 (brm, 7H), 2.10-1.82 (brm, 4H), 1.73 (brm, 2H), 1.42 (s, 4.5H), 1.40 (s, 4.5H), 1.13 (brd, 6H)
Mass Spectral Analysis *m/z* = 569.43 $(M+H)^+$

[1025] Preparation of **45.2**:

45.1 (1 g, 1.76 mmol, 1 eq) was resolved using Chiral HPLC method:
Column: Chiral Technologies Chiralcel OD-H, 4.6 x 250mm
Mobile Phase: 90% Hexane / 0.2% Diisopropylethylamine 10% Isopropanol
Flow: 1.0 mL min
Detector: UV 275 nm
Yield: 25%
Mass Spectral Analysis *m/z* = 569.78 $(M+H)^+$
Chiral HPLC Method: t_R = 11.024 min. (*ee* = 97.96%)

[1026] Preparation of **45A**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (0.6 mL, 2.42 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **45.2** (0.25 g, 0.44 mmol, 1 eq) in anhydrous methanol (4 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.
Yield: 80%
^{1}HNMR (400MHz, DMSO d_6) δ 9.92 (s, 1H), 9.19 (brs, 2H), 7.15 (d, 1H), 7.00 (m, 1H), 6.93 (m, 2H), 6.84 (d, 1H), 6.42 (dd, 1H), 5.84 (s, 1H), 3.42 (brs, 2H), 3.23 (brm, 5H), 3.08 (brs, 1H), 2.20 (brm, 3H), 1.95 (m, 2H), 1.77 (brm, 1H), 1.12 (brs, 6H)
Mass Spectral Analysis *m/z* = 425.80 $(M+H)^+$
Elemental analysis:
$C_{25}H_{29}FN_2O_3$, 1HCl, $0.5H_2O$
Theory: %C 63.89; %H 6.65; %N 5.96
Found: %C 63.70; %H 6.51; %N 5.67
$[\alpha]_D^{25}$ = +1.87 (c. 0.01, MeOH)

EXAMPLE 45B

[1027] Preparation of **45.3**:

45.1 (1 g, 1.76 mmol, 1 eq) was resolved using Chiral HPLC method:
Column: Chiral Technologies Chiralcel OD-H, 4.6 x 250mm
Mobile Phase: 90% Hexane / 0.2% Diisopropylethylamine 10% Isopropanol
Flow: 1.0 mL min
Detecor: UV 275 nm
Yield: 25%
^{1}HNMR (400MHz, DMSO d_6) δ 7.26 (d, 1H), 7.13 (s, 1H), 7.04 (d, 1H), 6.98 (m, 1H), 6.90 (m, 1H), 6.37 (dd, 1H), 5.85 (s, 0.5H), 5.83 (s, 0.5H), 5.14 (s, 1H), 5.13 (s, 1H), 4.12 (q, 2H), 3.46 (brm, 4H), 3.30-3.16 (brm, 5H), 2.14-1.84 (brm, 4H), 1.73 (brm, 2H), 1.41 (s, 4.5H), 1.40 (s, 4.5H), 1.13 (brd, 6H)
Mass Spectral Analysis *m/z* = 569.98 $(M+H)^+$
Chiral HPLC Method: t_R = 18.406 min. (*ee* = 98.27%)

[1028] Preparation of **45B**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (0.6 mL, 2.51 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **45.3** (0.26 g, 0.46 mmol, 1 eq) in anhydrous methanol (4 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.
Yield: 99%
^{1}H NMR (400MHz, DMSO d_6) δ 9.94 (br s, 1H), 9.23 (br s, 2H), 7.15 (d, 1H), 6.99 (m, 1H), 6.93 (m, 2H), 6.83 (d, 1H), 6.41 (dd, 1H), 5.83 (s, 1H), 3.42 (br s, 2H), 3.24 (m, 4H), 3.09 (m, 2H), 2.24 (m, 2H), 2.15 (m, 1H), 1.95 (m, 2H), 1.77 (m, 1H), 1.12 (br s, 6H)
Mass Spectral Analysis *m/z* = 425.8 $(M+H)^+$
$[\alpha]_D^{25}$ = -3.05 (c. 0.01, MeOH)

EXAMPLE 45C

[1029] Preparation of **45C**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (1.38 mL, 5.50 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **45.1** (0.57 g, 1.00 mmol, 1 eq) in anhydrous methanol (5 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.

Yield: 99%

^{1}HNMR (400MHz, DMSO d_6) δ 9.92 (brs, 1H), 9.20 (brs, 2H), 7.14 (d, 1H), 6.97 (m, 2H), 6.91 (s, 1H), 6.84 (d, 1H), 6.42 (dd, 1H), 5.84 (s, 1H), 3.64 (brs, 3H), 3.42 (brs, 2H), 3.18 (brm, 3H), 2.20 (m, 3H), 1.95 (m, 2H), 1.76 (brm, 1H), 1.12 (brs, 6H)

Mass Spectral Analysis $m/z = 425.4\ (M+H)^+$

EXAMPLE 45D

[1030] Preparation of **45.4**:

To a round bottomed flask was added successively **2.1** (15.21 g, 0.1 mol) followed by pyrrolidine (20.7 mL, 0.25 mol, 2.5 eq), **21.4** (21.33 g, 0.10 mol) and a minimum amount of methanol used to wash any remaining material. The resultant reaction was heated to 80°C for 30 min to dissolve all solids. The mixture was then cooled to room temperature and diluted with ethyl acetate (100 mL). The mixture was washed with a 1N aqueous solution of hydrochloric acid, water, brine and dried over sodium sulfate. The crude material was used for the next step without further purification.

Yield: 100% (crude)

[1031] Preparation of **45.5**:

To a cooled (0°C) and stirring solution of **45.4** (34.74 g, 0.10 mol) and imidazole (14.30 g, 0.21 mol, 2.1 eq) in anhydrous *N,N*-dimethylformamide (200 mL) was added drop wise, a solution of **2.3** (17.33 g, 0.12 mol, 1.2 eq) in *N,N*-dimethylformamide. The resultant mixture was allowed to warm to room temperature and stirring was continued for 16h at room temperature. The *N,N*-dimethylformamide was removed and the residue diluted with ethyl acetate. The organic solution was washed with water, brine and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 51%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.22 (d, 1H), 6.95 (dd, 1H), 6.80 (d, 1H), 3.72-3.44 (m, 2H), 3.33-3.21 (m, 2H), 2.75-2.58 (m, 2H), 2.20-2.07 (m, 2H), 2.02-1.52 (m, 4H), 1.43 (s, 9H), 0.94 (s, 9H), 0.15 (s, 6H)

[1032] Preparation of **45.6**:

To a solution of **45.5** (23.55 g, 51.0 mmol) in tetrahydrofuran (250 mL) at -78°C under argon was added drop wise, a 1.0M solution of LiHMDS in tetrahydrofuran (59 mL). The mixture was stirred for 1h at -78°C. A solution of **1.4** (21.08 g, 59.0 mmol, 1.16 eq) in tetrahydrofuran (175 mL) was added drop wise to the mixture, which was warmed slowly to room temperature. Stirring was continued for a further 15h at room temperature. The mixture was then poured into ice water and the two phases were separated. The organic phase was washed with a 1N aqueous solution of hydrochloric acid, a 1N aqueous solution of sodium hydroxide, brine and dried over sodium sulfate. The crude product was used for the next step without further purification.

Yield: 100% (crude)

^{1}H NMR (400MHz, $CDCl_3$) δ 7.13 (m, 1H), 6.75-6.68 (m, 2H), 5.58 (s, 1H), 3.78-3.50 (m, 2H), 3.37-3.20 (m, 2H), 2.27-2.04 (m, 3H), 1.97-1.62 (m, 3H), 1.47 (s, 9H), 0.98 (s, 9H), 0.19 (s, 6H)

[1033] Preparation of **45.7:**

To a solution of **45.6** (9.50 g, 16.0 mmol) and **1.7** (4.87 g, 16.0 mmol, 1 eq) in dimethoxyethane (DME) (165 mL) was added sequentially a 2N aqueous solution of sodium carbonate (24 mL, 48.0 mmol, 3 eq), lithium chloride (2.03 g, 48.0 mmol, 3 eq) and tetrakis(triphenylphosphine)palladium(0) (0.56 g, 0.48 mmol, 0.03 eq). The reaction mixture was evacuated for 2 min, purged with argon and heated under reflux for 23h. The mixture was then cooled to room temperature, diluted with ethyl acetate (150 mL) and filtered through a 1 inch plug of celite. The cake was further washed with ethyl acetate. The organic layer was washed with water followed by brine and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 47%

^{1}H NMR (300MHz, $CDCl_3$) δ 8.46 (br.s, 1H), 7.77-7.72 (m, 1H), 7.51 (dd, 1H), 6.87-6.81 (m, 1H), 6.76 (dd, 1H), 6.35 (m, 1H), 5.62 and 5.61 (s, 1H), 3.76-3.55 (m, 2H), 3.51 (q, 2H), 3.35 (q, 2H), 3.31-3.19 (m, 2H), 2.19-2.02 (m, 2H), 1.86-1.55 (m, 4H), 1.44 and 1.43 (s, 9H),1.26-1.17 (m, 3H), 1.14 (t, 3H)

Mass Spectral Analysis *m/z* = 508.37 $(M+H)^+$

[1034] Preparation of **45.8**:

45.7 (1 g, 1.97 mmol, 1 eq) was resolved using Chiral HPLC method:

Column: Chiral Technologies Chiralcel OD-H, 4.6 x 250mm

Mobile Phase: 90% Hexane / 0.2% Diisopropylethylamine 10% Ethanol

Flow: 1.0 mL min

Detector: UV 275 nm

Yield: 40%

^{1}H NMR (400MHz, DMSO d_6) δ 8.98 (s, 1H), 8.54 (d, 1H), 7.86 (m, 1H), 7.60 (dd, 1H), 6.77 (dd, 1H), 6.62 (dd, 1H), 6.34 (d, 1H), 5.96 (s, 0.5H), 5.92 (s, 0.5H), 3.47 (brm, 4H), 3.30 (brm, 4H), 2.08-1.84 (brm, 4H), 1.70 (brm, 2H), 1.42 (s, 4.5H), 1.41 (s, 4.5H), 1.17 (t, 3H), 1.11 (t, 3H)

Mass Spectral Analysis *m/z* = 508.39 $(M+H)^+$

Chiral HPLC Method: t_R = 8.583 min. (*ee* = 97.58%)

[1035] Preparation of **45D**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (1.1 mL, 4.33 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **45.8** (0.40 g, 0.79 mmol, 1 eq) in anhydrous methanol (4 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.

Yield: 95%

^{1}H NMR (400MHz, DMSO d_6) δ 9.31 (brs, 2H), 8.56 (d, 1H), 7.89 (dd, 1H), 7.62 (d, 1H), 6.82 (d, 1H), 6.65 (dd, 1H), 6.36 (d, 1H), 6.00 (s, 1H), 3.48 (q, 2H), 3.30 (q, 2H), 3.15 (brm, 4H), 2.22 (brm, 2H), 2.14 (m, 1H), 1.94 (m, 2H), 1.78 (brm, 1H), 1.18 (t, 3H), 1.11 (t, 3H)

Mass Spectral Analysis *m/z* = 408.3 $(M+H)^+$

Elemental analysis:

$C_{24}H_{29}N_3O_3$, 1.9HCl, 1.6H_2O

Theory: %C 57.01; %H 6.80; %N 8.31, %Cl 13.32

Found: %C 57.24; %H 6.82; %N 8.24, %Cl 13.40

$[\alpha]_D^{25}$ = +1.71 (c. 0.01, MeOH)

EXAMPLE 45E

[1036] Preparation of **45.9**:

45.7 (1 g, 1.97 mmol, 1 eq) was resolved using Chiral HPLC method:

Column: Chiral Technologies Chiralcel OD-H, 4.6 x 250mm

Mobile Phase: 90% Hexane / 0.2% Diisopropylethylamine 10% Ethanol

Flow: 1.0 mL min

Detector: UV 275 nm

Yield: 35%

^{1}H NMR (400MHz, DMSO d_6) δ 8.99 (s, 1H), 8.54 (d, 1H), 7.86 (m, 1H), 7.60 (dd, 1H), 6.77 (dd, 1H), 6.62 (dd, 1H), 6.34 (d, 1H), 5.96 (s, 0.5H), 5.92 (s, 0.5H), 3.47 (brm, 4H), 3.30 (brm, 4H), 2.08-1.84 (brm, 4H), 1.70 (brm, 2H), 1.42 (s, 4.5H), 1.41 (s, 4.5H), 1.17 (t, 3H), 1.11 (t, 3H)

Mass Spectral Analysis *m/z* = 508.34 $(M+H)^+$

Chiral HPLC Method: t_R = 11.101 min. (*ee* > 99%)

[1037] Preparation of **45E**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (1.0 mL, 3.79 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **45.9** (0.35 g, 0.69

mmol, 1 eq) in anhydrous methanol (4 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.

Yield: 95%

^{1}H NMR (400MHz, DMSO d_6) δ 9.31 (brs, 2H), 8.56 (d, 1H), 7.89 (dd, 1H), 7.62 (d, 1H), 6.83 (d, 1H), 6.66 (dd, 1H), 6.36 (d, 1H), 6.00 (s, 1H), 3.48 (q, 2H), 3.30 (q, 2H), 3.16 (brm, 4H), 2.22 (brm, 2H), 2.13 (m, 1H), 1.94 (m, 2H), 1.78 (brm, 1H), 1.18 (t, 3H), 1.11 (t, 3H)

Mass Spectral Analysis m/z = 408.8 $(M+H)^+$

Elemental analysis:

$C_{24}H_{29}N_3O_3$, 1HCl, 2.25H_2O

Theory: %C 59.50; %H 7.18; %N 8.67

Found: %C 59.37; %H 7.05; %N 8.40

$[\alpha]_D^{25}$ = -2.98 (c. 0.01, MeOH)

EXAMPLE 45F

[1038] Preparation of **45F**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (1.38 mL, 5.50 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **45.7** (0.51 g, 1.00 mmol, 1 eq) in anhydrous methanol (5 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.

Yield: 99%

^{1}H NMR (400MHz, DMSO d_6) δ 9.38 (brs, 2H), 8.56 (d, 1H), 7.90 (dd, 1H), 7.63 (d, 1H), 6.83 (d, 1H), 6.66 (dd, 1H), 6.37 (d, 1H), 6.00 (s, 1H), 3.48 (q, 2H), 3.30 (q, 2H), 3.15 (brm, 4H), 2.23 (brm, 2H), 2.13 (m, 1H), 1.94 (m, 2H), 1.78 (brm, 1H), 1.18 (t, 3H), 1.12 (t, 3H)

Mass Spectral Analysis m/z = 408.4 $(M+H)^+$

EXAMPLES 46A, 46B

[1039] Preparation of **46.1**:

To a solution of **45.6** (8.91 g , 15.0 mmol) in dimethoxyethane (DME) (150 mL) was added sequentially a 2N aqueous solution of sodium carbonate (22.5 mL, 45.0 mmol, 3 eq), lithium chloride (1.91 g, 45.1 mmol, 3 eq), compound **45.6** (3.32 g, 15.0 mmol, 1 eq) and tetrakis(triphenylphosphine)palladium(0) (0.52 g, 0.45 mmol, 0.03 eq). The reaction mixture was evacuated for 2 min, purged with argon and heated under reflux for 42h. The mixture was then cooled to room temperature, diluted with ethyl acetate (120 mL) and the mixture was filtered through a 1 inch plug of celite. The cake was further washed with ethyl acetate, the organic layer was washed with water followed by brine and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 69%

^{1}H NMR (300MHz, $CDCl_3$) δ 7.37-7.29 (m, 4H), 6.75 (d, 1H), 6.64 (dd, 1H), 6.60-6.50 (m, 1H), 6.48 (d, 1H), 5.60 (s, 1H), 3.77-3.48 (m, 4H), 3.36-3.18 (m, 4H), 2.21-2.04 (m, 2H), 1.87-1.61 (m, 4H), 1.47 (s, 9H),1.31-1.08 (m, 6H)

[1040] Preparation of **46.2**:

To a solution of **46.1** (3.20 g, 6.32 mmol, 1.0 eq) in methylene chloride (100 mL) was added *N*,*N*-diisopropylethylamine (4.40 mL, 25.56 mmol, 4.0 eq) and then **11.3** (1.54 g, 18.95 mmol, 3.0 eq) was added drop wise to the reaction mixture. The reaction mixture was stirred for 48h at room temperature and then poured onto water (150 mL). The layers were separated and the aqueous was washed two times with methylene chloride (50 mL). The combined organics were washed with a 0.1N aqueous solution of hydrochloric acid, a saturated aqueous solution of sodium bicarbonate and brine. The organics were dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (eluent: methanol/methylene chloride mixtures of increasing polarity).

Yield: 50% Mass Spectral Analysis $m/z = 551.2\ (M+H)^+$

^{1}H NMR (400MHz, $CDCl_3$) δ 7.39 (m, 4H), 6.87 (m, 2H), 6.68 (d, 1H), 5.63 (s, 1H), 5.03 (s, 2H), 3.84-3.55 (brm, 4H), 3.43 (s, 3H), 3.31(brm, 4H), 2.16 (brm, 3H), 1.94-1.68 (brm, 3H), 1.49 (s, 4.5H), 1.47 (s, 4.5H), 1.21 (brd, 6H)

[1041] Preparation of **46.3** and **46.4**:

The racemic **46.2** was separated into pure enantiomers **46.3** and **46.4** by chiral chromatography.

Column: Chiral Technologies Chiralcel OD-H, 4.6 x 250mm
Mobile Phase: 90% Hexane / 0.2% Diisopropylethylamine 10% Isopropanol
Flow: 1.0 mL min
Detector: UV 275 nm

46.3: ^{1}HNMR (400MHz, $CDCl_3$) δ 7.39 (m, 4H), 6.87 (m, 2H), 6.68 (d, 1H), 5.63 (s, 1H), 5.03 (s, 2H), 3.84-3.52 (brm, 4H), 3.43 (s, 3H), 3.31(brm, 4H), 2.16 (brm, 3H), 1.93-1.68 (brm, 3H), 1.48 (s, 4.5H), 1.47 (s, 4.5H), 1.21 (brd, 6H)

46.4: ^{1}HNMR (400MHz, $CDCl_3$) δ 7.39 (m, 4H), 6.87 (m, 2H), 6.68 (d, 1H), 5.63 (s, 1H), 5.03 (s, 2H), 3.82-3.52 (brm, 4H), 3.43 (s, 3H), 3.31(brm, 4H), 2.17 (brm, 3H), 1.92-1.68 (brm, 3H), 1.48 (s, 4.5H), 1.47 (s, 4.5H), 1.21 (brd, 6H)

[1042] Preparation of **46A**:

To a solution of **46.3** (0.83 g, 1.51 mmol, 1.0 eq) in methanol (40 mL) under nitrogen was added a 4.0M solution of anhydrous hydrochloric acid in dioxane (3.80 mL, 15.1 mmol, 10.0 eq). The reaction was stirred for 16h at room temperature and concentrated. The crude product was purified by column chromatography (eluent: methanol/methylene chloride mixtures of increasing polarity). The resulting solid was triturated in diethyl ether and collected by vacuum filtration.

Yield: 93%
^{1}H NMR (400MHz, DMSO d_6) δ 9.19 (brs, 2H), 9.03 (s, 1H), 7.40 (q, 4H), 6.80 (d, 1H), 6.63 (dd, 1H), 6.40 (d, 1H), 5.86 (s, 1H), 3.45 (brs, 2H), 3.28-3.02 (brm, 6H), 2.20 (brm, 2H), 2.12 (m, 1H), 1.92 (brm, 2H), 1.76 (brm, 1H), 1.12 (brd, 6H)
Mass Spectral Analysis *m/z* = 407.4 $(M+H)^+$
Elemental analysis:
$C_{25}H_{30}N_2O_3$, 1HCl, $2H_2O$
Theory: %C 62.69; %H 7.36; %N 5.85
Found: %C 62.37; %H 7.20; %N 5.83
$[\alpha]_D$ = + 1.67 (c = 10.5 mg/mL, MeOH, 22.6°C)

[1043] Preparation of **46B**:

To a solution of **46.4** (0.86 g, 1.56 mmol, 1.0 eq) in methanol (40 mL) under nitrogen was added a 4.0M solution of anhydrous hydrochloric acid in dioxane (3.90 mL, 15.6 mmol, 10.0 eq). The reaction was stirred for 16h at room temperature and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: methanol/methylene chloride mixtures of increasing polarity). The resulting solid was triturated in diethyl ether and collected by vacuum filtration.

Yield: 85%

^{1}H NMR (400MHz, DMSO d_6) δ 9.22 (brs, 2H), 9.03 (s, 1H), 7.40 (q, 4H), 6.80 (d, 1H), 6.63 (dd, 1H), 6.40 (d, 1H), 5.86 (s, 1H), 3.45 (brs, 2H), 3.30-3.02 (brm, 6H), 2.20 (brm, 2H), 2.12 (m, 1H), 1.92 (brm, 2H), 1.76 (brm, 1H), 1.12 (brd, 6H)

Mass Spectral Analysis *m/z* = 407.4 $(M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_2O_3$, 1HCl, 2.3H_2O

Theory: %C 61.99; %H 7.41; %N 5.78

Found: %C 62.08; %H 7.38; %N 5.86

$[\alpha]_D$ = - 1.52 (c = 10.0 mg/mL, MeOH, 22.6°C)

EXAMPLE 46C

[1044] Preparation of compound **46.1:**

To a solution of **45.6** (8.91 g , 15.0 mmol) in dimethoxyethane (DME) (150 mL) was added sequentially a 2N aqueous solution of sodium carbonate (22.5 mL, 45.0 mmol, 3 eq), lithium chloride (1.91 g, 45.1 mmol, 3 eq) **1.6** (3.32 g, 15.0 mmol, 1 eq) and tetrakis(triphenylphosphine)palladium(0) (0.52 g, 0.45 mmol, 0.03 eq). The reaction mixture was evacuated for 2 min, purged with argon and heated under reflux for 42h. The mixture was then cooled to room temperature, diluted with ethyl acetate (120 mL) and filtered through a 1 inch plug of celite. The cake was further washed with ethyl acetate, the organic layer was washed with water followed by brine and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 69%

^{1}H NMR (400MHz, DMSO d_6) δ 8.94 (s, 1H), 7.39 (s, 4H), 6.75 (d, 1H), 6.60 (dd, 1H), 6.38 (d, 1H), 5.82 (s, 0.5H), 5.79 (s, 0.5H), 3.46 (brm, 4H), 3.24 (brm, 4H), 2.08-1.82 (brm, 4H), 1.68 (brm, 2H), 1.42 (s, 4.5H), 1.40 (s, 4.5H), 1.12 (brd, 6H)
Mass Spectral Analysis *m/z* = 507.59 $(M+H)^+$

[1045] Preparation of **46C**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (1.38 mL, 5.50 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **46.1** (0.51 g, 1.00 mmol, 1 eq) in anhydrous methanol (5 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the resulting oil and the mixture was stirred for 1 hour at room temperature. The resulting solids were isolated by vacuum filtration.
Yield: 99%
^{1}H NMR (400MHz, DMSO d_6) δ 9.21 (brs, 2H), 9.03 (brs, 1H), 7.40 (q, 4H), 6.80 (d, 1H), 6.63 (dd, 1H), 6.40 (d, 1H), 5.86 (s, 1H), 3.43 (brs, 2H), 3.16 (brm, 6H), 2.21 (brm, 2H), 2.12 (m, 1H), 1.92 (m, 2H), 1.76 (brm, 1H), 1.13 (brd, 6H)
Mass Spectral Analysis *m/z* = 407.4 $(M+H)^+$

EXAMPLE 47A

[1046] Preparation of **47.1**:

To a solution of **23.3a** (2.71 g, 6.20 mmol, 1.0 eq) and compound **1.7** (1.89 g, 6.20 mmol, 1.0 eq) in dimethoxyethane (DME) (65 mL) was added sequentially a 2N aqueous solution of sodium carbonate (9.30 mL, 18.60 mmol, 3.0 eq), lithium chloride (0.79 g, 18.60 mmol, 3.0eq) and tetrakis(triphenylphosphine)palladium(0) (0.23 g, 0.20 mmol, 0.03 eq). The reaction mixture was evacuated for 2 min. and purged with argon and heated under reflux for 19h. The mixture was then cooled to room temperature, diluted with ethyl acetate (100 mL) and filtered through a 1 inch plug of celite. The cake was washed with ethyl acetate. The organics were washed with water and brine, and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 61%

^{1}H NMR (400MHz, $CDCl_3$) δ 8.56 (brs, 1H), 7.75 (dd, 1H), 7.64 (d, 1H), 7.25-7.17 (m, 1H), 6.96-6.85 (m, 3H), 5.70 (brs, 1H), 3.94-3.81 (m, 1H), 3.68-3.54 (m, 3H), 3.48-3.33 (m, 3H), 2.46-2.39 (m, 1H), 2.00-1.80 (m, 1H), 1.82-1.69 (m, 1H), 1.47 (s, 9H), 1.28 (t, 3H), 1.19 (t, 3H)

[1047] Preparation of **47A**

To a solution of **47.1** (1.40 g, 3.02 mmol, 1.0 eq) in methylene chloride (40 mL) at 0°C under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (9.06 mL, 18.12 mmol, 6.0 eq). The reaction was warmed to room temperature and stirred for 48h at room temperature. Diethyl ether (15 mL) was added and stirring was continued for 10 min at room temperature. The solids were collected by vacuum filtration.

