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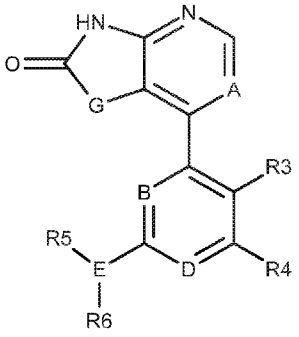
(54) Title: PKC-THETA MODULATORS

(57) Abstract: Disclosed are compounds, compositions and methods for treating disease, syndromes, conditions and disorders that are affected by the modulation of PKC-theta. Such compounds are represented by Formula I, wherein the variables are defined herein. (I)



I

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PKC-theta Modulators

TECHNICAL FIELD

The present disclosure relates to novel compounds capable of modulating PKC-theta phosphorylation activity. Such phosphorylation activity may be inhibited by the compounds described herein. The present invention further describes the synthesis of the compounds and their uses as medicaments in diseases or disorders where PKC-theta modulation may be beneficial.

BACKGROUND

Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a variety of signal transduction processes within the cell (see Hardie, G and Hanks, S. The Protein Kinase Facts Book, I and II, Academic Press, San Diego, CA: 1995).

The connection between abnormal protein phosphorylation and disease is well known. Accordingly, protein kinases are an important group of drug targets (see, for example, Cohen, Nature, vol. 1 (2002), pp 309-315, Gaestel et al. Curr. Med. Chem, 2007, pp 2214-223; Grimminger et al. Nat. Rev. Drug Disc. vol. 9(12), 2010, pp 956-970).

Protein kinase C (hereafter PKC) is a family of serine- and threonine-specific protein kinases. PKC family members phosphorylate a wide variety of protein targets and are known to be involved in diverse cellular signalling pathways. Each member of the PKC family has a specific expression profile and is believed to have a distinct role.

The PKC members can be classified into three groups: Group I (Ca^{2+} and diacylglycerol (DAG) dependent): PKC-alpha, PKC-βI, PKC-βII and PKC-γ; Group II (Ca^{2+} independent): PKC-δ (hereafter PKC-delta), PKC-e, PKC-η (or PKC-eta) and PKC-θ (hereafter PKC-theta); Group III (Ca^{2+} and DAG independent): PKC-i, PKC-ζ and PKC-μ (Brezar et al., 2015, Frontiers Immunol., 6:530).

The expression of the PKC-theta isoform of PKC is enriched in T lymphocytes and plays an important role in the T-cell receptor (TCR)-triggered activation of T-cells. PKC-theta signals through transcription factors, including NF-κB, NFAT and AP-1, leading to the release of cytokines such as IL-2 and IFN-gamma, and subsequently T-cell proliferation, differentiation and

survival (Brezar et al., 2015, Frontiers Immunol., 6:530). Unlike broader biommunosuppressive mechanisms, including those displayed by the calcineurin inhibitors, PKC-theta inhibition has demonstrated a selective effect on the immune system (Brezar et al., 2015, Frontiers Immunol., 6:530). Antiviral responses remain intact in mice lacking PKC-theta activity (Zhang et al., Adv Pharm. 2013 ; 66: 267–31). In regulatory T-cells (Tregs), PKC-theta signalling is not absolutely required for activation and function (Zhang et al. Adv Pharmacol. 2013 ; 66: 267–31). *Prkcq*$^{-/-}$ mice have a reduced but significant proportion of circulating Tregs and Tregs isolated from *Prkcq*$^{-/-}$ mice retain suppressive activity (Gupta, et al., Mol Immunol., 2008, 46(2):213–24). Pharmacological inhibition of PKC-theta protected Tregs from inactivation by TNFα and enhanced protection of mice from inflammatory colitis (Zanin-Zhorov, et al., Science, 2010, 328 (5976):372–6). Indeed, evidence has emerged that PKC-theta is a negative regulator of Tregs function (Zhang et al., Adv Pharm. 2013; 66: 267–31).

In human disease, associations of the Prkcq locus specific single nucleotide polymorphisms (SNP) have been identified with type 1 diabetes (T1D), rheumatoid arthritis (RA), and celiac disease by genome-wide association studies (GWAS; Brezar et al., 2015, Frontiers Immunol., 6:530). Further, pharmacological inhibition of PKC-theta rescued the defective activity of Tregs from rheumatoid arthritis patients (Zanin-Zhorov, et al., Science, 2010, 328 (5976):372–6).

PKC-theta activity is critically important in Th2 (allergic disease) and Th17 (autoimmune disease) responses and differentiation (Zhang et al., Adv Pharm., 2013; 66: 267–31).). The *Prkcq*$^{-/-}$ mouse is protected in Th2 models of allergic lung inflammation and parasite infection. Likewise, lack of PKC-theta activity is protective in Th17-driven mouse models such as experimental autoimmune encephalomyelitis (EAE), adjuvant-induced arthritis, and colitis.

PKC-theta is also implicated in various types of cancers and the PKC-theta-mediated signalling events controlling cancer initiation and progression. In these types of cancers, the high PKC-theta expression leads to aberrant cell proliferation, migration and invasion resulting in malignant phenotype (Nicolle, A et al., Biomolecules, 2021, 11, 221). Inhibition of PKC-theta may also benefit the treatment for cancers in which PKC-theta has been implicated.

Small molecule inhibitors of PKC-theta are known, for example inhibitors based on a pyrazolopyrimidine scaffold are described in WO 2011/139273, and WO 2015/095679 describes PKC-theta inhibitors based on a diaminopyrimidine core.

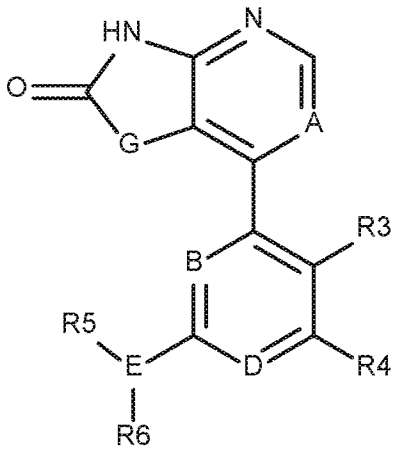
To date there is no effective and approved medical treatment available which is based on the inhibition of PKC-theta, largely due to the difficulties of securing potent inhibition alongside

suitable selectivity for the PKC-theta isoform over other isoforms, particularly PKC-delta in the PKC family (Group 2), and other kinases.

The present invention has been devised with the above observations in mind.

SUMMARY OF THE INVENTION

In one aspect of the invention there is provided a compound of structural Formula I:



I

or a pharmaceutically acceptable salt, solvate, stereoisomer or mixture of stereoisomers, tautomer, or isotopic form, or pharmaceutically active metabolite thereof, or combinations thereof, wherein:

A is selected from the group consisting of: N, C-R^a, where R^a is selected from hydrogen, halogen, C1-3 alkyl (e.g. Me, Et) and CN;

B is selected from the group consisting of: N; C-H, C-F and C-(C1-3 alkyl) (e.g. C-Me, C-Et);

D is selected from the group consisting of: N; C-H; C-R^b where R^b is selected from halogen (e.g. F, Cl, Br); C1-3 alkyl (e.g. Me, Et); and C1-3 haloalkyl (e.g. CHF_2, CF_3);

G is selected from the group consisting of: CR1R2; NR1; and O;

R1 and R2 are independently selected from the group consisting of: hydrogen, halogen (e.g. F, Cl, Br); C1-3 alkyl (e.g. Me, Et); C3-7 cycloalkyl (e.g. ^{c}Pr, ^{c}Hex); C1-3 alkoxyl (e.g. OMe, OEt); C2-6 cycloalkoxyl (e.g. oxetane, furan); C2-6 alkyl alkoxyl (e.g. CH_2OMe, $(CH_2)_2OMe$); hydroxyl; C1-3 alkyl hydroxyl (e.g. CH_2OH, $(CH_2)_2OH$); amino; C1-3 alkyl amino (e.g. CH_2NH_2,

$(CH_2)_2NH_2$); C1-4 amino alkyl (e.g. NMe_2, NMeEt); C2-7 alkyl amino alkyl (e.g. CH_2NMe_2, $(CH_2)_2NEt_2$); C1-3 haloalkyl (e.g. CHF_2, CF_3, CH_2CHF_2); aryl (e.g. phenyl); heteroaryl (e.g. pyridine, thiazole); alkyl aryl (e.g. benzyl) and alkyl heteroaryl (e.g. CH_2-pyridine, CH_2-thiazole); or

R1 and R2 together form a 3-5 membered optionally substituted spiro carbocyclic or heterocyclic ring (e.g. cyclopropane, cyclobutene, cyclopentane, oxetane, furan, pyrrolidine, piperidine);

R3 is selected from the group consisting of: hydrogen, C1-2 alkyl (e.g. Me, Et), OMe and halogen (e.g. F, Cl, Br);

R4 is selected from the group consisting of: hydrogen; C1-5 alkyl (e.g. Me, Et); C3-7 cycloalkyl (e.g. ^{c}Pr, ^{c}Hex); C1-5 haloalkyl (e.g. CHF_2, CF_3, CF_2Me, CH_2CHF_2); C1-5 alkoxyl (e.g. OMe, OEt); C1-5 haloalkoxyl (e.g. $OCHF_2$, OCF_3, OCH_2CHF_2); alkyl alkoxy (e.g. CH_2OMe, $(CH_2)_2OMe$); C2-6 heterocycloalkyl (e.g. piperidine, piperazine); CN and halogen (e.g. F, Cl, Br);

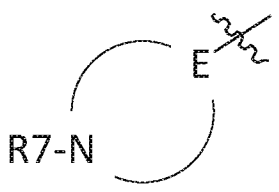
E is selected from the group consisting of: N; C-H; C-R^c, where R^c is selected from the group consisting of halogen (e.g. F, Cl, Br); hydroxyl; C1-3 alkyl hydroxyl (e.g. CH_2OH, $(CH_2)_2OH$); C1-3 alkyl amino (e.g. CH_2NH_2, $(CH_2)_2NH_2$); C1-3 haloalkyl (e.g. CH_2F ,CHF_2, CF_3, CH_2CHF_2); C2-6 alkyl alkoxyl (e.g. CH_2OMe, $(CH_2)_2OMe$); and CN;

R5 and R6 are each independently selected from the group consisting of: hydrogen; C2-5 alkyl (e.g. Me, Et); C1-C5 amino alkyl (e.g. NMe_2, NMeEt); 4-8-membered amino alkyl ring (e.g. piperidine, piperazine); C1-9 alkyl alkoxy (e.g. $(CH_2)_2OEt$; CH_2OMe); C1-9 alkyl amino alkyl (e.g. $(CH_2)_2NMe_2$; CH_2NHMe); or

R5 and R6 are joined together to form an optionally substituted, optionally bridged Ring Z, wherein Ring Z is a C3-10 heterocycloalkyl mono- or bicyclic ring (e.g. ^{c}Pr, oxetane, cHex, piperidine, piperazine, 1,4 diazacycloheptane); or

E, R5 and R6 together are J, wherein J is selected from the group consisting of: N-R^d; C(=O)R^d; SO_2R^d; O-R^d, wherein R^d is a 4-8-membered amino alkyl ring (e.g. piperidine, piperazine).

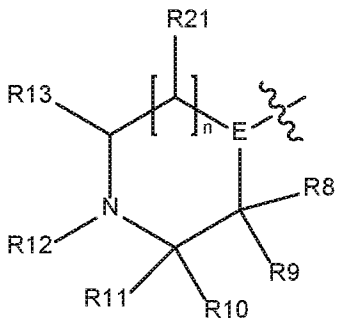
In embodiments, Ring Z is an optionally substituted, optionally bridged, 4-8-membered amino alkyl ring with the general Formula Ia;



Ia

wherein R7 is selected from the group consisting of: hydrogen; C1-3 alkyl (e.g. Me, Et); and C1-3 haloalkyl (e.g. CH_2CHF, CH_2CHF_2).

In embodiments, Ring Z is:



wherein R8, R9, R10, R11, R13 and R21 are each independently selected from the group consisting of: hydrogen, C1-3 alkyl (e.g. Me, Et), C1-3 alkyl alkoxy (e.g. CH_2OMe); C1-3 alkyl hydroxyl (e.g. CH_2OH); amino; C1-3 alkyl amino (e.g. CH_2NH_2); C1-6 alkyl amino alkyl (e.g. CH_2NMe_2); C1-3 haloalkyl (e.g. CHF_2, CF_3, CH_2CHF_2); alkyl heteroaryl (e.g. CH_2-pyridine, CH_2-thiazole);

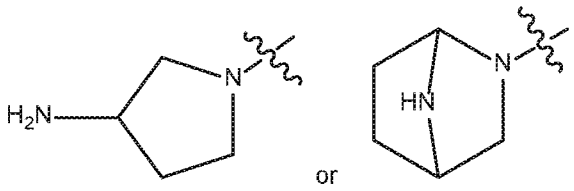
R12 is selected from the group consisting of: hydrogen; C1-3 alkyl (e.g. Me, Et); and C1-3 haloalkyl (e.g. CH_2CHF, CH_2CHF_2); or

any one of R8, R9, R10, R11, R12, R13 and R21 may be joined to another, different R8, R9, R10, R11, R12, R13 or R21 to form a 3-7-membered spiro or bicyclic carbocyclic or heterocyclic ring structure, and/or a 3-6 membered bridged carbocyclic or heterocyclic ring structure.

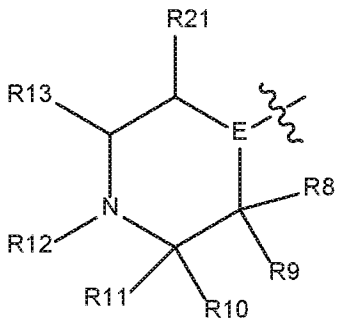
n is selected from the group consisting of: 0; 1; and 2; suitably n is 1 or 2.

In embodiments, when n=0, E is selected from the group consisting of: N; C-H; C-R^c, wherein R^c is selected from the group consisting of halogen (e.g. F, Cl, Br); hydroxy; C1-3 alkyl hydroxy (e.g. CH_2OH); C1-3 haloalkyl (e.g. CHF_2, CF_3, CH_2CHF_2); C2-5 alkyl alkoxy (e.g. CH_2OMe); C2-5 alkyl nitrile (e.g. CH_2CN).

In embodiments, Ring Z is:



In embodiments, G is CR1R2 and Ring Z is:



wherein;

A is selected from the group consisting of: C-H, C-F, C-Cl and C-Br;

B and D are each independently selected from the group consisting of: N and C-H;

E is selected from the group consisting of: N, C-F and C-H;

R1 is selected from the group consisting of: hydrogen, Me; Et; OMe; OEt; OH; NH_2 and NHMe; and

R2 is selected from the group consisting of: hydrogen, Me and Et; or

R1 and R2 together form a 3-6 membered spiro carbocyclic or heterocyclic ring;

R3 is hydrogen or halogen;

R4 is selected from the group consisting of: hydrogen; Me, Et, CF_2H; CF_3; CF_2Me; OMe; OEt; OCF_2H; OCF_3; CN; Cl and F; and

wherein:

R8 and R9 are each independently selected from the group consisting of: hydrogen; Me; Et; CH_2OH; $CHMeOH$; CMe_2OH; CH_2OMe; CH_2F and halogen;

R10 and R11 are each independently selected from the group consisting of: hydrogen; Me, Et, CH_2OH, $CHMeOH$, CMe_2OH, CH_2OMe, CH_2F CHF2; CH_2CF_3 and CH_2-heteroaryl;

R12 is selected from the group consisting of: hydrogen and Me;

R13 is selected from the group consisting of: hydrogen and Me;

R21 is selected from the group consisting of: hydrogen; and Me; or

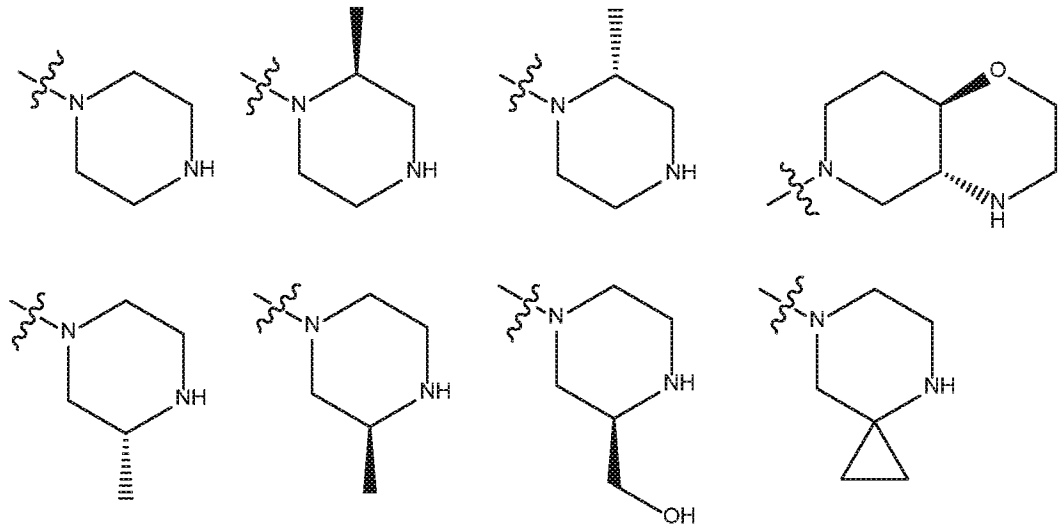
wherein:

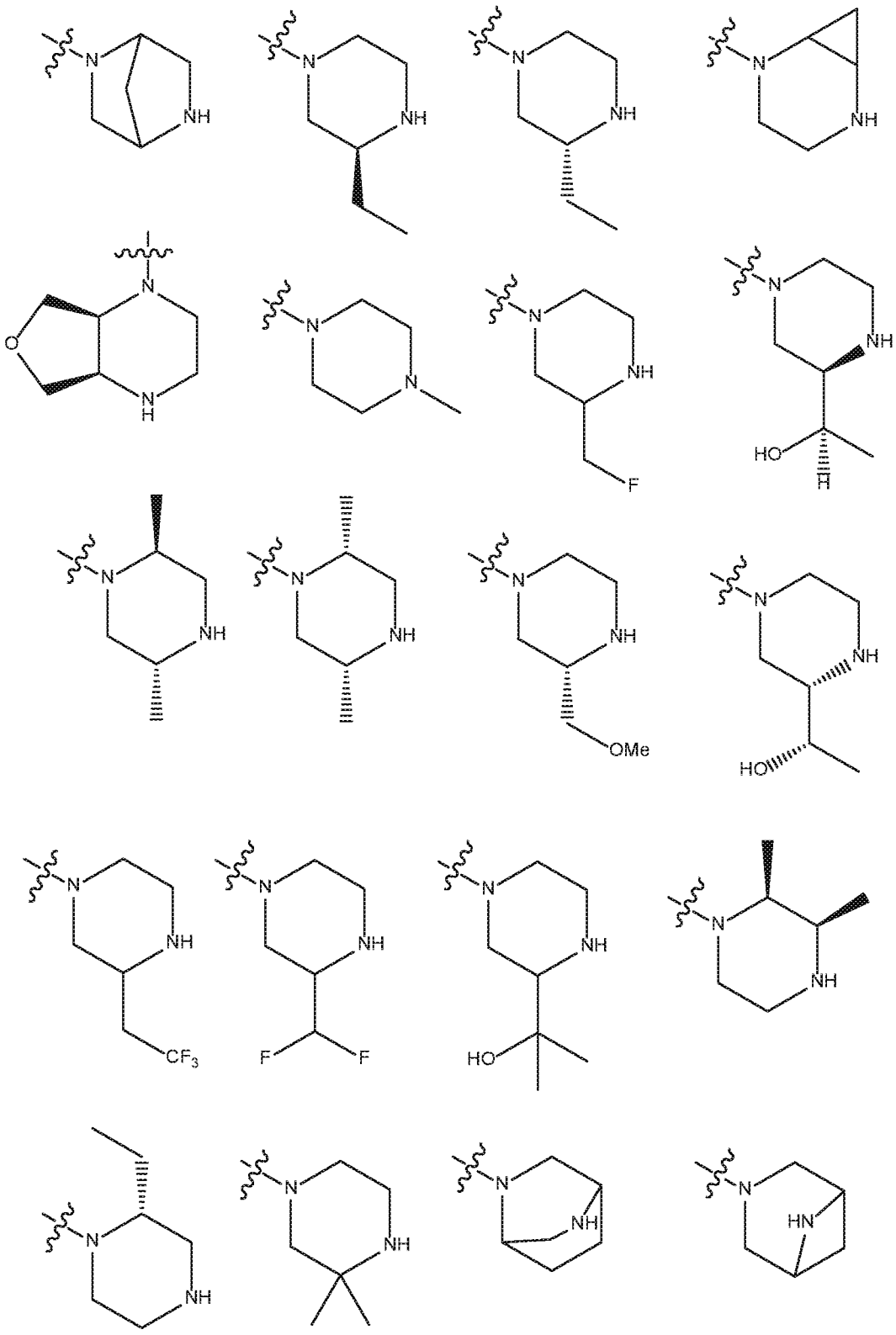
any one of R8, R9, R10, R11, R12, R13 and R21 may be joined to another, different R8, R9, R10, R11, R21, R13 or R21 to form a 3-7-membered spiro or bicyclic carbocyclic or heterocyclic ring structure, and/or a 3-6 membered bridged carbocyclic or heterocyclic ring structure.

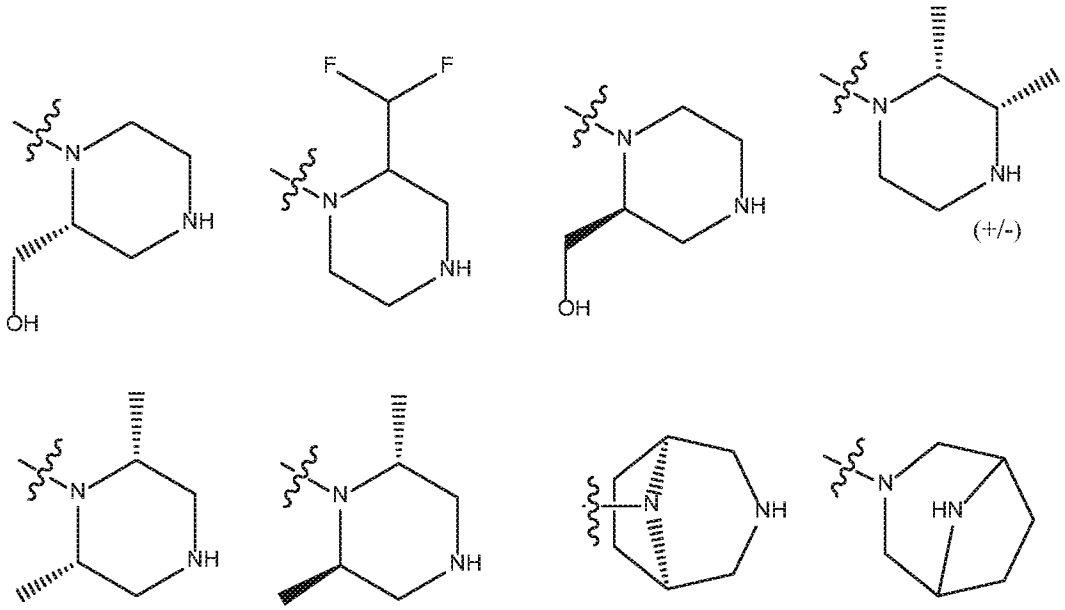
In embodiments:

a) one of R8 and R9 is joined to one of R10 and R11 to form a [6,3]-, [6,4]-, [6,5]-, [6,7]- or [6,8]-bicyclic structure;
b) one of R8 and R9 is joined to R13 to form a [6,5,5]-, [6,6,6]-, [6,7,7]- or [6,8,8]-, bridged structure;
c) one of R10 and R11 is joined to R13 to form a [6,6,4]-, [6,7,5]- or [6,8,6]-bridged structure;
d) one of R10 and R11 may be joined to R21 to form a [6,5,5]-, [6,6,6]-, [6,7,7]-, [6,8,8]-bridged structure;
e) one of R8 and R9 may be joined to R21 to form a [6,6,4]-, [6,7,5]-, [6,8,6]-, bridged structure;
f) R8 is joined to R9 to form a [6,3]-, [6,4-], [6,5]-, [6,6]- or [6,7]-spiro structure; or
g) R10 is joined to R11 to form a [6,3]-, [6,4-], [6,5]-, [6,6]- or [6,7]-spiro structure.

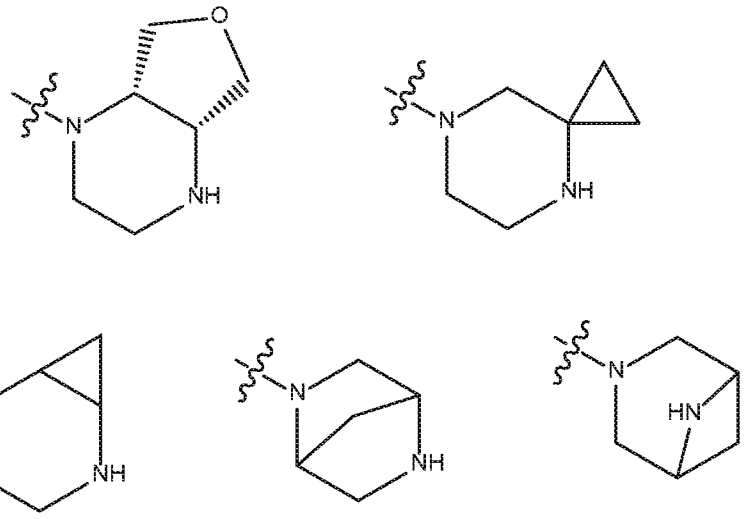
In embodiments, Ring Z is selected from the group consisting of:



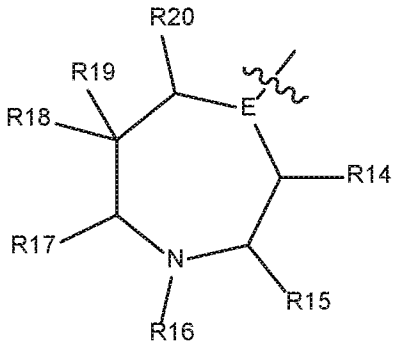




In embodiments, Ring Z is selected from the group consisting of:



In alternative embodiments of Formula I, G is CR1R2 and Ring Z is:



wherein;

A is selected from the group consisting of: C-H, C-F, C-Cl and C-Br;

B and D are each independently selected from the group consisting of: N and C-H;

E is selected from the group consisting of: N; C-H and CF;

R1 is selected from the group consisting of: hydrogen; Me; Et, OMe; OEt; OH; NH_2 and NHMe; and

R2 is selected from the group consisting of: hydrogen, Me and Et; or

R1 and R2 together form a 3-6 membered spiro carbocyclic or heterocyclic ring; particularly a 4-5 membered carbocyclic or heterocyclic spiro ring;

R3 is hydrogen or F;

R4 is selected from the group consisting of: Me; Et; CF_2H; CF_3; CF_2Me; OMe; OEt; OCF_2H; CN; Cl and F;

R14, R15, R17, R18, R19 and R20 is each independently selected from the group consisting of: hydrogen, Me and F.

R16 is selected from the group consisting of: hydrogen and Me.

In embodiments:

a) each of R14, R15, R16, R17, R18, R19 and R20 are hydrogen;

b) when one of R14, R15, R17, R18 and R20 is Me, R16 and R19 are hydrogen;

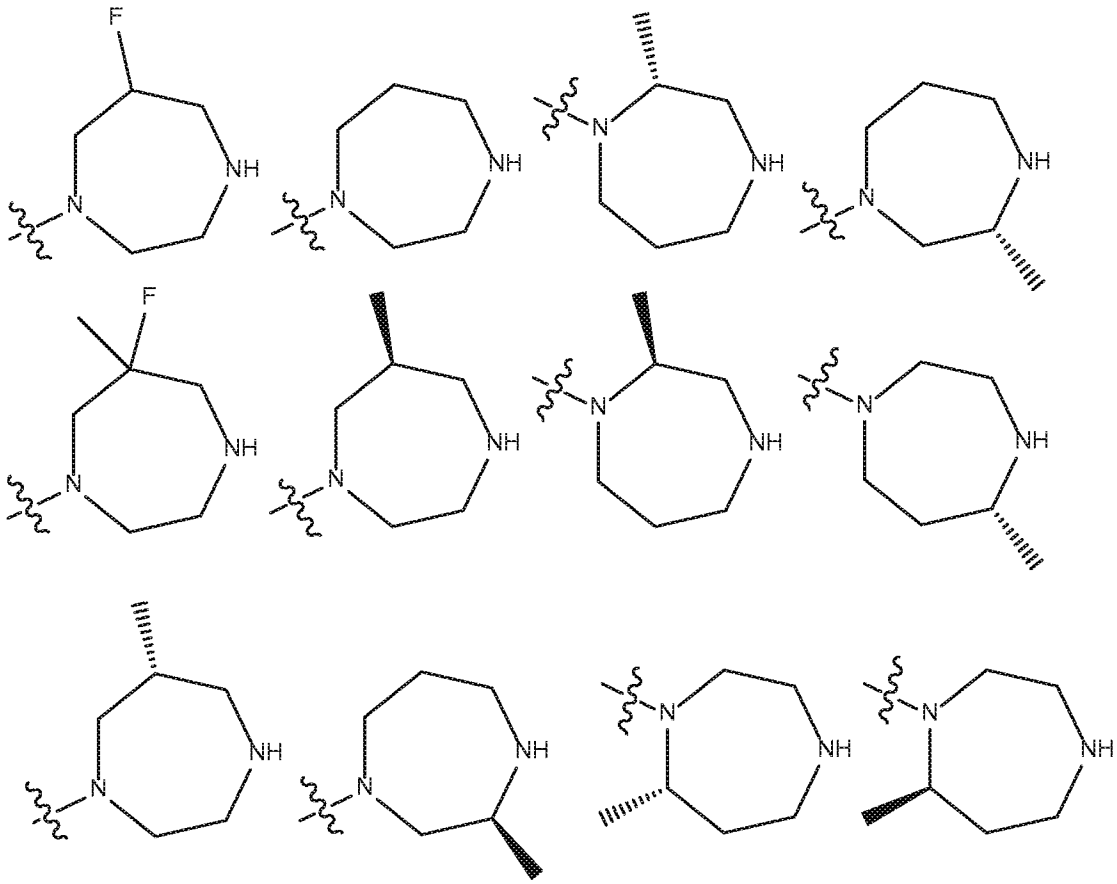
c) when R18 is F, R14, R15, R16, R17, R19 and R20 are hydrogen;

d) when R18 is F and R19 is Me, R14, R15, R16, R17 and R19 are hydrogen;

e) wherein R18 and R19 are both F and R14, R15, R17 and R20 are hydrogen; or

f) when E is C-H, and R14 or R20 is F.

In embodiments, Ring Z is selected from the group consisting of:



In embodiments, when G is N-H, B is N.

In a second aspect, the invention provides a compound according to Table 1 hereinbelow, or a pharmaceutically acceptable salt, solvate, stereoisomer or mixture of stereoisomers, tautomer, isotopic form, or pharmaceutically active metabolite thereof, or combinations thereof.

In a third aspect, the invention provides a pharmaceutical composition comprising one or more compound of the first or second aspects of the invention or a pharmaceutically acceptable salt, solvate, stereoisomer or mixture of stereoisomers, tautomer, isotopic form, or pharmaceutically active metabolite thereof, or combinations thereof, and one or more pharmaceutically acceptable carrier.

In a fourth aspect the invention provides the compound of the first or second aspects or the pharmaceutical composition of the third aspect for use in the treatment of a disorder or disease

selected from an autoimmune disorder and/or inflammatory disease and/or oncologic disease and/or cancer and/or HIV infection and replication.

In embodiments, the disorder or disease is selected from the group consisting of: rheumatoid arthritis, multiple sclerosis, psoriasis and atopic dermatitis.

In embodiments, the compound is an inhibitor of PKC-theta.

In embodiments, the use comprises administering the compound orally; topically; by inhalation; by intranasal administration; or systemically by intravenous, intraperitoneal, subcutaneous, or intramuscular injection.

In embodiments, the use comprises administering one or more compound according to the first or second aspects optionally in combination with one or more additional therapeutic agent. Suitably, the administering comprises administering the one or more compound according to any one of first or second embodiments simultaneously, sequentially or separately from the one or more additional therapeutic agent.

In embodiments, the use comprises administering to a subject an effective amount of the compound according to the first or second aspects, wherein the effective amount is between about 5 nM and about 10 μM in the blood, or component thereof, of the subject.

In a fifth aspect the invention provides a method of treatment of a disorder or disease selected from an autoimmune disorder and/or inflammatory disease and/or oncologic disease and/or cancer and/or HIV infection and replication using a compound of the first or second aspect or a pharmaceutical composition of the third aspect.

In embodiments the disorder or disease is selected from the group consisting of: rheumatoid arthritis, multiple sclerosis, psoriasis and atopic dermatitis.

In embodiments the compound is an inhibitor of PKC-theta.

Within the scope of this application, it is expressly intended that the various aspects, embodiments, examples and alternatives set out in the preceding paragraphs, in the claims and/or in the following description and drawings, and in particular the individual features thereof, may be taken independently or in any combination. That is, all embodiments and/or features of any embodiment can be combined in any way and/or combination, unless such features are

incompatible. More particularly, it is specifically intended that any embodiment of any aspect may form an embodiment of any other aspect, and all such combinations are encompassed within the scope of the invention. The applicant reserves the right to change any originally filed claim or file any new claim, accordingly, including the right to amend any originally filed claim to depend on and/or incorporate any feature of any other claim although not originally claimed in that manner.

DETAILED DESCRIPTION

Described herein are compounds and compositions (e.g., organic molecules, research tools, pharmaceutical formulations and therapeutics); uses for the compounds and compositions of the disclosure (*in vitro* and *in vivo*); as well as corresponding methods, whether diagnostic, therapeutic or for research applications. The chemical synthesis and biological testing of the compounds of the disclosure are also described. Beneficially, the compounds, compositions, uses and methods have utility in research towards and/or the treatment of diseases or disorders in animals, such as humans. Diseases or disorders which may benefit from PKC-theta modulation include, for example, autoimmune disorder, inflammatory disease, cancer and/or oncologic disease and/or HIV infection and replication, such as rheumatoid arthritis, multiple sclerosis, psoriasis, asthma, atopic dermatitis and Crohn's disease.

The compounds may also or alternatively be useful as lead molecules for the selection, screening and development of further derivatives that may have one or more improved beneficial drug property, as desired. Such further selection and screening may be carried out using the proprietary computational evolutionary algorithm described e.g. in the Applicant's earlier published patent application WO 2011/061548, which is hereby incorporated by reference in its entirety.

The disclosure also encompasses salts, solvates and functional derivatives of the compounds described herein. These compounds may be useful in the treatment of diseases or disorders which may benefit from PKC-theta modulation, such as the autoimmune disorders, inflammatory diseases, cancers and/or oncologic diseases and/or HIV infection and replication identified herein.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art (e.g. in organic, physical or theoretical chemistry; biochemistry and molecular biology).

Unless otherwise indicated, the practice of the present invention employs conventional techniques in chemistry and chemical methods, biochemistry, molecular biology, pharmaceutical formulation, and delivery and treatment regimens for patients, which are within the capabilities of a person of ordinary skill in the art. Such techniques are also described in the literature cited herein. All documents cited in this disclosure are herein incorporated by reference in their entirety.

Prior to setting forth the detailed description of the invention, a number of definitions are provided that will assist in the understanding of the disclosure.

In accordance with this disclosure, the terms 'molecule' or 'molecules' are used interchangeably with the terms 'compound' or 'compounds', and sometimes the term 'chemical structure'. The term 'drug' is typically used in the context of a pharmaceutical, pharmaceutical composition, medicament or the like, which has a known or predicted physiological or *in vitro* activity of medical significance; but such characteristics and qualities are not excluded in a molecule or compound of the disclosure. The term 'drug' is therefore used interchangeably with the alternative terms and phrases 'therapeutic (agent)', 'pharmaceutical (agent)', and 'active (agent)'. Therapeutics according to the disclosure also encompass compositions and pharmaceutical formulations comprising the compounds of the disclosure.

Prodrugs and solvates of the compounds of the disclosure are also encompassed within the scope of the disclosure. The term 'prodrug' means a compound (e.g. a drug precursor) that is transformed in vivo to yield a compound of the disclosure or a pharmaceutically acceptable salt, solvate or ester of the compound. The transformation may occur by various mechanisms (e.g. by metabolic or chemical processes), such as by hydrolysis of a hydrolysable bond, e.g. in blood (see Higuchi & Stella (1987), "Pro-drugs as Novel Delivery Systems", vol. 14 of the A.C.S. Symposium Series; (1987), "Bioreversible Carriers in Drug Design", Roche, ed., American Pharmaceutical Association and Pergamon Press). The compositions and medicaments of the disclosure therefore may comprise prodrugs of the compounds of the disclosure. In some aspects and embodiments the compounds of the disclosure are themselves prodrugs which may be metabolised in vivo to give the therapeutically effective compound.

The invention also includes various deuterated forms of the compounds of any of the Formulas disclosed herein, including Formulas I, II, or III (inc. corresponding subgeneric formulas defined herein), respectively, or a pharmaceutically acceptable salt and/or a corresponding tautomer form thereof (including subgeneric formulas, as defined above) of the present invention. Each available hydrogen atom attached to a carbon atom may be independently replaced with a

deuterium atom. A person of ordinary skill in the art will know how to synthesize deuterated forms of the compounds of any of the Formulas disclosed herein, including Formulas (I), (II), or (III) (inc. corresponding subgeneric formulas defined herein), respectively, or a pharmaceutically acceptable salt and/or a corresponding tautomer form thereof (including subgeneric formulas, as defined above) of the present invention. For example, deuterated materials, such as alkyl groups may be prepared by conventional techniques (see for example: methyl-d3 -amine available from Aldrich Chemical Co., Milwaukee, WI, Cat. No.489,689-2).

The subject invention also includes isotopically-labelled compounds which are identical to those recited in any of the Formulas disclosed herein, including Formulas (I), (II), or (III) (inc. corresponding subgeneric formulas defined herein), respectively, or a pharmaceutically acceptable salt and/or a corresponding tautomer form thereof (including subgeneric formulas, as defined above) of the present invention but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine, iodine and chlorine such as 3 H, 11 C, 14 C, 18 F, 123 I or 125 I. Compounds of the present invention and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically labelled compounds of the present invention, for example those into which radioactive isotopes such as 3 H or 14 C have been incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e. 3 H, and carbon-14, i.e. 14 C, isotopes are particularly preferred for their ease of preparation and detectability. 11 C and 18 F isotopes are particularly useful in PET (positron emission tomography).

In the context of the present disclosure, the terms 'individual', 'subject', or 'patient' are used interchangeably to indicate an animal that may be suffering from a medical (pathological) condition and may be responsive to a molecule, pharmaceutical drug, medical treatment or therapeutic treatment regimen of the disclosure. The animal is suitably a mammal, such as a human, cow, sheep, pig, dog, cat, bat, mouse or rat. In particular, the subject may be a human.

The term 'alkyl' refers to a monovalent, optionally substituted, saturated aliphatic hydrocarbon radical. Any number of carbon atoms may be present, but typically the number of carbon atoms in the alkyl group may be from 1 to about 20, from 1 to about 12, from 1 to about 6 or from 1 to about 4. Usefully, the number of carbon atoms is indicated, for example, a C1-12 alkyl (or C_{1-12} alkyl) refers to any alkyl group containing 1 to 12 carbon atoms in the chain. An alkyl group may be a straight chain (i.e. linear), branched chain, or cyclic. 'Lower alkyl' refers to an alkyl of 1 to 6

carbon atoms in the chain, and may have from 1 to 4 carbon atoms, or 1 to 2 carbon atoms. Thus, representative examples of lower alkyl radicals include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, isopropyl, isobutyl, isopentyl, amyl (C_5H_{11}), sec-butyl, tert-butyl, sec-amyl, tert-pentyl, 2-ethylbutyl, 2,3-dimethylbutyl, and the like. 'Higher alkyl' refers to alkyls of 7 carbons and above, including n-heptyl, n-octyl, n-nonyl, n-decyl, n-dodecyl, n-tetradecyl, n-hexadecyl, n-octadecyl, n-eicosyl, and the like, along with branched variations thereof. A linear carbon chain of say 4 to 6 carbons would refer to the chain length not including any carbons residing on a branch, whereas in a branched chain it would refer to the total number. Optional substituents for alkyl and other groups are described below.

The term 'substituted' means that one or more hydrogen atoms (attached to a carbon or heteroatom) is replaced with a selection from the indicated group of substituents, provided that the designated atom's normal valency under the existing circumstances is not exceeded. The group may be optionally substituted with particular substituents at positions that do not significantly interfere with the preparation of compounds falling within the scope of this invention and on the understanding that the substitution(s) does not significantly adversely affect the biological activity or structural stability of the compound. Combinations of substituents are permissible only if such combinations result in stable compounds. By 'stable compound' or 'stable structure', it is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture and/or formulation into an efficacious therapeutic agent. By 'optionally substituted' it is meant that the group concerned is either unsubstituted, or at least one hydrogen atom is replaced with one of the specified substituent groups, radicals or moieties.

Any radical / group / moiety described herein that may be substituted (or optionally substituted) may be substituted with one or more (e.g. one, two, three, four or five) substituents, which are independently selected from the designated group of substituents. Thus, substituents may be selected from the group: halogen (or 'halo', e.g. F, Cl and Br), hydroxyl (-OH), amino or aminyl ($-NH_2$), thiol (-SH), cyano (-CN), (lower) alkyl, (lower) alkoxy, (lower) alkenyl, (lower) alkynyl, aryl, heteroaryl, (lower) alkylthio, oxo, haloalkyl, hydroxyalkyl, nitro ($-NO_2$), phosphate, azido ($-N_3$), alkoxycarbonyl, carboxy, alkylcarboxy, alkylamino, dialkylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, thioalkyl, alkylsulfonyl, arylsulfinyl, alkylaminosulfonyl, arylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, arylcarbamoyl, alkylcarbonylamino, arylcarbonylamino, cycloalkyl, heterocycloalkyl, unless otherwise indicated. Alternatively, where the substituents are on an aryl or other cyclic ring system, two adjacent atoms may be substituted with a methylenedioxy or ethylenedioxy group. More suitably, the substituents are selected from: halogen, hydroxy, amino, thiol, cyano, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, aryl, aryl(C_1-C_6)alkyl, aryl(C_1-C_6)alkoxy,

heteroaryl, (C_1-C_6)alkylthio, oxo, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, nitro, phosphate, azido, (C_1-C_6)alkoxycarbonyl, carboxy, (C_1-C_6)alkylcarboxy, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl, thio(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl, arylsulfinyl, (C_1-C_6)alkylaminosulfonyl, arylaminosulfonyl, (C_1-C_6)alkylsulfonylamino, arylsulfonylamino, carbamoyl, (C_1-C_6)alkylcarbamoyl, di(C_1-C_6)alkylcarbamoyl, arylcarbamoyl, (C_1-C_6)alkylcarbonylamino, arylcarbonylamino, (C_1-C_6)cycloalkyl, and heterocycloalkyl. Still more suitably, the substituents are selected from one or more of: fluoro, chloro, bromo, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_5-C_6)aryl, a 5- or 6-membered heteroaryl, (C_4-C_6)cycloalkyl, a 4- to 6-membered heterocycloalkyl, cyano, (C_1-C_6)alkylthio, amino, -NH(alkyl), -NH((C_1-C_6)cycloalkyl), -N((C_1-C_6)alkyl)$_2$, -OC(O)-(C_1-C_6)alkyl, -OC(O)-(C_5-C_6)aryl, -OC(O)-(C_1-C_6)cycloalkyl, carboxy and -C(O)O-(C_1-C_6)alkyl. Most suitably, the substituents are selected from one or more of: fluoro, chloro, bromo, hydroxy, amino, (C_1-C_6)alkyl and (C_1-C_6)alkoxy, wherein alkyl and alkoxy are optionally substituted by one or more chloro. Particularly preferred substituents are: chloro, methyl, ethyl, methoxy and ethoxy.

The term 'halo' or 'halogen' refers to a monovalent halogen radical chosen from chloro, bromo, iodo, and fluoro. A 'halogenated' compound is one substituted with one or more halo substituent. Preferred halo groups are F, Cl and Br, and most preferred is F.

When used herein, the term 'independently', in reference to the substitution of a parent moiety with one or more substituents, means that the parent moiety may be substituted with any of the listed substituents, either individually or in combination, and any number of chemically possible substituents may be used. In any of the embodiments, where a group is substituted, it may contain up to 5, up to 4, up to 3, or 1 and 2 substituents. As a non-limiting example, useful substituents include: phenyl or pyridine, independently substituted with one or more lower alkyl, lower alkoxy or halo substituents, such as: chlorophenyl, dichlorophenyl, trichlorophenyl, tolyl, xylyl, 2-chloro-3-methylphenyl, 2,3-dichloro- 4-methylphenyl, etc.

As used herein, the term 'alkylene' or 'alkylenyl' means a difunctional group obtained by removal of a hydrogen atom from an alkyl group as defined above. Non-limiting examples of alkylene include methylene, ethylene and propylene. 'Lower alkylene' means an alkylene having from 1 to 6 carbon atoms in the chain, and may be straight or branched. Alkylene groups are optionally substituted.

The term 'alkenyl' refers to a monovalent, optionally substituted, unsaturated aliphatic hydrocarbon radical. Therefore, an alkenyl has at least one carbon-carbon double bond (C=C). The number of carbon atoms in the alkenyl group may be indicated, such as from 2 to about 20.

For example, a C2-12 alkenyl (or C_{2-12} alkenyl) refers to an alkenyl group containing 2 to 12 carbon atoms in the structure. Alkenyl groups may be straight (i.e. linear), branched chain, or cyclic. 'Lower alkenyl' refers to an alkenyl of 1 to 6 carbon atoms, and may have from 1 to 4 carbon atoms, or 1 to 2 carbon atoms. Representative examples of lower alkenyl radicals include ethenyl, 1-propenyl, 1-butenyl, 1-pentenyl, 1-hexenyl, isopropenyl, isobutenyl, and the like. Higher alkenyl refers to alkenyls of seven carbons and above, such as 1-heptenyl, 1-octenyl, 1-nonenyl, 1-decenyl, 1-dodecenyl, 1-tetradecenyl, 1-hexadecenyl, 1-octadecenyl, 1-eicosenyl, and the like, along with branched variations thereof. Optional substituents include are described elsewhere.

'Alkenylene' means a difunctional group obtained by removal of a hydrogen from an alkenyl group that is defined above. Non-limiting examples of alkenylene include -CH=CH-, $-C(CH_3)=CH-$, and $-CH=CHCH_2-$

'Alkynyl' and 'lower alkynyl' is defined similarly to the term 'alkenyl', except that it includes at least one carbon-carbon triple bond.

The term 'alkoxy' refers to a monovalent radical of the formula RO-, where R is any alkyl, alkenyl or alkynyl as defined herein. Alkoxy groups may be optionally substituted by any of the optional substituents described herein. 'Lower alkoxy' has the formula RO-, where the R group is a lower alkyl, alkenyl or alkynyl. Representative alkoxy radicals include methoxy, ethoxy, n-propoxy, n-butoxy, n-pentyloxy, n-hexyloxy, isopropoxy, isobutoxy, isopentyloxy, amyloxy, sec-butoxy, tert-butoxy, tert-pentyloxy, and the like. Preferred alkoxy groups are methoxy and ethoxy.

The term 'aryl' as used herein refers to a substituted or unsubstituted aromatic carbocyclic radical containing from 5 to about 15 carbon atoms; and preferably 5 or 6 carbon atoms. An aryl group may have only one individual carbon ring, or may comprise one or more fused rings in which at least one ring is aromatic in nature. A 'phenyl' is a radical formed by removal of a hydrogen atom from a benzene ring, and may be substituted or unsubstituted. A 'phenoxy' group, therefore, is a radical of the formula RO-, wherein R is a phenyl radical. 'Benzyl' is a radical of the formula $R-CH_2-$, wherein R is phenyl, and 'benzyloxy' is a radical of the formula RO-, wherein R is benzyl. Non-limiting examples of aryl radicals include, phenyl, naphthyl, benzyl, biphenyl, furanyl, pyridinyl, indanyl, anthraquinolyl, tetrahydronaphthyl, a benzoic acid radical, a furan-2-carboxylic acid radical, and the like.

A 'heteroaryl' group is herein defined as a substituted or unsubstituted 'aryl' group in which one or more carbon atoms in the ring structure has been replaced with a heteroatom, such as

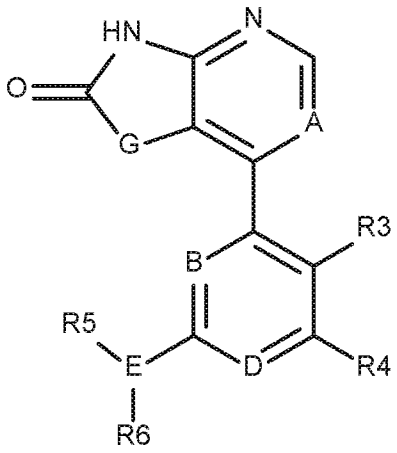
nitrogen, oxygen or sulphur. Generally, the heteroaryl group contains one or two heteroatoms. A preferred heteroatom is N. Exemplary heteroaryl groups include: furan, benzofuran, isobenzofuran, pyrrole, indole, isoindole, thiophene, benzothiophene, benzo[c]thiophene, imidazole, benzimidazole, purine, pyrazole, indazole, oxazole, benzoxazole, isoxazole, benzisoxazole, thiazole, benzothiazole, pyridine, quinoline, isoquinoline, pyrazine, quinoxaline, acridine, pyrimidine, quinazoline, pyridazine and cinnoline.

The terms 'heterocycle' or 'heterocyclic' group as used herein refer to a monovalent radical of from about 4- to about 15- ring atoms, and preferably 4-, 5- or 6,7- ring members. Generally the heterocyclic group contains one, two or three heteroatoms, selected independently from nitrogen, oxygen and sulphur. A preferred heteroatom is N. A heterocyclic group may have only one individual ring or may comprise one or more fused rings in which at least one ring contains a heteroatom. It may be fully saturated or partially saturated and may be substituted or unsubstituted as in the case or aryl and heteroaryl groups. Representative examples of unsaturated 5-membered heterocycles with only one heteroatom include 2- or 3-pyrrolyl, 2- or 3-furanyl, and 2- or 3-thiophenyl. Corresponding partially saturated or fully saturated radicals include 3-pyrrolin-2-yl, 2- or 3-pyrrolindinyl, 2- or 3-tetrahydrofuranyl, and 2- or 3-tetrahydrothiophenyl. Representative unsaturated 5-membered heterocyclic radicals having two heteroatoms include imidazolyl, oxazolyl, thiazolyl, pyrazolyl, and the like. The corresponding fully saturated and partially saturated radicals are also included. Representative examples of unsaturated 6-membered heterocycles with only one heteroatom include 2-, 3-, or 4-pyridinyl, 2H-pyranyl, and 4H-pryanyl. Corresponding partially saturated or fully saturated radicals include 2-, 3-, or 4-piperidinyl, 2-, 3-, or 4-tetrahydropyranyl and the like. Representative unsaturated 6-membered heterocyclic radicals having two heteroatoms include 3- or 4-pyridazinyl, 2-, 4-, or 5-pyrimidinyl, 2-pyrazinyl, morpholino, and the like. The corresponding fully saturated and partially saturated radicals are also included, e.g. 2-piperazine. The heterocyclic radical is bonded through an available carbon atom or heteroatom in the heterocyclic ring directly to the entity or through a linker such as an alkylene such as methylene or ethylene.

Unless defined otherwise, 'room temperature' is intended to mean a temperature of from about 18 to 28°C, typically between about 18 and 25°C, and more typically between about 18 and 22°C. As used herein, the phrase 'room temperature' may be shortened to 'rt' or 'RT'.

Molecules and Compounds

Disclosed herein is a compound having the structural Formula I:



I

or a pharmaceutically acceptable salt, solvate, stereoisomer or mixture of stereoisomers, tautomer, or isotopic form, or pharmaceutically active metabolite thereof, or combinations thereof, wherein:

A is selected from the group consisting of: N, C-R^a, where R^a is selected from hydrogen, halogen, C1-3 alkyl and CN;

B is selected from the group consisting of: N; C-H, C-F and C-(C1-3 alkyl);

D is selected from the group consisting of: N; C-H; C-R^b where R^b is selected from halogen; C1-3 alkyl; C1-3 haloalkyl;

G is selected from the group consisting of: CR1R2; NR1; and O;

R1 and R2 are independently selected from the group consisting of: hydrogen, halogen, C1-3 alkyl, C3-7 cycloalkyl (e.g. $CH_2{}^cPr$); C1-3 alkoxyl (e.g. OMe); C2-6 cycloalkoxyl (e.g. O^cPr); C2-6 alkyl alkoxy (e.g. CH_2OMe), hydroxyl, C1-3 alkyl hydroxyl (e.g. CH_2OH), amino, C1-3 alkyl amino (e.g. CH_2NH_2); C1-4 amino alkyl (e.g. NHMe or $N(Me)_2$), C2-7 alkyl amino alkyl (e.g. CH_2NHMe or $CH_2NH(Me)_2$); C1-3 haloalkyl; aryl (e.g. phenyl); heteroaryl (e.g. pyridine); alkyl aryl (e.g. benzyl) and alkyl heteroaryl; or

R1 and R2 together form a 3-5 membered optionally substituted spiro carbocyclic or heterocyclic ring; particularly a 4-5 membered optionally substituted carbocyclic or heterocyclic spiro ring; wherein in embodiments the carbocyclic or heterocyclic spiro ring is unsubstituted; wherein in alternative embodiments the carbocyclic or heterocyclic spiro ring is substituted with one or more substituents selected from the group consisting of: C1-2 alkyl, halogen; C1-2

haloalkyl; hydroxy; and C1-2 alkoxy; R3 is selected from the group consisting of: hydrogen, C1-2 alkyl, -OMe and halogen;

R4 is selected from the group consisting of: hydrogen; C1-5 alkyl (e.g. Me, Et); C3-7 cycloalkyl (e.g. cPr, cHex); C1-5 haloalkyl (e.g. CHF2, CF3, CF2Me, CH2CHF2); C1-5 alkoxyl (e.g. OMe, OEt); C1-5 haloalkoxyl (e.g. OCHF2, OCF3, OCH2CHF2); alkyl alkoxy (e.g. CH2OMe, (CH2)2OMe); C2-6 heterocycloalkyl (e.g. piperidine, piperazine); CN and halogen (e.g. F, Cl, Br);

E is selected from the group consisting of: N; C-H; C-R^c, where R^c is selected from the group consisting of halogen (e.g. F, Cl, Br); hydroxyl; C1-3 alkyl hydroxyl (e.g. CH_2OH, $(CH_2)_2OH$); C1-3 alkyl amino (e.g. CH_2NH_2, $(CH_2)_2NH_2$); C1-3 haloalkyl (e.g. CH_2F ,CHF_2, CF_3, CH_2CHF_2); C2-6 alkyl alkoxyl (e.g. CH_2OMe, $(CH_2)_2OMe$); and CN;

R5 and R6 are each independently selected from the group consisting of: hydrogen; C2-5 alkyl; C1-C5 amino alkyl (e.g. $-(CH_2)_2NH_2$); 4-8-membered amino alkyl ring (e.g. piperidine, suitably 4-piperidine); C1-9 alkyl alkoxy; (e.g. -CH_2OMe); C1-9 alkyl amino alkyl (e.g. $-(CH_2)_2NHMe$ or $-(CH_2)_2N(Me)_2$); or

R5 and R6 are joined together to form an optionally substituted, optionally bridged, C3-10 heterocycloalkyl mono- or bicyclic ring (hereinbefore defined as Ring Z); or

E, R5 and R6 together are J, wherein J is selected from the group consisting of: N-R^d; $C(=O)R^d$; SO_2R^d; O-R^d, wherein R^d is a 4-8-membered amino alkyl ring.

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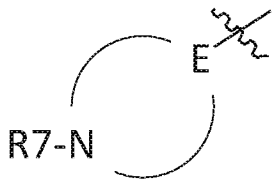
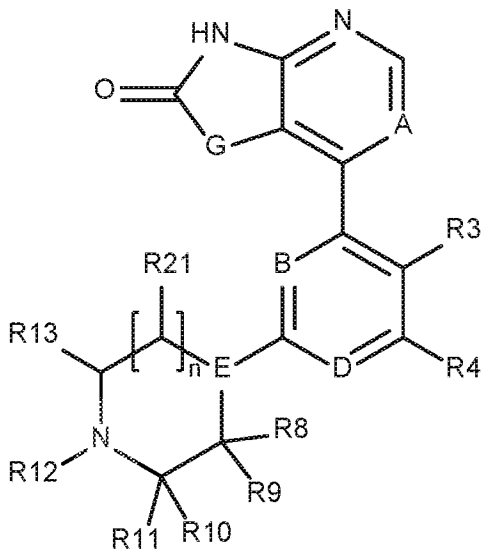
In certain embodiments, R5 and R6 are joined together to form an optionally substituted, optionally bridged, 4-8-membered, suitably 5-7-membered, amino alkyl ring (hereinbefore described as Ring Z), with the general Formula Ia;



Ia

wherein R7 is selected from the group consisting of: hydrogen; C1-3 alkyl (e.g. Me); and C1-3 haloalkyl (e.g. CH_2CHF, CH_2CHF_2).

In certain embodiments of Formula I, Formula Ia is an optionally substituted, optionally bridged, amino alkyl ring, i.e. general Formula II:



II

wherein A, B, D, E, G and R3 and R4 are as for Formula I; and wherein

R8, R9, R10, R11, R13 and R21 are each independently selected from the group consisting of: hydrogen, C1-3 alkyl, C1-3 alkyl alkoxy (e.g. CH_2OMe), C1-3 alkyl hydroxyl (e.g. CH_2OH, $CHMeOH$, CMe_2OH), amino, C1-3 alkyl amino (e.g. CH_2NH_2, $CHMeNH_2$, CMe_2NH_2), C1-6 alkyl amino alkyl (e.g. CH_2NHMe or $CH_2NH(Me)_2$); C1-3 haloalkyl (e.g. CH_2F); alkyl heteroaryl (e.g. CH_2-pyridyl, suitably CH_2-3-pyridyl; or CH_2-thiazole)

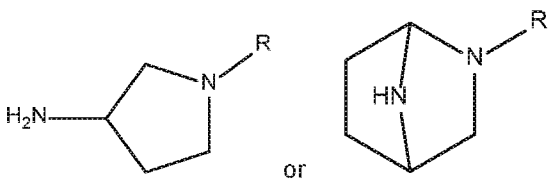
R12 is selected from the group consisting of: hydrogen; C1-3 alkyl; and C1-3 haloalkyl; or

any one of R8, R9, R10, R11, R12, R13 and R21 may be joined to another, different R8, R9, R10, R11, R12, R13 or R21 to form a 3-7-membered spiro or bicyclic carbocyclic or heterocyclic ring structure, and/or a 3-6 membered bridged carbocyclic or heterocyclic ring structure;

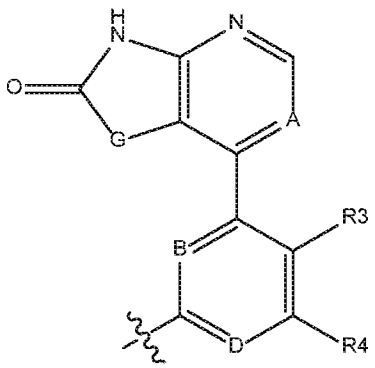
n is selected from the group consisting of: 0; 1; and 2; suitably n is 1 or 2.

In embodiments when n=0, E is suitably selected from the group consisting of: N; C-H; C-R^d, wherein R^d is selected from the group consisting of halogen; alkoxy; C1-3 alkylhydroxy (e.g. CH_2OH); C1-3 haloalkyl (e.g. CH_2F); C2-5 alkyl alkoxy (e.g. CH_2OMe); C2-5 alkyl nitrile (e.g. CH_2CN).

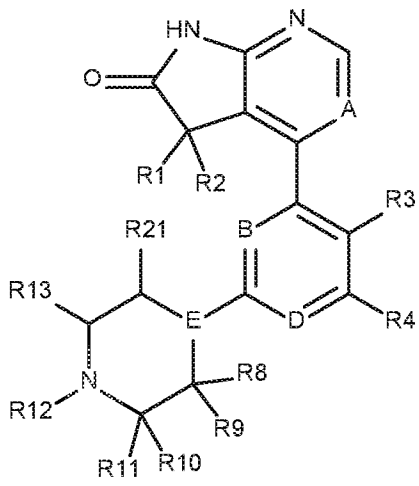
In specific embodiments of Formula I, or II, the ring defined hereinbefore as Ring Z may be:



wherein R in this context relates to the remaining structure of Formula I or II as follows:



In certain embodiments of Formula II, G is CR1R2 and n is 1 i.e. a compound of Formula IIa:



IIa

wherein;

A is selected from the group consisting of: C-H, C-F, C-Cl; and C-Br;

B and D are each independently selected from the group consisting of: N and CH;

E is selected from the group consisting of: N, C-F and C-H;

R1 is selected from the group consisting of: hydrogen, Me, Et, OMe, OEt, OH, NH_2, NHMe

R2 is selected from the group consisting of: hydrogen, Me, Et; suitably Me; or

R1 and R2 together form a 3-6 membered spiro carbocyclic or heterocyclic ring; particularly a 4-5 membered carbocyclic or heterocyclic spiro ring;

R3 is hydrogen or halogen;

R4 is selected from the group consisting of: hydrogen; Me, Et, CF_2H; CF_3; CF_2Me; OMe, OEt, OCF_2H; OCF3, CN, Cl; and F; and

wherein:

R8 and R9 are each independently selected from the group consisting of: hydrogen, Me, Et, CH_2OH, CHMeOH, CMe_2OH, CH_2OMe, and CH_2F; and halogen (e.g. F, when E is CH);

R10 and R11 are each independently selected from the group consisting of: H, Me, Et, CH_2OH, CHMeOH, CMe_2OH, CH_2OMe, CH_2F; CHF_2, CH_2-heteroaryl (e.g. pyridyl and thiazole), and CH_2CF_3;

R12 is selected from the group consisting of: hydrogen and Me;

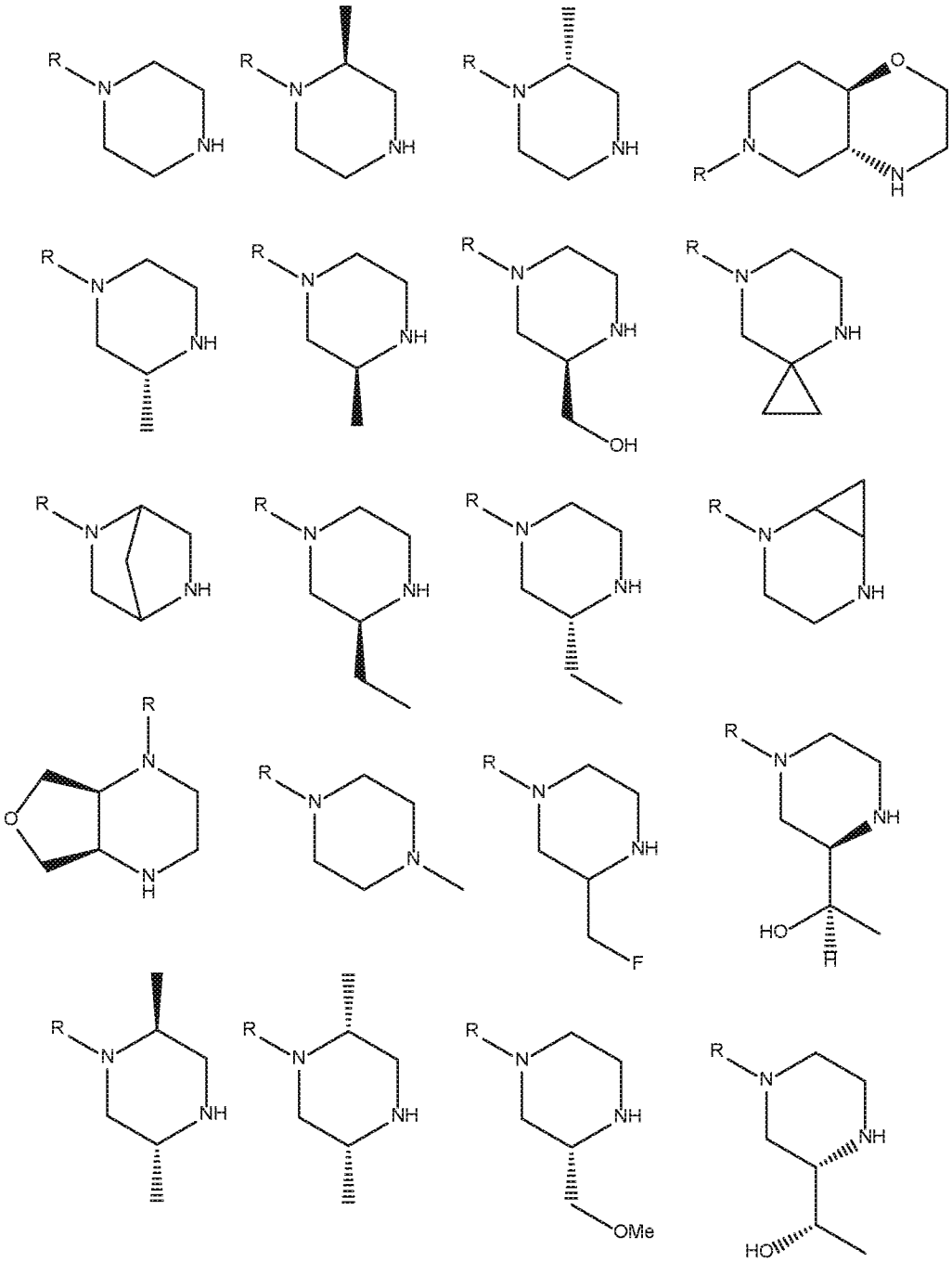
R13 is selected from the group consisting of: hydrogen and Me;

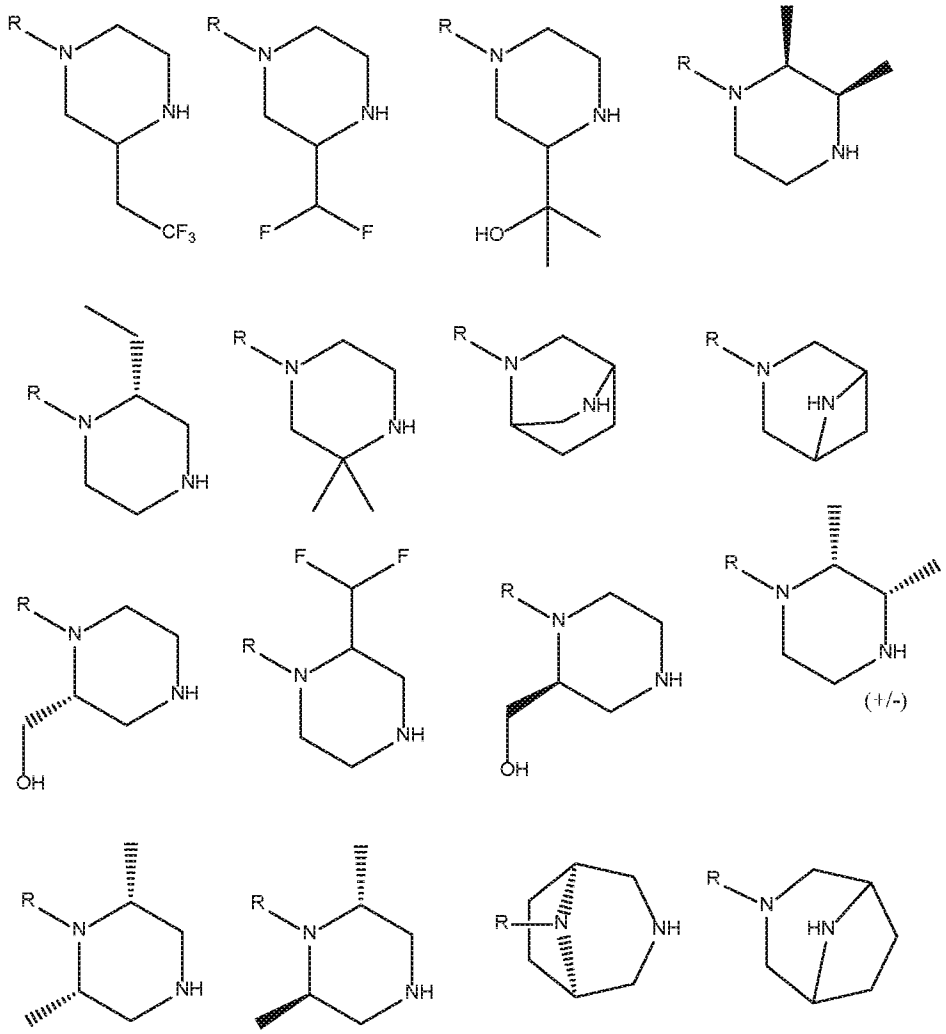
R21 is selected from the group consisting of: hydrogen; and methyl; or

wherein:

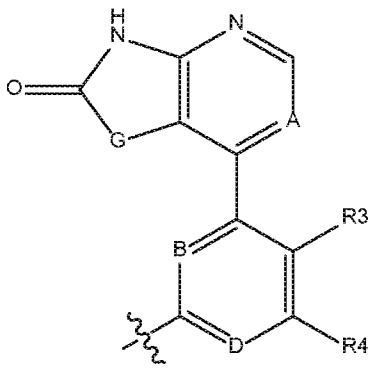
any one of R8, R9, R10, R11, R12, R13 and R21 may be joined to another, different R8, R9, R10, R11, R21, R13 or R21 to form a 3-7-membered spiro or bicyclic carbocyclic or heterocyclic ring structure, and/or a 3-6 membered bridged carbocyclic or heterocyclic ring structure.

