(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
07 November 2024 (07.11.2024)

WIPO | PCT

(10) International Publication Number
WO 2024/229221 A1

(51) International Patent Classification:
C07D 237/26 (2006.01) *A61K 31/025* (2006.01)
C07D 487/04 (2006.01) *A61P 35/00* (2006.01)
C07D 235/02 (2006.01)

(21) International Application Number:
PCT/US2024/027412

(22) International Filing Date:
02 May 2024 (02.05.2024)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/499,831 03 May 2023 (03.05.2023) US

(71) Applicant: **CAPULUS THERAPEUTICS, LLC** [US/US]; 535 Mission Street, 14th Floor, San Francisco, California 94105 (US).

(72) Inventors: **GREEN, Michael John**; c/o Capulus Therapeutics, LLC, 535 Mission Street, 14th Floor, San Francisco, California 94105 (US). **MUTTINENI, Ravikumar**; c/o Capulus Therapeutics, LLC, 535 Mission Street, 14th Floor, San Francisco, California 94105 (US). **GHOSH, Sumana**; c/o Capulus Therapeutics, LLC, 535 Mission Street, 14th Floor, San Francisco, California 94105 (US). **NAGANABOINA, Naveen**; c/o Capulus Therapeutics, LLC, 535 Mission Street, 14th Floor, San Francisco, California 94105 (US). **HART, Barry**; c/o Capulus Therapeutics, LLC, 535 Mission Street, 14th Floor, San Francisco, California 94105 (US).

(74) Agent: **REYNOLDS, Anne M.**; Casimir Jones S.C., 2275 Deming Way, Suite 310, Middleton, Wisconsin 53562 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

WO 2024/229221 A1

(54) Title: ANDROGEN RECEPTOR MODULATORS AND METHODS FOR THEIR USE

(57) Abstract: Androgen receptor modulators, and more particularly N-terminal domain androgen receptor inhibitors are presented. Related pharmaceutical compositions and methods are also presented.

ANDROGEN RECEPTOR MODULATORS AND METHODS FOR THEIR USE

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims a benefit of, and priority to, US Provisional Patent Application No 63/499,831, filed May 3rd, 2023, the disclosure of which is incorporated by reference in its entirety.

TECHNICAL FIELD

[0002] Embodiments of the present invention generally relate to androgen receptor modulators, and more particularly to N-terminal domain androgen receptor inhibitors.

BACKGROUND

[0003] Androgens mediate their effects through the androgen receptor (AR). Androgens play a role in a wide range of developmental and physiological responses and are involved in male sexual differentiation, maintenance of spermatogenesis, and male gonadotropin regulation. The androgen receptor (AR) is encoded by the NR3C4 gene and is within the nuclear receptor family. The binding of AR to its endogenous ligand 5α-dihydrotestosterone (DHT) and testosterone is responsible for starting male sexual development and differentiation. Testosterone is synthesized by the Leydig cells in the testes and circulates mostly bound to the serum sex hormone-binding globulin (SHBG) and albumin. The free form enters prostate cells, where testosterone is converted to the more potent form of DHT, which promotes growth and survival of prostate cells. High affinity binding of DHT to AR displaces other AR-bound proteins and drives the AR complex to the nucleus where it dimerizes and binds to androgen response elements (AREs) in the promoter region of target genes. The full-length AR protein has three major domains, the N-terminal domain (NTD), the DNA-binding domain (DBD), and the ligand-binding domain (LBD). All three are required for the proper regulation and function of AR. The AR can be activated in the absence of testicular androgens by alternative signal

transduction pathways in castration-resistant disease, which is consistent with the finding that nuclear AR protein is present in secondary prostate cancer tumors.

[0004] Prostate cancer is one of the most common male malignancies and is the second leading cause of cancer deaths among males in the United States. The current standard of care is androgen deprivation therapy, which is initially effective for the treatment of metastatic prostate cancer, but most patients develop castration-resistant prostate cancer (CRPC) that can further develop into metastatic CRPC (mCRPC).

[0005] Current AR targeting agents available for treatment primarily target the LBD of AR. However, point mutations, gene rearrangements resulting in overexpression of AR, development of constitutively active AR structural variants, and several other mechanisms may render AR-LBD targeting inhibitors ineffective. Multiple mechanisms may lead to resistance in prostate cancer cells, one of them being increased production of short AR splice variants. The most prominent variants in prostate and breast cancer are ARV7 and ARV567es.

[0006] Constitutively active AR structural variants (without LBD), of which AR splice variant-7 (AR-V7) is the most frequently detected, are considered a potential driver of castration-resistant prostate cancer (CRPC). AR-V7 is expressed in over 80% of CRPC patient samples in Stand Up to Cancer (SU2C) prostate cancer cohort. AR-V7 can dimerize without the presence of the receptor-ligand and drive AR response genes transcription in the nucleus, this provides them with the ability to drive prostate cancer even in the absence of LBD. ARV7 displays noncanonical nuclear import kinetics and short chromatin residence time as compared to ARFL. Further, in-vitro and in-vivo studies have shown that AR-V7 can drive prostate cancer and its inhibition leads to tumor growth control and induces tumor regression.

[0007] The AR pathway has also been implicated in breast cancer and may be a suitable target for triple-negative breast cancer (TNBC) where AR plays a role in the proliferation of breast cancer cells by either promoting proliferation or inhibiting

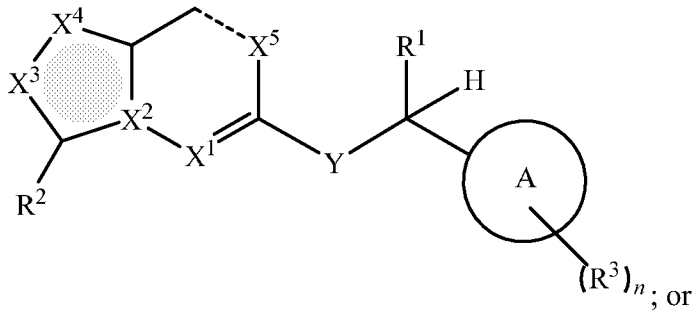
proliferation depending on the expression of estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2), as well as ovarian cancers. Up to 90% of breast cancer have AR expression and AR-V7 has been detected in primary breast cancer samples and cell lines.

[0008] Therefore, it is desirable to target domains other than LBD as a potential path for treating cancers such as prostate, breast, and ovarian cancers.

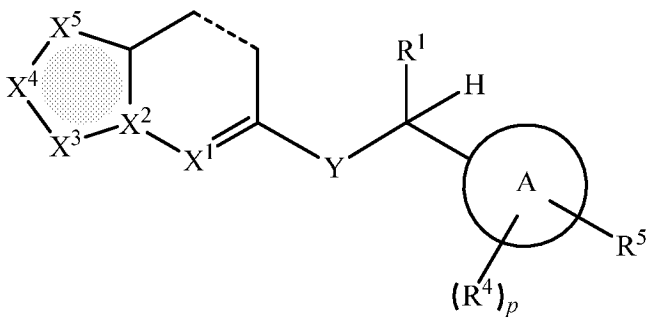
SUMMARY

[0009] The following summary is illustrative only and is not intended to be in any way limiting. In addition to the illustrative aspects, example embodiments, and features described, further aspects, example embodiments, and features will become apparent by reference to the following detailed description.

[0010] In some aspects of the present invention, a compound having formula (I) or (II) or a pharmaceutically acceptable salt thereof is presented:



(I) ; or



(II) ;

wherein

dotted line "-----" is a single bond or a double bond;

"n" is an integer from 0 to 5; "p" is an integer from 0 to 4;

A is a C_3-C_9 cycloalkyl group, a C_3-C_{12} heterocycloalkyl group, a C_6-C_{12} aryl group, or a C_3-C_{12} heteroaryl group;

X^1, X^3, X^4 and X^5 are independently at each occurrence nitrogen, NH, CH or CH_2;

X^2 is independently at each occurrence carbon or nitrogen;

wherein in formula (I) at least one of X^1, X^2, X^3, X^4 and X^5 is carbon, CH or CH_2 and at least two of X^1, X^2, X^3, X^4 and X^5 are nitrogen or NH, and in formula (II) at least two of X^1, X^2, X^3, X^4 and X^5 are nitrogen or NH;

Y is O, S, or NR^6;

R^1 is a C_1-C_6 alkyl group optionally substituted with one or more fluorine or deuterium or a C_3-C_7 cycloalkyl group optionally substituted with one or more fluorine or deuterium;

R^2 is a C_1-C_6 alkyl group optionally substituted with one or more fluorine, a C_3-C_7 cycloalkyl group optionally substituted with one or more fluorine, —OR^7, or SF_5;

R^3 is independently at each occurrence halogen, —CN, —OR^7, —$NHC(=O)R^7$, —$C(-C_6H_5)R^7R^8$, —$C(=O)NR^7R^8$, —NR^7R^8, —$P(=O)R^7R^8$, a C_1-C_6 alkyl group optionally substituted with one or more fluorine or deuterium, a C_3-C_7 cycloalkyl group optionally substituted with one or more fluorine or deuterium, a C_1-C_{12} heterocycloalkyl group optionally substituted with one or more R^9, or a C_1-C_{12} heteroaryl group optionally substituted with one or more R^9;

R^4 is independently at each occurrence halogen, —CN, —OR^7, —$NHC(=O)R^7$, —$C(=O)NR^7R^8$, —NR^7R^8, —$P(=O)R^7R^8$, a C_1-C_6 alkyl group optionally substituted with one or more fluorine or deuterium, or a C_3-C_7 cycloalkyl group optionally substituted with one or more fluorine or deuterium;

R^5 is a C_1-C_{12} heterocycloalkyl group or a C_1-C_{12} heteroaryl group optionally substituted with one or more R^9;

R^6 is hydrogen, a C_1-C_6 alkyl group, or a C_3-C_7 cycloalkyl group;

R^7 and R^8 are independently at each occurrence hydrogen, a C_1-C_6 alkyl group optionally substituted with one or more fluorine or an aminoalkyl group, a C_6-C_{10} aryl group optionally substituted with one or more fluorine, or R^7 and R^8 together with the carbon or nitrogen to which each is attached form a C_3-C_7 cycloalkyl group optionally substituted with one or more fluorine or a C_3-C_{15} heterocycloalkyl group optionally substituted with one or more fluorine; and

R^9 is independently at each occurrence halogen, —CN, —OR^7, —NHC(=O)R^7, —C(=O)NR^7R^8, —NR^7R^8, a C_1-C_6 alkyl group optionally substituted with one or more fluorine or a C_3-C_7 cycloalkyl group optionally substituted with one or more fluorine;

with the proviso that if in formula (I), A is a C_6-C_{12}aryl group, Y is NH, X^1, X^2, X^3 and X^4, are all nitrogen, R^1 is a C_1-C_6 alkyl group, R^2 is a C_1-C_6 alkyl group optionally substituted with one or more fluorine, n is 1, then R^3 is not a halogen.

[0011] In some aspects of the present invention, a pharmaceutical composition is presented. The pharmaceutical composition includes a compound having a formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, or co-crystal thereof, and a pharmaceutically carrier, diluent, or excipient.

[0012] In some aspects of the present invention, a method for modulation of androgen receptor activity for treatment of prostate cancer, breast cancer, ovarian cancer, or melanoma is presented. The method includes administering to a patient a therapeutically effective amount of a pharmaceutical composition including a compound of formula (I).

DETAILED DESCRIPTION OF EXAMPLE EMBODIMENTS

[0013] Various example embodiments will now be described more fully with reference to the accompanying drawings in which only some example embodiments are shown. Specific structural and functional details disclosed herein are merely representative for purposes of describing example embodiments. Example embodiments, however, may be embodied in many alternate forms and should not be construed as limited to only the example embodiments set forth herein. On the contrary, example embodiments are to

cover all modifications, equivalents, and alternatives thereof.

[0014] The terminology used herein is for the purpose of describing particular example embodiments only and is not intended to be limiting. Unless otherwise defined, all terms (including technical and scientific terms) used herein have the same meaning as commonly understood by one of ordinary skill in the art to which example embodiments belong. It will be further understood that terms, e.g., those defined in commonly used dictionaries, should be interpreted as having a meaning that is consistent with their meaning in the context of the relevant art and will not be interpreted in an idealized or overly formal sense unless expressly so defined herein.

[0015] As used herein, the singular forms "a," "an," and "the," are intended to include the plural forms as well, unless the context clearly indicates otherwise. As used herein, the terms "and/or" and "at least one of" include any and all combinations of one or more of the associated listed items. It will be further understood that the terms "comprises," "comprising," "includes," and/or "including," when used herein, specify the presence of stated features, integers, steps, operations, elements, and/or components, but do not preclude the presence or addition of one or more other features, integers, steps, operations, elements, components, and/or groups thereof.

[0016] Approximating language, as used herein throughout the specification and claims, may be applied to modify any quantitative representation that could permissibly vary without resulting in a change in the basic function to which it is related. Accordingly, a value modified by a term such as "about" is not to be limited to the precise value specified. Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention. At the very least each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

[0017] To more clearly and concisely describe and point out the subject matter of the claimed invention, the following definitions are provided for specific terms that are used in the following description and the claims appended hereto.

[0018] Definitions of specific functional groups and chemical terms are described in more detail below. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, the replacement of a carbon by a 13C- or 14C-enriched carbon, or the replacement of a fluorine by 18F-enriched fluorine, are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention.

[0019] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms.