Yield: 92%

^{1}H NMR (400MHz, DMSO d_6) δ 9.92 (brs, 1H), 9.70 (brs, 1H), 8.61 (m, 1H), 7.92 (dd, 1H), 7.63 (dd, 1H), 7.30 (m, 1H), 6.99 (m, 3H), 6.13 (s, 1H), 3.57 (brm, 1H), 3.45 (brm, 4H), 3.31 (m, 3H), 2.42 (brm, 1H), 2.16 (m, 1H), 1.18 (t, 3H), 1.11 (t, 3H)
Mass Spectral Analysis $m/z = 364.7$ $(M+H)^+$

EXAMPLE 47B

[1048] Preparation of **47.2**:

A solution of bis(pinacolato)diboron (**1.14**) (4.06 g, 16.0 mmol, 1.14 eq), potassium acetate (4.12 g, 42.0 mmol, 3.0 eq) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (0.31 g, 0.42 mmol, 0.03 eq) in anhydrous *N*,*N*-dimethylformamide (35 mL) was evacuated for 2 min, purged with argon and heated to 85°C. A solution of **23.3a** (6.10 g, 14.0 mmol, 1.0 eq) in anhydrous *N*,*N*-dimethylformamide (20 mL) was added to this reaction mixture, which was stirred at 85°C under argon for 15h. The mixture was then cooled to room temperature and concentrated. The residue was dissolved in ethyl acetate (120 mL) and filtered through a plug of celite. The cake was washed with ethyl acetate. The organics were washed with water and brine, and dried over sodium sulfate. The crude product was used for the next step without further purification.

Yield: 100% (crude)

[1049] Preparation of **47.3**:

To a solution of **47.2** (7.94 g, 19.2 mmol, 1.0 eq) and compound **35.8** (4.72 g, 13.0 mmol, 0.68 eq) in dimethoxyethane (DME) (110 mL) was added sequentially a 2N aqueous solution of sodium carbonate (19.5 mL, 39.0 mmol, 3.0 eq), lithium chloride (1.65 g, 39.0 mmol, 3.0 eq), and tetrakis(triphenylphosphine)palladium(0) (0.45 g, 0.39 mmol, 0.03 eq). The mixture was evacuated, purged with argon and heated under reflux for 17h. The mixture was then cooled to room temperature, diluted with ethyl acetate (60 mL) and filtered through a 1 inch plug of celite. The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 28%
^{1}H NMR (300MHz, $CDCl_3$) δ 7.26-7.02 (m, 4H), 6.82-6.69 (m, 2H), 6.85 (d, H), 5.60 (s, 1H), 5.30 (s, 2H), 3.95-3.83 (m, 1H), 3.69-3.43 (m, 3H), 3.40-3.23 (m, 3H), 3.26 (s, 3H), 2.49-2.40 (m, 1H), 2.00-1.88 (m, 1H), 1.76-1.64 (brs, 1H), 1.47 (s, 9H), 1.31-1.10 (m, 6H)

[1050] Preparation of **47B**

To a solution of **47.3** (2.16 g, 4.13 mmol, 1.0 eq) in methanol (35 mL) at 0°C under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (12.4 mL, 24.80 mmol, 6.0 eq). The reaction mixture was warmed to room temperature and stirred for 48h at room temperature. The reaction was concentrated to a solid and triturated in a mixture of methylene chloride (5 mL) and diethyl ether (25 mL). The solids were collected by vacuum filtration.
Yield: 100% Mass Spectral Analysis $m/z = 379.8$ $(M+H)^+$
^{1}H NMR (400MHz, DMSO d_6) δ 9.85 (brs, 1H), 9.65 (brs, 1H), 9.53 (brs, 1H), 7.19 (m, 2H), 6.87 (m, 4H), 6.74 (d, 1H), 5.84 (s, 1H), 3.57 (brm, 1H), 3.43 (brm, 4H), 3.25 (brm, 3H), 2.42 (brm, 1H), 2.12 (brm, 1H), 1.12 (brs, 6H)

EXAMPLE 47C

[1051] Preparation of **47.4**:

To a roud bottomed flask was added successively 2',6'-dihydroxyacetophenone (**11.1**) (9.12 g, 60.0 mmol, 1.0 eq) followed by pyrrolidine (12.4 mL, 150.0 mmol, 2.5 eq), *N*-Boc-pyrrolidin-3-one (**23.1a**) (11.11 g, 60.0 mmol, 1.0 eq) and a minimum amount of methanol used to wash any remaining material. The reaction mixture was heated to 80°C for 30 min. to dissolve all solids. The mixture was then cooled to room temperature and diluted with ethyl acetate (80 mL). The mixture was washed with a 1N aqueous solution of hydrochloric acid, water and brine, and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 52%

^{1}H NMR (400MHz, $CDCl_3$) δ 11.50 (s, 1H), 7.30 (dd, 1H), 6.52-6.32 (m, 2H), 3.82-3.40 (m, 3H), 3.38-3.20 (m, 1H), 3.00-2.60 (m, 2H), 2.34-2.20 (m, 1H), 1.98-1.74 (m, 1H), 1.43 (s, 9H)

[1052] Preparation of **47.5**:

To a solution of **47.4** (5.15 g, 16.1 mmol, 1.0 eq) and *N*,*N*-diisopropylethylamine (8.5 mL, 48.8 mmol, 3.0 eq) in methylene chloride (30 mL) was added drop wise compound **11.3** (3.7 mL, 48.7 mmol, 3.0 eq) under argon. The reaction mixture was heated under reflux for 15h and then allowed to cool to room temperature. The mixture was concentrated, diluted with ethyl acetate (50 mL) and washed with a 2N aqueous solution of hydrochloric acid until the aqueous layer was acidic. The organic layer was washed with brine and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 52%

[1053] Preparation of **47.6**:

To a solution of **47.5** (3.07 g, 8.4 mmol, 1.0 eq) in tetrahydrofuran (25 mL) at -78°C under argon was added drop wise a 1.0M solution of LiHMDS in tetrahydrofuran (10.1 mL, 10.1 mmol, 1.2 eq). The mixture was stirred for 1h at -78°C. A solution of *N*-phenyltrifluoromethanesulfonimide (**1.4**) (3.32 g, 9.29 mmol, 1.11 eq) in tetrahydrofuran (20 mL) was added drop wise to the reaction mixture. The mixture was warmed slowly to room temperature and stirring was continued for a further 15h at room temperature. The mixture was poured into ice water and the two phases were separated. The organic layer was washed with a 1N aqueous solution of hydrochloric acid, a 1N aqueous solution of sodium hydroxide and brine, and dried over sodium sulfate. The crude product was used for the next step without further purification.

Yield: 100% (crude)

[1054] Preparation of **47.7**:

To a solution of **47.6** (2.34 g, 4.7 mmol, 1.0 eq) in dimethoxyethane (DME) (50 mL) was added sequentially a 2N aqueous solution of sodium carbonate (6.75 mL, 13.5 mmol, 3.0 eq), lithium chloride (0.57 g, 13.5 mmol, 3.0 eq), compound **1.6** (1.00 g, 4.5 mmol, 0.96 eq) and tetrakis(triphenylphosphine) palladium(0) (0.16 g, 0.14 mmol, 0.03 eq). The reaction mixture was evacuated for 2 min, purged with argon and heated under reflux for 20h. The mixture was cooled to room temperature, diluted with ethyl acetate (40 mL) and filtered through a 1 inch plug of celite. The cake was rinsed with ethyl acetate. The filtrate was washed with water and brine, and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 51%

^{1}H NMR (300MHz, $CDCl_3$) δ 7.36-7.29 (m, 4H), 7.18-7.09 (m, 1H), 6.72-6.62 (m, 2H), 5.65 (s, 1H), 4.68 (s, 2H), 3.92-3.74 (m, 2H), 3.68-3.19 (m, 6H), 3.16 (s, 3H), 2.43-2.31 (m, 1H), 2.00-1.85 (m, 1H), 1.49 (s. 4.5H), 1.47 (s, 4.5H), 1.30-1.04 (m, 6H)

[1055] Preparation of **47C**

To a solution of **47.7** (1.29 g, 2.47 mmol, 1.0 eq) in methanol (20 mL) under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (7.40 mL, 14.81 mmol, 6.0 eq). The reaction was stirred for 24h at room temperature.

The reaction was concentrated to an oil and stirred in a 1:1 mixture of methylene chloride and diethyl ether for 20 min. The solids that precipitated were collected by vacuum filtration.

Yield: 73%

^{1}H NMR (400MHz, DMSO d_6) δ 9.62 (s, 1H), 9.55 (brs, 1H), 9.44 (brs, 1H), 7.27 (m, 4H), 7.08 (t, 1H), 6.49 (m, 2H), 5.86 (s, 1H), 3.56-3.16 (brm, 8H), 2.36 (m, 1H), 2.07 (m, 1H), 1.11 (brs, 6H)

Mass Spectral Analysis *m/z* = 379.3 $(M+H)^+$

EXAMPLE 47D

[1056] Preparation of **47.8:**

To a solution of **47.6** (2.34 g, 4.7 mmol, 1.0 eq) and compound **1.7** (1.37 g, 4.5 mmol, 0.96 eq) in dimethoxyethane (DME) (60 mL) was added sequentially a 2N aqueous solution of sodium carbonate (6.75 mL, 13.5 mmol, 3.0 eq), lithium chloride (0.57 g, 13.5 mmol, 3.0 eq) and tetrakis(triphenylphosphine)palladium(0) (0.16 g, 0.14 mmol, 0.03 eq). The reaction mixture was evacuated for 2 min, purged with argon and heated under reflux for 20h. The mixture was then cooled to room temperature, diluted with ethyl acetate (100 mL) and filtered through a 1 inch plug of celite. The cake was rinsed with ethyl acetate. The filtrate was washed with water, brine, and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 54%

^{1}H NMR (400MHz, $CDCl_3$) δ 8.42 (brs, 1H), 7.57 (dd, 1H), 7.38 (d, 1H), 7.17-7.07 (m, 1H), 6.73-6.60 (m, 2H), 5.65 (brs, 1H), 4.69 (s, 2H), 3.91-3.74 (m, 1H), 3.65-3.49 (m, 4H), 3.48-3.28 (m, 3H), 3.14 (s, 3H), 2.43-2.30 (m, 1H), 1.99-1.85 (m, 1H), 1.49 (s, 4.5H), 1.47 (s, 4.5H), 1.21 (t, 3H), 1.14 (t, 3H)

[1057] Preparation of **47D**

To a solution of **47.8** (1.36 g, 2.60 mmol, 1.0 eq) in methanol (20 mL) under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (7.79 mL, 15.58 mmol, 6.0 eq). The reaction was stirred for 24h at room temperature. The reaction was concentrated to a foamy solid and dissolved in methylene chloride

(5 mL). With stirring, diethyl ether (20 mL) was added and the mixture was stirred for 10 min at room temperature. The resulting solid was collected by vacuum filtration.

Yield: 87%

^{1}H NMR (400MHz, DMSO d_6) δ 9.79 (brs, 1H), 9.57 (brs, 1H), 9.46 (brs, 1H), 8.46 (dd, 1H), 7.71 (dd, 1H), 7.49 (dd, 1H), 7.11 (t, 1H), 6.50 (m, 2H), 5.98 (s, 1H), 3.58-3.25 (brm, 8H), 2.38 (m, 1H), 2.10 (m, 1H), 1.16 (t, 3H), 1.08 (t, 3H)

Mass Spectral Analysis *m/z* = 380.4 $(M+H)^+$

EXAMPLE 47E

Preparation of **47.9**:

To a round bottomed flask was added successively 2',5'-dihydroxyacetophenone (**2.1**) (10.19 g, 67.0 mmol, 0.96 eq) followed by pyrrolidine (14.5 mL, 175 mmol, 2.5 eq), *N*-Boc-pyrrolidin-3-one (**23.1a**) (12.97 g, 70.0 mmol, 1.0 eq) and a minimum amount of methanol used to wash any remaining material. The resultant reaction was heated to 80°C for 30 min. to dissolve all solids. The mixture was then cooled to room temperature and diluted with ethyl acetate (65 mL). The mixture was washed with a 1N aqueous solution of hydrochloric acid, water and brine, and dried over sodium sulfate. The crude material was used without further purification.

Yield: 100% (crude)

[1058] Preparation of **47.10**:

To a cooled (0°C) and stirring solution of **47.9** (19.55 g, 61.2 mmol, 1.0 eq) and imidazole (8.78 g, 129.0 mmol, 2.11 eq) in anhydrous *N,N*-dimethylformamide (110 mL) was added drop wise a solution of *tert*-butyldimethylsilyl chloride (**2.3**) (10.25 g, 68.0 mmol, 1.11 eq) under argon. The mixture was allowed to warm to room temperature and was stirred for 17h at room temperature. The *N,N*-dimethylformamide was removed and the residue was diluted with ethyl acetate. The organic phase was washed with water and brine, and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 65%

^{1}H NMR (300MHz, $CDCl_3$) δ 7.24 (d, 1H), 7.01-6.91 (m, 1H), 6.81 (d, 1H), 3.82-3.44 (m, 3H), 3.37-3.24 (m, 1H), 2.93-2.71 (m, 2H), 2.32-2.22 (m, 1H), 1.95-1.78 (m, 1H), 1.42 (s, 9H), 0.98 (s, 9H), 0.20 (s, 6H)

[1059] Preparation of **47.11**:

To a solution of **47.10** (17.34 g, 40.0 mmol, 1.0 eq) in tetrahydrofuran (150 mL) at -78°C under argon was added drop wise a 1.0M solution of LiHMDS in tetrahydrofuran (48 mL, 48 mmol, 1.2 eq). The mixture was stirred for 1h at -78°C. A solution of *N*-phenyltrifluoromethanesulfonimide (**1.4**) (15.72 g, 44.00 mmol, 1.1 eq) in tetrahydrofuran (100 mL) was added dropwise to the mixture. The mixture was warmed slowly to room temperature and stirring was continued for a further 16h at room temperature. The mixture was then poured into ice water and the layers were separated. The organics were washed with a 1N aqueous solution of hydrochloric acid, a 1N aqueous solution of sodium hydroxide, brine, and dried over sodium sulfate. The crude product was used for the next step without further purification.
Yield: 100% (crude)

[1060] Preparation of compound **47.12**:

To a solution of **47.11** (9.56 g, 17.4 mmol, 1.0 eq) in dimethoxyethane (DME) (190 mL) was added sequentially a 2N aqueous solution of sodium carbonate (21.75 mL, 43.5 mmol, 3.0 eq), lithium chloride (1.84 g, 43.5 mmol, 3.0 eq), compound **1.6** (3.20 g, 14.5 mmol, 0.83 eq) and tetrakis(triphenylphosphine)palladium(0) (0.51 g, 0.44 mmol, 0.03 eq). The reaction mixture was evacuated for 2 min, purged with argon and heated under reflux for 42h. The mixture was then cooled to room temperature, diluted with ethyl acetate (200 mL) and filtered through a 1 inch plug of celite. The cake was rinsed with ethyl acetate. The organic layer was washed with water, brine, and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 44%

^{1}H NMR (300MHz, $CDCl_3$) δ 7.39-7.31 (m, 4H), 6.95-6.66 (m, 3H), 6.49 (m, 1H), 5.67 (s, 1H), 3.94-3.80 (m, 1H), 3.66-3.50 (m, 4H), 3.41-3.27 (m, 3H), 2.47-2.37 (m, 1H), 2.02-1.85 (m, 1H), 1.47 (s, 4.5H), 1.45 (s, 4.5H), (s, 9H), 1.36-1.10 (m, 6H)

[1061] Preparation of **47E**

To a solution of **47.12** (3.66 g, 7.65 mmol, 1.0 eq) in methanol (40 mL) under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (15.3 mL, 30.59 mmol, 4.0 eq). The reaction mixture was stirred for 24h, concentrated to a foam and diethyl ether (20 mL) was added. The mixture was sonicated and methylene chloride (10 mL) was added with stirring. The mixture was stirred for 20 min. and the solids were collected by vacuum filtration.

Yield: 85%

^{1}H NMR (400MHz, DMSO d_6) δ 9.66 (brs, 1H), 9.51 (brs, 1H), 9.14 (brs, 1H), 7.43 (m, 4H), 6.81 (d, 1H), 6.66 (dd, 1H), 6.43 (d, 1H), 5.98 (s, 1H), 3.56-3.20 (brm, 8H), 2.38 (m, 1H), 2.08 (m, 1H), 1.11 (brd, 6H)

Mass Spectral Analysis $m/z = 379.8\ (M+H)^+$

EXAMPLE 47F

[1062] Preparation of **47.13**:

To a solution of **47.11** (9.56 g, 17.4 mmol, 1.2 eq) and compound **1.7** (4.41 g, 14.5 mmol, 1.0 eq) in dimethoxyethane (DME) (165 mL) was added sequentially a 2N aqueous solution of sodium carbonate (21.75 mL, 43.5 mmol, 3.0 eq), lithium chloride (1.84 g, 43.5 mmol, 3.0 eq) and tetrakis(triphenylphosphine)palladium(0) (0.51 g, 0.44 mmol, 0.03 eq). The reaction mixture was evacuated for 2 min, purged with argon and heated under reflux for 19h. The mixture was then cooled to room temperature, diluted with ethyl acetate (150 mL) and filtered through a 1 inch plug of celite, which was further rinsed with ethyl acetate. The organic layer was washed with water, brine, and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 33%

^{1}H NMR (300MHz, $CDCl_3$) δ 8.49 (brs, 1H), 7.77 (dd, 1H), 7.55-7.41 (m, 2H), 6.80-6.67 (m, 2H), 6.39 (brs, 1H), 5.70 (s, 1H), 3.90-3.78 (m, 1H), 3.64-3.50 (m, 4H), 3.43-3.27 (m, 3H), 2.44-2.34 (m, 1H), 1.95-1.83 (m, 1H), 1.48 (s, 4.5H), 1.46 (s, 4.5H), 1.25 (t, 3H), 1.17 (t, 3H)

[1063] Preparation of **47F**

To a solution of **47.13** (2.65 g, 5.53 mmol, 1.0 eq) in methanol (30 mL) under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (16.6 mL, 33.15 mmol, 6.0 eq). The reaction was stirred for 24h at room temperature, concentrated to a foam and diethyl ether (20 mL) was added. The mixture was sonicated and methylene chloride (10 mL) was added with stirring. The mixture was stirred for 20 min. and the solids were collected by vacuum filtration.
Yield: 81%
^{1}H NMR (400MHz, DMSO d_6) δ 9.88 (brs, 1H), 9.62 (brs, 1H), 8.59 (m, 1H), 7.92 (dd, 1H), 7.58 (m, 1H), 6.83 (d, 1H), 6.70 (dd, 1H), 6.40 (d, 1H), 6.11 (s, 1H), 3.56-3.26 (brm, 8H), 2.40 (m, 1H), 2.11 (m, 1H), 1.18 (t, 3H), 1.11 (t, 3H)
Mass Spectral Analysis *m/z* = 380.7 $(M+H)^+$

EXAMPLE 48A

[1064] Preparation of **48.1**:

To a solution of **1.5f** (20.0 g, 41.71 mmol, 1.0 eq) in dioxane (300 mL) was added potassium carbonate (17.3g, 125 mmol, 3.0 eq), water (50 mL), **14.1** (6.7 g, 45.88 mmol, 1.1 eq) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (1.70 g, 2.09 mmol, 0.05 eq). The mixture was stirred at room temperature for 1h. Water (500 mL) was added and product was extracted with ethyl acetate. The organics were combined, concentrated and the crude product was purified by column chromatography (eluent: ethyl acetate/hexane = 3:7). Pure Fractions were concentrated to an oil, which was dissolved in diethyl ether (30 mL). Hexane was added to the stirred solution and the precipitated solid was collected by vacuum filtration.
Yield: 76%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.59 (d, 2H), 7.31 (d, 2H), 7.19 (t, 1H), 6.67 (dd, 1H), 6.47 (d, 1H), 5.54 (s, 1H), 3.80 (brs, 2H), 3.42 (s, 3H), 3.32 (brs, 2H), 2.02 (brd, 2H), 1.68 (m, 2H), 1.47 (s, 9H)

Mass Spectral Analysis *m/z* = 433.5 $(M+H)^+$

[1065] Preparation of **48.2**:

To a suspension of **48.1** (5.0 g, 11.56 mmol, 1.0 eq) in isopropanol (100 mL) was added **14.3** (1.50 g, 23.12 mmol, 2.0 eq), zinc bromide (1.30 g, 5.78 mmol, 0.50 eq) and water (50 mL). The reaction mixture was heated to reflux (105°C). Additional amount of water (10 mL) and isopropanol (30 mL) were added to the reaction mixture, which was heated for 5 days at 105°C. The reaction mixture was then cooled to room temperature and then cooled in an ice/brine bath. A 3N aqueous solution of hydrochloric acid (10 mL) was slowly added to the mixture until the pH ~1. The homogeneous mixture was stirred for 10 min at room temperature. Water (200 mL) and ethyl acetate were added to the mixture followed by diethyl ether (100 mL). The organics were concentrated to a solid. This solid was triturated in methanol (20 mL) and collected by vacuum filtration. The filtrate was concentrated and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity, then methanol/ethyl acetate mixtures of increasing polarity). The starting material (**48.1**, 1.28 g white solid) was isolated along with 983 mg of the desired product (**48.2**).

Yield: 58%

^{1}H NMR (400MHz, $CDCl_3$) δ 8.01 (brd, 2H), 7.30 (m, 2H), 7.15 (t, 1H), 6.64 (d, 1H), 6.42 (d, 1H), 5.50 (s, 1H), 3.81 (brd, 2H), 3.33 (brs, 5H), 1.99 (m, 2H), 1.63 (m, 2H), 1.50 (s, 9H)

Mass Spectral Analysis *m/z* = 474.9 $(M-H)^-$

[1066] Preparation of **48A**:

To a solution of **48.2** (0.434 g, 0.913 mmol, 1.0 eq) in methylene chloride (15 mL) at 0°C under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (2.74 mL, 5.48 mmol, 6.0 eq). The reaction was warmed to room temperature, stirred for 3 days at room temperature and diluted with diethyl ether (10 mL). The solids were collected by vacuum filtration.

Yield: 87%

^{1}H NMR (400MHz, DMSO d_6) δ 8.89 (brs, 2H), 8.02 (d, 2H), 7.42 (d, 2H), 7.28 (t, 1H), 6.75 (dd, 1H), 6.69 (d, 1H), 5.92 (s, 1H), 3.41 (s, 3H), 3.20 (brm, 4H), 2.02 (brm, 4H)

Mass Spectral Analysis *m/z* = 376.3 $(M+H)^+$

Elemental analysis:

$C_{21}H_{21}N_5O_2$, 1HCl, $1H_2O$

Theory: %C 58.67; %H 5.63; %N 16.29

Found: %C 58.79; %H 5.30; %N 16.12

EXAMPLES 48B, 48C

[1067] Preparation of **48.3** and **48.4**:

To a solution of **48.2** (2.20 g, 4.63 mmol, 1.0 eq) in *N,N*-dimethylformamide (20 mL) under nitrogen was added potassium carbonate (3.20 g, 23.13 mmol, 5.0 eq) and **2.8c** (0.87 mL, 13.88 mmol, 3.0 eq). The mixture was stirred for 4 days at room temperature. Water was added and product was extracted with ethyl acetate. The combined organics were washed with brine, concentrated and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity). The major product was **48.3** (1.36 g) and the minor product was **48.4** (365 mg).

