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(54) Title: POTENT AND SELECTIVE DOPAMINE D3 RECEPTOR ANTAGONISTS

(57) Abstract: The present disclosure relates to potent and selective D_3 receptor modulators, inclusive of antagonists and agonists, with alleviated hERG liability and desirable pharmacokinetic properties, as well as compositions comprising, kits comprising, methods of administering, and methods of synthesizing the same.

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POTENT AND SELECTIVE DOPAMINE D_3 RECEPTOR ANTAGONISTS

BACKGROUND

Field

[0001] The present disclosure relates to potent and selective D_3 receptor modulators, inclusive of antagonists and agonists, with alleviated hERG liability and desirable pharmacokinetic properties, as well as compositions comprising, kits comprising, methods of administering, and methods of synthesizing the same.

Description of Related Art

[0002] There is an urgent need to find safe and efficacious modalities that can reverse addiction or in principle can be administered alongside opioids while avoiding development of addiction. Addictive drugs enhance dopamine signaling directly or indirectly in the mesolimbic areas of the brain, DA (dopamine) receptors are targets for developing drugs to combat opioid addiction. The D_3R receptor subtype is of particular interest due to its relative focal localization within the ventral striatum of the cerebrum and its enhanced expression in brains exposed to narcotics. Targeting the relatively low D_3R density in the dorsal striatum of cerebrum could avoid the undesirable motor coordination and extrapyramidal side effects often associated with non-selective D_2-like antagonists. Although several D_3R selective antagonists have displayed this advantage in pre-clinical models, they have failed to reach the market either due to their poor physicochemical properties (highly lipophilic) or due to their off-target liabilities (for example, undesirable effects on human EAG-related gene (hERG) (hERG) and K+ channels), *see, e.g.*, Micheli et al., J. Med. Chem., 53(1): 374-391 (2010). Design of dopamine selective modulators is complicated in that pharmacophore elements responsible for activity towards D_3Rs can also have activity towards hERG.

[0003] Ether-a-go-go (EAG) proteins are potassium channel proteins expressed in muscles, the brain, endocrine cells, and the heart. The EAG-related gene (ERG) channel proteins belong to an EAG subfamily including three isoforms—Kv11.1, Kv11.2, and Kv11.3. Four identical α-subunits each containing six transmembrane helices are encoded by the respective isoforms. Disfunction of the human ether-à-go-go-related gene (hERG) corresponding to the human isoform Kv11.1 is

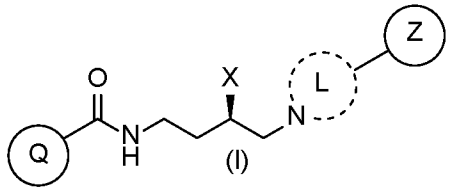
associated with prolongation of the QT interval as long QT syndrome (LQTS). LQTS can cause ventricular arrhythmia torsades de pointes (TdP), which can result in ventricular fibrillation and sudden death.

[0004] Dopamine receptors are G-protein-couple receptors (GPCRs) with characteristic seven helical membrane domains. Drug design of selective D_3R ligands has led to the development of bitopic D_3R compounds, characterized by two pharmacophores joined through a linker. While the basic amine in the primary pharmacophore is associated with binding to a conserved aspartic acid residue in the third transmembrane region (TM3), the occupancy of an allosteric pocket by the secondary pharmacophore can confer selectivity over homologous D_2 receptors. Unfortunately, the basic amine moiety associated with binding these biogenic amine GPCRs also presents a liability towards hERG channel activity. GSK598809, a selective D_3R antagonist that progressed to Phase 2 clinical trials for nicotine dependence, suffered from cardiovascular liabilities at high doses. Other selective D_3R antagonists that have progressed to clinical trials either suffer from low D_3R occupancy or poor physicochemical properties, highlighting a difficult balance between lipophilicity and attempts to develop these CNS-penetrating compounds. Crossing the blood-brain barrier with efflux mediated by P-glycoprotein (PGP) multi-drug transporters poses another challenge for obtaining successful CNS exposure. D_3R agonists, for example, for use in Parkinson patients pose similar challenges. Accordingly, there is a need for efficacious D_3R modulators that can cross the blood-brain barrier with minimal side effects.

BRIEF SUMMARY

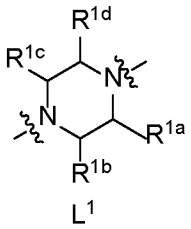
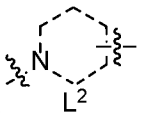
[0005] The present disclosure includes the following aspects/embodiments/features in any order and/or in any combination:

[0006] Disclosed is a therapeutic compound having Formula (I), its enantiomer, a racemate thereof, a prodrug thereof, a salt thereof, or any combination thereof:



;

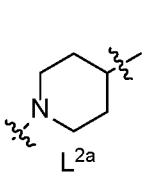
wherein Q is a first chemical moiety covalently bound through an amide bond to a n-butyl linker; X is a hydrogen, a hydroxyl, or a methyl group substituent of the n-butyl linker; L is a tertiary amine heterocyclic linker covalently bound to the n-butyl linker through the nitrogen of the tertiary amine; and Z is a second chemical moiety covalently bound to the tertiary amine heterocyclic linker;
wherein Q excludes indole, and wherein Z comprises a substituted aryl;

wherein L comprises  , or  , and R^{1a}, R^{1b}, R^{1c}, and R^{1d} are independently H, methyl, hydroxyl, or halogen, or R^{1a} and R^{1c} are bonds forming a bridge comprising methylene, or R^{1b} and R^{1d} are bonds forming a bridge comprising methylene; and wherein the therapeutic compound is a selective dopamine D_3 receptor modulator. A receptor modulator as used herein, unless defined otherwise, is a chemical compound that alters the activity of the receptor in a positive, negative or neutral direction, and may be categorized as activator, inhibitor, agonist, antagonist, partial agonist, partial antagonist, inverse agonist, inverse antagonist or any combination thereof. The modulator may be an allosteric or orthosteric binder, or any combination thereof.

[0007] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the therapeutic compound is a selective dopamine D_3 receptor antagonist.

[0008] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the therapeutic compound is a selective dopamine D_3 receptor agonist.

[0009] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the second linker L^2 is selected from one of the following:



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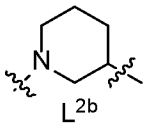

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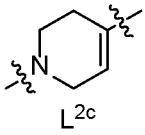

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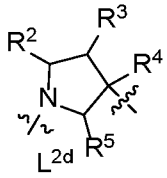

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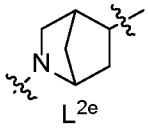

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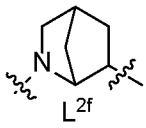

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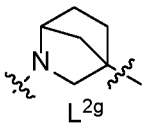
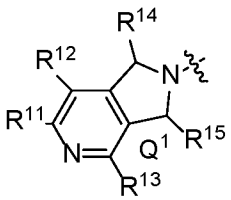


;

wherein R^2 and R^5 are independently H, methyl, hydroxyl, or halogen; and

[0010] wherein R^3 and R^4 can be, for example, independently H, methyl, hydroxyl, or halogen, or linked covalently at a methylene to form a three-carbon ring.

[0011] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Q is selected from one of the following:



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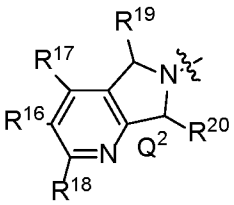

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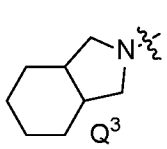

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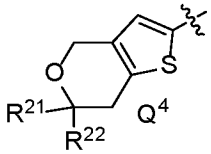

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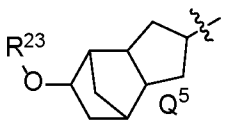

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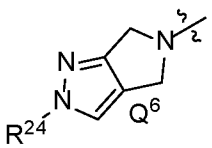

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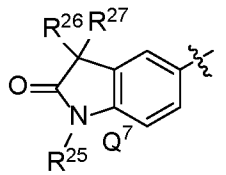

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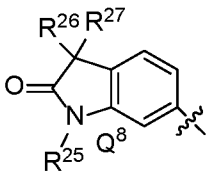

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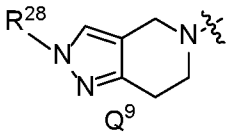

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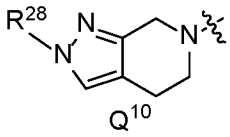

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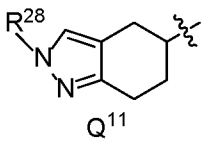

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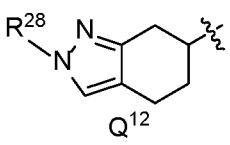

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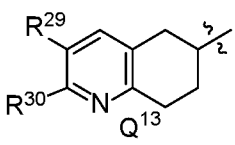

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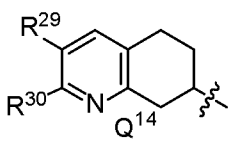

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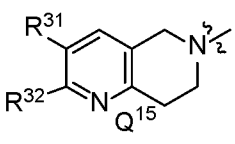

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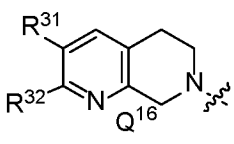

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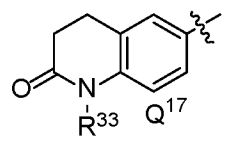

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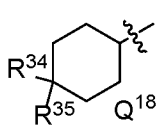

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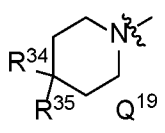

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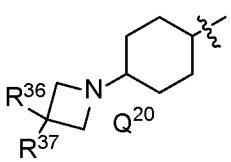

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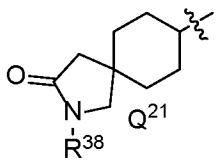

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wherein R^{11}, R^{12}, R^{13}, R^{16}, R^{17}, R^{18}, R^{29}, R^{30}, R^{31}, and R^{32} are independently H, methyl, ethyl, methoxy, ethoxy, or halogen;

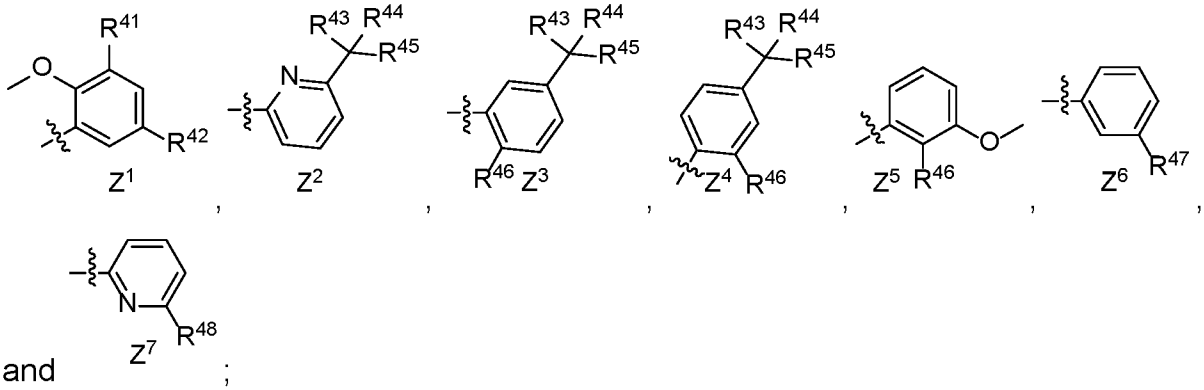
wherein R^{14}, R^{15}, R^{19}, R^{20}, R^{21}, R^{22}, R^{34}, R^{35}, R^{36}, and R^{37} are independently H, methyl, ethyl, methoxy, ethoxy, or halogen;

wherein R^{26} and R^{27} are independently H, methyl, ethyl, methoxy, ethoxy, or halogen, or methylenes covalently linked to form a three-carbon ring;

wherein R^{24}, R^{25}, R^{28}, R^{33}, and R^{38} are independently H, methyl, or halogen; and

wherein R^{23} is methyl or ethyl.

[0012] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Z is selected from one of the following:

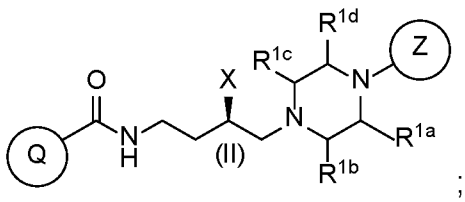


and ;

wherein R^{41}, R^{42}, R^{46}, R^{47}, and R^{48} are independently H, methyl, ethyl, or halogen; and

wherein R^{43}, R^{44}, and R^{45} are independently H or halogen.

[0013] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (II):



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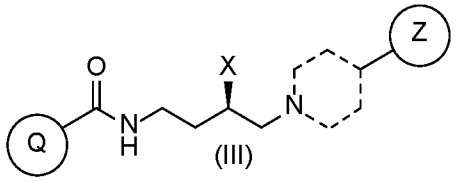
wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d} are independently H, methyl, hydroxyl, or halogen, or R^{1a} and R^{1c} are bonds forming a bridge comprising methylene, or R^{1b} and R^{1d} are bonds forming a bridge comprising methylene.

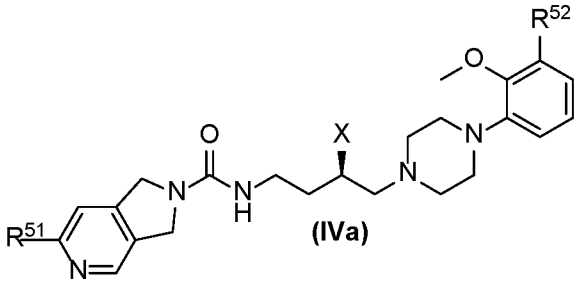
[0014] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or

salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (III):



.

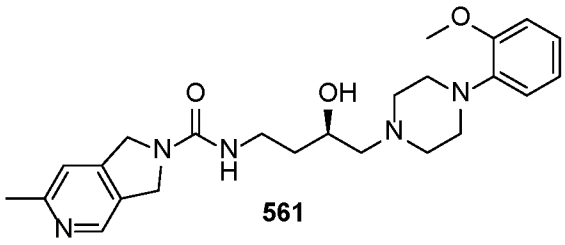
[0015] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (IVa):



; and

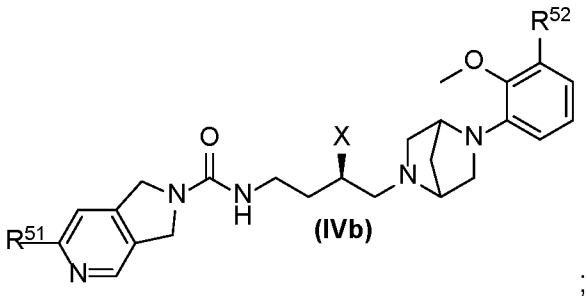
[0016] wherein R^{51} and R^{52} are independently H, methyl, ethyl, or halogen.

[0017] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the therapeutic compound comprises:



.

[0018] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (IVb):

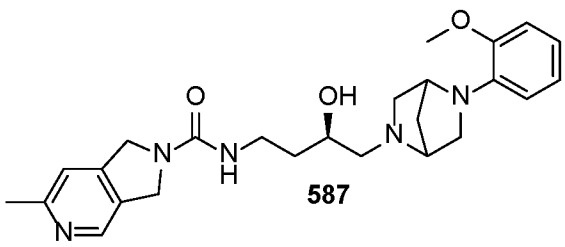


(IVb)

; and

wherein R^{51} and R^{52} are independently H, methyl, ethyl, or halogen.

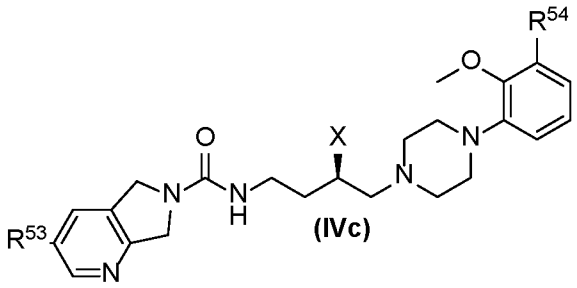
[0019] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the therapeutic compound comprises:



587

.

[0020] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (IVc):

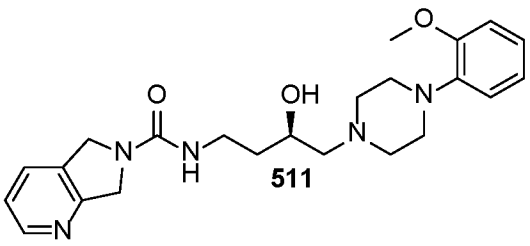


(IVc)

;

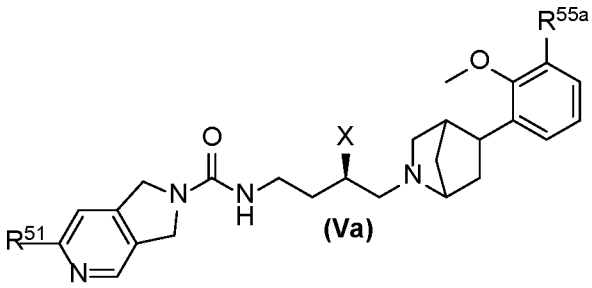
wherein R^{53} and R^{54} are independently H, methyl, ethyl, or halogen.

[0021] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the therapeutic compound comprises:



.

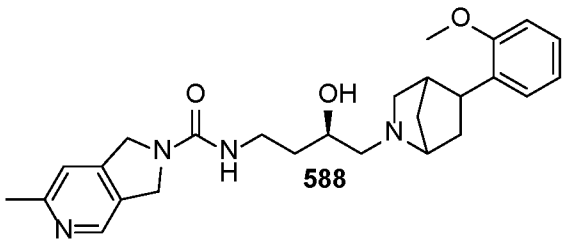
[0022] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (Va):



; and

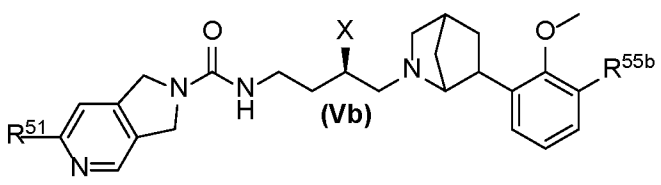
wherein R^{51} and R^{55b} are independently H, methyl, ethyl, or halogen.

[0023] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the therapeutic compound comprises:



.

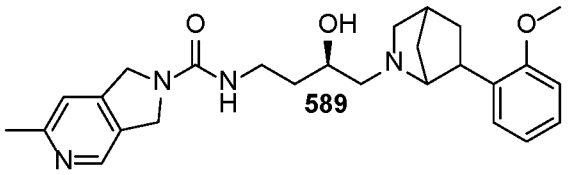
[0024] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (Vb):



; and

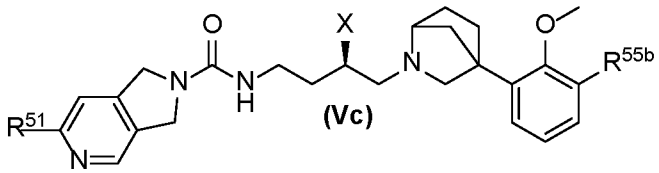
wherein R^{51} and R^{55b} are independently H, methyl, ethyl, or halogen.

[0025] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the therapeutic compound comprises:



.

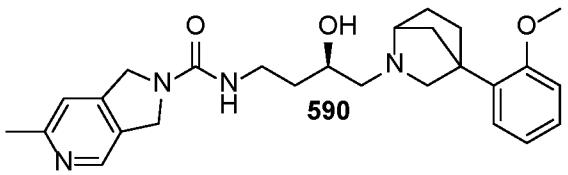
[0026] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (Vc):



; and

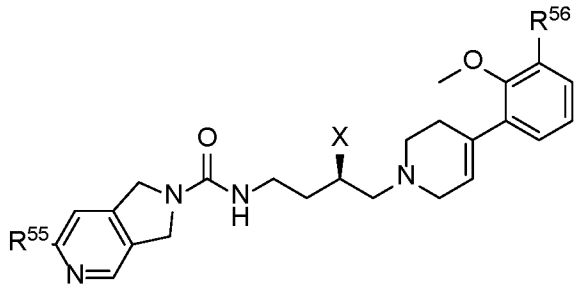
wherein R^{51} and R^{55b} are independently H, methyl, ethyl, or halogen.

[0027] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the therapeutic compound comprises:



.

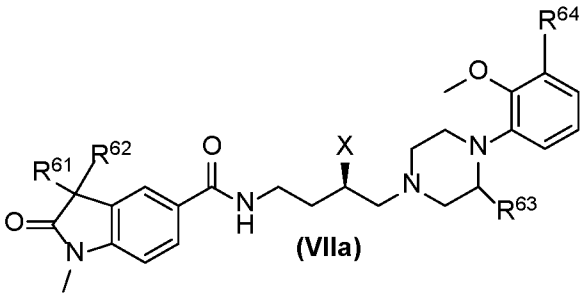
[0028] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (VI):



(VI) ;

wherein R^{55} and R^{56} are independently H, methyl, ethyl, or halogen.

[0029] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (VIIa):



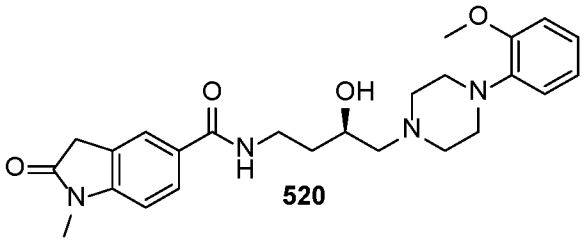
(VIIa) ;

wherein R^{61} and R^{62} are independently H or methyl, or methylenes covalently linked to form a three-carbon ring;

wherein R^{63} is H, methyl, hydroxyl, or halogen; and

wherein R^{64} is methyl, ethyl, or halogen.

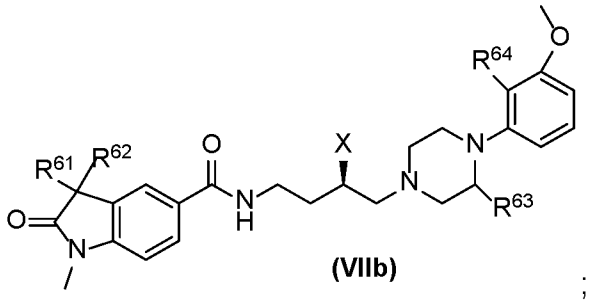
[0030] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the therapeutic compound comprises:



520 .

[0031] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or

salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (VIIb):



(VIIb)

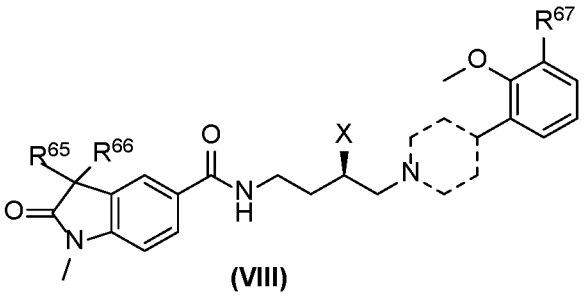
;

wherein R^{61} and R^{62} are independently H or methyl, or methylenes covalently linked to form a three-carbon ring;

wherein R^{63} is H, methyl, hydroxyl, or halogen; and

wherein R^{64} is methyl, ethyl, or halogen.

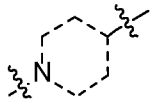
[0032] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (VIII):

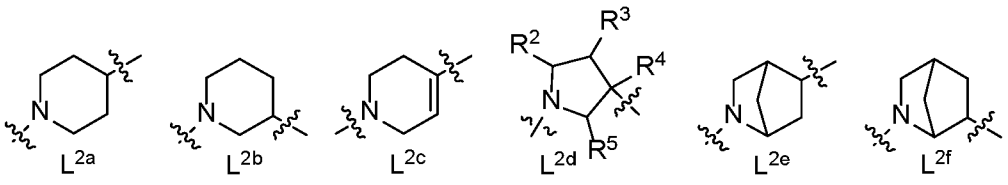


(VIII)

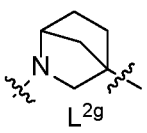
;

wherein R^{65} and R^{66} are independently H or methyl, or methylenes covalently linked to form a three-carbon ring;

wherein  is selected from one of the following:



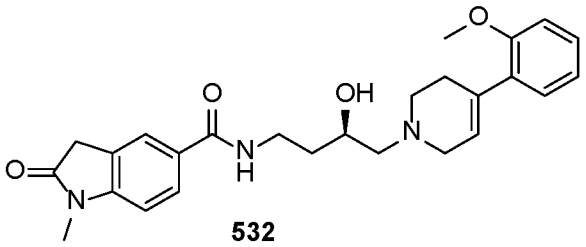
, and



;

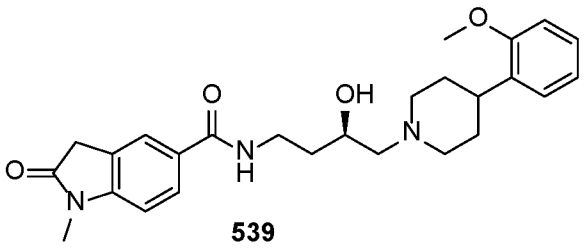
wherein R^2, R^3, R^4, and R^5 are independently H, methyl, hydroxyl, or halogen; and wherein R67 is methyl, ethyl, or halogen.

[0033] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the therapeutic compound comprises:



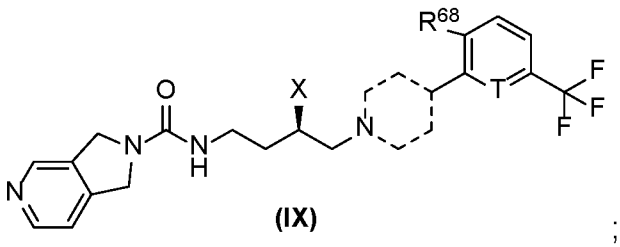
532

[0034] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the therapeutic compound comprises:



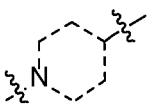
539

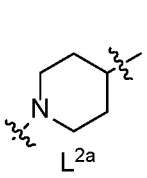
[0035] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (IX):

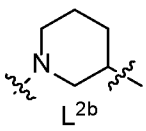


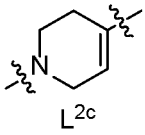
(IX)

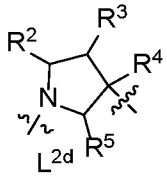
;

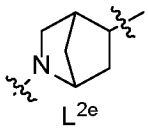
wherein  is selected from one of the following:

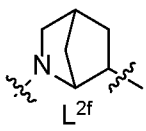


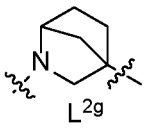
,


,


,


,


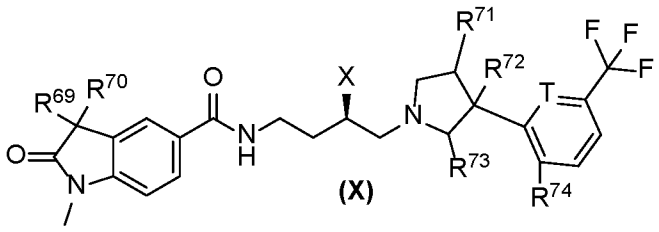
,


, and


;

wherein R^2, R^3, R^4, and R^5 are independently H, methyl, hydroxyl, or halogen;
wherein R^{68} is H or halogen; and
wherein T is C or N.

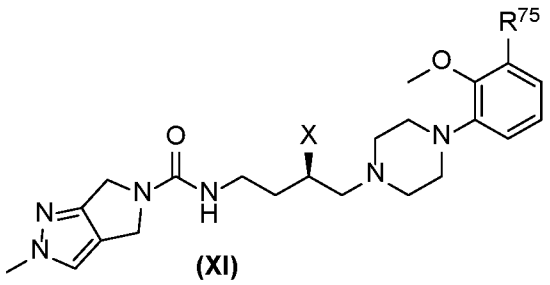
[0036] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (X):



;

wherein R^{69} and R^{70} are independently H or methyl, or methylenes covalently linked to form a three-carbon ring;
wherein R^{71} and R^{72} are independently H, methyl, halogen, or linked covalently at a methylene to form a three-carbon ring;
wherein R^{73} is H, methyl, or halogen;
wherein R^{74} is H or halogen; and
wherein T is C or N.

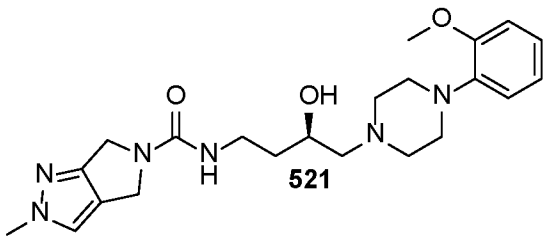
[0037] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (XI):



(XI) ;

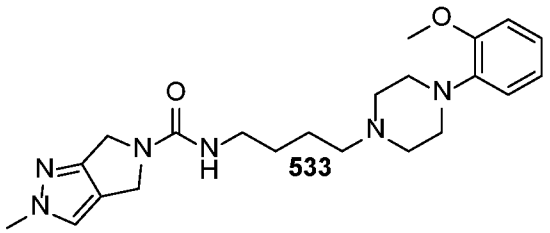
wherein R^{75} is H or halogen.

[0038] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the therapeutic compound comprises:



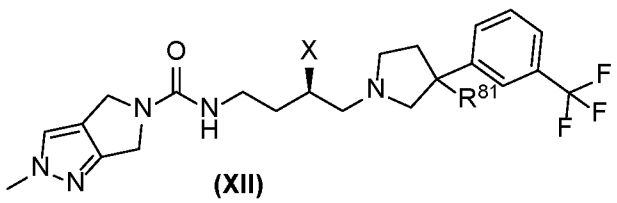
521 .

[0039] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the therapeutic compound comprises:



533 .

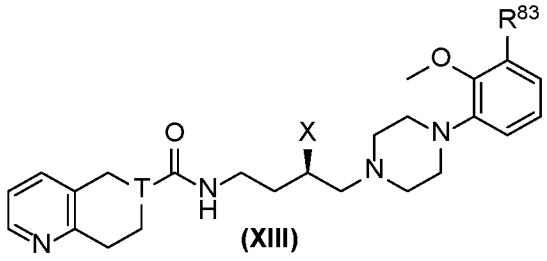
[0040] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (XII):



(XII) ;

wherein R^{81} is H, methyl, or halogen.

[0041] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (XIII):

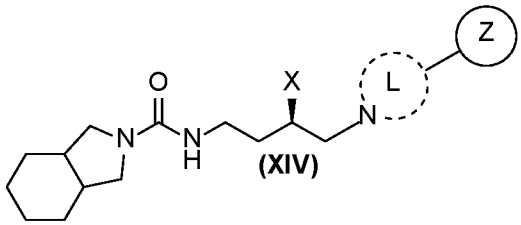


;

wherein T is C or N; and

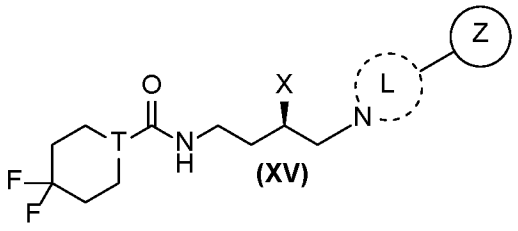
wherein R^{83} is H or halogen.

[0042] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (XIV):



.

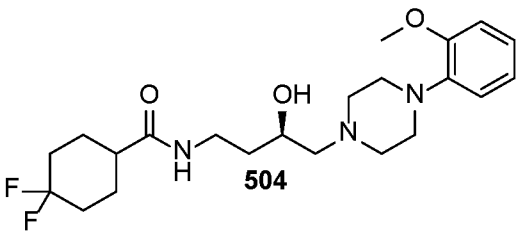
[0043] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (XV):



;

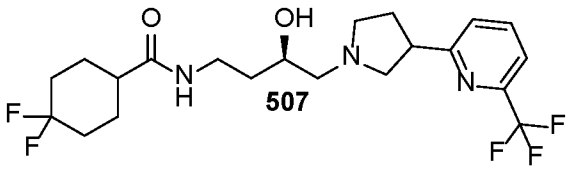
wherein T is C or N.

[0044] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the therapeutic compound comprises:



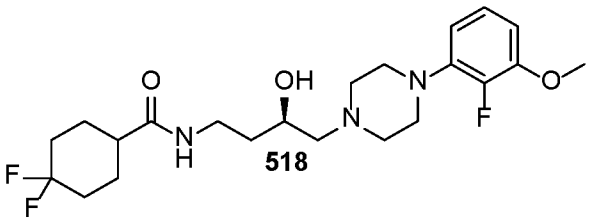
504

[0045] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the therapeutic compound comprises:



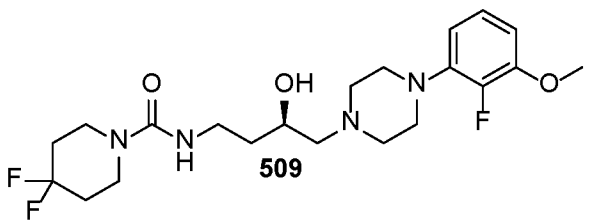
507

[0046] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the therapeutic compound comprises:



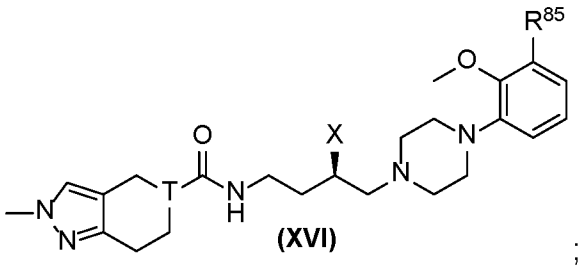
518

[0047] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the therapeutic compound comprises:



509

[0048] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (XVI):

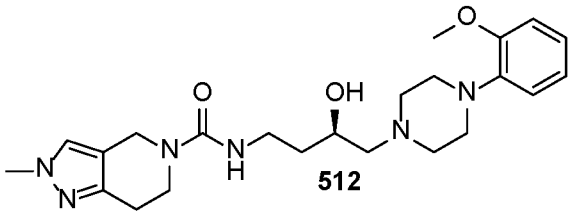


;

wherein T is C or N; and

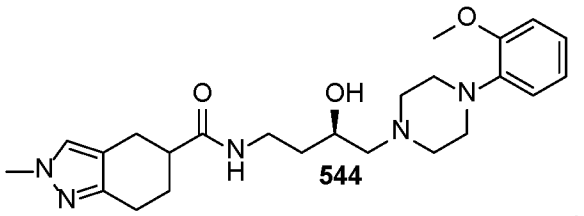
wherein R^{85} is H or halogen.

[0049] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the therapeutic compound comprises:



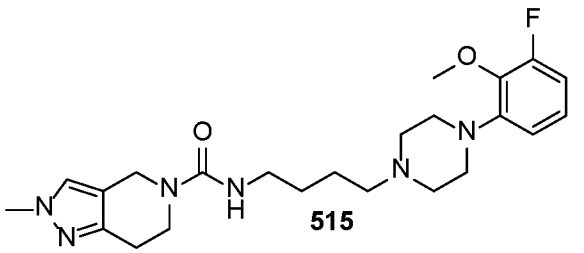
.

[0050] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the therapeutic compound comprises:



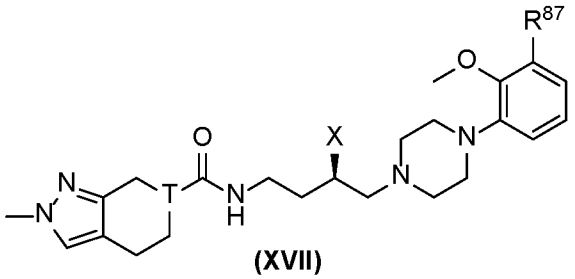
.

[0051] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the therapeutic compound comprises:



.

[0052] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (XVII):

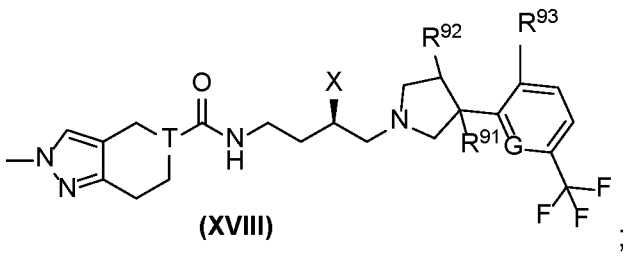


(XVII) ;

wherein T is C or N; and

wherein R87 is H or halogen.

[0053] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (XVIII):



(XVIII) ;

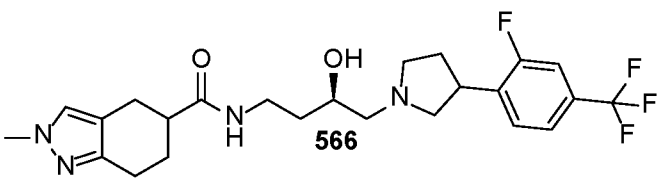
wherein T is C or N;

wherein R^{91} and R^{92} are independently H, methyl, halogen, or linked covalently at a methylene to form a three-carbon ring;

wherein R^{93} is H or halogen; and

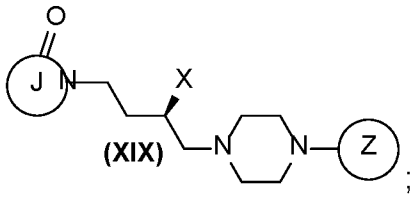
wherein G is C or N.

[0054] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the therapeutic compound comprises:



566 .

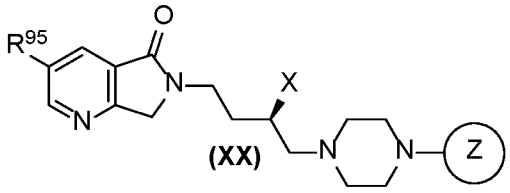
[0055] A therapeutic compound having Formula (XIX), its enantiomer, a racemate thereof, a prodrug thereof, a salt thereof, or any combination thereof:



(XIX);

[0056] wherein J is a cyclic, heterocyclic, bicyclic, or heterobicyclic lactam ring bound to a n-butyl linker through the lactam nitrogen; X is a hydrogen, a hydroxyl, or a methyl group substituent of the n-butyl linker; and Z is a substituted aryl bound to the n-butyl linker through a piperazine group.

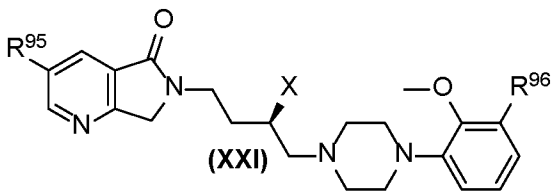
[0057] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (XIX) is represented by Formula (XX):



(XX); and

wherein R^{95} is H, methyl, ethyl, or halogen.

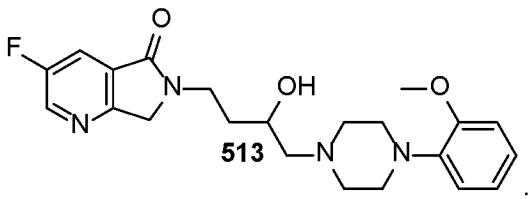
[0058] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (XIX) is represented by Formula (XXI):



(XXI); and

wherein R^{95} and R^{96} are independently H, methyl, ethyl, or halogen.

[0059] The therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the therapeutic compound comprises:



[0060] A pharmaceutical composition comprising a therapeutically effective amount of the therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, a salt thereof, or any combination thereof, together with a pharmaceutically acceptable carrier.

[0061] The pharmaceutical composition of any preceding or following embodiment/feature/aspect, wherein the therapeutic compound is a selective dopamine D_3 receptor antagonist, or a selective dopamine D_3 receptor agonist, or both.

[0062] The pharmaceutical composition of any preceding or following embodiment/feature/aspect, wherein the therapeutic compound has greater than 50 times D_3 receptor selectivity relative to D_2 receptor selectivity.

[0063] The pharmaceutical composition of any preceding or following embodiment/feature/aspect, wherein the therapeutic compound has greater than 100 times D_3 receptor selectivity relative to D_2 receptor selectivity.

[0064] The pharmaceutical composition of any preceding or following embodiment/feature/aspect, wherein the therapeutic compound has at least a 10-fold therapeutic window as measured by the IC_{50} hERG toxicity relative to the minimally effective therapeutic dose.

[0065] The pharmaceutical composition of any preceding or following embodiment/feature/aspect, wherein the therapeutic compound has at least a 30-fold therapeutic window as measured by the IC_{50} hERG toxicity dose relative to the minimally effective therapeutic dose.

[0066] The pharmaceutical composition of any preceding or following embodiment/feature/aspect, wherein the therapeutic compound is a first therapeutic compound, and the pharmaceutical composition further comprises a second therapeutic compound.

[0067] The pharmaceutical composition of any preceding or following embodiment/feature/aspect, wherein the second therapeutic compound comprises a selective dopamine D_1 receptor modulator, a selective dopamine D_2 receptor modulator, a selective dopamine D_4 receptor modulator, or a selective dopamine D_5 receptor modulator, or any combination thereof.

[0068] The pharmaceutical composition of any preceding or following embodiment/feature/aspect, wherein the second therapeutic compound comprises a selective dopamine D_1 receptor modulator, a selective dopamine D_2 receptor modulator, or both.

[0069] The pharmaceutical composition of any preceding or following embodiment/feature/aspect, wherein the second therapeutic compound comprises a selective dopamine D_1 receptor modulator, a selective dopamine D_5 receptor modulator, or both.

[0070] The pharmaceutical composition of any preceding or following embodiment/feature/aspect, wherein the second therapeutic compound comprises a selective dopamine D_2 receptor modulator, a selective dopamine D_4 receptor modulator, or both.

[0071] The pharmaceutical composition of any preceding or following embodiment/feature/aspect, wherein the first therapeutic compound comprises a selective dopamine D_2 receptor agonist, and the second therapeutic compound comprises a selective dopamine D_3 antagonist.

[0072] The pharmaceutical composition of any preceding or following embodiment/feature/aspect, wherein the second therapeutic compound comprises an antidepressant, or an antipsychotic, or both.

[0073] The pharmaceutical composition of any preceding or following embodiment/feature/aspect, wherein the second therapeutic compound is a Parkinson disease therapeutic compound.

[0074] A method of treating drug misuse or drug addiction, comprising administering to a patient in need thereof a composition comprising a therapeutically effective amount of the therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, a salt thereof, or any combination thereof optionally in combination with one or more additional active ingredients.

[0075] The method of any preceding or following embodiment/feature/aspect, wherein the patient has a history of misusing a stimulant, a depressant, an opioid, a cannabinoid, lysergic acid diethylamide (LSD), mescaline, psilocybin, nicotine, ethanol, a benzodiazepine, phencyclidine, ketamine, cocaine, or an amphetamine, or any combination thereof.

[0076] A method of treating a substance use disorder, comprising administering to a patient in need thereof a composition comprising a therapeutically effective amount of the therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, a salt thereof, or any combination thereof optionally in combination with one or more additional active ingredients.

[0077] The method of any preceding or following embodiment/feature/aspect, wherein the patient has one or more affective disorders, schizophrenia, or both.

[0078] The method of any preceding or following embodiment/feature/aspect, wherein the substance use disorder comprises a psychostimulant use disorder.

[0079] The method of any preceding or following embodiment/feature/aspect, wherein the patient has a history of misusing a stimulant comprising cocaine, an amphetamine, a methamphetamine, dextroamphetamine, levoamphetamine, methylenedioxymethamphetamine (MDMA), methylphenidate, modafinil, armodafinil, midodrine, oxymetazoline, dobutamine, ephedrine, pseudoephedrine, or phenylephrine, or any combination thereof.

[0080] A method of treating Parkinson Disease, comprising administering to a patient in need thereof a composition comprising a therapeutically effective amount of the therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, a salt thereof, or any combination thereof optionally in combination with one or more additional active ingredients.

[0081] The method of treating of treating Parkinson Disease of any preceding or following embodiment/feature/aspect, further comprising administering levodopa.

[0082] The method of treating of treating Parkinson Disease of any preceding or following embodiment/feature/aspect, wherein the therapeutic compound is a selective dopamine D_3 receptor agonist.

[0083] The method of treating Attention Deficit/Hyperactivity Disorder ("ADHD") of any preceding or following embodiment/feature/aspect, wherein the therapeutic compound is a selective dopamine D_3 receptor agonist.

[0084] A method of treating ADHD, comprising administering to a patient in need thereof a composition comprising a therapeutically effective amount of the therapeutic compound of any preceding or following embodiment/feature/aspect, its enantiomer, a racemate thereof, a prodrug thereof, a salt thereof, or any combination thereof optionally in combination with one or more additional active ingredients.

[0085] A kit comprising the therapeutic compound of any preceding or following embodiment/feature/aspect and a second therapeutic compound.

[0086] A method of synthesizing the therapeutic compound of any preceding or following embodiment/feature/aspect.

[0087] D_3R selective brain penetrant modulators are disclosed that possess superior physicochemical properties while minimizing hERG liability. D_3R selective modulators are provided that exhibit good aqueous kinetic solubility, permeability, and microsomal stabilities across different species. These compounds demonstrate a therapeutic window against hERG channel activity, which can be measured by a manual patch clamp assay. These compounds also have physicochemical properties that can provide higher free fractions in the brain that are 5 to15-fold above the binding concentrations for pharmacological action. The higher free fraction for these compounds as measured by the rat brain homogenate can lead to lower nonspecific binding in the human clinical studies and can lead to higher occupancy in the desired D_3R regions of the brain for pharmacological action.

[0088] D_3R selectivity over highly homologous D_2Rs and minimized hERG liability can be achieved. These compounds can address opioid addiction and can be, in principle, administered with oxycodone (and other opioids) to address the development of addiction without ameliorating the anti-nociceptic properties of the opioids. Use for substance use disorder (SUD), for example, with respect to methamphetamine and cocaine, is possible.

[0089] The disclosed compounds provide tools to treat addiction and has proven efficacious in the preclinical animal models both in attenuating self-administration and in reducing drug seeking behavior leading to reinstatement. As the D_3R antagonists have been shown to not diminish the antinociceptive actions of

oxycodone when administered together with the opioid, these can provide a new therapeutic modality to treat addiction and pain.

BRIEF DESCRIPTION OF THE DRAWINGS

[0090] For a further understanding of the nature, objects, and advantages of the present disclosure, reference should be had to the following detailed description, read in conjunction with the following drawings, wherein like reference numerals denote like elements.

[0091] FIGS. 1A-16B show chemical formulas and structures in accordance with the present disclosure.

[0092] FIGS. 17-81 show synthetic schemes in accordance with the present disclosure.

[0093] FIGS. 82-95 show graphs of data in accordance with the present disclosure.

DETAILED DESCRIPTION

[0094] Compounds are described using standard nomenclature. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this disclosure belongs.

[0095] The terms “a” and “an” do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced items. The term “or” means “and/or”. The terms “comprising,” “having,” “including,” and “containing” are to be construed as open-ended terms (*i.e.*, meaning “including, but not limited to”).

[0096] Recitation of ranges of values are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges are included within the range and independently combinable.

[0097] All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (for example, “such as”), is intended merely to better illustrate the disclosure and does not pose a limitation on the scope of the disclosure unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of

the disclosure as used herein. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art of this disclosure.

[0098] Furthermore, the disclosure encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims are introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, for example, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group.

[0099] All compounds are understood to include all possible isotopes of atoms occurring in the compounds. Isotopes include those atoms having the same atomic number but different mass numbers and encompass heavy isotopes and radioactive isotopes. By way of general example, and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include ^{11}C, ^{13}C, and ^{14}C. Accordingly, the compounds disclosed herein can include heavy or radioactive isotopes in the structure of the compounds or as substituents attached thereto. Examples of useful heavy or radioactive isotopes include ^{18}F, ^{15}N, ^{18}O, ^{76}Br, ^{125}I, and ^{131}I. Formulas, subformulas thereof, and compounds thereof include all pharmaceutically acceptable salts of the same.

[0100] The term “substituted” means that any one or more hydrogens on the designated atom or group is replaced with a selection from the indicated group, provided that the designated atom’s normal valence is not exceeded. Combinations of substituents and/or variables are permissible, for example, if such combinations result in stable compounds or useful synthetic intermediates. A stable compound or stable structure can be a compound that is sufficiently robust to survive isolation from a reaction mixture, and subsequent formulation into an effective therapeutic agent. A substituent or combination of substituents described with respect to one formula, subformula, or compound, can also be used in any other formula, subformula, or compound where consistent with valence, polarity, size, structure, and other parameters, unless otherwise indicated. Any substituent or combination of substituents described herein with respect to a particular atom or atoms can also be

excluded as an option for replacing one or more hydrogens at the particular atom, atoms, or subset thereof.

[0101] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent.

[0102] "Alkyl" refers to a group derived from a straight or branched chain saturated aliphatic hydrocarbon having the specified number of carbon atoms and having a valence of one, optionally substituted with one or more substituents where indicated, provided that the valence of the alkyl group is not exceeded.

[0103] "Cycloalkyl" refers to a group that comprises one or more saturated and/or partially saturated rings in which all ring members are carbon, the group having the specified number of carbon atoms. Cycloalkyl groups do not include an aromatic ring or a heterocyclic ring. "Heterocyclic" or "Heterocycloakyl" refers to a cycloalkyl group in which at least one carbon atom is replaced by N, O, P, S or an atom other than carbon.

[0104] "Alkanoyl" refers to a group having formula "alkyl-C(=O)-", wherein "alkyl" is the same as defined above.

[0105] "Cycloalkanoyl" refers to a group having formula "cycloalkyl-C(=O)-", wherein "cycloalkyl" is the same as defined above.

[0106] "Aryl" refers to a cyclic group in which all ring members are carbon and all rings are aromatic, the group having the specified number of carbon atoms, and having a valence of one, optionally substituted with one or more substituents where indicated, provided that the valence of the aryl group is not exceeded. More than one ring can be present, and any additional rings can be fused, pendant, spirocyclic, or a combination thereof.

[0107] "Heteroaryl" means a monovalent carbocyclic ring group that includes one or more aromatic rings, in which at least one ring member (for example, one, two or three ring members) is a heteroatom selected from nitrogen (N), oxygen (O), sulfur (S), and phosphorus (P), the group having the specified number of carbon atoms.

[0108] "Halogen" means fluoro, chloro, bromo, or iodo, and are defined herein to include all isotopes of the same, including heavy isotopes and radioactive isotopes. Examples of useful halo isotopes include ^{18}F, ^{76}Br, and ^{131}I. Additional isotopes will be readily appreciated by one of skill in the art.

[0109] "Substituted" means that the compound or group is substituted with at least one (for example, 1, 2, 3, or 4) substituent independently selected from a halogen (-F, -Cl, -Br, -I), a hydroxyl (-OH), a C_1-C_9 alkoxy, a C_1-C_9 haloalkoxy, an oxo (=O), a nitro ($-NO_2$), a cyano (-CN), an amino ($-NR_2$, wherein each R is independently hydrogen or C_1-C_{10} alkyl), an azido ($-N_3$), an amidino ($-C(=NH)NH_2$), a hydrazino ($-NHNH_2$), a hydrazono ($-C(=NNH_2)-$), a carbonyl (-C(=O)-), a carbamoyl group ($-C(O)NH_2$), a sulfonyl ($-S(=O)_2-$), a thiol (-SH), a thiocyano (-SCN), a tosyl ($CH_3C_6H_4SO_2-$), a carboxylic acid (-C(=O)OH), a carboxylic C_1-C_6 alkyl ester (-C(=O)OR wherein R is C_1-C_{10} alkyl), a carboxylic acid salt (-C(=O)OM) wherein M is an organic or inorganic anion, a sulfonic acid ($-SO_3H_2$), a sulfonic mono- or dibasic salt ($-SO_3MH$ or $-SO_3M_2$ wherein M is an organic or inorganic anion), a phosphoric acid ($-PO_3H_2$), a phosphoric acid mono- or dibasic salt ($-PO_3MH$ or $-PO_3M_2$ wherein M is an organic or inorganic anion), a C_1-C_{12} alkyl, a C_3-C_{12} cycloalkyl, a C_2-C_{12} alkenyl, a C_5-C_{12} cycloalkenyl, a C_2-C_{12} alkynyl, a C_6-C_{12} aryl, a C_7-C_{13} arylalkylene, a C_4-C_{12} heterocycloalkyl, and a C_3-C_{12} heteroaryl instead of hydrogen, provided that the substituted atom's normal valence is not exceeded.

[0110] "Pharmaceutical composition" means a composition comprising at least one active agent, such as a compound or salt of Formula (I), and at least one other substance, such as a carrier. Pharmaceutical compositions can meet the U.S. FDA's GMP (good manufacturing practice) standards for human or non-human drugs.

[0111] "Carrier" means a diluent, excipient, or vehicle with which an active compound is administered. A "pharmaceutically acceptable carrier" means a substance, for example, excipient, diluent, or vehicle, that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and can include a carrier that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable carrier" includes both one and more than one such carrier.

[0112] A "patient" means a human or non-human animal in need of medical treatment. Medical treatment can include treatment of an existing condition, such as a disease or disorder or diagnostic treatment. For example, the patient can be a human patient.

[0113] "Providing" means giving, administering, selling, distributing, transferring (for profit or not), manufacturing, compounding, or dispensing.

[0114] "Treatment" or "treating" means providing an active compound to a patient in an amount sufficient to measurably reduce any disease symptom, slow disease progression or cause disease regression. Treatment of the disease can be commenced before the patient presents symptoms of the disease.

[0115] A "therapeutically effective amount" of a pharmaceutical composition means an amount effective, when administered to a patient, to provide a therapeutic benefit such as an amelioration of symptoms, decrease disease progression, or cause disease regression.

[0116] A "therapeutic compound" means a compound which can be used for diagnosis or treatment of a disease. The compounds can be small molecules, peptides, proteins, or other kinds of molecules.

[0117] Compounds of formulas can contain one or more asymmetric elements such as stereogenic centers, stereogenic axes and the like, for example, asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. For compounds with two or more asymmetric elements, these compounds can additionally be mixtures of diastereomers. For compounds having asymmetric centers, all optical isomers in pure form and mixtures thereof are encompassed. In these situations, the single enantiomers, *i.e.*, optically active forms can be obtained by asymmetric synthesis, synthesis from optically pure precursors, or by resolution of the racemates. Resolution of the racemates can also be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column. All forms are contemplated herein regardless of the methods used to obtain them.

[0118] All forms (for example solvates, optical isomers, enantiomeric forms, polymorphs, free compound and salts) of an active agent can be employed either alone or in combination.

[0119] The term "chiral" refers to molecules, which have the property of non-superimposability of the mirror image partner.

[0120] "Stereoisomers" are compounds, which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

[0121] A "diastereomer" is a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different

physical properties, for example, melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers can separate under high resolution analytical procedures such as electrophoresis, crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column.

[0122] "Enantiomers" refer to two stereoisomers of a compound, which are non-superimposable mirror images of one another. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which can occur where there has been no stereoselection or stereospecificity in a chemical reaction or process.

[0123] Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory.

[0124] A "racemic mixture" or "racemate" is an equimolar (or 50:50) mixture of two enantiomeric species, devoid of optical activity. A racemic mixture can occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. Combinations of two enantiomeric species other than 50:50 racemic mixtures are also provided by the present disclosure, for example, 1:10,000, 1:1,000, 1:100, 1:10, 1:9, 1:7.5, 1:5, 1:3, 1:2.5, 1:2, or 1:1.5, or any opposite ratio, or any intervening ratio.

[0125] "Pharmaceutically acceptable salts" include derivatives of the disclosed compounds in which the parent compound is modified by making inorganic and organic, non-toxic, acid or base addition salts thereof. The salts of the present compounds can be synthesized from a parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate, or the like), or by reacting free base forms of these compounds with a

stoichiometric amount of the appropriate acid. Such reactions can be carried out in water or in an organic solvent, or in a mixture of the two. Generally, non-aqueous media such as ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are used, where practicable. Salts of the present compounds further include solvates of the compounds and of the compound salts.

[0126] 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 and the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, conventional non-toxic acid salts include those derived from inorganic acids, for example, hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids, for example, acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, mesylic, esylic, besylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, HOOC-(CH2)n-COOH where n is 0-4, and the like. Any suitable pharmaceutical salt can be used.

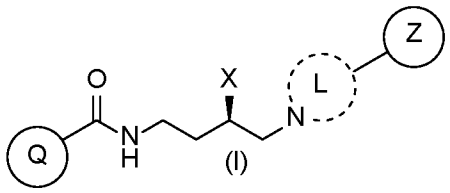
[0127] As used herein, “prodrug” is intended to include any covalently bonded carriers which release the active parent drug, for example, as according to a formula described herein, or other formulas or compounds employed in the methods of the present disclosure in vivo when such prodrug is administered to a mammalian subject. Because prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (for example, solubility, bioavailability, manufacturing, etc.) the compounds employed in the present methods can, if desired, be delivered in prodrug form. Thus, the present disclosure contemplates methods of delivering prodrugs. Prodrugs of the compounds employed in the present disclosure can 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. 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, iso-butyl, sec-butyl, tert-butyl, cyclopropyl, phenyl, benzyl, and phenethyl esters, and the like.

[0128] As used herein the term "beta-arrestin" is meant to encompass other notations commonly used in the art including "Beta-Arrestin", "β-arrestin", "β-Arrestin", "b-arrestin" and the like. As used herein the pain to be treated by the methods is not particularly limiting and can include chronic pain, acute pain, breakthrough pain, post-operative pain, perioperative pain, mild pain, moderate pain, severe pain, bone and joint pain, soft tissue pain, nerve pain, pain due to a disease or disorder, pain due to trauma, and the like, and a combination thereof.

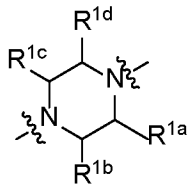
[0129] As used herein, the term Attention Deficit/Hyperactivity Disorder ("ADHD") also encompasses related disorders, including but not limited to Attention Deficit Disorder ("ADD"), Oppositional Defiant Disorder ("ODD"), Minimal Brain Dysfunction ("MBD"), Hyperkinetic Disorder, and the like.

[0130] Disclosed is a therapeutic compound having Formula (I), its enantiomer, a racemate thereof, a prodrug thereof, a salt thereof, or any combination thereof:



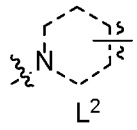
(I)

[0131] Q can be a first chemical moiety covalently bound through an amide bond to a n-butyl linker. X can be a hydrogen, a hydroxyl, or a methyl group substituent of the n-butyl linker. L can be a tertiary amine heterocyclic linker covalently bound to the n-butyl linker through the nitrogen of the tertiary amine. Z can be a second chemical moiety covalently bound to the tertiary amine heterocyclic linker. Q can



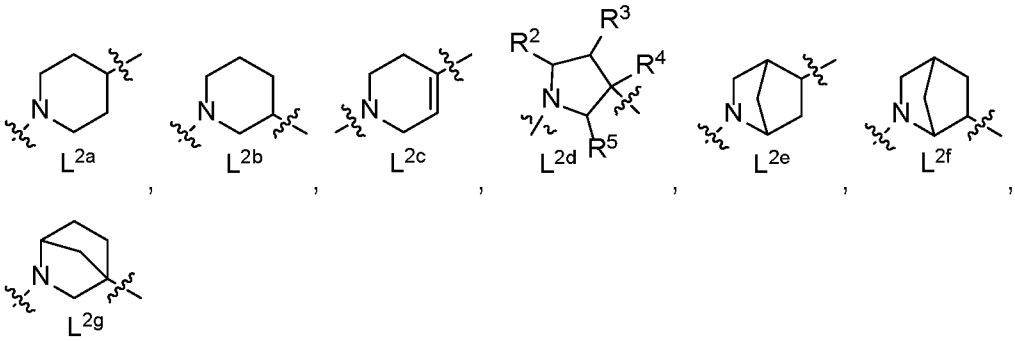
L^1

exclude indole and Z can comprise a substituted aryl. L can comprise



or , and R^{1a}, R^{1b}, R^{1c}, and R^{1d} are independently H, methyl, hydroxyl, or halogen, or R^{1a} and R^{1c} are bonds forming a bridge comprising methylene, or R^{1b} and R^{1d} are bonds forming a bridge comprising methylene. The therapeutic compound can be a selective dopamine D_3 receptor modulator. The therapeutic compound can be a selective dopamine D_3 receptor antagonist. The therapeutic compound can be a selective dopamine D3 receptor agonist.

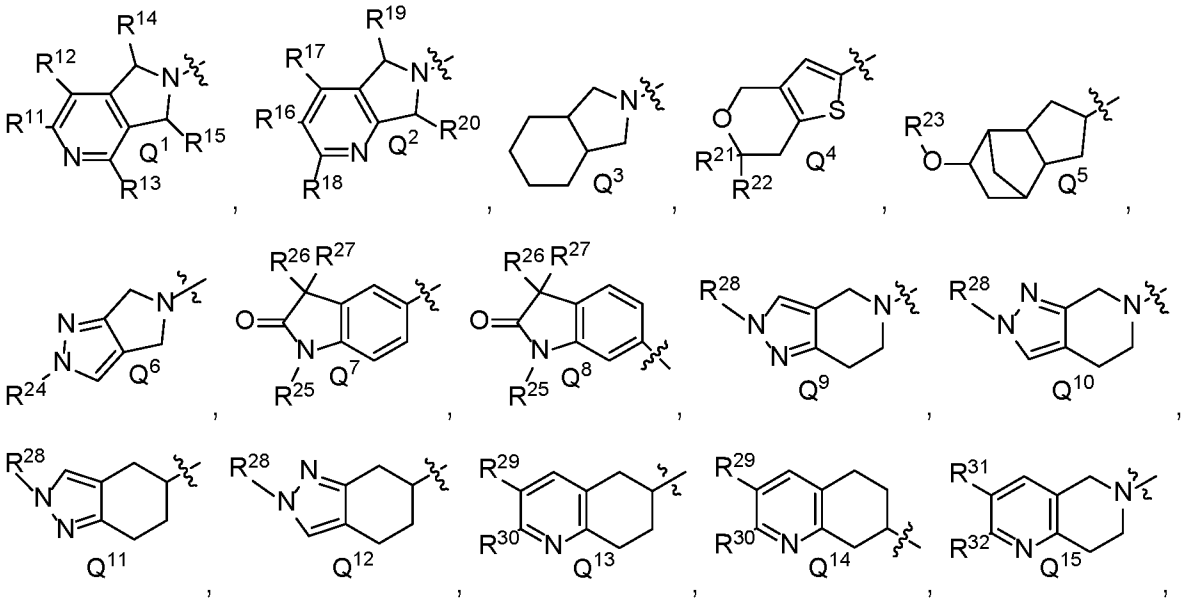
[0132] The second linker L2 can be, for example, selected from one of the following:

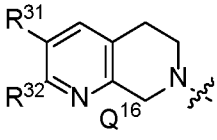
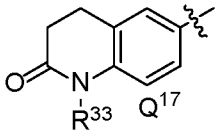
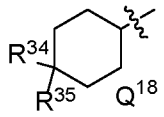
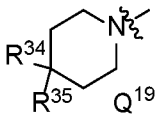
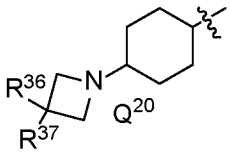
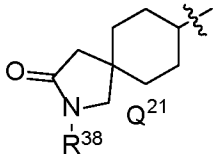


, and .

[0133] R^2 and R^5 can be, for example, independently H, methyl, hydroxyl, or halogen. R^3 and R^4 can be, for example, independently H, methyl, hydroxyl, or halogen, or linked covalently at a methylene to form a three-carbon ring.

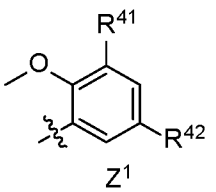
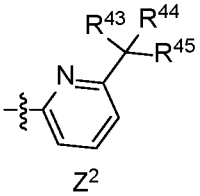
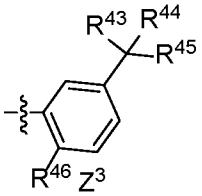
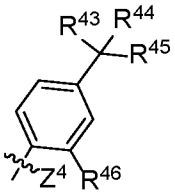
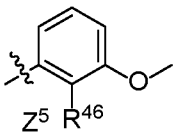
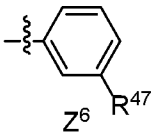
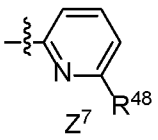
[0134] Q can be a first pharmacophore of the therapeutic compound. Q can be, for example, selected from one of the following:








, and

;

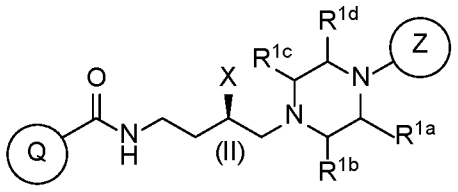
R^{11}, R^{12}, R^{13}, R^{16}, R^{17}, R^{18}, R^{29}, R^{30}, R^{31}, and R^{32} can be, for example, independently H, methyl, ethyl, methoxy, ethoxy, or halogen. R^{14}, R^{15}, R^{19}, R^{20}, R^{21}, R^{22}, R^{34}, R^{35}, R^{36}, and R^{37} can be, for example, independently H, methyl, ethyl, methoxy, ethoxy, or halogen. R^{26} and R^{27} can be, for example, independently H, methyl, ethyl, methoxy, ethoxy, or halogen, or methylenes covalently linked to form a three-carbon ring. R^{24}, R^{25}, R^{28}, R^{33}, and R^{38} can be, for example, independently H, methyl, or halogen. R^{23} can be, for example, methyl or ethyl.

[0135] Z can be a second pharmacophore of the therapeutic compound. Z can be, for example, selected from one of the following:







,
and

;

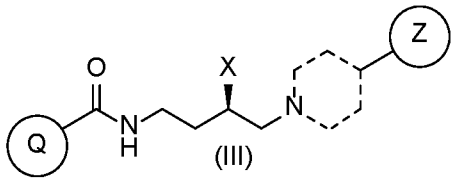
R^{41}, R^{42}, R^{46}, R^{47}, and R^{48} can be, for example, independently H, methyl, ethyl, or halogen. R^{43}, R^{44}, and R^{45} can be, for example, independently H or halogen.

[0136] Formula (I) can be, for example, represented by Formula (II):


;

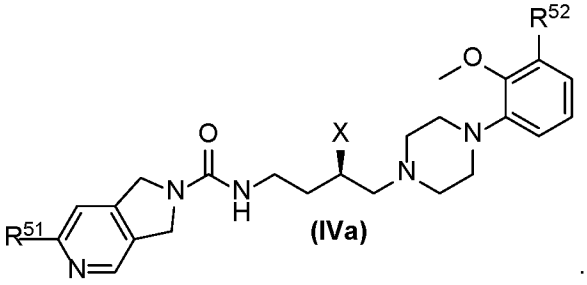
wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d} are independently H, methyl, hydroxyl, or halogen, or R^{1a} and R^{1c} are bonds forming a bridge comprising methylene, or R^{1b} and R^{1d} are bonds forming a bridge comprising methylene.

[0137] Formula (I) can be, for example, represented by Formula (III):



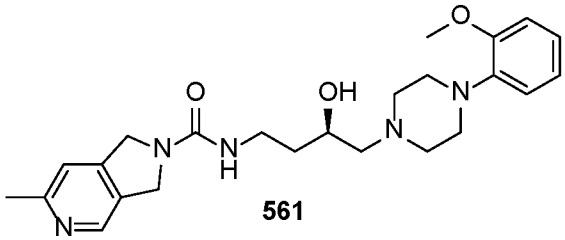
.

[0138] Formula (I) can be, for example, represented by Formula (IVa):



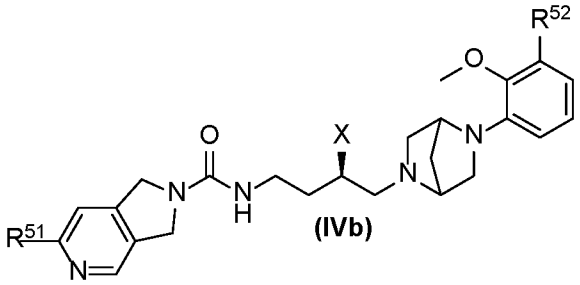
;

and.R^{51} and R^{52} can be, for example, independently H, methyl, ethyl, or halogen. The therapeutic compound can be, for example, one or more compounds set forth in FIG. 2A. For example, the therapeutic compound can be



.

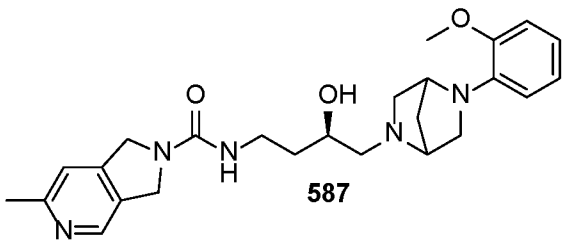
[0139] Formula (I) can be, for example, represented by Formula (IVb):



; and

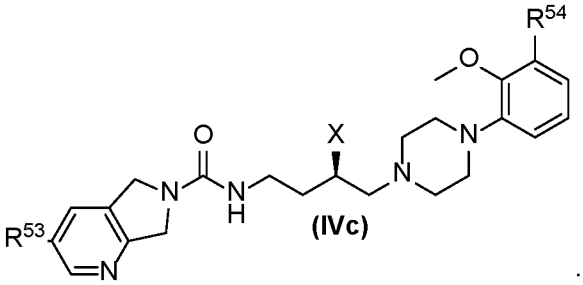
wherein R^{51} and R^{52} are independently H, methyl, ethyl, or halogen.

[0140] The therapeutic compound can be, for example, one or more compounds set forth in FIG. 2B. For example, the therapeutic compound can be



.

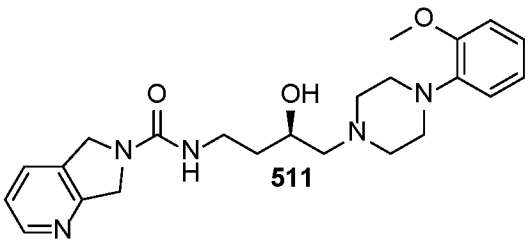
[0141] Formula (I) can be, for example, represented by Formula (IVc):



;

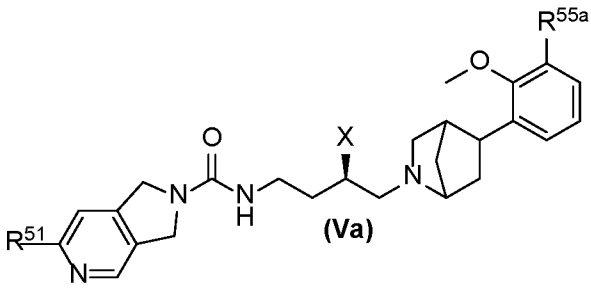
wherein R^{53} and R^{54} are independently H, methyl, ethyl, or halogen.

[0142] The therapeutic compound can be, for example, one or more compounds set forth in FIG. 2C. For example, the therapeutic compound can be



.

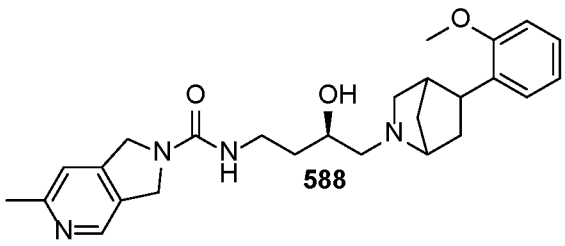
[0143] Formula (I) can be, for example, represented by Formula (Va):



; and

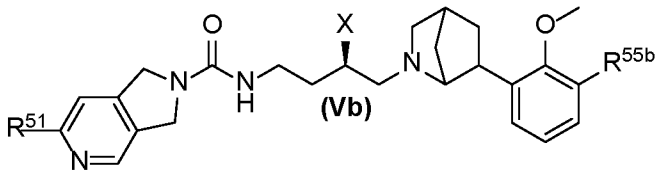
wherein R^{51} and R^{55b} are independently H, methyl, ethyl, or halogen.

[0144] The therapeutic compound can be, for example, one or more compounds set forth in FIG. 3A. For example, the therapeutic compound can be



.

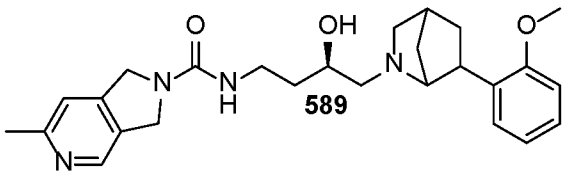
[0145] Formula (I) can be, for example, represented by Formula (Vb):



; and

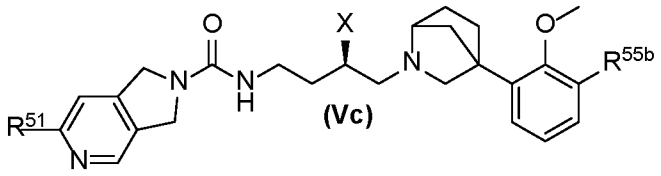
wherein R^{51} and R^{55b} are independently H, methyl, ethyl, or halogen.

[0146] The therapeutic compound can be, for example, one or more compounds set forth in FIG. 3B. For example, the therapeutic compound can be



.

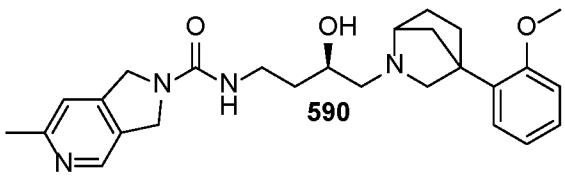
[0147] Formula (I) can be, for example, represented by Formula (Vc):



; and

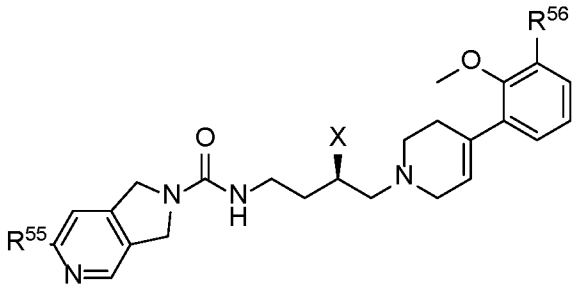
wherein R^{51} and R^{55b} are independently H, methyl, ethyl, or halogen.

[0148] The therapeutic compound can be, for example, one or more compounds set forth in FIG. 3C. For example, the therapeutic compound can be



.

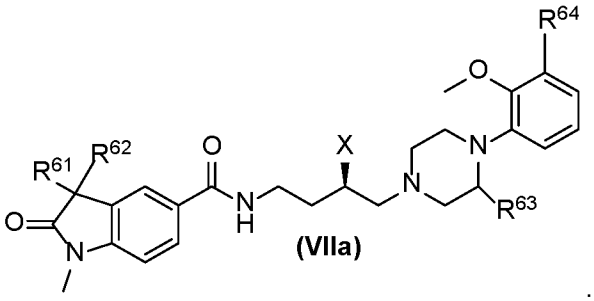
[0149] Formula (I) can be, for example, represented by Formula (VI):



(VI)

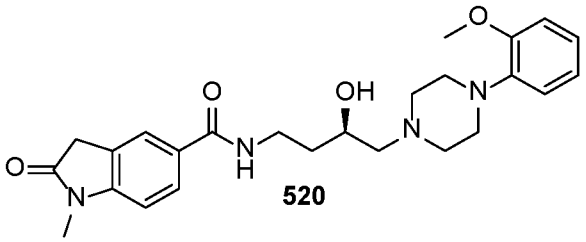
R^{55} and R^{56} are independently H, methyl, ethyl, or halogen. The therapeutic compound can be, for example, one or more compounds set forth in FIG. 4.

[0150] Formula (I) can be, for example, represented by Formula (VIIa):



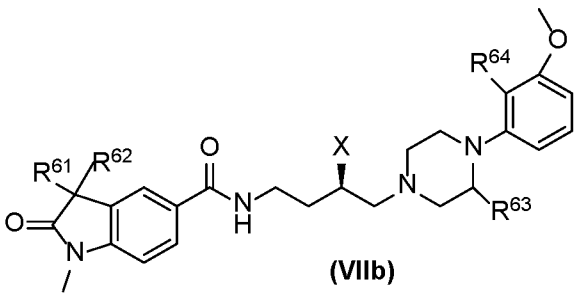
(VIIa)

[0151] R^{61} and R^{62} can be, for example, independently H or methyl, or methylenes covalently linked to form a three-carbon ring. R^{63} can be, for example, H, methyl, hydroxyl, or halogen. R^{64} can be methyl, ethyl, or halogen. The therapeutic compound can be, for example, one or more compounds set forth in FIG. 5A. For example, the therapeutic compound can be:



520

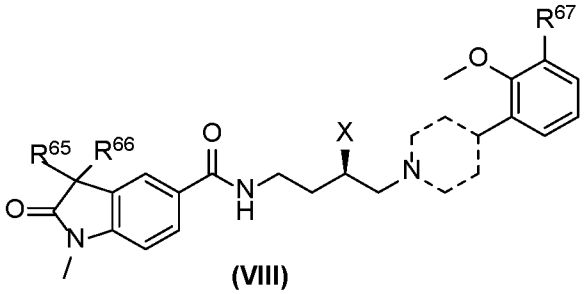
[0152] Formula (I) can be, for example, represented by Formula (VIIb):



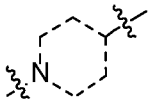
(VIIb)

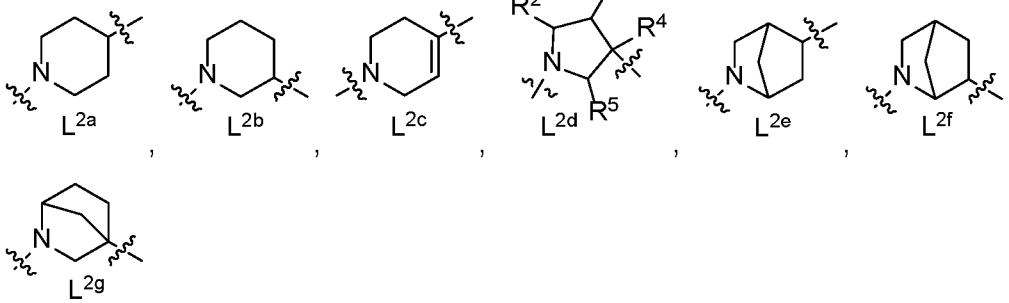
[0153] R^{61} and R^{62} can be, for example, independently H or methyl, or methylenes covalently linked to form a three-carbon ring. R^{63} can be, for example, H, methyl, hydroxyl, or halogen. R64 can be, for example, methyl, ethyl, or halogen. The therapeutic compound can be, for example, a compound set forth in FIG. 5B.

[0154] Formula (I) can be, for example, represented by Formula (VIII):



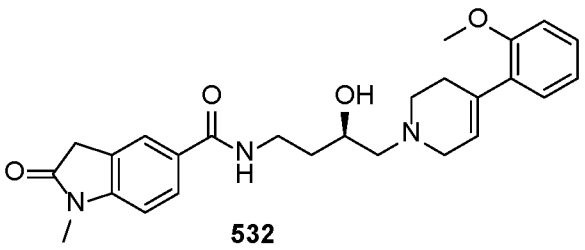
(VIII)

[0155] R^{65} and R^{66} can be, for example, independently H or methyl, or methylenes covalently linked to form a three-carbon ring to form a three-carbon ring. Linker  can be selected from one of the following:



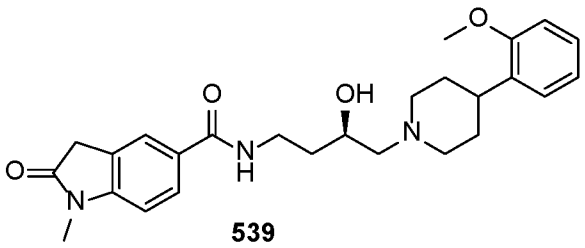
L^{2a}, **L^{2b}**, **L^{2c}**, **L^{2d}**, **L^{2e}**, **L^{2f}**, and **L^{2g}**.

[0156] R^{2}, and R^{5} can be, for example, independently H, methyl, hydroxyl, or halogen. R^{67} can be methyl, ethyl, or halogen. R^{3} and R^{4} can be, for example, independently H, methyl, hydroxyl, or halogen, or methylenes covalently linked to form a three-carbon ring. The therapeutic compound can be, for example, one or more compounds set forth in FIG. 6. For example, the therapeutic compound can be



532

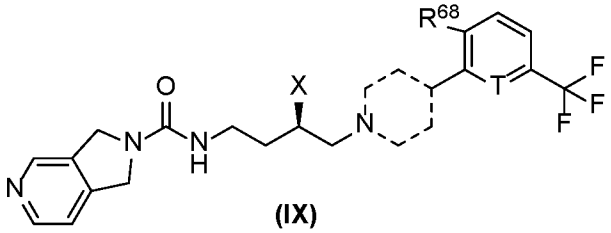
, or



539

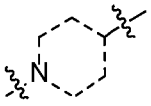
, or both.

[0157] Formula (I) can be, for example, represented by Formula (IX):

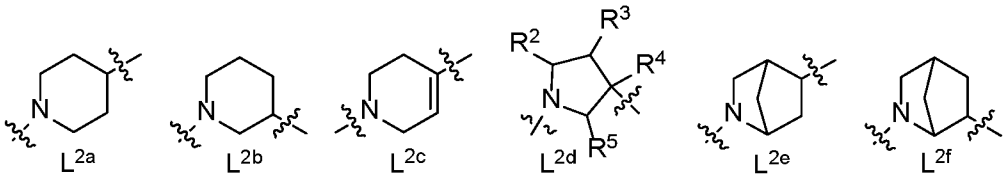


(IX)

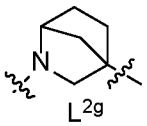
.



can be, for example, selected from one of the following:



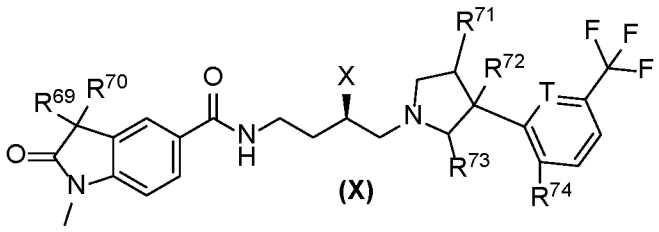
, and



.

[0158] R^2, R^3, R^4, and R^5 can be, for example, independently H, methyl, hydroxyl, or halogen. R^{68} can be, for example, H or halogen. T can be C or N. The therapeutic compound can be, for example, one or more compounds set forth in FIG. 7.

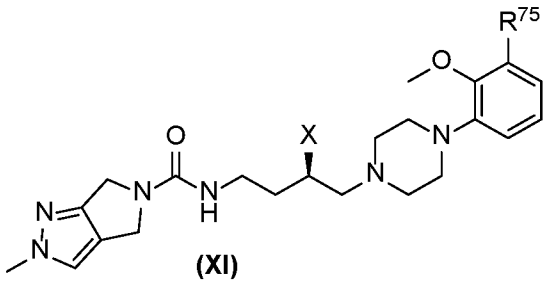
[0159] Formula (I) can be, for example, represented by Formula (X):



(X)

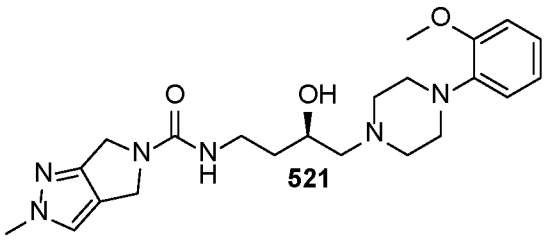
[0160] R^{69} and R^{70} can be, for example, independently H or methyl, or methylene covalently linked to form a three-carbon ring. R^{71} and R^{72} can be, for example, independently H, methyl, halogen, or linked covalently at a methylene to form a three-carbon ring. R^{73} can be, for example, H, methyl, or halogen. R^{74} can be, for example, H or halogen. T can be, for example, C or N. The therapeutic compound can be, for example, one or more compounds set forth in FIG. 8.

[0161] Formula (I) can be, for example, represented by Formula (XI):



(XI)

[0162] R^{75} can be, for example, H or halogen. The therapeutic compound can be, for example, one or more compounds set forth in FIG. 9. For example, the therapeutic compound can be:



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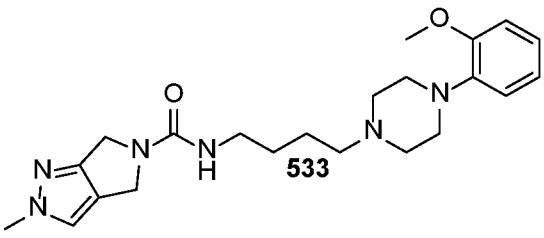
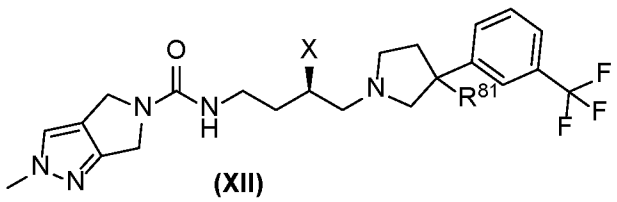
, or



533

, or both.

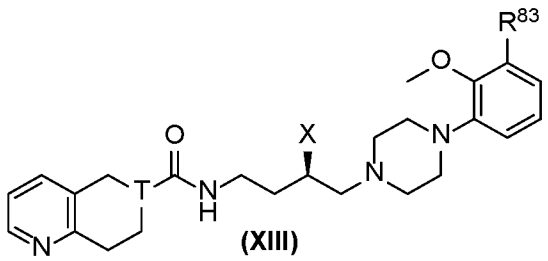
[0163] Formula (I) can be, for example, represented by Formula (XII):



(XII)

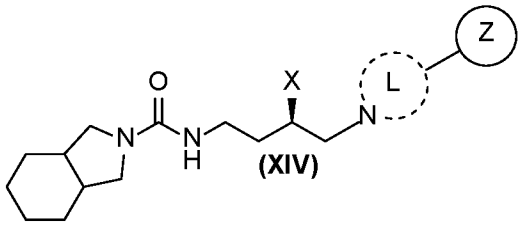
R^{81} can be, for example, H, methyl, or halogen. The therapeutic compound can be, for example, one or more compounds set forth in FIG. 10.

[0164] Formula (I) can be, for example, represented by Formula (XIII):



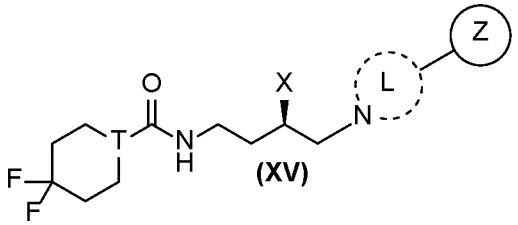
[0165] T can be, for example, C or N. R^{83} can be, for example, H or halogen. The therapeutic compound can be, for example, one or more compounds set forth in FIG. 11.

[0166] Formula (I) can be, for example, represented by Formula (XIV):

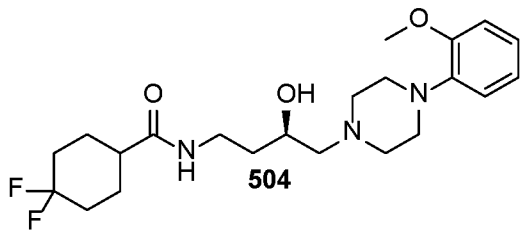


[0167] The therapeutic compound can be, for example, one or more compounds set forth in FIG. 12.

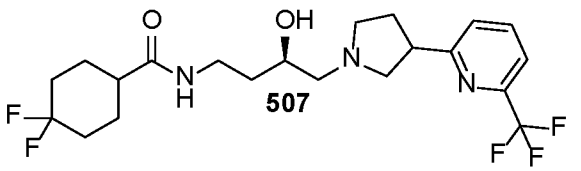
[0168] Formula (I) can be, for example, represented by Formula (XV):



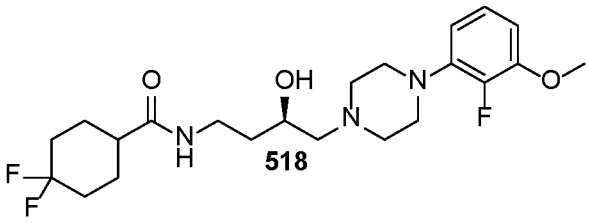
[0169] T can be, for example, C or N. The therapeutic compound can be, for example, one or more compounds set forth in FIG. 13. For example, the therapeutic compound can be:



,



,



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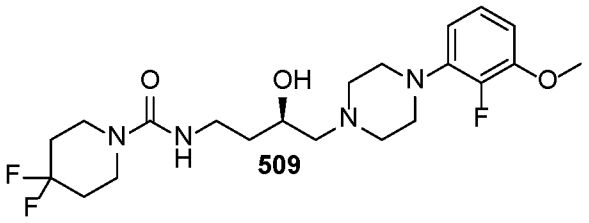
, or

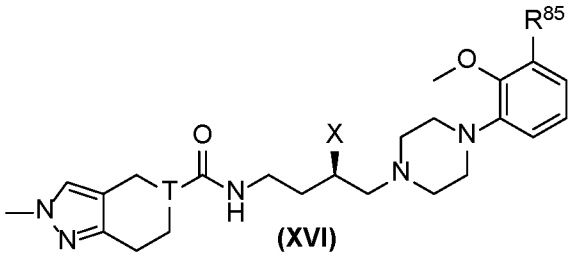


509

, or

any combination thereof.

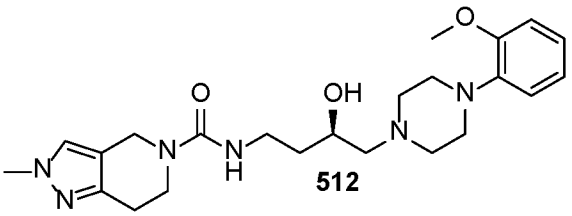
[0170] Formula (I) can be, for example, represented by Formula (XVI):



(XVI)

.