In specific embodiments of Formula I, or II, the ring defined hereinbefore as Ring Z may be selected from the group consisting of:



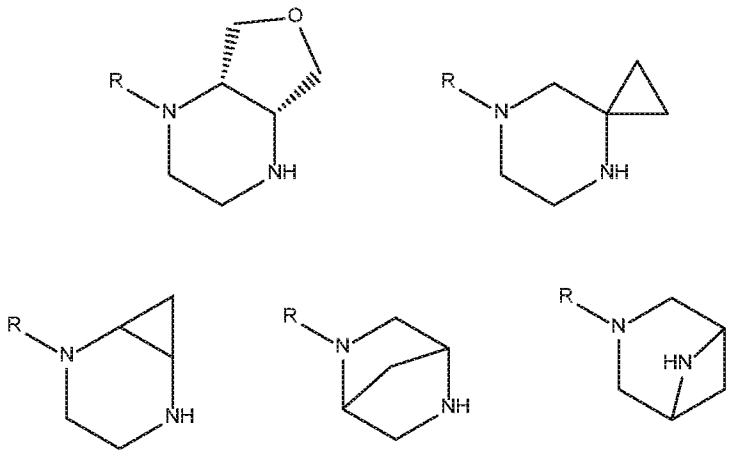


wherein R in this context relates to the remaining structure of Formula II (or Formula IIa when G is CR1R2) as follows:

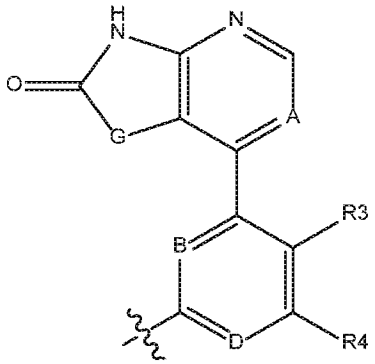


In further specific embodiments of Formula II or IIa, any one of R8 to R13 or R21 may be joined to another, different R8 to R13 or R21 to form a 3-7-membered carbocyclic or heterocyclic ring and/or a 3-6 membered bridged carbocyclic or heterocyclic ring structure. In embodiments, one of R8 and R9 may be joined to one of R10 and R11 to form a [6,3]-, [6,4]-, [6,5]-, [6,7]-, [6,8]-bicyclic structure. In other embodiments, one of R8 and R9 may be joined to R13 to form a [6,5,5]-, [6,6,6]-, [6,7,7]-, [6,8,8]-, bridged structure. In other embodiments, one of R10 and R11 may be joined to R13 to form a [6,6,4]-, [6,7,5]-, [6,8,6]-bridged structure. In other embodiments, one of R10 and R11 may be joined to R21 to form a [6,5,5]-, [6,6,6]-, [6,7,7]-, [6,8,8]-bridged structure. In other embodiments, one of R8 and R9 may be joined to R21 to form a [6,6,4]-, [6,7,5]-, [6,8,6]-, bridged structure. In other embodiments, R8 and R9 may be joined, or R10 and R11 may be joined, to form a [6,3]-, [6,4-], [6,5]-, [6,6]-, [6,7]- spiro structure.

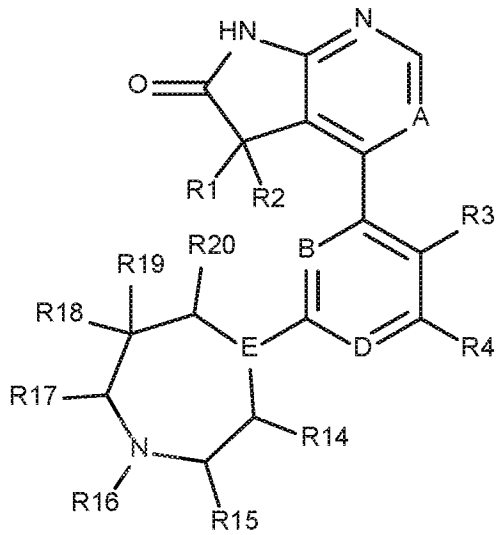
Suitable bicyclic, bridged or spiro structures may be selected from the group consisting of:



wherein R in this context is the portion of Formula II (or Formula IIa when G is CR1R2) defined as follows:



In certain embodiments of Formula II, G is CR1R2 and n is 2 i.e. a compound having the structure of Formula IIb:



IIb

wherein;

A is selected from the group consisting of: C-H, C-F, C-Cl; and C-Br;

B and D are each independently selected from the group consisting of: N and CH;

E is selected from the group consisting of: N; CH; and C-F;

R1 is selected from the group consisting of: hydrogen, Me, Et, OMe, OEt, OH, NH_2, NHMe

R2 is selected from the group consisting of: hydrogen, Me, Et; suitably Me; or

R1 and R2 together form a 3-6 membered spiro carbocyclic or heterocyclic ring; particularly a 4-5 membered carbocyclic or heterocyclic spiro ring;

R3 is selected from the group consisting of: hydrogen or halogen (e.g. F);

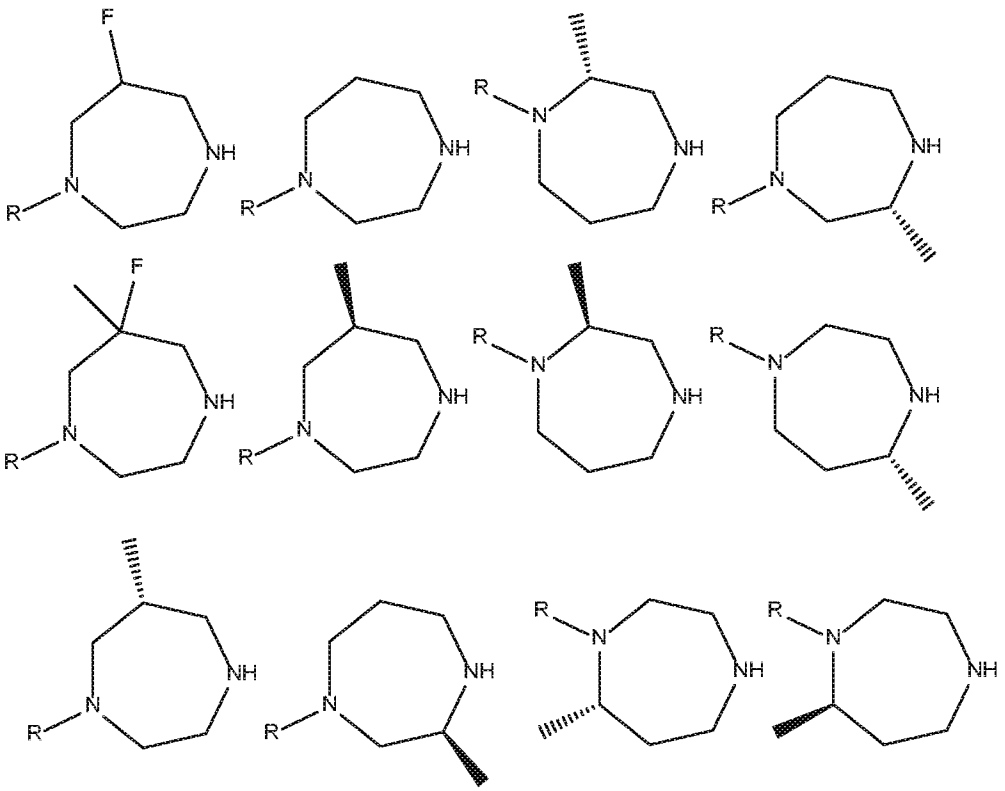
R4 is selected from the group consisting of: Me, Et, CF_2H; CF_3; CF_2Me; OMe, OEt, CN, OCF_2H; OCF_3, Cl; F;

R14, R15, R17, R18, R19 and R20 is each independently selected from the group consisting of: hydrogen; methyl and fluoro.

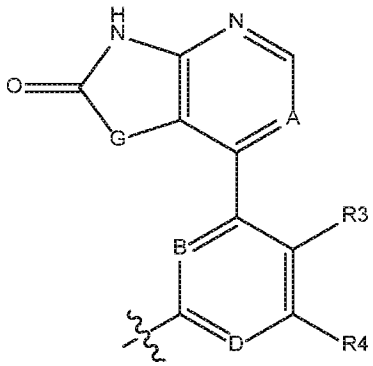
R16 is selected from the group consisting of: hydrogen and Me.

In a specific embodiment of Formula IIb, each of R14, R15, R16, R17, R18, R19 and R20 are H. In another specific embodiment of Formula IIb, R14, R15, R17, R18, R19 and R20 is each independently selected from the group consisting of: hydrogen and methyl when E is N. In another specific embodiment of Formula IIb, when one of R14, R15, R17, R18 and R20 are Me, R16 and R19 are hydrogen. In a further specific embodiment of Formula IIb, when R18 is F, R14, R15, R16, R17, R19 and R20 are H. In another specific embodiment of Formula IIb, when R18 is F and R19 is Me, R14, R15, R16, R17 and R19 are hydrogen. In another specific embodiment of Formula IIb, R18 and R19 are both fluoro and R14, R15, R17 and R20 are hydrogen. In another specific embodiment of Formula IIb, when E is C-H, R14 or R20 is fluoro.

In specific embodiments of Formula IIb, the ring defined herein before Ring Z may be selected from the group consisting of:

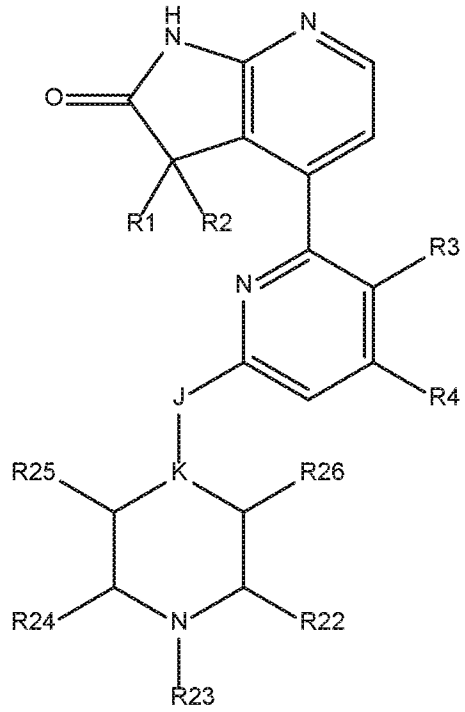


wherein R in this context is the portion of Formula II (or Formula IIb when G is R1R2) defined as follows:



In further specific embodiments of Formulas I, II, and/or III, when G is N-H, B is N.

In certain embodiments of Formula I, G is CR1R2 and E, R5 and R6 together are J, wherein J is selected from the group consisting of: N-R^d; C(=O)R^d; SO_2R^d; O-R^d, wherein R^d is a 4-8-membered amino alkyl ring, for example, a compound having the structure of Formula III:



III

wherein R1, R2, R3 and R4 are as for any of Formula I, II, IIa or IIb; and

wherein;

K is selected from the group consisting of: N and C-H;

when K is N, J is selected from the group consisting of: CH_2; CHMe; CMe_2; CO; and SO_2; or

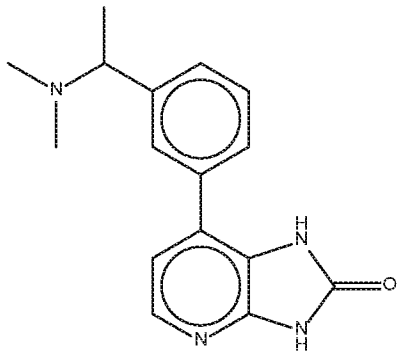
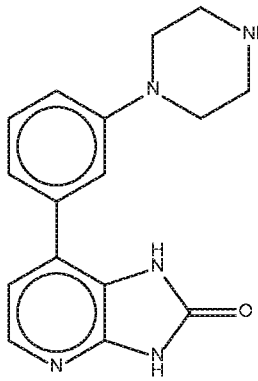
when K is C-H, J is selected from the group consisting of: O and N-R^e; wherein R^e is selected from the group consisting of: hydrogen; Me; Et; Propyl; CH_2CF_3; CH_2CH_2F; CH_2CH_2OMe; CH_2-oxetane;

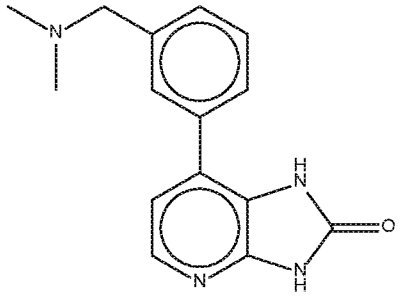
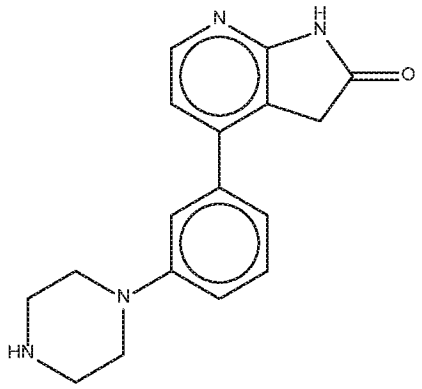
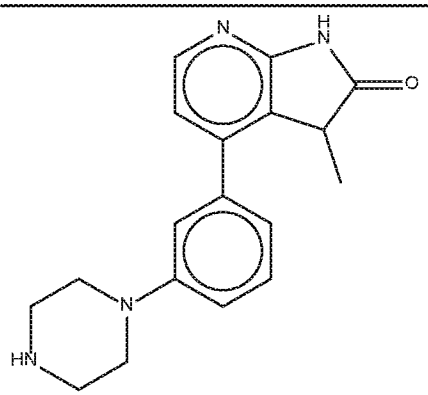
R22, R23, R24, R25, R26 are each independently selected from the group consisting of: hydrogen; fluoro and Me.

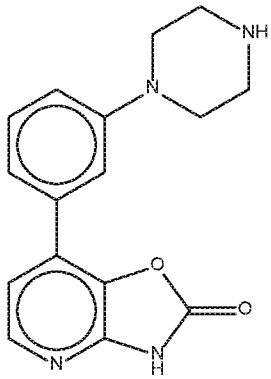
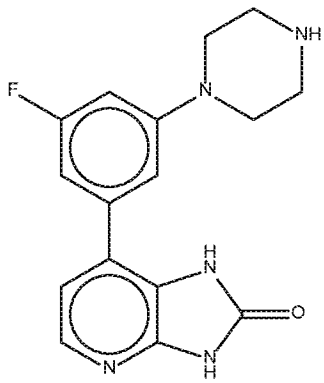
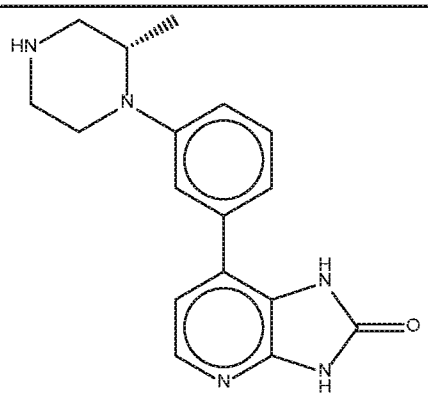
In certain embodiments, R22, R23, R24, R25, R26 are each independently selected from the group consisting of: hydrogen; Me and fluoro only when J is C-H and E is NR^e, otherwise R22,

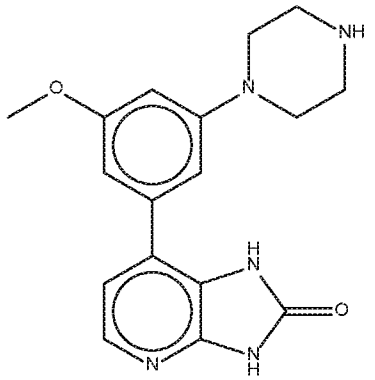
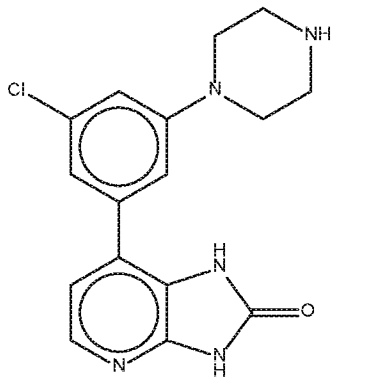
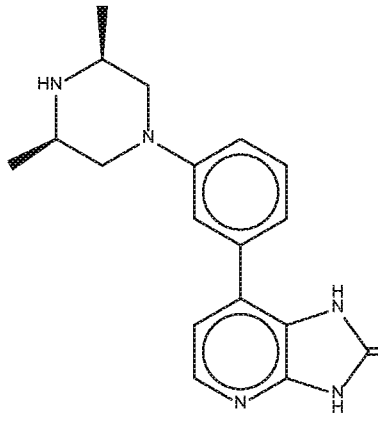
R23, R24, R25, R26 are each independently selected from the group consisting of: hydrogen; and Me.

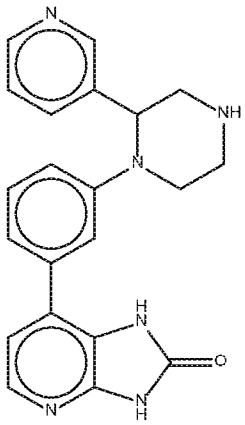
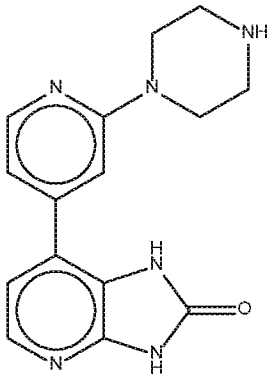
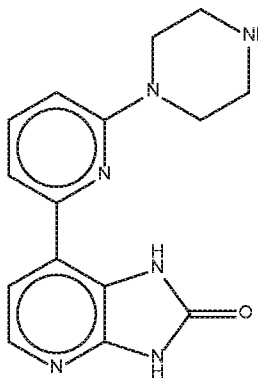
The compounds of the invention may have the structure as described below:

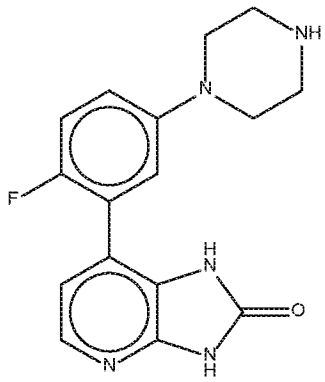
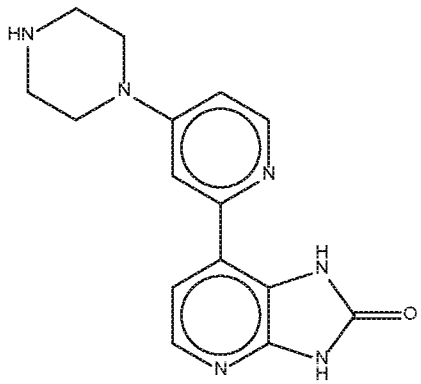
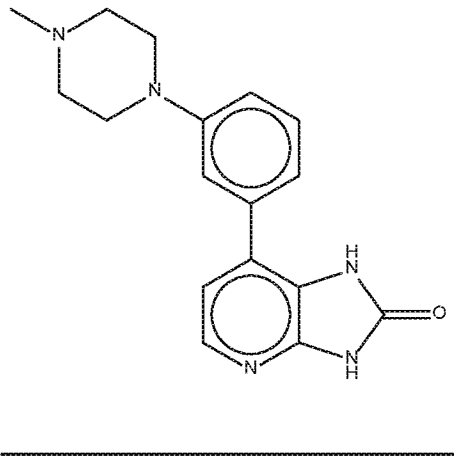
Example no.	Structure	Synthesis route	M+H	NMR
1		Phenyl 1	283.2	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.46 (br s, 1H), 11.01 (s, 1H), 7.95 (d, J = 5.6 Hz, 1H), 7.47-7.66 (m, 4H), 7.07 (d, J = 5.4 Hz, 1H), 3.91 (br s, 1H), 2.36 (br s, 6H), 1.49 (br s, 3H)
2		Phenyl 3	296.2	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.50 (br s, 1H), 11.05 (s, 1H), 9.16 (br s, 2H), 7.93 (d, J = 5.6 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.05-7.13 (m, 4H), 3.44-3.52 (m, 4H), 3.23 (br s, 4H)

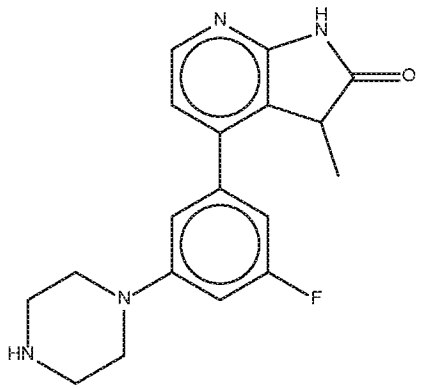
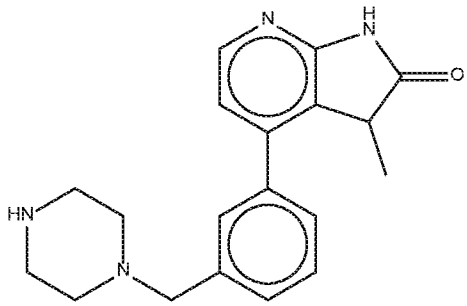
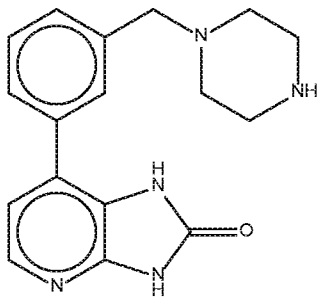
3		Phenyl 1	269.2	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.42 (s, 1H), 11.03 (s, 1H), 7.93 (d, J = 5.4 Hz, 1H), 7.44-7.53 (m, 3H), 7.37 (d, J = 7.3 Hz, 1H), 7.05 (d, J = 5.4 Hz, 1H), 3.48 (s, 2H), 2.17 (s, 6H)
4		Phenyl 3	295.2	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.13 (br s, 1H), 9.18 (br s, 2H), 8.12 (d, J = 5.6 Hz, 1H), 7.39 (t, J = 7.9 Hz, 1H), 7.19-7.22 (m, 1H), 7.12 (d, J = 7.8 Hz, 1H), 7.10 (d, J = 5.6 Hz, 1H), 7.08 (dd, J = 8.2, 2.3 Hz, 1H), 4.94-5.02 (m, 1H), 3.77 (s, 2H), 3.39-3.49 (m, 4H), 3.22 (br s, 4H)
5		Phenyl 3	309.2	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.09 (s, 1H), 9.11 (br s, 2H), 8.11 (d, J = 5.4 Hz, 1H), 7.38 (t, J = 7.9 Hz, 1H), 7.17-7.19 (m, 1H), 7.05-7.10 (m, 2H), 7.01 (d, J = 5.6 Hz, 1H), 4.08 (q, J = 7.5 Hz, 1H), 3.64 (br s, 1H), 3.41-3.47 (m, 4H), 3.19-3.25 (m, 4H), 0.95 (d, J = 7.6 Hz, 3H)

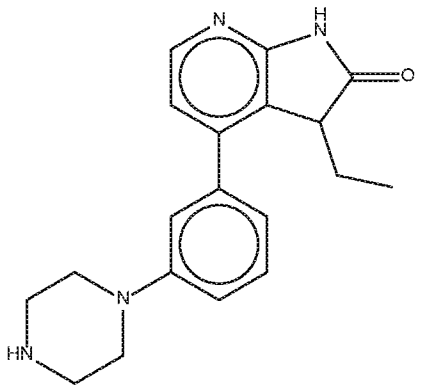
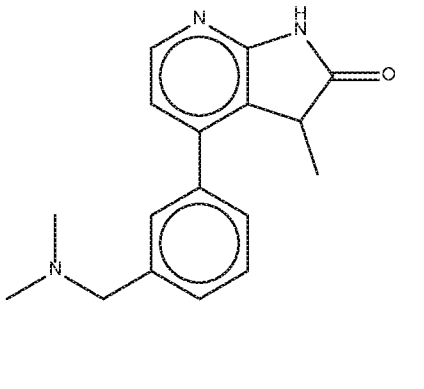
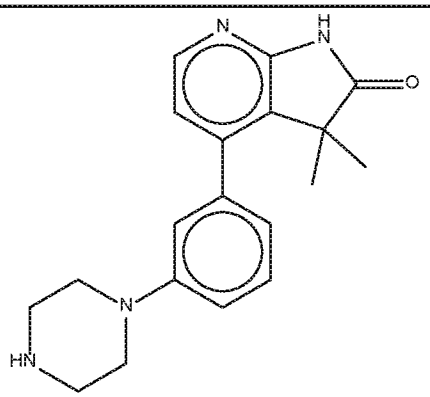
6		Phenyl 3	297.1	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 12.32 (br s, 1H), 9.19 (br s, 2H), 8.10 (d, J = 5.6 Hz, 1H), 7.40-7.49 (m, 3H), 7.36 (d, J = 7.6 Hz, 1H), 7.15 (dd, J = 8.2, 2.1 Hz, 1H), 5.37 (br s, 1H), 3.43-3.50 (m, 4H), 3.25 (br s, 4H)
7		Phenyl 3	314.2	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.45 (s, 1H), 11.07 (s, 1H), 9.05 (br s, 2H), 7.93 (d, J = 5.6 Hz, 1H), 7.06 (d, J = 5.4 Hz, 1H), 6.90-6.96 (m, 2H), 6.86 (dd, J = 8.9, 1.3 Hz, 1H), 3.47-3.57 (m, 4H), 3.22 (br s, 4H)
8		Phenyl 3	310.2	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.53 (br s, 1H), 11.07 (s, 1H), 9.49 (br s, 1H), 9.03 (br s, 1H), 7.93 (d, J = 5.6 Hz, 1H), 7.41 (t, J = 8.1 Hz, 1H), 7.08-7.16 (m, 3H), 7.06 (d, J = 5.6 Hz, 1H), 5.58 (br s, 1H), 4.17-4.41 (m, 1H), 3.63 (br d, J = 13.0 Hz, 1H), 3.18-3.37 (m, 4H), 3.03-3.13 (m, 1H), 1.11 (d, J = 6.8 Hz, 3H)

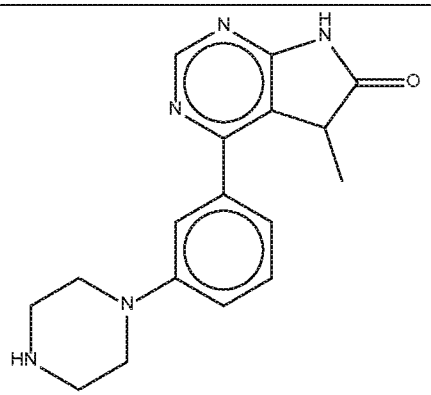
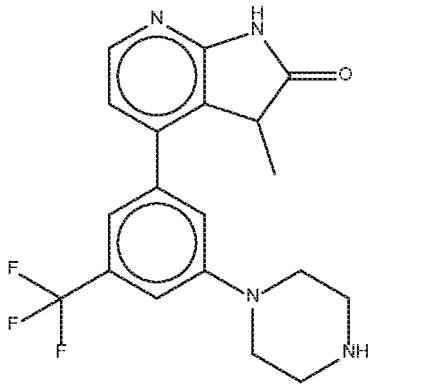
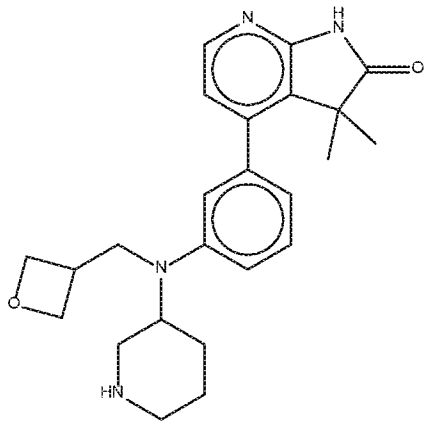
9		Phenyl 3	326.2	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.48 (br s, 1H), 11.04 (s, 1H), 9.17 (br s, 2H), 7.91 (d, J = 5.6 Hz, 1H), 7.05 (d, J = 5.6 Hz, 1H), 6.71 (s, 1H), 6.61 (br d, J = 12.2 Hz, 2H), 5.64 (br s, 1H), 3.82 (s, 3H), 3.41-3.51 (m, 4H), 3.05-3.25 (m, 4H)
10		Phenyl 3	330,3 ; 332,3	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.45 (s, 1H), 11.12 (s, 1H), 9.04 (br s, 2H), 7.92 (d, J = 5.6 Hz, 1H), 7.10-7.17 (m, 1H), 7.02-7.07 (m, 3H), 3.47-3.57 (m, 4H), 3.41 (br s, 1H), 3.21 (br s, 4H)
11		Phenyl 3	324.2	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.48 (br s, 1H), 11.02 (s, 1H), 9.50 (br s, 1H), 8.86 (br s, 1H), 7.93 (d, J = 5.6 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.15 (d, J = 1.7 Hz, 1H), 7.11 (dd, J = 8.3, 2.2 Hz, 1H), 7.04-7.08 (m, 2H), 4.61 (br s, 1H), 3.97 (br d, J = 12.2 Hz, 2H), 3.28-3.44 (m, 2H), 2.76 (br t, J = 12.2 Hz, 2H), 1.32 (d, J = 6.6 Hz, 6H)

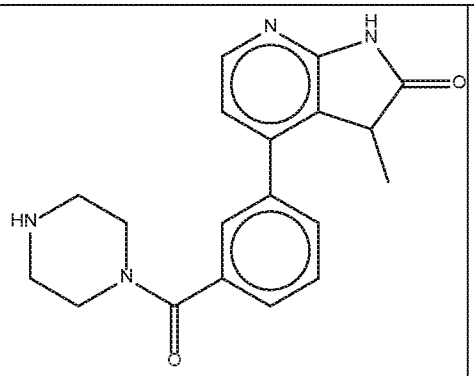
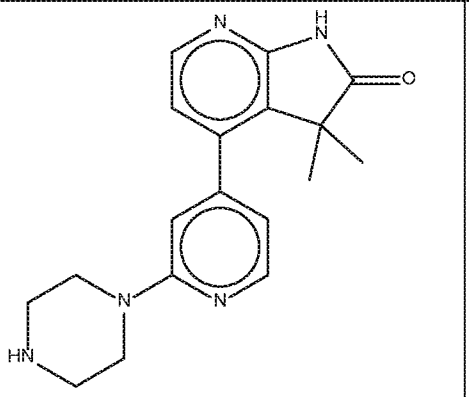
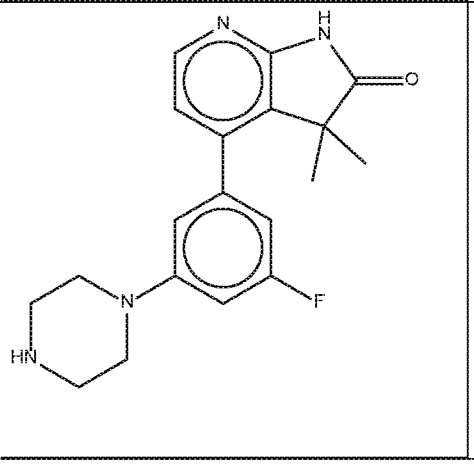
12		Phenyl 3	373.2	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.47 (br s, 1H), 11.01 (s, 1H), 9.61 (br s, 1H), 9.43 (br s, 1H), 8.87 (br s, 1H), 8.71 (br s, 1H), 8.34 (br s, 1H), 7.91 (d, J = 5.4 Hz, 1H), 7.83 (br s, 1H), 7.29-7.36 (m, 1H), 7.24 (s, 1H), 7.12 (d, J = 7.8 Hz, 1H), 7.03 (dd, J = 8.3, 2.0 Hz, 1H), 6.95 (d, J = 5.6 Hz, 1H), 5.28 (br s, 1H), 5.09 (br s, 1H), 3.68 (br t, J = 4.5 Hz, 2H), 3.58 (br s, 2H), 3.23-3.39 (m, 2H)
13		Pyridine	297.2	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.58 (br s, 1H), 11.22 (s, 1H), 9.26 (br s, 2H), 8.24 (d, J = 5.6 Hz, 1H), 7.98 (d, J = 5.4 Hz, 1H), 7.18 (s, 1H), 7.12 (d, J = 5.6 Hz, 1H), 7.01 (d, J = 5.6 Hz, 1H), 3.88-3.92 (m, 4H), 3.80 (br s, 1H), 3.19-3.25 (m, 4H)
14		Pyridine	297.2	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.59 (br d, J = 1.0 Hz, 1H), 10.63 (s, 1H), 9.36 (br s, 2H), 7.95 (d, J = 5.6 Hz, 1H), 7.75 (dd, J = 8.6, 7.6 Hz, 1H), 7.38 (d, J = 5.6 Hz, 1H), 7.27 (d, J = 7.3 Hz, 1H), 7.00 (d, J = 8.8 Hz, 1H), 4.92 (br s, 1H), 3.71-3.93 (m, 4H), 3.20 (br s, 4H)

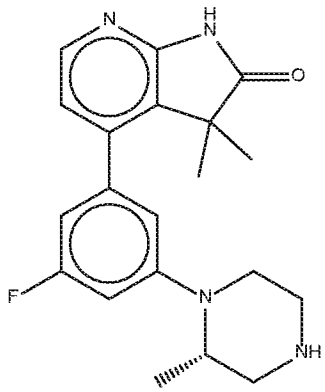
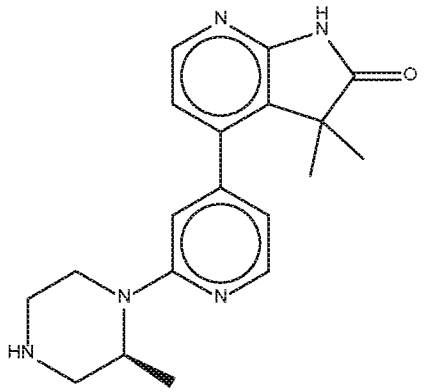
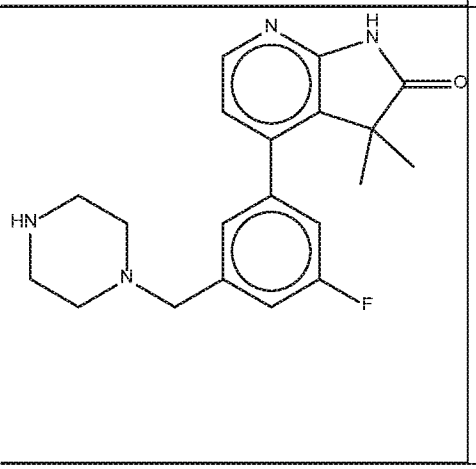
15		Phenyl 3	314.3	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.50 (br s, 1H), 10.98 (s, 1H), 9.23 (br s, 2H), 7.93 (d, J = 5.4 Hz, 1H), 7.21-7.28 (m, 1H), 7.13 (dt, J = 9.0, 3.7 Hz, 1H), 7.04 (dd, J = 6.1, 2.9 Hz, 1H), 6.99 (d, J = 5.4 Hz, 1H), 6.21 (br s, 1H), 3.34-3.48 (m, 4H), 3.21 (br s, 4H)
16		Pyridine	297.3	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 13.73 (br s, 1H), 11.75 (s, 1H), 11.50 (br s, 1H), 9.65 (br s, 2H), 8.40 (d, J = 7.3 Hz, 1H), 8.06 (d, J = 5.6 Hz, 1H), 7.45 (d, J = 2.7 Hz, 1H), 7.27 (dd, J = 7.3, 2.7 Hz, 1H), 7.23 (d, J = 5.4 Hz, 1H), 3.96-4.13 (m, 4H), 3.27 (br s, 4H)
17		Phenyl 3	310.2	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.40 (s, 1H), 10.98 (s, 1H), 9.63 (br s, 1H), 7.92 (d, J = 5.6 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.05-7.12 (m, 3H), 7.04 (d, J = 5.4 Hz, 1H), 3.35-4.31 (m, 3H), 2.90-3.27 (m, 4H), 2.54-2.86 (m, 3H)

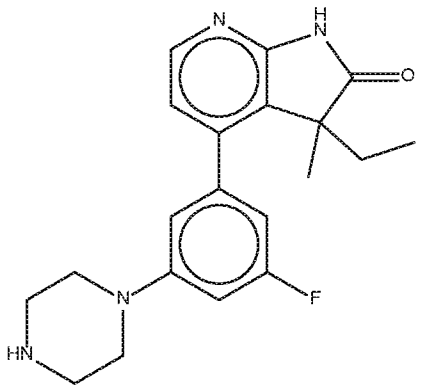
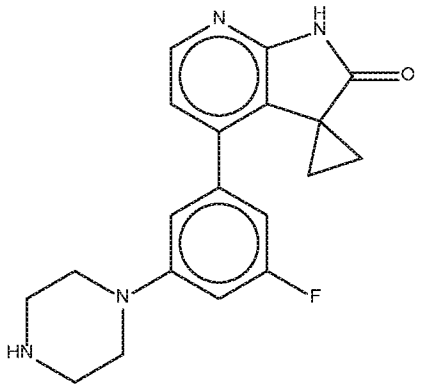
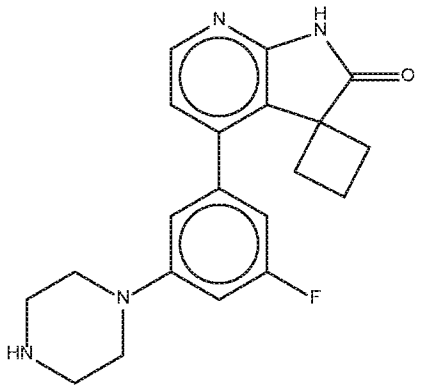
18		Phenyl 3	327	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.11 (s, 1H), 9.16 (br s, 2H), 8.12 (d, J = 5.6 Hz, 1H), 7.02 (d, J = 5.4 Hz, 1H), 6.99-7.01 (m, 1H), 6.93 (dt, J = 12.3, 2.2 Hz, 1H), 6.90 (dt, J = 9.3, 1.2 Hz, 1H), 4.62 (br s, 1H), 4.11 (q, J = 7.6 Hz, 1H), 3.46-3.55 (m, 4H), 3.20 (br s, 4H), 0.98 (d, J = 7.6 Hz, 3H)
19		Phenyl 2	323.2	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 12.25 (br s, 1H), 11.12 (s, 1H), 9.44 (br s, 2H), 8.16 (d, J = 5.4 Hz, 1H), 7.87-8.06 (m, 1H), 7.69-7.79 (m, 2H), 7.57-7.65 (m, 1H), 7.11 (br d, J = 3.9 Hz, 1H), 4.37-4.59 (m, 2H), 4.15-4.30 (m, 3H), 3.92 (br s, 1H), 3.41-3.51 (m, 2H), 3.13-3.34 (m, 3H), 0.96 (d, J = 7.6 Hz, 3H)
20		Phenyl 2	310.2	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 12.26 (br s, 1H), 11.54 (br d, J = 0.7 Hz, 1H), 11.09 (s, 1H), 9.72 (br s, 2H), 7.94-7.99 (m, 2H), 7.70-7.77 (m, 2H), 7.57-7.64 (m, 1H), 7.18 (d, J = 5.4 Hz, 1H), 4.48 (br s, 2H), 3.53-3.66 (m, 2H), 3.44-3.53 (m, 4H), 3.23-3.41 (m, 2H)

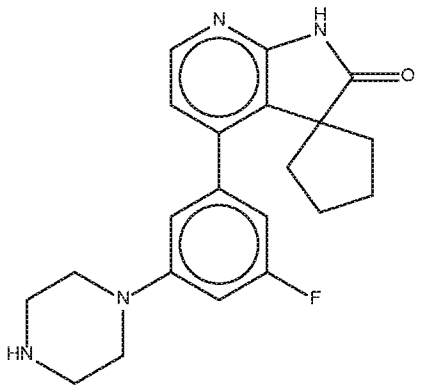
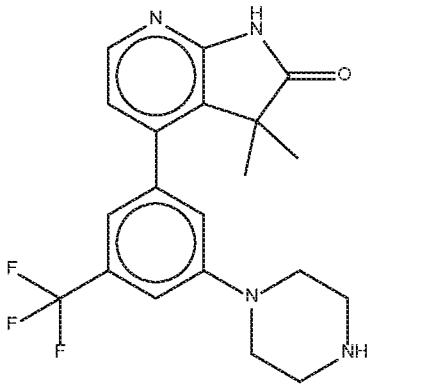
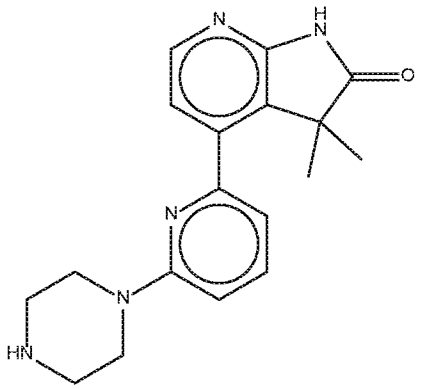
21		Specific Phenyl 1	323.2	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.10 (s, 1H), 9.10 (br s, 2H), 8.12 (d, J = 5.4 Hz, 1H), 7.38 (t, J = 7.9 Hz, 1H), 7.18 (t, J = 1.8 Hz, 1H), 7.05-7.10 (m, 2H), 7.00 (d, J = 5.4 Hz, 1H), 4.14-4.20 (m, 1H), 4.11 (br s, 1H), 3.44 (br d, J = 4.9 Hz, 4H), 3.18-3.26 (m, 4H), 1.68 (ddd, J = 13.8, 7.4, 4.0 Hz, 1H), 1.31-1.44 (m, 1H), 0.41 (t, J = 7.3 Hz, 3H)
22		Phenyl 1	282.2	1H NMR (500 MHz, DMSO-d6) δ ppm 11.05 (s, 1 H) 8.12 (d, J=5.38 Hz, 1 H) 7.51 (m, J=1.50 Hz, 2 H) 7.43 - 7.48 (m, 1 H) 7.38 (m, J=7.30 Hz, 1 H) 6.99 (d, J=5.62 Hz, 1 H) 4.03 (d, J=7.58 Hz, 1 H) 3.41 - 3.51 (m, 2 H) 2.16 (s, 6 H) 0.93 (d, J=7.58 Hz, 3 H)
23		Phenyl 3	323.3	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.11 (s, 1H), 9.03 (br s, 2H), 8.08 (d, J = 5.3 Hz, 1H), 7.36 (t, J = 7.9 Hz, 1H), 7.07 (br dd, J = 8.2, 1.9 Hz, 1H), 6.90 (t, J = 1.8 Hz, 1H), 6.79 (dt, J = 7.5, 1.0 Hz, 1H), 6.76 (d, J = 5.3 Hz, 1H), 4.48 (br s, 1H), 3.36-3.43 (m, 4H), 3.21 (br s, 4H), 1.09 (s, 6H)

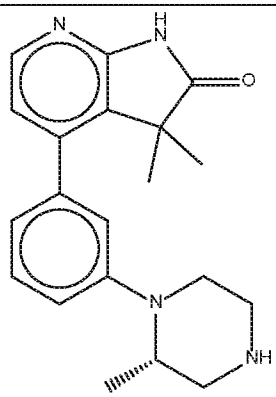
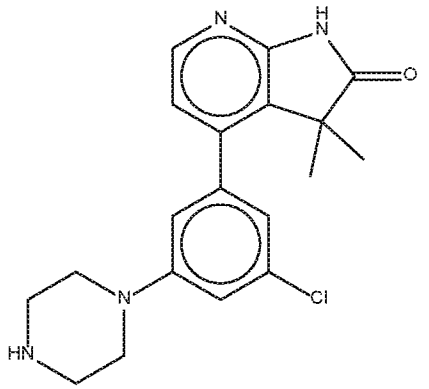
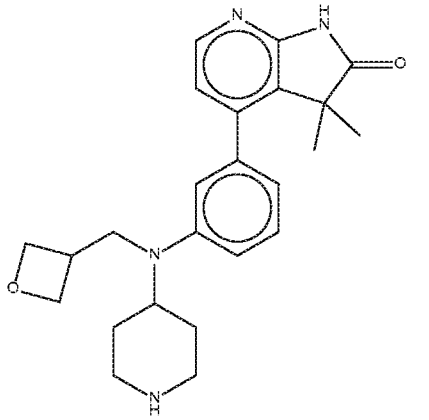
24		Specific Phenyl 2	310.3	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.69 (br s, 1H), 9.24 (br s, 2H), 8.79 (s, 1H), 7.36-7.49 (m, 3H), 7.17 (br dd, J = 7.8, 1.5 Hz, 1H), 5.73 (br s, 1H), 4.29 (q, J = 7.6 Hz, 1H), 3.45 (br d, J = 2.2 Hz, 4H), 3.23 (br s, 4H), 1.11 (d, J = 7.6 Hz, 3H)
25		Phenyl 3	377.1	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.13 (s, 1H), 9.04 (br s, 2H), 8.15 (d, J = 5.4 Hz, 1H), 7.44 (t, J = 2.2 Hz, 1H), 7.32-7.36 (m, 2H), 7.07 (d, J = 5.6 Hz, 1H), 4.12 (q, J = 7.6 Hz, 1H), 3.63 (br s, 1H), 3.56 (dd, J = 6.5, 4.0 Hz, 4H), 3.20-3.27 (m, 4H), 0.95 (d, J = 7.6 Hz, 3H)
26		phenyl 3 (using Specific Phenyl 3 as compound II)	407.2	1H NMR (500 MHz, DMSO-d6) δ ppm 10.49 - 11.52 (m, 1 H) 8.00 (br d, J=4.89 Hz, 1 H) 7.20 - 7.29 (m, 1 H) 6.78 - 6.94 (m, 1 H) 6.58 (br d, J=14.67 Hz, 3 H) 4.53 - 4.62 (m, 2 H) 4.32 (m, J=6.10 Hz, 2 H) 3.93 - 4.20 (m, 2 H) 3.39 - 3.64 (m, 4 H) 3.02 - 3.15 (m, 1 H) 2.25 - 2.46 (m, 2 H) 1.44 - 1.83 (m, 4 H) 1.07 (s, 6 H)

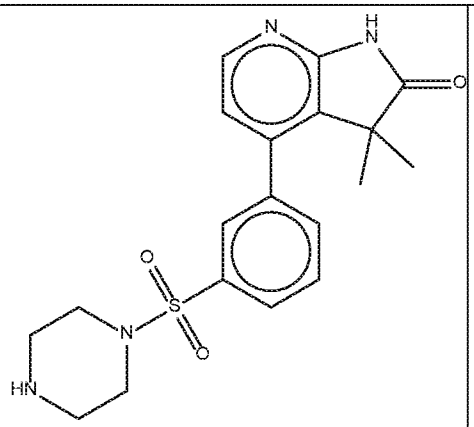
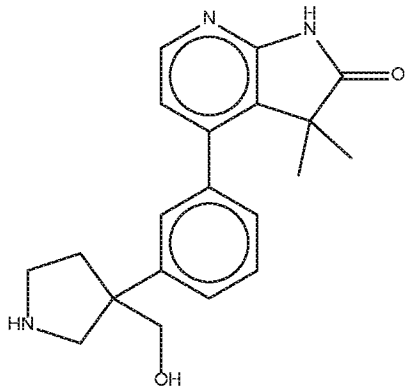
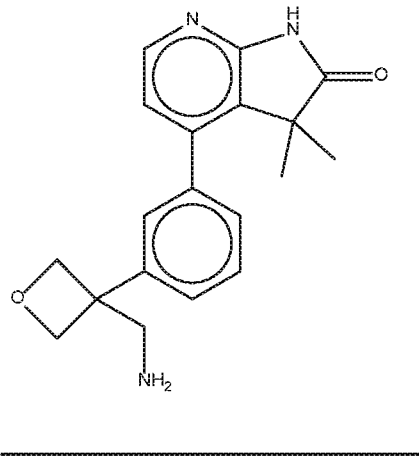
27		Phenyl 2	337.4	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.12 (s, 1H), 9.26 (br s, 2H), 8.16 (d, J = 5.4 Hz, 1H), 7.74 (dt, J = 7.8, 1.2 Hz, 1H), 7.69 (t, J = 1.5 Hz, 1H), 7.61 (t, J = 7.7 Hz, 1H), 7.54 (dt, J = 7.8, 1.2 Hz, 1H), 7.04 (d, J = 5.4 Hz, 1H), 4.11 (q, J = 7.7 Hz, 1H), 3.61-3.93 (m, 4H), 3.33 (br s, 1H), 3.17 (br d, J = 2.2 Hz, 4H), 0.95 (d, J = 7.6 Hz, 3H)
28		Pyridine	324.1	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.21 (s, 1H), 9.31 (br s, 2H), 8.23 (d, J = 5.1 Hz, 1H), 8.13 (d, J = 5.4 Hz, 1H), 6.99 (br s, 1H), 6.79 (d, J = 5.4 Hz, 1H), 6.77 (d, J = 5.1 Hz, 1H), 5.61 (br s, 1H), 3.78-3.95 (m, 4H), 3.10-3.33 (m, 4H), 1.14 (s, 6H)
29		Phenyl 3	341.1	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.15 (s, 1H), 9.18 (br s, 2H), 8.09 (d, J = 5.4 Hz, 1H), 6.93 (dt, J = 13.0, 2.0 Hz, 1H), 6.78 (d, J = 5.4 Hz, 1H), 6.73 (s, 1H), 6.60 (d, J = 8.6 Hz, 1H), 3.67 (br s, 1H), 3.44-3.50 (m, 4H), 3.17-3.23 (m, 4H), 1.11 (s, 6H)

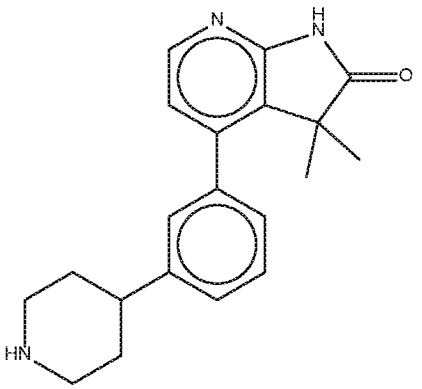
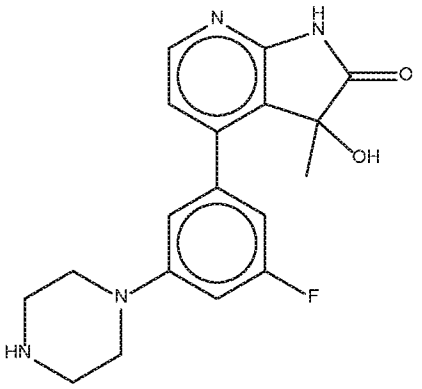
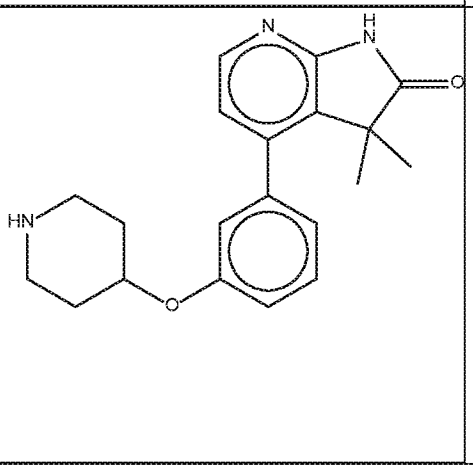
30		Phenyl 3	355.1	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.14 (s, 1H), 9.45 (br s, 1H), 8.95 (br s, 1H), 8.09 (d, J = 5.4 Hz, 1H), 6.88 (dt, J = 12.7, 2.2 Hz, 1H), 6.78 (d, J = 5.4 Hz, 1H), 6.68 (s, 1H), 6.56-6.61 (m, 1H), 4.28 (dtt, J = 6.8, 4.4, 3.3 Hz, 1H), 3.78 (br s, 1H), 3.54-3.61 (m, 1H), 3.11-3.34 (m, 4H), 2.98-3.10 (m, 1H), 1.13 (d, J = 6.8 Hz, 3H), 1.11 (s, 6H)
31		Pyridine	338.1	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.20 (s, 1H), 9.52 (br s, 1H), 9.08 (br s, 1H), 8.23 (d, J = 5.4 Hz, 1H), 8.13 (d, J = 5.4 Hz, 1H), 6.89 (s, 1H), 6.78 (d, J = 5.4 Hz, 1H), 6.73 (d, J = 5.1 Hz, 1H), 4.94 (br s, 1H), 4.70-4.78 (m, 1H), 4.28-4.37 (m, 1H), 3.17-3.34 (m, 4H), 2.95-3.05 (m, 1H), 1.26 (d, J = 7.1 Hz, 3H), 1.13 (s, 6H)
32		Phenyl 2	355.1	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.81-12.85 (m, 1H), 11.19 (s, 1H), 9.52 (br s, 2H), 8.13 (d, J = 5.4 Hz, 1H), 7.61-7.78 (m, 1H), 7.45 (br s, 1H), 7.33 (br d, J = 8.6 Hz, 1H), 6.83 (d, J = 5.4 Hz, 1H), 3.95-4.33 (m, 7H), 3.11-3.34 (m, 3H), 1.10 (s, 6H)

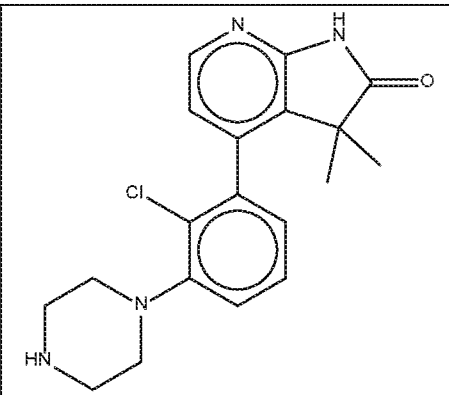
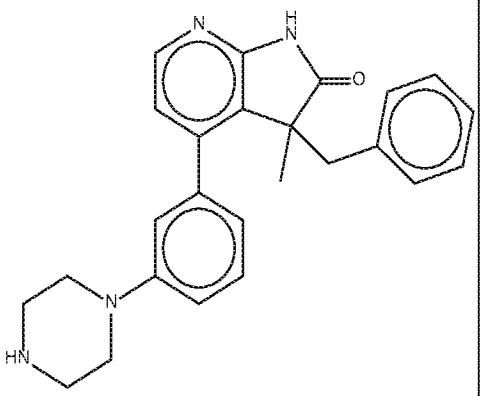
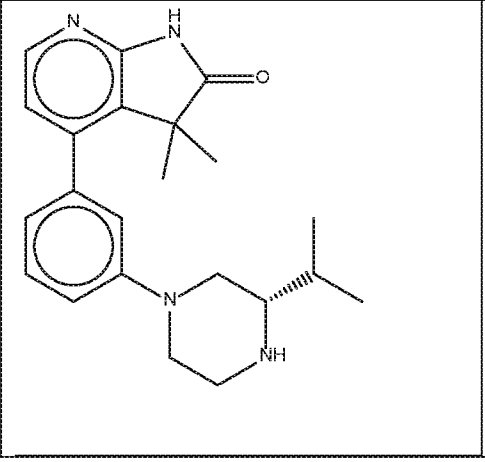
33		Phenyl 3	355.1	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.16 (s, 1H), 9.06 (br s, 2H), 8.10 (d, J = 5.3 Hz, 1H), 6.94 (dt, J = 12.5, 2.2 Hz, 1H), 6.78 (d, J = 5.3 Hz, 1H), 6.69 (s, 1H), 6.57 (d, J = 8.8 Hz, 1H), 3.84 (br s, 1H), 3.40-3.50 (m, 4H), 3.19 (br s, 4H), 1.62 (dd, J = 13.6, 7.4 Hz, 1H), 1.21-1.33 (m, 1H), 1.15 (s, 3H), 0.48 (t, J = 7.4 Hz, 3H)
34		Specific Phenyl 4a	339.1	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.32 (s, 1H), 8.72 (br s, 2H), 8.07 (d, J = 5.4 Hz, 1H), 6.91 (br dt, J = 12.5, 2.2 Hz, 1H), 6.74 (d, J = 5.4 Hz, 1H), 6.72 (t, J = 1.5 Hz, 1H), 6.60 (dt, J = 8.6, 1.2 Hz, 1H), 3.42-3.46 (m, 4H), 3.18-3.23 (m, 4H), 1.28-1.37 (m, 2H), 1.22 (q, J = 4.0 Hz, 2H)
35		Specific Phenyl 4b	353.1	1H NMR (500 MHz, DMSO-d6) δ ppm 10.48 - 11.39 (m, 1 H) 8.04 (d, J=5.38 Hz, 1 H) 6.81 - 6.87 (m, 2 H) 6.80 (d, J=5.38 Hz, 1 H) 6.61 - 6.67 (m, 1 H) 3.24 - 3.30 (m, 1 H) 3.10 - 3.14 (m, 4 H) 2.76 - 2.81 (m, 4 H) 2.21 - 2.37 (m, 4 H) 1.73 - 1.90 (m, 1 H) 1.12 - 1.31 (m, 1 H)

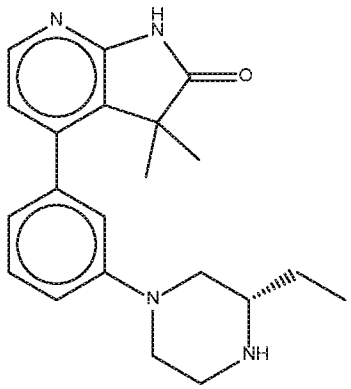
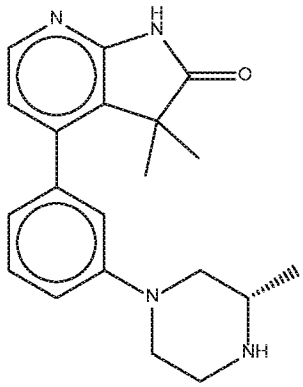
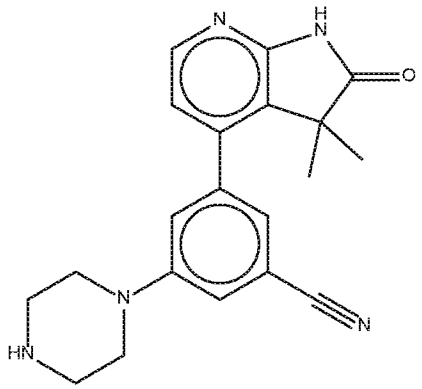
36		Phenyl 3	367.1	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.00 (s, 1H), 9.12 (br s, 2H), 8.06 (d, J = 5.4 Hz, 1H), 6.92 (br dt, J = 12.5, 2.4 Hz, 1H), 6.79 (s, 1H), 6.76 (d, J = 5.4 Hz, 1H), 6.65 (br d, J = 8.8 Hz, 1H), 3.42-3.48 (m, 4H), 3.18 (br s, 4H), 1.87 (br t, J = 6.0 Hz, 4H), 1.64 (br d, J = 4.6 Hz, 2H), 1.15 (br d, J = 5.4 Hz, 2H)
37		Phenyl 3	391.1	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.18 (s, 1H), 9.24 (br s, 2H), 8.12 (d, J = 5.4 Hz, 1H), 7.35 (s, 1H), 7.20 (s, 1H), 7.06 (s, 1H), 6.83 (d, J = 5.4 Hz, 1H), 4.49 (br s, 1H), 3.51-3.56 (m, 4H), 3.17-3.24 (m, 4H), 1.08 (s, 6H)
38		Pyridine	324	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.10 (s, 1H), 9.12 (br s, 2H), 8.12 (d, J = 5.4 Hz, 1H), 7.75 (dd, J = 8.6, 7.3 Hz, 1H), 7.01 (d, J = 8.6 Hz, 1H), 6.89 (d, J = 5.4 Hz, 1H), 6.82 (d, J = 7.1 Hz, 1H), 4.23 (br s, 1H), 3.74-3.79 (m, 4H), 3.15-3.20 (m, 4H), 1.19 (s, 6H)

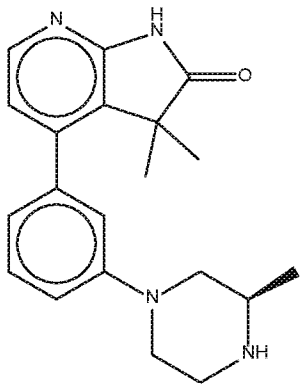
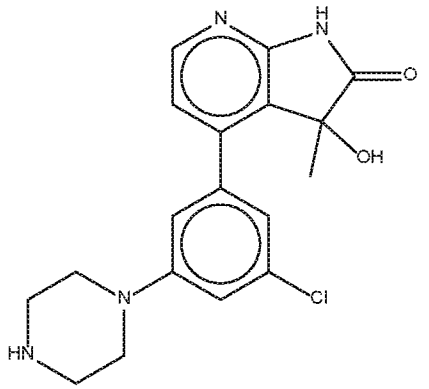
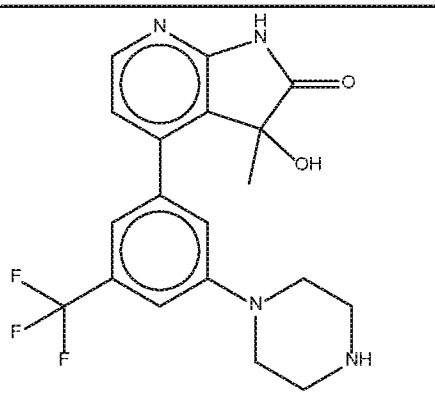
39		Phenyl 3	337.1	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.10 (s, 1H), 9.28 (br s, 1H), 8.84 (br s, 1H), 8.08 (d, J = 5.4 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 7.05 (dd, J = 8.3, 2.2 Hz, 1H), 6.87 (t, J = 2.2 Hz, 1H), 6.80 (d, J = 7.3 Hz, 1H), 6.76 (d, J = 5.1 Hz, 1H), 4.10-4.21 (m, 1H), 3.43-3.51 (m, 1H), 3.36 (br s, 1H), 3.22-3.29 (m, 2H), 3.05-3.22 (m, 3H), 1.09 (s, 6H), 1.07 (d, J = 6.8 Hz, 3H)
40		Phenyl 3	357 ; 359	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.15 (s, 1H), 9.12 (br s, 2H), 8.09 (d, J = 5.4 Hz, 1H), 7.13 (t, J = 2.1 Hz, 1H), 6.87 (dd, J = 2.1, 1.3 Hz, 1H), 6.81 (t, J = 1.5 Hz, 1H), 6.78 (d, J = 5.4 Hz, 1H), 4.82 (br s, 1H), 3.39-3.53 (m, 4H), 3.15-3.23 (m, 4H), 1.11 (s, 6H)
41		phenyl 3 (using Specific Phenyl 3 as compound II)	407.1	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.08 (br s, 1H), 8.06 (d, J = 5.4 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 6.91 (dd, J = 8.4, 2.3 Hz, 1H), 6.76 (d, J = 5.4 Hz, 1H), 6.73 (t, J = 1.7 Hz, 1H), 6.65 (d, J = 7.3 Hz, 1H), 7.17 (br s, 2H), 4.56 (dd, J = 7.8, 5.9 Hz, 2H), 4.28 (t, J = 6.2 Hz, 2H), 3.73-3.82 (m, 1H), 3.45 (d, J = 6.8 Hz, 2H), 3.22 (br d, J = 12.5 Hz, 2H), 3.07-3.15 (m, 1H), 2.76-2.90 (m, 2H), 1.65-1.79 (m, 4H), 1.09 (s, 6H)

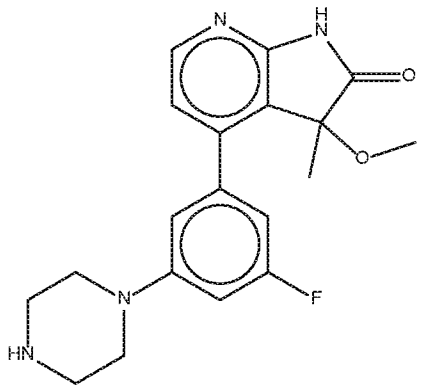
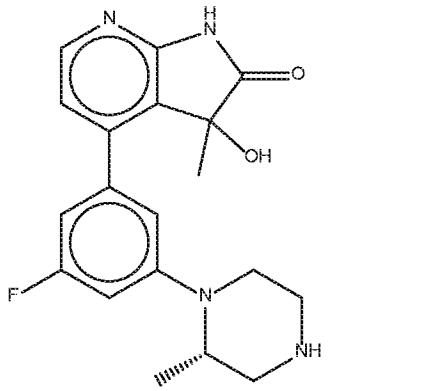
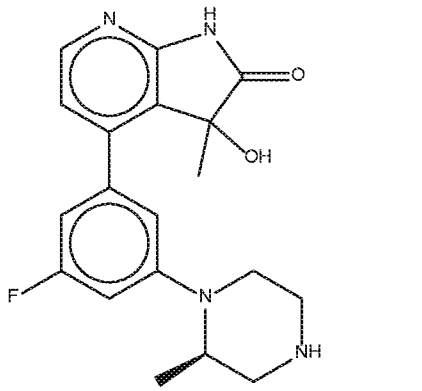
42		Phenyl 2	387.1	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.22 (s, 1H), 8.75 (br s, 2H), 8.16 (d, J = 5.1 Hz, 1H), 7.91 (dt, J = 7.8, 1.5 Hz, 1H), 7.84 (t, J = 7.7 Hz, 1H), 7.78 (dt, J = 7.6, 1.5 Hz, 1H), 7.71 (t, J = 1.6 Hz, 1H), 6.83 (d, J = 5.4 Hz, 1H), 3.73 (br s, 1H), 3.18 (br s, 8H), 1.09 (s, 6H)
43		phenyl 3 (using Specific Phenyl 5 as compound II)	338.2	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.12 (s, 1H), 8.99-9.19 (m, 2H), 8.09 (d, J = 5.4 Hz, 1H), 7.43-7.50 (m, 1H), 7.37-7.42 (m, 1H), 7.19-7.25 (m, 2H), 6.77 (d, J = 5.4 Hz, 1H), 4.03 (br s, 1H), 3.86 (br s, 1H), 3.63-3.69 (m, 1H), 3.51 (dd, J = 8.8, 6.1 Hz, 2H), 3.23-3.37 (m, 3H), 2.43 (ddd, J = 12.8, 7.8, 4.6 Hz, 1H), 2.16 (dt, J = 13.0, 9.0 Hz, 1H), 1.07 (d, J = 2.0 Hz, 6H)
44		phenyl 3 (using Specific Phenyl 6 as compound II)	324.1	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.08 (br s, 1H), 8.08 (d, J = 5.1 Hz, 1H), 7.46 (t, J = 7.7 Hz, 1H), 7.19 (dd, J = 7.8, 1.7 Hz, 2H), 7.02 (t, J = 1.6 Hz, 1H), 6.79 (d, J = 5.4 Hz, 1H), 4.73 (d, J = 6.1 Hz, 2H), 4.67 (d, J = 5.9 Hz, 2H), 3.00 (s, 2H), 1.42 (br s, 2H), 1.07 (s, 6H)

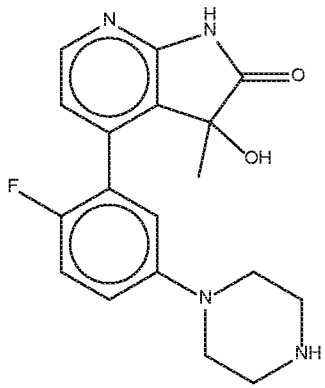
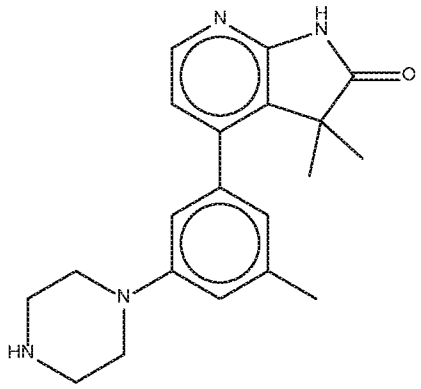
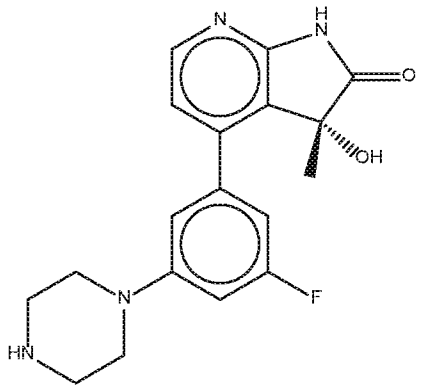
45		Specific Phenyl 7	322.1	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.13 (s, 1H), 8.55-8.87 (m, 2H), 8.09 (d, J = 5.3 Hz, 1H), 7.41-7.48 (m, 1H), 7.33 (dt, J = 7.8, 1.5 Hz, 1H), 7.19 (dt, J = 7.6, 1.3 Hz, 1H), 7.15 (t, J = 1.5 Hz, 1H), 6.77 (d, J = 5.3 Hz, 1H), 4.65 (br s, 1H), 3.36 (br d, J = 12.6 Hz, 2H), 2.95-3.03 (m, 2H), 2.92 (tt, J = 12.0, 3.5 Hz, 1H), 1.96 (br d, J = 13.2 Hz, 2H), 1.80-1.90 (m, 2H), 1.06 (s, 6H)
46		Phenyl 3	343.1	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.05 (s, 1H), 9.10 (br s, 2H), 8.15 (d, J = 5.6 Hz, 1H), 7.33 (dd, J = 1.9 Hz, 1H), 7.08-7.12 (m, 1H), 7.04 (d, J = 5.4 Hz, 1H), 6.95 (dt, J = 12.3, 2.2 Hz, 1H), 6.49 (br s, 1H), 3.95 (br s, 1H), 3.44-3.53 (m, 4H), 3.17-3.24 (m, 4H), 1.15 (s, 3H)
47		Phenyl 2	338.3	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.12 (s, 1H), 8.62-8.88 (m, 2H), 8.08 (d, J = 5.3 Hz, 1H), 7.37-7.43 (m, 1H), 7.10 (ddd, J = 8.4, 2.5, 0.7 Hz, 1H), 6.94 (dd, J = 2.3, 1.6 Hz, 1H), 6.90 (dt, J = 7.5, 1.1 Hz, 1H), 6.77 (d, J = 5.3 Hz, 1H), 4.69 (dt, J = 7.6, 4.0 Hz, 1H), 4.53 (br s, 1H), 3.19-3.27 (m, 2H), 3.00-3.12 (m, 2H), 2.10 (ddd, J = 10.1, 6.9, 3.4 Hz, 2H), 1.83 (ddt, J = 13.2, 8.7, 4.2 Hz, 2H), 1.09 (s, 6H)