Yield: 76% (combined yield)

48.3: ^{1}H NMR (400MHz, DMSO d_6) δ 7.99 (d, 2H), 7.34 (d, 2H), 7.23 (t, 1H), 6.66 (m, 2H), 5.83 (s, 1H), 4.43 (s, 3H), 3.64 (m, 2H), 3.39 (s, 3H), 3.27 (brs, 2H), 1.84 (m, 2H), 1.71 (m, 2H), 1.41 (s, 9H)

Mass Spectral Analysis *m/z* = 490.4 $(M+H)^+$

48.4: ^{1}H NMR (400MHz, DMSO d_6) δ 7.81 (d, 2H), 7.40 (d, 2H), 7.24 (t, 1H), 6.67 (m, 2H), 5.85 (s, 1H), 4.19 (s, 3H), 3.66 (m, 2H), 3.41 (s, 3H), 3.28 (brs, 2H), 1.84 (m, 2H), 1.72 (m, 2H), 1.42 (s, 9H)

Mass Spectral Analysis *m/z* = 490.6 $(M+H)^+$

[1068] Preparation of **48B**:

To a solution of **48.3** (0.40 g, 0.817 mmol, 1.0 eq) in methylene chloride (10 mL) at 0°C under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (1.63 mL, 3.27 mmol, 4.0 eq). The reaction was warmed to room temperature, stirred for 16h at room temperature and diluted with diethyl ether (10 mL). The solids were collected by vacuum filtration.

Yield: 84%

^{1}H NMR (400MHz, DMSO d_6) δ 8.88 (brs, 2H), 8.01 (d, 2H), 7.38 (d, 2H), 7.27 (t, 1H), 6.74 (d, 1H), 6.67 (d, 1H), 5.90 (s, 1H), 4.44 (s, 3H), 3.40 (s, 3H), 3.19 (m, 4H), 2.01 (m, 4H)

Mass Spectral Analysis *m/z* = 390.5 $(M+H)^+$

Elemental analysis:

$C_{22}H_{23}N_5O_2$, 1HCl

Theory: %C 62.04; %H 5.68; %N 16.44

Found: %C 62.05; %H 5.79; %N 16.51

[1069] Preparation of **48C**:

To a solution of **48.4** (0.36 g, 0.735 mmol, 1.0 eq) in methylene chloride (10 mL) at 0°C under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (1.47 mL, 2.94 mmol, 4.0 eq). The reaction was stirred for 16h at room temperature and diluted with diethyl ether (10 mL). The solids were collected by vacuum filtration.

Yield: 80%

^{1}H NMR (400MHz, DMSO d_6) δ 8.96 (brs, 2H), 7.82 (d, 2H), 7.43 (d, 2H), 7.28 (t, 1H), 6.75 (d, 1H), 6.69 (d, 1H), 5.92 (s, 1H), 4.19 (s, 3H), 3.42 (s, 3H), 3.19 (m, 4H), 2.06 (m, 4H)

Mass Spectral Analysis *m/z* = 390.4 $(M+H)^+$

EXAMPLE 48D

[1070] Preparation of **48.5**:

To a mixture of **1.14** (2.91 g, 11.47 mmol, 1.1 eq), potassium carbonate (2.16 g, 15.64 mmol, 1.5 eq), dichlorobis(triphenylphosphine)palladium (II) (0.22 g, 0.313 mmol, 0.03 eq) and triphenylphosphine (0.17 g, 0.626 mmol, 0.06 eq) in dioxane (75 mL) was added **1.5f** (5.0 g, 10.43 mmol, 1.0 eq). The reaction was heated at 50°C for 16h. Additional amount of dichlorobis(triphenylphosphine)palladium (II) (0.22 g) and triphenylphosphine (0.17 g) were added to the reaction mixture, which was heated for another 2 days at 50°C. The mixture was then cooled to room temperature. Water was added and the product was extracted with ethyl acetate. The organics were concentrated and purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 64%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.06 (t, 1H), 6.51 (dd, 1H), 6.45 (d, 1H), 5.82 (s, 1H), 3.81 (brs, 5H), 3.25 (brs, 2H), 1.93 (brd, 2H), 1.57 (m, 2H), 1.46 (s, 9H), 1.34 (s, 12H)

Mass Spectral Analysis *m/z* = 458.4 $(M+H)^+$

[1071] Preparation of **48.6**:

To a solution of **48.5** (1.96 g, 4.29 mmol, 1.0 eq) in dioxane (40 mL) was added potassium carbonate (1.78 g, 12.86 mmol, 3.0 eq), water (6 mL), **34.1c** (1.24 g, 4.71 mmol, 1.1 eq) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (0.17 g, 0.214 mmol, 0.05 eq). The reaction was stirred at room temperature for 16h. Water was added and the product was extracted with ethyl acetate. The organics were concentrated and purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 48%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.23 (d, 1H), 7.18 (t, 1H), 6.82 (d, 1H), 6.64 (dd, 1H), 6.50 (d, 1H), 5.70 (s, 1H), 3.78 (brs, 2H), 3.56 (m, 7H), 3.32 (brs, 2H), 2.00 (m, 2H), 1.67 (m, 2H), 1.47 (s, 9H), 1.26 (t, 6H)

Mass Spectral Analysis *m/z* = 513.4 $(M+H)^+$

[1072] Preparation of **48D**:

To a solution of **48.6** (1.06 g, 2.07 mmol, 1.0 eq) in methylene chloride (15 mL) at 0°C under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (4.14 mL, 8.27 mmol, 4.0 eq). The reaction mixture was warmed to room temperature and stirred for 16h, diluted with diethyl ether (10 mL) and stirred for an additional 30 min at room temperature. The solids were collected by vacuum filtration.

Yield: 86%

^{1}H NMR (400MHz, DMSO d_6) δ 9.02 (brs, 2H), 7.34 (m, 2H), 7.00 (d, 1H), 6.77 (m, 2H), 6.05 (s, 1H), 3.59 (s, 3H), 3.54 (brm, 4H), 3.23 (brm, 4H), 2.12-1.99 (brm 4H), 1.23 (brt, 6H)

Mass Spectral Analysis m/z = 413.7 $(M+H)^+$

Elemental analysis:

$C_{23}H_{28}N_2O_3S$, 1HCl, $1H_2O$

Theory: %C 59.36; %H 6.50; %N 5.86

Found: %C 59.15; %H 6.69; %N 6.00

EXAMPLE 48E

[1073] Preparation of **48.7**:

To a solution of **48.5** (2.0 g, 4.37 mmol, 1.0 eq) in dioxane (40 mL) was added potassium carbonate (1.81 g, 13.12 mmol, 3.0 eq), water (6 mL), **34.1d** (1.40 g, 4.81 mmol, 1.1 eq) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (0.18 g, 0.22 mmol, 0.05 eq). The reaction mixture was stirred at room temperature for 24h. Water was added and the product was extracted with ethyl acetate. The combined organics were concentrated and purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 49%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.17 (t, 1H), 7.07 (d, 1H), 6.79 (d, 1H), 6.63 (d, 1H), 6.50 (d, 1H), 5.70 (s, 1H), 4.00 (brs, 2H), 3.77 (brs, 2H), 3.57 (s, 3H), 3.32 (brs, 2H), 1.99 (m, 2H), 1.67 (m, 2H), 1.46 (s, 9H), 1.37 (brd, 12H)

Mass Spectral Analysis m/z = 541.8 $(M+H)^+$

[1074] Preparation of **48E**:

To a solution of **48.7** (1.16 g, 2.15 mmol, 1.0 eq) in methylene chloride (30 mL) at 0°C under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (4.29 mL, 8.58 mmol, 4.0 eq). The reaction mixture was warmed to room temperature, stirred for 16h and concentrated to a foam. Diethyl ether (15 mL) was added to the mixture, which was stirred for 1h at room temperature. The solids were collected by vacuum filtration.

Yield: 77%

^{1}H NMR (400MHz, DMSO d_6) δ 8.83 (brs, 2H), 7.14 (t, 1H), 6.96 (d, 1H), 6.78 (d, 1H), 6.57 (m, 2H), 5.83 (s, 1H), 3.82 (brs, 2H), 3.39 (s, 3H), 3.02 (brm, 4H), 1.94-1.80 (brm, 4H), 1.16 (brd, 6H)

Mass Spectral Analysis m/z = 441.4 $(M+H)^+$

Elemental analysis:

$C_{25}H_{32}N_2O_3S$, 1HCl, $1H_2O$

Theory: %C 60.65; %H 7.13; %N 5.66

Found: %C 61.02; %H 6.90; %N 5.57

EXAMPLE 48F

[1075] Preparation of **48.8**:

To a solution of **48.5** (1.50 g, 3.28 mmol, 1.0 eq) in dioxane (30 mL) was added potassium phosphate (1.04 g, 4.92 mmol, 1.5 eq), potassium bromide (0.43 g, 3.61 mmol, 1.1 eq), **34.1a** (0.93 g, 3.61 mmol, 1.1 eq) and tetrakis(triphenylphosphine) palladium(0) (0.38g, 0.328 mmol, 0.10 eq). The mixture was heated at 100°C for 6 days and then cooled to room temperature. Ethyl acetate and water were added and the layers were separated. The organics were concentrated and purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity). The resulting solid was triturated in diethyl ether and filtered. The filtrate, which contained the product, was concentrated.

Yield: 40%

^{1}H NMR (400MHz, $CDCl_3$) δ 8.60 (dd, 1H), 7.67 (m, 2H), 7.19 (m, 1H), 6.67 (dd, 1H), 6.48 (d, 1H), 5.87 (s, 1H), 3.82 (brs, 2H), 3.57 (brs, 2H), 3.44 (s, 3H), 3.32 (brs, 4H), 2.04 (brd, 2H), 1.72 (m, 2H), 1.47 (s, 9H), 1.22 (brd, 6H)

Mass Spectral Analysis *m/z* = 508.5 $(M+H)^+$

[1076] Preparation of **48F**:

To a solution of **48.8** (0.668 g, 1.32 mmol, 1.0 eq) in methylene chloride (15 mL) at 0°C under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (3.95 mL, 7.89 mmol, 6.0 eq). The reaction mixture was warmed to room temperature, stirred for 16h at room temperature and concentrated to a foam. Diethyl ether (15 mL) was added to the mixture and the solids were collected by vacuum filtration.

Yield: 75%

^{1}H NMR (400MHz, DMSO d_6) δ 9.11 (brd, 2H), 8.54 (s, 1H), 7.90 (d, 1H), 7.43 (d, 1H), 7.21 (t, 1H), 6.68 (dd, 1H), 6.61 (d, 1H), 6.07 (s, 1H), 3.41 (brm, 2H), 3.32 (s, 3H), 3.13 (brm, 6H), 1.98 (brm, 4H), 1.07 (brd, 6H)

Mass Spectral Analysis *m/z* = 408.4 $(M+H)^+$

Elemental analysis:

$C_{24}H_{29}N_3O_3$, 2HCl, $1H_2O$

Theory: %C 57.83; %H 6.67; %N 8.43; %Cl 14.23

Found: %C 57.98; %H 6.41; %N 8.29; %Cl 14.21

EXAMPLE 49A

[1077] Preparation of **49.2**:

Pyrrolidine (2.09 mL, 25.09 mmol, 1.0 eq) was added at 0°C to **1.2** (5.00 g, 25.09 mmol, 1.0 eq) and **49.1** (3.87 g, 25.09 mmol, 1.0 eq) in methanol (50 mL). The solution was stirred overnight at room temperature and then concentrated under reduced pressure. Ethyl acetate (100 mL) was added to the mixture. The organic mixture was washed with a 1N aqueous solution of hydrochloric acid, a 1N aqueous solution of sodium hydroxide, brine and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 40%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.56 (m, 1H), 6.92 (d, 1H), 6.83 (m, 1H), 3.69 (m, 2H), 3.12 (m, 2H), 2.83 (s, 2H), 1.86 (d, 2H), 1.63 (m, 2H), 1.40 (s, 9H)

Mass Spectral Analysis *m/z* = 336.14 $(M+H)^+$

[1078] Preparation of **49.3**:

To a solution of **49.2** (3.00 g, 8.95 mmol, 1 eq) in tetrahydrofuran (10 mL) at -78°C under nitrogen was added drop wise a 1M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (10.73 mL, 10.73 mmol, 1.2 eq). The mixture was stirred for 1 hour at -78°C. A solution of **1.4** (3.83 g, 10.73 mmol, 1.2 eq) in tetrahydrofuran (2 mL) was added drop wise to the mixture. The mixture was warmed slowly to room temperature and stirring was continued for 1 hour at room temperature. The reaction was then concentrated under reduced pressure. The crude product was used without further purification.

Yield: 85%

^{1}H NMR (400MHz, DMSO d_6) δ 7.38 (m, 1H), 6.92 (m, 1H), 6.74 (m, 1H), 6.23 (s, 1H), 3.71 (m, 2H), 3.17 (br s, 2H), 1.89 (m, 2H), 1.76 (m, 2H), 1.41 (s, 9H)

Mass Spectral Analysis m/z = 468.48 $(M+H)^+$

[1079] Preparation of **49.4**:

To a solution of **49.3** (1.00 g, 2.14 mmol, 1.0 eq) in dimethoxyethane (5 mL) was added sequentially a 2N aqueous solution of sodium carbonate (3.2 mL, 6.42 mmol, 3 eq), lithium chloride (0.27 g, 6.42 mmol, 3 eq), **1.6** (0.52 g, 2.35 mmol, 1.1 eq) and tetrakis(triphenylphosphine)palladium(0) (0.05 g, 0.04 mmol, 0.02 eq). The mixture was refluxed for 16 hours under nitrogen, then cooled to room temperature. Water (250 mL) was added to the mixture, which was extracted with ethyl acetate. The organic layer was further washed with brine and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 50%

Mass Spectral Analysis m/z = 495.36 $(M+H)^+$

[1080] Preparation of **49A**:

A 2M anhydrous solution of hydrochloric acid in diethyl ether (2.95 mL, 5.89 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **49.4** (0.53 g, 1.07 mmol, 1 eq) in anhydrous dichloromethane (6 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity).

Yield: 97%

^{1}H NMR (400MHz, DMSO d_6) δ 9.15 (m, 2H), 7.35 (m, 5H), 6.99 (d, 1H), 6.82 (m, 1H), 6.03 (s, 1H), 3.44 (br s, 2H), 3.19 (m, 6H), 2.07 (m, 4H), 1.10 (m, 6H)

Mass Spectral Analysis m/z = 395.3 $(M+H)^+$

Elemental analysis:

$C_{24}H_{27}FN_2O_2$, 1HCl, $1H_2O$

Theory: %C 64.21; %H 6.74; %N 6.24

Found: %C 64.27; %H 6.30; %N 6.28

EXAMPLE 49B

[1081] Preparation of **49.5**:

3.4k (270.8 mL, 3.24 mmol, 5.0 eq) was added at room temperature to a solution of **49.2** (100 mg, 0.65 mmol, 1.0 eq) in *N,N*-dimethylformamide (5 mL). The solution was stirred overnight at 80°C and then concentrated under reduced pressure. The crude product was used for the next step without further purification.
Yield: 90%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.23 (t, 1H), 6.38 (d, 1H), 6.25 (d, 1H), 3.69 (m, 2H), 3.10 (m, 6H), 2.70 (s, 2H), 1.94 (m, 2H), 1.87 (m, 4H), 1.62 (m, 2H), 1.39 (s, 9H)
Mass Spectral Analysis *m/z* = 387.25 $(M+H)^+$

[1082] Preparation of **49.6**:

To a solution of **49.5** (7.50 g, 19.40 mmol, 1 eq) in tetrahydrofuran (20 mL) at -78°C under nitrogen was added drop wise a 1M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (23.29 mL, 23.29 mmol, 1.2 eq). The mixture was stirred for 1 hour at -78°C. A solution of **1.4** (8.32 g, 23.29 mmol, 1.2 eq) in tetrahydrofuran (5 mL) was added drop wise to the mixture, which was warmed slowly to room temperature. Stirring was continued for 16 hours at room temperature. The reaction was then concentrated under reduced pressure and dissolved in ethyl acetate. The organic solution was washed with a 1N aqueous solution of hydrochloric acid, a 1N aqueous solution of sodium hydroxide, brine and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 50%

^{1}H NMR (400MHz, DMSO d_6) δ 7.15 (t, 1H), 6.56 (d, 1H), 6.50 (d, 1H), 5.91 (s, 1H), 3.61 (m, 2H), 3.21 (br s, 2H), 3.10 (m, 4H), 1.86 (m, 6H), 1.76 (m, 2H), 1.40 (s, 9H)
Mass Spectral Analysis *m/z* = 519.30 $(M+H)^+$

[1083] Preparation of **49.7**:

To a solution of **49.6** (1.00 g, 1.93 mmol, 1.0 eq) in dimethoxyethane (5 mL) was added sequentially a 2N aqueous solution of sodium carbonate (2.9 mL, 5.79

mmol, 3 eq), lithium chloride (0.25 g, 5.79 mmol, 3 eq), **1.6** (0.47 g, 2.12 mmol, 1.1 eq) and tetrakis(triphenylphosphine)palladium(0) (0.05 g, 0.04 mmol, 0.02 eq). The mixture was refluxed for 16 hours under nitrogen, then cooled to room temperature. Water (250 mL) was added to the mixture, which was extracted with ethyl acetate. The organic layer was further washed with brine and dried over sodium sulfate. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).
Yield: 10%

Mass Spectral Analysis *m/z* = 546.47 $(M+H)^+$

[1084] Preparation of **49B**:

A 2M anhydrous solution of hydrochloric acid in diethyl ether (0.4 mL, 0.81 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **49.7** (0.08 g, 0.15 mmol, 1 eq) in anhydrous dichloromethane (4 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity).
Yield: 97%
^{1}H NMR (400MHz, DMSO d_6) δ 9.01 (m, 2H), 7.26 (q, 4H), 7.15 (t, 1H), 6.55 (m, 2H), 5.89 (s, 1H), 3.54 (br s, 5H), 3.42 (br s, 2H), 3.18 (m, 6H), 2.76 (br s, 2H), 2.11 (m, 4H), 1.28 (br s, 2H), 1.08 (m, 6H)
Mass Spectral Analysis *m/z* = 446.8 $(M+H)^+$

EXAMPLES 49C, 49D

[1085] Preparation of **49.8**:

To a solution of **1.5d** (14.02 g, 30 mmol, 1 eq.) in *N,N*-dimethylformamide (150 mL) at 0°C was added successively potassium acetate (8.83 g, 90 mmol, 3 eq.), *bis*(pinacolato)diboron **1.14** (9.14 g, 36 mmol, 1.2 eq.) and 1,1'-*bis*(diphenylphosphino)ferrocene palladium(II) chloride complex with dichloromethane (658 mg, 0.9 mmol, 0.03 eq.). The reaction mixture was stirred at 100-110°C for 10h. The mixture was cooled to room temperature. Diethyl ether (300 mL) and water (300 mL) were added to the mixture, which was stirred for an additional 30 minutes at room temperature. The two phases were separated and the organic phase was washed with water (2 x 150 mL), brine (200 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 82 %

^{1}H NMR (400MHz, $CDCl_3$) δ 7.49 (dd, 1H), 6.78 (m, 2H), 6.34 (s, 1H), 3.95-3.72 (m, 2H), 3.37-3.15 (m, 2H), 1.97-1.87 (m, 2H), 1.66-1.53 (m, 2H), 1.46 (s, 9H), 1.34 (s, 12H)

Mass Spectral Analysis *m/z* = 446.31 $(M+H)^+$

Preparation of **49.9**:

To a solution of a 2M aqueous solution of potassium carbonate (3.08 mL, 6.15 mmol, 3 eq.) was added dioxane (20 mL), **35.8** (0.745 g, 2.05 mmol, 1 eq.), and **49.8** (1.37 g, 3.075 mmol, 1.5 eq.) successively. The reaction flask was purged with nitrogen and 1,1'-*bis*(diphenylphosphino)ferrocene palladium(II) chloride complex with dichloromethane (75 mg, 0.1 mmol, 0.05 eq) was added to the mixture. The mixture was stirred at room temperature for 1h and then heated at 55°C for 10h. The mixture was then cooled to room temperature. Water (50 mL) and ethyl acetate (150 mL) were added and the two phases were separated. The organic phase was washed with brine (100 mL) and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 94%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.23-7.17 (m, 2H), 7.06 (dd, 1H), 6.88-6.78 (m, 2H), 6.47 (dd, 1H), 5.59 (s, 1H), 5.07 (s, 2H), 3.97-3.77 (m, 2H), 3.63-3.47 (m, 2H), 3.42-3.22 (m, 7H), 2.11-2.01 (m, 2H), 1.73-1.61 (m, 2H), 1.48 (s, 9H)

Mass Spectral Analysis *m/z* = 555.47 $(M+H)^+$

[1086] Preparation of **49C**:

To a solution of **49.9** (1.2 g, 2.16 mmol, 1 eq.) in methanol (50 mL) was slowly added a 4M anhydrous solution of hydrogen chloride in dioxane (3.2 mL, 12.8

mmol, 6 eq.). The reaction mixture was stirred at room temperature for 10h. Additional amount of 4M anhydrous solution of hydrogen chloride in dioxane (2.16 mL, 8.64 mmol, 4 eq.) was slowly added to the mixture, which was stirred at room temperature for an additional 10h. The mixture was concentrated under reduced pressure. The resulting foamy solids were soaked in diethyl ether to give the fine powders, which were collected by filtration, washed with ethyl acetate and diethyl ether.

Yield: 90%

^{1}H NMR (400MHz, DMSO-d$_6$) δ 9.87 (s, 1H), 9.00-8.75 (m, 2H), 7.18 (d, 1H), 7.07-6.97 (m, 2H), 6.91-6.82 (m, 2H), 6.44 (dd, 1H), 5.89 (s, 1H), 3.53-3.10 (m, 8H), 2.15-2.05 (m, 2H), 2.03-1.92 (m, 2H), 1.20-1.03 (m, 6H)

Mass Spectral Analysis *m/z* = 411.7 (M+H)$^+$

Elemental analysis:

$C_{24}H_{27}FN_2O_3$, 1HCl, 0.5H_2O

Theory: %C 63.22; %H 6.41; %N 6.14

Found: %C 63.32; %H 6.34; %N 6.13

[1087] Preparation of **49D**:

To a stirred solution of **49C** (0.20 g, 0.45 mmol, 1 eq.) in methanol (20 mL) was added palladium [40 mg, 10 wt.% (dry basis) on activated carbon, 20% wt. eq]. The reaction mixture was stirred under hydrogen atmosphere using a hydrogen balloon at room temperature for 10h. The mixture was filtered through celite and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixture of increasing polarity).

Yield: 80%

^{1}H NMR (400MHz, DMSO-d$_6$) δ 9.87 (s, 1H), 8.85-8.55 (m, 2H), 7.08-6.89 (m, 3H), 6.84 (s, 1H), 6.75 (dd, 1H), 6.41 (dd, 1H), 4.47 (m, 1H), 3.50-2.91 (m, 8H), 2.15-1.74 (m, 6H), 1.20-1.11 (m, 6H)

Mass Spectral Analysis *m/z* = 413.7 (M+H)$^+$

EXAMPLE 50A

[1088] Preparation of **50.1**:

To a solution of **2.5** (15.00 g, 25.88 mmol, 1.0 eq) in dimethoxyethane (78 mL) was added sequentially a 2N aqueous solution of sodium carbonate (38.8 mL, 77.63 mmol, 3 eq), lithium chloride (3.29 g, 77.63 mmol, 3 eq), **31.1g** (3.47 g, 28.46 mmol, 1.1 eq) and palladium, 10 weight % (dry basis) on activated carbon, wet, (Degussa type E101) (0.28 g, 0.13 mmol, 0.005 eq). The mixture was refluxed for 6 days under nitrogen. The mixture was then cooled to room temperature and diluted with dichloromethane (350 mL). The mixture was then filtered through a celite plug. The filtrate was dried over sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (eluent: ethyl acetate/hexanes mixtures of increasing polarity).

Yield: 49%

^{1}H NMR (400MHz, DMSO d_6) δ 8.98 (br s, 1H), 7.42 (m, 3H), 7.33 (m, 2H), 6.79 (d, 1H), 6.58 (m, 1H), 6.38 (m, 1H), 5.76 (s, 1H), 3.68 (m, 2H), 3.23 (m, 2H), 1.82 (m, 2H), 1.65 (m, 2H), 1.41 (s, 9H)

Mass Spectral Analysis *m/z* = 394.46 $(M+H)^+$

[1089] Preparation of **50.2**:

To a solution of **50.1** (4.30 g, 10.9 mmol, 1.0 eq) in dichloromethane (20 mL) was added sequentially triethylamine (1.83 mL, 13.1 mmol, 1.2 eq) and **1.4** (4.29 g, 12.0 mmol, 1.1 eq). The mixture was stirred at room temperature overnight under nitrogen. The mixture was then concentrated under reduced pressure. Ethyl acetate (800 mL) was added. The organic mixture was washed with a 1N aqueous solution of sodium hydroxide, water, brine and dried over sodium sulfate. The crude product was used for the next step without further purification.