T can be, for example, C or N. R^{85} can be, for example, H or halogen. The therapeutic compound can be, for example, one or more compounds set forth in FIG. 14A. For example, the therapeutic compound can be:



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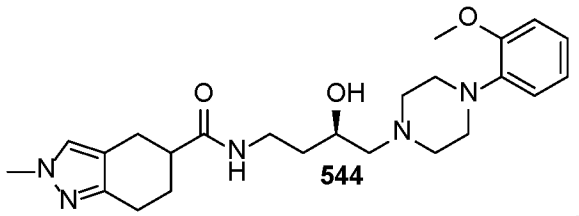
,



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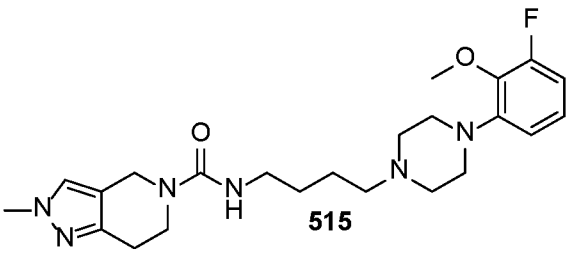
,

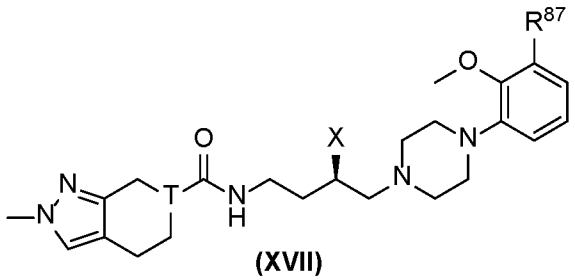
or



515

, or any combination thereof.

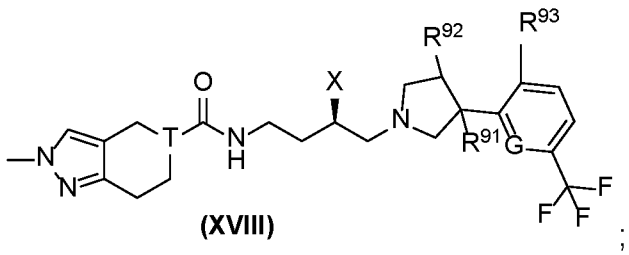
[0171] Formula (I) can be, for example, represented by Formula (XVII):



(XVII)

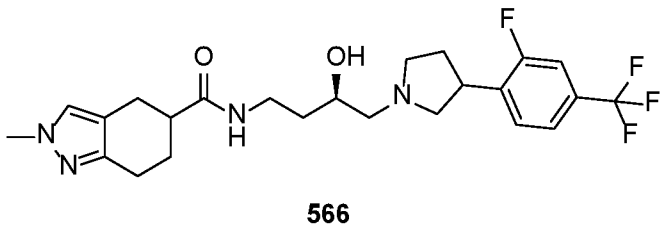
T can be, for example, C or N. R^{87} can be, for example, H or halogen. The therapeutic compound can be, for example, a compound set forth in FIG. 14B.

[0172] Formula (I) can be, for example, represented by Formula (XVIII):



(XVIII);

T can be, for example, C or N. R^{91} and R^{92} can be, for example, independently H, methyl, halogen, or linked covalently at a methylene to form a three-carbon ring. R^{93} can be, for example, H or halogen. G can be, for example, C or N. The therapeutic compound can be, for example, one or more compounds set forth in FIG. 15. For example, the therapeutic compound can be:



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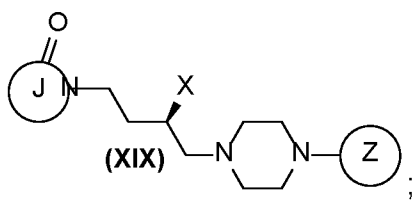
[0173] The therapeutic compound can be, for example, one or more compounds set forth in FIG. 16A, its enantiomer, a racemate thereof, a prodrug thereof, a salt thereof, or any combination thereof.

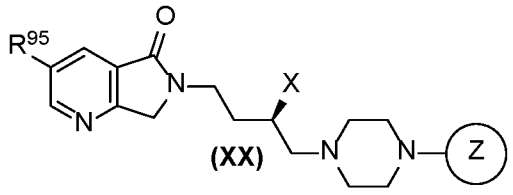
[0174] A therapeutic compound having Formula (XIX), its enantiomer, a racemate thereof, a prodrug thereof, a salt thereof, or any combination thereof is provided:



(XIX);

wherein J is a cyclic, heterocyclic, bicyclic, or heterobicyclic lactam ring bound to a n-butyl linker through the lactam nitrogen; X is a hydrogen, a hydroxyl, or a methyl group substituent of the n-butyl linker; and Z is a substituted aryl bound to the n-butyl linker through a piperazine group.

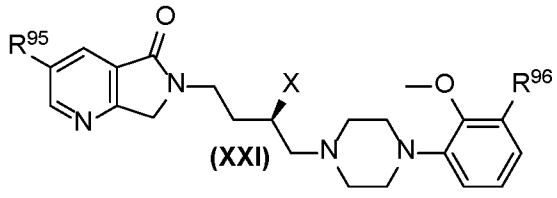
[0175] Formula (XIX) can be, for example, represented by Formula (XX):



(XX) ; and

wherein R^{95} is H, methyl, ethyl, or halogen.

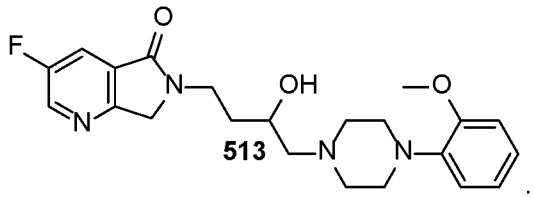
[0176] Formula (XIX) can be, for example, represented by Formula (XXI):



(XXI) ; and

wherein R^{95} and R^{96} are independently H, methyl, ethyl, or halogen.

[0177] The therapeutic compound can be, for example, one or more compounds set forth in FIG. 16B. For example, the therapeutic compound can be



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[0178] A pharmaceutical composition is provided that can comprise a therapeutically effective amount of the therapeutic compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, a salt thereof, or any combination thereof, together with a pharmaceutically acceptable carrier. The therapeutic compound is a selective dopamine D_3 receptor antagonist, or a selective dopamine D_3 receptor agonist, or both. The therapeutic compound can have greater than 5 times, greater than 10 times, greater than 25 times, greater than 100 times greater than 150 times, greater than 200 times, greater than 250 times, greater than 350 times, or greater than 500 times, or any range times therebetween, or any intervening value times D_3 receptor selectivity relative to D_2 receptor selectivity. The

therapeutic compound can have at least a 2-fold, at least a 5-fold, at least a 10-fold, at least a 15-fold, at least a 20-fold, at least a 25-fold, at least a 50-fold, or at least a 100-fold, or any range-fold therebetween, or any intervening value-fold, therapeutic window as measured by the IC_{50} hERG toxicity relative to the minimally effective therapeutic dose.

[0179] The therapeutic compound can be a first therapeutic compound, and the pharmaceutical composition can further comprise a second therapeutic compound. The pharmaceutical second therapeutic compound can comprise a selective dopamine D_1 receptor modulator, a selective dopamine D_2 receptor modulator, a selective dopamine D_4 receptor modulator, or a selective dopamine D_5 receptor modulator, or any combination thereof. The second therapeutic compound can comprise, for example, a selective dopamine D_1 receptor modulator, a selective dopamine D_2 receptor modulator, or both. The second therapeutic compound can comprise a selective dopamine D_1 receptor modulator, a selective dopamine D5 receptor modulator, or both. The second therapeutic compound can comprise a selective dopamine D_2 receptor modulator, a selective dopamine D_4 receptor modulator, or both. The first therapeutic compound can comprise a selective dopamine D_2 receptor agonist, and the second therapeutic compound comprise a selective dopamine D_3 antagonist. Dopamine receptors can be characterized as one of five subtypes—D_1 receptors, D_2 receptors, D_3 receptors, D_4 receptors, and D_5 receptors. Dopamine receptors and their modulators can be groups into two families—the D_1 receptor family (D_1 and D_5 receptors) and the D_2 receptor family (D_2, D_3, and D_4 receptors). The therapeutic compound of the present disclosure and a second therapeutic compound can affect the same receptor subtype, or family, or both. The therapeutic compound of the present disclosure and a second therapeutic compound can affect different receptor subtypes, or different families, or both. The second therapeutic compound can comprise an antidepressant, or an antipsychotic, or both. The second therapeutic compound can be a Parkinson disease therapeutic compound.

[0180] Pharmaceutical compositions are provided by the present disclosure. For example, a pharmaceutical composition is provided that can comprise a therapeutically effective amount of one or more compounds disclosed herein, their enantiomers, racemates thereof, prodrugs thereof, salts thereof, or any combination

thereof, together with a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier can be, for example, selected from the group consisting of binders, buffering agents, coloring agents, diluents, disintegrants, emulsifiers, flavorants, glidants, lubricants, preservatives, stabilizers, surfactants, tableting agents, and wetting agents, and combinations thereof. The compound of the pharmaceutical composition can be a first therapeutic compound and the pharmaceutical composition can further comprise a second therapeutic compound. The first and second therapeutic compounds can act additively or synergistically.

[0181] The second therapeutic compound can comprise, for example, an antidepressant, or an antipsychotic, or both. Antidepressants can include one or more of a selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine uptake inhibitor (SNRI), a 5-HT modulator, a unicyclic antidepressant, a tricyclic antidepressant (TCA), a tetracyclic antidepressant, a mixed norepinephrine/serotonin reuptake inhibitor or receptor blocker, a NMDA antagonist, a GABA modulator, a mixed-action drug, and a monoamine oxidase inhibitor. For example, the antidepressant can include one or more of fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram, amitriptyline, nortriptyline, protriptyline, imipramine, desipramine, doxepin, clomipramine, trimipramine, venlafaxine, desvenlafaxine, duloxetine, maprotiline, milnacipran, mirtazapine, vilazodone, bupropion, trazodone, nefazodone, vortioxetine, amoxapine, phenelzine, tranylcypromine, isocarboxid, selegiline, esketamine, and brexanolone. Antipsychotics can include, for example, a first-generation antipsychotic agent, or a second antipsychotic agent, or both. Antipsychotics can include, for example, one or more of a phenothiazine, a thioxanthene, a butyrophenone, a dibenzodiazepine, a benzisoxazole, a thienobenzodiazepine, a dibenzothiazepine, a dihydroindolone, and a dihydrocarbostyril. For example, the antipsychotic can include one or more chlorpromazine, thioridazine, perphenazine, loxapine, molindone, pimoizide, loxapine, haloperidol, fluphenazine, trifluoperazine, thiothixene, clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, iloperidone, asenapine, and lurasidone. The second therapeutic compound can include an anxiolytic, for example, one or more of diazepam, flurazepam, triazolam, lorazepam, alprazolam, chlordiazepoxide, oxazepam, temazepam, clonazepam, and buspirone. The anxiolytic can be a benzodiazepine, or a non-bezodiazepine. The

second therapeutic compound can include a mood stabilizer. The mood stabilizer can include, for example, one or more of lithium, valproic acid, carbamazepine, oxcarbazepine, and lamotrigine. For methods of treatment, a second or further therapeutic compound can be administered separately or in combination with the first therapeutic agent.

[0182] Compounds disclosed herein can be administered as the neat chemical, or can be administered as a pharmaceutical composition. Accordingly, the disclosure encompasses pharmaceutical compositions comprising a therapeutically effective amount of a compound or pharmaceutically acceptable salt of a compound, together with at least one pharmaceutically acceptable carrier. The pharmaceutical composition can contain a therapeutically effective amount of the compound or salt as the only active agent, and can contain at least one additional active agent. The pharmaceutical composition can be in a dosage form that contains from about 0.1 mg to about 2000 mg, from about 10 mg to about 1000 mg, from about 100 mg to about 800 mg, or from about 200 mg to about 600 mg of a compound, and optionally from about 0.1 mg to about 2000 mg, from about 10 mg to about 1000 mg, from about 100 mg to about 800 mg, or from about 200 mg to about 600 mg of an additional active agent in a unit dosage form. The pharmaceutical composition can be in a dosage form that contains about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg of a compound, and optionally about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg of an additional active agent in a unit dosage form. The pharmaceutical composition can also include a molar ratio of a compound and an additional active agent. For example, the pharmaceutical composition can contain a molar ratio of about 0.5:1, about 1:1, about 2:1, about 3:1 or from about 1.5:1 to about 4:1 of an additional active agent to a compound.

[0183] Compounds disclosed herein can be administered orally, topically, parenterally, by inhalation or spray, sublingually, transdermally, via buccal

administration, rectally, as an ophthalmic solution, or by other means, in dosage unit formulations containing conventional pharmaceutically acceptable carriers. The pharmaceutical composition can be formulated as any pharmaceutically useful form, for example, as an aerosol, a cream, a gel, a pill, a capsule, a tablet, a syrup, a transdermal patch, or an ophthalmic solution. Some dosage forms, such as tablets and capsules, are subdivided into suitably sized unit doses containing appropriate quantities of the active components, for example, a therapeutically effective amount to achieve the desired purpose.

[0184] Carriers include excipients and diluents of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the patient being treated. The carrier can be inert or it can possess pharmaceutical benefits of its own. The amount of carrier employed in conjunction with the compound is sufficient to provide a practical quantity of material for administration per unit dose of the compound.

[0185] Classes of carriers include, but are not limited to binders, buffering agents, coloring agents, diluents, disintegrants, emulsifiers, flavorants, glidants, lubricants, preservatives, stabilizers, surfactants, tableting agents, and wetting agents. Some carriers can be listed in more than one class, for example vegetable oil can be used as a lubricant in some formulations and a diluent in others. Exemplary pharmaceutically acceptable carriers include sugars, starches, celluloses, powdered tragacanth, malt, gelatin, talc, and vegetable oils. Optional active agents can be included in a pharmaceutical composition, which do not substantially interfere with the activity of the compound of the present disclosure.

[0186] The pharmaceutical compositions/combinations can be formulated for oral administration. These compositions contain between 0.1 and 99 weight % (wt%) of a compound and usually at least about 5 wt% of a compound of Formula (I). Compositions can contain from about 25 wt% to about 50 wt% or from about 5 wt% to about 75 wt% of the compound. Compositions can contain about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, or 95 wt% of the compound.

[0187] Methods of treatment are provided by the present disclosure that employ one or more compounds disclosed herein. The patient (subject) can be a mammal, and more specifically, a human, or non-human patients such as companion animals, for

example, cats, dogs, and livestock animals. A method of treating drug misuse or drug addiction is provided. The method can comprise administering to a patient in need thereof a composition comprising a therapeutically effective amount of a therapeutic compound of the present disclosure, its enantiomer, a racemate thereof, a prodrug thereof, a salt thereof, or any combination thereof optionally in combination with one or more additional active ingredients. The patient can be or have been taking methadone, or buprenorphine, or both. The patient can have had a history of misusing a stimulant, a depressant, an opioid, a cannabinoid, lysergic acid diethylamide (LSD), mescaline, psilocybin, nicotine, ethanol, a benzodiazepine, phencyclidine, ketamine, cocaine, or an amphetamine, or any combination thereof. For example, the patient can be being treated with one or more partial μ-opioid agonists to reduce cravings and blunt the effect of withdrawal.

[0188] A method of treating a substance use disorder is provided. The method can comprise administering to a patient in need thereof a composition comprising a therapeutically effective amount of a therapeutic compound of the present disclosure, its enantiomer, a racemate thereof, a prodrug thereof, a salt thereof, or any combination thereof optionally in combination with one or more additional active ingredients. The patient can have, for example, one or more affective disorders, schizophrenia, or both. The substance use disorder can comprise, for example, a psychostimulant use disorder. The patient can have had a history of misusing a stimulant comprising, for example, cocaine, an amphetamine, a methamphetamine, dextroamphetamine, levoamphetamine, methylenedioxymethamphetamine (MDMA), methylphenidate, modafinil, armodafinil, midodrine, oxymetazoline, dobutamine, ephedrine, pseudoephedrine, or phenylephrine, or any combination thereof. The method can comprise administering to a patient in need thereof a composition comprising a therapeutically effective amount of a therapeutic compound of the present disclosure, its enantiomer, a racemate thereof, a prodrug thereof, a salt thereof, or any combination thereof in combination with one or more additional active ingredients. Exemplary additional active ingredients that can be used in combination with the therapeutic compound of present disclosure include bremazocine, buprenorphine, butorphanol, carfentanyl, codeine, cyclazocine, dezocine, diamorphine, dihydrocodeine, dihydromorphine, dihydromorphinone (aka hydromorphone), enadoline, eseroline, ethylmorphine, etonitazine, etorphine,

fentanyl, hydrocodone, levophenacylmorphan, levorphanol, meperidine/pethidine, methadone, morphine, nalbuphine, nicomorphine, oxycodone, oxymorphone, pentazocine, phenazocine, picenadol, tramadol, tapentadol, or a combination thereof.

[0189] A method of treating pain is provided. The method can comprise administering to a patient in need thereof a composition comprising a therapeutically effective amount of a therapeutic compound of the present disclosure, its enantiomer, a racemate thereof, a prodrug thereof, a salt thereof, or any combination thereof optionally in combination with one or more additional active ingredients. The method can comprise administering to a patient in need thereof a composition comprising a therapeutically effective amount of a therapeutic compound of the present disclosure, its enantiomer, a racemate thereof, a prodrug thereof, a salt thereof, or any combination thereof in combination with one or more additional active ingredients. Exemplary additional active ingredients that can be used in combination with the therapeutic compound of present disclosure include bremazocine, buprenorphine, butorphanol, carfentanyl, codeine, cyclazocine, dezocine, diamorphine, dihydrocodeine, dihydromorphine, dihydromorphinone (aka hydromorphone), enadoline, eseroline, ethylmorphine, etonitazine, etorphine, fentanyl, hydrocodone, levophenacylmorphan, levorphanol, meperidine/pethidine, methadone, morphine, nalbuphine, nicomorphine, oxycodone, oxymorphone, pentazocine, phenazocine, picenadol, tramadol, tapentadol, or a combination thereof.

[0190] A method of treating Parkinson Disease is provided. The method can comprise administering to a patient in need thereof a composition comprising a therapeutically effective amount of a therapeutic compound of the present disclosure, its enantiomer, a racemate thereof, a prodrug thereof, a salt thereof, or any combination thereof optionally in combination with one or more additional active ingredients. The therapeutic compound can be, for example, a selective dopamine D_3 receptor agonist. The patient can have issues with locomotion, catalepsy, or hyperprolactinemia, or any combination thereof. The method can further comprise administering levodopa. Levodopa can be administered with carbidopa or other carboxylase inhibitor to reduce the amount levodopa converted to dopamine before the levodopa crosses the blood-brain barrier. The dopamine and levodopa can be

administered together as an oral disintegrating dosage form, for example, PARCOPA, or as a controlled release formulation, for example, as RYTARY. A combination of levodopa, carbidopa, and a catechol-O-methyl transferase (COMT) inhibitor, for example, STALEVO. Levodopa and/or other therapeutic compounds can be administered orally and/or locally, for example, in the small intestine. One or more therapeutic compounds of the present disclosure can be administered in combination with one or more additional Parkinson dopamine receptor modulators, for example, agonists. Additional agonists can comprise D_2 receptor agonists, for example, PARLODEl (bromocriptine, PERMAX (pergolide), REQUIP (ropinirole), or any combination thereof. The dopamine receptor agonist can comprise an ergot derivative. Additional agonists can comprise D_3 receptor agonists, for example, MIRAPEX (pramipexole). The second therapeutic compound can comprise a dopamine catabolic enzyme, for example, monoamine oxidase (MAO) inhibitor, or a catechol-O-methyl transferase (COMT) inhibitor, or both. The MAO inhibitor can comprise an inhibitor of a MAO A, or a MAO B, or both. The monoamine oxidase inhibitor can comprise, for example, SELEGILINE (deprenyl), AZILECT (rasagiline), or Xadago (safinamide), or any combination thereof. The COMT inhibitor can comprise, for example, TASMAR (tolcapone), COMTAN (entacapone), or ONGENTYS (opicapone), or any combination thereof. An acetylcholine-blocking agent can be used in combination with the therapeutic compositions of the present disclosure. Acetylcholine-blocking agents can comprise, for example, benztropine mesylate, biperiden, orphenadrine, procyclidine, or trihexyphenidyl, or any combination thereof. Other therapeutic compounds that can be used in combination with the therapeutic compounds of the present disclosure include, for example, apomorphine, amantadine, or istradefylline, or any combination thereof. Examples of therapeutic compounds for use in Parkinson disease can comprise compound **509**, or compound **518**, or both. Therapeutic compounds of the present disclosure can be administered in combination with performance of one or more additional therapies, for example, surgical procedures, neuroprotective therapy, or gene therapy, or any combination thereof.

[0191] The methods of treatment disclosed herein include providing any suitable dosage amounts of a compound to a patient. Dosage levels of each compound of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in

the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of compound that can be combined with the carrier materials to produce a single dosage form will vary depending upon the patient treated and the particular mode of administration. Dosage unit forms can contain, for example, between from about 1 mg to about 500 mg of each active compound. For example, 25 mg to 500 mg, or 25 mg to 200 mg of a compound can be provided daily to a patient. Frequency of dosage can also vary. A dosage regimen of 4 times daily or less can be used, or a dosage regimen of 1 or 2 or 3 times daily can be used. The specific dose level for any particular patient can depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

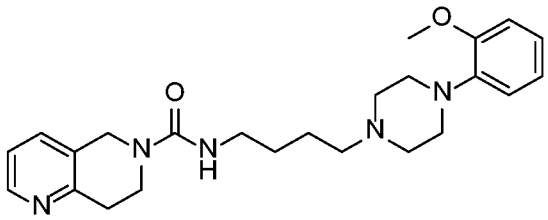
[0192] A kit is provided in accordance with the present disclosure. The kit can comprise one or more therapeutic compounds of the present disclosure and, optionally, a second therapeutic compound.

[0193] A method of synthesizing one or more therapeutic compounds of the present disclosure is provided. The method can comprise one or more synthetic schemes described herein and/or depicted in FIGS. 17-81. Intermediates as well as final products of such schemes are part of the present disclosure.

CHEMISTRY

[0194] All chemicals and reagents were purchased from commercial sources and used directly without further purification. Anhydrous solvents (CH_3CN, EtOH, $^{i}PrOH$) were purchased from Aldrich and were used without further purification. Dry solvents (DMF, THF, CH_2Cl_2) were dispensed under nitrogen from a solvent purification system. All non-aqueous reactions were performed under an atmosphere of nitrogen in oven-dried glassware. Reaction progress was monitored by thin layer chromatography using silica gel plates (silica gel 60 F_{254}) and eluted TLC plates were visualized with UV light (254 nm) or I_2. The products were isolated and purified by flash column chromatography. Yields were un-optimized other than common intermediates. NMR experiments were performed on a 400/100 MHz instrument. NMR spectra were processed with the MestReNova program. Chemical shifts are

reported as ppm referenced to $CDCl_3$ (7.26 ppm for ^1H, 77.0 ppm for ^{13}C), CD_3OD (3.31 and 4.87 ppm for ^1H, 49.1 ppm for ^{13}C), CD_2Cl_2 (5.32 ppm for ^1H, 54.0 for ^{13}C), and DMSO-d_6 (2.50 ppm for ^1H, 39.5 ppm for ^{13}C). ^1H NMR coupling constants (J) are expressed in Hz, and multiplicity is described as follows: s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; br = broad; m = multiplet. Compounds purity was analyzed with UPLC/MS. The UPLC analyses and mass spectra (LC-MS) were obtained on Waters ACQUITY system (Waters, Milford, CT,USA) with a QDa Mass Detector with ESI inlet and UV PDA detector. The Waters UPLC BEH C18, 1.7 µm (2.1 x 50 mm), column was used at 40 °C temperature. Sample was dissolved in between 200 µL and 600 µL of DMSO depending on the solubility of the sample. Sample is then diluted to approximately 0.1 mg/mL in MeOH for injection onto the LCMS. The LCMS parameters are as follows: mobile Phase A (10 mM ammonium bicarbonate in water), mobile Phase B (ACN or MeOH), a flow rate of 0.6 mL/min, injection volume 7.5 µL, run time 6.0 min. Gradient Operation as follows: Hold at 95:5 A:B for 0.5 min. Linear gradient to 5:95 A:B for 3 min. Hold at 5:95 A:B for 0.5 min. Linear gradient to 95:5 A:B for 0.5 min. Hold at 95:5 A:B for 1.5 min. The mass detector ran a positive scan from 150 – 1000 Da.

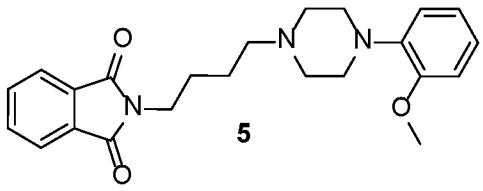


501

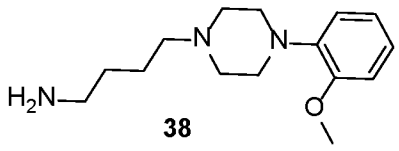
Synthesis of: .

[0195] Compound **501** synthesis according to Scheme 1 is depicted in FIG. 17. A general procedure for *N*-alkylation ("Method N") was utilized as follows. To a solution *N*-aryl piperazine (1 equiv) in CH_3CN (5 mL/mmol) was added anhydrous K_2CO_3 (3 equiv) and stirred at room temperature for 10 min under nitrogen. Alkyl bromide (0.95 equiv) and KI (10 mol%) were added to the above mixture and heated at 80 °C for 16 hours. After cooling the reaction to room temperature, water was added to the reaction mixture and extracted with EtOAc (x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure, and the resulting residue was purified by flash chromatography

(silica gel, 0-60% acetone in hexanes or MeOH in DCM 0-10%) to give the alkylated product.

Synthesis of:  5 .

[0196] 2-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)isoindoline-1,3-dione (Compound 5): Compound **5** was synthesized according to general method **N**, using **17** (0.428 g, 2.23 mmol), **34** (0.600 g, 2.12 mmol), K_2CO_3 (0.880 g, 6.38 mmol) and KI (0.0353 g, 0.21 mmol). The pure product, Compound **5** (0.794 g, 95%) was obtained as a colorless oil. The spectral data of the title compound was in agreement with that found in the literature.[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.05 – 6.81 (m, 4H), 3.85 (s, 3H), 3.73 (t, *J* = 7.0 Hz, 2H), 3.10 (s, 4H), 2.67 (s, 4H), 2.47 (s, 2H), 1.74 (p, *J* = 7.1 Hz, 2H), 1.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 168.4, 152.2, 141.1, 133.9, 132.1, 123.2, 122.9, 120.9, 118.2, 111.1, 58.0, 55.3, 53.3, 50.4, 37.8, 26.6, 24.0.

Synthesis of:  38 .

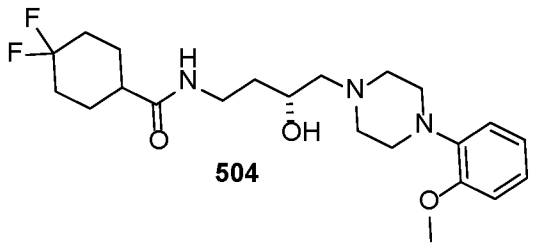
[0197] 4-(4-(2-Methoxyphenyl)piperazin-1-yl)butan-1-amine (38): Compound **38** was synthesized according to general method **D**, using Compound **5** (0.750 g, 1.91 mmol), and Anhydrous hydrazine (0.305 g, 9.53 mmol). The product, **38** (0.43 g, 86%) was obtained after solvent removal as a viscous oil, which was used for the preparation of urea and amide analogs without further purification. UPLC/MS $C_{15}H_{25}N_3O$, MW 263.39, observed 264.17 $[M+1]^+$.

[0198] A general procedure for preparation of urea ("Method O") was utilized as follows. *N*,*N*-Diisopropylethylamine (DIPEA) and 4-Nitrophenylchloroformate were added to a solution of amine in anhydrous DCM (5 mL/1 mmol) at 0 °C. After stirring at room temperature for 2 hours, the solution was diluted with DCM (10 mL), washed with water (2 X 10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to give the 4-nitrophenyl carbamate as yellow viscous oil, which was

used for next step without further purification. A mixture of 4-nitrophenyl carbamate, amine (1 equiv) and DIPEA (2 equiv) in dry DMF or dioxane was stirred at 90 °C to 100 °C for 16 hours. The reaction mixture was diluted with saturated brine solution, diluted with water and extracted with EtOAc (x 4). The combined organic layers were washed with saturated Na_2CO_3 solution (x 2), brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure, and the resulting residue was purified by flash chromatography (silica gel, 0 – 10% MeOH in DCM) to give urea compound.

[0199] ***N*-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxamide (Compound 501):** Compound **501** was synthesized according to general method **O**, using compound **38** (80 mg, 0.30 mmol), 4-Nitrophenylchloroformate (61 mg, 0.30 mmol), N,N-Diisopropylethylamine (DIPEA) (53 µL, 0.30 mmol) to get 4-Nitrophenyl carbamate as yellow viscous oil, which was used without further purification. Crude 4-Nitrophenyl carbamate (128 mg) reacted with amine **37** (45 mg, 0.33 mmol) and DIPEA (106 µL, 0.60 mmol). The pure product, **compound 501** (84 mg, 65%) was obtained as a yellow foam. ^{1}H NMR (400 MHz, MeOD) δ 8.35 (dd, *J* = 4.9, 1.6 Hz, 1H), 7.63 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.27 (dd, *J* = 7.8, 4.9 Hz, 1H), 7.15 – 6.80 (m, 4H), 4.62 (s, 2H), 3.85 (s, 3H), 3.76 (t, *J* = 5.9 Hz, 2H), 3.29 – 3.22 (m, 2H), 3.07 (s, 4H), 2.99 (t, *J* = 6.0 Hz, 2H), 2.70 (s, 4H), 2.50 (t, *J* = 7.3 Hz, 2H), 1.62 – 1.56 (m, 4H); ^{13}C NMR (100 MHz, MeOD) δ 160.1, 155.9, 154.1, 148.3, 142.2, 136.6, 131.5, 124.9, 123.4, 122.3, 119.6, 113.0, 59.5, 56.1, 54.4, 51.5, 46.1, 42.4, 41.7, 32.5, 29.4, 24.8. UPLC/MS purity >98% (CH_3CN: 98.7%, t_R= 1.93 min), (MeOH: 98.9%, t_R= 2.71 min), $C_{24}H_{33}N_5O_2$ MW 423.56, observed $[M+H]^+$ 424.33.

Synthesis of:



504

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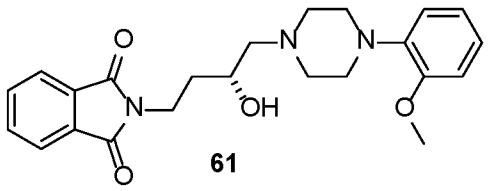
[0200] Compound 504 synthesis according to Scheme 2 is depicted in FIG. 18. Compound 504 was prepared in accordance with a general procedure for epoxide (*R*)-3 and (*S*)-3 opening with pyrrolidines and piperazines and other 2°-amines

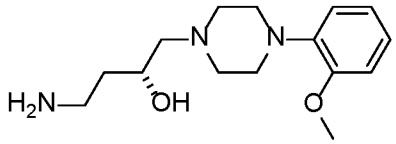
("Method C"). To a solution of (*R*)-3 or (*S*)-3 (1 equiv) in 2-propanol (6 mL/mmol) was added pyrrolidines or piperazines (1 equiv). The insoluble reaction mixture was heated to 70 °C to 80 °C to get a clear solution and then stirred at room temperature for 24 to 48 hours. The solvent was removed *in vacuo*, and the crude product was purified by flash column chromatography (silica gel, 0-100% acetone in hexanes or MeOH in DCM (0-10%) to give epoxide opened products.

Synthesis of: 

61 .

[0201] (*R*)-2-(3-Hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)isoindoline-1,3-dione (Compound 61): Compound **61** was synthesized according to general method **C**, using **(*R*)-3** (1.00 g, 4.60 mmol), and compound **17** (885 mg, 4.60 mmol). The pure product, compound **61** (1.60 g, 85%) was obtained as a colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.76 – 7.69 (m, 2H), 7.15 – 6.74 (m, 4H), 5.16 (s, 1H), 4.35 (s, 1H), 3.93 – 3.72 (m, 7H), 3.71 – 3.10 (m, 8H), 2.00 – 1.77 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 152.3, 134.3, 132.0, 123.6, 121.5, 112.0, 77.3, 64.0, 63.5, 55.8, 48.0, 34.2, 33.9.

[0202] A general procedure for phthalyl deprotection ("Method D") was utilized to synthesize intermediate compound **61B**. Anhydrous hydrazine (5 equiv) was added to a suspension of phthalyl protected amine (1 equiv) in anhydrous ethanol (10 mL/mmol), and the mixture was refluxed for 3 h under nitrogen atmosphere. Solvents were removed, and the resulting residue was partitioned between DCM and a 20% aqueous K_2CO_3 solution. The layers were separated, and the organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the amine, which was used for the next step without further purification.



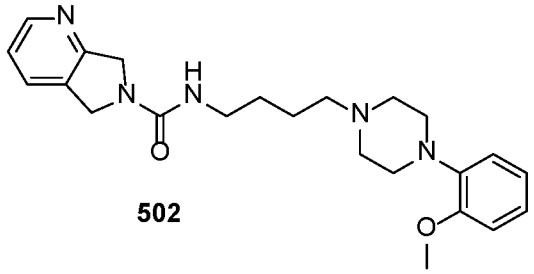
61B

Synthesis of: .

[0203] **(*R*)-4-amino-1-(4-(2-methoxyphenyl)piperazin-1-yl)butan-2-ol (Compound 61B):** Compound **61** was synthesized according to general method **D**, using compound **61** (1.50 g, 3.66 mmol), and anhydrous hydrazine (587 mg, 18.3 mmol). The product, compound **61B** (0.80 g, 78%) was obtained after solvent removal as a viscous oil, which was used for the preparation amide analog without further purification. A general procedure for preparation of amide using HATU ("Method Q") was used to produce Compound 504 from Compound 61B. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved acid (1 equiv) in DMF (5 mL) or DCM (5 mL). Diisopropylethylamine DIPEA or TEA (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture and stirred for 10 minutes at room temperature, and then the primary amine was added at room temperature. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with EtOAc or DCM (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM) to get amide.

[0204] **(*R*)-4,4-Difluoro-*N*-(3-hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)cyclohexane-1-carboxamide (Compound 504:** Compound **504** was synthesized according to general method **Q**, using compound **61B** (80 mg, 0.29 mmol), DIPEA (0.01 mL, 0.57 mmol), HATU (0.14 g, 0.37 mmol) and compound **53** (60 mg, 0.37 mmol). The pure product, compound **504** (120 mg, 81%) was obtained as a white solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.97 (ddd, *J* = 7.9, 5.7, 3.3 Hz, 1H), 6.91 – 6.81 (m, 3H), 6.43 (s, 1H), 3.82 (s, 4H), 3.55 (dtd, *J* = 13.5, 6.7, 5.0 Hz, 1H), 3.27 – 3.13 (m, 1H), 3.07 (s, 4H), 2.83 (dt, *J* = 10.1, 4.8 Hz, 2H), 2.60 (d, *J* = 9.4 Hz, 2H), 2.46 – 2.35 (m, 2H), 2.11 (tp, *J* = 12.7, 10.3, 4.5 Hz, 3H), 1.90 (dt, *J* = 11.8, 2.8 Hz, 2H), 1.83 – 1.60 (m, 5H), 1.46 (dtd, *J* = 13.9, 8.5, 5.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 174.0, 152.8, 141.7, 123.1, 121.3, 118.5, 111.8, 66.3, 64.2, 55.6, 50.8, 43.0, 37.8, 34.0, 33.4, 33.2, 33.2, 32.9, 26.3, 26.2; UPLC/MS purity >98%

(CH_3CN: 98.2%, t_R= 2.18 min), (MeOH: 99.9%, t_R= 3.01 min), $C_{22}H_{33}F_2N_3O_3$ MW 425.52, observed $[M+1]^+$ 426.28.



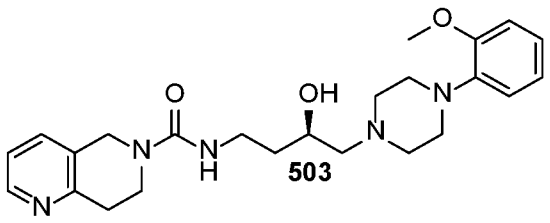
502

Synthesis of: .

[0205] Compound **502** synthesis according to Scheme 3 is depicted in FIG. 19. Compound **502** was prepared in accordance with a general procedure for preparation of urea ("**Method O**"). *N*,*N*-Diisopropylethylamine (DIPEA) and 4-Nitrophenylchloroformate was added to a solution of amine in anhydrous DCM (5 mL/1 mmol) at 0 °C. After stirring at room temperature for 2 hours, the solution was diluted with DCM (10 mL), washed with water (2 X 10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to give the 4-nitrophenyl carbamate as yellow viscous oil, which was used for next step without further purification. A mixture of 4-nitrophenyl carbamate, amine (1 equiv) and DIPEA (2 equiv) in dry DMF or dioxane was stirred at 90 °C to 100 °C for 16 hours. The reaction mixture was diluted with saturated brine solution, diluted with water and extracted with EtOAc (x 4). The combined organic layers were washed with saturated Na_2CO_3 solution (x 2), brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure, and the resulting residue was purified by flash chromatography (silica gel, 0 – 10% MeOH in DCM) to give urea compound.

[0206] ***N*-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridine-6-carboxamide (Compound 502):** Compound **502** was synthesized according to general method **O**, using compound **38** (80 mg, 0.30 mmol), 4-Nitrophenylchloroformate (61 mg, 0.30 mmol), N,N-diisopropylethylamine (DIPEA) (0.11 mL, 0.61 mmol) to get 4-Nitrophenyl carbamate as yellow viscous oil, which was used without further purification. Crude 4-Nitrophenyl carbamate was reacted with 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine (47 mg, 0.39 mmol) and DIPEA (0.11 mL, 0.76 mmol). The pure product, compound **502** (9 mg, 7%) was obtained as a yellow oil along with 33% (56 mg) of compound **510**. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.46 (dd, *J* = 4.9, 1.4 Hz, 1H), 7.61 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.20 (dd, *J* = 7.8, 4.9

Hz, 1H), 7.02 – 6.73 (m, 4H), 4.79 – 4.57 (m, 5H), 3.83 (s, 3H), 3.31 (q, *J* = 6.3 Hz, 2H), 3.05 (s, 4H), 2.60 (s, 4H), 2.43 (q, *J* = 5.2, 3.3 Hz, 2H), 1.59 (p, *J* = 3.5 Hz, 4H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 158.3, 156.9, 152.8, 149.3, 142.0, 131.1, 131.1, 122.9, 122.6, 121.2, 118.5, 111.8, 58.5, 55.6, 52.6, 50.9, 50.8, 40.9, 30.0, 28.7, 24.5; UPLC/MS purity >94% (CH_3CN: 94.3%, t_R = 1.85 min), MeOH: 97.3%, t_R = 2.89 min)), $C_{24}H_{31}N_5O_2$ MW 409.53, $[M+1]^+$ 410.31.

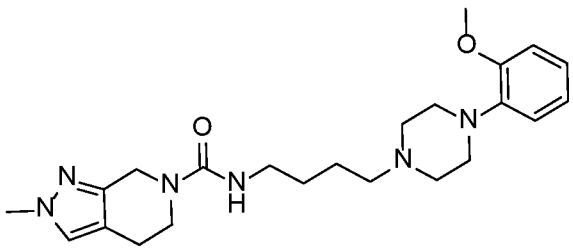
Synthesis of: 

.

[0207] Compound **503** synthesis according to Scheme 4 is depicted in FIG. 20. **4-Nitrophenyl 7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (37-carbamate): 37-Carbamate** was synthesized by reacting 5.6,7,8-tetrahydro-1,6-naphthyridine (150 mg, 1.12 mmol) with 4-nitrophenyl carbonochloridate (225 mg, 1.12 mmol) in the presence of DIPEA (0.40 mL, 2.24 mmol) in DCM (8 mL) for 2 hours at room temperature. The reaction was monitored by TLC (10% MeOH/DCM). Water was added and the organic layer was extracted with DCM (3 x 15 mL). The combined organic layers were dried on Na_2SO_4, filtered and concentrated under reduced pressure. The and the crude product was purified by flash column chromatography (silica gel, 0-10% MeOH in DCM) to give **37-Carbamate** as a beige color solid (0.26 g, 78%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.44 (t, *J* = 4.1 Hz, 1H), 8.24 (dd, *J* = 9.3, 2.6 Hz, 2H), 7.55 – 7.42 (m, 1H), 7.42 – 7.27 (m, 2H), 7.23 – 7.09 (m, 1H), 4.85 (s, 1H), 4.72 (s, 1H), 3.99 (t, *J* = 6.0 Hz, 1H), 3.88 (t, *J* = 6.0 Hz, 1H), 3.10 (dt, *J* = 12.5, 6.1 Hz, 2H).

[0208] A general procedure for preparation of urea from 2°-amine carbamates **("**Method S**")** was utilized to produce compound 37-carbamate**.** A mixture of 2°-amine carbamate, hydroxy amine (1 equiv) and DIPEA (2-6 equiv) in anhydrous DMF was stirred at 100 °C for 16 hours. Water was added to reaction mixture and extracted with EtOAc (x 3). The combined organic layers were washed with saturated Na2CO3 solution (x 2), brine, dried over Na2SO4 and filtered. The solvent was removed under reduced pressure, and the resulting residue was purified by flash chromatography (silica gel, 0-10% MeOH in DCM) to give urea analog.

[0209] (*R*)-*N*-(3-Hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxamide (Compound 503): Compound 503 was synthesized according to general method S, using 37-carbamate (0.12 g, 0.39 mmol), compound 127 (84 mg, 0.30 mmol), N,N-diisopropylethylamine (DIPEA) (0.11 mL, 0.60 mmol). The pure product, compound 503 (40 mg, 30%) was obtained as a yellow oil.^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.48 – 8.32 (m, 1H), 7.53 – 7.37 (m, 1H), 7.12 (dd, *J* = 7.7, 4.8 Hz, 1H), 6.98 (ddd, *J* = 7.8, 5.9, 3.3 Hz, 1H), 6.93 – 6.84 (m, 3H), 5.66 (t, *J* = 4.9 Hz, 1H), 4.55 (s, 2H), 3.83 (s, 5H), 3.67 (t, *J* = 6.0 Hz, 2H), 3.56 (dtd, *J* = 13.3, 6.7, 4.8 Hz, 1H), 3.27 (dddd, *J* = 13.2, 8.3, 4.7, 3.6 Hz, 1H), 3.15 – 2.95 (m, 6H), 2.85 – 2.75 (m, 2H), 2.63 – 2.52 (m, 2H), 2.45 – 2.30 (m, 2H), 1.70 (dddd, *J* = 14.2, 7.2, 4.7, 2.7 Hz, 1H), 1.57 – 1.42 (m, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 158.14, 156.17, 153.42, 149.24, 141.52, 135.30, 130.55, 123.59, 121.90, 121.45, 118.67, 112.70, 66.84, 63.70, 55.81, 51.23, 45.40, 41.15, 38.65, 35.10, 33.11; UPLC/MS purity >93% ((CH_3CN: 93.2%, t_R = 1.85 min), (MeOH: 95.4%, t_R = 2.83 min)), $C_{24}H_{33}N_5O_3$ MW 439.26, $[M+1]^+$ 440.29.



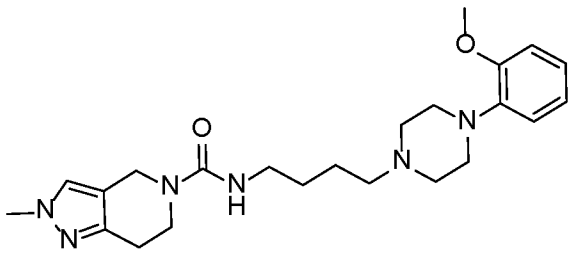
505

Synthesis of: .

[0210] Compound 505 synthesis according to Scheme 5 is depicted in FIG. 21. General procedure for preparation of urea ("Method O") is utilized. *N*,*N*-Diisopropylethylamine (DIPEA) and 4weretrophenylchloroformate was added to a solution of amine in anhydrous DCM (5 mL/1 mmol) at 0 °C. After stirring at room temperature for 2 h, the solution was diluted with DCM (10 mL), washed with water (2 X 10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to give the 4-nitrophenyl carbamate as yellow viscous oil, which was used for next step without further purification. A mixture of 4-nitrophenyl carbamate, amine (1 equiv) and DIPEA (2 equiv) in dry DMF or dioxane was stirred at 90 °C to 100 °C for 16 hours. The reaction mixture was diluted with saturated brine solution, diluted with water and extracted with EtOAc (x 4). The combined organic layers were washed

with saturated Na_2CO_3 solution (x 2), brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure, and the resulting residue was purified by flash chromatography (silica gel, 0 – 10% MeOH in DCM) to give urea compound.

[0211] *N*-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)-2-methyl-2,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridine-6-carboxamide (Compound 505): Compound 505 was synthesized according to general method O, using compound 38 (100 mg, 0.380 mmol), 4-Nitrophenylchloroformate (76.6 mg, 0.380 mmol), triethylamine (TEA) (0.11 mL, 0.76 mmol) to get compound 204 as yellow viscous oil, which was used without further purification. Crude carbamate compound 204 (160 mg, 0.373 mmol) was reacted with amine C (84.2 mg, 0.485 mmol) and DIPEA (0.33 mL, 1.87 mmol). The pure product, TDB-D3-104 (103 mg, 65%) was obtained as a yellow oil. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.09 (s, 1H), 7.03 (ddd, *J* = 8.0, 6.8, 2.3 Hz, 1H), 6.96 – 6.85 (m, 3H), 5.73 (s, 1H), 4.48 (s, 2H), 3.82 (s, 3H), 3.77 (s, 3H), 3.63 (t, *J* = 5.8 Hz, 2H), 3.45 – 3.01 (m, 10H), 2.92 (t, *J* = 7.8 Hz, 2H), 2.59 (t, *J* = 5.8 Hz, 2H), 1.89 (p, *J* = 7.0 Hz, 2H), 1.60 (p, *J* = 6.7 Hz, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 158.2, 152.6, 146.1, 140.0, 127.3, 124.1, 121.3, 119.0, 114.5, 111.8, 56.7, 55.6, 52.7, 48.2, 43.2, 42.7, 39.2, 38.9, 27.1, 21.2; UPLC/MS purity >97% ((CH_3CN: 97.1%, t_R = 1.96 min), (MeOH: 99.3%, t_R = 2.78 min)), $C_{23}H_{34}N_6O_2$ MW 426.57, observed $[M+1]^+$ 427.38.



506

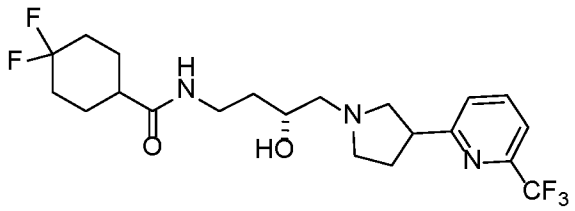
Synthesis of: .

[0212] Compound 506 synthesis according to Scheme 6 is depicted in FIG. 22.

[0213] *N*-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)-2-methyl-2,4,6,7-tetrahydro-5*H*-pyrazolo[4,3-*c*]pyridine-5-carboxamide (Compound 506):

[0214] Compound **506** was synthesized according to general method **O**, using **38** (100 mg, 0.380 mmol), 4-Nitrophenylchloroformate (76.6 mg, 0.380 mmol), DIPEA (0.13 mL, 0.76 mmol) to get 4-Nitrophenyl carbamate as yellow viscous oil, which was used without further purification. Crude 4-Nitrophenyl carbamate was reacted with amine **B** (62.6 mg, 0.456 mmol) and DIPEA (0.13 mL, 0.76 mmol). The pure

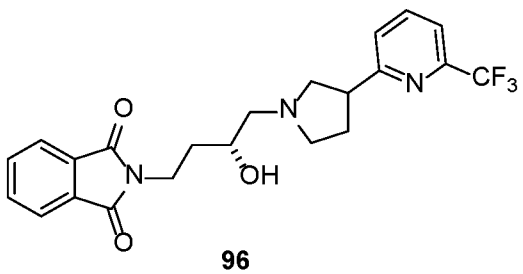
product, compound **506** (68 mg, 42%) was obtained as a yellow oil. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.10 (s, 1H), 6.95 (ddd, *J* = 7.8, 5.7, 3.4 Hz, 1H), 6.90 – 6.80 (m, 3H), 4.95 (t, *J* = 5.5 Hz, 1H), 4.38 (s, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 3.62 (t, *J* = 5.8 Hz, 2H), 3.30 – 3.15 (m, 2H), 3.02 (s, 4H), 2.69 (t, *J* = 5.8 Hz, 2H), 2.55 (t, *J* = 5.1 Hz, 4H), 2.42 – 2.34 (m, 2H), 1.53 (h, *J* = 3.4 Hz, 4H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 158.1, 152.8, 146.9, 142.0, 125.9, 122.8, 121.2, 118.4, 113.4, 111.8, 58.5, 55.6, 50.9, 42.5, 41.2, 40.7, 38.9, 28.5, 24.7, 24.0; UPLC/MS purity >92% ((CH_3CN: 92.7%, t_R = 1.88 min), (MeOH: 96.4%, t_R = 2.81 min)), $C_{23}H_{34}N_6O_2$ MW 426.57, observed $[M+1]^+$ 427.34.



507

Synthesis of: .

[0215] Compound 507 synthesis according to Scheme 7 is depicted in FIG. 23. A general procedure for epoxide (*R*)-3 and (*S*)-3 opening with pyrrolidines and piperazines and other 2°-amines ("Method C") was utilized. To a solution of **(*R*)-3** or **(*S*)-3** (1 equiv) in 2-propanol (6 mL/mmol) was added pyrrolidines or piperazines (1 equiv). The insoluble reaction mixture was heated to 70 °C to 80 °C to get a clear solution and then stirred at room temperature for 24 to 48 hours. The solvent was removed *in vacuo*, and the crude product was purified by flash column chromatography (silica gel, 0-100% acetone in hexanes or MeOH in DCM (0-10%) to give epoxide opened products.



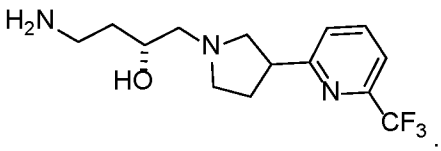
96

Synthesis of: .

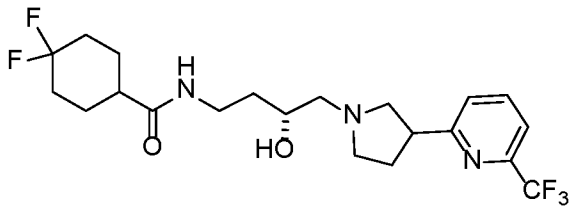
[0216] **2-((3*R*)-3-Hydroxy-4-(3-(6-(trifluoromethyl)pyridin-2-yl)pyrrolidin-1-yl)butyl)isoindoline-1,3-dione (Compound 96):** Compound **96** was synthesized following general method **C** from **12** (0.680 g, 1 equiv, 3.15 mmol) and **(*R*)-3** (683

mg, 1 equiv, 3.15 mmol) in 2-propanol (18.50 mL, 0.17 molar). The product was purified using flash column chromatography (0-70% acetone-hexane) to obtain compound **64** (898 mg, 66%) as pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.80 (m, 2H), 7.76 (t, *J* = 7.9 Hz, 1H), 7.73 – 7.67 (m, 2H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.42 (dd, *J* = 8.0, 4.6 Hz, 1H), 3.96 – 3.79 (m, 2H), 3.78 – 3.68 (m, 1H), 3.65 – 3.54 (m, 1H), 3.16 (dd, *J* = 9.4, 7.8 Hz, 0.5H), 3.02 (dd, *J* = 9.4, 7.9 Hz, 0.5H), 2.93 (qd, *J* = 8.9, 6.3 Hz, 1.5H), 2.79 – 2.71 (m, 1.5H), 2.65 (ddd, *J* = 15.0, 12.1, 9.9 Hz, 1H), 2.48 (ddd, *J* = 12.1, 6.6, 3.3 Hz, 1H), 2.40 – 2.26 (m, 1H), 2.07 (dddd, *J* = 15.3, 8.8, 7.5, 4.5 Hz, 1H), 1.87 – 1.71 (m, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 165.5, 165.3, 137.8, 134.0, 132.3, 124.8, 124.7, 123.4, 123.0, 118.1, 118.07, 118.05, 66.5, 66.5, 61.6, 61.5, 60.6, 60.4, 54.5, 54.4, 53.6, 45.4, 45.3, 35.2, 35.16, 33.9, 33.9, 31.9, 31.8.

[0217] A general procedure for phthalyl deprotection ("Method D") was utilized. Anhydrous hydrazine (5 equiv) was added to a suspension of phthalyl protected amine (1 equiv) in anhydrous ethanol (10 mL/mmol), and the mixture was refluxed for 3 h under nitrogen atmosphere. Solvents were removed, and the resulting residue was partitioned between DCM and a 20% aqueous K_2CO_3 solution. The layers were separated, and the organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the amine, which was used for the next step without further purification.

Synthesis of:  .

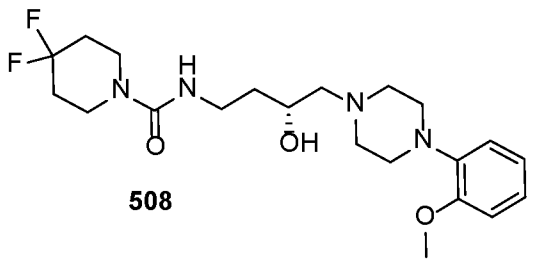
[0218] **(2*R*)-4-Amino-1-(3-(6-(trifluoromethyl)pyridin-2-yl)pyrrolidin-1-yl)butan-2-ol (Compound 98):** Compound **98** was synthesized following the general method **D** from Compound **96** (809 mg, 1 equiv, 1.87 mmol) and using anhydrous hydrazine (0.29 mL, 5 equiv, 9.33 mmol) in ethanol (26.7 mL, 0.07 molar) The crude amine (509 mg, 90%) was carried further for the next reaction without any purification.



507

Synthesis of: .

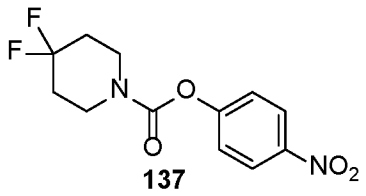
[0219] 4,4-Difluoro-*N*-((3*R*)-3-hydroxy-4-(3-(6-(trifluoromethyl)pyridin-2-yl)pyrrolidin-1-yl)butyl)cyclohexane-1-carboxamide (Compound 507): To a stirring solution of 4,4-difluorocyclohexane-1-carboxylic acid (70 mg, 429 µmol) in DCM (4.71 mL, 0.07 M) were added Hunig's base (0.12 mL, 660 µmol) and HATU (163 mg, 429 µmol) and the resulting mixture was stirred for 30 minutes. To this solution was added amine compound 98 (100, 330 mmol) and the reaction mixture was stirred for room temperature for 18 hours. The crude product was purified using flash column chromatography (0-100% acetone-hexane) to obtain the target compound 507 in 67% yield as a mixture of diastereomers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (t, *J* = 7.8 Hz, 1H), 7.61 (dd, *J* = 7.8, 4.2 Hz, 2H), 3.78 (tt, *J* = 8.0, 4.1 Hz, 1H), 3.70 – 3.60 (m, 1H), 3.34 – 3.26 (m, 2H), 3.24 – 3.17 (m, 1H), 3.01 – 2.90 (m, 1H), 2.89 – 2.76 (m, 2H), 2.68 – 2.55 (m, 2H), 2.40 – 2.23 (m, 2H), 2.17 – 2.03 (m, 3H), 1.92 – 1.68 (m, 7H), 1.62 – 1.50 (m, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 177.53, 177.51, 166.24, 166.19, 150.0, 148.64, 148.62, 148.3, 147.96, 139.59, 139.57, 127.2, 126.6, 126.3, 124.5, 123.93, 123.91, 121.8, 121.5, 119.4, 119.32, 119.29, 119.26, 68.7, 68.6, 63.41, 63.39, 61.8, 61.6, 56.0, 55.8, 46.2, 46.1, 43.80, 43.78, 37.27, 37.25, 36.2, 34.1, 34.0, 33.89, 33.87, 33.6, 32.5, 32.4, 27.2, 27.1, 27.1, 27.0.; UPLC/MS purity >97% (CH_3CN: 97.7%, t_R = 2.17 min), MeOH: 98.9%, t_R = 3.00 min), $C_{21}H_{28}F_5N_3O_2$ MW 449.5, [M+H]+ 450.2



508

Synthesis of: .

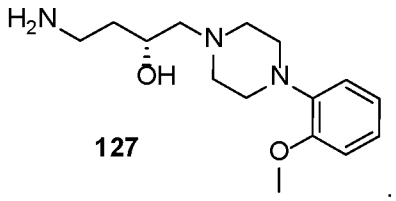
[0220] Compound 508 synthesis according to Scheme 8 is depicted in FIG. 24.

Synthesis of:  .

137

[0221] 4-Nitrophenyl 4,4-difluoropiperidine-1-carboxylate (Compound 137): A 25 mL round bottomed flask, equipped with a stirring bar, was charged with 4,4-difluoropiperidine hydrogen chloride (500 mg, 3.17 mmol) and DIPEA (1.10 mL, 6.35 mmol) in DCM (12 mL) and cooled it to 0 °C. Then 4-nitrophenyl carbonochloridate (640 mg, 3.17 mmol) was added to the reaction mixture. The reaction mixture was then stirred at room temperature for 16 hours. After completion of the reaction, the crude carbamate was purified by flash chromatography (silica gel, 0-30% EtOAc in hexanes) to get pure compound **137** (0.45 g, 50%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 – 8.08 (m, 2H), 7.33 – 7.27 (m, 2H), 3.77 (dt, *J* = 34.5, 5.8 Hz, 4H), 2.09 (q, *J* = 11.5 Hz, 4H).

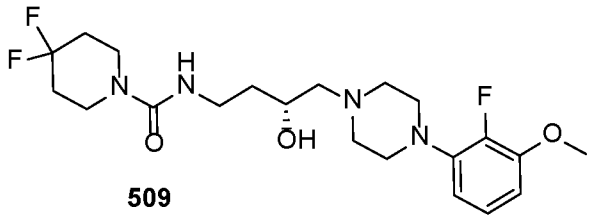
[0222] A general procedure for preparation of urea from 2°-amine carbamates ("Method R") is utilized. A mixture of 2°-amine carbamate, hydroxy amine (1 equiv) and DIPEA or NMM (2-6 equiv) in anhydrous DMF was stirred at 100 °C for 16 hours. Water was added to reaction mixture and extracted with EtOAc (x 3). The combined organic layers were washed with saturated Na_2CO_3 solution (x 2), brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure, and the resulting residue was purified by flash chromatography (silica gel, 0-10% MeOH in DCM) to give urea analog. Note: Polymer bound DMAP (0.5 equiv) was added for some analogs.

Synthesis of:  .

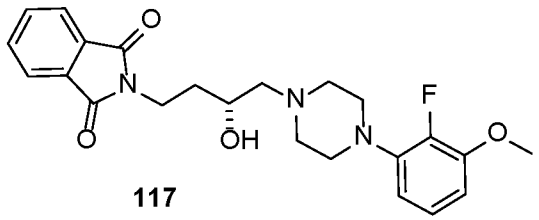
127

[0223] (*R*)-4,4-Difluoro-*N*-(3-hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)piperidine-1-carboxamide (Compound 508): Compound **508** was synthesized according to general method **R**, using compound **137** (0.14 g, 0.48 mmol), compound **127** (90 mg, 0.32 mmol), N,N-diisopropylethylamine (DIPEA) (0.17 mL, 0.97 mmol) and DMAP-polymer-bound, 3 mmol/g (53 mg, 0.16 mmol). The

pure product, compound **508** (25 mg, 18%) was obtained as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 6.99 (m, 1H), 6.99 – 6.79 (m, 3H), 5.95 (d, *J* = 6.3 Hz, 1H), 4.30 (s, 1H), 3.87 (s, 3H), 3.53 (t, *J* = 5.9 Hz, 6H), 3.45 – 3.17 (m, 9H), 2.92 (s, 2H), 1.97 (tt, *J* = 13.3, 5.9 Hz, 4H), 1.75 (ddt, *J* = 12.6, 8.1, 3.9 Hz, 1H), 1.57 (dtd, *J* = 13.8, 6.4, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 152.2, 124.3, 121.3, 118.8, 111.4, 64.3, 63.6, 55.6, 53.5, 48.2, 41.3, 37.7, 35.0, 34.2, 34.0, 33.8; UPLC/MS purity >95% (CH_3CN: 95.0%, t_R= 2.09 min), (MeOH: 96.5%, t_R= 2.88 min), $C_{21}H_{32}F_2N_4O_3$ MW 426.51, observed $[M+1]^+$ 427.31.

Synthesis of:  **509** .

[0224] Compound 509 synthesis according to Scheme 9 is depicted in FIG. 25. A general procedure for epoxide (R)-3 and (S)-3 opening with pyrrolidines and piperazines and other 2°-amines ("Method C") was utilized. To a solution of **(*R*)-3** or **(*S*)-3** (1 equiv) in 2-propanol (6 mL/mmol) was added pyrrolidines or piperazines (1 equiv). The insoluble reaction mixture was heated to 70 °C to 80 °C to get a clear solution and then stirred at room temperature for 24 to 48 hours. The solvent was removed *in vacuo*, and the crude product was purified by flash column chromatography (silica gel, 0-100% acetone in hexanes or MeOH in DCM (0-10%) to give epoxide opened products.

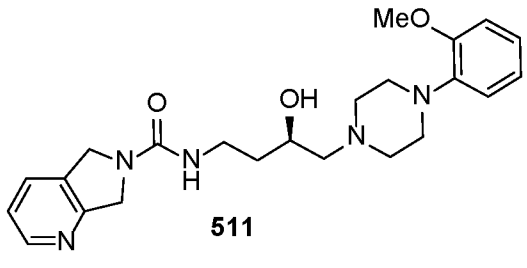
Synthesis of:  **117** .

[0225] **(*R*)-2-(4-(4-(2-Fluoro-3-methoxyphenyl)piperazin-1-yl)-3-hydroxybutyl)isoindoline-1,3-dione (Compound 117):** Compound **117** was synthesized according to general method **C**, using **(*R*)-3** (800 mg, 3.68 mmol), and 1-(2-fluoro-3-methoxyphenyl)piperazine (774 mg, 3.68 mmol). The pure product, compound **117** (1.38 g, 88%) was obtained as a white solid. ^{1}H NMR (400 MHz,

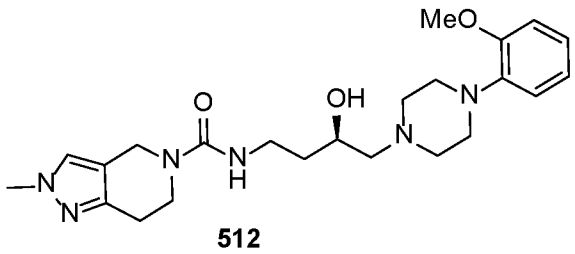
$CDCl_3$) δ 7.84 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.70 (dd, *J* = 5.4, 3.1 Hz, 2H), 6.95 (td, *J* = 8.3, 2.0 Hz, 1H), 6.63 (ddd, *J* = 8.6, 7.6, 1.4 Hz, 1H), 6.55 (ddd, *J* = 8.6, 7.4, 1.5 Hz, 1H), 3.95 – 3.82 (m, 5H), 3.78 (dtd, *J* = 9.8, 7.1, 6.2, 2.8 Hz, 1H), 3.54 (s, 1H), 3.09 (td, *J* = 6.2, 3.5 Hz, 4H), 2.89 – 2.73 (m, 2H), 2.64 – 2.52 (m, 2H), 2.49 – 2.30 (m, 2H), 1.78 (q, *J* = 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 148.7, 148.6, 146.9, 144.5, 141.0, 140.9, 134.0, 132.3, 123.6, 123.5, 123.3, 111.2, 111.1, 107.2, 64.6, 63.9, 56.5, 53.4, 50.76, 50.73, 35.2, 33.7.

[0226] A general procedure for preparation of urea from 2°-amine carbamates ("Method R") was utilized. A mixture of 2°-amine carbamate, hydroxy amine (1 equiv) and DIPEA or NMM (2-6 equiv) in anhydrous DMF was stirred at 100 °C for 16 hours. Water was added to reaction mixture and extracted with EtOAc (x 3). The combined organic layers were washed with saturated Na_2CO_3 solution (x 2), brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure, and the resulting residue was purified by flash chromatography (silica gel, 0-10% MeOH in DCM) to give urea analog. Note: Polymer bound DMAP (0.5 equiv) was added for some analogs.

[0227] (*R*)-4,4-Difluoro-*N*-(4-(4-(2-fluoro-3-methoxyphenyl)piperazin-1-yl)-3-hydroxybutyl)piperidine-1-carboxamide (Compound 509): Compound 509 was synthesized according to general method R, using compound 137 (0.13 g, 0.45 mmol), compound 118 (90 mg, 0.30 mmol), 4-Methylmorpholine (NMM) (67 µL, 0.61 mmol) and DMAP-polymer-bound, 3 mmol/g (50 mg, 0.15 mmol). The pure product, compound 509 (15 mg, 11%) was obtained as a yellow oil. ^1H NMR (400 MHz, CD_2Cl_2) δ 6.98 (td, *J* = 8.3, 2.0 Hz, 1H), 6.66 (td, *J* = 8.0, 1.5 Hz, 1H), 6.58 (ddd, *J* = 8.6, 7.5, 1.5 Hz, 1H), 5.63 (s, 1H), 3.81– 3.86 (m, 4H), 3.59 – 3.40 (m, 5H), 3.22 (dddd, *J* = 13.1, 8.3, 4.5, 3.5 Hz, 1H), 3.11 (td, *J* = 6.4, 3.3 Hz, 4H), 2.89 – 2.79 (m, 2H), 2.60 (dt, *J* = 10.7, 5.1 Hz, 2H), 2.45 – 2.33 (m, 2H), 1.94 (tt, *J* = 13.9, 5.8 Hz, 4H), 1.67 (dddd, *J* = 14.1, 7.1, 4.6, 2.7 Hz, 1H), 1.49 (ddd, *J* = 14.0, 9.4, 4.9 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 157.5, 149.0, 123.9, 123.9, 111.4, 107.4, 66.7, 64.2, 56.6, 53.7, 51.0, 51.0, 41.46, 41.40, 39.6, 34.4, 34.3, 34.2; UPLC/MS purity >92% (CH_3CN: 92.4%, t_R= 2.16 min), (MeOH: 96.7%, t_R= 2.88 min), $C_{21}H_{31}F_3N_4O_3$ MW 444.50, observed $[M+1]^+$ 445.26.\

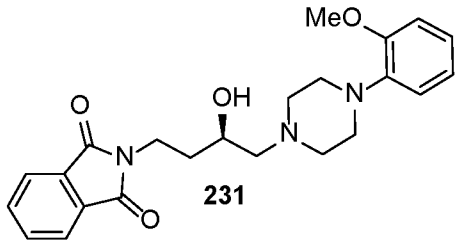
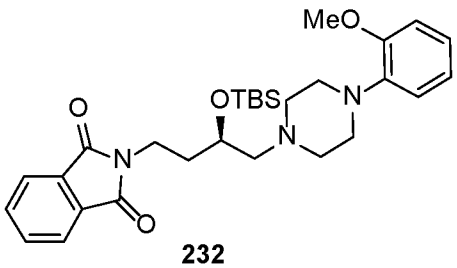
Synthesis of:  and

511



512

[0228] Compound 511 synthesis according to Scheme 10 is depicted in FIG. 26. Compound 512 synthesis according to Scheme 11 is depicted in FIG. 26. TBS protection of amine ("Method S") was utilized. To a stirring solution of epoxide opened compound (1 equiv) dissolved in DCM (0.10M) was added 2,6-lutidine (3 equiv). The resulting solution was cooled to 0 °C and TBSOTf (1.5 equiv) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 2-16 hours till the disappearance of starting material. The organic layer was washed with saturated K_2CO_3 solution and dried over Na_2SO_4. The crude product was purified using flash column chromatography (0-100% acetone-hexane) to obtain TBS protected compound.

Synthesis of:  and 

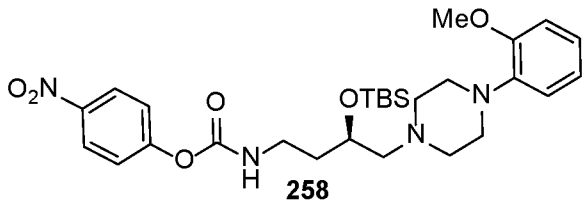
231

232

[0229] **(*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-4-(4-(2-methoxyphenyl)piperazin-1-yl)butan-1-amine (Compound 232):** Compound **232** was synthesized according to general method **S**, using compound **231** (3.50 g, 8.55 mmol), 2,6-lutidine (4.00 mL, 34.2 mmol), and TBSOTf (3.39 g, 12.8 mmol). The pure product, compound **232** (3.14 g, 70%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.82 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.72 (td, *J* = 5.2, 3.4 Hz, 2H), 6.95 (ddd, *J* = 7.6, 5.4, 2.4

Hz, 2H), 6.92 – 6.79 (m, 2H), 3.94 (qd, *J* = 6.3, 4.3 Hz, 1H), 3.89 – 3.66 (m, 5H), 3.13 – 2.90 (m, 4H), 2.61 (dq, *J* = 11.4, 6.1, 5.4 Hz, 4H), 2.46 – 2.29 (m, 2H), 2.07 – 1.92 (m, 1H), 1.85 – 1.71 (m, 1H), 0.92 (d, *J* = 1.2 Hz, 9H), 0.12 (s, 6H).

[0230] A general procedure for phthalyl deprotection ("Method D") was utilized. Anhydrous hydrazine (5 equiv) was added to a suspension of phthalyl protected amine (1 equiv) in anhydrous ethanol (10 mL/mmol), and the mixture was refluxed for 3 hours under nitrogen atmosphere. Solvents were removed, and the resulting residue was partitioned between DCM and a 20% aqueous K_2CO_3 solution. The layers were separated, and the organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the amine, which was used for the next step without further purification. A general procedure for preparation of 4-nitrophenyl carbamate ("Method T") was utilized. *N*,*N*-Diisopropylethylamine (DIPEA) or triethylamine (TEA) or NMM (3 equiv) and bis(4-nitrophenyl) carbonate (1.5 equiv) was added to a solution of TBS protected amine (1 equiv) in anhydrous DCM (5 mL/1 mmol) at 0 °C. After stirring at room temperature for 16 hours, the solvent was removed under reduced pressure to give the 4-Nitrophenyl carbamate as yellow viscous oil. The crude product was purified using flash column chromatography (0-50% acetone-hexane) to obtain pure carbamate.

Synthesis of:  **258** .

[0231] 4-Nitrophenyl(*R*)-(3-((*tert*-butyldimethylsilyl)oxy)-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)carbamate (Compound 258):

[0232] Phthalyl was deprotected following the general method **D,** using compound **232** (3.00 g, 5.92 mmol) and using anhydrous hydrazine (948 mg,29.6 mmol) in ethanol (50 mL). The crude amine was used for the next step without further purification. Compound **258** was synthesized according to general method **T**, using TBS protected amine (1.30 g, 3.30 mmol), TEA (1.40 mL, 9.91 mmol), and bis(4-nitrophenyl) carbonate (1.51 g, 4.95 mmol). The pure product, compound **258** (1.33 g, 72%) was obtained as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 7.98 (m,

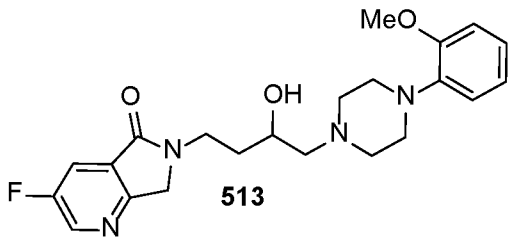
2H), 7.00 (dt, *J* = 7.9, 4.6 Hz, 1H), 6.92 – 6.88 (m, 2H), 6.88 – 6.82 (m, 3H), 3.93 (p, *J* = 5.9 Hz, 1H), 3.84 (s, 3H), 3.41 – 3.17 (m, 2H), 3.12 – 2.95 (m, 4H), 2.74 – 2.57 (m, 4H), 2.42 (dd, *J* = 6.2, 3.2 Hz, 2H), 1.94 – 1.80 (m, 1H), 1.74 (dd, *J* = 13.9, 6.3 Hz, 1H), 0.89 (s, 9H), 0.08 (d, *J* = 7.5 Hz, 6H).

[0233] Urea analog synthesis and TBS deprotection ("Method U") was utilized. To a stirring solution of amine or amine•HCl salt (1.3-3 equiv) in 1,4-dioxane (0.10M) was added Hunig's base (5-6 equiv) and the reaction was stirred for 30 minutes. To this was added carbamate (1 equiv) and the resulting mixture was stirred at 90 ºC for 24 hours. Then TBAF 1 M solution in THF (6 equiv) was added to the reaction mixture and stirred for another 16 hours. *p*-Nitrophenol (6 equiv) was added to the reaction mixture to remove excess TBAF and formed yellow precipitate which was removed by filtration. The filtrate was concentrated under reduced pressure. The crude product was purified using flash column chromatography (0-50% DCM-MeOH and 5-10% NH_4OH) to obtain pure urea compound.

[0234] (*R*)-*N*-(3-Hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridine-6-carboxamide (Compound 511): Compound 511 was synthesized according to general method U, using compound 258 (600 mg, 1.07 mmol), *N*,*N*-Diisopropylethylamine (DIPEA) (1.10 mL, 6.44 mmol), and 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine dihydrochloride (270 mg, 1.40 mmol), TBAF 1M solution (6.44 mL, 6.44 mmol) and p-nitrophenol (896 mg, 6.44 mmol). The pure product, compound 511 (340 mg, 75%) was obtained as a brown oil. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.46 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.60 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.20 (dd, *J* = 7.7, 4.9 Hz, 1H), 6.97 (ddd, *J* = 7.7, 6.1, 3.0 Hz, 1H), 6.93 – 6.84 (m, 3H), 5.50 – 5.37 (m, 1H), 4.76 – 4.60 (m, 4H), 3.88 (tdd, *J* = 8.5, 5.6, 2.7 Hz, 1H), 3.82 (s, 3H), 3.61 (dtd, *J* = 13.5, 6.8, 4.8 Hz, 1H), 3.32 (ddt, *J* = 11.5, 8.4, 4.5 Hz, 1H), 3.07 (s, 4H), 2.82 (dt, *J* = 10.4, 4.6 Hz, 2H), 2.59 (d, *J* = 10.6 Hz, 2H), 2.47 – 2.35 (m, 2H), 1.72 (dddd, *J* = 14.5, 7.4, 4.9, 2.7 Hz, 1H), 1.53 (dddd, *J* = 14.0, 9.1, 7.8, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 158.4, 157.2, 152.8, 149.3, 141.9, 131.1, 123.0, 122.5, 121.2, 118.5, 111.8, 66.4, 64.3, 55.6, 52.6, 51.0, 50.7, 39.1, 34.8; UPLC/MS purity >93% (CH_3CN: 93.1%, t_R= 1.84 min), (MeOH: 93.7%, t_R= 2.69 min), $C_{23}H_{31}N_5O_3$ MW 425.53, observed $[M+1]^+$ 426.34.

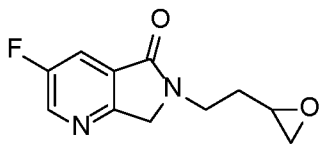
[0235] (*R*)-*N*-(3-Hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-2-methyl-2,4,6,7-tetrahydro-5*H*-pyrazolo[4,3-*c*]pyridine-5-carboxamide (Compound 512):

Compound 512 was synthesized according to general method U, using compound 258 (600 mg, 1.07 mmol), *N*,*N*-Diisopropylethylamine (DIPEA) (1.10 mL, 6.44 mmol), and 2-methyl-4,5,6,7-tetrahydro-2*H*-pyrazolo[4,3-*c*]pyridine dihydrochloride (242 mg, 1.40 mmol), TBAF 1M solution (6.44 mL, 6.44 mmol) and p-nitrophenol (896 mg, 6.44 mmol). The pure product, compound 512 (360 mg, 76%) was obtained as a brown oil. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.12 (s, 1H), 6.97 (ddd, *J* = 7.9, 5.8, 3.3 Hz, 1H), 6.93 – 6.80 (m, 3H), 5.59 (dd, *J* = 6.4, 3.6 Hz, 1H), 4.39 (s, 2H), 3.83 (s, 4H), 3.79 (s, 3H), 3.63 (dd, *J* = 6.8, 4.9 Hz, 2H), 3.53 (dtd, *J* = 13.4, 6.7, 4.7 Hz, 1H), 3.24 (dddd, *J* = 13.2, 8.3, 4.8, 3.7 Hz, 1H), 3.06 (s, 4H), 2.80 (dt, *J* = 10.1, 4.1 Hz, 2H), 2.70 (t, *J* = 5.8 Hz, 2H), 2.56 (p, *J* = 5.1, 4.7 Hz, 2H), 2.44 – 2.33 (m, 2H), 1.68 (dddd, *J* = 14.3, 7.3, 4.8, 2.7 Hz, 1H), 1.48 (dddd, *J* = 14.0, 9.2, 7.9, 4.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 152.3, 146.7, 125.8, 123.3, 121.1, 118.3, 113.6, 111.3, 61.8, 55.4, 54.2, 50.2, 45.6, 43.1, 39.0, 38.8, 25.1, 23.8; UPLC/MS purity >95% (CH_3CN: 95.2%, t_R= 1.79 min), (MeOH: 95.7%, t_R= 2.62 min), $C_{23}H_{34}N_6O_3$ MW 442.56, observed $[M+1]^+$ 443.31.

Synthesis of: 

513.

[0236] Compound 513 synthesis according to Scheme 12 is depicted in FIG. 27.



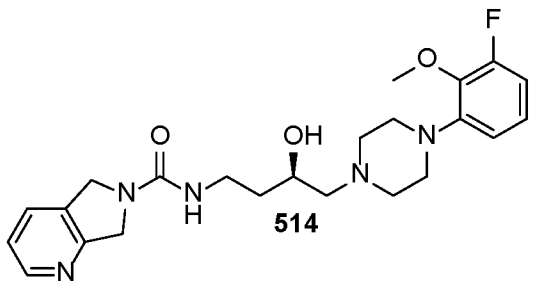
207

Synthesis of: .

[0237] 3-Fluoro-6-(2-(oxiran-2-yl)ethyl)-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (Compound 207): 3-Fluoro-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (100 mg, 0.657 mmol) in DMF (1 mL) was added to ^{t}BuOK (103 mg, 0.920 mmol, 1.4 equiv) in DMF (1 mL) in ice bath and the reaction mixture was stirred for 5 min at ambient temperature and 30 min at room temperature. Then, 2-(2-bromoethyl)oxirane (139

mg, 0.920 mmol, 1.4 equiv) in DMF (1 mL) was added to the reaction mixture in ice bath and the reaction mixture was stirred at room temperature for 24 hours. The reaction was monitored by TLC with 10% MeOH/DCM. Water was added to the reaction mixture and the product was extracted with DCM (3 x 20 mL). The organic layer was dried with $MgSO_4$ and concentrated. The product was purified by chromatography with silica gel with 0 → 10% gradient of MeOH/DCM. The product was obtained as a brown oil (98 mg, 67% yield): R_f 0.64 (10% MeOH/DCM); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.57 (dd, *J* = 2.8, 1.7 Hz, 1H), 7.78 (dd, *J* = 7.3, 2.8 Hz, 1H), 4.46 (s, 2H), 3.80 (h, *J* = 7.1 Hz, 2H), 2.97 (dtd, *J* = 6.8, 4.0, 2.6 Hz, 1H), 2.72 (dd, *J* = 5.0, 4.0 Hz, 1H), 2.47 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.05 (dtd, *J* = 13.9, 6.9, 4.1 Hz, 1H), 1.77 (dt, *J* = 14.3, 7.1 Hz, 1H). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 166.14, 161.53, 158.64 (d, *J* = 71.6 Hz), 141.69 (d, *J* = 26.5 Hz), 128.27 (d, *J* = 5.2 Hz), 118.42 (d, *J* = 20.3 Hz), 51.77, 50.54, 46.95, 40.35, 32.02.

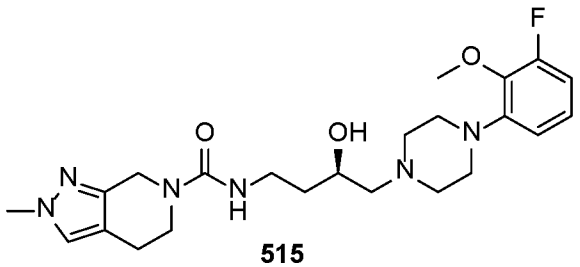
[0238] 3-Fluoro-6-(3-hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (Compound 513) was synthesized by treating 3-Fluoro-6-(2-(oxiran-2-yl)ethyl)-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (98 mg, 0.44 mmol) with 1-(2-methoxyphenyl)piperazine (85 mg, 0.44 mmol, 1.0 equiv) in 2-propanol (4 mL) at 80 °C for 24 hours. The reaction was monitored by TLC (10% MeOH/DCM). The solvent was removed under reduced pressure and the product was purified by column chromatography with silica gel using 0 → 10% MeOH/DCM gradient. 107 mg of product was obtained as a yellow gel (59% yield); R_f 0.49 (10% MeOH/DCM); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.55 (dd, *J* = 2.8, 1.6 Hz, 1H), 7.75 (dd, *J* = 7.4, 2.7 Hz, 1H), 6.95 (ddd, *J* = 7.9, 5.3, 3.8 Hz, 1H), 6.89 - 6.78 (m, 3H), 4.45 (d, *J* = 1.4 Hz, 2H), 3.91 - 3.68 (m, 6H), 3.03 (d, *J* = 8.4 Hz, 4H), 2.76 (dt, *J* = 10.2, 4.6 Hz, 2H), 2.54 (dt, *J* = 10.5, 4.6 Hz, 2H), 2.47 - 2.29 (m, 2H), 1.82 (dtd, *J* = 13.7, 7.7, 3.3 Hz, 1H), 1.76 - 1.61 (m, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 166.18 (d, *J* = 2.9 Hz), 160.17 (d, *J* = 255.0 Hz), 158.35 (d, *J* = 3.2 Hz), 152.88, 142.00, 141.49 (d, *J* = 26.5 Hz), 128.36 (d, *J* = 5.2 Hz), 123.11, 121.38, 118.59, 118.32 (d, *J* = 20.3 Hz), 111.96, 64.77, 64.60, 55.74, 54.09 (2C), 51.97, 51.12 (2C), 40.23, 33.95; UPLC/MS purity (CH_3CN: 97.7%, t_R = 1.995 min), MeOH: 99.7%, t_R = 2.791 min)), $C_{22}H_{27}FN_4O_3$ MW 414.48, observed $[M+H]^+$ 415.27.

Synthesis of:  .

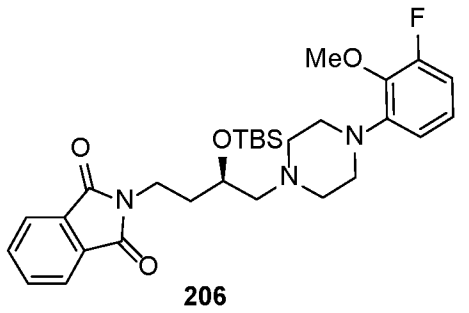
514

[0239] Compound 514 synthesis according to Scheme 13 is depicted in FIG. 28. A general procedure for preparation of urea from 2°-amine carbamates ("Method R") was utilized. A mixture of 2°-amine carbamate, hydroxy amine (1 equiv) and DIPEA or NMM (2-6 equiv) in anhydrous DMF was stirred at 100 °C for 16 hours. Water was added to reaction mixture and extracted with EtOAc (x 3). The combined organic layers were washed with saturated Na_2CO_3 solution (x 2), brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure, and the resulting residue was purified by flash chromatography (silica gel, 0-10% MeOH in DCM) to give urea analog. Note: Polymer bound DMAP (0.5 equiv) was added for some analogs.

[0240] (*R*)-*N*-(4-(4-(3-Fluoro-2-methoxyphenyl)piperazin-1-yl)-3-hydroxybutyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridine-6-carboxamide (Compound 514): Compound 514 was synthesized according to general method R, using compound 151 (0.14 g, 0.48 mmol), compound 71 (95 mg, 0.32 mmol), and N,N-diisopropylethylamine (DIPEA) (0.17 mL, 0.96 mmol). The pure product, compound 514 (20 mg, 14%) was obtained as a yellow oil. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.50 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.64 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.24 (dd, *J* = 7.7, 4.9 Hz, 1H), 6.98 (td, *J* = 8.2, 6.0 Hz, 1H), 6.82 – 6.67 (m, 2H), 4.83 – 4.61 (m, 4H), 3.91 (d, *J* = 0.8 Hz, 5H), 3.64 (dtd, *J* = 13.7, 7.0, 4.8 Hz, 1H), 3.42 – 3.29 (m, 1H), 3.26 – 3.09 (m, 5H), 2.87 (dt, *J* = 10.4, 4.6 Hz, 2H), 2.64 (dt, *J* = 10.7, 5.0 Hz, 2H), 2.47 (d, *J* = 6.8 Hz, 2H), 1.76 (dddd, *J* = 14.6, 7.5, 4.9, 2.8 Hz, 1H), 1.61 – 1.49 (m, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 158.4, 158.2, 157.2, 155.8, 149.4, 147.1, 140.9, 140.8, 131.0, 124.0, 123.9, 122.6, 114.14, 114.12, 110.3, 110.1, 66.4, 64.3, 60.27, 60.23, 54.2, 52.6, 50.8, 50.7, 39.0, 34.9; UPLC/MS purity >89% (CH_3CN: 90.1%, t_R= 2.08 min), (MeOH: 89.7%, t_R= 2.94 min), $C_{23}H_{30}FN_5O_3$ MW 443.52, observed $[M+1]^+$ 444.28.

Synthesis of:  **515** .

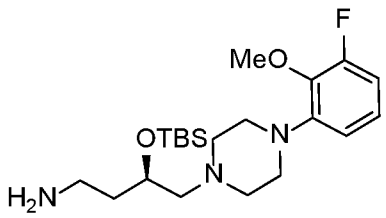
[0241] Compound 515 synthesis according to Scheme 14 is depicted in FIG. 29. TBS protection of amine ("Method S") was utilized. To a stirring solution of epoxide opened compound (1 equiv) dissolved in DCM (0.10M) was added 2,6-lutidine (3 equiv). The resulting solution was cooled to 0 ºC and TBSOTf (1.5 equiv) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 2-16 hours till the disappearance of starting material. The organic layer was washed with saturated K_2CO_3 solution and dried over Na_2SO_4. The crude product was purified using flash column chromatography (0-100% acetone-hexane) to obtain TBS protected compound.

Synthesis of:  **206** .

[0242] (*R*)-2-(3-((*tert*-Butyldimethylsilyl)oxy)-4-(4-(3-fluoro-2-methoxyphenyl)piperazin-1-yl)butyl)isoindoline-1,3-dione (Compound 206): Compound 206 was synthesized according to general method S, using compound 203 (0.51 g, 1.2 mmol), 2,6-lutidine (0.38 mL, 3.6 mmol), and TBSOTf (0.36 mL, 1.6 mmol). The pure product, compound 206 (0.47 g, 73%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dt, *J* = 5.3, 2.8 Hz, 2H), 7.69 (dt, *J* = 5.3, 2.4 Hz, 2H), 6.90 (tdd, *J* = 8.2, 6.0, 2.2 Hz, 1H), 6.71 (ddt, *J* = 10.3, 8.3, 1.9 Hz, 1H), 6.63 (dq, *J* = 8.2, 1.6 Hz, 1H), 3.98 – 3.68 (m, 6H), 3.17 – 2.97 (m, 4H), 2.63 (qd, *J* = 11.0, 10.3, 4.9 Hz, 4H), 2.52 – 2.36 (m, 2H), 2.08 – 1.94 (m, 1H), 1.85 (ddt, *J* = 12.7, 9.6, 6.1 Hz, 1H), 0.90 (d, *J* = 1.2 Hz, 9H), 0.13 – 0.05 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 157.8, 155.4, 146.87, 146.83, 140.5, 140.4, 133.9, 132.3, 123.6,

123.5, 123.1, 113.7, 113.6, 110.0, 109.8, 68.5, 64.5, 60.0, 59.9, 54.6, 50.4, 35.0, 34.5, 25.9, 18.2, -4.0, -4.6.

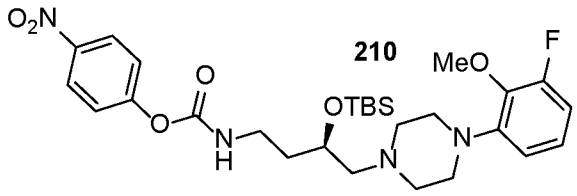
[0243] General procedure for phthalyl deprotection ("Method D") was utilized. Anhydrous hydrazine (5 equiv) was added to a suspension of phthalyl protected amine (1 equiv) in anhydrous ethanol (10 mL/mmol), and the mixture was refluxed for 3 hours under nitrogen atmosphere. Solvents were removed, and the resulting residue was partitioned between DCM and a 20% aqueous K_2CO_3 solution. The layers were separated, and the organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the amine, which was used for the next step without further purification.



209

Synthesis of:

[0244] **(*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-4-(4-(3-fluoro-2-methoxyphenyl)piperazin-1-yl)butan-1-amine (Compound 209):** Compound **209** as synthesized according to general method **D**, using compound **206** (0.47 g, 0.87 mmol), and anhydrous hydrazine (0.14 g, 4.3 mmol). The product, compound **209** (0.29 g, 81%) was obtained after solvent removal as a viscous oil, which was used for the next step without further purification. A general procedure for preparation of 4-nitrophenyl carbamate ("Method T") was utilized. *N*,*N*-Diisopropylethylamine (DIPEA) or triethylamine (TEA) or NMM (3 equiv) and bis(4-nitrophenyl) carbonate (1.5 equiv) was added to a solution of TBS protected amine (1 equiv) in anhydrous DCM (5 mL/1 mmol) at 0 °C. After stirring at room temperature for 16 hours, the solvent was removed under reduced pressure to give the 4-Nitrophenyl carbamate as yellow viscous oil. The crude product was purified using flash column chromatography (0-50% acetone-hexane) to obtain pure carbamate.