[0020] Where a particular enantiomer is preferred, it may, in some embodiments be provided substantially free of the corresponding enantiomer, and may also be referred to as "optically enriched." "Optically-enriched," as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In certain embodiments,

the compound is made up of at least about 90% by weight of a preferred enantiomer. In other embodiments, the compound is made up of at least about 95%, 98%, or 99% by weight of a preferred enantiomer. Preferred enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high-pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by asymmetric syntheses.

[0021] As used herein, the term "alkyl group" refers to a saturated monovalent group consisting of a linear or branched array of atoms that is not cyclic. Alkyl groups are defined to include at least one carbon atom and are represented by formula C_nH_{2n+1}. The array of atoms included in the alkyl group may be composed exclusively of carbon and hydrogen. By way of example, the term "C_1–C_{10} alkyl group" contains at least one but no more than 10 carbon atoms. A methyl group (i.e. CH_3—) is an example of a monovalent C_1 alkyl group. A decyl group (i.e., $CH_3(CH_2)_9$—) is an example of a monovalent C_{10} alkyl group. Non-limiting examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like.

[0022] As used herein the term "cycloalkyl group" refers to a group having a valence of at least three, and consisting of a saturated or a partially unsaturated array of atoms which is cyclic but which is not aromatic. A "cycloalkyl" may include one or more noncyclic components. For example, a cyclohexylmethyl group ($C_6H_{11}CH_2$—) is a cycloalkyl group which includes a cyclohexyl ring (the array of atoms which is cyclic but which is not aromatic) and a methylene group (the noncyclic component). Further, a cycloalkyl group may be monocyclic or may include one or more ring systems. By way of example, the term "a C_3–C_{10} cycloalkyl group" includes cycloalkyl groups containing at least three but no more than 10 carbon atoms. The cycloalkyl group 2-tetrahydrofuranyl (C_4H_7O—) represents a C_4 cycloalkyl group. The cyclohexylmethyl group ($C_6H_{11}CH_2$—) represents a C_7 cycloalkyl group.

[0023] As used herein the term "aryl group" refers to a monovalent aromatic hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Aryl group encompasses 5- and 6-membered

carbocyclic aromatic rings, for example, benzene; bicyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, naphthalene, indane, and tetralin; and tricyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, fluorene.

[0024] The term "aryl group "also encompasses multiple ring systems having at least one carbocyclic aromatic ring fused to at least one carbocyclic aromatic ring, cycloalkyl ring, or heterocycloalkyl ring. For example, aryl group includes 5- and 6-membered carbocyclic aromatic rings fused to a 5- to 7-membered heterocycloalkyl ring containing one or more heteroatoms chosen from N, O, and S. For such fused, bicyclic ring systems wherein only one of the rings is a carbocyclic aromatic ring, the point of attachment may be at the carbocyclic aromatic ring or the heterocycloalkyl ring. Examples of aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, as-indacene, s-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, trinaphthalene, and the like. In certain embodiments, an aryl group can include from 5 to 20 carbon atoms, and in certain embodiments, from 5 to 12 carbon atoms.

[0025] As used herein, the term "heteroaryl group" refers to a monovalent heteroaromatic radical derived by the removal of one hydrogen atom from a single atom of a parent heteroaromatic ring system. Heteroaryl group encompasses multiple ring systems having at least one aromatic ring fused to at least one other ring, which can be aromatic or non-aromatic in which at least one ring atom is a heteroatom. Heteroaryl group encompasses 5- to 12-membered aromatic, monocyclic rings (such as 5- to 7-membered rings) containing one or more, for example, from 1 to 4, or in certain embodiments, from 1 to 3, heteroatoms chosen from N, O, and S, with the remaining ring atoms being carbon; and bicyclic heterocycloalkyl rings containing one or more, for example, from 1 to 4, or in certain embodiments, from 1 to 3, heteroatoms chosen from N, O, and S, with the remaining

ring atoms being carbon and wherein at least one heteroatom is present in an aromatic ring. For example, heteroaryl includes a 5- to 7-membered heteroaromatic ring fused to a 5- to 7-membered cycloalkyl ring. For such fused, bicyclic heteroaryl ring systems wherein only one of the rings contains one or more heteroatoms, the point of attachment may be at the heteroaromatic ring or the cycloalkyl ring. In certain embodiments, when the total number of N, S, and O atoms in the heteroaryl group exceeds one, the heteroatoms are not adjacent to one another. In certain embodiments, the total number of N, S, and O atoms in the heteroaryl group is not more than two. In certain embodiments, the total number of N, S, and O atoms in the aromatic heterocycle is not more than one. By way of example, the term "C_5–C_{10} heteroaryl group" contains at least 5 but no more than 10 carbon atoms. The heteroaryl group benzoimidazolyl ($C_7H_5N_2$—) represents a C_7 heteroaryl group. The pyridyl group (C_5H_4N—) represents a C_5 heteroaryl group.

[0026] As used herein, the term "heterocycloalkyl group" refers to non-aromatic group having a valence of one which consists of at least one heteroatom selected from the group consisting of nitrogen, oxygen and sulfur. Unless stated otherwise specifically in the specification, the heterocycloalkyl group can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocycloalkyl group can be optionally oxidized; the nitrogen atom can be optionally quaternized; and the heterocycloalkyl group can be partially or fully saturated. By way of example, the term "C_4–C_7 heterocycloalkyl group" contains at least 4 but no more than 7 carbon atoms. The heterocycloalkyl group dioxyl ($C_4H_7O_2$—) represents a C_4 heterocycloalkyl group. The piperidyl group (C_5H_9N—) represents a C_5 heterocycloalkyl group.

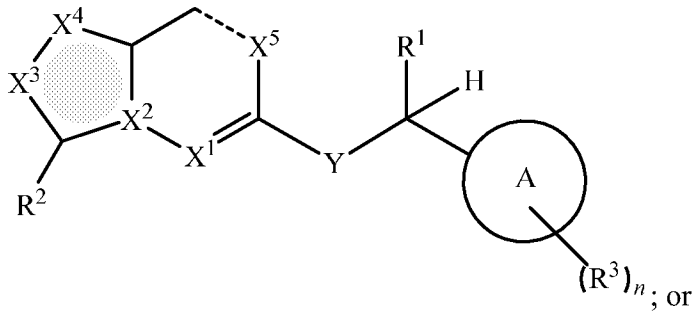
[0027] Examples of heteroaryl and heterocycloalkyl groups include, but are not limited to, groups derived from acridine, arsindole, carbazole, beta-carboline, chromane, chromene, cinnoline, furan, furazan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine,

pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene, and the like.

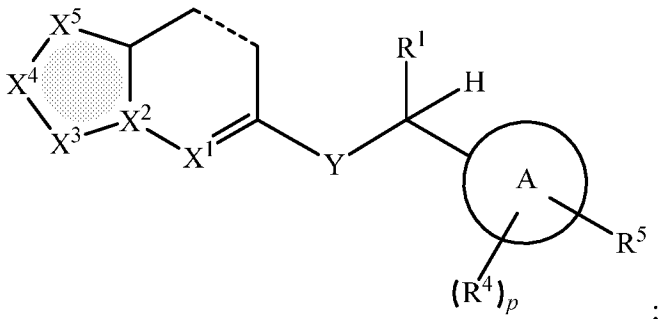
[0028] As used herein, the term "therapeutically effective amount" refers to an amount (of a compound) that is sufficient to provide a therapeutic benefit to a patient in the treatment or management of a disease or disorder, or to delay or minimize one or more symptoms associated with the disease or disorder.

[0029] As used herein, the term "pharmaceutically acceptable salt" refers to any salt suitable for administration to a patient. Examples of salts include, but are not limited to, acid-derived, base-derived, organic, inorganic, amine, and alkali or alkaline earth metal salts, including but not limited to calcium salts, magnesium salts, potassium salts, sodium salts, salts of hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like.

[0030] In some embodiments, a compound having formula (I) or (II) or a pharmaceutically acceptable salt thereof is presented:



(I) ; or



(II) ;

wherein

dotted line "-----" is a single bond or a double bond;

"n" is an integer from 0 to 5; "p" is an integer from 0 to 4;

A is a C_3-C_9 cycloalkyl group, a C_3-C_{12} heterocycloalkyl group, a C_6-C_{12} aryl group, or a C_3-C_{12} heteroaryl group;

X^1, X^3, X^4 and X^5 are independently at each occurrence nitrogen, NH, CH or CH_2;

X^2 is independently at each occurrence carbon or nitrogen;

wherein in formula (I) at least one of X^1, X^2, X^3, X^4 and X^5 is carbon, CH or CH_2 and at least two of X^1, X^2, X^3, X^4 and X^5 are nitrogen or NH, and in formula (II) at least two of X^1, X^2, X^3, X^4 and X^5 are nitrogen or NH;

Y is O, S, or NR^6;

R^1 is a C_1-C_6 alkyl group optionally substituted with one or more fluorine or deuterium or a C_3-C_7 cycloalkyl group optionally substituted with one or more fluorine or deuterium;

R^2 is a C_1-C_6 alkyl group optionally substituted with one or more fluorine, a C_3-C_7 cycloalkyl group optionally substituted with one or more fluorine, —OR^7, or SF_5;

R^3 is independently at each occurrence halogen, —CN, —OR^7, —$NHC(=O)R^7$, —$C(-C_6H_5)R^7R^8$, —$C(=O)NR^7R^8$, —NR^7R^8, —$P(=O)R^7R^8$, a C_1-C_6 alkyl group optionally

substituted with one or more fluorine or deuterium, a C_3-C_7 cycloalkyl group optionally substituted with one or more fluorine or deuterium, a C_1-C_{12} heterocycloalkyl group optionally substituted with one or more R^9, or a C_1-C_{12} heteroaryl group optionally substituted with one or more R^9;

R^4 is independently at each occurrence halogen, —CN, —OR^7, —NHC(=O)R^7, —C(=O)NR^7R^8, —NR^7R^8, —P(=O)R^7R^8, a C_1-C_6 alkyl group optionally substituted with one or more fluorine or deuterium, or a C_3-C_7 cycloalkyl group optionally substituted with one or more fluorine or deuterium;

R^5 is a C_1-C_{12} heterocycloalkyl group or a C_1-C_{12} heteroaryl group optionally substituted with one or more R^9;

R^6 is hydrogen, a C_1-C_6 alkyl group, or a C_3-C_7 cycloalkyl group;

R^7 and R^8 are independently at each occurrence hydrogen, a C_1-C_6 alkyl group optionally substituted with one or more fluorine or an aminoalkyl group, a C_6-C_{10} aryl group optionally substituted with one or more fluorine, or R^7 and R^8 together with the carbon or nitrogen to which each is attached form a C_3-C_7 cycloalkyl group optionally substituted with one or more fluorine or a C_3-C_{15} heterocycloalkyl group optionally substituted with one or more fluorine; and

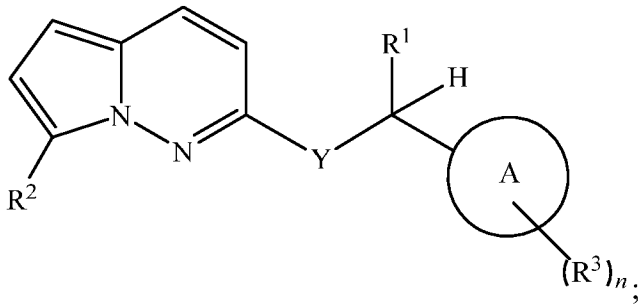
R^9 is independently at each occurrence halogen, —CN, —OR^7, —NHC(=O)R^7, —C(=O)NR^7R^8, —NR^7R^8, a C_1-C_6 alkyl group optionally substituted with one or more fluorine or a C_3-C_7 cycloalkyl group optionally substituted with one or more fluorine;

with the proviso that if in formula (I), A is a C_6-C_{12}aryl group, Y is NH, X^1, X^2, X^3 and X^4, are all nitrogen, R^1 is a C_1-C_6 alkyl group, R^2 is a C_1-C_6 alkyl group optionally substituted with one or more fluorine, n is 1, then R^3 is not a halogen.