Yield: 87%

Mass Spectral Analysis *m/z* = 525.93 $(M+H)^+$

[1090] Preparation of **50.3**:

A solution of **50.2** (5.00 g, 9.51 mmol, 1.0 eq), triethylamine (2.9 mL, 20.93 mmol, 2.2 eq), palladium(II) acetate (0.21 g, 0.95 mmol, 0.1 eq) and 1,1'-bis(diphenylphosphino)ferrocene (1.05 g, 1.90 mmol, 0.2 eq) was stirred at 65°C under a carbon monoxide atmosphere for 4 days. The mixture was then cooled to room temperature and diluted with ethyl acetate (350 mL). The mixture was then filtered through a celite plug. The filtrate was washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: ethyl acetate/hexanes mixtures of increasing polarity).

Yield: 49%

^{1}H NMR (400MHz, DMSO d$_6$) δ 7.82 (m, 1H), 7.57 (m, 1H), 7.47 (m, 3H), 7.35 (m, 2H), 7.07 (d, 1H), 5.90 (s, 1H), 3.74 (s, 3H), 3.34 (m, 4H), 1.91 (m, 2H), 1.75 (m, 2H), 1.42 (s, 9H)

Mass Spectral Analysis *m/z* = 436.07 $(M+H)^+$

[1091] Preparation of **50A**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (1.6 mL, 6.31 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **50.3** (0.50 g, 1.15 mmol, 1 eq) in anhydrous methanol (5 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity).

Yield: 10%

^{1}H NMR (400MHz, DMSO d$_6$) δ 9.07 (m, 2H), 7.87 (m, 1H), 7.58 (d, 1H), 7.48 (m, 3H), 7.38 (m, 2H), 7.17 (d, 1H), 5.97 (s, 1H), 3.75 (s, 3H), 3.24 (m, 4H), 2.08 (m, 4H)

Mass Spectral Analysis *m/z* = 336.4 $(M+H)^+$

EXAMPLE 50B

[1092] Preparation of **50.4**:

To a solution of **50.3** (0.90 g, 2.07 mmol, 1.0 eq) in tetrahydrofuran (3 mL) and methanol (3 mL) was added a solution of lithium hydroxide monohydrate (0.48 g, 11.37 mmol, 5.5 eq) dissolved in water (3 mL). The reaction was stirred at room temperature overnight. The mixture was concentrated under reduced pressure. Water (100 mL) was added and any undissolved material was removed by filtration. A 6N aqueous solution of hydrochloric acid was added dropwise to the filtrate until the solution was acidic (pH = 2). The precipitate was collected by vacuum filtration. The crude product was further purified by column chromatography (eluent: ethyl acetate/hexanes mixtures of increasing polarity).

Yield: 40%

Mass Spectral Analysis $m/z = 420.31$ $(M-H)^-$

[1093] Preparation of **50B**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (1.11 mL, 4.44 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **50.4** (0.34 g, 0.81 mmol, 1 eq) in anhydrous methanol (4 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity).

Yield: 10%

^{1}H NMR (400MHz, DMSO d_6) δ 12.76 (br s, 1H), 9.17 (br s, 2H), 7.83 (m, 1H), 7.58 (d, 1H), 7.48 (m, 3H), 7.37 (d, 2H), 7.13 (d, 1H), 5.95 (s, 1H), 3.23 (m, 4H), 2.08 (m, 4H)

Mass Spectral Analysis $m/z = 322.1$ $(M+H)^+$

EXAMPLE 50C

[1094] Preparation of **50.5**:

O-Benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (0.10 g, 0.31 mmol, 1.1 eq) was added to a cooled (0°C) solution of **50.4** (0.12 g, 0.28 mmol, 1.0 eq), **1.12** (0.034 g, 0.31 mmol, 1.1 eq), and *N,N*-diisopropylethylamine (0.11 mL, 0.63 mmol, 2.2 eq) dissolved in acetonitrile (5 mL). The solution was stirred for 2 hours at room temperature and then concentrated under reduced pressure. Ethyl acetate (10 mL) and a saturated aqueous solution of sodium hydrogenocarbonate (10 mL) were added to the crude product and the resulting mixture was stirred for 20 minutes at room temperature. The phases were separated and the organic phase was washed with a saturated aqueous solution of sodium hydrogenocarbonate, brine dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 55%

Mass Spectral Analysis m/z = 477.43 $(M+H)^+$

[1095] Preparation of **50C**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (0.17 mL, 0.69 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **50.5** (60 mg, 0.13 mmol, 1 eq) in anhydrous methanol (4 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity).

Yield: 54%

^{1}H NMR (400MHz, DMSO d_6) δ 9.12 (br s, 2H), 7.45 (m, 3H), 7.36 (m, 2H), 7.27 (m, 1H), 7.09 (d, 1H), 6.89 (d, 1H), 5.93 (s, 1H), 3.23 (br s, 8H), 2.07 (m, 4H), 1.02 (br s, 6H)

Mass Spectral Analysis m/z = 377.7 $(M+H)^+$

EXAMPLE 50D

[1096] Preparation of **50D**:

A 4M anhydrous solution of hydrochloric acid in 1,4-dioxane (1.7 mL, 6.99 mmol, 5.5 eq) was added drop wise to a cooled (0°C) solution of **50.1** (0.50 g, 1.27 mmol, 1 eq) in anhydrous methanol (3 mL). The mixture was warmed to room temperature and stirring was continued for an additional 16 hours at room temperature. The reaction mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity).

Yield: 55%

^{1}H NMR (400MHz, DMSO d_6) δ 9.04 (s, 3H), 7.46 (m, 3H), 7.35 (m, 2H), 6.84 (d, 1H), 6.64 (d, 1H), 6.42 (s, 1H), 5.83 (s, 1H), 3.16 (m, 4H), 2.07 (m, 2H), 1.96 (m, 2H)

Mass Spectral Analysis m/z = 294.1 $(M+H)^+$

Elemental analysis:

$C_{19}H_{19}NO_2$, 1HCl, 1H_2O

Theory: %C 65.61; %H 6.38; %N 4.03

Found: %C 65.89; %H 6.29; %N 3.95

EXAMPLES 51A, 51B, 51C

[1097] Preparation of **51.2**:

To a solution of **51.1** (2.0 g, 9.38 mmol, 1.0 eq) in methanol (50 mL) was added **1.1a** (1.13 mL, 9.38 mmol, 1.0 eq) and pyrrolidine (2.11 mL, 25.51 mmol, 2.72 eq). The reaction mixture was refluxed for 16h and then concentrated. The crude product was dissolved in ethyl acetate. The organic solution was washed with water, with a 1N aqueous solution of sodium hydroxide and then brine. The organics were concentrated and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 29%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.88 (dd, 1H), 7.50 (m, 1H), 7.02 (t, 1H), 6.96 (d, 1H), 4.38 (brs, 1H), 3.96 (brd, 1H), 3.30 (brt, 1H), 2.66 (q, 2H), 2.05 (m, 2H), 1.65 (m, 2H), 1.46 (s, 9H), 1.28 (d, 3H)

Mass Spectral Analysis *m/z* = 332.3 $(M+H)^+$

[1098] Preparation of **51.3**:

To a solution of **51.2** (0.89 g, 2.69 mmol, 1.0 eq) in tetrahydrofuran (30 mL) at -78°C under nitrogen was added drop wise a 1.0M solution of LiHMDS in tetrahydrofuran (3.22 mL, 3.22 mmol, 1.2 eq). The mixture was stirred for 1h at -78°C. A solution of **1.4** (1.15 g, 3.22 mmol, 1.2 eq) in tetrahydrofuran (10 mL) was added drop wise to the mixture. The mixture was warmed slowly to room temperature and stirring was continued for 5h at room temperature. Ice was added to the reaction mixture, which was stirred for 5 min. Ethyl acetate and a 1N aqueous solution of sodium hydroxide were added to the mixture and the layers were separated. The organics were washed with a 1N aqueous solution of sodium hydroxide and then brine. The mixture was concentrated and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 78%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.28 (m, 2H), 6.99 (t, 1H), 6.89 (d, 1H), 5.46 (s, 1H), 4.38 (brs, 1H), 3.97 (brd, 1H), 3.33 (brt, 1H), 2.18 (m, 1H), 2.06 (m, 1H), 1.72 (m, 1H), 1.62 (m, 1H), 1.47 (s, 9H), 1.34 (d, 3H)
Mass Spectral Analysis *m/z* = 464.1 $(M+H)^+$

[1099] Preparation of **51.4**:

To a solution of **51.3** (0.95 g, 2.05 mmol, 1.0 eq) in dioxane (25 mL) was added **1.6** (0.50 g, 2.25 mmol, 1.1 eq), potassium phosphate (0.65 g, 3.07 mmol, 1.5 eq), potassium bromide (0.27 g, 2.25 mmol, 1.1 eq) and tetrakis(triphenylphosphine) palladium(0) (0.12 g, 0.102 mmol, 0.05 eq). The mixture was heated at 100°C for 16h and then cooled to room temperature. Ethyl acetate and water were added to the mixture and the layers were separated. The organics were concentrated and the crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity). The resulting solid was triturated in diethyl ether (15 mL) and collected by vacuum filtration.

Yield: 75%
^{1}H NMR (400MHz, $CDCl_3$) δ 7.40 (d, 2H), 7.36 (d, 2H), 7.19 (m, 1H), 7.00 (dd, 1H), 6.93 (d, 1H), 6.85 (t, 1H), 5.46 (s, 1H), 4.39 (brs, 1H), 3.96 (brd, 1H), 3.57 (brs, 2H), 3.33 (brm, 3H), 2.14 (m, 1H), 2.04 (m, 1H), 1.72 (m, 1H), 1.63 (m, 1H), 1.48 (s, 9H), 1.39 (d, 3H), 1.21 (brd, 6H)
Mass Spectral Analysis *m/z* = 491.2 $(M+H)^+$

[1100] Preparation of **51.5** and **51.6**:

Chiral separation of **51.4** (720mg) gave the two enantiomers **51.5** and **51.6**.
Column: Chiralpak ADH, 21 x 250nm, 35°C; SFC
Eluent: 20% EtOH / 80% CO_2; 50mL/min, 200 bar

UV wavelength: 260 nm

Polarimeter: 670 nm

Sample: 10 mg/mL in MeOH, 2.1mL injected

Negative polarimeter peak elutes first at about 5 minutes and the positive polarimeter peak elutessecond at about 6.5 minutes in 20% EtOH/ CO_2

51.5: (+) enantiomer; ee >99% (226mg) **51.6**: (-) enantiomer; ee >98% (238mg)

[1101] Preparation of **51A**:

To a solution of **51.5** (0.226 g, 0.461 mmol, 1.0 eq) in methylene chloride (7 mL) at 0°C under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (0.92 mL, 1.84 mmol, 4.0 eq). The reaction was warmed to room temperature and stirred for an additional 16h at room temperature. The reaction was concentrated to a solid, which was triturated in diethyl ether (5 mL), and the solids were collected by vacuum filtration.

Yield: 79%

^{1}H NMR (400MHz, DMSO d_6) δ 9.04 (brs, 1H), 8.62 (brs, 1H), 7.40 (d, 2H), 7.35 (d, 2H), 7.18 (m, 1H), 6.89 (m, 3H), 6.23 (s, 1H), 3.48 (brs, 2H), 3.37 (brs, 2H), 3.24 (brs, 1H), 3.14 (brs, 2H), 2.12 (brm, 2H), 1.86 (brm, 1H), 1.67 (brm, 1H), 1.19 (d, 3H), 1.04 (brd, 6H)

Mass Spectral Analysis *m/z* = 391.4 $(M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_2O_2$, 1HCl, $0.5H_2O$

Theory: %C 68.87; %H 7.40; %N 6.43

Found: %C 69.01; %H 7.36; %N 6.39

$[\alpha]_D$ = -4.62 (c = 8.25 mg/mL, MeOH)

[1102] Preparation of **51B**:

To a solution of **51.6** (0.238 g, 0.485 mmol, 1.0 eq) in methylene chloride (7 mL) at 0°C under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (0.97 mL, 1.94 mmol, 4.0 eq). The reaction was warmed to room temperature and stirred for an additional 16h at room temperature. The reaction was concentrated to a solid, which was triturated in diethyl ether (5 mL), and the solids were collected by vacuum filtration.

Yield: 77%

^{1}H NMR (400MHz, DMSO d_6) δ 9.12 (brs, 1H), 8.72 (brs, 1H), 7.40 (d, 2H), 7.34 (d, 2H), 7.17 (m, 1H), 6.89 (m, 3H), 6.23 (s, 1H), 3.47 (brs, 2H), 3.36 (brs, 2H), 3.23 (brs, 1H), 3.14 (brs, 2H), 2.10 (brm, 2H), 1.87 (brm, 1H), 1.68 (t, 1H), 1.19 (d, 3H), 1.04 (brd, 6H)

Mass Spectral Analysis *m/z* = 391.4 $(M+H)^+$

Elemental analysis:
$C_{25}H_{30}N_2O_2$, 1HCl, $0.33H_2O$
Theory: %C 69.35; %H 7.37; %N 6.47
Found: %C 69.44; %H 7.37; %N 6.46
$[\alpha]_D = +5.89$ (c = 9.60 mg/mL, MeOH)

[1103] Preparation of **51C**:

To a solution of **51.4** (0.75 g, 1.53 mmol, 1.0 eq) in methylene chloride (15 mL) at 0°C under nitrogen was added a 2.0M solution of anhydrous hydrochloric acid in diethyl ether (3.06 mL, 6.11 mmol, 4.0 eq). The reaction was warmed to room temperature and stirred for an additional 16h at room temperature. The reaction mixture was diluted with diethyl ether (20 mL) and the mixture was stirred for 15 min at room temperature. The solids were collected by vacuum filtration.

Yield: 95%

^1H NMR (400MHz, DMSO d_6) δ 9.24 (brs, 1H), 8.87 (brs, 1H), 7.49 (d, 2H), 7.42 (d, 2H), 7.26 (m, 1H), 6.97 (m, 3H), 6.31 (s, 1H), 3.55 (brs, 1H), 3.45 (brs, 2H), 3.26 (brm, 4H), 2.19 (brm, 2H), 1.96 (brm, 1H), 1.77 (t, 1H), 1.28 (d, 3H), 1.12 (brd, 6H)

Mass Spectral Analysis $m/z = 391.4\ (M+H)^+$

EXAMPLE 52A

[1104] Preparation of **52.1**:

4.1 (1.78 mL, 12.60 mmol, 1.2 eq) was added dropwise to a cooled (0 °C) solution of **Example 21C** (4.10 g, 10.50 mmol, 1.0 eq) and triethylamine (4.39 mL, 31.50 mmol, 3.0 eq) in tetrahydrofuran (25 mL). The reaction was stirred overnight at room temperature. Dichloromethane (10 mL) was added to help solubilize the reaction. An additional portion of **4.1** (1.00 mL, 7.11 mmol, 0.68 eq) was added dropwise and stirring was continued for 3 hours. The reaction was diluted with an aqueous solution of 1N hydrochloric acid (200 mL) and extracted with dichloromethane (2 x 100 mL). The organic extracts were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 85%

^{1}H NMR (400MHz, DMSO-d6) δ 7.39 (q, 4H), 7.23 (t, 1H), 6.93 (m, 3H), 5.87 (d, 1H), 3.51-3.78 (br m, 4H), 3.44 (br s, 2H), 3.23 (br s, 2H), 1.91-2.29 (br m, 4H), 1.80 (m, 2H), 1.12 (m, 6H)
Mass Spectral Analysis *m/z* = 487.45 $(M+H)^+$

[1105] Preparation of **52.2**:
To a solution of **52.1** (4.22 g, 8.67 mmol, 1.0 eq) in 1,2-dichloroethane (20 mL) was added **4.3** (1.99 g, 13.01 mmol, 1.5 eq) portionwise. The reaction mixture was refluxed at 65 °C overnight. The reaction mixture was cooled to room temperature and then to 0 °C in an ice/brine bath. A 2M solution of oxalyl chloride in methylene chloride (6.94 mL, 13.88 mmol, 1.6 eq) was added dropwise to the reaction mixture. The reaction mixture was warmed to room temperature, then heated to 65 °C for 3 hours. The reaction was quenched by cooling to 0 °C and adding water (50 mL). The layers were separated and the aqueous was extracted with dichloromethane (2 x 100 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 58%

^{1}H NMR (400MHz, DMSO d_6) δ 7.44 (t, 3H), 7.36 (d, 2H), 7.25 (s, 1H), 6.87 (q, 1H), 5.88 (d, 1H), 3.51-3.78 (br m, 4H), 3.45 (br s, 2H), 3.25 (br s, 2H), 1.91-2.34 (br m, 4H), 1.79 (m, 2H), 1.12 (m, 6H)
Mass Spectral Analysis *m/z* = 585.44 $(M+H)^+$

[1106] Preparation of **52.3**:
To a solution of **52.2** (2.50 g, 4.27 mmol, 1.0 eq) and tetrahydrofuran (10 mL) at 0 °C under an atmosphere of nitrogen was added **5.1** (0.88 mL, 28.20 mmol, 6.6 eq) dropwise. The reaction mixture was stirred at 0 °C for 30 minutes. The reaction mixture was concentrated under reduced pressure. Dichloromethane (50 mL) and water (50 mL) were added and the reaction mixture was stirred for 10 minutes. The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 50 mL). The organic extracts were combined, dried over sodium sulfate, filtered,

and concentrated under reduced pressure. The crude product was used without further purification.

Yield: 90%

^{1}H NMR (400MHz, DMSO-d6) 8.23 (s, 1H), 7.65 (d, 1H), 7.44 (m, 5H), 7.11 (q, 1H), 6.01 (d, 1H), 4.06 (m, 2H), 3.52-3.80 (br m, 4H), 3.45 (br s, 2H), 3.23 (br s, 2H), 1.95-2.34 (br m, 4H), 1.85 (m, 2H), 1.13 (m, 6H)

Mass Spectral Analysis *m/z* = 581.45 $(M+H)^+$

[1107] Preparation of **52.4**:

To a solution of **52.3** (2.00 g, 3.44 mmol, 1.0 eq) in ethanol (10 mL) at room temperature under an atmosphere of nitrogen was added sodium acetate (1.89 g, 23.08 mmol, 6.7 eq) and **2.8c** (1.18 mL, 18.94 mmol, 5.5 eq). The reaction mixture was refluxed at 90 °C overnight. The reaction mixture was concentrated under reduced pressure. The resulting oil was diluted with water (50 mL) then extracted with dichloromethane (3 x 50 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 82%

^{1}H NMR (400MHz, DMSO-d6) δ 7.80 (m, 1H), 7.45 (m, 5H), 7.15 (q, 1H), 6.04 (d, 1H), 3.53-3.81 (br m, 4H), 3.45 (br s, 2H), 3.23 (br s, 2H), 3.13 (s, 3H), 1.99-2.36 (br m, 4H), 1.84 (m, 2H), 1.12 (m, 6H)

Mass Spectral Analysis *m/z* = 565.51 $(M+H)^+$

[1108] Preparation of **52A**:

To a solution of **52.4** (1.50 g, 2.66 mmol, 1.0 eq) in methanol (9 mL) and water (1 mL) at room temperature and under an atmosphere of nitrogen was added potassium carbonate (2.42 g, 17.53 mmol, 6.6 eq). The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with water and ethyl acetate. The phases were separated and the organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was used without further purification.

Yield: 93%

^{1}H NMR (400MHz, DMSO d_6) δ 7.75 (m, 1H), 7.44 (m, 5H), 7.16 (d, 1H), 6.06 (d, 1H), 3.17-3.55 (br m, 8H), 2.72-2.96 (br m, 4H), 1.98-2.16 (br m, 4H), 1.83 (br s, 1H), 1.62 (br s, 1H), 1.12 (m, 6H)

Mass Spectral Analysis *m/z* = 469.43 $(M+H)^+$

EXAMPLE 53A

[1109] Preparation of **53A**:

To a solution of **48.2** (0.335 g, 0.704 mmol, 1.00 eq) in acetic acid (4 mL) was added a 48% aqueous solution of HBr (4 mL). The reaction mixture was refluxed at 110°C for 8 hours and then cooled to room temperature. The reaction mixture was concentrated and a saturated aqueous solution of sodium bicarbonate was added until the mixture was basic. The product was extracted with 5% methanol/methylene chloride and purified by HPLC using the following conditions to give 40 mg of a light orange solid.

HPLC conditions:

Column: Waters Xterra Prep RP18 OBD Column, 19 x 150mm

Detection: UV 210 nm

Flow: 15 mL/min

Mobile Phase A: 0.1% TFA in HPLC Water

Mobile Phase B: Acetonitrile

Gradient: Linear, 15%B to 90%B in 15 min.

Yield: 12%

^{1}H NMR (400MHz, DMSO) δ 9.58 (s, 1H), 8.62 (brs, 2H), 7.98 (d, 2H), 7.46 (d, 2H), 7.09 (t, 1H), 6.56 (dd, 1H), 6.46 (dd, 1H), 5.85 (s, 1H), 3.20 (brm, 4H), 2.08-1.92 (brm, 4H)

Mass Spectral Analysis *m/z* = 360.8 $(M-H)^-$

EXAMPLE 53B

[1110] Preparation of **53B**:

To a solution of **48.3** (0.500 g, 1.02 mmol, 1.00 eq) in acetic acid (5 mL) was added a 48% aqueous solution HBr (5 mL). The reaction mixture was refluxed at 110°C for 8 hours and then cooled to room temperature and stirred for an additional 48h at room temperature. A precipitate formed and the reaction was concentrated. The solid was collected by filtration. The crude product was purified by column chromatography (eluent: methanol/methylene chloride mixtures of increasing polarity, methanol contained 5% ammonium hydroxide). The resulting solid was triturated in a methylene chloride/diethyl ether mixture (5 mL/10 mL), filtered, and dried to give 168 mg of a white solid.

Yield: 44%

^{1}H NMR (400MHz, DMSO) δ 9.39 (brs, 1H), 7.97 (d, 2H), 7.38 (d, 2H), 7.02 (t, 1H), 6.46 (d, 1H), 6.39 (d, 1H), 5.74 (s, 1H), 4.43 (s, 3H), 2.86 (brm, 2H), 2.70 (brm, 2H), 1.70 (brm, 4H)

Mass Spectral Analysis *m/z* = 376.8 $(M+H)^+$

EXAMPLE 53C

[1111] Preparation of **53C**:

To a solution of **53D** (0.300 g, 0.802 mmol, 1.00 eq) in anhydrous methanol (15 mL) was added concentrated hydrochloric acid (0.50 mL) and the reaction mixture was refluxed for 16 hours and then concentrated. The crude product was dissolved in methanol (2 mL) and then diethyl ether (10 mL) was added with stirring. The resulting solid was filtered, rinsed with diethyl ether, and dried to give 272 mg of an off-white solid.

Yield: 87%

^{1}H NMR (400MHz, DMSO) δ 9.56 (s, 1H), 8.86 (brs, 2H), 7.89 (d, 2H), 7.37 (d, 2H), 7.08 (t, 1H), 6.55 (dd, 1H), 6.46 (dd, 1H), 5.82 (s, 1H), 3.86 (s, 3H), 3.18 (brm, 4H), 2.08-1.92 (brm, 4H)

Mass Spectral Analysis *m/z* = 352.7 $(M+H)^+$

$C_{21}H_{21}NO_4$, $0.5H_2O$, 1HCl

Theory: %C 63.56; %H 5.84; %N 3.53

Found: %C 63.39; %H 5.72; %N 3.53

EXAMPLE 53D

[1112] Preparation of **53.2**:

To a solution of **11.5** (0.500 g, 0.981 mmol, 1.00 eq) in dioxane (8 mL) was added potassium carbonate (0.407 g, 2.94 mmol, 3.00 eq), water (2 mL), **53.1** (0.180 g, 1.08 mmol, 1.10 eq) and tetrakis(triphenylphosphine)palladium(0) (0.060 g, 0.05 mmol, 0.05 eq). The reaction mixture was stirred for 30 minutes at room temperature and no

product was detected by LC/MS. Water (5 mL) was added and the reaction was homogeneous. The reaction mixture was heated at 50 °C for 20 hours. Additional quantities of tetrakis(triphenylphosphine)palladium(0) (0.060 g, 0.05 mmol, 0.05 eq) were added and the reaction mixture was heated at 80 °C for 3 hours. The reaction mixture was complete by LC/MS. The reaction mixture was cooled, acidified with a 1N aqueous solution of hydrochloric acid and product was extracted two times with ethyl acetate. The crude product was concentrated and purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity, then methanol/ethyl acetate mixtures of increasing polarity). The product was dissolved in diethyl ether (3 mL) and hexane (10 mL) was added to precipitate the product, which was filtered and rinsed with hexane to give 400 mg of a pale orange solid.
Yield: 85%
^{1}H NMR (400MHz, DMSO) δ 7.89 (d, 2H), 7.32 (d, 2H), 7.19 (t, 1H), 6.70 (m, 2H), 5.83 (s, 1H), 4.71 (s, 2H), 3.65 (brm, 2H), 3.32 (s, 2H), 3.01 (s, 3H), 1.84-1.70 (brm, 4H), 1.41 (s, 9H)
Mass Spectral Analysis *m/z* = 480.6 $(M-H)^-$

[1113] Preparation of **53D**:
A 2.0 M solution of hydrochloric acid in diethyl ether (1.66 mL, 3.32 mmol, 4.00 eq) was added dropwise to a solution of **53.2** (0.400 g, 0.83 mmol, 1.00 eq) in anhydrous methylene chloride (15 mL). The reaction mixture was stirred for 3 days. The precipitate was filtered and purified by HPLC using the following conditions to give 75 mg of an off-white solid.
HPLC conditions:
Column: Waters Xterra Prep RP18 OBD Column, 19 x 150mm
Detection: UV 210 nm
Flow: 15 mL/min
Mobile Phase A: 0.2% Ammonium Hydroxide in HPLC Water
Mobile Phase B: Acetonitrile
Gradient: Linear, 15%B to 90%B in 15 min.
Yield: 27%
^{1}H NMR (400MHz, DMSO) δ 7.91 (d, 2H), 7.37 (d, 2H), 7.09 (t, 1H), 6.57 (dd, 1H), 6.48 (dd, 1H), 5.82 (s, 1H), 3.24 (brm, 4H), 2.08 (brm, 2H), 1.97 (brm, 2H)

Mass Spectral Analysis m/z = 338.7 $(M+H)^+$

$C_{20}H_{19}NO_4$, $1H_2O$

Theory: %C 67.59; %H 5.96; %N 3.94

Found: %C 67.57; %H 5.92; %N 4.00

EXAMPLE 53F

[1114] Preparation of **53.4**:

To a solution of **53.2** (0.600 g, 1.25 mmol, 1.00 eq), *N,N*-diisopropylethylamine (0.65 mL, 3.75 mmol, 3.00 eq), and ethylamine hydrochloride (**3.4c**) (0.203 g, 2.50 mmol, 2.00 eq) in acetonitrile (15 mL) under nitrogen and cooled in an ice/water bath was added *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) (0.480 g, 1.50 mmol, 1.20 eq). The ice bath was removed and the reaction was stirred at room temperature for 2 hours and then concentrated. The residue was dissolved in ethyl acetate and the resulting mixture was washed with water and brine. The organic extracts were concentrated and purified by column chromatography (eluent: methanol/methylene chloride mixtures of increasing polarity, methanol contained 5% ammonium hydroxide) to give 520 mg of a pale yellow foam.