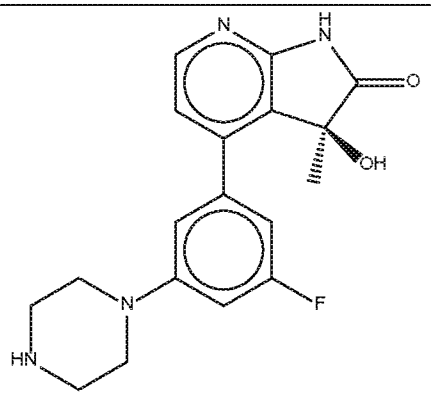
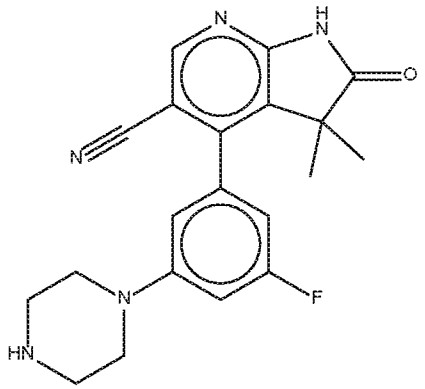
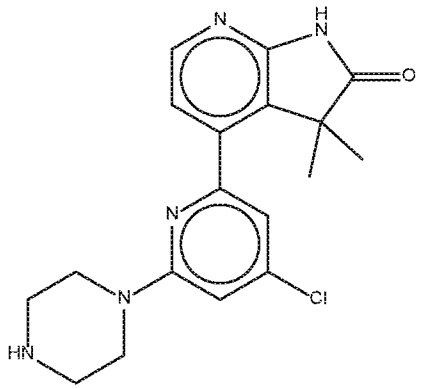
48		Phenyl 3	357,0 ; 358,9	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.17 (s, 1H), 9.08 (br s, 2H), 8.12 (d, J = 5.4 Hz, 1H), 7.41-7.48 (m, 1H), 7.33 (dd, J = 8.1, 1.5 Hz, 1H), 7.10 (dd, J = 7.6, 1.5 Hz, 1H), 6.72 (d, J = 5.4 Hz, 1H), 4.19 (br s, 1H), 3.18-3.32 (m, 8H), 1.10 (s, 3H), 0.95 (s, 3H)
49		Specific Phenyl 8	399.1	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 10.91 (s, 1H), 9.28 (br s, 2H), 8.00 (d, J = 5.4 Hz, 1H), 7.44 (t, J = 8.1 Hz, 1H), 7.14 (dd, J = 8.3, 2.0 Hz, 1H), 7.07-7.11 (m, 3H), 6.95-6.99 (m, 2H), 6.79 (d, J = 5.4 Hz, 1H), 6.76 (dd, J = 6.6, 2.9 Hz, 2H), 5.25 (br s, 1H), 3.36-3.50 (m, 4H), 3.22 (br s, 4H), 2.84 (d, J = 13.2 Hz, 1H), 2.56 (d, J = 13.2 Hz, 1H), 1.38 (s, 3H)
50		Phenyl 3	365.1	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.12 (s, 1H), 8.97-9.27 (m, 2H), 8.08 (d, J = 5.4 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.07-7.15 (m, 1H), 6.92-6.99 (m, 1H), 6.75-6.81 (m, 2H), 4.32 (br s, 1H), 3.77-3.89 (m, J = 12.5 Hz, 2H), 3.26-3.37 (m, J = 12.2 Hz, 1H), 2.95-3.18 (m, 3H), 2.75-2.95 (m, 1H), 1.87-2.09 (m, 1H), 1.10 (d, J = 5.1 Hz, 6H), 1.03 (dd, J = 12.2, 6.8 Hz, 6H)

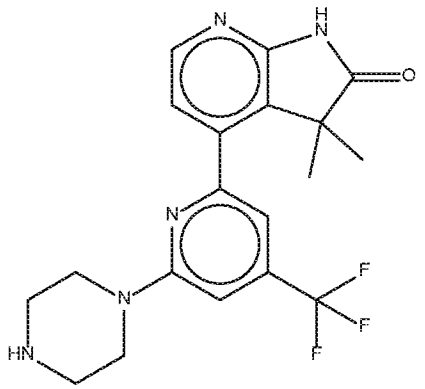
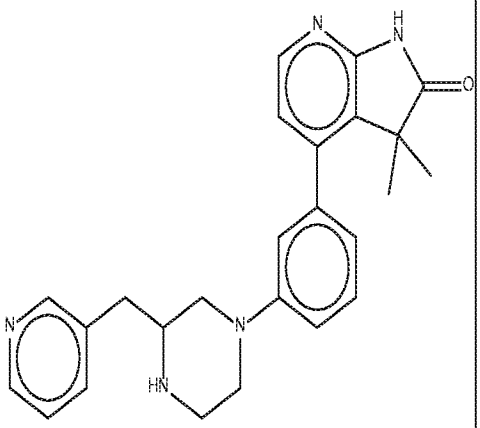
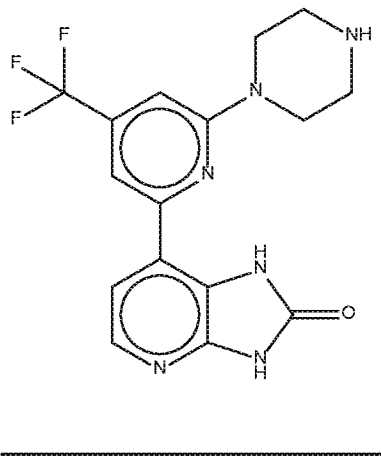
51		Phenyl 3	351.2	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.12 (s, 1H), 9.02-9.28 (m, 2H), 8.08 (d, J = 5.4 Hz, 1H), 7.33-7.39 (m, 1H), 7.10 (dd, J = 8.3, 2.4 Hz, 1H), 6.94 (t, J = 2.0 Hz, 1H), 6.78-6.80 (m, 1H), 6.77 (d, J = 5.4 Hz, 1H), 5.07 (br s, 1H), 3.70-3.94 (m, 2H), 3.33 (br d, J = 12.2 Hz, 1H), 3.14-3.24 (m, 1H), 2.99-3.13 (m, 2H), 2.80 (dd, J = 13.2, 10.8 Hz, 1H), 1.57-1.76 (m, 2H), 1.09 (d, J = 1.7 Hz, 6H), 0.99 (t, J = 7.5 Hz, 3H)
52		Phenyl 3	337.2	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.11 (s, 1H), 9.36 (br s, 1H), 9.09 (br s, 1H), 8.08 (d, J = 5.4 Hz, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.08 (dd, J = 8.4, 2.3 Hz, 1H), 6.91 (s, 1H), 6.76-6.79 (m, 2H), 4.89 (br s, 1H), 3.80 (dd, J = 18.3, 11.7 Hz, 2H), 3.28-3.40 (m, 2H), 2.95-3.14 (m, 2H), 2.79 (dd, J = 12.0, 2.0 Hz, 1H), 1.28 (d, J = 6.6 Hz, 3H), 1.09 (s, 6H)
53		Phenyl 3	348.1	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.17 (s, 1H), 8.93 (br s, 2H), 8.11 (d, J = 5.4 Hz, 1H), 7.53 (s, 1H), 7.25 (s, 1H), 7.21 (s, 1H), 6.79 (d, J = 5.4 Hz, 1H), 3.47-3.56 (m, 4H), 3.17-3.22 (m, 4H), 1.09 (s, 6H)

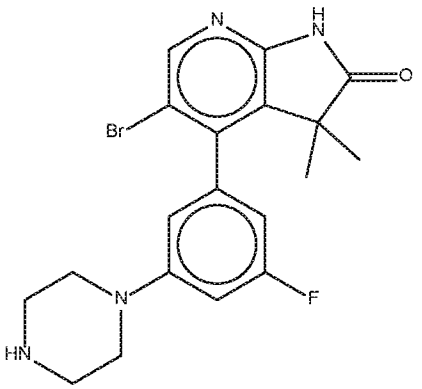
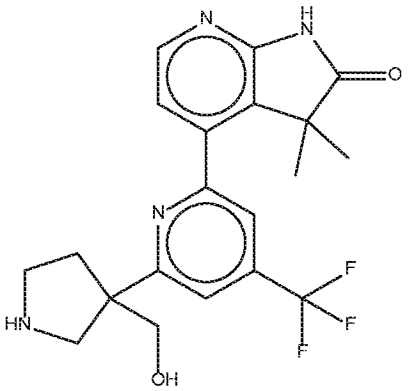
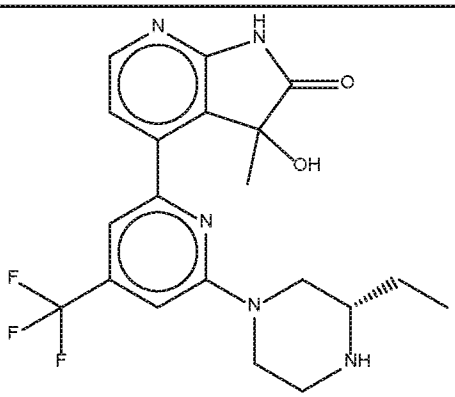
54		Phenyl 3	337.1	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.12 (s, 1H), 9.08-9.58 (m, 2H), 8.08 (d, J = 5.4 Hz, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.08 (dd, J = 8.4, 2.3 Hz, 1H), 6.91 (s, 1H), 6.75-6.80 (m, 2H), 4.93 (br s, 1H), 3.73-3.87 (m, 2H), 3.28-3.37 (m, 2H), 2.95-3.17 (m, 2H), 2.80 (dd, J = 13.0, 10.8 Hz, 1H), 1.28 (d, J = 6.6 Hz, 3H), 1.09 (s, 6H)
55		Phenyl 3	359 ; 360,9	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.06 (s, 1H), 8.93 (br s, 2H), 8.15 (d, J = 5.6 Hz, 1H), 7.46 (d, J = 1.5 Hz, 1H), 7.29 (t, J = 1.3 Hz, 1H), 7.13-7.17 (m, 1H), 7.03 (d, J = 5.6 Hz, 1H), 6.52 (s, 1H), 3.40-3.55 (m, 4H), 3.22 (br s, 4H), 1.14 (s, 3H)
56		Phenyl 3	393	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.08 (s, 1H), 9.08 (br s, 2H), 8.18 (d, J = 5.4 Hz, 1H), 7.74 (s, 1H), 7.59 (s, 1H), 7.37 (s, 1H), 7.08 (d, J = 5.6 Hz, 1H), 6.47 (br s, 1H), 3.81 (br s, 1H), 3.48-3.56 (m, 4H), 3.24 (br s, 4H), 1.12 (s, 3H)

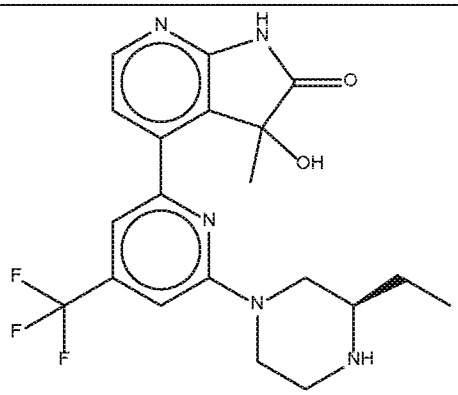
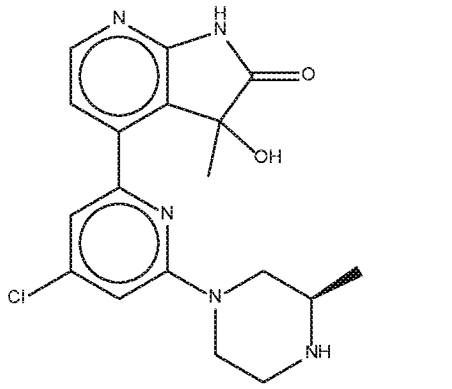
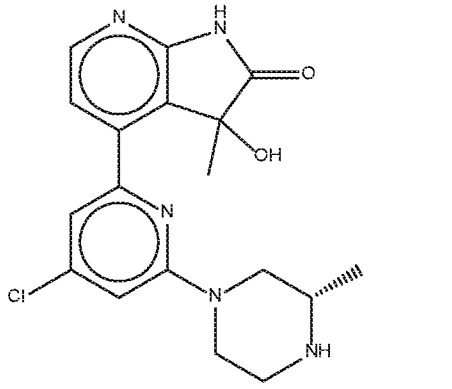
57		Phenyl 3	357.1	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.39 (s, 1H), 9.06 (br s, 2H), 8.22 (d, J = 5.4 Hz, 1H), 7.10 (d, J = 5.4 Hz, 1H), 7.04-7.05 (m, 1H), 6.98 (dt, J = 12.3, 2.1 Hz, 1H), 6.88 (dt, J = 9.4, 1.6 Hz, 1H), 4.05 (br s, 1H), 3.43-3.54 (m, 4H), 3.19-3.26 (m, 4H), 3.10 (s, 3H), 1.19 (s, 3H)
58		Phenyl 3	357	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.06 (br d, J = 4.4 Hz, 1H), 8.94-9.67 (m, 2H), 8.15 (dd, J = 5.4, 2.4 Hz, 1H), 7.24-7.38 (m, 1H), 7.02-7.09 (m, 2H), 6.90 (br dt, J = 12.2, 2.2 Hz, 1H), 5.59 (br s, 1H), 5.32 (br s, 1H), 4.15-4.34 (m, 1H), 3.57-3.67 (m, 1H), 3.14-3.34 (m, 4H), 2.99-3.10 (m, 1H), 1.16 (d, J = 6.8 Hz, 3H), 1.14 (d, J = 1.7 Hz, 3H)
59		Phenyl 3	357	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.05 (d, J = 4.6 Hz, 1H), 8.66-9.50 (m, 2H), 8.15 (dd, J = 5.5, 2.3 Hz, 1H), 7.26-7.39 (m, 1H), 7.03-7.10 (m, 1H), 7.03 (dd, J = 5.4, 1.2 Hz, 1H), 6.90 (dt, J = 12.5, 2.2 Hz, 1H), 6.52 (d, J = 9.8 Hz, 1H), 4.18-4.40 (m, 1H), 3.48-3.70 (m, 1H), 3.02-3.30 (m, 6H), 1.14 (br d, J = 1.7 Hz, 6H)

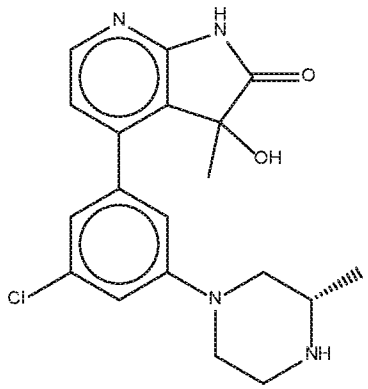
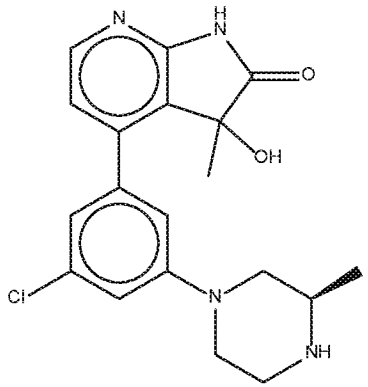
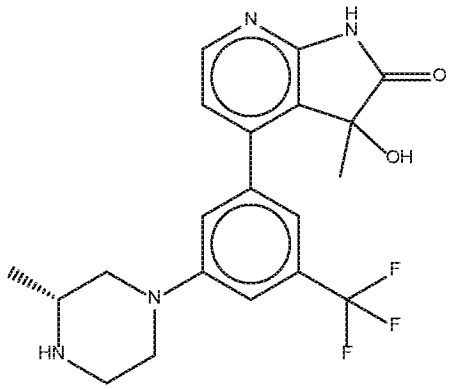
60		Phenyl 3	343	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.05 (s, 1H), 9.06 (br s, 2H), 8.12 (d, J = 5.4 Hz, 1H), 7.28 (dd, J = 6.4, 2.9 Hz, 1H), 7.20-7.26 (m, 1H), 7.08-7.14 (m, 1H), 6.91 (dd, J = 5.4, 1.5 Hz, 1H), 4.82 (br s, 1H), 4.71 (br s, 1H), 3.27-3.40 (m, 4H), 3.19-3.25 (m, 4H), 1.10 (s, 3H)
61		Phenyl 3	337	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.11 (s, 1H), 9.13 (br s, 2H), 8.06 (d, J = 5.4 Hz, 1H), 6.90 (s, 1H), 6.75 (d, J = 5.4 Hz, 1H), 6.69 (s, 1H), 6.61 (s, 1H), 4.81 (br s, 1H), 3.36-3.46 (m, 4H), 3.19 (br s, 4H), 2.32 (s, 3H), 1.10 (s, 6H)
62		Phenyl 3 (using compound II' obtained from OHMe isomer 2)	343	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.01 (br s, 1H), 8.12 (d, J = 5.6 Hz, 1H), 7.22-7.26 (m, 1H), 7.01 (d, J = 5.4 Hz, 1H), 6.96-6.99 (m, 1H), 6.80 (dt, J = 12.8, 2.2 Hz, 1H), 6.47 (s, 1H), 3.09-3.16 (m, 4H), 2.81 (t, J = 5.1 Hz, 4H), 2.25 (br s, 1H), 1.15 (s, 3H)

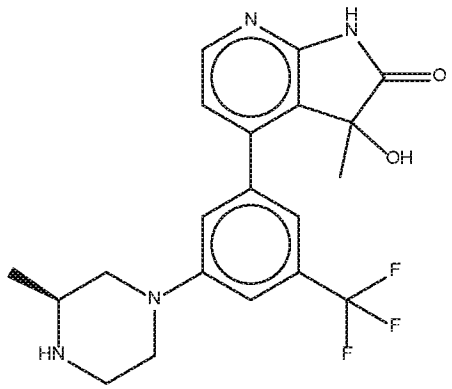
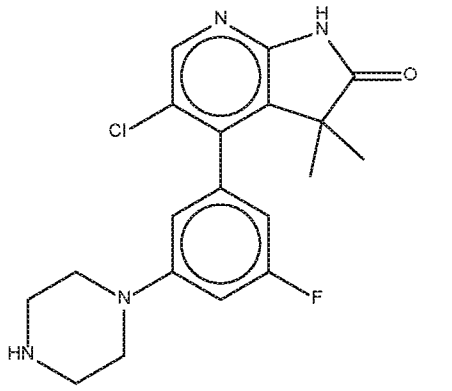
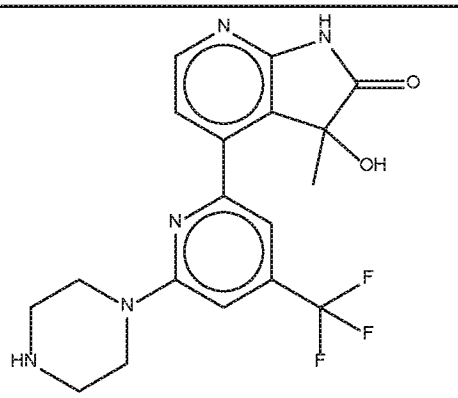
63		Phenyl 3 (using compound II' obtained from OHMe isomer 1)	343	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.00 (br s, 1H), 8.12 (d, J = 5.4 Hz, 1H), 7.25 (t, J = 1.6 Hz, 1H), 7.01 (d, J = 5.6 Hz, 1H), 6.98 (br dt, J = 9.4, 1.6 Hz, 1H), 6.80 (dt, J = 12.8, 1.9 Hz, 1H), 6.47 (s, 1H), 3.09-3.16 (m, 4H), 2.81 (t, J = 5.0 Hz, 4H), 2.32 (br s, 1H), 1.15 (s, 3H)
64		Phenyl 3	366.2	1H NMR (500 MHz, DMSO-d6) δ 8.60 (s, 1H), 6.87 (d, J = 13.0 Hz, 1H), 6.71 (s, 1H), 6.55 (d, J = 8.0 Hz, 1H), 3.18 – 3.05 (m, 4H), 2.80 (t, J = 4.9 Hz, 4H), 2.54 (s, 1H), 1.17 – 0.94 (m, 6H).
65		Pyridine	358,0 ; 360,0	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.14 (s, 1H), 9.17 (br s, 2H), 8.13 (d, J = 5.4 Hz, 1H), 7.15 (d, J = 1.5 Hz, 1H), 6.91 (d, J = 5.4 Hz, 1H), 6.89 (d, J = 1.2 Hz, 1H), 4.04 (br s, 1H), 3.73-3.86 (m, 4H), 3.16 (br s, 4H), 1.20 (s, 6H)

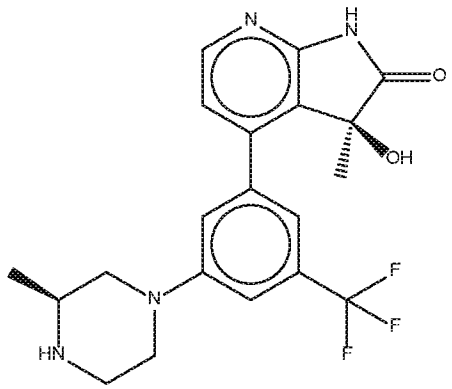
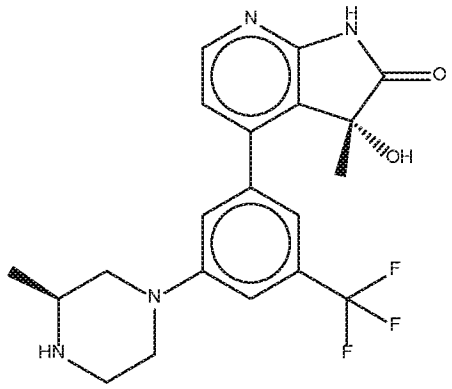
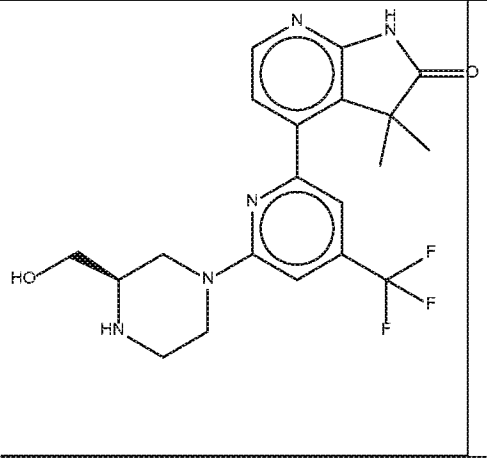
66		Pyridine	392	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.16 (s, 1H), 9.15 (br s, 2H), 8.15 (d, J = 5.4 Hz, 1H), 7.32 (s, 1H), 7.04 (s, 1H), 6.95 (d, J = 5.4 Hz, 1H), 4.83 (br s, 1H), 3.80-3.94 (m, 4H), 3.19 (br s, 4H), 1.19 (s, 6H)
67		Phenyl 3 (using specific phenyl 9 as compound II)	414.1	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.12 (s, 1H), 9.26-10.03 (m, 2H), 8.94 (s, 1H), 8.77 (d, J = 5.6 Hz, 1H), 8.48 (br d, J = 7.8 Hz, 1H), 8.09 (d, J = 5.4 Hz, 1H), 7.92-7.97 (m, 1H), 7.34 (t, J = 7.9 Hz, 1H), 7.11 (dd, J = 8.4, 2.1 Hz, 1H), 6.90 (s, 1H), 6.77 (d, J = 5.4 Hz, 1H), 6.75 (d, J = 7.3 Hz, 1H), 5.05 (br s, 1H), 4.55-4.60 (m, 1H), 3.66 (br d, J = 13.2 Hz, 1H), 3.56 (br dd, J = 13.7, 9.8 Hz, 1H), 3.40-3.48 (m, 1H), 3.33 (br d, J = 12.5 Hz, 1H), 2.99-3.19 (m, 4H), 1.07 (s, 3H), 1.06 (s, 3H)
68		Pyridine	365	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.55 (br s, 1H), 10.83 (s, 1H), 9.22 (br s, 2H), 7.97 (d, J = 5.4 Hz, 1H), 7.38-7.43 (m, 2H), 7.28 (s, 1H), 4.53 (br s, 2H), 3.90-3.94 (m, 4H), 3.22 (br s, 4H)

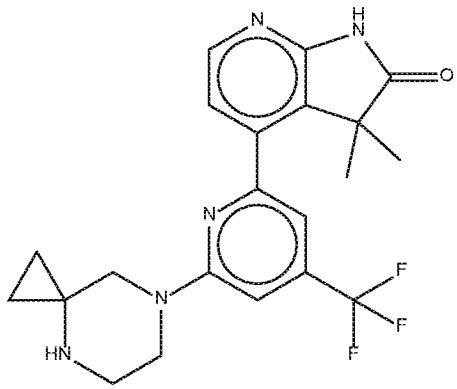
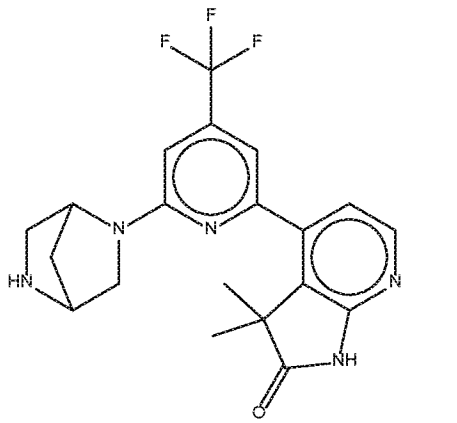
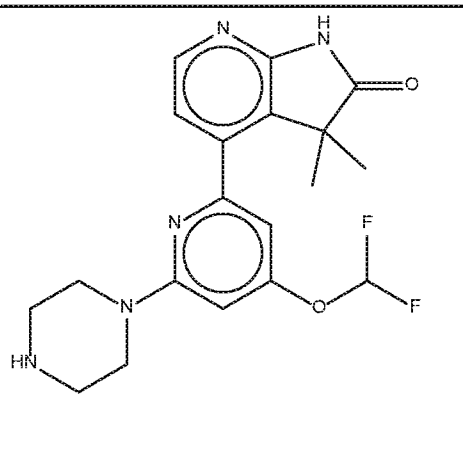
69		Phenyl 3	419	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.31 (s, 1H), 9.00 (br s, 2H), 8.34 (s, 1H), 6.95 (dt, J = 12.5, 2.2 Hz, 1H), 6.73 (dd, J = 2.1, 1.2 Hz, 1H), 6.56-6.59 (m, 1H), 3.41-3.50 (m, 4H), 3.36 (br s, 1H), 3.20 (br s, 4H), 1.07 (s, 3H), 1.04 (s, 3H)
70		Pyridine (using Specific Pyridine 2 as compound II)	406.9	1H NMR (500 MHz, DMSO-d6): δ ppm 11.20 (s, 1 H), 8.78 - 9.63 (m, 2 H), 8.20 (d, J=5.38 Hz, 1 H), 7.91 (s, 1 H), 7.86 (s, 1 H), 7.07 (d, J=5.38 Hz, 1 H), 4.70 - 5.91 (m, 1 H), 3.65 - 3.77 (m, 3 H), 3.47 - 3.58 (m, 1 H), 3.16 - 3.40 (m, 2 H), 2.30 - 2.44 (m, 2 H), 1.25 (s, 3 H), 1.18 (s, 3 H)
71		Pyridine	422.1	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.12 (s, 1H), 9.15-9.43 (m, 2H), 8.21 (d, J = 5.6 Hz, 1H), 8.16 (d, J = 4.2 Hz, 1H), 7.42 (dd, J = 10.1, 5.5 Hz, 1H), 7.39 (d, J = 2.2 Hz, 1H), 6.56 (br s, 1H), 4.56 (br t, J = 12.7 Hz, 2H), 3.66 (br s, 1H), 3.27-3.40 (m, 2H), 2.99-3.25 (m, 3H), 1.61-1.78 (m, 2H), 1.28 (d, J = 6.4 Hz, 3H), 1.03 (tt, J = 7.8 Hz, 3H)

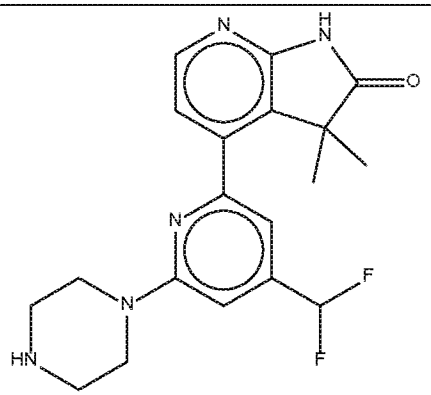
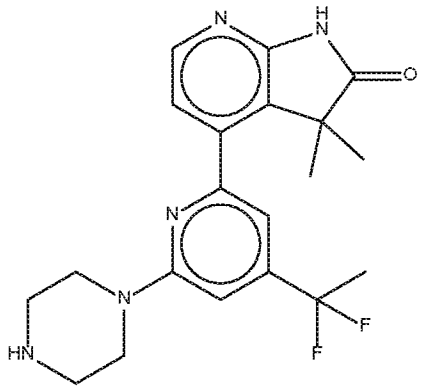
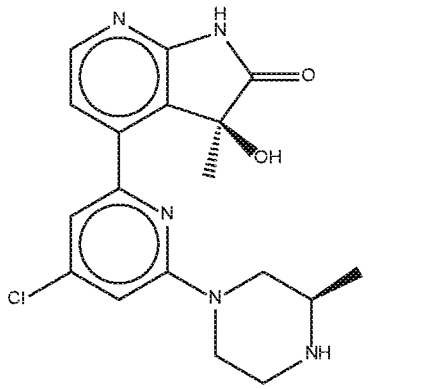
72		Pyridine	422	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.09 (s, 1H), 8.20 (d, J = 5.6 Hz, 1H), 8.01 (d, J = 7.3 Hz, 1H), 7.39 (dd, J = 5.6, 2.0 Hz, 1H), 7.19 (s, 1H), 6.55 (br d, J = 5.1 Hz, 1H), 4.19-4.37 (m, 2H), 3.31 (br s, 1H), 2.94-3.04 (m, 1H), 2.60-2.92 (m, 2H), 2.51-2.58 (m, 2H), 1.32-1.49 (m, 2H), 1.29 (d, J = 3.7 Hz, 3H), 0.94 (tt, J = 7.6 Hz, 3H)
73		Pyridine	374 ; 375,9	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.10 (s, 1H), 8.95-9.41 (m, 2H), 8.19 (d, J = 5.6 Hz, 1H), 7.89 (dd, J = 2.6, 1.3 Hz, 1H), 7.37 (d, J = 5.6 Hz, 1H), 7.20 (d, J = 1.5 Hz, 1H), 6.40 (br s, 1H), 4.35-4.58 (m, 2H), 3.66 (br s, 1H), 3.20-3.40 (m, 3H), 2.97-3.13 (m, 2H), 1.27-1.31 (m, 6H)
74		Pyridine	373,9; 375,9	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.10 (s, 1H), 9.00-9.65 (m, 2H), 8.19 (d, J = 5.4 Hz, 1H), 7.89 (dd, J = 2.2, 1.5 Hz, 1H), 7.37 (d, J = 5.6 Hz, 1H), 7.20 (d, J = 1.2 Hz, 1H), 5.04 (br s, 2H), 4.36-4.52 (m, 2H), 2.93-3.42 (m, 5H), 1.28-1.32 (m, 6H)

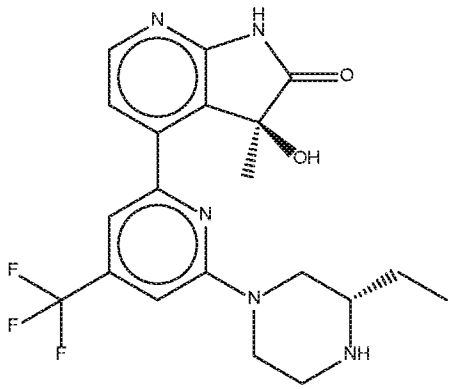
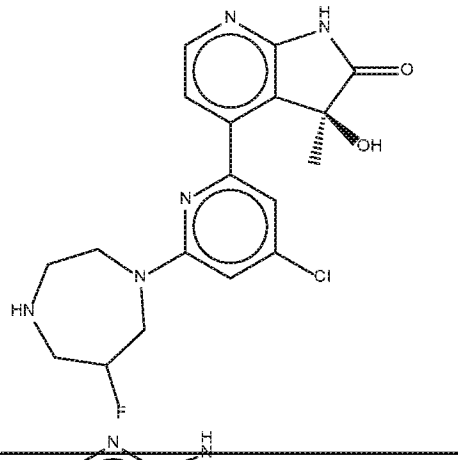
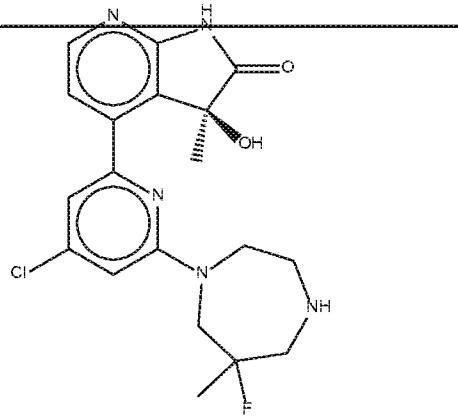
75		Phenyl 3	373 ; 375	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.07 (s, 1H), 9.41 (br s, 1H), 9.20 (br s, 1H), 8.15 (d, J = 5.4 Hz, 1H), 7.44 (q, J = 2.0 Hz, 1H), 7.28 (t, J = 1.5 Hz, 1H), 7.17 (dt, J = 4.0, 2.0 Hz, 1H), 7.03 (dd, J = 5.6, 1.2 Hz, 1H), 6.35 (br s, 1H), 4.65 (br s, 1H), 3.80-3.99 (m, 2H), 3.29-3.38 (m, 2H), 3.05-3.13 (m, 2H), 2.89 (ddd, J = 13.3, 10.7, 2.7 Hz, 1H), 1.29 (dd, J = 6.6, 3.7 Hz, 3H), 1.14 (s, 3H)
76		Phenyl 3	373 ; 375	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.06 (s, 1H), 9.27 (br s, 2H), 9.03 (br s, 1H), 8.15 (d, J = 5.4 Hz, 1H), 7.44 (s, 1H), 7.28 (s, 1H), 7.17 (dt, J = 3.7, 1.9 Hz, 1H), 7.03 (dd, J = 5.5, 1.1 Hz, 1H), 4.08 (br s, 1H), 3.81-3.97 (m, 2H), 3.30-3.42 (m, 2H), 3.06-3.15 (m, 2H), 2.87 (ddd, J = 13.3, 10.9, 2.2 Hz, 1H), 1.28 (dd, J = 6.5, 3.5 Hz, 3H), 1.14 (s, 3H)
77		Phenyl 3	407	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.08 (s, 1H), 9.23 (br s, 1H), 8.97 (br s, 1H), 8.18 (d, J = 5.4 Hz, 1H), 7.73 (t, J = 3.2 Hz, 1H), 7.58 (s, 1H), 7.39 (br dt, J = 6.0, 1.9 Hz, 1H), 7.08 (dd, J = 5.4, 1.2 Hz, 1H), 6.57 (s, 1H), 3.87-4.04 (m, 2H), 3.33-3.41 (m, 3H), 3.08-3.17 (m, 2H), 2.85-2.93 (m, 1H), 1.29 (dd, J = 6.5, 5.1 Hz, 3H), 1.11 (s, 3H)

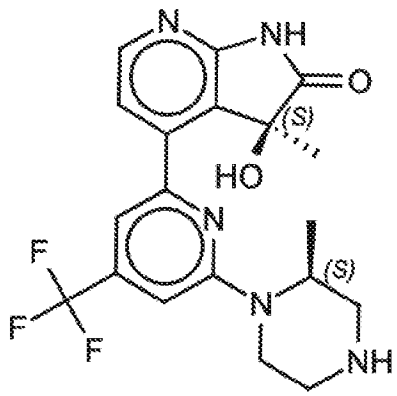
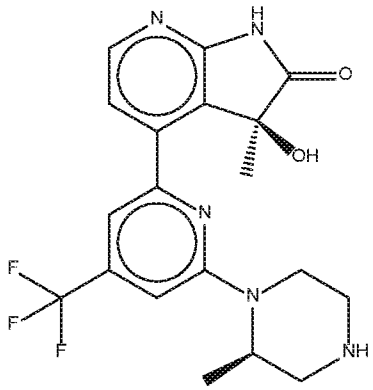
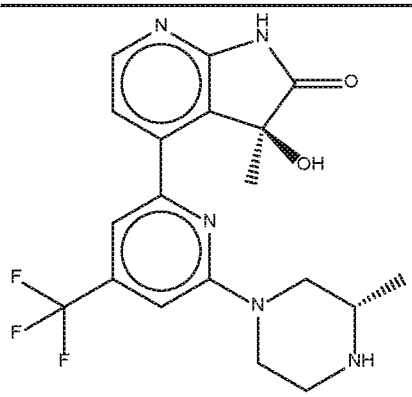
78		Phenyl 3	407	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.09 (s, 1H), 9.35 (br s, 1H), 9.11 (br s, 1H), 8.18 (d, J = 5.4 Hz, 1H), 7.73 (br s, 1H), 7.58 (s, 1H), 7.39 (br d, J = 4.9 Hz, 1H), 7.08 (d, J = 5.4 Hz, 1H), 6.52 (br s, 1H), 4.25 (br s, 1H), 3.87-4.04 (m, 2H), 3.31-3.44 (m, 2H), 3.08-3.18 (m, 2H), 2.88-2.95 (m, 1H), 1.30 (dd, J = 6.4, 4.4 Hz, 3H), 1.11 (s, 3H)
79		Phenyl 3	375 ; 377	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.30 (s, 1H), 9.04 (br s, 2H), 8.24 (s, 1H), 6.95 (dt, J = 12.5, 2.2 Hz, 1H), 6.75-6.76 (m, 1H), 6.59-6.62 (m, 1H), 4.05 (br s, 1H), 3.40-3.51 (m, 4H), 3.15-3.25 (m, 4H), 1.08 (s, 3H), 1.04 (s, 3H)
80		Pyridine	393.9	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.12 (s, 1H), 9.12 (br s, 2H), 8.21 (d, J = 5.4 Hz, 1H), 8.18 (s, 1H), 7.43 (d, J = 5.4 Hz, 1H), 7.33 (s, 1H), 6.57 (br s, 1H), 3.85-4.01 (m, 4H), 3.18-3.27 (m, 4H), 1.28 (s, 4H)

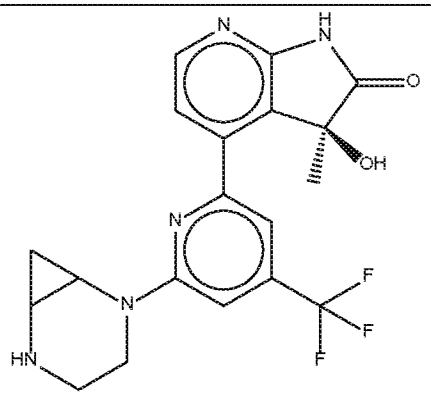
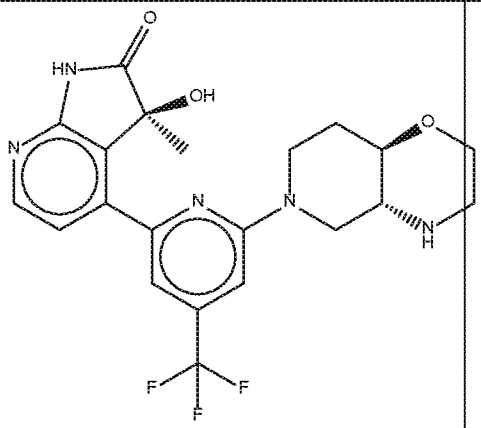
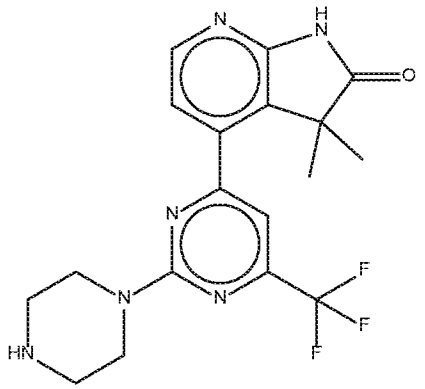
81		Phenyl 3 (using compound II' obtained from OHMe isomer 1)	406.9	1H NMR (600 MHz, DMSO-d6) δ ppm 11.08 (s, 1 H), 8.81 - 9.68 (m, 2 H), 8.18 (d, J=5.58 Hz, 1 H), 7.73 (d, J=1.00 Hz, 1 H), 7.58 (d, J=1.00 Hz, 1 H), 7.30 - 7.44 (m, 1 H), 7.08 (d, J=5.43 Hz, 1 H), 5.75 - 6.94 (m, 1 H), 3.94 (m, J=10.90 Hz, 2 H), 3.30 - 3.45 (m, 2 H), 3.05 - 3.21 (m, 2 H), 2.83 - 2.97 (m, 1 H), 1.31 (d, J=6.60 Hz, 3 H), 1.11 (s, 3 H)
82		Phenyl 3 (using compound II' obtained from OHMe isomer 2)	406.9	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.09 (s, 1H), 8.94-9.57 (m, 2H), 8.18 (d, J = 5.6 Hz, 1H), 7.73 (s, 1H), 7.58 (s, 1H), 7.39 (s, 1H), 7.08 (d, J = 5.6 Hz, 1H), 4.09-4.45 (m, 1H), 4.02 (br d, J = 13.0 Hz, 2H), 3.85-3.96 (m, 1H), 3.29-3.47 (m, 2H), 3.06-3.20 (m, 2H), 2.88-2.94 (m, 1H), 1.30 (d, J = 6.6 Hz, 3H), 1.11 (s, 3H)
83		Pyridine	421.9	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.16 (s, 1H), 8.98-9.54 (m, 2H), 8.15 (d, J = 5.4 Hz, 1H), 7.34 (s, 1H), 7.04 (s, 1H), 6.95 (d, J = 5.3 Hz, 1H), 4.42-4.54 (m, 3H), 3.59-3.74 (m, 2H), 3.23-3.37 (m, 3H), 3.18 (dd, J = 13.9, 10.9 Hz, 1H), 2.98-3.13 (m, 1H), 1.18 (d, J = 19.1 Hz, 6H)

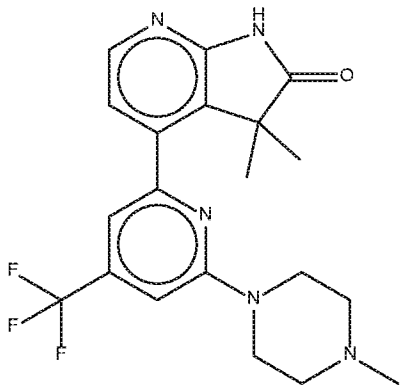
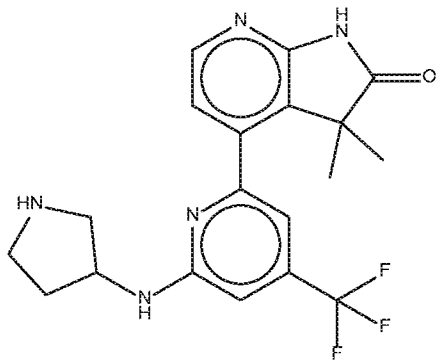
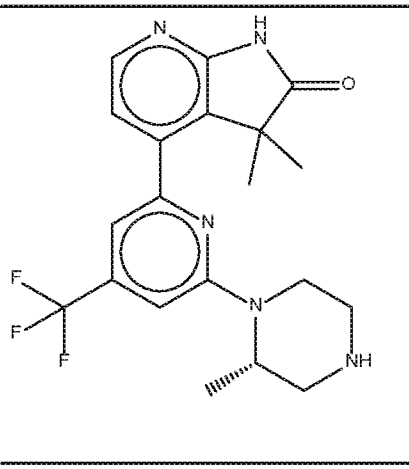
84		Pyridine	418.3	1H NMR (500 MHz, DMSO-d6, 300K) δ ppm 11.16 (s, 1 H), 9.68 (br s, 2 H), 8.15 (d, J=5.4 Hz, 1 H), 7.34 (s, 1 H), 7.04 (s, 1 H), 6.95 (d, J=5.4 Hz, 1 H), 3.92 - 3.98 (m, 2 H), 3.81 (s, 2 H), 3.28 (br s, 2 H), 1.17 (s, 6 H), 1.04 - 1.14 (m, 2 H), 0.84 - 0.94 (m, 2 H)
85		Pyridine	404.2	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.15 (s, 1H), 9.45 (br s, 1H), 8.83 (br s, 1H), 8.16 (d, J = 5.4 Hz, 1H), 7.02 (s, 2H), 6.99 (d, J = 5.6 Hz, 1H), 4.41-5.05 (m, 2H), 3.68 (br s, 2H), 3.15-3.34 (m, 2H), 1.93-2.22 (m, 2H), 1.16-1.37 (m, 6H)
86		Pyridine	390	1H NMR (500 MHz, DMSO-d6) δ ppm 11.13 (s, 1 H), 8.71 - 9.26 (m, 2 H), 8.14 (d, J=5.38 Hz, 1 H), 7.25 - 7.74 (m, 1 H), 6.91 (d, J=5.38 Hz, 1 H), 6.76 (d, J=1.96 Hz, 1 H), 6.65 (d, J=1.71 Hz, 1 H), 3.68 - 3.92 (m, 4 H), 3.10 - 3.24 (m, 4 H), 1.21 (s, 6 H)

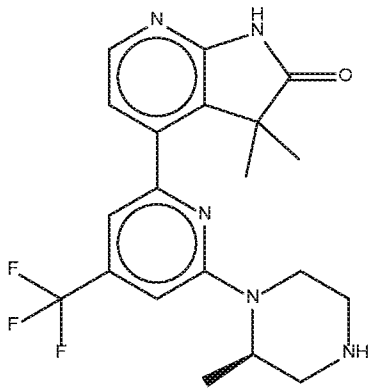
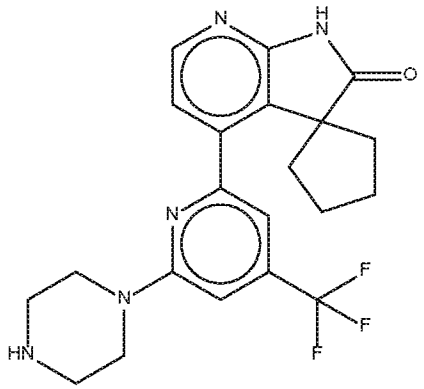
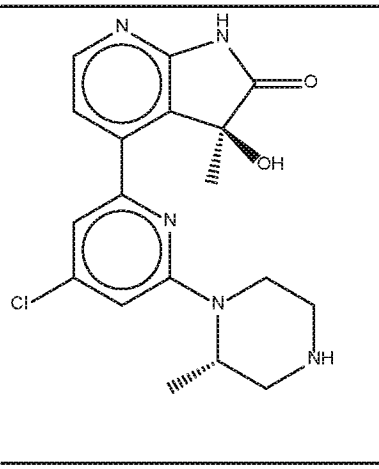
87		Pyridine	374	1H NMR (500 MHz, DMSO-d6) Shift 11.14 (s, 1H), 9.19 (br s, 2H), 8.14 (d, J=5.38 Hz, 1H), 7.16-7.19 (m, 1H), 7.12-7.16 (m, 1H), 6.89-7.15 (m, 3H), 3.80-3.87 (m, 4H), 3.18 (br d, J=8.80 Hz, 4H), 1.18-1.24 (m, 6H)
88		Pyridine (using compound I synthetized by Specific pyridine 1 route)	388	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.13 (s, 1H), 8.48-9.15 (m, 2H), 8.14 (d, J = 5.4 Hz, 1H), 7.10 (s, 1H), 6.94 (d, J = 5.4 Hz, 1H), 6.91 (s, 1H), 3.72-3.88 (m, 4H), 3.16 (br t, J = 4.4 Hz, 4H), 1.92-2.07 (m, 3H), 1.19 (s, 6H)
89		Pyridine (using compound II' obtained from OHMe isomer 1)	374; 376	1H NMR (600 MHz, DMSO-d6): δ ppm 11.09 (s, 1 H), 8.98 - 9.52 (m, 2 H), 8.19 (d, J=5.58 Hz, 1 H), 7.89 (d, J=1.32 Hz, 1 H), 7.36 (d, J=5.58 Hz, 1 H), 7.20 (d, J=1.32 Hz, 1 H), 5.16 - 6.97 (m, 1 H), 4.40 - 4.51 (m, 2 H), 3.34 - 3.41 (m, 1 H), 3.28 - 3.33 (m, 1 H), 3.19 - 3.27 (m, 1 H), 2.97 - 3.14 (m, 2 H), 1.22 - 1.36 (m, 6 H)

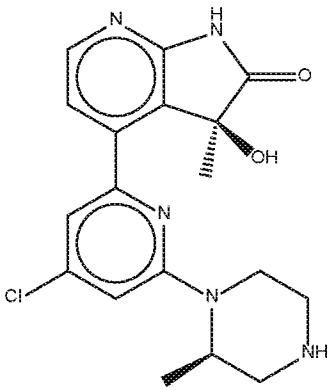
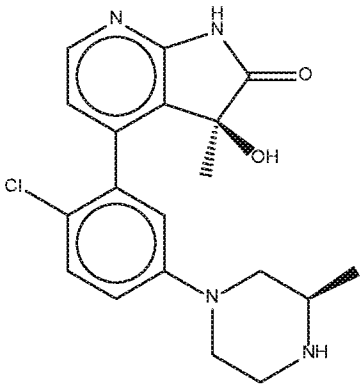
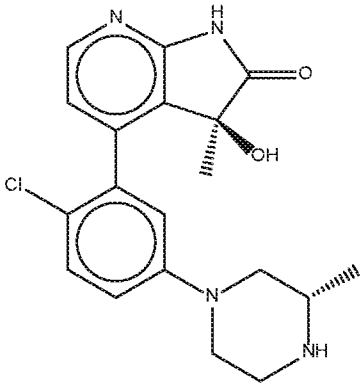
90		Pyridine (using compound II' obtained from OHMe isomer 1)	421.9	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.12 (s, 1H), 8.91-9.57 (m, 2H), 8.22 (d, J = 5.6 Hz, 1H), 8.17 (s, 1H), 7.41 (d, J = 5.6 Hz, 1H), 7.39 (s, 1H), 5.80-6.90 (m, 1H), 4.52-4.60 (m, 2H), 3.31-3.42 (m, 2H), 3.15-3.25 (m, 1H), 3.01-3.14 (m, 2H), 1.60-1.80 (m, 2H), 1.28 (s, 3H), 1.04 (t, J = 7.6 Hz, 3H)
91		Pyridine (using compound II' obtained from OHMe isomer 1)	391,9; 393,7	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.10 (s, 1H), 8.76-10.01 (m, 2H), 8.20 (dd, J = 5.4, 1.2 Hz, 1H), 7.91 (dd, J = 17.0, 1.3 Hz, 1H), 7.38 (dd, J = 18.7, 5.5 Hz, 1H), 7.09 (s, 1H), 5.98-6.81 (m, 1H), 5.23-5.39 (m, 1H), 4.26-4.48 (m, 1H), 3.81-4.15 (m, 3H), 3.19-3.64 (m, 4H), 1.31 (d, J = 9.0 Hz, 3H)
92		Pyridine (using compound II' obtained from OHMe isomer 1)	406,2; 408,2	1H NMR (DMSO-d6, 500 MHz (2 diastereosomers 45/55 at 300K): δ (ppm) 11.10 (s, 1H), 8.43-10.22 (m, 2H), 8.20 (dd, J = 5.6, 3.7 Hz, 1H), 7.93 (d, J = 1.2 Hz, 0.45H), 7.88 (d, J = 1.2 Hz, 0.55H), 7.41 (d, J = 5.6 Hz, 0.45H), 7.35 (d, J = 5.6 Hz, 0.55H), 7.06-7.13 (m, 1H), 5.43-6.91 (m, 1H), 4.47-4.65 (m, 1H), 4.27-4.36 (m, 2H), 3.21-3.74 (m, 6H), 1.44-1.57 (m, 3H), 1.33 (s , 1.35H), 1.30 (s , 1.65H)

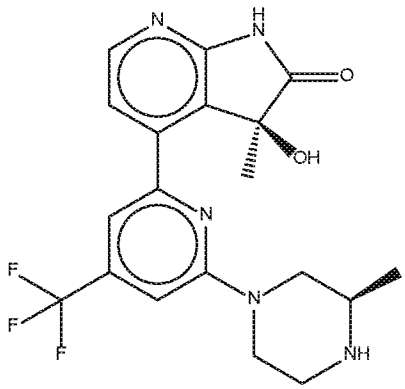
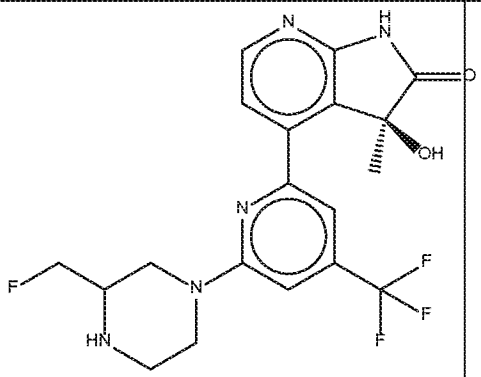
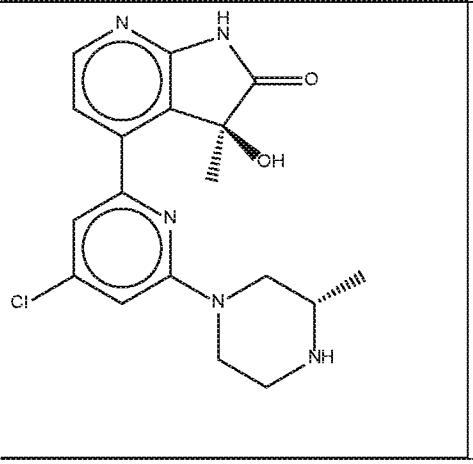
93		Pyridine (using compound II' obtained from OHMe isomer 1)	408.3	1H NMR (500 MHz, DMSO-d6, 300K) δ ppm 11.13 (s, 1 H), 9.45 (br d, J=10.5 Hz, 1 H), 8.88 - 9.15 (m, 1 H), 8.19 - 8.23 (m, 2 H), 7.41 (d, J=5.6 Hz, 1 H), 7.26 (s, 1 H), 5.95 - 7.02 (m, 1 H), 4.82 - 5.07 (m, 1 H), 4.32 - 4.58 (m, 1 H), 3.26 - 3.40 (m, 3 H), 3.17 (s, 1 H), 3.14 - 3.25 (m, 1 H), 2.96 - 3.10 (m, 1 H), 1.33 (d, J=6.8 Hz, 3 H), 1.28 (s, 3 H)
94		Pyridine (using compound II' obtained from OHMe isomer 1)	407.9	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.12 (s, 1H), 9.29 (br s, 2H), 8.21 (d, J = 5.4 Hz, 1H), 8.17 (s, 1H), 7.43 (d, J = 5.6 Hz, 1H), 7.25 (s, 1H), 6.01 (br s, 1H), 4.95 (br s, 1H), 4.50 (br d, J = 14.9 Hz, 1H), 4.10 (br s, 1H), 3.30-3.36 (m, 2H), 3.27-3.30 (m, 1H), 3.21 (br s, 1H), 3.01 (br s, 1H), 1.26-1.31 (m, 6H)
95		Pyridine (using compound II' obtained from OHMe isomer 1)	408.2	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.12 (s, 1H), 9.02-9.55 (m, 2H), 8.21 (d, J = 5.6 Hz, 1H), 8.15 (s, 1H), 7.43 (d, J = 5.6 Hz, 1H), 7.37 (s, 1H), 6.45 (br s, 1H), 4.73 (br s, 1H), 4.51-4.61 (m, 2H), 3.25-3.43 (m, 3H), 3.08 (dd, J = 13.8, 10.9 Hz, 2H), 1.32 (d, J = 6.6 Hz, 3H), 1.28 (s, 3H)

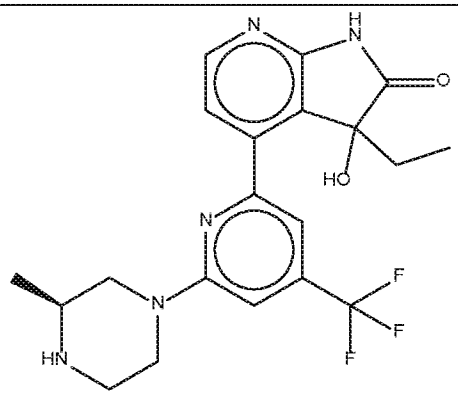
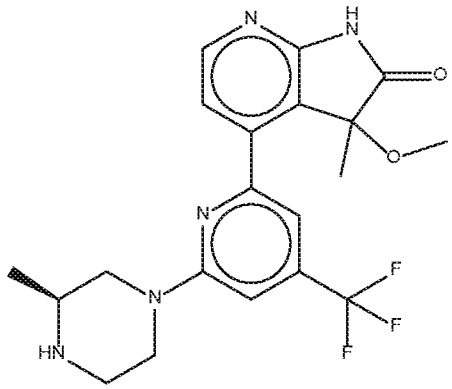
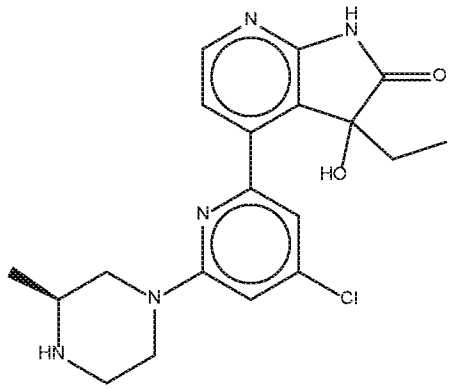
96		Pyridine (using compound II' obtained from OHMe isomer 1)	405.9	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.13 (d, J = 4.2 Hz, 1H), 9.41-10.19 (m, 2H), 8.22 (dd, J = 5.4, 3.9 Hz, 1H), 8.21 (d, J = 33.3 Hz, 1H), 7.39-7.53 (m, 1H), 7.17 (d, J = 3.7 Hz, 1H), 6.53 (br s, 1H), 4.35-4.53 (m, 1H), 3.69-4.24 (m, 1H), 3.07-3.37 (m, 5H), 1.32-1.39 (m, 1H), 1.30 (d, J = 9.3 Hz, 3H), 1.09-1.19 (m, 1H)
97		Pyridine (using compound II' obtained from OHMe isomer 1 and specific pyridine 3 as compound II)	450	1H NMR (500 MHz, DMSO-d6) Shift 11.12 (s, 1H), 8.71-9.86 (m, 2H), 8.22 (d, J=5.51 Hz, 1H), 8.18 (d, J=4.36 Hz, 1H), 7.50 (t, J=5.75 Hz, 1H), 7.26 (s, 1H), 6.62 (d, J=7.34 Hz, 1H), 4.51 (br d, J=11.25 Hz, 1H), 3.65-4.13 (m, 5H), 3.44-3.55 (m, 1H), 3.33-3.40 (m, 1H), 3.18-3.28 (m, 1H), 3.08 (br dd, J=2.69, 12.96 Hz, 1H), 1.94 (dt, J=3.55, 14.24 Hz, 1H), 1.78-1.88 (m, 1H), 1.29 (d, J=1.96 Hz, 3H)
98		Pyrimidine	393	1H NMR (500 MHz, DMSO-d6): δ ppm 11.19 (s, 1 H), 8.85 - 9.93 (m, 2 H), 8.22 (d, J=5.38 Hz, 1 H), 7.61 (d, J=5.62 Hz, 1 H), 7.47 (s, 1 H), 3.95 - 4.16 (m, 4 H), 3.16 - 3.30 (m, 4 H), 1.45 (s, 6 H)

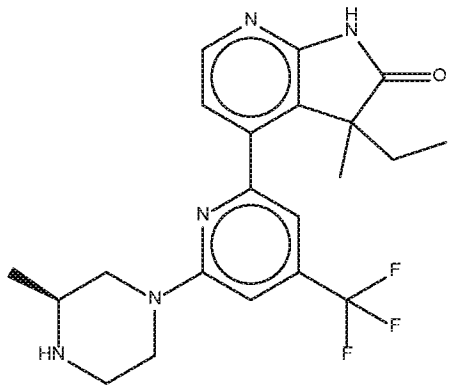
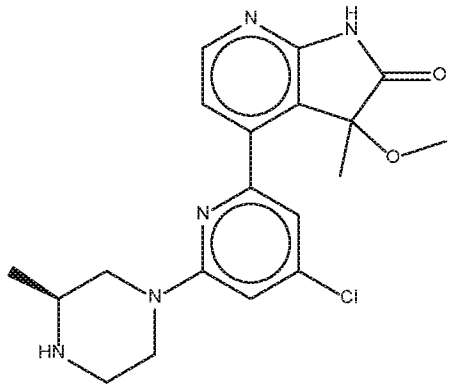
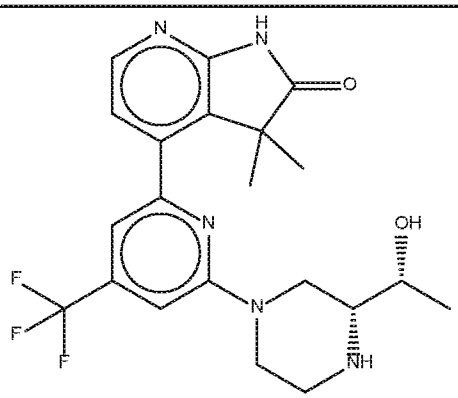
99		Pyridine	406	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.13 (s, 1H), 10.17 (br s, 1H), 8.14 (d, J = 5.3 Hz, 1H), 7.25 (br s, 1H), 6.98 (br s, 1H), 6.95 (d, J = 5.4 Hz, 1H), 3.33-4.08 (m, 4H), 2.53-3.10 (m, 4H), 2.26 (br s, 3H), 1.19 (s, 6H)
100		Pyridine (using specific pyridine 4 as compound II)	391.9	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.14 (s, 1H), 8.78-9.30 (m, 2H), 8.14 (d, J = 5.3 Hz, 1H), 7.77 (br d, J = 5.6 Hz, 1H), 6.96 (d, J = 5.4 Hz, 1H), 6.90 (s, 2H), 4.45-4.58 (m, 1H), 3.28-3.47 (m, 2H), 2.99-3.28 (m, 2H), 1.83-2.28 (m, 2H), 1.11-1.30 (m, 6H)
101		Pyridine	405.9	1H NMR (500 MHz, DMSO-d6) Shift 11.16 (s, 1H), 8.64-9.51 (m, 2H), 8.15 (d, J=5.38 Hz, 1H), 7.25 (s, 1H), 7.03 (s, 1H), 6.94 (d, J=5.38 Hz, 1H), 4.86-4.92 (m, 1H), 4.35-4.42 (m, 1H), 3.33-3.38 (m, 1H), 3.24-3.29 (m, 2H), 3.14-3.23 (m, 1H), 2.96-3.06 (m, 1H), 1.23-1.30 (m, 3H), 1.18 (d, J=5.14 Hz, 6H)

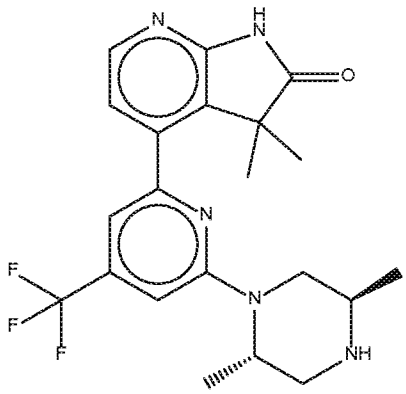
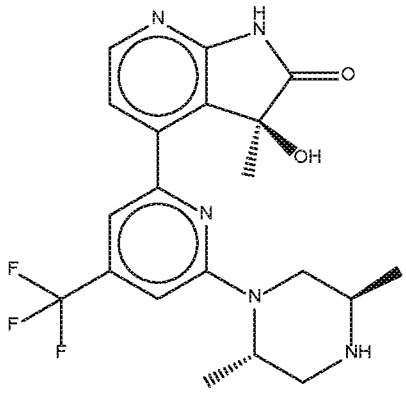
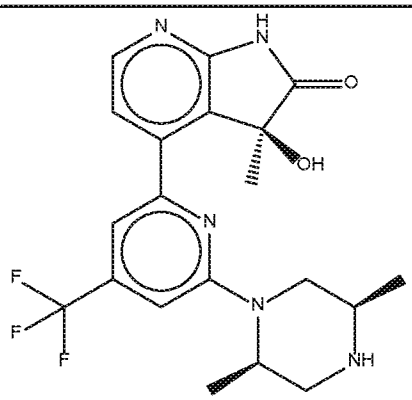
102		Pyridine	405.9	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.16 (s, 1H), 8.86-9.54 (m, 2H), 8.15 (d, J = 5.4 Hz, 1H), 7.25 (s, 1H), 7.02 (s, 1H), 6.94 (d, J = 5.4 Hz, 1H), 4.71-5.04 (m, 1H), 4.27-4.46 (m, 1H), 3.22-3.34 (m, 3H), 3.12-3.21 (m, 1H), 2.91-3.04 (m, 1H), 1.28 (d, J = 6.9 Hz, 3H), 1.18 (d, J = 7.6 Hz, 6H)
103		Pyridine	418.1	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.03 (s, 1H), 9.22 (br s, 2H), 8.13 (d, J = 5.4 Hz, 1H), 7.32 (s, 1H), 7.08 (s, 1H), 6.92 (d, J = 5.4 Hz, 1H), 4.43-4.48 (m, 1H), 3.83-3.89 (m, 4H), 3.13-3.22 (m, 4H), 1.83-2.07 (m, 4H), 1.65-1.82 (m, 2H), 1.22-1.32 (m, 2H)
104		Pyridine (using compound II' obtained from OHMe isomer 1)	373,9; 375,8	1H NMR (600 MHz, DMSO-d6): δ ppm 11.11 (s, 1 H), 8.52 - 9.76 (m, 2 H), 8.19 (d, J=5.58 Hz, 1 H), 7.93 (d, J=1.32 Hz, 1 H), 7.36 (d, J=5.43 Hz, 1 H), 7.09 (d, J=1.32 Hz, 1 H), 6.40 - 6.69 (m, 1 H), 4.71 - 4.96 (m, 1 H), 4.30 - 4.39 (m, 1 H), 3.29 - 3.35 (m, 1 H), 3.21 - 3.29 (m, 2 H), 3.11 - 3.19 (m, 1 H), 2.92 - 3.06 (m, 1 H), 1.30 - 1.33 (m, 3 H), 1.28 - 1.30 (m, 3 H)

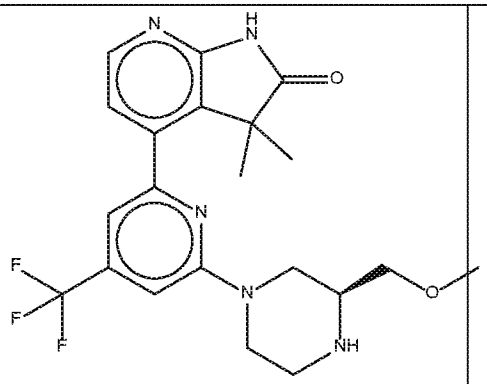
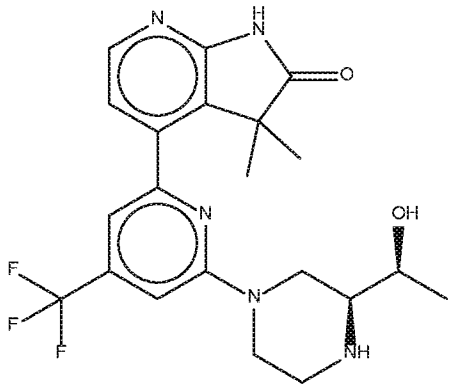
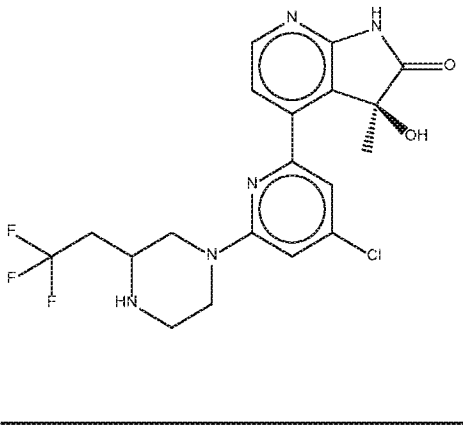
105		Pyridine (using compound II' obtained from OHMe isomer 1)	373,9; 375,8	1H NMR (600 MHz, DMSO-d6) Shift 11.09 (s, 1H), 9.41 (br d, J=9.83 Hz, 1H), 8.96 (br d, J=9.83 Hz, 1H), 8.18 (d, J=5.57 Hz, 1H), 7.90 (d, J=1.32 Hz, 1H), 7.37 (d, J=5.43 Hz, 1H), 7.10 (d, J=1.32 Hz, 1H), 5.95-6.90 (m, 1H), 4.72-4.90 (m, 1H), 4.41 (br d, J=13.35 Hz, 1H), 3.16-3.33 (m, 5H), 2.94-3.02 (m, 1H), 1.29 (s, 3H), 1.26 (d, J=7.04 Hz, 3H)
106		Phenyl 3	372,9 ; 374,8	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.04 (s, 1H), 8.80-9.48 (m, 2H), 8.12 (d, J = 5.4 Hz, 1H), 7.41 (d, J = 8.6 Hz, 1H), 7.03-7.14 (m, 2H), 6.81 (d, J = 5.4 Hz, 1H), 6.24 (br s, 1H), 3.81 (br d, J = 12.5 Hz, 1H), 3.70 (br d, J = 12.0 Hz, 1H), 3.25-3.41 (m, 2H), 2.96-3.14 (m, 2H), 2.80 (dd, J = 13.0, 10.8 Hz, 1H), 1.26 (d, J = 6.4 Hz, 3H), 1.08 (br s, 3H)
107		Phenyl 3	373; 374,9	1H NMR (600 MHz, DMSO-d6): δ ppm 11.04 (s, 1 H), 8.72 - 9.58 (m, 2 H), 8.12 (d, J=5.43 Hz, 1 H), 7.35 - 7.47 (m, 1 H), 7.08 - 7.13 (m, 1 H), 7.08 (s, 1 H), 6.72 - 6.83 (m, 1 H), 5.31 - 6.35 (m, 1 H), 3.76 (m, J=14.10 Hz, 2 H), 3.26 - 3.40 (m, 2 H), 2.97 - 3.13 (m, 2 H), 2.82 (m, J=12.80, 10.90 Hz, 1 H), 1.26 (d, J=6.46 Hz, 3 H), 1.07 (br s, 3 H)