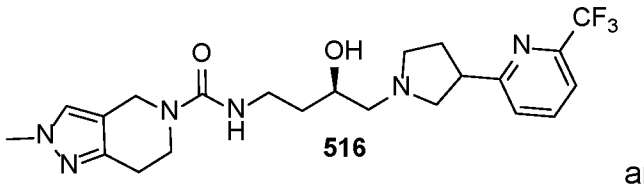
Synthesis of: 

[0245] 4-Nitrophenyl (*R*)-(3-((*tert*-butyldimethylsilyl)oxy)-4-(4-(3-fluoro-2-methoxyphenyl)piperazin-1-yl)butyl)carbamate (Compound 210): Compound 210 was synthesized according to general method T, using amine compound 209 (350 mg, 0.850 mmol), TEA (0.36 mL, 2.55 mmol), and bis(4-nitrophenyl) carbonate (388 mg, 1.27 mmol). The pure product, compound 210 (342 mg, 70%) was obtained as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 – 8.20 (m, 2H), 7.34 – 7.27 (m, 2H), 7.25 (d, *J* = 4.9 Hz, 1H), 6.93 (td, *J* = 8.2, 5.9 Hz, 1H), 6.77 (ddd, *J* = 10.1, 8.3, 1.5 Hz, 1H), 6.64 (dt, *J* = 8.2, 1.5 Hz, 1H), 4.04 (t, *J* = 5.5 Hz, 1H), 3.93 (d, *J* = 0.9 Hz, 3H), 3.56 – 3.43 (m, 1H), 3.35 (ddt, *J* = 12.9, 8.4, 4.3 Hz, 1H), 3.19 (s, 4H), 2.78 – 2.66 (m, 4H), 2.52 (d, *J* = 6.1 Hz, 2H), 1.94 (ddt, *J* = 11.4, 6.9, 4.9 Hz, 2H), 0.94 (s, 9H), 0.14 (d, *J* = 4.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 156.3, 155.4, 153.0, 146.58, 146.54, 144.6, 140.67, 140.5, 125.2, 123.7, 123.6, 121.9, 113.65, 113.62, 110.5, 110.3, 69.4, 63.9, 60.2, 60.1, 54.5, 50.2, 37.81, 34.8, 25.9, 18.1, -4.3, -4.6.

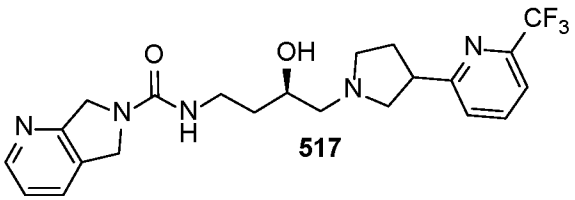
[0246] Urea analog synthesis and TBS deprotection ("Method U") was utilized. To a stirring solution of amine or amine•HCl salt (1.3-3 equiv) in 1,4-dioxane (0.10M) was added Hunig's base (5-6 equiv) and the reaction was stirred for 30 minutes. To this was added carbamate (1 equiv) and the resulting mixture was stirred at 90 ºC for 24 hours. Then TBAF 1 M solution in THF (6 equiv) was added to the reaction mixture and stirred for another 16 hours. *p*-Nitrophenol (6 equiv) was added to the reaction mixture to remove excess TBAF and formed yellow precipitate which was removed by filtration. The filtrate was concentrated under reduced pressure. The crude product was purified using flash column chromatography (0-50% DCM-MeOH and 5-10% NH_4OH) to obtain pure urea compound.

[0247] (*R*)-*N*-(4-(4-(3-Fluoro-2-methoxyphenyl)piperazin-1-yl)-3-hydroxybutyl)-2-methyl-2,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridine-6-carboxamide (Compound 515): Compound 515 was synthesized according to general method U, using compound 210 (150 mg, 0.260 mmol), *N*,*N*-Diisopropylethylamine (DIPEA) (0.27 mL, 1.56 mmol), and 2-methyl-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*c*]pyridine (46.4 mg,

0.338 mmol), TBAF 1M solution (1.56 mL, 1.56 mmol) and p-nitrophenol (217 mg, 1.56 mmol). The pure product, compound 515 (74 mg, 62%) was obtained as a yellow viscous oil. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.13 (s, 1H), 6.94 (td, *J* = 8.3, 6.1 Hz, 1H), 6.83 – 6.63 (m, 2H), 5.61 – 5.43 (m, 1H), 4.39 (s, 2H), 3.94 – 3.76 (m, 7H), 3.63 (t, *J* = 5.9 Hz, 2H), 3.53 (dtd, *J* = 13.4, 6.8, 4.7 Hz, 1H), 3.32 – 3.04 (m, 5H), 2.83 (t, *J* = 9.0 Hz, 2H), 2.71 (t, *J* = 5.8 Hz, 2H), 2.59 (d, *J* = 11.2 Hz, 2H), 2.41 (dd, *J* = 6.9, 3.0 Hz, 2H), 1.68 (dtd, *J* = 14.5, 4.7, 2.4 Hz, 1H), 1.59 – 1.38 (m, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 158.3, 155.8, 146.9, 140.8, 125.9, 124.0, 123.9, 114.14, 114.11, 113.5, 110.3, 110.1, 66.5, 64.3, 60.28, 60.24, 50.7, 42.5, 40.6, 39.3, 39.0, 34.7, 24.0; UPLC/MS purity >90% (CH_3CN: 90.7%, t_R= 2.05 min), (MeOH: 89.6%, t_R= 2.87 min), $C_{23}H_{33}FN_6O_3$ MW 460.55, observed $[M+1]^+$ 461.32.

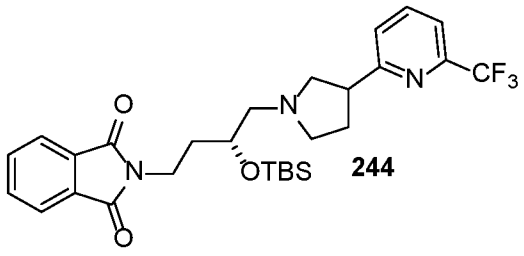
Synthesis of:  and

516



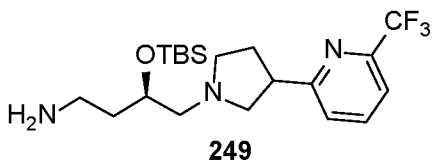
517

[0248] Compounds 516 and 517 synthesis according to Schemes 15 and 16 are depicted in FIG. 30. TBS protection of amine ("Method S") was utilized. To a stirring solution of epoxide opened compound (1 equiv) dissolved in DCM (0.10M) was added 2,6-lutidine (3 equiv). The resulting solution was cooled to 0 ºC and TBSOTf (1.5 equiv) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 2-16 hours till the disappearance of starting material. The organic layer was washed with saturated K_2CO_3 solution and dried over Na_2SO_4. The crude product was purified using flash column chromatography (0-100% acetone-hexane) to obtain TBS protected compound.

Synthesis of:  **244**.

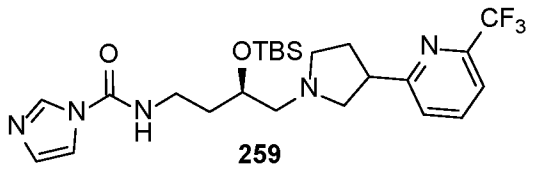
[0249] 2-((3*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-4-(3-(6-(trifluoromethyl)pyridin-2-yl)pyrrolidin-1-yl)butyl)isoindoline-1,3-dione (Compound 244): Compound 244 was synthesized following general method S from compound 242 (4 g, 9.00 mmol) and 2,6-lutidine (3 mL, 0.03 mol) and TBSOTf (3 mL, 0.01 mol) in anhydrous dichloromethane (0.09 L, 0.10 M). The crude product was purified using flash column chromatography (0-100% acetone-hexane) to obtain the Compound 244 as a mixture of diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.76 (m, 3H), 7.72 – 7.66 (m, 2H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.47 (dt, *J* = 7.6, 1.3 Hz, 1H), 3.94 – 3.69 (m, 3H), 3.54 (d, *J* = 7.2 Hz, 1H), 3.03 – 2.72 (m, 2H), 2.62 (tt, *J* = 17.4, 9.2 Hz, 2H), 2.38 – 2.21 (m, 1H), 2.12 – 1.69 (m, 4H), 1.18 (d, *J* = 21.6 Hz, 1H), 0.89 (s, 9H), 0.07 (dd, *J* = 7.5, 3.0 Hz, 6H).

[0250] A general procedure for phthalyl deprotection ("Method D") was utilized. Anhydrous hydrazine (5 equiv) was added to a suspension of phthalyl protected amine (1 equiv) in anhydrous ethanol (10 mL/mmol), and the mixture was refluxed for 3 hours under nitrogen atmosphere. Solvents were removed, and the resulting residue was partitioned between DCM and a 20% aqueous K_2CO_3 solution. The layers were separated, and the organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the amine, which was used for the next step without further purification.

Synthesis of:  **249**.

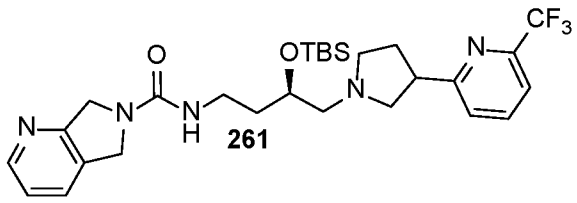
[0251] (3*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-4-(3-(6-(trifluoromethyl)pyridin-2-yl)pyrrolidin-1-yl)butan-1-amine (Compound 249): Compound 249 was synthesized following the general method D from compound **243** (3.80 g, 1 equiv, 6.90 mmol) and using anhydrous hydrazine (1.10 mL, 5 equiv, 35 mmol) in ethanol (69 mL, 0.10

molar) The crude amine was carried further for the next reaction without any purification. CDI Carbamate formation was performed via "Method V" as follows. To a stirring solution of CDI (1 equiv) in DCM (0.10 M) was added TBS-protected amine (1 equiv) dropwise at 0 ºC. The reaction mixture was warmed to room temperature and stirred for 1 hour. The crude product was purified using flash column chromatography (0-100% acetone-hexane) to obtain the target compound.

Synthesis of:  **259** .

[0252] *N*-((3*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-4-(3-(6-(trifluoromethyl)pyridin-2-yl)pyrrolidin-1-yl)butyl)-1*H*-imidazole-1-carboxamide (Compound 259): Compound 259 was synthesized following the general method V from compound 249 (500 mg, 1.20 mmol) and CDI (252 mg, 1.56 mmol) in DCM (12 mL, 0.10 M). The crude product was purified using flash column chromatography (0-100% acetone-hexane) to obtain the target compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.09 (dt, *J* = 12.4, 1.0 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.41 – 7.31 (m, 2H), 6.97 (dt, *J* = 5.9, 1.2 Hz, 1H), 3.97 – 3.91 (m, 1H), 3.56 (ddd, *J* = 17.9, 7.8, 3.4 Hz, 2H), 3.05 – 2.95 (m, 1H), 2.90 (ddd, *J* = 9.7, 7.3, 5.1 Hz, 1H), 2.80 – 2.58 (m, 3.5H), 2.47 (dd, *J* = 12.3, 4.5 Hz, 0.5H), 2.28 (ddt, *J* = 13.0, 9.6, 6.3 Hz, 1H), 2.10 – 1.83 (m, 3H), 0.84 (d, *J* = 0.9 Hz, 9H), 0.03 (dd, *J* = 2.7, 1.8 Hz, 6H).

[0253] Urea analog synthesis was performed ("Method W"). To a stirring solution of amine or amine•HCl salt (1.3-3 equiv) in 1,4-dioxane (0.10M) was added Hunig's base (5-6 equiv) and the reaction was stirred for 30 minutes. To this was added carbamate (1 equiv) and the resulting mixture was stirred at 90 ºC for 24 hours. The solvent was removed under reduced pressure and the crude product was purified using flash column chromatography (0-50% DCM-MeOH and 5-10% NH_4OH) to obtain pure urea compound.

Synthesis of:  .

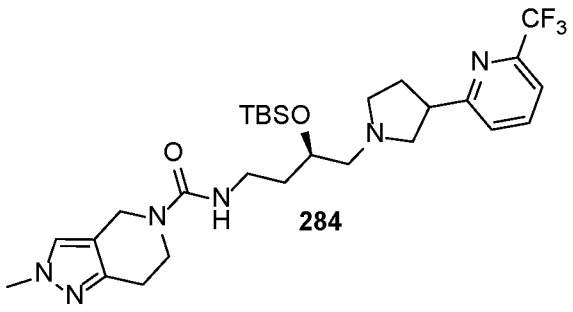
261

[0254] *N*-((3*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-4-(3-(6-(trifluoromethyl)pyridin-2-yl)pyrrolidin-1-yl)butyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridine-6-carboxamide (Compound 261): Compound 261 was synthesized following the general method W from Compound 259 (365 mg, 713 µmol) and amine•HCl salt (275 mg, 2 equiv, 1.43 mmol), Hunig's base (0.50 mL, 2.85 mmol) in 1,4-dioxane (7.13 mL, 0.10M). The crude product was carried forward for further reaction without purification. TBS-deprotection with 4N HCl in dioxane ("Method X") was utilized. To a stirring solution of TBS-protected urea compound (1 equiv) in 1,4-dioxane (0.05M) was added HCl (4 M in 1,4-dioxane; 3-6 equiv) at 0 ºC. The resulting mixture was stirred at room temperature for 2-4 hours. The solvent was evaporated, and the crude product was purified using flash column chromatography (0-100% acetone-MeOH (2% aq. NH_3 added) to obtain the final target compound.

[0255] *N*-((3*R*)-3-Hydroxy-4-(3-(6-(trifluoromethyl)pyridin-2-yl)pyrrolidin-1-yl)butyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridine-6-carboxamide (Compound 517): Compound 517 was synthesized following the general method X from compound 261 (211 mg, 374 µmol) in 1,4-dioxane (7.50 mL, 0.05M) and HCl in 1,4-dioxane (0.20 mL, 748 µmol). The solvent was evaporated, and the crude product was purified using flash column chromatography (0-100% acetone-MeOH (2% aq. NH_3 added) to obtain the target compound 517 in 65% yield as a mixture of diastereomers; ^{1}H NMR (400 MHz, MeOD) δ 8.42 (d, *J* = 5.0 Hz, 1H), 7.93 (t, *J* = 7.8 Hz, 1H), 7.78 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.61 (dd, *J* = 7.8, 1.9 Hz, 2H), 7.33 (dd, *J* = 7.8, 5.0 Hz, 1H), 4.68 (dt, *J* = 23.2, 2.9 Hz, 4H), 3.92 (pd, *J* = 5.6, 4.8, 1.9 Hz, 1H), 3.78 – 3.63 (m, 1H), 3.49 – 3.32 (m, 3H), 3.12 (dq, *J* = 9.7, 7.4 Hz, 1H), 2.97 (dtd, *J* = 17.9, 8.9, 6.0 Hz, 2H), 2.86 – 2.69 (m, 2H), 2.38 (dddd, *J* = 19.3, 9.4, 6.4, 2.8 Hz, 1H), 2.12 (ddt, *J* = 12.9, 8.2, 6.3 Hz, 1H), 1.80 (dtd, *J* = 14.4, 7.4, 3.7 Hz, 1H), 1.61 (ddt, *J* = 15.3, 8.9, 6.1 Hz, 1H); ^{13}C NMR (100 MHz, MeOD) δ 165.8, 159.5, 158.5, 149.5, 148.7, 148.3, 139.6, 133.2, 132.8, 126.7, 124.4, 124.1, 121.7, 119.4, 119.4, 68.5, 68.5, 63.2, 61.6, 61.4, 56.0, 55.8, 53.0, 51.4, 46.01, 45.96, 38.5, 37.2, 32.4, 32.3; UPLC/MS purity >95%

(CH_3CN: 95.6%, t_R = 1.90 min), MeOH: 96.3%, t_R = 2.72 min), $C_{22}H_{26}F_3N_5O_2$ MW 449.48, [M+H]+ 450.3

[0256] Urea analog synthesis was performed ("Method W"). To a stirring solution of amine or amine•HCl salt (1.3-3 equiv) in 1,4-dioxane (0.10M) was added Hunig's base (5-6 equiv) and the reaction was stirred for 30 minutes. To this was added carbamate (1 equiv) and the resulting mixture was stirred at 90 ºC for 24 hours. The solvent was removed under reduced pressure and the crude product was purified using flash column chromatography (0-50% DCM-MeOH and 5-10% NH_4OH) to obtain pure urea compound.

Synthesis of: 

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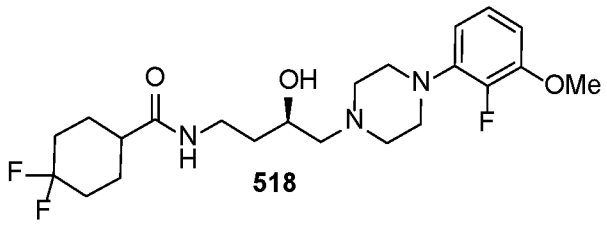
[0257] *N*-((3*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-4-(3-(6-(trifluoromethyl)pyridin-2-yl)pyrrolidin-1-yl)butyl)-2-methyl-2,4,6,7-tetrahydro-5*H*-pyrazolo[4,3-*c*]pyridine-5-carboxamide (Compound 284): Compound 284 was synthesized following the general method W from compound 259 (300 mg, 586 µmol) and amine•HCl salt (370 mg, 3 equiv, 1.76 mmol), Hunig's base (0.61 mL, 3.52 mmol) in 1,4-dioxane (5.86 mL, 0.10M). The crude product was carried forward for further reaction without purification. TBS-deprotection with 4N HCl in dioxane ("Method X") was utilized. To a stirring solution of TBS-protected urea compound (1 equiv) in 1,4-dioxane (0.05M) was added HCl (4 M in 1,4-dioxane; 3-6 equiv) at 0 ºC. The resulting mixture was stirred at room temperature for 2-4 hours. The solvent was evaporated, and the crude product was purified using flash column chromatography (0-100% acetone-MeOH (2% aq. NH_3 added) to obtain the final target compound.

[0258] *N*-((3*R*)-3-Hydroxy-4-(3-(6-(trifluoromethyl)pyridin-2-yl)pyrrolidin-1-yl)butyl)-2-methyl-2,4,6,7-tetrahydro-5*H*-pyrazolo[4,3-*c*]pyridine-5-carboxamide (Compound 516): Compound 516 was synthesized following the general method X from compound 284 (600 mg, 1.03 mmol) in 1,4-dioxane (20.7 mL, 0.05M) and HCl in 1,4-dioxane (0.52 mL, 2.07 mmol). The solvent was evaporated, and the crude product

was purified using flash column chromatography (0-100% acetone-MeOH (2% aq. NH_3 added) to obtain the target compound 516 in 60% yield (calculated from CDI intermediate) as a mixture of diastereomers; ^{1}H NMR (400 MHz, MeOD) δ 8.01 (dtd, *J* = 7.9, 4.7, 2.3 Hz, 1H), 7.75 – 7.62 (m, 3H), 4.50 – 4.43 (m, 2H), 4.09 – 3.97 (m, 3H), 3.97 – 3.91 (m, 4H), 3.84 (dddd, *J* = 17.8, 12.1, 9.5, 4.0 Hz, 1H), 3.77 – 3.63 (m, 2H), 3.61 – 3.31 (m, 4H), 3.28 – 3.19 (m, 1H), 2.78 (q, *J* = 6.0 Hz, 2H), 2.68 – 2.48 (m, 1H), 2.35 – 2.13 (m, 1H), 1.71 (ddq, *J* = 14.9, 7.6, 3.8 Hz, 1H), 1.59 (ddd, *J* = 14.0, 8.3, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, MeOD) δ 162.1, 161.9, 160.2, 148.5, 146.5, 140.6, 140.5, 140.4, 131.38, 131.36, 127.5, 124.3, 121.6, 120.5, 116.09, 116.06, 65.33, 65.30, 65.2, 65.1, 61.7, 61.6, 60.5, 60.3, 58.3, 57.7, 57.1, 56.4, 54.8, 54.0, 44.9, 44.9, 44.5, 44.4, 42.23, 42.19, 40.91, 40.87, 38.57, 38.56, 37.8, 36.7, 32.4, 32.3, 31.7, 31.6, 23.1; UPLC/MS purity >94% (CH_3CN: 94.6%, t_R = 1.81 min), MeOH: 96.7%, t_R = 2.58 min), $C_{22}H_{29}F_3N_6O_2$ MW 466.5, [M+H]+ 467.3

Synthesis of: 

518

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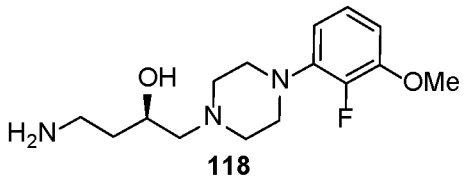
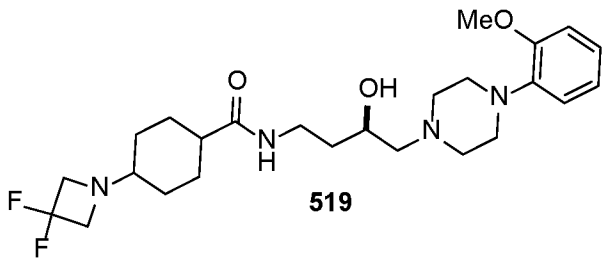
[0259] Compound 518 synthesis according to Scheme 17 is depicted in FIG. 31. A general procedure for preparation amide with HATU ("Method Q") was utilized. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved acid (1 equiv) in DMF (5 mL) or DCM (5 mL). Diisopropylethylamine DIPEA or TEA (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture and stirred for 10 minutes at room temperature, and then the primary amine was added at room temperature. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with EtOAc or DCM (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM) to get amide.



118

Synthesis of: .

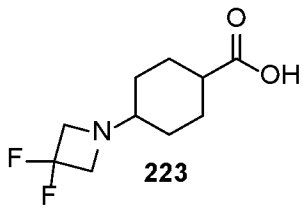
[0260] (*R*)-4,4-Difluoro-*N*-(4-(4-(2-fluoro-3-methoxyphenyl)piperazin-1-yl)-3-hydroxybutyl)cyclohexane-1-carboxamide (Compound 518): Compound 518 was synthesized according to general method Q, using compound 118 (75 mg, 0.25 mmol), TEA (69 μL, 0.50 mmol), HATU (96 mg, 0.25 mmol) and 4,4-difluorocyclohexane-1-carboxylic acid (41 mg, 0.25 mmol). The pure product, compound 518 (84 mg, 75%) was obtained as a white solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.98 (td, *J* = 8.3, 2.0 Hz, 1H), 6.70 – 6.63 (m, 1H), 6.62 – 6.54 (m, 1H), 6.44 (t, *J* = 5.3 Hz, 1H), 3.84 (s, 4H), 3.56 (dtd, *J* = 13.6, 6.9, 5.0 Hz, 1H), 3.30 – 3.03 (m, 6H), 2.92 – 2.80 (m, 2H), 2.62 (dt, *J* = 11.1, 5.2 Hz, 2H), 2.52 – 2.34 (m, 2H), 2.13 (qd, *J* = 10.4, 6.3 Hz, 3H), 1.99 – 1.60 (m, 7H), 1.46 (dtd, *J* = 13.9, 8.3, 5.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 174.0, 149.0, 148.9, 147.2, 144.7, 141.39, 141.32, 125.8, 123.9, 123.8, 123.4, 121.0, 111.4, 111.3, 107.3, 66.4, 64.1, 56.6, 53.7, 51.1, 51.0, 43.0, 37.8, 34.0, 33.4, 33.24, 33.22, 32.9, 26.3, 26.2; UPLC/MS purity >99% (CH_3CN: 99.0%, t_R= 2.23 min), (MeOH: 99.6%, t_R= 2.90 min), $C_{22}H_{32}F_3N_3O_3$ MW 443.51, observed $[M+1]^+$ 444.30.



519

Synthesis of: .

[0261] Compound 519 synthesis according to Scheme 18 is depicted in FIG. 32.



223

Synthesis of: .

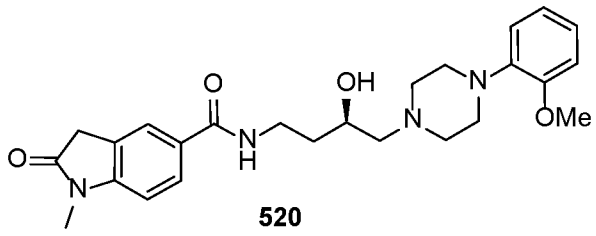
[0262] 4-(3,3-Difluoroazetidin-1-yl)cyclohexane-1-carboxylic acid (Compound 223): 3,3-Difluoroazetidine hydrochloride (164 mg, 1.76 mmol) in anhydrous DCM

(10 mL) was treated with TEA at room temperature and stirred for 10 min. Then 4-oxocyclohexane-1-carboxylic acid (250 mg, 1.76 mmol) was added to the above mixture and stirred overnight, then then $Na(OAc)_3BH$ (1.12 g, 5.28 mmol) was added to the reaction mixture and stirred for another 16 hours. The reaction mixture was quenched with aqueous saturated $NaHCO_3$ solution, and the product was extracted with DCM. The DCM extract was dried (Na_2SO_4) and concentrated under reduced pressure to get crude compound **223** which was purified by flash column chromatography (silica gel, 0-100% acetone in hexanes) to get pure compound **223** in 26% yield. ^1H NMR (400 MHz, CD_2Cl_2) δ 14.02 (s, 1H), 3.76 (t, *J* = 12.0 Hz, 4H), 2.55 (t, *J* = 3.8 Hz, 1H), 2.40 – 2.13 (m, 3H), 1.64 (dt, *J* = 14.2, 3.8 Hz, 2H), 1.53 – 1.09 (m, 4H).

[0263] A general procedure for preparation amide with HATU ("Method Q") was followed**.** In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved acid (1 equiv) in DMF (5 mL) or DCM (5 mL). Diisopropylethylamine DIPEA or TEA (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture and stirred for 10 minutes at room temperature, and then the primary amine was added at room temperature. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with EtOAc or DCM (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM) to get amide.

[0264] (*R*)-4-(3,3-Difluoroazetidin-1-yl)-*N*-(3-hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)cyclohexane-1-carboxamide (Compound 519): Compound 519 was synthesized according to general method Q, using compound 127 (70 mg, 0.25 mmol), TEA (69 μL, 0.50 mmol), HATU (95 mg, 0.25 mmol) and compound 223 (55 mg, 0.25 mmol). The pure product, compound 519 (88 mg, 73%) was obtained as a white solid. ^1H NMR (400 MHz, CD_2Cl_2) δ 7.01 (ddd, *J* = 7.9, 6.0, 3.2 Hz, 1H), 6.97 – 6.83 (m, 3H), 6.35 (s, 1H), 3.87 (s, 4H), 3.65 – 3.46 (m, 5H), 3.35 – 3.20 (m, 1H), 3.11 (s, 4H), 2.94 – 2.81 (m, 2H), 2.64 (d, *J* = 5.9 Hz, 2H), 2.49 – 2.41 (m, 2H), 2.39 (d, *J* = 7.3 Hz, 1H), 2.13 (dt, *J* = 10.5, 3.7 Hz, 1H (overlapped with acetone)), 1.91 – 1.76 (m, 3H), 1.74 – 1.36 (m, 8H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 175.5, 152.8, 141.8, 123.1, 121.3, 118.5, 116.7, 111.8, 66.1, 64.3, 63.2, 63.0, 62.8,

62.3, 55.6, 50.9, 44.5, 37.5, 34.3, 31.0, 27.7, 24.4, 24.4; UPLC/MS purity >98% (CH_3CN: 98.9%, t_R= 2.24 min), (MeOH: 99.2%, t_R= 3.01 min), $C_{25}H_{38}F_2N_4O_3$ MW 480.60, observed $[M+1]^+$ 481.37.

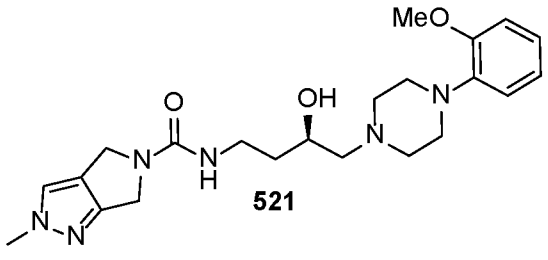
Synthesis of: 

520 .

[0265] Compound 520 synthesis according to Scheme 19 is depicted in FIG. 33. A general procedure for preparation amide with HATU ("Method Q") was performed. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved acid (1 equiv) in DMF (5 mL) or DCM (5 mL). Diisopropylethylamine DIPEA or TEA (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture and stirred for 10 minutes at room temperature, and then the primary amine was added at room temperature. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with EtOAc or DCM (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM) to get amide.

[0266] **(*R*)-*N*-(3-Hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-1-methyl-2-oxoindoline-5-carboxamide (Compound 520):** Compound **520** was synthesized according to general method **Q**, using compound **127** (70 mg, 0.25 mmol), TEA (69 μL, 0.50 mmol), HATU (95 mg, 0.25 mmol) and 1-Methyl-2-oxoindoline-5-carboxylic acid (48 mg, 0.25 mmol). The pure product, compound **520** (70 mg, 62%) was obtained as a white solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.75 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.69 (d, *J* = 1.8 Hz, 1H), 7.23 (s, 1H), 6.98 (ddd, *J* = 7.9, 5.8, 3.3 Hz, 1H), 6.92 – 6.83 (m, 4H), 3.91 (tdd, *J* = 9.1, 4.6, 2.7 Hz, 1H), 3.83 (s, 4H), 3.52 (s, 2H), 3.41 (ddt, *J* = 13.1, 8.5, 4.2 Hz, 1H), 3.19 (s, 3H), 3.07 (s, 4H), 2.84 (dt, *J* = 10.4, 4.7 Hz, 2H), 2.67 – 2.54 (m, 2H), 2.49 – 2.36 (m, 2H), 1.79 (dddd, *J* = 14.0, 7.0, 4.6, 2.6 Hz, 1H), 1.64 – 1.49 (m, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 175.2, 166.8, 152.8, 148.4, 141.8, 129.2, 127.5, 125.1, 123.4, 123.1, 121.2, 118.5, 111.8, 107.8, 66.8, 64.2,

55.6, 50.9, 38.7, 35.8, 33.8, 26.5; UPLC/MS purity >96% (CH_3CN: 96.1%, t_R= 1.91 min), (MeOH: 97.8%, t_R= 2.70 min), $C_{25}H_{32}N_4O_4$ MW 452.56, observed $[M+1]^+$ 453.32.

Synthesis of: 

521

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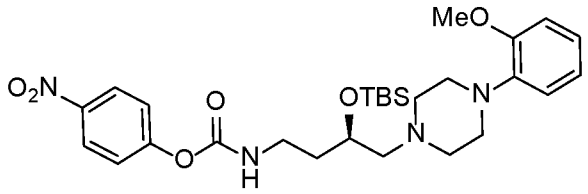
[0267] Compound 521 synthesis according to Scheme 20 is depicted in FIG. 34.Urea analog synthesis and TBS deprotection ("Method U") was utilized. To a stirring solution of amine or amine•HCl salt (1.3-3 equiv) in 1,4-dioxane (0.10M) was added Hunig's base (5-6 equiv) and the reaction was stirred for 30 minutes. To this was added carbamate (1 equiv) and the resulting mixture was stirred at 90 ºC for 24 hours. Then TBAF 1 M solution in THF (6 equiv) was added to the reaction mixture and stirred for another 16 hours. *p*-Nitrophenol (6 equiv) was added to the reaction mixture to remove excess TBAF and formed yellow precipitate which was removed by filtration. The filtrate was concentrated under reduced pressure. The crude product was purified using flash column chromatography (0-50% DCM-MeOH and 5-10% NH_4OH) to obtain pure urea compound.

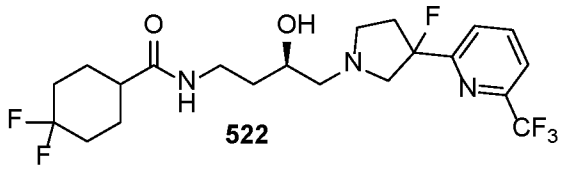


233

Synthesis of: .

[0268] (*R*)-*N*-(3-Hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-2-methyl-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5(4*H*)-carboxamide (Compound 521): Compound 521 was synthesized according to general method U, using compound 233 (90 mg, 0.16 mmol), *N*,*N*-Diisopropylethylamine (DIPEA) (0.19 mL, 0.97 mmol), and 2-methyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole hydrochloride (33 mg, 0.21 mmol), TBAF 1M solution (0.97 mL, 0.97 mmol) and p-nitrophenol (0.13 g, 0.97 mmol). The pure product, compound 521 (24 mg, 35%) was obtained as a brown oil. ^1H NMR (400

MHz, CD_2Cl_2) δ 7.13 (s, 1H), 6.98 (ddd, *J* = 7.8, 6.1, 2.9 Hz, 1H), 6.94 – 6.82 (m, 3H), 5.19 (s, 1H), 4.40 (s, 4H), 3.86 (s, 4H), 3.83 (s, 3H), 3.63 – 3.50 (m, 1H), 3.29 (ddt, *J* = 12.4, 7.5, 4.5 Hz, 1H), 3.09 (s, 4H), 2.85 (s, 2H), 2.63 (s, 2H), 2.45 (d, *J* = 6.9 Hz, 2H), 1.70 (dddd, *J* = 12.3, 7.7, 4.9, 2.8 Hz, 1H), 1.57 – 1.45 (m, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 157.5, 154.2, 152.8, 123.7, 123.1, 121.3, 119.1, 118.5, 111.8, 66.1, 64.3, 55.6, 50.8, 45.5, 45.3, 39.4, 38.8, 35.0; UPLC/MS purity >90% (CH_3CN: 90.0%, t_R= 1.78 min), (MeOH: 96.6%, t_R= 2.59 min), $C_{22}H_{32}N_6O_3$ MW 428.54, observed $[M+1]^+$ 429.28.

Synthesis of: 

522

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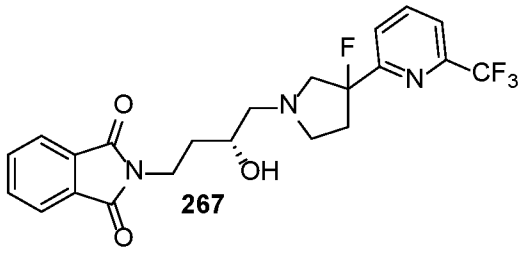
[0269] Compound 522 synthesis according to Scheme 21 is depicted in FIG. 35. General procedure for epoxide (*R*)-3 and (*S*)-3 opening with pyrrolidines and piperazines and other 2°-amines ("Method C") was utilized. To a solution of **(*R*)-3** or **(*S*)-3** (1 equiv) in 2-propanol (6 mL/mmol) was added pyrrolidines or piperazines (1 equiv). The insoluble reaction mixture was heated to 70 °C to 80 °C to get a clear solution and then stirred at room temperature for 24 to 48 hours. The solvent was removed *in vacuo*, and the crude product was purified by flash column chromatography (silica gel, 0-100% acetone in hexanes or MeOH in DCM (0-10%) to give epoxide opened products.

Synthesis of: 

267

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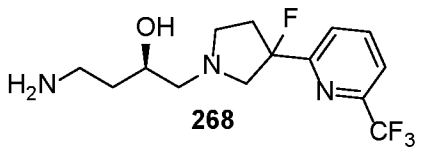
[0270] 2-((3*R*)-4-(3-Fluoro-3-(6-(trifluoromethyl)pyridin-2-yl)pyrrolidin-1-yl)-3-hydroxybutyl)isoindoline-1,3-dione (Compound 267): Compound 267 was synthesized according to general method C, using (*R*)-3 (148 mg, 0.683 mmol), and compound 266 (160 mg, 0.683 mmol). The pure product, compound 267 (230 mg, 75%) was obtained as a viscous oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (t, *J* = 7.9 Hz, 1H), 7.82 (dt, *J* = 5.2, 2.3 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.72 – 7.65 (m, 2H), 7.58

(d, *J* = 7.7 Hz, 1H), 3.96 – 3.78 (m, 2H), 3.74 (pd, *J* = 8.3, 7.5, 4.0 Hz, 1H), 3.60 (s, 1H), 3.37 – 3.06 (m, 3H), 3.03 – 2.78 (m, 1H), 2.74 – 2.48 (m, 3H), 2.43 – 2.22 (m, 1H), 1.79 (q, *J* = 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 161.1, 160.8, 147.8, 147.4, 138.1, 134.0, 132.2, 123.3, 122.2, 122.1, 119.35, 119.32, 105.1, 104.9, 103.2, 103.1, 66.6, 66.5, 66.3, 66.1, 65.9, 65.7, 61.8, 61.6, 54.1, 53.6, 39.2, 39.0, 35.08, 35.06, 33.7.

[0271] A general procedure for phthalyl deprotection ("Method D") was utilized. Anhydrous hydrazine (5 equiv) was added to a suspension of phthalyl protected amine (1 equiv) in anhydrous ethanol (10 mL/mmol), and the mixture was refluxed for 3 hours under nitrogen atmosphere. Solvents were removed, and the resulting residue was partitioned between DCM and a 20% aqueous K_2CO_3 solution. The layers were separated, and the organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the amine, which was used for the next step without further purification.

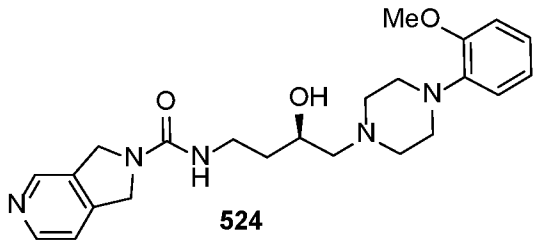
Synthesis of: 

268.

[0272] **(2*R*)-4-Amino-1-(3-fluoro-3-(6-(trifluoromethyl)pyridin-2-yl)pyrrolidin-1-yl)butan-2-ol (Compound 268):** Compound **268** was synthesized according to general method **D**, using compound **267** (230 mg, 0.510 mmol), and anhydrous hydrazine (81.7 mg, 2.55 mmol). The product, compound **S268** (138 mg, 84%) was obtained after solvent removal as a viscous oil, which was used for the preparation amide analog without further purification. A general procedure for preparation amide with HATU ("Method Q") was utilized. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved acid (1 equiv) in DMF (5 mL) or DCM (5 mL). Diisopropylethylamine DIPEA or TEA (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture and stirred for 10 minutes at room temperature, and then primary–amine was added at room temperature. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with EtOAc or DCM (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced

pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM) to get amide.

[0273] 4,4-Difluoro-*N*-((3*R*)-4-(3-fluoro-3-(6-(trifluoromethyl)pyridin-2-yl)pyrrolidin-1-yl)-3-hydroxybutyl)cyclohexane-1-carboxamide (Compound 522): Compound 522 was synthesized according to general method Q, using compound 268 (60 mg, 0.19 mmol), TEA (51 μL, 0.37 mmol), HATU (71 mg, 0.19 mmol) and 4,4-difluorocyclohexane-1-carboxylic acid (31 mg, 0.19 mmol). The pure product, compound 522 (75 mg, 86%) was obtained as a white solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.96 (t, *J* = 7.9 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.64 (dd, *J* = 7.8, 1.0 Hz, 1H), 6.47 (q, *J* = 5.5 Hz, 1H), 3.80 – 3.67 (m, 1H), 3.66 – 3.53 (m, 1H), 3.37 – 2.94 (m, 5H), 2.87 – 2.48 (m, 4H), 2.48 – 2.27 (m, 1H), 2.24 – 2.05 (m, 4H), 1.99 – 1.63 (m, 5H (overlapped with acetone)), 1.49 (dddt, *J* = 11.6, 7.0, 4.4, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 175.2, 175.1, 175.0, 161.4, 161.1, 147.8, 147.4, 138.8, 125.7, 123.3, 123.2, 122.7, 122.6, 121.0, 120.5, 119.8, 105.3, 105.2, 103.5, 103.4, 67.6, 67.4, 66.2, 66.0, 65.7, 61.65, 61.60, 43.0, 39.5, 39.3, 37.2, 37.1, 34.5, 34.4, 33.4, 33.1, 32.9, 31.0, 26.3, 26.29, 26.20; UPLC/MS purity >96% (CH_3CN: 97.6%, t_R= 2.41 min), (MeOH: 96.9%, t_R= 3.08 min), $C_{24}H_{27}F_6N_3O_2$ MW 467.46, observed [M]+1$^+$ 468.26.

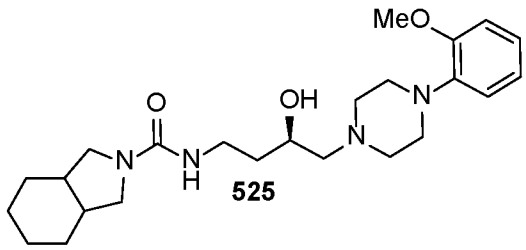
Synthesis of: 

524 .

[0274] Compound 524 synthesis according to Scheme 22 is depicted in FIG. 36. Urea analog synthesis and TBS deprotection ("Method U") were performed. To a stirring solution of amine or amine•HCl salt (1.3-3 equiv) in 1,4-dioxane (0.10M) was added Hunig's base (5-6 equiv) and the reaction was stirred for 30 minutes. To this was added carbamate (1 equiv) and the resulting mixture was stirred at 90 ºC for 24 hours. Then TBAF 1 M solution in THF (6 equiv) was added to the reaction mixture and stirred for another 16 hours. *p*-Nitrophenol (6 equiv) was added to the reaction mixture to remove excess TBAF and formed yellow precipitate which was removed by filtration. The filtrate was concentrated under reduced pressure. The crude

product was purified using flash column chromatography (0-50% DCM-MeOH and 5-10% NH_4OH) to obtain pure urea compound.

[0275] (*R*)-*N*-(3-Hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridine-2-carboxamide (Compound 524): Compound 524 was synthesized according to general method U, using compound 233 (120 mg, 0.215 mmol), *N*,*N*-Diisopropylethylamine (DIPEA) (77 μL, 0.430 mmol), and 2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine (33.6 mg, 0.280 mmol), TBAF 1M solution (645 μL, 0.645 mmol) and *p*-nitrophenol (0.15 g, 1.08 mmol). The pure product, compound 524 (54 mg, 59%) was obtained as a brown viscous oil. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.52 (s, 1H), 8.47 (d, *J* = 5.0 Hz, 1H), 7.23 (d, *J* = 5.0 Hz, 1H), 6.97 (ddd, *J* = 7.9, 6.0, 3.1 Hz, 1H), 6.93 – 6.81 (m, 3H), 5.45 (dd, *J* = 6.8, 4.0 Hz, 1H), 4.68 (q, *J* = 2.7 Hz, 4H), 3.92 (dq, *J* = 11.2, 4.1, 2.9 Hz, 1H), 3.81 (s, 3H), 3.58 (dtd, *J* = 13.6, 6.9, 4.7 Hz, 1H), 3.37 – 3.24 (m, 1H), 3.10 (s, 4H), 2.94 – 2.82 (m, 2H), 2.68 (d, *J* = 7.1 Hz, 2H), 2.52 – 2.42 (m, 2H), 1.71 (dddd, *J* = 14.5, 7.5, 4.7, 2.9 Hz, 1H), 1.52 (dddd, *J* = 13.9, 9.1, 7.7, 4.7 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 157.1, 152.7, 148.6, 146.7, 144.9, 141.6, 133.9, 123.2, 121.3, 118.5, 118.3, 111.8, 66.2, 64.3, 55.6, 51.9, 50.6, 50.2, 39.0, 34.8; UPLC/MS purity >93% (CH_3CN: 93.3%, t_R= 1.78 min), (MeOH: 95.2%, t_R= 2.64 min), $C_{23}H_{31}N_5O_3$ MW 425.53, observed $[M+1]^+$ 426.33

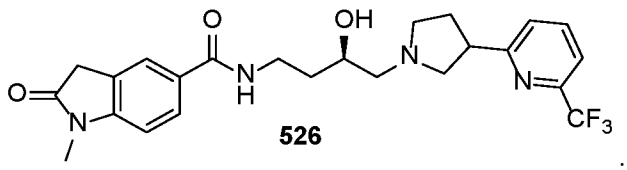
Synthesis of: 

525.

[0276] Compound 525 synthesis according to Scheme 23 is depicted in FIG. 37. Urea analog synthesis and TBS deprotection ("Method U") was utilized. To a stirring solution of amine or amine•HCl salt (1.3-3 equiv) in 1,4-dioxane (0.10M) was added Hunig's base (5-6 equiv) and the reaction was stirred for 30 minutes. To this was added carbamate (1 equiv) and the resulting mixture was stirred at 90 ºC for 24 hours. Then TBAF 1 M solution in THF (6 equiv) was added to the reaction mixture and stirred for another 16 hours. *p*-Nitrophenol (6 equiv) was added to the reaction mixture to remove excess TBAF and formed yellow precipitate which was removed by filtration. The filtrate was concentrated under reduced pressure. The crude

product was purified using flash column chromatography (0-50% DCM-MeOH and 5-10% NH_4OH) to obtain pure urea compound.

[0277] ***N*-((*R*)-3-Hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)octahydro-2*H*-isoindole-2-carboxamide (Compound 525):** Compound **525** was synthesized according to general method **U**, using compound **233** (125 mg, 0.224 mmol), *N*,*N*-Diisopropylethylamine (DIPEA) (80 μL, 0.448 mmol), and octahydro-1*H*-isoindole (36.4 mg, 0.291 mmol), TBAF 1M solution (672 μL, 0.672 mmol) and *p*-nitrophenol (156 mg, 1.12 mmol). The pure product, compound **525** (62 mg, 64%) was obtained as a yellow viscous oil. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.97 (ddd, *J* = 7.9, 6.0, 3.1 Hz, 1H), 6.92 – 6.83 (m, 3H), 4.94 (t, *J* = 5.8 Hz, 1H), 3.83 (s, 4H), 3.57 – 3.42 (m, 1H), 3.40 – 2.97 (m, 9H), 2.79 (dt, *J* = 10.3, 4.6 Hz, 2H), 2.63 – 2.49 (m, 2H), 2.39 (d, *J* = 6.7 Hz, 2H), 2.21 (p, *J* = 5.7 Hz, 2H), 1.72 – 1.30 (m, 10H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 157.9, 152.8, 141.9, 123.0, 121.2, 118.5, 111.8, 66.1, 64.4, 51.0, 49.8, 38.6, 37.6, 35.4, 26.3, 23.3; UPLC/MS purity >98% (CH_3CN: 99.4%, t_R= 2.35 min), (MeOH: 98.9%, t_R= 3.19 min), $C_{24}H_{38}N_4O_3$ MW 430.59, observed $[M+1]^+$ 431.36.

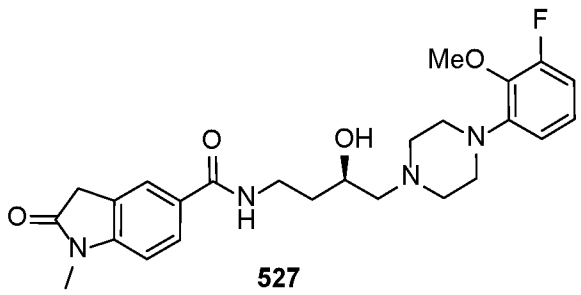
Synthesis of: 

526.

[0278] Compound 526 synthesis according to Scheme 24 is depicted in FIG. 38.

[0279] *N*-((3*R*)-3-Hydroxy-4-(3-(6-(trifluoromethyl)pyridin-2-yl)pyrrolidin-1-yl)butyl)-1-methyl-2-oxoindoline-5-carboxamide (Compound 526; Compound 269): To a stirring solution of 1-methyl-2-oxoindoline-5-carboxylic acid (40 mg, 0.21 mmol) in DCM (3.30 mL, 0.07 M) were added triethylamine (96 μL, 0.69 mmol) and HATU (79 mg, 0.21 mmol) and the resulting mixture was stirred for 30 minutes. To this solution was added amine compound 263 (70 mg, 0.23 mmol) and the reaction mixture was stirred at room temperature for 18 hours. The crude product was purified using flash column chromatography (0-100% acetone-hexane) to obtain the target compound 526 in 50% yield as a mixture of diastereomers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (t, *J* = 7.9 Hz, 2H), 7.69 (t, *J* = 1.6 Hz, 1H), 7.55 – 7.43 (m, 2H), 7.38 (t, *J* = 7.3 Hz, 1H), 6.81 (dd, *J* = 8.2, 1.5 Hz, 1H), 3.93 – 3.77 (m, 2H), 3.67 – 3.55 (m, 1H), 3.52 (bs, 2H), 3.43 – 3.36 (m, 1H), 3.21 (d, *J* = 1.0 Hz, 3H), 3.09 – 2.59 (m, 6H), 2.55 – 2.41 (m, 1H), 2.34 (qd, *J* = 8.0, 3.8 Hz, 1H), 2.15 – 2.02 (m, 1H), 1.82 (ddt, *J* = 13.8, 6.9,

3.4 Hz, 1H), 1.61 (dtd, *J* = 18.1, 9.0, 8.2, 3.8 Hz, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 167.1, 147.9, 137.8, 129.0, 127.7, 124.6, 123.2, 107.7, 68.6, 61.3, 59.6, 54.3, 50.8, 44.9, 38.6, 35.6, 31.7, 26.5.; UPLC/MS purity >92% (CH_3CN: 94.1%, t_R = 1.91 min), MeOH: 92.6%, t_R = 2.66 min), $C_{24}H_{27}F_3N_4O_3$ MW 476.5, [M+H]+ 477.3

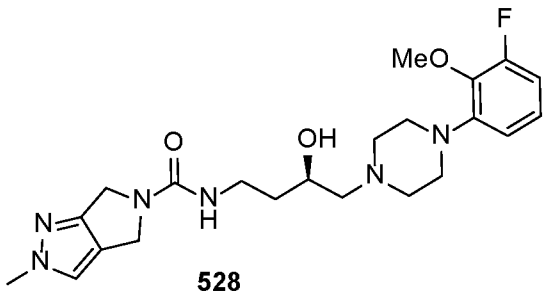
Synthesis of: 

527 .

[0280] Compound 527 synthesis according to Scheme 25 is depicted in FIG. 39. A general procedure for preparation amide with HATU ("Method Q") was utilized. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved acid (1 equiv) in DMF (5 mL) or DCM (5 mL). Diisopropylethylamine DIPEA or TEA (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture and stirred for 10 minutes at room temperature, and then the primary amine was added at room temperature. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with EtOAc or DCM (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM) to get amide.

[0281] (R)-N-(4-(4-(3-Fluoro-2-methoxyphenyl)piperazin-1-yl)-3-hydroxybutyl)-1-methyl-2-oxoindoline-5-carboxamide (Compound 527): To a solution of (R)-4-amino-1-(4-(3-fluoro-2-methoxyphenyl)piperazin-1-yl)butan-2-ol (199 mg, 523 µmol), triethylamine (106mg, 1.05 mmol) and 1-methyl-2-oxoindoline-5-carboxylic acid (100 mg, 523 µmol) in DCM (40 mL) was added 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate (199 mg, 523 µmol). The reaction mass was stirred for 24 hours at room temperature. Then added saturated K_2CO_3 solution 25 mL and extracted twice with DCM. The combined DCM layer was washed with brine solution and dried over sodium sulfate (**Method Q)**. The compound was isolated through column chromatography using DCM: MeOH,

afforded the final product (R)-N-(4-(4-(3-fluoro-2-methoxyphenyl)piperazin-1-yl)-3-hydroxybutyl)-1-methyl-2-oxoindoline-5-carboxamide (**Compound 527**) as yellow solid (181 mg, 73.5%) (mixture of diastereomers). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (t, J = 5.4 Hz, 1H), 7.76 (dd, J = 8.2, 1.8 Hz, 1H), 7.69 (d, J = 1.7 Hz, 1H), 6.99 – 6.87 (m, 2H), 6.78 - 6.73 (m, 1H), 6.69 – 6.61 (m, 1H), 4.40 (s, 1H), 3.73 (s, 3H), 3.66 (s, 1H), 3.52 (s, 2H), 3.40 – 3.29 (m, 1H), 3.08 (s, 3H), 2.96 (s, 4H), 2.59 (s, 4H), 2.31 (d, J = 25.6 Hz, 2H), 1.76 – 1.64 (m, 1H), 1.52 – 1.39 (m, 1H). ^{13}C NMR (100 MHz, DMSO) δ 174.60, 165.90, 157.68, 157.10, 147.43, 139.68, 128.19, 127.27, 124.46, 123.05, 113.87, 107.53, 59.46, 53.68, 53.67, 49.87, 49.86, 48.56, 40.13, 39.92, 39.71, 39.50, 39.29, 39.08, 38.87, 36.49, 36.49, 35.26, 34.94, 25.97; UPLC/MS purity >97% (CH_3CN: 97.97%, t_R= 2.13min), MeOH: 97.44%, t_R= 2.95min)), $C_{25}H_{31}FN_4O_4$ MW 470.5, observed $[M+H]^+$ 471.3

Synthesis of: 

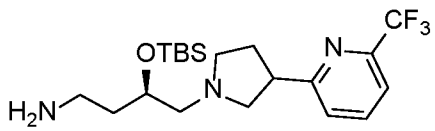
528 .

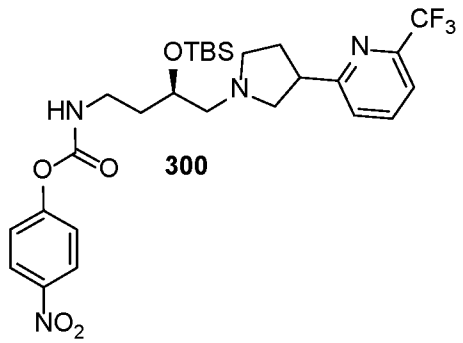
[0282] Compound 528 synthesis according to Scheme 26 is depicted in FIG. 40.

[0283] (R)-N-(4-(4-(3-Fluoro-2-methoxyphenyl)piperazin-1-yl)-3-hydroxybutyl)-2-methyl-2,6-dihydropyrrolo[3,4-c]pyrazole-5(4H)-carboxamide: To the solution of (R)-N-(3-((tert-butyldimethylsilyl)oxy)-4-(4-(3-fluoro-2-methoxyphenyl)piperazin-1-yl)butyl)-2-methyl-2,6-dihydropyrrolo[3,4-c]pyrazole-5(4H)-carboxamide (332 mg, 592 µmol), 1,4-dioxane (40 mL) was cooled to 0 °C. Then 4.0 M HCl in 1,4-dioxane (10 mL) was added at 0 °C and slowly temp raised to room temperature. (After adding HCl solution reaction mass turned to gummy lump). The reaction mass stirred vigorously for 4 hours at room temperature. Then solvent was removed completely under reduced pressure. Then saturated K_2CO_3 solution was added and extracted twice with DCM, washed with brine and dried over Na_2SO_4. The compound was isolated through column chromatography using DCM:MeOH (90:10%) afforded (R)-N-(4-(4-(3-fluoro-2-methoxyphenyl)piperazin-1-yl)-3-hydroxybutyl)-2-methyl-2,6-dihydropyrrolo[3,4-c]pyrazole-5(4H)-carboxamide (Compound 528)as a white solid

(105 mg, 39.7%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (s, 1H), 7.03 - 6.97 (m, 1H), 6.84 (ddd, J = 9.8, 8.4, 1.4 Hz, 1H), 6.75 - 6.72 (m, 1H), 4.51 (d, J = 4.4 Hz, 1H), 4.30 (s, 4H), 3.82 (s, 3H), 3.80 (s, 3H), 3.73 (s, 1H), 3.27 – 3.14 (m, 2H), 3.04 (d, J = 5.9 Hz, 4H), 2.59 (s, 4H), 2.38 - 2.28 (m, 2H), 1.78 – 1.63 (m, 1H), 1.50 – 1.36 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 156.84, 154.69, 153.15, 146.46, 139.54, 124.14, 118.09, 113.94, 113.92, 109.53, 65.43, 64.52, 59.47, 59.44, 54.88, 53.71, 49.89, 44.79, 44.67, 37.13, 36.17. (mixture of diastereomers).; UPLC/MS purity >99% (CH3CN: 99.3%, t_R= 2.04 min), MeOH: 99.3%, t_R = 2.89 min)), $C_{22}H_{31}FN_6O_3$ MW 446.2, observed $[M+H]^+$ 447.3

[0284] Compound 529 synthesis according to Scheme 27 is depicted in FIG. 41. A general procedure for preparation of 4-nitrophenyl carbamate ("Method T") was followed. *N*,*N*-Diisopropylethylamine (DIPEA) or triethylamine (TEA) or NMM (3 equiv) and bis(4-nitrophenyl) carbonate (1.5 equiv) was added to a solution of TBS protected amine (1 equiv) in anhydrous DCM (5 mL/1 mmol) at 0 °C. After stirring at room temperature for 16 h, the solvent was removed under reduced pressure to give the 4-Nitrophenyl carbamate as yellow viscous oil. The crude product was purified using flash column chromatography (0-50% acetone-hexane) to obtain pure carbamate.

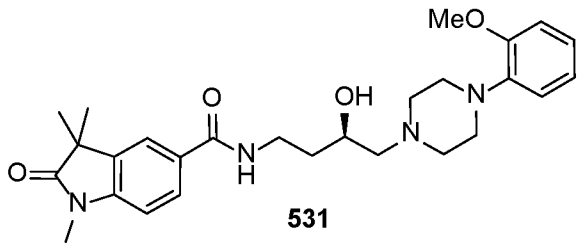
Synthesis of:  **299** and

 **300**

[0285] 4-Nitrophenyl ((3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-4-(3-(6-(trifluoromethyl)pyridin-2-yl)pyrrolidin-1-yl)butyl)carbamate (Compound 300): Compound 300 was synthesized according to general method T, using TBS protected amine compound 299 (1.00 g, 2.39 mmol), TEA (0.98 mL, 7.18 mmol), and

bis(4-nitrophenyl) carbonate (1.09 g, 3.59 mmol). Compound 300 (0.98 g, 70%) was obtained as a yellow oil. TBS-deprotection with 4N HCl in dioxane ("Method X") was followed. To a stirring solution of TBS-protected urea compound (1 equiv) in 1,4-dioxane (0.05M) was added HCl (4 M in 1,4-dioxane; 3-6 equiv) at 0 ºC. The resulting mixture was stirred at room temperature for 2-4 hours. The solvent was evaporated, and the crude product was purified using flash column chromatography (0-100% acetone-MeOH (2% aq. NH_3 added) to obtain the final target compound.

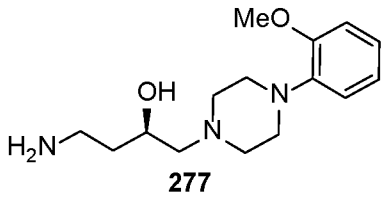
[0286] *N*-((3*R*)-3-Hydroxy-4-(3-(6-(trifluoromethyl)pyridin-2-yl)pyrrolidin-1-yl)butyl)octahydro-2*H*-isoindole-2-carboxamide (Compound 529): To a stirring solution of octahydro-1*H*-isoindole (28 mg, 0.224 mmol) in 1,4-dioxane (8 mL) was added DIPEA (60 μL, 0.344) and the reaction was stirred for 30 minutes. To this compound 300 (100 mg, 0.172 mmol) was added and the resulting mixture was stirred at 80 ºC for 24 hours. Dioxane was removed under reduced pressure. The crude product was purified using flash column chromatography (silica gel, 0-100% acetone-hexane) to obtain silyl protected urea. Compound 529 was synthesized according to general method X, using 4N HCl in dioxane and dioxane (1:1, 10 mL). The pure product Compound 529 was obtained as a viscous brown oil (41 mg, 53%). ^{1}H NMR (400 MHz, MeOD) δ 7.93 (t, *J* = 7.8 Hz, 1H), 7.61 (dd, *J* = 7.9, 1.9 Hz, 2H), 4.00 – 3.75 (m, 1H), 3.64 (tt, *J* = 7.4, 2.5 Hz, 1H), 3.47 – 3.11 (m, 9H), 3.04 – 2.88 (m, 1H), 2.90 – 2.71 (m, 2H), 2.70 – 2.47 (m, 2H), 2.43 – 2.17 (m, 3H), 2.10 (ddd, *J* = 12.6, 6.4, 1.8 Hz, 1H), 1.84 – 1.31 (m, 9H); ^{13}C NMR (100 MHz, MeOD) δ 166.3, 166.2, 160.1, 148.6, 139.55, 139.53, 126.6, 121.7, 119.26, 119.23, 68.98, 68.91, 63.4, 61.8, 61.6, 56.0, 55.8, 46.2, 46.1, 38.37, 38.34, 37.2, 32.4, 32.3, 26.94, 26.90, 23.9, 23.8; UPLC/MS purity >99% (CH_3CN: 99.2%, t_R= 2.40 min), (MeOH: 99.2%, t_R= 3.18 min), $C_{23}H_{33}F_3N_4O_2$ MW 454.54, observed $[M+1]^+$ 455.30.

Synthesis of: 

531.

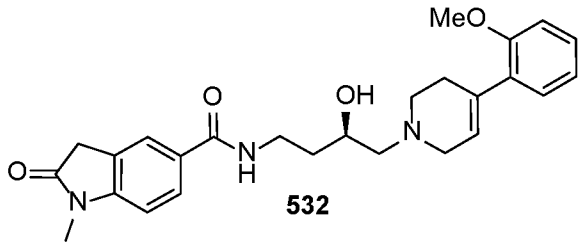
[0287] Compound 531 synthesis according to Scheme 28 is depicted in FIG. 42. A general procedure for preparation amide with HATU ("Method Q") was followed. In a

25 mL round-bottomed flask or a screw capped vial equipped with, a magnetic stir bar was dissolved acid (1 equiv) in DMF (5 mL) or DCM (5 mL). Diisopropylethylamine DIPEA or TEA (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture and stirred for 10 minutes at room temperature, and then the primary amine was added at room temperature. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with EtOAc or DCM (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM) to get amide.

Synthesis of: 

277 .

[0288] ***R*)-*N*-(3-Hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-1,3,3-trimethyl-2-oxoindoline-5-carboxamide (Compound 531):** Compound **531** was synthesized according to general method **Q**, using compound **277** (58 mg, 0.21 mmol), TEA (57 μL, 0.42 mmol), HATU (79 mg, 0.21 mmol) and 1,3,3-trimethyl-2-oxoindoline-5-carboxylic acid (46 mg, 0.21 mmol). The pure product, compound **531** (80 mg, 80%) was obtained as a white solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.70 (dq, *J* = 3.2, 1.8 Hz, 2H), 7.19 (t, *J* = 5.3 Hz, 1H), 6.97 (ddd, *J* = 7.9, 5.9, 3.3 Hz, 1H), 6.93 – 6.83 (m, 4H), 3.90 (tdd, *J* = 9.0, 4.7, 2.7 Hz, 1H), 3.83 (s, 4H), 3.43 (ddt, *J* = 13.1, 8.6, 4.4 Hz, 1H), 3.20 (s, 3H), 3.07 (s, 4H), 2.84 (dd, *J* = 10.9, 5.2 Hz, 2H), 2.58 (h, *J* = 5.3, 3.8 Hz, 2H), 2.48 – 2.37 (m, 2H), 1.79 (dddd, *J* = 14.1, 7.1, 4.8, 2.6 Hz, 1H), 1.60 (ddd, *J* = 14.0, 9.5, 5.0 Hz, 1H), 1.36 (s, 6H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 181.5, 167.0, 152.8, 145.9, 141.8, 136.3, 129.4, 127.1, 123.1, 121.7, 121.2, 118.5, 111.8, 107.8, 66.7, 64.2, 55.6, 51.0, 44.3, 38.6, 33.9, 26.5, 24.4; UPLC/MS purity >93% (CH_3CN: 94.7%, t_R= 2.1- min), (MeOH: 93.0%, t_R= 2.92 min), $C_{27}H_{36}N_4O_4$ MW 480.61, observed $[M+1]^+$ 481.37

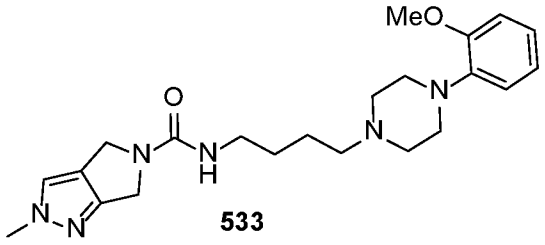
Synthesis of:  **532** .

[0289] Compound 532 synthesis according to Scheme 29 is depicted in FIG. 43.

[0290] A general procedure for preparation amide with HATU ("Method Q"). In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved acid (1 equiv) in DMF (5 mL) or DCM (5 mL). Diisopropylethylamine DIPEA or TEA (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture and stirred for 10 minutes at room temperature, and then the primary amine was added at room temperature. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with EtOAc or DCM (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM) to get amide.

[0291] (R)-N-(3-Hydroxy-4-(4-(2-methoxyphenyl)-3,6-dihydropyridin-1(2H)-yl)butyl)-1-methyl-2-oxoindoline-5-carboxamide (Compound 532): To a solution of (R)-4-amino-1-(4-(2-methoxyphenyl)-3,6-dihydropyridin-1(2H)-yl)butan-2-ol (88 mg, 0.32 mmol), triethylamine (61 mg, 0.60 mmol) and 1-methyl-2-oxoindoline-5-carboxylic acid (57 mg, 0.30 mmol) in DCM (40 mL) was added 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate (110 mg, 0.30 mmol). The reaction mass was stirred for 24 hours at room temperature. Then added saturated K_2CO_3 solution 25 mL and extracted twice with DCM. The combined DCM layer was washed with brine solution and dried over sodium sulfate (**Method Q**). The compound was isolated through column chromatography using DCM: MeOH, afforded the final product (R)-N-(3-hydroxy-4-(4-(2-methoxyphenyl)-3,6-dihydropyridin-1(2H)-yl)butyl)-1-methyl-2-oxoindoline-5-carboxamide (**Compound 532**) as yellow gummy compound (69 mg, 51%) ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (t, J = 5.4 Hz, 1H), 7.83 (dd, J = 8.3, 1.8 Hz, 1H), 7.76 (d, J = 1.6 Hz, 1H), 7.25 - 7.21 (m, 1H), 7.10 (dd, J = 7.5, 1.8 Hz, 1H), 7.03 (d, J = 8.2 Hz, 1H), 7.00 – 6.94 (m, 1H), 6.91 - 6.87 (m, 1H), 5.72 (s, 1H), 4.54 (s, 1H), 3.75

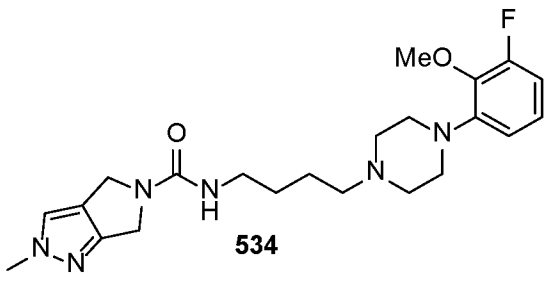
(s, 4H), 3.60 (s, 2H),3.46 - 3.38 (m, 2H), 3.15 (s, 3H), 3.12 (s, 2H), 2.65 (s, 2H), 2.43 (s, 4H), 1.83 - 1.75 (m, 1H), 1.56 - 1.47 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 174.63, 165.86, 156.44, 147.43, 139.53, 136.12, 134.53, 128.68, 128.18, 124.51, 123.05, 120.37, 119.12, 111.26, 107.59, 75.94, 69.62, 55.24, 54.89, 48.57, 42.77, 36.51, 31.30, 26.00. (mixture of diastereomers).; UPLC/MS purity >65% (CH_3CN: 96.6%, t_R= 2.11min), MeOH: 96.6%, t_R= 2.94min)), $C_{26}H_{31}N_3O_4$, MW 449.5, observed $[M+H]^+$ 450.3

Synthesis of: 

533

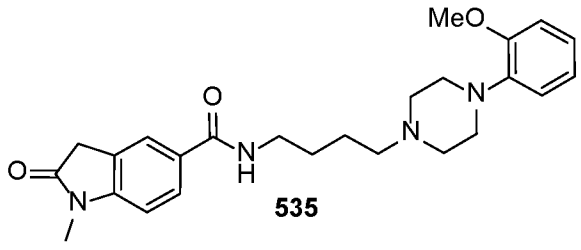
[0292] Compound 533 synthesis according to Scheme 30 is depicted in FIG. 44.

[0293] ***N*-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)-2-methyl-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5(4*H*)-carboxamide (Compound 533):** To a stirring solution of 2-methyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole hydrochloride (100 mg, 629 µmol) in 1,4-dioxane (10 mL) was added DIPEA (325 mg, 2.52 mmol) and the reaction was stirred for 10 minutes at room temperature. Then *N*-(4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-1*H*-imidazole-1-carboxamide (260 mg, 728 µmol) was added and slowly raised the temperature to 90 °C, stirred for 16 hours. The reaction mixture was diluted with saturated K_2CO_3 solution and extracted twice with DCM (2 x 30 mL), washed with brine and dried over Na_2SO_4 filtered, and the solvent was evaporated under reduced pressure to give crude product. The crude compound was purified through column chromatography using (0-50% DCM-MeOH & 2% aq. NH_3 added) to afford compound **533** as brown solid (102 mg, 59%). ^{1}H NMR (400 MHz, DMSO) δ 7.50 (s, 1H), 7.00 – 6.85 (m, 4H), 6.29 (t, *J* = 5.6 Hz, 1H), 4.30 (s, 4H), 3.82 (s, 3H), 3.77 (s, 3H), 3.10 (m, 3H), 2.99 (s, 4H), 2.59 (2, 3H), 2.42 (s, 2H), 1.61 – 1.38 (m, 4H); ^{13}C NMR (100 MHz, DMSO) δ 156.6, 153.1, 151.9, 141.0, 131.7, 124.1, 122.4, 120.8, 118.1, 117.8, 111.8, 102.1, 77.6, 57.3, 55.2, 52.8, 49.6, 44.8, 44.6, 38.7, 27.8, 19.5. UPLC/MS purity >95% (CH_3CN: 95.9%, t_R = 1.88 min), (MeOH: 94.6%, t_R = 2.78 min), $C_{23}H_{31}N_5O_2$ MW 412.5, observed $[M+H]^+$413.3.

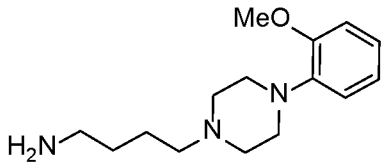
Synthesis of:  **534** .

[0294] Compound 534 synthesis according to Scheme 31 is depicted in FIG. 45.

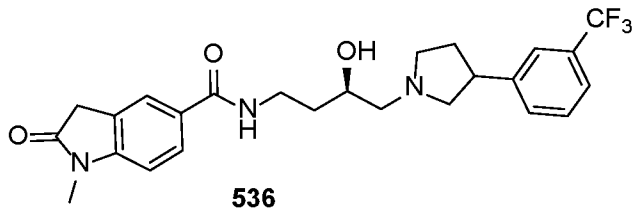
[0295] ***N*-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)-2-methyl-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5(4*H*)-carboxamide (Compound 534):** To a stirring solution of 2-methyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole hydrochloride (250 mg, 999 µmol) in 1,4-dioxane (20 mL) was added DIPEA (325 mg, 2.52 mmol) and the reaction was stirred for 10 minutes at room temperature. Then *N*-(4-(4-(3-Fluoro-2 methoxyphenyl) piperazin-1-yl)butyl)-1*H*-imidazole-1-carboxamide (250 mg, 666 µmol) was added and slowly raised the temperature to 90 °C, stirred for 16 hours. The reaction mixture was diluted with saturated K_2CO_3 solution was added and extracted twice with DCM (2x30 mL), washed with brine and dried over Na_2SO_4 filtered, and the solvent was evaporated under reduced pressure to give crude product. The crude compound was purified through column chromatography using (0-50% DCM-MeOH & 2% aq. NH3 added) to afford compound **534** as brown solid (70 mg, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 1H), 6.96 - 6.90 (m, 1H), 6.80 - 6.75 (m, 1H), 6.68 - 6.65 (dm, 1H), 4.99 (s, 1H), 4.47 (s, 3H), 4.40 (d, *J* = 13.3 Hz, 1H), 3.90 – 3.87 (m, 6H), 3.38 - 3.32 (m, 6H), 2.98 (s, 4H), 2.82 – 2.74 (m, 2H), 1.86 - 1.78 (m, 2H), 1.71 – 1.59 (m, 2H);^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 157.1, 155.2, 153.9, 152.6, 145.3, 140.4, 124.2, 123.7, 118.8, 113.9, 110.9, 77.2, 60.4, 57.3, 52.9, 48.8, 45.2, 44.1, 39.2, 27.6, 22.3. UPLC/MS purity >95% (CH_3CN: 95.2%, t_R = 2.13 min), (MeOH: 97.0%, t_R = 3.02 min), $C_{22}H_{31}FN_6O_2$ MW 430.5, observed $[M+H]^+$431.3.

Synthesis of:  535 .

[0296] Compound 535 synthesis according to Scheme 32 is depicted in FIG. 46. A general procedure for preparation amide with HATU ("Method C"). In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved 1°–amine (1 equiv), acid (0.95 equiv) in DCM (8 mL/mmol). Triethylamine (TEA) (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were washed with K_2CO_3 (10 mL), brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM or 0-100% acetone in hexanes) to get amide.

Synthesis of:  6 .

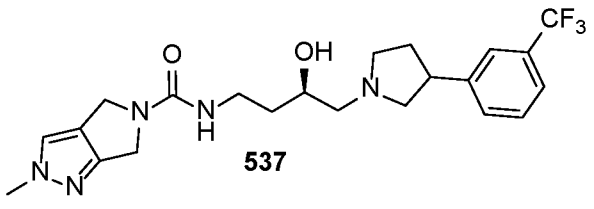
[0297] ***N*-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)-1-methyl-2-oxoindoline-5-carboxamide (Compound 535):** Compound **535** was synthesized according to general method **C**, using 1-methyl-2-oxoindoline-5-carboxylic acid (58 mg, 0.30 mmol), TEA (85 μL, 0.61 mmol), HATU (0.12 g, 0.30 mmol) and compound **6** (80 mg, 0.30 mmol). The pure product, compound **535** (97 mg, 73%) was obtained as a white solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.71 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.67 (d, *J* = 1.9 Hz, 1H), 6.96 (td, *J* = 7.5, 1.8 Hz, 1H), 6.91 – 6.73 (m, 5H), 3.82 (s, 3H), 3.49 (s, 2H), 3.43 (q, *J* = 6.1 Hz, 2H), 3.18 (s, 3H), 3.01 (s, 4H), 2.59 (s, 4H), 2.45 (t, *J* = 6.6 Hz, 2H), 1.75 – 1.59 (m, 4H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 175.1, 167.3, 152.8, 141.9, 129.6, 127.6, 125.1, 123.5, 123.0, 121.2, 118.3, 111.8, 107.7, 58.3, 55.6, 50.7, 40.3, 35.8, 27.8, 26.5, 24.8. UPLC/MS purity >96% (CH_3CN: 96%, t_R= 2.00 min), (MeOH: 97%, t_R= 2.80 min), $C_{25}H_{32}N_4O_3$ MW 436.56, observed $[M+1]^+$ 437.33.

Synthesis of:  **536** .

[0298] Compound 536 synthesis according to Scheme 33 is depicted in FIG. 47. A general procedure for preparation amide with HATU ("Method A") was followed. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved 1°–amine (1 equiv), acid (0.95 equiv) in DCM (8 mL/mmol). Triethylamine (TEA) (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were washed with K_2CO_3 (10 mL), brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM or 0-100% acetone in hexanes) to get amide.

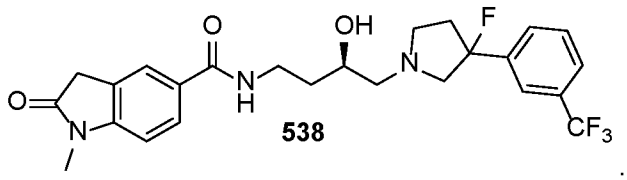
[0299] *N*-((3*R*)-3-Hydroxy-4-(3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)butyl)-1-methyl-2-oxoindoline-5-carboxamide (Compound 536): Compound 536 was synthesized according to general method A, using 1-methyl-2-oxoindoline-5-carboxylic acid (57 mg, 0.30 mmol), triethylamine (60 mg, 0.60 mmol), HATU (110 mg, 0.30 mmol) and (2*R*)-4-amino-1-(3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)butan-2-ol (90 mg, 0.30 mmol) was added. The crude compound was purified by flash column chromatography (silica gel, 10-30% MeOH in DCM) to obtain compound 536 as off white solid (95 mg, 67%). ^{1}H NMR (400 MHz, DMSO) δ 8.30 – 8.22 (m, 1H), 7.76 - 7.72 (m, 1H), 7.69 - 7.67 (m, 1H), 7.57 - 7.54 (m, 2H), 7.48 - 7.43 (m, 2H), 6.96 (dd, *J* = 8.2, 2.7 Hz, 1H), 4.46 (s, 1H), 3.60 (s, 1H), 3.52 (s, 2H), 3.10 (d, *J* = 5.1 Hz, 1H), 3.07 (s, 3H), 2.87 (t, *J* = 7.0 Hz, 1H), 2.74 - 2.68 (m 1H), 2.63 - 2.57 (m, 1H), 2.54 – 2.46 (m, 1H), 2.42 - 2.36 (m, 2H), 2.19 (m, 1H), 2.02 (s, 2H), 1.77 – 1.61 (m, 2H), 1.52 – 1.39 (m, 1H); ^{13}C NMR (100 MHz, DMSO) δ 178.4, 174.6, 165.8, 147.4, 131.3, 129.3, 128.2, 127.2, 124.5, 123.6, 123.0, 122.7, 109.0, 107.5, 72.7, 66.8, 62.0, 54.4, 52.5, 42.2, 40.1, 39.90, 39.69, 39.48, 39.28, 39.07, 38.8, 36.4, 35.1, 34.9, 30.6, 25.9. UPLC/MS purity >95% (CH_3CN: 95.2%, t_R = 2.24

min), (MeOH: 95.3%, t_R = 3.09 min), $C_{25}H_{28}F_3N_3O_3$ MW 475.5, observed $[M+H]^+$476.3.

Synthesis of:  **537** .

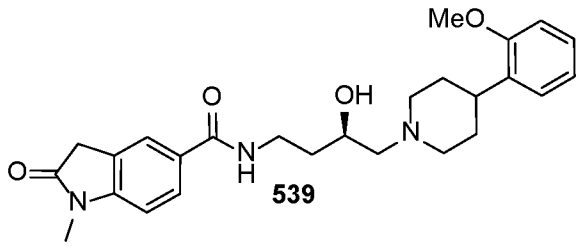
[0300] Compound 537 synthesis according to Scheme 34 is depicted in FIG. 48. TBS-deprotection with 4N HCl in dioxane ("Method B") was followed. To a stirring solution of TBS-protected urea compound (1 equiv) in 1,4-dioxane (0.05 M) was added HCl (4 M in 1,4-dioxane; 3-6 equiv) at 0 ºC. The resulting mixture was stirred at room temperature for 2-16 hours. The solvent was evaporated and washed with saturated K_2CO_3 solution (x 2) and dried over Na_2SO_4, and the crude product was purified using flash column chromatography (0-100% acetone-MeOH (2% aq. NH_3 added) to obtain the final target compound.

[0301] *N*-((3*R*)-3-Hydroxy-4-(3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)butyl)-2-methyl-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5(4*H*)-carboxamide (Compound 537): Compound 537 was synthesized according to general method B, using *N*-((3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-4-(3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)butyl)-2-methyl-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5(4*H*)-carboxamide (163 mg, 288 µmol) and 4N HCl in 1,4-dioxane (10 mL). The crude compound was purified through column chromatography using (0-50% DCM-MeOH & 2% aq. NH3 added) to afford compound 537 as colorless gummy compound (75 mg, 58%).^{1}H NMR (400 MHz, DMSO) δ 7.62 (d, *J* = 3.9 Hz, 2H), 7.53 - 7.51 (m, 2H), 7.48 (s, 1H), 6.27 (q, *J* = 5.5 Hz, 1H), 4.58 – 4.50 (m, 1H), 4.29 (d, *J* = 3.3 Hz, 4H), 3.82 (s, 3H), 3.81 - 3.76 (m, 1H), 3.66 (s, 1H), 3.45 – 3.35 (m, 2H), 2.93 (t, *J* = 8.5 Hz, 1H), 2.80 - 2. 75 (m, 1H), 2.70 - 2.64 (m, 1H), 2.59 - 2.54 (m, 1H), 2.49 – 2.38 (m, 2H), 2.34 (d, *J* = 1.9 Hz, 1H), 1.79 – 1.65 (m, 2H), 1.49 - 1.40 (m, 1H); ^{13}C NMR (100 MHz, DMSO) δ 171.5, 163.7, 156.8, 153.1, 147.2, 131.2, 129.3, 124.0, 123.6, 118.0, 85.8, 79.1, 73.2, 66.9, 62.0, 44.6, 42.2, 38.6, 37.1, 36.0, 32.9, 25.4. UPLC/MS purity >95% (CH_3CN: 98.6%, t_R = 2.13 min), (MeOH: 98.9%, t_R = 3.00 min), $C_{22}H_{28}F_3N_5O_2$ MW 451.4, observed $[M+H]^+$452.3.

Synthesis of:  538 .

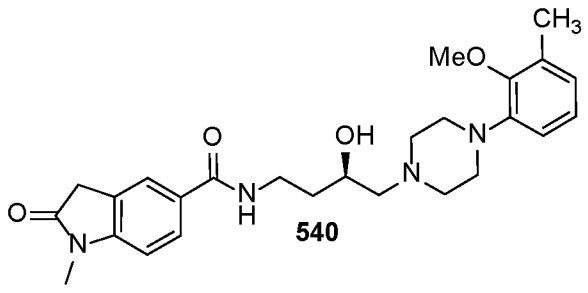
[0302] Compound 538 synthesis according to Scheme 35 is depicted in FIG. 49. A general procedure for preparation amide with HATU ("Method A") was followed. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved the primary amine (1 equiv), acid (0.95 equiv) in DCM (8 mL/mmol). Triethylamine (TEA) (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were washed with K_2CO_3 (10 mL), brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM or 0-100% acetone in hexanes) to get amide.

[0303] *N*-((3*R*)-4-(3-Fluoro-3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)-3-hydroxybutyl)-1-methyl-2-oxoindoline-5-carboxamide (Compound 538): Compound 538 was synthesized according to general method A, using 1-methyl-2-oxoindoline-5-carboxylic acid (54 mg, 0.28 mmol), triethylamine (57 mg, 0.56 mmol), HATU (110 mg, 0.28 mmol) and (2*R*)-4-amino-1-(3-fluoro-3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)butan-2-ol (90 mg, 0.28 mmol). The residue was purified by flash column chromatography (silica gel, 10-30% MeOH in DCM) to obtain the final compound 538 as light brown solid (92 mg, 66%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 - 8.32 (m 1H), 7.84 - 7.81 (m, 1H), 7.78 – 7.70 (m, 4H), 7.68 - 7.63 (m, 1H), 7.03 (dd, *J* = 8.2, 2.8 Hz, 1H), 4.60 (s, 1H), 3.70 - 3.65 (m, 1H), 3.60 (s, 2H), 3.46 – 3.35 (m, 2H), 3.15 (s, 4H), 3.08 – 2.92 (m, 2H), 2.86 (s, 1H), 2.59 - 2.54 (m, 2H), 2.42 – 2.31 (m, 1H), 2.29 - 2.26 (m, 1H), 1.85 – 1.74 (m, 1H), 1.60 – 1.47 (m, 1H). ^{13}C NMR (100 MHz, DMSO) δ 174.6, 165.8, 147.4, 129.6, 128.9, 128.6, 128.6, 128.1, 127.2, 125.4, 124.5, 123.0, 122.7, 120.62, 120.60, 107.5, 101.9, 66.9, 61.8, 53.5, 53.4, 36.4, 35.1, 34.9, 25.9. UPLC/MS purity >95% (CH_3CN: 98.8%, t_R = 2.35 min), (MeOH: 96.8%, t_R = 3.13 min), $C_{25}H_{27}F_4N_3O_3$ MW 493.5, observed $[M+H]^+$494.3.

Synthesis of:  539 .

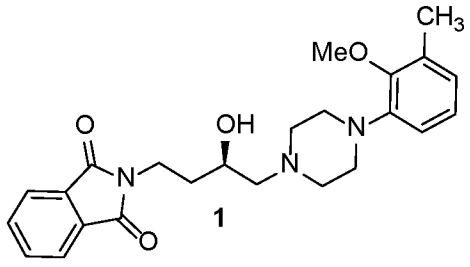
[0304] Compound 539 synthesis according to Scheme 36 is depicted in FIG. 50. A general procedure for preparation amide with HATU ("Method A") was followed. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved the primary amine (1 equiv), acid (0.95 equiv) in DCM (8 mL/mmol). Triethylamine (TEA) (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were washed with K_2CO_3 (10 mL), brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM or 0-100% acetone in hexanes) to get amide.

[0305] **(*R*)-*N*-(3-Hydroxy-4-(4-(2-methoxyphenyl)piperidin-1-yl)butyl)-1-methyl-2-oxoindoline-5-carboxamide (Compound 539):** Compound **539** was synthesized according to general method **A**, using 1-methyl-2-oxoindoline-5-carboxylic acid (69 mg, 359 µmol) in DMF (30 mL), triethylamine (73 mg, 718 µmol), HATU (137 mg, 359 µmol) and (*R*)-4-amino-1-(4-(2-methoxyphenyl)piperazin-1-yl)butan-2-ol (100 mg, 359 µmol). The crude compound was purified by flash column chromatography (silica gel, 10-30% MeOH in DCM) to obtain compound **539** (98 mg, 60%). ^{1}H NMR (400 MHz, DMSO) δ 8.50 (s, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 1.7 Hz, 1H), 7.25 - 7.21 (m, 1H), 7.14 (d, *J* = 7.4 Hz, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 7.03 – 6.91 (m, 2H), 4.04 (s, 1H), 3.80 (s, 3H), 3.61 (s, 4H), 3.39 (d, *J* = 7.4 Hz, 2H), 3.32 (s, 2H), 3.16 (s, 7H), 2.18 – 1.80 (m, 4H), 1.78 – 1.51 (m, 2H); ^{13}C NMR (100 MHz, DMSO) δ 180.8, 174.6, 170.3, 166.1, 163.1, 156.3, 153.2, 147.5, 127.3, 124.5, 123.1, 120.6, 112.1, 110.9, 107.6, 104.5, 98.8, 86.6, 69.0, 63.0, 58.8, 55.3, 34.9, 26.0. UPLC/MS purity >95% (CH_3CN: 97.1%, t_R = 2.04 min), (MeOH: 98.5 %, t_R = 2.84 min), $C_{26}H_{33}N_3O_4$: MW 451.5, observed $[M+H]^+$452.3.

Synthesis of:  .

[0306] Compound 540 synthesis according to Scheme 37 is depicted in FIG. 51. A general procedure for epoxide (*R*)-3 and (*S*)-3 opening with pyrrolidines and piperazines and other secondary amines ("Method A") was followed.

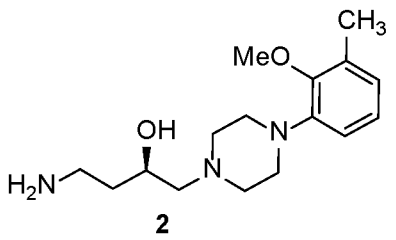
[0307] To a solution of **(*R*)-3** or **(*S*)-3** (1 equiv) in 2-propanol (10 mL/mmol) was added pyrrolidines or piperazines (1 equiv). The reaction mixture was heated at 80 °C and stirred at the same temperature for 24 hours. The solvent was removed *in vacuo*, and the crude product was purified by flash column chromatography (silica gel, 0-100% acetone in hexanes or MeOH in DCM (0-10%) to give epoxide opened products.

Synthesis of:  .

[0308] **(*R*)-2-(3-Hydroxy-4-(4-(2-methoxy-3-methylphenyl)piperazin-1-yl)butyl)isoindoline-1,3-dione (Compound 1)**; Compound **1** was synthesized according to general method **A**, using (R)-2-(2-(oxiran-2-yl)ethyl)isoindoline-1,3-dione (998 mg, 4.59 mmol), and 1-(2-methoxy-3-methylphenyl)piperazine (948 mg, 4.59 mmol) in Isopropanol (10 mL, 0.46 molar). The crude product was purified using flash column chromatography (0-100% ethyl acetate-hexane) to obtain the target compound **1,** 1.286 g in 66% as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.82 (m, 2H), 7.74 – 7.68 (m, 2H), 6.93 (t, *J* = 7.7 Hz, 1H), 6.82 (d, *J* = 7.0 Hz, 1H), 6.75 (d, *J* = 7.9 Hz, 1H), 3.99 – 3.83 (m, 2H), 3.83 – 3.74 (m, 4H), 3.60 (d, *J* = 23.6 Hz, 1H), 3.09 (s, 4H), 2.84 – 2.73 (m, 2H), 2.56 (d, *J* = 5.1 Hz, 2H), 2.46 – 2.34 (m, 2H), 2.24 (s, 3H), 1.79 (q, *J* = 6.7 Hz, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6,

151.0, 145.0, 134.0, 132.3, 132.1, 124.6, 124.0, 123.3, 116.4, 64.6, 64.0, 58.5, 50.5, 35.2, 33.7, 16.2.