Yield: 82%

^1H NMR (400MHz, DMSO) δ 8.46 (t, 1H), 7.80 (d, 2H), 7.27 (d, 2H), 7.19 (t, 1H), 6.71 (m, 2H), 5.80 (s, 1H), 4.70 (s, 2H), 3.65 (brm, 2H), 3.29 (brm, 4H), 3.02 (s, 3H), 1.83 (brm, 2H), 1.71 (brm, 2H), 1.41 (s, 9H), 1.13 (t, 3H)

Mass Spectral Analysis m/z = 509.5 $(M+H)^+$

[1115] Preparation of **53F**:

A 2.0 M solution of hydrochloric acid in diethyl ether (4.05 mL, 8.10 mmol, 8.00 eq) was added drop wise to a solution of **53.4** (0.515 g, 1.01 mmol, 1.00 eq) in anhydrous methanol (10 mL) cooled in an ice/water bath. The mixture was warmed to room temperature and stirring was continued for an additional 3.5 hours. Diethyl ether (10 mL) was added to the solution and the resulting precipitate was collected by filtration, washed with diethyl ether, and dried to give 275 mg of a white solid.

Yield: 68%

^{1}H NMR (400MHz, DMSO) δ 9.50 (s, 1H), 8.92 (brs, 2H), 8.47 (t, 1H), 7.78 (d, 2H), 7.29 (d, 2H), 7.07 (t, 1H), 6.54 (dd, 1H), 6.46 (dd, 1H), 5.76 (s, 1H), 3.30-3.11 (brm, 6H), 2.00 (brm, 4H), 1.13 (t, 3H)

Mass Spectral Analysis *m/z* = 365.8 $(M+H)^+$

Elemental analysis:

$C_{22}H_{24}N_2O_3$, 1HCl

Theory: %C 65.91; %H 6.29; %N 6.99

Found: %C 65.54; %H 6.20; %N 6.87

EXAMPLE 54A

[1116] Preparation of **54.1**:

To a suspension of the crude HCl salt of ketone **21.3** (mother liquor of the recrystallization) (61 g, 400 mmol) in methylene chloride (1200 mL) at 0°C was added triethylamine (223 mL, 1.6 mol, 4 eq) followed by dropwise addition of benzyl chloroformate (112.6 mL, 800 mmol, 2 eq). The reaction mixture was slowly warmed up to room temperature and stirred overnight, washed with 1 N aqueous solution of hydrochloric acid, 1 N aqueous solution of sodium hydroxide and brine. The organic layer was separated, dried over sodium sulfate, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 19%

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.12 (s, 2H), 3.68 (m, 4H), 2.78 (s, 2H), 2.65 (m, 4H), 1.80 (m, 2H).

[1117] Preparation of **54.2**:

To a solution of Meldrum's acid (**38.1**) (11.07 g, 76.8 mmol) in methanol (190 mL) was added ammonium acetate (1.18 g, 15.36 mmol, 0.2 eq) followed by compound **54.1** in one portion. The reaction mixture was stirred at room temperature overnight, and concentrated *in vacuo*. The residue was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity), to yield 26 g (90.6%) of the crude product contaminated with Meldrum's acid and **54.1**, which was used without further purification for the next step.

[1118] Preparation of **54.3**:

To a suspension of CuI (270 mg, 1.4 mmol, 0.03 eq) in anhydrous tetrahydrofuran (200 mL) was added dropwise a 2.0 M solution of benzylmagnesium chloride (**28.3a**) (35.25 mL, 70.5 mmol, 1.5 eq) in anhydrous tetrahydrofuran under nitrogen atmosphere at -10°C. After the reaction mixture was stirred at -10°C for 15 min, a solution of crude **54.2** (17.7 g, 47 mmol, 1eq) in anhydrous tetrahydrofuran (100 mL) was added during a 30 min period. After the addition, the reaction mixture was stirred between -10°C and -5°C for 3 hours, and then quenched by a mixture of conc. NH_4OH: sat. NH_4Cl:H_2O (200 mL, 1:2:3). The mixture was extracted with ethyl acetate, and the combined organic layers were washed with a mixture of conc. NH_4OH: sat. NH_4Cl:H_2O (1:2:3) and brine, dried over sodium sulfate, and concentrated *in vacuo*. Diethyl ether was added to the residue and the mixture was stirred at room temperature overnight. The resulting solid was collected by filtration, washed with diethyl ether, and dried *in vacuo*.

Yield: 60.6%

^{1}H NMR (400MHz, DMSO-d_6) δ 7.31–7.08 (m, 10H), 5.02 (d, 1H), 4.90 (d, 1H), 3.50-2.85 (m, 7H), 2.70 (d, 1H), 1.53 (m, 2H), 1.43 (s, 6H), 1.0 (m, 1H), 0.75 (m, 1H).

[1119] Preparation of **54.4**:

Compound **54.3** (14 g, 28.72 mmol) was dissolved in a mixture of *N*,*N*-dimethylformamide (70 mL) and water (70 mL) and the reaction mixture was heated at ~120°C overnight, then cooled to room temperature. The reaction mixture was acidified by adding 1 N aqueous solution of hydrochloric acid to pH 2-3, and kept overnight at room temperature. The upper solvent was decanted, and the sticky residue at the bottom was dissolved in diethyl ether (400 mL). This solution was washed with water, brine, and dried over sodium sulfate. Evaporation of the solvent provided the crude product, which was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 86%

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.7 (brs, 1H), 7.35-7.20 (m, 10H), 5.12 (s, 2H), 3.50 (m, 4H), 2.80 (m, 2H), 2.29 (s, 2H), 1.82-1.50 (m, 6H).

[1120] Preparation of **54.5**:

To a solution of **54.4** (9.5 g, 24.9 mmol, 1 eq) in anhydrous methylene chloride (150 mL) was added oxalyl chloride (4.36 mL, 49.8 mmol, 2 eq) in one portion followed by 5 drops of anhydrous *N,N*-dimethylformamide. The reaction mixture was stirred at room temperature for 2 hours and then concentrated *in vacuo*. The resulting acyl chloride was dissolved in anhydrous methylene chloride (450 mL) and aluminum chloride (6.7 g, 49.8 mmol, 2 eq) was added in one portion. The reaction mixture was stirred at room temperature overnight and then quenched by water (400 mL) followed by addition of concentrated ammonium hydroxide to make the aqueous layer basic. The organic layer was separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were dried over sodium sulfate, and concentrated in vacuo.

To the solution of the above crude product in methylene chloride (250 mL) was added triethylamine (6.94 mL, 49.8 mmol, 2 eq) followed by di-*tert*-butyl dicarbonate (**4.7**) (7.08 g, 32.37 mmol, 1.3 eq.). The reaction mixture was stirred at room temperature overnight, washed with 0.5 N aqueous solution of hydrochloric acid, brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 85%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.0 (m, 1H), 7.50 (t, 1H), 7.30 (m, 1H), 7.22 (m, 6H), 3.50-3.23 (m, 4H), 2.92 (d, 1H), 2.83 (d, 1H), 2.60 (d, 1H), 2.52 (d, 1H), 1.60 (m, 6H), 1.47 (s, 9H).

[1121] Preparation of **54.6**:

A 1.0 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (25.4 mL, 25.4 mmol, 1.2 eq) was added at -78°C to a solution of compound **54.5** (7 g, 21 mmol, 1 eq) in tetrahydrofuran (200mL). After 1 hour, a solution of N-phenyltrifluoromethanesulfonimide (**1.4**) (9.1 g, 25.4 mmol, 1.2 eq) in tetrahydrofuran (80 mL) was added dropwise. The reaction mixture was then slowly warmed up to room temperature, stirred overnight at room temperature and concentrated *in vacuo*. The residue was dissolved in diethyl ether, washed with 0.5 N aqueous solution of hydrochloric acid, 1 N aqueous solution of sodium hydroxide, brine, dried over sodium sulfate, and concentrated *in vacuo*.

Yield: 100%.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.33 (m, 1H), 7.27 (m, 2H), 7.16 (m, 1H), 5.90 (s, 1H), 3.40 (m, 4H), 2.80 (m, 2H), 1.70 (m, 6H), 1.49 (s, 9H).

[1122] Preparation of **54.7**:

To a solution of **54.6** (1.48 g, 3.2 mmol, 1.0 eq) in dioxane (50 mL) was added sequentially a 2N aqueous solution of potassium carbonate (4.8 mL, 9.6 mmol, 3.0 eq), **1.6** (780 mg, 3.52 mmol, 1.1 eq) and tetrakis(triphenylphosphine)palladium(0) (111 mg, 0.096 mmol, 0.03 eq). The mixture was stirred at room temperature for 2 hours under nitrogen. Ethyl acetate (200 mL) and water (100 mL) were added. The organic layer was separated, washed with water, brine, dried over sodium sulfate, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 83%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.40 (m, 4H), 7.18 (m, 1H), 7.11 (m, 1H), 7.0 (d, 1H), 5.90 (d, 1H), 3.54-3.30 (m, 8H), 2.78 (m, 2H), 1.82-1.62 (m, 6H), 1.50 (s, 9H), 1.23 (m, 3H), 1.12 (m, 3H).

Preparation of 54A:

[1123] To the solution of **54.7** (1.3 g, 2.6 mmol) in methylene chloride (50 mL) was added a 2.0 M solution of hydrochloric acid in diethyl ether (7.8 mL, 15.6 mmol, 6 eq). The mixture was stirred at ambient temperature for 24 hours and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (eluent: methylene chloride/methanol mixtures of increasing polarity).

Yield: 44.3%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (brs, 2H), 7.40 (s, 4H), 7.20 (m, 3H), 6.90 (d, 1H), 6.0 (s, 1H), 3.43 (m, 2H), 3.20 (m, 4H), 3.10 (m, 2H), 2.79 (s, 2H), 1.83-1.62 (m, 6H), 1.10 (m, 6H).

Mass Spectral Analysis *m/z* = 389.98 $(M+H)^+$

EXAMPLE 54B

[1124] Preparation of **54.8**:

To a solution of **54.6** (1.55 g, 3.3 mmol, 1.0 eq) in dioxane (50 mL) was added sequentially a 2N aqueous solution of potassium carbonate (5.0 mL, 10 mmol, 3.0 eq), 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine-2-carboxylic acid diethylamide (**1.7**) (1.1 g, 3.63 mmol, 1.1 eq) and 1,1'-bis(diphenylphosphin0)ferrocene palladium (II) chloride complex with methylene chloride (72 mg, 0.099 mmol, 0.03 eq). The mixture was stirred at room temperature for 45 min under nitrogen. Ethyl acetate (200 mL) and water (100 mL) were added. The organic layer was separated, washed with water, brine, dried over sodium sulfate, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 81%

^{1}H NMR (400MHz, $CDCl_3$) δ 8.56 (δ, 1H), 7.78 (m, 1H), 7.60 (t, 1H), 7.18 (m, 2H), 7.11 (m, 1H), 6.92 (d, 1H), 5.93 (d, 1H), 3.58-3.30 (m, 8H), 2.80 (m, 2H), 1.82-1.62 (m, 6H), 1.49 (s, 9H), 1.22 (m, 6H).

Preparation of 54B:

[1125] To the solution of **54.8** (1.31 g, 2.6 mmol) in methylene chloride (50 mL) was added a 2.0 M solution of hydrochloric acid in diethyl ether (9.1 mL, 18.2 mmol, 7 eq). The mixture was stirred at ambient temperature for 24 hours and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (eluent: methylene chloride/methanol mixtures of increasing polarity).

Yield: 44.2%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (brs, 2H), 8.55 (s, 1H), 7.83 (d, 1H), 7.59 (d, 1H), 7.26 (m, 2H), 7.16 (t, 1H), 6.88 (d, 1H), 6.13 (s, 1H), 3.48 (q, 2H), 3.30 (q, 2H), 3.20-3.10 (m, 4H), 2.80 (s, 2H), 1.86-1.62 (m, 6H), 1.16 (t, 3H), 1.10 (t, 3H).

Mass Spectral Analysis $m/z = 390.88\ (M+H)^+$

EXAMPLE 55A

[1126] Preparation of **55.2**:

To a suspension of CuI (343 mg, 1.8 mmol, 0.036 eq) in anhydrous tetrahydrofuran (500 mL) was added dropwise a 0.25 M solution of 3,5-dimethoxybenzylmagnesium chloride (**55.1**) (500 mL, 125 mmol, 2,5 eq) in tetrahydrofuran under a nitrogen atmosphere at -10°C. After the reaction mixture was stirred at -10°C for 30 min, 4-(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidene)-piperidine-1-carboxylic acid benzyl ester (**38.2**) (17.95 g, 50 mmol, 1.0 eq) was added in ten portions to the mixture in a 1 hour period. After the addition, the reaction mixture was stirred between -10°C and 0°C for 3 hours, and then quenched by a mixture of conc. NH_4OH: sat. NH_4Cl:H_2O (300 mL, 1:2:3). The mixture was extracted with ethyl acetate, and the combined organic layers were washed with a mixture of conc. NH_4OH: sat. NH_4Cl:H_2O (1:2:3), brine, dried over sodium sulfate, and concentrated *in vacuo*. To the residue was added diethyl ether and the mixture was stirred overnight. The solid was collected by filtration, washed with diethyl ether, and dried *in vacuo*.

Yield: 100%

^{1}H NMR (400MHz, DMSO-d_6) δ 7.32 (m, 5H), 6.23 (s, 1H), 6.20 (s, 2H), 5.0 (s, 2H), 3.70 (s+m, 8H), 2.98 (m, 2H), 2.81 (m, 2H), 2.70 (s, 2H), 1.46 (s, 6H), 0.90 (m, 2H).

[1127] Preparation of **55.3**:

Compound **55.2** (26 g, 48.8 mmol) was dissolved in a mixture of *N*,*N*-dimethylformamide (150 mL) and water (150 mL) and heated at ~120°C for 3 days, then cooled to room temperature. To the reaction mixture was added 1 N aqueous solution of sodium hydroxide (125 mL) and water (500 mL). The resulting mixture was extracted with diethyl ether. The aqueous phase was then acidified with 6 N aqueous hydrochloric acid, and extracted with diethyl ether. The combined organic extracts were washed with water and brine, dried over sodium sulfate, and concentrated *in vacuo*.

Yield: 98.4%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.0 (brs, 1H), 7.35 (m, 5H), 5.10 (s, 2H), 3.75 (s+m, 8H), 3.32 (m, 2H), 2.78 (s, 2H), 2.38 (s, 2H), 1.59 (m, 4H).

[1128] Preparation of **55.4**:

To a solution of compound **55.3** (23.8 g, 55.73 mmol) in trifluoroacetic acid (250 mL) was added dropwise trifluoroacetic anhydride (93 mL, 669 mmol, 12 eq) under nitrogen atmosphere at room temperature. The reaction was stirred for 2 hours and concentrated *in vacuo*. The residue was dissolved in methylene chloride. The

mixture was washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-methylene chloride, 1:1), to yield the spiro ketone **55.4.**
Yield: 70.8%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H), 6.33 (s, 1H), 6.30 (s, 1H), 5.10 (s, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 3.59 (m, 2H), 3.41 (m, 2H), 2.85 (s, 2H), 2.56 (s, 2H), 1.50 (m, 4H).

[1129] Preparation of **55.5**:
A 1.0 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (28 mL, 28 mmol, 1.24 eq) was added at -78°C to a solution of compound **55.4** (9.26 g, 22.64 mmol, 1 eq) in tetrahydrofuran (200 mL). After 45 minutes, a solution of N-phenyltrifluoromethanesulfonimide (**1.4**) (9.8 g, 27.4 mmol, 1.2 eq) in tetrahydrofuran (80 mL) was added dropwise. The reaction mixture was then warmed up to room temperature and stirred for 2 hours at room temperature, quenched by addition of water (200 mL), and extracted with a mixture of hexane and diethyl ether (1:1). The organic extracts were combined and washed with water, brine and dried over sodium sulfate. Evaporation of the solvent gave the crude compound, which was purified by column chromatography on silica gel (hexane-ethyl acetate, 2:1), to yield the enol triflate derivative **55.5**.
Yield: 83.3%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.33 (m, 5H), 6.33 (m, 2H), 5.70 (s, 1H), 5.11 (s, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 3.73 (m, 2H), 3.29 (m, 2H), 2.69 (s, 2H), 1.61 (m, 2H), 1.45 (m, 2H).

[1130] Preparation of **55.6**:
To a solution of the enol triflate derivative **55.5** (9.8 g, 18.12 mmol) in dimethoxyethane (150 mL) was added sequentially a 2 N aqueous solution of sodium carbonate (30 mL, 60 mmol, 3.3 eq), lithium chloride (2.6 g, 61.3 mmol, 3.4 eq), 4-(*N*,*N*-diethylaminocarbonyl)phenylboronic acid) **1.6** (4.81 g, 21.77 mmol, 1.2 eq) and tetrakis(triphenylphosphine)palladium(0) (630 mg, 0.55 mmol, 0.03 eq). The reaction mixture was refluxed overnight, cooled to room temperature, diluted with water (200

mL) and extracted with diethyl ether. The combined organic extracts were dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography (eluent: hexane-ethyl acetate, 1:2).
Yield: 98.2%

^{1}H NMR (400MHz, $CDCl_3$) δ 7.36-7.22 (m, 10H), 6.40 (s, 1H), 6.30 (s, 1H), 5.89 (s, 1H), 5.11 (s, 2H), 3.81 (s, 3H), 3.78 (m, 2H), 3.53 (m, 2H), 3.39 (s, 3H), 3.30 (m, 4H), 2.68 (s, 2H), 1.62 (m, 2H), 1.43 (m, 2H), 1.22 (m, 3H), 1.10 (m, 3H).

[1131] Preparation of **55A**:
To a solution of **55.6** (3.41 g, 6 mmol) in methylene chloride (60 mL) was added dropwise a 1.0 M solution of boron tribromide in methylene chloride (60 mL, 60 mmol, 10 eq) under nitrogen atmosphere at –40°C. The reaction was slowly warmed to room temperature and stirred overnight at room temperature. A 1 N aqueous solution of hydrochloric acid was added to quench the reaction and the resulting mixture was extracted with diethyl ether. The aqueous layer was basified to pH 9 with a 3 N aqueous solution of sodium hydroxide, and extracted with methylene chloride. The organic extracts were combined, dried over sodium sulfate, and concentrated *in vacuo* to yield 1.46 g (60%) of the crude product, which was further purified by column chromatography (eluent: methylene chloride-methanol-ammonium hydroxide, 20:1:1).
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (s, 1H), 9.07 (s, 1H), 8.90 (br, 2H), 7.28 (d, 2H), 7.20 (d, 2H), 6.20 (s, 1H), 6.13 (s, 1H), 5.80 (s, 1H), 3.33-3.10 (m, 8H), 2.55 (s, 2H), 1.68 (m, 2H), 1.58 (m, 2H), 1.10 (m, 6H).
Mass Spectral Analysis *m/z* = 407.51 $(M+H)^+$

EXAMPLE 55B

[1132] Preparation of **55.7**:
To the solution of crude **55A** (1.46 g, 3.6 mmol) in methylene chloride (50 mL) was added triethylamine (2 mL, 14.4 mmol, 4 eq) followed by di-t-butyl dicarbonate **(4.7)** (787 mg, 3.6 mmol, 1.0 eq.). The reaction mixture was stirred at room temperature for 1 hour, and then concentrated *in vacuo*. The residue was purified by column chromatography (eluent: hexane-acetone, 3:2).
Yield: 42.8% for two steps.

^{1}H NMR (400MHz, CDCl$_3$) δ 8.30 (s, 1H), 7.39 (s, 4H), 6.35 (s, 1H), 5.80 (s, 1H), 5.66 (s, 1H), 5.02 (s, 1H), 3.60 (m, 4H), 3.30 (m, 4H), 2.60 (s, 2H), 2.00 (m, 1H), 1.60 (m, 2H), 1.43 (s+m, 11H), 1.28 (m, 3H), 1.12 (m, 3H).

[1133] Preparation of **55.8**:

To a solution of **55.7** (506 mg, 1 mmol) in dichloromethane was added added triethylamine (0.35 mL, 2.5 mmol, 2.5 eq) followed by *N*-phenyltrifluoromethanesulfonimide (**1.4**) (368 mg, 1.03 mmol, 1.03 eq). The reaction mixture was stirred at room temperature overnight and additional quantities of *N*-phenyltrifluoromethanesulfonimide (**1.4**) (90 g, 0.25 mmol, 0.25 eq) were added to the reaction mixture. The reaction mixture was stirred for an additional 24 hours at room temperature, washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane-acetone-triethylamine, 3:1:0.1), to yield **55.8**.

Yield: 50.2%

^{1}H NMR (400MHz, CDCl$_3$) δ 7.40 (d, 2H), 7.37 (d, 2H), 6.73 (s, 1H), 6.70 (s, 1H), 6.06 (s, 1H), 3.69 (m, 2H), 3.55 (m, 2H), 3.28 (m, 2H), 2.73 (s, 2H), 1.60 (m, 2H), 1.48 (s+m, 11H), 1.28 (m, 3H), 1.12 (m, 3H).

[1134] Preparation of **55.9**:

To a mixture of **55.8** (383 mg, 0.6 mmol), palladium acetate (4.5 mg, 0.02 mmol), 1,3-bis(diphenylphosphine)propane (8 mg, 0.02 mmol) in anhydrous *N,N*-dimethylformamide (6 mL) was added under nitrogen atmosphere at 60°C triethylsilane (0.40 mL, 2.5 mmol). The reaction mixture was stirred at 60°C for 24 hours, cooled to room temperature, and diluted with diethyl ether. The mixture was washed successively with water, a saturated aqueous solution of sodium bicarbonate, brine and dried over sodium sulfate. Evaporation of the solvent provided the crude residue, which was purified by column chromatography on silica gel (ethyl acetate-methylene chloride 1:3), to yield 80 mg (30%) of the desired phenol **55.9**, and 120 mg (33%) of the corresponding silyl ether.

Compound **55.9**: ^{1}H NMR (400MHz, $CDCl_3$) δ 7.42 (s, 4H), 7.10 (t, 1H), 6.80 (d, 1H), 6.72 (d, 1H), 6.0 (s, 1H), 5.0 (s, 1H), 3.64 (m, 2H), 3.52 (m, 2H), 3.28 (m, 4H), 2.71 (s, 2H), 1.60 (m, 2H), 1.45 (s+m, 11H), 1.23 (m, 3H), 1.12 (m, 3H).