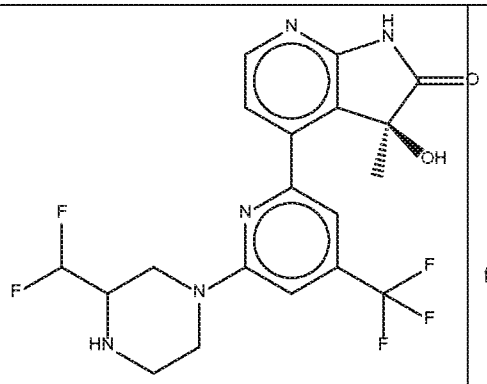
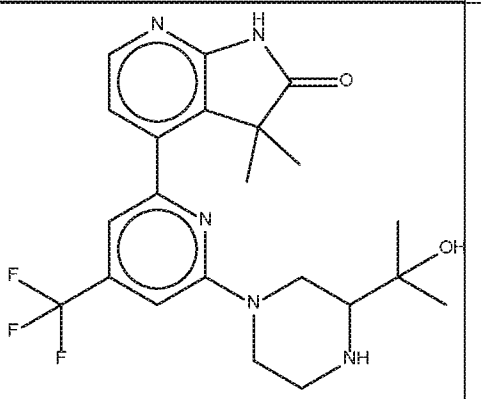
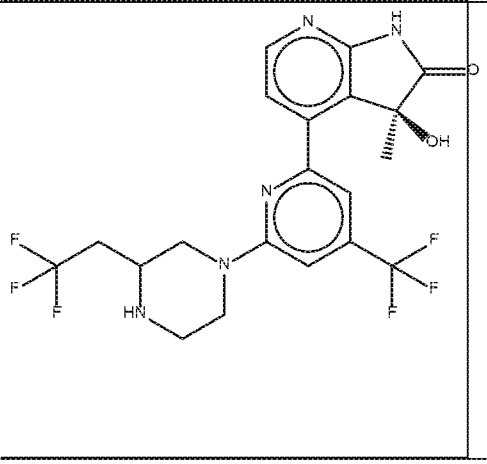
108		Pyridine (using compound II' obtained from OHMe isomer 1)	407.9	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.11 (s, 1H), 9.09-9.51 (m, 2H), 8.21 (d, J = 5.4 Hz, 1H), 8.15 (s, 1H), 7.43 (d, J = 5.4 Hz, 1H), 7.37 (s, 1H), 6.47 (br s, 1H), 4.41-4.66 (m, 2H), 3.81 (br s, 1H), 3.24-3.44 (m, 3H), 3.05-3.15 (m, 2H), 1.31 (d, J = 6.6 Hz, 3H), 1.28 (s, 3H)
109		Pyridine (using compound II' obtained from OHMe isomer 1)	426	1H NMR (500 MHz, DMSO-d6): δ ppm 11.13 (s, 1 H), 8.98 - 10.21 (m, 2 H), 8.21 - 8.24 (m, 1 H), 8.20 (d, J=3.42 Hz, 1 H), 7.45 (dd, J=5.38, 2.69 Hz, 1 H), 7.38 (s, 1 H), 6.28 - 6.93 (m, 1 H), 4.68 - 4.90 (m, 2 H), 4.48 - 4.67 (m, 2 H), 3.64 - 3.68 (m, 1 H), 3.16 - 3.48 (m, 4 H), 1.28 (s, 3 H)
110		Pyridine (using compound II' obtained from OHMe isomer 1)	373,9; 375,8	1H NMR (500 MHz, DMSO-d6): δ ppm 11.11 (s, 1 H), 8.96 - 10.00 (m, 2 H), 8.19 (d, J=5.38 Hz, 1 H), 7.88 (d, J=1.22 Hz, 1 H), 7.37 (d, J=5.38 Hz, 1 H), 7.20 (d, J=1.22 Hz, 1 H), 5.56 - 5.77 (m, 1 H), 4.40 - 4.47 (m, 2 H), 3.21 - 3.41 (m, 3 H), 2.95 - 3.10 (m, 2 H), 1.31 (d, J=6.60 Hz, 3 H), 1.29 (s, 3 H)

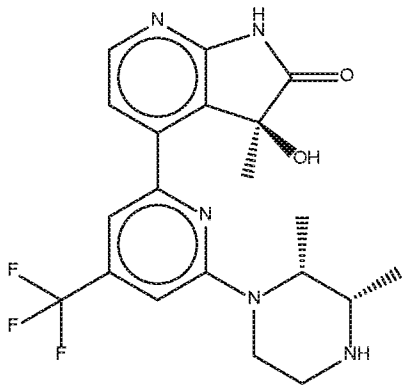
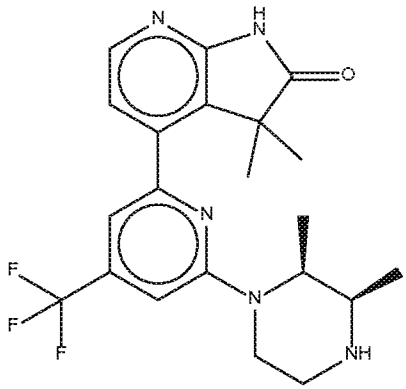
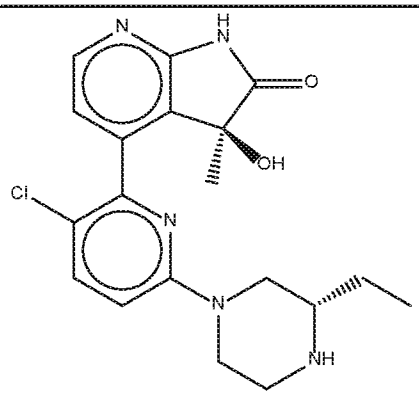
111		Pyridine	422	1H NMR (500 MHz, DMSO-d6): δ ppm 11.15 (s, 1 H), 8.72 - 9.83 (m, 2 H), 8.23 (d, J=5.38 Hz, 1 H), 8.09 (d, J=5.62 Hz, 1 H), 7.42 (dd, J=5.38, 2.69 Hz, 1 H), 7.36 (s, 1 H), 5.90 - 6.90 (m, 1 H), 4.46 - 4.64 (m, 2 H), 3.24 - 3.41 (m, 3 H), 2.99 - 3.15 (m, 2 H), 1.63 - 1.92 (m, 2 H), 1.31 (d, J=6.36 Hz, 3 H), 0.29 - 0.43 (m, 3 H)
112		Pyridine	422	1H NMR (500 MHz, DMSO-d6) δ ppm 11.49 (s, 1 H), 8.78 - 9.71 (m, 2 H), 8.29 (d, J=5.62 Hz, 1 H), 7.63 - 7.66 (m, 1 H), 7.45 - 7.49 (m, 1 H), 7.36 - 7.41 (m, 1 H), 4.36 - 4.72 (m, 2 H), 3.38 (m, J=2.90 Hz, 1 H), 3.31 - 3.36 (m, 1 H), 3.24 - 3.31 (m, 1 H), 3.06 - 3.15 (m, 2 H), 3.03 - 3.06 (m, 3 H), 1.32 - 1.39 (m, 3 H), 1.26 - 1.32 (m, 3 H)
113		Pyridine	388; 389,9	1H NMR (500 MHz, DMSO-d6): δ ppm 11.13 (s, 1 H), 8.69 - 9.65 (m, 2 H), 8.20 (d, J=5.62 Hz, 1 H), 7.81 (dd, J=5.87, 1.22 Hz, 1 H), 7.30 - 7.40 (m, 1 H), 7.18 - 7.23 (m, 1 H), 6.06 - 6.90 (m, 1 H), 4.33 - 4.56 (m, 2 H), 3.30 - 3.40 (m, 2 H), 3.18 - 3.27 (m, 1 H), 2.96 - 3.10 (m, 2 H), 1.65 - 1.95 (m, 2 H), 1.29 (d, J=6.36 Hz, 3 H), 0.38 (t, J=7.46 Hz, 3 H)

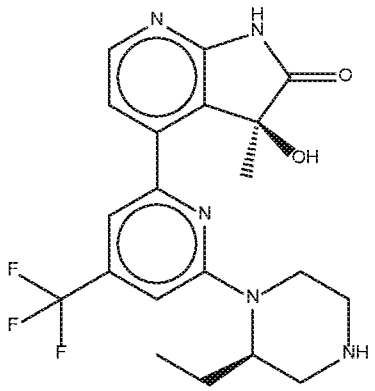
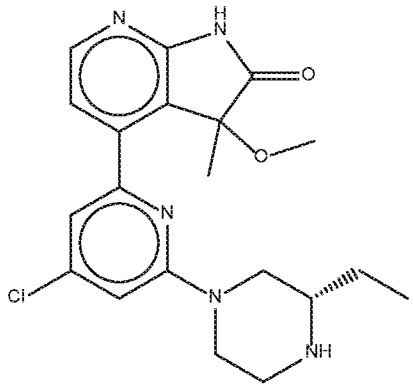
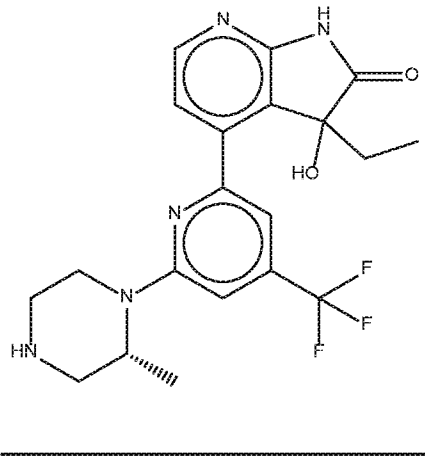
114		Pyridine	420	1H NMR (500 MHz, DMSO-d6): δ ppm 11.12 (s, 1 H), 8.83 - 9.44 (m, 2 H), 8.16 (d, J=5.38 Hz, 1 H), 7.36 (s, 1 H), 7.01 (s, 1 H), 6.95 (d, J=5.38 Hz, 1 H), 4.29 - 4.52 (m, 2 H), 3.36 - 3.41 (m, 1 H), 3.30 - 3.35 (m, 1 H), 3.21 - 3.29 (m, 1 H), 2.99 - 3.12 (m, 2 H), 1.46 - 1.73 (m, 2 H), 1.27 (dd, J=6.60, 1.47 Hz, 3 H), 1.16 (d, J=4.65 Hz, 3 H), 0.50 (td, J=7.34, 1.47 Hz, 3 H)
115		Pyridine	388,0; 389.9	1H NMR (500 MHz, DMSO-d6): δ ppm 11.40 (s, 1 H), 8.90 - 9.62 (m, 2 H), 8.26 (d, J=5.62 Hz, 1 H), 7.40 - 7.42 (m, 1 H), 7.38 - 7.40 (m, 1 H), 7.14 - 7.25 (m, 1 H), 4.38 - 4.57 (m, 2 H), 3.34 - 3.41 (m, 1 H), 3.30 (m, J=10.10, 7.00, 3.20 Hz, 1 H), 3.20 - 3.27 (m, 1 H), 3.01 - 3.11 (m, 5 H), 1.35 (s, 3 H), 1.23 - 1.31 (m, 3 H)
116		Pyridine	436	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.17 (s, 1H), 8.86-9.21 (m, 2H), 8.16 (d, J = 5.4 Hz, 1H), 7.37 (s, 1H), 7.05 (s, 1H), 6.95 (d, J = 5.4 Hz, 1H), 4.80-6.04 (m, 1H), 4.45 (br t, J = 13.6 Hz, 2H), 4.13-4.18 (m, 1H), 3.82 (t, J = 6.4 Hz, 1H), 3.25-3.37 (m, 2H), 3.04-3.21 (m, 3H), 1.16-1.22 (m, 9H)

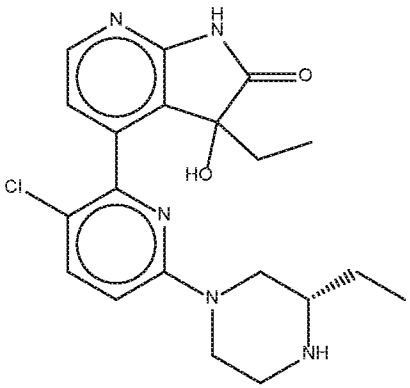
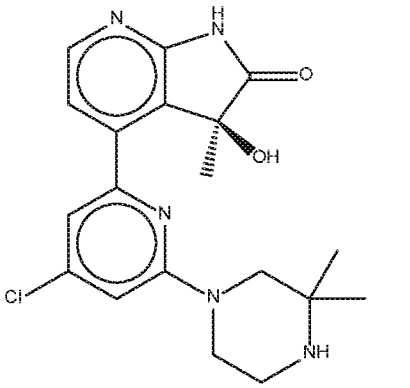
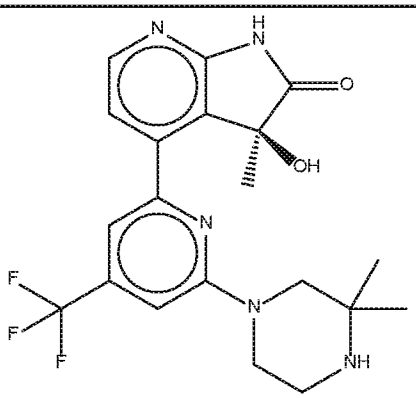
117		Pyridine	420	1H NMR (500 MHz, DMSO-d6): δ ppm 11.20 (s, 1 H), 8.88 - 9.72 (m, 2 H), 8.15 (d, J=5.38 Hz, 1 H), 7.24 (s, 1 H), 7.00 (s, 1 H), 6.95 (d, J=5.38 Hz, 1 H), 4.72 - 4.87 (m, 1 H), 4.22 - 4.26 (m, 1 H), 3.65 - 3.72 (m, 1 H), 3.42 - 3.47 (m, 1 H), 3.34 - 3.39 (m, 1 H), 3.06 - 3.13 (m, 1 H), 1.25 - 1.31 (m, 6 H), 1.14 - 1.21 (m, 6 H)
118		Pyridine (using compound II' obtained from OHMe isomer 1)	422	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.13 (s, 1H), 9.01-9.45 (m, 2H), 8.22 (d, J = 5.6 Hz, 1H), 8.21 (s, 1H), 7.41 (d, J = 5.4 Hz, 1H), 7.24 (s, 1H), 6.07-6.85 (m, 1H), 4.78-4.89 (m, 1H), 4.28 (br d, J = 13.7 Hz, 1H), 3.69-3.78 (m, 1H), 3.46-3.52 (m, 2H), 3.32-3.34 (m, 1H), 3.11 (br dd, J = 13.1, 2.3 Hz, 1H), 1.34 (d, J = 3.9 Hz, 3H), 1.33 (d, J = 3.9 Hz, 3H), 1.28 (s, 3H)
119		Pyridine (using compound II' obtained from OHMe isomer 1)	422	1H NMR (500 MHz, DMSO-d6, 300K) δ ppm 11.12 (s, 1 H), 9.41 - 9.69 (m, 1 H), 8.63 - 8.91 (m, 1 H), 8.22 (d, J=5.4 Hz, 1 H), 8.14 (s, 1 H), 7.42 (d, J=5.6 Hz, 1 H), 7.30 (s, 1 H), 6.28 - 6.89 (m, 1 H), 5.00 (br d, J=2.0 Hz, 1 H), 4.41 - 4.60 (m, 1 H), 3.18 - 3.35 (m, 3 H), 3.01 (dd, J=14.4, 11.5 Hz, 1 H), 1.35 (d, J=6.6 Hz, 3 H), 1.20 - 1.30 (m, 6 H)

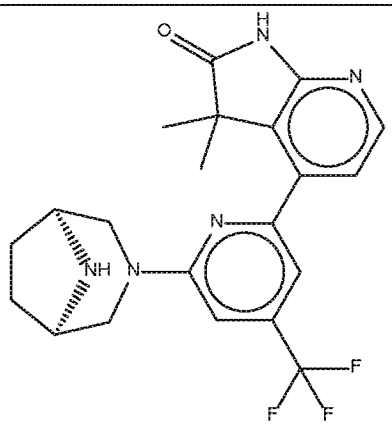
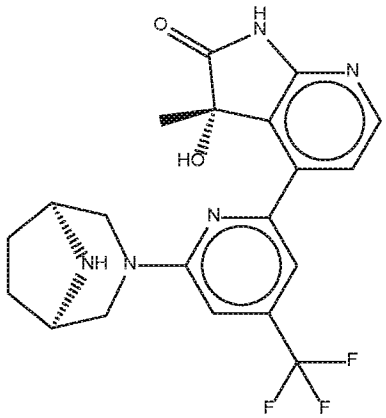
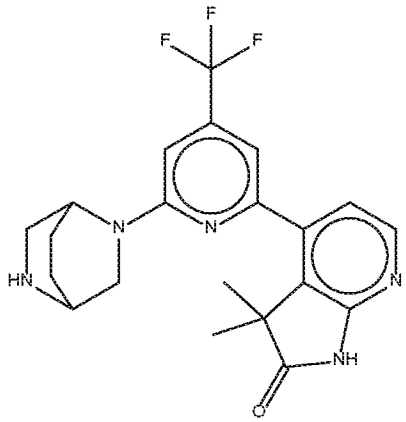
120		Pyridine	436	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.16 (s, 1H), 9.03-9.44 (m, 2H), 8.15 (d, J = 5.4 Hz, 1H), 7.35 (s, 1H), 7.05 (s, 1H), 6.95 (d, J = 5.4 Hz, 1H), 4.42-4.54 (m, 2H), 3.56-3.64 (m, 3H), 3.42-3.46 (m, 1H), 3.34 (s, 3H), 3.26-3.33 (m, 2H), 3.18 (dd, J = 14.1, 10.7 Hz, 1H), 3.06-3.15 (m, 1H), 1.19 (s, 3H), 1.17 (s, 3H)
121		Pyridine	436	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.16 (s, 1H), 8.98 (br s, 2H), 7.94-8.39 (m, 1H), 7.29-7.42 (m, 1H), 7.05 (s, 1H), 6.95 (d, J = 5.3 Hz, 1H), 5.20-6.08 (m, 1H), 4.45 (br t, J = 14.9 Hz, 2H), 3.81 (br dd, J = 12.8, 6.5 Hz, 1H), 3.25-3.36 (m, 2H), 2.96-3.22 (m, 3H), 1.05-1.31 (m, 9H)
122		Pyridine (using compound II' obtained from OHMe isomer 1)	442,0; 443,9	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.11 (s, 1H), 9.30-9.96 (m, 2H), 8.12-8.24 (m, 1H), 7.97 (dd, J = 13.8, 1.3 Hz, 1H), 7.34 (dd, J = 18.0, 5.4 Hz, 1H), 7.18 (dd, J = 8.8, 1.3 Hz, 1H), 6.47 (br s, 1H), 4.49-4.71 (m, 1H), 4.32 (br t, J = 13.8 Hz, 1H), 4.03-4.06 (m, 1H), 3.64-3.75 (m, 1H), 3.28-3.48 (m, 3H), 3.14-3.25 (m, 1H), 2.77-2.94 (m, 2H), 1.30 (d, J = 7.5 Hz, 3H)

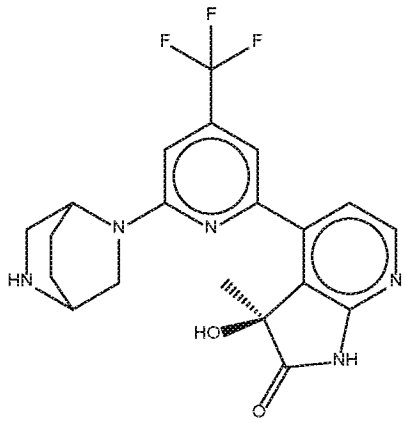
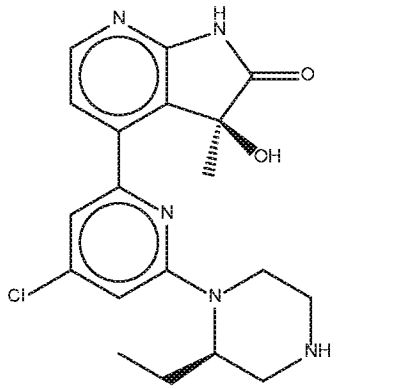
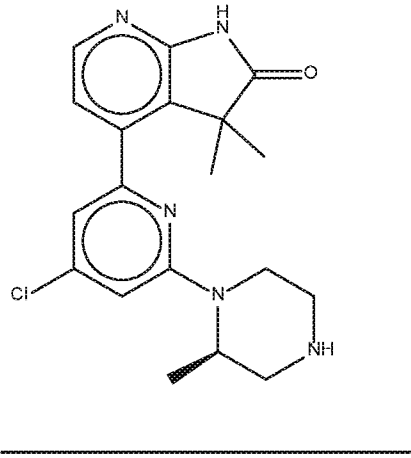
123		Pyridine (using compound II' obtained from OHMe isomer 1)	444	1H NMR (500 MHz, DMSO-d6): δ ppm 11.13 (s, 1 H), 9.52 - 10.51 (m, 2 H), 8.14 - 8.36 (m, 2 H), 7.42 - 7.46 (m, 1 H), 7.38 - 7.41 (m, 1 H), 5.95 - 7.08 (m, 2 H), 4.76 (m, J=13.90 Hz, 1 H), 4.50 - 4.61 (m, 1 H), 3.97 - 4.01 (m, 1 H), 3.38 - 3.46 (m, 2 H), 3.27 - 3.37 (m, 1 H), 3.18 - 3.25 (m, 1 H), 1.28 (s, 3 H)
124		Pyridine	450.1	1H NMR (500 MHz, DMSO-d6, 300K) δ ppm 11.17 (s, 1 H), 8.57 - 8.95 (m, 2 H), 8.16 (d, J=5.4 Hz, 1 H), 7.36 (s, 1 H), 7.06 (s, 1 H), 6.95 (d, J=5.4 Hz, 1 H), 5.03 - 5.75 (m, 1 H), 4.38 - 4.71 (m, 2 H), 2.94 - 3.35 (m, 5 H), 1.09 - 1.33 (m, 12 H)
125		Pyridine	476	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.11 (s, 1H), 8.20 (dd, J = 5.4, 2.9 Hz, 1H), 8.14 (d, J = 12.5 Hz, 1H), 7.40 (dd, J = 6.8, 5.6 Hz, 1H), 7.24 (br d, J = 4.6 Hz, 1H), 6.58 (d, J = 13.0 Hz, 1H), 4.42-4.60 (m, 1H), 4.28 (br t, J = 12.2 Hz, 1H), 2.86-3.29 (m, 6H), 2.52-2.69 (m, 2H), 1.29 (d, J = 5.4 Hz, 3H)

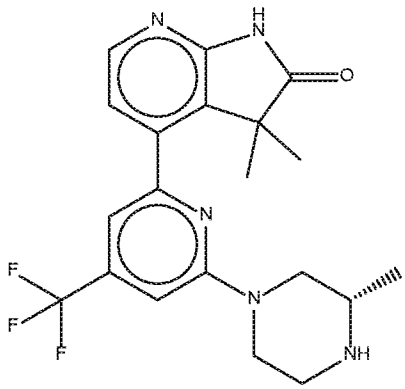
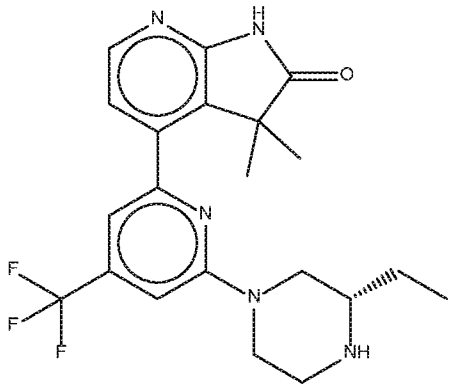
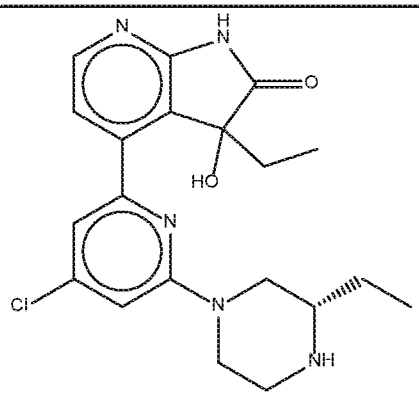
126		Pyridine	422	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.11 (s, 1H), 9.55 (br s, 1H), 9.00 (br s, 1H), 8.21 (t, J = 5.1 Hz, 1H), 8.16 (d, J = 17.5 Hz, 1H), 7.42 (dd, J = 10.2, 5.5 Hz, 1H), 7.30 (d, J = 4.4 Hz, 1H), 6.56 (br s, 1H), 4.72-4.89 (m, 1H), 4.46-4.62 (m, 1H), 3.72-3.76 (m, 1H), 3.44-3.54 (m, 1H), 3.34 (br t, J = 11.0 Hz, 1H), 3.17-3.24 (m, 1H), 2.99-3.13 (m, 1H), 1.18-1.30 (m, 9H)
127		Pyridine	420	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.15 (s, 1H), 9.43-9.70 (m, 1H), 8.95-9.08 (m, 1H), 8.15 (d, J = 5.4 Hz, 1H), 7.29 (s, 1H), 7.02 (s, 1H), 6.95 (d, J = 5.3 Hz, 1H), 4.71-4.84 (m, 1H), 4.44 (br d, J = 13.8 Hz, 1H), 3.89-3.92 (m, 1H), 3.41-3.52 (m, 1H), 3.32 (br d, J = 12.0 Hz, 1H), 3.13-3.22 (m, 1H), 2.98-3.06 (m, 1H), 1.23 (d, J = 6.7 Hz, 3H), 1.17-1.21 (m, 6H), 1.16 (s, 3H)
128		Pyridine (using compound II' obtained from OHMe isomer 1)	388,0; 389,9	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.01 (s, 1H), 9.20 (br s, 2H), 8.14 (d, J = 5.4 Hz, 1H), 7.80 (d, J = 9.1 Hz, 1H), 7.07 (d, J = 9.2 Hz, 1H), 6.85 (d, J = 5.3 Hz, 1H), 4.90-6.21 (m, 1H), 4.33 (br d, J = 12.6 Hz, 1H), 4.24 (br d, J = 13.9 Hz, 1H), 3.84-3.86 (m, 1H), 3.31 (br d, J = 12.6 Hz, 1H), 3.19-3.26 (m, 1H), 3.07-3.16 (m, 1H), 2.99-3.05 (m, 1H), 2.97 (dd, J = 13.9, 10.6 Hz, 1H), 1.57-1.70 (m, 2H), 1.24 (s, 3H), 0.96 (t, J = 7.6 Hz, 3H)

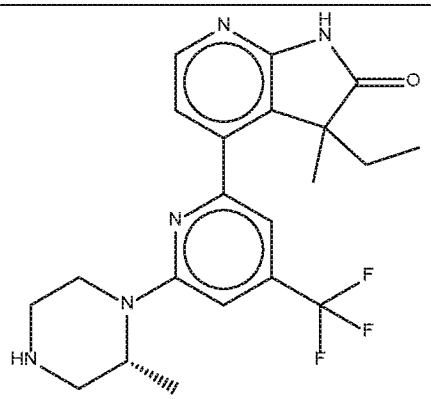
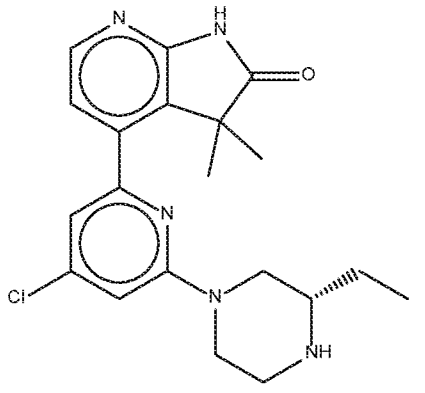
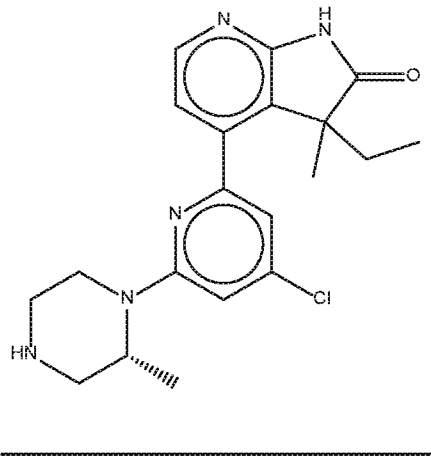
129		Pyridine (using compound II' obtained from OHMe isomer 1)	422	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.11 (s, 1H), 9.42 (br d, J = 10.4 Hz, 1H), 8.93-9.13 (m, 1H), 8.21 (d, J = 5.6 Hz, 1H), 8.11 (s, 1H), 7.44 (d, J = 5.4 Hz, 1H), 7.28 (s, 1H), 6.44 (br s, 1H), 4.76 (br s, 1H), 4.56 (br d, J = 14.4 Hz, 1H), 3.89 (br s, 1H), 3.24-3.39 (m, 3H), 3.16 (br d, J = 11.7 Hz, 1H), 2.98 (br d, J = 10.7 Hz, 1H), 1.75-1.91 (m, 2H), 1.28 (s, 3H), 0.84 (t, J = 7.3 Hz, 3H)
130		Pyridine	402	1H NMR (500 MHz, DMSO-d6, 300K) δ ppm 11.41 (s, 1 H), 9.04 - 9.39 (m, 2 H), 8.26 (d, J=5.6 Hz, 1 H), 7.42 (dd, J=5.1, 1.2 Hz, 1 H), 7.39 (dd, J=5.5, 1.3 Hz, 1 H), 7.24 (dd, J=2.7, 1.5 Hz, 1 H), 4.41 - 4.55 (m, 2 H), 2.98 - 3.43 (m, 8 H), 1.54 - 1.79 (m, 2 H), 1.36 (d, J=5.1 Hz, 3 H), 1.01 (td, J=7.7, 6.1 Hz, 3 H)
131		Pyridine	422	1H NMR (500 MHz, DMSO-d6) Shift 11.15 (d, J=3.18 Hz, 1H), 9.34 (br d, J=10.27 Hz, 1H), 8.90 (br d, J=8.07 Hz, 1H), 8.22 (t, J=5.45 Hz, 1H), 8.04-8.16 (m, 1H), 7.40 (t, J=5.01 Hz, 1H), 7.25 (s, 1H), 6.21-6.91 (br s, 1H), 4.95 (br d, J=5.38 Hz, 1H), 4.41-4.51 (m, 1H), 3.17-3.36 (m, 5H), 2.97-3.10 (m, 1H), 1.66-1.85 (m, 2H), 1.21-1.38 (m, 3H), 0.36 (dt, J=2.32, 7.52 Hz, 3H)

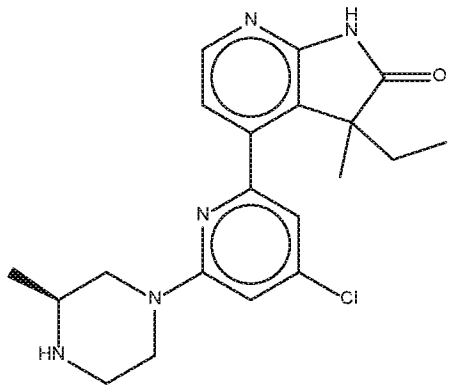
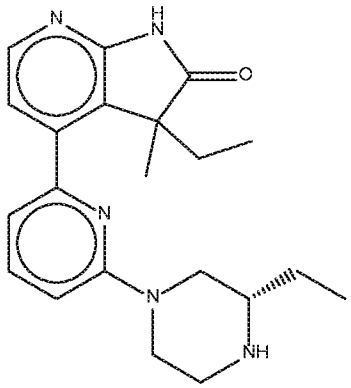
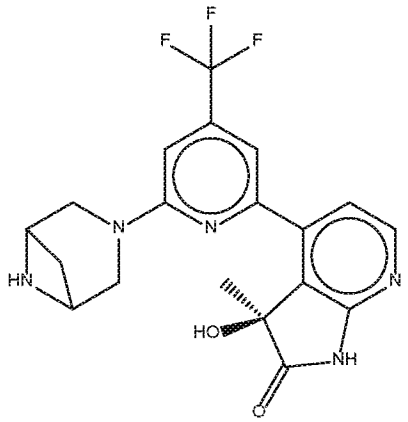
132		Pyridine	402,0; 403,9	1H NMR (500 MHz, DMSO-d6) Shift 11.05 (s, 1H), 9.08 (br s, 1H), 8.99 (br s, 1H), 8.15 (d, J=5.38 Hz, 1H), 7.81 (d, J=9.05 Hz, 1H), 7.07 (d, J=9.05 Hz, 1H), 6.86 (d, J=5.62 Hz, 1H), 5.75-5.78 (m, 1H), 4.19-4.44 (m, 2H), 2.85-3.24 (m, 5H), 1.46-1.80 (m, 4H), 0.96 (q, J=7.58 Hz, 3H), 0.53 (t, J=7.46 Hz, 3H)
133		Pyridine (using compound II' obtained from OHMe isomer 1)	388,0; 389.9	1H NMR (500 MHz, DMSO-d6): δ ppm 11.10 (s, 1 H), 8.80 - 9.73 (m, 2 H), 8.19 (d, J=5.38 Hz, 1 H), 7.86 (d, J=1.22 Hz, 1 H), 7.34 - 7.40 (m, 1 H), 7.20 (d, J=1.22 Hz, 1 H), 5.86 - 6.93 (m, 1 H), 3.85 - 3.89 (m, 2 H), 3.72 - 3.76 (m, 2 H), 3.18 - 3.31 (m, 2 H), 1.32 - 1.38 (m, 6 H), 1.28 - 1.31 (m, 3 H)
134		Pyridine (using compound II' obtained from OHMe isomer 1)	422	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.11 (s, 1H), 9.35 (br s, 2H), 8.21 (d, J = 5.6 Hz, 1H), 8.12 (s, 1H), 7.42 (d, J = 5.6 Hz, 1H), 7.36 (s, 1H), 5.98-6.90 (m, 1H), 4.15 (br s, 1H), 3.94 (br t, J = 5.2 Hz, 2H), 3.78-3.84 (m, 1H), 3.74 (d, J = 13.9 Hz, 1H), 3.22-3.27 (m, 2H), 1.36 (d, J = 7.0 Hz, 6H), 1.28 (s, 3H)

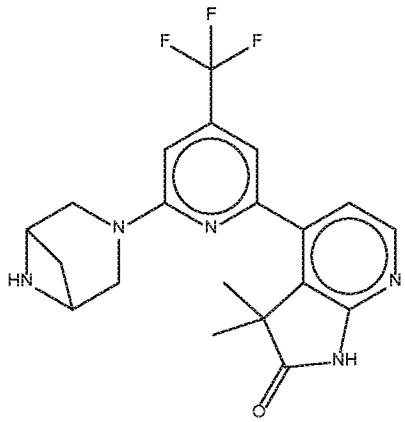
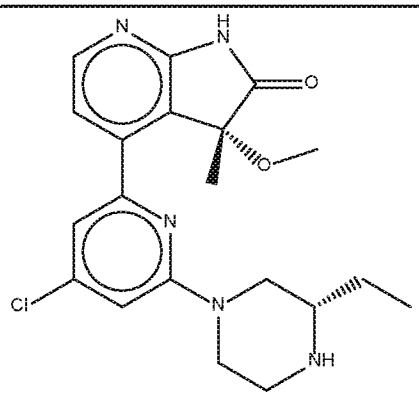
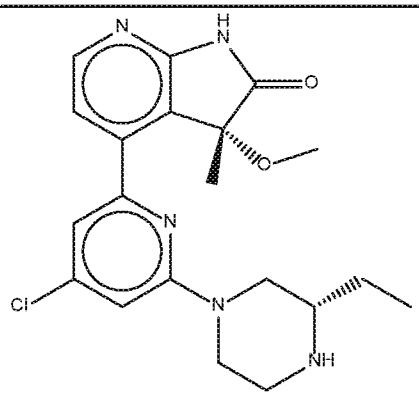
135		Pyridine	418	1H NMR (500 MHz, DMSO-d6) Shift 11.16 (s, 1H), 9.16-9.43 (m, 2H), 8.15 (d, J=5.38 Hz, 1H), 7.23 (s, 1H), 7.06 (s, 1H), 6.96 (d, J=5.38 Hz, 1H), 4.24 (br d, J=12.96 Hz, 2H), 4.16 (br s, 2H), 3.51 (s, 1H), 3.34 (d, J=12.47 Hz, 2H), 1.93-2.00 (m, 2H), 1.80-1.91 (m, 2H), 1.17-1.22 (m, 6H)
136		Pyridine (using compound II' obtained from OHMe isomer 1)	420	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 10.93-11.29 (m, 1H), 9.03-9.57 (m, 2H), 8.12-8.31 (m, 2H), 7.44 (d, J = 5.4 Hz, 1H), 7.25 (s, 1H), 6.18-6.94 (m, 1H), 4.25-4.42 (m, 2H), 4.18 (br s, 2H), 3.24-3.40 (m, 2H), 1.74-2.16 (m, 4H), 1.29 (s, 3H)
137		Pyridine	418	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.15 (s, 1H), 9.06-9.24 (m, 2H), 8.15 (d, J = 5.4 Hz, 1H), 6.97-7.05 (m, 2H), 6.96 (d, J = 5.4 Hz, 1H), 4.68-4.99 (m, 1H), 3.57-3.92 (m, 4H), 3.30-3.38 (m, 2H), 1.79-2.18 (m, 4H), 1.25 (s, 3H), 1.17 (s, 3H)

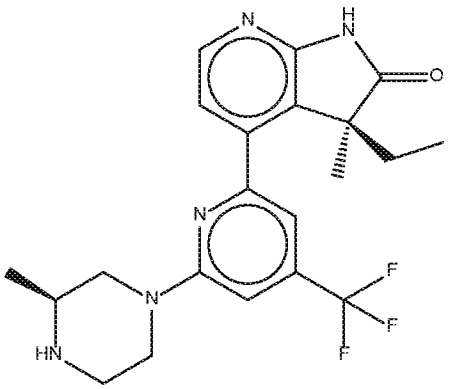
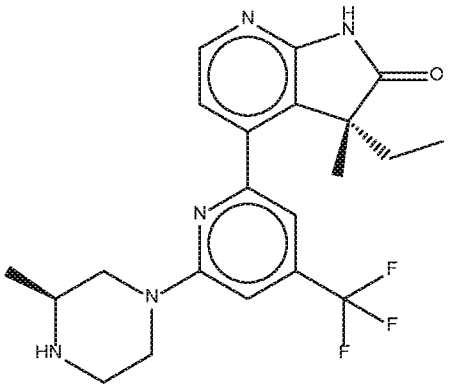
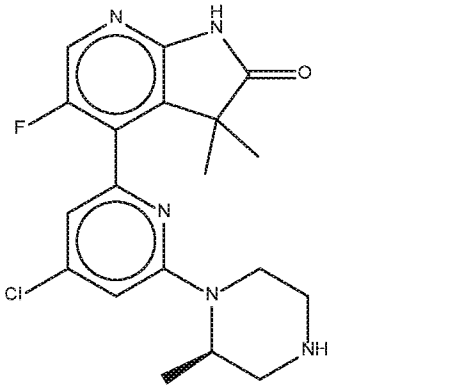
138		Pyridine (using compound II' obtained from OHMe isomer 1)	420	1H NMR (500 MHz, DMSO-d6): δ ppm 11.11 (s, 1 H), 8.92 - 9.58 (m, 2 H), 8.15 - 8.27 (m, 1 H), 8.05 - 8.11 (m, 1 H), 7.37 - 7.54 (m, 1 H), 6.86 - 7.15 (m, 1 H), 5.99 - 6.81 (m, 1 H), 4.49 - 5.23 (m, 1 H), 3.82 - 3.95 (m, 2 H), 3.67 - 3.75 (m, 1 H), 3.30 - 3.41 (m, 2 H), 1.75 - 2.25 (m, 4 H), 1.30 (s, 3 H)
139		Pyridine (using compound II' obtained from OHMe isomer 1)	388; 389,9	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.09 (s, 1H), 9.23 (br s, 1H), 8.85 (br s, 1H), 8.18 (d, J = 5.6 Hz, 1H), 7.84 (d, J = 1.3 Hz, 1H), 7.37 (d, J = 5.6 Hz, 1H), 7.12 (d, J = 1.3 Hz, 1H), 6.50 (br s, 1H), 4.64 (br s, 1H), 4.47 (br d, J = 14.4 Hz, 1H), 3.95-4.05 (m, 1H), 3.34 (br d, J = 12.6 Hz, 1H), 3.20-3.27 (m, 2H), 3.09-3.16 (m, 1H), 2.91-3.00 (m, 1H), 1.69-1.85 (m, 2H), 1.29 (s, 3H), 0.84 (t, J = 7.4 Hz, 3H)
140		Pyridine	372; 373,9	1H NMR (500 MHz, DMSO-d6) Shift 11.13 (s, 1H), 9.42 (br d, J=9.05 Hz, 1H), 8.98 (br d, J=9.05 Hz, 1H), 8.13 (d, J=5.72 Hz, 1H), 7.08 (s, 1H), 6.91 (d, J=5.70 Hz, 1H), 6.87 (s, 1H), 4.74-4.83 (m, 1H), 4.28 (br d, J=13.45 Hz, 1H), 3.12-3.32 (m, 4H), 2.92-3.02 (m, 1H), 1.25 (d, J=6.85 Hz, 3H), 1.19 (d, J=6.11 Hz, 6H)

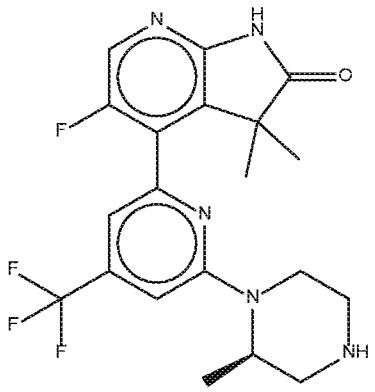
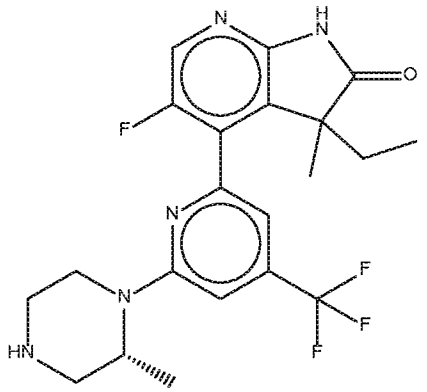
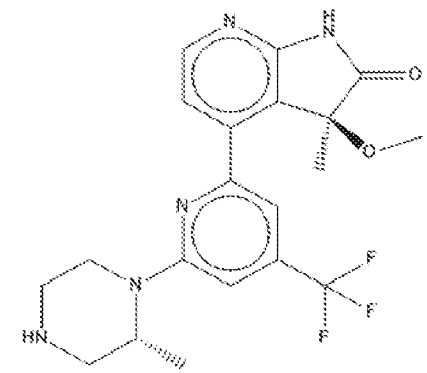
141		Pyridine	406.1	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.15 (s, 1H), 8.85-9.36 (m, 2H), 8.15 (d, J = 5.3 Hz, 1H), 7.36 (s, 1H), 7.04 (s, 1H), 6.95 (d, J = 5.3 Hz, 1H), 4.39-4.53 (m, 2H), 3.53-3.61 (m, 1H), 3.23-3.38 (m, 3H), 3.08 (br dd, J = 14.2, 10.6 Hz, 2H), 1.27 (d, J = 6.5 Hz, 3H), 1.19 (d, J = 14.4 Hz, 6H)
142		Pyridine	420.1	1H NMR (600 MHz, DMSO-d6) Shift 11.16 (s, 1H), 9.20-9.27 (m, 1H), 9.16 (br d, J=9.98 Hz, 1H), 8.15 (d, J=5.28 Hz, 1H), 7.37 (s, 1H), 7.04 (s, 1H), 6.95 (d, J=5.43 Hz, 1H), 4.42-4.55 (m, 2H), 3.26-3.41 (m, 2H), 3.12-3.20 (m, 1H), 3.02-3.12 (m, 2H), 1.60-1.72 (m, 2H), 1.16-1.27 (m, 6H), 0.97 (t, J=7.56 Hz, 3H)
143		Pyridine	402,0; 403,9	1H NMR (600 MHz, DMSO-d6) δ ppm 11.12 (s, 1 H), 8.85 - 9.60 (m, 2 H), 8.20 (d, J=5.58 Hz, 1 H), 7.80 (dd, J=7.34, 1.32 Hz, 1 H), 7.29 - 7.38 (m, 1 H), 7.19 - 7.25 (m, 1 H), 6.55 (s, 1 H), 4.34 - 4.56 (m, 2 H), 3.24 - 3.37 (m, 2 H), 3.11 - 3.20 (m, 1 H), 3.00 - 3.10 (m, 2 H), 1.81 (m, J=7.60 Hz, 2 H), 1.59 - 1.72 (m, 2 H), 1.01 (q, J=7.63 Hz, 3 H), 0.37 (td, J=7.48, 1.32 Hz, 3 H)

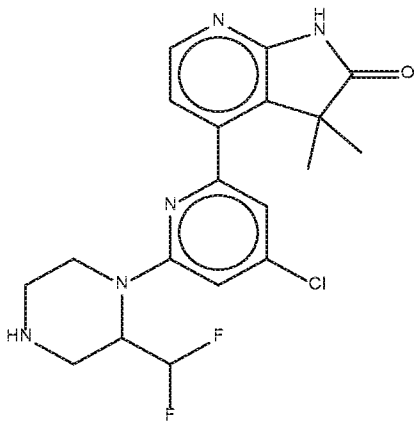
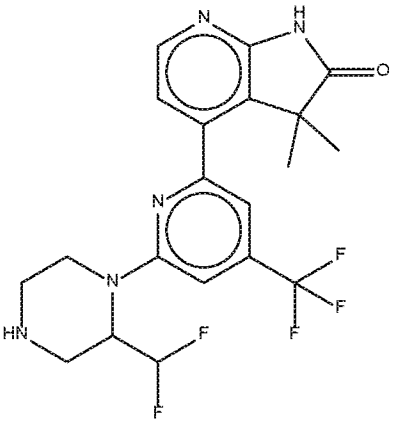
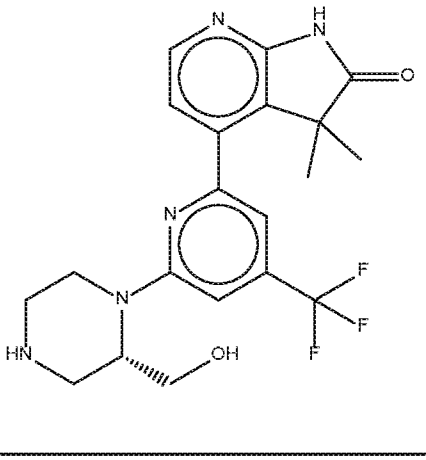
144		Pyridine	420	1H NMR (500 MHz, DMSO-d6) Shift 11.19 (s, 1H), 9.40 (br d, J=10.52 Hz, 1H), 8.96 (br s, 1H), 8.16 (dd, J=0.86, 5.26 Hz, 1H), 7.25 (d, J=4.40 Hz, 1H), 6.99 (s, 1H), 6.94 (t, J=4.82 Hz, 1H), 4.87 (br d, J=5.87 Hz, 1H), 4.36 (br d, J=12.72 Hz, 1H), 3.24-3.36 (m, 3H), 3.14-3.23 (m, 1H), 2.95-3.05 (m, 1H), 1.65-1.73 (m, 1H), 1.39-1.50 (m, 1H), 1.27 (d, J=7.09 Hz, 3H), 1.16 (d, J=3.91 Hz, 3H), 0.49 (dt, J=4.40, 7.34 Hz, 3H)
145		Pyridine	386	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.14 (s, 1H), 9.01-9.34 (m, 2H), 8.13 (d, J = 5.4 Hz, 1H), 7.21 (d, J = 1.2 Hz, 1H), 6.92 (d, J = 5.4 Hz, 1H), 6.89 (d, J = 1.2 Hz, 1H), 4.32-4.47 (m, 2H), 2.91-3.38 (m, 5H), 1.49-1.81 (m, 2H), 1.15-1.28 (m, 6H), 0.97 (t, J = 7.5 Hz, 3H)
146		Pyridine	386; 387,9	1H NMR (500 MHz, DMSO-d6) Shift 11.17 (s, 1H), 9.40 (br s, 1H), 8.95 (br s, 1H), 8.14 (d, J=5.38 Hz, 1H), 7.08 (d, J=3.42 Hz, 1H), 6.90 (dd, J=3.79, 5.26 Hz, 1H), 6.85 (s, 1H), 4.77 (br s, 1H), 4.27 (br d, J=13.69 Hz, 1H), 2.88-3.35 (m, 5H), 1.64-1.74 (m, 1H), 1.47-1.58 (m, 1H), 1.16-1.28 (m, 6H), 0.48 (dt, J=3.42, 7.21 Hz, 3H)

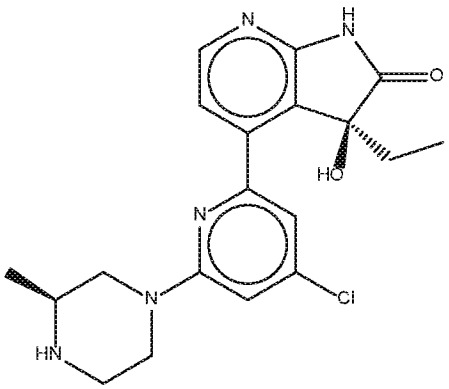
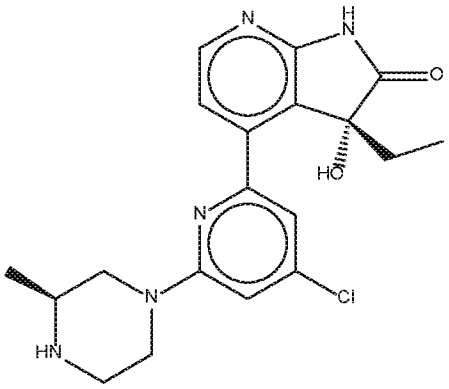
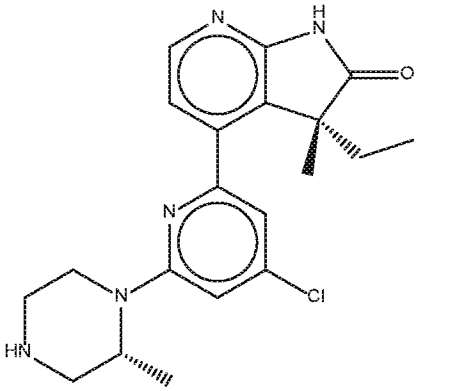
147		Pyridine	386; 388	1H NMR (600 MHz, DMSO-d6) δ 11.16 (s, 1H), 9.35 (br d, J=9.68 Hz, 1H), 9.18 (br d, J=9.39 Hz, 1H), 8.14 (d, J=5.28 Hz, 1H), 7.18 (d, J=1.32 Hz, 1H), 6.91 (d, J=5.28 Hz, 1H), 6.86 (d, J=1.47 Hz, 1H), 4.31-4.40 (m, 2H), 3.21-3.36 (m, 3H), 2.97-3.09 (m, 2H), 1.65-1.72 (m, 1H), 1.54-1.62 (m, 1H), 1.26 (dd, J=1.98, 6.53 Hz, 3H), 1.18 (d, J=6.60 Hz, 3H), 0.49 (dt, J=2.57, 7.37 Hz, 3H)
148		Pyridine	366.1	1H NMR (600 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.12 (br d, J=9.24 Hz, 1H), 9.01 (br s, 1H), 8.13 (d, J=5.28 Hz, 1H), 7.75 (dd, J=7.56, 8.29 Hz, 1H), 7.04 (dd, J=2.05, 8.66 Hz, 1H), 6.88 (d, J=5.28 Hz, 1H), 6.79 (dd, J=1.54, 7.12 Hz, 1H), 4.34-4.48 (m, 1H), 4.27-4.33 (m, 1H), 2.88-3.24 (m, 5H), 1.55-1.71 (m, 4H), 1.18 (d, J=5.58 Hz, 3H), 0.97 (dt, J=5.50, 7.52 Hz, 3H), 0.47 (dt, J=1.98, 7.37 Hz, 3H)
149		Pyridine (using compound II' obtained from OHMe isomer 1)	406	1H NMR (600 MHz, DMSO-d6) Shift 11.10 (s, 1H), 8.21 (d, J=5.58 Hz, 1H), 8.06 (s, 1H), 7.48 (d, J=5.43 Hz, 1H), 6.94 (s, 1H), 6.65 (s, 1H), 3.65-3.79 (m, 6H), 2.51-2.57 (m, 1H), 1.67-2.18 (m, 1H), 1.51 (d, J=8.51 Hz, 1H), 1.31 (s, 3H)

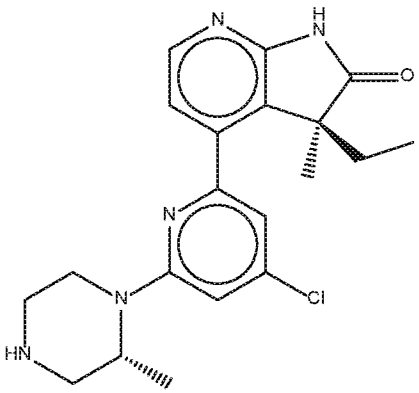
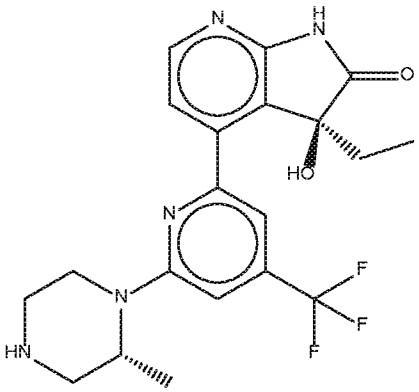
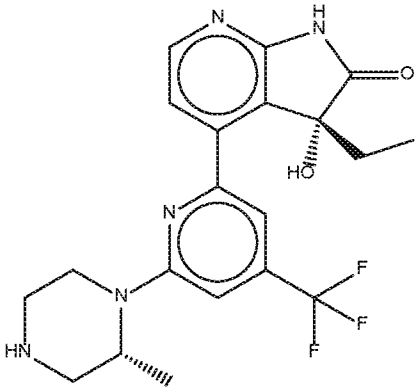
150		Pyridine	404	1H NMR (600 MHz, DMSO-d6) Shift 11.12 (s, 1H), 8.14 (d, J=5.43 Hz, 1H), 6.91-6.97 (m, 3H), 3.65-3.78 (m, 6H), 2.51-2.58 (m, 1H), 1.52 (d, J=8.66 Hz, 1H), 1.21-1.27 (s, 6H), 1.07-1.62 (br s, 1H)
151		Pyridine (using compound II' obtained from OHMe isomer 2)	402,0; 403,9	1H NMR (600 MHz, DMSO-d6, 300K) δ ppm 9.12 - 11.20 (m, 1 H), 8.36 (d, J=5.4 Hz, 1 H), 7.48 (d, J=5.4 Hz, 1 H), 7.40 (d, J=1.3 Hz, 1 H), 7.14 (d, J=1.3 Hz, 1 H), 4.21 - 4.42 (m, 2 H), 3.13 (s, 3 H), 3.05 - 3.10 (m, 1 H), 2.93 (td, J=12.1, 3.2 Hz, 1 H), 2.73 - 2.79 (m, 1 H), 2.52 - 2.59 (m, 2 H), 2.68 - 2.25 (br s, 1 H), 1.40 - 1.57 (m, 5 H), 1.05 (t, J=7.6 Hz, 3 H)
152		Pyridine (using compound II' obtained from OHMe isomer 2)	402,0; 403,9	1H NMR (600 MHz, DMSO-d6, 300K) δ ppm 8.24 (d, J=5.4 Hz, 1 H), 7.36 (d, J=5.6 Hz, 1 H), 7.27 (d, J=1.3 Hz, 1 H), 7.01 (d, J=1.3 Hz, 1 H), 4.14 - 4.33 (m, 2 H), 3.00 (s, 2 H), 2.93 - 2.99 (m, 2 H), 2.79 (td, J=12.0, 3.2 Hz, 1 H), 2.66 (td, J=11.7, 3.1 Hz, 1 H), 2.41 - 2.49 (m, 2 H), 1.27 - 1.48 (m, 6 H), 0.92 (t, J=7.6 Hz, 3 H)

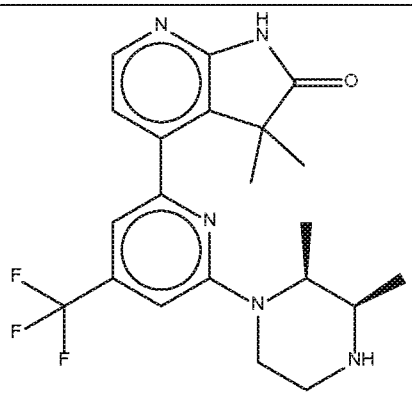
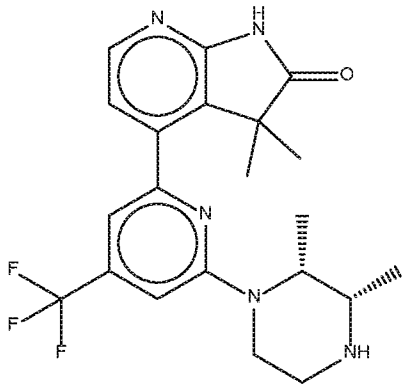
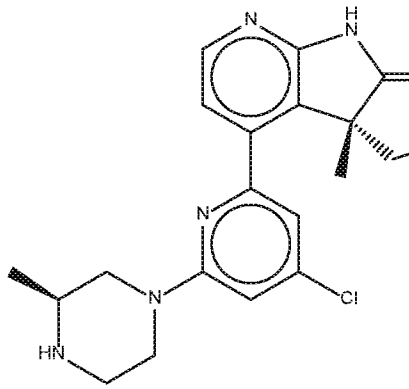
153		Pyridine (using compound II' obtained from MeEt isomer 1)	420.1	1H NMR (600 MHz, DMSO-d6) δ 11.15 (s, 1H), 8.15 (d, J=5.28 Hz, 1H), 7.17 (s, 1H), 6.94 (d, J=5.43 Hz, 1H), 6.86 (s, 1H), 4.26 (br dd, J=13.94, 16.58 Hz, 2H), 2.99 (br d, J=12.03 Hz, 1H), 2.81-2.93 (m, 1H), 2.67-2.77 (m, 2H), 1.51-1.77 (m, 3H), 1.11-1.19 (m, 4H), 1.01-1.05 (m, 3H), 0.48 (t, J=7.34 Hz, 2H), 0.41-0.56 (m, 1H)
154		Pyridine (using compound II' obtained from OHMe isomer 2)	420.1	1H NMR (600 MHz, DMSO-d6) δ 11.15 (s, 1H), 8.14 (d, J=5.43 Hz, 1H), 7.14 (s, 1H), 6.94 (d, J=5.43 Hz, 1H), 6.83 (s, 1H), 4.25 (br d, J=11.59 Hz, 1H), 4.20 (br d, J=12.47 Hz, 1H), 2.88-2.98 (m, 1H), 2.82 (dt, J=3.08, 12.10 Hz, 1H), 2.60-2.71 (m, 2H), 2.43-2.48 (m, 1H), 1.57-1.72 (m, 2H), 1.09-1.19 (m, 3H), 1.00 (d, J=6.31 Hz, 3H), 0.49 (t, J=7.34 Hz, 3H)
155		Pyridine	390,3; 392,2	1H NMR (500 MHz, DMSO-D6, 300 K) δ (ppm) = 11.21 (s, 1H), 9.30 (br d, J = 10.5 Hz, 1H), 8.98 - 8.70 (m, 1H), 8.18 (d, J = 2.0 Hz, 1H), 7.12 (d, J = 1.5 Hz, 1H), 6.96 (d, J = 1.0 Hz, 1H), 5.02 - 4.64 (m, 1H), 4.27 (br d, J = 13.7 Hz, 1H), 3.32 - 3.11 (m, 4H), 2.99 (br d, J = 11.7 Hz, 1H), 1.23 (d, J = 6.8 Hz, 3H), 1.14 (s, 3H), 1.13 (s, 3H)

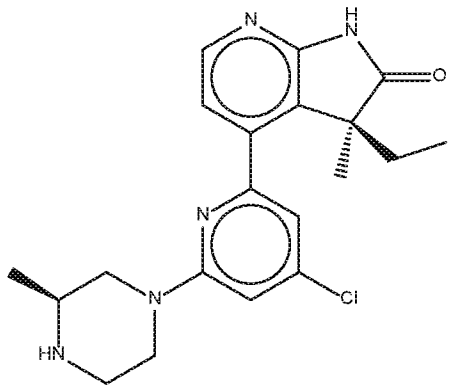
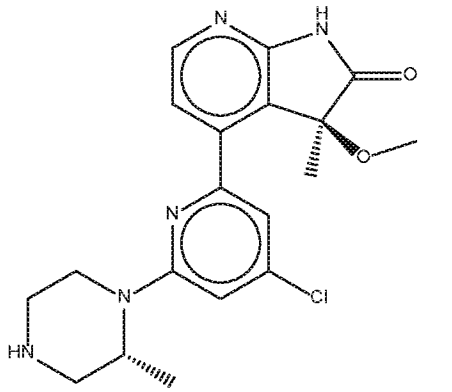
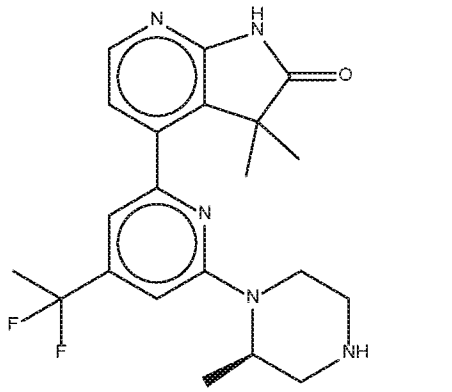
156		Pyridine	424.3	1H NMR (500 MHz, DMSO-D6, 300 K) δ (ppm) = 11.24 (s, 1H), 9.48 - 9.13 (m, 1H), 9.03 - 8.69 (m, 1H), 8.20 (d, J = 2.0 Hz, 1H), 7.29 (s, 1H), 7.13 (s, 1H), 4.93 - 4.78 (m, 1H), 4.43 - 4.30 (m, 1H), 3.29 - 2.93 (m, 5H), 1.25 (d, J = 7.1 Hz, 3H), 1.11 (d, J = 3.7 Hz, 6H)
157		Pyridine	438.3	1H NMR (500 MHz, DMSO-d6) δ 11.27 (s, 1H), 9.82 – 8.55 (m, 2H), 8.21 (s, 1H), 7.41 – 7.22 (m, 1H), 7.17 – 7.03 (m, 1H), 4.99 – 4.73 (m, 1H), 4.48 – 4.23 (m, 1H), 3.30 – 3.24 (m, 4H), 3.09 – 2.92 (m, 1H), 1.73 – 1.54 (m, 1H), 1.35 – 1.21 (m, 4H), 1.11 (s, 3H), 0.66 – 0.24 (m, 3H)
158		Pyridine (using compound II' obtained from OHMe isomer 1)	422.1	1H NMR (500 MHz, DMSO-D6, 300 K) δ (ppm) = 11.15 (s, 1H), 9.85 - 8.38 (m, 2H), 8.15 (d, J = 5.4 Hz, 1H), 7.26 (s, 1H), 6.99 (s, 1H), 6.94 (d, J = 5.4 Hz, 1H), 5.14 (br t, J = 5.0 Hz, 1H), 4.72 - 4.59 (m, 1H), 4.49 (br d, J = 14.4 Hz, 1H), 3.83 - 3.63 (m, 2H), 3.48 (br d, J = 13.0 Hz, 1H), 3.32 (br s, 2H), 3.24 - 3.11 (m, 1H), 3.08 - 2.91 (m, 1H), 1.20 (s, 3H), 1.16 (s, 3H)

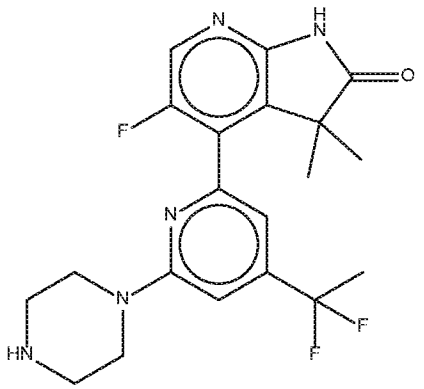
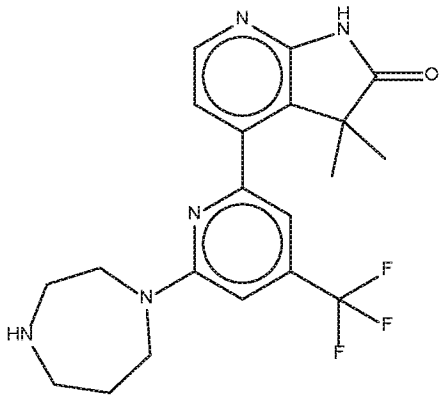
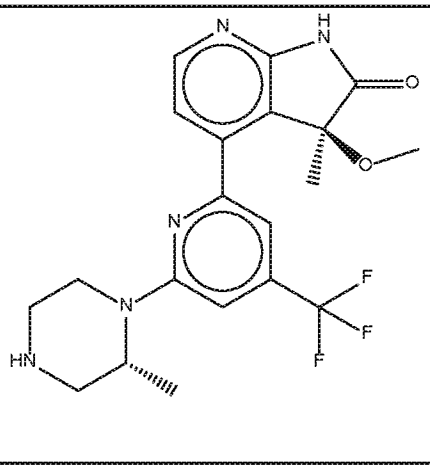
159		Pyridine	408, 410	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.13 (s, 1H), 9.07-9.70 (m, 2H), 8.13 (d, J = 5.4 Hz, 1H), 7.24 (d, J = 1.3 Hz, 1H), 6.94 (d, J = 1.3 Hz, 1H), 6.90 (d, J = 5.4 Hz, 1H), 6.68 (td, J = 55.0, 5.8 Hz, 1H), 5.07-5.21 (m, 1H), 4.46 (br d, J = 14.2 Hz, 1H), 3.32-3.53 (m, 4H), 2.98-3.09 (m, 1H), 1.15-1.22 (m, 6H)
160		Pyridine	442.3	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.17 (s, 1H), 9.00-9.61 (m, 2H), 8.16 (d, J = 5.4 Hz, 1H), 7.42 (s, 1H), 7.11 (s, 1H), 6.95 (d, J = 5.4 Hz, 1H), 6.65 (td, J = 55.0, 5.4 Hz, 1H), 5.15-5.33 (m, 1H), 4.47-4.66 (m, 1H), 3.77-3.79 (m, 1H), 3.52-3.57 (m, 1H), 3.31-3.52 (m, 3H), 3.00-3.15 (m, 1H), 1.19 (s, 3H), 1.15 (s, 3H)
161		Pyridine	422.4	1H NMR (600 MHz, DMSO-D6, 300 K) δ (ppm) = 11.15 (s, 1H), 9.81 - 8.21 (m, 2H), 8.15 (d, J = 5.4 Hz, 1H), 7.25 (s, 1H), 6.99 (s, 1H), 6.94 (d, J = 5.4 Hz, 1H), 5.28 - 4.97 (m, 1H), 4.66 (br d, J = 5.6 Hz, 1H), 4.48 (br d, J = 13.5 Hz, 1H), 3.85 - 3.60 (m, 2H), 3.47 (br d, J = 12.9 Hz, 1H), 3.33 (br d, J = 2.9 Hz, 2H), 3.16 (dd, J = 4.9, 13.0 Hz, 1H), 3.05 - 2.91 (m, 1H), 1.20 (s, 3H), 1.16 (s, 3H)