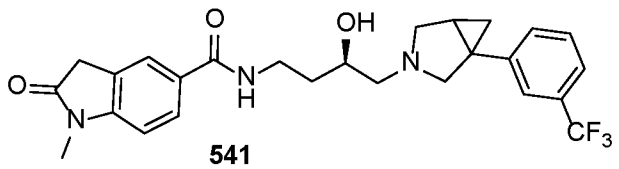
[0309] A general procedure for phthalyl deprotection ("Method B") was followed. Anhydrous hydrazine (5 equiv) was added to a suspension of phthalyl protected amine (1 equiv) in anhydrous ethanol (10 mL/mmol), and the mixture was refluxed overnight under nitrogen atmosphere. Solvent was removed, and the resulting residue was partitioned between DCM and a 20% aqueous K_2CO_3 solution. The layers were separated, and the organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the amine, which was used for the next step without further purification.

Synthesis of: 

2 .

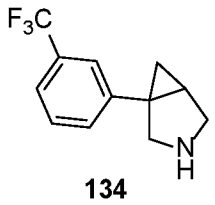
[0310] **(*R*)-4-Amino-1-(4-(2-methoxy-3-methylphenyl)piperazin-1-yl)butan-2-ol (Compound 2);** Compound **2** was synthesized following the general method **B** from compound **1** (1.28 g, 3.03 mmol) and using anhydrous hydrazine (476 µL, 15.18 mmol) in ethanol (10.0 mL, 0.3 molar) The crude product was used for the next step without further purification. After this operation 891.4 mg oil isolated. A general procedure for preparation amide with HATU ("Method C") was followed. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved acid (0.95 equiv), in DCM (5 mL). TEA (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture and stirred for 10 minutes at room temperature, and then the primary amine (1 equiv) was added at room temperature. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were washed with 20% aqueous K_2CO_3 solution (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-100% acetone in hexanes or 0-40% MeOH in DCM) to get amide.

[0311] (*R*)-N-(3-Hydroxy-4-(4-(2-methoxy-3-methylphenyl)piperazin-1-yl)butyl)-1-methyl-2-oxoindoline-5-carboxamide (Compound 540): Compound 540 was synthesized following the general method C using 1-methyl-2-oxoindoline-5-carboxylic acid (88 mg, 0.47 mmol), compound 2 (140 mg, 0.47 mmol), DIPEA (0.2 mL, 1.2 mmol) and HATU (270 mg, 0.7 mmol) in CH_2Cl_2 (10 mL, 0.46 molar). The crude product was purified using flash column chromatography (0-20% MeOH/DCM) to obtain the target compound 540, 123 mg in 49% as a colorless oil; ^{1}H NMR (400 MHz, CDCl3) δ 7.79 (dd, J = 8.1, 1.8 Hz, 1H), 7.71 (d, J = 1.7 Hz, 1H), 7.37 (dd, J = 7.0, 3.5 Hz, 1H), 6.94 (t, J = 7.7 Hz, 1H), 6.83 (dd, J = 8.8, 2.4 Hz, 2H), 6.76 (dd, J = 8.0, 1.7 Hz, 1H), 3.98 – 3.82 (m, 1H), 3.82 (s, 3H), 3.55 (s, 2H), 3.45 (ddt, J = 13.5, 9.5, 4.0 Hz, 1H), 3.23 (s, 3H), 3.13 (s, 4H), 2.85 (q, J = 6.4 Hz, 2H), 2.60 (d, J = 10.3 Hz, 2H), 2.50 – 2.38 (m, 1H), 2.25 (s, 3H), 2.17 (s, 1H), 1.88 – 1.77 (m, 1H), 1.61 (dtd, J = 13.7, 9.1, 4.3 Hz, 1H).; ^{13}C NMR (100 MHz, CDCl3) δ 175.1, 166.8, 150.9, 147.8, 144.7, 132.1, 128.9, 127.5, 124.7, 124.5, 123.9, 123.1, 116.2, 107.6, 66.7, 63.8, 58.4, 50.4, 38.6, 35.5, 33.2, 26.3, 16.1. UPLC/MS purity (CH_3CN: 96%, t_R = 2.28 min), MeOH: 95%, t_R = 3.17 min), $C_{26}H_{34}N_4O_4$ MW 466.58, observed $[M+H]^+$ 467.33.

Synthesis of:  **541** .

[0312] Compound 541 synthesis according to Scheme 38 is depicted in FIG. 52. ***tert*-Butyl 1-(3-(trifluoromethyl)phenyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate:** To a stirring solution of 1-iodo-3-(trifluoromethyl)benzene (282 mg, 1.04 mmol) and tert-butyl 1-(trifluoro-l4-boraneyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate, potassium salt (300 mg, 1.04 mmol) in toluene (25.9 mL, 0.04 molar)and H_2O (2.59 mL, 0.40 molar) was added cesium carbonate (1.01 g, 3.11 mmol). The solution was degassed with N_2 for 10 minutes and palladium(II) acetate (23.3 mg, 104 µmol) and di((3S,5S,7S)-adamantan-1-yl)(butyl)phosphane (74.4 mg, 208 µmol)were added. The reaction was refluxed for 18 hours at 90 ºC. The crude product was purified using flash column chromatography (0-100% ethyl acetate-hexane) to obtain the target compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.33 (m, 4H), 3.96 (dd, *J* = 40.4, 10.5 Hz, 1H), 3.71 (dd, *J* = 37.8, 10.7 Hz, 1H), 3.57 (dt, *J* =

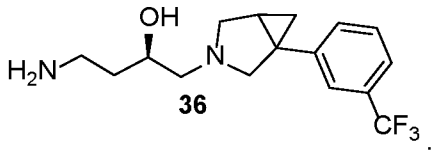
15.3, 9.7 Hz, 2H), 1.86 (dt, *J* = 8.3, 4.2 Hz, 1H), 1.47 (s, 9H), 1.12 (dd, *J* = 8.2, 5.1 Hz, 1H), 0.92 (d, *J* = 4.5 Hz, 1H).

Synthesis of:  **134** .

[0313] 1-(3-(Trifluoromethyl)phenyl)-3-azabicyclo[3.1.0]hexane (Compound 134): To a stirring solution of *tert*-Butyl 1-(3-(trifluoromethyl)phenyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (242 mg, 739 µmol) in methylene chloride (3.08 mL, 0.24 M), was added trifluoroacetic acid (0.33 mL, 334 µmol). The mixture was stirred for 16 hours at ambient temperature after which the solvent was evaporated. The crude product was directly taken forward for the next reaction without purification. A general procedure for epoxide (*R*)-3 and (*S*)-3 opening with pyrrolidines and piperazines and other secondary amines ("Method C") was followed. To a solution of **(*R*)-3** or **(*S*)-3** (1 equiv) in 2-propanol (6 mL/mmol) was added pyrrolidines or piperazines (1 equiv). The insoluble reaction mixture was heated to 70 °C to 80 °C to get a clear solution and then stirred at room temperature for 24 to 48 hours. The solvent was removed *in vacuo*, and the crude product was purified by flash column chromatography (silica gel, 0-100% acetone in hexanes or MeOH in DCM (0-10%) to give epoxide opened products.

[0314] ((3*R*)-3-Hydroxy-4-(5-(3-(trifluoromethyl)phenyl)-2-azabicyclo[3.1.0]hexan-2-yl)butyl)isoindoline-1,3-dione was synthesized following general method **C** from compound **34** (200 mg, 1 equiv, 880 µmol) and **(*R*)-3** (191 mg, 1 equiv, 880 µmol) in 2-propanol (5.18 mL, 0.17 molar). The product was carried forward for further reaction without purification. A general procedure for phthalyl deprotection ("Method D") was followed. Anhydrous hydrazine (5 equiv) was added to a suspension of phthalyl protected amine (1 equiv) in anhydrous ethanol (10 mL/mmol), and the mixture was refluxed for 3 hours under nitrogen atmosphere. Solvents were removed, and the resulting residue was partitioned between DCM and a 20% aqueous K_2CO_3 solution. The layers were separated, and the organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered,

and the solvent removed *in vacuo* to give the amine, which was used for the next step without further purification.

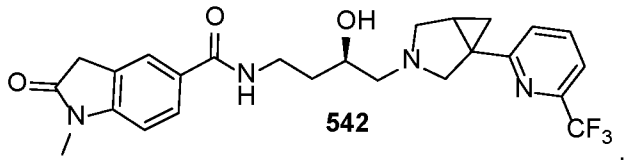
Synthesis of: 

36.

[0315] **(2*R*)-4-Amino-1-(5-(3-(trifluoromethyl)phenyl)-2-azabicyclo[3.1.0]hexan-2-yl)butan-2-ol (Compound 36):** Compound **36** was synthesized following the general method **D** from ((3*R*)-3-Hydroxy-4-(5-(3-(trifluoromethyl)phenyl)-2-azabicyclo[3.1.0]hexan-2-yl)butyl)isoindoline-1,3-dione (130 mg, 1 equiv, 407 µmol) and using anhydrous hydrazine (46 µL, 5 equiv, 1.46 mmol) in ethanol (4.18 mL, 0.07 molar) The crude amine was carried further for the next reaction without any purification. A general procedure for preparation amide with HATU ("Method C"). In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved the primary amine (1 equiv), acid (0.95 equiv) in DCM (8 mL/mmol). Triethylamine (TEA) (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were washed with K_2CO_3 (10 mL), brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM or 0-100% acetone in hexanes) to get amide.

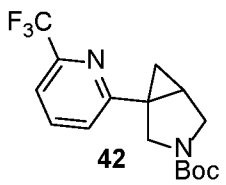
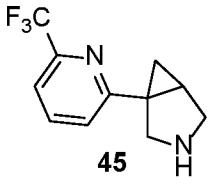
[0316] *N*-((3*R*)-3-Hydroxy-4-(1-(3-(trifluoromethyl)phenyl)-3-azabicyclo[3.1.0]hexan-3-yl)butyl)-1-methyl-2-oxoindoline-5-carboxamide (Compound 541): Compound 541 was synthesized according to general method C, using compound 36 (80 mg, 0.25 mmol), TEA (70 µL, 0.51 mmol), HATU (97 mg, 0.25 mmol) and 1-methyl-2-oxoindoline-5-carboxylic acid (46 mg, 0.24 mmol). The pure product, compound 541 (91 mg, 73%) was obtained as a white solid. ^{1}H NMR (400 MHz, MeOD) δ 7.84 (dt, *J* = 8.2, 1.8 Hz, 1H), 7.76 (t, *J* = 1.5 Hz, 1H), 7.52 – 7.42 (m, 4H), 7.04 (d, *J* = 8.2 Hz, 1H), 3.91 – 3.81 (m, 1H), 3.62 – 3.45 (m, 3H), 3.32 – 3.28 (m, 3H (overlapped with MeOD)), 3.24 (d, *J* = 0.9 Hz, 3H), 2.99 – 2.66 (m, 4H), 2.01 – 1.78 (m, 2H), 1.76 – 1.60 (m, 1H), 1.52 (t, *J* = 4.6 Hz, 1H), 0.95 (dd, *J* = 8.7, 4.6 Hz, 1H). UPLC/MS purity

>95% (CH_3CN: 96%, t_R= 2.53 min), (MeOH: 95%, t_R= 3.27 min), $C_{26}H_{28}F_3N_3O_3$ MW 487.52, observed $[M+1]^+$ 488.30.

Synthesis of:  **542**.

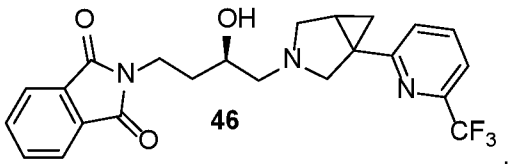
[0317] Compound 542 synthesis according to Scheme 39 is depicted in FIG. 53.

[0318] ***tert*-Butyl 1-(6-(trifluoromethyl)pyridin-2-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (Compound 42):** To a stirring solution of 2-iodo-6-(trifluoromethyl)pyridine (566 mg, 2.08 mmol) and tert-butyl 1-(trifluoro-l4-boraneyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate, potassium salt (600 mg, 2.08 mmol) in toluene (25.9 mL, 0.04 molar)and H_2O (2.59 mL, 0.40 molar) was added cesium carbonate (2.03 g, 6.23 mmol). The solution was degassed with N_2 for 10 mins and palladium(II) acetate (46.6 mg, 208 µmol) and di((3S,5S,7S)-adamantan-1-yl)(butyl)phosphane (149 mg, 415 µmol) were added. The reaction was refluxed for 18 hours at 90 ºC. The crude product was purified using flash column chromatography (0-100% ethyl acetate-hexane) to obtain the target compound **42** (538 mg, 79%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (t, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.32 – 7.20 (m, 1H), 4.07 – 3.82 (m, 2H), 3.70 (dd, *J* = 40.8, 10.8 Hz, 1H), 3.50 (dd, *J* = 10.8, 4.0 Hz, 1H), 2.19 (d, *J* = 17.1 Hz, 1H), 1.48 (s, 10H), 1.02 (t, *J* = 4.8 Hz, 1H).

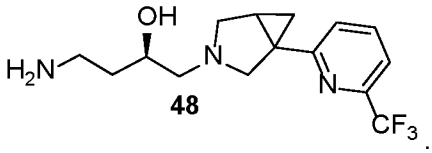
Synthesis of:  **42** and  **45**.

[0319] **1-(6-(Trifluoromethyl)pyridin-2-yl)-3-azabicyclo[3.1.0]hexane (Compound 45):** To a stirring solution of compound **42** (538 mg, 1.64 mmol) in methylene chloride (10 mL), was added trifluoroacetic acid (2 mL). The mixture was stirred for 16 hours at ambient temperature after which the solvent was evaporated. The crude product was directly taken forward for the next reaction without purification. A general procedure for epoxide (*R*)-3 opening with pyrrolidines and piperazines and other secondary amines ("Method A") was followed. To a solution of

(*R*)-3 (1 equiv) in 2-propanol (10 mL/mmol) was added pyrrolidines or piperazines (1 equiv). The insoluble reaction mixture was heated at 80 °C to get a clear solution and then stirred at the same temperature for 24 hours. The solvent was removed *in vacuo*, and the crude product was purified by flash column chromatography (silica gel, 0-100% acetone in hexanes or MeOH in DCM (0-10%) to give epoxide opened products.

Synthesis of:  **46**.

[0320] 2-((3*R*)-3-Hydroxy-4-(1-(6-(trifluoromethyl)pyridin-2-yl)-3-azabicyclo[3.1.0]hexan-3-yl)butyl)isoindoline-1,3-dione (Compound 46): Compound 46 was synthesized according to general method A, using (R)-2-(2-(oxiran-2-yl)ethyl)isoindoline-1,3-dione (381 mg, 1.75 mmol), and compound 45 (400 mg, 1.75 mmol). The pure product, compound 46 (600 mg, 77%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dt, *J* = 5.5, 2.7 Hz, 2H), 7.71 (dtd, *J* = 7.3, 3.7, 1.7 Hz, 3H), 7.50 – 7.36 (m, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 4.10 – 3.03 (m, 7H), 2.95 – 2.41 (m, 3H), 2.06 (ddt, *J* = 10.3, 8.2, 4.2 Hz, 1H), 1.88 – 1.66 (m, 2H), 1.56 (s, 1H), 1.29 (dt, *J* = 9.2, 4.7 Hz, 1H). A general procedure for phthalyl deprotection ("Method B") was followed. Anhydrous hydrazine (5 equiv) was added to a suspension of phthalyl protected amine (1 equiv) in anhydrous ethanol (10 mL/mmol), and the mixture was refluxed for 3-12 hours under nitrogen atmosphere. Solvent was removed, and the resulting residue was partitioned between DCM and a 20% aqueous K_2CO_3 solution. The layers were separated, and the organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the amine, which was used for the next step without further purification.

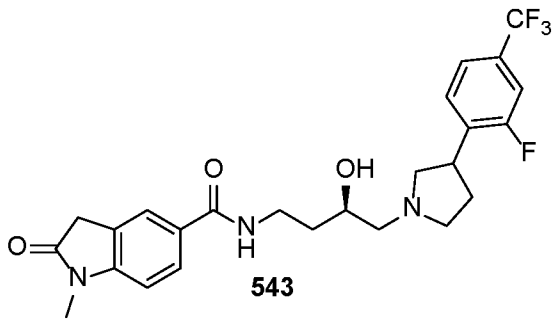
Synthesis of:  **48**.

[0321] (2*R*)-4-Amino-1-(1-(6-(trifluoromethyl)pyridin-2-yl)-3-azabicyclo[3.1.0]hexan-3-yl)butan-2-ol (Compound 48): Compound 48 was synthesized according to general

method B, using Compound 46 (0.590 mg, 1.32 mmol), and anhydrous hydrazine (0.233 mL, 6.62 mmol). The product, Compound 48 was obtained after solvent removal as a viscous oil, which was used for the preparation amide analog without further purification. A general procedure for preparation amide with HATU ("Method C") was followed. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved the primary amine (1 equiv), acid (0.95 equiv) in DCM (8 mL/mmol). Triethylamine (TEA) (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were washed with K_2CO_3 (10 mL), brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM or 0-100% acetone in hexanes) to get amide.

[0322] *N*-((3*R*)-3-Hydroxy-4-(1-(6-(trifluoromethyl)pyridin-2-yl)-3-azabicyclo[3.1.0]hexan-3-yl)butyl)-1-methyl-2-oxoindoline-5-carboxamide (Compound 542): Compound 542 was synthesized according to general method C, using compound 48 (80 mg, 0.25 mmol), TEA (69 μL, 0.51 mmol), HATU (96 mg, 0.25 mmol) and 1-methyl-2-oxoindoline-5-carboxylic acid (46 mg, 0.24 mmol). The pure product, compound 542 (95 mg, 77%) was obtained as a white solid.

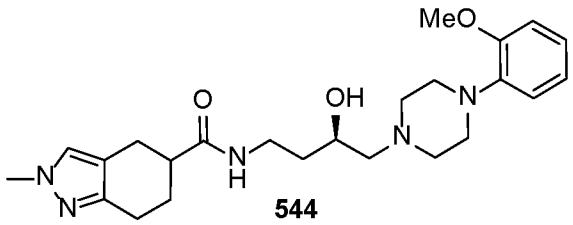
[0323] ^{1}H NMR (400 MHz, MeOD) δ 7.92 (t, *J* = 7.9 Hz, 1H), 7.85 (ddd, *J* = 8.2, 2.9, 1.9 Hz, 1H), 7.77 (dd, *J* = 3.1, 1.8 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.04 (dd, *J* = 8.2, 3.6 Hz, 1H), 4.03 – 3.83 (m, 1H), 3.73 (t, *J* = 9.8 Hz, 1H), 3.63 – 3.40 (m, 4H), 3.33 (p, *J* = 1.7 Hz, 2H), 3.24 (d, *J* = 2.8 Hz, 3H), 3.19 – 2.84 (m, 3H), 2.24 (d, *J* = 8.8 Hz, 1H), 1.87 (dddd, *J* = 11.5, 7.5, 3.7, 2.5 Hz, 1H), 1.77 – 1.55 (m, 2H), 1.46 (dd, *J* = 8.4, 5.0 Hz, 1H); ^{13}C NMR (100 MHz, MeOD) δ 177.6, 170.1, 149.5, 148.5, 148.2, 139.3, 129.75, 129.74, 128.9, 126.2, 124.3, 124.3, 123.6, 123.58 118.6, 109.1, 67.2, 62.0, 58.3, 57.4, 56.5, 54.8, 37.6, 36.0, 28.1, 26.6. UPLC/MS purity >95% (CH_3CN: 95%, t_R= 2.30 min), (MeOH: 95%, t_R= 3.09 min), $C_{25}H_{27}F_3N_4O_3$ 488.51, observed $[M+1]^+$ 489.29.

Synthesis of: 

543 .

[0324] Compound 543 synthesis according to Scheme 40 is depicted in FIG. 54. A general procedure for preparation amide with HATU ("Method A") was followed. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved the primary amine (1 equiv), acid (0.95 equiv) in DCM (8 mL/mmol). Triethylamine (TEA) (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were washed with K_2CO_3 (10 mL), brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM or 0-100% acetone in hexanes) to get amide.

[0325] *N*-((3*R*)-4-(3-(2-Fluoro-4-(trifluoromethyl)phenyl)pyrrolidin-1-yl)-3-hydroxybutyl)-1-methyl-2-oxoindoline-5-carboxamide (Compound 543): Compound 543 was synthesized according to general method A, using 1-methyl-2-oxoindoline-5-carboxylic acid (98 mg, 512 µmol), triethylamine (104 mg, 1.02 mmol), HATU (195 mg, 512 µmol) and (2*R*)-4-amino-1-(3-(2-fluoro-4-(trifluoromethyl)phenyl)pyrrolidin-1-yl)butan-2-ol (164 mg, 512 µmol). The crude compound was purified by flash column chromatography (silica gel, 10-30% MeOH in DCM) to obtain compound 543 as light brown solid (139 mg, 55%). ^{1}H NMR (400 MHz, DMSO) δ 8.36 – 8.32 (m, 1H), 7.84 - 7.76 (m, 1H), 7.75 (t, *J* = 2.1 Hz, 1H), 7.73 - 7.71 (m, 1H), 7.62 – 7.46 (m, 2H), 7.03 (dd, *J* = 8.2, 3.5 Hz, 1H), 4.55 (s, 1H), 3.68 (s, 1H), 3.62 – 3.51 (m, 3H), 3.45 - 3.36 (m, 2H), 3.15 (s, 3H), 2.95 – 2.84 (m, 1H), 2.77 (t, *J* = 7.2 Hz, 1H), 2.72 – 2.58 (m, 2H), 2.49 – 2.41 (m, 1H), 2.32 – 2.16 (m, 1H), 1.89 – 1.69 (m, 2H), 1.57 - 1.47 (m, 1H); ^{13}C NMR (100 MHz, DMSO) δ 174.6, 165.8, 160.8, 158.3, 147.4, 129.9, 128.1, 127.2, 124.5, 123.0, 121.4, 112.5, 111.0, 107.5, 106.4, 72.5, 66.8, 61.9, 60.2, 54.2, 36.4, 35.1, 34.9, 31.5, 25.9. UPLC/MS purity >95% (CH_3CN: 95.5%, t_R = 2.34 min), (MeOH: 95.3%, t_R = 3.21 min), $C_{25}H_{27}F_4N_3O_3$ MW 493.5, observed $[M+H]^+$494.3.

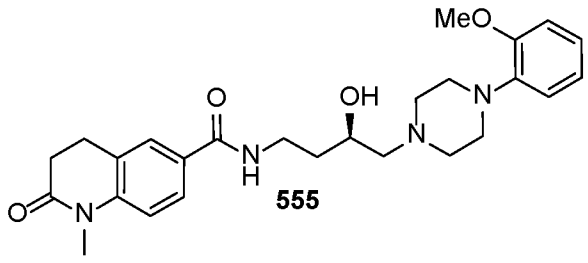
Synthesis of: 

544

[0326] Compound 544 synthesis according to Scheme 41 is depicted in FIG. 55.

[0327] A general procedure for preparation amide with HATU ("Method C"). In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved the primary amine (1 equiv), acid (0.95 equiv) in DCM (8 mL/mmol). Triethylamine (TEA) (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were washed with K_2CO_3 (10 mL), brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM or 0-100% acetone in hexanes) to get amide.

[0328] *N*-((*R*)-3-Hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-2-methyl-4,5,6,7-tetrahydro-2*H*-indazole-5-carboxamide (Compound 544): Compound 544 was synthesized according to general method C, using 2-methyl-4,5,6,7-tetrahydro-2*H*-indazole-5-carboxylic acid (45 mg, 0.25 mmol), TEA (74 μL, 0.53 mmol), HATU (0.10 g, 0.26 mmol) and compound 277 (74 mg, 0.26 mmol). The pure product, compound 544 (87 mg, 74%) was obtained as a white solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.08 (s, 1H), 7.02 – 6.83 (m, 4H), 6.42 (s, 1H), 3.83 (s, 4H), 3.76 (s, 3H), 3.56 (dddt, *J* = 15.7, 6.8, 5.2, 2.7 Hz, 1H), 3.32 – 3.19 (m, 1H), 3.14 – 3.00 (m, 4H), 2.94 – 2.54 (m, 9H), 2.47 – 2.35 (m, 3H), 2.10 (dt, *J* = 13.7, 2.7 Hz, 1H), 1.84 (dtdd, *J* = 13.5, 11.3, 5.6, 2.4 Hz, 1H), 1.73 – 1.59 (m, 1H), 1.55 – 1.40 (m, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 175.3, 152.8, 147.9, 141.7, 127.4, 123.1, 121.3, 118.5, 114.7, 111.8, 66.0, 64.3, 55.6, 50.8, 42.9, 38.8, 37.6, 34.2, 27.6, 24.3, 24.2, 22.9. UPLC/MS purity >96% (CH_3CN: 97%, t_R= 1.84 min), (MeOH: 96%, t_R= 2.69 min), $C_{24}H_{35}N_5O_3$ MW 441.58, observed $[M+1]^+$ 442.37.

Synthesis of: 

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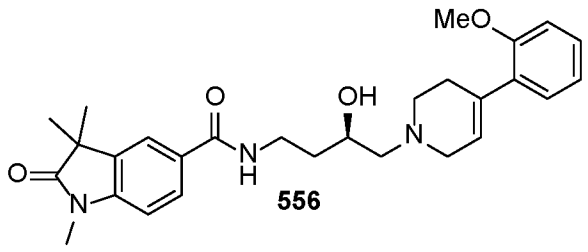
[0329] Compound 555 synthesis according to Scheme 42 is depicted in FIG. 56. A general procedure for preparation amide with HATU ("Method C") was followed. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved the primary amine (1 equiv), acid (0.95 equiv) in DCM (8 mL/mmol). Triethylamine (TEA) (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were washed with K_2CO_3 (10 mL), brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM or 0-100% acetone in hexanes) to get amide.

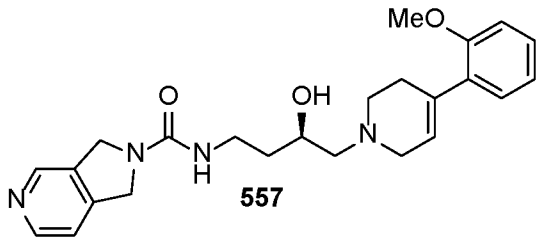
[0330] (*R*)-*N*-(3-Hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-1-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-6-carboxamide (Compound 555): Compound 555 was synthesized according to general method C, using 1-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-6-carboxylic acid (42 mg, 0.20 mmol), TEA (60 μL, 0.43 mmol), HATU (82 mg, 0.21 mmol) and compound 277 (60 mg, 0.21 mmol). The pure product, compound 555 (60 mg, 60%) was obtained as a white solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.72 – 7.59 (m, 2H), 7.20 (s, 1H), 7.06 – 6.94 (m, 2H), 6.93 – 6.83 (m, 3H), 3.93 (s, 1H), 3.83 (s, 3H), 3.77 (ddd, *J* = 13.4, 6.8, 4.8 Hz, 1H), 3.42 (dq, *J* = 13.4, 4.2 Hz, 1H), 3.33 (s, 3H), 3.10 (s, 4H), 2.97 – 2.80 (m, 4H), 2.62 (dd, *J* = 8.6, 6.2 Hz, 4H), 2.47 (d, *J* = 9.0 Hz, 2H), 1.79 (td, *J* = 10.7, 8.9, 4.6 Hz, 1H), 1.59 (dtd, *J* = 13.7, 8.7, 4.7 Hz, 1H). UPLC/MS purity >89% (CH_3CN: 89%, t_R= 1.97 min), (MeOH: 91%, t_R= 2.76 min), $C_{26}H_{34}N_4O_4$ MW 466.58, observed $[M+1]^+$ 467.41.

Synthesis of:  .

556

[0331] Compound 556 synthesis according to Scheme 43 is depicted in FIG. 57. A general procedure for preparation amide with HATU ("Method A") was followed. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved the primary amine (1 equiv), acid (0.95 equiv) in DCM (8 mL/mmol). Triethylamine (TEA) (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were washed with K_2CO_3 (10 mL), brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM or 0-100% acetone in hexanes) to get amide.

[0332] (*R*)-*N*-(3-Hydroxy-4-(4-(2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)butyl)-1,3,3-trimethyl-2-oxoindoline-5-carboxamide (Compound 556): Compound 556 was synthesized according to general method A, using 1,3,3-trimethyl-2-oxoindoline-5-carboxylic acid (56 mg, 0.25 mmol), triethylamine (51 mg, 0.51 mmol), HATU (96 mg, 0.25 mmol) and (*R*)-4-amino-1-(4-(2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)butan-2-ol (70 mg, 0.25 mmol). The crude compound was purified by flash column chromatography (silica gel, 10-30% MeOH in DCM) to obtain compound 556 as off white solid (84 mg, 69%). ^{1}H NMR (400 MHz, DMSO) δ 8.37 (s, 1H), 7.87 – 7.79 (m, 2H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.15 – 7.05 (m, 2H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.91 (t, *J* = 7.4 Hz, 1H), 5.74 (s, 1H), 4.62 (s, 1H), 3.81 (s, 1H), 3.76 (s, 3H), 3.46 - 3.43 (m, 3H), 3.31 (s, 2H), 3.18 (s, 1H), 3.17 (s, 3H), 2.09 (s, 4H), 1.79 (d, *J* = 11.3 Hz, 1H), 1.55 (s, 1H), 1.29 (s, 6H);^{13}C NMR (100 MHz, $CDCl_3$) δ 181.6, 159.7, 156.6, 145.4, 143.6, 135.9, 129.2, 128.7, 127.1, 121.7, 120.7, 113.3, 110.8, 107.5, 104.4, 92.1, 88.0, 77.9, 77.2, 65.6, 60.2, 55.4, 52.2, 50.0, 44.2, 26.3. UPLC/MS purity >86% (CH_3CN: 89.6%, t_R = 2.31 min), (MeOH: 86.4%, t_R = 3.13 min), $C_{28}H_{35}N_3O_4$ MW 477.6, observed $[M+H]^+$478.3.

Synthesis of: 

557

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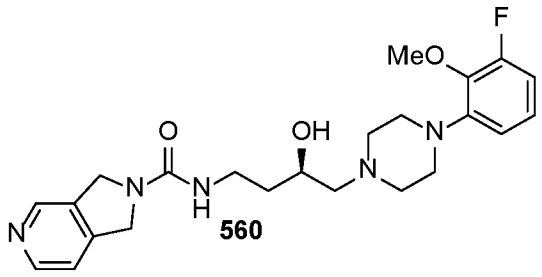
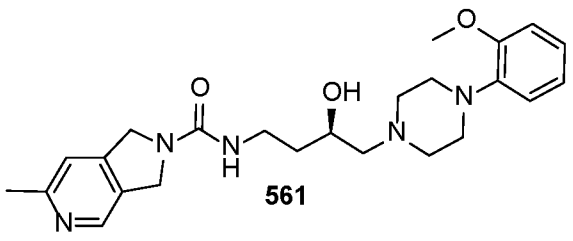
[0333] Compound 557 synthesis according to Scheme 44 is depicted in FIG. 58. TBS-deprotection with TBAF ("Method C") was followed. To a stirring solution of TBS-protected urea compound (1 equiv) in THF (0.05 M) was added TBAF (1 M in THF; 2-3 equiv) at 0 ºC. The resulting mixture was stirred at room temperature for 2-16 hours. The solvent was evaporated, and the crude product was purified using flash column chromatography (0-100% acetone-MeOH (2% aq. NH_3 added) to obtain the final target compound.

[0334] (*R*)-*N*-(3-Hydroxy-4-(4-(2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)butyl)-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridine-2-carboxamide (Compound 557): Compound 557 was synthesized according to general method C, using (*R*)-*N*-(3-((*tert*-butyldimethylsilyl)oxy)-4-(4-(2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)butyl)-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridine-2-carboxamide (322 mg, 600 µmol) and 1M TBAF in THF solution (10 mL) at 0 °C. The crude compound was purified through column chromatography using (0-50% DCM-MeOH & 2% aq. NH3 added) to afford compound 557 as light brown gummy (120 mg, 47%). ^{1}H NMR (400 MHz, DMSO) δ 8.56 (s, 1H), 8.47 (d, *J* = 5.1 Hz, 1H), 7.38 (d, *J* = 5.0 Hz, 1H), 7.23 (ddd, *J* = 8.7, 7.3, 1.8 Hz, 1H), 7.11 (dd, *J* = 7.5, 1.8 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.89 (td, *J* = 7.4, 1.0 Hz, 1H), 6.44 (t, *J* = 5.5 Hz, 1H), 5.75 – 5.69 (m, 1H), 4.62 (dd, *J* = 6.6, 2.4 Hz, 4H), 4.57 (s, 1H), 3.75 (s, 4H), 3.30 – 3.12 (m, 4H), 3.13 (s, 1H), 2.66 (s, 2H), 2.43 (s, 4H), 1.76 - 1.68 (m, 1H), 1.57 (s, 1H), 1.49 -1.41 (m, 1H), 1.34 - 1.27 (m, 1H), 0.94 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 168.1, 156.5, 156.4, 147.8, 146.3, 144.3, 134.5, 133.6, 128.6, 128.1, 120.3, 118.2, 111.2, 55.2, 51.3, 50.5, 49.6, 45.9, 37.1, 36.0, 33.6, 29.1, 23.0, 13.4. UPLC/MS purity >95% (CH_3CN: 95.0%, t_R = 2.01 min), (MeOH: 96.6%, t_R = 2.93 min), $C_{24}H_{30}N_4O_3$ MW 422.5, observed $[M+H]^+$423.3.

Synthesis of:  **560** .

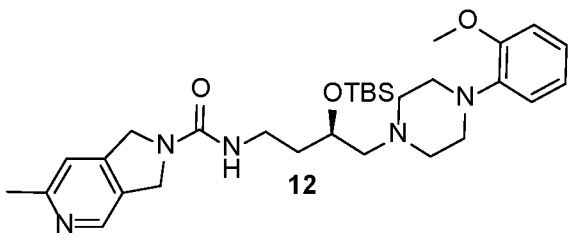
[0335] Compound 560 synthesis according to Scheme 45 is depicted in FIG. 59. TBS-deprotection with 4N HCl in dioxane ("Method B") was followed. To a stirring solution of TBS-protected urea compound (1 equiv) in 1,4-dioxane (0.05 M) was added HCl (4 M in 1,4-dioxane; 3-6 equiv) at 0 ºC. The resulting mixture was stirred at room temperature for 2-16 hours. The solvent was evaporated and washed with saturated K_2CO_3 solution (x 2) and dried over Na_2SO_4, and the crude product was purified using flash column chromatography (0-100% acetone-MeOH (2% aq. NH_3 added) to obtain the final target compound.

[0336] (*R*)-*N*-(4-(4-(3-Fluoro-2-methoxyphenyl)piperazin-1-yl)-3-hydroxybutyl)-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridine-2-carboxamide (Compound 560): Compound 560 was synthesized according to general method B, using (*R*)-*N*-(3-((*tert*-Butyldimethylsilyl)oxy)-4-(4-(3-fluoro-2-methoxyphenyl)piperazin-1-yl)butyl)-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridine-2-carboxamide (255 mg, 457 µmol), and 4N HCl in 1,4-dioxane (10 mL). The crude compound was purified through column chromatography using (0-50% DCM-MeOH & 2% aq. NH3 added) to obtain compound 560 as light pink gummy liquid (68 mg, 39%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.51 – 8.45 (m, 1H), 7.41 (d, *J* = 5.0 Hz, 1H), 7.05 - 6.99 (m, 1H), 6.92 – 6.83 (m, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.53 (t, *J* = 5.6 Hz, 1H), 5.16 (s, 0.5H), 4.64 (s, 2H), 4.62 (s, 2H), 4.24 (s, 0.5H), 3.89 (s, 1H), 3.80 (s, 3H), 3.22 - 3.02 (m, 8H), 3.02 (s, 2H), 2.76 (s, 2H), 1.70 – 1.59 (m, 1H), 1.54 – 1.45 (m, 1H); ^{13}C NMR (100 MHz, DMSO) δ 157.0, 156.7, 154.6, 147.8, 146.4, 144.2, 139.68, 139.56, 133.5, 124.10, 124.00, 118.3, 114.1, 109.9, 59.8, 59.7, 51.3, 49.6, 48.5, 36.6, 35.7, 30.6. UPLC/MS purity >95% (CH_3CN: 98.9%, t_R = 2.01 min), (MeOH: 97.7%, t_R = 2.94 min), $C_{23}H_{30}FN_5O_3$ MW 443.5, observed $[M+H]^+$444.3.

Synthesis of:  .

561

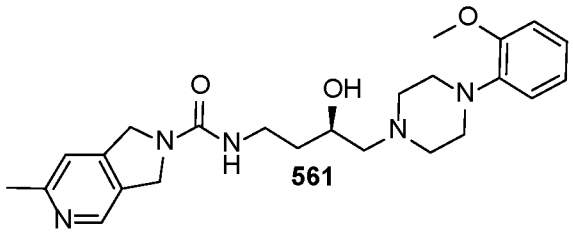
[0337] Compound 561 synthesis according to Scheme 46 is depicted in FIG. 60. Urea analog synthesis ("Method F") was followed. To a stirring solution of amine or amine•HCl salt (1.2-3 equiv) in 1,4-dioxane (0.10 *M*) was added Hunig's base (5-6 equiv) and the reaction was stirred for 30 minutes. To this was added carbamate or 4-Nitrophenylchloroformate (1 equiv) and the resulting mixture was stirred at 90 °C for 24 hours. The solvent was removed under reduced pressure to get the crude product, which was purified using flash column chromatography (0-50% DCM-MeOH and 5-10% NH_4OH) to obtain pure urea compound.

Synthesis of:  .

12

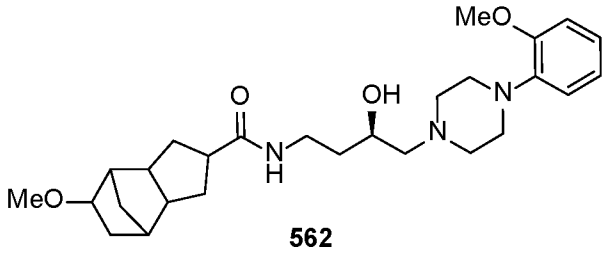
[0338] (*R*)-*N*-(3-((*tert*-Butyldimethylsilyl)oxy)-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-6-methyl-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide (Compound 12): Compound 12 was synthesized following the general method F from compound 233 (370 mg, 0.662 mmol), 6-methyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine hydrochloride (113 mg, 0.662 mmol) and using DIPEA (577 µL, 3.31 mmol) in 1,4-dioxane (6.0 mL, 0.1 molar), the crude urea compound was used for the next reaction without further purification. TBS-deprotection with 4 N HCl in dioxane ("Method G") was followed. To a stirring solution of TBS-protected urea compound (1 equiv) in 1,4-dioxane (0.05 M) was added HCl (4 *N* in 1,4-dioxane; 3-6 equiv) at 0 °C. The resulting mixture was stirred at room temperature for 2-4 hours. The solvent was evaporated, then the crude was diluted with CH_2Cl_2 and washed with saturated K_2CO_3 solution at 0 °C and stir for 15 minutes. The reaction was extracted with DCM, washed with brine, dried over Na_2SO_4, filtered, and concentrated to give the crude

product, which was purified using flash column chromatography (0-50% DCM-MeOH (2-5% aq. NH_3 added) to obtain the final target compound.

Synthesis of:  .

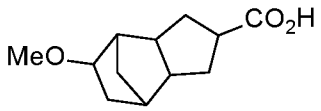
561

[0339] (*R*)-*N*-(3-Hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-6-methyl-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxamide (Compound 561): Compound 561 was synthesized following the general method G using compound 12 (250 mg, 0.514 mmol), 4 *N* HCl in dioxane (770 µL, 3.08 mmol), in dioxane (8.00 mL, 0.06 molar). The crude product was purified using flash column chromatography (0-20% DCM-MeOH and 5% NH_4OH) to obtain the target compound 561 in 64% yield as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.09 (s, 1H), 7.05 – 6.98 (m, 1H), 6.97 – 6.90 (m, 2H), 6.87 (d, *J* = 7.7 Hz, 1H), 5.56 (dd, *J* = 14.7, 11.5 Hz, 1H), 4.68 (s, 4H), 3.87 (s, *J* = 5.1 Hz, 3H), 3.70 (ddd, *J* = 13.1, 10.9, 6.5 Hz, 1H), 3.33 (ddd, *J* = 12.9, 7.9, 3.8 Hz, 1H), 3.10 (s, 4H), 2.89 (dd, *J* = 10.6, 5.0 Hz, 2H), 2.63 (d, *J* = 5.9 Hz, 2H), 2.57 (s, 3H), 2.47 – 2.37 (m, 2H), 1.82 – 1.70 (m, 2H), 1.55 (dtd, *J* = 13.5, 8.9, 4.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 156.9, 152.4, 147.2, 143.7, 141.2, 130.6, 123.2, 121.1, 118.3, 117.6, 111.3, 66.8, 63.9, 55.5, 53.5, 51.5, 50.9, 49.6, 39.4, 34.0, 24.4. UPLC/MS purity (CH_3CN: 98%, t_R = 1.88 min), MeOH: 97%, t_R = 2.83 min), $C_{24}H_{33}N_5O_3$ MW 439.56, observed $[M+H]^+$ 440.33.

Synthesis of:  .

562

[0340] Compound 562 synthesis according to Scheme 47 is depicted in FIG. 61.

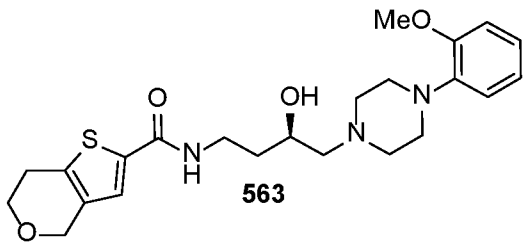


47

Synthesis of: .

[0341] 5-Methoxyoctahydro-1*H*-4,7-methanoindene-2-carboxylic acid (Compound 47): The aldehyde (200 mg, 1.03 mmol) was dissolved in DMF (0.1 M). Oxone (633 mg, 1.03 mmol) was added in one portion and stirred at room temperature for 3 hours. The reactions were monitored by TLC. 1N HCl was used to dissolve the salts and EtOAc was added to extract the products. The organic extract was washed with 1N HCl (3x) and brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure to obtain the crude compound 47 (168 mg, 78%), which was used in the next step without further purification. A general procedure for preparation amide with HATU ("Method C") was followed. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved the primary amine (1 equiv), acid (0.95 equiv) in DCM (8 mL/mmol). Triethylamine (TEA) (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were washed with K_2CO_3 (10 mL), brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM or 0-100% acetone in hexanes) to get amide.

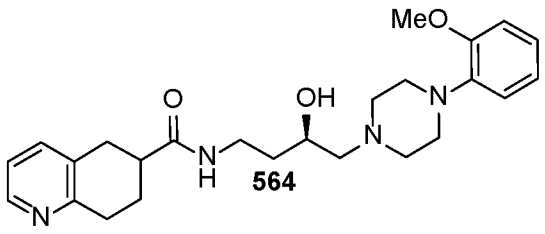
[0342] *N*-((*R*)-3-Hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-5-methoxyoctahydro-1*H*-4,7-methanoindene-2-carboxamide (Compound 562): Compound 562 was synthesized according to general method C, using compound 47 (64 mg, 0.31 mmol), TEA (91 μL, 0.64 mmol), HATU (0.12 g, 0.32 mmol) and compound 277 (90 mg, 0.32 mmol). The pure product, compound 562 (120 mg, 79%) was obtained as a white solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.06 – 6.94 (m, 1H), 6.94 – 6.81 (m, 3H), 6.48 – 6.26 (m, 1H), 4.79 (s, 1H), 3.83 (s, 4H), 3.66 – 3.47 (m, 1H), 3.32 – 2.49 (m, 15H), 2.25 – 1.16 (m, 14H), 1.12 – 0.93 (m, 1H). UPLC/MS purity >98% (CH_3CN: 98%, t_R= 2.28 min, 2.32 min, 2.34 min), (MeOH: 99%, t_R= 3.12 min, 3.19 min), $C_{27}H_{41}N_3O_4$ MW 471.64, observed $[M+1]^+$ 472.41.

Synthesis of:  .

563

[0343] Compound 563 synthesis according to Scheme 48 is depicted in FIG. 62. A general procedure for preparation amide with HATU ("Method C") was followed. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved the primary amine (1 equiv), acid (0.95 equiv) in DCM (8 mL/mmol). Triethylamine (TEA) (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were washed with K_2CO_3 (10 mL), brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM or 0-100% acetone in hexanes) to get amide.

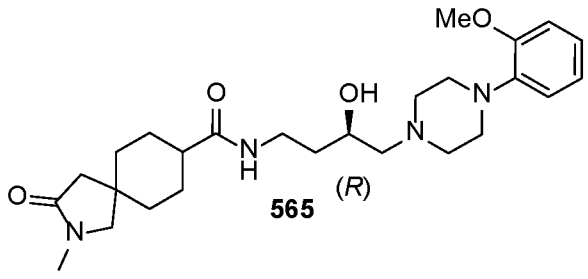
[0344] (*R*)-*N*-(3-Hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-6,7-dihydro-4*H*-thieno[3,2-*c*]pyran-2-carboxamide (Compound 563): Compound 563 was synthesized according to general method C, using 6,7-dihydro-4*H*-thieno[3,2-*c*]pyran-2-carboxylic acid (53 mg, 0.29 mmol), TEA (86 μL, 0.61 mmol), HATU (0.12 g, 0.30 mmol) and compound 277 (85 mg, 0.30 mmol). The pure product, compound 563 (0.11 g, 81%) was obtained as a white solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.11 (s, 1H), 7.05 (d, *J* = 5.6 Hz, 1H), 7.01 – 6.92 (m, 1H), 6.92 – 6.80 (m, 3H), 4.62 (d, *J* = 1.7 Hz, 2H), 4.29 (s, 1H), 3.97 – 3.85 (m, 3H), 3.82 (s, 3H), 3.73 (dtd, *J* = 13.8, 6.9, 4.7 Hz, 1H), 3.42 – 3.30 (m, 1H), 3.10 (s, 4H), 2.97 – 2.81 (m, 4H), 2.70 (d, *J* = 10.2 Hz, 2H), 2.58 – 2.42 (m, 2H), 1.76 (dddd, *J* = 14.4, 7.3, 4.7, 2.7 Hz, 1H), 1.56 (tdd, *J* = 9.4, 8.0, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 162.3, 152.8, 141.4, 138.0, 136.6, 135.1, 124.8, 123.3, 121.3, 118.5, 111.9, 66.27, 66.25, 65.0, 63.9, 55.6, 50.5, 38.3, 33.9, 26.0. UPLC/MS purity >97% (CH_3CN: 97%, t_R= 2.08 min), (MeOH: 97%, t_R= 2.89 min), $C_{23}H_{31}N_3O_4S$ MW 445.58, observed $[M+1]^+$ 446.27.

Synthesis of: 

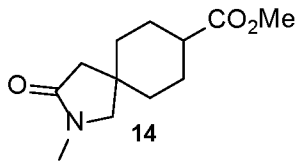
.

[0345] Compound 564 synthesis according to Scheme 49 is depicted in FIG. 63. A general procedure for preparation amide with HATU ("Method A") was followed. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved the primary amine (1 equiv), acid (0.95 equiv) in DCM (8 mL/mmol). Triethylamine (TEA) (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were washed with K_2CO_3 (10 mL), brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM or 0-100% acetone in hexanes) to get amide.

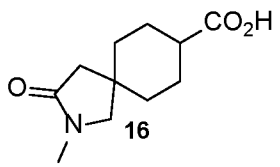
[0346] ***N*-((*R*)-3-Hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-*yl*)butyl)-5,6,7,8-tetrahydroquinoline-6-carboxamide (Compound 564):** Compound **564** was synthesized according to general method **A**, using 5,6,7,8-tetrahydroquinoline-6-carboxylic acid (51 mg, 0.21 mmol), triethylamine (59 mg), HATU (110 mg, 0.29 mmol) and (*R*)-4-amino-1-(4-(2-methoxyphenyl)piperazin-1-yl)butan-2-ol (81 mg, 0.29 mmol). The crude compound was purified by flash column chromatography (silica gel, 10-30% MeOH in DCM) to obtain compound **564** as white solid, (80 mg, 63%).^{1}H NMR (400 MHz, DMSO) δ 8.29 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.92 (t, *J* = 5.6 Hz, 1H), 7.51 – 7.44 (m, 1H), 7.12 (dd, *J* = 7.7, 4.7 Hz, 1H), 6.99 – 6.90 (m, 2H), 6.90 – 6.82 (m, 2H), 4.43 (s, 1H), 3.77 (s, 3H), 3.70 (s, 1H), 3.31 – 3.09 (m, 3H), 2.95 (s, 4H), 2.92 - 2.77 (m, 4H), 2.69 – 2.52 (m, 4H), 2.34 (s, 2H), 2.01 (t, *J* = 8.4 Hz, 1H), 1.88 – 1.73 (m, 1H), 1.72 – 1.60 (m, 1H), 1.46 – 1.39 (m, 1H); ^{13}C NMR (100 MHz, DMSO) δ 174.0, 155.7, 151.9, 146.5, 141.4, 136.5, 130.7, 130.6, 128.2, 122.3, 121.1, 120.8, 117.8, 111.8, 82.8, 70.3, 55.2, 53.5, 50.0, 35.6, 35.3, 31.2, 30.97, 30.92, 26.2. UPLC/MS purity >95% (CH_3CN: 99.1%, t_R = 1.94 min), (MeOH: 99.2%, t_R = 2.81 min), $C_{25}H_{34}N_4O_3$ MW 438.5, observed $[M+H]^+$439.3.

Synthesis of: 
565

[0347] Compound 565 synthesis according to Scheme 50 is depicted in FIG. 64.

Synthesis of: 
14

[0348] **Methyl 2-methyl-3-oxo-2-azaspiro[*4.5*]decane-8-carboxylate (Compound 14):**To a cooled solution of 3-Oxo-2-azaspiro[*4.5*]decane-8-carboxylic acid (200 mg, 1.0 mmol) in anhydrous *N,N*-Dimethylformamide (5.0 mL) was added sodium hydride (60% dispersion in mineral oil, 122 mg, 3.03 mmol) and the resulting mixture was stirred for 10 minutes after which iodomethane (0.19 mL, 3.03 mmol) was added. The cooling batch was removed, and the reaction mixture was stirred for 2 hours at room temperature. The reaction was quenched with aqueous saturated ammonium chloride (15 mL) and the aqueous phase was extracted with ethyl acetate (2×50 mL). The combined organic phase was washed with water (3x50 mL) and brine solution, dried over Na_2SO_4, filtered, and evaporated. The crude product was purified using flash column chromatography (0-100% ethyl acetate-hexane) to obtain the target compound **14** (120 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.10 (s, 2H), 2.83 (s, 3H), 2.34 – 2.22 (m, 3H), 1.88 (dt, *J* = 13.0, 3.9 Hz, 2H), 1.79 – 1.66 (m, 2H), 1.65 – 1.48 (m, 2H), 1.39 (td, *J* = 12.9, 3.7 Hz, 2H).

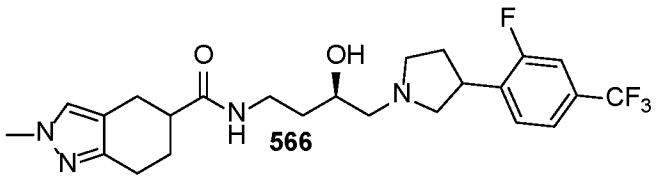
Synthesis of: 
16

[0349] **2-Methyl-3-oxo-2-azaspiro[*4.5*]decane-8-carboxylic acid (Compound 16):** To a solution of compound **14** (120 mg, 0.53 mmol) in a 2:2:1 THF/MeOH/H2O mixture (5 mL) was added lithium hydroxide monohydrate (38.3 mg, 1.6 mmol) at 25 °C. The reaction mixture was stirred for 16 hours, The solvents were distilled under

reduced pressure and 10 mL water added, washed with *n*-Hexanes (15 mL). To the aq. Layer pH was adjusted between pH 4 and pH 6 by dropwise addition of a 0.5 *N* HCl solution. The mixture was extracted with EtOAc (3 x 25 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The resulting residue was used for the preparation of the amide analog without further purification compound **16** (75 mg, 67%). ^{1}H NMR (400 MHz, DMSO) δ 12.04 (s, 1H), 3.06 (s, 2H), 2.69 (s, 3H), 2.20 (ddd, *J* = 14.4, 8.6, 3.5 Hz, 1H), 2.10 (s, 2H), 1.75 (dt, *J* = 13.7, 3.9 Hz, 2H), 1.64 – 1.52 (m, 2H), 1.51 – 1.29 (m, 5H).

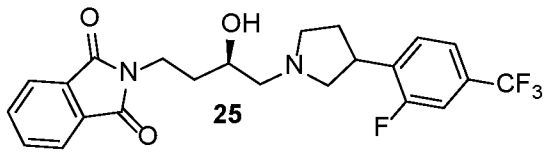
[0350] A general procedure for preparation amide with HATU ("Method C") was followed. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved the primary amine (1 equiv), acid (0.95 equiv) in DCM (8 mL/mmol). Triethylamine (TEA) (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were washed with K_2CO_3 (10 mL), brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM or 0-100% acetone in hexanes) to get amide.

[0351] (*R*)-*N*-(3-Hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-2-methyl-3-oxo-2-azaspiro[4.5]decane-8-carboxamide (Compound 565): Compound 565 was synthesized according to general method C, using compound 4 (100 mg, 0.36 mmol), TEA (150 μL, 1.07 mmol), HATU (136 mg, 0.36 mmol) and compound 16 (75 mg, 0.36 mmol). The pure product, compound 565 (120 mg, 71%) was obtained as a white solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.97 (td, *J* = 6.7, 3.1 Hz, 1H), 6.93 – 6.81 (m, 3H), 6.46 (s, 1H), 3.82 (s, 4H), 3.52 (dt, *J* = 13.0, 6.4 Hz, 1H), 3.22 (ddt, *J* = 13.1, 8.8, 4.8 Hz, 1H), 3.06 (s, 5H), 2.85 – 2.70 (m, 5H), 2.62 – 2.49 (m, 2H), 2.43 – 2.31 (m, 2H), 2.23 (s, 2H), 2.04 (tt, *J* = 11.8, 3.6 Hz, 1H), 1.86 – 1.60 (m, 5H), 1.60 – 1.18 (m, 7H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 175.3, 173.6, 152.7, 141.8, 123.0, 121.2, 118.5, 111.8, 66.2, 64.3, 63.0, 55.6, 51.0, 44.9, 41.7, 37.6, 36.5, 35.8, 34.2, 29.5, 26.4; UPLC/MS purity >97% (CH_3CN: 98.7%, t_R= 1.88 min), (MeOH: 97.3%, t_R= 2.73 min), $C_{26}H_{40}N_4O_4$ MW 472.63, observed $[M+1]^+$ 473.32.

Synthesis of: 

566 .

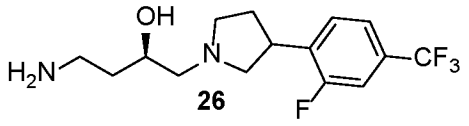
[0352] Compound 566 synthesis according to Scheme 51 is depicted in FIG. 65. A general procedure for epoxide (*R*)-3 and (*S*)-3 opening with pyrrolidines and piperazines and other secondary amines ("Method A") was followed. To a solution of **(*R*)-3** or **(*S*)-3** (1 equiv) in 2-propanol (10 mL/mmol) was added pyrrolidines or piperazines (1 equiv). The reaction mixture was heated at 80 °C and stirred at the same temperature for 24 hours. The solvent was removed *in vacuo*, and the crude product was purified by flash column chromatography (silica gel, 0-100% acetone in hexanes or MeOH in DCM (0-10%) to give epoxide opened products.

Synthesis of: 

25 .

[0353] 2-((3*R*)-4-(3-(2-Fluoro-4-(trifluoromethyl)phenyl)pyrrolidin-1-yl)-3-hydroxybutyl)isoindoline-1,3-dione (Compound 25): Compound 25 was synthesized according to general method A, using (R)-2-(2-(oxiran-2-yl)ethyl)isoindoline-1,3-dione (1.1 g, 5.1 mmol), and 3-(2-fluoro-4-(trifluoromethyl)phenyl)pyrrolidine (1.19 g, 5.1 mmol) in Isopropanol (10 mL, 0.51 molar). The crude product was purified using flash column chromatography (0-20% MeOH/DCM) to obtain the target compound 25, 1.62 g in 71% as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.82 (m, 2H), 7.74 – 7.68 (m, 2H), 7.44 (td, *J* = 7.6, 3.9 Hz, 1H), 7.35 (dd, *J* = 8.1, 2.5 Hz, 1H), 7.29 – 7.23 (m, 1H), 3.95 – 3.80 (m, 2H), 3.79 – 3.60 (m, 2H), 3.45 (d, *J* = 28.0 Hz, 1H), 3.12 – 2.85 (m, 2H), 2.81 – 2.60 (m, 3H), 2.52 – 2.43 (m, 1H), 2.41 – 2.27 (m, 1H), 1.94 – 1.73 (m, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 129.2, 129.1, 124.8, 121.2, 112.9, 112.6, 68.8, 68.7, 62.34, 62.30, 60.58, 60.51, 54.4, 40.0, 39.9, 37.5, 37.4, 36.1, 31.9. A general procedure for phthalyl deprotection ("Method B") was followed. Anhydrous hydrazine (5 equiv) was added to a suspension of phthalyl protected amine (1 equiv) in anhydrous ethanol (10 mL/mmol), and the mixture was refluxed overnight under nitrogen atmosphere. Solvent was removed, and the resulting residue was partitioned between DCM and a 20% aqueous K_2CO_3 solution.

The layers were separated, and the organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the amine, which was used for the next step without further purification.

Synthesis of:  **26** .

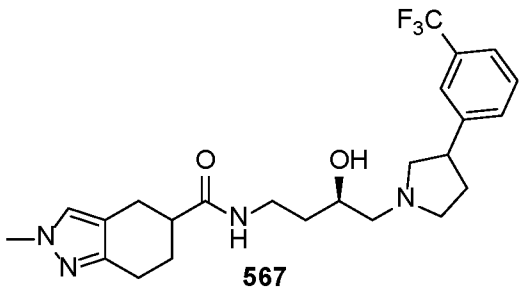
[0354] **(2*R*)-4-Amino-1-(3-(2-fluoro-4-(trifluoromethyl)phenyl)pyrrolidin-1-yl)butan-2-ol** (**Compound 26**): Compound **26** was synthesized following the general method **B** from compound **25** (1.62 g, 3.60 mmol) and using anhydrous hydrazine (580 µL, 18.0 mmol) in ethanol (20.0 mL, 0.18 molar) The crude product was used for the next step without further purification. After this operation 1.07 g oil isolated.

[0355] A general procedure for preparation amide with HATU ("Method C") was followed. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved acid (0.95 equiv), in DCM (5 mL). TEA (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture and stirred for 10 minutes at room temperature, and then the primary amine (1 equiv) was added at room temperature. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were washed with 20% aqueous K_2CO_3 solution (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-100% acetone in hexanes or 0-40% MeOH in DCM) to get amide.

[0356] N-((3*R*)-4-(3-(2-Fluoro-4-(trifluoromethyl)phenyl)pyrrolidin-1-yl)-3-hydroxybutyl)-2-methyl-4,5,6,7-tetrahydro-2H-indazole-5-carboxamide (Compound 566): Compound 566 was synthesized following the general method C using 2-methyl-4,5,6,7-tetrahydro-2H-indazole-5-carboxylic acid (142 mg, 0.788 mmol), Compound 26 (252 mg, 0.788 mmol), DIPEA (0.41 mL, 2.36 mmol) and HATU (300 mg, 0.788 mmol) in CH_2Cl_2 (10 mL, 0.79 molar). The crude product was purified using flash column chromatography (0-20% MeOH/DCM) to obtain the target compound 566, 157 mg in 66% as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 13.0, 7.3 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.22 (d, *J* = 10.2 Hz, 1H), 7.00 (s, 1H), 6.87 (d, *J* = 5.0 Hz, 1H), 3.86 – 3.77 (m, 1H), 3.74 (s, 3H), 3.67 (dd, *J* = 15.6,

7.7 Hz, 1H), 3.61 – 3.49 (m, 1H), 3.30 – 2.95 (m, 3H), 2.91 – 2.49 (m, 8H), 2.37 (dddd, *J* = 21.2, 16.9, 11.3, 5.6 Hz, 2H), 2.12 – 2.03 (m, 1H), 1.99 – 1.77 (m, 2H), 1.75 – 1.62 (m, 1H), 1.54 – 1.44 (m, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.76, 175.73, 175.71, 161.5, 159.0, 147.7, 135.0, 134.9, 130.6, 130.3, 130.2, 129.2, 129.1, 127.4, 124.6, 121.9, 121.28, 121.24, 121.21, 114.4, 113.0, 112.9, 112.7, 67.1, 67.1, 61.4, 59.8, 54.2, 54.1, 53.6, 53.4, 42.4, 41.9, 38.6, 36.8, 36.2, 36.1, 34.1, 31.4, 27.19, 27.14, 24.0, 23.9, 22.5, 18.0, 12.1. UPLC/MS purity (CH_3CN: 97%, t_R = 2.29 min), MeOH: 97%, t_R = 3.17 min), $C_{24}H_{30}F_4N_4O_2$ MW 482.52, observed $[M+H]^+$ 483.30.

Synthesis of:



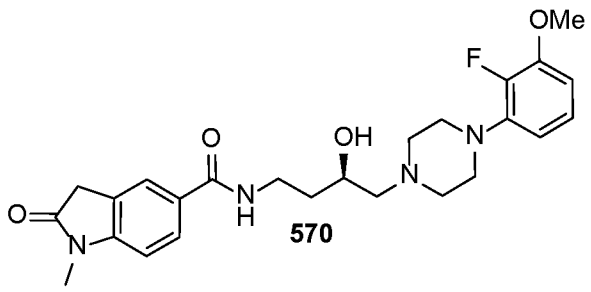
567

[0357] Compound 567 synthesis according to Scheme 52 is depicted in FIG. 66. A general procedure for preparation amide with HATU ("Method A") was followed. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved the primary amine (1 equiv), acid (0.95 equiv) in DCM (8 mL/mmol). Triethylamine (TEA) (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were washed with K_2CO_3 (10 mL), brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM or 0-100% acetone in hexanes) to get amide.

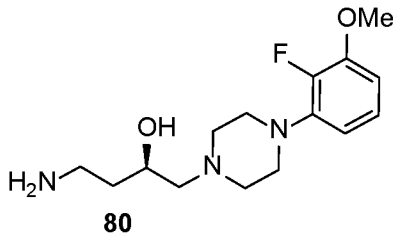
[0358] *N*-((3*R*)-3-Hydroxy-4-(3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)butyl)-2-methyl-4,5,6,7-tetrahydro-2*H*-indazole-5-carboxamide (Compound 567): Compound 567 was synthesized according to general method A, using 2-methyl-4,5,6,7-tetrahydro-2*H*-indazole-5-carboxylic acid (48 mg, 0.26 mmol), triethylamine (54 mg, 0.53 mmol), HATU (100 mg, 0.26 mmol) and (2*R*)-4-Amino-1-(3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)butan-2-ol (80 mg, 0.26 mmol). The crude

compound was purified by flash column chromatography (silica gel, 10-30% MeOH in DCM) to obtain compound 567 (82 mg, 67%).^{1}H NMR (400 MHz, DMSO) δ 7.91 – 7.83 (m, 1H), 7.68 – 7.60 (m, 2H), 7.55 (d, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 2.5 Hz, 1H), 4.65 (s, 1H), 3.71 (s, 3H), 3.66 (s, 1H), 3.50 – 3.41 (m, 1H), 3.26 – 3.09 (m, 3H),2.90 (s, 1H), 2.79 (s, 1H), 2.65 - 2.55 (m, 5H), 2.49 – 2.33 (m, 3H), 2.30 (d, *J* = 7.8 Hz, 1H), 1.95 - 1.91 (m, 1H), 1.79 (s, 1H), 1.71 - 1.60 (m, 2H), 1.48 - 1.39 (m, 1H); ^{13}C NMR (100 MHz, DMSO) δ 174.5, 146.4, 137.7, 131.4, 129.4, 127.4, 123.71 122.9, 113.7, 101.3, 82.0, 66.0, 61.6, 54.8, 54.4, 42.0, 40.1, 39.90, 39.70, 39.49, 39.28, 39.07, 38.8, 38.1, 35.4, 35.1, 27.0, 23.5, 22.1. UPLC/MS purity >95% (CH_3CN: 95.4%, t_R = 2.22 min), (MeOH: 95.4%, t_R = 3.07 min), $C_{24}H_{31}F_3N_4O_2$ MW 464.5, observed $[M+H]^+$465.3.

Synthesis of:

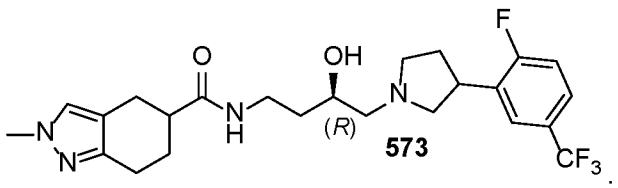


[0359] Compound 570 synthesis according to Scheme 53 is depicted in FIG. 67. A general procedure for preparation amide with HATU ("Method Q") was followed. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved acid (1 equiv) in DMF (5 mL) or DCM (5 mL). Diisopropylethylamine DIPEA or TEA (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture and stirred for 10 minutes at room temperature, and then the primary amine was added at room temperature. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with EtOAc or DCM (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM) to get amide.

Synthesis of: 

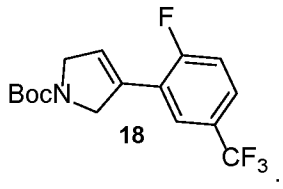
80.

[0360] (*R*)-*N*-(4-(4-(2-Fluoro-3-methoxyphenyl)piperazin-1-yl)-3-hydroxybutyl)-1-methyl-2-oxoindoline-5-carboxamide (Compound 570): Compound 570 was synthesized according to general method Q, using compound 80 (83 mg, 0.28 mmol), TEA (76 μL, 0.56 mmol), HATU (0.11 g, 0.28 mmol) and 2-methyl-4,5,6,7-tetrahydro-2*H*-indazole-5-carboxylic acid (51 mg, 0.27 mmol). The pure product, compound 570 (100 mg, 76%) was obtained as a white solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.75 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.68 (d, *J* = 1.8 Hz, 1H), 7.20 (d, *J* = 6.1 Hz, 1H), 6.98 (td, *J* = 8.3, 1.9 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.71 – 6.63 (m, 1H), 6.59 (td, *J* = 8.7, 8.1, 1.5 Hz, 1H), 3.91 (tdd, *J* = 9.1, 4.5, 2.8 Hz, 1H), 3.84 (s, 3H), 3.78 (dtd, *J* = 13.3, 6.6, 4.8 Hz, 1H), 3.52 (s, 2H), 3.41 (ddt, *J* = 13.0, 8.5, 4.3 Hz, 1H), 3.19 (s, 3H), 3.10 (tt, *J* = 11.4, 5.7 Hz, 4H), 2.93 – 2.80 (m, 2H), 2.60 (dt, *J* = 10.6, 4.7 Hz, 2H), 2.50 – 2.34 (m, 2H), 1.78 (dtd, *J* = 14.1, 4.5, 2.3 Hz, 1H), 1.66 – 1.49 (m, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 175.2, 166.8, 149.0, 148.9, 148.4, 144.7, 141.3, 141.2, 129.2, 127.5, 125.1, 123.9, 123.8, 123.4, 111.4, 111.3, 107.8, 107.3, 66.7, 64.1, 56.6, 51.0, 51.0, 38.6, 35.8, 33.8, 26.5. UPLC/MS purity >97% (CH_3CN: 97%, t_R= 2.02 min), (MeOH: 98%, t_R= 2.77 min), $C_{25}H_{31}FN_4O_4$ MW 470.55, observed $[M+1]^+$ 471.33.

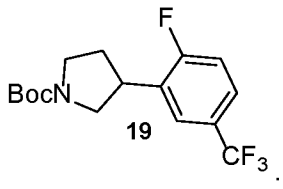
Synthesis of: 

573.

[0361] Compound 573 synthesis according to Scheme 54 is depicted in FIG. 68.

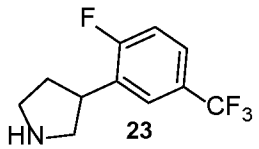
Synthesis of: 

[0362] ***tert*-Butyl 3-(2-Fluoro-5-(trifluoromethyl)phenyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (Compound 18):** To a stirred solution of 1-fluoro-2-iodo-4-(trifluoromethyl)benzene (1.8 g, 6.2 mmol), *tert*-Butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (2.0 g, 6.8 mmol) and cesium carbonate (Cs_2CO_3) (5.1 g, 16 mmol) was taken in 4:1 mixture of 1,4-dioxane/water (30 mL). The reaction mixture was purged with nitrogen gas for 15 minutes. [*1,1'*-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (100 mg, 0.12 mmol) was added quickly under positive nitrogen atmosphere, the mixture was purged with nitrogen gas for another 10 minutes. Then the reaction mixture was stirred for 16 hours at 90 °C under nitrogen atmosphere. The reaction mixture was cooled to room temperature, filtered through celite pad, washed with ethyl acetate (100 mL), filtrate was washed with water (100 mL). The aqueous layer was extracted with ethyl acetate (50 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The resulting residue was purified using flash column chromatography (silica gel, (0-20% hexane-ethyl acetate) to provide compound **18** as a half white solid (1.9 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.45 (m, 2H), 7.21 (dd, *J* = 11.0, 8.6 Hz, 1H), 6.44 (d, *J* = 18.0 Hz, 1H), 4.53 (dd, *J* = 26.2, 4.9 Hz, 2H), 4.35 (d, *J* = 18.8 Hz, 2H), 1.52 (d, *J* = 6.9 Hz, 9H).

Synthesis of: 

[0363] ***tert*-Butyl 3-(2-Fluoro-5-(trifluoromethyl)phenyl)pyrrolidine-1-carboxylate (Compound 19):** To a stirred solution of compound **18** (1.5 g, 4.5 mmol), ammonium formate (1.4 g, 23 mmol) and 10%Pd/C (120 mg) was taken in EtOH (30 mL). The reaction mixture was stirred for 2 hours at 70 °C (intensive gas evolution observed). The rection mixture was cooled to room temperature, filtered through celite and filtrated was evaporated under reduced pressure. Residue was

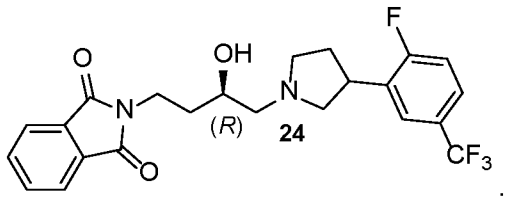
dissolved in ethyl acetate (100 mL), washed with water (50 mL), brine solution and the organic layer was dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The resulting residue was purified using flash column chromatography (0-100% hexane-ethyl acetate) to obtain the target compound **19** (1.36 g, 90%) as viscous liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (t, *J* = 6.4 Hz, 2H), 7.15 (t, *J* = 9.2 Hz, 1H), 3.84 (dt, *J* = 19.7, 9.5 Hz, 1H), 3.71 – 3.50 (m, 2H), 3.36 (dt, *J* = 46.3, 10.7 Hz, 2H), 2.28 (s, 1H), 2.10 – 1.99 (m, 1H), 1.48 (s, 9H).

Synthesis of: 

23.

[0364] **3-(2-Fluoro-5-(trifluoromethyl)phenyl)pyrrolidine (Compound 23):** Boc-protected **Compound 19** (1.7 g, 5.1 mmol) was dissolved in dioxane (8 mL/mmol) and cooled to 0 °C. 4*N* HCl in dioxane (8 mL/mmol) was added and stirred for 1 hour at room temperature. The solvent was removed under vacuo and the resulted residue was dissolved in dichloromethane (50 mL) and washed with 20% aqueous K_2CO_3 solution (20 mL). The organic phase was dried over sodium sulfate, filtered, and the solvent was removed under reduced pressure to give amine compound **23** (1.1 g, 92%) as colorless oil, which was used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.41 (m, 2H), 7.12 (t, *J* = 9.2 Hz, 1H), 3.56 – 3.34 (m, 2H), 3.28 – 3.04 (m, 2H), 2.95 – 2.82 (m, 1H), 2.33 – 2.14 (m, 2H), 1.87 (dq, *J* = 12.6, 7.9 Hz, 1H).

[0365] A general procedure for epoxide (*R*)-3 opening with pyrrolidines and piperazines and other secondary amines ("Method A") was followed. To a solution of **(*R*)-3** (1 equiv) in 2-propanol (10 mL/mmol) was added pyrrolidines or piperazines (1 equiv). The insoluble reaction mixture was heated at 80 °C to get a clear solution and then stirred at the same temperature for 24 hours. The solvent was removed *in vacuo*, and the crude product was purified by flash column chromatography (silica gel, 0-100% acetone in hexanes or MeOH in DCM (0-10%) to give epoxide opened products.

Synthesis of: 

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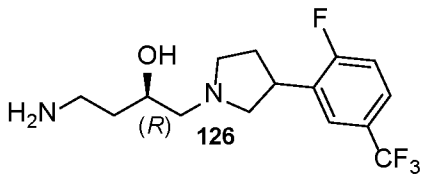
[0366] **2-((3*R*)-4-(3-(2-Fluoro-5-(trifluoromethyl)phenyl)pyrrolidin-1-*yl*)-3 hydroxybutyl)isoindoline-1,3-dione (Compound 24):** Compound **24** was synthesized according to general method **A**, using (*R*)-2-(2-(oxiran-2-*yl*)ethyl)isoindoline-1,3-dione (1.0 g, 4.7 mmol), and compound **23** (1.1 g, 4.7 mmol). The pure product, compound **24** (1.6 g, 75%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 7.78 (m, 2H), 7.78 – 7.64 (m, 2H), 7.57 (dt, *J* = 6.2, 2.8 Hz, 1H), 7.46 (dd, *J* = 9.3, 4.0 Hz, 1H), 7.20 – 7.02 (m, 1H), 4.00 – 3.81 (m, 2H), 3.82 – 3.57 (m, 2H), 3.44 (s, 1H), 3.25 – 2.91 (m, 2H), 2.68 (dddd, *J* = 31.4, 19.7, 12.9, 8.2 Hz, 3H), 2.56 – 2.43 (m, 1H), 2.40 – 2.27 (m, 1H), 1.91 (tt, *J* = 13.9, 7.1 Hz, 1H), 1.81 (td, *J* = 7.1, 5.0 Hz, 2H).

[0367] A general procedure for phthalyl deprotection ("Method B") was followed. Anhydrous hydrazine (5 equiv) was added to a suspension of phthalyl protected amine (1 equiv) in anhydrous ethanol (10 mL/mmol), and the mixture was refluxed for 3-12 hours under nitrogen atmosphere. Solvents were removed, and the resulting residue was partitioned between DCM and a 20% aqueous K_2CO_3 solution. The layers were separated, and the organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the amine, which was used for the next step without further purification.

Synthesis of: 

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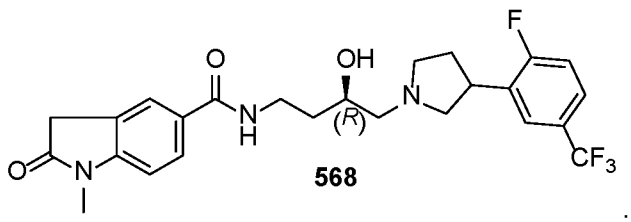
[0368] **(2*R*)-4-Amino-1-(3-(2-fluoro-5-(trifluoromethyl)phenyl)pyrrolidin-1-*yl*)butan-2-ol (Compound 126):** Compound **126** was synthesized according to general method **B**, using compound **24** (200 mg, 4.44 mmol), and anhydrous hydrazine (71.2 mg, 2.22 mmol). The product, compound **126** (100 mg, 70%) was obtained after solvent removal as a viscous oil, which was used for the preparation of amide analog without further purification. A general procedure for preparation

amide with HATU ("Method C") was followed. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved the primary amine (1 equiv), acid (0.95 equiv) in DCM (8 mL/mmol). Triethylamine (TEA) (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were washed with K_2CO_3 (10 mL), brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM or 0-100% acetone in hexanes) to get amide.

[0369] *N*-((3*R*)-4-(3-(2-Fluoro-5-(trifluoromethyl)phenyl)pyrrolidin-1-yl)-3-hydroxybutyl)-2-methyl-4,5,6,7-tetrahydro-2H-indazole-5-carboxamide (Compound 573): Compound 573 was synthesized according to general method C, using compound 126 (100 mg, 0.312 mmol), TEA (130 μL, 0.936 mmol), HATU (119 mg, 0.312 mmol) and 1-methyl-2-oxoindoline-5-carboxylic acid (56 mg, 0.312 mmol). The pure product, compound 573 (67 mg, 67%) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.53 (m, 1H), 7.49 (s, 1H), 7.18 – 7.03 (m, 2H), 6.50 (s, 1H), 3.82 (s, 4H), 3.74 – 3.63 (m, 2H), 3.34 – 2.99 (m, 3H), 2.92 – 2.60 (m, 7H), 2.62 – 2.32 (m, 3H), 2.16 (d, *J* = 12.6 Hz, 1H), 2.05 – 1.86 (m, 2H), 1.84 – 1.67 (m, 1H), 1.54 (t, *J* = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 148.0, 127.5, 126.0, 116.3, 114.5, 77.3, 72.7, 67.8, 61.5, 60.0, 54.2, 54.1, 42.7, 38.8, 36.4, 34.0, 31.5, 27.2, 24.0, 22.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.70, -61.76, -61.8, -111.8; UPLC/MS purity >95% (CH_3CN: 95.0%, t_R= 3.0 min), (MeOH: 97.4%, t_R= 3.29 min), $C_{24}H_{30}F_4N_4O_2$ MW 482.52, observed $[M+1]^+$ 483.23.

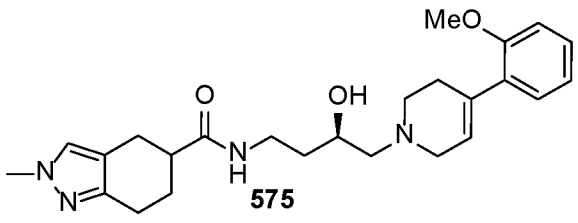
Synthesis of: 

568.

[0370] Compound 568 synthesis according to Scheme 55 is depicted in FIG. 69. A general procedure for preparation amide with HATU ("Method C") was followed. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved the primary amine (1 equiv), acid (0.95 equiv) in DCM (8

mL/mmol). Triethylamine (TEA) (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were washed with K_2CO_3 (10 mL), brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM or 0-100% acetone in hexanes) to get amide.

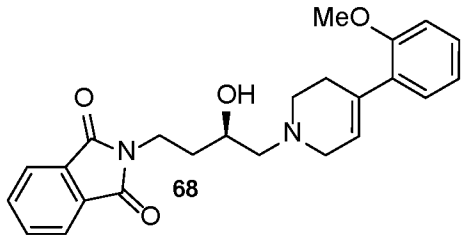
[0371] *N*-((3*R*)-4-(3-(2-Fluoro-5-(trifluoromethyl)phenyl)pyrrolidin-1-*yl*)-3-hydroxybutyl)-1-methyl-2-oxoindoline-5-carboxamide (Compound 568): Compound 568 was synthesized according to general method C, using compound 62 (150 mg, 0.468 mmol), TEA (196 μL, 1.40 mmol), HATU (178 mg, 0.468 mmol) and 1-methyl-2-oxoindoline-5-carboxylic acid (90 mg, 0.468 mmol). The pure product, compound 568 (120 mg, 52%) was obtained as a white solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.74 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.69 – 7.61 (m, 2H), 7.48 (ddd, *J* = 7.7, 4.6, 2.3 Hz, 1H), 7.25 (s, 1H), 7.14 (t, *J* = 9.2 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 3.92 – 3.71 (m, 2H), 3.70 – 3.59 (m, 1H), 3.50 (s, 2H), 3.46 – 3.35 (m, 1H), 3.18 (s, 3H), 3.11 (dd, *J* = 9.4, 7.7 Hz, 1H), 3.03 – 2.85 (m, 2H), 2.81 – 2.61 (m, 3H), 2.39 (dddt, *J* = 44.6, 17.5, 8.6, 4.2 Hz, 2H), 1.97 – 1.73 (m, 2H), 1.68 – 1.51 (m, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 175.2, 167.0, 148.4, 133.6, 133.5, 133.4, 133.3, 129.1, 127.6, 125.1, 123.4, 123.1, 116.4, 116.2, 107.8, 68.5, 61.7, 60.4, 38.4, 36.5, 36.4, 35.8, 34.1, 32.0, 26.4; ^{19}F NMR (376 MHz, CD_2Cl_2) δ -61.9, -112.5. UPLC/MS purity >95% (CH_3CN: 98.6%, t_R= 2.28 min), (MeOH: 95.6%, t_R= 3.14 min), $C_{25}H_{27}F_4N_3O_3$ MW 493.5, observed $[M+1]^+$ 494.29.

Synthesis of: 

575 .

[0372] Compound 575 synthesis according to Scheme 56 is depicted in FIG. 70. A general procedure for epoxide (*R*)-3 opening with pyrrolidines and piperazines and other secondary amines ("Method A") was followed. To a solution of (*R*)-3 (1 equiv) in 2-propanol (10 mL/mmol) was added pyrrolidines or piperazines (1 equiv). The insoluble reaction mixture was heated at 80 °C to get a clear solution and then

stirred at the same temperature for 24 hours. The solvent was removed *in vacuo*, and the crude product was purified by flash column chromatography (silica gel, 0-100% acetone in hexanes or MeOH in DCM (0-10%) to give epoxide opened products.

Synthesis of: 

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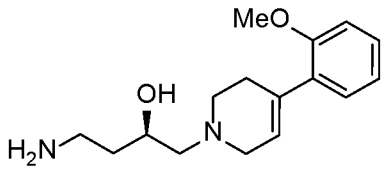
[0373] **(*R*)-2-(3-Hydroxy-4-(4-(2-Methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)butyl)isoindoline-1,3-dione (Compound 68):** Compound **68** was synthesized according to general method **A**, using (*R*)-2-(2-(oxiran-2-*yl*)ethyl)isoindoline-1,3-dione (1.1 g, 5.3 mmol), and 4-(2-methoxyphenyl)-1,2,3,6-tetrahydropyridine (1.0 g, 5.3 mmol). The pure product, compound **68** (1.0 g, 47%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.22 (td, *J* = 7.8, 1.8 Hz, 1H), 7.14 (dd, *J* = 7.5, 1.9 Hz, 1H), 6.98 – 6.81 (m, 2H), 5.74 (tt, *J* = 3.4, 1.6 Hz, 1H), 3.90 (ddt, *J* = 30.4, 13.7, 6.9 Hz, 3H), 3.80 (s, 3H), 3.31 (dd, *J* = 16.8, 3.1 Hz, 1H), 3.14 (dd, *J* = 16.7, 3.1 Hz, 1H), 2.88 (dt, *J* = 11.0, 5.4 Hz, 1H), 2.64 (dt, *J* = 11.0, 5.6 Hz, 1H), 2.58 – 2.51 (m, 2H), 2.51 – 2.37 (m, 2H), 1.84 – 1.75 (m, 2H).

[0374] A general procedure for phthalyl deprotection ("Method B") was followed. Anhydrous hydrazine (5 equiv) was added to a suspension of phthalyl protected amine (1 equiv) in anhydrous ethanol (10 mL/mmol), and the mixture was refluxed for 3-12 hours under nitrogen atmosphere. Solvents were removed, and the resulting residue was partitioned between DCM and a 20% aqueous K_2CO_3 solution. The layers were separated, and the organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the amine, which was used for the next step without further purification.

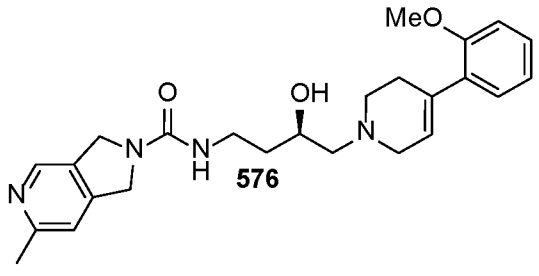


Synthesis of: **69** .

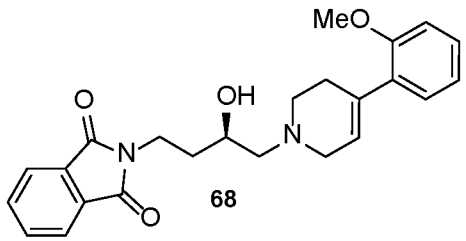
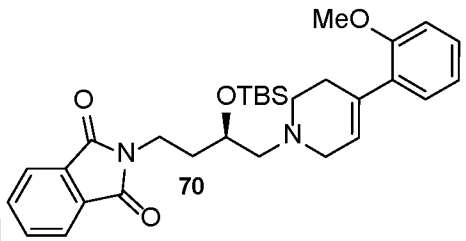
[0375] **(*R*)-4-Amino-1-(4-(2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)butan-2-ol (Compound 69):** Compound **69** was synthesized according to general method **B**, using compound **68** (0.400 mg, 0.984 mmol), and anhydrous hydrazine (158 mg, 4.92 mmol). The product, compound **69** (260 mg, 95%) was obtained after solvent removal as a viscous oil, which was used for the preparation of amide analog without further purification. A general procedure for preparation amide with HATU ("Method C") was followed. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved the primary amine (1 equiv), acid (0.95 equiv) in DCM (8 mL/mmol). Triethylamine (TEA) (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were washed with K_2CO_3 (10 mL), brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-40% MeOH in DCM or 0-100% acetone in hexanes) to get amide.

[0376] *N*-((*R*)-3-Hydroxy-4-(4-(2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)butyl)-2-methyl-4,5,6,7-tetrahydro-2H-indazole-5-carboxamide (Compound 575): Compound 575 was synthesized according to general method C, using Compound 69 (130 mg, 0.47 mmol), TEA (197 μL, 1.41 mmol), HATU (179 mg, 0.47 mmol) and 2-methyl-4,5,6,7-tetrahydro-2*H*-indazole-5-carboxylic acid (85 mg, 0.47 mmol). The pure product, compound 575 (120 mg, 58%) was obtained as a white solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.22 (td, *J* = 7.8, 1.8 Hz, 1H), 7.14 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.07 (s, 1H), 6.96 – 6.83 (m, 2H), 6.46 (s, 1H), 5.75 (p, *J* = 1.8 Hz, 1H), 3.87 – 3.81 (m, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.57 (dddd, *J* = 13.6, 6.8, 4.7, 1.9 Hz, 1H), 3.36 – 3.21 (m, 2H), 3.16 – 3.05 (m, 1H), 2.86 (dt, *J* = 10.9, 5.4 Hz, 1H), 2.78 (d, *J* = 5.3 Hz, 1H), 2.76 – 2.66 (m, 2H), 2.61 (dt, *J* = 11.3, 5.3 Hz, 2H), 2.56 – 2.49 (m, 2H), 2.47 – 2.35 (m, 3H), 2.15 – 2.04 (m, 1H), 1.93 – 1.79 (m, 1H), 1.76 – 1.62 (m, 2H), 1.49 (dtd, *J* = 13.9, 8.2, 5.1 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 175.2, 157.2, 147.9, 136.1, 132.1, 129.5, 128.5, 127.4, 123.9, 120.9, 114.7, 111.2, 66.6, 66.5, 64.1, 55.6,

53.6, 50.8, 42.9, 38.8, 37.7, 34.3, 34.2, 30.0, 27.68, 27.67, 24.32, 24.29, 22.9; UPLC/MS purity >97% (CH_3CN: 97.7%, t_R= 2.05 min), (MeOH: 98.4%, t_R= 2.96 min), $C_{25}H_{34}N_4O_3$ MW 438.57, observed $[M+1]^+$ 439.37.

Synthesis of:  .

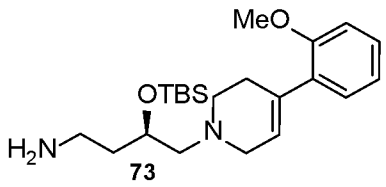
[0377] Compound 576 synthesis according to Scheme 57 is depicted in FIG. 71. TBS protection of secondary Alcohols ("Method D") was followed. To a stirring solution of epoxide opened compound (1 equiv) dissolved in DCM (0.10 M) was added 2,6-lutidine (3 equiv). The resulting solution was cooled to 0 ºC and TBSOTf (1.5 equiv) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 2-16 hours till the disappearance of starting material. The organic layer was washed with saturated K_2CO_3 solution and dried over Na_2SO_4. The crude product was purified using flash column chromatography (0-100% acetone-hexane or EtOAc-hexanes) to obtain TBS protected compound.

Synthesis of:  and  .

[0378] (*R*)-2-(3-((*tert*-Butyldimethylsilyl)oxy)-4-(4-(2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)butyl)isoindoline-1,3-dione (Compound 70): was synthesized following general method D. Using compound 68 (600 mg, 1.48 mmol), 2,6-lutidine (513 µL, 4.43 mmol), and TBSOTf (563 µL, 2.95 mmol). The pure product, compound 70 (600 mg, 78%) was obtained as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.69 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.25 – 7.11 (m, 2H), 6.94 – 6.77 (m, 2H), 5.79 – 5.66 (m, 1H), 3.97 (s, 1H), 3.87 (ddd, *J* = 13.4, 9.9, 5.6 Hz, 1H), 3.80 (s, 4H), 3.15 (s, 2H), 2.69 (d, *J* = 6.0 Hz, 2H), 2.51 (d, *J* = 5.8

Hz, 4H), 2.03 (ddd, *J* = 14.5, 9.3, 5.0 Hz, 1H), 1.93 – 1.80 (m, 1H), 0.91 (s, 9H), 0.10 (d, *J* = 2.2 Hz, 6H).

[0379] A general procedure for phthalyl deprotection ("Method B") was followed. Anhydrous hydrazine (5 equiv) was added to a suspension of phthalyl protected amine (1 equiv) in anhydrous ethanol (10 mL/mmol), and the mixture was refluxed for 3-12 hours under nitrogen atmosphere. Solvents were removed, and the resulting residue was partitioned between DCM and a 20% aqueous K_2CO_3 solution. The layers were separated, and the organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the amine, which was used for the next step without further purification.