[1135] Preparation of **55B**:

To the solution of **55.9** (78 mg, 0.16 mmol) in methylene chloride (4 mL) was added a 2.0 M hydrochloric acid in diethyl ether (10 mL, 20 mmol). The mixture was stirred at ambient temperature for 2 days. To the solution of the silyl ether of **55.9** (110 mg, 0.18 mmol) in methylene chloride (4 mL) was added 2.0 M hydrochloric acid in diethyl ether (10 mL, 20 mmol). The mixture was stirred at ambient temperature for 2 days. The two reaction mixtures were diluted with diethyl ether, combined and filtered. The solid was collected and dried *in vacuo*.

Yield: 75.3%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (s, 1H), 8.90 (brs, 1H), 8.72 (brs, 1H), 7.30 (d, 2H), 7.21 (d, 2H), 7.06 (t, 1H), 6.75 (d, 1H), 6.69 (d, 1H), 6.03 (s, 1H), 3.50-3.10 (m, 8H), 2.66 (s, 2H), 1.68 (m, 2H), 1.53 (m, 2H), 1.10 (m, 6H).

Mass Spectral Analysis $m/z = 391.53$ $(M+H)^+$

EXAMPLE 55C

[1136] Iodotrimethylsilane (0.62 mL, 4.4 mmol, 2.9 eq) was added to the solution of compound **55.6** (852 mg, 1.5 mmol) in anhydrous methylene chloride (10 mL) under nitrogen. The reaction mixture was stirred at room temperature for 1 hour, quenched with 1 N aqueous solution of hydrochloric acid (20 mL), and extracted with diethyl ether. The aqueous phase was basified to pH 9-10 with a 3 N aqueous solution of sodium hydroxide, and extracted with methylene chloride. The organic extracts were combined, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (methylene chloride-methanol-ammonium hydroxide, 10:1:1).

Yield: 60%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, 2H), 7.25 (d, 2H), 7.21 (d, 2H), 6.43 (d, 1H), 6.30 (d, 1H), 5.93 (s, 1H), 3.80 (s, 3H), 3.53 (m, 2H), 3.38 (s, 3H), 2.90 (m, 4H), 2.68 (s, 2H), 1.60 (m, 2H), 1.41 (m, 2H), 1.22 (m, 3H), 1.12 (m, 3H).

Mass Spectral Analysis m/z = 435.70 $(M+H)^+$

Elemental analysis:

$C_{27}H_{34}N_2O_3$, 1 H_2O

Theory: %C 71.65; %H 8.02; %N 6.19

Found: %C 71.32; %H 7.80; %N 6.11

EXAMPLE 56A

[1137] To a solution of **28.8b** (3.23 g, 6 mmol) in methylene chloride (50 mL) was added dropwise a 1.0 M solution of boron tribromide in methylene chloride (60 mL, 60 mmol, 10 eq) under nitrogen atmosphere at –50°C. The reaction was kept between -50°C and –10°C for 1 hour, and then slowly warmed up to room temperature and stirred overnight at room temperature. A 1 N aqueous solution of hydrochloric acid was added to quench the reaction mixture, which was extracted with diethyl ether. The aqueous layer was basified to pH 9 with a 3 N aqueous solution of sodium hydroxide, and extracted with methylene chloride (small amount of methanol was added to increase the solubility). The organic extracts were combined, dried over sodium sulfate, and concentrated *in vacuo*.

Yield: 98.3%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (brs, 1H), 9.07 (s, 1H), 7.38 (d, 2H), 7.32 (d, 2H), 7.03 (d, 1H), 6.58 (dd, 1H), 6.35 (d, 1H), 6.0 (s, 1H), 3.40-3.25 (m, 4H), 2.72 (m, 4H), 2.63 (s, 2H), 1.42 (m, 2H), 1.35 (m, 2H), 1.10 (m, 6H).

Mass Spectral Analysis m/z = 391.45 $(M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_2O_2$, 1/4 H_2O

Theory: %C 76.01; %H 7.78; %N 7.09

Found: %C 75.90; %H 7.67; %N 7.09

EXAMPLE 56B

[1138] Compound **56A** (190 mg, 1 mmol) was dissolved in methanol (30 mL), and hydrogenated in the presence of 10% Pd/C (120 mg) using a hydrogen balloon. After 3 days at room temperature, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (eluent: methylene chloride-methanol-conc. ammonia hydroxide, 8:1:1).

Yield: 94.4%

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, 2H), 7.18 (d, 2H), 6.91 (d, 1H), 6.60 (dd, 1H), 6.19 (d, 1H), 4.4 (br, 1H), 3.97 (m, 1H), 3.50 (m, 2H), 3.25 (m, 2H), 2.80 (m, 2H), 2.75 (m, 2H), 2.54 (d, 1H), 2.0 (m, 1H), 1.55-1.43 (m, 4H), 1.21 (m, 3H), 1.11 (m, 3H).

Mass Spectral Analysis $m/z = 393.59\ (M+H)^+$

EXAMPLE 56C

[1139] To a solution of **40.3** (850 mg, 1.58 mmol) in methylene chloride (15 mL) was added dropwise a 1.0 M solution of boron tribromide in methylene chloride (11 mL, 11 mmol, 7 eq) under nitrogen atmosphere at –50°C. The reaction was kept between -50°C - –10°C for 1 hour, and then slowly warmed up to room temperature and stirred overnight at room temperature. A 1 N aqueous solution of hydrochloric acid was added to quench the reaction mixture, which was extracted with diethyl ether. The aqueous layer was basified to pH 9 with a 3 N aqueous solution of sodium hydroxide, and extracted with methylene chloride (small amount of methanol was added to increase the solubility). The organic extracts were combined, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (methylene chloride-methanol-ammonium hydroxide, 6:1:1).

Yield: 73%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (brs, 1H), 8.51 (d, 1H), 7.83 (dd, 1H), 7.58 (d, 1H), 7.04 (d, 1H), 6.60 (dd, 1H), 6.30 (d, 1H), 6.12 (s, 1H), 3.48 (q, 2H), 3.30 (q, 2H), 2.77 (m, 4H), 2.69 (s, 2H), 1.50 (m, 2H), 1.32 (m, 2H), 1.18 (t, 3H), 1.11 (t, 3H)..

Mass Spectral Analysis $m/z = 392.44\ (M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_2O_2$, 1/4 H_2O

Theory: %C 71.44; %H 7.58; %N 10.41

Found: %C 71.44; %H 7.40; %N 10.38

EXAMPLE 56D

[1140] Compound **56C** (190 mg, 1 mmol) was dissolved in methanol (20 mL) and hydrogenated in the presence of 10% Pd/C (120 mg) using a hydrogen balloon. After 3 days at room temperature, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (eluent: methylene chloride-methanol-conc. ammonia hydroxide, 8:1:1).

Yield: 53.9%

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, 1H), 7.52 (dd, 1H), 7.48 (d, 1H), 6.96 (d, 1H), 6.62 (dd, 1H), 6.12 (d, 1H), 4.50 (br, 1H), 4.01 (m, 1H), 3.53 (q, 2H), 3.40 (q, 2H), 2.88 (m, 2H), 2.80 (m, 2H), 2.60 (d, 1H), 2.0 (m, 1H), 1.50 (m, 4H), 1.25 (t, 3H), 1.18 (m, 3H).

Mass Spectral Analysis *m/z* = 394.51 $(M+H)^+$

EXAMPLE 57D

[1141] Preparation of **57.1**:

4.1 (0.27 mL, 1.91 mmol, 1.2 eq) was added dropwise to a cooled 0 °C solution of **31J** (0.50 g, 1.59 mmol, 1.0 eq) and triethylamine (0.67 mL, 4.78 mmol, 3.0 eq) in tetrahydrofuran (5 mL). The reaction mixture was stirred overnight at room temperature. Dichloromethane (1 mL) was added to help solubilizing the reaction mixture. An additional portion of **4.1** (1.00 mL, 7.11 mmol, 4.5 eq) was added dropwise. Stirring was continued for 3 hours. The reaction mixture was diluted with a 1N aqueous solution of hydrochloric acid (100 mL) and extracted with dichloromethane (2 x 100 mL). The organic extracts were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 87%

^{1}H NMR (400MHz, DMSO-d6) δ 7.43 (m, 3H), 7.33 (m, 2H), 7.23 (t, 1H), 7.01 (d, 1H), 6.97 (m, 1H), 6.91 (m, 1H), 5.81 (s, 1H), 4.11 (m, 1H), 3.79 (m, 1H), 3.66 (m, 1H), 3.40 (m, 1H), 2.04 (m, 2H), 1.85 (m, 2H)

[1142] Preparation of **57.2**:

To a solution of **57.1** (0.50 g, 1.34 mmol, 1.0 eq) in 1,2-dichloroethane (5 mL) was added **4.3** (0.31 g, 2.01 mmol, 1.5 eq) portionwise. The reaction mixture was refluxed at 65 °C overnight. The reaction mixture was cooled to room temperature and then to 0 °C in an ice/brine bath. A 2M solution of oxalyl chloride in methylene chloride (1.07 mL, 2.14 mmol, 1.6 eq) was added dropwise to the reaction mixture. The reaction mixture was warmed to room temperature, then heated to 65 °C for 3 hours. The reaction mixture was cooled to 0 °C and quenched by addition of water (50 mL). The layers were separated and the aqueous was extracted with dichloromethane (2 x 100 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 74%

^{1}H NMR (400MHz, DMSO d$_6$) δ 7.46 (m, 4H), 7.31 (m, 2H), 7.24 (d, 1H), 6.95 (d, 1H), 5.81 (s, 1H), 4.10 (m, 1H), 3.75 (m, 1H), 3.66 (m, 1H), 3.40 (m, 1H), 2.04 (m, 2H), 1.85 (m, 2H)

[1143] Preparation of **57.4**:

To a solution of **57.2** (0.40 g, 0.85 mmol, 1.0 eq) in tetrahydrofuran (5 mL) at 0 °C under an atmosphere of nitrogen was added **5.1** (0.18 mL, 5.60 mmol, 6.6 eq) dropwise. The reaction mixture was stirred at 0 °C for 30 minutes. The reaction mixture was concentrated under reduced pressure. Dichloromethane (50 mL) and water (50 mL) were added and the reaction mixture was stirred for 10 minutes. The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 50 mL). The organic extracts were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 67% Mass Spectral Analysis *m/z* = 466.43 (M-H)$^-$

^{1}H NMR (400MHz, DMSO-d6) δ 8.22 (s, 1H), 7.65 (m, 1H), 7.47 (m, 4H), 7.39 (m, 2H), 7.20 (d, 1H), 5.94 (s, 1H), 4.13 (m, 1H), 3.80 (m, 1H), 3.68 (m, 1H), 3.41 (m, 1H), 3.34 (s, 2H), 2.07 (m, 2H), 1.91 (m, 2H)

[1144] Preparation of **57.5**:

To a solution of **57.4** (0.25 g, 0.54 mmol, 1.0 eq) in ethanol (5 mL) at room temperature under an atmosphere of nitrogen was added sodium acetate (0.29 g, 3.58 mmol, 6.7 eq) and **2.8c** (0.18 mL, 2.94 mmol, 5.5 eq). The reaction mixture was refluxed at 90 °C overnight. The reaction mixture was concentrated under reduced pressure. The resulting oil was diluted with water (50 mL) then extracted with dichloromethane (3 x 50 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 73%

^{1}H NMR (400MHz, DMSO-d6) δ 7.81 (m, 1H), 7.48 (m, 4H), 7.38 (m, 2H), 7.26 (d, 1H), 5.97 (s, 1H), 4.14 (m, 1H), 3.79 (m, 1H), 3.69 (m, 1H), 3.41 (m, 1H), 3.13 (s, 3H), 2.08 (m, 2H), 1.93 (m, 2H)

Mass Spectral Analysis *m/z* = 451.33 $(M+H)^+$

[1145] Preparation of **57D**:

To a solution of **57.5** (0.15 g, 0.33 mmol; 1.0 eq) in methanol (4 mL) and water (1 mL) at room temperature and under an atmosphere of nitrogen was added potassium carbonate (0.30 g, 2.19 mmol, 6.6 eq). The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with water and ethyl acetate. The phases were separated and the organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure.

Yield: 94%

^{1}H NMR (400MHz, DMSO d_6) δ 7.76 (m, 1H), 7.47 (m, 4H), 7.37 (m, 2H), 7.20 (d, 1H), 5.96 (s, 1H), 3.12 (s, 3H), 3.03 (s, 1H), 2.93 (m, 2H), 2.83 (m, 2H), 1.85 (m, 2H), 1.78 (m, 2H)

Mass Spectral Analysis *m/z* = 356.30 $(M+H)^+$

EXAMPLE 58A

[1146] Preparation of **58.1a**:

To a solution of **2.5** (3.58 g, 6.18 mmol, 1.0 eq) in 1,4-dioxane (18 mL) at room temperature and under an atmosphere of nitrogen was added 2M solution of potassium carbonate in water (9.26 mL, 18.53 mmol, 3.0 eq), **3.6a** (1.11 g, 6.79 mmol, 1.1 eq) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (0.25 g, 0.31 mmol, 0.05 eq). The reaction mixture was heated at 60 °C for 4 hours. The reaction mixture was cooled to room temperature then diluted with water (20 mL) and stirred for an additional 20 minutes at room temperature. The mixture was then extracted with diethyl ether (1 x 20 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 54%

^{1}H NMR (400MHz, DMSO-d6) δ 8.61 (d, 1H), 8.56 (s, 1H), 7.77 (m, 1H), 7.47 (m, 1H), 6.88 (d, 1H), 6.72 (m, 1H), 6.31 (d, 1H), 5.95 (s, 1H), 3.69 (m, 2H), 3.34 (m, 2H), 1.84 (m, 2H), 1.70 (m, 2H), 1.41 (s, 9H), 0.87 (s, 9H), 0.83 (s, 6H)

Mass Spectral Analysis *m/z* = 509.56 $(M+H)^+$

[1147] Preparation of **58A**:

To a solution of **58.1a** (0.60 g, 1.18 mmol, 1.0 eq) in methanol (5 mL) at room temperature and under an atmosphere of nitrogen was added a 4M solution of hydrogen chloride in 1,4-dioxane (0.59 mL, 2.40 mmol, 2.0 eq). The reaction mixture was stirred for 2 days at room temperature. The reaction mixture was concentrated under reduced pressure to dryness. The resulting oil was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity, methanol contains 10% ammonium hydroxide).

Yield: 25%

^{1}H NMR (400MHz, DMSO d_6) δ 9.38 (br s, 2H), 9.19 (br s, 1H), 8.74 (s, 2H), 8.04 (d, 1H), 7.70 (m, 1H), 6.90 (d, 1H), 6.68 (d, 1H), 6.37 (s, 1H), 6.06 (s, 1H), 4.05 (br s, 1H), 3.17 (m, 4H), 2.06 (m, 4H)

Mass Spectral Analysis *m/z* = 295.32 $(M+H)^+$

EXAMPLE 58B

[1148] **Example 58B** was obtained according to a procedure similar to the one described for **58A**, with the following exceptions:

Step 58.1: **3.6a** was replaced by **31.1n**.

Step 58.2: **58.1a** was replaced by **58.1b**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.20 (s, 1H), 9.14 (br s, 2H), 8.00 (m, 1H), 7.89 (m, 1H), 7.58 (s, 1H), 7.42 (m, 2H), 6.90 (m, 2H), 6.72 (m, 1H), 6.14 (s, 1H), 3.17 (m, 4H), 2.02 (m, 4H)

Mass Spectral Analysis $m/z = 350.33\ (M+H)^+$

EXAMPLE 58C

[1149] Preparation of **58.2**:

To a solution of **2.5** (15.00 g, 25.87 mmol, 1.00 eq) in 1,4-dioxane (65 mL) at room temperature and under an atmosphere of nitrogen was added a solution of potassium carbonate (10.73 g, 77.63 mmol, 3.0 eq) in water (32 mL), phenylboronic acid (3.47 g, 28.46 mmol, 1.1 eq) and tetrakis(triphenylphosphine)palladium(0) (1.49 g, 1.29 mmol, 0.05 eq). The reaction mixture was stirred at 80 °C overnight. The reaction mixture was cooled to room temperature then diluted with water (20 mL) and stirred for an additional 20 minutes at room temperature. The mixture was then extracted with diethyl ether (1 x 20 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 39%

Mass Spectral Analysis $m/z = 508.53\ (M+H)^+$

[1150] Preparation of **58.3**:

To a solution of **58.2** (5.11 g, 10.06 mmol, 1.0 eq) in tetrahydrofuran (10 mL) at 0 °C, under an atmosphere of nitrogen, was added dropwise a 1M solution of tetra-n-butylammonium fluoride in tetrahydrofuran (30.19 mL, 30.19 mmol, 3.0 eq). The reaction mixture was allowed to warm to room temperature and stirred overnight at room temperature. The reaction mixture was diluted with saturated sodium bicarbonate (50 mL) then extracted with ethyl acetate (2 x 50 mL). The organic layer was washed with a 1N aqueous solution of hydrogen chloride (50 mL) then brine (50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The product was triturated with diethyl ether then isolated by vacuum filtration and dried under vacuum overnight

Yield: 89%

^{1}H NMR (400MHz, DMSO d_6) δ 8.92 (s, 1H), 7.43 (m, 3H), 7.34 (m, 2H), 6.78 (d, 1H), 6.58 (m, 1H), 6.40 (d, 1H), 5.77 (s, 1H), 3.71 (m, 2H), 3.23 (m, 2H), 1.82 (m, 2H), 1.65 (m, 2H), 1.41 (s, 9H)

Mass Spectral Analysis *m/z* = 394.44 $(M+H)^+$

[1151] Preparation of **58.5a**:

To a solution of **58.3** (0.50 g, 1.27 mmol, 1.0 eq) and potassium carbonate (0.58 g, 4.19 mmol, 3.3 eq) in *N,N*-dimethylformamide (5 mL) at 0 °C and under an atmosphere of nitrogen was added dropwise **2.8c** (0.26 mL, 4.19 mmol, 3.3 eq). The reaction mixture was stirred for 3 days at 100 °C. The reaction mixture was cooled to room temperature and partitioned between water (50 mL) and diethyl ether (50 mL). The phases were separated and the organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 58%

^{1}H NMR (400MHz, DMSO-d6) δ 7.43 (m, 3H), 7.35 (m, 2H), 6.92 (d, 1H), 6.81 (m, 1H), 6.46 (d, 1H), 5.84 (s, 1H), 3.71 (m, 2H), 3.61 (s, 3H), 3.24 (m, 2H), 1.83 (m, 2H), 1.68 (m, 2H), 1.41 (s, 9H)

Mass Spectral Analysis *m/z* = 408.86 $(M+H)^+$

[1152] Preparation of **58C**:

To a solution of **58.5a** (0.30 g, 0.74 mmol, 1.0 eq) in methylene chloride (4 mL) at room temperature and under an atmosphere of nitrogen was added a 2M solution of hydrogen chloride in diethyl ether (2.02 mL, 4.04 mmol, 5.5 eq). The reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, then triturated with ethyl acetate. The product was isolated by vacuum filtration and dried under vacuum overnight.

Yield: 69%

^{1}H NMR (400MHz, DMSO d_6) δ 9.17 (br s, 2H), 7.44 (m, 3H), 7.37 (m, 2H), 7.00 (d, 1H), 6.84 (m, 1H), 6.47 (d, 1H), 5.90 (s, 1H), 3.62 (s, 3H), 3.20 (m, 4H), 2.03 (m, 4H)

Mass Spectral Analysis *m/z* = 308.28 $(M+H)^+$

EXAMPLE 58D

[1153] **58D** was obtained according to a procedure similar to the one described for **58C**, with the following exceptions:

Step 58.5: **2.8c** was replaced by **58.4**.

Step 58.6: **58.5a** was replaced by **58.5b**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.07 (br s, 2H), 7.45 (m, 3H), 7.37 (m, 2H), 6.97 (d, 1H), 6.82 (m, 1H), 6.45 (d, 1H), 5.89 (s, 1H), 3.64 (d, 2H), 3.20 (m, 4H), 2.01 (m, 4H), 1.10 (m, 1H), 0.50 (m, 2H), 0.22 (m, 2H)

Mass Spectral Analysis *m/z* = 348.26 $(M+H)^+$

EXAMPLE 59A

[1154] Preparation of **59.4a**:

To a solution of **59.2a** (3.00 g, 14.6 mmol, 1.00 eq) in methanol (75 mL) was added triethylamine (2.24 mL, 16.1 mmol, 1.10 eq). The solution was cooled in an ice/water bath and **59.3** (1.92 mL, 16.1 mmol, 1.10 eq) was added slowly. The reaction mixture was stirred at 0°C for 2.5 hours and then concentrated. The residue was dissolved in methylene chloride. The organic phase was washed with water, a saturated solution of sodium bicarbonate and brine. The organic extracts were concentrated under reduced pressure and dried to give 2.85 g of a white solid.

Yield: 89%

^{1}H NMR (400MHz, DMSO) δ 9.67 (brs, 1H), 3.59 (m, 4H)

[1155] Preparation of **59.6**:

To a solution of **59.5** (20.0 g, 0.110 mol, 1.00 eq) in *N,N*-dimethylformamide (100 mL) was added sodium azide (7.86 g, 0.121 mol, 1.10 eq) and ammonium chloride (6.46 g, 0.121 mol, 1.10 eq). The reaction mixture was heated at 125°C for 20 hours, cooled to room temperature and then cooled in a brine/ice bath. A 1N solution of hydrochloric acid (50 mL) was slowly added to the reaction mixture. A thick precipitate formed and water (200 mL) was added to facilitate stirring. To reach pH 1, a 6N solution of hydrochloric acid (20 mL) was added carefully. The solids were filtered and dried to give 25 g of a off-white solid.

Yield: 100%

^{1}H NMR (400MHz, DMSO) δ 8.00 (d, 2H), 7.84 (d, 2H)

Mass Spectral Analysis *m/z* = 223.5 $(M-H)^-$

[1156] Preparation of **59.7a**:

To a solution of **59.6** (2.33 g, 10.4 mmol, 1.00 eq) in *N,N*-dimethylformamide (50 mL) was added triethylamine (2.89 mL, 20.7 mmol, 2.00 eq). **59.4a** (2.85 g, 13.0 mmol, 1.25 eq) was then added to the reaction mixture, which was stirred at room temperatue for 16 hours. The reaction was not complete as evidenced by LC/MS, so it was heated at 50°C for 24 hours. The reaction mixture was diluted with cold water and the product was extracted two times with ethyl acetate. The crude product was concentrated and purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity) and the resulting solid was triturated in hexanes, filtered, and dried to give 1.67 g of a white solid.

Yield: 44%

^{1}H NMR (400MHz, DMSO) δ 9.64 (t, 1H), 7.99 (d, 2H), 7.79 (d, 2H), 4.90 (m, 2H), 3.76 (m, 2H)

Mass Spectral Analysis *m/z* = 362.2 $(M-H)^-$

[1157] Preparation of **59.8a**:

To a solution of **59.7a** (1.00 g, 2.75 mmol, 1.00 eq), **32.1** (2.35 g, 5.49 mmol, 2.00 eq), and potassium carbonate (1.14, 8.24 mmol, 3.00 eq) in dioxane (25 mL) and water (5 mL) was added tetrakis(triphenylphosphine)palladium(0) (0.200 g, 0.10 mmol, 0.05 eq). The reaction mixture was stirred at room temperature for 16 hours, heated at 45°C for 1 hour, and then diluted with water. Methylene chloride was added and the layers were separated. The aqueous layer was washed again with methylene chloride and the organic extracts were combined and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent:

hexane/ethyl acetate mixtures of increasing polarity) to give 1.52 g of a light yellow foam.

Yield: 95%

^{1}H NMR (400MHz, $CDCl_3$) δ 8.15 (d, 2H), 7.49 (d, 2H), 7.20 (m, 1H), 7.08 (brs, 1H), 7.02 (dd, 1H), 6.96 (dd, 1H), 6.87 (m, 1H), 5.62 (s, 1H), 4.90 (m, 2H), 4.07 (m, 2H), 3.87 (m, 2H), 3.34 (m, 2H), 2.06 (m, 2H), 1.68 (m, 2H), 1.48 (s, 9H)

Mass Spectral Analysis *m/z* = 583.6 $(M-H)^-$

[1158] Preparation of **59.9a**:

To a solution of **59.8a** (1.50 g, 2.56 mmol, 1.00 eq) in methanol (40 mL) was added potassium carbonate (1.77 g, 12.8 mmol, 5.00 eq). The reaction mixture was heated at 50°C for 24 hours and then at 60°C for an additional 24 hours. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography (eluent: methanol/methylene chloride mixtures of increasing polarity, methanol containing 5% ammonium hydroxide) to give 1.11 g of a light orange foam.