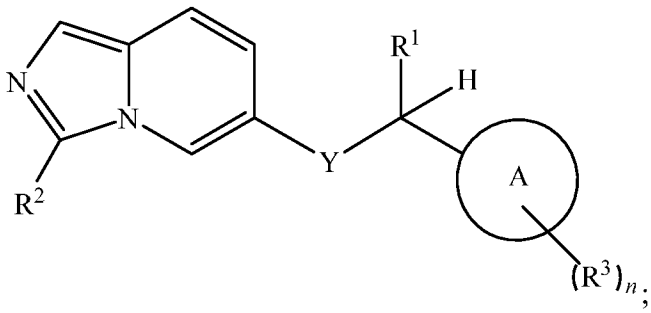
Series A

[0031] In some embodiments, the compound has formula (I) and is selected from

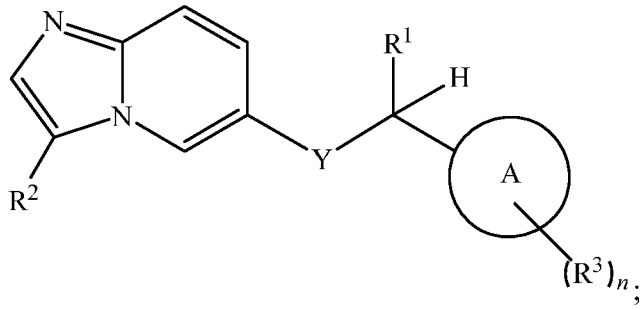
the group consisting of:



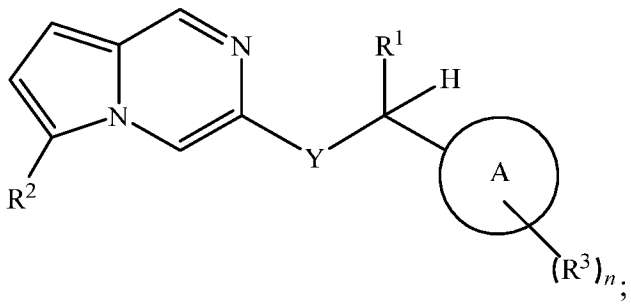
(III)



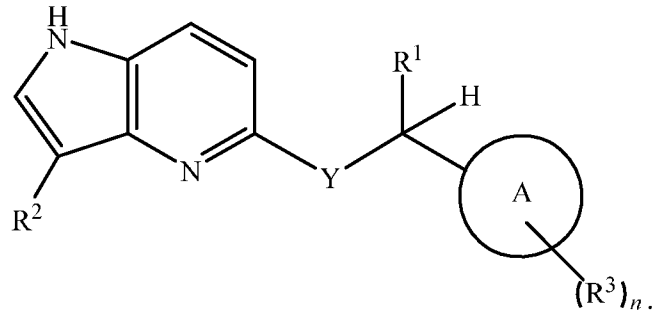
(IV)



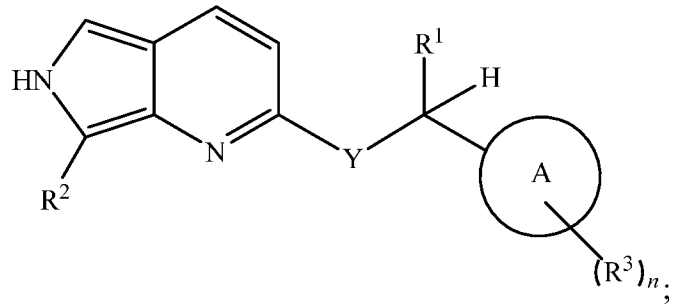
(V)



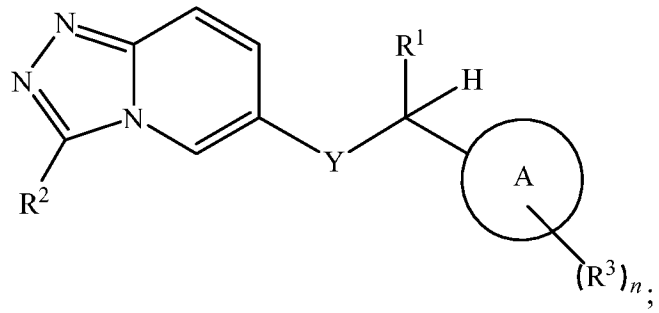
(VI)



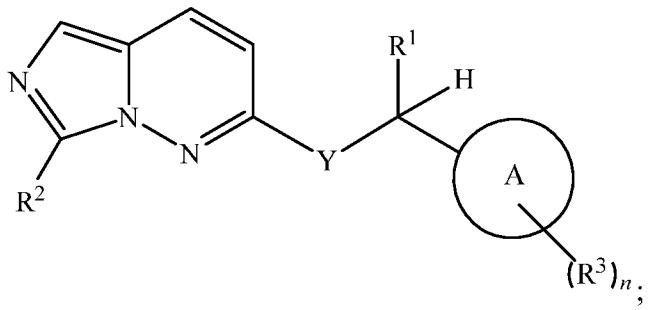
(VII)



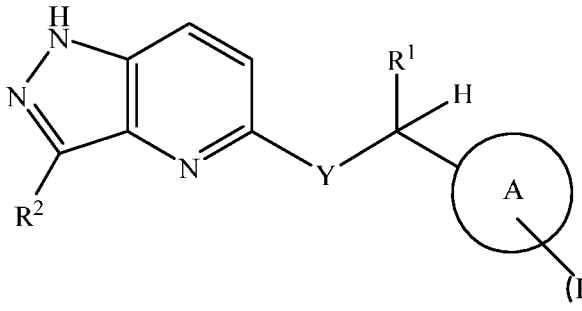
(VIII)



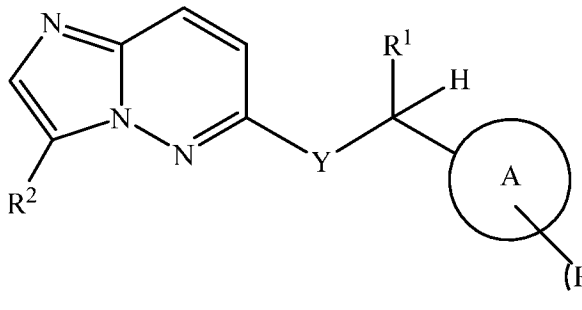
(IX)



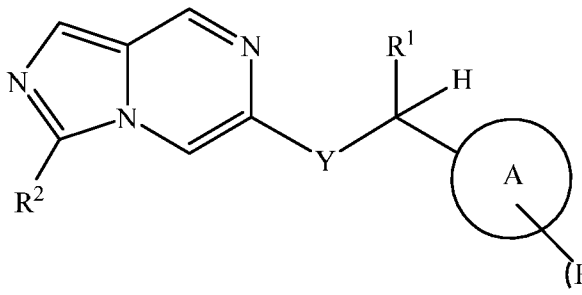
(X)



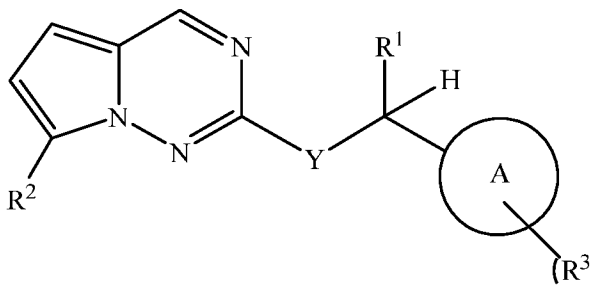
(XI);



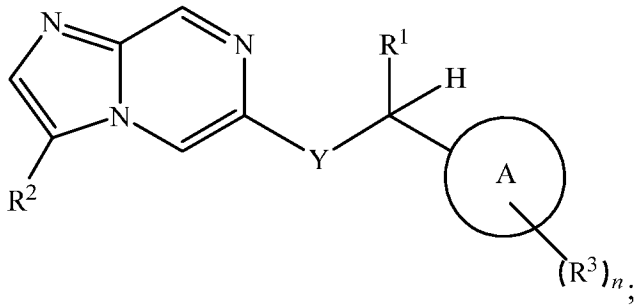
(XII);



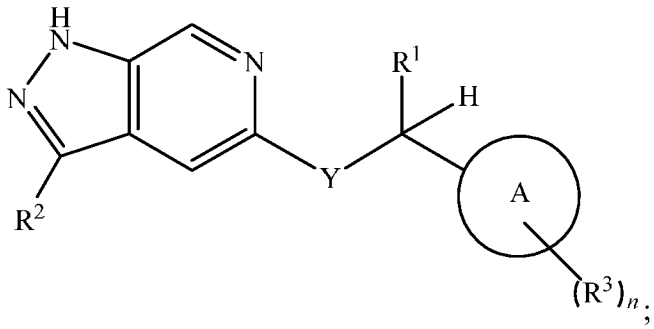
(XIII);



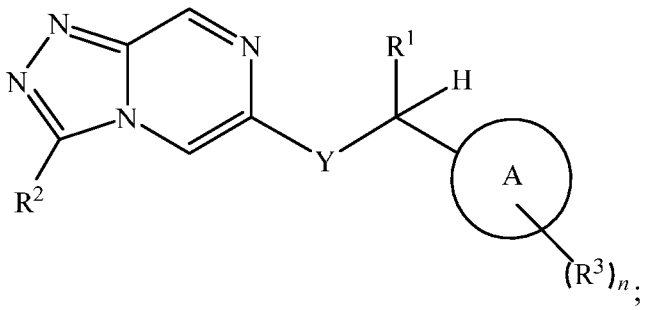
(XIV);



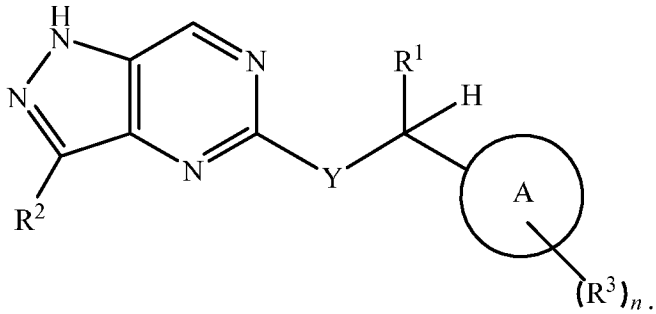
(XV);



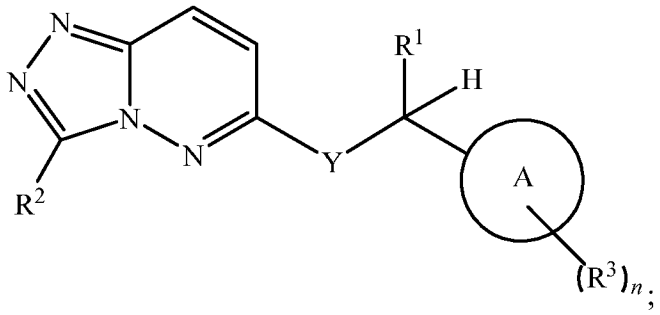
(XVI);



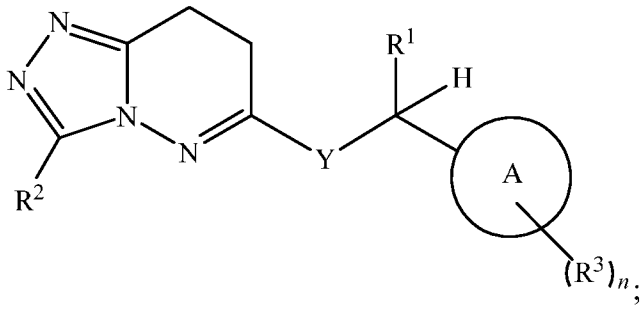
(XVII);



(XVIII);



(XIX)



(XX)

and any pharmaceutically acceptable salts thereof.

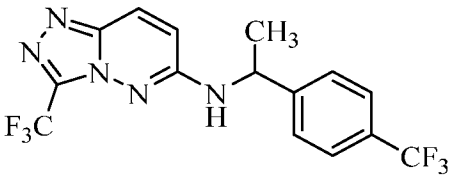
[0032] In some embodiments, the compound has formula (III) to (XX), wherein Y is O, S, or NR^6, R^1 is a C_1-C_3 alkyl group optionally substituted with one or more fluorine, R^2 is a C_1-C_3 alkyl group substituted with one or more fluorine, and R^6 is hydrogen, a C_1-C_6 alkyl group, or a C_3-C_7 cycloalkyl group.

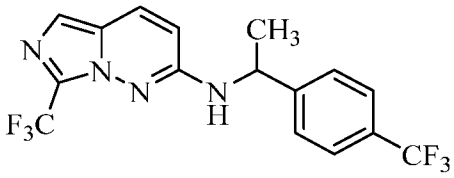
[0033] In some embodiments, the compound has formula (III) to (XX), wherein Y is O, S, or NR^6, R^1 is a C_1-C_3 alkyl group optionally substituted with one or more fluorine, R^2 is a C_1-C_3 alkyl group substituted with one or more fluorine, R^3 is independently at each occurrence halogen, —CN, —OR^7, or a C_1-C_3 alkyl group substituted with one or more fluorine, and R^6 is hydrogen, a C_1-C_6 alkyl group, or a C_3-C_7 cycloalkyl group.

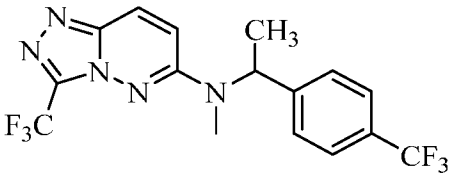
[0034] In some embodiments, the compound has formula (III) to (XX), wherein Y is O, S, or NR^6, R^1 is a C_1-C_3 alkyl group optionally substituted with one or more fluorine, R^2 is a C_1-C_3 alkyl group substituted with one or more fluorine, R^3 is independently at each occurrence a C_1-C_3 alkyl group substituted with one or more fluorine, and R^6 is hydrogen, a C_1-C_6 alkyl group, or a C_3-C_7 cycloalkyl group.

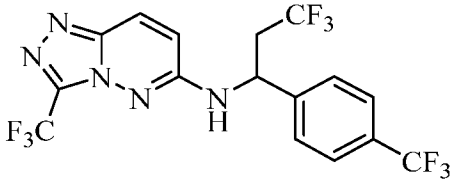
[0035] In some embodiments, the compound has formula (III) to (XX), wherein Y is NR^6, R^1 is a C_1-C_3 alkyl group optionally substituted with one or more fluorine, R^2 is a C_1-C_3 alkyl group substituted with one or more fluorine, R^3 is independently at each occurrence a C_1-C_3 alkyl group substituted with one or more fluorine, and R^6 is a C_1-C_3 alkyl group.