Synthesis of: 

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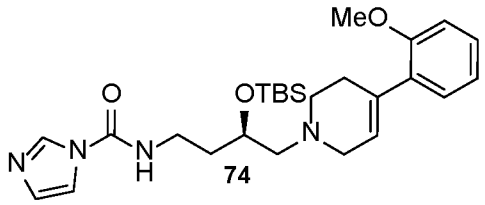
[0380] **(*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-4-(4-(2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)butan-1-amine (Compound 73):** Compound **73** was synthesized according to general method **B**, using compound **70** (600 mg, 1.15 mmol), and anhydrous hydrazine (185 mg, 5.76 mmol). The product, compound **73** (400 mg, 89%) was obtained after solvent removal as a viscous oil, which was used for the preparation of urea analog without further purification. CDI Carbamate formation ("Method E") was followed. To a stirring solution of TBS-protected amine (1 equiv) in DCM (0.10 M) was added CDI (1 equiv) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2-6 hours. The solvent was removed *in vacuo*, and the crude product was purified by flash column chromatography (silica gel, 0-100% acetone-hexane) to obtain the target compound.

Synthesis of: 

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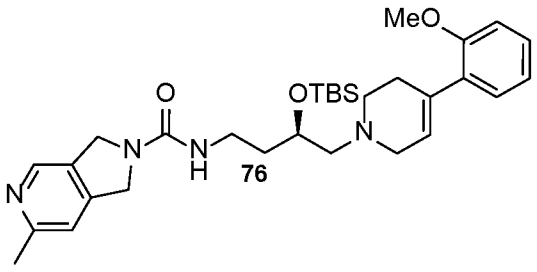
[0381] (*R*)-*N*-(3-((*tert*-Butyldimethylsilyl)oxy)-4-(4-(2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-*yl*)butyl)-1*H*-imidazole-1-carboxamide (Compound 74):

Compound 74 was synthesized following the general method E from compound 73 (450 mg, 1.15 mmol) and CDI (280 mg, 1.73 mmol) in DCM (15 mL). The crude product was purified using flash column chromatography (0-100% hexane-ethyl acetate) to obtain the target compound 74 (400 mg, 72%) as viscous liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.08 (s, 1H), 7.36 (dd, *J* = 9.8, 5.7 Hz, 1H), 7.24 – 7.03 (m, 2H), 6.92 – 6.67 (m, 3H), 5.64 (td, *J* = 3.3, 1.6 Hz, 1H), 4.08 (s, 1H), 3.69 (s, 3H), 3.55 – 3.30 (m, 2H), 3.15 (s, 2H), 2.80 (s, 2H), 2.57 (d, *J* = 27.5 Hz, 3H), 1.99 – 1.78 (m, 3H), 0.80 (s, 9H), -0.00 (d, *J* = 0.9 Hz, 6H).

[0382] Urea analog synthesis ("Method F") was followed. To a stirring solution of amine or amine•HCl salt (1.3-3 equiv) in 1,4-dioxane (0.10M) was added TEA (3-6 equiv) and the reaction was stirred for 30 minutes. To this was added carbamate (1 equiv) and the resulting mixture was stirred at 90 ºC for 24 hours. The solvent was removed under reduced pressure and the crude product was purified using flash column chromatography (0-50% DCM-MeOH and 5-10% NH_4OH) to obtain pure urea compound.

Synthesis of: 

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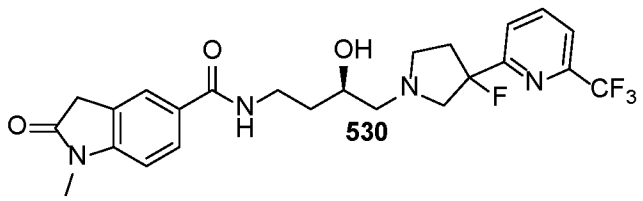
[0383] (*R*)-*N*-(3-((*tert*-Butyldimethylsilyl)oxy)-4-(4-(2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-*yl*)butyl)-6-methyl-1,3-dihydro-2*H*-pyrrolo[3,4-c]pyridine-2-carboxamide (Compound 76): Compound 76 was synthesized following the general method F from compound 74 (200 mg, 413 μmol) and 6-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine•HCl salt (129 mg, 619 μmol), Triethylamine (0.292 mL, 2.89 mmol) in 1,4-dioxane (10 mL). The crude product was purified using flash column chromatography (0-10% methanol-dichloromethane) to obtain the target compound 76 (130 mg, 57%) as viscous liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.28 – 7.21 (m, 1H), 7.15 (dd, *J* = 7.5, 1.8 Hz, 1H), 6.91 (td, *J* = 7.5, 1.1 Hz, 1H), 6.87 – 6.79 (m, 2H), 6.01 (s, 1H), 5.91 – 5.72 (m, 1H), 4.64 (d, *J* = 9.2 Hz, 4H), 4.05 (s, 1H), 3.69 (s, 3H), 3.52 – 3.33 (m, 2H), 3.19 (s, 2H), 2.76 (s, 2H), 2.64 – 2.50 (m, 4H), 2.46 (s, 3H), 1.91 (d, *J* = 5.8 Hz, 2H), 0.90 (s, 9H), 0.09 (d, *J* = 1.2 Hz, 6H).

[0384] TBS-deprotection with TBAF ("Method I") was followed: To a stirring solution of TBS-protected urea compound (1 equiv) in THF (0.05 M) was added TBAF (1 M in THF; 2-3 equiv) at 0 ºC. The resulting mixture was stirred at room temperature for 2-16 hours. The solvent was evaporated, and the crude product was purified using flash column chromatography (0-100% acetone-MeOH (2% aq. NH_3 added) to obtain the final target compound.

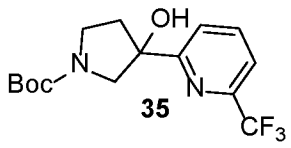
[0385] (*R*)-*N*-(3-Hydroxy-4-(4-(2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-*yl*)butyl)-6-methyl-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridine-2-carboxamide (Compound 576): Compound 576 was synthesized following the general method I from compound 76 (130 mg, 236 μmol) and 1M TBAF in THF solution (472 μL, 472 μmol) in THF (5 mL). The crude product was purified using flash column chromatography (0-20% DCM-MeOH (2% aq. NH_3 added) to obtain the final target compound 576 (78 mg, 76%) as half white solid. ^{1}H NMR (400 MHz, MeOD) δ 8.36 (s, 1H), 7.26 (s, 1H), 7.22 (ddd, *J* = 8.2, 7.4, 1.8 Hz, 1H), 7.12 (dd, *J* = 7.4, 1.8 Hz, 1H), 6.95 – 6.84 (m, 2H), 5.73 (dq, *J* = 3.5, 1.7 Hz, 1H), 4.69 (s, 4H), 3.97 (dt, *J* = 8.6, 2.9 Hz, 1H), 3.77 (s, 3H), 3.48 – 3.33 (m, 2H), 3.30 – 3.16 (m, 2H), 2.87 (t, *J* = 5.7 Hz, 2H), 2.60 (dd, *J* = 11.5, 4.5 Hz, 4H), 2.53 (s, 3H), 1.87 – 1.71 (m, 1H), 1.67 – 1.57 (m, 1H); ^{13}C NMR (100 MHz, MeOD) δ 159.3, 158.2, 158.1, 149.5, 143.9, 137.2, 132.6, 132.5, 130.0, 129.5, 123.6, 121.6, 119.2, 112.1, 67.3, 65.1, 55.7, 54.3, 52.5, 51.8, 50.7, 38.4, 37.2, 29.9, 24.7, 23.6, 13.9; UPLC/MS purity >98% (CH_3CN: 98.0%, t_R= 2.07 min), (MeOH: 98.0%, t_R= 3.04 min), $C_{25}H_{32}N_4O_3$ MW 436.56, observed $[M+1]^+$ 437.36.

Synthesis of:



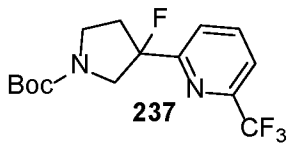
[0386] Compound 530 synthesis according to Scheme 58 is depicted in FIG. 72.

Synthesis of:



[0387] ***tert*-Butyl 3-hydroxy-3-(6-(trifluoromethyl)pyridin-2-yl)pyrrolidine-1-carboxylate (Compound 35):** 2-Iodo-6-(trifluoromethyl)pyridine (1.50 mg, 5.49

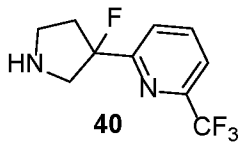
mmol) was dissolved in dry THF (40 mL) and cooled to – 78 °C. n-BuLi (1.6 M solution in hexanes, 3.43 mL, 5.49 mmol) was added drop wise to the above reaction mixture and stirred for 1 hour at – 78° C. Then *tert*-Butyl 3-oxopyrrolidine-1-carboxylate (1.02 g, 5.49 mmol) was added to the reaction mixture at – 78 °C. It was then stirred at – 78° C. for 1 hour. The reaction mixture was quenched with aqueous saturated ammonium chloride solution, and the product was extracted with ethyl acetate. The ethyl acetate extract was dried over Na_2SO_4 and concentrated under reduced pressure to get crude compound **35** which was purified by flash column chromatography (silica gel, 0-70% EtOAc in hexanes) to get pure compound **35** (1.20 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (t, *J* = 7.9 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 7.7 Hz, 1H), 4.34 (d, *J* = 3.4 Hz, 1H), 3.83 – 3.58 (m, 4H), 2.39 (q, *J* = 10.7, 10.2 Hz, 1H), 2.20 – 2.08 (m, 1H), 1.47 (d, *J* = 11.2 Hz, 9H).



237

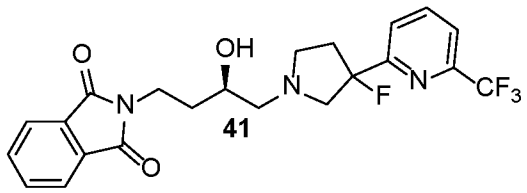
Synthesis of:

[0388] ***tert*-Butyl 3-fluoro-3-(6-(trifluoromethyl)pyridin-2-yl)pyrrolidine-1-carboxylate (Compound 237):** To compound **35** (400 mg, 1.20 mmol) was added anhydrous dichloromethane (15 mL) and the reaction mixture was cooled to −78 °C. Maintaining the same temperature, DAST (0.155 mL, 1.20 mmol) dissolved in anhydrous DCM (2 mL) was added dropwise, and the reaction was stirred at −78 °C for 1 hour. Thin layer chromatography was used to monitor the progress of the reaction. Once the reaction was completed, ice cold water was added to the reaction mixture and the product was extracted with ethyl acetate (EtOAc) and purified by flash column chromatography (silica gel, 0-20% EtOAc in hexanes) to get compound **237** as colorless viscous oil (310 mg, 77%) as a major product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (t, *J* = 7.9 Hz, 1H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.64 (d, *J* = 7.7 Hz, 1H), 4.06 – 3.72 (m, 3H), 3.65 (td, *J* = 10.9, 6.6 Hz, 1H), 2.83 – 2.57 (m, 1H), 2.30 (dddt, *J* = 17.0, 13.9, 6.7, 1.6 Hz, 1H), 1.48 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -67.87, -157.18.

Synthesis of:  **40**.

[0389] **2-(3-Fluoropyrrolidin-3-yl)-6-(trifluoromethyl)pyridine (Compound 40):** To a stirred solution of compound **237** (300 mg, 0.897 mmol) in DCM (2 mL) was added TFA (8 mL) at °C and the reaction mixture was stirred at the same temperature for 2 hours. After completion of reaction solvent was removed and neutralized with saturated K_2CO_3 and the product was extracted with DCM. The DCM extract was dried over Na_2SO_4 and concentrated under reduced pressure to get crude compound **40** which was used for the next step without further purification. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.84 (t, *J* = 7.9 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.51 (dd, *J* = 7.8, 1.0 Hz, 1H), 3.26 – 2.99 (m, 4H), 2.39 (dddd, *J* = 33.3, 14.2, 8.9, 7.4 Hz, 1H), 2.23 – 2.04 (m, 2H); ^{19}F NMR (376 MHz, CD_2Cl_2) δ -68.45, -151.70.

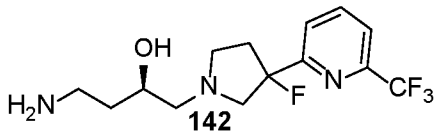
[0390] A general procedure for epoxide (*R*)-3 and (*S*)-3 opening with pyrrolidines and piperazines and other secondary amines ("Method C") was followed. To a solution of **(*R*)-3** or **(*S*)-3** (1 equiv) in 2-propanol (6 mL/mmol) was added pyrrolidines or piperazines (1 equiv). The insoluble reaction mixture was heated to 70 °C to 80 °C to get a clear solution and then stirred at room temperature for 24 to 48 hours. The solvent was removed *in vacuo*, and the crude product was purified by flash column chromatography (silica gel, 0-100% acetone in hexanes or MeOH in DCM (0-10%) to give epoxide opened products.

Synthesis of:  **41**.

[0391] 2-((3*R*)-4-(3-Fluoro-3-(6-(trifluoromethyl)pyridin-2-yl)pyrrolidin-1-yl)-3-hydroxybutyl)isoindoline-1,3-dione (Compound 41): Compound 41 was synthesized according to general method C, using (*R*)-3 (148 mg, 0.683 mmol), and compound 40 (160 mg, 0.683 mmol). The pure product, compound 41 (230 mg, 75%) was obtained as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (t, *J* = 7.9 Hz, 1H), 7.82 (dt, *J* = 5.2, 2.3 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.72 – 7.65 (m, 2H), 7.58 (d, *J* = 7.7 Hz, 1H), 3.96 – 3.78 (m, 2H), 3.74 (pd, *J* = 8.3, 7.5, 4.0 Hz, 1H), 3.60 (s, 1H),

3.37 – 3.06 (m, 3H), 3.03 – 2.78 (m, 1H), 2.74 – 2.48 (m, 3H), 2.43 – 2.22 (m, 1H), 1.79 (q, *J* = 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 161.1, 160.8, 147.8, 147.4, 138.1, 134.0, 132.2, 123.3, 122.2, 122.1, 119.35, 119.32, 105.1, 104.9, 103.2, 103.1, 66.6, 66.5, 66.3, 66.1, 65.9, 65.7, 61.8, 61.6, 54.1, 53.6, 39.2, 39.0, 35.08, 35.06, 33.7.2

[0392] A general procedure for phthalyl deprotection ("Method D") was followed. Anhydrous hydrazine (5 equiv) was added to a suspension of phthalyl protected amine (1 equiv) in anhydrous ethanol (10 mL/mmol), and the mixture was refluxed for 3 h under nitrogen atmosphere. Solvents were removed, and the resulting residue was partitioned between DCM and a 20% aqueous K_2CO_3 solution. The layers were separated, and the organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the amine, which was used for the next step without further purification.

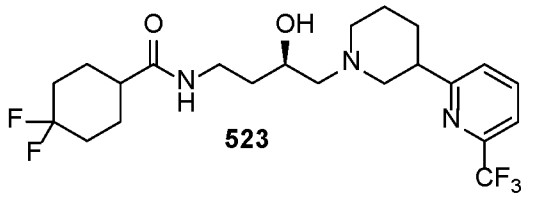
Synthesis of: 

142 .

[0393] **2*R*)-4-Amino-1-(3-fluoro-3-(6-(trifluoromethyl)pyridin-2-yl)pyrrolidin-1-yl)butan-2-ol (Compound 142):** Compound **142** was synthesized according to general method **D**, using compound **41** (230 mg, 0.510 mmol), and anhydrous hydrazine (81.7 mg, 2.55 mmol). The product, compound **142** (138 mg, 84%) was obtained after solvent removal as a viscous oil, which was used for the preparation of an amide analog without further purification. A general procedure for preparation amide with HATU ("Method Q") was followed. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved acid (0.95 equiv), in DCM (5 mL). TEA (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture and stirred for 10 minutes at room temperature, and then the primary amine (1 equiv) was added at room temperature. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were washed with 20% aqueous K_2CO_3 solution (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column

chromatography (silica gel, 0-100% acetone in hexanes or 0-40% MeOH in DCM) to get amide.

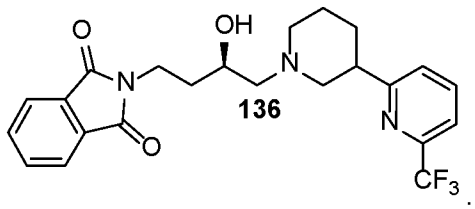
[0394] 4,4-Difluoro-N-((3*R*)-3-hydroxy-4-(3-(6-(trifluoromethyl)pyridin-2-yl)piperidin-1-yl)butyl)cyclohexane-1-carboxamide (Compound 530): Compound 530 was synthesized following the general method Q using 1-methyl-2-oxoindoline-5-carboxylic acid (60 mg, 0.31 mmol), compound 142 (110 mg, 0.35 mmol), triethylamine (0.13 mL, 0.94 mmol) and HATU (180 mg, 0.47 mmol) in CH_2Cl_2 (4.0 mL, 0.08 molar). The crude product was purified using flash column chromatography (0-100% Ethyl acetate-hexane) to obtain the target compound 530 (90 mg, 58%) yield as a mixture of diastereomers; ^{1}H NMR (400 MHz, MeOD) δ 8.07 (t, *J* = 7.9 Hz, 1H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.82 (dt, *J* = 8.2, 1.8 Hz, 1H), 7.74 (dd, *J* = 4.8, 2.9 Hz, 2H), 7.02 (dd, *J* = 8.2, 1.6 Hz, 1H), 3.86 (dq, *J* = 12.6, 4.2 Hz, 1H), 3.62 – 3.45 (m, 2H), 3.37 (dd, *J* = 16.0, 7.2 Hz, 1H), overlapped with CD_3OD 3.34-3.27 (m, 2H), 3.29 – 3.24 (m, 1H), 3.23 (s, 3H), 3.21 – 3.12 (m, 1H), 2.89 (ddd, *J* = 23.6, 15.3, 8.5 Hz, 1H), 2.76 – 2.52 (m, 3H), 2.44 – 2.28 (m, 1H), 1.92 – 1.82 (m, 1H), 1.69 (td, *J* = 14.2, 7.1 Hz, 1H).; ^{13}C NMR (100 MHz, MeOD) δ 177.7, 169.9, 162.3, 162.0, 149.4, 148.6, 148.3, 140.1, 129.9, 128.9, 126.2, 124.3, 124.2, 123.7, 123.6, 121.5, 120.73, 120.70, 109.1, 106.1, 106.08, 104.3, 104.2, 69.0, 68.9, 67.48, 67.45, 67.24, 67.21, 63.4, 55.4, 54.8, 40.0, 39.89, 39.82, 39.6, 38.0, 36.15, 36.11, 26.6: UPLC/MS purity (CH_3CN: 95%, t_R = 4.40 min), MeOH: 97%, t_R = 3.19 min), $C_{24}H_{26}F_4N_4O_3$ MW 494.49, observed $[M+H]^+$ 495.26.

Synthesis of: 

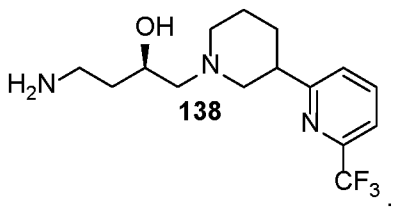
523.

[0395] Compound 523 synthesis according to Scheme 59 is depicted in FIG. 73. A general procedure for epoxide (R)-3 and (S)-3 opening with pyrrolidines and piperazines and other secondary amines ("Method A"). To a solution of (*R*)-3 or (*S*)-3 (1 equiv) in 2-propanol (10 mL/mmol) was added pyrrolidines or piperazines (1 equiv). The reaction mixture was heated at 80 °C and stirred at the same temperature for 24 hours. The solvent was removed *in vacuo*, and the crude product

was purified by flash column chromatography (silica gel, 0-100% acetone in hexanes or MeOH in DCM (0-10%) to give epoxide opened products.

Synthesis of: 

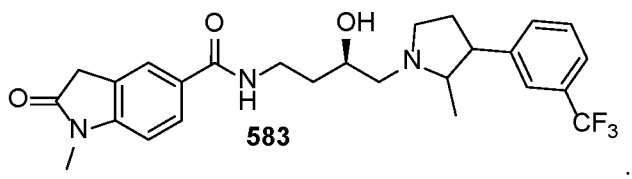
[0396] 2-((3*R*)-3-Hydroxy-4-(3-(6-(trifluoromethyl)pyridin-2-yl)piperidin-1-yl)butyl)isoindoline-1,3-dione (Compound 136): Compound 136 was synthesized according to general method A, using (R)-2-(2-(oxiran-2-yl)ethyl)isoindoline-1,3-dione (200 mg, 0.921 mmol), and 2-(piperidin-3-yl)-6-(trifluoromethyl)pyridine (221 mg, 0.921 mmol) in Isopropanol (8 mL, 0.1 molar). The crude product was purified using flash column chromatography (0-100% acetone-hexane) to obtain compound 136 (350 mg, 85%) as a yellow oil. General procedure for phthalyl deprotection ("Method B") was followed. Anhydrous hydrazine (5 equiv) was added to a suspension of phthalyl protected amine (1 equiv) in anhydrous ethanol (10 mL/mmol), and the mixture was refluxed overnight under nitrogen atmosphere. Solvents were removed, and the resulting residue was partitioned between DCM and a 20% aqueous K_2CO_3 solution. The layers were separated, and the organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the amine, which was used for the next step without further purification.

Synthesis of: 

[0397] **(2*R*)-4-Amino-1-(3-(6-(trifluoromethyl)pyridin-2-yl)piperidin-1-yl)butan-2-ol (Compound 138):** Compound **138** was synthesized following the general method **B** from compound **136** (300 mg, 670 µmol) and using anhydrous hydrazine (105 µL, 3.35 mmol) in ethanol (8.0 mL, 0.08 molar). The product, compound **138** (180 mg, 85%) was obtained after solvent removal as a viscous oil, which was used for the preparation of amide analog without further purification. A general procedure for

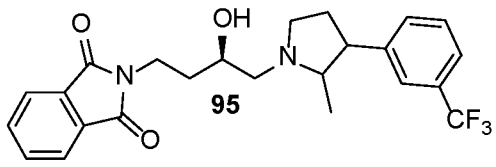
preparation amide with HATU ("Method C") was followed. In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved acid (0.95 equiv), in DCM (5 mL). TEA (2 equiv) and HATU (1 equiv) were added sequentially to the reaction mixture and stirred for 10 minutes at room temperature, and then 1°-amine (1 equiv) was added at room temperature. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were washed with 20% aqueous K_2CO_3 solution (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 0-100% acetone in hexanes or 0-40% MeOH in DCM) to get amide.

[0398] 4,4-Difluoro-*N*-((3*R*)-3-hydroxy-4-(3-(6-(trifluoromethyl)pyridin-2-yl)piperidin-1-yl)butyl)cyclohexane-1-carboxamide (Compound 523): Compound 523 was synthesized following the general method C using 4,4-difluorocyclohexane-1-carboxylic acid (52 mg, 0.32 mmol), compound 138 (110 mg, 0.35 mmol), triethylamine (0.13 mL, 0.95 mmol) and HATU (180 mg, 0.48 mmol) in CH_2Cl_2 (5.0 mL, 0.06 molar). The crude product was purified using flash column chromatography (0-100% Ethyl acetate-hexane) to obtain the target compound 523, 106 mg in 74% yield as a mixture of diastereomers; ^{1}H NMR (400 MHz, MeOD) δ 7.95 (t, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 3.83 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.14 (dt, *J* = 19.1, 11.8 Hz, 2H), 3.03 (t, *J* = 12.6 Hz, 1H), 2.54 – 2.22 (m, 5H), 2.21 – 1.95 (m, 4H), 1.92 – 1.62 (m, 11H), 1.60 – 1.47 (m, 1H).; ^{13}C NMR (100 MHz, MeOD) δ 177.4, 165.6, 148.6, 148.3, 148.0, 139.53, 139.51, 126.2, 124.4, 123.8, 121.7, 121.4, 119.3, 67.0, 66.8, 65.9, 60.7, 59.7, 55.8, 54.8, 45.2, 43.7, 37.2, 36.2, 36.1, 34.0, 33.8, 33.6, 31.17, 31.11, 27.1, 27.0, 26.0; UPLC/MS purity (CH_3CN: 96%, t_R = 3.22 min), MeOH: 95%, t_R = 3.61 min), $C_{22}H_{30}F_5N_3O_2$ MW 463.49, observed $[M+H]^+$ 464.36.

Synthesis of: 

583.

[0399] Compound 583 synthesis according to Scheme 60 is depicted in FIG. 74.

Synthesis of: 

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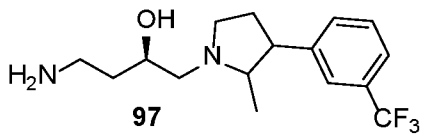
[0400] 2-((3*R*)-3-Hydroxy-4-(2-methyl-3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)butyl)isoindoline-1,3-dione (Compound 95): To a solution of (*R*)-2-(2-(oxiran-2-yl)ethyl)isoindoline-1,3-dione (250 mg, 1.15 mmol) in 2-propanol (5 mL) was added 2-methyl-4-(3-(trifluoromethyl)phenyl)pyrrolidine (264 mg, 1.15 mmol). The reaction mixture was heated to 80 °C and stirred at the same temperature for 16 hours. The reaction mixture was cooled to room temperature and solvent was removed *in vacuo*, and the crude product was purified by flash column chromatography (silica gel, 50-70% EtOAc in hexanes to give 2-((3*R*)-3-hydroxy-4-(2-methyl-3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)butyl)isoindoline-1,3-dione **(Compound 95)** (335 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (ddd, *J* = 5.4, 3.0, 2.0 Hz, 2H), 7.66 (ddd, *J* = 5.4, 3.1, 1.9 Hz, 2H), 7.46 – 7.31 (m, 4H), 3.98 – 3.60 (m, 3H), 3.48 – 3.03 (m, 2H), 2.97 – 2.53 (m, 3H), 2.53 – 2.08 (m, 3H), 2.08 – 1.64 (m, 3H), 0.98 (t, *J* = 5.9 Hz, 2H), 0.59 (t, *J* = 5.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 168.5, 168.4, 168.4, 145.0, 144.5, 143.7, 133.9, 133.9, 133.8, 132.1, 132.1, 132.1, 132.0, 131.3, 131.2, 130.8, 130.8, 130.5, 130.5, 130.3, 130.0, 128.9, 128.9, 128.4, 128.4, 125.6, 125.5, 125.3, 125.2, 124.4, 124.4, 124.4, 124.3, 123.3, 123.2, 123.2, 123.1, 123.1, 122.9, 122.9, 122.8, 122.8, 68.5, 67.5, 67.4, 67.1, 65.7, 63.2, 59.6, 59.5, 59.4, 54.9, 53.6, 53.0, 52.3, 52.3, 47.9, 35.1, 35.0, 34.9, 34.5, 34.1, 33.6, 31.9, 31.4, 29.6, 17.3, 17.0, 15.2.

Synthesis of: 

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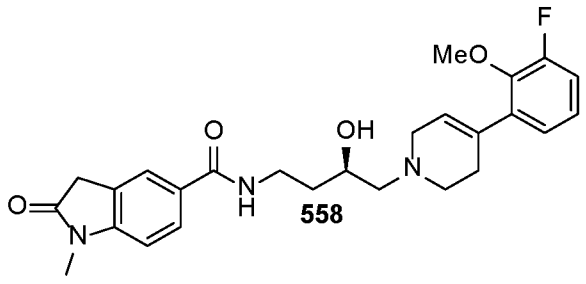
[0401] (2*R*)-4-Amino-1-(2-methyl-3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)butan-2-ol (Compound 97): Anhydrous hydrazine (0.11 mL, 3.0 mmol) was added to a suspension of 2-((3*R*)-3-hydroxy-4-(2-methyl-3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)butyl)isoindoline-1,3-dione **(Compound 95)** (300 mg, 3.00 mmol) in anhydrous ethanol (5 mL), and the mixture was refluxed overnight under nitrogen atmosphere. Solvents were removed, and the resulting residue was partitioned between DCM and a 20% aqueous K_2CO_3 solution. The

layers were separated, and the organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the crude (2*R*)-4-amino-1-(2-methyl-3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)butan-2-ol **(Compound 97)** (150 mg, 70%), which was used for the next step without further purification.

[0402] N-((3*R*)-3-Hydroxy-4-(2-methyl-3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)butyl)-1-methyl-2-oxoindoline-5-carboxamide (Compound 583): In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved 1-methyl-2-oxoindoline-5-carboxylic acid (90.6 mg, 0.47 mmol), in DCM (3 mL). TEA (0.21mL, 1.4 mmol) and HATU (180 mg, 0.47 mmol) were added sequentially to the reaction mixture and stirred for 10 minutes at room temperature, and then (2*R*)-4-amino-1-(2-methyl-3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)butan-2-ol (Compound 97) (150 mg, 0.47 mmol) was added at room temperature. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 X 10 mL). The combined organic layers were washed with 20% aqueous K_2CO_3 solution (2 X 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 10-30% MeOH in DCM) to get N-((3*R*)-3-hydroxy-4-(2-methyl-3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)butyl)-1-methyl-2-oxoindoline-5-carboxamide (Compound 583) (50 mg, 22%); ^{1}H NMR (400 MHz, MeOD) δ 7.93 – 7.73 (m, 2H), 7.54 (tdd, *J* = 16.8, 11.1, 7.9 Hz, 4H), 7.04 (dd, *J* = 8.2, 2.4 Hz, 1H), 3.94 (dt, *J* = 8.4, 4.1 Hz, 1H), 3.72 – 3.38 (m, 3H), 3.31 (p, *J* = 1.6 Hz, 2H), 3.23 (d, *J* = 1.0 Hz, 3H), 3.16 – 2.87 (m, 3H), 2.88 – 2.20 (m, 3H), 2.20 – 1.59 (m, 3H), 1.16 (dd, *J* = 17.6, 6.0 Hz, 2.1H), 0.75 (d, *J* = 6.6 Hz, 0.9H); ^{13}C NMR (101 MHz, MeOD) δ 177.6, 170.1, 170.1, 149.5, 149.5, 133.7, 132.7, 131.9, 130.7, 130.6, 129.9, 129.8, 129.8, 129.7, 129.0, 128.9, 127.0, 126.5, 126.3, 125.5, 125.0, 124.7, 124.4, 124.3, 109.1, 70.2, 70.1, 68.4, 66.6, 65.0, 61.0, 60.7, 55.7, 53.8, 52.8, 52.3, 37.8, 37.7, 36.6, 36.3, 36.2, 32.4, 31.9, 26.6, 16.1; UPLC/MS purity >95% (CH_3CN: 97%, t_R = 2.35 min, MeOH: 97%, t_R = 3.16 min), $C_{26}H_{30}F_3N_3O_3$ MW 489.22, $[M+H]^+$ 490.23.

Synthesis of: 

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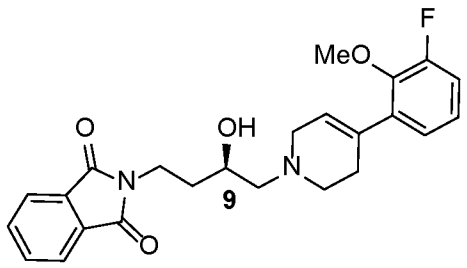
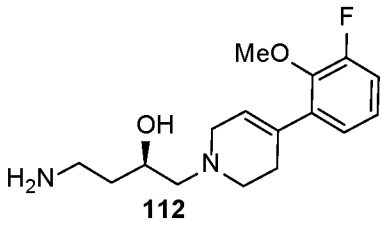
[0403] Compound 558 synthesis according to Scheme 61 is depicted in FIG. 75.

Synthesis of: 

and 

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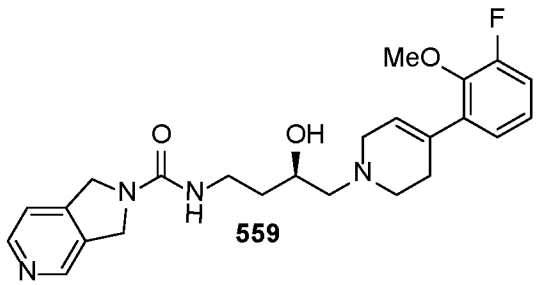
[0404] **(*R*)-4-Amino-1-(4-(3-fluoro-2-methoxyrefluxeddihydropyridin-1(2*H*)-yl)butan-2-ol (Compound 112):** Anhydrous hydrazine (0.20 mL, 7.01 mmol) was added to a suspension of (*R*)-2-(4-(4-(3-fluoro-2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)-3-hydroxybutyl)isoindoline-1,3-dione **(Compound 9)** (600 mg, 1.41 mmol) in anhydrous ethanol (6 mL), and the mixture was refluxed overnight under nitrogen atmosphere. Solvents were removed, and the resulting residue was partitioned between DCM and a 20% aqueous K_2CO_3 solution. The layers were separated, and the organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the crude (*R*)-4-amino-1-(4-(3-fluoro-2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)butan-2-ol **(Compound 112)** (320 mg, 77%), which was used for the next step without further purification.

[0405] (*R*)-*N*-(4-(4-(3-Fluoro-2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)-3-hydroxybutyl)-1-methyl-2-oxoindoline-5-carboxamide (Compound 558): In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved 1-methyl-2-oxoindoline-5-carboxylic acid (65 mg, 0.34 mmol), in DCM (3 mL). TEA (0.14 mL, 1.02 mmol) and HATU (100 mg, 0.41 mmol) were added sequentially to the reaction mixture and stirred for 10 minutes at room temperature, and then (*R*)-4-amino-1-(4-(3-fluoro-2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)butan-2-ol (100 mg, 0.34 mmol) was added at room temperature. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 X

10 mL). The combined organic layers were washed with 20% aqueous K_2CO_3 solution (2 X 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 10-30% MeOH in DCM) to get (*R*)-*N*-(4-(4-(3-fluoro-2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)-3-hydroxybutyl)-1-methyl-2-oxoindoline-5-carboxamide (Compound 558) (75 mg, 41%); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.80 – 7.71 (m, 1H), 7.69 (q, *J* = 1.3 Hz, 1H), 7.25 (s, 1H), 7.08 – 6.89 (m, 3H), 6.84 (d, *J* = 8.1 Hz, 1H), 5.83 (dt, *J* = 3.4, 1.8 Hz, 1H), 4.00 – 3.88 (m, 1H), 3.84 (d, *J* = 1.4 Hz, 3H), 3.78 (ddd, *J* = 13.3, 6.7, 4.7 Hz, 1H), 3.52 (s, 2H), 3.49 – 3.27 (m, 2H), 3.19 (s, 3H), 3.16 – 3.07 (m, 1H), 2.91 (dt, *J* = 11.0, 5.5 Hz, 1H), 2.65 (dt, *J* = 11.2, 5.6 Hz, 1H), 2.58 – 2.44 (m, 4H), 1.84 – 1.76 (m, 1H), 1.66 – 1.56 (m, 1H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 175.2, 166.8, 156.2 (d, *J* = 246.4 Hz, CF), 148.4, 138.1, 134.6, 129.2, 127.5, 125.1, 124.7, 124.0, 123.9, 123.4, 115.8, 115.6, 107.8, 67.1, 63.9, 61.5, 61.5, 50.7, 38.7, 35.8, 33.9, 30.1, 26.5; UPLC/MS purity >86% (CH_3CN: 87%, t_R = 2.19 min, MeOH: 86%, t_R = 3.03 min), $C_{26}H_{30}FN_3O_4$ MW 467.22, $[M+H]^+$ 468.22.

Synthesis of: 

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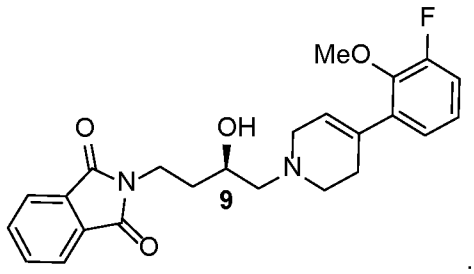
[0406] Compound 559 synthesis according to Scheme 62 is depicted in FIG. 76.

Synthesis of: 

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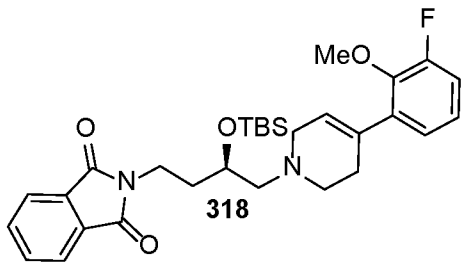
[0407] **(*R*)-2-(4-(4-(3-Fluoro-2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)-3-hydroxybutyl)isoindoline-1,3-dione (Compound 9):** To a solution of (*R*)-2-(2-(oxiran-2-yl)ethyl)isoindoline-1,3-dione (1.00 g, 4.60 mmol) in 2-propanol (10 mL) was added 4-(3-fluoro-2-methoxyphenyl)-1,2,3,6-tetrahydropyridine (0.95 g, 4.60

mmol). The reaction mixture was heated to 80 °C and stirred at the same temperature for 16 hours. The reaction mixture was cooled room temperature and solvent was removed *in vacuo*, and the crude product was purified by flash column chromatography (silica gel, 50-70% EtOAc in hexanes to give (*R*)-2-(4-(4-(3-fluoro-2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)-3-hydroxybutyl)isoindoline-1,3-dione **(Compound 9)** (1.37 g, 70%); ^{1}H NMR (400 MHz, MeOD) δ 7.94 – 7.76 (m, 4H), 7.08 – 6.92 (m, 3H), 5.82 (dt, *J* = 3.5, 1.8 Hz, 1H), 3.96 – 3.75 (m, 6H), 3.23 (dq, *J* = 6.2, 2.9 Hz, 2H), 2.79 (dd, *J* = 5.7, 4.2 Hz, 2H), 2.61 – 2.50 (m, 4H), 1.97 – 1.85 (m, 1H), 1.77 (dtd, *J* = 14.2, 8.1, 6.3 Hz, 1H).

Synthesis of: 

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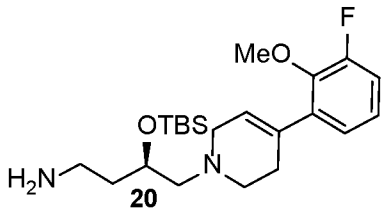
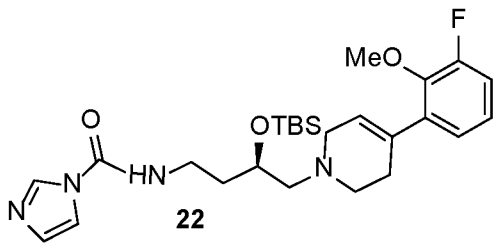
[0408] (*R*)-2-(3-((*tert*-Butyldimethylsilyl)oxy)-4-(4-(3-fluoro-2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)butyl)isoindoline-1,3-dione (Compound 318): To a stirring solution of (*R*)-2-(4-(4-(3-fluoro-2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)-3-hydroxybutyl)isoindoline-1,3-dione (Compound 9) (500 mg, 1.18 mmol) dissolved in DCM (5 mL) was added 2,6-lutidine (0.27 mL, 2.21 mmol). The resulting solution was cooled to 0 ºC and TBSOTf (0.32 mL, 1.40 mmol) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 16 hours till the disappearance of starting material. The organic layer was washed with saturated K_2CO_3 solution and dried over Na_2SO_4. The crude product was purified using flash column chromatography (40-50% EtOAc-hexane) to obtain (*R*)-2-(3-((*tert*-butyldimethylsilyl)oxy)-4-(4-(3-fluoro-2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)butyl)isoindoline-1,3-dione (Compound 318) (420 mg, 66%); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.82 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.03 – 6.90 (m, 3H), 5.80 (dq, *J* = 3.4, 1.7 Hz, 1H), 3.97 (qd, *J* = 6.2, 4.1 Hz, 1H), 3.90 – 3.56 (m, 5H), 3.14 (dq, *J* = 5.8, 3.0 Hz, 2H), 2.70 (h, *J* = 5.5 Hz, 2H), 2.57 – 2.43 (m, *J* = 5.2, 4.6 Hz, 4H), 2.06 – 1.94 (m, 1H), 1.89 – 1.76 (m, 1H), 0.92 (s, 9H), 0.11 (s, 6H).

Synthesis of 

20.

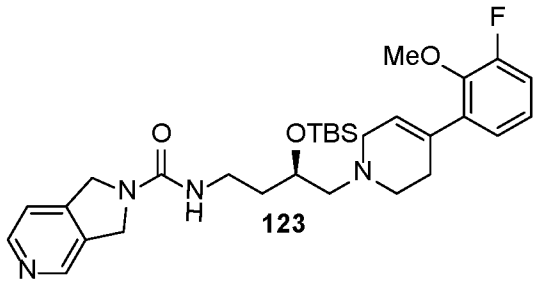
[0409] **(*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-4-(4-(3-fluoro-2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)butan-1-amine (Compound 20):** Anhydrous hydrazine (0.11 mL, 3.70 mmol) was added to a suspension of (*R*)-2-(3-((*tert*-butyldimethylsilyl)oxy)-4-(4-(3-fluoro-2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)butyl)isoindoline-1,3-dione **(Compound 318)** (400 mg, 0.74 mmol) in anhydrous ethanol (5 mL), and the mixture was refluxed overnight under nitrogen atmosphere. Solvents were removed, and the resulting residue was partitioned between DCM and a 20% aqueous K_2CO_3 solution. The layers were separated, and the organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the crude (*R*)-3-((*tert*-butyldimethylsilyl)oxy)-4-(4-(3-fluoro-2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)butan-1-amine **(Compound 20)** (250 mg, 82%), which was used for the next step without further purification.

Synthesis of: 

22.

[0410] (*R*)-*N*-(3-((*tert*-Butyldimethylsilyl)oxy)-4-(4-(3-fluoro-2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)butyl)-1*H*-imidazole-1-carboxamide (Compound 22): To a stirring solution of CDI (104 mg, 0.64 mmol) in DCM (5 mL) was added (*R*)-3-((*tert*-butyldimethylsilyl)oxy)-4-(4-(3-fluoro-2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)butan-1-amine (Compound 20) (250 mg, 0.64 mmol) at 0 ºC. The reaction mixture was warmed to room temperature and stirred for 16 hours. The crude product was purified using flash column chromatography (0-10% MeOH-DCM) to obtain (*R*)-*N*-(3-((*tert*-butyldimethylsilyl)oxy)-4-(4-(3-fluoro-2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)butyl)-1*H*-imidazole-1-carboxamide (Compound 22) (200 mg, 62%); ^{1}H

NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.98 (s, 1H), 8.02 (s, 1H), 7.12 – 6.94 (m, 4H), 5.78 (s, 1H), 4.63 (s, 1H), 3.95 – 3.74 (m, 5H), 3.59 – 3.05 (m, 6H), 2.48 – 2.08 (m, 2H), 2.02 – 1.84 (m, 2H), 0.87 (s, 9H), 0.10 (d, J = 3.3 Hz, 6H).

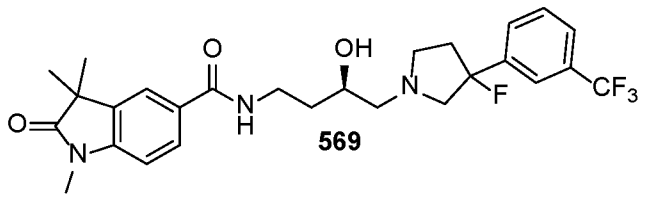
Synthesis of: 

123.

[0411] (*R*)-*N*-(3-((*tert*-Butyldimethylsilyl)oxy)-4-(4-(3-fluoro-2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)butyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridine-6-carboxamide (Compound 123): To a stirring solution of 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine•2HCl salt (55 mg, 0.46 mmol) in 1,4-dioxane (2 mL) was added DIPEA (0.21 mL, 1.21 mmol) and the reaction was stirred for 30 minutes. To this was added (*R*)-*N*-(3-((*tert*-butyldimethylsilyl)oxy)-4-(4-(3-fluoro-2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)butyl)-1*H*-imidazole-1-carboxamide (Compound 22) (120 mg, 0.23 mmol) and the resulting mixture was stirred at 90 ºC for 16 hours. The solvent was removed under reduced pressure to and the crude product was purified using flash column chromatography (0-50% DCM-MeOH) to obtain (*R*)-*N*-(3-((*tert*-butyldimethylsilyl)oxy)-4-(4-(3-fluoro-2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)butyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridine-6-carboxamide (Compound 123) (110 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 5.0 Hz, 1H), 7.64 (d, *J* = 7.3 Hz, 1H), 7.20 (t, *J* = 6.4 Hz, 1H), 7.10 – 6.90 (m, 2H), 6.58 (s, 1H), 5.77 (s, 1H), 4.84 (q, *J* = 14.8 Hz, 4H), 4.61 (s, 1H), 4.19 (t, *J* = 13.8 Hz, 1H), 3.90 (s, 3H), 3.82 – 3.69 (m, 2H), 3.45 – 3.13 (m, 3H), 2.85 – 2.68 (m, 1H), 2.33 – 1.78 (m, 4H), 0.86 (s, 9H), 0.12 (d, *J* = 10.4 Hz, 6H).

[0412] (*R*)-*N*-(4-(4-(3-Fluoro-2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)-3-hydroxybutyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridine-6-carboxamide (Compound 559): To a stirring solution of (*R*)-*N*-(3-((*tert*-butyldimethylsilyl)oxy)-4-(4-(3-fluoro-2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)butyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridine-6-carboxamide (Compound 123) (100 mg, 0.18 mmol) in 1,4-dioxane (2 mL) was added 4M HCl in 1,4-dioxane (0.18 mL, 1 mL/1 mmol) at 0 ºC. The resulting mixture was stirred at room temperature for 2 hours. The solvent was

evaporated, and the crude product was purified using flash column chromatography (0-50% DCM-MeOH & 2% aq. NH_3 added) to afford (*R*)-*N*-(4-(4-(3-fluoro-2-methoxyphenyl)-3,6-dihydropyridin-1(2*H*)-yl)-3-hydroxybutyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridine-6-carboxamide (Compound 559) (50 mg, 63%); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.46 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.60 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.20 (dd, *J* = 7.7, 4.9 Hz, 1H), 7.05 – 6.95 (m, 3H), 5.86 – 5.79 (m, 1H), 5.39 (s, 1H), 4.73 – 4.62 (m, 4H), 4.06 – 3.87 (m, 1H), 3.84 (d, *J* = 1.4 Hz, 3H), 3.61 (dtd, *J* = 13.6, 6.9, 4.8 Hz, 1H), 3.38 – 3.26 (m, 2H), 3.19 – 3.08 (m, 1H), 2.89 (dt, J = 11.1, 5.5 Hz, 1H), 2.66 (dt, *J* = 11.3, 5.6 Hz, 1H), 2.53 (q, *J* = 3.8 Hz, 2H), 2.50 – 2.43 (m, 2H), 1.74 (dddd, *J* = 14.6, 7.5, 4.9, 2.8 Hz, 1H), 1.54 (dddd, *J* = 14.0, 9.1, 7.7, 4.8 Hz, 1H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 158.4, 157.2, 156.4 (d, *J* = 244.0 Hz, 1CF), 149.3, 145.6, 138.1, 134.6, 131.1, 125.2, 124.8, 124.0, 123.9, 122.6, 115.8, 66.7, 64.1, 61.5, 61.5, 54.3, 54.3, 54.1, 53.8, 53.5, 53.3, 52.61, 50.8, 39.1, 34.9, 30.1; UPLC/MS purity >90% (CH_3CN: 90%, t_R = 2.13 min, MeOH: 93%, t_R = 3.06 min), $C_{24}H_{29}FN_4O_3$ MW 440.22, $[M+H]^+$ 441.23.

Synthesis of: 

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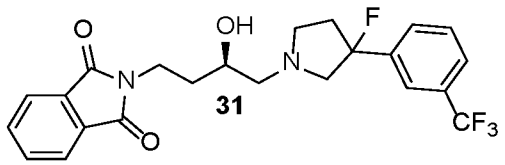
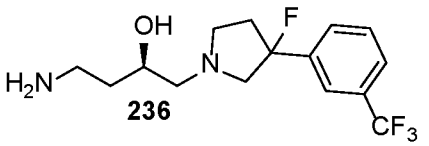
[0413] Compound 569 synthesis according to Scheme 63 is depicted in FIG. 77.

Synthesis of: 

and



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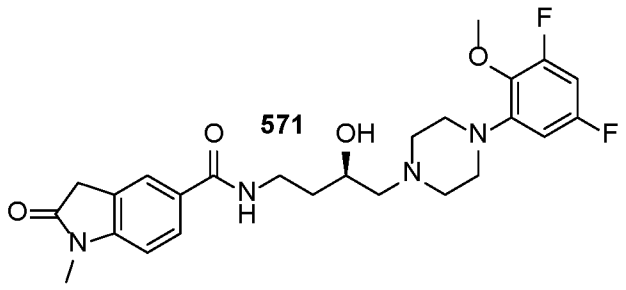
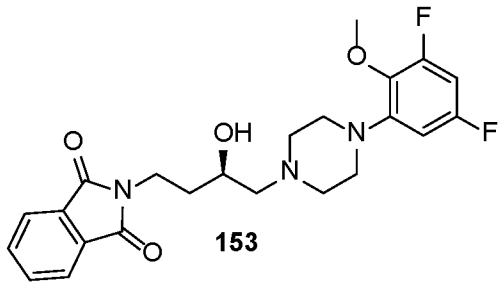
[0414] **(2*R*)-4-Amino-1-(3-fluoro-3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)butan-2-ol (Compound 236):** Anhydrous hydrazine (0.25 mL, 8.01 mmol) was added to a suspension of 2-((3*R*)-4-(3-fluoro-3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)-3-hydroxybutyl)isoindoline-1,3-dione **(Compound 31)** (800 mg, 1.78 mmol) in anhydrous ethanol (10 mL), and the mixture was refluxed overnight under nitrogen

atmosphere. Solvents were removed, and the resulting residue was partitioned between DCM and a 20% aqueous K_2CO_3 solution. The layers were separated, and the organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the crude (2*R*)-4-amino-1-(3-fluoro-3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)butan-2-ol **(Compound 236)** (400 mg, 70%), which was used for the next step without further purification.

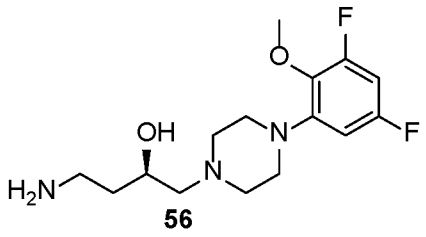
[0415] *N*-((3*R*)-4-(3-Fluoro-3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)-3-hydroxybutyl)-1,3,3-trimethyl-2-oxoindoline-5-carboxamide (Compound 569): In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved 1,3,3-trimethyl-2-oxoindoline-5-carboxylic acid (100 mg, 0.45 mmol), in DCM (5 mL). TEA (0.19 mL, 1.40 mmol) and HATU (200 mg, 0.52 mmol) were added sequentially to the reaction mixture and stirred for 10 minutes at room temperature, and then (2*R*)-4-amino-1-(3-fluoro-3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)butan-2-ol (Compound 236) (146 mg, 0.45 mmol) was added at room temperature. The reaction mixture was stirred overnight, diluted with water (10 mL), and extracted with DCM (3 X 15 mL). The combined organic layers were washed with 20% aqueous K_2CO_3 solution (2 X 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 10-30% MeOH in DCM) to get *N*-((3*R*)-4-(3-fluoro-3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)-3-hydroxybutyl)-1,3,3-trimethyl-2-oxoindoline-5-carboxamide (Compound 569) (45 mg, 18%); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.76 – 7.49 (m, 6H), 7.04 (s, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 5.33 (s, 1H), 3.93 – 3.74 (m, 2H), 3.49 – 3.31 (m, 2H), 3.20 (s, 3H), 3.19 – 3.09 (m, 2H), 2.98 (d, *J* = 9.0 Hz, 1H), 2.82 – 2.63 (m, 2H), 2.54 – 2.31 (m, 2H), 1.88 – 1.78 (m, 1H), 1.62 (dddd, *J* = 14.1, 9.4, 7.2, 4.6 Hz, 1H), 1.35 (s, 6H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 181.5, 167.7, 167.7, 146.1, 136.4, 130.8, 129.5, 128.6 (q, *J* = 73.7 Hz, CF_3), 127.3, 125.1, 123.1, 121.7, 121.6, 121.5, 107.9, 103.0 (d, *J* = 181.8 Hz, CF), 67.9, 67.7, 61.9, 44.3, 40.6, 40.4, 38.0, 34.4, 26.5, 24.4; UPLC/MS purity >94% (CH_3CN: 95%, t_R = 2.71 min, MeOH: 94%, t_R = 3.58 min), $C_{27}H_{31}F_4N_3O_3$ MW 521.23, $[M+H]^+$ 522.23.

Synthesis of:  571 .

[0416] Compound 571 synthesis according to Scheme 64 is depicted in FIG. 78.

Synthesis of:  153 .

[0417] **(*R*)-2-(4-(4-(3,5-Difluoro-2-methoxyphenyl)piperazin-1-yl)-3-hydroxybutyl)isoindoline-1,3-dione (Compound 153):** To a solution of (*R*)-2-(2-(oxiran-2-yl)ethyl)isoindoline-1,3-dione (200 mg, 0.921 mmol) in 2-propanol (5 mL) was added 1-(3,5-difluoro-2-methoxyphenyl)piperazine (210 mg, 0.921 mmol). The reaction mixture was heated at 80 °C and stirred at the same temperature for 16 hours. The reaction mixture was cooled room temperature and solvent was removed *in vacuo*, and the crude product was purified by flash column chromatography (silica gel, 50-70% EtOAc in hexanes to give (*R*)-2-(4-(4-(3,5-difluoro-2-methoxyphenyl)piperazin-1-yl)-3-hydroxybutyl)isoindoline-1,3-dione **(Compound 153)** (280 mg, 68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.72 (dd, *J* = 5.4, 3.0 Hz, 2H), 6.47 (ddd, *J* = 10.9, 8.3, 3.0 Hz, 1H), 6.37 (ddd, *J* = 10.7, 3.0, 1.9 Hz, 1H), 3.97 – 3.77 (m, 6H), 3.59 (d, *J* = 43.0 Hz, 1H), 3.13 (s, 4H), 2.81 (s, 2H), 2.60 (s, 2H), 2.43 (d, *J* = 12.4 Hz, 2H), 1.79 (q, *J* = 6.7 Hz, 2H).

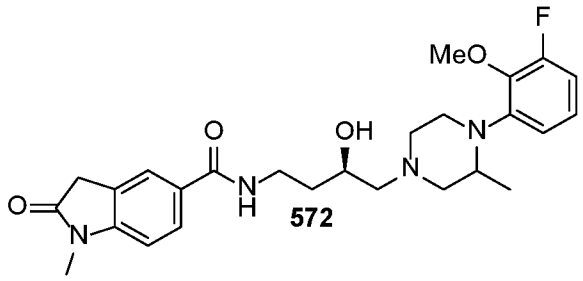
Synthesis of:  .

56

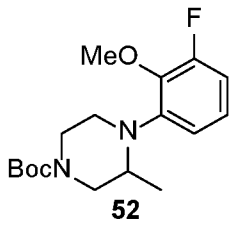
[0418] (*R*)-4-Amino-1-(4-(3,5-difluoro-2-methoxyphenyl)piperazin-1-yl)butan-2-ol (Compound 56): Anhydrous hydrazine (0.13 mL, 4.0 mmol) was added to a suspension of (*R*)-2-(4-(4-(3,5-difluoro-2-methoxyphenyl)piperazin-1-yl)-3-hydroxybutyl)isoindoline-1,3-dione **(Compound 153)** (250 mg, 0.561 mmol) in anhydrous ethanol (3 mL), and the mixture was refluxed overnight under nitrogen atmosphere. Solvents were removed, and the resulting residue was partitioned between DCM and a 20% aqueous K_2CO_3 solution. The layers were separated, and the organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the crude (*R*)-4-amino-1-(4-(3,5-difluoro-2-methoxyphenyl)piperazin-1-yl)butan-2-ol **(Compound 56)** (125 mg, 71%), which was used for the next step without further purification.

[0419] (*R*)-*N*-(4-(4-(3,5-Difluoro-2-methoxyphenyl)piperazin-1-yl)-3-hydroxybutyl)-1-methyl-2-oxoindoline-5-carboxamide (Compound 571): In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved 1-methyl-2-oxoindoline-5-carboxylic acid (61 mg, 0.317 mmol), in DCM (3 mL). TEA (0.13 mL, 0.954 mmol) and HATU (144 mg, 0.42 mmol) were added sequentially to the reaction mixture and stirred for 10 minutes at room temperature, and then (*R*)-4-amino-1-(4-(3,5-difluoro-2-methoxyphenyl)piperazin-1-yl)butan-2-ol **(Compound 56)** (100 mg, 0.317 mmol) was added at room temperature. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 X 10 mL). The combined organic layers were washed with 20% aqueous K_2CO_3 solution (2 X 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 10-30% MeOH in DCM) to get (*R*)-*N*-(4-(4-(3,5-difluoro-2-methoxyphenyl)piperazin-1-yl)-3-hydroxybutyl)-1-methyl-2-oxoindoline-5-carboxamide **(Compound 571)** (68 mg, 44%); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.73 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.66 (d, *J* = 1.8 Hz, 1H), 7.13 (s, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.56 – 6.46 (m, 1H), 6.41 (dt, *J* = 10.8, 2.3 Hz, 1H), 3.96 (td,

J = 9.6, 4.8 Hz, 1H), 3.82 (s, 4H), 3.50 (s, 2H), 3.44 – 3.35 (m, 1H), 3.24 – 3.18 (m, 7H), 2.99 (d, *J* = 5.0 Hz, 2H), 2.82 (s, 2H), 2.69 – 2.56 (m, 2H), 1.81 (dddd, *J* = 14.8, 7.5, 4.7, 2.7 Hz, 1H), 1.59 (dddd, *J* = 14.0, 9.3, 7.4, 4.6 Hz, 1H). ^{13}C NMR (101 MHz, CD_2Cl_2) δ 175.2, 167.1, 159.8, 157.9, 157.5, 157.4, 155.6, 148.5, 147.4, 137.2, 137.1, 129.0, 127.6, 125.1, 123.4, 107.8, 101.4, 101.2, 101.2, 98.0, 97.7, 97.5, 66.6, 64.0, 60.4, 60.4, 54.2, 50.4, 50.4, 48.0, 38.5, 35.8, 33.9, 26.5. UPLC/MS purity >95% (CH_3CN: 99%, t_R = 4.49 min, MeOH: 97%, t_R = 3.27 min), $C_{25}H_{30}F_2N_4O_4$ MW 488.22, $[M+H]^+$ 489.23.

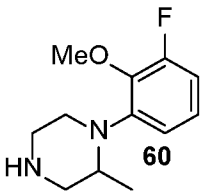
Synthesis of:  **572** .

[0420] Compound 572 synthesis according to Scheme 65 is depicted in FIG. 79.

Synthesis of:  **52** .

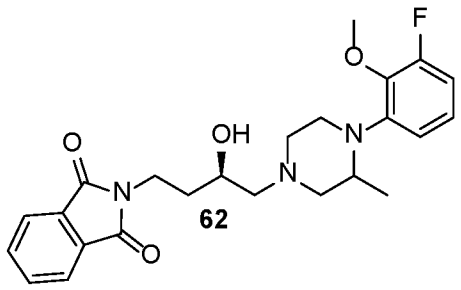
[0421] ***tert*-Butyl 4-(3-fluoro-2-methoxyphenyl)-3-methylpiperazine-1-carboxylate (Compound 52):** 1-bromo-3-fluoro-2-methoxybenzene (500 mg, 2.44 mmol) was weighed in a 50 mL two neck round-bottomed flask which was equipped with reflux condenser, stirring bar and a rubber septa. The flask was purged with nitrogen for five minutes. *tert*-butyl 3-methylpiperazine-1-carboxylate (489 mg, 2.44 mmol), tris(dibenzylideneacetone)dipalladium(0) (120 mg, 0.13 mmol), (±)-BINAP (227 mg, 0.36 mmol), sodium *tert*-butoxide (NaO^tBu) (376 mg, 3.91 mmol) were added quickly through side neck under positive nitrogen. Anhydrous toluene (20 mL, degassed for 10 minutes) was added to the flask *via* syringe. The resulting reaction mixture was degassed and back filled with nitrogen. This cycle was repeated three times. Then the reaction was heated to 100 °C while stirring for 24 hours under nitrogen atmosphere. The reaction mixture was cooled to room temperature, filtered

through pad of Celite, and washed with ethyl acetate (3 X 20 mL). Water (30 ml) was added to filtrate and then organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 X 20 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The resulting residue was purified using flash column chromatography (silica gel, hexanes/ethyl acetate, 100:00 to 90:10) to provide *tert*-butyl 4-(3-fluoro-2-methoxyphenyl)-3-methylpiperazine-1-carboxylate **(Compound 52)** (200 mg, 25%); ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (td, *J* = 8.1, 5.9 Hz, 1H), 6.87 – 6.77 (m, 1H), 6.68 (t, *J* = 8.0 Hz, 1H), 3.91 (s, 3H), 3.64 – 3.13 (m, 6H), 2.81 (s, 1H), 1.49 (s, 9H),0.93 (d, *J* = 2.8 Hz, 3H).

Synthesis of: 

60 .

[0422] 1-(3-Fluoro-2-methoxyphenyl)-2-methylpiperazine (Compound 60): *tert*-butyl 4-(3-fluoro-2-methoxyphenyl)-3-methylpiperazine-1-carboxylate **(Compound 52)** (200 g, 0.61 mmol) was dissolved in DCM (3 mL) and cooled to 0 °C. TFA (0.61 mL, 1 mL/mmol) was added and stirred for 4 hours at room temperature. The solvent was removed *in vacuo* and the resulting residue was dissolved in water and washed with EtOAc (2 X 20 mL) to remove organic impurities. The aqueous layer was neutralized with aqueous K_2CO_3 (20%), and extracted with DCM (3 X 20 mL). The organic phase was dried over sodium sulfate, filtered and the solvent was removed under reduced pressure to get 1-(3-fluoro-2-methoxyphenyl)-2-methylpiperazine **(Compound 60)** (100 mg, 72%) which was used for the next step without further purification.

Synthesis of: 

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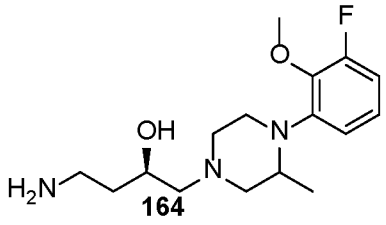
[0423] 2-((3*R*)-4-(4-(3-Fluoro-2-methoxyphenyl)-3-methylpiperazin-1-yl)-3-hydroxybutyl)isoindoline-1,3-dione (Compound 62): To a solution of (*R*)-2-(2-(oxiran-2-yl)ethyl)isoindoline-1,3-dione (97 mg, 0.44 mmol) in 2-propanol (2 mL) was added 1-(3-fluoro-2-methoxyphenyl)-2-methylpiperazine **(Compound 60)** (100 mg, 0.44 mmol). The reaction mixture was heated at 80 °C and stirred at the same temperature for 16 hours. The reaction mixture was cooled room temperature and solvent was removed *in vacuo*, and the crude product was purified by flash column chromatography (silica gel, 50-70% EtOAc in hexanes to give 2-((3*R*)-4-(4-(3-fluoro-2-methoxyphenyl)-3-methylpiperazin-1-yl)-3-hydroxybutyl)isoindoline-1,3-dione **(Compound 62)** (145 mg, 73%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.0 Hz, 2H), 6.92 (td, *J* = 8.2, 6.0 Hz, 1H), 6.83 – 6.68 (m, 2H), 3.90 (s, 3H), 3.89 – 3.71 (m, 3H), 3.63 (s, 2H), 3.32 – 3.19 (m, 1H), 2.94 – 2.63 (m, 3H), 2.57 – 2.48 (m, 1H), 2.43 – 2.29 (m, 2H), 1.79 (q, *J* = 6.7 Hz, 2H), 0.95 (d, *J* = 6.4 Hz, 3H).

Synthesis of: 

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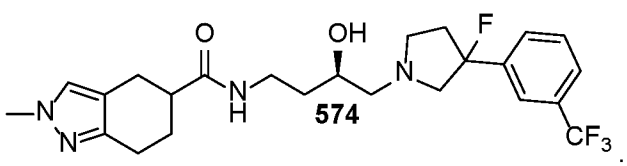
[0424] (2*R*)-4-Amino-1-(4-(3-fluoro-2-methoxyphenyl)-3-methylpiperazin-1-yl)butan-2-ol (Compound 164): Anhydrous hydrazine (0.04 mL, 1.33 mmol) was added to a suspension of 2-((3*R*)-4-(4-(3-fluoro-2-methoxyphenyl)-3-methylpiperazin-1-yl)-3-hydroxybutyl)isoindoline-1,3-dione **(Compound 62)** (140 mg, 0.31 mmol) in anhydrous ethanol (10 mL), and the mixture was refluxed overnight under nitrogen atmosphere. Solvents were removed, and the resulting residue was partitioned between DCM and a 20% aqueous K_2CO_3 solution. The layers were separated, and the organic layer was washed with water and brine. The organic

layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the crude (2*R*)-4-amino-1-(4-(3-fluoro-2-methoxyphenyl)-3-methylpiperazin-1-yl)butan-2-ol **(Compound 164)** (84 mg, 85%), which was used for the next step without further purification.

[0425] *N*-((3*R*)-4-(4-(3-Fluoro-2-methoxyphenyl)-3-methylpiperazin-1-yl)-3-hydroxybutyl)-1-methyl-2-oxoindoline-5-carboxamide (Compound 572): In a 10 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved 1-methyl-2-oxoindoline-5-carboxylic acid (37 mg, 0.19 mmol), in DCM (2 mL). TEA (0.10 mL, 0.70 mmol) and HATU (100 mg, 0.263 mmol) were added sequentially to the reaction mixture and stirred for 10 minutes at room temperature, and then (2*R*)-4-amino-1-(4-(3-fluoro-2-methoxyphenyl)-3-methylpiperazin-1-yl)butan-2-ol (Compound 164) (60 mg, 0.19 mmol) was added at room temperature. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 X 10 mL). The combined organic layers were washed with 20% aqueous K_2CO_3 solution (2 X 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 10-30% MeOH in DCM) to get *N*-((3*R*)-4-(4-(3-fluoro-2-methoxyphenyl)-3-methylpiperazin-1-yl)-3-hydroxybutyl)-1-methyl-2-oxoindoline-5-carboxamide (Compound 572) (25 mg, 27%); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.74 (d, *J* = 8.2 Hz, 1H), 7.67 (s, 1H), 7.19 (s, 1H), 6.95 (q, *J* = 7.6 Hz, 1H), 6.89 – 6.68 (m, 3H), 3.93 (d, *J* = 8.4 Hz, 1H), 3.88 (s, 3H), 3.82 – 3.57 (m, 2H), 3.49 (s, 2H), 3.46 – 3.36 (m, 1H), 3.26 (d, *J* = 15.9 Hz, 1H), 3.18 (s, 3H), 3.00 – 2.79 (m, 3H), 2.72 – 2.30 (m, 4H), 1.87 – 1.73 (m, 1H), 1.59 (d, *J* = 8.4 Hz, 1H), 0.97 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 175.3, 167.4, 158.1, 155.7, 148.5, 145.5, 128.9, 127.6, 125.1, 123.6, 123.6, 123.4, 118.4, 111.7, 107.9, 66.4, 66.2, 64.0, 63.9, 60.8, 60.2, 52.1, 52.0, 38.3, 35.8, 34.1, 34.0, 31.0, 26.5; UPLC/MS purity >95% (CH_3CN: 96%, t_R = 2.30 min, MeOH: 95%, t_R = 3.08 min), $C_{26}H_{33}FN_4O_4$ MW 484.24, $[M+H]^+$ 485.25.

Synthesis of: 

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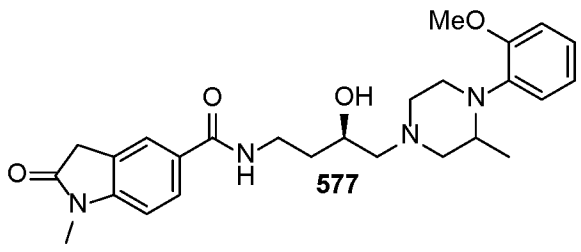
[0426] Compound 574 synthesis according to Scheme 66 is depicted in FIG. 80.

[0427] *N*-((3*R*)-4-(3-Fluoro-3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)-3-hydroxybutyl)-2-methyl-4,5,6,7-tetrahydro-2*H*-indazole-5-carboxamide (Compound 574): In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved 2-methyl-4,5,6,7-tetrahydro-2*H*-indazole-5-carboxylic acid (112 mg, 0.62 mmol), in DCM (5 mL). TEA (0.26 mL, 1.89 mmol) and HATU (250 mg, 0.65 mmol) were added sequentially to the reaction mixture and stirred for 10 minutes at room temperature, and then (2*R*)-4-amino-1-(3-fluoro-3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)butan-2-ol (Compound 236) (200 mg, 0.62 mmol) was added at room temperature. The reaction mixture was stirred overnight, diluted with water (10 mL), and extracted with DCM (3 X 15 mL). The combined organic layers were washed with 20% aqueous K_2CO_3 solution (2 X 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 10-40% MeOH in DCM) to get *N*-((3*R*)-4-(3-fluoro-3-(3-(trifluoromethyl)phenyl)pyrrolidin-1-yl)-3-hydroxybutyl)-2-methyl-4,5,6,7-tetrahydro-2*H*-indazole-5-carboxamide (Compound 574) (60 mg, 20%); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.70 (s, 1H), 7.66 – 7.49 (m, 3H), 7.07 (s, 1H), 6.34 (s, 1H), 3.76 (s, 3H), 3.75 – 3.66 (m, 1H), 3.65 – 3.53 (m, 1H), 3.33 – 2.91 (m, 5H), 2.89 – 2.25 (m, 10H), 2.16 – 2.03 (m, 1H), 1.84 (ddt, *J* = 11.3, 5.6, 2.1 Hz, 1H), 1.70 (dtd, *J* = 13.3, 5.2, 2.6 Hz, 1H), 1.56 – 1.45 (m, 1H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 175.6, 147.9, 143.8, 130.8 (q, *J* = 63.7 Hz, CF_3), 129.4, 128.3, 127.4, 125.9, 124.9, 121.5, 114.6, 103.1 (d, *J* = 181.8 Hz, CF), 67.8, 67.7, 61.9, 42.9, 41.1, 40.9, 38.8, 37.3, 34.5, 27.6, 24.2, 22.9; UPLC/MS purity >95% (CH_3CN: 95%, t_R = 2.54 min, MeOH: 97%, t_R = 3.61 min), $C_{24}H_{30}F_4N_4O_2$ MW 482.23, $[M+H]^+$ 483.23.

Synthesis of: 

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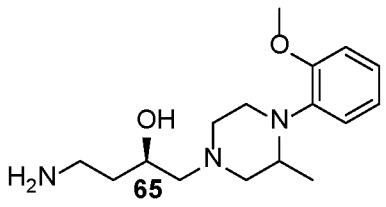
[0428] Compound 577 synthesis according to Scheme 67 is depicted in FIG. 81.

Synthesis of:  .

[0429] ***N*-((3*R*)-3-Hydroxy-4-(4-(2-methoxyphenyl)-3-methylpiperazin-1-yl)butyl)-1-methyl-2-oxoindoline-5-carboxamide (Compound 577):** In a 25 mL round-bottomed flask or a screw capped vial equipped with a magnetic stir bar was dissolved 1-methyl-2-oxoindoline-5-carboxylic acid (72 mg, 0.37 mmol), in DCM (2 mL). TEA (0.15 mL, 1.12 mmol) and HATU (160 mg, 0.42 mmol) were added sequentially to the reaction mixture and stirred for 10 minutes at room temperature, and then (2*R*)-4-amino-1-(4-(2-methoxyphenyl)-3-methylpiperazin-1-yl)butan-2-ol **(Compound 65)** (110 mg, 0.37 mmol) was added at room temperature. The reaction mixture was stirred overnight, diluted with water (5 mL), and extracted with DCM (3 X 10 mL). The combined organic layers were washed with 20% aqueous K_2CO_3 solution (2 X 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to get crude residue. The residue was purified by flash column chromatography (silica gel, 10-30% MeOH in DCM) to get *N*-((3*R*)-3-hydroxy-4-(4-(2-methoxyphenyl)-3-methylpiperazin-1-yl)butyl)-1-methyl-2-oxoindoline-5-carboxamide **(Compound 577)** (65 mg, 37%); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.75 (dt, *J* = 8.2, 1.6 Hz, 1H), 7.69 (t, *J* = 1.5 Hz, 1H), 7.25 (d, *J* = 6.5 Hz, 1H), 7.09 – 6.94 (m, 2H), 6.94 – 6.80 (m, 3H), 3.96 – 3.84 (m, 1H), 3.82 (s, 4H), 3.52 (s, 3H), 3.47 – 3.33 (m, 1H), 3.19 (s, 4H), 2.98 – 2.55 (m, 4H), 2.54 – 2.19 (m, 4H), 1.78 (q, *J* = 6.8 Hz, 1H), 1.59 (ddt, *J* = 13.8, 9.1, 4.4 Hz, 1H), 0.91 (dd, *J* = 6.3, 2.6 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 175.2, 166.8, 154.8, 148.4, 140.1, 129.3, 127.5, 125.1, 124.4, 124.3, 123.4, 121.0, 112.2, 107.8, 66.9, 66.8, 64.2, 64.2, 60.1, 55.7, 52.1, 38.8, 35.8, 33.8, 33.8, 26.5. UPLC/MS purity >95% (CH_3CN: 98%, t_R = 2.06 min, MeOH: 95%, t_R = 2.88 min), $C_{26}H_{34}N_4O_4$ MW 466.25, $[M+H]^+$ 467.26.

EXAMPLES

[0430] The D_3R modulators disclosed demonstrate superior pharmacological properties. For example, compound 561 has an hERG IC_{50}> 30 μM, optimal 143-fold D_3 relative to D_2 receptor selectivity (D_2/D_3 receptor selectivity), and acceptable plasma and brain PK profile (36% bioavailability and AUC_b/AUC_p =0.6). Compound

561 has good DMPK properties with optimal brain exposure, and is efficacious in a rat model of oxycodone addiction. These newly developed D3 selective chemotypes were able to display a better hERG liability window, which was seen as a challenge in the past by many researchers including the leading pharmaceutical companies.

[0431] Medicinal chemical endpoints can include, for example, D_3/D_2 receptor binding selectivity (K_i >100 fold), D_3/D_2 receptor cell-based beta-arrestin activity (>25 fold), cAMP (>10 fold) mediated response, hERG liability window, solubility, passive permeability, high PAMPA-BBB permeability, high MDCK-MDR1 permeability, low P-glycoprotein (Pgp) efflux, higher unbound free fraction in (rat) brain homogenate, and free drug in the brain – 5 to 10-fold over D_3 receptor K_i. Pharmacological endpoints can include, for example, measurement of dose dependent response in oxycodone self-administration model- fixed ratio (FR) and progressive ratio (PR) schedules, and measurement of dose dependent response in an oxycodone relapse model.

[0432] Binding assays were performed and can be performed using the protocols set forth in Gogarnoiu et al., J. Med. Chem. 66:1809-1834 (2023). Beta-arrestin assays for antagonists and agonists were performed and can be performed as follows. F12K medium (30-2004) was purchased from ATCC (Gaithersburg, MD), Hyclone FBS (Cat #SH30071.03) was purchased from GE Healthcare (Logan, UT). The following items were purchased from ThermoFisher (Waltham, MA): G418 sulfate (Cat #10131), Hygromycin (Cat #10687010), TrypLE Express (Cat #12605), Opti-MEM Reduce Serum Medium (Cat #31985088), and DPBS with calcium and magnesium (Cat #14040). Dopamine hydrochloride (Cat #3548) was purchased from Tocris Bioscience (Bristol, United Kingdom). Pathhunter bioassay detection kit (Cat #93-001) was purchased from Eurofins DiscoverX. 384-well, white, tissue culture treated microplate (Cat #781073) and 384-well polypropylene microplate (Cat #781201) were purchased from Greiner Bio-One.

[0433] beta-arrestin recruitment assays for DRD3 and DRD2: The PathHunter beta-arrestin recruitment assay (DiscoverX) was performed as previously described (Furman et al, Eur Neuropsychopharmacol. 2015 Sep;25(9):1448-61).

[0434] DRD3 beta-arrestin -coupled antagonist assay: CHO-K1 cells expressing the D3 dopamine receptor (CHOK1-DRD3) (Cat #93-0591C2, DiscoverX) were cultured in growth media (F12, 10% FBS, 0.8 mg/mL G418, 0.3 mg/ml hygromycin, 1x Pen/Strep). Cells were harvested with TrypLE Express at 80-90% confluence and

resuspended in assay media (Opti-MEM, 1% FBS, 1x Pen/Strep) at a density of 400,000 cells/mL. Then, 20 µL of cells (8,000 cells/well) were dispensed into 384-well white, solid-bottom, tissue culture treated plates using a Multidrop Combi dispenser (ThermoFisher, Waltham, MA). The assay plates were incubated at 37ºC and 5% CO_2 overnight to allow cell attachment. Compounds were titrated in DMSO and dispensed via pin transfer at 46 nL/well with an Automated Pintool Workstation (Wako Automation, San Diego, CA). Then, 5 µL/well of DPBS with calcium and magnesium containing 100 nM of dopamine (20 nM final concentration) was dispensed with a Multidrop Combi dispenser. The assay plates were incubated for 90 minutes at room temperature before 12.5 uL/well of PathHunter Detection Kit (Cat #93-001, DiscoverX). The assay plates were incubated for 60 minutes at room temperature, then luminescence signal was read on a PHERAstar FSX plate reader (BMG Labtech, Cary, NC). Data were normalized with 20 nM dopamine treated wells as 0% activity, and no dopamine treatment as -100% activity.

[0435] DRD3 beta-arrestin-coupled agonist assay: CHO-K1 cells expressing the D3 dopamine receptor (CHOK1-DRD3) (Cat #93-0591C2, DiscoverX) were cultured in growth media (F12, 10% FBS, 0.8 mg/ml G418, 0.3 mg/mL hygromycin, 1x Pen/Strep). Cells were harvested with TrypLE Express at 80-90% confluence and resuspended in assay media (Opti-MEM, 1% FBS, 1x Pen/Strep) at a density of 400,000 cells/mL. Then, 20 µL of cells (8,000 cells/well) were dispensed into 384-well white, solid-bottom, tissue culture treated plates using a Multidrop Combi dispenser (ThermoFisher, Waltham, MA). The assay plates were incubated at 37 ºC and 5% CO_2 overnight to allow cell attachment. Compounds were titrated in DMSO and dispensed via pin transfer at 46 nL/well with an Automated Pintool Workstation (Wako Automation, San Diego, CA). The assay plates were incubated for 90 minutes at room temperature before 12.5 µL/well of PathHunter Detection Kit (Cat #93-001, DiscoverX). The assay plates were incubated for 60 minutes at room temperature, then luminescence signal was read on a PHERAstar FSX plate reader (BMG Labtech, Cary, NC). Data were normalized with 1 uM dopamine treated wells as 100% activity, and no dopamine treatment as 0% activity.

[0436] DRD2 beta-arrestin-coupled antagonist assay: CHO-K1 cells expressing the D2 dopamine receptor long isoform (CHOK1-DRD2L) (Cat #93-0579C2, DiscoverX) were cultured in growth media (F12, 10% FBS, 0.8 mg/mL G418, 0.3 mg/mL

hygromycin, 1x Pen/Strep). Cells were harvested with TrypLE Express at 80-90% confluence and resuspended in assay media (Opti-MEM, 1% FBS, 1x Pen/Strep) at a density of 400,000 cells/mL. Then, 20 µL of cells (8,000 cells/well) were dispensed into 384-well white, solid-bottom, tissue culture treated plates using a Multidrop Combi dispenser (ThermoFisher, Waltham, MA). The assay plates were incubated at 37 ºC and 5% CO_2 overnight to allow cell attachment. Compounds were titrated in DMSO and dispensed via pin transfer at 46 nL/well with an Automated Pintool Workstation (Wako Automation, San Diego, CA). Then, 5 µL/well of DPBS with calcium and magnesium containing 2 µM of dopamine (400 nM final concentration) was dispensed with a Multidrop Combi dispenser. The assay plates were incubated for 90 minutes at room temperature before 12.5 µL/well of PathHunter Detection Kit (Cat #93-001, DiscoverX). The assay plates were incubated for 60 minutes at room temperature, then luminescence signal was read on a PHERAstar FSX plate reader (BMG Labtech, Cary, NC). Data were normalized with 400 nM dopamine treated wells as 0% activity, and no dopamine treatment as 100% activity.

[0437] DRD2 beta-arrestin-coupled agonist assay: CHO-K1 cells expressing the D2 dopamine receptor long isoform (CHOK1-DRD2L) (Cat #93-0579C2, DiscoverX) were cultured in growth media (F12, 10% FBS, 0.8 mg/mL G418, 0.3 mg/mL hygromycin, 1x Pen/Strep). Cells were harvested with TrypLE Express at 80-90% confluence and resuspended in assay media (Opti-MEM, 1% FBS, 1x Pen/Strep) at a density of 400,000 cells/mL. Then, 20 µL of cells (8,000 cells/well) were dispensed into 384-well white, solid-bottom, tissue culture treated plates using a Multidrop Combi dispenser (ThermoFisher, Waltham, MA). The assay plates were incubated at 37 ºC and 5% CO_2 overnight to allow cell attachment. Compounds were titrated in DMSO and dispensed via pin transfer at 46 nL/well with an Automated Pintool Workstation (Wako Automation, San Diego, CA). The assay plates were incubated for 90 minutes at room temperature before addition of 12.5 µL/well of PathHunter Detection Kit (Cat #93-001, DiscoverX). The assay plates were incubated for 90 minutes at room temperature, then luminescence signal was read on a PHERAstar FSX plate reader (BMG Labtech, Cary, NC). Data were normalized with 1 µM dopamine treated wells as 100% activity, and no dopamine treatment as 0% activity.

EXAMPLE 1

[0438] Parameters were determined for various disclosed compounds as set forth in Tables 1-4.

TABLE 1

	CMP 561	CMP 511	CMP 520	CMP 539	CMP 532	CMP 533
TPSA	82.4	82.4	86.5	83.3	83.3	67.07
CLogP	0.57	0.52	0.99	1.54	1.36	1.38
CLogD	0.34	0.29	0.66	0.21	0.68	0.82
Hydrogen bond donor (HBD)	3	3	3	3	3	2
pKa	7.55	7.54	7.54	8.74	8.1	7.93
CNS Score	4.43	4.53	4.59	4.23	4.56	5.13

TABLE 2

Parameter	CMP 561	CMP 511	CMP 520	CMP 539	CMP 532	CMP 533
Binding- D_3R Ki (nM)	18.2	24.4	5.8	4	8.2	1.8
Binding- D_2R Ki (nM)	2620	1620	733	614	1870	258
D_2/D_3	143	66	126	136	228	143
Beta-arrestin Assay: D_3R IC_{50} (nM); D_2/D_3	31; 56	64; 38	12.4; 63	12; 45	11; 45	6; 35

cAMP Assay: D3R IC_{50} (nM); D_2/D_3	17; 22	85; 5	21; 6	30; 9	24; 12	4; 6

TABLE 3:

Parameter	CMP 561	CMP 511	CMP 520	CMP 539	CMP 532	CMP 533
HLM ($t_{1/2}$) (min)	91	>120	112.8	>120	>120	>120
MLM ($t_{1/2}$) (min)	>120	119	111	>120	82	>120
RLM ($t_{1/2}$) (min)	>120	>120	>120	>120	55	>120
Solubility (µg/mL)	30.8	>63	>45	>45	>44	>41
PAMPA (10^{-6} cm/sec)	241.7	88.3	186.8	289	118	ND
PAMPA-BBB (10^{-6} cm/sec)	5.5	5.4	12	15	12	3.4
PPB-Fu (%)-Mouse	18.5	42	31	20.9	19.7	34.8
Rat Brain Homogenate -Fu (%)	26.5	78.1	36.5	19.3	25.3	49.5
hERG (IC_{50}) (µM)	>30	20% at 10 µM	>30	20.2	9	20.3

HLM- Human Liver Microsomal Stability; RLM- Rat Liver Microsomal Stability; MLM- Mouse Liver microsomal Stability; PAMPA- Parallel Artificial Membrane Permeability Assay; BBB- Blood Brain Barrier; PPB- Plasma Protein Binding; Fu- Unbound Fraction; hERG-human Ether-a-go-go Related Gene

[0439] Pharmacokinetic data obtained for hERG toxicity, IC_{50} (µM), relative to plasma C_{max} (µM) which were the therapeutic "fold" windows between the efficacious

concentration of a particular compound and the IC_{50} concentration. These results (Table 4) show very favorable therapeutic windows for several compounds—demonstrating that efficacious compounds with relatively low toxicity can be achieved with the compounds of the present disclosure.

TABLE 4

	CMP 561	CMP 511	CMP 520	CMP 539	CMP 532	CMP 533
Plasma C_{max} (μg/mL), 30 mpk PO	524	1853	1283	348	321	1337
Plasma C_{max} (μM), 30 mpk PO	1.19	4.35	2.83	0.77	0.71	3.24
hERG IC_{50} (μM)	>30	20% @ 10uM	>30	20.2	9	20.3
Fold Window	>30		>10	26	12.6	7

EXAMPLE 2

[0440] Additional data obtained are as follows.

TABLE 5 (Compound 561)

D_3 Ki (nM)	18
Binding Selectivity (D2/D3)	143
Aq. Solubility (μg/mL)	31
PPB-Fu (%)-Mouse	18
CNS MPO Score	4.4
hERG (IC_{50}) (μM)	>30

TABLE 6 (Compound 561)

$C_{max,b,u}$ (nM)	143.3
$C_{max,b,u}$ – Fold over D_3 K_i	8

$K_{p,u,u}$	0.8

[0441] Data for Compound 561 are also set forth in graphs depicted in FIGS. 82 and 83.

EXAMPLE 3

[0442] Pharmacokinetic data were also obtained for various disclosed compounds as depicted in FIGS. 84-95: Compound 511 (FIGS. 84 and 85), Compound 504 (FIGS. 86 and 87), Compound 520 (FIGS. 88 and 89), Compound 536 (FIGS. 90 and 91), Compound 507 (FIGS. 92 and 93), Compound 566 (FIG. 94), and Compound 533 (FIG. 95).

[0443] The present disclosure can include any combination of these various features or embodiments above and/or below as set forth in sentences and/or paragraphs. Any combination of disclosed features herein is considered part of the present disclosure. Further, when an amount, concentration, or other value or parameter is given as either a range, or a list of upper values and lower values, all ranges formed from any pair of any upper range limit or value and any lower range limit or value are also disclosed, regardless of whether ranges are separately disclosed. Where a range of numerical values is recited herein, unless otherwise stated, the range is intended to include the endpoints thereof, and all subranges, integers, and fractions within the range. The scope of the disclosure is not limited to the specific values recited in a range. All references cited in this specification are herein incorporated in their entireties by reference as though each reference was specifically and individually indicated to be incorporated by reference. Each of the elements described herein, or two or more together, are also within the scope of the present disclosure.

[0444] Additional data obtained are as follows

Table 7. In vitro pharmacology assays. In Column 1, “+” represents IC50 >500nM, “++” represents 100nM ≤ IC50 ≤ 500nM, and “+++” represents IC50 < 100nM; In Column 2, “+” represents D2/D3 < 20, “++” represents 20 ≤ D2/D3 ≤ 40, and “+++” represents D2/D3 > 40; and In Column 3, “+” represents Ki < 50, “++” represents 50 ≤ Ki ≤ 100, and “+++” represents Ki > 100

	Column 1	Column 2	Column 3
Compound ID	Beta-Arrestin Assay, D3, IC50 (nM)	Beta-Arrestin Assay, D2/D3	Binding Affinity Ki D2/D3
501	+++	+	+
502	+++	++	ND
503	+++	+	+
504	++	++	ND
505	+++	+	ND
506	+++	+	ND
507	+++	+++	++
508	++	+	+
509	+++	+	ND
510	+	++	ND
511	++	++	++
512	++	+	ND
513	+	+	ND
514	+++	++	+++
515	++	+	ND
516	++	+	ND
517	++	+	ND
518	+++	+++	ND
519	++	+	ND
520	+++	+++	+++
521	+++	++	++
522	+++	+	ND
523	+	+	ND

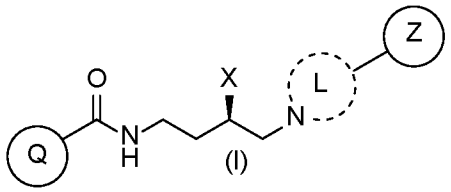
524	+++	+++	+++
525	+++	++	ND
526	+++	+++	+++
527	+++	+++	+++
528	++	++	ND
529	+++	++	+++
530	+++	+++	ND
531	+++	+++	+
532	++	+++	+++
533	+++	++	+++
534	+++	++	+++
535	+++	+	++
536	+++	++	+++
537	++	+	ND
538	+++	+++	++
539	+++	+++	+++
540	+++	++	+++
541	+++	+++	+++
542	+++	+	++
543	+++	+++	+++
544	++	+++	+
555	+++	++	++
556	+++	++	+++
557	+++	+++	+++
558	+++	+++	ND
559	++	++	ND
560	+++	+++	++
561	+++	+++	+++
562	+++	++	++
563	+++	++	+++
564	++	++	ND
565	+++	+++	ND

566	++	+++	+++
567	+++	++	+++
568	+++	++	++
569	+++	+	ND
570	+++	++	ND
571	+++	++	ND
572	+++	+++	ND
573	+++	++	ND
574	++	++	+++
575	++	+++	ND
576	+++	+++	+++
577	+++	+++	+++

CLAIMS

What is claimed is:

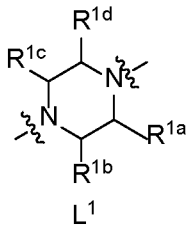
1. A compound having Formula (I), its enantiomer, a racemate thereof, a prodrug thereof, a salt thereof, or any combination thereof:

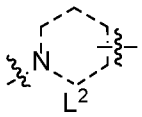


;

wherein Q is a first chemical moiety covalently bound through an amide bond to a n-butyl linker; X is a hydrogen, a hydroxyl, or a methyl group substituent of the n-butyl linker; L is a tertiary amine heterocyclic linker covalently bound to the n-butyl linker through the nitrogen of the tertiary amine; and Z is a second chemical moiety covalently bound to the tertiary amine heterocyclic linker;

wherein Q excludes indole, wherein Z comprises a substituted aryl;

wherein L comprises 

L^1 ,or 

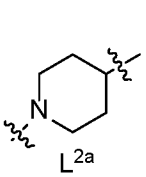
L^2 and R^{1a}, R^{1b}, R^{1c}, and R^{1d} are independently H, methyl, hydroxyl, or halogen, or R^{1a} and R^{1c} are bonds forming a bridge comprising methylene, or R^{1b} and R^{1d} are bonds forming a bridge comprising methylene; and

wherein the compound is a selective dopamine D_3 receptor modulator.

2. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the compound is a selective dopamine D_3 receptor antagonist.

3. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the compound is a selective dopamine D_3 receptor agonist.

4. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the second linker L^2 is selected from one of the following:



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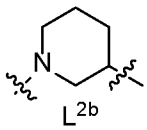

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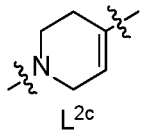

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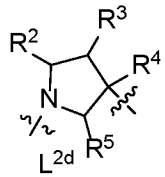

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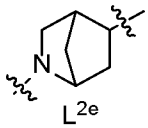

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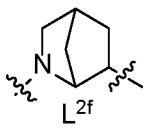
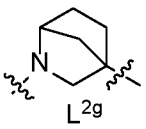
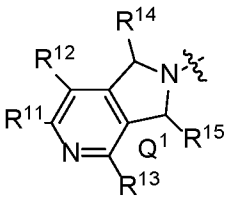


, and


;

wherein R^2 and R^5 are independently H, methyl, hydroxyl, or halogen; and wherein R^3 and R^4 can be, for example, independently H, methyl, hydroxyl, or halogen, or linked covalently at a methylene to form a three-carbon ring.

5. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Q is selected from one of the following:



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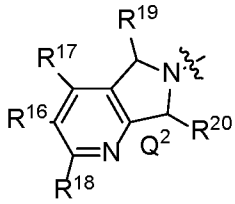

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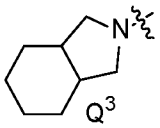

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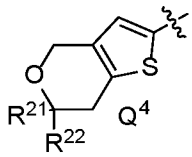

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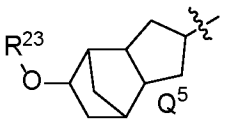

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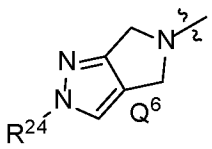

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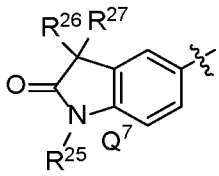

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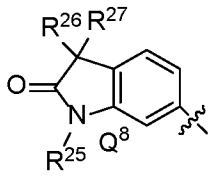

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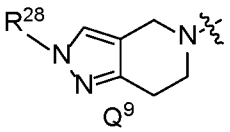

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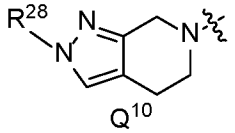

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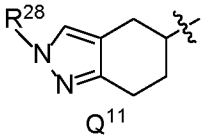

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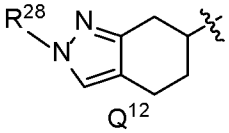

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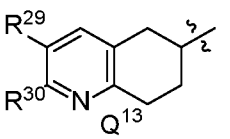

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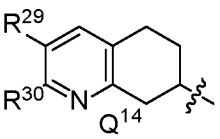

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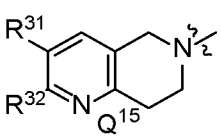

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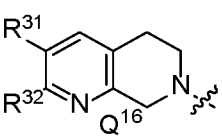

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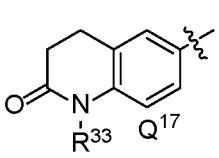
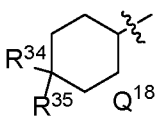
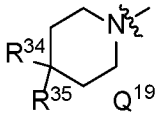
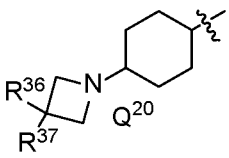
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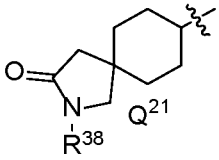

;

wherein R^{11}, R^{12}, R^{13}, R^{16}, R^{17}, R^{18}, R^{29}, R^{30}, R^{31}, and R^{32} are independently H, methyl, ethyl, methoxy, ethoxy, or halogen;

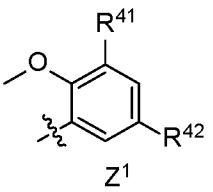
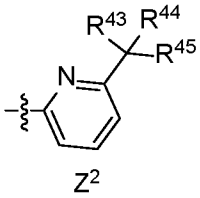
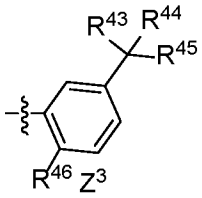
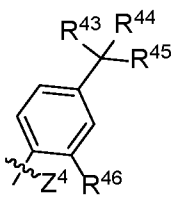
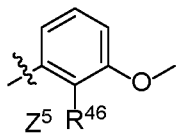
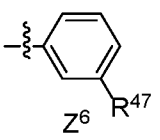
wherein R^{14}, R^{15}, R^{19}, R^{20}, R^{21}, R^{22}, R^{34}, R^{35}, R^{36}, and R^{37} are independently H, methyl, ethyl, methoxy, ethoxy, or halogen;

wherein R^{26} and R^{27} are independently H, methyl, ethyl, methoxy, ethoxy, or halogen, or methylenes covalently linked to form a three-carbon ring;

wherein R^{24}, R^{25}, R^{28}, R^{33}, and R^{38} are independently H, methyl, or halogen; and

wherein R^{23} is methyl or ethyl.

6. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Z is selected from one of the following: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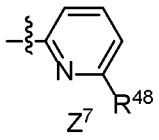
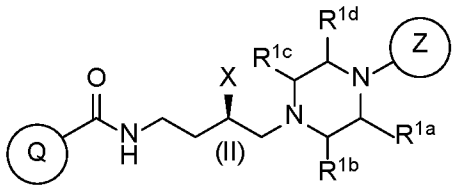

;

wherein R^{41}, R^{42}, R^{46}, R^{47}, and R^{48} are independently H, methyl, ethyl, or halogen; and

wherein R^{43}, R^{44}, and R^{45} are independently H or halogen.

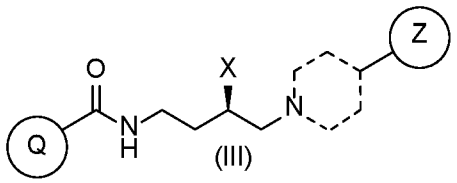
7. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (II):



;

wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d} are independently H, methyl, hydroxyl, or halogen, or R^{1a} and R^{1c} are bonds forming a bridge comprising methylene, or R^{1b} and R^{1d} are bonds forming a bridge comprising methylene.

8. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (III):



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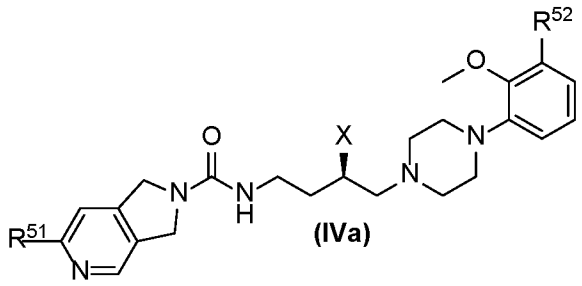
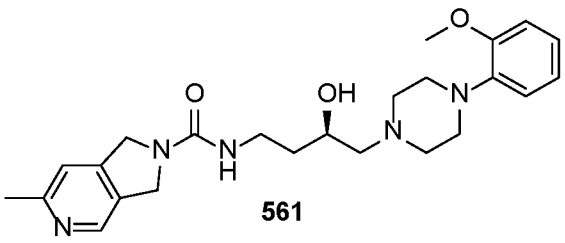
9. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (IVa):



; and

wherein R^{51} and R^{52} are independently H, methyl, ethyl, or halogen.

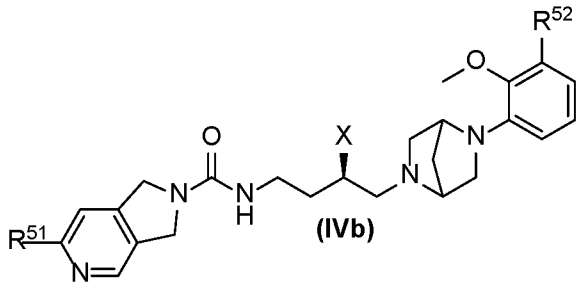
10. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the compound comprises:



561

.

11. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (IVb):

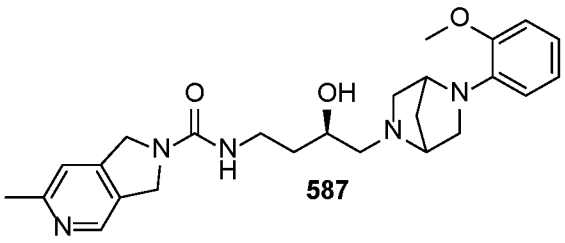


(IVb)

; and

wherein R^{51} and R^{52} are independently H, methyl, ethyl, or halogen.

12. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the compound comprises:



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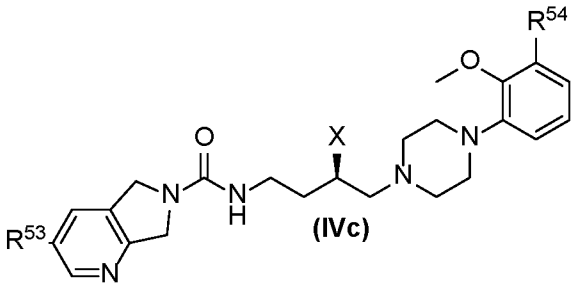
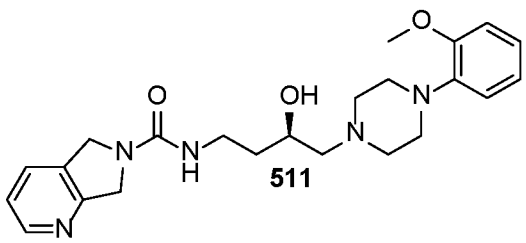
13. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (IVc):



;

wherein R^{53} and R^{54} are independently H, methyl, ethyl, or halogen.

14. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the compound comprises:



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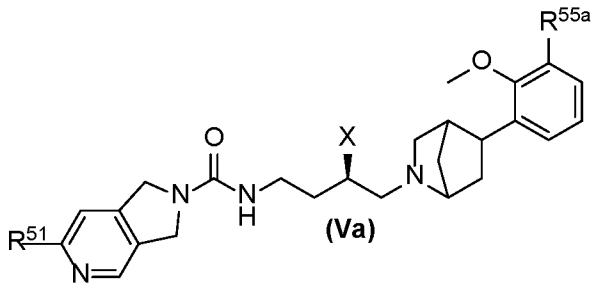
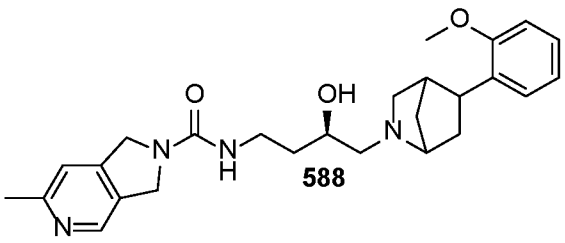
15. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (Va):



; and

wherein R^{51} and R^{55b} are independently H, methyl, ethyl, or halogen.

16. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the compound comprises:



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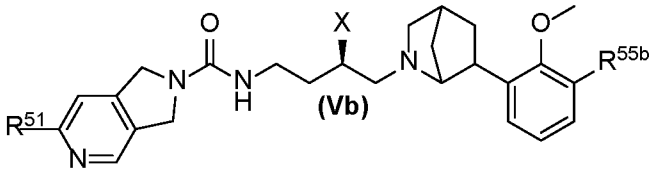
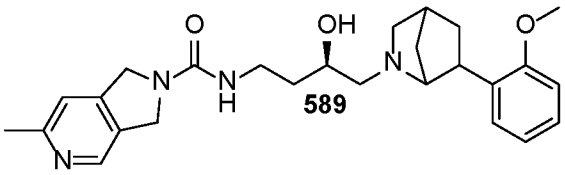
17. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (Vb):



; and

wherein R^{51} and R^{55b} are independently H, methyl, ethyl, or halogen.

18. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the compound comprises:



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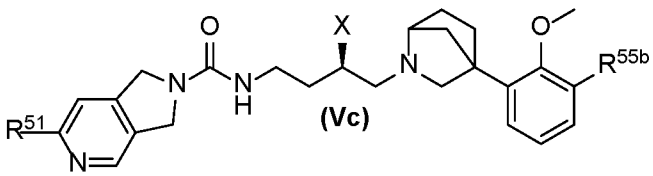
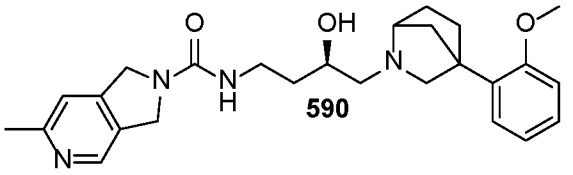
19. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (Vc):



; and

wherein R^{51} and R^{55b} are independently H, methyl, ethyl, or halogen.

20. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the compound comprises:



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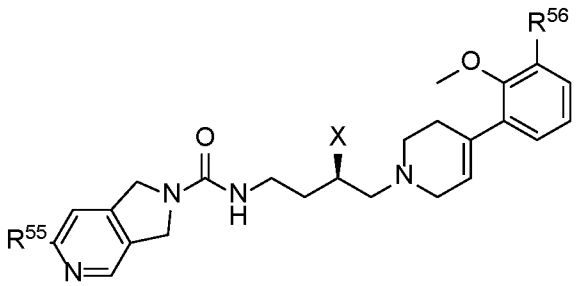
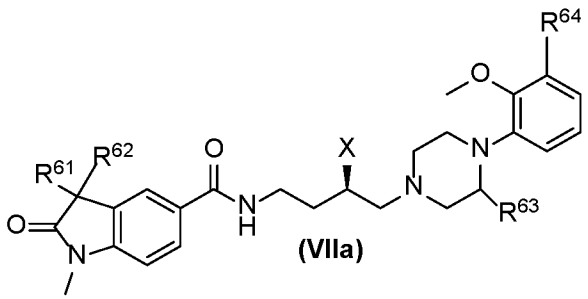
21. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (VI):



;

wherein R^{55} and R^{56} are independently H, methyl, ethyl, or halogen.

22. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (VIIa):



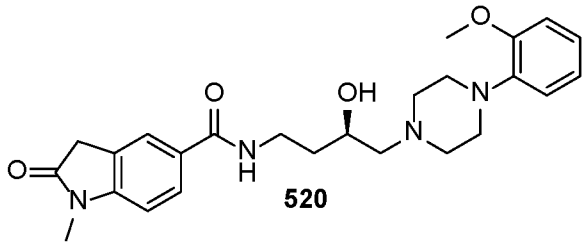
;

wherein R^{61} and R^{62} are independently H or methyl, or methylenes covalently linked to form a three-carbon ring;

wherein R^{63} is H, methyl, hydroxyl, or halogen; and

wherein R^{64} is methyl, ethyl, or halogen.

23. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the compound comprises:



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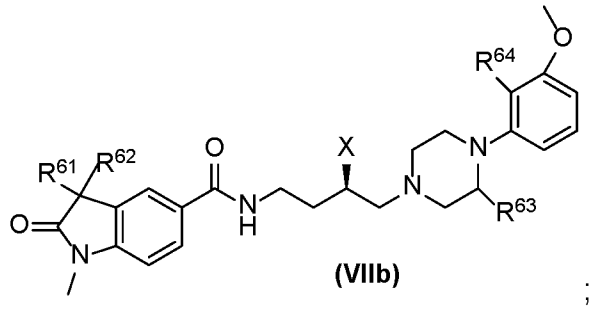
24. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (VIIb):



(VIIb)

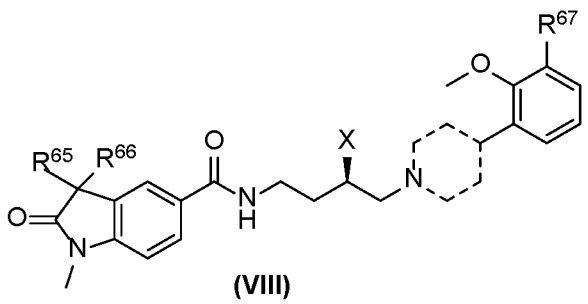
;

wherein R^{61} and R^{62} are independently H or methyl, or methylenes covalently linked to form a three-carbon ring;

wherein R^{63} is H, methyl, hydroxyl, or halogen; and

wherein R^{64} is methyl, ethyl, or halogen.

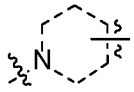
25. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (VIII):

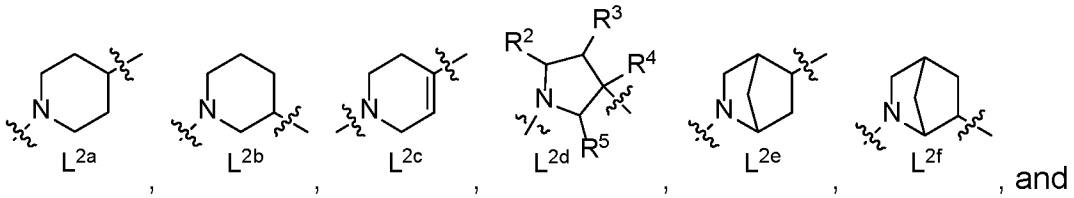


(VIII)

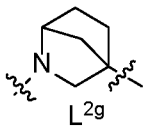
;

wherein R^{65} and R^{66} are independently H or methyl, or methylenes covalently linked to form a three-carbon ring;

wherein  is selected from one of the following:



, and

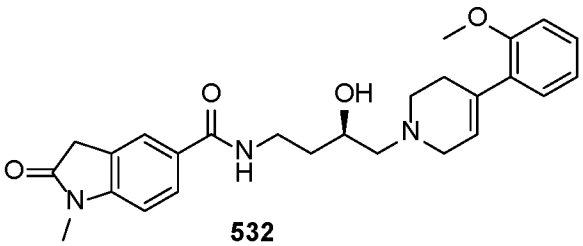


;

wherein R^2, R^3, R^4, and R^5 are independently H, methyl, hydroxyl, or halogen; and

wherein R^{67} is methyl, ethyl, or halogen.

26. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the compound comprises:



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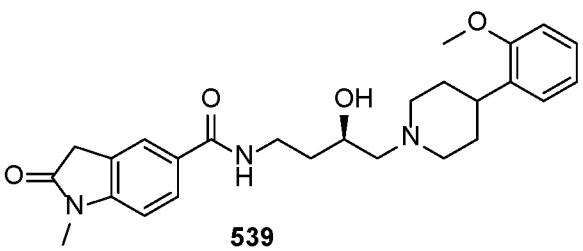
27. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the compound comprises:



539

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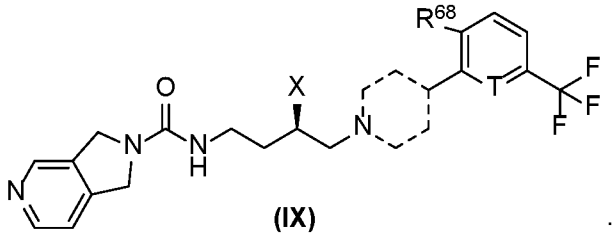
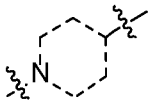
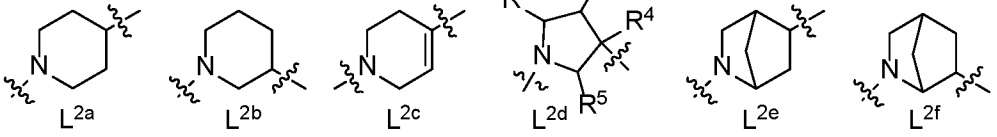
28. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (IX):



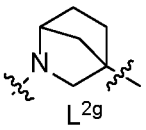
(IX)

;

wherein  is selected from one of the following:



L2a , L2b , L2c , L2d , L2e , L2f , and



L2g ;

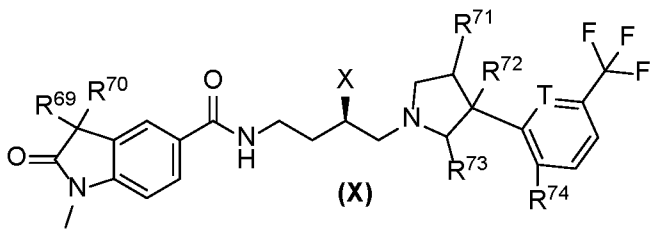
wherein R^2, R^3, R^4, and R^5 are independently H, methyl, hydroxyl, or halogen;

wherein R^{68} is H or halogen;

and

wherein T is C or N.

29. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (X):



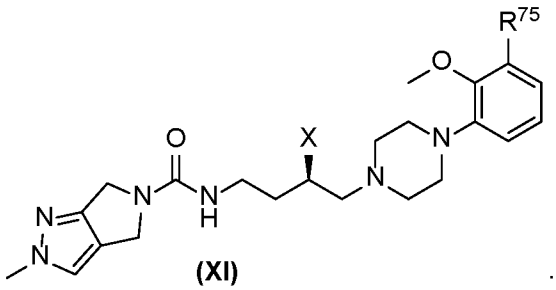
(X)

;

wherein R^{69} and R^{70} are independently H or methyl, or methylenes covalently linked to form a three-carbon ring;

wherein R^{71} and R^{72} are independently H, methyl, halogen, or linked covalently at a methylene to form a three-carbon ring;
wherein R^{73} is H, methyl, or halogen;
wherein R^{74} is H or halogen; and
wherein T is C or N.

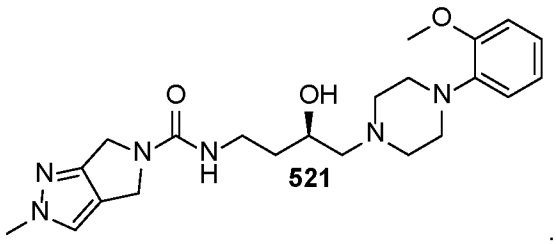
30. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (XI):



(XI) ;

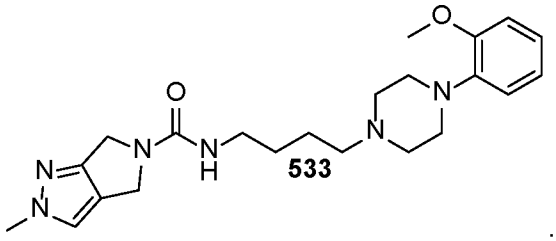
wherein R^{75} is H or halogen.

31. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the compound comprises:



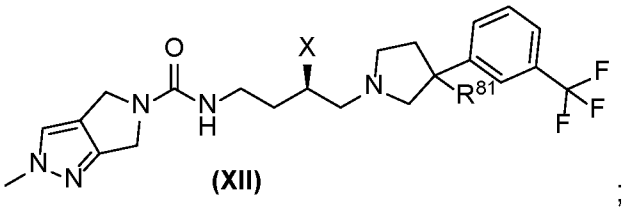
521 .

32. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the compound comprises:



533 .

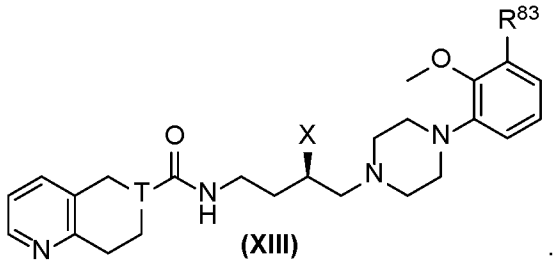
33. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (XII):



(XII) ;

wherein R^{81} is H, methyl, or halogen.

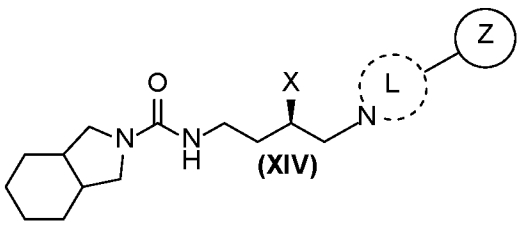
34. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (XIII):



(XIII) ;

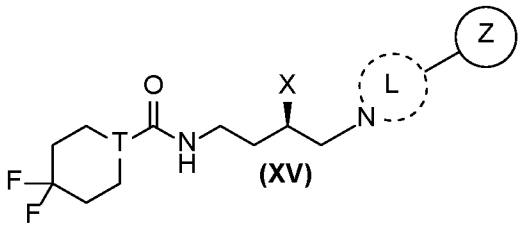
wherein T is C or N; and
wherein R^{83} is H or halogen.

35. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (XIV):



(XIV) .

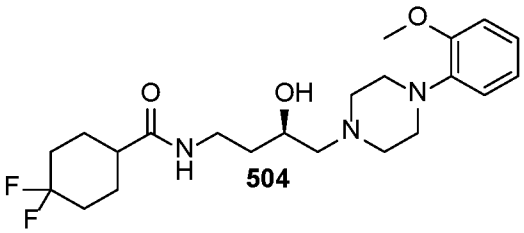
36. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (XV):



;

wherein T is C or N.

37. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the compound comprises:



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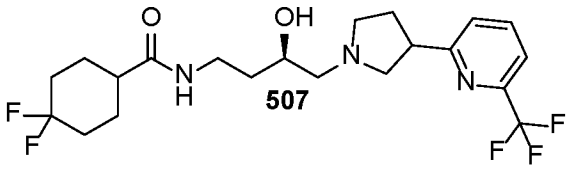
38. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the compound comprises:



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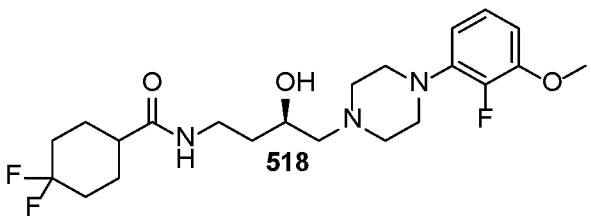
39. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the compound comprises:



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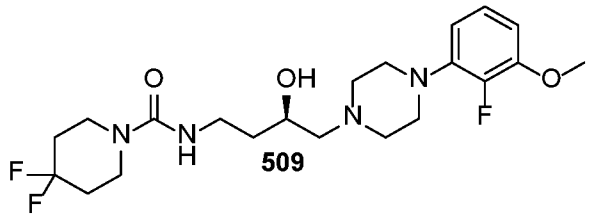
40. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the compound comprises:



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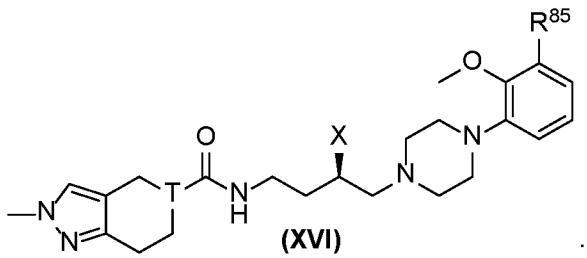
41. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (XVI):



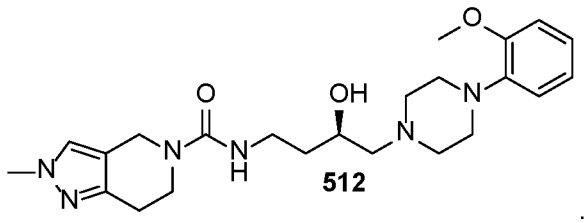
(XVI)

;

wherein T is C or N; and

wherein R^{85} is H or halogen.

42. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the compound comprises;



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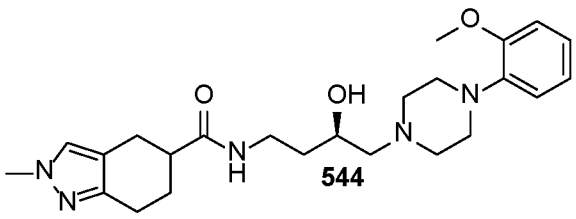
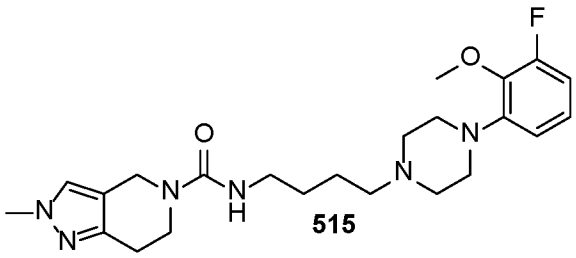
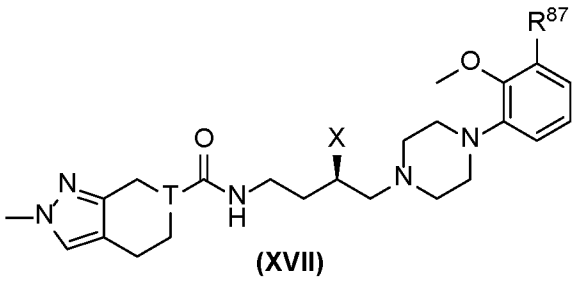
43. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the compound comprises:



44. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the compound comprises:



45. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (XVII):

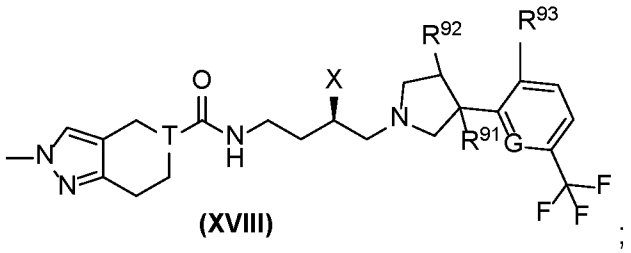


;

wherein T is C or N; and

wherein R87 is H or halogen.

46. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (XVIII):



(XVIII);

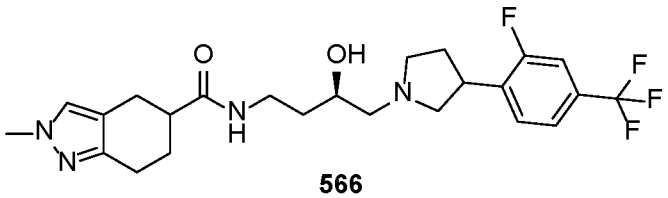
wherein T is C or N;

wherein R^{91} and R^{92} are independently H, methyl, halogen, or linked covalently at a methylene to form a three-carbon ring;

wherein R^{93} is H or halogen; and

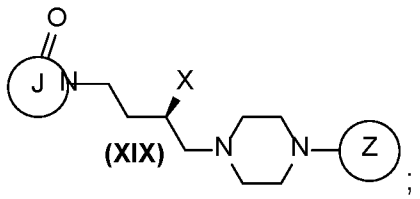
wherein G is C or N.

47. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the compound comprises:



566.

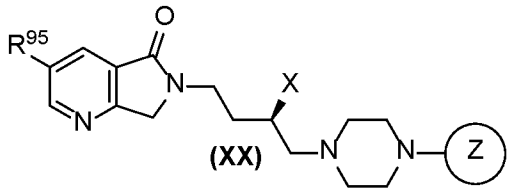
48. A compound having Formula (XIX), its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof:



(XIX);

wherein J is a cyclic, heterocyclic, bicyclic, or heterobicyclic lactam ring bound to a n-butyl linker through the lactam nitrogen; X is a hydrogen, a hydroxyl, or a methyl group substituent of the n-butyl linker; and Z is a substituted aryl bound to the n-butyl linker through a piperazine group.

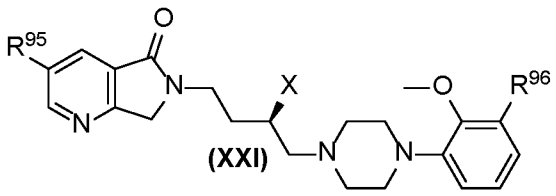
49. The therapeutic compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (XIX) is represented by Formula (XX):



(XX) ; and

wherein R^{95} and R^{96} are independently H, methyl, ethyl, or halogen.

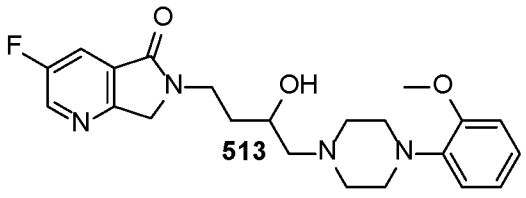
50. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein Formula (I) is represented by Formula (XXI):



(XXI) ; and

wherein R^{95} and R^{96} are independently H, methyl, ethyl, or halogen.

51. The compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, or salt thereof, or any combination thereof, wherein the compound comprises:



513 .

52. A pharmaceutical composition, comprising a therapeutically effective amount of the compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, a salt thereof, or any combination thereof, together with a pharmaceutically acceptable carrier.

53. The pharmaceutical composition of any preceding claim, wherein the compound is a selective dopamine D_3 receptor antagonist, or a selective dopamine D_3 receptor agonist.

54. The pharmaceutical composition of any preceding claim, wherein the compound has greater than 50 times D_3 receptor selectivity relative to D_2 receptor selectivity.

55. The pharmaceutical composition of any preceding claim, wherein the compound has greater than 100 times D_3 receptor selectivity relative to D_2 receptor selectivity.

56. The pharmaceutical composition of any preceding claim, wherein the compound has at least a 10-fold therapeutic window as measured by the IC_{50} hERG toxicity relative to the minimally effective therapeutic dose.

57. The pharmaceutical composition of any preceding claim, wherein the compound has at least a 30-fold therapeutic window as measured by the IC_{50} hERG toxicity dose relative to the minimally effective therapeutic dose.

58. The pharmaceutical composition of any preceding claim, wherein the compound is a first therapeutic compound, and the pharmaceutical composition further comprises a second therapeutic compound.

59. The pharmaceutical composition of any preceding claim, wherein the second compound comprises a selective dopamine D_1 receptor modulator, a selective dopamine D_2 receptor modulator, a selective dopamine D_4 receptor modulator, or a selective dopamine D_5 receptor modulator, or any combination thereof.

60. The pharmaceutical composition of any preceding claim, wherein the second compound comprises a selective dopamine D_1 receptor modulator, a selective dopamine D_5 receptor modulator, or both.

61. The pharmaceutical composition of any preceding claim, wherein the second compound comprises a selective dopamine D_2 receptor modulator, a selective dopamine D_4 receptor modulator, or both.

62. The pharmaceutical composition of any preceding claim, wherein the first compound comprises a selective dopamine D_2 receptor agonist, and the second therapeutic compound comprises a selective dopamine D_3 antagonist.

63. The pharmaceutical composition of any preceding claim, wherein the second compound comprises an antidepressant, or an antipsychotic, or both.

64. The pharmaceutical composition of any preceding claim, wherein the second compound is a Parkinson disease therapeutic compound.

65. A method of treating drug misuse or drug addiction, comprising administering to a patient in need thereof a composition comprising a therapeutically effective amount of the compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, a salt thereof, or any combination thereof optionally in combination with one or more additional active ingredients.

66. The method of any preceding claim, wherein the patient has a history of misusing a stimulant, a depressant, an opioid, a cannabinoid, lysergic acid diethylamide (LSD), mescaline, psilocybin, nicotine, ethanol, a benzodiazepine, phencyclidine, ketamine, cocaine, or an amphetamine, or any combination thereof.

67. A method of treating a substance use disorder, comprising administering to a patient in need thereof a composition comprising a therapeutically effective amount of the compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, a salt thereof, or any combination thereof optionally in combination with one or more additional active ingredients.

68. The method of any preceding claim, wherein the patient has one or more affective disorders, schizophrenia, or both.

69. The method of any preceding claim, wherein the substance use disorder comprises a psychostimulant use disorder.

70. The method of any preceding claim, wherein the patient has a history of misusing a stimulant comprising cocaine, an amphetamine, a methamphetamine, dextroamphetamine, levoamphetamine, methylenedioxymethamphetamine (MDMA), methylphenidate, modafinil, armodafinil, midodrine, oxymetazoline, dobutamine, ephedrine, pseudoephedrine, or phenylephrine, or any combination thereof.

71. The method of any preceding claim, comprising administering to a patient in need thereof a composition comprising a therapeutically effective amount of the compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, a salt thereof, or any combination thereof and one or more additional active ingredients selected from the group consisting of bremazocine, buprenorphine, butorphanol, carfentanyl, codeine, cyclazocine, dezocine, diamorphine, dihydrocodeine, dihydromorphine, dihydromorphinone (aka hydromorphone), enadoline, eseroline, ethylmorphine, etonitazine, etorphine, fentanyl, hydrocodone, levophenacylmorphan, levorphanol, meperidine/pethidine, methadone, morphine, nalbuphine, nicomorphine, oxycodone, oxymorphone, pentazocine, phenazocine, picenadol, tramadol, tapentadol, or a combination thereof.

72. The method of any preceding claim, wherein the additional active ingredient is selected from the group consisting of methadone, naltrexone and buprenorphine.

73. A method of treating Parkinson Disease, comprising administering to a patient in need thereof a composition comprising a therapeutically effective amount of the compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, a salt thereof, or any combination thereof optionally in combination with one or more additional active ingredients.

74. The method of treating Parkinson Disease of any preceding claim, further comprising administering levodopa.

75. The method of treating Parkinson Disease of any preceding claim, wherein the compound is a selective dopamine D_3 receptor agonist.

76. A method of treating Attention Deficit/ Hyperactivity Disorder ("ADHD"), comprising administering to a patient in need thereof a composition comprising a therapeutically effective amount of the compound of any preceding claim, its enantiomer, a racemate thereof, a prodrug thereof, a salt thereof, or any combination thereof optionally in combination with one or more additional active ingredients.

77. A kit comprising the compound of any preceding claim and a second therapeutic compound.

78. A method of synthesizing the compound of any preceding claim.

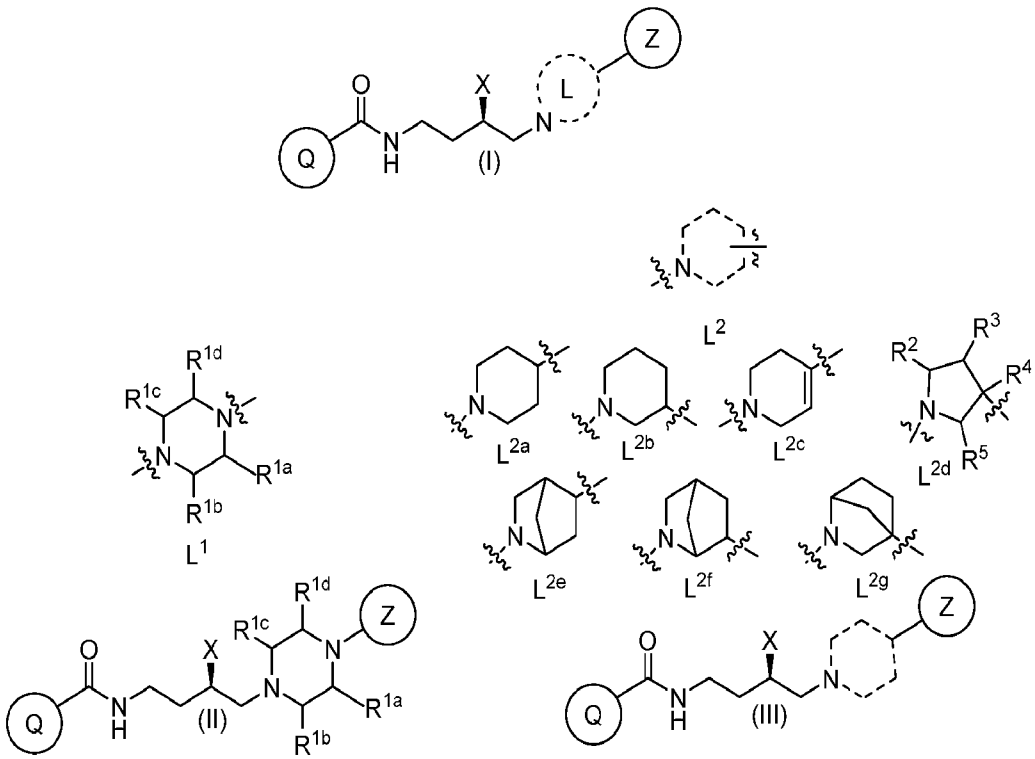

Z
O
X
L
Q
N
H
(I)
R1d
R1c
N
N
R1a
R1b
L1
L2
L2a
L2b
L2c
R3
R2
R4
N
L2d
R5
L2e
L2f
L2g
Z
R1d
R1c
O
X
N
Q
N
H
(II)
N
R1a
R1b
Z
O
X
Q
N
H
(III)
N

FIG. 1A

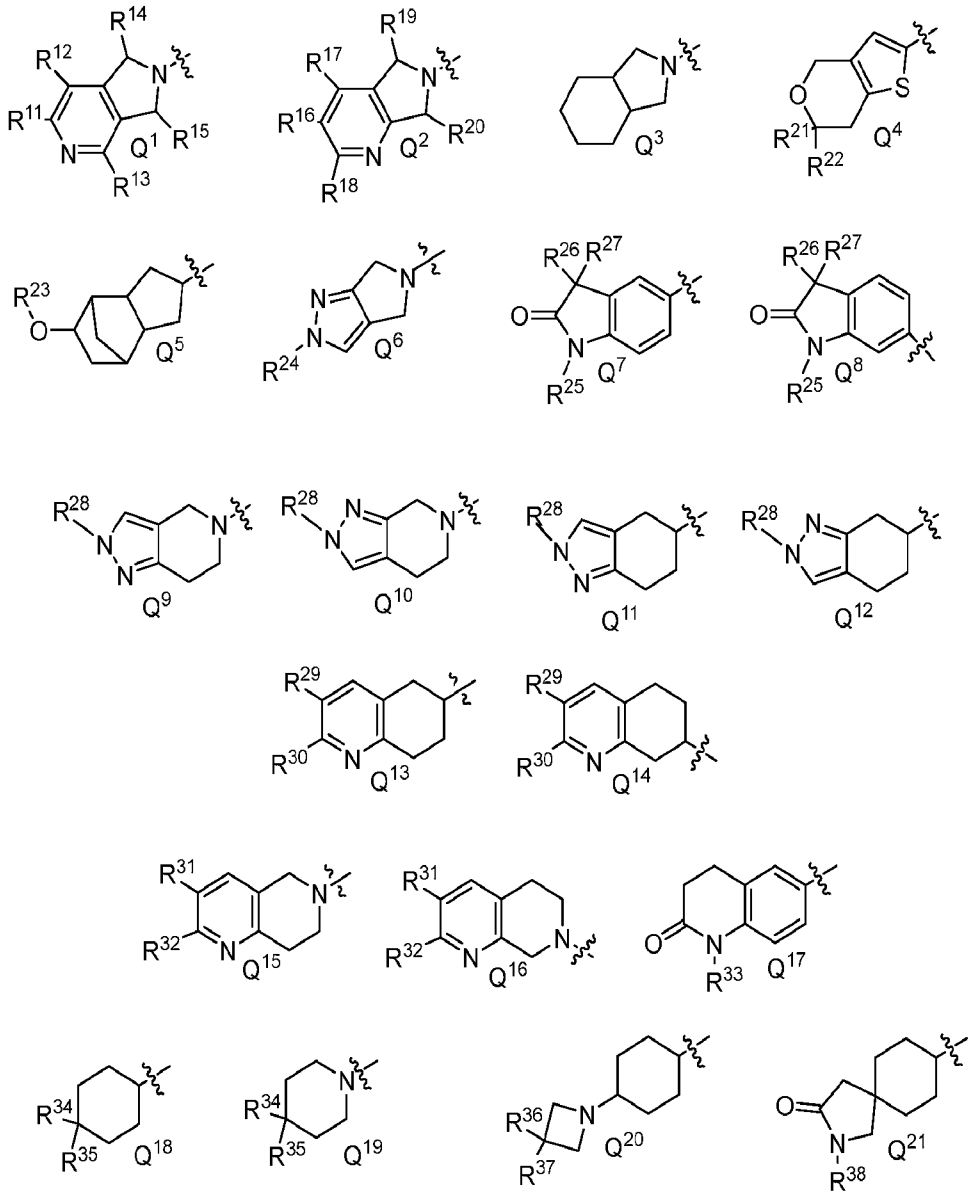

Q1
Q2
Q3
Q4
Q5
Q6
Q7
Q8
Q9
Q10
Q11
Q12
Q13
Q14
Q15
Q16
Q17
Q18
Q19
Q20
Q21

FIG. 1B

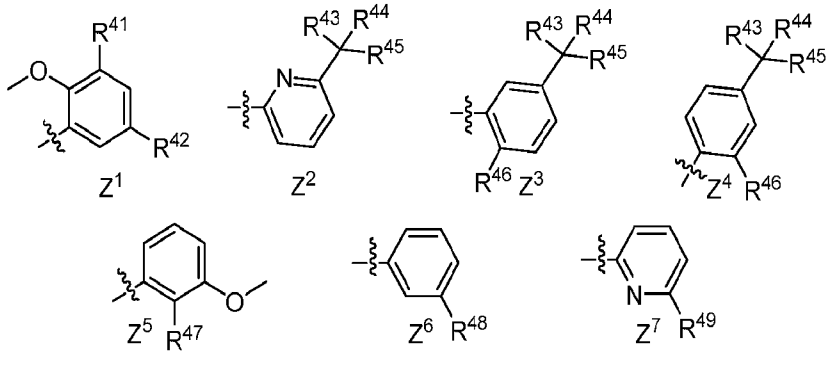

Z1
Z2
Z3
Z4
Z5
Z6
Z7

FIG. 1C

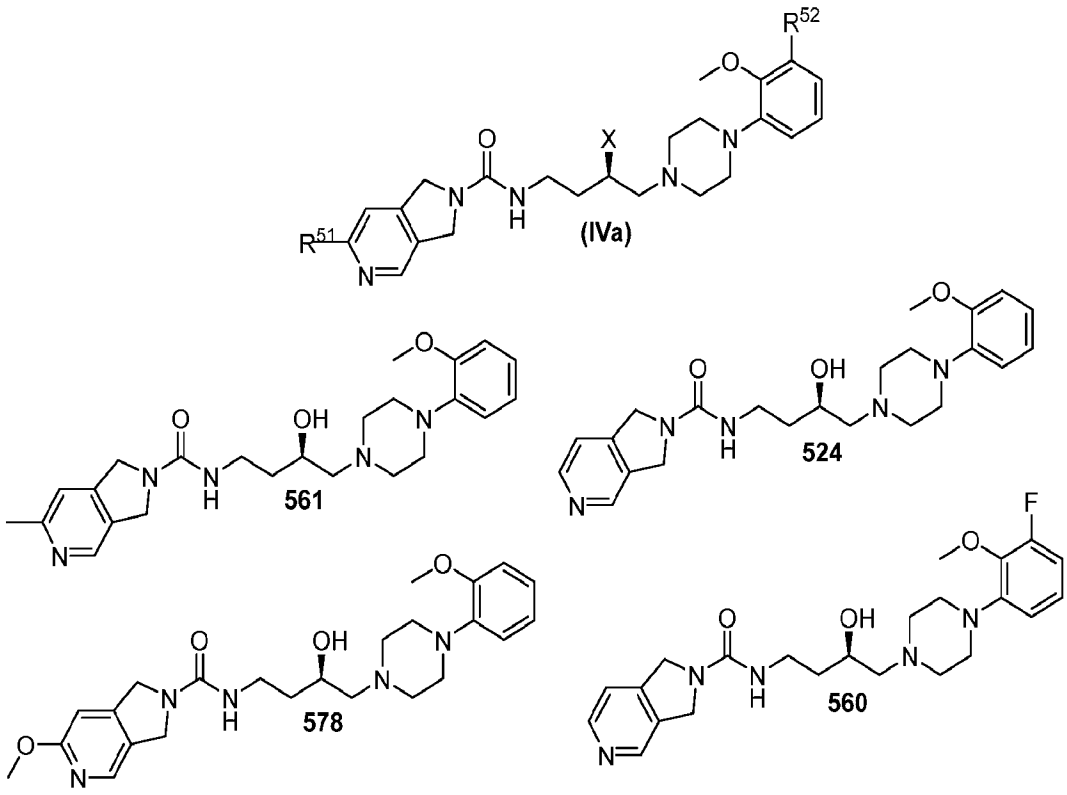


FIG. 2A

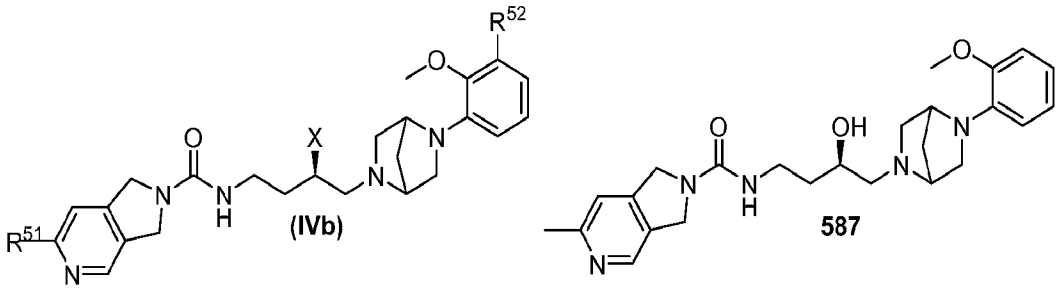
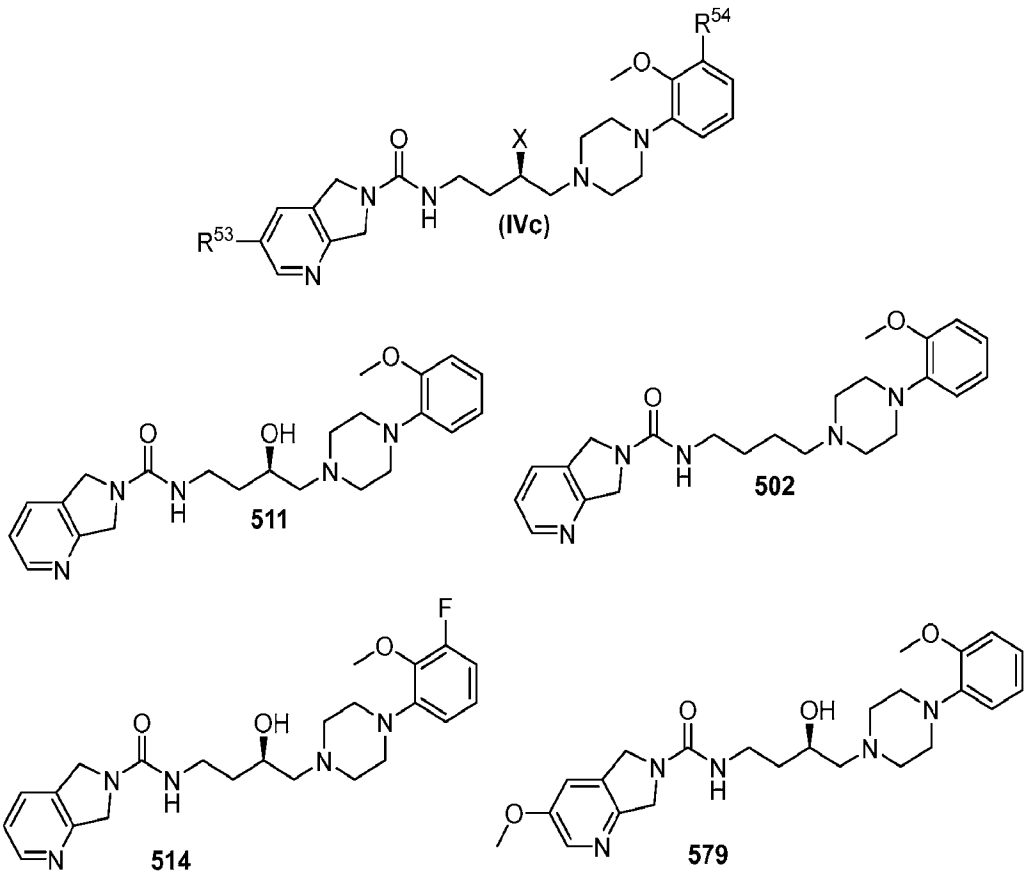


FIG. 2B


R54
O
X
O
N
N
N
H
N
R53
N
(IVc)
O
OH
O
N
N
N
H
N
511
O
O
N
N
N
H
N
502
F
O
OH
O
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N
H
N
514
O
OH
O
N
N
N
H
O
N
579

FIG. 2C

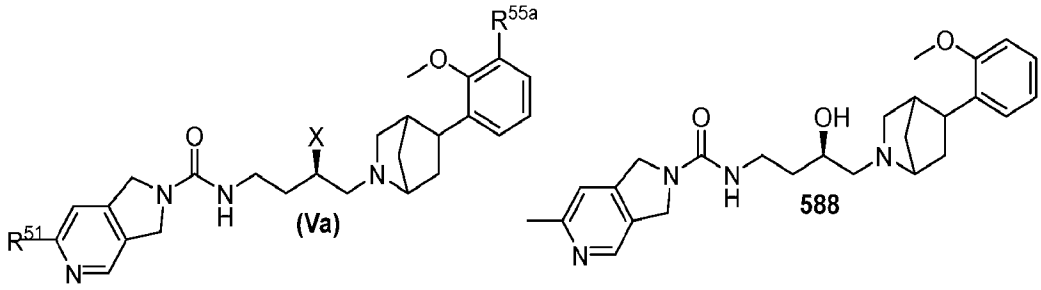


FIG. 3A

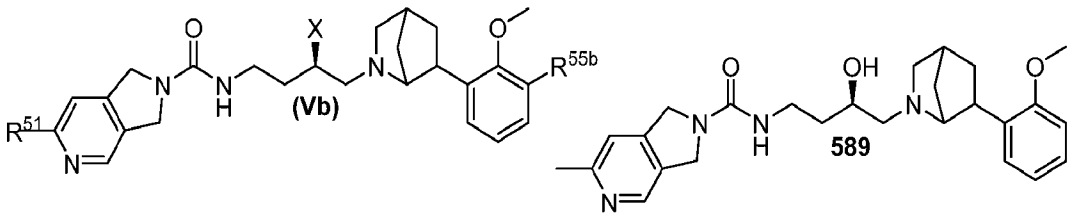


FIG. 3B

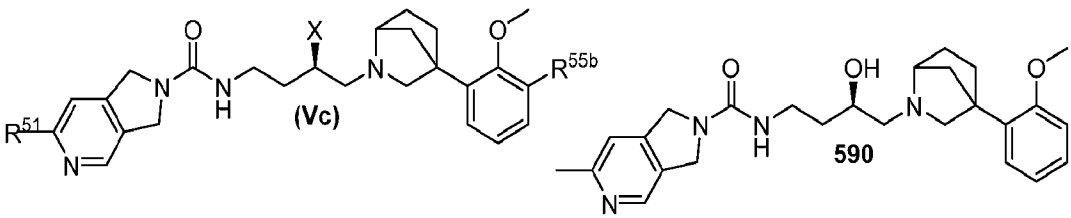


FIG. 3C

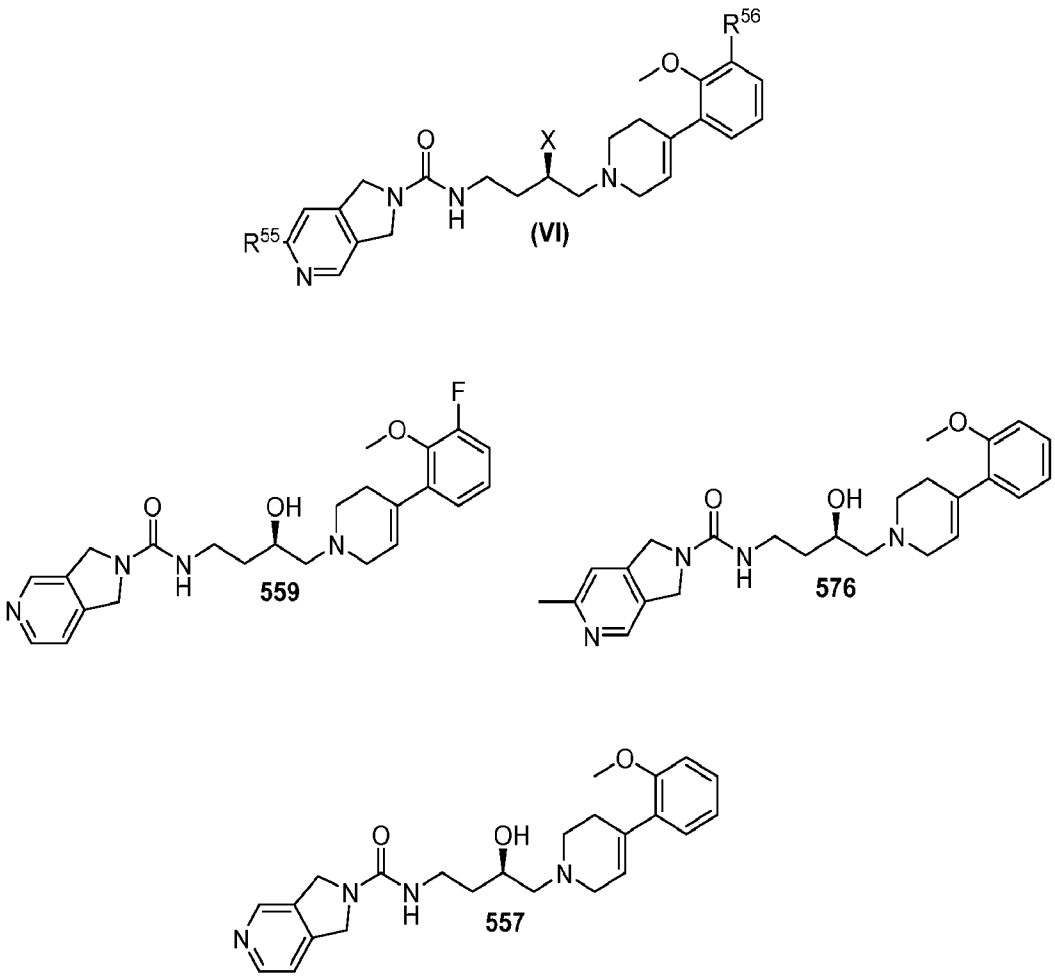

R56
O
X
O
N
N
H
N
R55
N
(VI)
F
O
OH
O
N
N
H
N
N
559
O
OH
O
N
N
H
N
N
576
O
OH
O
N
N
H
N
N
557

FIG. 4

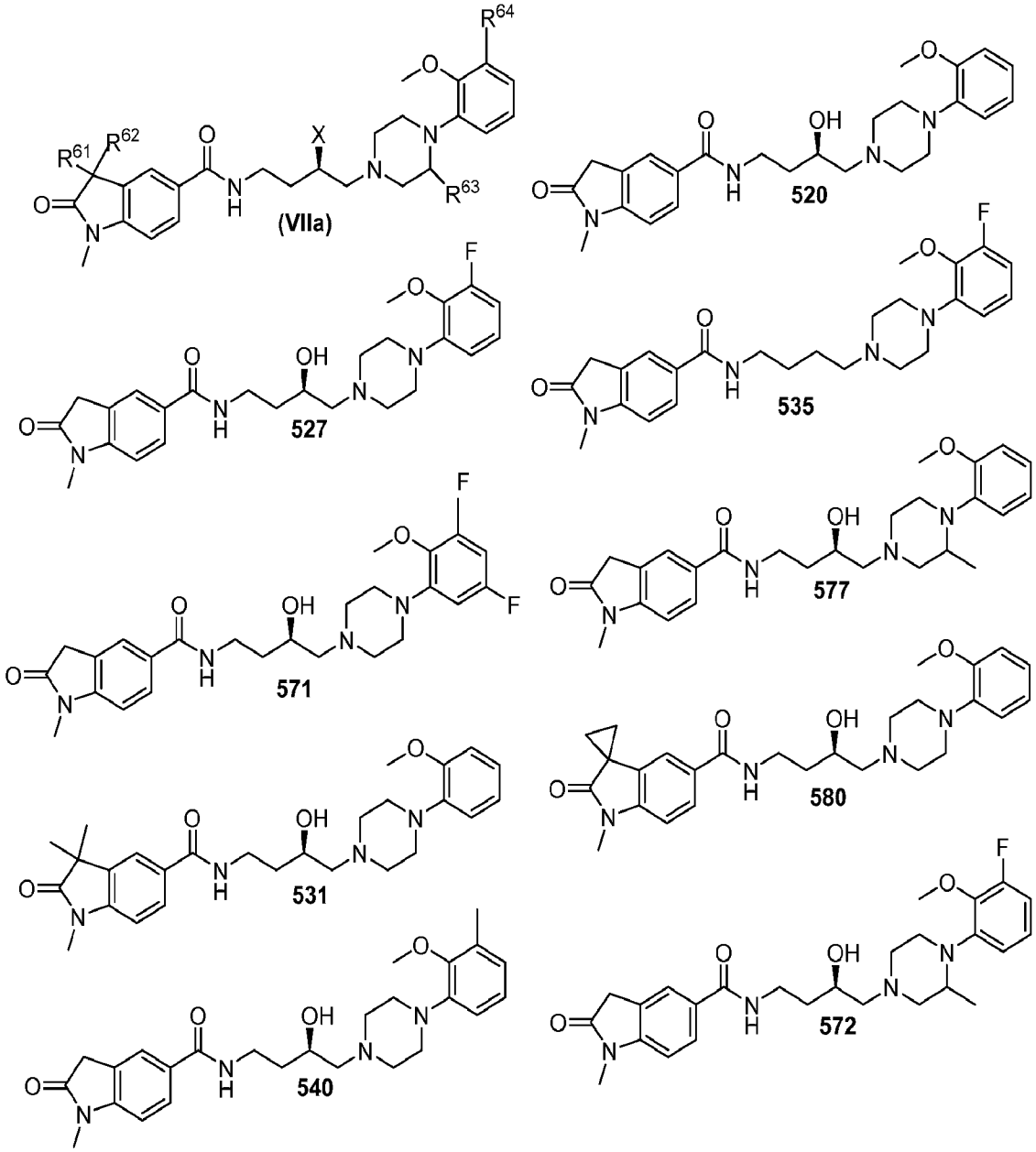


FIG. 5A

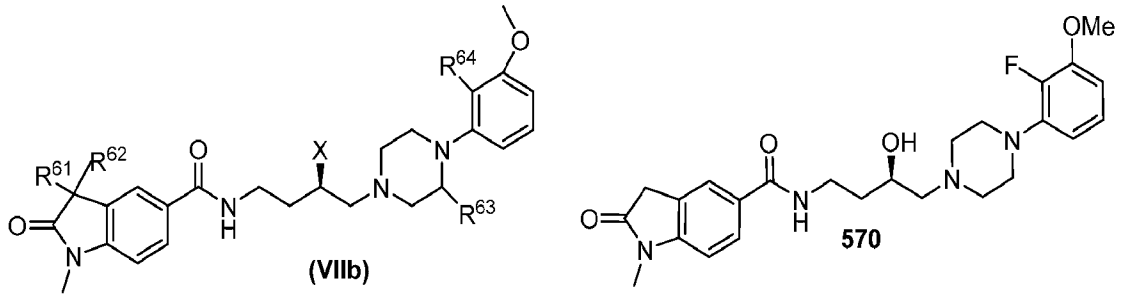


FIG. 5B

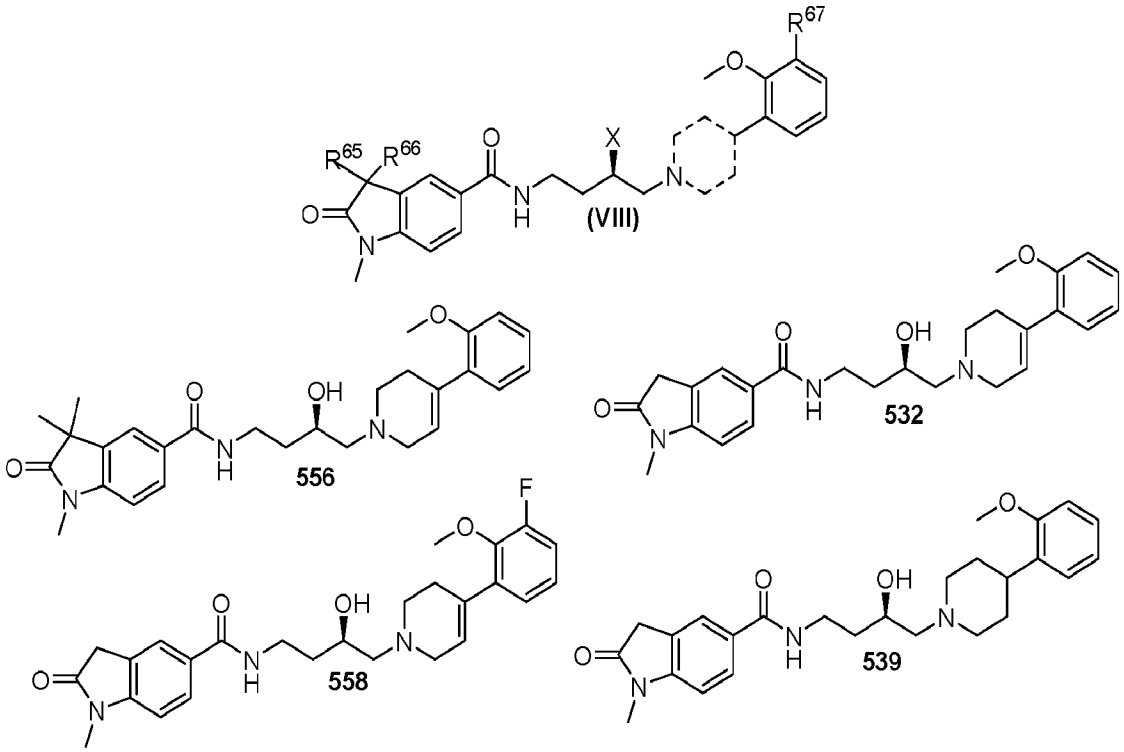


FIG. 6

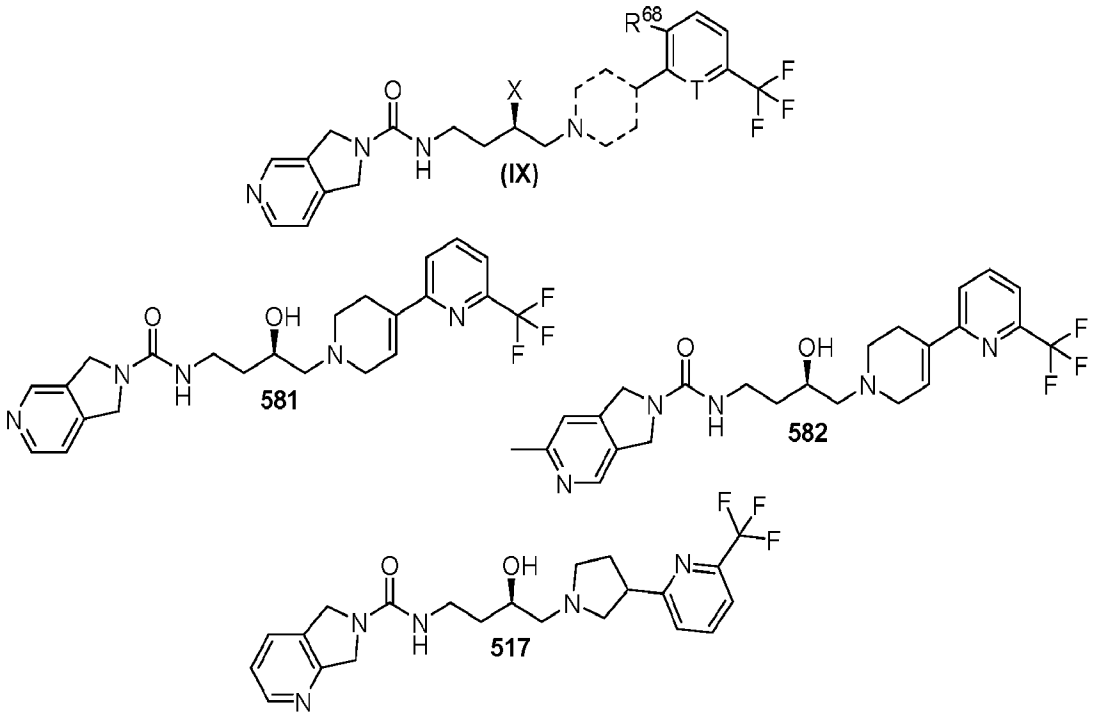


FIG. 7

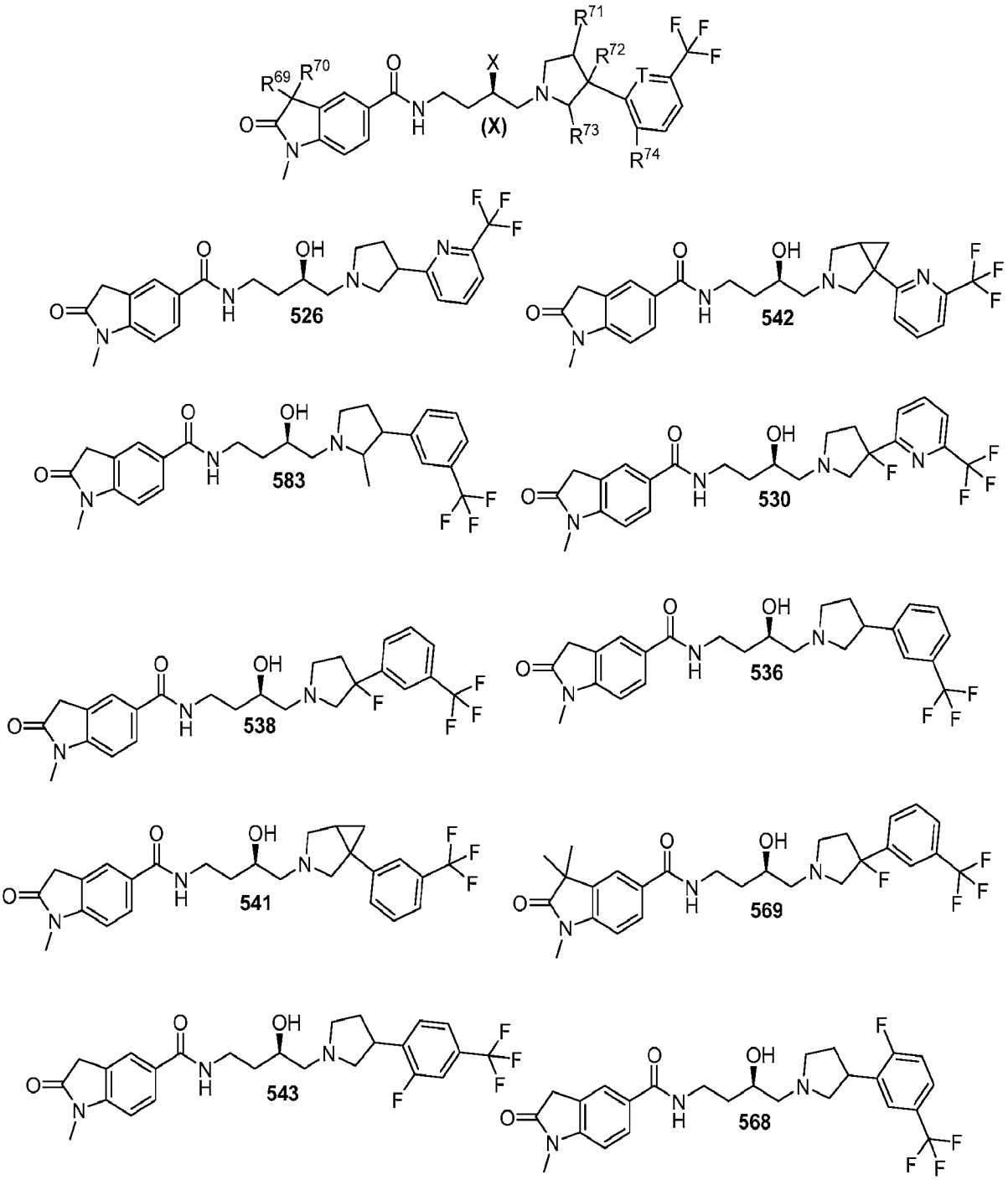
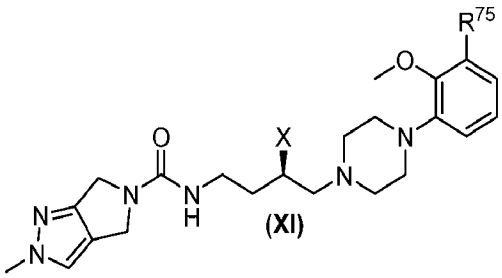
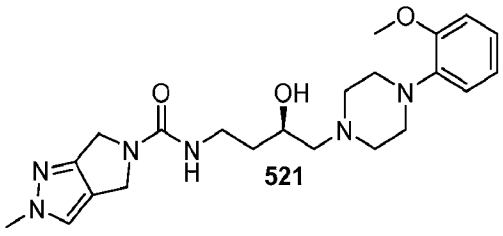


FIG. 8



(XI)



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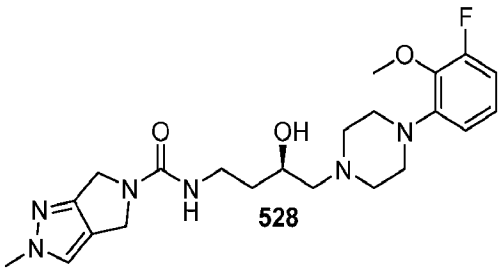

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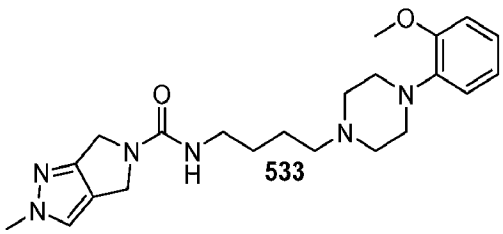

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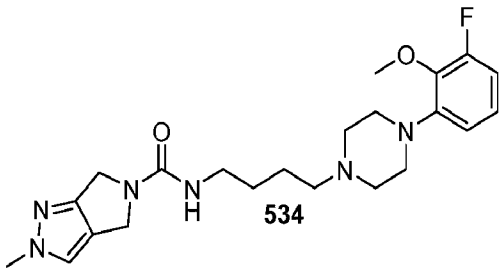
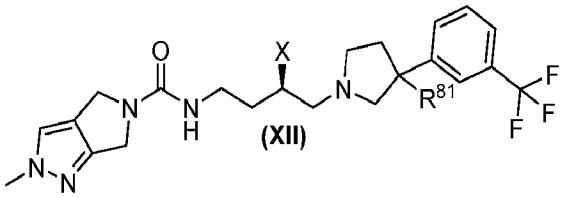


534

FIG. 9



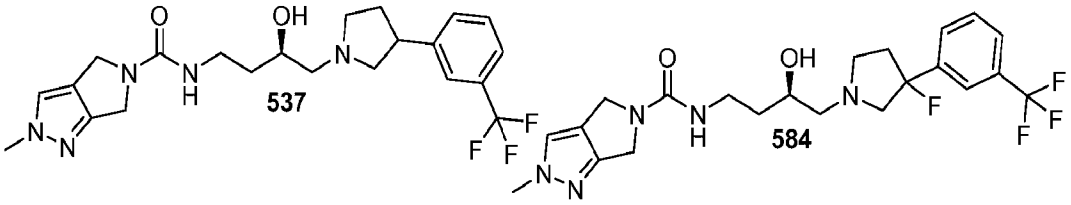


FIG. 10

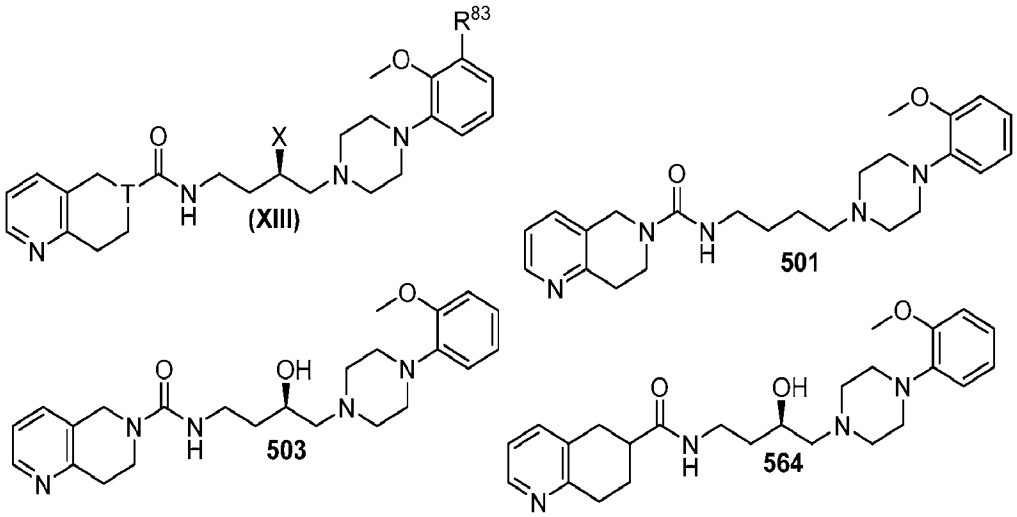
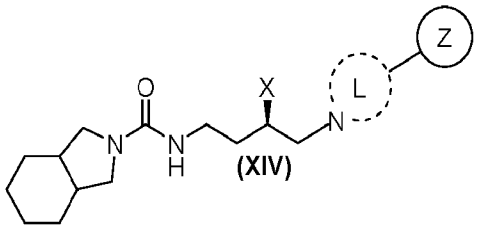


FIG. 11



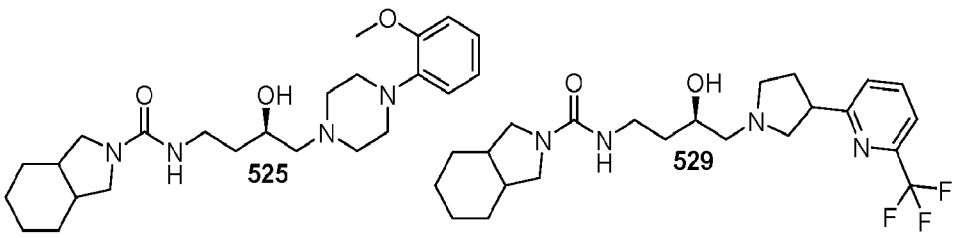


FIG. 12

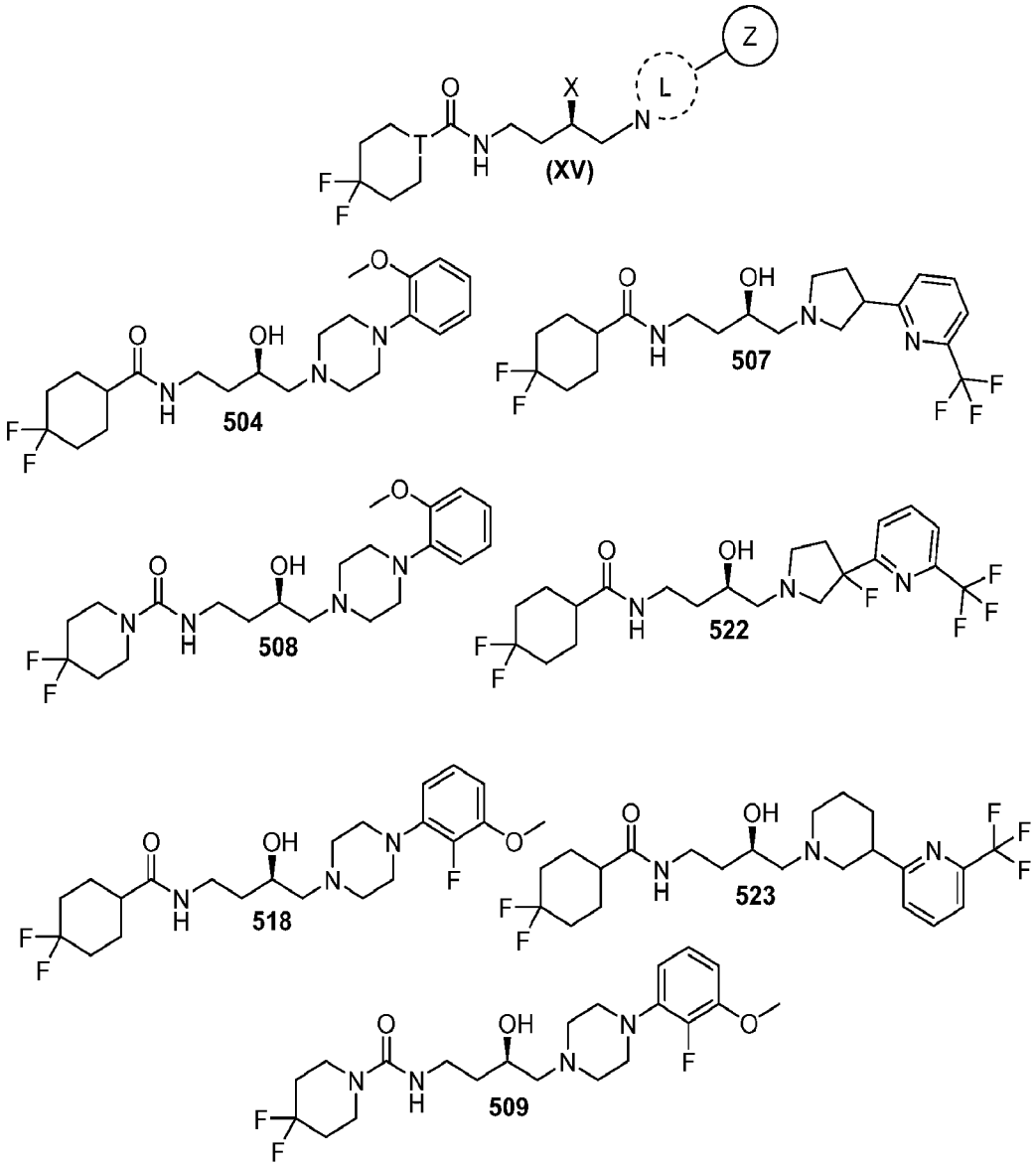


FIG. 13

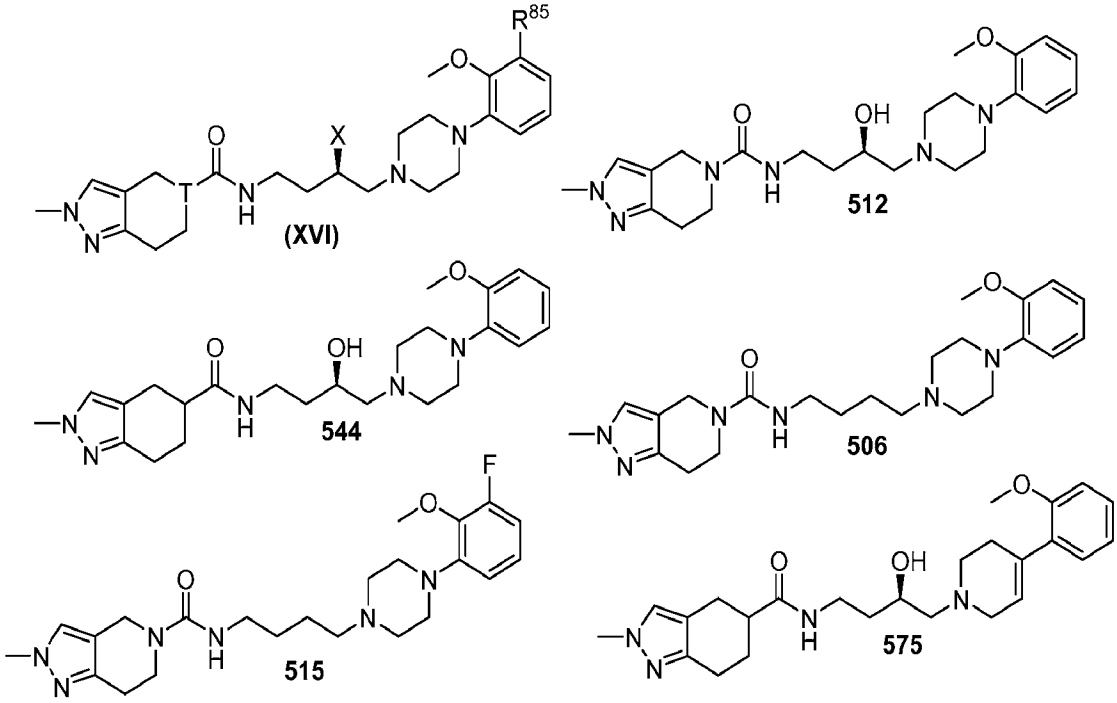


FIG. 14A

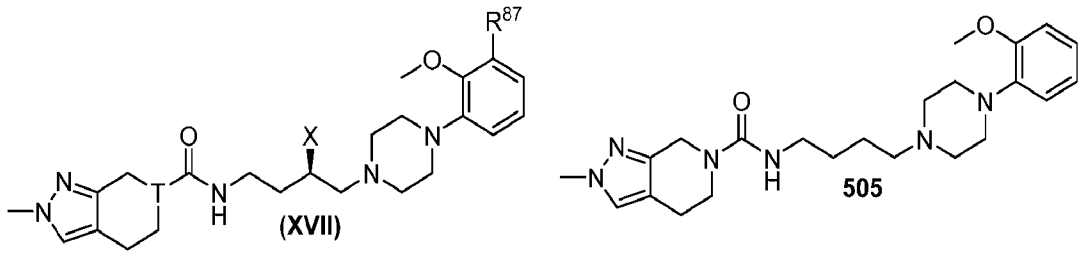


FIG. 14B

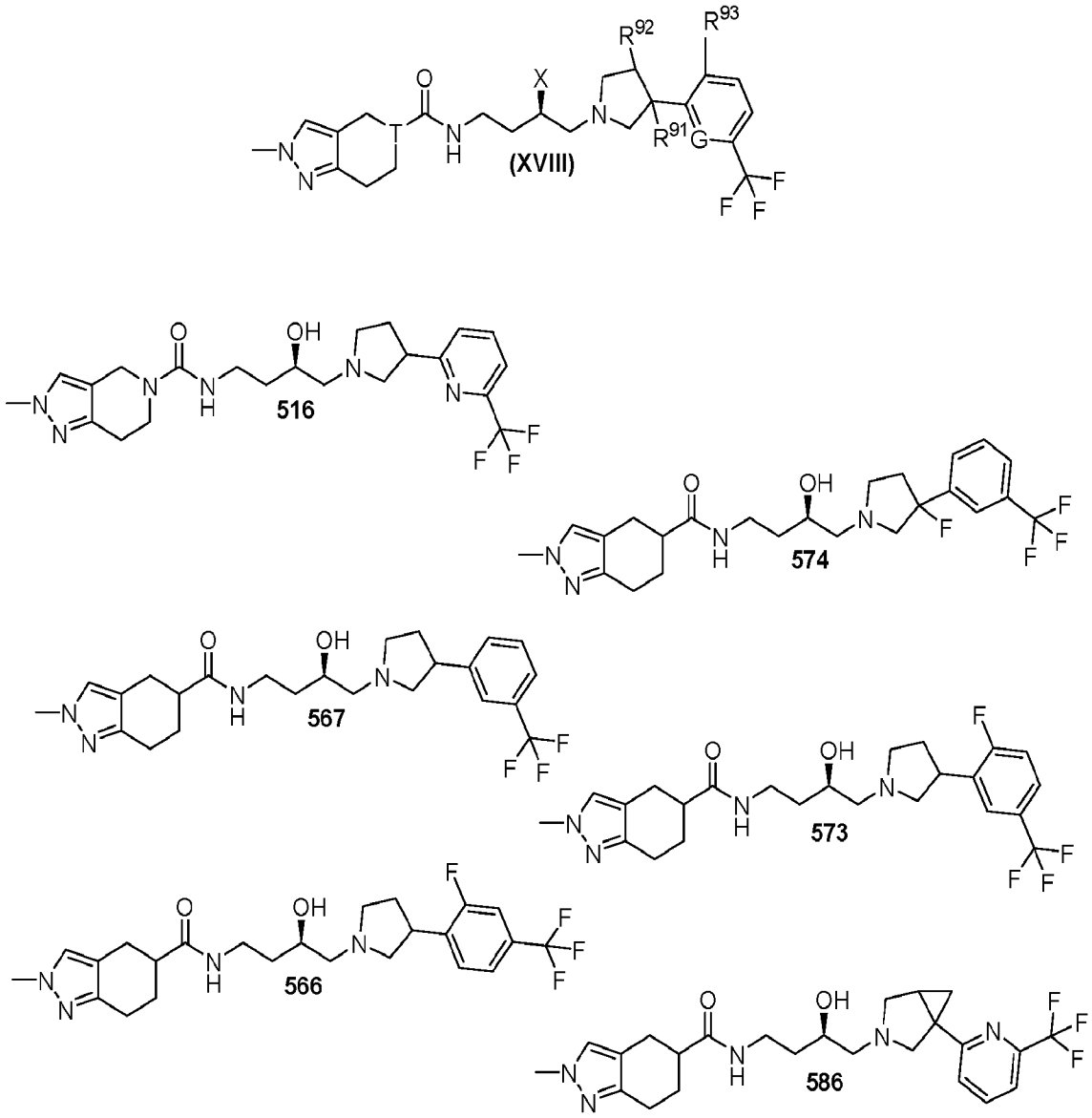


FIG. 15

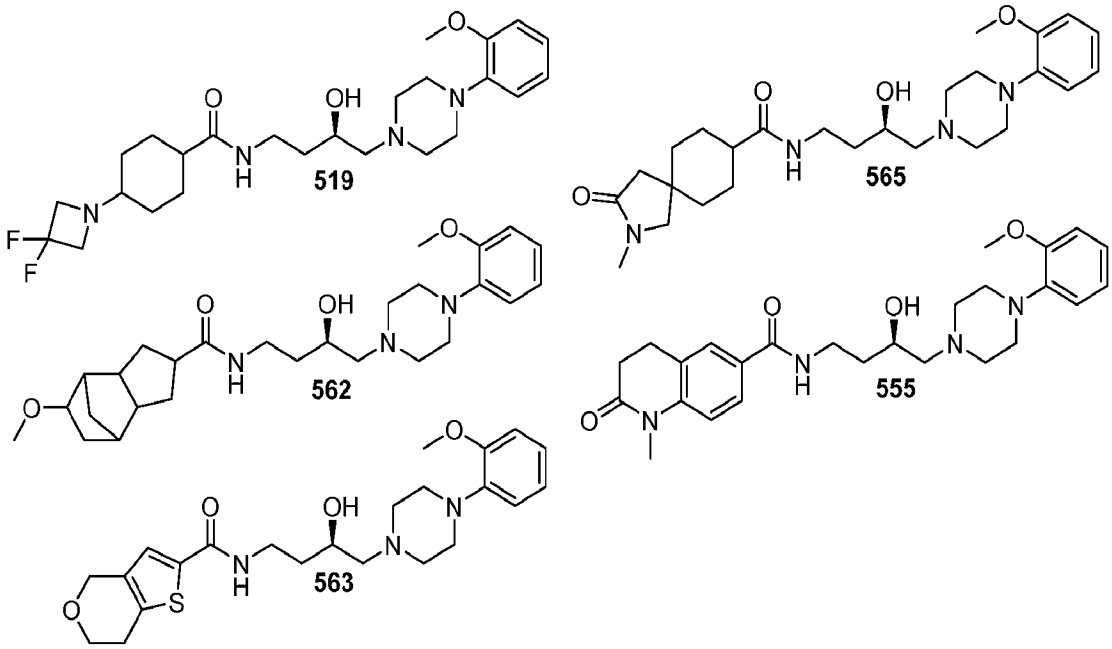


FIG. 16A

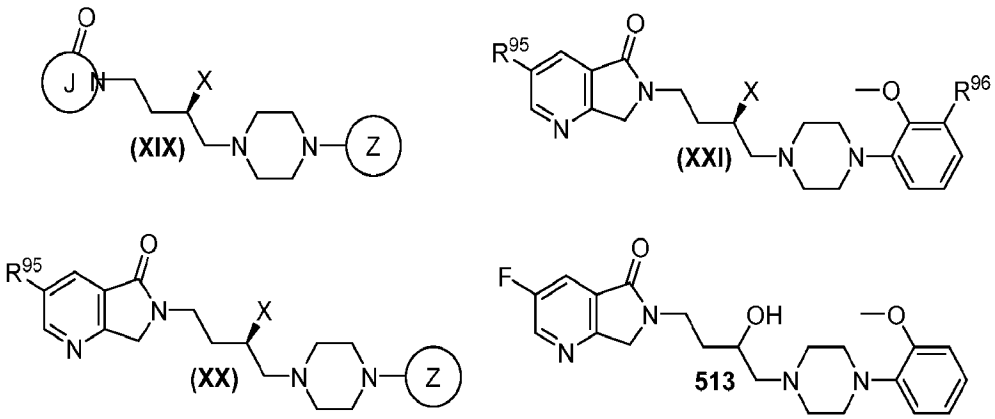
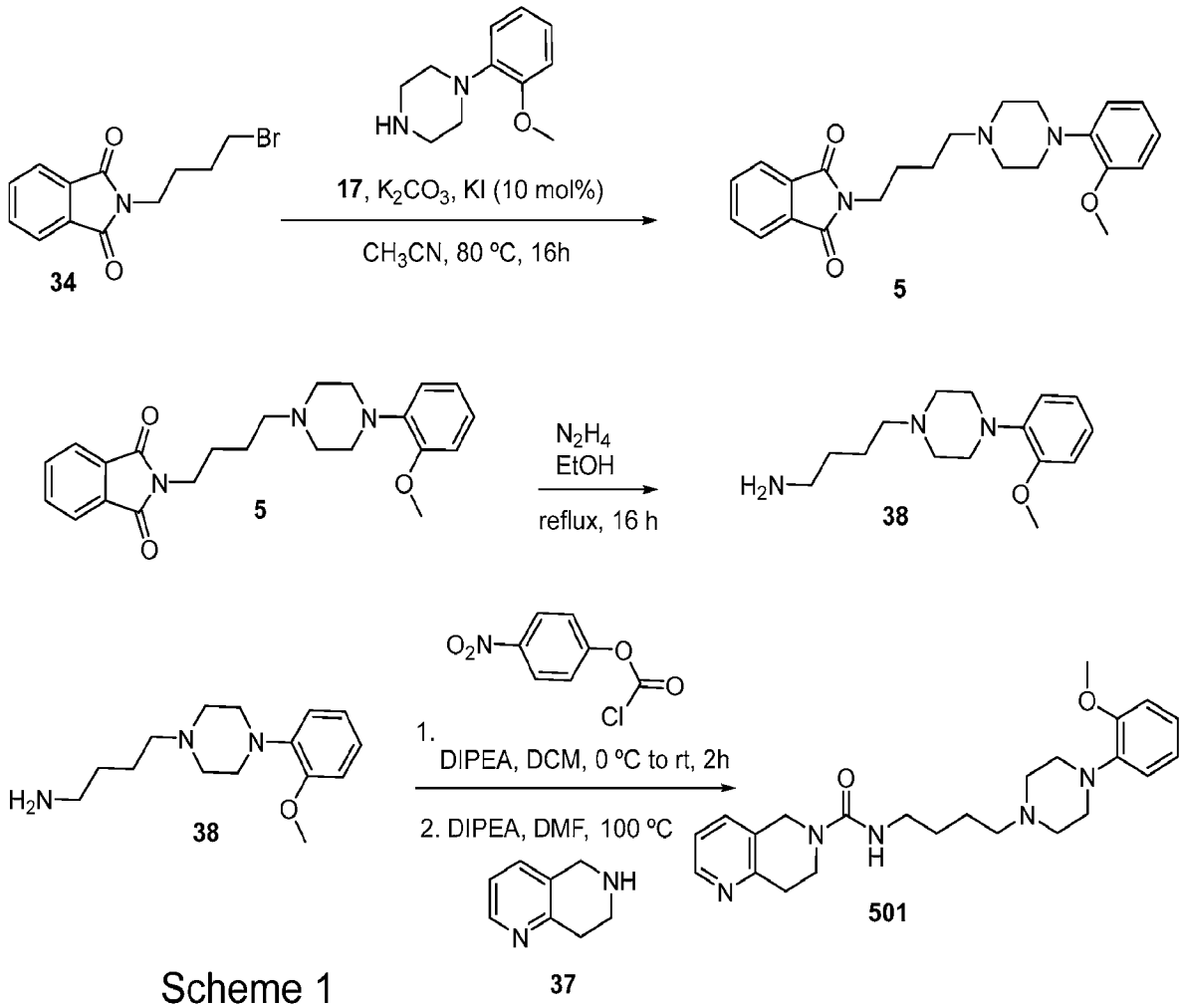
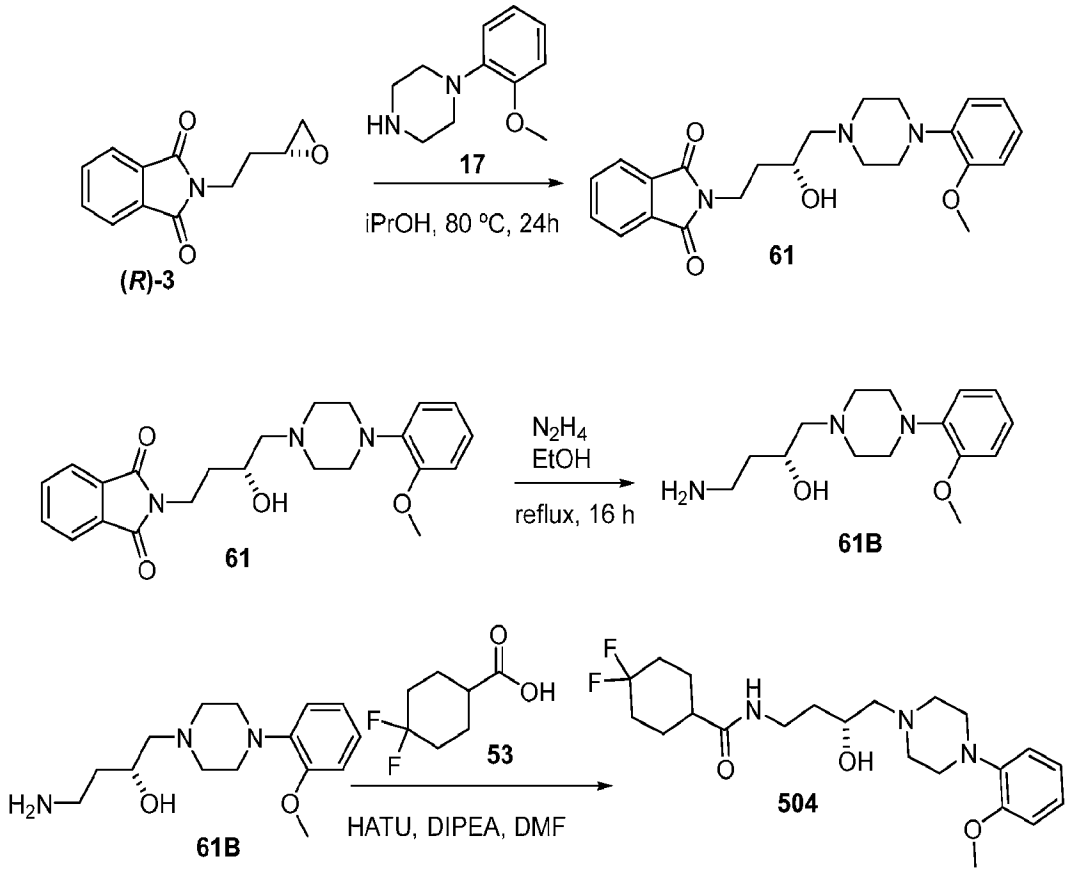