Yield: 88%

^{1}H NMR (400MHz, DMSO) δ 8.13 (d, 2H), 7.54 (d, 2H), 7.23 (m, 1H), 7.00 (m, 2H), 6.92 (m, 1H), 5.93 (s, 1H), 4.69 (t, 2H), 3.73 (m, 2H), 3.33 (s, 2H), 3.13 (t, 2H), 1.89 (m, 2H), 1.73 (m, 2H), 1.42 (s, 9H)

Mass Spectral Analysis *m/z* = 489.5 $(M+H)^+$

[1159] Preparation of **59A**:

To a solution of **59.9a** (0.500 g, 1.02 mmol, 1.00 eq) in methylene chloride (15 mL) was added a 2.0 M solution of hydrochloric acid in diethyl ether (3.10 mL, 6.10 mmol, 6.00 eq). The reaction mixture was stirred at room temperature for 3 days. The resulting solid was filtered, rinsed with diethyl ether, and dried to give 458 mg of a pale orange solid.

Yield: 96%

^{1}H NMR (400MHz, DMSO) δ 9.05 (brs, 2H), 8.27 (brs, 3H), 8.17 (d, 2H), 7.60 (d, 2H), 7.29 (m, 1H), 7.07 (dd, 1H), 7.04 (dd, 1H), 6.97 (m, 1H), 6.00 (s, 1H), 5.05 (t, 2H), 3.51 (t, 2H), 3.22 (brm, 4H), 2.05 (brm, 4H)

Mass Spectral Analysis *m/z* = 389.4 $(M+H)^+$

Elemental analysis:

$C_{22}H_{24}N_6O$, 2HCl, $1.5H_2O$

Theory: %C 54.10; %H 5.98; %N 17.21; %Cl 14.52

Found: %C 54.43; %H 5.94; %N 16.90; %Cl 14.80

EXAMPLE 59B

[1160] **59B** was obtained according to a procedure similar to the one described for **59A**, with the following exceptions:

Step 59.2: **59.2a** was replaced by **59.2b**.

Step 59.4: **59.4a** was replaced by **59.4b**.

Step 59.5: **59.7a** was replaced by **59.7b**.

Step 59.6: **59.8a** was replaced by **59.8b**.

Step 59.7: **59.9a** was replaced by **59.9b**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.21 (brs, 2H), 8.15 (m, 5H), 7.59 (d, 2H), 7.28 (m, 1H), 7.07 (m, 1H), 7.03 (dd, 1H), 6.96 (m, 1H), 5.99 (s, 1H), 4.91 (t, 2H), 3.22 (brm, 4H), 2.93 (brm, 2H), 2.32 (m, 2H), 2.06 (brm, 4H)

Mass Spectral Analysis *m/z* = 403.4 $(M+H)^+$

Elemental analysis:

$C_{23}H_{26}N_6O$, 2HCl, $1H_2O$

Theory: %C 55.99; %H 6.13; %N 17.03

Found: %C 56.01; %H 6.23; %N 16.93

EXAMPLE 59C

[1161] Preparation of **59.2c**:

A solution of **59.1a** (4.79 g, 46.4 mmol, 1.00 eq) in 48% aqueous hydrobromic acid (10 mL) was refluxed at 105°C for 4 hours. The reaction was concentrated and dried to give 10.1 g of a sticky, tan solid.

Yield: 88%

^{1}H NMR (400MHz, DMSO) δ 7.76 (brs, 3H), 3.54 (t, 1H), 3.35 (m, 1H), 2.78 (brm, 2H), 1.82 (m, 1H), 1.60-1.30 (brm, 5H)

59C was obtained according to a procedure similar to the one described for **59A**, with the following exceptions:

Step 59.2: **59.2a** was replaced by **59.2c**.

Step 59.4: **59.4a** was replaced by **59.4c**.

Step 59.5: **59.7a** was replaced by **59.7c**.

Step 59.6: **59.8a** was replaced by **59.8c**.

Step 59.7: **59.9a** was replaced by **59.9c**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.16 (brs, 2H), 8.14 (d, 2H), 7.90 (brs, 3H), 7.58 (d, 2H), 7.28 (m, 1H), 7.07 (m, 1H), 7.02 (m, 1H), 6.96 (m, 1H), 5.98 (s, 1H), 4.77 (t, 2H), 3.21 (brm, 4H), 2.77 (m, 2H), 2.06 (brm, 6H), 1.61 (m, 2H), 1.36 (m, 2H)

Mass Spectral Analysis $m/z = 431.5$ $(M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_6O$, 2HCl, 2/3H_2O

Theory: %C 58.25; %H 6.52; %N 16.30; %Cl 13.76

Found: %C 58.01; %H 6.45; %N 16.24; %Cl 14.10

EXAMPLE 59D

[1162] Preparation of **59.2d**:

A solution of **59.1b** (5.00 g, 42.7 mmol, 1.00 eq) in 48% aqueous hydrobromic acid (10 mL) was refluxed at 105°C for 4 hours. The reaction was concentrated and dried to give 9.27 g of an orange/brown oil.

Yield: 83%

^{1}H NMR (400MHz, DMSO) δ 7.70 (brs, 3H), 3.38 (m, 3H), 2.77 (m, 2H), 1.53 (m, 2H), 1.35 (brm, 5H)

59D was obtained according to a procedure similar to the one described for **59A**, with the following exceptions:

Step 59.2: **59.2a** was replaced by **59.2d**.

Step 59.4: **59.4a** was replaced by **59.4d**.

Step 59.5: **59.7a** was replaced by **59.7d**.

Step 59.6: **59.8a** was replaced by **59.8d**.

Step 59.7: **59.9a** was replaced by **59.9d**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.18 (brs, 2H), 8.14 (d, 2H), 7.91 (brs, 3H), 7.58 (d, 2H), 7.28 (m, 1H), 7.07 (dd, 1H), 7.03 (dd, 1H), 6.96 (m, 1H), 5.98 (s, 1H), 4.77 (t, 2H), 3.22 (brm, 4H), 2.75 (brs, 2H), 2.13-1.96 (brm, 6H), 1.55 (m, 2H), 1.34 (brm, 4H)

Mass Spectral Analysis *m/z* = 445.5 $(M+H)^+$

Elemental analysis:

$C_{26}H_{32}N_6O$, 2HCl, $1.25H_2O$

Theory: %C 57.83; %H 6.81; %N 15.56

Found: %C 57.99; %H 6.83; %N 15.63

EXAMPLE 59E

[1163] Preparation of **59.10a**:

To a solution of **59.9a** (0.400 g, 0.82 mmol, 1.00 eq) and triethylamine (0.342 mL, 2.46 mmol, 3.00 eq) in methylene chloride (20 mL) in an ice/water bath was added acetic anhydride (0.085 mL, 0.900 mmol, 1.10 eq). The reaction mixture was warmed to room temperature, stirred for an additional 6 hours at room temperature and diluted with a 1N solution of hydrochloric acid. The layers were separated and the aqueous phase was extracted with methylene chloride. The organic extracts were combined and concentrated under reduced pressure. The crude residue was purified by column chromatography (eluent: ethyl acetate/hexane mixtures of increasing polarity) to give 400 mg of a white foam.

Yield: 91%

^{1}H NMR (400MHz, DMSO) δ 8.14 (d, 2H), 8.07 (t, 1H), 7.55 (d, 2H), 7.24 (m, 1H), 7.00 (m, 2H), 6.92 (m, 1H), 5.93 (s, 1H), 4.78 (m, 2H), 3.73 (m, 2H), 3.63 (m, 2H), 3.31 (s, 2H), 1.89 (m, 2H), 1.77 (s, 3H), 1.72 (m, 2H), 1.42 (s, 9H)

Mass Spectral Analysis *m/z* = 531.4 $(M+H)^+$

[1164] Preparation of **59E**:

To a solution of **59.10a** (0.390 g, 0.735 mmol, 1.00 eq) in methylene chloride (10 mL) was added a 2.0 M solution of hydrochloric acid in diethyl ether (1.50 mL, 2.90 mmol, 4.00 eq). The reaction mixture was stirred at room temperature for 3 days. The solids were filtered, rinsed with methylene chloride and diethyl ether, and dried to give 335 mg of a white solid.

Yield: 98%

^{1}H NMR (400MHz, DMSO) δ 8.93 (brs, 2H), 8.15 (d, 2H), 8.09 (t, 1H), 7.58 (d, 2H), 7.28 (m, 1H), 7.05 (m, 2H), 6.96 (m, 1H), 6.00 (s, 1H), 4.78 (m, 2H), 3.63 (m, 2H), 3.22 (brm, 4H), 2.05 (brm, 4H), 1.77 (s, 3H)

Mass Spectral Analysis m/z = 431.5 $(M+H)^+$

Elemental analysis:

$C_{24}H_{26}N_6O_2$, 1HCl, $0.5H_2O$

Theory: %C 60.56; %H 5.93; %N 17.66

Found: %C 60.39; %H 5.81; %N 17.53

EXAMPLE 59F

[1165] **59F** was obtained according to a procedure similar to the one described for **59E**, with the following exceptions:

Step 59.8: **59.9a** was replaced by **59.9b**.

Step 59.9: **59.10a** was replaced by **59.10b**.

^{1}H NMR (400MHz, DMSO) δ 8.98 (brs, 2H), 8.14 (d, 2H), 8.01 (brt, 1H), 7.57 (d, 2H), 7.28 (m, 1H), 7.05 (m, 2H), 6.96 (m, 1H), 6.00 (s, 1H), 4.77 (t, 2H), 3.22 (brm, 4H), 3.13 (m, 2H), 2.16-1.97 (brm, 6H), 1.80 (s, 3H)

Mass Spectral Analysis m/z = 445.5 $(M+H)^+$

Elemental analysis:

$C_{25}H_{28}N_6O_2$, 1HCl, $1.5H_2O$

Theory: %C 59.11; %H 6.35; %N 16.54

Found: %C 59.46; %H 6.27; %N 16.60

EXAMPLE 59G

[1166] **59G** was obtained according to a procedure similar to the one described for **59E**, with the following exceptions:

Step 59.8: **59.9a** was replaced by **59.9c**.

Step 59.9: **59.10a** was replaced by **59.10c**.

^{1}H NMR (400MHz, DMSO) δ 8.88 (brs, 2H), 8.14 (d, 2H), 7.82 (brt, 1H), 7.58 (d, 2H), 7.28 (m, 1H), 7.07 (dd, 1H), 7.03 (dd, 1H), 6.96 (m, 1H), 5.99 (s, 1H), 4.75 (t, 2H), 3.22 (brm, 4H), 3.00 (q, 2H), 2.10 (m, 2H), 1.99 (brm, 4H), 1.76 (s, 3H), 1.43 (m, 2H), 1.29 (m, 2H)

Mass Spectral Analysis m/z = 473.5 $(M+H)^+$

Elemental analysis:

$C_{27}H_{32}N_6O_2$, 1HCl, 2/3H_2O

Theory: %C 62.24; %H 6.64; %N 16.13

Found: %C 61.92; %H 6.65; %N 15.91

EXAMPLE 59H

[1167] **59H** was obtained according to a procedure similar to the one described for **59E**, with the following exceptions:

Step 59.8: **59.9a** was replaced by **59.9d**.

Step 59.9: **59.10a** was replaced by **59.10d**.

^{1}H NMR (400MHz, DMSO) δ 8.99 (brs, 2H), 8.14 (d, 2H), 7.80 (brt, 1H), 7.57 (d, 2H), 7.28 (m, 1H), 7.07 (dd, 1H), 7.03 (dd, 1H), 6.96 (m, 1H), 5.99 (s, 1H), 4.75 (t, 2H), 3.22 (brm, 4H), 2.99 (q, 2H), 2.12-1.94 (brm, 6H), 1.77 (s, 3H), 1.34 (brm, 6H)

Mass Spectral Analysis *m/z* = 487.5 $(M+H)^+$

Elemental analysis:

$C_{28}H_{34}N_6O_2$, 1HCl, 1H_2O

Theory: %C 62.15; %H 6.89; %N 15.53

Found: %C 62.27; %H 6.83; %N 15.48

EXAMPLE 59I

[1168] Preparation of **59.11a**:

To a solution of **59.9a** (0.250 g, 0.512 mmol, 1.00 eq) and triethylamine (0.214 mL, 1.54 mmol, 3.00 eq) in methylene chloride (20 mL) cooled in an ice/water bath was added methanesulfonyl chloride (**7.4**) (0.044 mL, 0.563 mmol, 1.10 eq). The reaction was stirred at 0°C for 30 minutes and diluted with water. The layers were separated and the aqueous was extracted with methylene chloride. The organic extracts were combined and concentrated under reduced pressure. The crude residue was purified by column chromatography (eluent: ethyl acetate/hexane mixtures of increasing polarity) to give 164 mg of a white foam.

Yield: 57%

^{1}H NMR (400MHz, DMSO) δ 8.14 (d, 2H), 7.56 (d, 2H), 7.38 (brs, 1H), 7.23 (m, 1H), 7.00 (m, 2H), 6.92 (m, 1H), 5.93 (s, 1H), 4.85 (t, 2H), 3.73 (m, 2H), 3.61 (m, 2H), 3.32 (brs, 2H), 2.91 (s, 3H), 1.89 (m, 2H), 1.73 (m, 2H), 1.42 (s, 9H)

Mass Spectral Analysis m/z = 565.6 $(M-H)^-$

[1169] Preparation of **59I**:

To a solution of **59.11a** (0.155 g, 0.274 mmol, 1.00 eq) in methylene chloride (10 mL) was added a 2.0 M solution of hydrochloric acid in diethyl ether (0.55 mL, 1.10 mmol, 4.00 eq). The reaction was stirred at room temperature for 16 hours. The solids were filtered, rinsed with methylene chloride and diethyl ether, and dried to give 83 mg of a white solid.

Yield: 58%

^{1}H NMR (400MHz, DMSO) δ 9.04 (brs, 2H), 8.15 (d, 2H), 7.58 (d, 2H), 7.41 (t, 1H), 7.28 (m, 1H), 7.05 (m, 2H), 6.96 (m, 1H), 6.00 (s, 1H), 4.85 (t, 2H), 3.62 (m, 2H), 3.23 (brm, 4H), 2.92 (s, 3H), 2.07 (brm, 4H)

Mass Spectral Analysis m/z = 467.3 $(M+H)^+$

Elemental analysis:

$C_{23}H_{26}N_6O_3S$, 1HCl, $0.5H_2O$

Theory: %C 53.95; %H 5.51; %N 16.41

Found: %C 54.00; %H 5.39; %N 16.10

EXAMPLE 59J

[1170] **59J** was obtained according to a procedure similar to the one described for **59I**, with the following exceptions:

Step 59.10: **59.9a** was replaced by **59.9b**.

Step 59.11: **59.11a** was replaced by **59.11b**.

^{1}H NMR (400MHz, DMSO) δ 8.90 (brs, 2H), 8.15 (d, 2H), 7.57 (d, 2H), 7.28 (m, 1H), 7.21 (t, 1H), 7.05 (m, 2H), 6.96 (m, 1H), 6.00 (s, 1H), 4.83 (t, 2H), 3.22 (brm, 4H), 3.06 (q, 2H), 2.92 (s, 3H), 2.20 (m, 2H), 2.11 (brm, 2H), 2.01 (brm, 2H)

Mass Spectral Analysis m/z = 481.5 $(M+H)^+$

Elemental analysis:

$C_{24}H_{28}N_6O_3S$, 1HCl, $0.5H_2O$

Theory: %C 54.80; %H 5.75; %N 15.98

Found: %C 54.96; %H 5.64; %N 15.67

EXAMPLE 59K

[1171] **59K** was obtained according to a procedure similar to the one described for **59I**, with the following exceptions:

Step 59.10: **59.9a** was replaced by **59.9c**.

Step 59.11: **59.11a** was replaced by **59.11c**.

^{1}H NMR (400MHz, DMSO) δ 8.13 (d, 2H), 7.54 (d, 2H), 7.22 (m, 1H), 6.98 (m, 3H), 6.90 (m, 1H), 5.92 (s, 1H), 4.76 (t, 2H), 2.92 (brm, 4H), 2.86 (s, 3H), 2.78 (m, 2H), 1.99 (m, 2H), 1.82 (m, 2H), 1.73 (m, 2H), 1.51 (m, 2H), 1.33 (m, 2H)

Mass Spectral Analysis *m/z* = 509.5 $(M+H)^+$

Elemental analysis:

$C_{26}H_{32}N_6O_3S$, 1.45H_2O

Theory: %C 58.40; %H 6.58; %N 15.71

Found: %C 58.79; %H 6.58; %N 15.31

EXAMPLE 59L

[1172] **59L** was obtained according to a procedure similar to the one described for **59I**, with the following exceptions:

Step 59.10: **59.9a** was replaced by **59.9d**.

Step 59.11: **59.11a** was replaced by **59.11d**.

^{1}H NMR (400MHz, DMSO) δ 8.92 (brs, 2H), 8.14 (d, 2H), 7.57 (d, 2H), 7.28 (m, 1H), 7.07 (dd, 1H), 7.03 (dd, 1H), 6.96 (m, 2H), 5.99 (s, 1H), 4.76 (t, 2H), 3.22 (brm, 4H), 2.91 (q, 2H), 2.86 (s, 3H), 2.05 (brm, 6H), 1.39 (brm, 6H)

Mass Spectral Analysis *m/z* = 523.6 $(M+H)^+$

Elemental analysis:

$C_{27}H_{34}N_6O_3S$, 1HCl, 0.5H_2O

Theory: %C 57.08; %H 6.39; %N 14.79

Found: %C 57.36; %H 6.34; %N 14.81

EXAMPLE 60A

[1173] Preparation of **60.2**:

To a solution of **60.1** (5.00 g, 56.1 mmol, 1.00 eq) and triethylamine (15.6 mL, 112 mmol, 2.00 eq) in methanol (100 mL) cooled in an ice/water bath was added **59.3** (7.34 mL, 61.7 mmol, 1.10 eq). The reaction mixture was stirred at 0°C for 1.5 hours

and then concentrated. The mixture was dissolved in methylene chloride and washed with a 0.5N solution of hydrochloric acid. The aqueous phase was extracted three times with 5% methanol/methylene chloride. The organic extracts were combined, concentrated, and dried to give 6.96 g of an orange oil.
Yield: 67%

^{1}H NMR (400MHz, $CDCl_3$) δ 3.72 (t, 2H), 3.41 (q, 2H), 1.94 (s, 1H), 1.70 (m, 4H)

[1174] Preparation of **60.3**:
To a solution of **60.2** (3.69 g, 19.9 mmol, 1.00 eq) and triethylamine (5.56 mL, 39.9 mmol, 2.00 eq) in methylene chloride (100 mL) cooled in an ice/water bath was added **7.4** (2.31 mL, 29.9 mmol, 1.50 eq). The reaction mixture was warmed to room temperature, stirred for an additional 1 hour at room temperature and then diluted with water. The layers were separated and the aqueous phase was extracted with methylene chloride. The organic extracts were combined and washed with a 0.5M solution of hydrochloric acid. The organic extracts were concentrated and dried to give 4.96 g of an orange oil.
Yield: 95%
^{1}H NMR (400MHz, DMSO) δ 9.46 (brm, 1H), 4.21 (t, 2H), 3.22 (q, 2H), 3.16 (s, 3H), 1.62 (m, 4H)
Mass Spectral Analysis *m/z* = 262.6 $(M-H)^-$
60A was obtained according to a procedure similar to the one described for **59A**, with the following exceptions:
Step 60.3: **59.4a** from Step 59.4 was replaced by **60.3**.
Step 60.4: **59.7a** from Step 59.5 was replaced by **60.4**.
Step 60.5: **59.8a** from Step 59.6 was replaced by **60.5**.
Step 60.6: **59.9a** from Step 59.7 was replaced by **60.6**.
^{1}H NMR (400MHz, DMSO d_6) δ 9.22 (brs, 2H), 8.14 (d, 2H), 7.97 (brs, 3H), 7.57 (d, 2H), 7.28 (m, 1H), 7.08 (dd, 1H), 7.02 (dd, 1H), 6.96 (m, 1H), 5.99 (s, 1H), 4.82 (t, 2H), 3.21 (brm, 4H), 2.83 (t, 2H), 2.06 (brm, 6H), 1.61 (m, 2H)
Mass Spectral Analysis *m/z* = 417.5 $(M+H)^+$
Elemental analysis:
$C_{24}H_{28}N_6O$, 2HCl, $3/2H_2O$

Theory: %C 55.81; %H 6.44; %N 16.27; %Cl 13.73

Found: %C 55.95; %H 6.48; %N 16.28; %Cl 14.00

EXAMPLE 60B

[1175] **60B** was obtained according to a procedure similar to the one described for **59E**, with the following exceptions:

Step 60.7: **59.9a** from Step 59.8 was replaced by **60.6**.

Step 60.8: **59.10a** from Step 59.9 was replaced by **60.7**.

^{1}H NMR (400MHz, DMSO d_6) δ 9.09 (brs, 2H), 8.14 (d, 2H), 7.90 (brt, 1H), 7.57 (d, 2H), 7.28 (m, 1H), 7.07 (dd, 1H), 7.03 (dd, 1H), 6.96 (m, 1H), 5.99 (s, 1H), 4.78 (t, 2H), 3.22 (brm, 4H), 3.07 (q, 2H), 2.04 (brm, 6H), 1.78 (s, 3H), 1.42 (m, 2H)

Mass Spectral Analysis *m/z* = 459.5 $(M+H)^+$

Elemental analysis:

$C_{26}H_{30}N_6O$, 1HCl, 3/2H_2O

Theory: %C 59.82; %H 6.56; %N 16.10

Found: %C 59.77; %H 6.31; %N 16.05

EXAMPLE 60C

[1176] **60C** was obtained according to a procedure similar to the one described for **59I**, with the following exceptions:

Step 60.9: **59.9a** from Step 59.10 was replaced by **60.6**.

Step 60.10: **59.11a** from Step 59.11 was replaced by **60.8**.

^{1}H NMR (400MHz, DMSO d_6) δ 8.13 (d, 2H), 7.54 (d, 2H), 7.23 (m, 1H), 7.01 (m, 3H), 6.91 (m, 1H), 5.93 (s, 1H), 4.78 (t, 2H), 2.97 (m, 4H), 2.88 (s, 3H), 2.84 (m, 2H), 2.03 (m, 2H), 1.86 (m, 2H), 1.76 (m, 2H), 1.50 (m, 2H)

Mass Spectral Analysis *m/z* = 495.5 $(M+H)^+$

Elemental analysis:

$C_{25}H_{30}N_6O_3S$, 1H_2O

Theory: %C 58.58; %H 6.29; %N 16.39

Found: %C 58.78; %H 5.94; %N 16.40

EXAMPLE 61A, 61B

[1177] Preparation of **61.1**:

To a stirred solution of **49.9** (1.47 g, 2.65 mmol, 1 eq) in methanol (80 mL) was added 10% Pd/C (294 mg). The reaction mixture was stirred under a hydrogen atmosphere using a hydrogen balloon overnight. The reaction mixture was then filtered, the catalyst was washed with methanol, and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: ~ 100%.

Preparation of **61.2a, 61.2b**:

Compound **61.1** (1.47 g, 2.64 mmol) was subjected to chiral separation to yield two enantiomeric pure isomers **61.2a** (600mg, 40.8%) and **61.2b** (550 mg, 37.4%).

HPLC conditions:

Column: Chiralcel AD 2x15 cm

Flow: 20 mL/min, 75% A, 25% B

Detection: UV 254 nm

Mobile phase A: hexane

Mobile phase B: 60 EtOH/40 MeOH

[1178] **61.2a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 1H), 7.08 (m, 1H), 6.99 (d, 1H), 6.80 (m, 2H), 6.46 (dd, 1H), 5.12 (brs, 2H), 4.58 (m, 1H), 3.89 (m, 2H), 3.53 (m, 2H), 3.38-3.10 (m, 7H), 1.98 (m, 3H), 1.78 (m, 1H), 1.67-1.52 (m, 2H), 1.48 (s, 9H), 1.27 (m, 3H), 1.18 (m, 3H).

$[\alpha]^{25}_D$ -62.10° (c = 1.34, MeOH)

[1179] **61.2b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 1H), 7.08 (m, 1H), 6.99 (d, 1H), 6.80 (m, 2H), 6.46 (dd, 1H), 5.12 (brs, 2H), 4.58 (m, 1H), 3.89 (m, 2H), 3.53 (m, 2H), 3.38-3.10 (m, 7H), 1.98 (m, 3H), 1.78 (m, 1H), 1.67-1.52 (m, 2H), 1.48 (s, 9H), 1.27 (m, 3H), 1.18 (m, 3H).