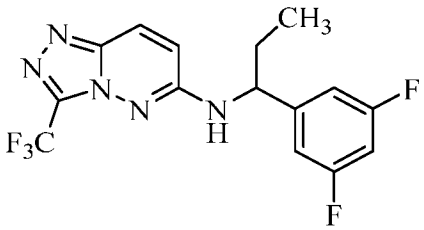
[0036] Non-limiting examples of compounds having a formula (I) include:

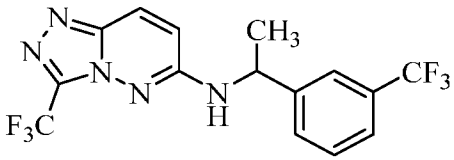


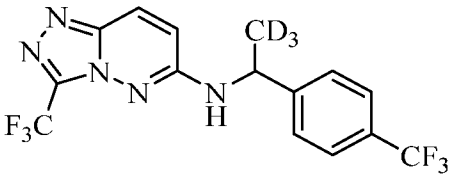


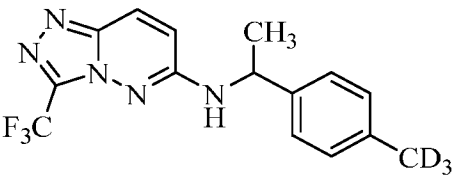


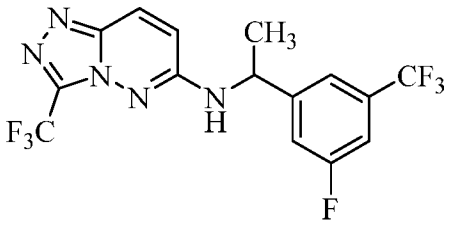


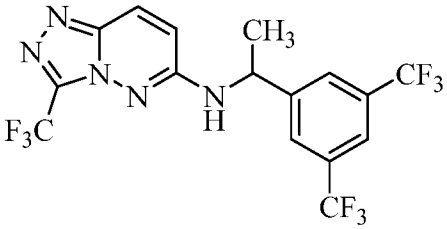


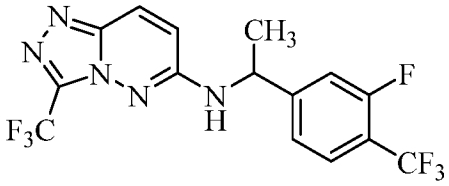


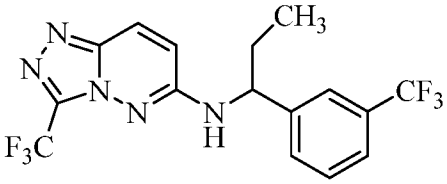


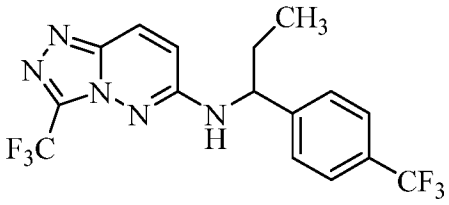


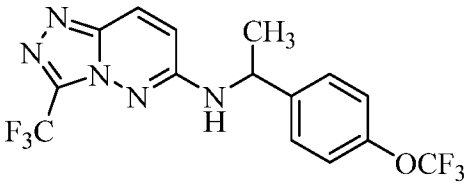


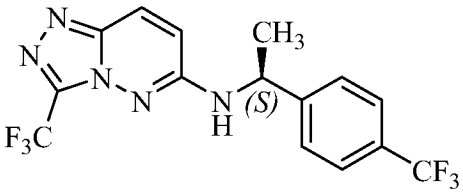


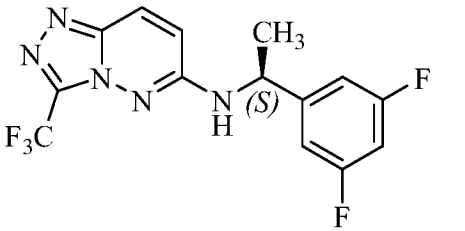


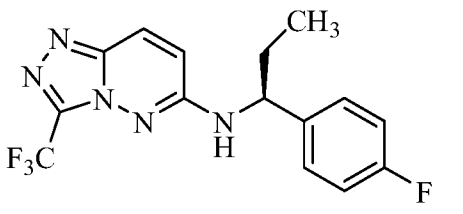


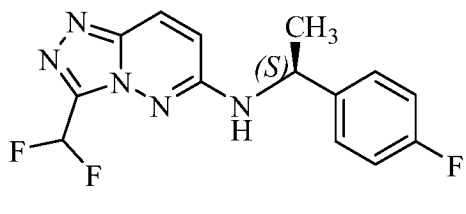


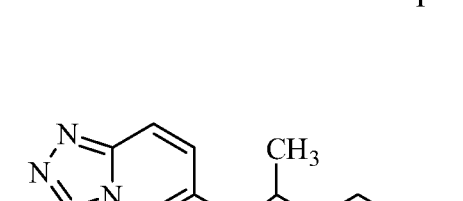


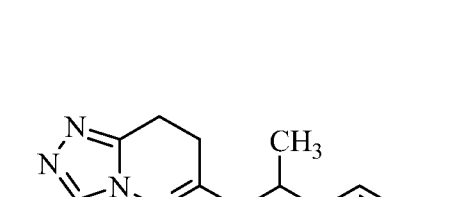


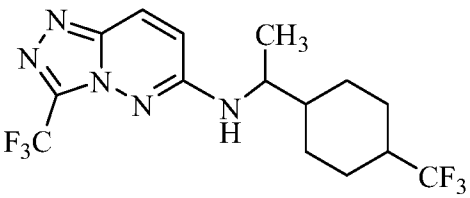


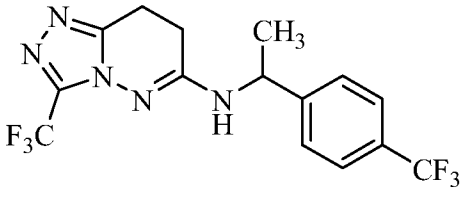


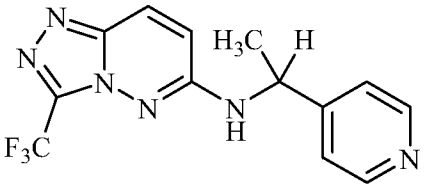


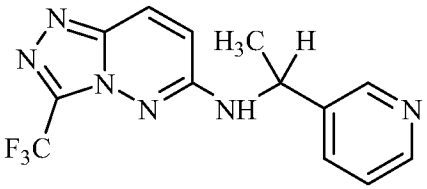


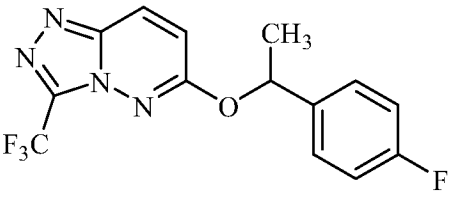


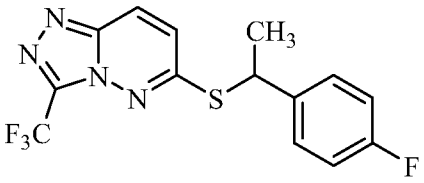


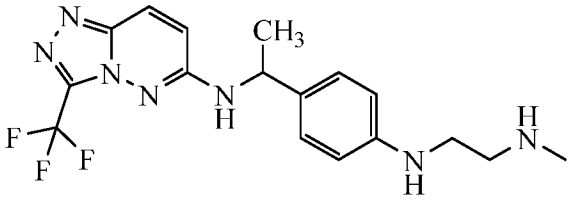


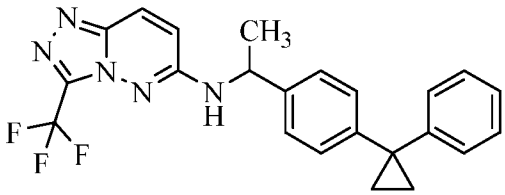


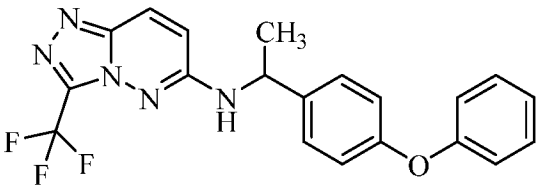


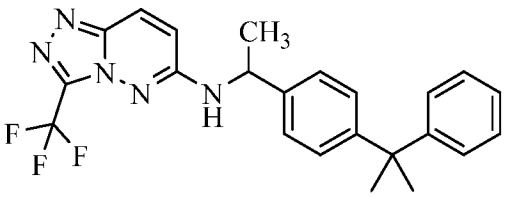


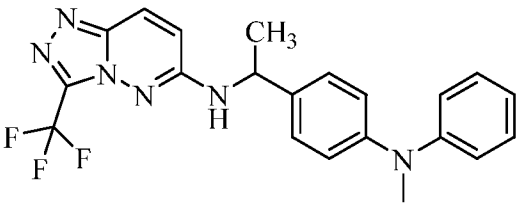


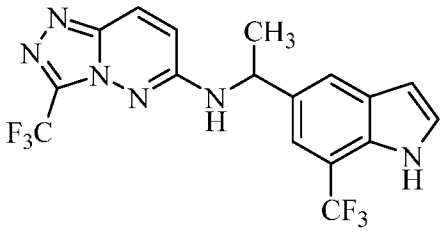


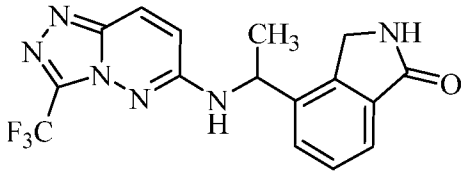


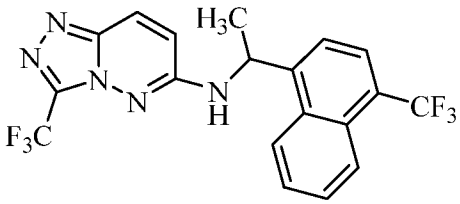








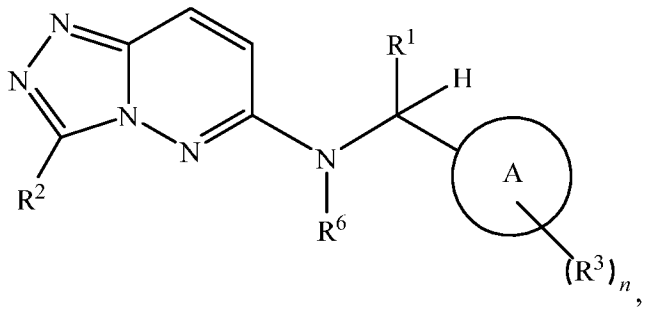




.

Series B

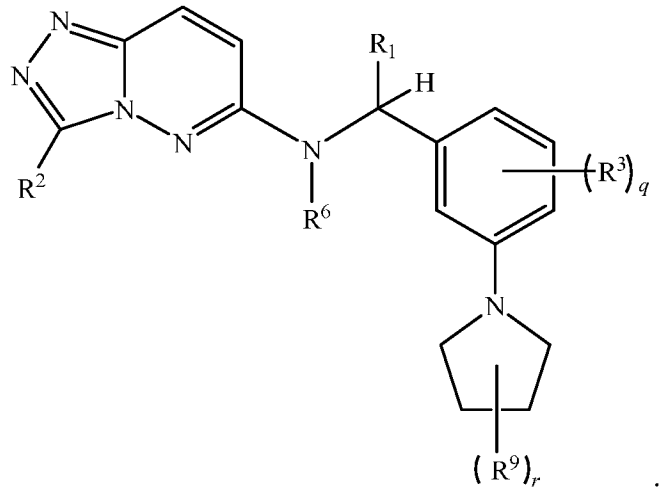
[0037] In some embodiments, the compound has a formula (XXI) or any pharmaceutically acceptable salt thereof:



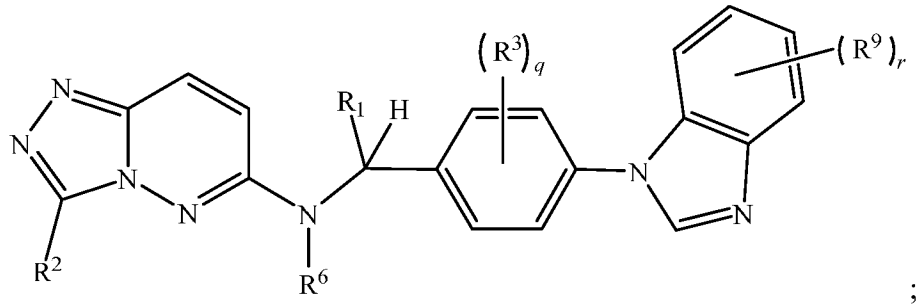
(XXI)

wherein "n" is an integer from 1 to 5, and at least one R^3 is a C_1-C_{12} heterocycloalkyl group optionally substituted with one or more R^9 or a C_1-C_{12} heteroaryl group optionally substituted with one or more R^9.