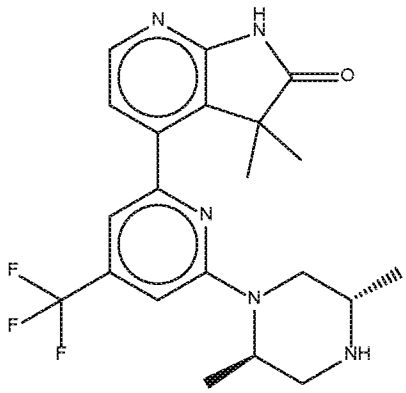
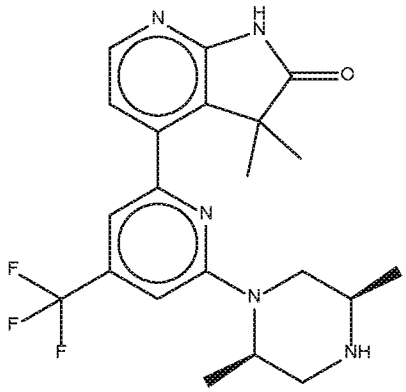
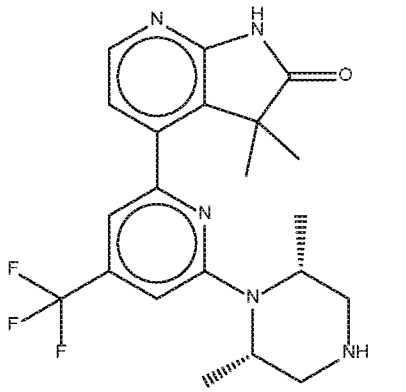
162		Pyridine (using racemic mixture and chiral separation with method A, OHEt isomer 1)	388,1; 399,0	1H NMR (500 MHz, DMSO-D6, 300 K) δ (ppm) = 11.27 - 10.86 (m, 1H), 8.19 (d, J = 5.4 Hz, 1H), 7.63 (d, J = 1.5 Hz, 1H), 7.31 (d, J = 5.6 Hz, 1H), 7.01 (d, J = 1.5 Hz, 1H), 6.55 (s, 1H), 4.16 (br d, J = 12.2 Hz, 2H), 2.94 (br d, J = 11.5 Hz, 1H), 2.82 - 2.61 (m, 3H), 2.43 (dd, J = 10.5, 12.5 Hz, 1H), 1.88 - 1.69 (m, 2H), 1.02 (d, J = 6.4 Hz, 4H), 0.39 (t, J = 7.5 Hz, 3H)
163		Pyridine (using racemic mixture and chiral separation with method A, OHEt isomer 2)	388,1; 399,0	1H NMR (500 MHz, DMSO-D6, 300 K) δ (ppm) = 11.34 - 10.88 (m, 1H), 8.19 (d, J = 5.4 Hz, 1H), 7.62 (d, J = 1.5 Hz, 1H), 7.31 (d, J = 5.4 Hz, 1H), 7.01 (d, J = 1.5 Hz, 1H), 6.55 (s, 1H), 4.22 - 4.10 (m, 2H), 2.97 - 2.90 (m, 1H), 2.86 - 2.74 (m, 1H), 2.73 - 2.60 (m, 2H), 2.41 (dd, J = 10.4, 12.3 Hz, 1H), 1.87 - 1.72 (m, 2H), 1.19 (br d, J = 5.9 Hz, 1H), 1.02 (d, J = 6.4 Hz, 3H), 0.39 (t, J = 7.5 Hz, 3H)
164		Pyridine (using compound II' obtained from MeEt isomer 2)	386,3; 388,3	1H NMR (600 MHz, DMSO-d6) δ ppm 11.12 (br s, 1 H), 8.12 (d, J=5.43 Hz, 1 H), 6.90 (d, J=5.43 Hz, 1 H), 6.88 (d, J=1.32 Hz, 1 H), 6.69 (d, J=1.32 Hz, 1 H), 4.37 - 4.45 (m, 1 H), 3.89 - 3.96 (m, 1 H), 3.26 - 3.29 (m, 1 H), 2.90 - 3.00 (m, 2 H), 2.73 - 2.84 (m, 2 H), 2.53 - 2.63 (m, 1 H), 1.52 - 1.76 (m, 2 H), 1.19 (s, 3 H), 1.14 (d, J=6.75 Hz, 3 H), 0.47 (t, J=7.34 Hz, 3 H)

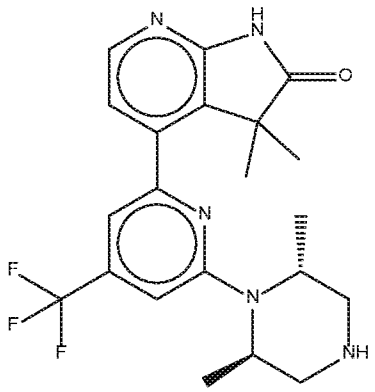
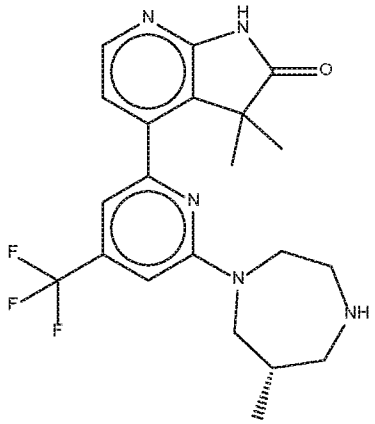
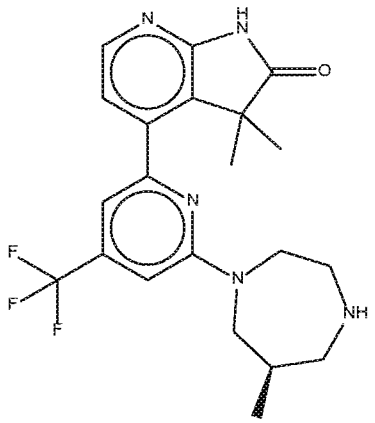
165		Pyridine (using compound II' obtained from MeEt isomer 1)	386,3; 388,3	1H NMR (600 MHz, DMSO-d6) δ ppm 11.21 (s, 1 H), 8.12 (d, J=5.43 Hz, 1 H), 6.89 - 6.92 (m, 1 H), 6.87 - 6.89 (m, 1 H), 6.68 - 6.70 (m, 1 H), 4.36 - 4.48 (m, 1 H), 3.88 - 3.97 (m, 1 H), 3.22 - 3.29 (m, 1 H), 2.89 - 3.00 (m, 2 H), 2.73 - 2.86 (m, 2 H), 2.54 - 2.64 (m, 1 H), 1.55 - 1.81 (m, 2 H), 1.18 (s, 3 H), 1.14 (d, J=6.75 Hz, 3 H), 0.45 - 0.50 (m, 3 H)
166		Pyridine (using racemic mixture and chiral separation with method B, OHEt isomer 1)	422.1	1H NMR (600 MHz, DMSO-d6) δ ppm 11.05 (s, 1 H), 8.20 (d, J=5.58 Hz, 1 H), 7.87 (s, 1 H), 7.29 - 7.42 (m, 1 H), 7.07 (s, 1 H), 6.55 (s, 1 H), 4.45 - 4.59 (m, 1 H), 4.02 - 4.13 (m, 1 H), 3.31 - 3.33 (m, 1 H), 2.95 - 3.07 (m, 2 H), 2.73 - 2.88 (m, 2 H), 2.55 - 2.65 (m, 1 H), 1.66 - 1.86 (m, 2 H), 1.14 (d, J=6.60 Hz, 3 H), 0.37 (t, J=7.48 Hz, 3 H)
167		Pyridine (using racemic mixture and chiral separation with method B, OHEt isomer 2)	422.1	1H NMR (600 MHz, DMSO-d6) δ ppm 11.10 (s, 1 H), 8.21 (d, J=5.58 Hz, 1 H), 7.97 (s, 1 H), 7.38 (d, J=5.58 Hz, 1 H), 7.00 - 7.12 (m, 1 H), 6.57 (s, 1 H), 4.47 - 4.60 (m, 1 H), 3.94 - 4.09 (m, 1 H), 2.93 - 3.07 (m, 2 H), 2.77 - 2.85 (m, 2 H), 2.57 - 2.67 (m, 1 H), 1.66 - 1.85 (m, 2 H), 1.20 (d, J=6.60 Hz, 3 H), 0.37 (t, J=7.56 Hz, 3 H)

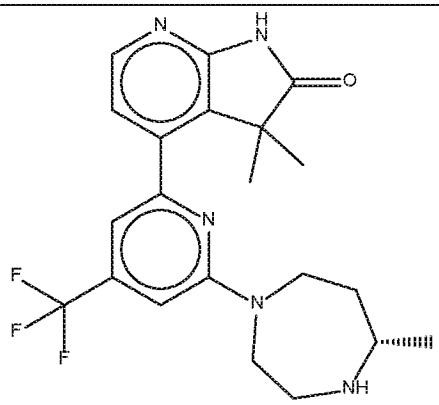
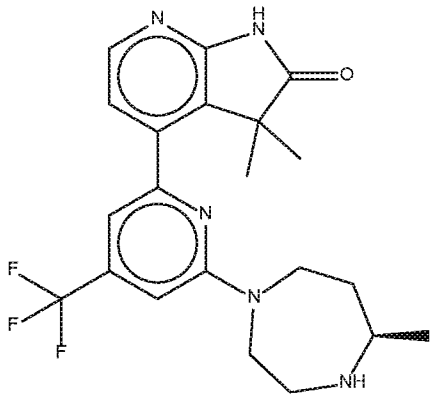
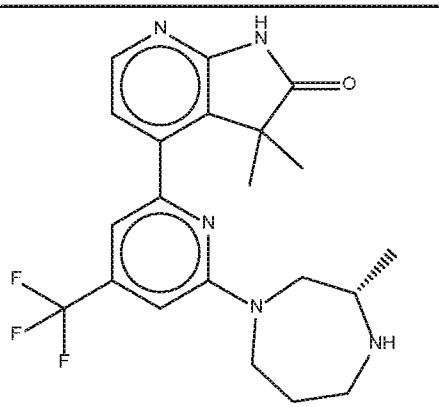
168		Pyridine	420.1	1H NMR (600 MHz, DMSO-d6) δ ppm 11.13 (s, 1 H), 8.14 (d, J=5.43 Hz, 1 H), 7.35 - 8.02 (m, 1 H), 7.15 - 7.28 (m, 1 H), 6.95 (s, 2 H), 4.53 - 4.78 (m, 1 H), 4.15 - 4.33 (m, 1 H), 3.17 - 3.24 (m, 1 H), 3.11 - 3.17 (m, 1 H), 2.99 - 3.12 (m, 1 H), 2.79 - 2.95 (m, 1 H), 1.17 - 1.21 (m, 6 H), 1.07 - 1.14 (m, 6 H)
169		Pyridine	420.1	1H NMR (600 MHz, DMSO-d6) δ ppm 11.12 (s, 1 H), 8.14 (d, J=5.43 Hz, 1 H), 7.34 - 8.01 (m, 1 H), 7.14 (s, 1 H), 6.95 (d, J=5.43 Hz, 1 H), 6.89 (s, 1 H), 4.41 - 4.62 (m, 1 H), 3.99 - 4.26 (m, 1 H), 2.70 - 3.12 (m, 4 H), 1.18 (d, J=13.94 Hz, 6 H), 1.03 - 1.07 (m, 6 H)
170		Pyridine (using compound II' obtained from MeEt isomer 2)	386,1; 388,0	1H NMR (600 MHz, DMSO-d6) δ ppm 11.05 (s, 1 H), 8.12 (d, J=5.43 Hz, 1 H), 6.96 (d, J=1.32 Hz, 1 H), 6.90 (d, J=5.43 Hz, 1 H), 6.69 (d, J=1.32 Hz, 1 H), 4.02 - 4.20 (m, 2 H), 3.66 - 3.90 (m, 1 H), 2.85 - 2.95 (m, 1 H), 2.72 - 2.81 (m, 1 H), 2.55 - 2.69 (m, 2 H), 2.40 (dd, J=12.40, 10.34 Hz, 1 H), 1.61 - 1.74 (m, 2 H), 1.16 (s, 3 H), 0.99 (d, J=6.16 Hz, 3 H), 0.49 (t, J=7.34 Hz, 3 H)

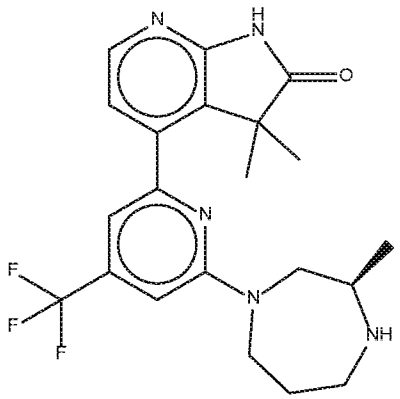
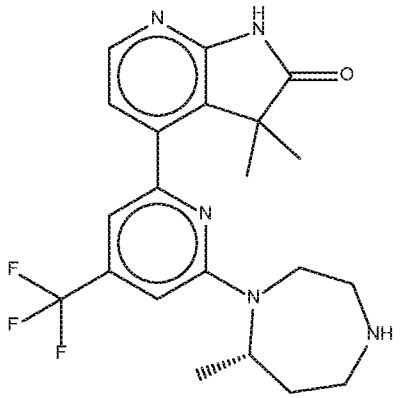
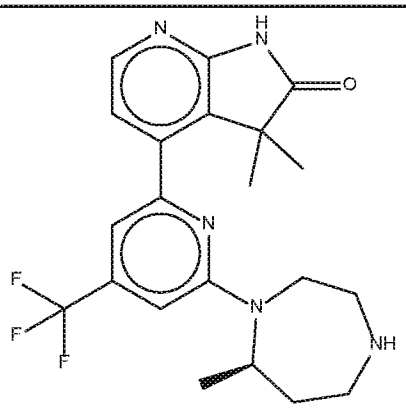
171		Pyridine (using compound II' obtained from MeEt isomer 1)	386,1; 388,1	1H NMR (600 MHz, DMSO-d6) δ ppm 11.15 (s, 1 H), 8.12 (d, J=5.28 Hz, 1 H), 6.95 - 6.98 (m, 1 H), 6.90 (d, J=5.28 Hz, 1 H), 6.70 (d, J=1.32 Hz, 1 H), 4.07 - 4.19 (m, 2 H), 3.15 - 3.26 (m, 1 H), 2.58 - 2.93 (m, 4 H), 2.36 - 2.43 (m, 1 H), 1.61 - 1.73 (m, 2 H,) 1.18 (s, 3 H), 0.98 (d, J=6.46 Hz, 3 H), 0.48 (t, J=7.48 Hz, 3 H)
172		Pyridine (using compound II' obtained from OHMe isomer 1)	388,3; 390,2	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.41 (s, 1H), 9.43 (br d, J = 10.3 Hz, 1H), 8.99 (br d, J = 10.0 Hz, 1H), 8.26 (d, J = 5.4 Hz, 1H), 7.34-7.55 (m, 2H), 7.11 (d, J = 1.0 Hz, 1H), 4.82-4.98 (m, 1H), 4.32-4.50 (m, 1H), 3.09-3.36 (m, 4H), 3.03 (s, 3H), 2.91-3.01 (m, 1H), 1.35 (s, 3H), 1.26 (d, J = 6.8 Hz, 3H)
173		Pyridine (using specific pyridine 1 as compound II)	402.3	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.13 (s, 1H), 9.24-9.53 (m, 1H), 8.78-9.08 (m, 1H), 8.14 (d, J = 5.4 Hz, 1H), 7.04 (s, 1H), 6.93 (d, J = 5.4 Hz, 1H), 6.90 (s, 1H), 4.77-4.91 (m, 1H), 4.33 (br d, J = 15.2 Hz, 1H), 2.88-3.36 (m, 5H), 1.99 (t, J = 19.1 Hz, 3H), 1.26 (d, J = 7.1 Hz, 3H), 1.18 (d, J = 9.3 Hz, 6H)

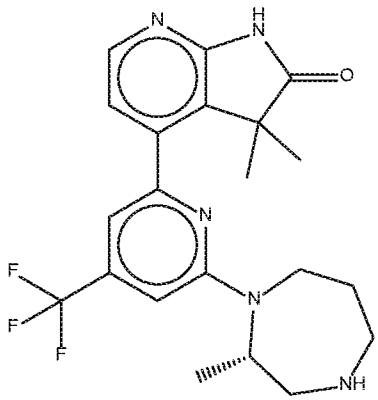
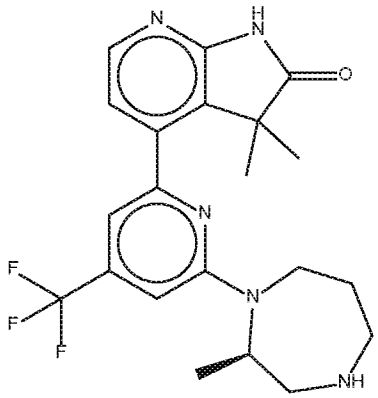
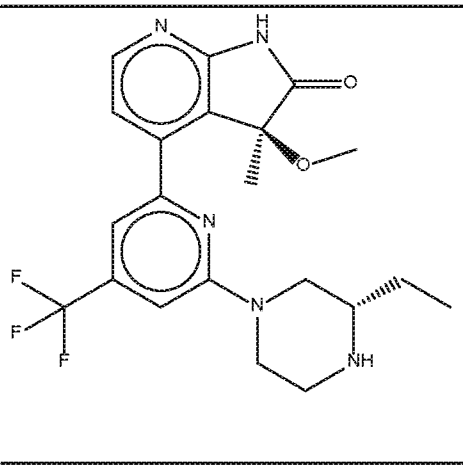
174		Pyridine (using specific pyridine 1 as compound II)	406.1	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.20 (s, 1H), 9.00 (br s, 2H), 8.18 (d, J = 1.9 Hz, 1H), 7.14 (s, 1H), 6.97 (s, 1H), 3.76-3.86 (m, 4H), 3.36-3.38 (m, 1H), 3.18 (br s, 4H), 1.98 (t, J = 19.2 Hz, 3H), 1.11 (s, 6H)
175		Pyridine	406.3	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.15 (s, 1H), 9.01 (br s, 2H), 8.15 (d, J = 5.4 Hz, 1H), 7.08 (s, 1H), 6.89-6.99 (m, 2H), 3.97-4.02 (m, 2H), 3.77 (t, J = 5.9 Hz, 2H), 3.12-3.29 (m, 4H), 2.07 (dt, J = 10.7, 5.5 Hz, 2H), 1.12-1.30 (m, 6H)
176		Pyridine (using compound II' obtained from OHMe isomer 1)	422	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.12-11.63 (m, 1H), 8.27 (d, J = 5.6 Hz, 1H), 7.53 (s, 1H), 7.46 (d, J = 5.6 Hz, 1H), 7.09 (s, 1H), 4.47-4.66 (m, 1H), 4.13 (br d, J = 13.0 Hz, 1H), 2.74-3.09 (m, 8H), 2.55-2.66 (m, 1H), 1.35 (s, 3H), 1.17 (d, J = 6.6 Hz, 3H)

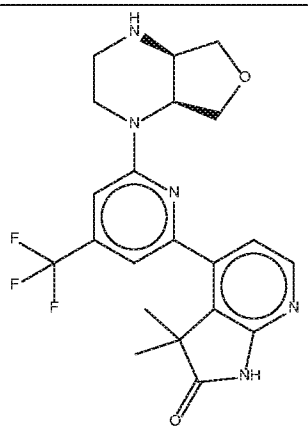
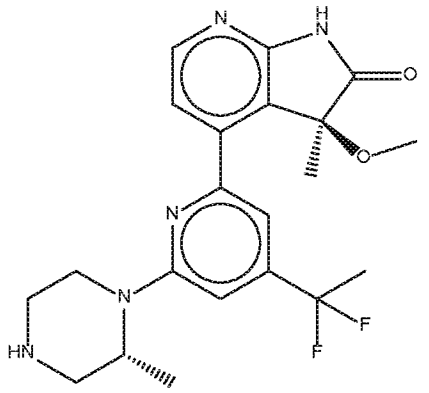
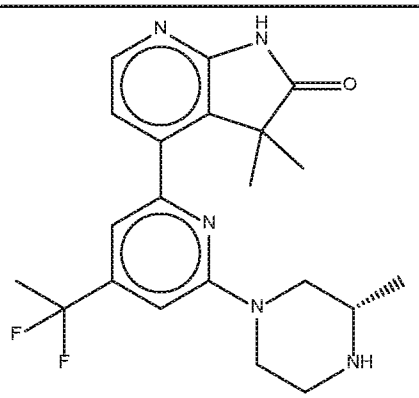
177		Pyridine	420.1	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.16 (s, 1H), 8.92-9.34 (m, 2H), 8.15 (d, J = 5.4 Hz, 1H), 7.24 (s, 1H), 7.01 (s, 1H), 6.95 (d, J = 5.4 Hz, 1H), 4.73-4.86 (m, 1H), 4.24 (br d, J = 14.2 Hz, 1H), 3.63-3.75 (m, 1H), 3.32-3.49 (m, 2H), 3.10 (br dd, J = 13.2, 2.0 Hz, 1H), 1.25-1.30 (m, 6H), 1.10-1.22 (m, 6H)
178		Pyridine	420.1	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.16 (s, 1H), 9.63 (br d, J = 9.8 Hz, 1H), 8.83 (br d, J = 9.8 Hz, 1H), 8.15 (d, J = 5.4 Hz, 1H), 7.29 (s, 1H), 7.02 (s, 1H), 6.95 (d, J = 5.4 Hz, 1H), 4.92 (br s, 1H), 4.41 (br d, J = 13.4 Hz, 1H), 3.17-3.32 (m, 3H), 2.99 (dd, J = 14.1, 11.9 Hz, 1H), 1.33 (d, J = 6.6 Hz, 3H), 1.27 (d, J = 7.1 Hz, 3H), 1.15-1.22 (m, 6H)
179		Pyridine	420.4	1H NMR (500 MHz, DMSO-d6) δ ppm 11.17 (s, 1 H), 8.87 - 9.94 (m, 2 H), 8.15 (d, J=5.38 Hz, 1 H), 7.11 (s, 1 H), 7.03 (s, 1 H), 6.90 - 6.97 (m, 1 H), 4.65 - 4.85 (m, 2 H), 3.11 - 3.33 (m, 4 H), 1.27 - 1.34 (m, 6 H), 1.17 (s, 6 H)

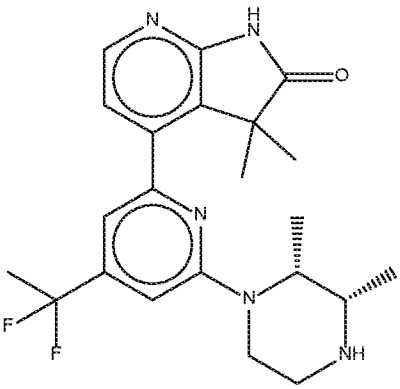
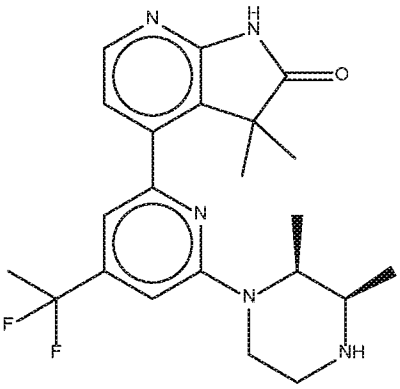
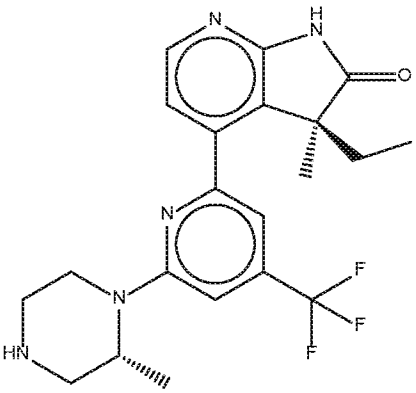
180		Pyridine	420.3	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.13 (br s, 1H), 8.14 (d, J = 5.3 Hz, 1H), 7.14 (s, 1H), 7.03 (s, 1H), 6.97 (d, J = 5.4 Hz, 1H), 3.99-4.07 (m, 2H), 3.21-3.26 (m, 1H), 3.14 (dd, J = 12.3, 3.8 Hz, 2H), 2.69 (dd, J = 12.3, 4.4 Hz, 2H), 1.33 (s, 3H), 1.13 (s, 3H), 1.12 (s, 3H), 1.10 (s, 3H)
181		Pyridine	420.4	1H NMR (500 MHz, DMSO-d6) δ ppm 11.12 (br s, 1 H), 8.13 (d, J=5.38 Hz, 1 H), 6.93 (d, J=5.38 Hz, 2 H), 6.80 (s, 1 H), 4.03 (br d, J=9.29 Hz, 2 H), 3.33 - 3.40 (m, 1 H), 3.26 - 3.30 (m, 1 H), 3.06 - 3.15 (m, 1 H), 2.88 - 2.95 (m, 1 H), 2.76 - 2.86 (m, 1 H), 2.63 - 2.71 (m, 1 H), 2.40 - 2.48 (m, 1 H), 1.81 - 2.03 (m, 1 H), 1.17 - 1.26 (m, 6 H), 0.74 - 0.90 (m, 3 H)
182		Pyridine	420.3	1H NMR (500 MHz, DMSO-d6) δ ppm 11.11 (s, 1 H), 8.13 (d, J=5.38 Hz, 1 H), 0.00 (d, J=5.38 Hz, 1 H), 6.90 - 6.93 (m, 1 H), 6.80 (s, 1 H), 4.03 (br dd, J=10.27, 2.20 Hz, 2 H), 3.32 - 3.39 (m, 1 H), 3.27 - 3.30 (m, 1 H), 3.06 - 3.14 (m, 1 H), 2.78 - 2.95 (m, 2 H), 2.61 - 2.70 (m, 1 H), 2.40 - 2.46 (m, 1 H), 1.89 - 2.04 (m, 1 H), 1.21 (s, 6 H), 0.84 (d, J=6.85 Hz, 3 H)

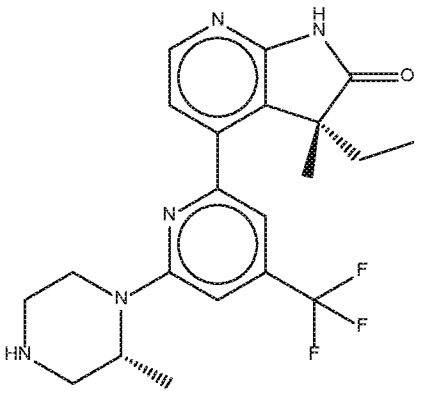
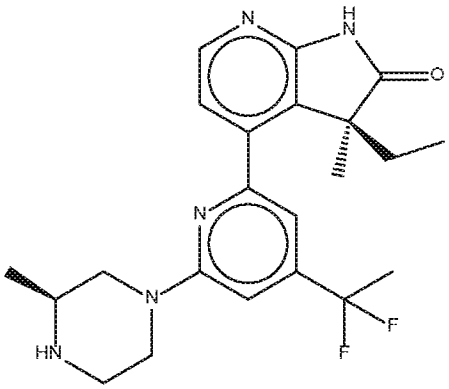
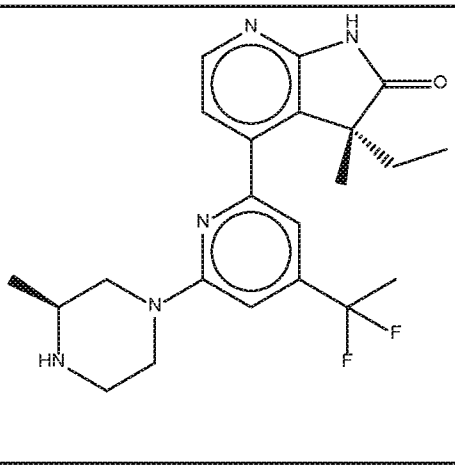
183		Pyridine	420.3	1H NMR (500 MHz, DMSO-d6) δ 11.09 (br s, 1H), 8.13 (d, J = 5.4 Hz, 1H), 7.00 – 6.92 (m, 1H), 6.91 – 6.87 (m, 1H), 6.80 (s, 1H), 4.01 – 3.88 (m, 1H), 3.86 – 3.73 (m, 1H), 3.62 – 3.54 (m, 1H), 3.52 – 3.43 (m, 1H), 3.39 – 3.32 (m, 1H), 3.11 – 3.00 (m, 1H), 2.82 – 2.73 (m, 1H), 2.66 – 2.56 (m, 1H), 1.90 – 1.79 (m, 1H), 1.38 – 1.28 (m, 1H), 1.21 (s, 6H), 1.00 (d, J = 6.4 Hz, 3H)
184		Pyridine	420.3	1H NMR (600 MHz, DMSO-d6) δ 12.16 – 9.15 (m, 1H), 8.13 (d, J = 5.4 Hz, 1H), 6.94 (d, J = 5.4 Hz, 1H), 6.89 (s, 1H), 6.80 (s, 1H), 4.08 – 3.88 (m, 1H), 3.86 – 3.75 (m, 1H), 3.64 – 3.53 (m, 1H), 3.51 – 3.44 (m, 1H), 3.40 – 3.32 (m, 1H), 3.10 – 3.03 (m, 1H), 2.83 – 2.74 (m, 1H), 2.66 – 2.56 (m, 1H), 1.88 – 1.81 (m, 1H), 1.39 – 1.29 (m, 1H), 1.21 (s, 6H), 0.99 (d, J = 6.3 Hz, 3H)
185		Pyridine	420.3	1H NMR (500 MHz, DMSO-d6) δ ppm 11.16 (s, 1 H), 8.79 - 9.35 (m, 2 H), 8.15 (d, J=5.38 Hz, 1 H), 7.07 - 7.11 (m, 1 H), 6.94 - 6.96 (m, 1 H), 6,92 (d, J=5.38 Hz, 1 H), 4.21 (m, J=1.50 Hz, 1 H), 4.00 (m, J=6.60 Hz, 1 H), 3.44 - 3.61 (m, 3 H), 3.27 - 3.37 (m, 1 H), 2.98 (m, J=13.40, 5.10 Hz, 1 H), 2.05 - 2.20 (m, 2 H), 1,25 (d, J=6.60 Hz, 3 H), 1.20 (s, 6 H)

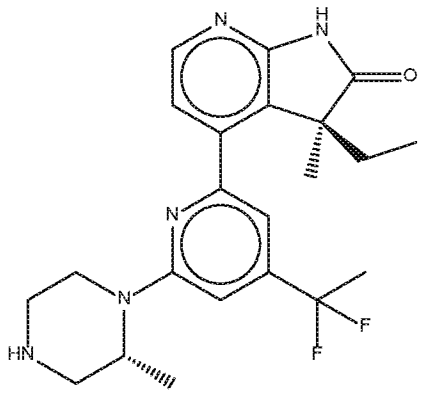
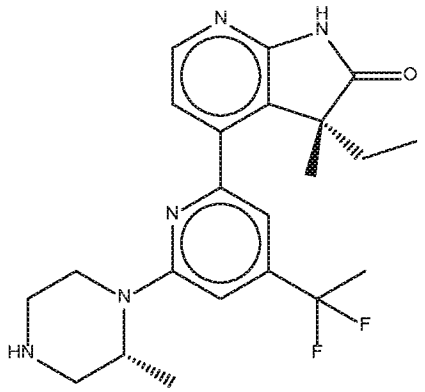
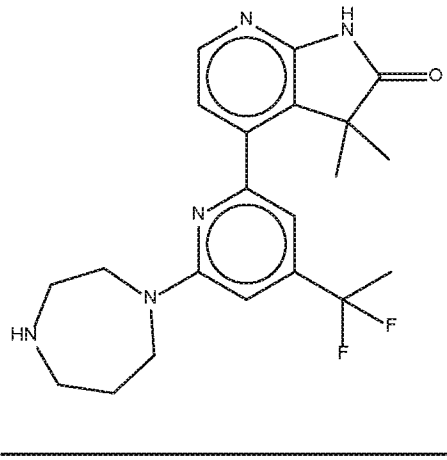
186		Pyridine	420.3	1H NMR (500 MHz, DMSO-d6) δ ppm 11.16 (s, 1 H), 8.60 - 9.37 (m, 2 H), 8.15 (d, J=5.38 Hz, 1 H), 7.06 - 7.16 (m, 1 H), 6.94 - 6.97 (m, 1 H), 6.91 - 6.94 (m, 1 H), 4.22 - 4.26 (m, 1 H), 3.96 - 4.01 (m, 1 H), 3.55 - 3.62 (m, 1 H), 3.43 - 3.53 (m, 2 H), 2.93 - 3.38 (m, 2 H), 2.00 - 2.21 (m, 2 H), 1.23 - 1.27 (m, 3 H), 1.20 (s, 6 H)
187		Pyridine	420.3	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.16 (s, 1H), 8.72-9.03 (m, 2H), 8.14 (d, J = 5.4 Hz, 1H), 7.06 (s, 1H), 6.94 (s, 1H), 6.93 (d, J = 5.4 Hz, 1H), 4.34-4.60 (m, 1H), 4.17-4.33 (m, 1H), 4.02-4.05 (m, 1H), 3.29-3.54 (m, 3H), 2.81-2.97 (m, 2H), 2.20-2.32 (m, 1H), 2.00 (dt, J = 16.1, 10.8 Hz, 1H), 1.21 (s, 3H), 1.18 (s, 3H), 1.13 (d, J = 6.1 Hz, 3H)
188		Pyridine	420	1H NMR (600 MHz, DMSO-d6, 300K) δ ppm 11.15 (s, 1 H), 8.59 - 9.16 (m, 2 H), 8.14 (d, J=5.4 Hz, 1 H), 7.06 (s, 1 H), 6.93 (s, 1 H), 6.92 (d, J=5.4 Hz, 1 H), 4.09 - 4.72 (m, 2 H), 3.45 - 3.56 (m, 1 H), 3.26 - 3.40 (m, 2 H), 2.78 - 3.00 (m, 2 H), 2.17 - 2.32 (m, 1 H), 2.01 (br d, J=16.4 Hz, 1 H), 1.20 (d, J=15.6 Hz, 6 H), 1.12 (d, J=6.2 Hz, 3 H)

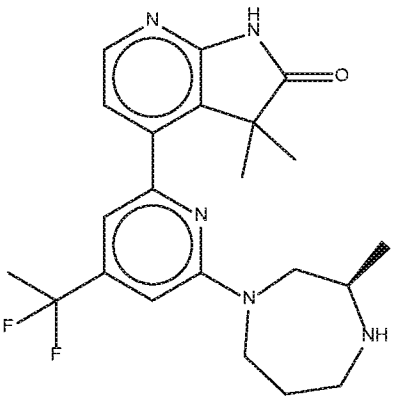
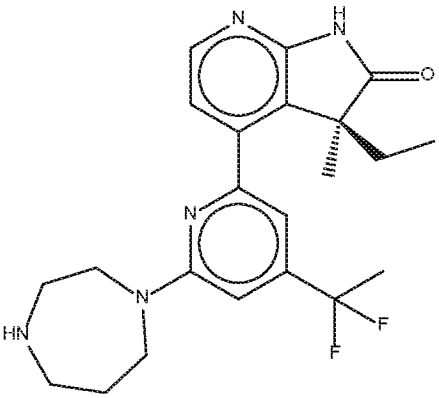
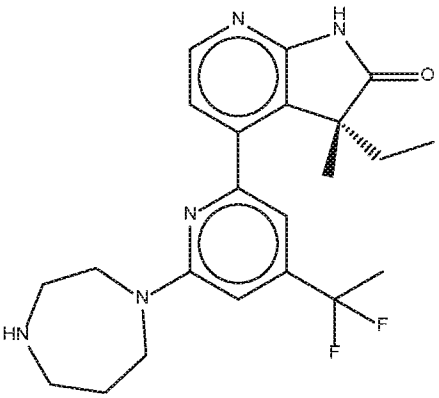
189		Pyridine	420.4	1H NMR (500 MHz, DMSO-d6) δ 11.11 (s, 1H), 8.13 (d, J=5.38 Hz, 1H), 6.93 (d, J=5.38 Hz, 1H), 6.88 (s, 1H), 6.78 (s, 1H), 3.83-4.75 (m, 2H), 3.26-3.29 (m, 1H), 3.21 (br dd, J=5.99, 14.31 Hz, 2H), 2.96 (br d, J=12.23 Hz, 1H), 2.51-2.56 (m, 1H), 2.32-2.48 (m, 1H), 1.49-1.65 (m, 2H), 1.16-1.30 (m, 6H), 0.96-1.06 (m, 3H)
190		Pyridine	420.3	1H NMR (500 MHz, DMSO-d6) δ 11.15 (s, 1H), 9.32 (br d, J = 2.2 Hz, 1H), 8.67 – 8.28 (m, 1H), 8.15 (d, J = 5.4 Hz, 1H), 7.00 (s, 1H), 6.94 (s, 1H), 6.90 (d, J = 5.4 Hz, 1H), 4.74 – 4.40 (m, 1H), 4.36 – 3.95 (m, 1H), 3.56 (br s, 2H), 3.36 – 3.10 (m, 2H), 3.03 – 2.86 (m, 1H), 1.92 – 1.70 (m, 2H), 1.27 (s, 3H), 1.18 (s, 3H), 1.13 (d, J = 6.4 Hz, 3H)
191		Pyridine (using compound II' obtained from OHMe isomer 1)	436.4	1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.11-11.59 (m, 1H), 8.27 (d, J = 5.6 Hz, 1H), 7.52 (s, 1H), 7.43 (d, J = 5.4 Hz, 1H), 7.19 (s, 1H), 4.21-4.39 (m, 2H), 3.03 (s, 3H), 2.81-3.00 (m, 2H), 2.66 (td, J = 11.8, 3.1 Hz, 1H), 2.50 (dt, J = 3.7, 1.8 Hz, 2H), 1.26-1.52 (m, 5H), 0.94 (t, J = 7.6 Hz, 3H) (il manque le NH piperazine)

192		Pyridine	434.3	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.16 (s, 1H), 8.15 (d, J = 5.4 Hz, 1H), 7.38-9.01 (m, 2H), 7.28 (s, 1H), 7.03 (s, 1H), 6.93 (d, J = 5.4 Hz, 1H), 5.04-5.17 (m, 1H), 4.26 (br d, J = 13.4 Hz, 1H), 3.90-4.00 (m, 2H), 3.83 (d, J = 10.0 Hz, 1H), 3.63-3.73 (m, 2H), 3.26 (br d, J = 12.5 Hz, 1H), 3.18 (br d, J = 11.2 Hz, 1H), 2.94-3.06 (m, 1H), 1.18 (s, 3H), 1.16 (s, 3H)
193		Pyridine (using compound II' obtained from OHMe isomer 1 and specific pyridine 1 as compound II)	418.3	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.40 (s, 1H), 9.24-9.58 (m, 1H), 8.92 (br d, J = 10.0 Hz, 1H), 8.27 (d, J = 5.4 Hz, 1H), 7.54 (s, 1H), 7.46 (d, J = 5.4 Hz, 1H), 7.06 (s, 1H), 4.89-4.99 (m, 1H), 4.47 (br d, J = 13.7 Hz, 1H), 3.13-3.38 (m, 4H), 3.04 (s, 3H), 2.95-3.04 (m, 1H), 1.99 (t, J = 19.1 Hz, 3H), 1.33 (s, 3H), 1.27 (d, J = 7.1 Hz, 3H)
194		Pyridine (using specific pyridine 1 as compound II)	402.1	1H NMR (600 MHz, DMSO-d6) δ 11.13 (s, 1H), 9.30 – 8.97 (m, 2H), 8.14 (d, J = 5.3 Hz, 1H), 7.14 (s, 1H), 6.94 (d, J = 5.4 Hz, 1H), 6.92 (s, 1H), 4.42 (br d, J = 14.1 Hz, 2H), 3.73 – 3.71 (m, 1H), 3.38 – 3.28 (m, 2H), 3.27 – 3.01 (m, 3H), 1.99 (t, J = 19.1 Hz, 3H), 1.28 (d, J = 6.5 Hz, 3H), 1.20 (s, 3H), 1.18 (s, 3H)

195		Pyridine (using specific pyridine 1 as compound II)	416.3	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.08 (s, 1H), 8.12 (d, J = 5.4 Hz, 1H), 6.93 (d, J = 5.4 Hz, 1H), 6.88 (s, 1H), 6.74 (s, 1H), 4.36 (br s, 1H), 3.91-4.05 (m, 1H), 2.93 (br t, J = 11.0 Hz, 2H), 2.80-2.87 (m, 1H), 2.63-2.69 (m, 1H), 2.09-2.46 (m, 1H), 1.98 (t, J = 19.2 Hz, 3H), 1.16-1.24 (m, 6H), 1.00 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H)
196		Pyridine (using specific pyridine 1 as compound II)	416.3	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.08 (s, 1H), 8.12 (d, J = 5.4 Hz, 1H), 6.93 (d, J = 5.4 Hz, 1H), 6.88 (s, 1H), 6.74 (s, 1H), 4.35 (br s, 1H), 3.88-4.05 (m, 1H), 2.87-2.97 (m, 2H), 2.81-2.87 (m, 1H), 2.60-2.71 (m, 1H), 2.06-2.32 (m, 1H), 1.98 (t, J = 19.1 Hz, 3H), 1.20 (d, J = 12.2 Hz, 6H), 1.00 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H)
197		Pyridine (using compound II' obtained from MeEt isomer 1)	420.4	1H NMR (500 MHz, DMSO-D6, 300 K) δ (ppm) = 11.20 (s, 1H), 9.50 - 9.20 (m, 1H), 9.08 - 8.72 (m, 1H), 8.16 (d, J = 5.4 Hz, 1H), 7.24 (s, 1H), 6.99 (s, 1H), 6.94 (d, J = 5.4 Hz, 1H), 4.96 - 4.78 (m, 1H), 4.44 - 4.29 (m, 1H), 3.37 - 3.13 (m, 4H), 2.99 (br d, J = 11.2 Hz, 1H), 1.68 (dd, J = 7.3, 13.4 Hz, 1H), 1.43 (dd, J = 7.5, 13.6 Hz, 1H), 1.27 (d, J = 7.1 Hz, 3H), 1.17 (s, 3H), 0.48 (t, J = 7.3 Hz, 3H)

198		Pyridine (using compound II' obtained from MeEt isomer 2)	420.1	1H NMR (500 MHz, DMSO-d6) δ 11.19 (s, 1H), 9.46 (br d, J = 10.3 Hz, 1H), 9.01 (br d, J = 10.8 Hz, 1H), 8.16 (d, J = 5.4 Hz, 1H), 7.25 (s, 1H), 6.99 (s, 1H), 6.95 (d, J = 5.4 Hz, 1H), 4.92 – 4.80 (m, 1H), 4.35 (br d, J = 15.2 Hz, 1H), 3.35 – 2.93 (m, 6H), 1.73 – 1.65 (m, 1H), 1.51 – 1.42 (m, 1H), 1.27 (d, J = 6.8 Hz, 3H), 1.16 (s, 3H), 0.49 (t, J = 7.3 Hz, 3H)
199		Pyridine (using compound II' obtained from MeEt isomer 1 and Specific pyridine 1 as compound II)	416.3	1H NMR (500 MHz, DMSO-d6) δ 11.16 (s, 1H), 9.16 (br d, J = 10.5 Hz, 1H), 9.03 – 8.81 (m, 1H), 8.15 (d, J = 5.4 Hz, 1H), 7.13 (s, 1H), 6.93 (d, J = 5.4 Hz, 1H), 6.88 (s, 1H), 4.41 (br d, J = 13.7 Hz, 2H), 3.43 – 2.95 (m, 5H), 1.99 (t, J = 19.2 Hz, 3H), 1.74 – 1.47 (m, 2H), 1.26 (d, J = 6.4 Hz, 3H), 1.16 (s, 3H), 0.49 (t, J = 7.5 Hz, 3H)
200		Pyridine (using compound II' obtained from MeEt isomer 2 and Specific pyridine 1 as compound II)	416.1	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.17 (s, 1H), 9.37 (br s, 1H), 9.20 (br s, 1H), 8.15 (d, J = 5.4 Hz, 1H), 7.13 (s, 1H), 6.93 (d, J = 5.4 Hz, 1H), 6.88 (s, 1H), 4.40 (br d, J = 13.7 Hz, 2H), 4.02 (br s, 1H), 3.36-3.39 (m, 1H), 3.21-3.33 (m, 2H), 3.01-3.09 (m, 2H), 1.99 (t, J = 19.1 Hz, 3H), 1.68 (dd, J = 13.4, 7.3 Hz, 1H), 1.53 (dd, J = 13.2, 7.3 Hz, 1H), 1.28 (d, J = 6.6 Hz, 3H), 1.16 (s, 3H), 0.49 (t, J = 7.3 Hz, 3H)

201		Pyridine (using compound II' obtained from MeEt isomer 1 and Specific pyridine 1 as compound II)	416.3	1H NMR (500 MHz, DMSO-d6) δ 11.16 (s, 1H), 9.59 – 8.74 (m, 2H), 8.15 (d, J = 5.4 Hz, 1H), 7.02 (s, 1H), 6.92 (d, J = 5.4 Hz, 1H), 6.85 (s, 1H), 4.92 – 4.73 (m, 1H), 4.32 (br d, J = 13.7 Hz, 1H), 3.36 – 3.11 (m, 4H), 2.97 (br d, J = 11.5 Hz, 1H), 1.99 (t, J = 19.2 Hz, 3H), 1.74 – 1.36 (m, 2H), 1.25 (d, J = 7.1 Hz, 3H), 1.17 (s, 3H), 0.47 (t, J = 7.5 Hz, 3H)
202		Pyridine (using compound II' obtained from MeEt isomer 2 and Specific pyridine 1 as compound II)	416.1	1H NMR (600 MHz, DMSO-d6, 300K) δ ppm 11.15 (s, 1 H), 9.35 (br d, J=11.0 Hz, 1 H), 8.71 - 9.00 (m, 1 H), 8.15 (d, J=5.4 Hz, 1 H), 7.03 (s, 1 H), 6.92 (d, J=5.4 Hz, 1 H), 6.86 (s, 1 H), 4.78 - 4.88 (m, 1 H), 4.31 (br d, J=13.4 Hz, 1 H), 3.12 - 3.36 (m, 4 H), 2.94 - 3.05 (m, 1 H), 1.99 (t, J=19.1 Hz, 3 H), 1.61 - 1.75 (m, 1 H), 1.43 - 1.55 (m, 1 H), 1.25 (d, J=7.0 Hz, 3 H), 1.16 (s, 3 H), 0.48 (t, J=7.3 Hz, 3 H)
203		Pyridine (using Specific pyridine 1 as compound II)	402.3	1H NMR (600 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.02 (br s, 2H), 8.13 (d, J = 5.3 Hz, 1H), 6.92 (d, J = 5.4 Hz, 1H), 6.87 (s, 1H), 6.82 (s, 1H), 4.04 – 3.94 (m, 2H), 3.84 – 3.66 (m, 2H), 3.25 – 3.21 (m, 2H), 3.20 – 3.15 (m, 2H), 2.12 – 2.04 (m, 2H), 1.99 (t, J = 19.1 Hz, 3H), 1.21 (s, 6H)

204		Pyridine (using Specific pyridine 1 as compound II)	416.3	1H NMR (600 MHz, DMSO-d6) δ 11.13 (s, 1H), 9.48 – 8.81 (m, 2H), 8.13 (d, J = 5.4 Hz, 1H), 6.91 (d, J = 5.3 Hz, 1H), 6.87 (s, 1H), 6.82 (s, 1H), 4.26 – 4.18 (m, 1H), 4.01 – 3.64 (m, 1H), 3.62 – 3.40 (m, 3H), 3.33 (dt, J = 9.1, 4.7 Hz, 1H), 3.02 – 2.88 (m, 1H), 2.19 – 2.08 (m, 2H), 1.99 (t, J = 19.1 Hz, 3H), 1.28 – 1.14 (m, 9H)
205		Pyridine (using compound II' obtained from MeEt isomer 1 and Specific pyridine 1 as compound II)	416.3	1H NMR (500 MHz, DMSO-d6) δ 11.10 (s, 1H), 9.25 – 8.68 (m, 2H), 8.14 (d, J = 5.4 Hz, 1H), 6,90 (d, J = 5.4 Hz, 1H), 6.88 – 6.85 (m, 1H), 6.82 – 6.75 (m, 1H), 3.96 (br t, J = 4.3 Hz, 2H), 3.72 (br s, 2H), 3.28 – 3.12 (m, 4H), 2.11 – 2.04 (m, 2H), 1.99 (t, J = 19.1 Hz, 3H), 1.77 – 1.49 (m, 2H), 1.20 (s, 3H), 0.48 (s, 3H)
206		Pyridine (using compound II' obtained from MeEt isomer 2 and Specific pyridine 1 as compound II)	416.4	1H NMR (500 MHz, DMSO-d6) δ 11.16 (s, 1H), 9.05 (br s, 2H), 8.14 (d, J = 5.4 Hz, 1H), 6.91 (d, J = 5.4 Hz, 1H), 6.87 (s, 1H), 6.79 (s, 1H), 4.15 – 3.57 (m, 4H), 3.28 – 3.10 (m, 4H), 2.14 – 2.04 (m, 2H), 1.99 (t, J = 19.1 Hz, 3H), 1.81 – 1.46 (m, 2H), 1.20 (s, 3H), 0.48 (t, J = 7.3 Hz, 3H)

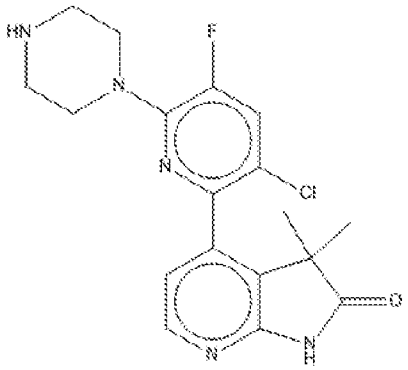
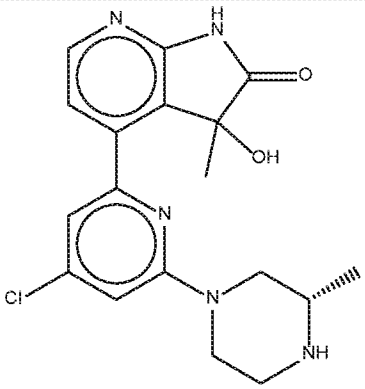
207		Pyridine	376.3	1H NMR (600 MHz, DMSO-d6) δ 11.20 (s, 1H), 9.71 – 8.96 (m, 2H), 8.15 (d, J = 5.3 Hz, 1H), 8.09 (d, J = 12.3 Hz, 1H), 6.83 (d, J = 5.3 Hz, 1H), 3.73 – 3.54 (m, 4H), 3.22 – 3.16 (m, 4H), 1.16 (br s, 6H)
208		Pyridine	373,9; 375,9	1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.10 (s, 1H), 9.00-9.65 (m, 2H), 8.19 (d, J = 5.4 Hz, 1H), 7.89 (dd, J = 2.2, 1.5 Hz, 1H), 7.37 (d, J = 5.6 Hz, 1H), 7.20 (d, J = 1.2 Hz, 1H), 5.04 (br s, 2H), 4.36-4.52 (m, 2H), 2.93-3.42 (m, 5H), 1.28-1.32 (m, 6H)

Table 1: Specific PKC-theta inhibitor compounds of the disclosure.

In another aspect the invention provides a pharmaceutical composition comprising a compound according to this disclosure.

PKC-theta Activity, Prodrugs and Metabolites of Compounds

PKC-theta is selectively expressed in T lymphocytes and plays an important role in the T cell antigen receptor (TCR)-triggered activation of mature T cells, and the subsequent release of cytokines such as IL-2 and T cell proliferation (Isakov and Altman, Annu. Rev. Immunol., 2002, 20, 761-94). Thus, reduction of IL-2 levels is indicative of a desirable response that could provide a treatment of diseases and disorders as described herein, such as autoimmune and oncological disease.

Due to its involvement in T-cell activation, selective inhibition of PKC-theta may reduce harmful inflammation mediated by Th17 (mediating autoimmune diseases) or by Th2 (causing allergies) (Madouri et al, Journal of Allergy and Clinical Immunology. 139 (5): 2007, pp 1650–1666). without diminishing the ability of T cells to get rid of viral-infected cells. Inhibitors could be used in T-cell mediated adaptive immune responses. Inhibition of PKC-theta downregulates transcription factors (NF-κB, NF-AT) and results in lower production of IL-2. It was observed that animals without PKC-theta are resistant to some autoimmune diseases. (Zanin-Zhorov et al., Trends in Immunology. 2011, 32(8): 358–363). PKC-theta is therefore an interesting target for potential cancer and autoimmune therapies.

Studies in PKC-theta-deficient mice have demonstrated that while antiviral responses are independent of PKC-theta activity, T cell responses associated with autoimmune diseases are PKC-theta-dependent (Jimenez et al., J. Med. Chem. 2013, 56(5) pp 1799-1810). Thus, potent and selective inhibition of PKC-theta is expected to block autoimmune T cell responses without compromising antiviral immunity. However, the similarity of the PKC isoforms, particularly PKC-delta, and selectivity over other protein kinases represents a challenge to the development of a suitable PKC-inhibitor for clinical use.

In order to address such concerns, in aspects and embodiments, compounds (or 'active agents') of the disclosure may beneficially provide a potent and selective (having a selectivity of greater than 5-fold, preferably greater than 20-fold by a suitable measure, such as pIC50 in a suitable assay) PKC-theta inhibition over other PKC-isoforms, such as PKC-delta, and other kinases.

The active agents or compounds of the present invention may be provided as prodrugs of compounds of the disclosure.

The term 'active agent' is typically used to refer to a compound according to the disclosure which has inhibition activity against PKC-theta; especially under physiological conditions. However, it is often the case that the active agent may be difficult to administer or deliver to the physiological site of relevance, e.g. due to solubility, half-life or many other chemical or biological reasons. Therefore, it is known to use 'prodrugs' of the active agent in order to overcome physiochemical, biological or other barriers in drug efficiency and/or toxicity.

An active agent may be formed from a compound or prodrug of the disclosure by metabolism of the drug *in vivo*, and/or by chemical or enzymatic cleavage of the prodrug *in vivo*. Typically, a prodrug may be a pharmacologically inactive compound that requires chemical or enzymatic

transformation to become an effective, active agent inside the body in which it is intended to have its therapeutic effect. On the other hand, since a prodrug may, in some embodiments, have very close structural similarity to the active agent, in some such embodiments, the prodrug may also have activity against the PKC-theta target. This may be particularly the case where the active agent is formed from a compound of prodrug of the disclosure by metabolism or a minor chemical transformation, such that the metabolite is closely related to the parent compound / prodrug. Accordingly, prodrugs of the disclosure may be active inhibitors of PKC-theta. Suitably, however, such prodrugs may be characterised by having lower inhibition activity against PKC-theta than the drug / active agent that is derived from the prodrug of the disclosure.

On the other hand, where the therapeutic effect is derived from the release of the active agent from a larger chemical entity, then the eventual active agent / compound / drug may have significant structural differences compared to the prodrug from which it was derived. In such cases, the prodrug can effectively 'mask' the form(s) of the active agent, and in such cases the prodrug may be completely (or essentially) completely inactive under physiological conditions.

Dosage Forms, Medicaments and Pharmaceuticals

The compounds, molecules or agents of the disclosure may be used to treat (e.g. cure, alleviate or prevent) one or more diseases, infections or disorders. Thus, in accordance with the disclosure, the compounds and molecules may be manufactured into medicaments or may be incorporated or formulated into pharmaceutical compositions.

The molecules, compounds and compositions of the disclosure may be administered by any convenient route, for example, methods of administration include intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intranasal, intravaginal, transdermal, rectally, by inhalation, or topically to the skin. Delivery systems are also known to include, for example, encapsulation in liposomes, microgels, microparticles, microcapsules, capsules, etc. Any other suitable delivery system known in the art is also envisioned in use. Administration can be systemic or local. The mode of administration may be left to the discretion of the practitioner.

The dosage administered will, of course, vary depending upon known factors, such as the pharmacodynamic properties of the particular active agent; the chosen mode and route of administration; the age, health and weight of the recipient; the nature of the disease or disorder to be treated; the extent of the symptoms; any simultaneous or concurrent treatments; the frequency of treatment; and the effect desired. In general, a daily dosage of active agent of

between about 0.001 and about 1,000 mg/kg of body weight can be expected. For some applications, the dosage may suitably be within the range of about 0.01 to about 100 mg/kg; between about 0.1 to about 25 mg/kg, or between about 0.5 and 10 mg/kg.

Depending on known factors, such as those noted above, the required dosage of the active agent may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of e.g. two, three, or four times daily. Suitably, the therapeutic treatment regime according to the disclosure is devised for a single daily dose or for a divided daily dose of two doses.

Dosage forms of the pharmaceutical compositions of the disclosure suitable for administration may contain from about 1 mg to about 2,000 mg of the active ingredient per unit. Typically, the daily dosage of compounds may be at least about 10 mg and at most about 1,500 mg per human dose; such as between about 25 and 1,250 mg or suitably between about 50 and 1,000 mg. Typically, the daily dosage of compounds may be at most about 1000 mg. In such compositions the compound of the invention will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

The 'effective amount' or 'therapeutically effective amount' is meant to describe an amount of compound or a composition of the disclosure that is effective in curing, inhibiting, alleviating, reducing or preventing the adverse effects of the diseases or disorders to be treated, or the amount necessary to achieve a physiological or biochemically-detectable effect. Thus, at the effective amount, the compound or agent is able to produce the desired therapeutic, ameliorative, inhibitory or preventative effect in relation to disease or disorder. Beneficially, an effective amount of the compound or composition of the disclosure may have the effect of inhibiting PKC-theta. Diseases or disorders which may benefit from PKC-theta inhibition include, for example, autoimmune disorders, inflammatory diseases, cancers and/or oncologic diseases, such as rheumatoid arthritis, multiple sclerosis, psoriasis, Sjogren's syndrome and systemic lupus erythematosus or vasculitic conditions, cancers of hematopoietic origin or solid tumors, including chronic myelogenous leukemia, myeloid leukemia, non-Hodgkin lymphoma and other B cell lymphomas.

For therapeutic applications, the effective amount or therapeutically effective amount of a compound / active agent of the disclosure may be at least about 50 nM or at least about 100 nM; typically at least about 200 nM or at least about 300 nM in the blood of the subject. The effective amount or therapeutically effective amount may be at most about 5 μM, at most about 3 μM, suitably at most about 2 μM and typically at most about 1 μM in the blood of the subject. For

example, the therapeutically effective amount may be at most about 500 nM, such as between about 100 nM and 500 nM. In some embodiments the amount of therapeutic compound is measured in serum of the subject and the above concentrations may then apply to serum concentration of the compounds of the disclosure.

When administered to a subject, a compound of the disclosure is suitably administered as a component of a composition that comprises a pharmaceutically acceptable carrier or vehicle. One or more additional pharmaceutical acceptable carrier (such as diluents, adjuvants, excipients or vehicles) may be combined with the compound of the disclosure in a pharmaceutical composition. Suitable pharmaceutical carriers are described in *"Remington's Pharmaceutical Sciences"* by E. W. Martin. Pharmaceutical formulations and compositions of the disclosure are formulated to conform to regulatory standards and according to the chosen route of administration.

Acceptable pharmaceutical vehicles can be liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The pharmaceutical vehicles can be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea, and the like. In addition, auxiliary, stabilising, thickening, lubricating and colouring agents may be used. When administered to a subject, the pharmaceutically acceptable vehicles are generally sterile. Water is a suitable vehicle when the compound is to be administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid vehicles, particularly for injectable solutions. Suitable pharmaceutical vehicles also include excipients such as starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or buffering agents.

The medicaments and pharmaceutical compositions of the disclosure can take the form of solutions, suspensions, emulsion, tablets, pills, pellets, powders, gels, capsules (for example, capsules containing liquids or powders), modified-release formulations (such as slow or sustained-release formulations), suppositories, emulsions, aerosols, sprays, suspensions, or any other form suitable for use. Other examples of suitable pharmaceutical vehicles are described in Remington's Pharmaceutical Sciences, Alfonso R. Gennaro ed., Mack Publishing Co. Easton, Pa., 19th ed., 1995, see for example pages 1447-1676.

Suitably, the therapeutic compositions or medicaments of the disclosure are formulated in accordance with routine procedures as a pharmaceutical composition adapted for oral administration (more suitably for humans). Compositions for oral delivery may be in the form of tablets, lozenges, aqueous or oily suspensions, granules, powders, emulsions, capsules, syrups, or elixirs, for example. Thus, in one embodiment, the pharmaceutically acceptable vehicle is a capsule, tablet or pill.

Orally administered compositions may contain one or more agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavouring agents such as peppermint, oil of wintergreen, or cherry; colouring agents; and preserving agents, to provide a pharmaceutically palatable preparation. When the composition is in the form of a tablet or pill, the compositions may be coated to delay disintegration and absorption in the gastrointestinal tract, so as to provide a sustained release of active agent over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving compound are also suitable for orally administered compositions. In these dosage forms, fluid from the environment surrounding the capsule is imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These dosage forms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time delay material such as glycerol monostearate or glycerol stearate may also be used. Oral compositions can include standard vehicles such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Such vehicles are preferably of pharmaceutical grade. For oral formulations, the location of release may be the stomach, the small intestine (the duodenum, the jejunem, or the ileum), or the large intestine. One skilled in the art is able to prepare formulations that will not dissolve in the stomach yet will release the material in the duodenum or elsewhere in the intestine. Suitably, the release will avoid the deleterious effects of the stomach environment, either by protection of the compound (or composition) or by release of the compound (or composition) beyond the stomach environment, such as in the intestine. To ensure full gastric resistance a coating impermeable to at least pH 5.0 would be essential. Examples of the more common inert ingredients that are used as enteric coatings are cellulose acetate trimellitate (CAT), hydroxypropylmethylcellulose phthalate (HPMCP), HPMCP 50, HPMCP 55, polyvinyl acetate phthalate (PVAP), Eudragit L30D, Aquateric, cellulose acetate phthalate (CAP), Eudragit L, Eudragit S, and Shellac, which may be used as mixed films.

While it can be beneficial to provide therapeutic compositions and/or compounds of the disclosure in a form suitable for oral administration, for example, to improve patient compliance and for ease of administration, in some embodiments compounds or compositions of the disclosure may cause undesirable side-effects, such as intestinal inflammation which may lead to premature

termination of a therapeutic treatment regime. Thus, in some embodiments, the therapeutic treatment regime is adapted to accommodate 'treatment holidays', e.g. one or more days of non-administration. For example, treatment regimens and therapeutic methods of the disclosure may comprise a repetitive process comprising administration of the therapeutic composition or compound for a number of consecutive days, followed by a treatment holiday of one or more consecutive days. For example, a treatment regime of the disclosure may comprise a repetitive cycle of administration of the therapeutic composition or compound for between 1 and 49 consecutive days, between 2 and 42 days, between 3 and 35 days, between 4 and 28 days, between 5 and 21 days, between 6 and 14 days, or between 7 and 10 days; followed by a treatment holiday of between 1 and 14 consecutive days, between 1 and 12 days, between 1 and 10 days, or between 1 and 7 days (e.g. 1, 2, 3, 4, 5, 6 or 7 days).

To aid dissolution of the therapeutic agent into the aqueous environment a surfactant might be added as a wetting agent. Surfactants may include anionic detergents such as sodium lauryl sulfate, dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate. Cationic detergents might be used and could include benzalkonium chloride or benzethomium chloride. Potential nonionic detergents that could be included in the formulation as surfactants include: lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 50 and 60, glycerol monostearate, polysorbate 20, 40, 60, 65 and 80, sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose. These surfactants, when used, could be present in the formulation of the compound or derivative either alone or as a mixture in different ratios.

Typically, compositions for intravenous administration comprise sterile isotonic aqueous buffer. Where necessary, the compositions may also include a solubilising agent.

Another suitable route of administration for the therapeutic compositions of the disclosure is via pulmonary or nasal delivery.

Additives may be included to enhance cellular uptake of the therapeutic agent of the disclosure, such as the fatty acids oleic acid, linoleic acid and linolenic acid.

The therapeutic agents of the disclosure may also be formulated into compositions for topical application to the skin of a subject.

Where the invention provides more than one active compound / agent for use in combination, generally, the agents may be formulated separately or in a single dosage form, depending on the prescribed most suitable administration regime for each of the agents concerned. When the

therapeutic agents are formulated separately, the pharmaceutical compositions of the invention may be used in a treatment regime involving simultaneous, separate or sequential administration with the other one or more therapeutic agent. The other therapeutic agent(s) may comprise a compound of the disclosure or a therapeutic agent known in the art).

The compounds and/or pharmaceutical compositions of the disclosure may be formulated and suitable for administration to the central nervous system (CNS) and/or for crossing the blood-brain barrier (BBB).

The invention will now be described by way of the following non-limiting examples.

EXAMPLES

Materials and Methods

Sample preparation: Powders were solubilized in DMSO-d_6, vortexed vigorously until the solution was clear and transferred to a NMR tube for data acquisition.

NMR spectroscopy:

Liquid-state NMR experiments were recorded on a 600 MHz (14.1 Tesla) Bruker Avance III NMR spectrometer (600 MHz for ^{1}H, 151 MHz for ^{13}C) using a triple-resonance ^{1}H,^{15}N,^{13}C CP-TCI 5 mm cryoprobe (Bruker Biospin, Germany).

Liquid-state NMR experiments were recorded on a 500 MHz (11.75 Tesla) Bruker Avance I NMR spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C) using a Dual Resonance BBI 5 mm probe (Bruker Biospin, Germany).

Liquid-state NMR experiments were recorded on a 400 MHz (9.4 Tesla) Bruker Avance NEO NMR spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C) using a SEI 5 mm probe (Bruker Biospin, Germany).

All the experiments used for the resonance assignment procedure and the elucidation of the products structure (1D ^{1}H, 2D ^{1}H-^{1}H-COSY, 2D ^{1}H-^{1}H-ROESY, 2D ^{1}H-^{13}C-HSQC, 2D ^{1}H-^{13}C-HMBC) were recorded at 300 K. ^{1}H chemical shifts are reported in δ (ppm) as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), m (multiplet) or br s (broad singlet)

LCMS chromatography:

LCMS chromatography were recorded the following apparatus using:

- Waters HPLC : Alliance 2695, UV : PDA 996, MS : ZQ (simple Quad) ZQ2
- Waters UPLC : Acquity, UV : Acquity PDA, MS : Qda
- Waters UPLC : Acquity, UV : Acquity TUV, MS : Qda
- Waters UPLC : Acquity, UV : Acquity PDA, MS : QDa, ELSD

The apparatus was tested using a column Gemini NX-C18 Phenomenex (30 x 2 mm) 3µm for the Waters HPLC or a CSH C18 Waters (50 x 2.1 mm), 1,7 µm for the UPLC Waters. All of them used a combination of the following eluents: H_2O + 0.05% TFA (v/v) and ACN + 0.035% TFA (v/v) and a positive electrospray ES+ as ionization mode. The UV detection was set up at 220 and 254 nm.

Temperatures are given in degrees Celsius (°C). The reactants used in the examples below may be obtained from commercial sources or they may be prepared from commercially available starting materials as described herein or by methods known in the art. All of the compounds of the invention are synthesized according to the Examples described herein. The progress of the reactions described herein were followed as appropriate by e.g. LC, GC or TLC, and as the skilled person will readily realise, reaction times and temperatures may be adjusted accordingly.

Chiral purification:

Method A:
Instrument: Waters Prep SFC80;
Stationary Phase: Chiralcel OJ-H 5µm, 250 x 21mm
Mobile phase: CO_2 / (EtOH + 0.5% IPAm) 80/20
Flowrate: 50 mL/min
UV detection: λ=210 nm
Temperature: 40°C - Pressure: 100 bars

Method B:
Instrument: Waters Prep SFC80;
Stationary Phase: Chiralcel OJ-H 5µm, 250 x 20mm
Mobile phase: CO_2 / (EtOH + 0.5% IPAm) 70/30
Flowrate: 50 mL/min
UV detection: λ=210 nm

Temperature: 40°C - Pressure: 100 bars

Abbreviations

In addition to the definitions above, the following abbreviations are used in the synthetic schemes above and the examples below. If an abbreviation used herein is not defined, it has its generally accepted meaning:

Ac	Acetyl
ACN	Acetonitrile
AcOH	Acetic acid
Boc	*tert*-butyloxycarbonyl
Boc_2O	Di-tert-butyl Dicarbonate
BzBr	Benzyl bromide
DCM	Dichloromethane
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethyl formamide
DMSO	Dimethylsulfoxide
Et	Ethyl
EtI	Ethyl iodide
EtOAc	Ethyl acetate
Et_3N	Triethylamine
EtOH	Ethanol
Et_2O	Diethyl ether
h	hour
H_2O	water
HCl	Hydrochloric acid
KOAc	Potassium acetate
KOtBu	Potassium terbutoxide
LiAlH4	Lithium aluminium hydride
LiHMDS	Lithium bis(trimethylsilyl)amide
LiBH4	Lithium borohydride
min	minutes
Me	Methyl
MeCN	Acetonitrile

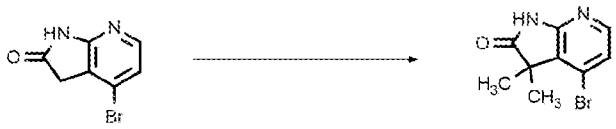
MeI	Methyl iodide
MeO or OMe	Methoxy
MeOH	Methanol
$MgSO_4$	Magnesium sulfate
MS	Mass spectrometry
$NaBH_3CN$	Sodium cyanoborohydride
NaOAc	Sodium acetate
NaOH	Sodium hydroxide
NaOtBu	Sodium terbutoxide
Na_2CO_3	Sodium carbonate
Na_2SO_4	Sodium sulfate
nBuLi	n-Butyl Lithium
NaH	Sodium hydride
$NaHCO_3$	Sodium bicarbonate
NH_4Cl	Ammonium chloride
NH_4HCO_2	Amonium formate
ovnt	overnight
$Pd(OAc)_2$	Palladium Acetate
$Pd(OH)_2$	Palladium hydroxide
$Pd(PPh_3)_4$	tetrakistriphenylphosphine palladium
$Pd(dppf)Cl_2$	bis(diphenylphosphino)ferrocene] dichloropalladium(II)
Ph	Phenyl
Pyr	Pyridine
rt	Room temperature (18 to 22 °C)
t-BuLi	terbutyl lithium
t-BuOH	Terbutanol
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

Example 1 – Chemical Synthesis Routes

Scaffolds

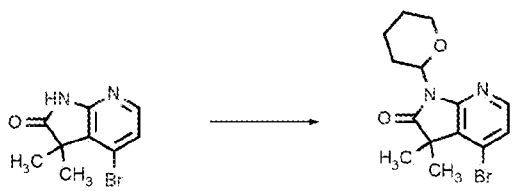
Dimethyl Scaffold Synthesis

Synthesis of 4-bromo-3,3-dimethyl-1H-pyrrolo[2,3-b]pyridin-2-one



In a 250 mL three-necked round bottom flask, 1 M lithium bis(trimethylsilyl)amide solution (33 mL, 33.4 mmol, 3.8 eq.) was added dropwise via an additional funnel to a solution of 4-bromo-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (2.00 g, 8.92 mmol, 1 eq.) in anhydrous THF (44 mL, 0.2 N) at -78°C. The mixture was stirred at -78°C for 10 min. Then iodomethane (1.4 mL, 22.3 mmol, 2.5 eq.) was added. The reaction was allowed to warm up to room temperature and stirred at room temperature for 1h. Then a saturated aqueous solution of NH_4Cl and ethyl acetate were added. The two phases were separated and the aqueous phase was extracted with ethyl acetate. Combined organic phases were dried over Na_2SO_4, filtered and evaporated to give crude product. The crude material was purified by flash chromatography on silica gel using a gradient of dichloromethane/ ethyl acetate. It was transferred via solid phase on Dicalite. Relevant fractions were collected and concentrated under vacuum to afford 4-bromo-3,3-dimethyl-1H-pyrrolo[2,3-b]pyridin-2-one as a pale yellow powder (63% Yield). ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 11.26 (s, 1H), 7.95 (d, *J*=5.7 Hz, 1H), 7.19 (d, *J*=5.7 Hz, 1H), 1.39 (s, 6H); m/z = 241.2, 243.2 [M+H]+.