FIG. 16B



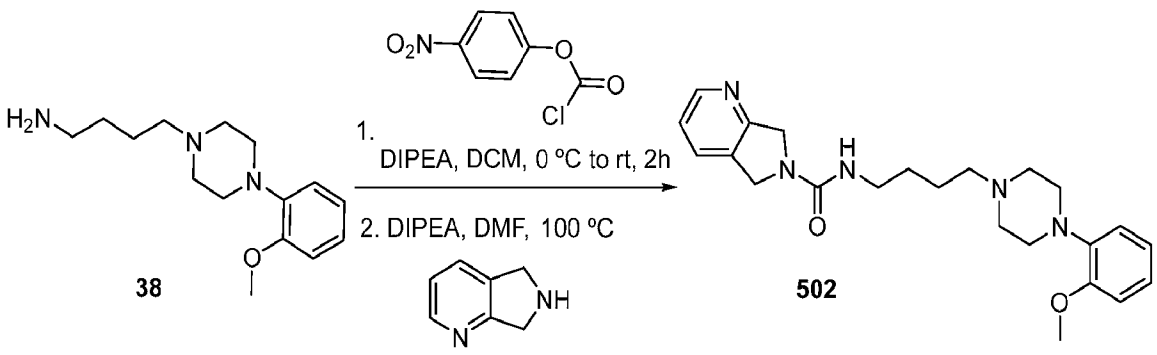
Scheme 1

FIG. 17



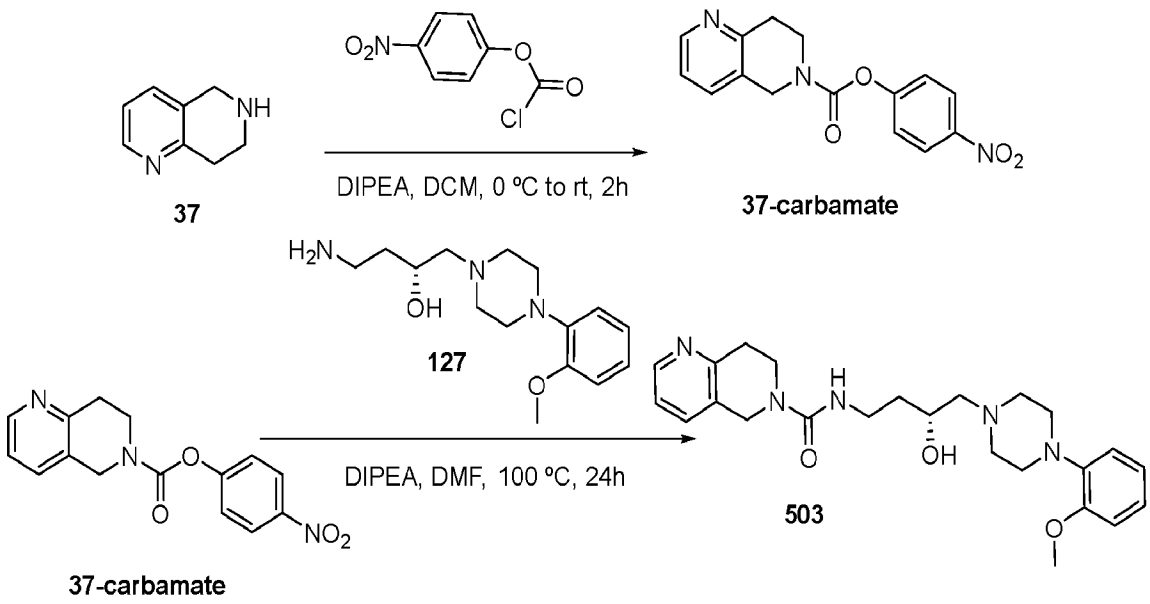
Scheme 2

FIG. 18



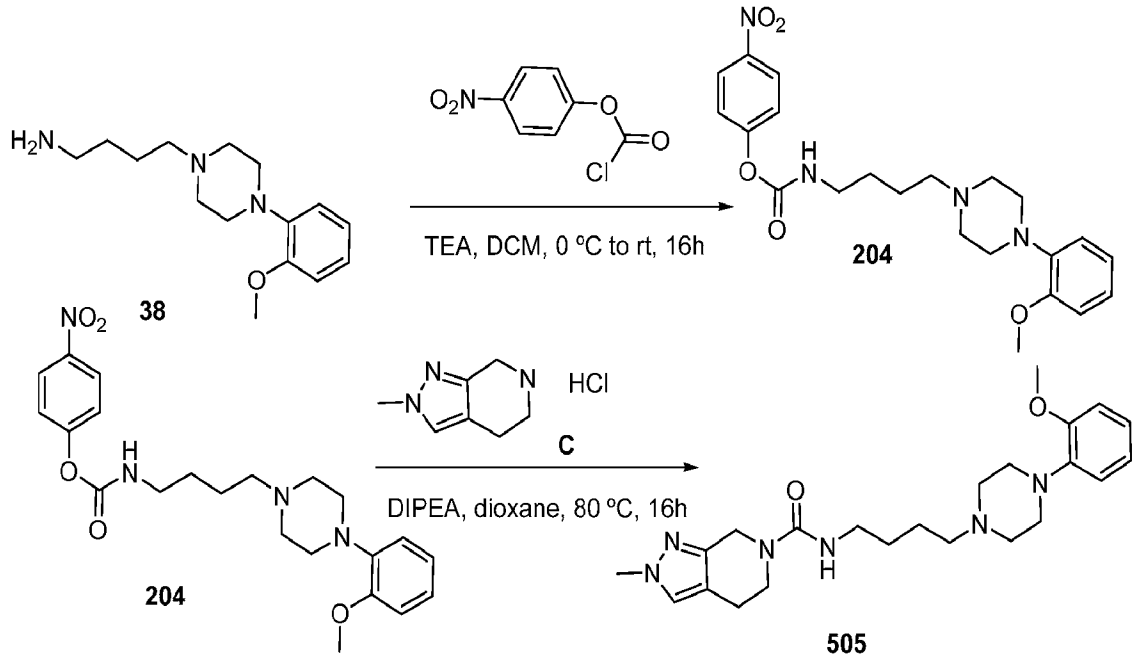
Scheme 3

FIG. 19



Scheme 4

FIG. 20



Scheme 5

FIG. 21

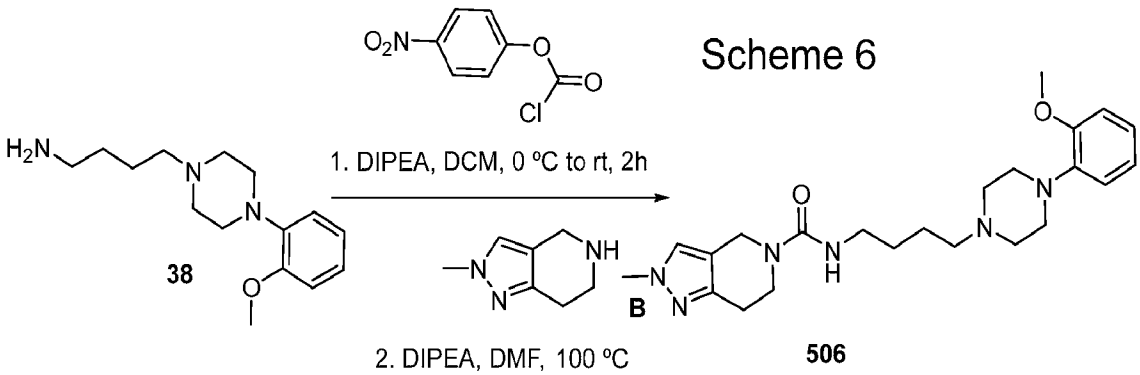

Scheme 6
1. DIPEA, DCM, 0 °C to rt, 2h
2. DIPEA, DMF, 100 °C
38
B
506

FIG. 22

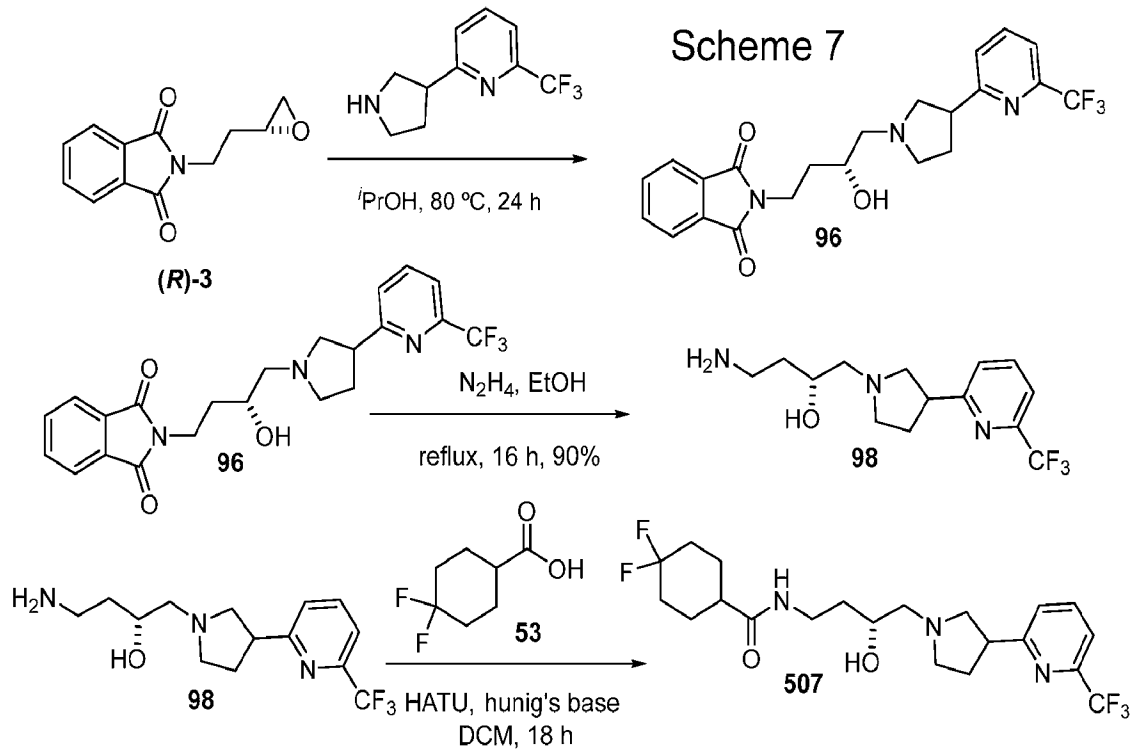

Scheme 7
(R)-3
iPrOH, 80 °C, 24 h
96
N2H4, EtOH
reflux, 16 h, 90%
98
53
HATU, hunig's base
DCM, 18 h
507

FIG. 23

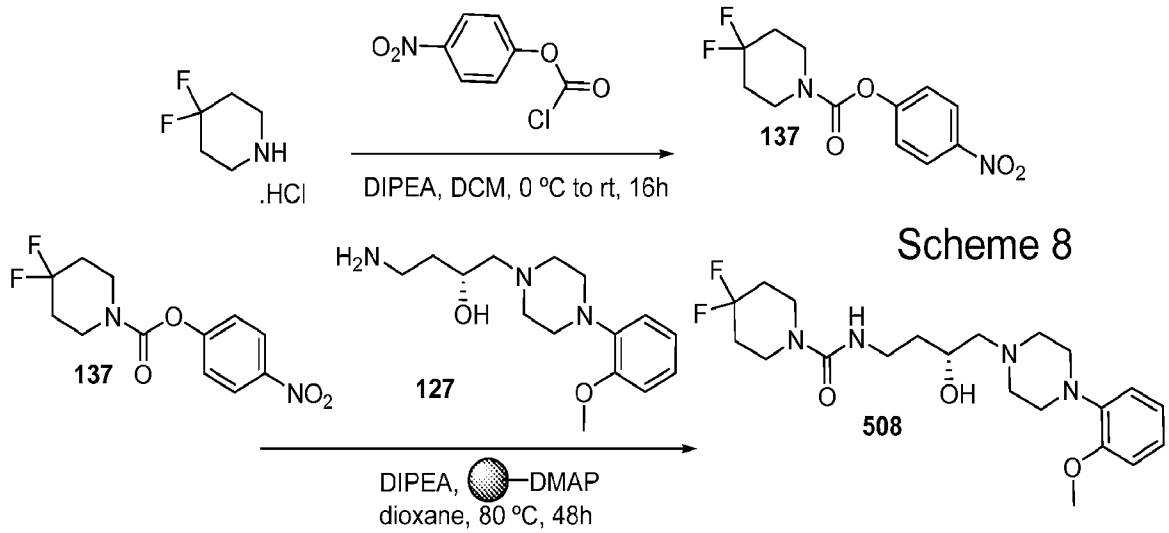

Scheme 8
.HCl
DIPEA, DCM, 0 °C to rt, 16h
137
127
508
DIPEA, DMAP
dioxane, 80 °C, 48h

FIG. 24

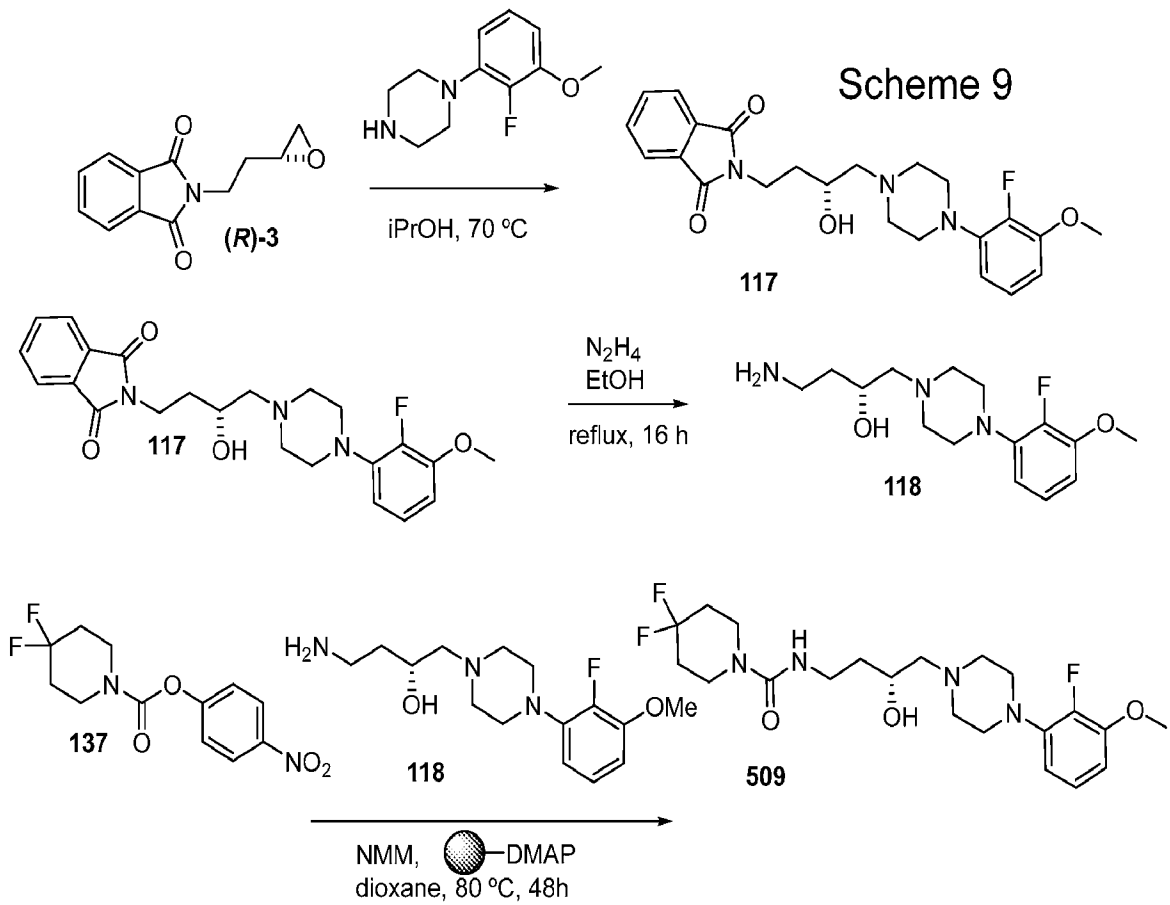
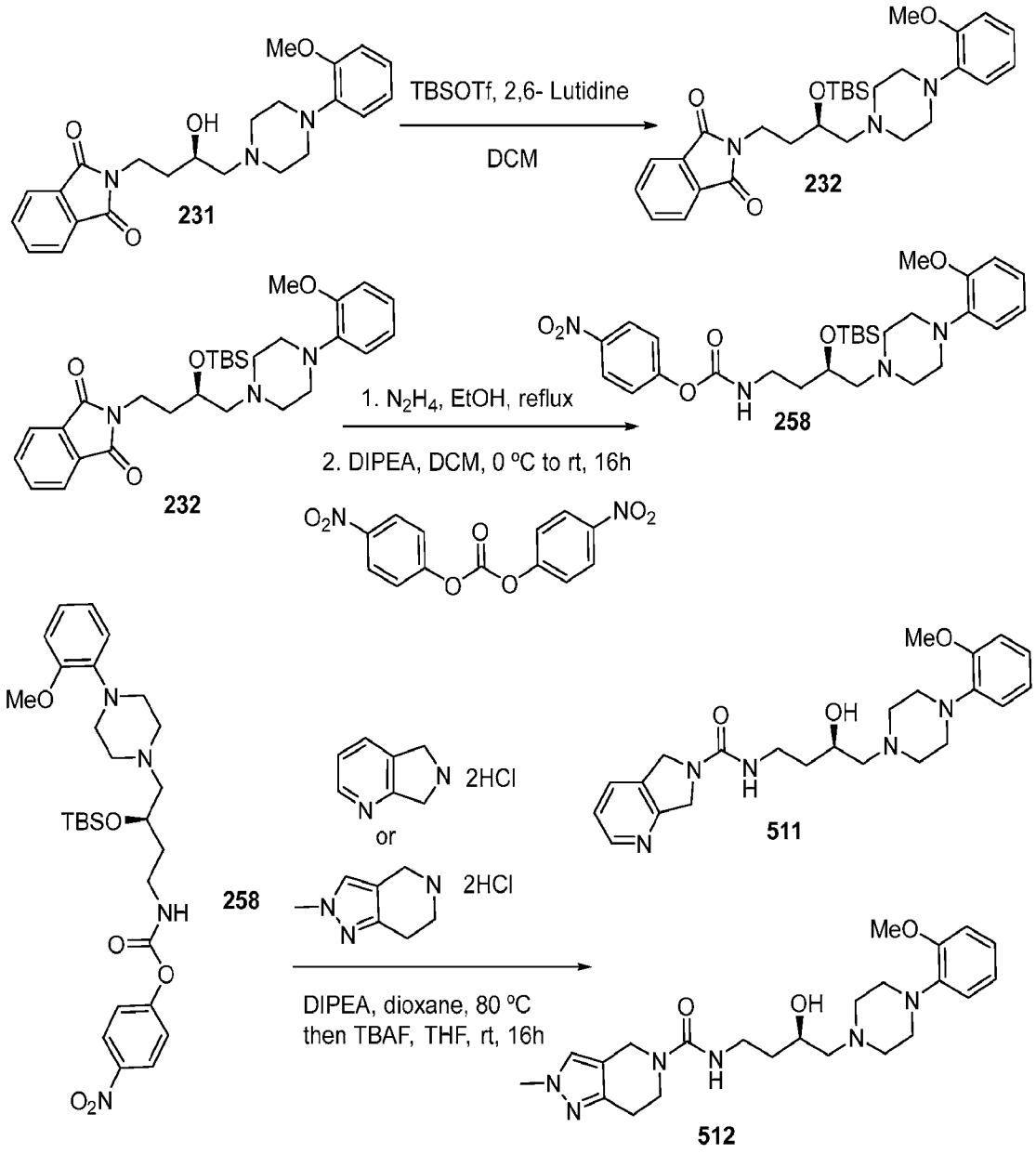

Scheme 9
(R)-3
iPrOH, 70 °C
117
N2H4
EtOH
reflux, 16 h
118
137
509
NMM, DMAP
dioxane, 80 °C, 48h

FIG. 25



Schemes 10 & 11

FIG. 26

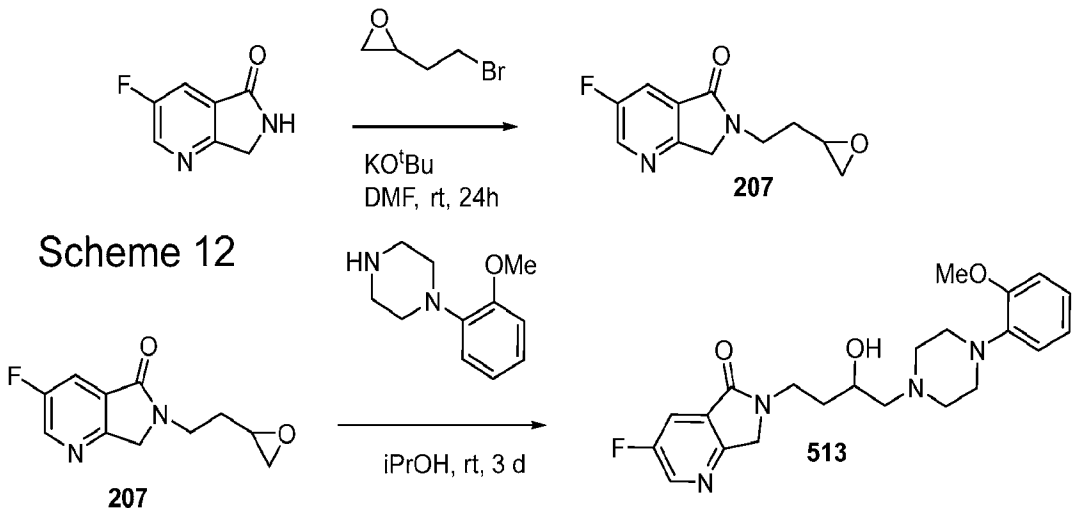

Br
KO^{t}Bu
DMF, rt, 24h
207
Scheme 12
HN
OMe
MeO
OH
iPrOH, rt, 3 d
207
513

FIG. 27

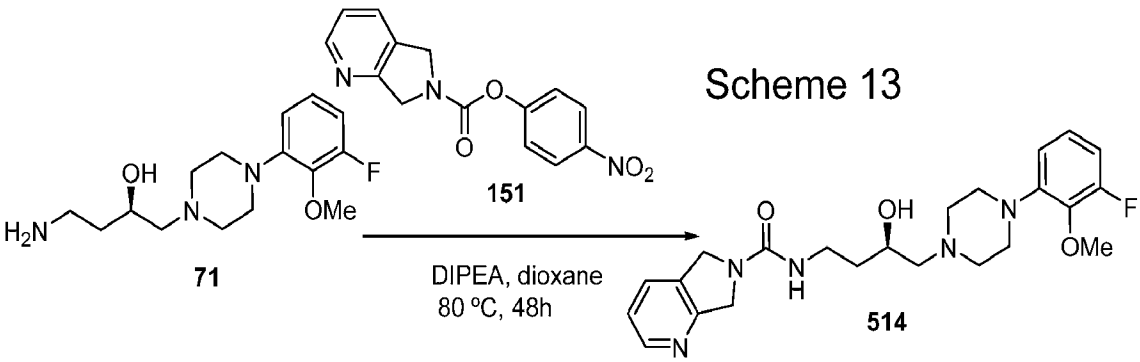
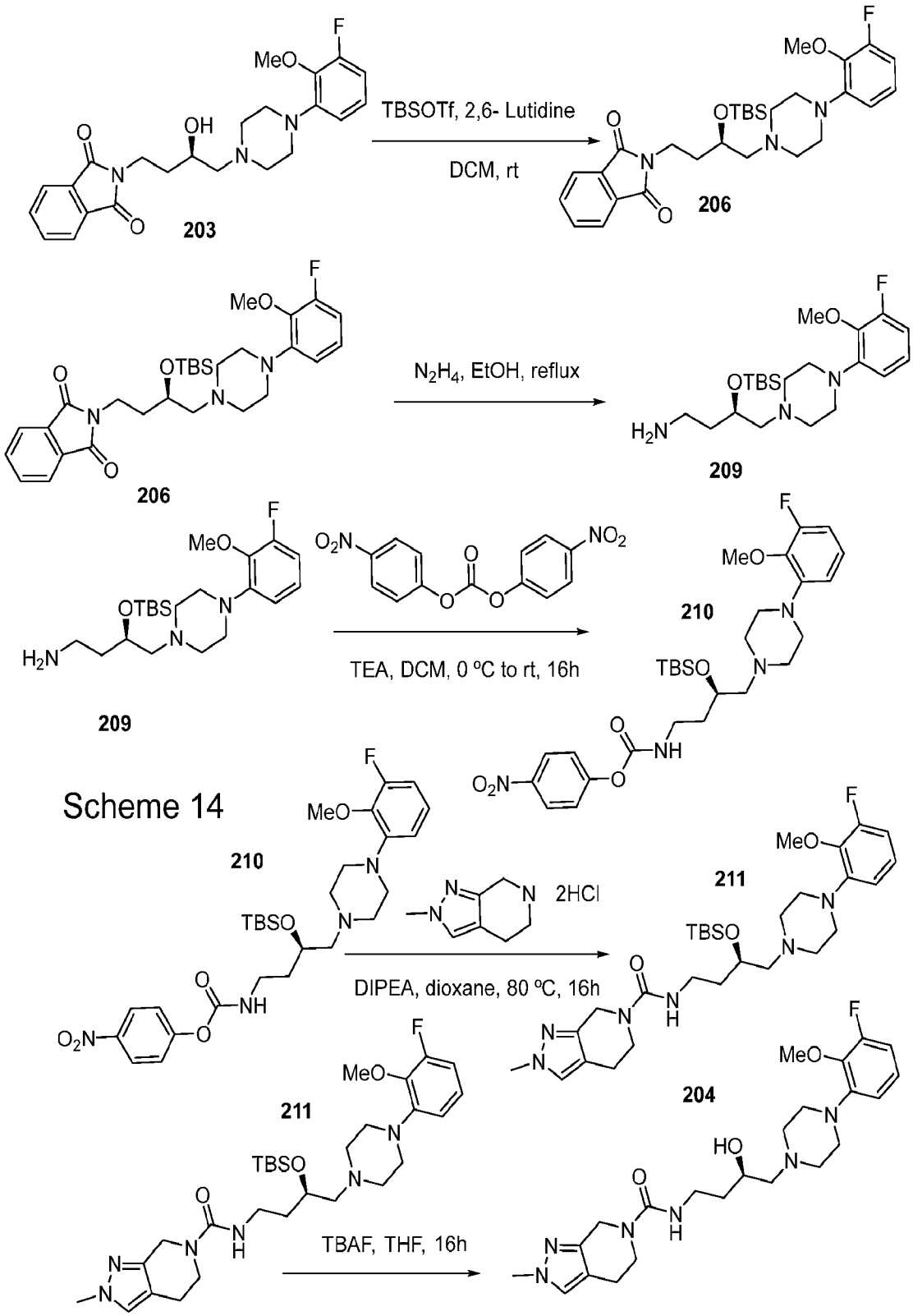

Scheme 13
OH
F
OMe
H_2N
71
151
NO_2
DIPEA, dioxane
80 °C, 48h
514

FIG. 28



Scheme 14

FIG. 29

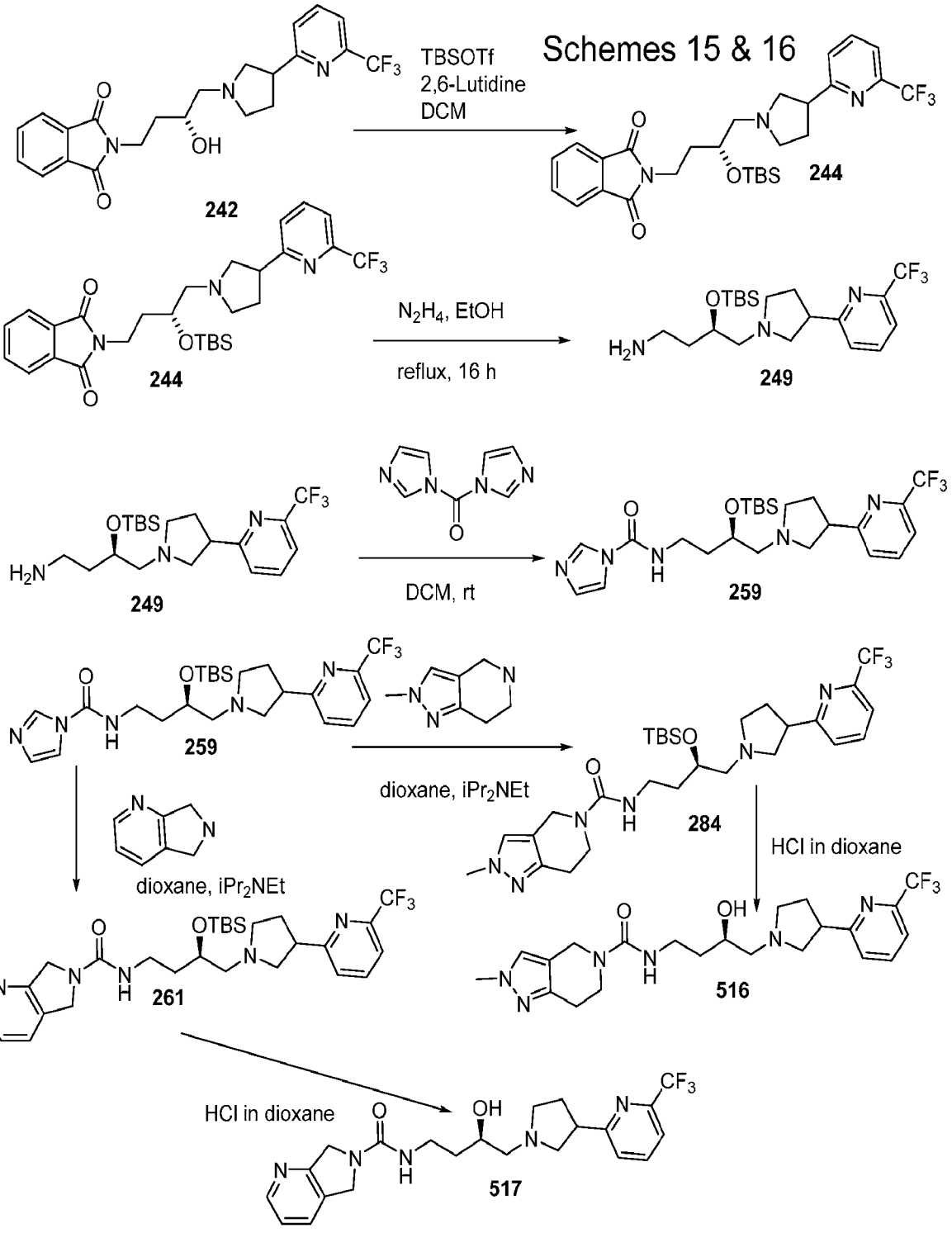

Schemes 15 & 16
TBSOTf
2,6-Lutidine
DCM
242
244
N_2H_4, EtOH
reflux, 16 h
249
DCM, rt
259
dioxane, iPr_2NEt
284
HCl in dioxane
261
516
517

FIG. 30

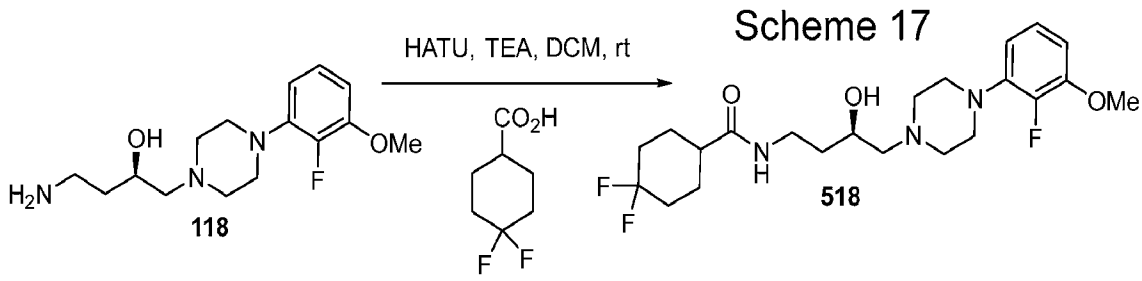


FIG. 31

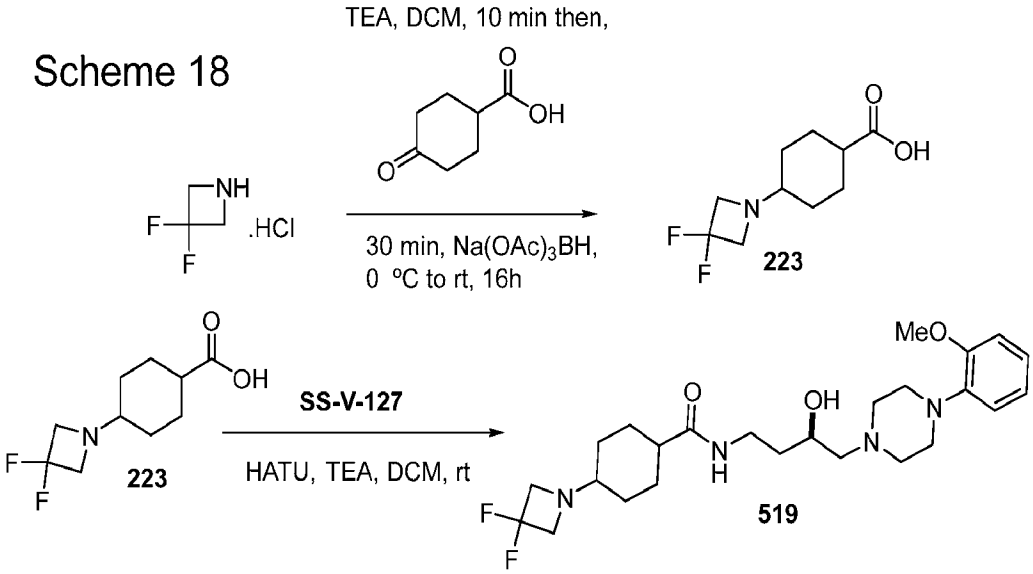


FIG. 32

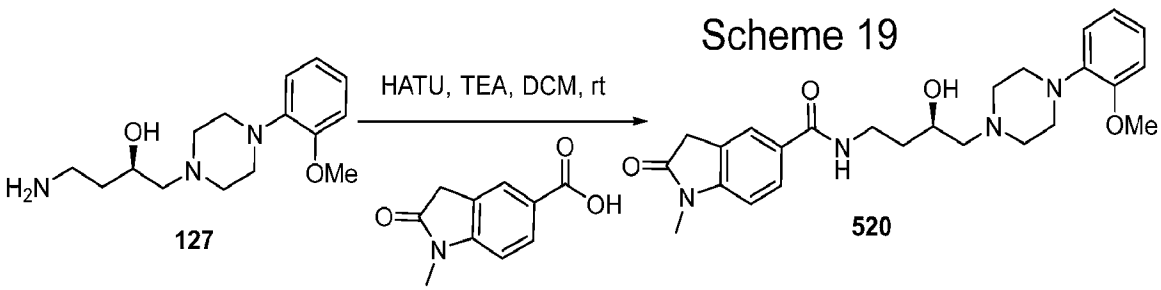
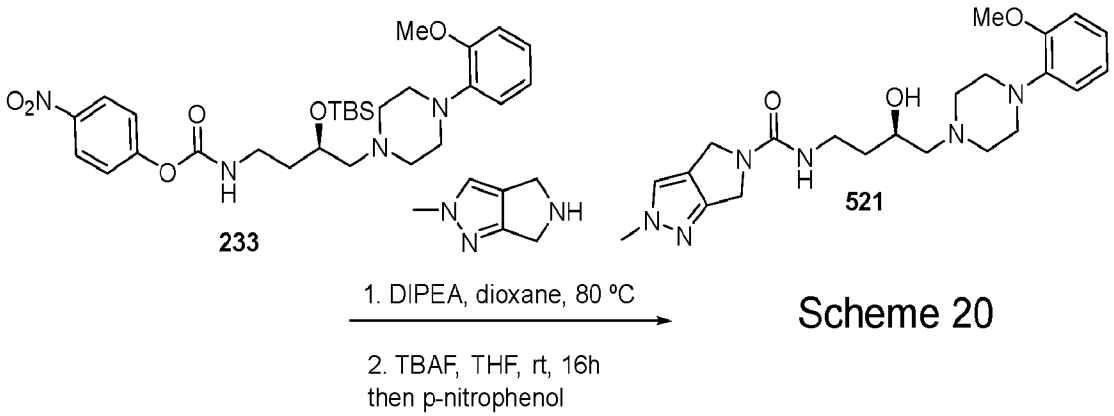


FIG. 33



Scheme 20

FIG. 34

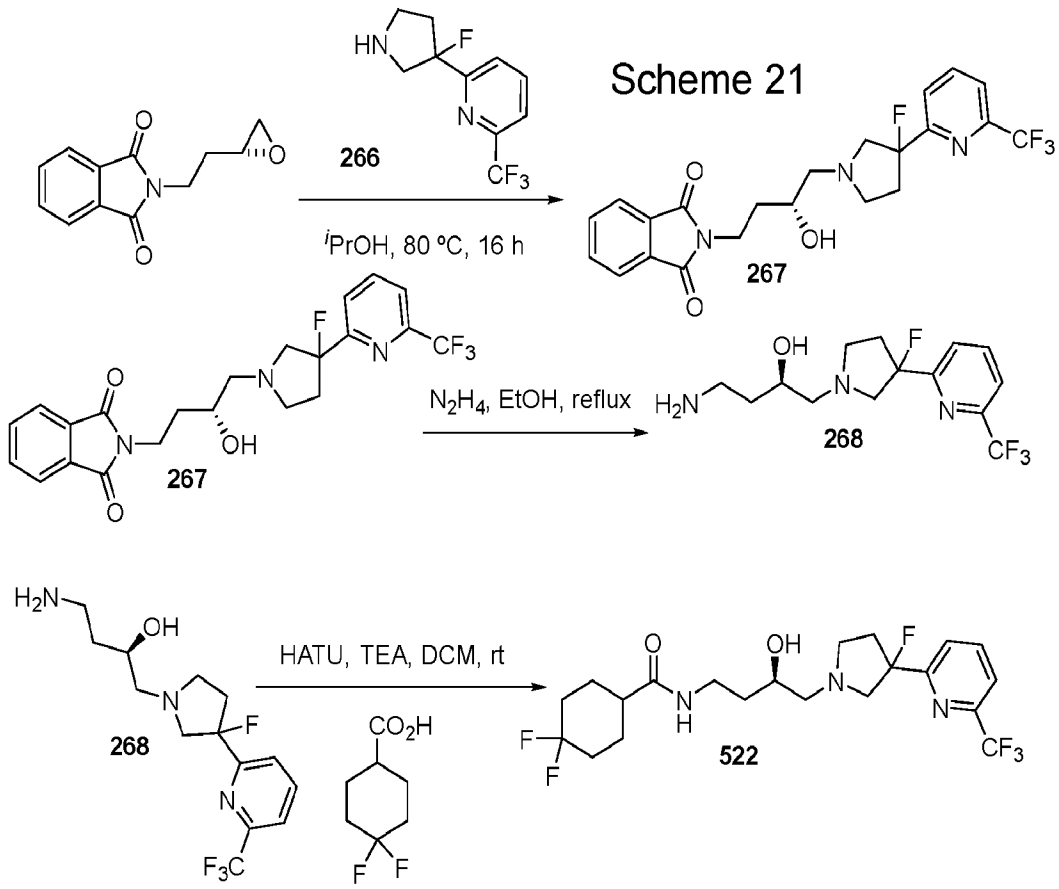


FIG. 35

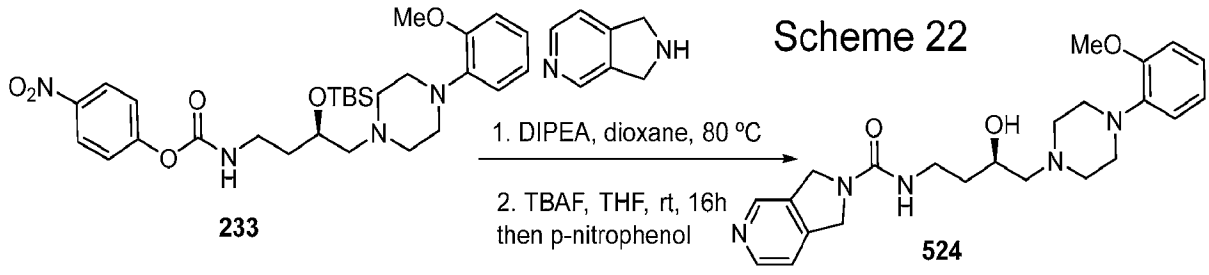


FIG. 36

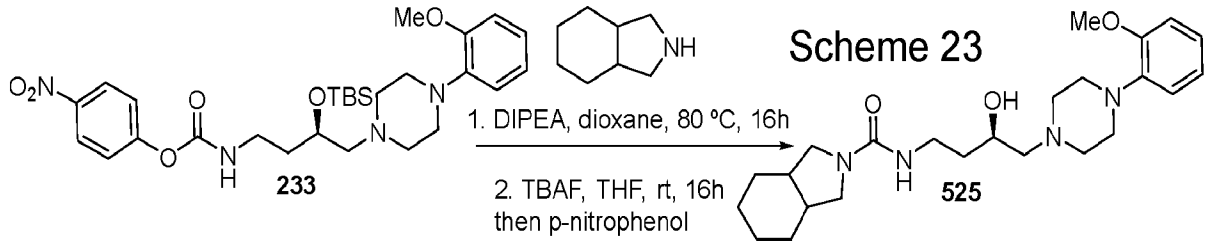


FIG. 37

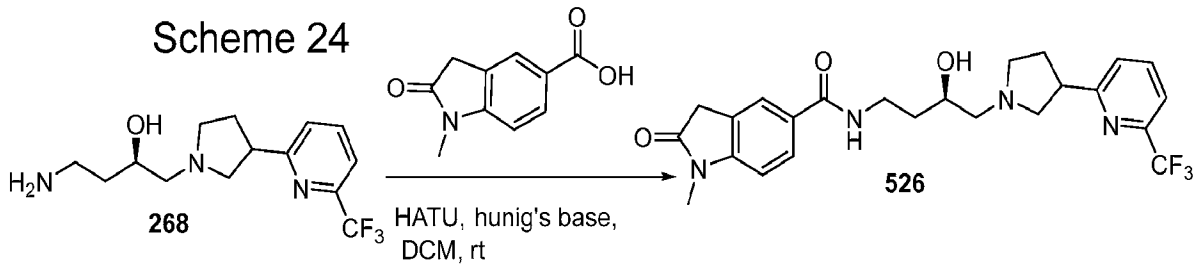


FIG. 38

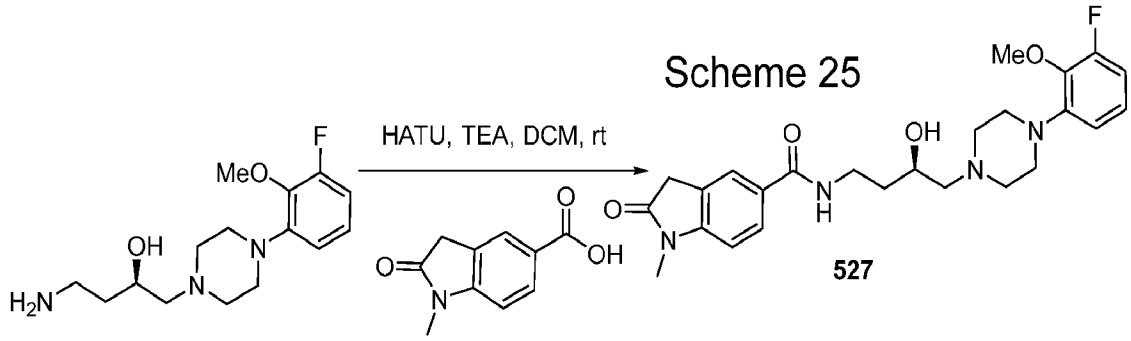


FIG. 39

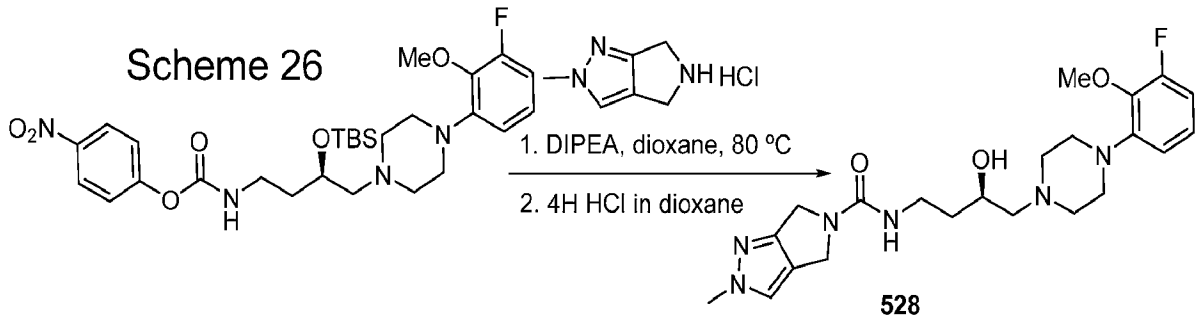


FIG. 40

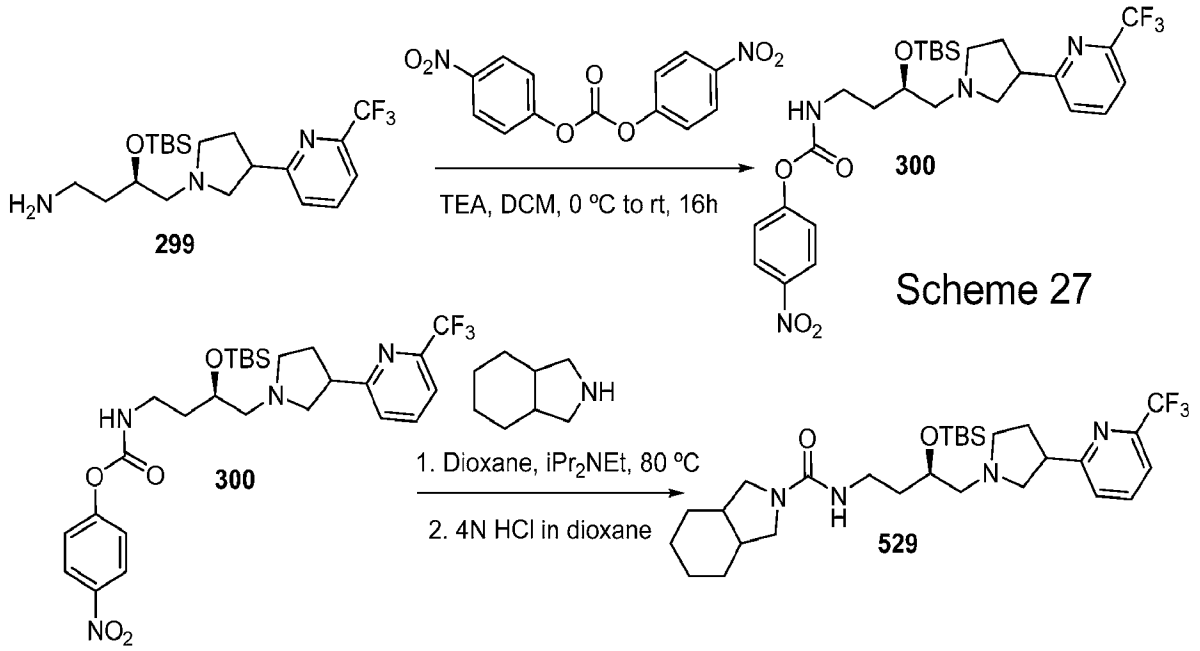


FIG. 41

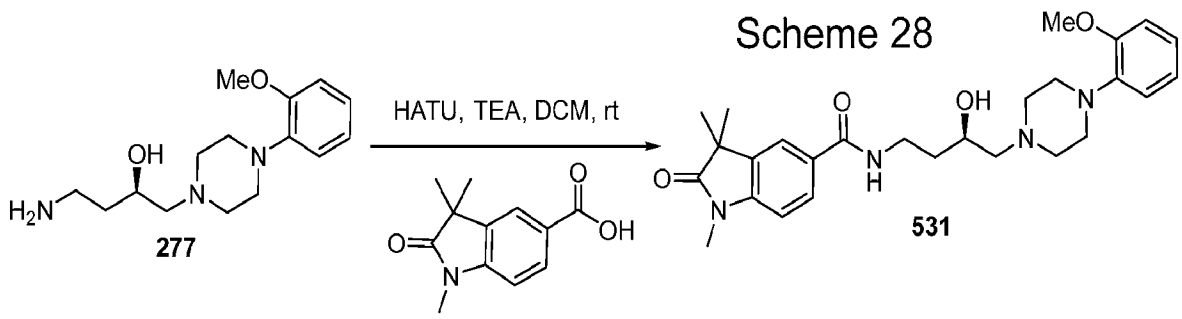


FIG. 42

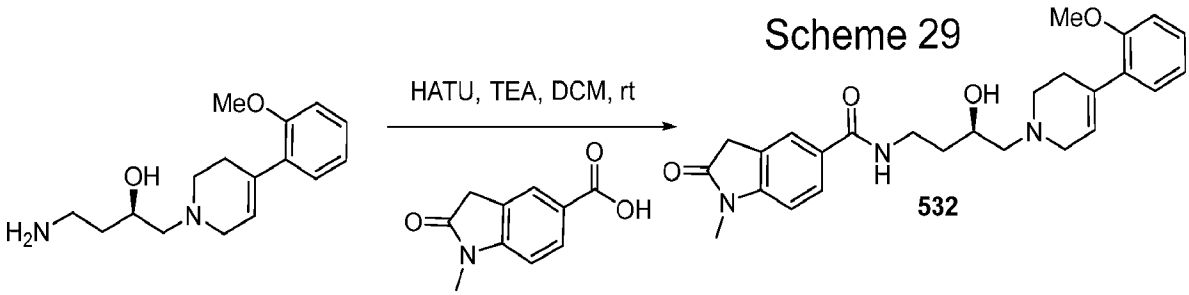


FIG. 43

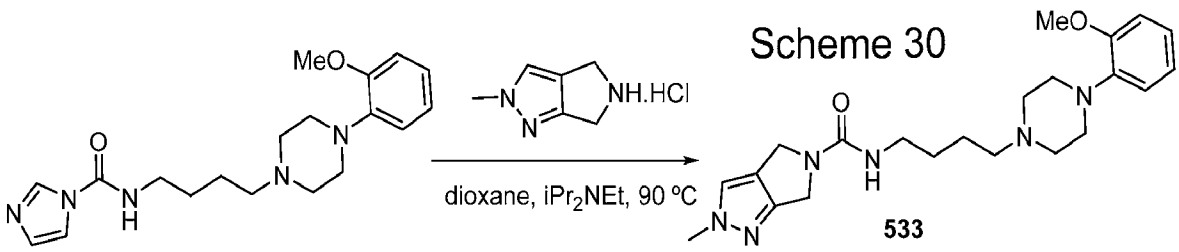


FIG. 44

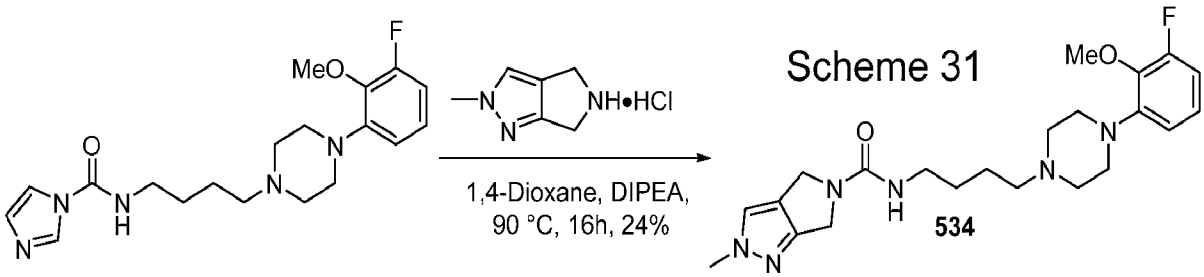


FIG. 45

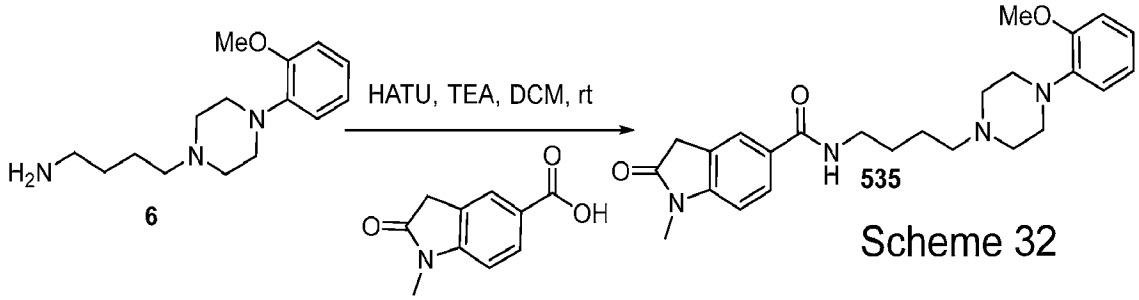


FIG. 46

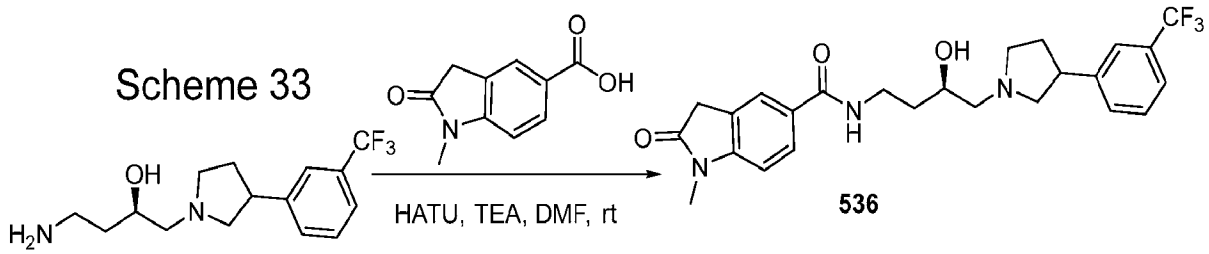


FIG. 47

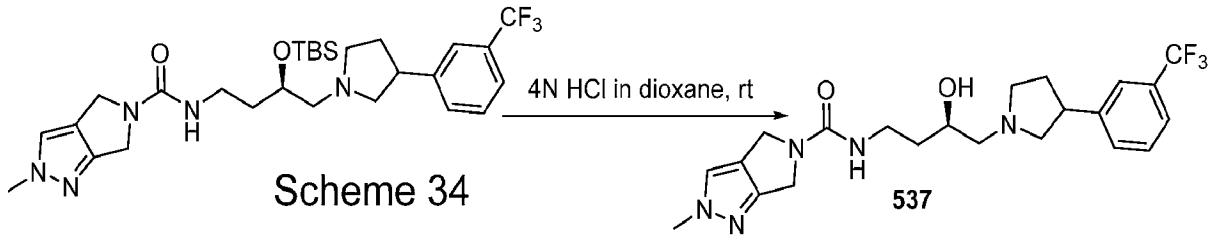


FIG. 48

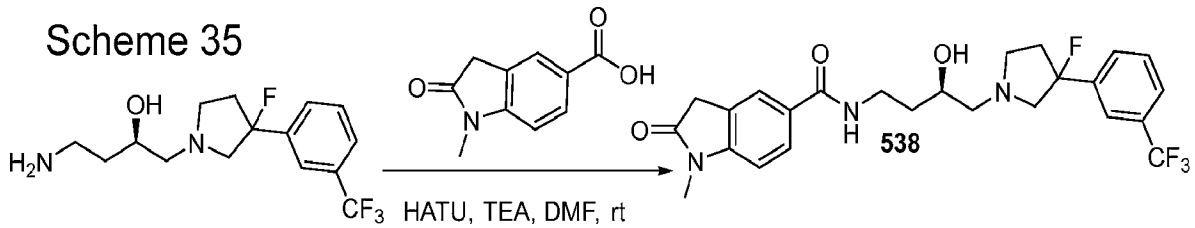


FIG. 49

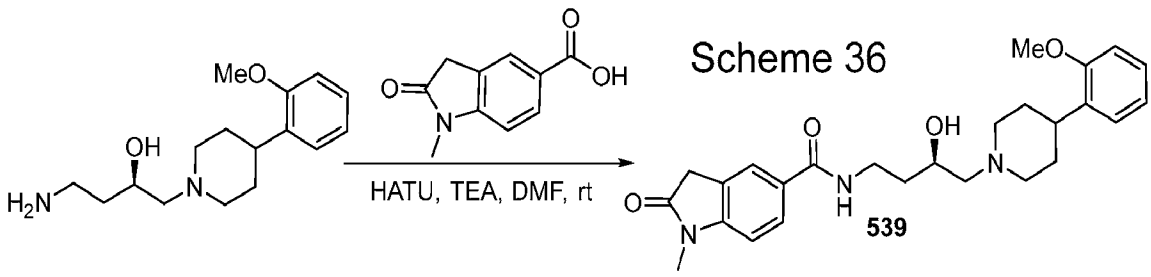


FIG. 50

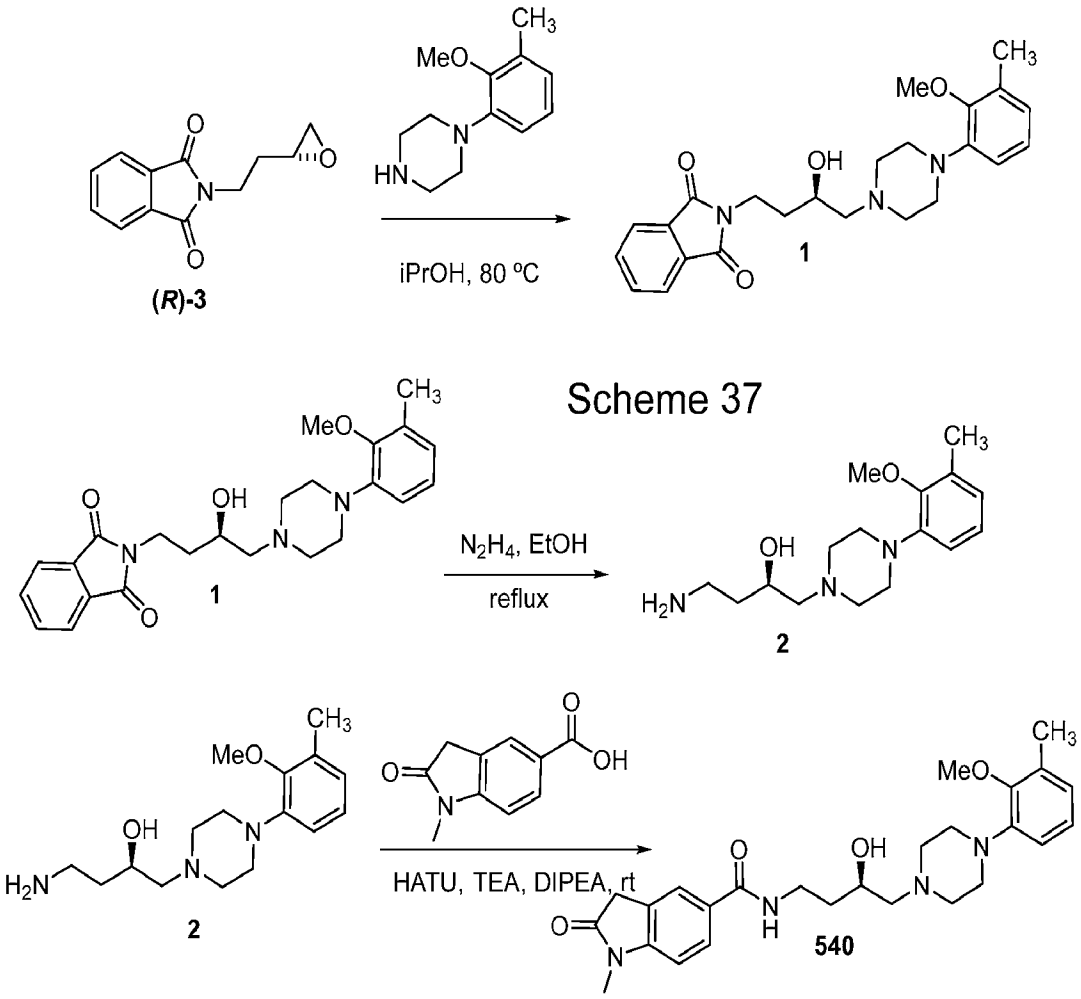

(R)-3
iPrOH, 80 °C
1
Scheme 37
N2H4, EtOH
reflux
2
HATU, TEA, DIPEA, rt
540

FIG. 51

Scheme 38

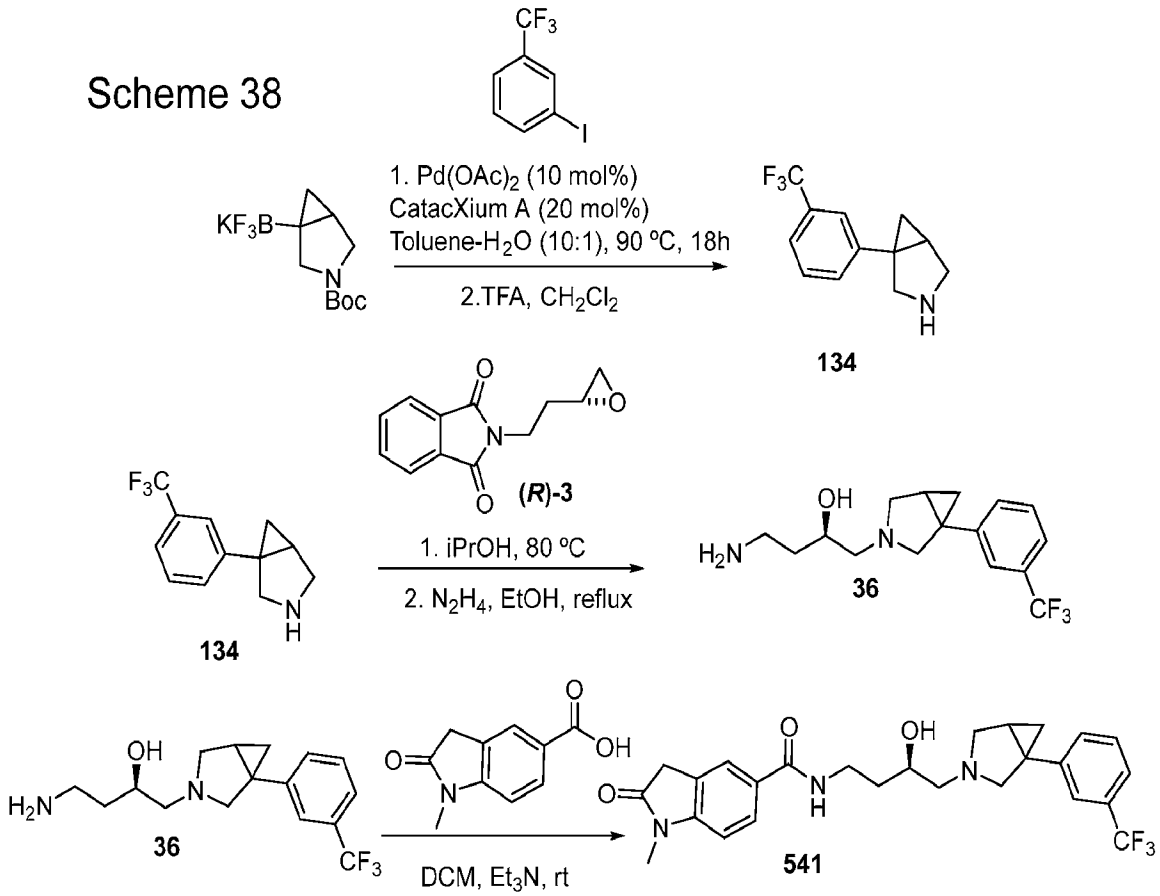


FIG. 52

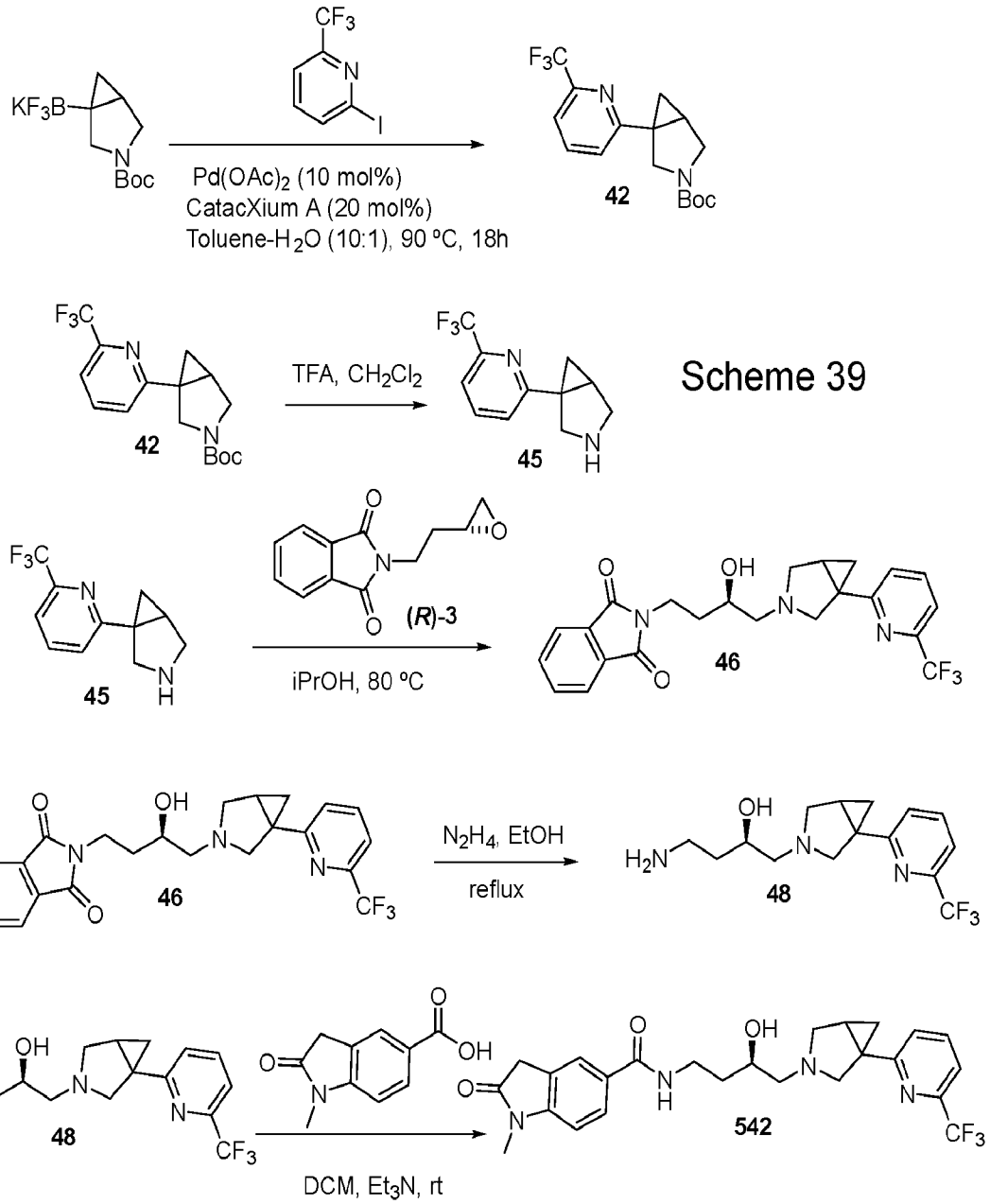

KF3B
N
Boc
CF3
N
I
Pd(OAc)2 (10 mol%)
CatacXium A (20 mol%)
Toluene-H2O (10:1), 90 °C, 18h
F3C
N
N
Boc
42
TFA, CH2Cl2
F3C
N
N
H
45
Scheme 39
O
O
N
O
(R)-3
iPrOH, 80 °C
OH
N
N
CF3
46
N2H4, EtOH
reflux
H2N
48
DCM, Et3N, rt
542

FIG. 53

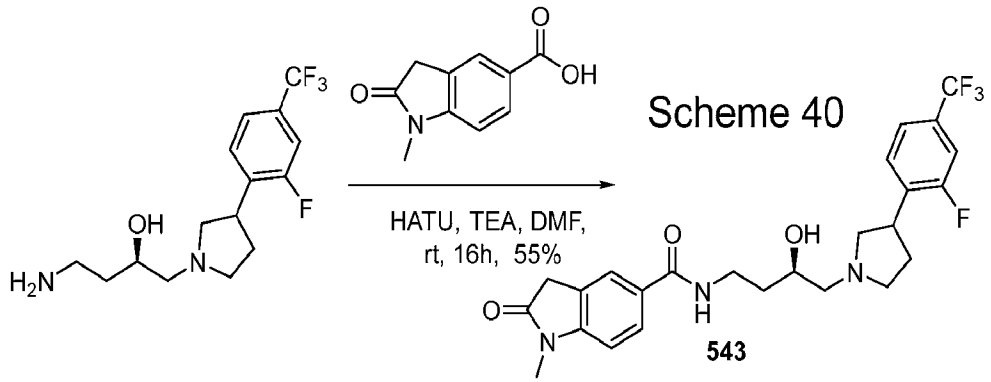


FIG. 54

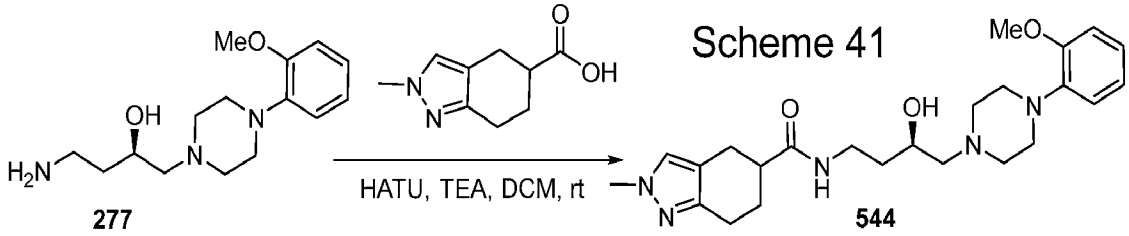


FIG. 55

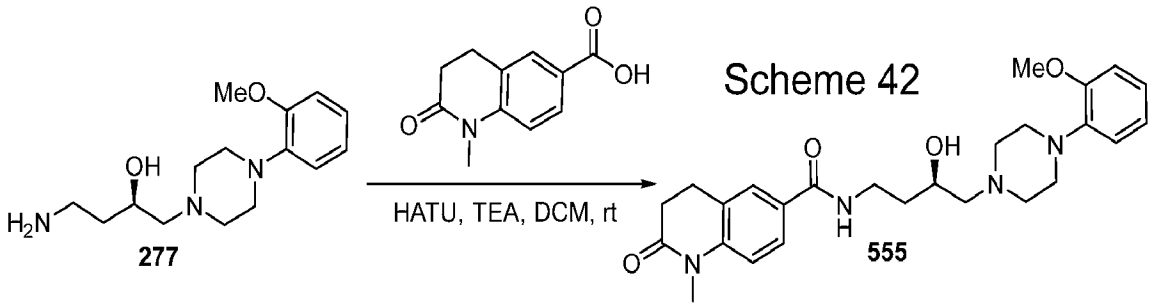


FIG. 56

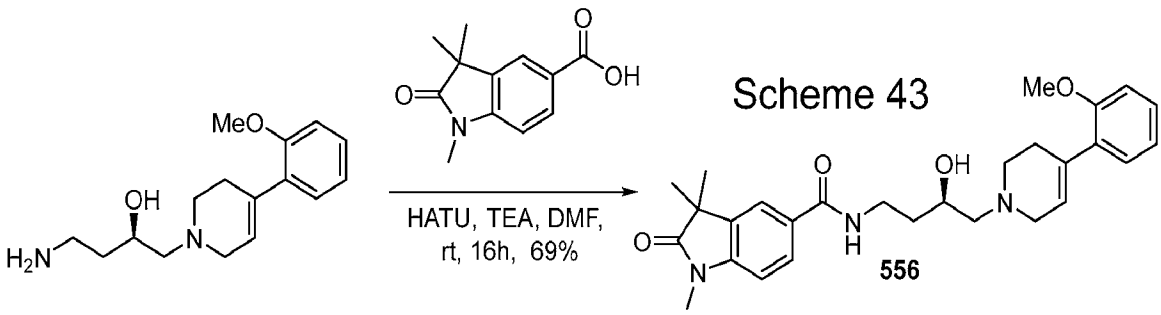
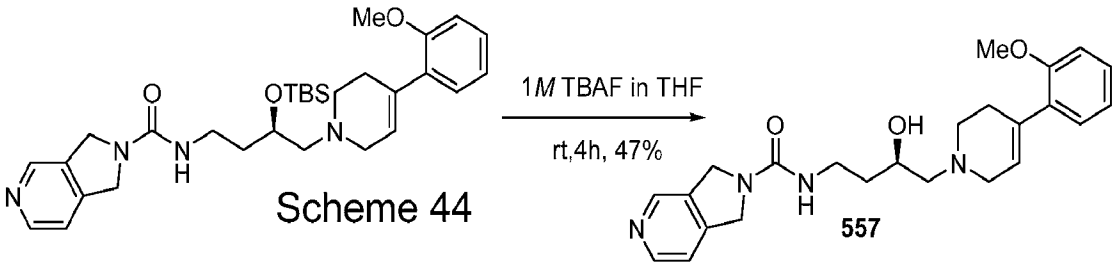
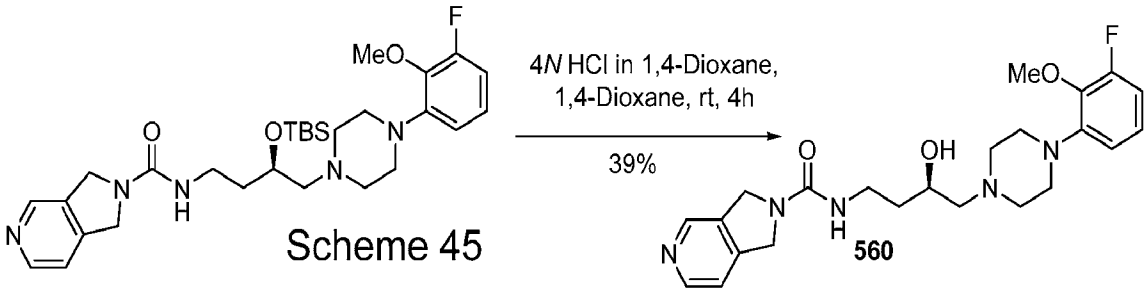


FIG. 57



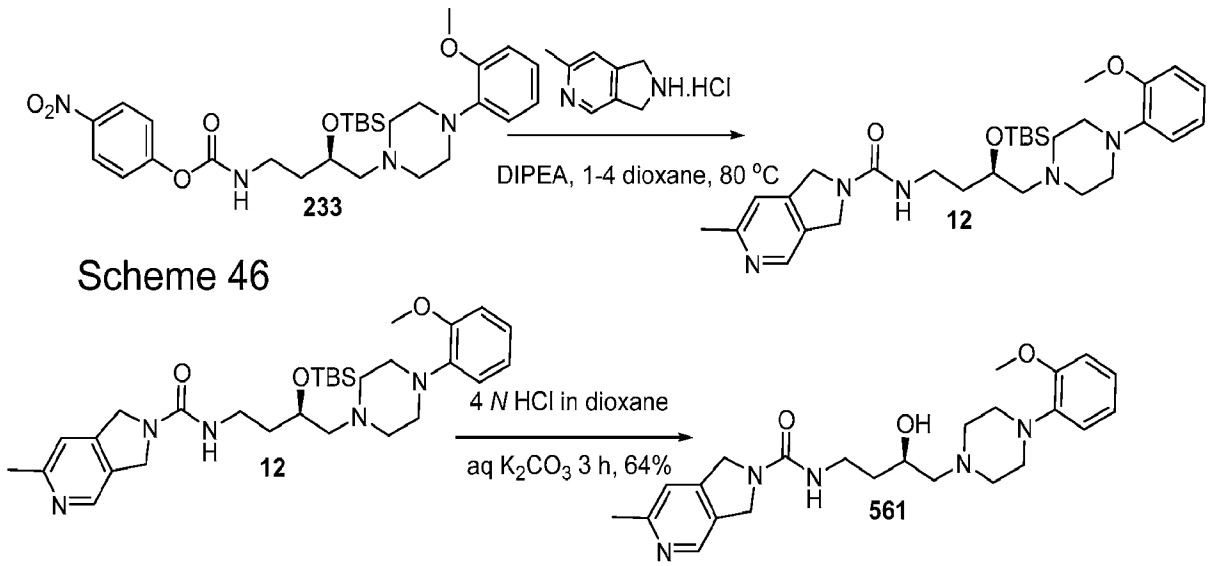
Scheme 44

FIG. 58



Scheme 45

FIG. 59



Scheme 46

FIG. 60

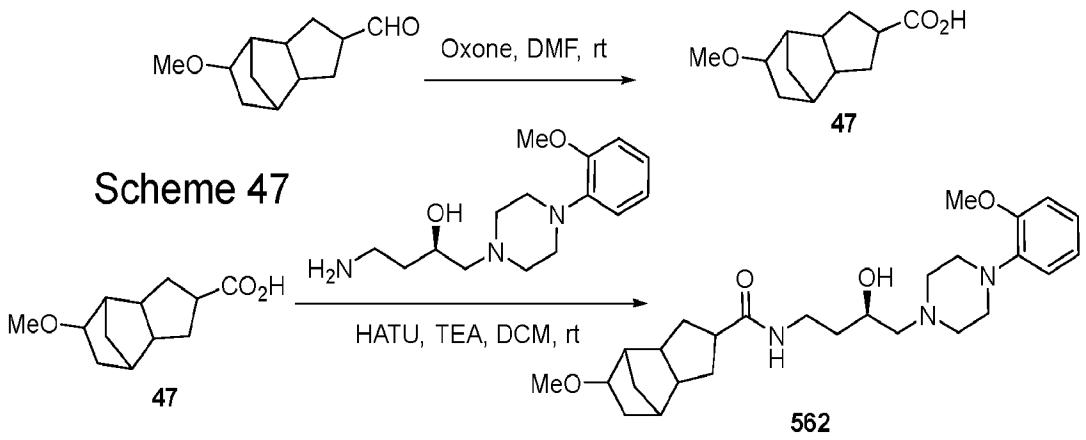


FIG. 61

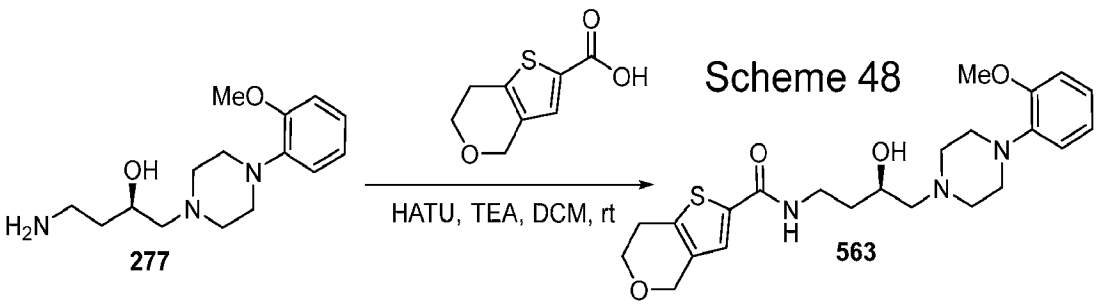


FIG. 62

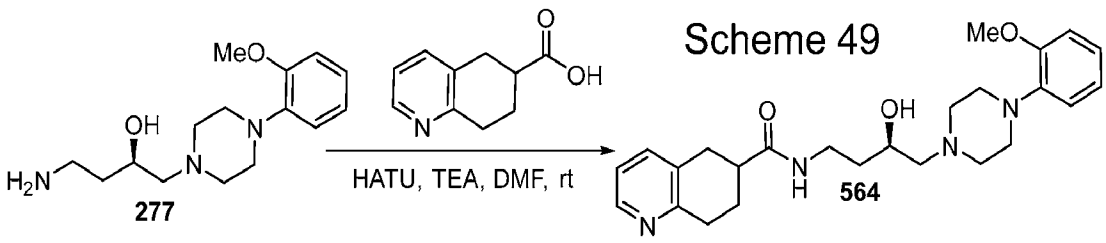
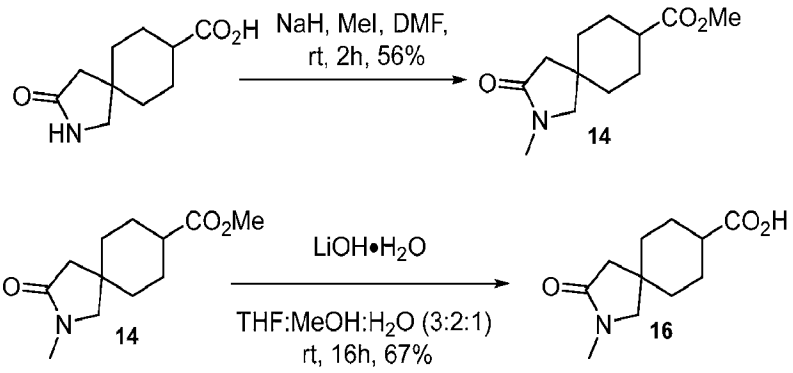