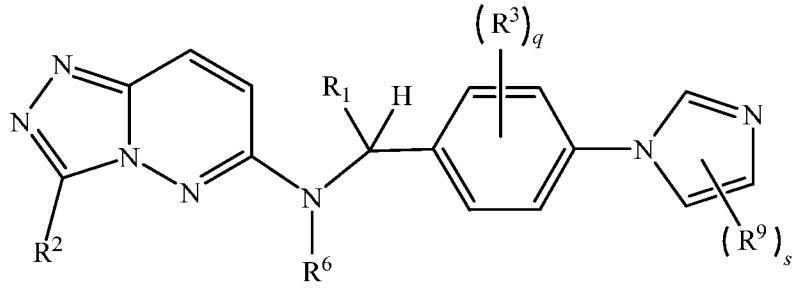
[0038] In some embodiments, the compound has a formula (XXI) and is selected from the group consisting of:



(XXII) ;



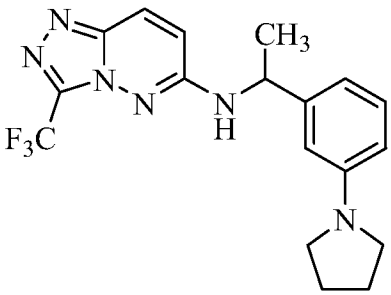
(XXIII) ;

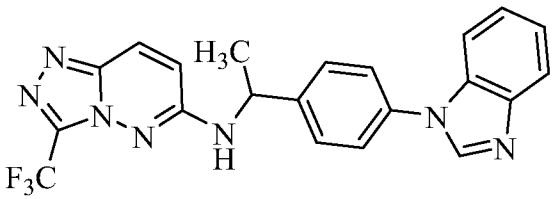


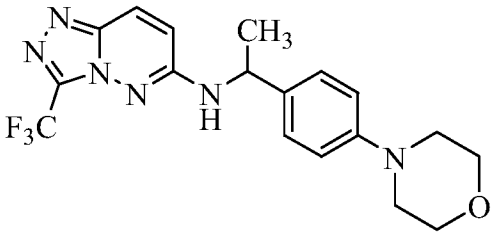
(XXIV) ; and any pharmaceutically acceptable salts thereof, wherein "q" is an integer from 0 to 4; "r" is an integer from 0 to 4, and "s" is an integer from 0 to 3.

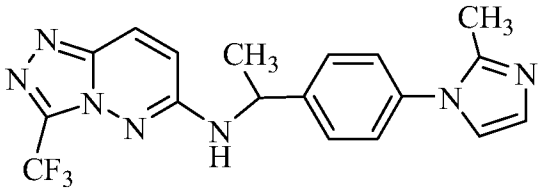
[0039] In some embodiments, the compound has formula (XXII) to (XXIV), and R^1 is a C_1-C_3 alkyl group optionally substituted with one or more fluorine, R^2 is a C_1-C_3 alkyl group substituted with one or more fluorine, and R^6 is hydrogen.

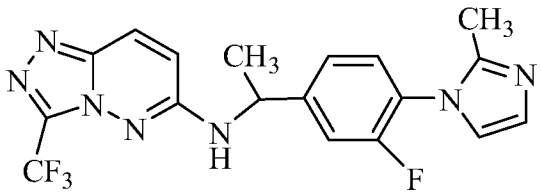
[0040] Non-limiting examples of compounds having a formula (XXI) include:

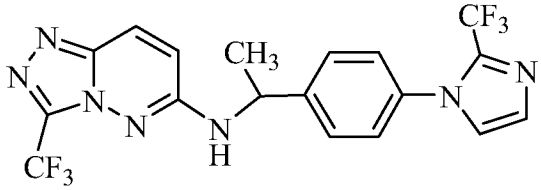








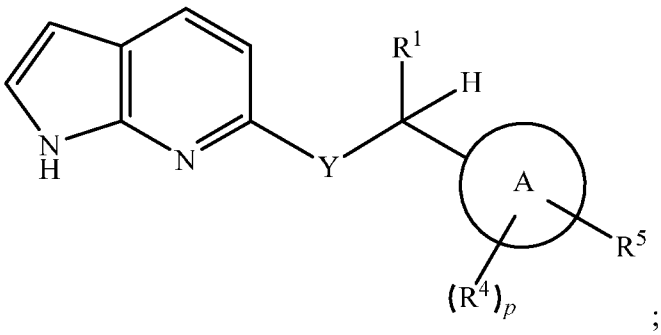




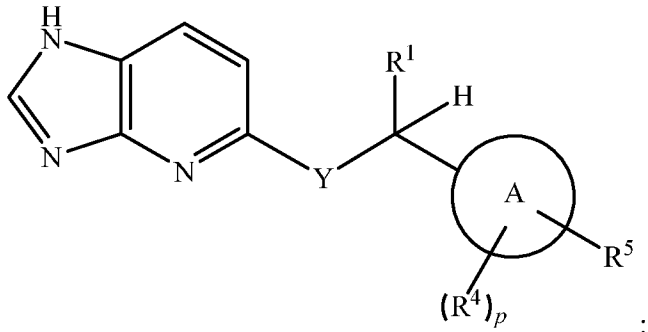
.

Series C

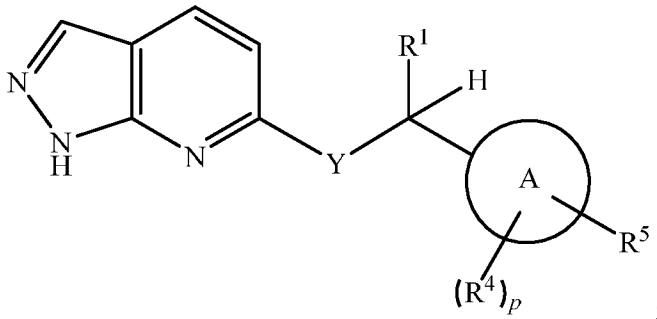
[0041] In some embodiments, the compound has formula (II) and is selected from the group consisting of:



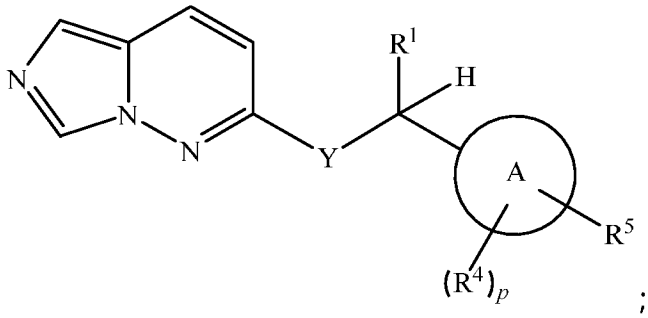
(XXV) ;



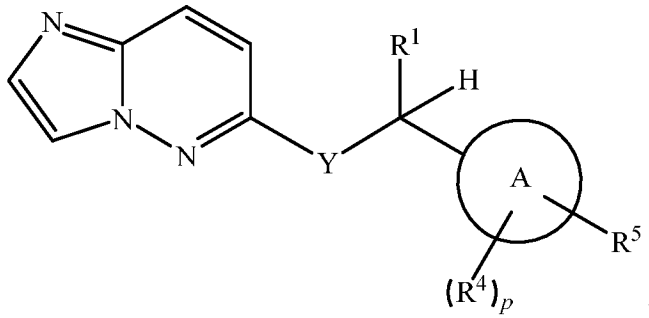
(XXVI) ;



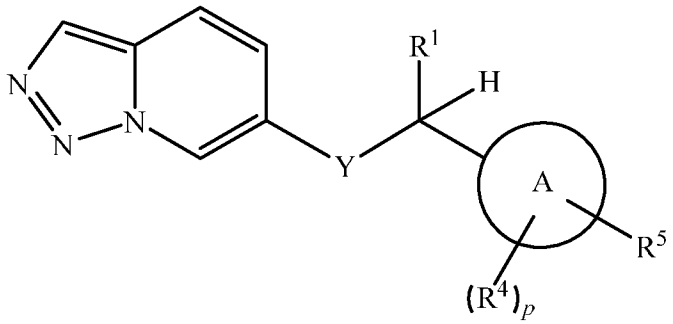
(XXVII) ;



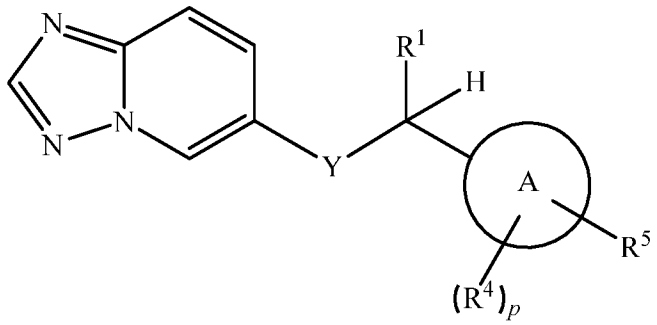
(XXVIII) ;



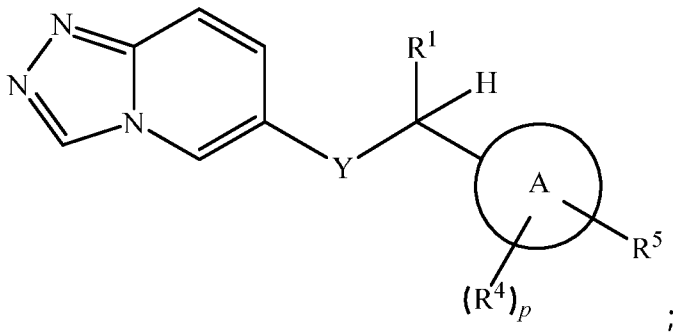
(XXIX) ;



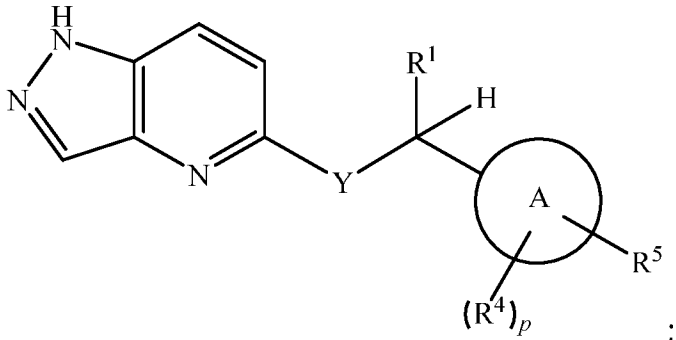
(XXX) ;



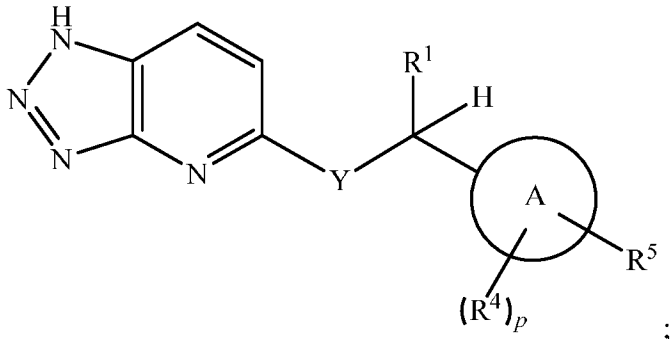
(XXXI) ;



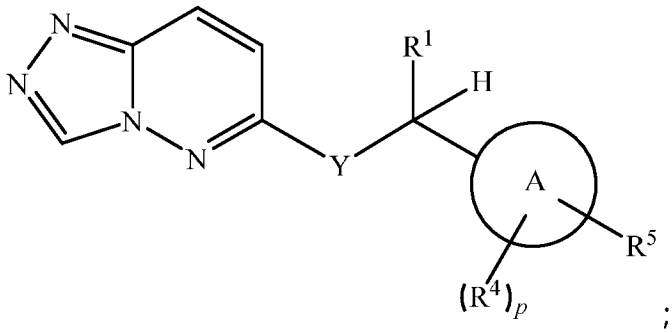
(XXXII) ;



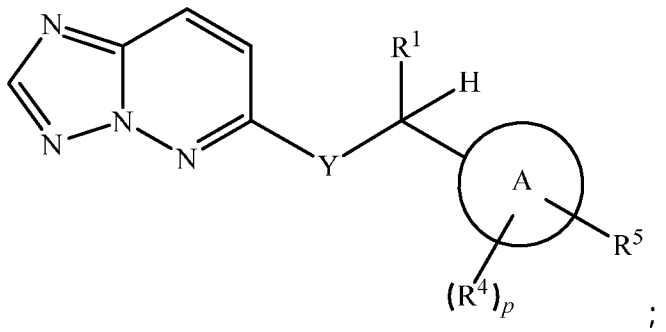
(XXXIII) ;



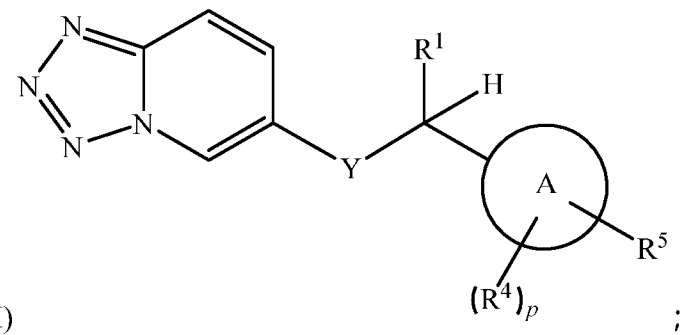
(XXXIV) ;



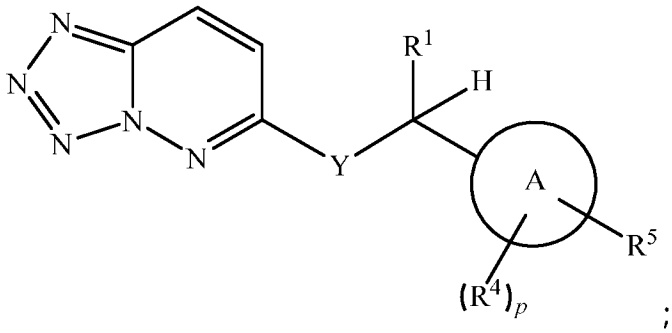
(XXXV) ;



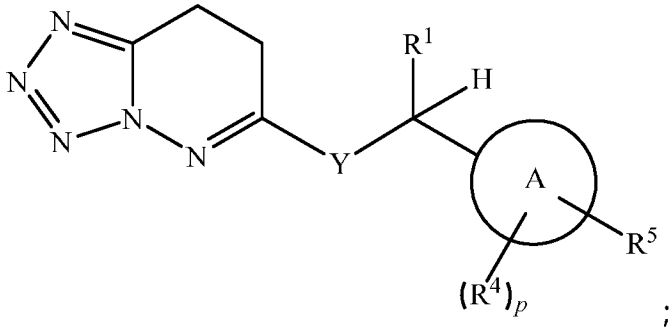
(XXXVI) ;



(XXXVII) ;

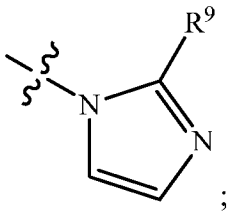


(XXXVIII) ;

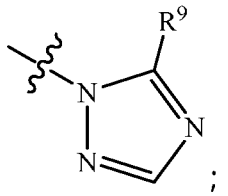


(XXXIX) ; and any pharmaceutically acceptable salts thereof.