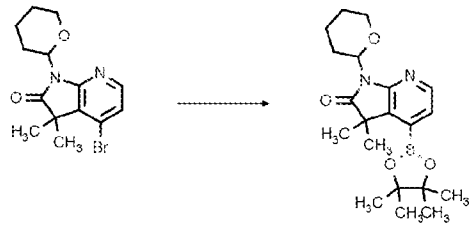
Synthesis of 4-bromo-3,3-dimethyl-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-2-one



In a 20 mL microwave vial, 3,4-dihydro-2H-pyran (0.68 mL, 7.47 mmol, 3 eq.) was added to a stirred solution of 4-bromo-3,3-dimethyl-1H-pyrrolo[2,3-b]pyridin-2-one (600 mg, 2.49 mmol) and

p-toluene sulfonic acid hydrate (95 mg, 0.498 mmol, 0.2 eq.) in anhydrous toluene (12 mL, 0.2 N). The reaction was stirred at 90°C for 5h. The solvent was removed under vacuum to give crude material as an orange oil. The crude material was purified by flash chromatography on silica gel using a gradient of heptane / ethyl acetate. Relevant fractions were collected and concentrated under vacuum to afford 4-bromo-3,3-dimethyl-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-2-one (750mg, 93% Yield). ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.07 (d, *J*=5.6 Hz, 1H), 7.32 (d, *J*=5.6 Hz, 1H), 5.40 (dd, *J*=11.3, 2.1 Hz, 1H), 3.97 (d, *J*=10.8 Hz, 1H), 3.56 (qd, *J*=11.2, 10.8, 5.0 Hz, 1H), 2.85 (qd, *J*=13.7, 12.7, 3.8 Hz, 1H), 2.01 – 1.86 (m, 1H), 1.68 – 1.48 (m, 4H), 1.42 (s, 6H), m/z = 325.2, 327.0 [M+H]+.

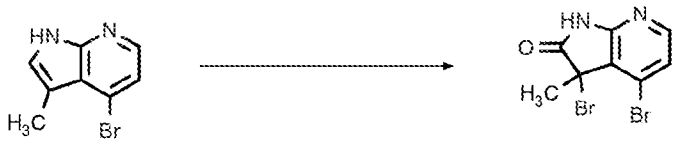
Synthesis of 3,3-dimethyl-1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-b]pyridin-2-one



A sealed vial was charged under nitrogen with 4-bromo-3,3-dimethyl-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-2-one (0.75 g, 2.31mmol), bis(pinacolato)diboron (0.88 g, 3.46 mmol, 1.5 eq.), potassium acetate (715 mg, 6.92 mmol, 3 eq.) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II), complex with dichloromethane (193 mg, 0.231 mmol, 0.1 eq.) in anhydrous dioxane (8 mL, 0.3 N). The vial was sealed and degassed with nitrogen. The reaction mixture was stirred at 100°C overnight. The reaction mixture was filtered through a pad of Dicalite and the filtrate was evaporated to dryness to give crude material as a dark oil. The crude product was purified by flash chromatography on silica gel using a gradient of heptane / ethyl acetate. Relevant fractions were collected and concentrated under vacuum to afford 3,3-dimethyl-1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-b]pyridin-2-one (490mg, 57% Yield) as a yellow oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.19 (d, *J*=5.1 Hz, 1H), 7.24 (d, *J*=5.1 Hz, 1H), 5.42 (dd, *J*=11.3, 2.0 Hz, 1H), 3.96 (d, *J*=11.1 Hz, 1H), 3.64 – 3.44 (m, 1H), 2.89 (d, *J*=11.4 Hz, 1H), 1.91 (s, 1H), 1.73 – 1.46 (m, 4H), 1.40 (s, 6H), 1.35 (s, 12H). m/z = 373.4 [M+H]+.

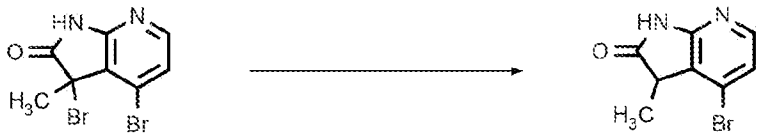
Ethyl/Methyl Scaffold Synthesis

Synthesis of 3,4-dibromo-3-methyl-1H-pyrrolo[2,3-b]pyridin-2-one



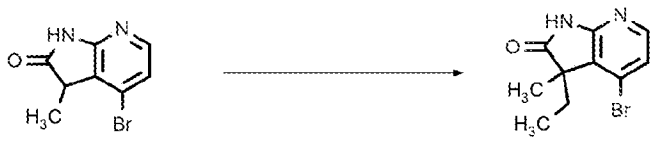
To a stirred solution of 4-bromo-3-methyl-1H-pyrrolo[2,3-b]pyridine (460 mg, 2.07 mmol) in tert-butanol (16 mL, 0.13 N) was added in small portions pyridinium bromide-perbromide (1.46 g, 4.56 mmol, 2.2 eq.) over 10 min. The reaction was stirred at room temperature overnight. t-Butanol was removed under vacuum. Water was added followed by ethyl acetate. The two phases were separated and the aqueous phase was extracted with EtOAc. Combined organic phases were washed with water, dried over Na_2SO_4, concentrated under high vacuum to give 3,4-dibromo-3-methyl-1H-pyrrolo[2,3-b]pyridin-2-one (660mg, 96% Yield) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 11.77 (s, 1H), 8.04 (d, *J*=5.7 Hz, 1H), 7.32 (d, *J*=5.7 Hz, 1H), 2.07 (s, 3H); (*product not stable in LCMS*)

Synthesis of 4-bromo-3-methyl-1,3-dihydropyrrolo[2,3-b]pyridin-2-one



In a 50 mL round-bottomed flask, at room temperature, zinc powder (847 mg, 13.0 mmol, 2 eq.) was added in portions to a stirred suspension of 3,4-dibromo-3-methyl-1H-pyrrolo[2,3-b]pyridin-2-one (2.00 g, 6.01 mmol) in a mixture of methanol (30 mL) and acetic acid (15 mL). The reaction was stirred at room temperature for 10 min. The mixture was neutralized with an aqueous solution of $NaHCO_3$ until pH=6. The solution was filtered and the aqueous phase was extracted with EtOAc. Combined organic phases were washed with brine, dried over Na_2SO_4, filtered and evaporated to give 4-bromo-3-methyl-1,3-dihydropyrrolo[2,3-b]pyridin-2-one (1.08g, 76% Yield) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 11.22 (s, 1H), 7.95 (dd, *J*=5.7, 0.8 Hz, 1H), 7.18 (d, *J*=5.7 Hz, 1H), 3.66 – 3.49 (m, 1H), 1.43 (d, *J*=7.6 Hz, 3H); m/z = 227.1, 229.1 [M+H]+.

Synthesis of 4-bromo-3-ethyl-3-methyl-1H-pyrrolo[2,3-b]pyridin-2-one (MeEt)



At -78°C, under an argon stream, 1 M lithium [bis(trimethylsilyl)amide] solution (2.2 mL, 2.16 mmol, 2 eq.) was added dropwise to a solution of 4-bromo-3-methyl-1,3-dihydropyrrolo[2,3-b]pyridin-2-one (350 mg, 1.08 mmol) in anhydrous tetrahydrofuran (2.7 mL, 0.4 N). The reaction was stirred at -78°C for 10 min. Then iodoethane (0.087 mL, 1.08 mmol, 1 eq.) was added and the mixture was stirred at room temperature under argon stream for 1h. Then an aqueous solution of HCl 1N was added slowly to reach pH 6-7 followed by ethyl acetate. The two phases were separated and the aqueous phase was extracted with ethyl acetate. Combined organic phases were dried using a phase separator and evaporated to give crude material as an orange solid. The crude material was purified by flash chromatography on silica gel using a gradient of heptane / ethyl acetate. It was transferred via solid phase. Relevant fractions were collected and concentrated under vacuum to afford 4-bromo-3-ethyl-3-methyl-1H-pyrrolo[2,3-b]pyridin-2-one (155mg, 56% Yield) as a beige powder. 1H NMR (400 MHz, DMSO-d6) δ 11.30 (s, 1H), 7.96 (d, J = 5.7 Hz, 1H), 7.21 (d, J = 5.7 Hz, 1H), 2.21 – 2.05 (m, 1H), 1.77 (dq, J = 14.7, 7.4 Hz, 1H), 1.38 (s, 3H), 0.50 (t, J = 7.4 Hz, 3H); m/z = 255.1, 257.1 [M+H]+.

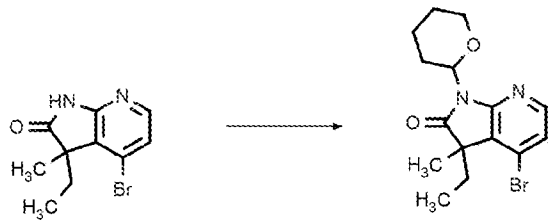
The two enantiomers were obtained from chiral separation of the racemic mixture is SFC conditions.

Instrument: Novasep SFC Superprep
Stationary Phase: Chiralpak AD-H 20µm, 300 x 50mm
Mobile phase: CO_2 / MeOH 73/27
Flowrate: 1000 g/min UV detection: λ=295 nm
Temperature: 45°C
Pressure: 130 bars
Sample: dissolution in MeOH
rt (MeEt isomer 1) = 4.74 min and rt (MeEt isomer 2) = 7.06 min

The S-isomer has been arbitrarily assigned as MeEt isomer 1 and the *R*-isomer has been arbitrarily assigned as MeEt isomer 2. The same nomenclature has been used to describe all related derivatives.

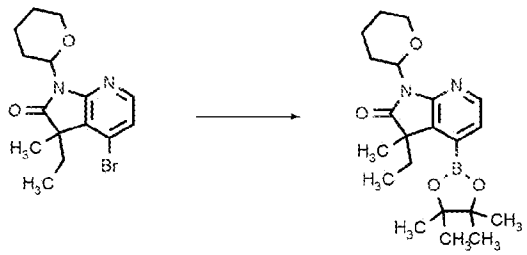
The next steps were the same for racemic mixture and the pure enantiomers. The boronic esters synthesis will be described for the racemic mixture.

Synthesis of 4-bromo-3-ethyl-3-methyl-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-2-one



A 50 mL vial was charged with 4-bromo-3-ethyl-3-methyl-1H-pyrrolo[2,3-b]pyridin-2-one (2.14 g, 6.79 mmol), 3,4-dihydro-2H-pyran (1.9 mL, 20.4 mmol, 3 eq.), and p-toluene sulfonic acid hydrate (271 mg, 1.43 mmol, 0.2 eq.) in anhydrous toluene (34 mL, 0.2 N). The reaction mixture was stirred at 80°C overnight. The reaction mixture was cooled to room temperature. Then water was added and the reaction mixture was extracted with EtOAc. Combined organic layers were dried using a phase separator and concentrated under vacuum to give crude material as an orange solid. The crude material was purified by flash chromatography on silica gel using a gradient of Cyclohexane/ EtOAc. It was transferred via solid phase on Dicalite. Relevant fractions were collected and concentrated under vacuum to afford 4-bromo-3-ethyl-3-methyl-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-2-one (1.45 g, 62.951% Yield) as a yellow oil. 1H NMR (400 MHz, DMSO-d6) δ 8.08 (d, J = 5.6 Hz, 1H), 7.33 (d, J = 5.7 Hz, 1H), 5.42 (dd, J = 11.4, 1.8 Hz, 1H), 3.97 (d, J = 10.9 Hz, 1H), 3.54 (tt, J = 11.2, 2.9 Hz, 1H), 2.86 (pd, J = 13.1, 3.9 Hz, 1H), 2.18 (ddh, J = 15.0, 7.5, 3.5 Hz, 1H), 1.93 (d, J = 10.8 Hz, 1H), 1.81 (dqd, J = 14.7, 7.3, 1.7 Hz, 1H), 1.69 – 1.45 (m, 4H), 1.40 (d, J = 0.8 Hz, 3H), 0.45 (t, J = 7.4 Hz, 3H). m/z = 338.9, 340.8 [M+H]+.

Synthesis of 3-ethyl-3-methyl-1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-b]pyridin-2-one

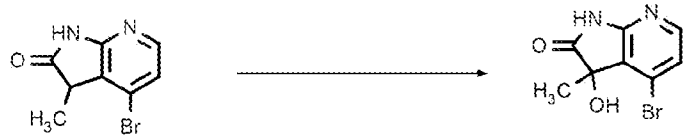


In a 20 mL microwave-vial were introduced bis(pinacolato)diboron (2.19 g, 8.61 mmol, 2 eq.), potassium acetate (1.33 g, 12.9 mmol, 3 eq.), 4-bromo-3-ethyl-3-methyl-1-tetrahydropyran-2-yl-

pyrrolo[2,3-b]pyridin-2-one (1460 mg, 4.30 mmol) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II), complex with dichloromethane (352 mg, 0.430 mmol, 0.1 eq.) in anhydrous dioxane (43 mL, 0.1 N). The mixture was degassed with nitrogen and then stirred at 100°C for 2h. The reaction mixture was allowed to reach room temperature and filtered through a Dicalite pad. The Dicalite was washed with EtOAc. Combined organic layers were concentrated under vacuum to give crude material as a brown oil. The crude material was purified by flash chromatography on silica gel using a gradient of Cyclohexane/ EtOAc. It was transferred via solid phase on Dicalite. Relevant fractions were collected and concentrated under vacuum to afford 3-ethyl-3-methyl-1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-b]pyridin-2-one (1.08 g, 52 % Yield) as a pale yellow oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.19 (d, *J*=5.2 Hz, 1H), 7.25 (d, *J*=5.1 Hz, 1H), 5.43 (dd, *J*=11.4, 2.0 Hz, 1H), 3.96 (d, *J*=11.1 Hz, 1H), 3.64 – 3.49 (m, 1H), 3.01 – 2.79 (m, 1H), 2.33 – 2.16 (m, 1H), 1.93 (d, *J*=11.0 Hz, 1H), 1.87 – 1.73 (m, 2H), 1.71 – 1.43 (m, 6H), 1.34 (s, 12 H), 0.38 (t, *J*=7.4 Hz, 3H); m/z = 387.0 [M+H]+.

Me/OH Scaffold Synthesis

Synthesis of 4-bromo-3-hydroxy-3-methyl-1H-pyrrolo[2,3-b]pyridin-2-one (OHMe)



A round bottom flask was charged with sodium hydride (60%, 203 mg, 5.09 mmol, 1.1 eq.) in THF (10 mL) under N_2. The mixture was cooled down to 0°C and 4-bromo-3-methyl-1,3-dihydropyrrolo[2,3-b]pyridin-2-one (1.05 g, 4.62 mmol) in THF (13 mL) was added dropwise. Then the reaction was opened and left to the air overnight at room temperature. Then an aqueous solution of HCl 1N was added. The aqueous phase was extracted with ethyl acetate. Combined organic phases were dried over phase separator and evaporated to give crude material. The product was triturated in DCM to afford 4-bromo-3-hydroxy-3-methyl-1H-pyrrolo[2,3-b]pyridin-2-one (697mg, 62% Yield) as a pale yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 11.11 (s, 1H), 7.95 (d, *J*=5.7 Hz, 1H), 7.18 (d, *J*=5.7 Hz, 1H), 6.11 (s, 1H), 1.50 (s, 3H); m/z = 243.1, 245.1 [M+H]+.

The two enantiomers were obtained from chiral separation of the racemic mixture in SFC conditions.

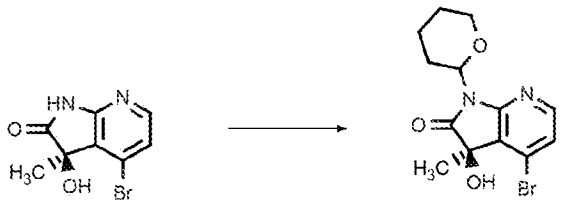
Instrument: Waters prep SFC Supersep

Stationary Phase: Chiralpak AD-H 20µm, 250 x 50mm
Mobile phase: CO2 / MeOH 87/13
Flowrate: 1000g/min UV detection: λ=290 nm
Temperature: 40°C
Pressure: 150 bars
Sample: dissolution in MeOH
rt (OHMe isomer 1) = 6.05 min and rt (OHMe isomer 2) = 8.34 min

The S-isomer has been arbitrarily assigned as OHMe isomer 1 and the *R*-isomer has been arbitrarily assigned as OHMe isomer 2. The same nomenclature has been used to describe all related derivatives.

The next steps were the same for racemic mixture and the pure enantiomers. The boronic esters synthesis will be described starting from OHMe isomer 1.

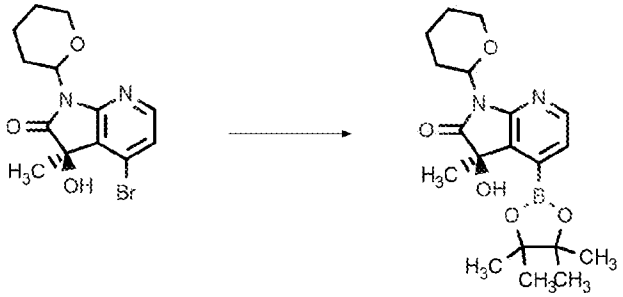
Synthesis of (3R)-4-bromo-3-hydroxy-3-methyl-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-2-one



In a sealed vial, 3,4-dihydro-2H-pyran (3.0 mL, 32.9 mmol, 4 eq.) was added to a stirred solution of (3R)-4-bromo-3-hydroxy-3-methyl-1H-pyrrolo[2,3-b]pyridin-2-one (2.00 g, 8.23 mmol) and p-toluene sulfonic acid hydrate (313 mg, 1.65 mmol, 0.2 eq.) in anhydrous toluene (27 mL, 0.3 N). The reaction was stirred at 90°C overnight. Then the mixture was cooled at 0°C and 4 M hydrogen chloride (4.1 mL, 16.5 mmol, 2 eq.) was added. The mixture was stirred for 2h at room temperature. The solution was concentrated under vacuum. Dichloromethane and a saturated aqueous solution of $NaHCO_3$ were added. The aqueous phase was extracted by dichloromethane. The organic phase was dried on a phase separator and concentrated under vacuum. The crude material was purified by flash chromatography on silica gel using a gradient of heptane / EtOAc. Relevant fractions were collected and evaporated to afford (3R)-4-bromo-3-hydroxy-3-methyl-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-2-one (1.02g, 36% Yield). ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.07 (dd, *J*=5.6, 1.2 Hz, 1H), 7.31 (dd, *J*=5.7, 0.8 Hz, 1H), 6.28 (d, *J*=6.8 Hz, 1H), 5.37 (dd, *J*=11.3, 1.9 Hz, 1H), 4.02 – 3.90 (m, 1H), 3.54 (td, *J*=11.0, 10.6,

3.2 Hz, 1H), 2.90 – 2.73 (m, 1H), 1.93 (d, *J*=10.0 Hz, 1H), 1.69 – 1.44 (m, 7H); m/z = 327.0, 328.9 [M+H]+.

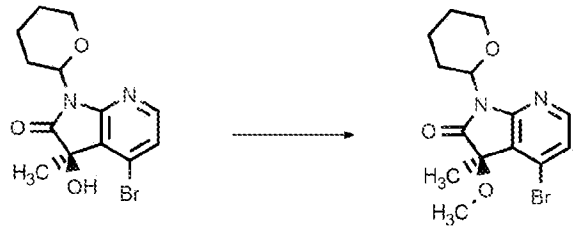
Synthesis of (3R)-3-hydroxy-3-methyl-1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-b]pyridin-2-one



A vial was charged with *bis*(*pinacolato*)diboron (640 mg, 2.52 mmol, 1.5 eq.), potassium acetate (521 mg, 5.04 mmol, 3 eq.), (3R)-4-bromo-3-hydroxy-3-methyl-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-2-one (0.55 g, 1.68 mmol) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II), complex with dichloromethane (140 mg, 0.168 mmol, 0.1 eq.) in anhydrous dioxane (5.6 mL, 0.3N). The vial was sealed and degassed with nitrogen. The reaction mixture was stirred at 100°C for 2h. The reaction mixture was filtered through a pad of Dicalite and the filtrate was evaporated to dryness to give crude material as a dark oil. The crude material was purified by flash chromatography on silica gel using a gradient of dichloromethane / ethyl acetate. It was transferred via solid phase on Dicalite. Fractions were collected and concentrated under vacuum to afford (3R)-3-hydroxy-3-methyl-1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-b]pyridin-2-one (211mg, 28% Yield) was obtained as a yellow gum. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.18 (d, *J*=5.0 Hz, 1H), 7.14 (d, *J*=5.1 Hz, 1H), 5.92 (d, *J*=6.4 Hz, 1H), 5.38 (d, *J*=9.9 Hz, 1H), 3.96 (d, *J*=11.0 Hz, 1H), 3.59 – 3.49 (m, 1H), 2.86 (q, *J*=13.4, 12.5 Hz, 1H), 1.92 (s, 1H), 1.70 – 1.41 (m, 7H), 1.33 (d, *J*=7.0 Hz, 12H); m/z = 293.2 [M+H]+.

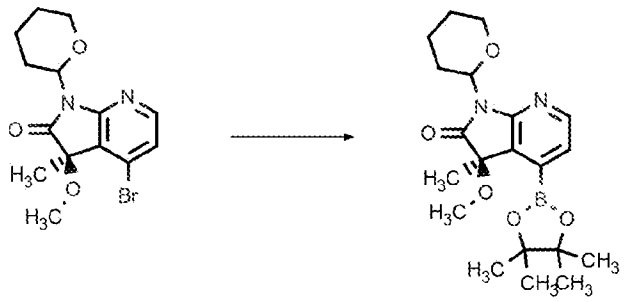
Me/OMe Scaffold Synthesis

Synthesis of (3R)-4-bromo-3-methoxy-3-methyl-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-2-one



In a 50 mL round-bottomed flask, at 0°C, under nitrogen, sodium hydride (60%, 378 mg, 9.44 mmol, 1.5 eq.) was added to a stirred solution of (3R)-4-bromo-3-hydroxy-3-methyl-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-2-one (2.06 g, 6.30 mmol) in anhydrous DMF (32 mL, 0.2 N). The reaction was stirred at room temperature for 30mn. Then 2 M iodomethane in tert-butylmethyl ether (6.3 mL, 12.6 mmol, 2 eq.) was added dropwise at 0°C. The reaction was stirred at 0°C for 15 min and allowed to reach room temperature. After 45 min at room temperature, the reaction was quenched with water and EtOAc was added. The two phases were separated and the aqueous phase was extracted with EtOAc. Combined organic phases were washed with water, dried using a phase separator and evaporated to give (3R)-4-bromo-3-methoxy-3-methyl-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-2-one as an orange gum (1.49g, 63% Yield). ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.16 (d, *J*=5.6 Hz, 1H), 7.40 (dd, *J*=5.6, 0.8 Hz, 1H), 5.42 (dt, *J*=11.4, 2.6 Hz, 1H), 4.00 – 3.93 (m, 1H), 3.61 – 3.49 (m, 1H), 2.91 (s, 3H), 2.87 – 2.75 (m, 1H), 1.94 (d, *J*=10.9 Hz, 1H), 1.70 – 1.41 (m, 7H); m/z = 341.1, 343.1 [M+H]+.

Synthesis of (3R)-3-methoxy-3-methyl-1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-b]pyridin-2-one

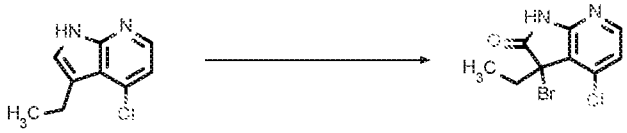


A reacti-vial, under a nitrogen atmosphere, was charged with tricyclohexylphosphane (459 µL, 0.290 mmol, 0.075 eq.), *bis*(pinacolato)diboron (1.96 g, 7.73 mmol, 4 eq.), (3R)-4-bromo-3-

methoxy-3-methyl-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-2-one (1.45 g, 3.87 mmol) and anhydrous dioxane (19 mL, 0.2 N). Then potassium acetate (767 mg, 7.73 mmol, 4 eq.) and tris(dibenzylideneacetone)dipalladium(0) (186 mg, 0.193 mmol, 0.05 eq.) were added. The reaction was stirred at 100°C for 2 h. The solvent was evaporated. Then water and dichloromethane were added. The two phases were separated and the aqueous phase was extracted with dichloromethane. Combined organic phases were dried using a phase separator and evaporated to give crude material as an orange gum. The crude material was purified by flash chromatography on silica gel using a gradient of heptane / ethyl acetate. It was transferred via solid phase. Relevant fractions were collected and concentrated under vacuum to afford (3R)-3-methoxy-3-methyl-1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-b]pyridin-2-one (665 mg, 43% Yield) as an orange gum. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.26 (d, *J*=5.1 Hz, 1H), 7.22 (dd, *J*=5.1, 1.7 Hz, 1H), 5.42 (ddd, *J*=11.4, 5.4, 2.1 Hz, 1H), 4.01 – 3.94 (m, 1H), 3.62 – 3.48 (m, 1H), 2.89 – 2.76 (m, 4H), 1.94 (d, *J*=11.4 Hz, 1H), 1.73 – 1.46 (m, 7H), 1.33 (d, *J*=2.6 Hz, 12H); m/z = 307.2 [M+H]+ (acid form).

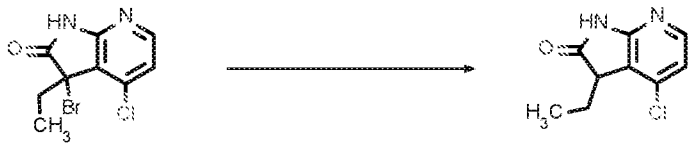
Et/OH Scaffold Synthesis

Synthesis of 3-bromo-4-chloro-3-ethyl-1H-pyrrolo[2,3-b]pyridin-2-one



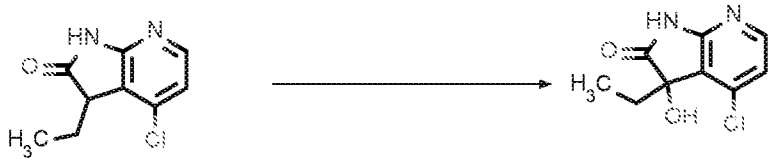
To a stirred solution of 4-chloro-3-ethyl-1H-pyrrolo[2,3-b]pyridine hydrochloride (3.00 g, 13.8 mmol) in tert-butanol (106 mL, 0.13 N) was added in small portions pyridinium bromide-perbromide (11.05 g, 34.5 mmol) . The reaction was stirred at room temperature during 3h. tert-butanol was removed under vacuum. The product was triturated in water and filtered to afford 3-bromo-4-chloro-3-ethyl-1H-pyrrolo[2,3-b]pyridin-2-one (2.95g, 77% Yield) as a beige solid. 1H NMR(DMSO-d6, 400 MHz): δ (ppm) 11.89 (s, 1H), 8.18 (d, J=5.7 Hz, 1H), 7.21 (d, J=5.7 Hz, 1H), 2.84 – 2.56 (m, 1H), 2.47 – 2.23 (m, 1H), 0.62 (t, J=7.4 Hz, 3H)

Synthesis of 4-chloro-3-ethyl-1,3-dihydropyrrolo[2,3-b]pyridin-2-one



To a stirred suspension of 3-bromo-4-chloro-3-ethyl-1H-pyrrolo[2,3-b]pyridin-2-one (2.95 g, 10.7 mmol) in THF (33 mL, 0.3 N), at rt, was added zinc (1.05 g, 16.1 mmol) and then water (0.58 mL, 32.1 mmol) dropwise.The mixture was stirred at room temperature during 2h. Then the solution was filtered under Dicalite to remove all residue of zinc. The filtrate was concentrated under vacuum to afford 4-chloro-3-ethyl-1,3-dihydropyrrolo[2,3-b]pyridin-2-one (2.1g, 98% Yield) as a yellow solid; m/z = 197.1, 199.1 [M+H]+.

Synthesis of 4-chloro-3-ethyl-3-hydroxy-1H-pyrrolo[2,3-b]pyridin-2-one



An aqueous solution of sodium hydroxide 10N (2.7 mL, 26.7 mmol) was added to a solution of 4-chloro-3-ethyl-1,3-dihydropyrrolo[2,3-b]pyridin-2-one (2.10 g, 10.7 mmol) in ethanol (49 mL, 0.2 N). The mixture was stirred at room temperature overnight. The mixture was concentrated under vacuum and a mixture of an aqueous solution of NH_4Cl and MeTHF was added. Phases were separated and the organic phase dried and concentrated under vacuum to afford 4-chloro-3-ethyl-3-hydroxy-1H-pyrrolo[2,3-b]pyridin-2-one (2.2 g, 94% Yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, J = 5.7 Hz, 1H), 7.06 (d, J = 5.7 Hz, 1H), 6.19 (s, 1H), 2.13 (tt, J = 14.3, 7.8 Hz, 1H), 2.03 – 1.87 (m, 1H), 0.55 (t, J = 7.5 Hz, 3H); m/z = 213.1, 215.1 [M+H]+.

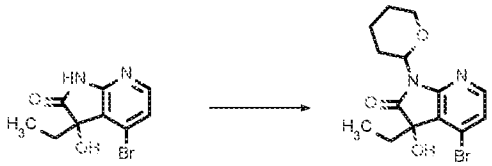
The two enantiomers were obtained from chiral separation of the racemic mixture in SFC conditions:

Instrument: Waters prep SFC200
Stationary Phase: Chiralpak IC 5µm, 250 x 30mm
Mobile phase: CO2 / MeOH 80/20
Flowrate: 100 mL/min UV detection: λ=210 nm
Temperature: 40°C
Pressure: 100 bars
Sample: dissolution in MeOH
rt (OHEt isomer 1) = 4.82 min and rt (OHEt isomer 2) = 6.74 min

The S-isomer has been arbitrarily assigned as OHEt isomer 1 and the *R*-isomer has been arbitrarily assigned as OHEt isomer 2. The same nomenclature has been used to describe all related derivatives.

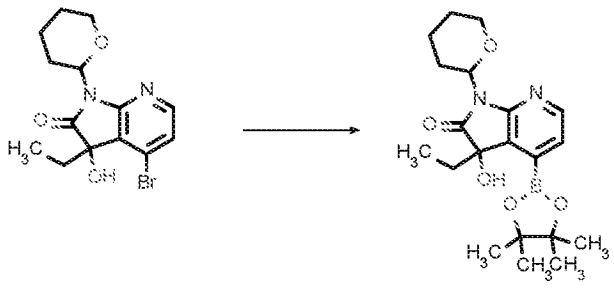
The following protocols were described for racemic mixture.

Synthesis of 4-bromo-3-ethyl-3-hydroxy-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-2-one



In a sealed vial, 3,4-dihydro-2H-pyran (0.59 mL, 6.50 mmol) was added to a stirred solution of 4-bromo-3-ethyl-3-hydroxy-1H-pyrrolo[2,3-b]pyridin-2-one (0.56 g, 2.17 mmol) and para-toluenesulfonic acid (82 mg, 0.433 mmol) in anhydrous toluene (11 mL, 0.2 N). The reaction was stirred at 90°C overnight. Then the mixture was cooled at 0°C and 4 M hydrogen chloride (1.1 mL, 4.33 mmol) was added. The mixture was stirred during 3h at room temperature. The solution was concentrated under vacuum. DCM and an aqueous solution of NaHCO3 were added. The compound was resolubilized under free base form and the aqueous phase was extracted by DCM. The organic phase was dried on a phase separator and concentrated under vacuum. The crude material was purified by flash chromatography on silica gel using a gradient of heptane / AcOEt. It was transferred via solid pause on Dicalite on a 24g column. Fractions were collected and evaporated to afford 4-bromo-3-ethyl-3-hydroxy-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-2-one (200mg, 26% Yield) as a orange oil. m/z = 341.0, 343.0 [M+H]+.

Synthesis of 3-ethyl-3-hydroxy-1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-b]pyridin-2-one

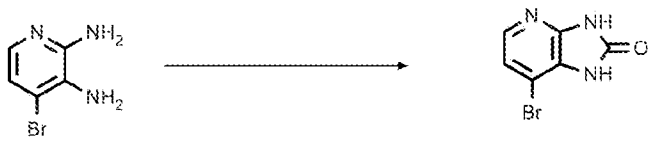


A reacti-vial, under a nitrogen atmosphere, was charged with *bis*(pinacolato)diboron (223 mg, 0.879 mmol, 4 eq.), 4-bromo-3-ethyl-3-hydroxy-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-2-

one (200 mg, 0.586 mmol) and anhydrous dioxane (1.9 mL, 0.3 N). Then potassium acetate (182 mg, 1.76 mmol, 4 eq.) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II), complex with dichloromethane (49 mg, 0.0586 mmol, 0.1 eq.) were added. The reaction was stirred at 100°C for 3 h. The mixture was filtered on a Dicalite pad and the solvant was evaporated. The crude material was purified by flash chromatography on silica gel using a gradient of DCM / ethyl acetate. It was transferred via solid phase. Relevant fractions were collected and concentrated under vacuum to afford 3-ethyl-3-hydroxy-1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-b]pyridin-2-one (97mg, 42.62% Yield) as an yellow gum. m/z = 307.1 [M+H]+ (acid form).

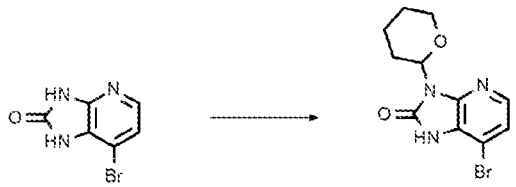
Other Scaffolds

Synthesis of 7-bromo-1,3-dihydroimidazo[4,5-b]pyridin-2-one



4-bromopyridine-2,3-diamine (5.00 g, 25.3 mmol) and 1,1'-carbonyldiimidazole (8.19 g, 50.5 mmol) were introduced to a sealed vial. THF (140 mL) was added and the mixture was stirred at 60°C overnight. The flask was cooled with an ice-bath for 5min. The precipitate was filtered through a glass-frit and washed once with cold THF followed by water. The solid was dried under vacuum. 7-bromo-1,3-dihydroimidazo[4,5-b]pyridin-2-one was afforded as a brown powder (5.14g, 94%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 11.60 (s, 1H), 11.39 (s, 1H), 7.74 (d, *J*=5.7 Hz, 1H), 7.17 (d, *J*=5.7 Hz, 1H); m/z = 214.0, 216.0 [M+H]+.

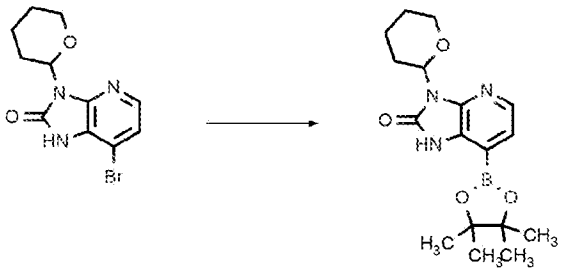
Synthesis of 7-bromo-3-tetrahydropyran-2-yl-1H-imidazo[4,5-b]pyridin-2-one



To a solution of 7-bromo-1,3-dihydroimidazo[4,5-b]pyridin-2-one (500 mg, 2.34 mmol) in anhydrous THF (17.5 mL, 0.1 N) was added 3,4-dihydro-2H-pyran (0.64 mL, 7.01 mmol, 3 eq.) and p-toluene sulfonic acid hydrate (89 mg, 0.467 mmol, 0.2 eq.) . The mixture was stirred at 75°C overnight. 3,4-dihydro-2H-pyran (0.64 mL, 7.01 mmol, 3 eq.) was added and the reaction

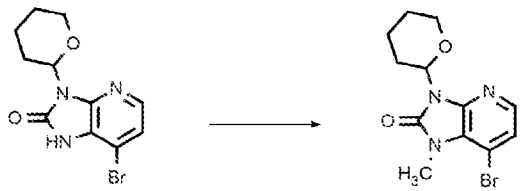
mixture was stirred at 75°C for 3h. The reaction was allowed to reach room temperature and quenched with water. EtOAc was added and the two layers were separated. Aqueous layer was extracted with EtOAc. Combined organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum to give crude material as a brown oil. The crude mixture was purified by flash chromatography using a gradient of cyclohexane/ EtOAc. It was transferred via solid deposit on Dicalite. Relevant fractions were collected and concentrated under vacuum to afford 7-bromo-3-tetrahydropyran-2-yl-1H-imidazo[4,5-b]pyridin-2-one (452 mg, 65% Yield) as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 11.77 (s, 1H), 7.84 (d, *J*=5.6 Hz, 1H), 7.28 (d, *J*=5.7 Hz, 1H), 5.41 (dd, *J*=11.3, 2.2 Hz, 1H), 4.02 – 3.92 (m, 1H), 3.58 (td, *J*=11.3, 3.4 Hz, 1H), 2.94 (qd, *J*=12.6, 4.1 Hz, 1H), 1.99 – 1.90 (m, 1H), 1.76 – 1.45 (m, 4H); m/z = 298.0; 300.0 [M+H]+.

Synthesis of 3-tetrahydropyran-2-yl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-imidazo[4,5-b]pyridin-2-one



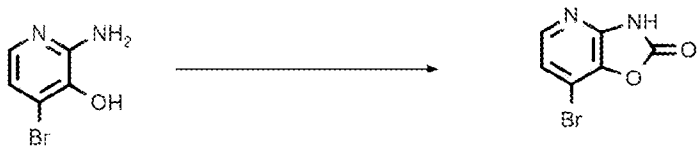
To a solution of 7-bromo-3-tetrahydropyran-2-yl-1H-imidazo[4,5-b]pyridin-2-one (300 mg, 1.01 mmol) in anhydrous dioxane (10 mL, 0.1 N) was added potassium acetate (420 mg, 4.02 mmol, 4 eq.) and bis(pinacolato)diboron (767 mg, 3.02 mmol, 3 eq.). The mixture was degassed with N_2 and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (78 mg, 0.101 mmol, 0.1 eq.) was added. The resulting mixture was stirred 2h at 95°C under N_2. The mixture was filtered on Dicalite and concentrated to give 3-tetrahydropyran-2-yl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-imidazo[4,5-b]pyridin-2-one (1.1 g, 57% Yield) as a dark oil. The crude material was engaged in next steps without more purification. m/z = 264.1 [M+H]+. (boronic acid).

Synthesis of 7-bromo-1-methyl-3-tetrahydropyran-2-yl-imidazo[4,5-b]pyridin-2-one



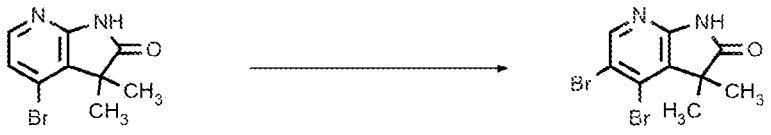
To a solution of 7-bromo-3-tetrahydropyran-2-yl-1H-imidazo[4,5-b]pyridin-2-one (502 mg, 1.63 mmol) in anhydrous DMF (8.3 mL, 0.1N) at 0°C was added sodium hydride (78 mg, 1.95 mmol, 1.2 eq., 60%). The mixture was stirred for 15 min and iodomethane (125 µL, 2.01 mmol, 1.2 eq.) was added at the same temperature. The reaction mixture was stirred for 1h. Water was added and the resulting precipitate was filtered and washed with water. The solid was dried at 40°C under vacuum to afford 7-bromo-1-methyl-3-tetrahydropyran-2-yl-imidazo[4,5-b]pyridin-2-one (0.40 g, 77% Yield) as a pinkish solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 7.86 (d, *J*=5.6 Hz, 1H), 7.32 (d, *J*=5.6 Hz, 1H), 5.49 (dd, *J*=11.3, 2.2 Hz, 1H), 3.97 (dd, *J*=11.2, 2.0 Hz, 1H), 3.59 (s, 4H), 2.92 (qd, *J*=13.5, 13.0, 4.4 Hz, 1H), 2.03 – 1.89 (m, 1H), 1.79 – 1.41 (m, 4H); m/z = 312.1, 314.1 [M+H]+.

Synthesis of 7-bromo-3H-oxazolo[4,5-b]pyridin-2-one



2-amino-4-bromopyridin-3-ol (200 mg, 1.01 mmol) and 1,1'-carbonyldiimidazole (0.33 g, 2.01 mmol, 2 eq.) were introduced in a sealed vial. THF (6 mL, 0.2 N) was added and the mixture was stirred at 60°C overnight. The solution was evaporated under vacuum and the crude triturated in DCM. The solid obtained was filtered and dried under vacuum to obtain 7-bromo-3H-oxazolo[4,5-b]pyridin-2-one as a brown powder (140mg, 32% Yield). ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 7.85 (d, *J*=5.8 Hz, 1H), 7.25 (d, *J*=5.8 Hz, 1H).

Synthesis of 4,5-dibromo-3,3-dimethyl-1H-pyrrolo[2,3-b]pyridin-2-one



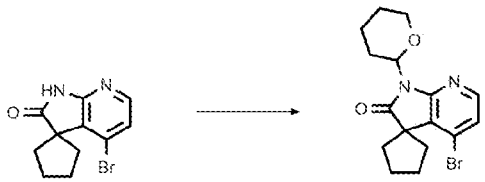
In a 25 mL round-bottomed flask, at room temperature, *N*-bromosuccinimide (236 mg, 1.33 mmol, 1.6 eq.) was added to a stirred suspension of 4-bromo-3,3-dimethyl-1H-pyrrolo[2,3-b]pyridin-2-one (200 mg, 0.830 mmol) and sodium acetate (34 mg, 0.415 mmol, 0.5 eq.) in acetic acid (1 mL, 0.8 N). The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with water and quenched with a 1M aqueous solution of $Na_2S_2O_3$. The solid obtained was filtered through a glass-frit to give 4,5-dibromo-3,3-dimethyl-1H-pyrrolo[2,3-b]pyridin-2-one

(223.1 mg, 82% Yield) as a yellow powder. The product was used in the next step without further purification. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 11.41 (s, 1H), 8.35 (s, 1H), 1.40 (s, 6H).

Synthesis of 4-bromospiro[1H-pyrrolo[2,3-b]pyridine-3,1'-cyclopentane]-2-one

A solution of 4-bromo-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (500 mg, 2.35 mmol) in anhydrous THF (7.8 mL, 0.3N) was cooled to -78 °C and 1 M lithium [bis(trimethylsilyl)amide] solution (8.2 mL, 8.21 mmol, 3.5 eq.) was added. After stirring for 30 minutes 1,4-diiodobutane (371 µL, 2.82 mmol, 1.2 eq.) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic phase was dried using a phase separator and evaporated to give crude material as an oil. The crude material was purified by flash chromatography on silica gel using a gradient of heptane/ EtOAC. It was transferred via solid phase on silica. Relevant fractions were collected and concentrated to give 4-bromospiro[1H-pyrrolo[2,3-b]pyridine-3,1'-cyclopentane]-2-one (258 mg, 41% yield). ^{1}H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 7.91 (d, J = 5.7 Hz, 1H), 7.19 (d, J = 5.7 Hz, 1H), 2.15 (dd, J = 8.1, 5.5 Hz, 2H), 2.08 – 1.82 (m, 6H); m/z = 267.1, 269.1 [M+H]+.

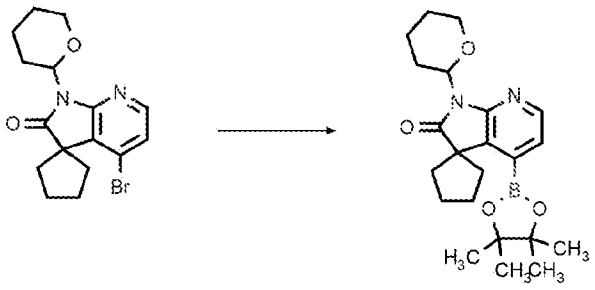
Synthesis of 4'-bromo-1'-tetrahydropyran-2-yl-spiro[cyclopentane-1,3'-pyrrolo[2,3-b]pyridine]-2'-one



3,4-dihydro-2H-pyran (0.26 mL, 2.90 mmol, 3 eq.) was added to a stirred solution of 4-bromospiro[1H-pyrrolo[2,3-b]pyridine-3,1'-cyclopentane]-2-one (258 mg, 0.966 mmol) and p-toluene sulfonic acid hydrate (37 mg, 0.193 mmol, 0.2 eq.) in anhydrous toluene (4.8 mL, 0.2 N). The reaction was stirred at 90°C overnight. The solvent was removed under vacuum. The crude material was purified by flash chromatography on silica gel using a gradient of heptane /

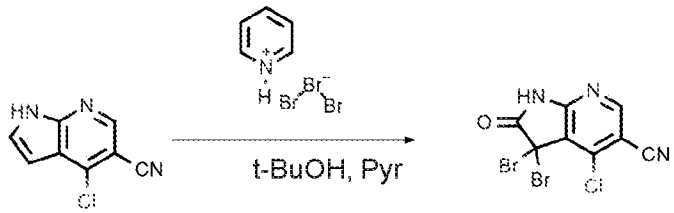
ethyl acetate. Relevant fractions were collected and concentrated under vacuum to afford 4'-bromo-1'-tetrahydropyran-2-yl-spiro[cyclopentane-1,3'-pyrrolo[2,3-b]pyridine]-2'-one (238mg, 70% Yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d,*J*= 5.6 Hz, 1H), 7.32 (d,*J*= 5.7 Hz, 1H), 5.37 (dd,*J*= 11.3, 2.1 Hz, 1H), 3.96 (d,*J*= 11.3 Hz, 1H), 3.53 (td,*J*= 11.2, 4.0 Hz, 1H), 2.95 – 2.76 (m, 1H), 2.17 (dd,*J*= 13.2, 5.9 Hz, 2H), 2.04 – 1.87 (m, 7H), 1.69 – 1.50 (m, 4H); m/z = 351.2-353.2 [M+H]+.

Synthesis of 1'-tetrahydropyran-2-yl-4'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[cyclopentane-1,3'-pyrrolo[2,3-b]pyridine]-2'-one



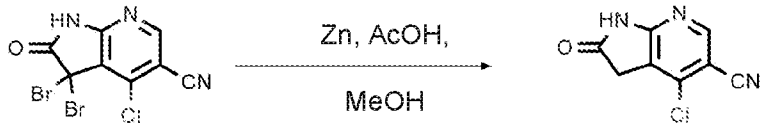
A vial was charged with bis(pinacolato)diboron (258 mg, 1.02 mmol, 1.5 eq.), potassium acetate (210 mg, 2.03 mmol, 3 eq.), 4'-bromo-1'-tetrahydropyran-2-yl-spiro[cyclopentane-1,3'-pyrrolo[2,3-b]pyridine]-2'-one (238 mg, 0.68 mmol) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II), complex with dichloromethane (57 mg, 0.068 mmol, 0.1 eq.) in anhydrous dioxane (2.2 mL, 0.3 N). The vial was sealed and degassed with nitrogen. The reaction mixture was stirred at 100°C overnight. The reaction mixture was filtered through a pad of celite and the filtrate was evaporated to dryness to give crude material as a dark oil. The crude material was purified by flash chromatography on silica gel using a gradient of dichloromethane / ethyl acetate. It was transferred via solid phase on Dicalite. Relevant fractions were collected and concentrated under vacuum to afford 1'-tetrahydropyran-2-yl-4'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[cyclopentane-1,3'-pyrrolo[2,3-b]pyridine]-2'-one (190 mg, 35 % Yield). ^{1}H NMR (Chloroform-*d*, 400 MHz): δ (ppm) 8.16 (d, *J*=5.2 Hz, 1H), 7.28 (d, *J*=5.1 Hz, 1H), 5.52 (dd, *J*=11.3, 2.2 Hz, 1H), 4.21 – 4.10 (m, 1H), 3.69 (td, *J*=11.9, 2.2 Hz, 1H), 3.00 (qd, *J*=13.1, 12.6, 4.1 Hz, 1H), 2.29 – 1.95 (m, 9H), 1.85 – 1.60 (m, 4H), 1.35 (s, 12H); m/z = 399.4 [M+H]+.

Synthesis of 3,3-dibromo-4-chloro-2-oxo-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile



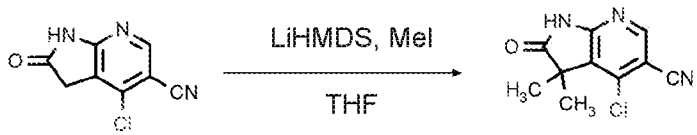
To a flask containing 4-chloro-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (1.00 g, 5.35 mmol) was added tert-butanol (62 mL). pyridinium bromide-perbromide (4.84 mg, 15.1 mmol, 3.5 eq.) was added portion-wise over 10 mins. Pyridine (1.24 mL) was added to aid solubility. The resulting solution was stirred for 6 h at 40 °C. The solution was concentrated to dryness under reduced pressure. To the resulting yellow solid was added water, resulting in a yellow suspension. The organic product was extracted into EtOAc. The combined organic extracts were washed with brine, separated and then dried over anhydrous $MgSO_4$. After filtration the organics were concentrated. The crude material was purified by flash column chromatography with a gradient of EtOAc in heptane. Relevant fractions were collected and concentrated giving the final compound as an off-white solid in sufficient purity for progression to the next step of the synthesis. m/z = 347.7, 349.7 [M-H]-

Synthesis of 4-chloro-2-oxo-1,3-dihydropyrrolo[2,3-b]pyridine-5-carbonitrile



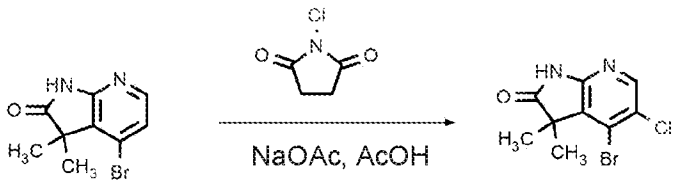
To a flask containing 3,3-dibromo-4-chloro-2-oxo-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (1.90 g, 3.84 mmol) was added methanol (18 mL) and acetic acid (18 mL). zinc (628 mg, 9.60 mmol, 2.5 eq.) was added portion-wise over 3 min. The suspension was stirred for 1.5h at room temperature. The solution was diluted with EtOAc and slowly neutralized by the addition of sat. aq. $NaHCO_3$. The aqueous layer was separated and the organic layer was washed with water, brine and then dried over anhydrous $MgSO_4$. After filtration the organic layer was concentrated to dryness to give a yellow solid. The solid was transferred as a suspension in water and filtered by Buchner filtration. The resulting solid was triturated with cold ether, heptane and then oven-dried for 1 h. This gave the final product as a beige solid (494 mg, 53%). 1H NMR (400 MHz, DMSO-d6) δ 11.81 (br. s, 1H), 8.65 (s, 1H), 3.70 (s, 2H); m/z = 192.1, 194.1 [M-H]-

Synthesis of 4-chloro-3,3-dimethyl-2-oxo-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile



To a flask containing 4-chloro-2-oxo-1,3-dihydropyrrolo[2,3-b]pyridine-5-carbonitrile (494 mg, 2.04 mmol) was added anhydrous THF (7 mL, 0.3 N) under nitrogen. The suspension was cooled to -78 °C and stirred for 5 min. 1 M lithium [bis(trimethylsilyl)amide] solution (7.7 mL, 7.66 mmol, 3.75 eq.) in THF was added slowly over 3 min and the resulting solution was stirred for 10 min. iodomethane (0.31 mL, 4.90 mmol, 2.4 eq.) was added dropwise and the solution was stirred at -78 °C for 30 min. The solution was warmed to room temperature and stirred for an additional 3 h. The solution was cooled to 0 °C and quenched by the dropwise addition of saturated aqueous ammonium chloride. The solution was diluted with EtOAc and washed with water and brine. The organics were then separated and dried (MgSO4) before concentration to dryness. The crude was then purified by flash column chromatography with a gradient of TBME in heptane. The desired fractions were concentrated to dryness in vacuum giving the desired compound as a yellow solid (195 mg, 43%). 1H NMR (500 MHz, CDCl3) δ 8.71 (s, 1H), 8.44 (s, 1H), 1.58 (s, 6H); m/z = 222.0-224.0 [M+H]+

Synthesis of 4-bromo-5-chloro-3,3-dimethyl-1H-pyrrolo[2,3-b]pyridin-2-one



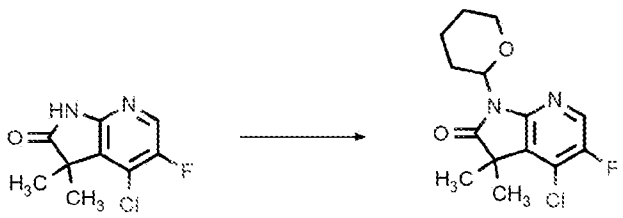
In a 50 mL round-bottomed flask, at room temperature, N-chlorosuccinimide (133 mg, 0.996 mmol, 1.6 eq.) was added to a stirred suspension of 4-bromo-3,3-dimethyl-1H-pyrrolo[2,3-b]pyridin-2-one (150 mg, 0.622 mmol) and sodium acetate (26 mg, 0.311 mmol, 0.5 eq.) in acetic acid (0.8 mL, 0.8 N). The mixture was heated at 60°C for 2h. N-chlorosuccinimide (133 mg, 0.996 mmol, 1.6 eq.) was added and the solution was stirred at 80°C overnight. The reaction mixture was diluted with water and quenched with an aqueous solution of $Na_2S_2O_3$ 1M. The solid obtained was filtered through a glass-frit to give 4-bromo-5-chloro-3,3-dimethyl-1H-pyrrolo[2,3-b]pyridin-2-

one (143mg, 82% Yield) as a yellow powder. The product was engaged in next step without further purification. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 11.41 (s, 1H), 8.27 (s, 1H), 1.41 (s, 6H); m/z = 275.0, 277.0 [M+H]+

Synthesis of 4-chloro-5-fluoro-3,3-dimethyl-1H-pyrrolo[2,3-b]pyridin-2-one

In a round-bottom flask, at 0°C, 1 M lithium [bis(trimethylsilyl)amide] solution (38 mL, 37.7 mmol, 3.7 eq.) was added dropwise to a stirred solution of 4-chloro-5-fluoro-1H,2H,3H-pyrrolo[2,3-b]pyridin-2-one (2.00 g, 10.2 mmol) in anhydrous 2-methyltetrahydrofuran (26 mL, 0.4 N). The mixture was stirred at 0°C for 10 min. Then iodomethane (1.6 mL, 25.5 mmol, 2.5 eq.) was added dropwise at 0°C and the mixture was stirred for 3h at this temperature. An saturated aqueous solution of NH_4Cl was added slowly. Water was added and the mixture was extracted with EtOAc. The combined organic layers were washed with water, brine, dried over phase separator and concentrated to afford a green solid. The crude product was triturated in a mixture of diisopropylether / Et_2O (50/50) and filtered to afford 4-chloro-5-fluoro-3,3-dimethyl-1H-pyrrolo[2,3-b]pyridin-2-one (1.8 g, 78% Yield) as a green solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 11.32 (s, 1H), 8.24 (d, *J*=2.2 Hz, 1H), 1.41 (s, 6H). m/z = 215.2, 217.2 [M+H]+

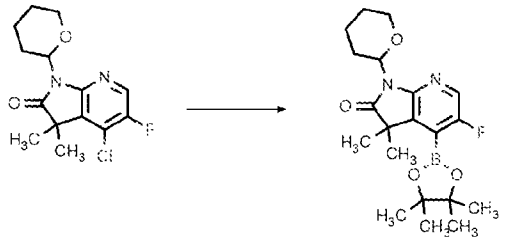
Synthesis of 4-chloro-5-fluoro-3,3-dimethyl-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-2-one



A 20 mL vial was successively charged with 4-chloro-5-fluoro-3,3-dimethyl-1H-pyrrolo[2,3-b]pyridin-2-one (830 mg, 3.87 mmol), anhydrous toluene (13 mL, 0.3 N), p-toluene sulfonic acid hydrate (147 mg, 0.773 mmol, 0.2 eq.) and 3,4-dihydro-2H-pyran (1.1 mL, 11.6 mmol, 3 eq.). The

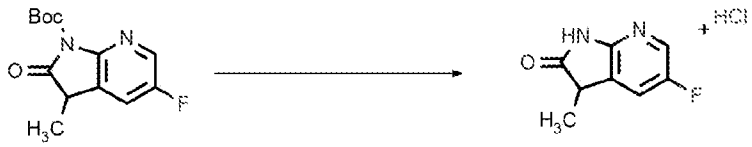
reaction was stirred overnight at 90°C. Then 3,4-dihydro-2H-pyran (0.5 mL) was added and the reaction was stirred at 90°C for another night. The solvent was evaporated to give crude material as a brown oil. The crude material was purified by flash chromatography on silica gel using a gradient of heptane / ethyl acetate. It was transferred via solid phase. Relevant fractions were collected and concentrated under vacuum to afford 4-chloro-5-fluoro-3,3-dimethyl-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-2-one (785 mg, 67% Yield) as an orange gum. 1H NMR (400 MHz, DMSO-d6) δ 8.37 (d, J = 2.0 Hz, 1H), 5.38 (dd, J = 11.3, 2.1 Hz, 1H), 3.97 (d, J = 10.7 Hz, 1H), 3.55 (td, J = 11.3, 4.0 Hz, 1H), 2.82 (qd, J = 13.7, 12.9, 4.1 Hz, 1H), 1.97 – 1.88 (m, 1H), 1.69 – 1.48 (m, 4H), 1.44 (s, 6H), m/z = 299.2, 301.2 [M+H]+

Synthesis of 5-fluoro-3,3-dimethyl-1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-b]pyridin-2-one



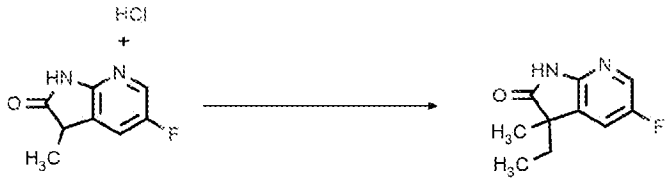
A reacti-vial, under nitrogen atmosphere, was charged with tricyclohexylphosphane (284 µL, 0.180 mmol, 0.075 eq.), bis(pinacolato)diboron (1.22 g, 4.79 mmol, 2 eq.), 4-chloro-5-fluoro-3,3-dimethyl-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-2-one (715 mg, 2.39 mmol) and anhydrous dioxane (12 mL, 0.2 N). Then potassium acetate (475 mg, 4.79 mmol, 2 eq.) and tris(dibenzylideneacetone)dipalladium(0) (115 mg, 0.120 mmol, 0.05 eq.) were added. The reaction was stirred overnight at 100°C. The mixture was filtered on Dicalite and concentrated to give crude material as a black oil. The crude material was purified by flash chromatography on silica gel using a gradient of heptane / ethyl acetate. 5-fluoro-3,3-dimethyl-1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-b]pyridin-2-one (670mg, 22% Yield) was obtained as a yellow solid (mixture of product and debrominated one). m/z = 391.4 [M+H]+

Synthesis of 5-fluoro-3-methyl-1,3-dihydropyrrolo[2,3-b]pyridin-2-one hydrochloride



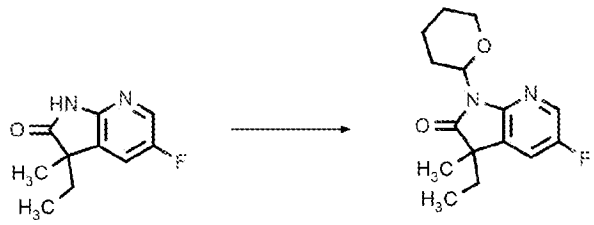
4 M hydrogen chloride in dioxane (1.0 mL, 4.00 mmol, 5 eq.) was added to a solution of tert-butyl 5-fluoro-3-methyl-2-oxo-3H-pyrrolo[2,3-b]pyridine-1-carboxylate (210 mg, 0.752 mmol) in anhydrous dioxane (2 mL, 0.3 N). The vial was sealed and the reaction was stirred at 60°C for 1h. The solution was concentrated to dryness to give 5-fluoro-3-methyl-1,3-dihydropyrrolo[2,3-b]pyridin-2-one hydrochloride (139 mg, 84% yield) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.01 (br s, 1H), 8.03 (t, *J*=1.83 Hz, 1H), 7.69 (dd, *J*=2.20, 8.31 Hz, 1H), 3.54-3.61 (m, 1H), 1.35 (d, *J*=7.58 Hz, 3H); m/z = 167.1 [M+H]+

Synthesis of 3-ethyl-5-fluoro-3-methyl-1H-pyrrolo[2,3-b]pyridin-2-one



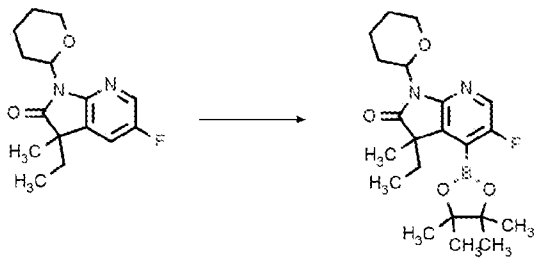
In a 2-5 mL vial, at 0°C, 1 M lithium [bis(trimethylsilyl)amide] solution (1.7 mL, 1.71 mmol, 3.8 eq.) was added dropwise via syringe to a stirred suspension of 5-fluoro-3-methyl-1,3-dihydropyrrolo[2,3-b]pyridin-2-one hydrochloride (98 mg, 0.445 mmol) in anhydrous 2-methyltetrahydrofurane (1.5 mL, 0.3 N). The reaction mixture was stirred at 0°C for 10min. iodoethane (0.065 mL, 0.813 mmol, 1.8 eq.) was added dropwise at 0°C and the reaction was stirred at room temperature over the weekend. Water was added and the mixture was acidified with an aqueous solution of HCl to pH=5. EtOAc was added. The two phases were separated and the aqueous phase was extracted with EtOAc. Combined organic phases were washed with brine, dried using a phase separator and evaporated to give 3-ethyl-5-fluoro-3-methyl-1H-pyrrolo[2,3-b]pyridin-2-one (104 mg, 90% yield) as an orange solid. 1H NMR (400 MHz, DMSO-d6) δ 11.05 (s, 1H), 8.05 (dd, J = 2.7, 1.9 Hz, 1H), 7.75 (dd, J = 8.3, 2.8 Hz, 1H), 1.86 – 1.69 (m, 2H), 1.28 (s, 3H), 0.57 (t, J = 7.4 Hz, 3H). m/z = 195.2 [M+H]+

Synthesis of 3-ethyl-5-fluoro-3-methyl-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-2-one



A 2-5 mL vial was charged with 3-ethyl-5-fluoro-3-methyl-1H-pyrrolo[2,3-b]pyridin-2-one (126 mg, 0.519 mmol), 3,4-dihydro-2H-pyran (0.14 mL, 1.56 mmol, 3 eq.) and p-toluene sulfonic acid hydrate (20 mg, 0.104 mmol, 0.2 N) in anhydrous toluene (1.7 mL, 0.3 N). The resulting mixture was stirred overnight at 95°C and concentrated to dryness. The crude material was purified by flash chromatography on silica gel using a gradient of Heptane/ EtOAc to afford 3-ethyl-5-fluoro-3-methyl-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-2-one (80 mg, 51% yield). ^{1}H NMR (DMSO-d_6, 600 MHz): δ (ppm) 8.17-8.18 (m, 1H), 7.85 (dd, *J* = 8.2, 2.8 Hz, 1H), 5.36 (d, *J* = 10.4 Hz, 1H), 3.95 (dt, *J* = 11.4, 2.0 Hz, 1H), 3.53 (tt, *J* = 11.4, 2.8 Hz, 1H), 2.79-2.94 (m, 1H), 1.89-1.95 (m, 1H), 1.74-1.86 (m, 2H), 1.53-1.65 (m, 2H), 1.45-1.55 (m, 2H), 1.29 (s, 3H), 0.51 (td, *J* = 7.4, 3.4 Hz, 3H) ; m/z = 279.2 [M+H]+.

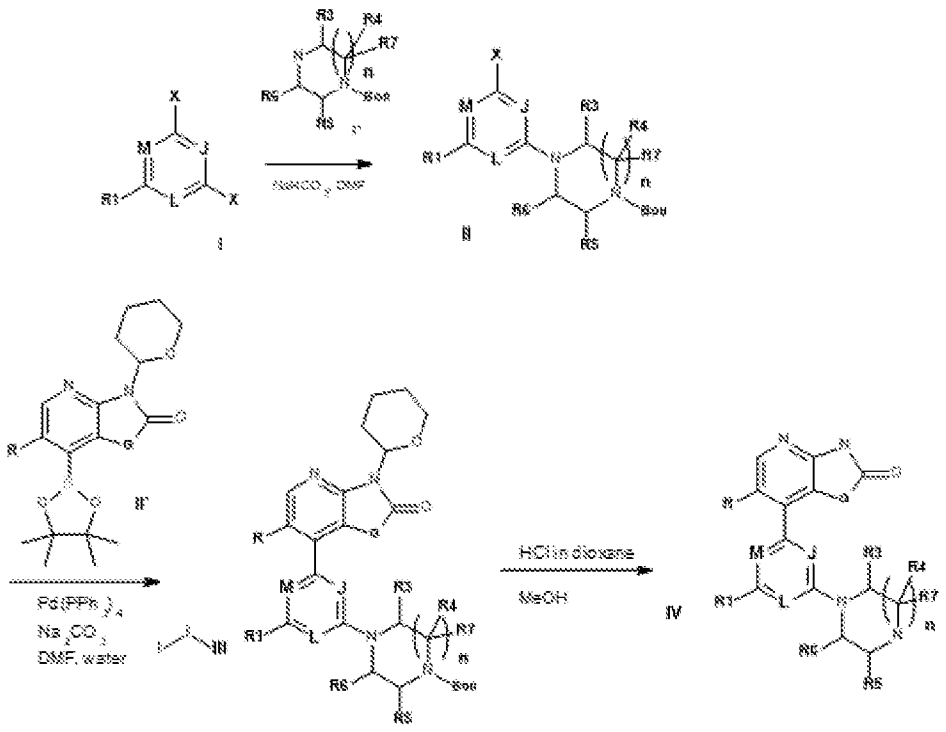
Synthesis of 5-ethyl-3-fluoro-5-methyl-7-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7H-cyclopenta[b]pyridin-6-one



In a 2-5 mL vial, sealed, at -60°C under N_2, 1 M lithium diisopropylamide solution (0.60 mL, 0.600 mmol, 2.3 eq.) was added dropwise to a stirred solution of 3-ethyl-5-fluoro-3-methyl-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-2-one (78 mg, 0.256 mmol) in anhydrous THF (2 mL, 0.1 N). The reaction was stirred at -60°C for 30mn. triisopropyl borate (0.15 mL, 0.650 mmol, 2.5 eq.) was added dropwise at -60°C.The reaction was stirred at -60°C for 30mn and the mixture was allowed to warm to room temperature for 4h. 2,3-dimethylbutane-2,3-diol (0.60 mL, 0.512 mmol, 2 eq.) was added to the mixture then after 10 min. stirring, acetic acid (0.015 mL, 0.269 mmol, 1.05 eq.) was added. The reaction was stirred at room temperature overnight. The mixture

was filtered through Dicalite. Solvent was partially evaporated under N_2 stream and the solution extracted by an aqueous solution of NaOH 5%. The resulting aqueous layer was collected and acidified down to pH=6 at 0°C, by dropwise addition of 3N HCl, then extracted with EtOAc. Combined organic phases were washed with brine, dried using a phase separator and evaporated to give 5-ethyl-3-fluoro-5-methyl-7-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7H-cyclopenta[b]pyridin-6-one (50 mg, 26% yield) as a brown gum. m/z = 323.2 [M+H]+ (acid form) (impure)

Scaffold coupling - General Procedure (pyridine)



G = NH, CMe_2, CMeOH, CEtOH, CMeOMe, CMeEt, C-cyclopentyl
X = Cl
R_1 = H, Me, Cl, CF_3, CHF_2, CF_2Me, $OCHF_2$
M = CH, CCl, N
R_3 = H, Me, Et, CH_2OH, CHF_2
R_4 = H, Me, Et, CH_2OH, CH_2F, CH(OHMe), CH_2OMe, CH_2CF_3, CHF_2, CMe_2OH
R_5, R_6 = H, Me or can form a CH_2 or CH_2OCH_2 bridge
R_7 = H, F, Me or R4 and R7 could form a cyclopropyl
R = H, F
J = CH, N
L = CH, N, CF
n = 1, 2
R_4 with R_5, or R_6 with R_4, or R_5 with R_6 can form a CH_2 or a CH_2CH_2 bridge

Included in this scheme are bridged piperidine structures, bicyclic piperidine structures, and diazacycloheptanes instead of piperidine.