FIG. 63



Scheme 50

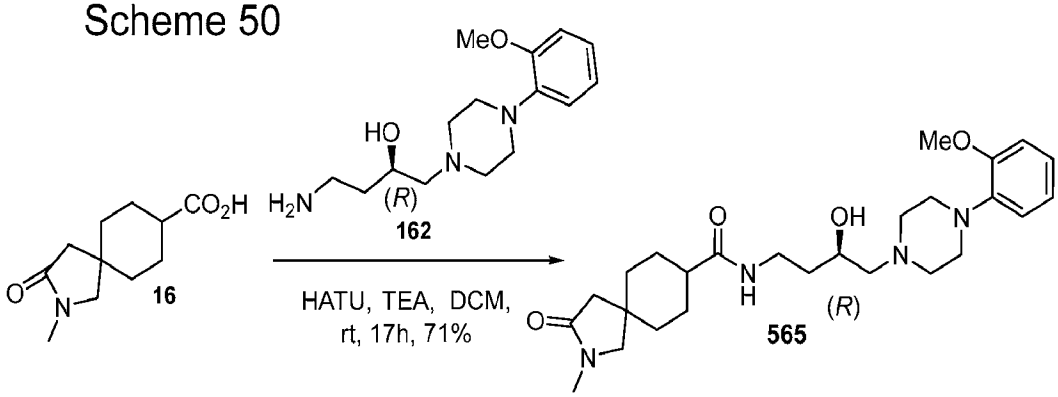
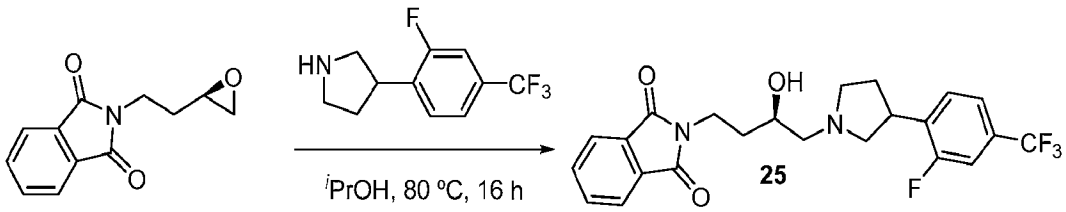
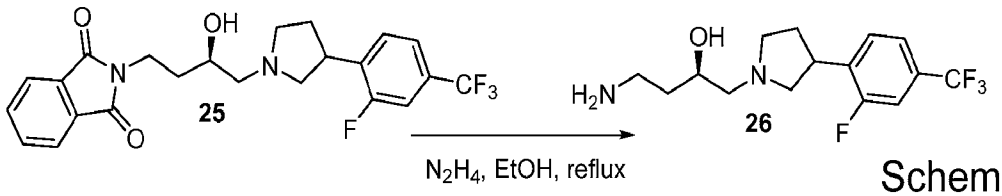


FIG. 64





Scheme 51

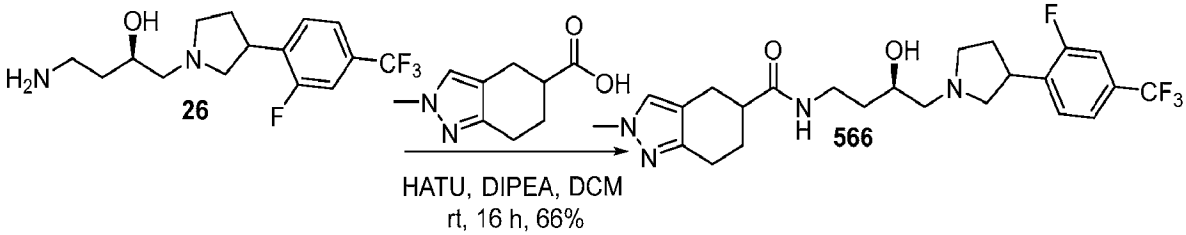


FIG. 65

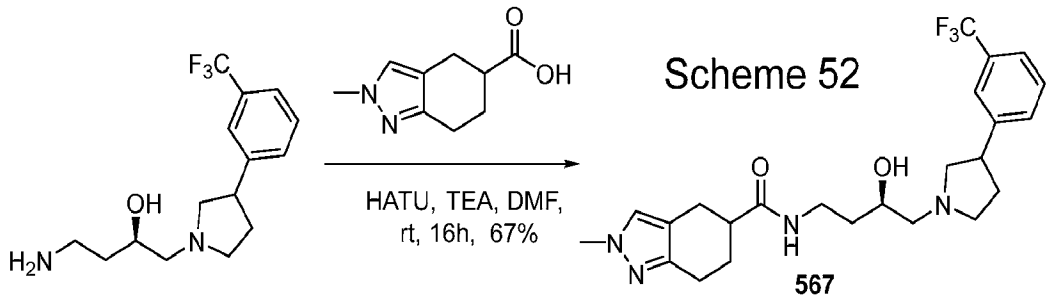

Scheme 52
HATU, TEA, DMF,
rt, 16h, 67%
567

FIG. 66

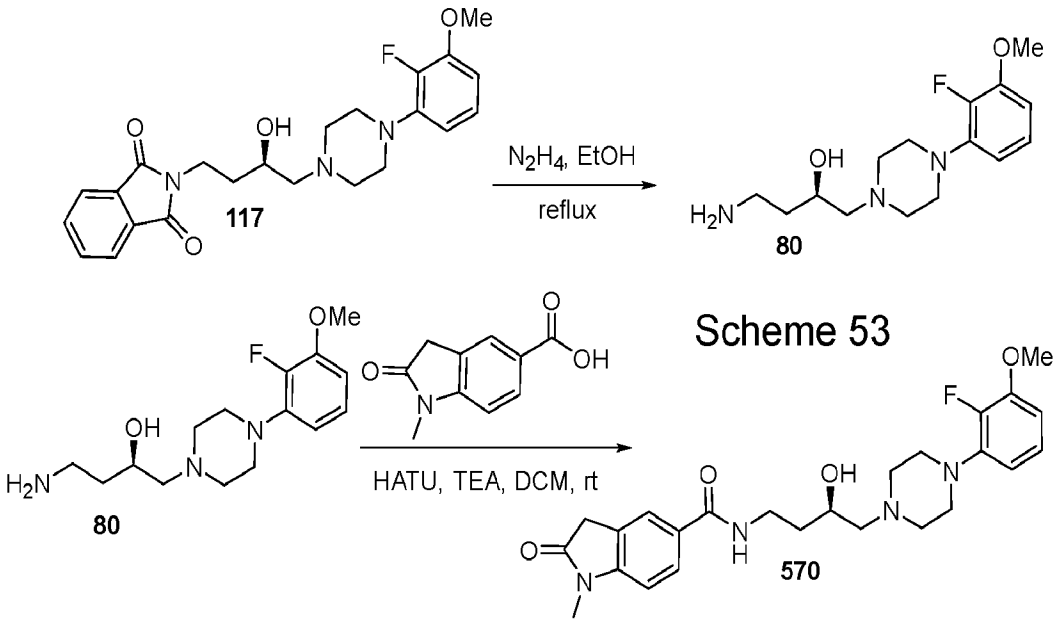
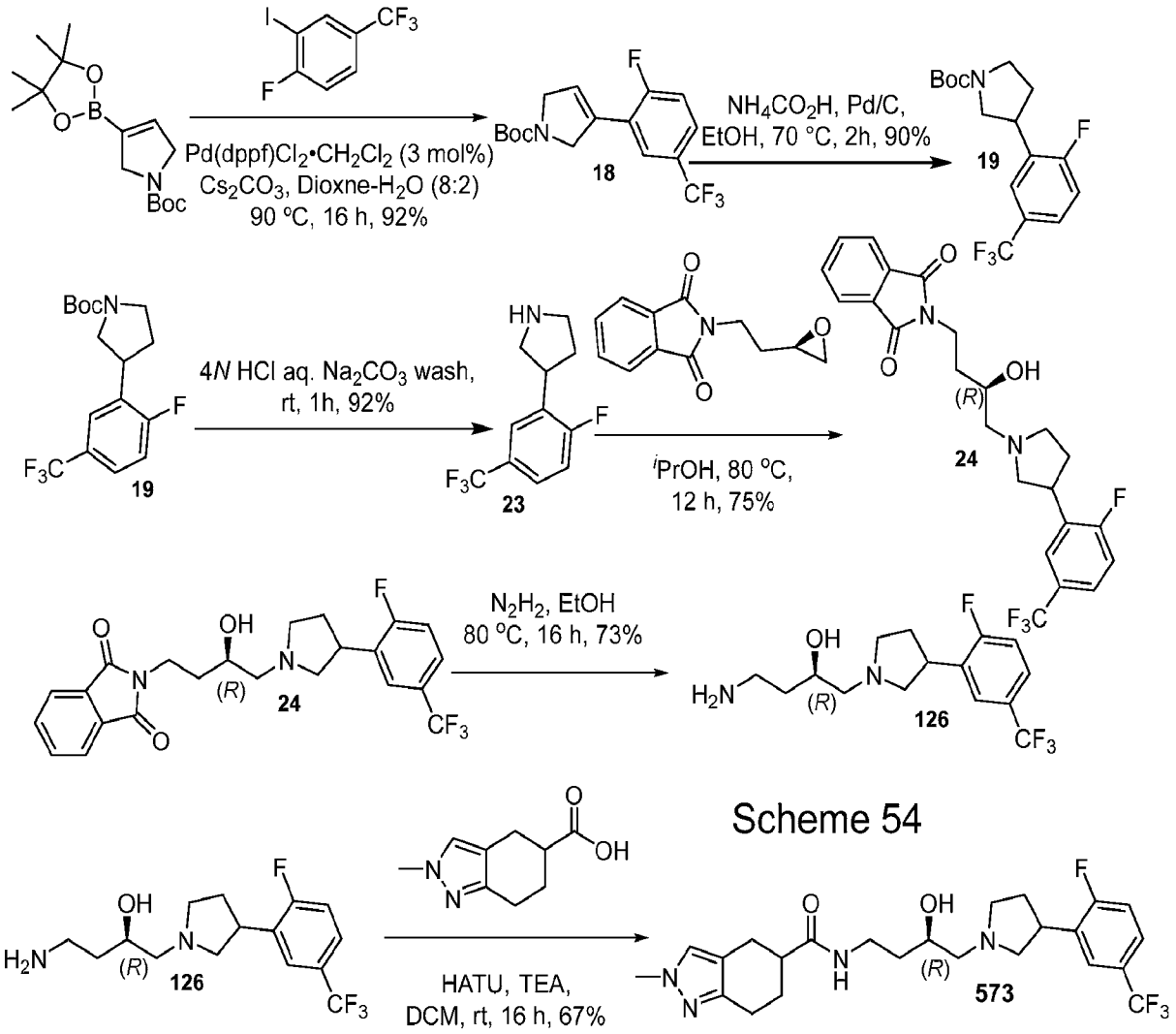

117
N_2H_4, EtOH
reflux
80
Scheme 53
80
HATU, TEA, DCM, rt
570

FIG. 67



Scheme 54

FIG. 68

Scheme 55

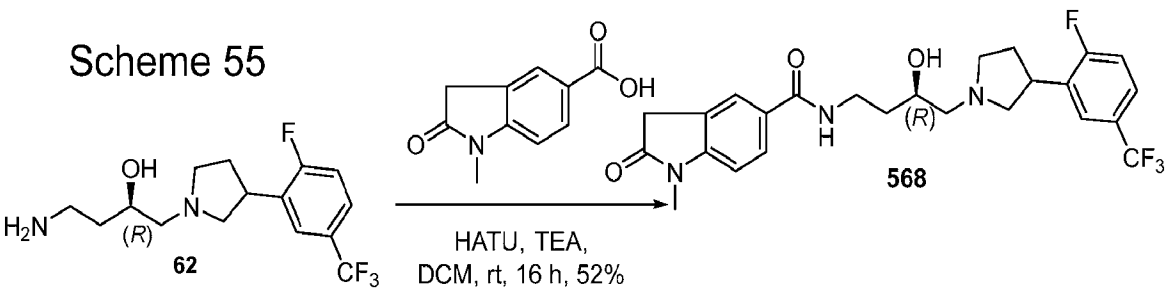


FIG. 69

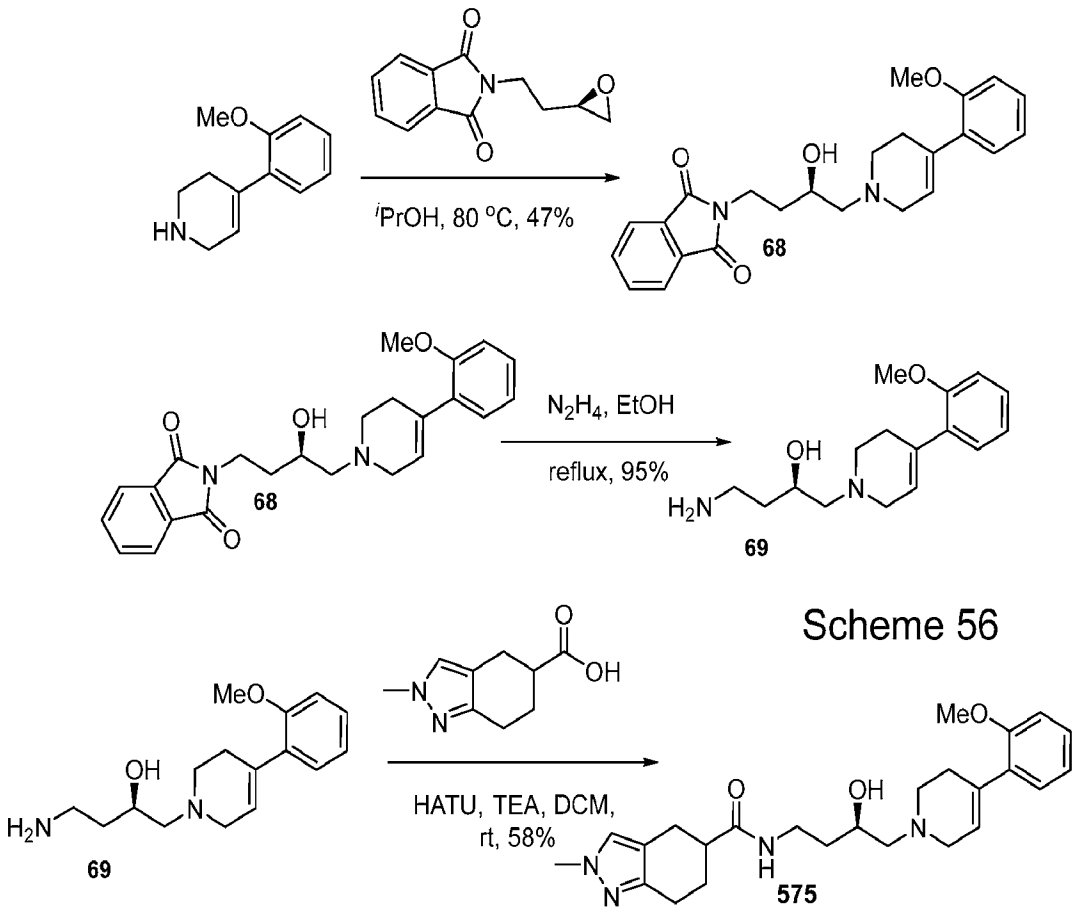
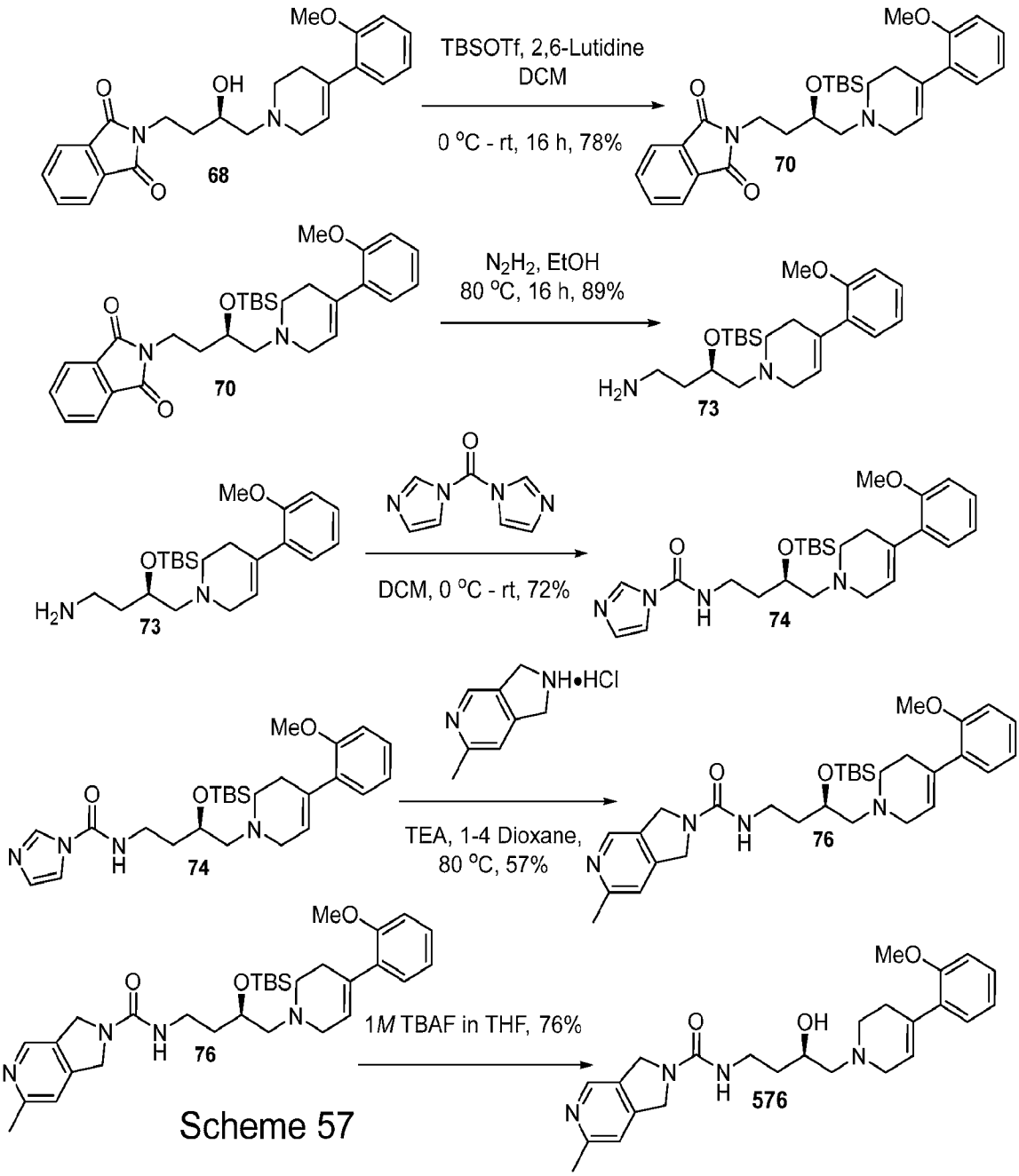

MeO
HN
O
N
O
O
iPrOH, 80 °C, 47%
MeO
OH
N
O
N
O
68
MeO
OH
N
O
N
O
68
N2H4, EtOH
reflux, 95%
MeO
OH
H2N
N
69
Scheme 56
MeO
OH
H2N
N
69
O
OH
N
N
HATU, TEA, DCM,
rt, 58%
MeO
O
OH
N
H
N
N
575

FIG. 70



Scheme 57

FIG. 71

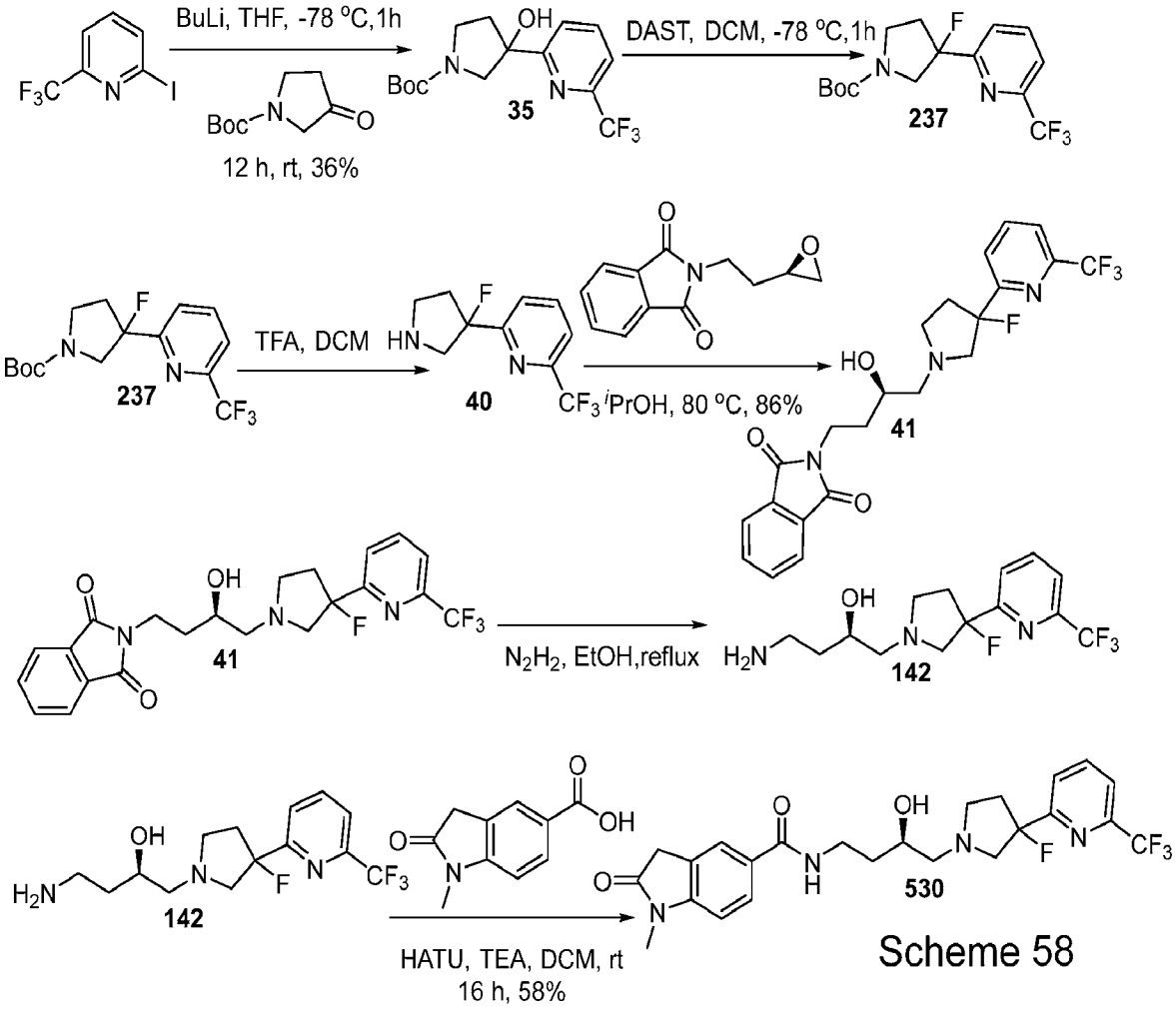

BuLi, THF, -78 °C,1h
12 h, rt, 36%
35
DAST, DCM, -78 °C,1h
237
TFA, DCM
40
iPrOH, 80 °C, 86%
41
N2H2, EtOH,reflux
142
HATU, TEA, DCM, rt
16 h, 58%
530
Scheme 58

FIG. 72

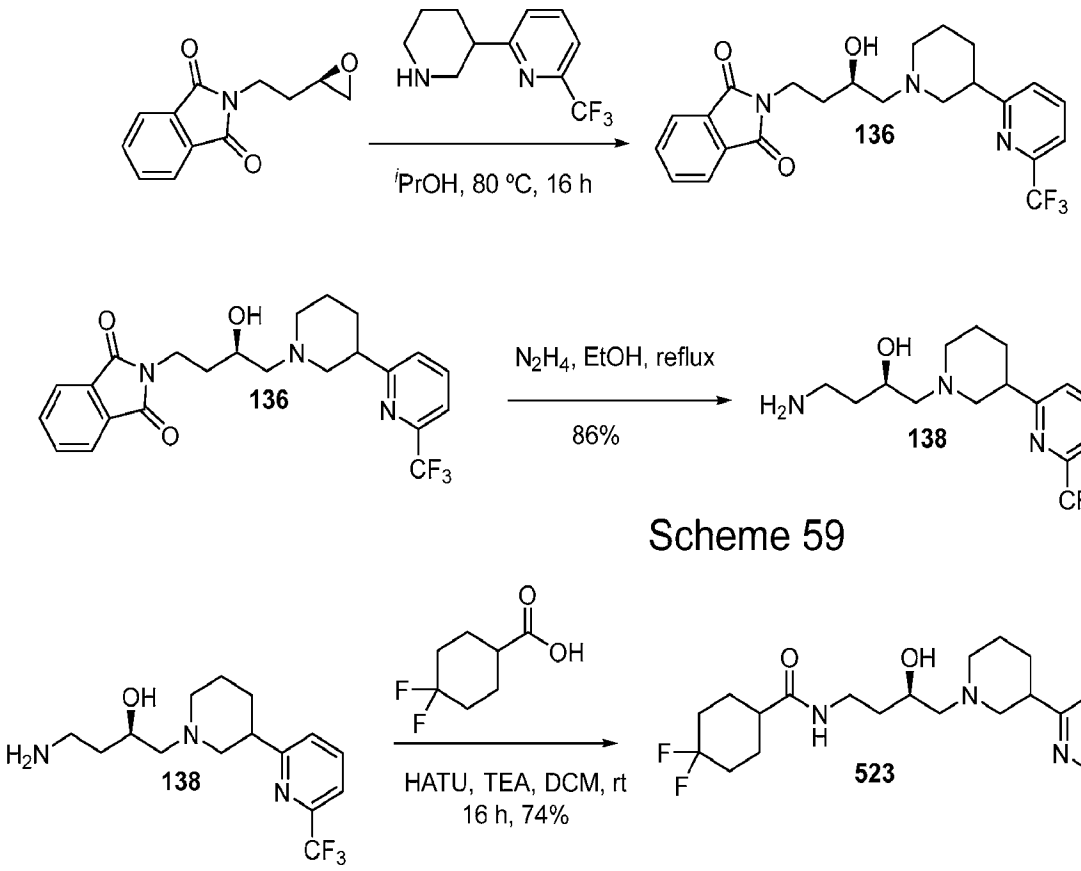
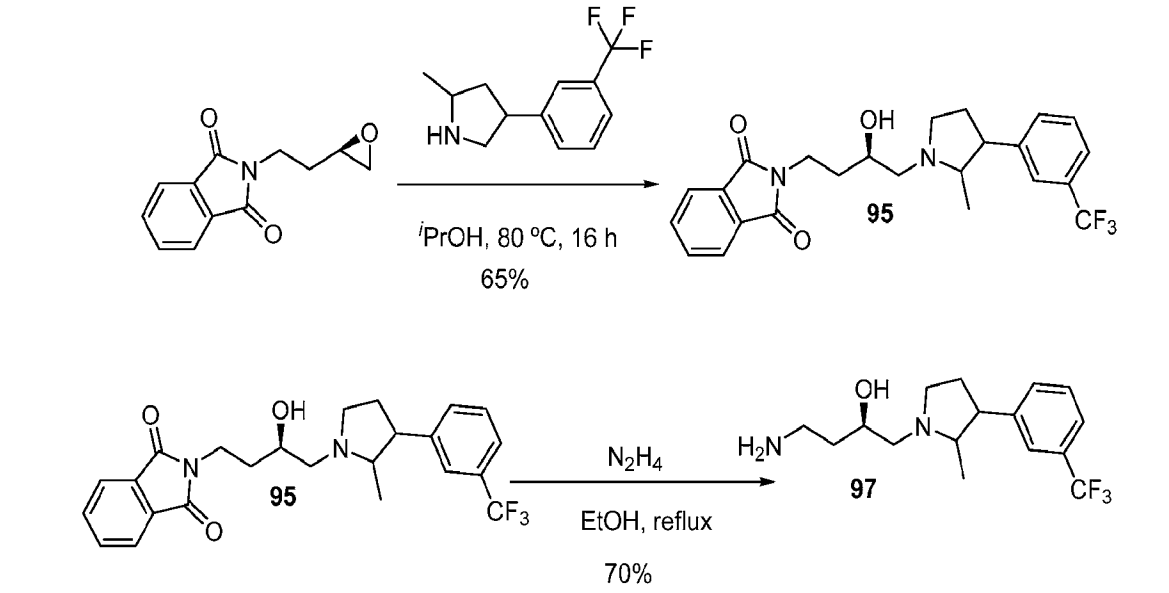

HN
N
CF3
iPrOH, 80 °C, 16 h
OH
136
N2H4, EtOH, reflux
86%
H2N
138
Scheme 59
F
F
OH
HATU, TEA, DCM, rt
16 h, 74%
523

FIG. 73



Scheme 60

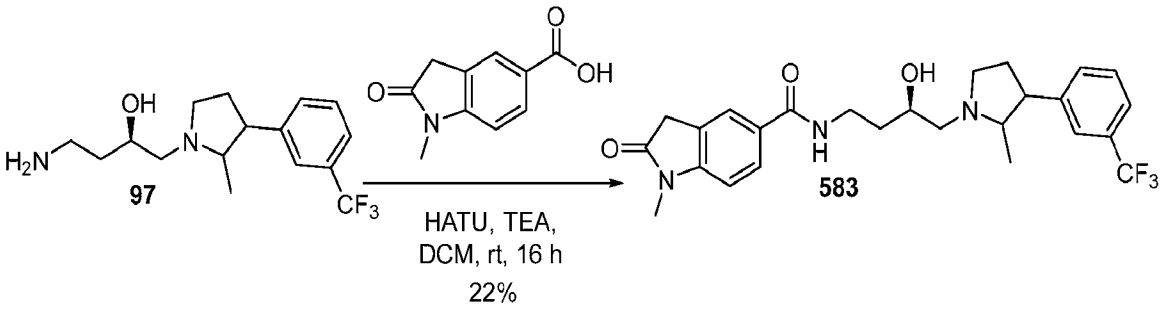
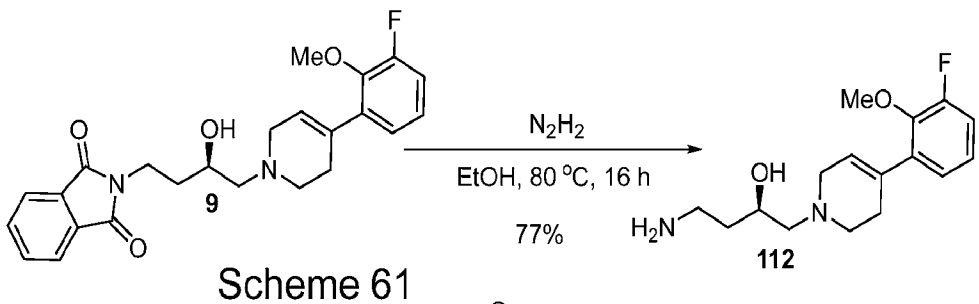


FIG. 74



Scheme 61

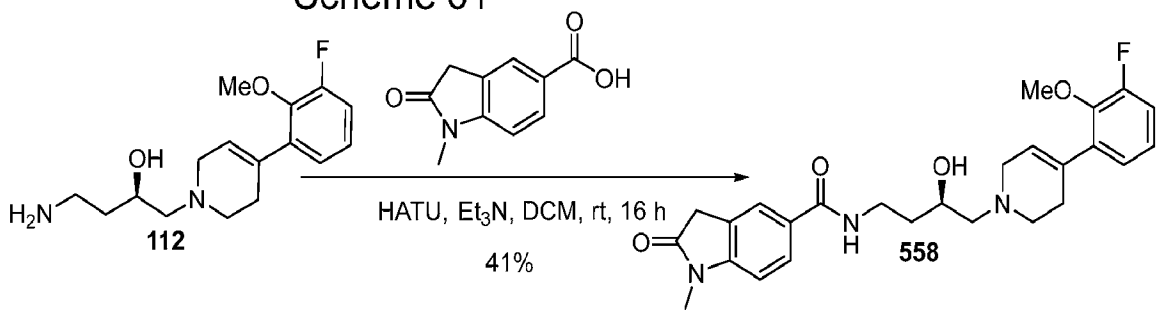


FIG. 75

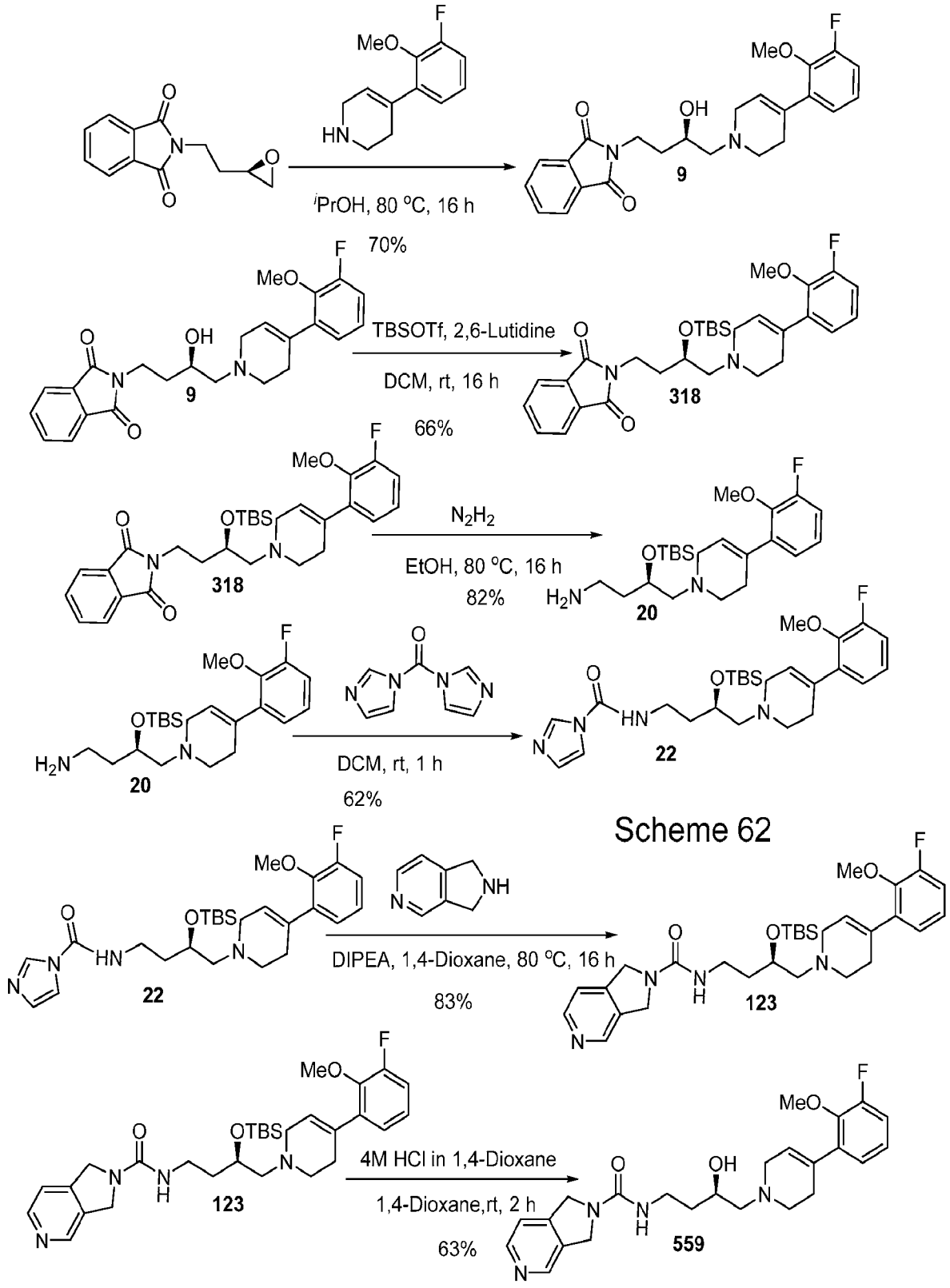

iPrOH, 80 °C, 16 h
70%
9
TBSOTf, 2,6-Lutidine
DCM, rt, 16 h
66%
318
N2H2
EtOH, 80 °C, 16 h
82%
20
DCM, rt, 1 h
62%
22
Scheme 62
DIPEA, 1,4-Dioxane, 80 °C, 16 h
83%
123
4M HCl in 1,4-Dioxane
1,4-Dioxane,rt, 2 h
63%
559

FIG. 76

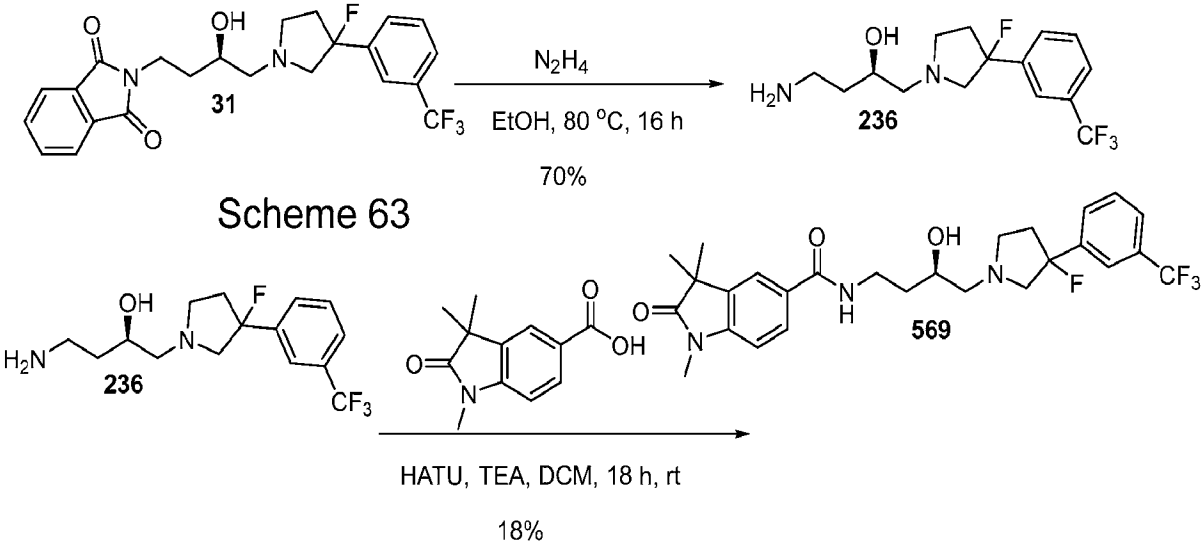

31
N_2H_4
EtOH, 80 °C, 16 h
70%
236
Scheme 63
236
569
HATU, TEA, DCM, 18 h, rt
18%

FIG. 77

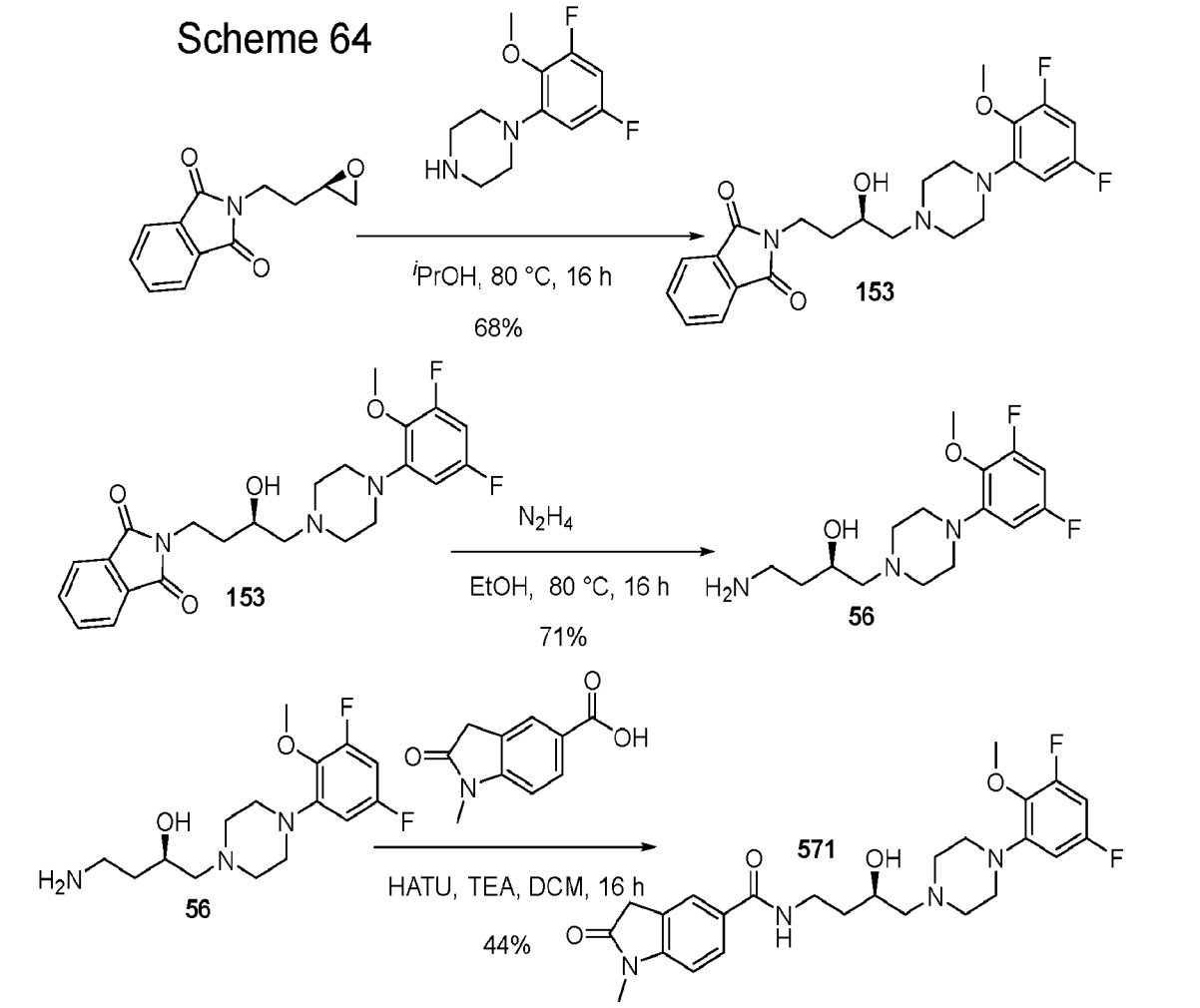
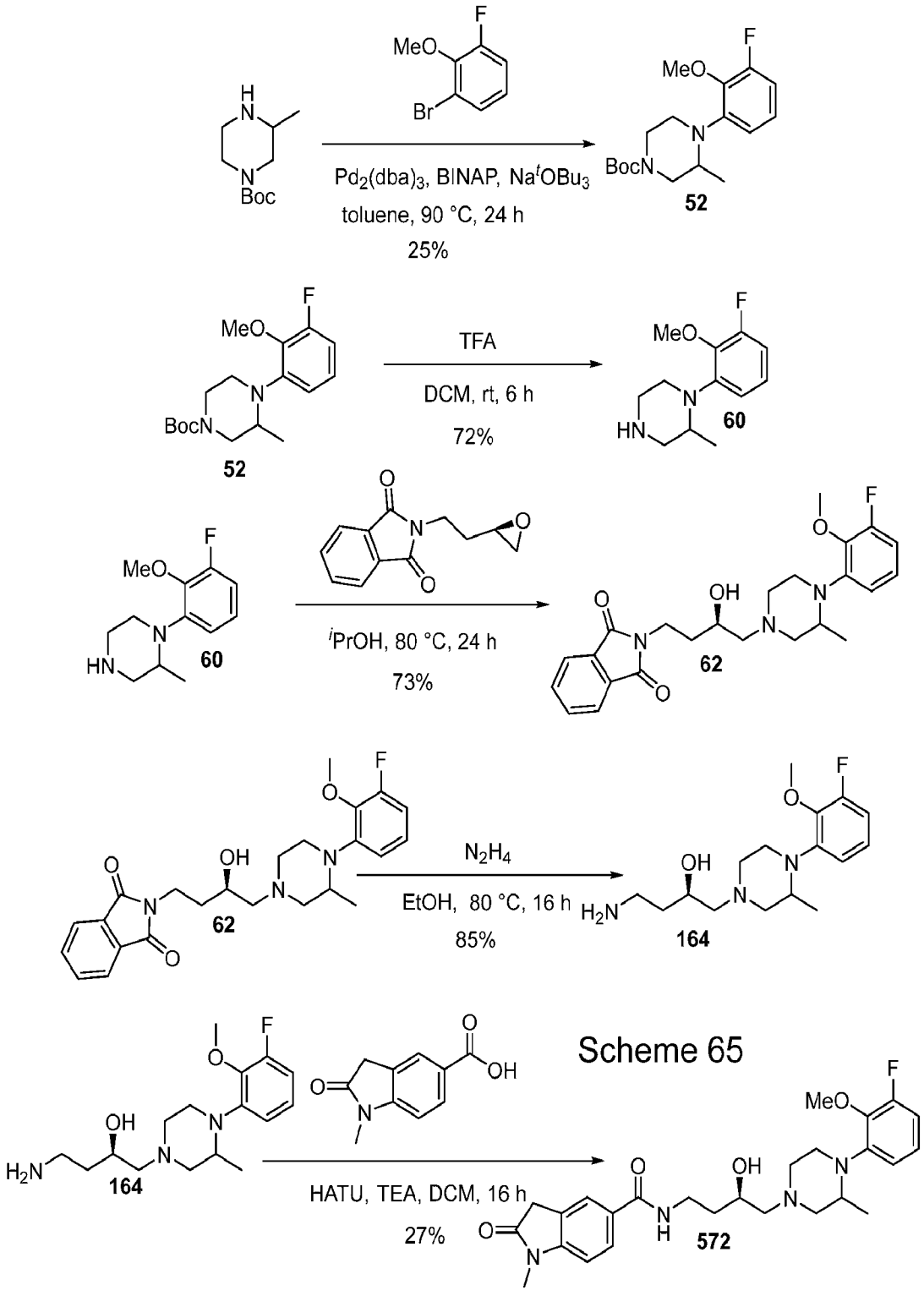

Scheme 64
^{i}PrOH, 80 °C, 16 h
68%
153
153
N_2H_4
EtOH, 80 °C, 16 h
71%
56
56
HATU, TEA, DCM, 16 h
44%
571

FIG. 78



Scheme 65

FIG. 79

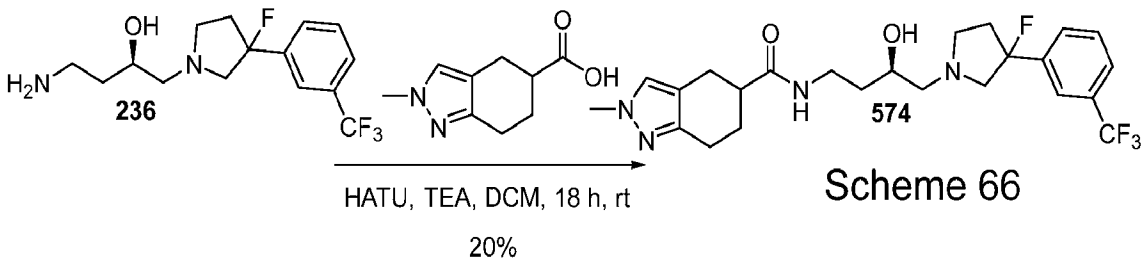

OH
F
H_2N
N
236
CF_3
O
OH
N
N
O
N
H
OH
574
HATU, TEA, DCM, 18 h, rt
20%
Scheme 66

FIG. 80

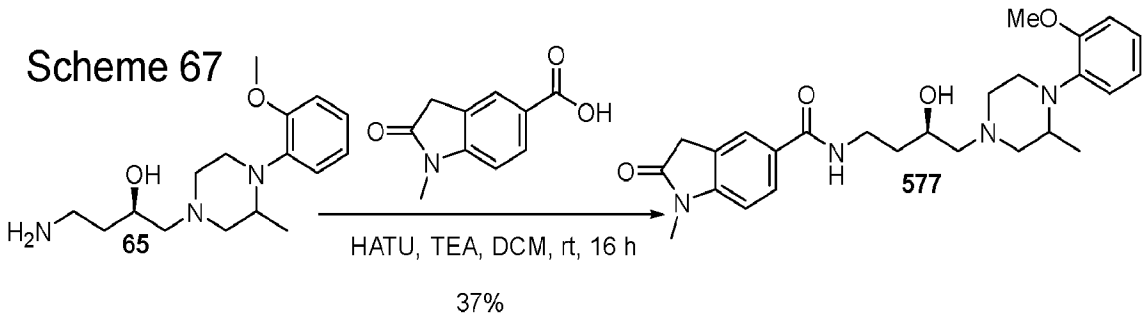

Scheme 67
O
OH
H_2N
N
65
O
OH
N
O
N
MeO
O
N
H
OH
577
HATU, TEA, DCM, rt, 16 h
37%

FIG. 81

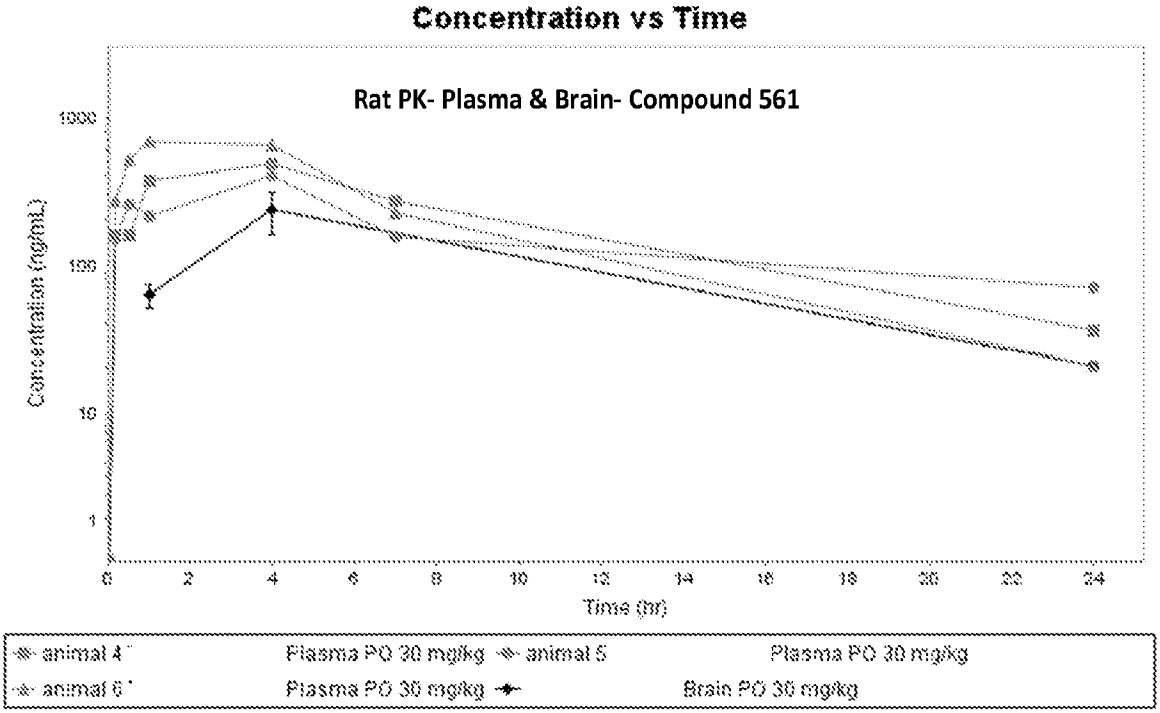

Concentration vs Time
Rat PK- Plasma & Brain- Compound 561
Concentration (ng/mL)
1000
100
10
1
0
2
4
6
8
10
12
14
16
18
20
22
24
Time (hr)
animal 4 Plasma PO 30 mg/kg
animal 5 Plasma PO 30 mg/kg
animal 6 Plasma PO 30 mg/kg
Brain PO 30 mg/kg

FIG. 82

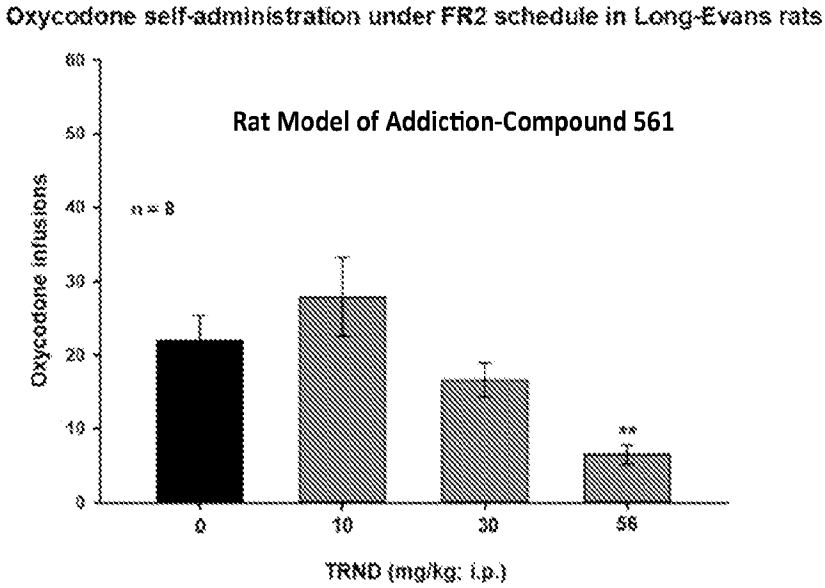

Oxycodone self-administration under FR2 schedule in Long-Evans rats
Rat Model of Addiction-Compound 561
Oxycodone infusions
60
50
40
30
20
10
0
n = 8
**
0
10
30
56
TRND (mg/kg; i.p.)

FIG. 83

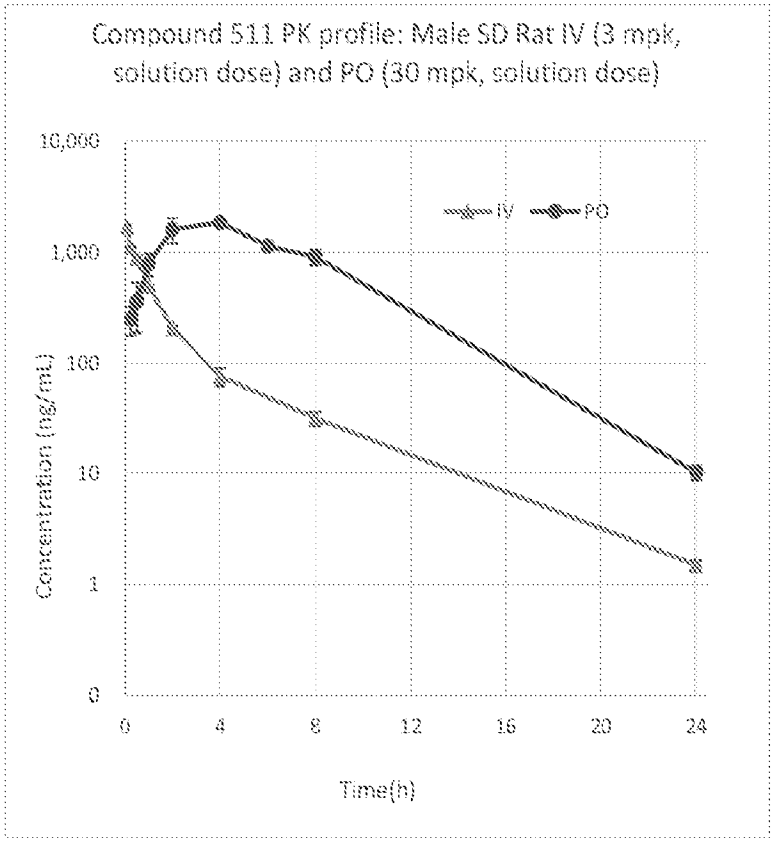

Compound 511 PK profile: Male SD Rat IV (3 mpk, solution dose) and PO (30 mpk, solution dose)
10,000
1,000
100
10
1
0
Concentration (ng/mL)
IV
PO
0
4
8
12
16
20
24
Time(h)

FIG. 84

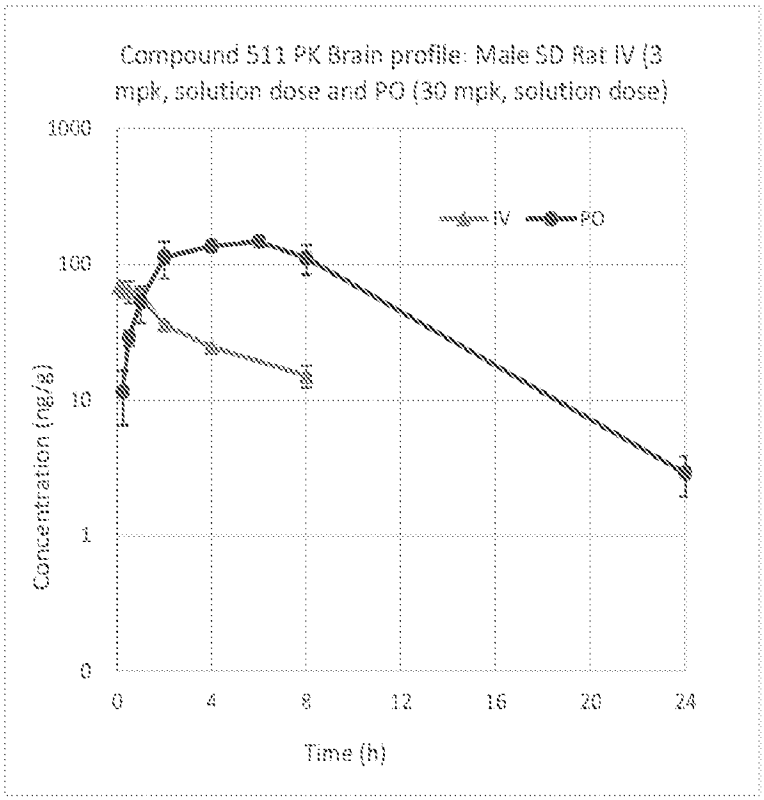

Compound 511 PK Brain profile: Male SD Rat IV (3 mpk, solution dose and PO (30 mpk, solution dose)
1000
100
10
1
0
Concentration (ng/g)
IV
PO
0
4
8
12
16
20
24
Time (h)

FIG. 85

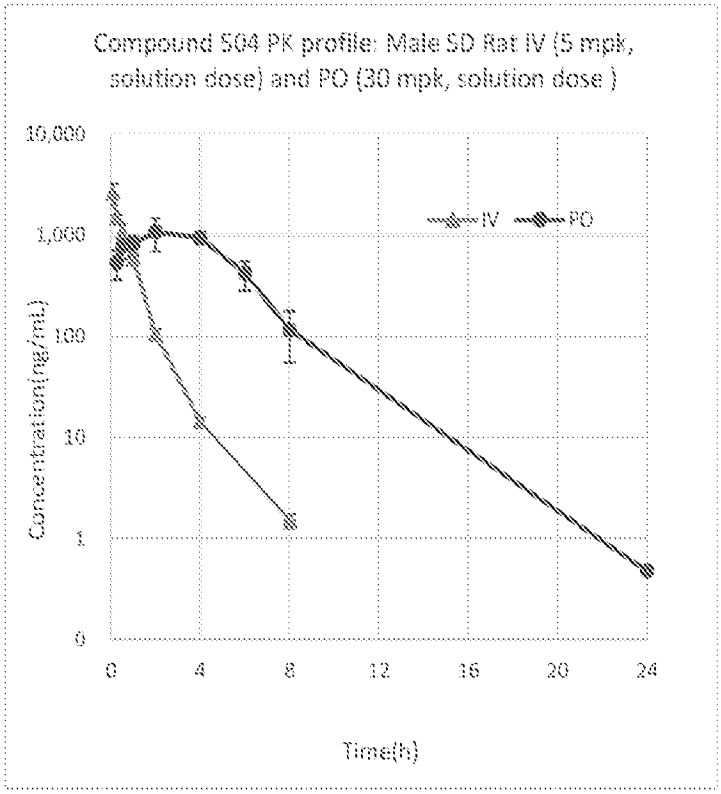

Compound 504 PK profile: Male SD Rat IV (5 mpk, solution dose) and PO (30 mpk, solution dose)
10,000
1,000
100
10
1
0
Concentration (ng/mL)
IV
PO
0
4
8
12
16
20
24
Time(h)

FIG. 86

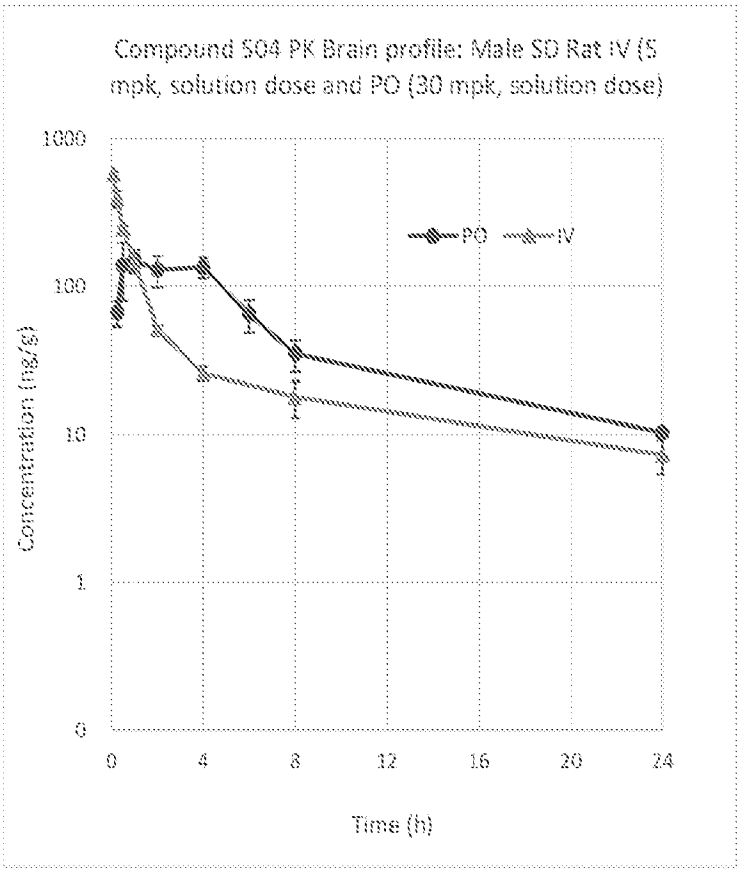

Compound 504 PK Brain profile: Male SD Rat IV (5 mpk, solution dose and PO (30 mpk, solution dose)
1000
100
10
1
0
Concentration (ng/g)
PO
IV
0
4
8
12
16
20
24
Time (h)

FIG. 87

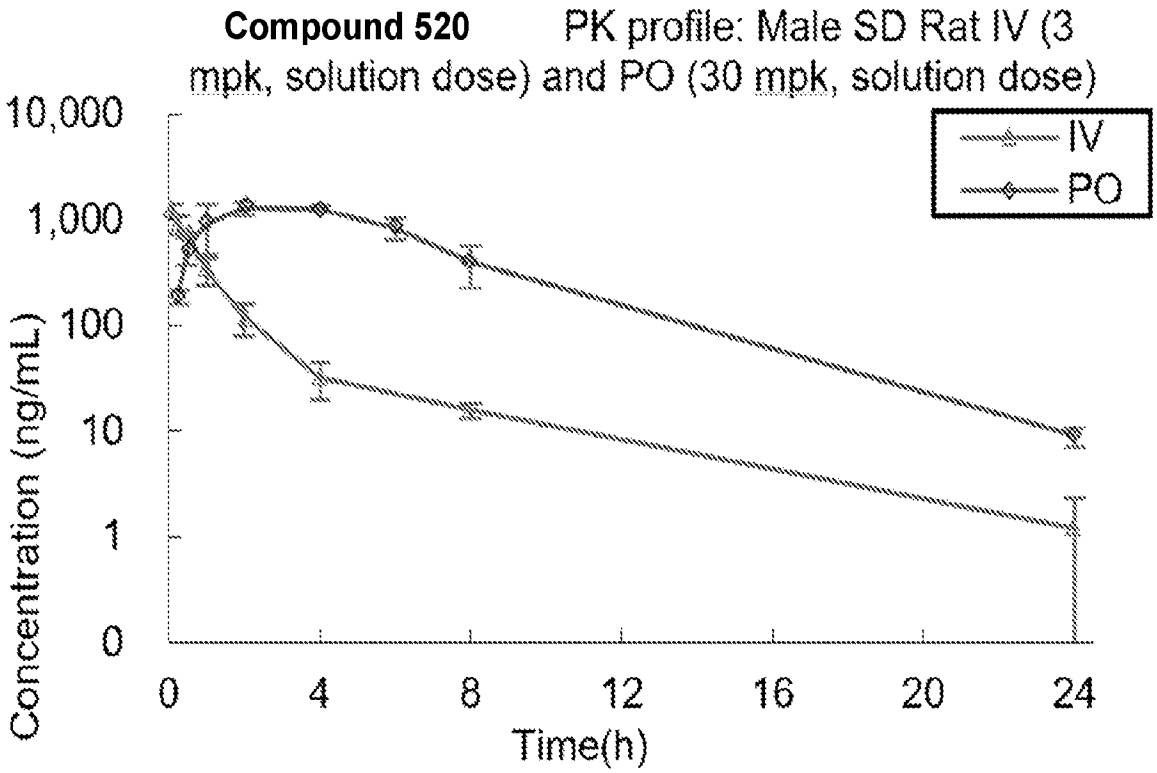

Compound 520 PK profile: Male SD Rat IV (3 mpk, solution dose) and PO (30 mpk, solution dose)
10,000
1,000
100
10
1
0
Concentration (ng/mL)
0
4
8
12
16
20
24
Time(h)
IV
PO

FIG. 88

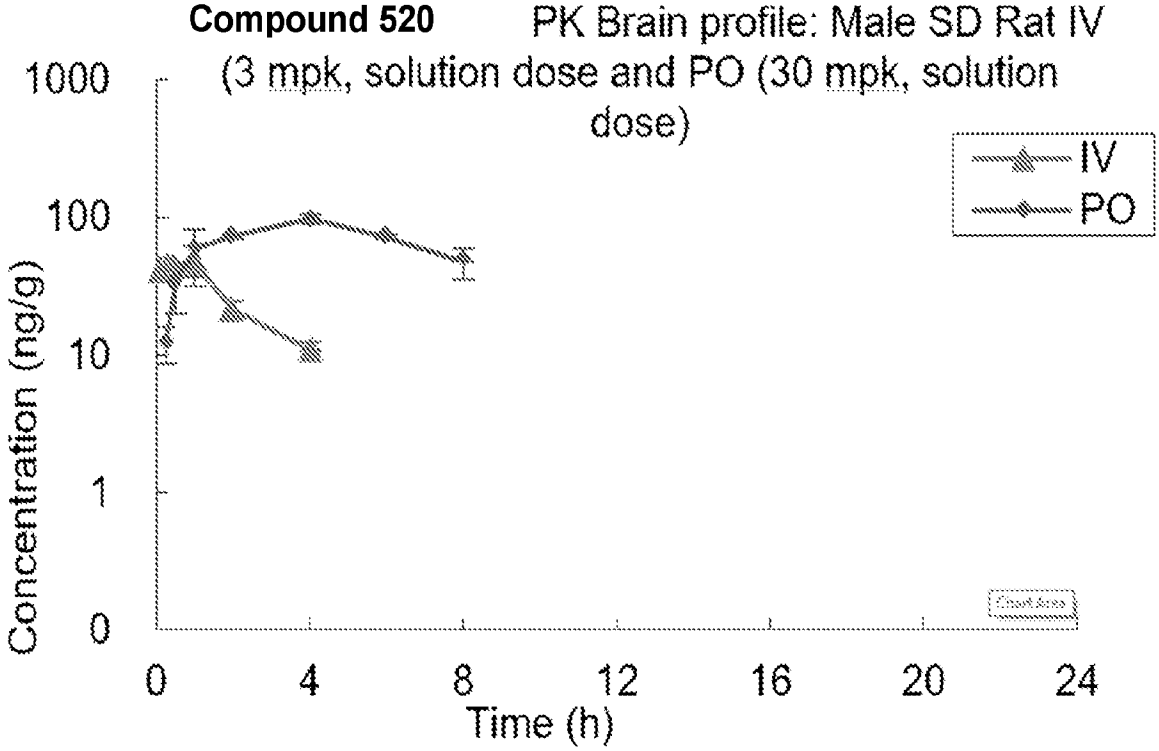

Compound 520 PK Brain profile: Male SD Rat IV (3 mpk, solution dose and PO (30 mpk, solution dose)
1000
100
10
1
0
Concentration (ng/g)
0
4
8
12
16
20
24
Time (h)
IV
PO

FIG. 89

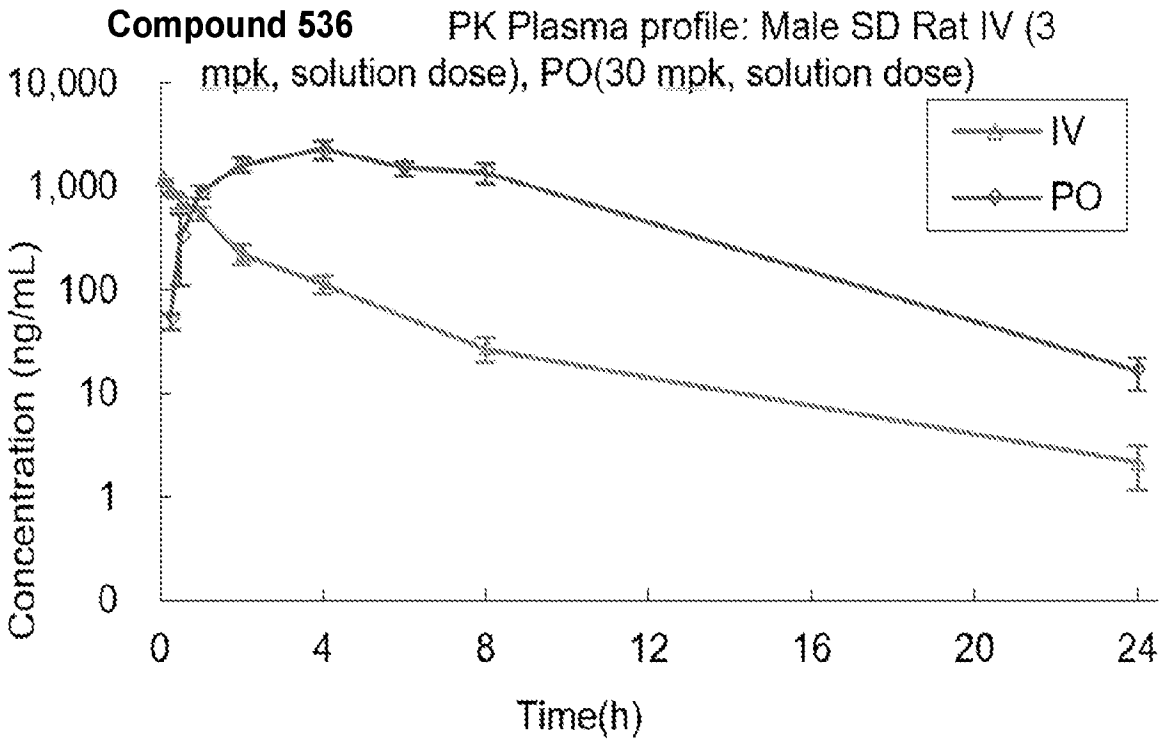

Compound 536 PK Plasma profile: Male SD Rat IV (3 mpk, solution dose), PO(30 mpk, solution dose)
10,000
1,000
100
10
1
0
Concentration (mg/mL)
IV
PO
0
4
8
12
16
20
24
Time(h)

FIG. 90

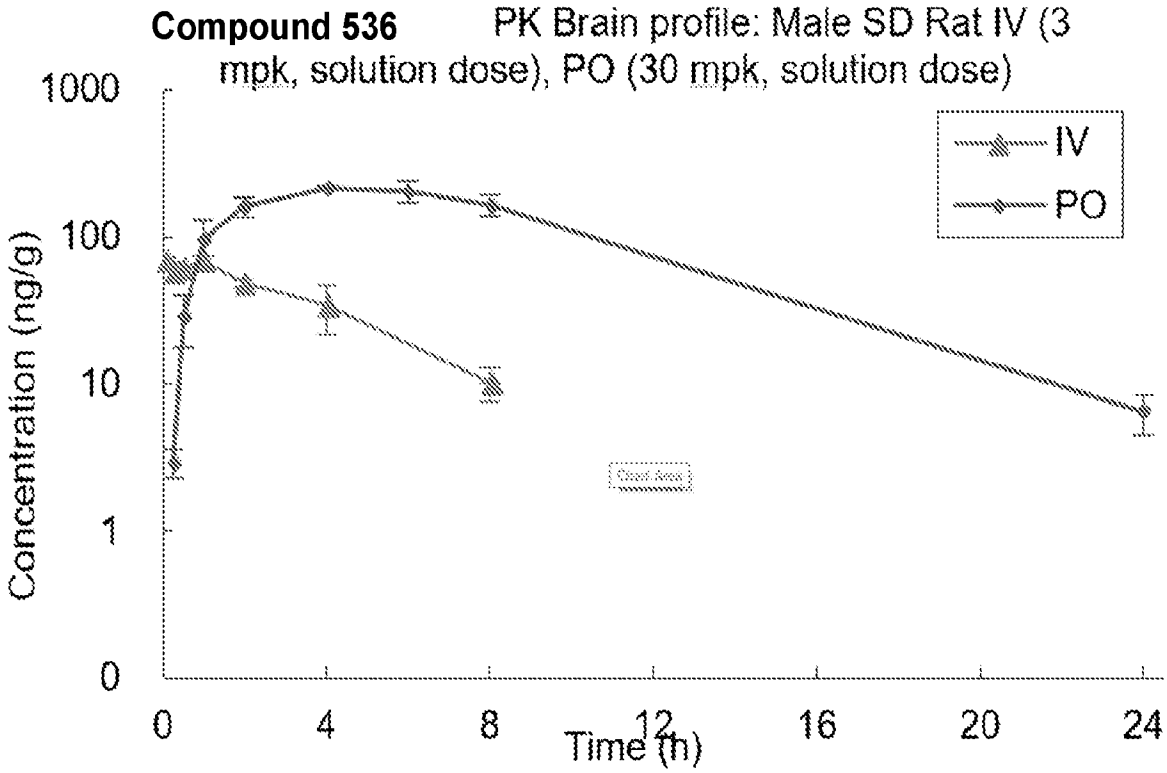

Compound 536 PK Brain profile: Male SD Rat IV (3 mpk, solution dose), PO (30 mpk, solution dose)
1000
100
10
1
0
Concentration (mg/g)
IV
PO
0
4
8
12
16
20
24
Time (h)

FIG. 91

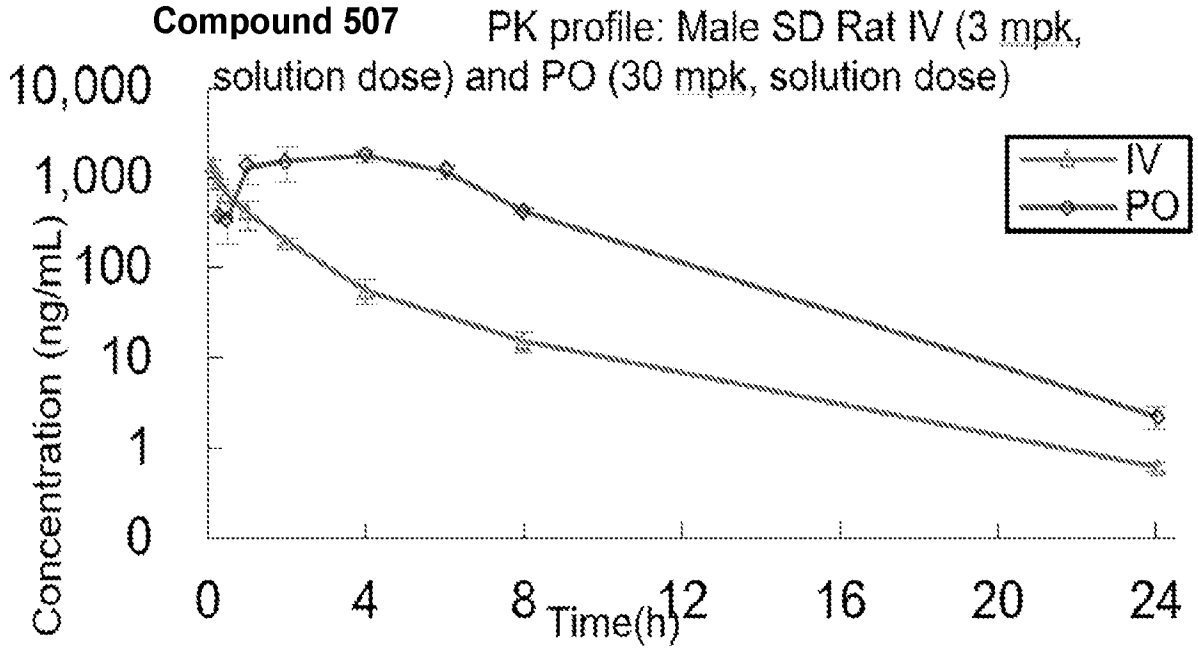

Compound 507
PK profile: Male SD Rat IV (3 mpk, solution dose) and PO (30 mpk, solution dose)
10,000
1,000
100
10
1
0
Concentration (ng/mL)
IV
PO
0
4
8
12
16
20
24
Time(h)

FIG. 92

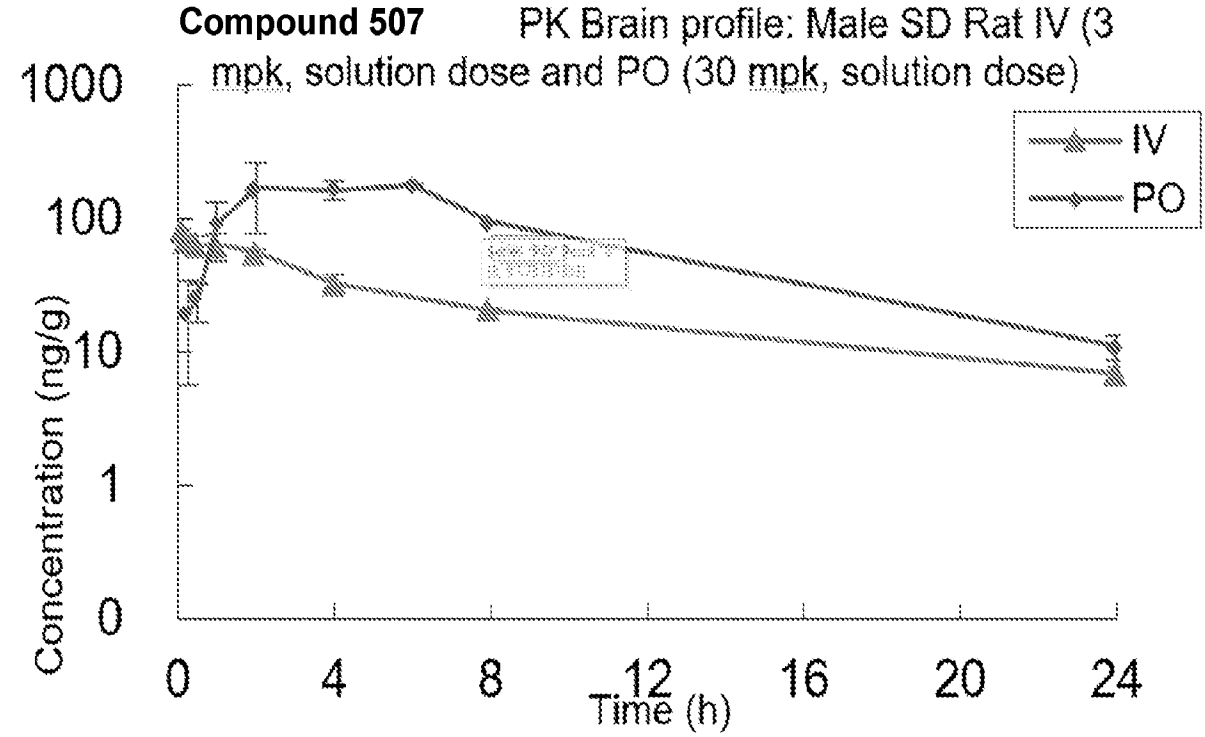

Compound 507
PK Brain profile: Male SD Rat IV (3 mpk, solution dose and PO (30 mpk, solution dose)
1000
100
10
1
0
Concentration (ng/g)
IV
PO
0
4
8
12
16
20
24
Time (h)

FIG. 93

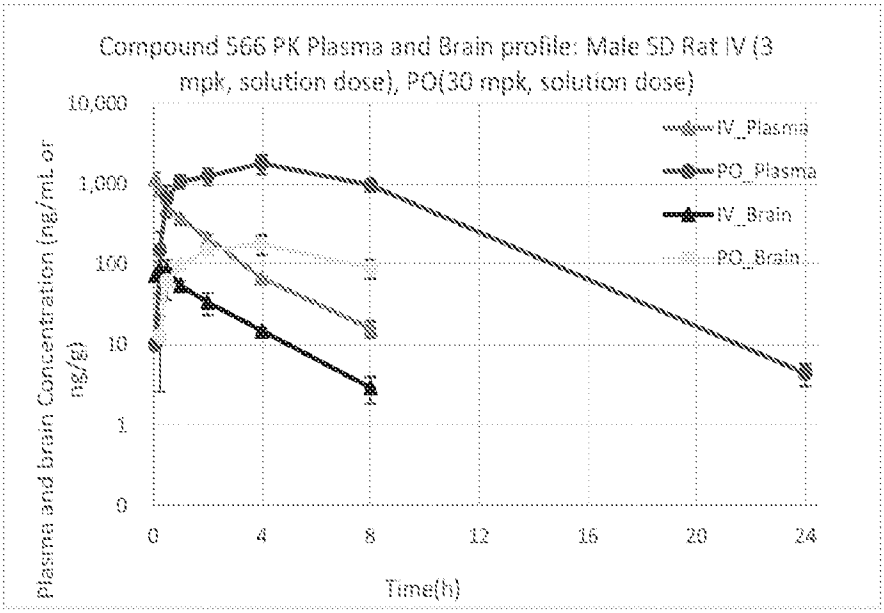

Compound 566 PK Plasma and Brain profile: Male SD Rat IV (3 mpk, solution dose), PO(30 mpk, solution dose)
Plasma and brain Concentration (ng/mL or ng/g)
10,000
1,000
100
10
1
0
0
4
8
12
16
20
24
Time(h)
IV_Plasma
PO_Plasma
IV_Brain
PO_Brain

FIG. 94

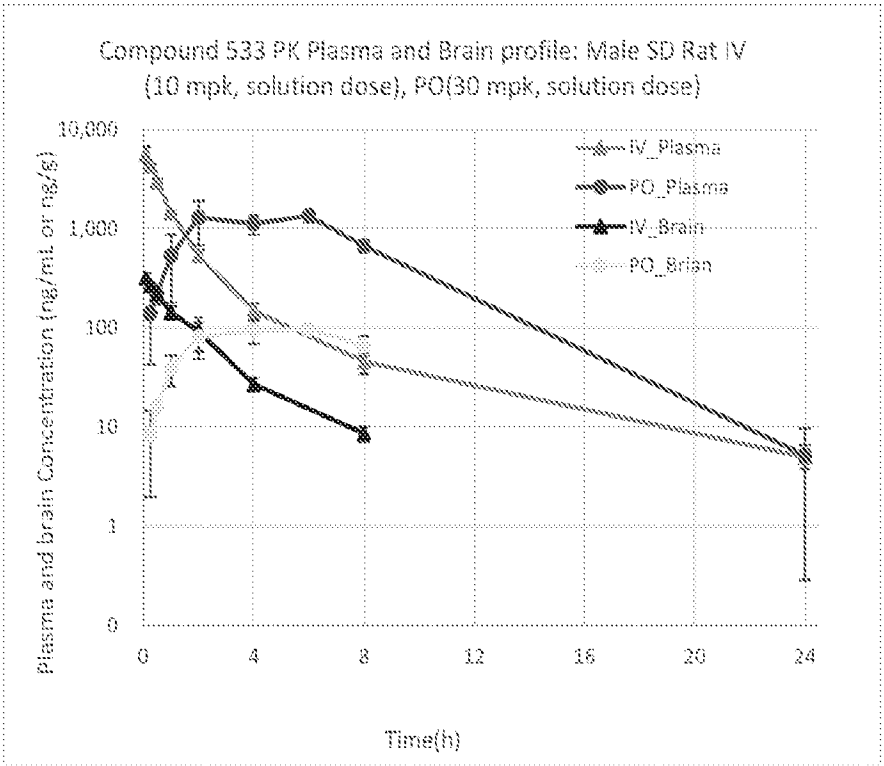

Compound 533 PK Plasma and Brain profile: Male SD Rat IV (10 mpk, solution dose), PO(30 mpk, solution dose)
Plasma and brain Concentration (ng/mL or ng/g)
10,000
1,000
100
10
1
0
0
4
8
12
16
20
24
Time(h)
IV_Plasma
PO_Plasma
IV_Brain
PO_Brain

FIG. 95

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/036149

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D295/13 C07D401/04 C07D401/12 C07D401/14 C07D403/12
C07D471/04 C07D495/04 A61P25/16 A61P25/18 A61P25/30
A61P25/36 A61K31/4025 A61K31/437 A61K31/451 A61K31/4545

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/059265 A1 (SOUTHERN RES INST [US]) 17 April 2014 (2014-04-17) abstract page 20 - page 64; examples 1-130 claim 1	1-78
X	US 8 748 608 B2 (NEWMAN AMY HAUCK [US]; GRUNDT PETER [US] ET AL.) 10 June 2014 (2014-06-10) abstract column 15 - column 28; compounds 9-49 claim 1	1-4, 6-51, 53-78

-/--

[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 October 2024	04/11/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bissmire, Stewart

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/036149

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017/160552 A1 (US HEALTH [US]) 21 September 2017 (2017-09-21) abstract page 42 - page 43; compounds 18-40 claim 1	1-4, 6-51, 53-78
X	WO 2020/055725 A1 (US HEALTH [US]) 19 March 2020 (2020-03-19) abstract page 63; compounds 18-40 claim 1	1-4, 6-51, 53-78
X	EP 0 445 701 A1 (SHIONOGI & CO [JP]) 11 September 1991 (1991-09-11) abstract page 21 - page 65; compounds III-17, Ia-17, Ia-107 claim 1	1-51, 53-78
X	AWADALLAH ET AL: "Synthesis of novel lactam derivatives and their evaluation as ligands for the dopamine receptors, leading to a D"4-selective ligand", BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER, AMSTERDAM, NL, vol. 15, no. 17, 19 July 2007 (2007-07-19), pages 5811-5818, XP022152370, ISSN: 0968-0896, DOI: 10.1016/J.BMC.2007.06.002 abstract page 5831; examples 9a-12d	48,53-78
X	CAO YONGKAI ET AL: "Design, synthesis, and evaluation of bitopic arylpiperazine-phthalimides as selective dopamine D 3 receptor agonists", MEDCHEMCOMM, vol. 9, no. 9, 1 January 2018 (2018-01-01), pages 1457-1465, XP093213675, United Kingdom ISSN: 2040-2503, DOI: 10.1039/C8MD00237A abstract figures 1-3; examples 1 HCl, 2HCl, 9a-11b	1-78

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2024/036149

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		DK 2906221 T3	22-07-2019
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		US 2015232435 A1	20-08-2015
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US 8748608 B2	10-06-2014	AU 2007354861 A1	18-12-2008
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		DK 3429993 T3	09-08-2021
		EP 3429993 A1	23-01-2019
		EP 3848351 A1	14-07-2021
		ES 2881267 T3	29-11-2021
		HR P20211182 T1	15-10-2021
		HU E055634 T2	28-12-2021
		PL 3429993 T3	15-11-2021
		PT 3429993 T	19-07-2021
		SI 3429993 T1	30-09-2021
		US 2022185798 A1	16-06-2022
		WO 2017160552 A1	21-09-2017
WO 2020055725 A1	19-03-2020	AU 2019340675 A1	11-03-2021
		AU 2024219951 A1	10-10-2024
		CA 3111785 A1	19-03-2020
		EP 3849963 A1	21-07-2021
		US 2021346373 A1	11-11-2021
		US 2022265643 A1	25-08-2022
		WO 2020055725 A1	19-03-2020
EP 0445701 A1	11-09-1991	AU 643258 B2	11-11-1993
		CA 2037566 A1	06-09-1991
		EP 0445701 A1	11-09-1991
		EP 0861832 A1	02-09-1998
		KR 910016697 A	05-11-1991
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