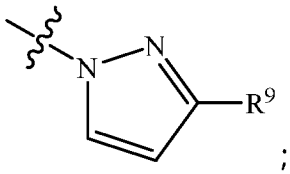
[0042] In some embodiments, the compound has formula (XXV) to (XXXIX), and R^5 is selected from the group consisting of:



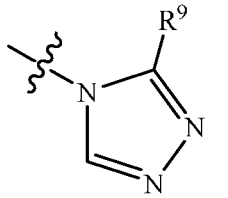
;



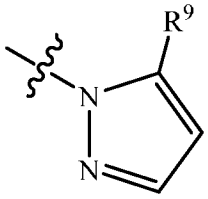
;



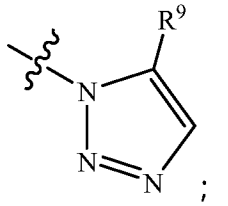
;



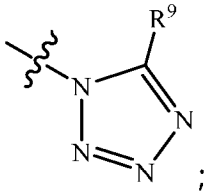
;

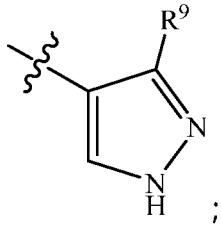


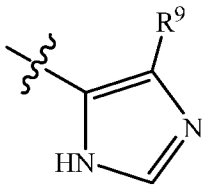
;



;


;


;

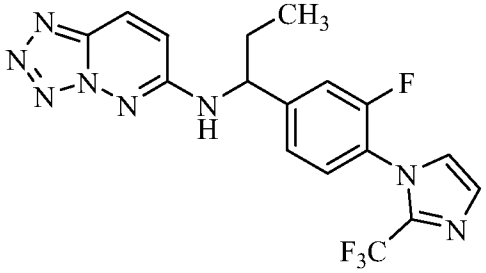

; and

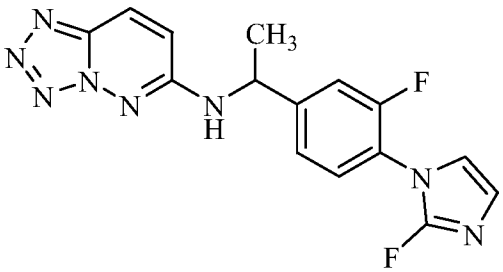
wherein R^9 is halogen or a C_1-C_3 alkyl group optionally substituted with one or more fluorine.

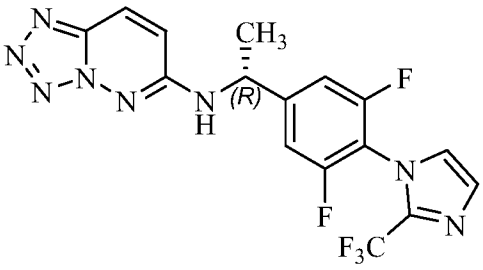
[0043] In some embodiments, the compound has formula (XXV) to (XXXIX), Y is O, S, or NR^6, R^1 is a C_1-C_3 alkyl group optionally substituted with one or more fluorine, R^4 is independently at each occurrence halogen, and R^6 is hydrogen, a C_1-C_6 alkyl group, or a C_3-C_7 cycloalkyl group.

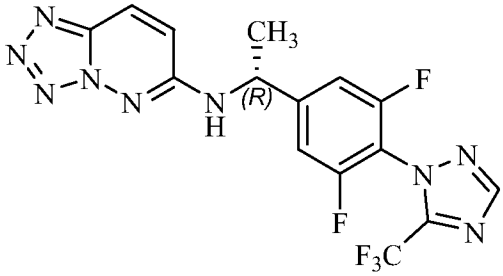
[0044] In some embodiments, the compound has formula (XXV) to (XXXIX), Y is NR^6, R^1 is a C_1-C_3 alkyl group optionally substituted with one or more fluorine, R^4 is independently at each occurrence halogen, and R^6 is a C_1-C_3 alkyl group.

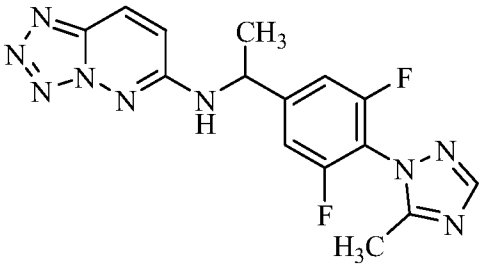
[0045] Non-limiting examples of compounds having a formula (II) include:

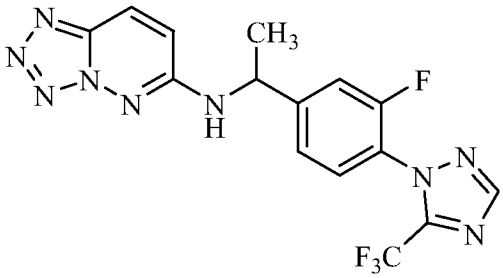


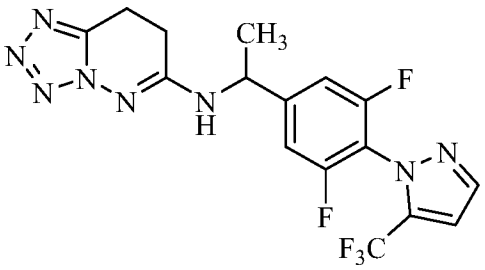


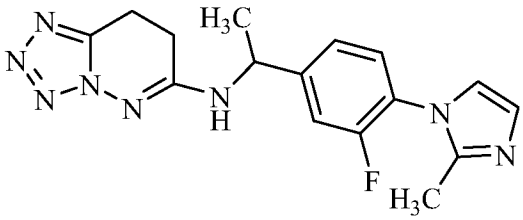


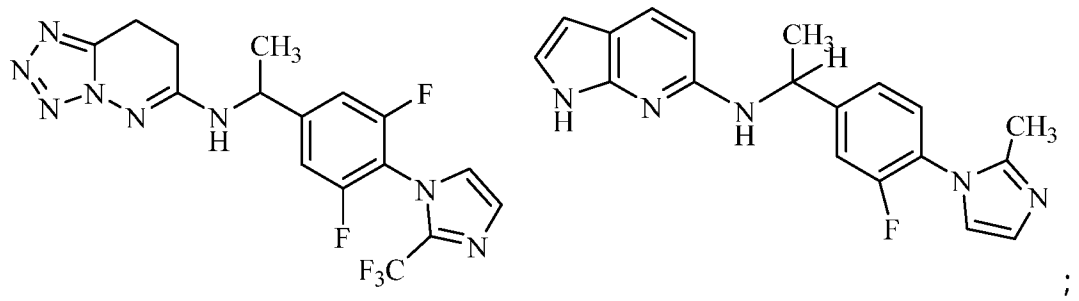












and any pharmaceutically acceptable salts thereof.

[0046] In some embodiments, the compound of the present invention is an optically enriched R-isomer. In some embodiments, the compound of the present invention is an optically enriched S-isomer. In some embodiments, the compound of the present invention is a mixture of R and S-isomers.

[0047] Without being bound by any theory it is believed that, in some embodiments, compounds of the present invention may be capable of targeting NTD of AR. As noted earlier, targeting NTD of AR may facilitate inhibition of AR function and also mitigate the current drug resistance mechanisms that may develop post androgen-deprivation or LBD inhibitor treatment. Further, targeting NTD may mitigate variant and LBD point mutation driven resistance thereby providing effective treatment against all stages of AR driven prostate cancer.

[0048] In some embodiments, the compounds of the present description may be capable of targeting NTD of ARV7. ARV7 may include NTD, DBD and a cryptic exon. NTD of ARV7 may include Tau1, Tau5 and a FXXLF motif. In some embodiments, the compounds of the present description may be capable of targeting FXXLF motif of ARV7.

[0049] In some embodiments, a pharmaceutical composition is presented. The pharmaceutical composition includes a compound as described herein above or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, or co-crystal thereof, and a pharmaceutically acceptable carrier, diluent, or excipient. In some embodiments, the

pharmaceutical composition includes a compound having a formula (I) to (XXXIX). The pharmaceutical composition may further one or more other additional anticancer therapeutic agents in some embodiments.

[0050] The pharmaceutical compositions of the present invention may be in any form that allows for the composition to be administered to a subject. For example, the composition may be in the form of a solid, liquid, or gas (aerosol). Pharmaceutical compositions may be formulated to allow the active ingredients contained therein to be bioavailable upon administration of the composition to a subject. To further optimize the pharmacokinetic profile of the compounds of the present invention, the compounds may be administered in conjunction with a suitable delivery vehicle (e.g., microcapsules, microspheres, biodegradable polymer films, lipid-based delivery systems such as liposomes and lipid foams, viscous instillates and absorbable mechanical barriers) useful for maintaining the necessary concentrations of the prodrugs or the therapeutic agent at the site of the disease.

[0051] A process for preparing a pharmaceutical composition is also presented. The process includes mixing a compound as described herein above or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, or co-crystal thereof with a pharmaceutically acceptable carrier, diluent, or excipient. In some embodiments, the process includes mixing a compound having a formula (I) to (XXXIX) or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, or co-crystal thereof with a pharmaceutically acceptable carrier, diluent, or excipient.

[0052] In some embodiments, methods of treating or reducing symptoms of a certain disease by administering a compound of the present invention are also presented. The compounds or derivatives thereof can be administered to any host, including a human, a non-human animal, and mammals, in an amount effective to treat a disorder. In some embodiments, methods of treating or reducing symptoms of a certain disease by administering a compound having a formula (I) to (XXXIX) is presented.

[0053] In some embodiments, the compounds of the present description may be used as single agents or in combination with other additional anticancer therapeutic agents for treating metastatic castration-resistant prostate cancer, metastatic castration-sensitive prostate cancer, non-metastatic castration-resistant prostate cancer, non-metastatic castration-sensitive prostate cancer, localized prostate cancer or metastatic/non-metastatic castration-resistant prostate cancer that exhibits intrinsic or acquired resistance to enzalutamide, abiraterone acetate or any other androgen signaling axis/receptor inhibitors.

[0054] In some embodiments, the compounds of the present description may be used as single agents or in combination with other additional anticancer therapeutic agents for treating AR-positive HER2 positive metastatic, advanced breast cancer, AR-positive advanced TNBC, ER-negative HER2 positive (ER-HER2+) breast cancer, or ER-positive HER2 negative (ER+HER2-) breast cancer that exhibit poor therapeutic efficacy against known ER antagonists.

[0055] In some embodiments, the compounds of the present description may be used as single agents or in combination with other additional anticancer therapeutic agents for treating ovarian cancer. In some embodiments, the compounds of the present description may be used as single agents or in combination with other additional anticancer therapeutic agents for treating BRAF/MEK targeted therapy resistant melanoma.

[0056] In some embodiments, the compounds of the present description may be used as single agents or in combination with other additional AR antagonists or AR LBD inhibitors. Non-limiting examples of other additional AR antagonists or AR LBD inhibitors include bicalutamide, enzalutamide, flutamide, nilutamide, apalutamide, darolutmide, proxalutamide, or combinations thereof. In some embodiments, the compounds of the present invention may be used in combination with docetaxel, olaparib, talazoparib (PARP inhibitors), selumetinib, capivasertib (AKT inhibitors), ribociclib (CDK inhibitor), BET inhibitors, or combinations thereof.

[0057] In some embodiments, the compounds of the present description may be

used as single agents or in combination with other antibody-radioligand conjugate, immune check point therapy like pembrolizumab, cell therapy like prostate targeting CART-T cell, prostate targeting bi-specific antibodies and combinations thereof.

[0058] In some embodiments, a method of treating prostate cancer, breast cancer ovarian cancer, or melanoma is presented. In some embodiments, a method of treating prostate cancer is presented. Non-limiting examples of prostate cancer include metastatic castration-resistant prostate cancer, metastatic castration-sensitive prostate cancer, non-metastatic castration-resistant prostate cancer, non-metastatic castration-sensitive prostate cancer, localized prostate cancer or metastatic/non-metastatic castration resistant prostate cancer that exhibits intrinsic or acquired resistance to enzalutamide, abiraterone acetate or any other androgen signalling axis/receptor inhibitors. Non-limiting examples of breast cancer include AR positive HER2 positive metastatic, advanced breast cancer, AR positive advanced TNBC, ER negative HER2 positive (ER-HER2+) breast cancer, and ER positive HER2 negative (ER+HER2-) breast cancer that exhibit poor therapeutic efficacy against known ER antagonists. Non-limiting example of melanoma includes BRAF/MEK targeted therapy resistant melanoma.