1. Substitution

A microwave tube was charged with piperazine I' (1.08 mmol, 1 eq.), pyridine I (1.08 mmol, 1 eq.), sodium hydrogen carbonate (1.08 mmol, 1 eq.) and anhydrous DMF (3 mL, 0.35 N). The resulting mixture was heated at 110°C overnight. Water was added and the mixture was extracted with EtOAc. Combined organic layers were washed with water, brine, dried over phase separator and concentrated under vacuum to afford a brown solid. The crude product was purified on silica gel column, solid deposit, with a gradient of cyclohexane/EtOAc. Relevant fractions were collected and concentrated under vacuum to afford expected products **II**.

Example 1: Synthesis of tert-butyl (3R)-4-(6-bromo-4-chloro-2-pyridyl)-3-methyl-piperazine-1-carboxylate (R_1 = Cl, R_2 = R_4 = R_5 = H; R_3 = Me, X=Br)

Beige solid; yield 48%, ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.92 (d, *J* = 21.3 Hz, 2H), 4.44 (s, 1H), 3.88 (dd, *J* = 79.1, 12.8 Hz, 3H), 3.19 – 2.81 (m, 3H), 1.43 (s, 9H), 1.05 (d, *J* = 6.6 Hz, 3H); m/z=390.0, 392.0 [M+H]+

2. Suzuki coupling

A reaction vial was charged with substituted pyridine **II** (0.201 mmol, 1eq.), boronic ester II' (0.201 mmol, 1 eq.) and disodium carbonate (0.604 mmol, 3 eq.) in a mixture of DMF (1.6 mL) and Water (0.4 mL). The reaction was degassed and tetrakis triphenylphosphine palladium (0.0201 mmol, 0.1 eq.) was added. The resulting mixture was stirred overnight at 95°C under N_2. Water was added to the mixture. The precipitate was filtered and dissolved in DCM. The organic phase was dried over phase separator and evaporated to afford crude material. It was then purified on silica gel column with a gradient of heptane/EtOAc. Relevant fractions were collected and concentrated under vacuum to afford Suzuki coupling products **III**.

Example 1: Synthesis of tert-butyl (3R)-4-[4-chloro-6-(3,3-dimethyl-2-oxo-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-4-yl)-2-pyridyl]-3-methyl-piperazine-1-carboxylate (R_1 = Cl, R_2 = R_4 = R_5 = H; R_3 = Me, G= CMe_2, X=Br)

White foam; Yield 46%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (d, *J* = 5.3 Hz, 1H), 7.02 (d, *J* = 5.3 Hz, 1H), 6.98 (s, 1H), 6.80 (s, 1H), 5.52 – 5.40 (m, 1H), 4.57 (s, 1H), 4.08 – 3.84 (m, 3H), 3.78 (d, *J* = 13.4 Hz, 1H), 3.63 – 3.49 (m, 1H), 3.19 – 3.00 (m, 2H), 3.00 – 2.83 (m, 2H), 1.97 (d, *J* =

22.9 Hz, 1H), 1.68 – 1.47 (m, 4H), 1.42 (s, 9H), 1.24 – 1.19 (m, 6H), 1.05 (d, *J* = 6.5 Hz, 3H); m/z = 556.2, 558.1 [M+H]+

3. Deprotection

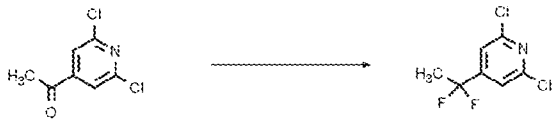
To a solution of Suzuki coupling products **III** (0.093 mmol) in anhydrous methanol (0.46 mL, 0.2N) was added 4 M hydrogen chloride (3.70 mmol, 40 eq.). The resulting mixture was stirred overnight at 60°C under N_2. The mixture was concentrated under vacuum. The product was solubilized in water. Then this aqueous phase was washed with DCM and evaporated to afford expected final products **IV** under salt forms.

Example 1: Synthesis of 4-[4-chloro-6-[(2R)-2-methylpiperazin-1-yl]-2-pyridyl]-3,3-dimethyl-1H-pyrrolo[2,3-b]pyridin-2-one;dihydrochloride (R_1 = Cl, R_2 = R_4 = R_5 = H; R_3 = Me, G= CMe_2)
Green powder; yield 79%, 1H NMR (500 MHz, DMSO-d6) Shift 11.13 (s, 1H), 9.42 (br d, J=9.05 Hz, 1H), 8.98 (br d, J=9.05 Hz, 1H), 8.13 (d, J=5.72 Hz, 1H), 7.08 (s, 1H), 6.91 (d, J=5.70 Hz, 1H), 6.87 (s, 1H), 4.74-4.83 (m, 1H), 4.28 (br d, J=13.45 Hz, 1H), 3.12-3.32 (m, 4H), 2.92-3.02 (m, 1H), 1.25 (d, J=6.85 Hz, 3H), 1.19 (d, J=6.11 Hz, 6H); m/z = 372.1, 374.1

<u>Scaffold coupling – specific examples</u>

The pyridine **I** was either obtained from commercial sources or synthesised by standard techniques according to the procedures that follow.

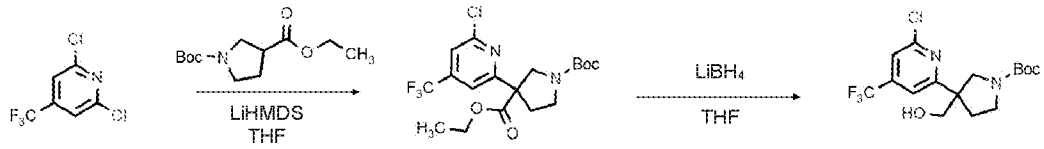
Synthesis of 2,6-dichloro-4-(1,1-difluoroethyl)pyridine (**specific pyridine 1**)



At room temperature, 1-(2,6-dichloro-4-pyridyl)ethanone (300 mg, 1.50 mmol) was added to a stirred solution of triethylamine (0.21 mL, 1.50 mmol, 1 eq.), N,N-diethylethanamine trihydrofluoride (0.50 mL, 3.00 mmol, 2 eq.) and Xtal fluor (687 mg, 3.00 mmol, 2 eq.) in anhydrous DCE (4.5 mL, 0.3 N).The reaction was stirred at 60°C overnight. The reaction was quenched with an aqueous solution of $NaHCO_3$ sat. Dichloromethane was added and the two phases were separated. Combined organic phases were dried using a phase separator and evaporated to give crude material as yellow oil. The crude material was purified by flash

chromatography on silica gel using a gradient of heptane / ethyl acetate. Relevant fractions were collected and concentrated under vacuum to afford 2,6-dichloro-4-(1,1-difluoroethyl)pyridine (124mg, 38% Yield) as a yellow oil. 1H NMR(DMSO-d6, 400 MHz): δ (ppm) 7.81 (s, 2H), 2.01 (t, J=19.3 Hz, 3H); m/z = 212.1, 214.1.

Synthesis of tert-butyl 3-[6-chloro-4-(trifluoromethyl)-2-pyridyl]-3-(hydroxymethyl)pyrrolidine-1-carboxylate (2 steps) (**specific pyridine 2**)



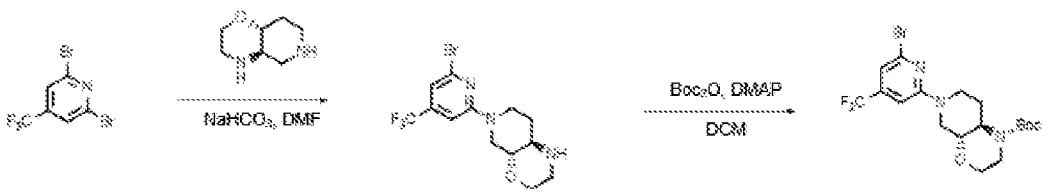
Step 1: Synthesis of O1-tert-butyl O3-ethyl 3-[6-chloro-4-(trifluoromethyl)-2-pyridyl]pyrrolidine-1,3-dicarboxylate

A 2-6 mL microwave vial was successively charged with {O}1-tert-butyl {O}3-ethyl pyrrolidine-1,3-dicarboxylate (436 mg, 1.70 mmol, 1.5 eq.), 2,6-dichloro-4-(trifluoromethyl)pyridine (250 mg, 1.13 mmol), anhydrous THF (6.25 mL, 0.18N) and 1 M lithium [bis(trimethylsilyl)amide] solution (2.3 mL, 2.27 mmol, 2 eq.) at 0°C. The reaction was stirred at room temperature for 1h. The reaction mixture was poured in a saturated aqueous solution of NH_4Cl. Dichloromethane was added and the two phases were separated. The aqueous phase was extracted with dichloromethane. Combined organic phases were washed with water, dried using a phase separator and evaporated to give crude material as an orange gum. The crude material was purified by flash chromatography on silica gel using a gradient of heptane/ Ethyl acetate. It was transferred via solid phase on Isolute HM-N. O1-tert-butyl O3-ethyl 3-[6-chloro-4-(trifluoromethyl)-2-pyridyl]pyrrolidine-1,3-dicarboxylate (408mg, 82 % Yield) was obtained as a colorless gum. 1H NMR (400 MHz, DMSO-d6) δ 8.01 (s, 1H), 7.85 (d, J = 5.6 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 4.07 (d, J = 11.2 Hz, 1H), 3.76 (dd, J = 11.1, 6.9 Hz, 1H), 3.35 (dd, J = 13.8, 7.2 Hz, 2H), 2.66 (dd, J = 12.3, 6.0 Hz, 1H), 2.51 (dt, J = 3.7, 1.9 Hz, 1H), 1.40 (d, J = 5.0 Hz, 9H), 1.11 (t, J = 7.1 Hz, 3H). m/z = 323.2, 325.2 [M+H-Boc]+

Step 2: Synthesis of tert-butyl 3-[6-chloro-4-(trifluoromethyl)-2-pyridyl]-3-(hydroxymethyl)pyrrolidine-1-carboxylate

O1-tert-butyl O3-ethyl 3-[6-chloro-4-(trifluoromethyl)-2-pyridyl]pyrrolidine-1,3-dicarboxylate (200 mg, 0.421 mmol) was dissolved in anhydrous THF (2 mL, 0.2 N). The mixture was cooled down to 0°C. 2 M lithium borohydride solution (0.42 mL, 0.842 mmol, 2 eq.) was added dropwise and the reaction mixture was stirred at room temperature for 2h. The reaction was quenched with Rochelle salts solution and dichloromethane was added. The two phases were separated and the aqueous phase was extracted with dichloromethane. Combined organic phases were dried using a phase separator and evaporated to give tert-butyl 3-[6-chloro-4-(trifluoromethyl)-2-pyridyl]-3-(hydroxymethyl)pyrrolidine-1-carboxylate as a colorless gum. 1H NMR (400 MHz, DMSO-d6) δ 7.88 (s, 1H), 7.69 (d, J = 6.4 Hz, 1H), 5.00 (t, J = 5.5 Hz, 1H), 3.71 – 3.51 (m, 3H), 3.35 (d, J = 7.8 Hz, 1H), 2.20 (d, J = 8.4 Hz, 2H), 1.81 – 1.74 (m, 2H), 1.41 (d, J = 6.6 Hz, 9H); m/z = 325-327[M+H-tBu]+.

Synthesis of tert-butyl rac-(4aR,8aR)-6-[6-bromo-4-(trifluoromethyl)-2-pyridyl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-4-carboxylate (**specific pyridine 3**)



Step 1: Synthesis of rac-(4aR,8aR)-6-[6-bromo-4-(trifluoromethyl)-2-pyridyl]-2,3,4,4a,5,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine

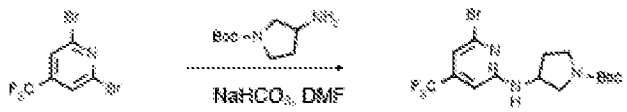
A microwave tube was charged with 2,6-dibromo-4-(trifluoromethyl)pyridine (150 mg, 0.467 mmol), (4aR,8aR)-octahydro-2H-pyrido[4,3-b]morpholine (70 mg, 0.467 mmol), sodium hydrogen carbonate (39 mg, 0.467 mmol) in anhydrous DMF (1.4 mL, 0.34 N). The resulting mixture was heated at 140°C under microwave irradiations for 15 min. Water was added and the mixture was extracted with AcOEt. The combined organic layers were washed with water, brine, dried over phase separator and concentrated to afford a brown oil. The crude product was purified on silica gel column with a gradient of DCM/MeOH. Relevant fractions were collected and concentrated under vacuum to afford rac-(4aR,8aR)-6-[6-bromo-4-(trifluoromethyl)-2-pyridyl]-2,3,4,4a,5,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine (124mg, 72% Yield) as a beige solid. ^{1}H

NMR (DMSO-d_6, 500 MHz): δ (ppm) 7.08 (s, 1H), 6.97 (s, 1H), 3.83-3.95 (m, 2H), 3.67-3.81 (m, 2H), 3.62 (dd, *J* = 13.2, 10.0 Hz, 1H), 3.46 (td, *J* = 10.5, 2.8 Hz, 1H), 3.20-3.28 (m, 1H), 2.93 (ddd, *J* = 12.7, 9.8, 3.4 Hz, 1H), 2.67-2.78 (m, 1H), 2.49-2.53 (m, 1H), 1.80-1.88 (m, 1H), 1.53-1.69 (m, 1H); m/z = 366.0, 368.0 [M+H]+.

Step 2: Synthesis of tert-butyl rac-(4aR,8aR)-6-[6-bromo-4-(trifluoromethyl)-2-pyridyl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-4-carboxylate

To a solution of tert-butoxycarbonyl tert-butyl carbonate (111 mg, 0.51 mmol) and N,N-dimethylpyridin-4-amine (4.2 mg, 0.0339 mmol) in anhydrous DCM (1.7 mL, 0.2 N) was added rac-(4aR,8aR)-6-[6-bromo-4-(trifluoromethyl)-2-pyridyl]-2,3,4,4a,5,7,8,8a-octahydropyrido[4,3-b][1,4]oxazine (124 mg, 0.339 mmol). The resulting mixture was stirred overnight at room temperature under N_2. Water was added and the mixture was extracted with AcOEt. The combined organic layers were washed with water, brine, dried over phase separator and concentrated to afford a brown gum. The crude product was purified on silica gel column with a gradient of Heptane/AcOEt. Relevant fractions were collected and concentrated under vacuum to afford tert-butyl rac-(4aR,8aR)-6-[6-bromo-4-(trifluoromethyl)-2-pyridyl]-3,4a,5,7,8,8a-hexahydro-2H-pyrido[4,3-b][1,4]oxazine-4-carboxylate (126mg, 77% Yield) as a colorless gum. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.16 – 6.97 (m, 2H), 4.40 – 3.77 (m, 4H), 3.68 (d,*J*= 14.5 Hz, 2H), 3.64 – 3.54 (m, 1H), 3.49 (t,*J*= 10.5 Hz, 1H), 3.20 – 2.90 (m, 2H), 1.80 (s, 2H), 1.45 (d,*J*= 6.6 Hz, 9H); m/z = 466.0, 468.0 [M+H]+.

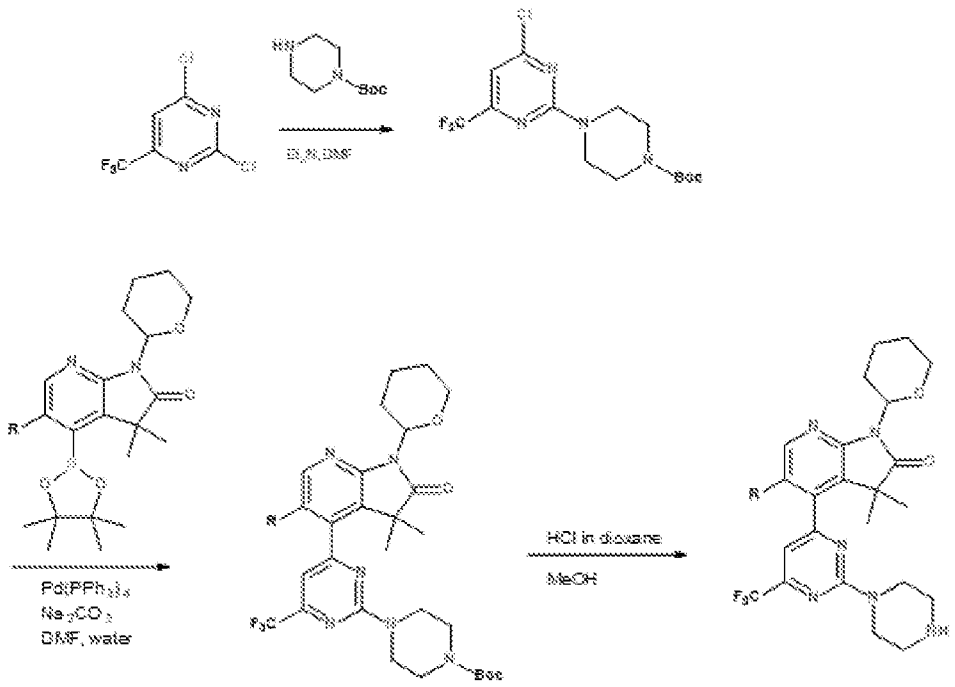
Synthesis of 3-[[6-bromo-4-(trifluoromethyl)-2-pyridyl]amino]pyrrolidine-1-carboxylate (**specific pyridine 4**)



A microwave tube was charged with 2,6-dibromo-4-(trifluoromethyl)pyridine (145 mg, 0.45 mmol), tert-butyl 3-aminopyrrolidine-1-carboxylate (84 mg, 0.452 mmol), sodium hydrogen carbonate (38 mg, 0.452 mmol) in anhydrous DMF (1.3 mL, 0.34 M). The resulting mixture was heated at 150°C under microwave irradiations for 10 min. The mixture was stirred 15 more minutes at 150°C under microwave irradiation. The mixture was stirred 15 more minutes at 150°C under microwave irradiations. Water was added and the mixture was extracted with EtOAc. The combined organic layers were washed with water, brine, dried over phase separator and concentrated to afford a brown oil. The crude product was purified on silica gel column with a

gradient of Heptane/EtOAc. Relevant fractions were collected and concentrated under vacuum to afford tert-butyl 3-[[6-bromo-4-(trifluoromethyl)-2-pyridyl]amino]pyrrolidine-1-carboxylate (108mg, 57% Yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, J = 6.6 Hz, 1H), 6.97 (s, 1H), 6.78 (s, 1H), 4.32 (d, J = 17.4 Hz, 1H), 3.62 – 3.51 (m, 1H), 3.45 – 3.34 (m, 2H), 3.11 (dd, J = 11.0, 4.2 Hz, 1H), 2.13 (s, 1H), 1.82 (s, 1H), 1.41 (d, J = 2.6 Hz, 9H); m/z = 353.9, 355.9 [M+H]+.

Synthesis of tert-butyl 4-[4-(3,3-dimethyl-2-oxo-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-4-yl)-6-(trifluoromethyl)pyrimidin-2-yl]piperazine-1-carboxylate (2 steps) (**pyrimidine**)



Step 1: Synthesis of tert-butyl 4-[4-chloro-6-(trifluoromethyl)pyrimidin-2-yl]piperazine-1-carboxylate

A 10 mL reacti-vial was charged with 2,4-dichloro-6-(trifluoromethyl)pyrimidine (16 mL, 1.11 mmol), tert-butyl piperazine-1-carboxylate (0.21 g, 1.11 mmol), and triethylamine (0.46 mL, 3.32 mmol, 3 eq.) in anhydrous DMF (2.9 mL, 0.4 M). The reaction was stirred at 100°C overnight. The reaction mixture was allowed to reach room temperature, then water was added followed by EtOAc. The two layers were separated and aqueous layer was extracted with EtOAc. Combined

organic phases were washed with water, dried using a phase separator and concentrated under vacuum to give crude material as a brown oil. The crude material was purified by flash chromatography on silica gel using a gradient of cyclohexane/ EtOAc. It was transferred via liquid injection in cyclohexane. Relevant fractions were collected and concentrated under vacuum to afford tert-butyl 4-[4-chloro-6-(trifluoromethyl)pyrimidin-2-yl]piperazine-1-carboxylate (295mg, 73 % Yield) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.32 (s, 1 H), 3.57 - 3.95 (m, 4 H), 3.36 - 3.52 (m, 4 H), 1.42 (s, 9 H); m/z = 367.1 [M+H]+

Step 2: Synthesis of tert-butyl 4-[4-(3,3-dimethyl-2-oxo-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-4-yl)-6-(trifluoromethyl)pyrimidin-2-yl]piperazine-1-carboxylate

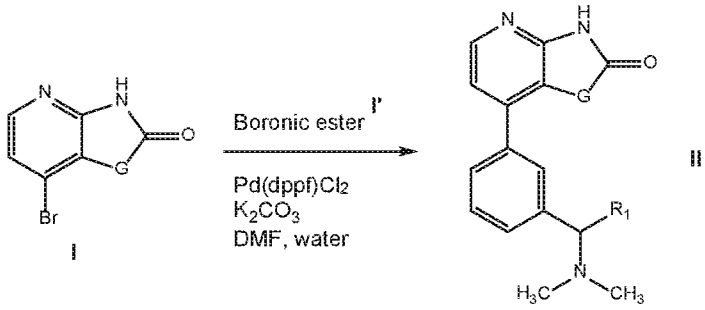
A 5mL reacti-vial was charged with 3,3-dimethyl-1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-b]pyridin-2-one (81 mg, 0.218 mmol), tetrakis triphenylphosphine palladium (50 mg, 0.0436 mmol, 0.1 eq.), tert-butyl 4-[4-chloro-6-(trifluoromethyl)pyrimidin-2-yl]piperazine-1-carboxylate (80 mg, 0.218 mmol) and disodium carbonate (69 mg, 0.65 mmol, 3 eq.) in DMF (1.9 mL) and water (0.4 mL). The reaction was stirred at 100°C for 2h. The reaction mixture was allowed to reach room temperature. Then, water was added. The solid obtained was filtered through a glass-frit and washed with water to give crude material as a brown solid. The crude material was purified by flash chromatography on silica gel using a gradient of cyclohexane/ EtOAc. It was transferred via solid deposit on Dicalite. Relevant fractions were collected and concentrated under vacuum to afford tert-butyl 4-[4-(3,3-dimethyl-2-oxo-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-4-yl)-6-(trifluoromethyl)pyrimidin-2-yl]piperazine-1-carboxylate (66.4mg, 52% Yield) as a pale yellow powder. 1H NMR(400 MHz, DMSO-d6) δ 8.34 (d, J = 5.5 Hz, 1H), 7.69 (d, J = 5.5 Hz, 1H), 7.38 (s, 1H), 5.49 (dd, J = 11.3, 2.0 Hz, 1H), 3.99 (d, J = 10.8 Hz, 1H), 3.84 (s, 3H), 3.56 (td, J = 11.3, 3.4 Hz, 1H), 3.51 – 3.45 (m, 4H), 3.00 – 2.83 (m, 1H), 1.94 (s, 1H), 1.70 – 1.48 (m, 5H), 1.48 – 1.37 (m, 15H). m/z = 577.2 [M+H]+

Step 3: Synthesis of 3,3-dimethyl-4-[2-piperazin-1-yl-6-(trifluoromethyl)pyrimidin-4-yl]-1H-pyrrolo[2,3-b]pyridin-2-one dihydrochloride

A microwave-vial was charged with tert-butyl 4-[4-(3,3-dimethyl-2-oxo-1-tetrahydropyran-2-yl-pyrrolo[2,3-b]pyridin-4-yl)-6-(trifluoromethyl)pyrimidin-2-yl]piperazine-1-carboxylate (66 mg, 0.113 mmol) and 4 M hydrogen chloride in dioxane (0.85 mL, 3.39 mmol, 30 eq.) in methanol (0.56 mL, 0.2 N). The reaction mixture was stirred at 60°C overnight. The solvent was removed under vacuum. Then water was added. Aqueous layer was extracted with EtOAc. Aqueous layer was then concentrated under vacuum to give 3,3-dimethyl-4-[2-piperazin-1-yl-6-

(trifluoromethyl)pyrimidin-4-yl]-1H-pyrrolo[2,3-b]pyridin-2-one dihydrochloride (42.5mg, 77% Yield) as a pale yellow powder. 1H NMR (500 MHz, DMSO-d6): δ ppm 11.19 (s, 1 H), 8.85 - 9.93 (m, 2 H), 8.22 (d, J=5.38 Hz, 1 H), 7.61 (d, J=5.62 Hz, 1 H), 7.47 (s, 1 H), 3.95 - 4.16 (m, 4 H), 3.16 - 3.30 (m, 4 H), 1.45 (s, 6 H); m/z = 393.0 [M+H]+.

Scaffold coupling - General Procedure (phenyl 1)



R_1 = H, Me
G = NH, CHMe

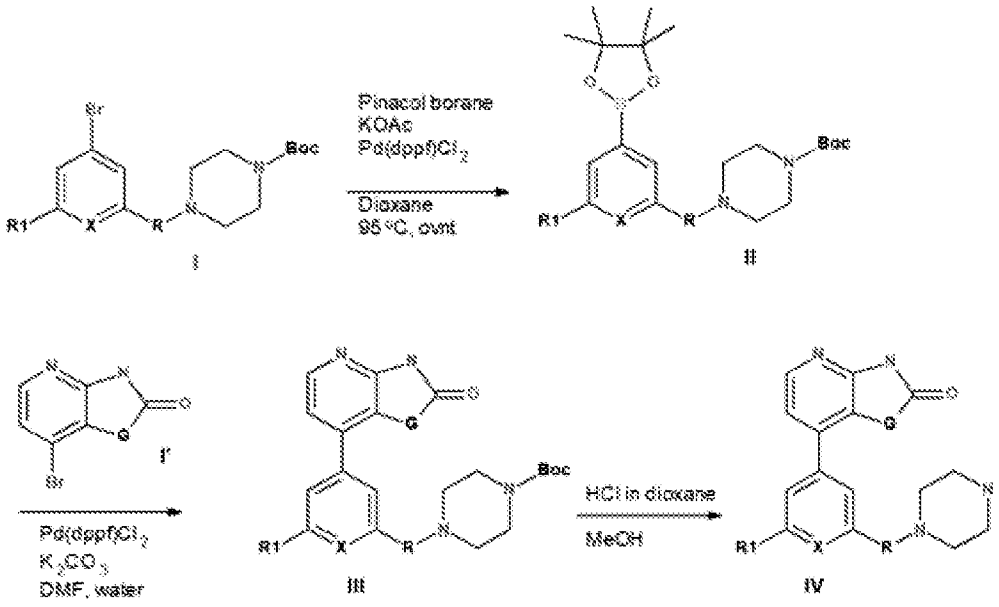
Suzuki coupling

A microwave vial was successively charged with bromine scaffold **I** (0.467 mmol, 1 eq.), dipotassium carbonate (1.40 mmol, 3 eq.) and boronic ester **I'** (0.701 mmol, 1.5 eq.) in a mixture of dioxane (4 mL) and water (0.5 mL). The mixture was degassed and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (II) (95%, 0.0467 mmol, 0.1 eq.) was added. The reaction was irradiated under microwaves and stirred at 140°C for 1h30. The reaction mixture was filtered through a pad of Dicalite, the filtrate was diluted with dichloromethane and passed through a phase separator to remove water. The organic layer was concentrated under vacuum to give crude material as a black solid. The crude material was purified by flash chromatography on silica gel using a gradient of dichloromethane / ethyl acetate. It was transferred via solid phase on Dicalite. Relevant fractions were collected and concentrated under vacuum. The result product was triturated in THF or diethyl ether, filtered and dried at 40°C under vacuum to obtain afforded compounds **II**.

Example 1: Synthesis of 7-[3-[(dimethylamino)methyl]phenyl]-1,3-dihydroimidazo[4,5-b]pyridin-2-one (R_1=H, G=NH)

Beige powder; 32% yield; ^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 11.42 (s, 1H), 11.03 (s, 1H), 7.93 (d, J = 5.4 Hz, 1H), 7.44-7.53 (m, 3H), 7.37 (d, J = 7.3 Hz, 1H), 7.05 (d, J = 5.4 Hz, 1H), 3.48 (s, 2H), 2.17 (s, 6H); m/z = 269.2 [M+H]+

Scaffold coupling - General Procedure (phenyl 2)



Synthesis of boronic ester *(Only in the case* of Example 32 *(X=C, R1=F, R=CH_2), others were commercial)*

To a solution of tert-butyl 4-[(3-bromo-5-fluorophenyl)methyl]piperazine-1-carboxylate (200 mg, 0.536 mmol) **I** in anhydrous dioxane (5.4 mL, 0.1N) was added potassium acetate (158 mg, 1.61 mmol, 3 eq.) and bis(pinacolato)diboron (275 mg, 1.07 mmol, 2 eq.). The solution was degassed with a flow of N_2. [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (39 mg, 0.0536

mmol, 0.1 eq.) was added to the mixture. It was then stirred overnight at 95°C. The solution was filtered on Dicalite and the filtrate was concentrated under vacuum to afford tert-butyl 4-[[3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl]piperazine-1-carboxylate **II** as a black oil. The crude was engaged without more purification in the next step. m/z = 421.5 [M+H]+

Suzuki coupling

To a solution of boronic esters **II** (481 mg, 0.458 mmol, 1.2 eq.) in DMF (3 mL) and Water (0.8 mL) were added bromine scaffold I' (90 mg, 0.373 mmol) and disodium carbonate (119 mg, 1.12 mmol, 3 eq.). The mixture was degassed with N_2 then tetrakis triphenylphosphine palladium (43 mg, 0.0373 mmol, 0.1 eq.) was added. The solution was then stirred overnight at 95°C. The mixture was filtered on a Dicalite pad, rinsed with EtOAc and solvents were evaporated under vacuum. The product was purified on a silica gel column, solid deposit, with a gradient of DCM/MeOH. Relevant fractions were collected and concentrated under vacuum to afford Suzuki coupling products **III**.

Example 32: Synthesis of tert-butyl 4-[[3-(3,3-dimethyl-2-oxo-1H-pyrrolo[2,3-b]pyridin-4-yl)-5-fluoro-phenyl]methyl]piperazine-1-carboxylate (*X=C, R_1=F, R=CH_2, A=CMe_2*)

Yellow oil; 15% yield, ^{1}H NMR(Chloroform-*d*, 400 MHz): δ (ppm) 8.13 (t, *J*=5.3 Hz, 2H), 7.15 (d, *J*=9.4 Hz, 1H), 7.07 (s, 1H), 6.89 (d, *J*=8.9 Hz, 1H), 6.78 (d, *J*=5.4 Hz, 1H), 3.54 (s, 2H), 3.43 (s, 4H), 2.40 (s, 4H), 1.46 (s, 9H), 1.25 (s, 6H); m/z = 455.4 [M+H]+

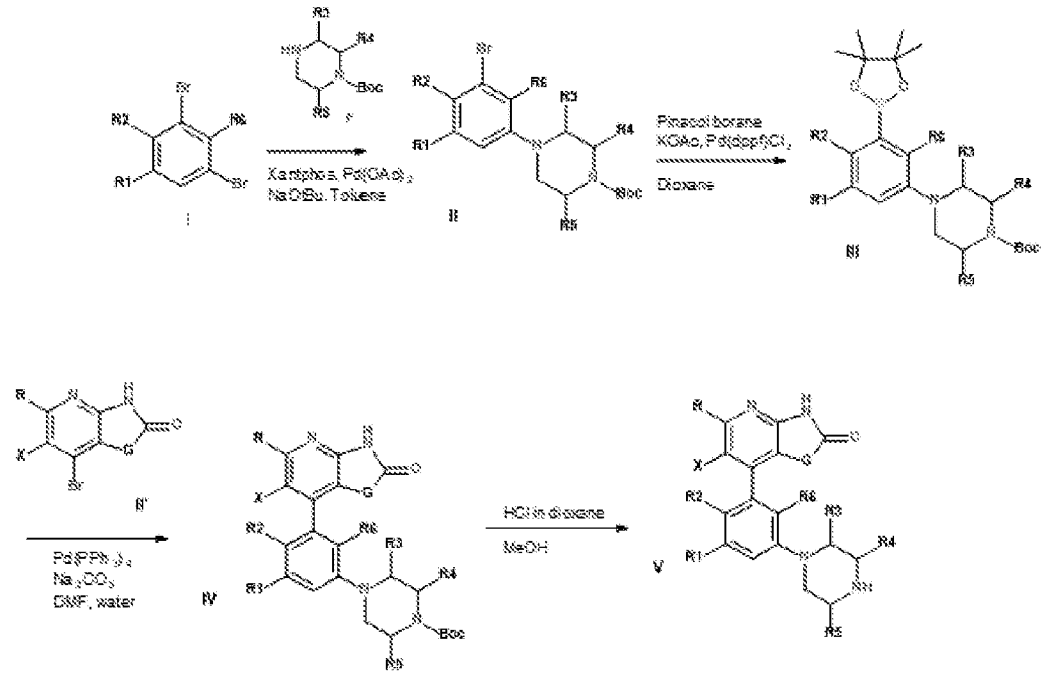
Deprotection

4 M hydrogen chloride solution in dioxane (0.11 mL, 0.447 mmol, 10 eq.) was added to a solution of Suzuki coupling products **III** (0.0447 mmol)) in methanol (0.22 mL, 0.2N). The mixture was stirred at room temperature overnight. The solvent was evaporated under vacuum and products were dried under vacuum at 40°C. Final compounds were afforded as hydrochloric salts **IV**.

Example 32: Synthesis of 4-[3-fluoro-5-(piperazin-1-ylmethyl)phenyl]-3,3-dimethyl-1H-pyrrolo[2,3-b]pyridin-2-one;dihydrochloride *(X=C, R_1=F, R=CH_2, A=CMe_2)*

Yellow solid; 93% yield; 1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.81-12.85 (m, 1H), 11.19 (s, 1H), 9.52 (br s, 2H), 8.13 (d, J = 5.4 Hz, 1H), 7.61-7.78 (m, 1H), 7.45 (br s, 1H), 7.33 (br d, J = 8.6 Hz, 1H), 6.83 (d, J = 5.4 Hz, 1H), 3.95-4.33 (m, 7H), 3.11-3.34 (m, 3H), 1.10 (s, 6H); M/Z = 355.1 [M+H]+

Scaffold coupling - General Procedure (phenyl 3)



G = NH, CH_2, CHMe, NMe, O, CHEt, CMe_2, CMeOH, CMeEt, C-cyclopentyl, CMeOMe
R_1 = H, F, Me, OMe, Cl, CN, CF_3, C(cyclopropyl)CN
R_2 = H, F, Cl
R_3 = H, Me, 3-Pyr
R_4 = H, Me, Et, $CHMe_2$,
R_5 = H, Me
R_6 = H, Cl
R = H, CN
X= H, Cl, CN, Br

Buchwald reaction

A reacti-vial was charged with Xantphos (0.022 mmol), 0.03 eq.), $Pd(OAc)_2$ (7.5 µmol, 0.01 eq.) and NaOtBu (1.12 mmol, 1.5 eq.) under N_2. Anhydrous toluene (1.9 mL, 0.4 M) was added followed by dibromobenzene product **I** (0.786 mmol, 1.05 eq.) and corresponding piperazine I' (0.749 mmol, 1 eq.). The reaction was heated at 80°C overnight. Water was added and the mixture extracted with DCM. The organic phase was dried on a phase separator and concentrated under vacuum. The crude material was purified by flash chromatography on

silica gel using a gradient of heptane/ EtOAc. It was transferred via liquid injection. Relevant fractions were collected and concentrated under vacuum to afford expect compounds **II**.

Example: Synthesis of tert-butyl (3S)-4-(3-bromophenyl)-3-methyl-piperazine-1-carboxylate (R_1 = R_2 = R_4 = R_5 = R_5 = H; R_3 = Me)
Yellow oil; 72% yield, ^{1}H NMR(DMSO-d_6, 400 MHz): δ (ppm) 7.15 (t, *J*=8.1 Hz, 1H), 7.02 (t, *J*=2.1 Hz, 1H), 6.93 – 6.86 (m, 2H), 4.03 (dd, *J*=6.6, 3.5 Hz, 1H), 3.93 (s, 1H), 3.75 (d, *J*=13.1 Hz, 1H), 3.29-3.33 (m, 2H), 3.18 (s, 1H), 3.05 – 2.83 (m, 2H), 1.43 (s, 9H), 0.92 (d, *J*=6.5 Hz, 3H); M/Z = 357.1 [M+H]+

1. Synthesis of boronic esters

In a 10 mL reacti-vial were introduced previous compounds **II** (0.538 mmol, 1 eq.), bis(pinacolato)diboron (0.645 mmol, 1.2 eq.) and potassium acetate (1.62 mmol, 3 eq.) in anhydrous dioxane (1.8 mL, 0.3 M). The mixture was degassed with N_2 and [1,1'-bis(diphenylphosphino)ferrocene] *dichloropalladium*(II) (0.0538 mmol, 0.1 eq.) was added. The solution was heated to 100°C overnight. The mixture was filtered and concentrated under vacuum. The crude material **III** was used without purification in the next step.

Example: Synthesis of tert-butyl (3S)-3-methyl-4-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate (R_1 = R_2 = R_4 = R_5 = R_5 = H; R_3 = Me)
Black oil; m/z = 403.2 [M+H]+

2. Suzuki coupling

A 10 mL reacti-vial was charged with bromine scaffold **II'** (0.327 mmol, 1 eq.), boronic ester **III** (0.523 mmol, 1.6 eq.), Na_2CO_3 (0.981 mmol, 3 eq.) in a solution of DMF (2.6 mL) and water (0.5 mL). The mixture was degassed and tetrakis triphenylphosphine palladium (0.0327 mmol, 0.1 eq.) was added. The reaction was heated at 100°C overnight. The solution was filtered on Dicalite and concentrated under vacuum. The crude material was purified by flash chromatography on silica gel using a gradient of heptane/ EtOAc. Relevant fractions were collected and concentrated under vacuum. The product was then triturated in DCM and dried under vacuum at 40°C overnight to expected compounds **IV**.

Example: Synthesis of tert-butyl (3S)-3-methyl-4-[3-(2-oxo-1,3-dihydroimidazo[4,5-b]pyridin-7-yl)phenyl]piperazine-1-carboxylate (G=NH; R = X = H; R_1 = R_2 = R_4 = R_5 = R_5 = H; R_3 = Me)
Pink powder; 22% yield; ^{1}H NMR(DMSO-d_6, 400 MHz): δ (ppm) 11.39 (s, 1H), 10.96 (s, 1H), 7.92 (d, *J*=5.4 Hz, 1H), 7.35 (t, *J*=7.9 Hz, 1H), 7.06 – 6.96 (m, 4H), 4.10 (s, 1H), 3.95 (s, 1H), 3.76 (d,

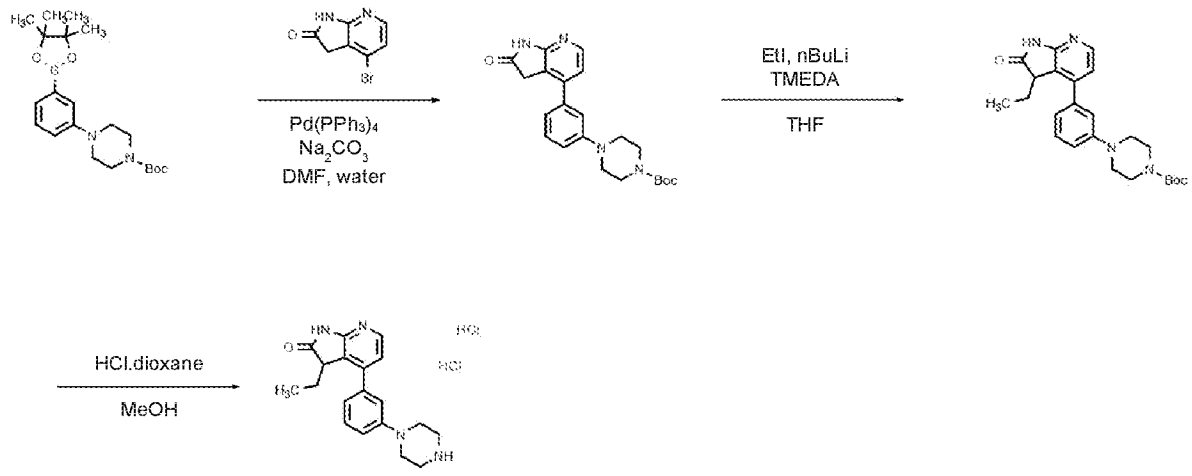
J=12.9 Hz, 1H), 3.42 (d, *J*=11.0 Hz, 1H), 3.25 (br s, 1H), 3.01 (s, 2H), 1.43 (s, 9H), 0.95 (d, *J*=6.4 Hz, 3H); m/z = 410.2 [M+H]+

3. Deprotection

4 M hydrogen chloride solution in dioxane (0.366 mmol, 5 eq.) was added to a solution of Suzuki coupling products **IV** (0.0733 mmol, 1 eq.) in methanol (0.7 mL, 0.1M). The mixture was stirred at room temperature overnight. The solution was concentrated under vacuum and the product triturated in DCM, filtered and dried under vacuum at 40°C to afford expected products **V** on hydrochloric salts forms.

Example 8: Synthesis of 7-[3-[(2S)-2-methylpiperazin-1-yl]phenyl]-1,3-dihydroimidazo[4,5-b]pyridin-2-one dihydrochloride (G=NH; R= X= H; R_1 = R_2 = R_4 = R_5 = H; R_3 = Me)
Brown powder; 80% yield; 1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.53 (br s, 1H), 11.07 (s, 1H), 9.49 (br s, 1H), 9.03 (br s, 1H), 7.93 (d, J = 5.6 Hz, 1H), 7.41 (t, J = 8.1 Hz, 1H), 7.08-7.16 (m, 3H), 7.06 (d, J = 5.6 Hz, 1H), 5.58 (br s, 1H), 4.17-4.41 (m, 1H), 3.63 (br d, J = 13.0 Hz, 1H), 3.18-3.37 (m, 4H), 3.03-3.13 (m, 1H), 1.11 (d, J = 6.8 Hz, 3H); m/z = 310.2 [M+H]+

<u>Scaffold coupling - Specific Procedure (specific phenyl 1)</u>



Synthesis of tert-butyl 4-[3-(2-oxo-1,3-dihydropyrrolo[2,3-b]pyridin-4-yl)phenyl]piperazine-1-carboxylate

A reacti-vial was charged with tetrakis triphenylphosphine palladium (103 mg, 0.0892 mmol, 0.1 eq.), Na_2CO_3 (284 mg, 2.68 mmol, 3 eq.), tert-butyl 4-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate (433 mg, 1.07 mmol, 1.2 eq.) in a solution of DMF (7.2 mL) and water (1.4 mL). The mixture was degassed and 4-bromo-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (200 mg, 0.892 mmol) was added. The reaction was heated at 100°C overnight. The solution was filtered on Dicalite and concentrated under vacuum. The crude material was purified by flash chromatography on silica gel using a gradient of DCM/ EtOAc. Relevant fractions were collected and evaporated to afford tert-butyl 4-[3-(2-oxo-1,3-dihydropyrrolo[2,3-b]pyridin-4-yl)phenyl]piperazine-1-carboxylate (266mg, 75% Yield) as a beige solid. m/z = 395.2 [M+H]+.

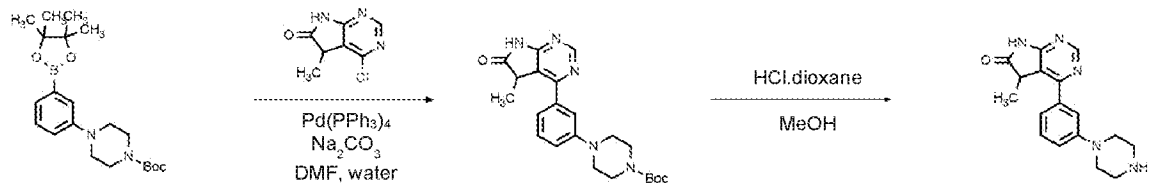
Synthesis of tert-butyl 4-[3-(3-ethyl-2-oxo-1,3-dihydropyrrolo[2,3-b]pyridin-4-yl)phenyl]piperazine-1-carboxylate

At -78°C, iodoethane (0.085 mL, 1.05 mmol, 3 eq.) was added dropwise to a solution of N,N,N',N'-tetramethylethylene diamine (0.16 mL, 1.05 mmol, 3 eq.) in anhydrous THF (0.88 mL) followed by addition of 1.6 M butyllithium solution (0.66 mL, 1.05 mmol, 3 eq.). The reaction was stirred at -78°C for 30 min. Then tert-butyl 4-[3-(2-oxo-1,3-dihydropyrrolo[2,3-b]pyridin-4-yl)phenyl]piperazine-1-carboxylate (140 mg, 0.351 mmol) was added and the mixture left to reach room temperature. The reaction was stirred at room temperature for 2 hours. Water was added and the mixture extracted with DCM. The organic phase was dried and concentrated under vacuum. The crude material was purified by flash chromatography on silica gel using a gradient of DCM /EtOAc. It was transferred via liquid injection in DCM. Relevant fractions were collected and concentrated under vacuum to afford tert-butyl 4-[3-(3-ethyl-2-oxo-1,3-dihydropyrrolo[2,3-b]pyridin-4-yl)phenyl]piperazine-1-carboxylate (20mg, 32% Yield) as a white oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 8.11 (d, J = 5.7 Hz, 1H), 7.40 – 7.32 (m, 1H), 7.14 (s, 1H), 7.07 – 6.97 (m, 3H), 4.21 – 4.11 (m, 1H), 3.54 – 3.36 (m, 4H), 3.11-3.20 (m, 4H), 1.79 – 1.62 (m, 1H), 1.42 (s, 9H), 1.31 – 1.40 (m, 1H), 0.41 (t, J = 7.4 Hz, 3H). m/z = 423.3 [M+H]+.

Synthesis of 3-ethyl-4-(3-piperazin-1-ylphenyl)-1,3-dihydropyrrolo[2,3-b]pyridin-2-one;dihydrochloride

4 M hydrogen chloride solution in dioxane (0.05 mL, 0.2 mmol, 4 eq.) was added to a solution of tert-butyl 4-[3-(3-ethyl-2-oxo-1,3-dihydropyrrolo[2,3-b]pyridin-4-yl)phenyl]piperazine-1-carboxylate (21 mg, 0.050 mmol) in methanol (0.5 mL, 0.1 N). The mixture was stirred at room temperature overnight. The solution was concentrated under vacuum and dried under vacuum at 40°C overnight to afford 3-ethyl-4-(3-piperazin-1-ylphenyl)-1,3-dihydropyrrolo[2,3-b]pyridin-2-one;dihydrochloride (11.8mg, 60% Yield) as a yellow powder. 1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.10 (s, 1H), 9.10 (br s, 2H), 8.12 (d, J = 5.4 Hz, 1H), 7.38 (t, J = 7.9 Hz, 1H), 7.18 (t, J = 1.8 Hz, 1H), 7.05-7.10 (m, 2H), 7.00 (d, J = 5.4 Hz, 1H), 4.14-4.20 (m, 1H), 4.11 (br s, 1H), 3.44 (br d, J = 4.9 Hz, 4H), 3.18-3.26 (m, 4H), 1.68 (ddd, J = 13.8, 7.4, 4.0 Hz, 1H), 1.31-1.44 (m, 1H), 0.41 (t, J = 7.3 Hz, 3H); m/z = 323.2 [M+H]+.

Scaffold coupling - Specific Procedure (specific phenyl 2)



Synthesis of tert-butyl 4-[3-(5-methyl-6-oxo-5,7-dihydropyrrolo[2,3-d]pyrimidin-4-yl)phenyl]piperazine-1-carboxylate

A reacti-vial was charged with tert-butyl 4-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate (264 mg, 0.654 mmol, 1.5 eq.), 4-chloro-5-methyl-5H,6H,7H-pyrrolo[2,3-d]pyrimidin-6-one (80 mg, 0.436 mmol), disodium carbonate (139 mg, 1.31 mmol) and tetrakis triphenylphosphine palladium (51 mg, 0.0436 mmol, 0.1 eq.) in a mixture of DMF (4.2 mL) and water (0.8351 mL). The vial was sealed, degassed with nitrogen and stirred at 120°C for 1h under microwave irradiation. The reaction was stopped and the reaction mixture was filtered through a Dicalite pad, then washed with EtOAc. The solvent was removed under vacuum to give crude material as a red oi. The crude material was purified by flash chromatography on silica gel using a gradient of Cyclohexane/ Acetone. It was transferred via solid pose on Dicalite. Relevant fractions were collected and concentrated under vacuum to

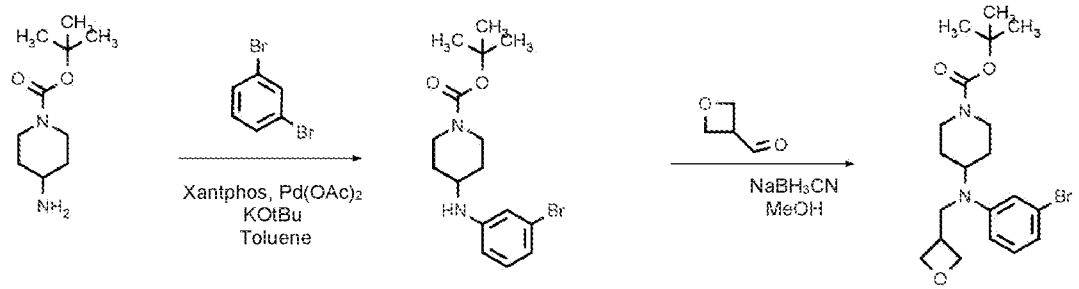
afford tert-butyl 4-[3-(5-methyl-6-oxo-5,7-dihydropyrrolo[2,3-d]pyrimidin-4-yl)phenyl]piperazine-1-carboxylate (53.1mg, 30% Yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.53 (s, 1H), 8.76 (d, J = 9.9 Hz, 1H), 7.44 (s, 3H), 7.12 (d, J = 9.4 Hz, 1H), 4.26 (q, J = 7.4 Hz, 1H), 3.49 (t, J = 5.0 Hz, 4H), 3.22 – 3.12 (m, 4H), 1.43 (s, 9H), 1.12 (d, J = 7.6 Hz, 3H); m/z = 410.3 [M+H]+.

Synthesis of 3-ethyl-4-(3-piperazin-1-ylphenyl)-1,3-dihydropyrrolo[2,3-b]pyridin-2-one;dihydrochloride

4 M hydrogen chloride solution in dioxane (0.32 mL, 1.3 mmol, 10 eq.) was added to a solution of tert-butyl 4-[3-(5-methyl-6-oxo-5,7-dihydropyrrolo[2,3-d]pyrimidin-4-yl)phenyl]piperazine-1-carboxylate (53 mg, 0.13 mmol) in methanol (1.2 mL, 0.1 N). The mixture was stirred at room temperature overnight. The solution was concentrated under vacuum. The product was triturated in DCM and dried under vacuum at 40°C overnight to afford 5-methyl-4-(3-piperazin-1-ylphenyl)-5,7-dihydropyrrolo[2,3-d]pyrimidin-6-one dihydrochloride (34.3 mg, 66% Yield) as a pale yellow solid. 1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.69 (br s, 1H), 9.24 (br s, 2H), 8.79 (s, 1H), 7.36-7.49 (m, 3H), 7.17 (br dd, J = 7.8, 1.5 Hz, 1H), 5.73 (br s, 1H), 4.29 (q, J = 7.6 Hz, 1H), 3.45 (br d, J = 2.2 Hz, 4H), 3.23 (br s, 4H), 1.11 (d, J = 7.6 Hz, 3H); m/z = 310.3 [M+H]+.

<u>Scaffold coupling - Specific Procedure (specific phenyl 3)</u>

(Method provided for 4-aminopiperidine variant. 3-aminopiperidine variant was prepared by the same method)



Synthesis of tert-butyl 4-(3-bromoanilino)piperidine-1-carboxylate

A reacti-vial was charged with diacetoxypalladium (3.3 mg, 0.0145 mmol, 0.01 eq.), Xantphos (25 mg, 0.0436 mmol, 0.03 eq.) and potassium tert-butylate (245 mg, 2.18 mmol, 1.5 eq.)

in anhydrous toluene (3.63 mL, 0.4 N) and stirred 5 min at room temperature. 1,3-dibromobenzene (360 mg, 1.53 mmol, 1.05 eq.) and tert-butyl 4-aminopiperidine-1-carboxylate (300 mg, 1.45 mmol) were successively added to the reaction. The resulting mixture was heated overnight at 80°C under N_2. diacetoxypalladium (0.01 eq), Xantphos (0.03 eq), potassium tert-butylate (1 eq) and tert-butyl 4-aminopiperidine-1-carboxylate (1.5 eq) were added again and the mixture was stirred one more night at 80°C. Water was added and the mixture was extracted with DCM. The combined organic layers were washed with water and brine, filtered on phase separator and concentrated under vacuum to give a yellow liquid. The crude product was purified on silica gel column, solid deposit, with a gradient of Heptane/EtOAc. Relevant fractions were collected and concentrated under vacuum to afford tert-butyl 4-(3-bromoanilino)piperidine-1-carboxylate (304mg, 58% Yield) as a white solid. ^{1}H NMR(DMSO-d_6, 400 MHz): δ (ppm) 6.99 (t, *J*=8.0 Hz, 1H), 6.75 (t, *J*=2.0 Hz, 1H), 6.66 – 6.61 (m, 1H), 6.57 (dd, *J*=8.3, 1.6 Hz, 1H), 5.81 (d, *J*=8.2 Hz, 1H), 3.86 (d, *J*=13.1 Hz, 2H), 3.50 – 3.34 (m, 1H), 2.92 (s, 2H), 1.85 (dd, *J*=12.8, 3.0 Hz, 2H), 1.41 (s, 9H), 1.31 – 1.12 (m, 2H); m/z = 355.0 [M+H]+

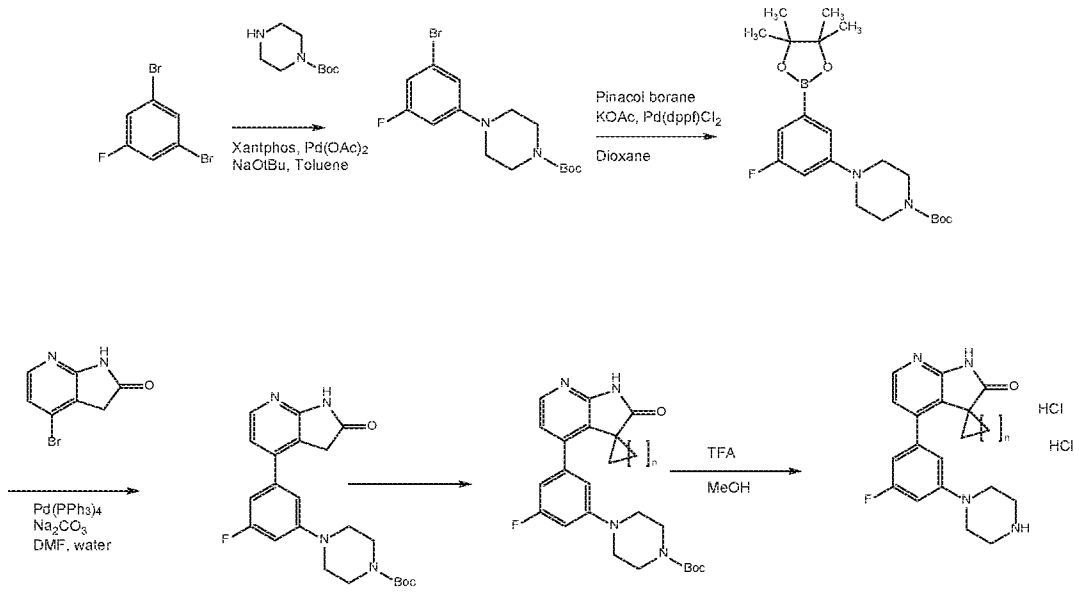
Synthesis of tert-butyl 4-[3-bromo-N-(oxetan-3-ylmethyl)anilino]piperidine-1-carboxylate

A reacti-vial was charged with tert-butyl 4-(3-bromoanilino)piperidine-1-carboxylate (293 mg, 0.808 mmol), oxetane-3-carbaldehyde (110 mg, 1.21 mmol, 1.5 eq.) and acetic acid (0.046 mL, 0.808 mmol, 1 eq.) in anhydrous methanol (4 mL, 0.2 N). The mixture was stirred 30 minutes and sodium cyanoborohydride (1010 mg, 2.02 mmol, 2.5 eq.) (resin) was added. The resulting mixture was stirred 7 days with several additions of oxetane-3-carbaldehyde at 50°C. The resin was filtered and washed with MeOH. The filtrate was concentrated under vacuum to give a colourless oil. The crude product was purified on silica gel column, solid deposit, with a gradient of heptane/EtOAc. Relevant fractions were collected and concentrated under vacuum to afford tert-butyl 4-[3-bromo-N-(oxetan-3-ylmethyl)anilino]piperidine-1-carboxylate (194mg, 56% Yield) as a colorless gum. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 7.11 (t, *J*=8.1 Hz, 1H), 6.96 (t, *J*=2.0 Hz, 1H), 6.82 (ddd, *J*=13.8, 8.2, 1.7 Hz, 2H), 4.55 (dd, *J*=7.9, 5.9 Hz, 2H), 4.31 (t, *J*=6.2 Hz, 2H), 4.02 (d, *J*=11.2 Hz, 2H), 3.72 (td, *J*=9.7, 7.9, 5.9 Hz, 1H), 3.43 (d, *J*=6.9 Hz, 2H), 3.11 (hept, *J*=6.8 Hz, 1H), 2.83 (s, 2H), 1.62 (d, *J*=10.3 Hz, 2H), 1.49 (qd, *J*=12.1, 4.3 Hz, 2H), 1.42 (s, 9H); m/z = 425.1, 427.1 [M+H]+

The next steps were similar to General Procedure – Phenyl 3.

.

Scaffold coupling - Specific Procedure (specific phenyl 4)



Synthesis of tert-butyl 4-(3-bromo-5-fluoro-phenyl)piperazine-1-carboxylate

A vial was charged with Xantphos (17 mg, 0.0300 mmol, 0.03 eq.), $Pd(OAc)_2$ (2.3 mg, 9.98 µmol, 0.01 eq.) and NaOtBu (107 mg, 0.474 mmol, 1.5 eq.) under N_2. Anhydrous toluene (118 mL, 0.4N) was added followed by 1,3-dibromo-5-fluorobenzene (12.6 g, 49.7 mmol, 1.05 eq.) and tert-butyl piperazine-1-carboxylate (9 g, 47.3 mmol). The reaction was heated at 80°C overnight. Water was added and the mixture extracted with DCM. The organic phase was washed with an aqueous solution of $MgCl_2$, dried on a phase separator and concentrated under vacuum to give tert-butyl 4-(3-bromo-5-fluoro-phenyl)piperazine-1-carboxylate as an orange oil (20.8 g, quantitative yield). The crude material was directly engaged in the next reaction. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 6.95 – 6.92 (m, 1H), 6.84 – 6.76 (m, 2H), 3.47 – 3.36 (m, 4H), 3.24 – 3.14 (m, 4H), 1.42 (s, 9H); m/z = 305.0 [M+H-tBu]+

Synthesis of tert-butyl 4-[3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate

In a 500 mL sealed vial were introduced tert-butyl 4-(3-bromo-5-fluoro-phenyl)piperazine-1-carboxylate (81%, 20.81 g, 46.9 mmol), bis(pinacolato)diboron (14.3 g, 56.3 mmol, 1.2

eq.) and potassium acetate (14.69 g, 0.141 mol, 3 eq.) in anhydrous dioxane (156 mL, 0.3 N). The mixture was degassed with N_2 and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II), complex with dichloromethane (3.84 g, 4.69 mmol, 0.1 eq.) was added. The solution was heated to 100°C overnight. The mixture was filtered and concentrated under vacuum. The crude material was purified by flash chromatography on silica gel using a gradient of heptane/ EtOAc. It was transferred via solid deposit on silica. Relevant fractions were collected and concentrated under vacuum to afford tert-butyl 4-[3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate as a brown foam (8.67 g, 46%). 1 H NMR (400 MHz, Chloroform-d) δ 7.12 (d, J = 2.2 Hz, 1H), 6.98 (dd, J = 8.3, 2.3 Hz, 1H), 6.67 (dt, J = 11.9, 2.3 Hz, 1H), 3.58 – 3.54 (m, 4H), 3.20 – 3.13 (m, 4H), 1.56 (s, 6H), 1.48 (s, 9H), 1.33 (s, 12H); m/z = 407.1 [M+H]+

Synthesis of tert-butyl 4-[3-fluoro-5-(2-oxo-1,3-dihydropyrrolo[2,3-b]pyridin-4-yl)phenyl]piperazine-1-carboxylate

A 50mL sealed tube was charged with 4-bromo-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (500 mg, 2.35 mmol), tert-butyl 4-[3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate (1.05 g, 2.58 mmol, 1.1 eq.) , disodium carbonate (746 mg, 7.04 mmol, 3 eq.) in a solution of DMF (17.5 mL) and Water (5 mL). The mixture was degassed and tetrakis(triphenylphosphine) palladium (542 mg, 0.469 mmol, 0.1 N) was added. The reaction was heated at 100°C overnight. The reaction mixture was diluted with water, filtered and the residue give crude material as yellowish powder. The crude material was purified by flash chromatography on silica gel using a gradient of Heptane/EtOAc. Relevant fractions were collected and concentrated under vacuum to afford tert-butyl 4-[3-fluoro-5-(2-oxo-1,3-dihydropyrrolo[2,3-b]pyridin-4-yl)phenyl]piperazine-1-carboxylate as orange powder (631 mg, 42%). ^{1}H NMR(DMSO-d_6, 400 MHz): δ (ppm) 11.08 (s, 1H), 8.12 (d, *J*=5.5 Hz, 1H), 7.09 (d, *J*=5.5 Hz, 1H), 6.97 (s, 1H), 6.88 (s, 1H), 6.85 (dd, *J*=3.8, 1.7 Hz, 1H), 3.78 (s, 2H), 3.52 – 3.41 (m, 4H), 3.29 – 3.21 (m, 4H), 1.43 (s, 9H); m/z = 413.2 [M+H]+

Specific Procedure (specific phenyl 4a)

Synthesis of tert-butyl 4-[3-fluoro-5-(2-oxospiro[1H-pyrrolo[2,3-b]pyridine-3,1'-cyclopropane]-4-yl)phenyl]piperazine-1-carboxylate (n=1)

To a 9 mL reacti-vial were added tert-butyl 4-[3-fluoro-5-(2-oxo-1,3-dihydropyrrolo[2,3-b]pyridin-4-yl)phenyl]piperazine-1-carboxylate (166 mg, 0.36 mmol), diphenylvinylsulfonium triflate (127

mg, 0.33 mmol, 0.9 eq.), zinc trifluoromethanesulfonate (276 mg, 0.74 mmol, 2 eq.) and molecular sieve (100mg) in DMF-Anhydrous (2.1 mL, 0.2 N). The mixture was stirred at room temperature for 10 min and 1,8-diazabicyclo[5.4.0]-7-undecene (167 µL, 1.11 mmol, 3 eq.) was added into it. The mixture was stirred for 3h and quenched with water, then was extracted with EtOAc. The combined organic layers were washed with brine, dried using a phase separator and evaporated to give crude material as an oil. The crude material was purified via preparative HPLC in TFA conditions (preparative HPLC with trifluoroacetic acid mobile phase). Relevant fractions were combined and concentrated under vacuum to give tert-butyl 4-[3-fluoro-5-(2-oxospiro[1H-pyrrolo[2,3-b]pyridine-3,1'-cyclopropane]-4-yl)phenyl]piperazine-1-carboxylate (89 mg, 54%) as a yellowish powder. m/z = 439.1 [M+H]+.

Synthesis of 4-(3-fluoro-5-piperazin-1-yl-phenyl)spiro[1H-pyrrolo[2,3-b]pyridine-3,1'-cyclopropane]-2-one;2,2,2-trifluoroacetic acid (n=1)

In a reacti-vial, trifluoroacetic acid (0.15 mL, 2.03 mmol, 10 eq.) was added to a stirred solution of tert-butyl 4-[3-fluoro-5-(2-oxospiro[1H-pyrrolo[2,3-b]pyridine-3,1'-cyclopropane]-4-yl)phenyl]piperazine-1-carboxylate (89 mg, 0.203 mmol) in anhydrous DCM (2 mL, 0.1 N). The reaction was stirred at room temperature for 1h. The reaction mixture was evaporated to dryness under vacuum to afford product as a yellow powder. The crude material was purified via preparative HPLC in TFA conditions (preparative HPLC with trifluoroacetic acid mobile phase). Relevant fractions were combined and concentrated to give a yellow oil. This oil was taken up in mixture of DCM/MeOH and under stirring, resin PL-HCO3 was added until the pH of the mixture was 8. The solution was filtered and concentrated then dried overnight under vacuum to afford 4-(3-fluoro-5-piperazin-1-yl-phenyl)spiro[1H-pyrrolo[2,3-b]pyridine-3,1'-cyclopropane]-2-one;2,2,2-trifluoroacetic acid (13.2mg, 14% Yield). 1H NMR (DMSO-d6, 500 MHz): δ (ppm) 11.32 (s, 1H), 8.72 (br s, 2H), 8.07 (d, J = 5.4 Hz, 1H), 6.91 (br dt, J = 12.5, 2.2 Hz, 1H), 6.74 (d, J = 5.4 Hz, 1H), 6.72 (t, J = 1.5 Hz, 1H), 6.60 (dt, J = 8.6, 1.2 Hz, 1H), 3.42-3.46 (m, 4H), 3.18-3.23 (m, 4H), 1.28-1.37 (m, 2H), 1.22 (q, J = 4.0 Hz, 2H). m/z = 339.1 [M+H]+.