$[\alpha]^{25}_D$ +62.82° (c = 1.19, MeOH)

[1180] Preparation of **61A**:

To a solution of pure enantiomer **61.2a** (590 mg, 1.06 mmol) in methanol (30 mL) was added 4.0 M hydrochloric acid in dioxane (2.65 mL, 10.6 mmol, 10 eq). The mixture was stirred at ambient temperature for 24 hours, An additional amount of a 4.0 M hydrochloric acid in dioxane (1.0 mL, 4 mmol, 3.8 eq) was added to the reaction mixture, which was stirred for another 3 days at room temperature. The solvent was evaporated *in vacuo*. The residue was purified by column chromatography (eluent: methylene chloride-methanol, 10:1).
Yield: 77.5%

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (brs, 1H), 8.93 (brs, 1H), 8.78 (brs, 1H), 7.02-6.86 (m, 4H), 6.73 (d, 1H), 6.40 (dd, 1H), 4.49 (m, 1H), 3.39-3.18 (m, 7H), 2.98 (m, 1H), 2.05-1.82 (m, 6H), 1.10 (m, 6H).

$[\alpha]^{25}_{D}$ –47.31° (c = 0.96, MeOH)

Mass Spectral Analysis *m/z* = 413.91 $(M+H)^+$
Elemental analysis:
$C_{24}H_{29}FN_2O_3$, 1 HCl, 9/10 H_2O
Theory: %C 61.97; %H 6.89; %N 6.02
Found: %C 61.89; %H 6.72; %N 5.95

[1181] Preparation of **61B**:

To a solution of pure enantiomer **61.2b** (550 mg, 0.988 mmol) in methanol (30 mL) was added 4.0 M hydrochloric acid in dioxane (2.47 mL, 9.88 mmol, 10 eq). The mixture was stirred at ambient temperature for 24 hours. An additional amount of a 4.0 M hydrochloric acid in dioxane (1.0 mL, 4 mmol, 4 eq) was added to the reaction mixture, which was stirred for another 3 days at room temperature. The solvent was evaporated *in vacuo*. The residue was purified by column chromatography (eluent: methylene chloride-methanol, 10:1).
Yield: 86%

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (brs, 1H), 9.08 (brs, 1H), 8.90 (brs, 1H), 7.0-6.86 (m, 4H), 6.72 (d, 1H), 6.40 (dd, 1H), 4.49 (m, 1H), 3.39-3.16 (m, 7H), 2.98 (m, 1H), 2.03-1.82 (m, 6H), 1.10 (m, 6H).

$[\alpha]^{25}_{D}$ +46.78° (c = 1.17, MeOH)

Mass Spectral Analysis *m/z* = 413.88 $(M+H)^+$

Elemental analysis:

$C_{24}H_{29}FN_2O_3$, 1 HCl, 13/10 H_2O

Theory: %C 61.02; %H 6.96; %N 5.93

Found: %C 61.00; %H 6.78; %N 5.88

[1182] Preparation of **61.4**:

O-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (0.41 g, 1.28 mmol, 1.1 eq) was added at 0°C to a solution of **21C** (0.50 g, 1.28 mmol, 1.1 eq), **61.3** (0.29g, 1.16 mmol, 1.0 eq) and diisopropylethylamine (0.46 mL, 2.56 mmol, 2.2 eq) in acetonitrile (4 mL). The reaction mixture was warmed to room temperature and stirred for an additional 2 days at room temperature. The reaction mixture was concentrated under reduced pressure, then re-dissolved in ethyl acetate. The solution was washed with a saturated aqueous solution of sodium hydrogen carbonate (50 mL) and brine (50 mL) then dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity).

Yield: 95%

^{1}H NMR (400MHz, DMSO d_6) δ 8.28 (s, 1H), 8.07 (d, 1H), 7.99 (m, 2H), 7.70 (m, 1H), 7.62 (m, 1H), 7.42 (m, 2H), 7.38 (d, 1H), 7.31 (d, 1H), 7.21 (m, 1H), 6.98 (m, 1H), 6.91 (m, 1H), 6.88 (m, 1H), 5.89 (d, 1H), 3.93 (m, 1H), 3.72 (m, 1H), 3.55 (m, 2H), 3.45 (m, 2H), 3.24 (m, 2H), 2.22 (m, 1H), 2.07 (m, 2H), 1.85 (m, 2H), 1.63 (m, 1H), 1.13 (m, 6H)

Mass Spectral Analysis *m/z* = 642.13 $(M+H)^+$

X-Ray Crystallography:

Single crystals were grown as plates by dissolving **61.4** (50 mg, 0.008 mmol, 1 eq) in an aqueous methanolic solution (MeOH/water = 80:20) and letting sit still at room temperature for 9 months.

Crystal data and structure refinement for **61.4:**

Empirical formula: C36 H35 Br N2 O3

Formula weight: 623.57

Temperature: 120(2) K

Wavelength: 0.71073 A

Crystal system, space group: Monoclinic, P2(1)

Unit cell dimensions:

a = 7.435(3) A; alpha = 90 deg.

b = 14.851(6) A; beta = 93.695(6) deg.

c = 13.628(5) A; gamma = 90 deg.

Volume: 1501.7(10) A^3.

Z, Calculated density: 2, 1.379 Mg/m^3

Absorption coefficient: 1.408 mm^{-1}

F(000): 648

Crystal size: 0.22 x 0.10 x 0.04 mm

Theta range for data collection: 2.03 to 28.27 deg.

Limiting indices: -9<=h<=9, -19<=k<=18, -17<=l<=17

Reflections collected / unique: 16930 / 6798 [R(int) = 0.0287]

Completeness to theta = 28.27: 94.1%

Absorption correction: Semi-empirical from equivalents

Max. and min. transmission: 0.9458 and 0.7470

Refinement method: Full-matrix least-squares on F^2

Data / restraints / parameters: 6798 / 1 / 381

Goodness-of-fit on F^2 - 1.034

Final R indices [I>2sigma(I)]: R1 = 0.0340, wR2 = 0.0846

R indices (all data): R1 = 0.0354, wR2 = 0.0857

Absolute structure parameter: -0.002(5)

Largest diff. peak and hole: 0.792 and -0.236 $e.A^{-3}$

Biological Methods

In vitro Assays

[1183] The potencies of the compounds listed in **Table 2** were determined by testing the ability of a range of concentrations of each compound to inhibit the binding of the non-selective opioid antagonist, [^{3}H]diprenorphine, to the cloned human μ, κ, and δ opioid receptors, expressed in separate cell lines. IC_{50} values were obtained by nonlinear analysis of the data using GraphPad Prism version 3.00 for

Windows (GraphPad Software, San Diego). K_i values were obtained by Cheng-Prusoff corrections of IC_{50} values.

Receptor binding

[1184] The receptor binding method (DeHaven and DeHaven-Hudkins, 1998) was a modification of the method of Raynor *et al.* (1994). After dilution in buffer A and homogenization as before, membrane proteins (10-80 μg) in 250 μL were added to mixtures containing test compound and [^{3}H]diprenorphine (0.5 to 1.0 nM, 40,000 to 50,000 dpm) in 250 μL of buffer A in 96-well deep-well polystyrene titer plates (Beckman). After incubation at room temperature for one hour, the samples were filtered through GF/B filters that had been presoaked in a solution of 0.5% (w/v) polyethylenimine and 0.1% (w/v) bovine serum albumin in water. The filters were rinsed 4 times with 1 mL of cold 50 mM Tris HCl, pH 7.8 and radioactivity remaining on the filters determined by scintillation spectroscopy. Nonspecific binding was determined by the minimum values of the titration curves and was confirmed by separate assay wells containing 10 μM naloxone. K_i values were determined by Cheng-Prusoff corrections of IC_{50} values derived from nonlinear regression fits of 12 point titration curves using GraphPad Prism® version 3.00 for Windows (GraphPad Software, San Diego, CA).

[1185] To determine the equilibrium dissociation constant for the inhibitors (K_i), radioligand bound (cpm) in the presence of various concentrations of test compounds was measured. The concentration to give half-maximal inhibition (EC_{50}) of radioligand binding was determined from a best nonlinear regression fit to the following equation,

$$Y = Bottom + \frac{(Top - Bottom)}{1 + 10^{X - LogEC50}}$$

where Y is the amount of radioligand bound at each concentration of test compound, Bottom is the calculated amount of radioligand bound in the presence of an infinite concentration of test compound, Top is the calculated amount of radioligand bound in the absence of test compound, X is the logarithm of the concentration of test compound, and $LogEC_{50}$ is the log of the concentration of test compound where the amount of radioligand bound is half-way between Top and Bottom. The nonlinear regression fit was performed using the program Prism® (GraphPad Software, San Diego, CA). The K_i values were then determined from the EC_{50} values by the following equation,

$$K_i = \frac{EC_{50}}{1 + \frac{[ligand]}{K_d}}$$

where [ligand] is the concentration of radioligand and K_d is the equilibrium dissociation constant for the radioligand.

Receptor-mediated [^{35}S]GTPγS binding

[1186] The potency and efficacy of compounds at each of the receptors are assessed by modifications of the methods of Selley et al., 1997 and Traynor and Nahorski, 1995 using receptor-mediated [35S]GTPγS binding in the same membrane preparations used to measure receptor binding. Assays are carried out in 96-well FlashPlates® (Perkin Elmer Life Sciences, Inc, Boston, MA). Membranes prepared from CHO cells expressing the appropriate receptor (50 -100 μg of protein) are added to assay mixtures containing agonist with or without antagonists, 100 pM [^{35}S]GTPγS (approx. 100,000 dpm), 3.0 μM GDP, 75 mM NaCl, 15 mM $MgCl_2$, 1.0 mM ethylene glycol-bis(β-aminoethyl ether)-*N,N,N',N'*-tetracetic acid, 1.1 mM dithiothreitol, 10 μg/mL leupeptin, 10 μg/mL pepstatin A, 200 μg/mL bacitracin, and 0.5 μg/mL aprotinin in 50 mM Tris-HCl buffer, pH 7.8. After incubation at room temperature for one hour, the plates are sealed, centrifuged at 800 x g in a swinging bucket rotor for 5 min and bound radioactivity determined with a TopCount microplate scintillation counter (Packard Instrument Co., Meriden, CT).

[1187] EC_{50} values for agonists are determined from nonlinear regression fits of 8- or 12-point titration curves to the 4-parameter equation for a sigmoidal dose-response with a slope factor of 1.0 using GraphPad Prism® version 3.00 for Windows (GraphPad Software, San Diego, CA).

[1188] To determine IC_{50} values, the concentrations to give half-maximal inhibition of agonist-stimulated $[^{35}S]GTP\gamma S$ binding, the amount of $[^{35}S]GTP\gamma S$ bound in the presence of a fixed concentration of agonist and various concentrations of antagonist was measured. The fixed concentration of agonist was the EC_{80}, the concentration to give 80% of the relative maximum stimulation of $[^{35}S]GTP\gamma S$ binding. The agonists loperamide (100 nM), U50,488 (50 nM), and BW373U86 (2.0 nM) were used to stimulate $[^{35}S]GTP\gamma S$ binding via the μ, δ, and κ opioid receptors, respectively. The IC_{50} value was determined from a best nonlinear regression fit of the data to the 4-parameter equation for a sigmoidal dose-response with a slope factor of 1.0 using GraphPad Prism® version 3.00 for Windows.

[1189] The potencies of the compounds were determined by testing the ability of a range of concentrations of each compound to inhibit the binding of the non-selective opioid antagonist, $[^{3}H]$diprenorphine, to the cloned human μ, κ, and δ opioid receptors, expressed in separate cell lines. All the compounds tested (compounds included in Table 2) bind with affinity to the human cloned δ opioid receptor less than 2 μM (K_i values). These compounds display high selectivity δ/κ and δ/μ (at least 10-fold). The potencies of the agonists were assessed by their abilities to stimulate $[^{35}S]GTP\gamma S$ binding to membranes containing the cloned human δ opioid receptors. All the compounds listed in Table 2 were shown to be agonists at the δ opioid receptor.

[1190] As example, **33M** (Table 2) binds to the delta, mu, and kappa opioid receptors with affinity (expressed as K_i value) of 9.7nM, >1000nM and >1000nM, respectively. Furthermore, **33M** displayed *in vitro* agonist activity (EC_{50} = 287 nM).

[1191] As further example, **43D** (Table 2) binds to the delta, mu, and kappa opioid receptors with affinity (expressed as K_i value) of 2.5nM, >1000nM and >1000nM, respectively. Furthermore, **43D** displayed potent *in vitro* agonist activity (EC_{50} = 63 nM).

[1192] Example **61A** (Table 3) and **61B** (enantiomeric analog of Example **61A**) bind to the δ opioid receptor with affinity (expressed as K_i value) of 0.59 nM, and 75 nM, respectively. Furthermore, Example **61A** displayed potent *in vitro* δ agonist activity (EC_{50} = 16.8 nM), whereas Example **61B** displayed weaker *in vitro* δ agonist activity (EC_{50} = 1282 nM), when compared to Example **61A**.

In vivo Assay

Freunds Complete Adjuvant (FCA)-Induced Hyperalgesia

[1193] Rats were injected intraplantar with FCA and 24h later treated with tested compounds administered orally. Paw Pressure Thresholds (PPT) was assessed 60minutes after drug treatment. In this assay, **43D** produced siginificant anti-hyperalgesic activity (193 ± 47% antihyperalgesia) after oral administration (3 mg/kg dose).

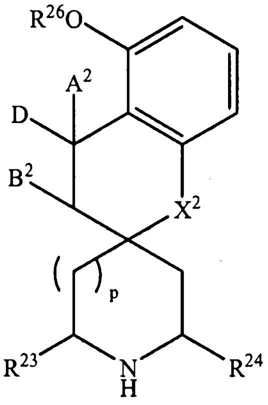
[1194] The disclosures of each patent, patent application and publication cited or described in this document are hereby incorporated herein by reference, in their entirety.

[1195] Those skilled in the art will appreciate that numerous changes and modifications can be made to the preferred embodiments of the invention and that such changes and modifications can be made without departing from the spirit of the invention. It is, therefore, intended that the appended claims cover all such equivalent variations as fall within the true spirit and scope of the invention.

[1196] Comprises/comprising and grammatical variations thereof when used in this specification are to be taken to specify the presence of stated features, integers, steps or components or groups thereof, but do not preclude the presence or addition of one or more other features, integers, steps, components or groups thereof.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

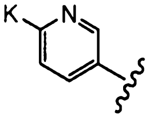
1. A compound of formula XXVIII:



XXVIII ;

wherein:

D is :



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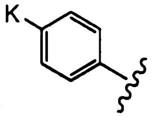

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K is carboxy (-COOH), $-C(=O)-O-C_1$ alkyl, heteroaryl having 5 members with 4 nitrogens; or N-alkylaminocarbonyl ($-C(=O)-NH(C_1-C_4$ alkyl));

R^{23} and R^{24} are each H;

R^{26} is C_1-C_6 alkyl or hydrogen;

p is 1;

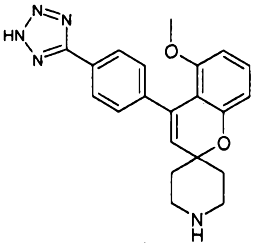
A^2 and B^2 are each H, or together form a double bond; and

X^2 is -O-;

or a stereoisomer or pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein R^{26} is H.

3. A compound according to claim 1, wherein the compound is:



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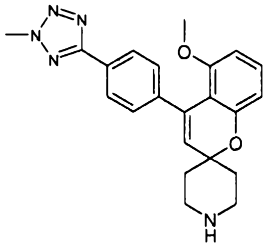

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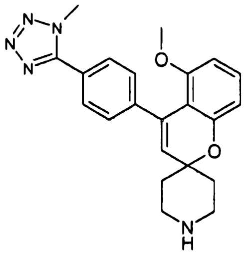

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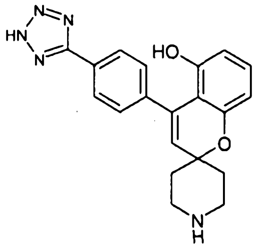

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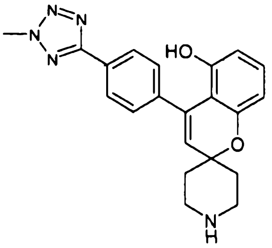

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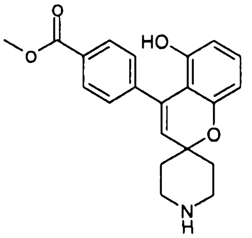

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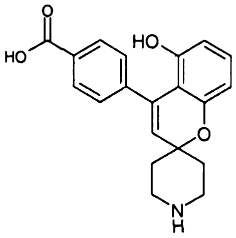

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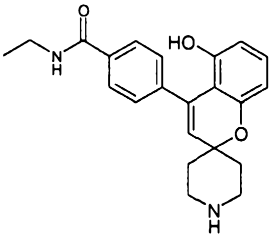

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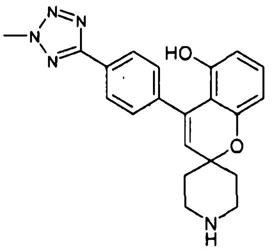
4. A compound according to claim 3, wherein the compound is:



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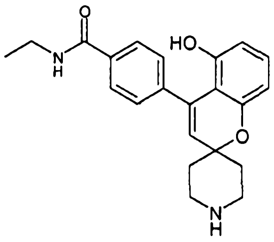

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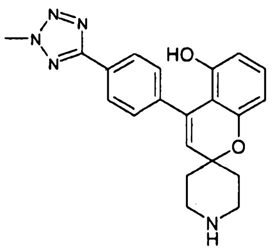
5. A compound according to claim 4, wherein the compound is: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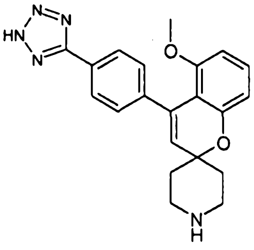
6. A pharmaceutical composition, comprising:
a pharmaceutically acceptable carrier; and a compound of any one of claims 1 to 5.

7. A method for binding δ opioid receptors in a patient in need thereof, the method comprising the step of administering to the patient a therapeutically effective amount of a compound according to any one claims 1 to 5 or a stereoisomer or pharmaceutically acceptable salt thereof, or of a pharmaceutical composition according to claim 6.

8. A method according to claim 7, wherein the compound binds with δ opioid receptors located in the central nervous system of the patient.

9. A method according to claim 7, wherein the compound binds with δ opioid receptors located peripherally to the central nervous system in the patient.

10. A method according to claim 7, wherein the compound is selected from the group consisting of: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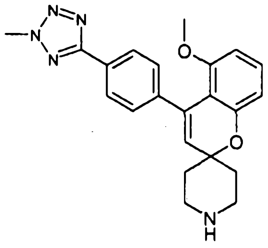
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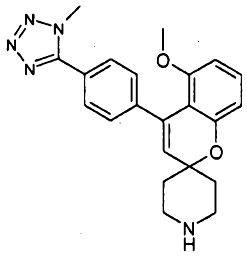
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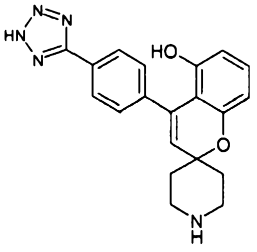
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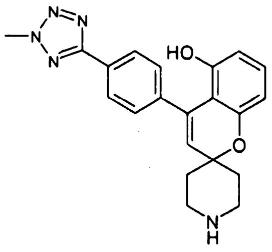
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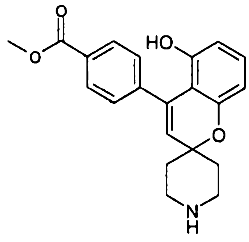
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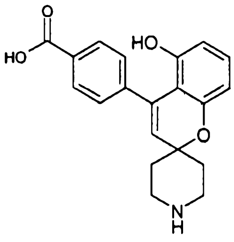
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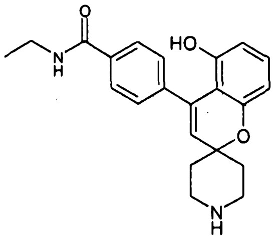
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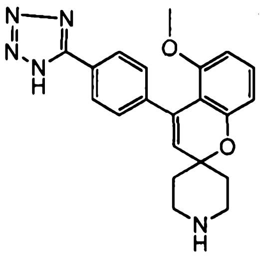
11. A method according to claim 10, wherein the compound is selected from the group consisting of: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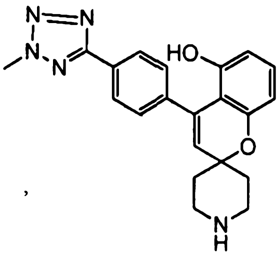
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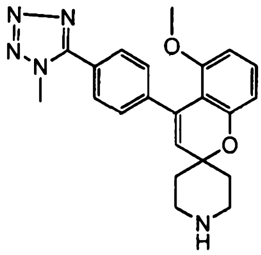
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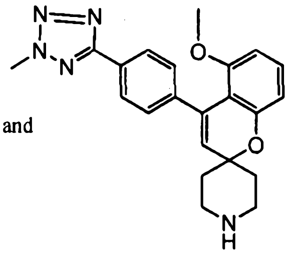
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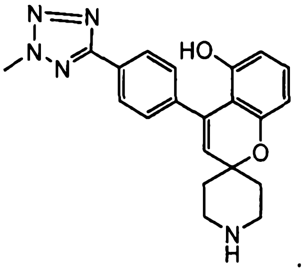
12. A method according to claim 7, wherein the compound is:

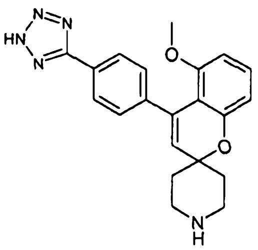
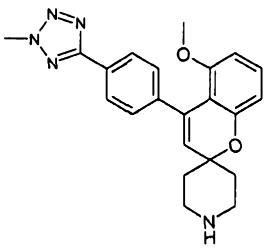
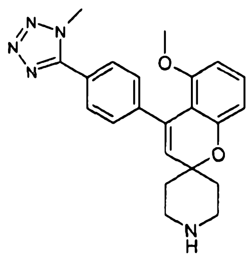


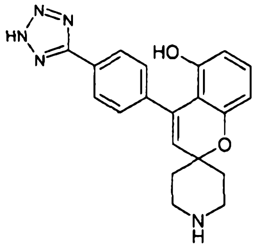
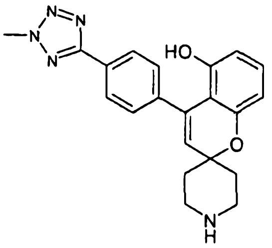
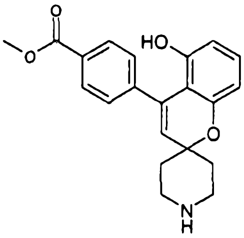
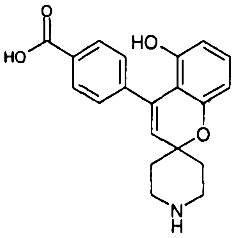
13. Use of a compound according to any one of claims 1 to 5 in the manufacture of a medicament for binding δ opioid receptors in a patient

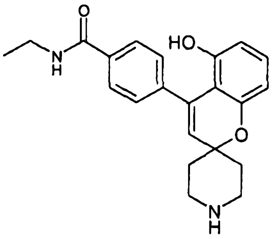
14. Use according to claim 13, wherein the compound binds with δ opioid receptors located in the central nervous system of the patient.

15. Use according to claim 13, wherein the compound binds with δ opioid receptors located peripherally to the central nervous system in the patient.

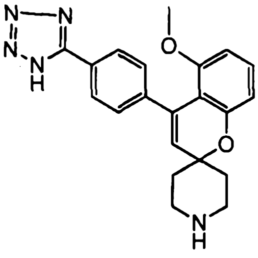
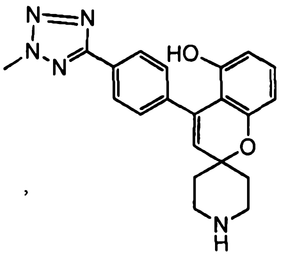
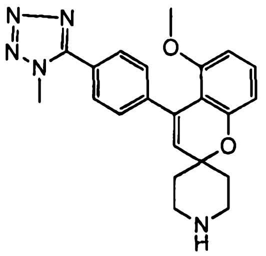
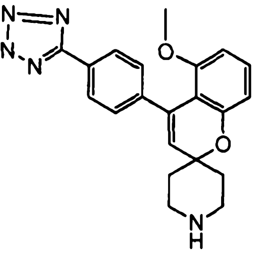
16. Use according to claim 13, wherein the compound is selected from the group consisting of:

 ,
 ,
 ,

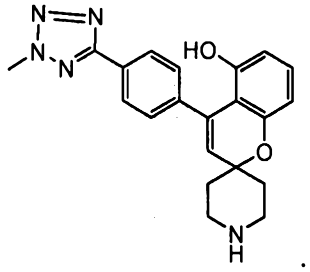
 ,
 ,
 ,
 ,

and  .

17. Use according to claim 16, wherein the compound is selected from the group consisting of:

 ,
 ,
 and
 .

18. Use according to claim 13, wherein the compound is:



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