[0059] The method includes administering to a patient an effective amount of a pharmaceutical composition including a compound of the present invention or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, or co-crystal thereof. The pharmaceutical composition may further one or more other additional anticancer therapeutic agents in some embodiments.

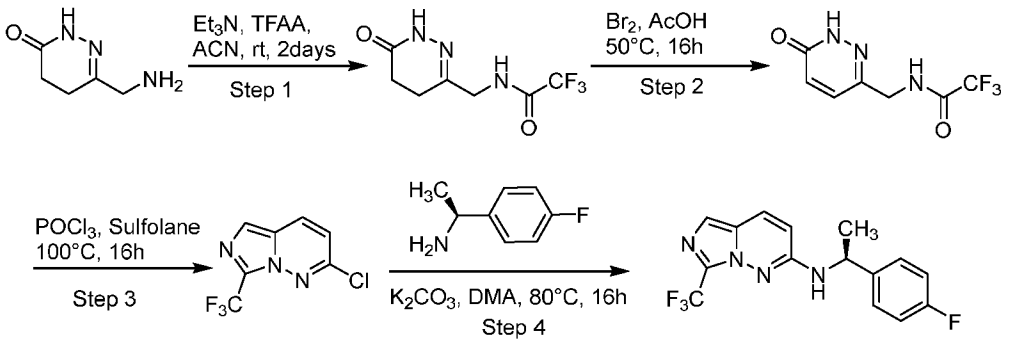
[0060] The pharmaceutical composition may be administered by any suitable method known to a person skilled in the art. Typical routes of administration include, without limitation, oral, topical, parenteral, sublingual, rectal, vaginal, ocular, and intranasal. The term parenteral as used herein includes intravenous, intraperitoneal, intramuscular, intradermal, and epidermal including subcutaneous and intradermal, oral, or application to mucosal surfaces, e.g, by intranasal administration using inhalation of aerosol suspensions, and by implanting to muscle or other tissue in the subject.

EXAMPLES

General methods for synthesis

Synthesis of compounds of Series A

[0061] Example 1: Synthesis of (S)-N-(1-(4-fluorophenyl)ethyl)-7-(trifluoromethyl)imidazo[1,5-b]pyridazin-2-amine (*Compound 1*)



[0062] Step 1: Synthesis of 2,2,2-trifluoro-N-((6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)methyl)acetamide

[0063] A stirred solution of 6-(aminomethyl)-4,5-dihydropyridazin-3(2H)-one (2.0 g, 15.7 mmol) in acetonitrile (20 mL), TFAA (3.3 mL, 23.5 mmol) and TEA (4.4 mL, 31.4 mmol) was stirred at rt. After 48h the reaction mass was diluted with water and the product was extracted into 10% MeOH in DCM, dried over sodium sulfate and concentrated under reduced pressure to obtain a crude product which was purified by column chromatography to give 2,2,2-trifluoro-N-((6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)methyl)acetamide as a yellow solid (1.4g, 34%).

[0064] Step 2: Synthesis of 2,2,2-trifluoro-N-((6-oxo-1,6-dihydropyridazin-3-yl)methyl)acetamide

[0065] The product of Step 1 (1.0 g, 4.48 mmol) in acetic acid (10 mL), bromine (0.23 mL, 4.48 mmol) and TEA (4.4 mL, 31.4 mmol) was heated at 50°C for 16h. The

reaction mixture was evaporated to dryness and the product was extracted into ethyl acetate, washed with saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated under reduced pressure to give 2,2,2-trifluoro-N-((6-oxo-1,6-dihydropyridazin-3-yl)methyl)acetamide as a yellow solid (700mg, 71%) which was used directly for the next step without further purification.

[0066] Step 3: Synthesis of 2-chloro-7-(trifluoromethyl)imidazo[1,5-b]pyridazine

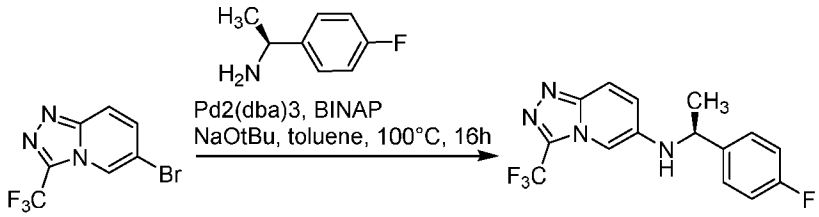
[0067] A stirred solution of the product of Step 2 (700 mg, 3.16 mmol) in sulpholane (10 mL) and POCl3 (2.36 mL, 25.3 mmol) was heated at 100¬°C for 16h. The reaction mixture was evaporated to dryness and the product was extracted into ethyl acetate, washed with saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated under reduced pressure to give a crude product which was purified by column chromatography to give 2-chloro-7-(trifluoromethyl)imidazo[1,5-b]pyridazine as a yellow solid (380 mg, 54%).

[0068] Step 4: Synthesis of(S)-N-(1-(4-fluorophenyl)ethyl)-7-(trifluoromethyl)imidazo[1,5-b]pyridazin-2-amine.

[0069] A mixture of the product of step 3 (150mg, 0.67mM) in DMA (5 mL), potassium carbonate (280 mg, 0.67 mmol) and (S)-1-(4-fluorophenyl)ethan-1-amine (94.2 mg, 0.67 mmol) was heated at 80°C for 16 h. The reaction mixture was diluted with ice water and the product was extracted into ethyl acetate. This extract was dried over sodium sulfate, filtered, concentrated under reduced pressure and purified by prep reverse chromatography to give (S)-N-(1-(4-fluorophenyl)ethyl)-7-(trifluoromethyl)imidazo[1,5-b]pyridazin-2-amine as a pale yellow solid (43 mg, 20%).

[0070] ^{1}H- NMR: (400 MHz, DMSO-d6): δ (ppm) 7.87 (d, J = 6.8 Hz, 1H), 7.84 (d, J = 10.00 Hz, 1H), 7.45-7.38 (m, 2H), 7.35 (s, 1H), 7.18-7.09 (m, 2H), 6.55 (d, J = 9.6 Hz, 1H), 4.89-4.81 (m, 1H), 1.48 (d, J = 6.8 Hz, 3H). LCMS: 99.43% (m/z = 325.26 $[M+H]^{+}$).

[0071] Example 2: Synthesis of (S)-N-(1-(4-fluorophenyl)ethyl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-amine (*Compound 2*)

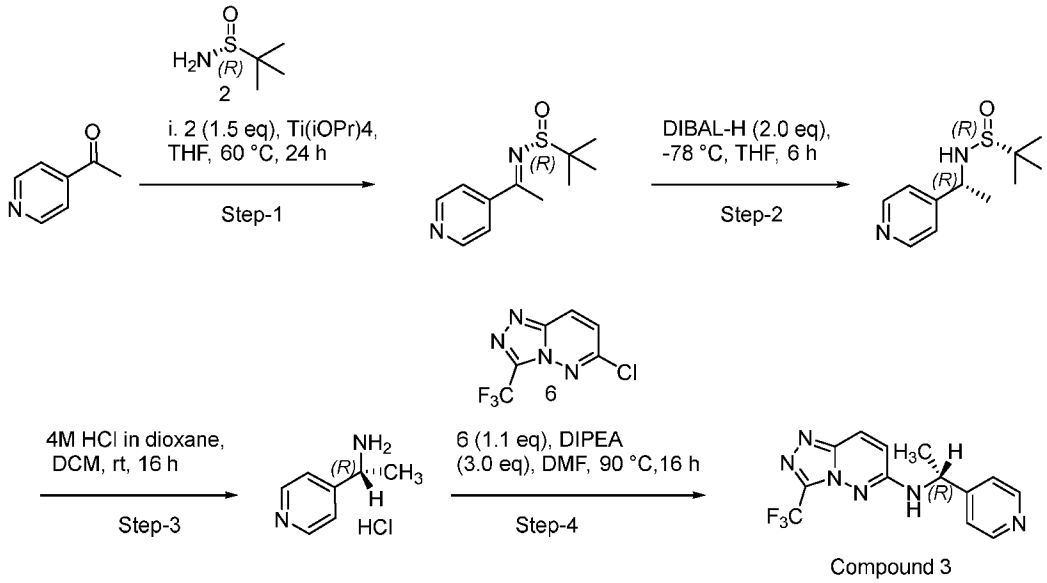


Compound 2

[0072] A suspension of 6-bromo-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine (0.15 g, 0.56 mmol), (S)-1-(4-fluorophenyl)ethan-1-amine (0.15 mg, 1.12 mmol) and NaOtBu (0.16 g, 1.69 mmol) in toluene (5 mL) in a glass tube was purged with nitrogen gas for 15 minutes. After adding Pd2(dba)3 (25 mg, 0.028 mmol) and racemic BINAP (26 mg, 0.042 mmol) the tube was sealed and the reaction mass was heated at 100°C for 16h. The reaction mixture was cooled, filtered through celite, and concentrated under reduced pressure. The residue was diluted with water (10 mL) and the product extracted into EtOAc, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography to give (S)-N-(1-(4-fluorophenyl)ethyl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-amine (94 mg, 51 %) as an off white solid.

[0073] ^{1}H-NMR (400 MHz, DMSO-d6): δ (ppm) 7.82 (d, J = 9.60 Hz, 1H), 7.46-7.42 (m, 2H), 7.33 (dd, J = 9.6 & 1.6 Hz, 1H), 7.18 (t, J = 8.80 Hz, 2H), 6.94 (s, 1H), 6.91 (d, J = 6.00 Hz, 1H), 4.53-4.46 (m, 1H), 1.45 (d, J = 6.80 Hz, 3H). LCMS: 96.5% (m/z = 325.2 $[M+H]^{+}$).

[0074] Example 3: Synthesis of (*R*)-*N*-(1-(pyridin-4-yl)ethyl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-amine (*Compound 3*)



Compound 3

[0075] To a sealed tube was added trifluoroacetic acid (60 mL) followed by 3-chloro-6-hydrazinopyridazine (11.0 g, 0.049 mol) at 0°C and heated at 100°C for 24 h. The reaction mixture was evaporated to dryness. The crude mass was dissolved in EtOAc and washed with aqueous solution of $NaHCO_3$ and the process was repeated for three times. The organic layer was separated, and the aqueous layer was extracted two times with EtOAc. The combined organic layers were then washed with brine, dried over Na2SO4, filtered, and concentrated under reduced pressure to obtain (6-Chloro-3-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine) as an off white solid (11.5 g, 31%).

[0076] Step 1: To the solution of 1-(pyridin-4-yl)ethanone (2.0 g, 0.016 mol) and (*R*)-2-methylpropane-2-sulfinamide (3.9 g, 0.033 mol) in anhydrous THF (20 ml) at 0 °C, was added $Ti(O^iPr)_4$ (10.4 ml, 0.033). The reaction was heated at 60 °C for 24 h. The reaction mixture was poured into crushed ice and extracted with DCM. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography, eluted with 50:50 mixture of EtOAc and hexanes providing (*R*, *E*)-2-methyl-N-(1-(pyridin-4-yl)ethylidene)propane-2-sulfinamide as a colourless liquid (1.4 g, 38%); Mass: 225 $[M+H]^+$.

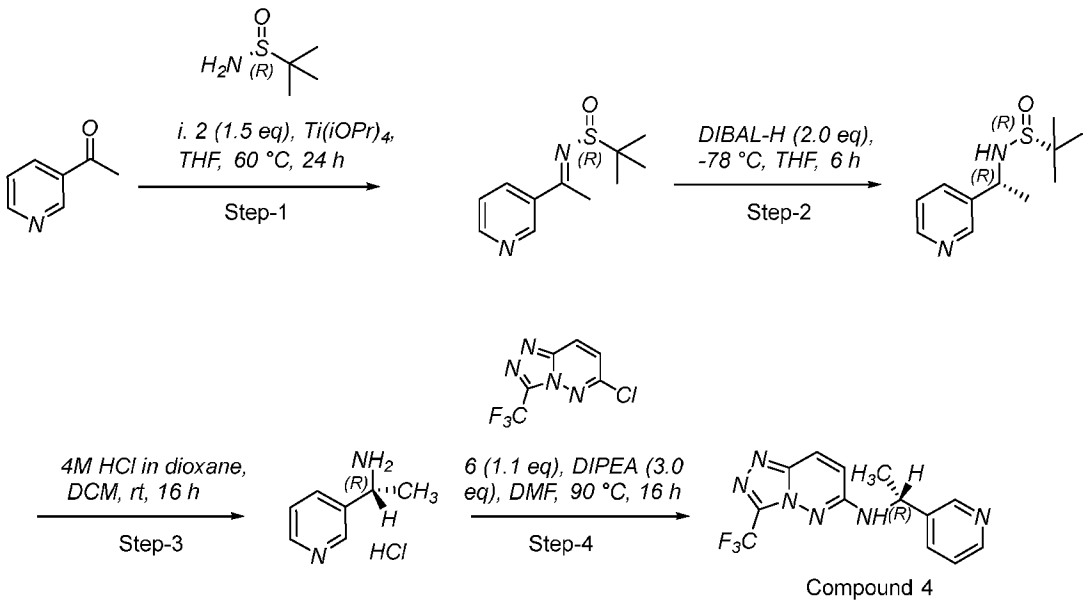
[0077] Step 2: To the solution of (*R*)-2-methyl-N-(1-(pyridin-4-yl)ethylidene)propane-2-sulfinamide (1.4 g, 0.0625 mol) was added DIBAL-H (12.5 ml, 0.0125 mol) at -78 °C and stirred for 6 h. The reaction mixture was quenched with ammonium chloride, poured over crushed ice and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography, eluted with 5% MeOH in DCM providing (*R*)-2-methyl-N-((*R*)-1-(pyridin-4-yl)ethyl)propane-2-sulfinamide as a colourless liquid (0.630 g, 45%); ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.59 (d, J = 4 Hz, 2H), 7.28 (t, J = 12 Hz, 2H), 4.54-4.51 (m, 1H), 1.52 (d, J = 8 Hz , 3H), 1.25 (s , 9H).