Specific Procedure (specific phenyl 4b)

Synthesis of tert-butyl 4-[3-fluoro-5-(2-oxospiro[1H-pyrrolo[2,3-b]pyridine-3,1'-cyclobutane]-4-yl)phenyl]piperazine-1-carboxylate (n=2)

To a solution of tert-butyl 4-[3-fluoro-5-(2-oxo-1,3-dihydropyrrolo[2,3-b]pyridin-4-yl)phenyl]piperazine-1-carboxylate (327 mg, 0.64 mmol) in anhydrous THF (6.4 mL, 0.1 N) was

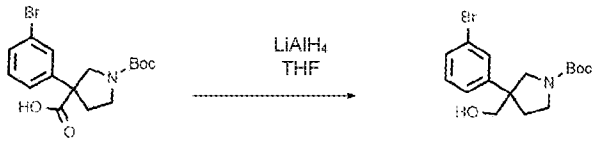
added dropwise 1 M lithium [bis(trimethylsilyl)amide] solution (1.4 mL, 1.41 mmol, 2.2 eq.) at -78°C under N_2. The mixture was stirred 5 min at this temperature. Then 1,3-diiodopropane (0.098 mL, 0.835 mmol, 1.3 eq.) was added dropwise at -78°C and the resulting mixture was stirred 1h letting it rise to room temperature. The mixture was quenched by an aqueous solution of NH_4Cl. Water was added and the mixture was extracted with EtOAc. Organic layers were washed with water and brine, dried over phase separator and concentrated to afford a brown oil. The crude product was purified via preparative HPLC in TFA conditions (preparative HPLC with trifluoroacetic acid mobile phase). Relevant fractions were combined and concentrated to give tert-butyl 4-[3-fluoro-5-(2-oxospiro[1H-pyrrolo[2,3-b]pyridine-3,1'-cyclobutane]-4-yl)phenyl]piperazine-1-carboxylate (39mg, 12%) as a brown solid. ^{1}H NMR(DMSO-d_6, 400 MHz): δ (ppm) 11.00 (s, 1H), 8.06 (d, *J*=5.4 Hz, 1H), 6.89 – 6.86 (m, 2H), 6.81 (d, *J*=5.3 Hz, 1H), 6.73 (d, *J*=9.2 Hz, 1H), 3.49 – 3.40 (m, 4H), 3.28 – 3.16 (m, 4H), 2.42 – 2.29 (m, 2H), 2.28 – 2.17 (m, 2H), 1.79-1.89 (m, 1H), 1.42 (d, *J*=3.8 Hz, 9H), 1.30 – 1.17 (m, 1H); m/z = 453.2 [M+H]+

Synthesis of 4-(3-fluoro-5-piperazin-1-yl-phenyl)spiro[1H-pyrrolo[2,3-b]pyridine-3,1'-cyclobutane]-2-one (n=2)

To a solution of tert-butyl 4-[3-fluoro-5-(2-oxospiro[1H-pyrrolo[2,3-b]pyridine-3,1'-cyclobutane]-4-yl)phenyl]piperazine-1-carboxylate (39 mg, 0.0767 mmol) in anhydrous DCM (0.4 mL, 0.2N) was added trifluoroacetic acid (57 µL, 0.767 mmol, 10 eq.). The resulting mixture was stirred 8h at room temperature under N_2. Then the solution was concentrated under vacuum. The crude product was purified via preparative HPLC in TFA conditions (preparative HPLC with trifluoroacetic acid mobile phase). Relevant fractions were combined and concentrated under vacuum. The product was taken up in a mixture of DCM/MeOH and resin PL-HCO_3 was added until pH = 8. The solution was filtered and concentrated under vacuum to afford 4-(3-fluoro-5-piperazin-1-yl-phenyl)spiro[1H-pyrrolo[2,3-b]pyridine-3,1'-cyclobutane]-2-one (11mg, 34%) as an orange solid. 1H NMR (500 MHz, DMSO-d6) δ ppm 10.48 - 11.39 (m, 1 H), 8.04 (d, J=5.38 Hz, 1 H), 6.81 - 6.87 (m, 2 H), 6.80 (d, J=5.38 Hz, 1 H), 6.61 - 6.67 (m, 1 H), 3.24 - 3.30 (m, 1 H), 3.10 - 3.14 (m, 4 H), 2.76 - 2.81 (m, 4 H), 2.21 - 2.37 (m, 4 H), 1.73 - 1.90 (m, 1 H), 1.12 - 1.31 (m, 1 H); m/z = 353.1 [M+H]+

Scaffold coupling - Specific Procedure (specific phenyl 5)

Synthesis of tert-butyl 3-(3-bromophenyl)-3-(hydroxymethyl)pyrrolidine-1-carboxylate

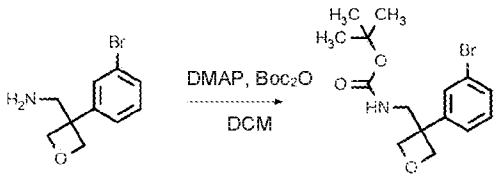


In a microwave flask, at 0°C under N_2, lithium aluminium hydride (0.68 mL, 1.35 mmol, 2 eq.) was added to a stirred solution of 3-(3-bromophenyl)-1-tert-butoxycarbonyl-pyrrolidine-3-carboxylic acid (250 mg, 0.675 mmol) in anhydrous THF (6.8 mL, 0.1 N). The reaction was stirred at 0°C overnight. The reaction mixture was diluted with EtOAc. Organic phase was washed with aqueous solutions of 20% Rochelle salt and 2% $NaHCO_3$, dried using a phase separator and evaporated to give crude material as colorless syrup. The crude material was purified by flash chromatography on silica gel using a gradient of DCM / MeOH. It was transferred via liquid injection in DCM. Relevant fractions were collected and concentrated under vacuum to afford tert-butyl 3-(3-bromophenyl)-3-(hydroxymethyl)pyrrolidine-1-carboxylate (169 mg, 38%) as a colorless syrup. m/z = 300.0, 302.0 [M+H-tBu]+

The next steps were similar to General Procedure – Phenyl 2.

Scaffold coupling - Specific Procedure (specific phenyl 6)

Synthesis of tert-butyl N-[[3-(3-bromophenyl)oxetan-3-yl]methyl]carbamate

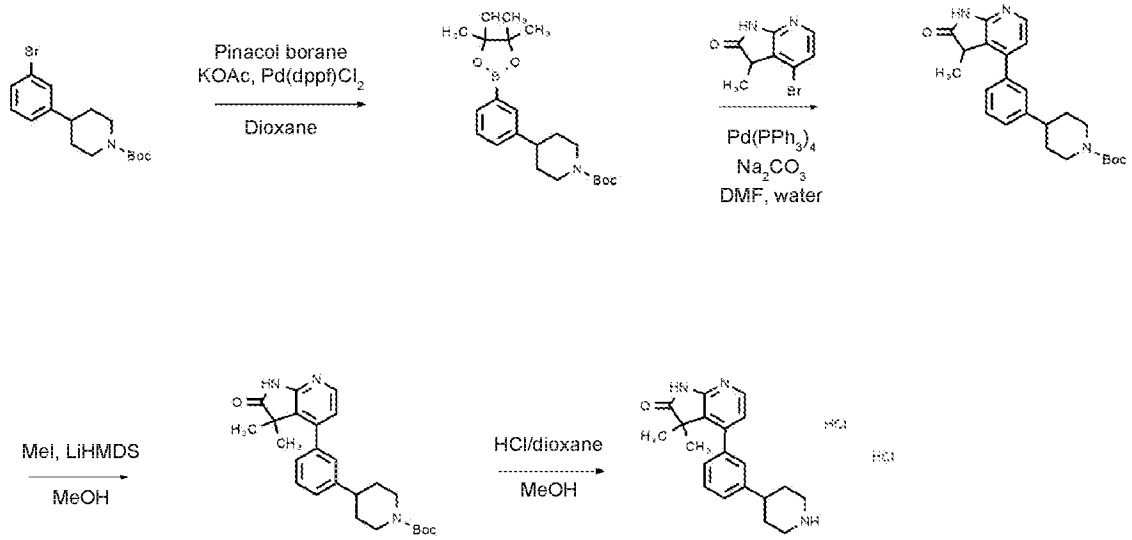


In a round-bottomed flask, at room temperature, 4-dimethylamino pyridine (0.13 g, 1.03 mmol, 1 eq.) was added to a stirred solution of [3-(3-bromophenyl)oxetan-3-yl]methanamine (0.25 g, 1.03 mmol) and tert-butoxycarbonyl tert-butyl carbonate (0.34 g, 1.55 mmol, 2 eq.) in DCM (5 mL, 0.2 N). The reaction was stirred at room temperature overnight. Water was added and the mixture extracted with DCM. The organic phase was dried and concentrated under vacuum. The crude material was purified by flash chromatography on silica gel using a gradient of DCM/ MeOH. It was transferred via solid phase on dicalite. Relevant fractions were collected and concentrated

under vacuum to afford tert-butyl N-[[3-(3-bromophenyl)oxetan-3-yl]methyl]carbamate (0.166g, 47% Yield) as a colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 7.43 (d, *J*=7.8 Hz, 1H), 7.34 – 7.26 (m, 2H), 7.12 (d, *J*=7.9 Hz, 1H), 4.62-4.77 (m, 4H), 3.44 (d, *J*=6.3 Hz, 2H), 1.31 (s, 9H); m/z = 286.1, 288.1 [M+H-tBu]+.

The next steps were similar to General Procedure – Phenyl 2.

Scaffold coupling - Specific Procedure (specific phenyl 7)



Synthesis of tert-butyl 4-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-1-carboxylate

To a solution tert-butyl 4-(3-bromophenyl)piperidine-1-carboxylate (200 mg, 0.58 mmol) in anhydrous dioxane (5.8 mL, 0.1 N) was added bis(pinacolato)diboron (293 mg, 1.15 mmol, 1.5 eq.) and potassium acetate (171 mg, 1.73 mmol, 3 eq.). The mixture was degassed with N_2 and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (42 mg, 0.0576 mmol) was added. The resulting mixture was stirred overnight at 95°C under N_2. The mixture was filtered on Dicalite and concentrated under vacuum to give tert-butyl 4-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-1-carboxylate (501mg, 88% Yield) as a dark oil. The crude product was used in the next reaction. m/z = 332.3 [M+H-tBu]+

Synthesis of tert-butyl 4-[3-(3-methyl-2-oxo-1,3-dihydropyrrolo[2,3-b]pyridin-4-yl)phenyl]piperidine-1-carboxylate

A reacti-vial was charged with tert-butyl 4-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-1-carboxylate (39%, 501 mg, 0.506 mmol, 1.2 eq.), 4-chloro-3-methyl-1H,2H,3H-pyrrolo[2,3-b]pyridin-2-one (81 mg, 0.421 mmol) and disodium carbonate (134 mg, 1.26 mmol, 3 eq.) in a mixture of DMF (3.3 mL) and water (0.9 mL). The mixture was degassed and tetrakis triphenylphosphine palladium (49 mg, 0.0421 mmol, 0.1 eq.) was added. The resulting mixture was stirred 4h at 95°C under N_2. The mixture was filtered on Dicalite and concentrated to give a brown oil. The crude product was purified on silica gel column, solid deposit, with a gradient of Heptane/EtOAc. Relevant fractions were collected and concentrated under vacuum to give tert-butyl 4-[3-(3-methyl-2-oxo-1,3-dihydropyrrolo[2,3-b]pyridin-4-yl)phenyl]piperidine-1-carboxylate (150mg, 65% Yield) as a yellow oil. m/z = 408.4 [M+H]+

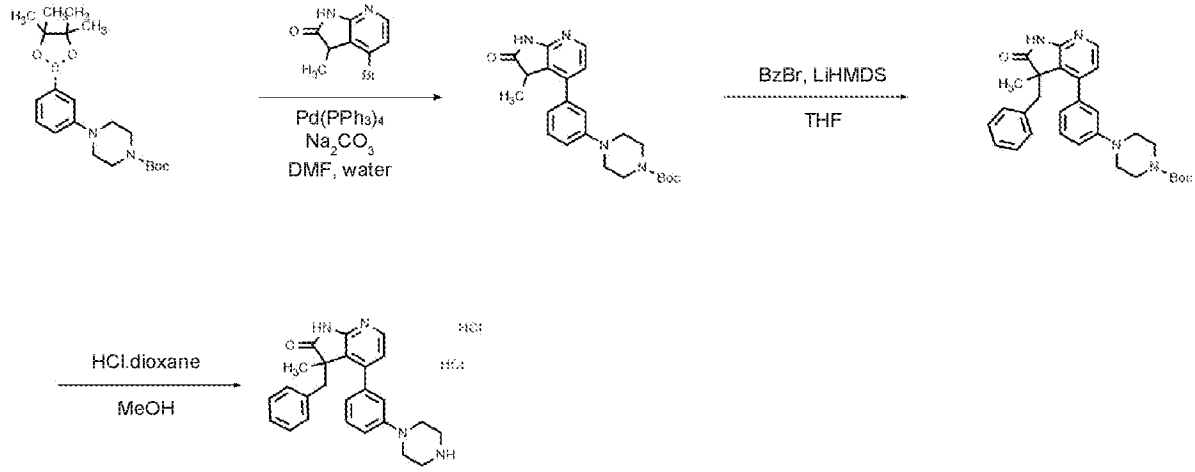
Synthesis of tert-butyl 4-[3-(3,3-dimethyl-2-oxo-1H-pyrrolo[2,3-b]pyridin-4-yl)phenyl]piperidine-1-carboxylate

A reacti-vial was charged with 1 M lithium [bis(trimethylsilyl)amide] solution (0.88 mL, 0.885 mmol, 3.3 eq.) in anhydrous THF (1.4 mL, 0.2N). The mixture was cooled to -78°C under N_2 and iodomethane (0.034 mL, 0.541 mmol, 2 eq.) was added dropwise. The resulting mixture was stirred 15 min at -78°C and tert-butyl 4-[3-(3-methyl-2-oxo-1,3-dihydropyrrolo[2,3-b]pyridin-4-yl)phenyl]piperidine-1-carboxylate (74%, 149 mg, 0.271 mmol) was added. The mixture was allowed to rise to RT and stirred 1h. The mixture was quenched with an aqueous solution of $NaHCO_{3\ sat}$ and water. The mixture was extracted with DCM. The combined organic layers were washed with water, brine, dried over phase separator and concentrated to afford an orange oil. The crude product was purified on silica gel column, solid deposit, with a gradient of heptane/EtOAc. Relevant fractions were collected and concentrated under vacuum to give tert-butyl 4-[3-(3,3-dimethyl-2-oxo-1H-pyrrolo[2,3-b]pyridin-4-yl)phenyl]piperidine-1-carboxylate (25mg, 21% Yield), as a yellowish solid. ^{1}H NMR(Chloroform-*d*, 400 MHz): δ (ppm) 8.09 (d, *J*=5.6 Hz, 1H), 7.40 (t, *J*=7.6 Hz, 1H), 7.30 (d, *J*=7.8 Hz, 1H), 7.15 – 7.07 (m, 2H), 6.84 (d, *J*=5.6 Hz, 1H), 4.25 (s, 2H), 2.89 – 2.63 (m, 3H), 1.86 (d, *J*=13.7 Hz, 2H), 1.64 (tt, *J*=12.9, 6.8 Hz, 2H), 1.47 (s, 9H), 1.23 (s, 6H); m/z = 422.4 [M+H]+.

Synthesis of 3,3-dimethyl-4-[3-(4-piperidyl)phenyl]-1H-pyrrolo[2,3-b]pyridin-2-one dihydrochloride

To a solution of tert-butyl 4-[3-(3,3-dimethyl-2-oxo-1H-pyrrolo[2,3-b]pyridin-4-yl)phenyl]piperidine-1-carboxylate (25 mg, 0.0575 mmol) in methanol (0.3 mL, 0.2 N) was added 4 M hydrogen chloride solution in dioxane (0.14 mL, 0.575 mmol, 10 eq.). The resulting mixture was stirred over 2 days at room temperature under N_2. The mixture was concentrated under vacuum to afford 3,3-dimethyl-4-[3-(4-piperidyl)phenyl]-1H-pyrrolo[2,3-b]pyridin-2-one dihydrochloride (21.3mg, 90% Yield) as a yellow solid. 1H NMR (DMSO-d6, 600 MHz): δ (ppm) 11.13 (s, 1H), 8.55-8.87 (m, 2H), 8.09 (d, J = 5.3 Hz, 1H), 7.41-7.48 (m, 1H), 7.33 (dt, J = 7.8, 1.5 Hz, 1H), 7.19 (dt, J = 7.6, 1.3 Hz, 1H), 7.15 (t, J = 1.5 Hz, 1H), 6.77 (d, J = 5.3 Hz, 1H), 4.65 (br s, 1H), 3.36 (br d, J = 12.6 Hz, 2H), 2.95-3.03 (m, 2H), 2.92 (tt, J = 12.0, 3.5 Hz, 1H), 1.96 (br d, J = 13.2 Hz, 2H), 1.80-1.90 (m, 2H), 1.06 (s, 6H); m/z = 322.1 [M+H]+.

Scaffold coupling - Specific Procedure (specific phenyl 8)



Synthesis of tert-butyl 4-[3-(3-methyl-2-oxo-1,3-dihydropyrrolo[2,3-b]pyridin-4-yl)phenyl]piperazine-1-carboxylate

In a microwave flask, at room temperature, tetrakis triphenylphosphine palladium (509 mg, 0.440 mmol, 0.1 eq.) was added to a stirred solution of tert-butyl 4-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate (214 mg, 0.528 mmol, 1.2 eq.) and 4-bromo-3-methyl-1,3-dihydropyrrolo[2,3-b]pyridin-2-one (100 mg, 0.440 mmol) in a mixture of DMF (3.6

mL) and water (0.70 mL). The reaction mixture was purged with argon for 15min. Disodium carbonate (140 mg, 1.32 mmol, 3 eq.) was added under argon and the reaction was stirred at 100°C overnight. The reaction mixture was diluted with EtOAc. Organic phase was washed with water, dried using a phase separator and evaporated to give crude material as a yellow solid. The crude material was purified by flash chromatography on silica gel using a gradient of cyclohexane / EtOAc. It was transferred via liquid injection in DCM. Relevant fractions were collected and concentrated under vacuum to afford tert-butyl 4-[3-(3-methyl-2-oxo-1,3-dihydropyrrolo[2,3-b]pyridin-4-yl)phenyl]piperazine-1-carboxylate (132mg, 56% Yield) as a yellowish solid. m/z = 409.4 [M+H]+

Synthesis of tert-butyl 4-[3-(3-benzyl-3-methyl-2-oxo-1H-pyrrolo[2,3-b]pyridin-4-yl)phenyl]piperazine-1-carboxylate

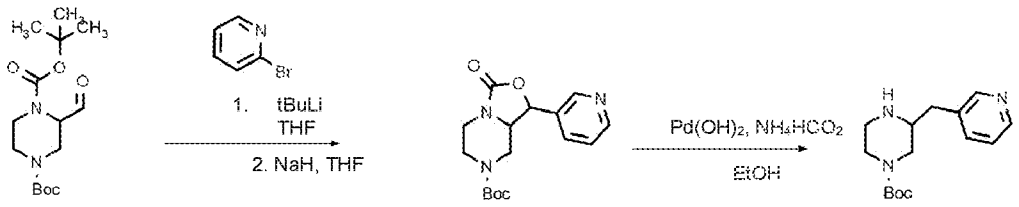
In a microwave flask, at -78°C under N_2, 1 M lithium [bis(trimethylsilyl)amide] solution (1.5 mL, 1.50 mmol, 4.7 eq.) was added to a stirred solution of tert-butyl 4-[3-(3-methyl-2-oxo-1,3-dihydropyrrolo[2,3-b]pyridin-4-yl)phenyl]piperazine-1-carboxylate (130 mg, 0.318 mmol) in anhydrous THF (3.2 mL, 0.1 N). The reaction was stirred at -78°C for 10 min, then bromomethylbenzene (0.045 mL, 0.382 mmol, 1.2 eq.) was added and the reaction was allowed to warm to room temperature and was stirred for 6h. The reaction mixture was diluted with EtOAc. Organic phase was washed with an aqueous solution of sat NH_4Cl, dried using a phase separator and evaporated to give crude material as a dark yellow syrup. Crude material was purified by flash chromatography on silica gel using a gradient of Toluene / Acetone. It was transferred via liquid injection in DCM. Relevant fractions were collected and concentrated under vacuum to afford tert-butyl 4-[3-(3-benzyl-3-methyl-2-oxo-1H-pyrrolo[2,3-b]pyridin-4-yl)phenyl]piperazine-1-carboxylate (128mg, 74% Yield) as a yellowish foam. m/z = 499.2 [M+H]+.

Synthesis of 3-benzyl-3-methyl-4-(3-piperazin-1-ylphenyl)-1H-pyrrolo[2,3-b]pyridin-2-one dihydrochloride

4 M hydrogen chloride solution in dioxane (0.6 mL, 2.5 mmol, 10 eq.) was added to a solution of tert-butyl 4-[3-(3-benzyl-3-methyl-2-oxo-1H-pyrrolo[2,3-b]pyridin-4-yl)phenyl]piperazine-1-carboxylate (125 mg, 0.251 mmol) in methanol (2.5 mL, 0.1 eq.). The mixture was stirred at room temperature overnight. The precipitate was filtered, washed with cold isopropanol and dried under high vacuum at 40°C overnight to afford 3-benzyl-3-methyl-4-(3-piperazin-1-ylphenyl)-1H-pyrrolo[2,3-b]pyridin-2-one dihydrochloride (58.6mg, 49.337% Yield) as a white powder. 1H NMR (DMSO-d6, 500 MHz): δ (ppm) 10.91 (s, 1H), 9.28 (br s, 2H), 8.00 (d, J = 5.4 Hz, 1H), 7.44

(t, J = 8.1 Hz, 1H), 7.14 (dd, J = 8.3, 2.0 Hz, 1H), 7.07-7.11 (m, 3H), 6.95-6.99 (m, 2H), 6.79 (d, J = 5.4 Hz, 1H), 6.76 (dd, J = 6.6, 2.9 Hz, 2H), 5.25 (br s, 1H), 3.36-3.50 (m, 4H), 3.22 (br s, 4H), 2.84 (d, J = 13.2 Hz, 1H), 2.56 (d, J = 13.2 Hz, 1H), 1.38 (s, 3H); m/z = 399.1 [M+H]+.

Scaffold coupling - Specific Procedure (specific phenyl 9)



Synthesis of tert-butyl 3-oxo-1-(3-pyridyl)-5,6,8,8a-tetrahydro-1H-oxazolo[3,4-a]pyrazine-7-carboxylate

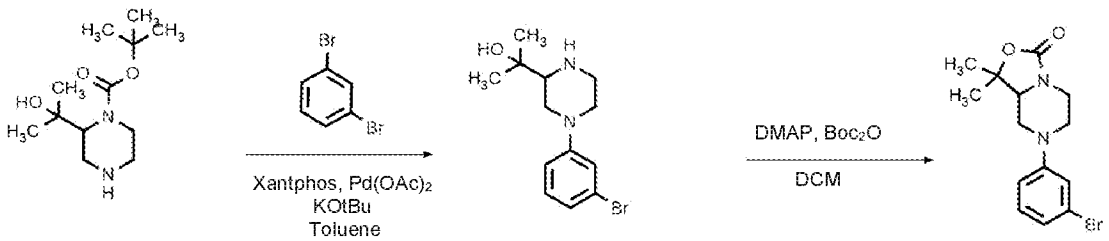
In a 50mL round-bottomed flask, at -78°C, 1.6 M tert-butyllithium solution (14.9 mL, 23.86 mmol) was slowly added to a stirred solution of 3-bromopyridine (1.17 mL, 11.93 mmol, 5 eq.) in anhydrous THF (20 mL). Then this solution was added dropwise at -78°C to a solution of ditert-butyl 2-formylpiperazine-1,4-dicarboxylate (750 mg, 2.39 mmol) in anhydrous THF (20 mL). The reaction was stirred at -78°C for 15 min. The reaction was quenched with a saturated aqueous solution of NH_4Cl. The two phases were separated and the aqueous phase was extracted with ethyl acetate. Combined organic phases were dried over Na_2SO_4, filtered and evaporated to give crude material as an orange gum. Then the residue was solubilized in anhydrous THF (8 mL) and was slowly added to a heterogeneous mixture of sodium hydride 60% (95 mg, 2.38 mmol, 1 eq.) in anhydrous THF (20 mL). The reaction was stirred at 60°C overnight. The reaction was quenched with water and ethyl acetate was added. The two phases were separated and the aqueous phase was extracted with ethyl acetate. Combined organic phases were dried over Na_2SO_4, filtered and evaporated to give crude material as an orange gum. The crude material was purified by flash chromatography on silica gel using a gradient of dichloromethane / ethyl acetate. It was transferred via liquid injection in DCM. Relevant fractions were collected and concentrated under vacuum to afford tert-butyl 3-oxo-1-(3-pyridyl)-5,6,8,8a-tetrahydro-1H-oxazolo[3,4-a]pyrazine-7-carboxylate (220 mg, 19% Yield) as a pale orange gum under 2 diastereoisomers forms. m/z = 394[M+H]+.

Synthesis of tert-butyl 3-(3-pyridylmethyl)piperazine-1-carboxylate.

A 4 mL vial was successively charged with ammonium formate (57 mg, 0.909 mmol, 2 eq.), tert-butyl 3-oxo-1-(3-pyridyl)-5,6,8,8a-tetrahydro-1H-oxazolo[3,4-a]pyrazine-7-carboxylate (220 mg, 0.455 mmol) in anhydrous ethanol (4.5 mL, 0.1N) and dihydroxypalladium (20%, 32 mg, 0.0455 mmol, 0.1 eq.). The reaction was stirred at 80°C for 5h. Then dihydroxypalladium (20%, 16 mg) and ammonium formate (29 mg) were added and the reaction was stirred at 80°C overnight. The reaction mixture was filtered through a pad of Dicalite and the filtrate was evaporated to dryness to give tert-butyl 3-(3-pyridylmethyl)piperazine-1-carboxylate (185mg, 94% Yield) as a colorless gum. ^{1}H NMR(DMSO-d_6, 400 MHz): δ (ppm) 8.45 – 8.40 (m, 2H), 7.65 (d, *J*=7.8 Hz, 1H), 7.32 (dd, *J*=7.6, 4.8 Hz, 1H), 3.68 (d, *J*=12.6 Hz, 2H), 2.83 (d, *J*=12.1 Hz, 1H), 2.76 – 2.56 (m, 4H), 2.49 – 2.36 (m, 2H), 1.37 (d, *J*=17.4 Hz, 9H); m/z = 278.3 [M+H]+.

The next steps were similar to General Procedure – Phenyl 3.

Scaffold coupling - Specific Procedure (specific phenyl 10)



Synthesis of 2-[4-(3-bromophenyl)piperazin-2-yl]propan-2-ol

A reacti-vial was charged with diacetoxypalladium (2.4 mg, 0.0106 mmol, 0.01 eq.), Xantphos (19 mg, 0.0318 mmol, 0.03 eq.) and potassium tert-butoxide (178 mg, 1.59 mmol, 1.5 eq.) in anhydrous toluene (2.6 mL, 0.4 N). Then 1,3-dibromobenzene (128 µL, 1.06 mmol, 1 eq.) and tert-butyl 2-(1-hydroxy-1-methyl-ethyl)piperazine-1-carboxylate (259 mg, 1.06 mmol) were successively added. The resulting mixture was stirred overnight at 95°C under N_2. Water was added and the mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over phase separator and concentrated under vacuum to afford a brown liquid. The crude product was purified on silica gel column, solid deposit, with a

gradient of DCM/MeOH. Relevant fractions were collected and concentrated under vacuum to afford 2-[4-(3-bromophenyl)piperazin-2-yl]propan-2-ol (163 mg, 51% Yield) as an orange oil. ^{1}H NMR(DMSO-d_6, 400 MHz): δ (ppm) 7.17 – 7.10 (m, 1H), 7.04 (t, *J*=2.1 Hz, 1H), 6.90 (ddd, *J*=12.9, 8.1, 1.8 Hz, 2H), 4.39 (s, 1H), 3.66 – 3.49 (m, 2H), 3.07 – 2.94 (m, 1H), 2.73 (td, *J*=11.8, 3.1 Hz, 1H), 2.59 – 2.52 (m, 1H), 2.48 (d, *J*=2.7 Hz, 1H), 2.34 (t, *J*=11.0 Hz, 1H), 2.14 (s, 1H), 1.14 (d, *J*=6.7 Hz, 6H); m/z = 299.1; 301.0 [M+H]+

Synthesis of 7-(3-bromophenyl)-1,1-dimethyl-5,6,8,8a-tetrahydrooxazolo[3,4-a]pyrazin-3-one

To a solution of 2-[4-(3-bromophenyl)piperazin-2-yl]propan-2-ol (239 mg, 0.799 mmol) in anhydrous DCM (4 mL, 0.2 N) was successively added dimethylaminopyridine (197 mg, 1.60 mmol, 2 eq.) and tert-butoxycarbonyl tert-butyl carbonate (349 mg, 1.60 mmol, 2 eq.). The resulting mixture was stirred overnight at room temperature under N_2. Water was added and the mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over phase separator and concentrated under vacuum to afford crude material. It was then purified on silica gel column, solid deposit, with a gradient of Heptane/EtOAc. Relevant fractions were collected and concentrated under vacuum to afford 7-(3-bromophenyl)-1,1-dimethyl-5,6,8,8a-tetrahydrooxazolo[3,4-a]pyrazin-3-one (190mg, 73% Yield) as a colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 7.21 – 7.14 (m, 2H), 7.01 (dd, *J*=8.1, 2.1 Hz, 1H), 6.96 (dd, *J*=7.8, 1.1 Hz, 1H), 3.84 (ddd, *J*=12.2, 3.5, 1.6 Hz, 1H), 3.74 – 3.66 (m, 1H), 3.65 – 3.58 (m, 1H), 3.49 (dd, *J*=11.2, 3.6 Hz, 1H), 3.07 (td, *J*=12.5, 3.8 Hz, 1H), 2.75 – 2.62 (m, 2H), 1.43 (s, 3H), 1.34 (s, 3H); m/z = 325.0; 327.0 [M+H]+

The next steps were similar to General Procedure – Phenyl 3.

Example 2 – Biological Assays

PKC-theta and PKC-delta inhibition assay

PKC-theta and PKC-delta biochemical activities were measured using the PKC-theta HTRF KinEASEkit kit, according to manufacturer's instructions (Cisbio, catalogue number 61ST1PEJ). Briefly, the kinase buffer component of the kit was supplemented with 10 mM MgCl2, 1 mM DTT and 0.1% Tween 20. For the PKC-theta assay, STK substrate and ATP were added to provide a final assay concentration of 525 nM and 6.5 µM, respectively. For the PKC-delta assay, STK substrate and ATP were added to provide a final assay concentration of

243 nM and 5.7 µM, respectively. The streptavidin_XL665 and STK antibody-cryptate detection reagents were mixed according to the manufacturer's instructions. Test compounds were diluted in DMSO in a series of 10 semi-log step doses; 10 nL of each compound dose were dispensed in 384 well plates. Recombinant human PKC-theta (His-tagged 362-706) or PKC-delta (His-tagged 345-676) was diluted into kinase buffer to provide a final assay concentration of 10 ng/mL and added to the test compound for 30 minutes on ice. The reaction was started by addition of the substrate and ATP and incubated at 25°C for 30 minutes or 20 minutes for the PKC-theta and PKC-delta assays, respectively. The detection reagents were added, and the plate was incubated in the dark for 2 hours. Fluorescence was measured on an Envision 2103 plate reader with optical setup for excitation at 665 nM and emission at 620 nM in the HTRF mode. The ratio of acceptor and donor emission signals was calculated for each well. Percent inhibition values were calculated from the HTRF ratios at different doses and fitted to a 4-parameter logistic curve to determine IC50 values (see Table 2).

Effector memory T cells IL-2 release assay

Test compound-mediated inhibition of NFκB signalling in T cells was assessed by quantification of the IL-2 secretion by human effector memory T cells (TEM) upon treatment and stimulation. Human TEM cells were isolated from buffy coats of healthy donors obtained from the French blood bank. First, peripheral blood mononuclear cells (PBMC) were purified from buffy coats diluted 1:1 with DPBS (Gibco, cat# 14190-094) by Pancoll (PAN BIOTECH, cat#P04-60500) density gradient centrifugation at 400 x g for 20 minutes. TEM cells were further enriched by negative immuno-magnetic cell sorting using a human CD4+ Effector Memory T Cell Isolation Kit (Miltenyi, cat#130-094-125) according to the manufacturer's instructions. Aliquots of 3 x 10E6 purified TEM cells were kept frozen in Cryo-SFM medium (PromoCell, cat#C-29912) in gas phase nitrogen until used. Cell purity was verified by flow cytometry analysis of 200 000 PFA-fixed cells previously labelled with monoclonal antibodies anti-CD4-PerCP-Cy5.5 (BD Pharmigen, cat#332772), anti-CD8-V500 (BD Biosciences, cat#561617), anti-CD14-Pacific Blue (Biolegend, cat#325616), anti-CD45 RA-FITC (Biolegend, cat#304106) and anti-CCR7-APC (in CD4+ Effector Memory T Cell Isolation Kit, Miltenyi, cat#130-094-125).

TEM cells were resuspended in complete RPMI medium composed of: RPMI 1640 (Gibco, cat#31870-025), 10 % heat inactivated fetal bovine serum (Sigma, cat#F7524), 2 mM GlutaMAX (Gibco, cat#35050-038), 1 mM sodium pyruvate 100X (Gibco, cat#11360-039), 1 % MEM non-essential amino acids solution (Gibco, cat#11140-035) and 100 U/mL penicillin, 100 µg/mL streptomycin (Sigma-Aldrich, cat#11074440001). 5,000 cells per well were plated onto flat clear

bottom 384 well plates (Corning, cat#3770). 5,000 Dynabeads Human T-Activator CD3/CD28 (Gibco, cat#11132D) were added to each well for cell stimulation. Finally, 10 doses of test compound, originally prepared in DMSO by serial semi-log step dilution, were also added to cells in triplicate wells. Final DMSO concentration in wells was 0.1% in a total volume of 100 µL complete medium. Plates were incubated for 24 h at 37°C in 5% CO_2 atmosphere. After incubation, cell suspensions were centrifuged at 400 x g and culture supernatants were recovered and stored at -80°C. Cell viability was assessed by flow cytometry after staining the cells with Fixable Viability Dye eFluor 780 (Invitrogen, cat# 65-0865-14). IL-2 levels were determined in cell supernatants using an HTRF human IL-2 detection kit (Cisbio, cat# 62HIL02PEH). IL-2 data at the different compound doses were fitted to a 4-parameter logistic curve to determine IC_{50} values, corresponding to the compound concentration leading to 50% reduction of the maximal IL-2 levels observed in each experiment. Viability data were analysed similarly to exclude cytotoxicity as a cause of IL-2 decrease (see Table 1).

Example no.	PKC-theta HTRF pIC50	PKC-theta HTRF pIC50 (binned)	PKC-theta IL2 pIC50	PKC-theta IL2 pIC50 (binned)	PKC-theta/ PKC-delta selectivity	PKC-theta/ PKC-delta selectivity (binned)
1	6.3	G	5.0	G	1	F
2	6.3	G	5.0	G	2	F
3	6.1	G	5.3	G	1	F
4	6.6	F	5.3	G	8	E
5	7.1	E	6.1	F	4	F
6	6.0	H	5.0	G	2	F
7	7.0	F	5.6	G	2	F
8	6.4	G	5.4	G	2	F
9	5.7	H	5.9	G	1	G
10	6.5	G	5.7	G	1	F
11	5.6	H	5.2	G	4	F
12	5.3	H	5.0	G	1	G
13	6.4	G	5.0	G	N/D	N/D
14	7.0	F	6.2	F	2	F
15	6.3	G	5.0	G	3	F
16	5.2	H	5.0	G	1	G
17	5.3	H	5.0	G	2	F
18	7.6	D	6.7	E	3	F
19	6.7	F	5.7	G	2	F
20	5.4	H	5.0	G	0	G
21	6.5	G	6.0	F	1	F
22	6.3	G	5.8	G	1	F

23	7.0	F	5.8	G	2	F
24	6.0	G	5.7	G	1	F
25	7.3	E	6.3	F	7	E
26	6.8	F	5.6	G	2	F
27	6.0	G	5.0	G	1	F
28	5.9	H	5.0	G	1	G
29	7.5	E	6.3	F	1	F
30	7.5	E	6.1	F	2	F
31	6.3	G	5.2	G	1	F
32	6.7	F	5.4	G	3	F
33	7.3	E	6.1	F	2	F
34	6.0	H	5.4	G	2	F
35	7.4	E	6.4	F	3	F
36	7.7	D	6.6	E	1	F
37	7.0	E	5.9	G	5	F
38	8.0	C	6.8	E	4	F
39	6.7	F	5.6	G	1	F
40	7.5	E	6.4	F	4	F
41	7.1	E	5.7	G	3	F
42	5.7	H	5.0	G	1	F
43	8.1	C	6.2	F	3	F
44	6.7	F	5.0	G	4	F
45	6.7	F	5.4	G	2	F
46	7.9	D	6.6	E	3	F
47	6.5	F	5.6	G	2	F
48	5.8	H	5.0	G	1	G
49	6.0	G	5.4	G	1	F
50	7.1	E	6.0	G	2	F
51	7.1	E	5.9	G	3	F
52	6.9	F	5.8	G	2	F
53	6.6	F	5.8	G	3	F
54	7.0	E	5.7	G	3	F
55	8.0	D	6.4	F	9	E
56	7.7	D	6.1	F	14	D
57	7.3	E	6.2	F	6	E
58	7.9	D	6.5	F	7	E
59	8.3	C	6.9	E	5	F
60	6.9	F	5.8	G	4	F
61	7.3	E	6.1	F	6	E
62	8.2	C	6.9	E	5	E
63	6.0	G	5.0	G	0	G

64	6.3	G	5.3	G	2	F
65	8.7	B	6.7	E	14	D
66	8.3	C	7.1	D	13	D
67	7.3	E	6.0	G	3	F
68	7.5	E	6.3	F	11	D
69	7.4	E	6.4	F	1	F
70	8.6	B	6.4	F	30	B
71	8.9	B	7.5	D	12	D
72	7.6	D	6.5	E	12	D
73	8.2	C	6.9	E	11	D
74	8.7	B	7.7	C	12	D
75	8.1	C	6.8	E	11	D
76	7.3	E	6.1	F	11	D
77	7.0	E	5.6	G	12	D
78	7.8	D	6.8	E	11	D
79	7.4	E	6.1	F	2	F
80	8.2	C	7.1	D	12	D
81	7.6	D	6.7	E	9	E
82	6.0	G	5.4	G	3	F
83	8.5	B	7.1	D	20	D
84	8.1	C	6.5	F	14	D
85	7.7	D	6.5	F	20	D
86	7.5	E	6.3	F	10	E
87	8.2	C	7.0	E	10	D
88	8.3	C	7.3	D	14	D
89	8.5	B	7.2	D	17	D
90	9.1	A	7.8	C	17	D
91	8.2	C	6.7	E	6	E
92	8.1	C	6.7	E	6	E
93	7.9	D	6.9	E	12	D
94	8.7	B	7.7	C	9	E
95	8.7	B	7.5	D	15	D
96	8.3	C	6.7	E	10	E
97	6.8	F	5.4	G	21	C
98	7.7	D	6.5	E	15	D
99	7.5	D	6.1	F	22	C
100	7.2	E	5.3	G	30	B
101	8.2	C	7.0	D	12	D
102	8.8	B	7.7	C	14	D
103	7.8	D	7.0	E	6	E
104	8.3	C	6.9	E	11	D

105	9.0	A	7.7	C	7	E
106	6.0	G	5.0	G	10	D
107	7.2	E	6.3	F	7	E
108	7.9	D	6.9	E	15	D
109	8.4	C	6.1	F	29	C
110	9.0	A	7.6	C	16	D
111	8.3	C	6.9	E	17	D
112	7.8	D	6.6	E	20	C
113	8.5	B	7.1	D	22	C
114	8.3	C	7.2	D	13	D
115	8.0	C	6.8	E	12	D
116	8.3	C	6.9	E	10	D
117	7.9	D	6.7	E	10	D
118	7.6	D	6.6	E	12	D
119	8.4	C	6.7	E	12	D
120	7.6	D	6.3	F	15	D
121	7.6	D	6.2	F	12	D
122	8.4	C	6.6	E	16	D
123	7.7	D	5.8	G	25	C
124	8.4	C	6.8	E	16	D
125	7.8	D	6.4	F	13	D
126	8.9	B	7.6	C	12	D
127	8.9	B	7.6	C	15	D
128	7.6	D	6.5	E	5	F
129	9.3	A	8.4	B	3	F
130	8.1	C	6.8	E	8	E
131	8.4	C	7.4	D	6	E
132	7.0	F	6.0	F	4	F
133	8.6	B	7.3	D	10	D
134	8.1	C	7.0	E	10	D
135	7.7	D	6.5	E	13	D
136	7.6	D	6.3	F	11	D
137	7.9	D	6.6	E	16	D
138	7.8	D	6.2	F	16	D
139	9.1	A	8.7	A	1	F
140	8.8	B	7.9	C	6	E
141	8.4	C	7.3	D	16	D
142	8.7	B	7.4	D	17	D
143	8.4	C	7.5	D	8	E
144	8.8	B	7.6	C	23	C
145	9.1	A	7.8	C	25	C

146	8.6	B	7.6	C	4	F
147	8.6	B	7.5	D	10	D
148	7.7	D	6.8	E	3	F
149	7.6	D	6.4	F	15	D
150	7.2	E	5.9	G	13	D
151	7.9	D	6.9	E	15	D
152	8.2	C	7.1	D	11	D
153	8.5	B	7.5	C	13	D
154	8.1	C	6.9	E	19	D
155	8.4	C	7.3	D	17	D
156	7.9	D	6.9	E	12	D
157	8.1	C	6.8	E	20	C
158	8.2	C	6.7	E	10	E
159	8.7	B	7.0	E	9	E
160	8.5	B	7.0	D	9	E
161	8.6	B	7.3	D	12	D
162	6.5	F	6.1	F	33	B
163	8.4	C	7.5	C	10	D
164	8.7	B	7.9	C	5	F
165	8.2	C	7.2	D	12	D
166	8.5	B	7.5	C	6	E
167	6.5	F	5.6	G	33	B
168	9.3	A	8.1	B	14	D
169	8.1	C	7.0	D	16	D
170	8.2	C	7.0	E	N/D	N/D
171	8.6	B	7.4	D	9	E
172	8.0	C	7.0	E	13	D
173	9.0	A	8.1	B	18	D
174	7.5	E	6.5	E	10	D
175	8.3	C	7.2	D	21	C
176	7.9	D	6.9	E	20	C
177	8.2	C	7.2	D	24	C
178	8.5	B	7.2	D	20	D
179	8.2	C	6.7	E	20	D
180	8.7	B	6.2	F	28	C
181	7.9	D	6.8	E	12	D
182	8.1	C	6.8	E	25	C
183	8.2	C	6.9	E	25	C
184	8.0	D	6.6	E	20	C
185	8.3	C	7.4	D	27	C
186	8.2	C	7.3	D	22	C

187	8.3	C	7.0	D	28	C
188	8.2	C	7.0	D	28	C
189	8.3	C	6.6	E	16	D
190	8.5	C	7.1	D	32	B
191	7.8	D	6.6	E	22	C
192	8.4	C	6.8	E	31	B
193	8.0	C	7.1	D	16	D
194	8.5	B	7.5	D	23	C
195	9.4	A	8.3	B	30	B
196	8.1	C	7.0	D	26	C
197	9.0	A	7.8	C	14	D
198	8.4	C	7.2	D	30	C
199	8.8	B	7.6	C	16	D
200	8.3	C	7.1	D	27	C
201	9.3	A	8.1	B	18	D
202	8.4	C	7.3	D	22	C
203	8.2	C	7.0	D	14	D
204	8.2	C	6.9	E	24	C
205	8.4	C	7.1	D	13	D
206	7.5	E	6.2	F	23	C
207	6.6	F	5.7	G	5	F
208	8.7	B	7.7	C	12	D

Table 2: Biochemical data for representative compounds of the disclosure. In the columns indicated, the data has been binned in a category of A to H as indicated below dependent on the measured value.

For PKC-theta HTRF:

A means a measured pIC50 of between 9.0 and 9.5;

B means a measured pIC50 of between 8.5 and 9.0;

C means a measured pIC50 of between 8.0 and 8.5;

D means a measured pIC50 of between 7.5 and 8.0;

E means a measured pIC50 of between 7.0 and 7.5;

F means a measured pIC50 of between 6.5 and 7.0;

G means a measured pIC50 of between 6.0 and 6.5;

H means a measured pIC50 <6.0.

For PKC-theta CD4Tc IL-2:

A means a measured pIC50 of between 8.5 and 9.0;

B means a measured pIC50 of between 8.0 and 8.5;

C means a measured pIC50 of between 7.5 and 8.0;

D means a measured pIC50 of between 7.0 and 7.5;

E means a measured pIC50 of between 6.5 and 7.0;

F means a measured pIC50 of between 6.0 and 6.5;

G means a measured pIC50 <6.0.

For PKC-theta/PKC-delta selectivity:

A means a ratio of between 50 and 120;

B means a ratio of between 30 and 50;

C means a ratio of between 20 and 30;

D means a ratio of between 10 and 20;

E means a ratio of between 5 and 10;

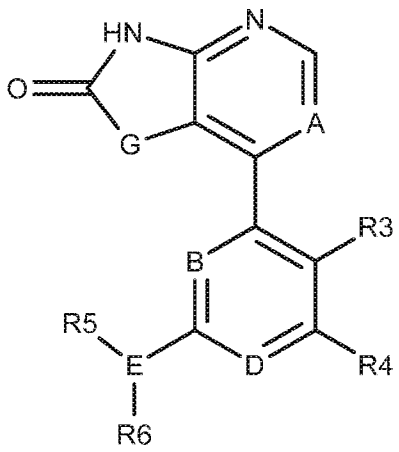
F means a ratio of between 1 and 5;

G means a ratio of 0 to 1.

Modifications may be made to the above examples without departing from the scope of the present invention as defined in the accompanying claims.

CLAIMS

1. A compound of structural Formula I:



I

or a pharmaceutically acceptable salt, solvate, stereoisomer or mixture of stereoisomers, tautomer, or isotopic form, or pharmaceutically active metabolite thereof, or combinations thereof, wherein:

A is selected from the group consisting of: N, C-R^a, where R^a is selected from hydrogen, halogen, C1-3 alkyl and CN;

B is selected from the group consisting of: N; C-H; C-F and C-(C1-3 alkyl);

D is selected from the group consisting of: N; C-H; C-R^b where R^b is selected from halogen; C1-3 alkyl; and C1-3 haloalkyl;

G is selected from the group consisting of: CR1R2; NR1; and O;

R1 and R2 are independently selected from the group consisting of: hydrogen, halogen, C1-3 alkyl; C3-7 cycloalkyl; C1-3 alkoxyl; C2-6 cycloalkoxyl; C2-6 alkyl alkoxy; hydroxyl; C1-3 alkyl hydroxyl; amino; C1-3 alkyl amino; C1-4 amino alkyl; C2-7 alkyl amino alkyl; C1-3 haloalkyl; aryl; heteroaryl; alkyl aryl and alkyl heteroaryl; or

R1 and R2 together form a 3-5 membered optionally substituted spiro carbocyclic or heterocyclic ring;

R3 is selected from the group consisting of: hydrogen, C1-2 alkyl, OMe and halogen;

R4 is selected from the group consisting of: hydrogen; C1-5 alkyl; C3-7 cycloalkyl; C1-5 haloalkyl; C1-5 alkoxyl; C1-5 haloalkoxyl; alkyl alkoxy; C2-6 heterocycloalkyl; CN and halogen;

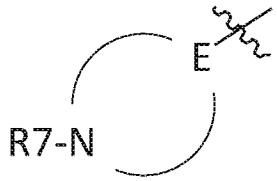
E is selected from the group consisting of: N; C-H; C-R^c, where R^c is selected from the group consisting of halogen; hydroxyl; C1-3 alkyl hydroxyl; C1-3 alkyl amino; C1-3 haloalkyl; C2-6 alkyl alkoxyl; and CN;

R5 and R6 are each independently selected from the group consisting of: hydrogen; C2-5 alkyl; C1-C5 amino alkyl; 4-8-membered amino alkyl ring; C1-9 alkyl alkoxy; C1-9 alkyl amino alkyl; or

R5 and R6 are joined together to form an optionally substituted, optionally bridged Ring Z, wherein Ring Z is a C3-10 heterocycloalkyl mono- or bicyclic ring; or

E, R5 and R6 together are J, wherein J is selected from the group consisting of: N-R^d; C(=O)R^d; SO_2R^d; O-R^d, wherein R^d is a 4-8-membered amino alkyl ring.

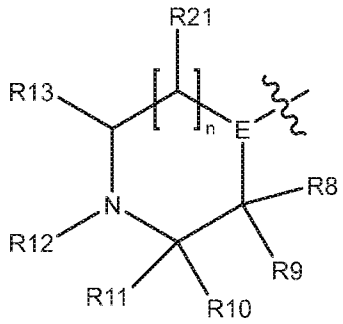
2. The compound of Claim 1, wherein Ring Z is an optionally substituted, optionally bridged, 4-8-membered amino alkyl ring with the general Formula Ia;



Ia

wherein R7 is selected from the group consisting of: hydrogen; C1-3 alkyl; and C1-3 haloalkyl.

3. The compound of Claim 1 or Claim 2, wherein Ring Z is:



wherein R8, R9, R10, R11, R13 and R21 are each independently selected from the group consisting of: hydrogen, C1-3 alkyl, C1-3 alkyl alkoxy; C1-3 alkyl hydroxyl; amino; C1-3 alkyl amino; C1-6 alkyl amino alkyl; C1-3 haloalkyl; alkyl heteroaryl;

R12 is selected from the group consisting of: hydrogen; C1-3 alkyl; and C1-3 haloalkyl; or

any one of R8, R9, R10, R11, R12, R13 and R21 may be joined to another, different R8, R9, R10, R11, R12, R13 or R21 to form a 3-7-membered spiro or bicyclic carbocyclic or heterocyclic ring structure, and/or a 3-6 membered bridged carbocyclic or heterocyclic ring structure.

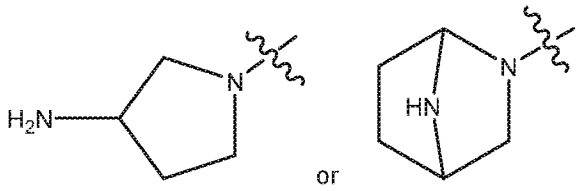
n is selected from the group consisting of: 0; 1; and 2.

4. The compound of any one of Claims 1 to 3, wherein:

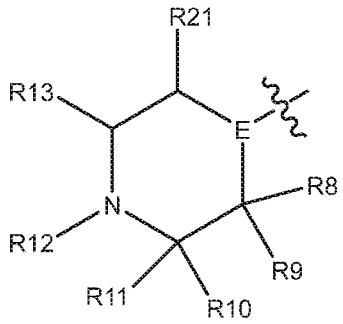
n=0; and

E is selected from the group consisting of: N; C-H; C-R^d, wherein R^d is selected from the group consisting of halogen; alkoxy; C1-3 alkylhydroxy; C1-3 haloalkyl; C2-5 alkyl alkoxy; C2-5 alkyl nitrile.

5. The compound of Claim 4, wherein Ring Z is:



6. The compound of any one of Claim 2 or Claim 3, wherein G is CR1R2 and Ring Z is:



wherein;

A is selected from the group consisting of: C-H, C-F, C-Cl and C-Br;

B and D are each independently selected from the group consisting of: N and C-H;

E is selected from the group consisting of: N, C-F and C-H;

R1 is selected from the group consisting of: hydrogen, Me; Et; OMe; OEt; OH; NH_2 and NHMe; and

R2 is selected from the group consisting of: hydrogen, Me and Et; or

R1 and R2 together form a 3-6 membered spiro carbocyclic or heterocyclic ring;

R3 is hydrogen or halogen;

R4 is selected from the group consisting of: hydrogen; Me, Et, CF_2H; CF_3; CF_2Me; OMe; OEt; OCF_2H; OCF_3; CN; Cl and F; and

wherein:

R8 and R9 are each independently selected from the group consisting of: hydrogen; Me; Et; CH_2OH; CHMeOH; CMe_2OH; CH_2OMe; CH_2F and halogen;

R10 and R11 are each independently selected from the group consisting of: hydrogen; Me, Et, CH_2OH, CHMeOH, CMe_2OH, CH_2OMe, CH_2F CHF2; CH_2CF_3 and CH_2-heteroaryl;

R12 is selected from the group consisting of: hydrogen and Me;

R13 is selected from the group consisting of: hydrogen and Me;

R21 is selected from the group consisting of: hydrogen; and Me; or

wherein:

any one of R8, R9, R10, R11, R12, R13 and R21 may be joined to another, different R8, R9, R10, R11, R21, R13 or R21 to form a 3-7-membered spiro or bicyclic carbocyclic or heterocyclic ring structure, and/or a 3-6 membered bridged carbocyclic or heterocyclic ring structure.

7. The compound of Claim 6, wherein:

a) one of R8 and R9 is joined to one of R10 and R11 to form a [6,3]-, [6,4]-, [6,5]-, [6,7]- or [6,8]-bicyclic structure;

b) one of R8 and R9 is joined to R13 to form a [6,5,5]-, [6,6,6]-, [6,7,7]- or [6,8,8]-, bridged structure;

c) one of R10 and R11 is joined to R13 to form a [6,6,4]-, [6,7,5]- or [6,8,6]-, bridged structure;

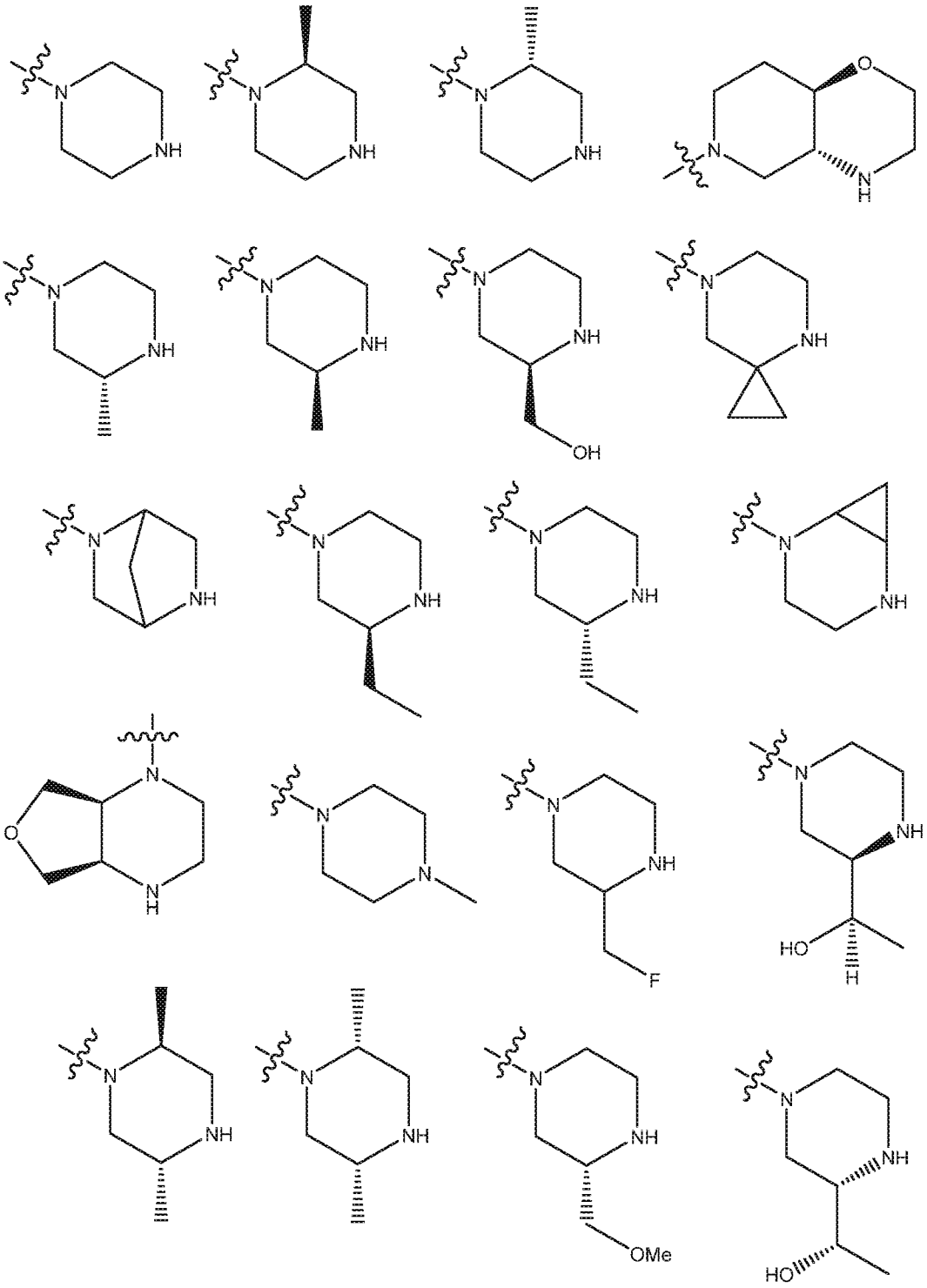
d) one of R10 and R11 may be joined to R21 to form a [6,5,5]-, [6,6,6]-, [6,7,7]-, [6,8,8]-, bridged structure;

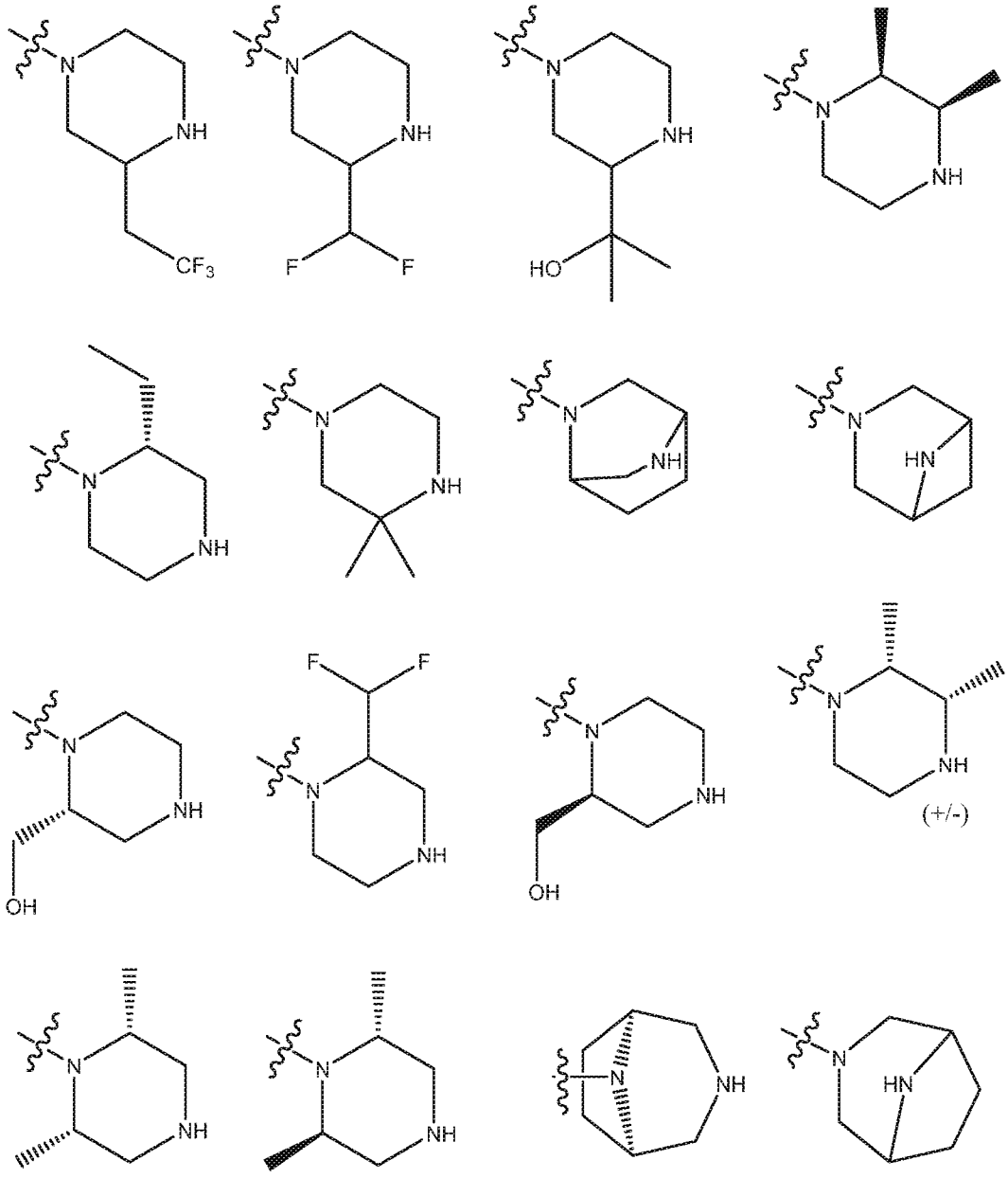
e) one of R8 and R9 may be joined to R21 to form a [6,6,4]-, [6,7,5]-, [6,8,6]-, bridged structure;

f) R8 is joined to R9 to form a [6,3]-, [6,4-], [6,5]-, [6,6]- or [6,7]-spiro structure; or

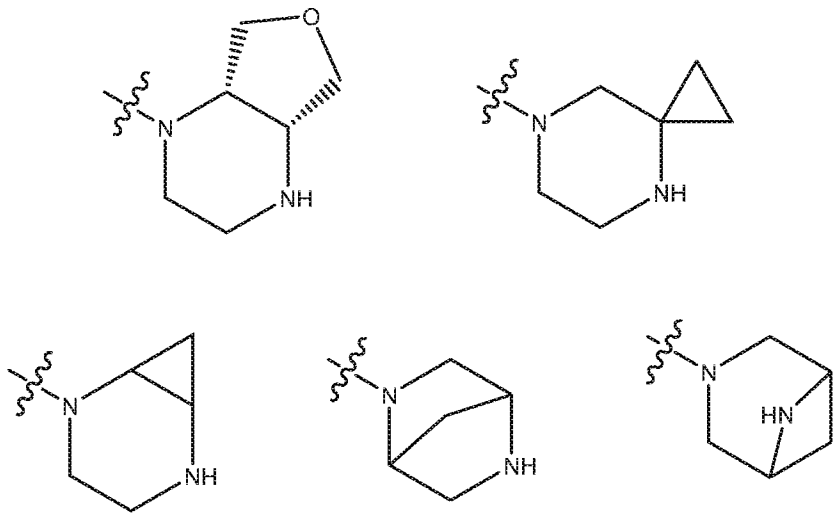
g) R10 is joined to R11 to form a [6,3]-, [6,4-], [6,5]-, [6,6]- or [6,7]-spiro structure.

8. The compound of any one of Claims 1, 2 or 6, wherein Ring Z is selected from the group consisting of:

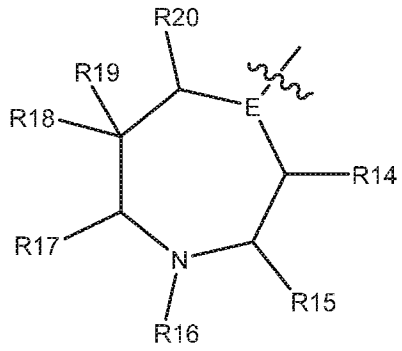



N
NH
CF3
F
F
HO
(+/-)
OH
HN

9. The compound of any one of Claims 1, 2, 6 or 8, wherein Ring Z is selected from the group consisting of:



10. The compound of Claim 2 or Claim 3, wherein G is CR1R2 and Ring Z is:



wherein;

A is selected from the group consisting of: C-H, C-F, C-Cl and C-Br;

B and D are each independently selected from the group consisting of: N and C-H;

E is selected from the group consisting of: N; C-H and C-F;

R1 is selected from the group consisting of: hydrogen; Me; Et, OMe; OEt; OH; NH_2 and NHMe; and

R2 is selected from the group consisting of: hydrogen, Me and Et; or

R1 and R2 together form a 3-6 membered spiro carbocyclic or heterocyclic ring; particularly a 4-5 membered carbocyclic or heterocyclic spiro ring;

R3 is selected from the group consisting of: hydrogen and F;

R4 is selected from the group consisting of: Me; Et; CF_2H; CF_3; CF_2Me; OMe; OEt; OCF_2H; CN; Cl and F;

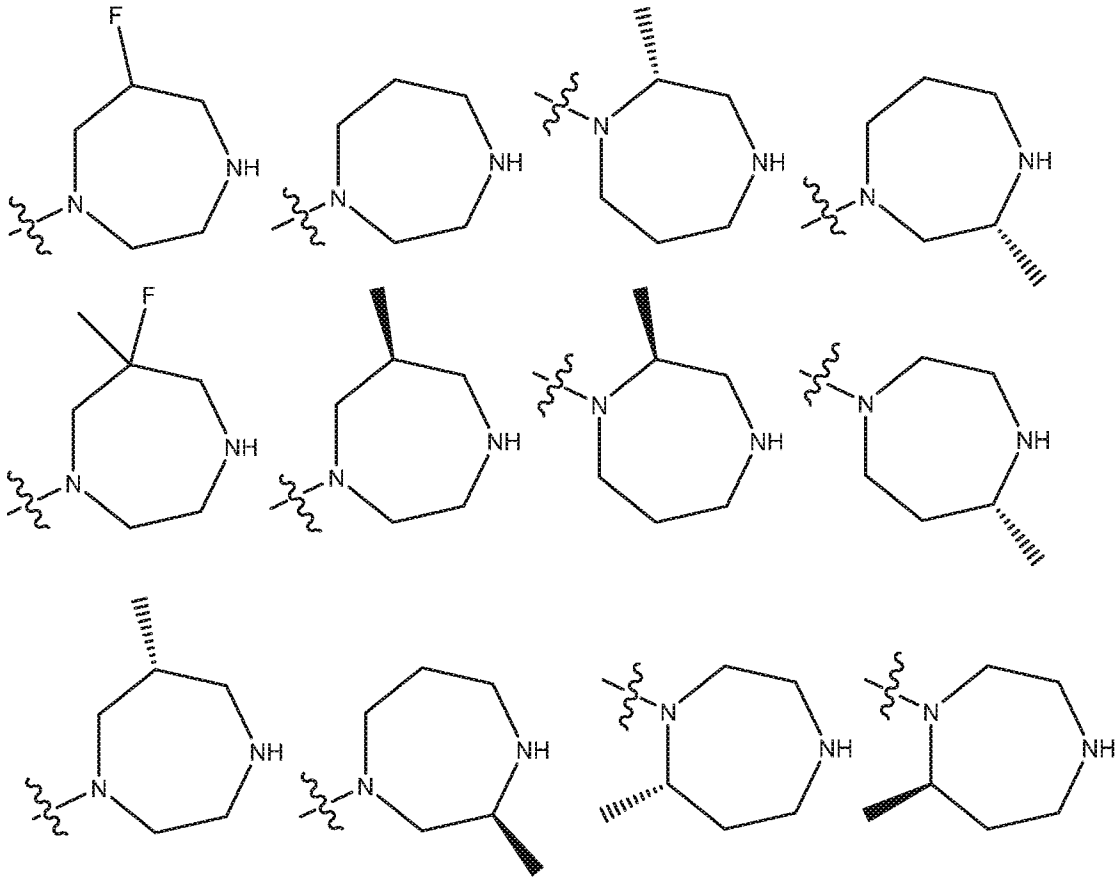
R14, R15, R17, R18, R19 and R20 is each independently selected from the group consisting of: hydrogen, Me and F.

R16 is selected from the group consisting of: hydrogen and Me.

11. The compound of Claim 10, wherein:

a) each of R14, R15, R16, R17, R18, R19 and R20 are hydrogen;
b) when one of R14, R15, R17, R18 and R20 is Me, R16 and R19 are hydrogen;
c) when R18 is F, R14, R15, R16, R17, R19 and R20 are hydrogen;
d) when R18 is F and R19 is Me, R14, R15, R16, R17 and R19 are hydrogen;
e) wherein R18 and R19 are both F and R14, R15, R17 and R20 are hydrogen;
f) when E is C-H, and R14 or R20 is F.

12. The compound of Claim 1 or Claim 10, wherein Ring Z is selected from the group consisting of:



13. The compound of any one of Claims 1 to 12, wherein when G is N-H, B is N.

14. A compound according to Table 1, or a pharmaceutically acceptable salt, solvate, stereoisomer or mixture of stereoisomers, tautomer, isotopic form, or pharmaceutically active metabolite thereof, or combinations thereof.

15. A pharmaceutical composition comprising one or more compound of any of Claims 1 to 14 or a pharmaceutically acceptable salt, solvate, stereoisomer or mixture of stereoisomers, tautomer, isotopic form, or pharmaceutically active metabolite thereof, or combinations thereof, and one or more pharmaceutically acceptable carrier.

16. The compound of any of Claim 1 to 14 or the pharmaceutical composition of Claim 15 for use in the treatment of a disorder or disease selected from an autoimmune disorder and/or inflammatory disease and/or oncologic disease and/or cancer and/or HIV infection and replication.

17. The compound or pharmaceutical composition for use according to Claim 16, wherein the disorder or disease is selected from the group consisting of: rheumatoid arthritis, multiple sclerosis, psoriasis and atopic dermatitis.

18. The compound or pharmaceutical composition for use according to Claim 16 or Claim 17, wherein the compound is an inhibitor of PKC-theta.

19. The compound or pharmaceutical composition for use according to any of Claims 16 to 18, wherein the use is in a method comprising administering the compound orally; topically; by inhalation; by intranasal administration; or systemically by intravenous, intraperitoneal, subcutaneous, or intramuscular injection.

20. The compound or pharmaceutical composition for use according to any of Claims 16 to 19, wherein the use is in a method comprising administering one or more compound according to any one of Claims 1 to 14 optionally in combination with one or more additional therapeutic agent.

21. The compound or pharmaceutical composition for use according to Claim 20, wherein the administering comprises administering the one or more compound according to any one of Claims 1 to 14 simultaneously, sequentially or separately from the one or more additional therapeutic agent.

22. The compound or pharmaceutical composition for use according to any of Claims 16 to 21, which comprises administering to a subject an effective amount of the compound according to any one of Claims 1 to 14, wherein the effective amount is between about 5 nM and about 10 μM in the blood of the subject.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2022/051166

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P31/18 A61P35/00 A61P37/00 C07D471/04 C07D471/08
C07D487/08 C07D491/04 C07D498/04 A61K31/437
ADD.
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 A61K

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, WPI Data, CHEM ABS 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 2018/035080 A1 (MERCK PATENT GMBH [DE]; CALDWELL RICHARD D [US]) 22 February 2018 (2018-02-22) paragraphs [0101] - [0112], [0138] - [0141]; claims 1, 12-13, 18	1,14-17, 19-22
X	WO 2015/099196 A1 (TAKEDA PHARMACEUTICAL [JP]) 2 July 2015 (2015-07-02) claims 1, 14, 17; compound 348	1,14-16
X	WO 2009/099594 A1 (CYTOKINETICS INC [US]; YANG ZHE [US] ET AL.) 13 August 2009 (2009-08-13) several specific compounds for instance on page 36, 38, 41 and 44.; paragraphs [0123], [0132]; claims 8, 36	1,14-17, 19-21

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[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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"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
10 September 2022	20/09/2022

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	Grégoire, Ariane

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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2022/051166

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE REGISTRY [Online] Chemical Abstacts Service, Columbus, OH, US; 4 June 2020 (2020-06-04), Enamine Llc: "Oxazolo(4,5-b)pyridin-2(3H)-one derivative", XP055957722, retrieved from STNext Database accession no. 2419260-74-3 abstract -----	1
A	CN 112 480 116 A (NANJING CHIA TAI TIANQING PHARMACEUTICAL CO LTD) 12 March 2021 (2021-03-12) paragraphs [0070], [0073] -----	1-22
A	WO 2011/139273 A1 (VERTEX PHARMA [US]; JIMENEZ JUAN-MIGUEL [GB]; MILLER ANDREW [GB]) 10 November 2011 (2011-11-10) cited in the application claims 1, 43 -----	1-22

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2022/051166

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		EP 2566866 A1	13-03-2013
		JP 2013525481 A	20-06-2013
		WO 2011139273 A1	10-11-2011