[0078] Step 3: To the solution of (*R*)-2-methyl-N-((*R*)-1-(pyridin-4-yl)ethyl)propane-2-sulfinamide (0.6 g, 0.0013 mol) in DCM (20 ml) was added 4M HCl in dioxane (10 ml) at 0 °C and stirred at RT for overnight. The reaction mixture was concentrated and co-precipitated with MeOH:Ether as co-solvent to provide (*R*)-1-(pyridin-4-yl)ethanamine hydrochloride as a white solid (0.5 g, 93%).

[0079] Step 4: To the solution of (*R*)-1-(pyridin-4-yl)ethanamine hydrochloride (0.200 g, 0.90 mol) in DMF (10 ml) was added DIPEA (0.313 ml, 0.90 mol) followed by 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.100 g, 0.81 mol). The reaction was sealed and heated at 80 °C for 16 h. The reaction mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography, eluted with 5% MeOH in DCM providing (*R*)-N-(1-(pyridin-4-yl)ethyl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-amine as an off-white solid (0. 1 g, 20%).

[0080] ^{1}H-NMR (400 MHz, DMSO- d6): δ (ppm) 8.50 (d, J = 4.4 Hz, 2H), 8.36 (d, J = 6.4 Hz, 1H), 8.11 (d, J = 10 Hz, 1H), 7.37-7.35 (m, 2H), 7.06 (d, J = 10 Hz , 1H), 4.85-4.78 (m, 1H), 1.50 (d, J = 7.2 Hz, 3H); Mass: 309.31 $[M+H]^+$; LCMS: 96.39%; SOR: $[\alpha]:_{\lambda}^{T}$ = + 194.94.

Example 4: Synthesis of Synthesis of (R)-N-(1-(pyridin-3-yl)ethyl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-amine (*Compound 4*).



[0081] Step 1: To the solution of 1-(pyridin-3-yl)ethanone (3.0 g, 0.024 mol) and (*R*)-2-methylpropane-2-sulfinamide (6.0 g, 0.048 mol) in anhydrous THF (60 ml) at 0 °C, was added $Ti(O^iPr)_4$ (10.2 ml, 0.036 mol). The reaction was heated at 60 °C for 24 h. The reaction mixture was poured into crushed ice and extracted with DCM. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was then purified by silica gel chromatography, eluted with a mixture of 50:50 EtOAc and hexane to obtain (*R, E*)-2-methyl-N-(1-(pyridin-3-yl)ethylidene)propane-2-sulfinamideas a colourless liquid (0.92 g, 34%). Mass: 225 $[M+H]^+$.

[0082] Step 2: To the solution of (*R*)-2-methyl-N-(1-(pyridin-3-yl)ethylidene)propane-2-sulfinamide (0.9 g, 0.004 mol) was added DIBAL-H (8 ml , 0.008 mol) at - 78 °C and stirred for 6 h. The reaction mixture was quenched with ammonium chloride and poured over crushed ice followed by extraction with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography, eluted with

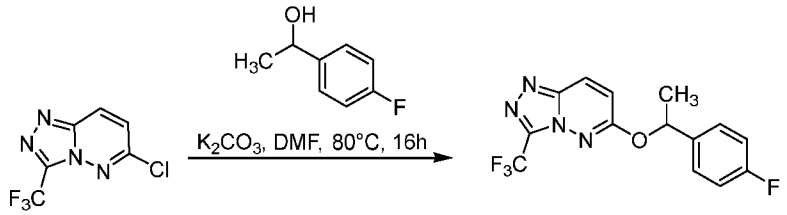
MeOH:DCM (5:95) mixture to obtain (*R*)-2-methyl-N-((*R*)-1-(pyridin-3-yl)ethyl)propane-2-sulfinamide as a colorless liquid (0.740 g, 81%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.61 (d, J = 4 Hz, 1H), 8.55 (d, J = 8 Hz, 1H), 7.70-7.67 (m, 1H), 1.30-1.26 (m, 1H), 4.62-4.56 (m, 1H) , 3.41 (s, 1H), 1.58 (d, J = 8.4 Hz , 3H), 1.24 (s, 9H).

[0083] Step 3: To the solution of (*R*)-2-methyl-N-((*R*)-1-(pyridin-3-yl)ethyl)propane-2-sulfinamide (0.9 g, 0.002 mol) in DCM (5 ml) was added 4M HCl in dioxane (15 ml) at 0 °C and stirred at RT for 16 h. The reaction mixture was concentrated and co-precipitated with MeOH: ether as co-solvent to provide (*R*)-1-(pyridin-3-yl)ethanamine hydrochloride as a white solid (0.51 g, 99.4%). (

[0084] Step 4: To the solution of (*R*)-1-(pyridin-3-yl)ethanamine hydrochloride (0.5 g, 0.0032 mol) in DMF (10 ml) in a reaction vessel was added DIPEA (1.67 ml, 0.0096 mol) followed by 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.780 g, 0.0035 mol). The reaction mixture was then placed in a seal tube and heated at 80 °C for 16 h. The reaction mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography, eluted with a mixture of (5:95) MeOH:CH_2Cl_2 providing (*R*)-N-(1-(pyridin-3-yl)ethyl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-amine as an off colour solid (0. 2 g, 22%).

[0085] ^{1}H-NMR (400 MHz, DMSO-d6): δ (ppm) 8.61 (d, J = 2 Hz, 1H), 8.43 (d, J = 4.8 Hz, 1H), 8.34 (d , J = 6.8 Hz , 1H), 8.09 (d, J = 10 Hz, 1H), 7.78-7.75 (m ,1H) , 7.35-7.32 (m, 1H), 7.025 (d, J = 12 Hz, 1H) ,4.87-4.84 (m , 1H), 1.52 (d, J = 6.8 Hz, 3H); Mass: 309.31 $[M+H]^+$; LCMS: 95.34% ; SOR: $[\alpha]_\lambda^T$ = +281.06.

[0086] Example 5: Synthesis of (R,S)-6-(1-(4-fluorophenyl)ethoxy)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (*Compound 5*)

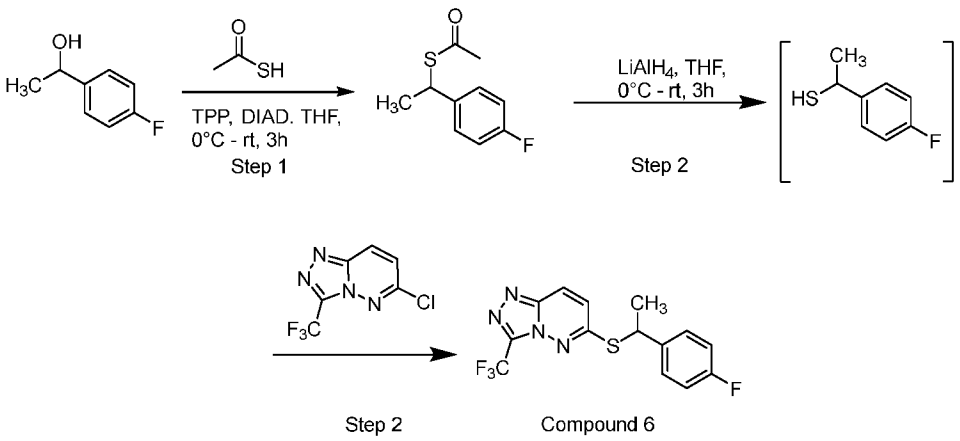


Compound 5

[0087] A mixture of (R,S)-1-(4-fluorophenyl)ethan-1-ol (0.15 g, 1.08mmol) in DMF (3 mL) and potassium carbonate (0.24 g, 1.8 mmol) was stirred at rt for 15 min. 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.2 g, 0. 9 mmol) was added and the reaction mixture was heated at 80°C for 16 h. The reaction was then diluted with water (20 mL) and the product extracted into EtOAc. The extract was dried over anhydrous sodium sulphate and concentrated under reduced pressure to give a crude product which was purified by silica gel column chromatography to give (R,S)-6-(1-(4-fluorophenyl)ethoxy)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine as a white solid (0.15 g, 51% yield).

[0088] ^{1}H-NMR (400 MHz, DMSO-d6): δ (ppm) 8.44 (d, J = 10.00 Hz, 1H), 7.56-7.53 (m, 2H), 7.31 (d, J = 10.00 Hz, 1H), 7.23-7.18 (m, 2H), 6.03 (q, J = 6.40 Hz, 1H), 1.68 (d, J = 6.80 Hz, 3H); LCMS: (M+H = 327.08).

[0089] Example 6: Synthesis of (R,S)-6-((1-(4-fluorophenyl)ethyl)thio)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (*Compound 6*)



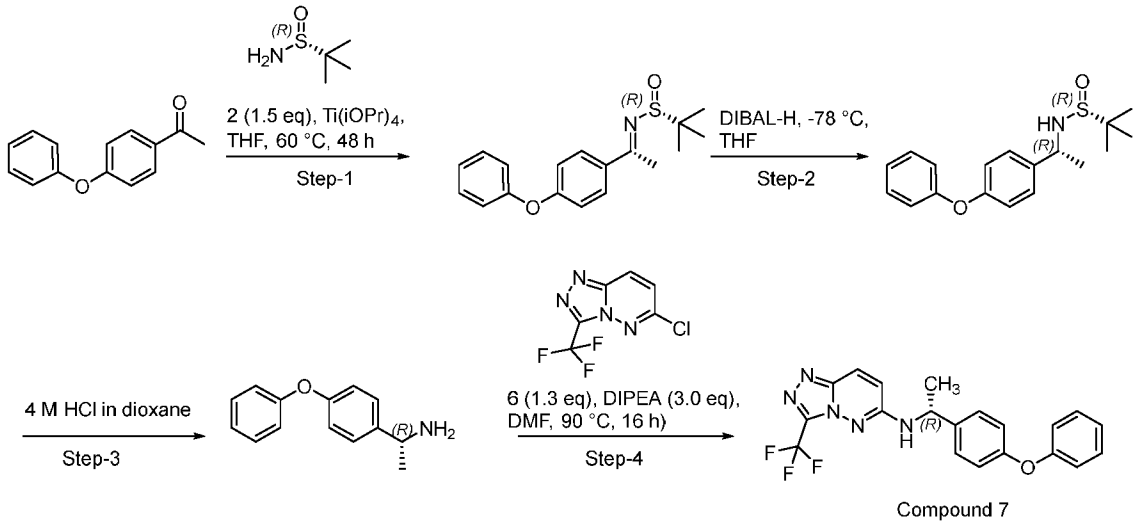
Step 2 Compound 6

[0090] Step 1: - S-(1-(4-fluorophenyl)ethyl) ethanethioate: To a stirred solution of 1-(4-fluorophenyl)ethan-1-ol (1g, 7.13mmol) and thioacetic acid (1.08g, 14.3mmol) in THF (3 mL) was added triphenylphosphine (3.74g, 14.3mmol) and diisopropyl azodicarboxylate (2.88g, 2.85mmol) at 0°C under argon. After stirring for 3h at RT, the solvent was removed under reduced pressure and the resulting mixture was suspended in n-pentane (20 mL). The suspension was filtered through a bed of celite and the filtrate was concentrated under vacuum to give a crude product that was purified by silica gel column chromatography to give S-(1-(4-fluorophenyl)ethyl) ethanethioate as a pale yellow thick liquid (0.25g, 25% yield).

[0091] Step 2: - (R,S)-6-((1-(4-fluorophenyl)ethyl)thio)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine: The product of step 1 (0.2g, 0.5mmol) was added to a stirred solution of LiAlH4 (0.14g, 1mmol) in THF at 0 °C. The reaction was allowed to warm up to RT and stirring was continued for a further 2h when 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.14g, 0.64mmol) was added. After stirring for a further 3hrs at RT, the reaction mixture was diluted with water and the product extracted into EtOAc. The organic extract was dried over anhydrous sodium sulphate and concentrated under reduced pressure to give a crude product which was purified by silica gel column chromatography to give (R,S)-6-((1-(4-fluorophenyl)ethyl)thio)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine as colorless sticky solid (40 mg, 18% yield).

[0092] ^{1}H-NMR (400 MHz, DMSO-d6): δ (ppm) 8.37 (d, J = 9.60 Hz, 1H), 7.58-7.54 (m, 2H), 7.48 (d, J = 9.60 Hz, 1H), 7.17 (t, J = 8.80 Hz, 2H), 5.01 (q, J = 7.20 Hz, 1H), 1.76 (d, J = 7.20 Hz, 3H). LCMS: (M+H = 343.23).

[0093] Example 7: Synthesis of (*R*)-N-(1-(4-phenoxyphenyl)ethyl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-amine (*Compound 7*)



Compound 7

[0094] Step 1: To the solution of 1-(4-phenoxyphenyl)ethanone (2.0 g, 0.009 mol) and (*R*)-2-methylpropane-2-sulfinamide (1.36 g, 0.0113 mol) in anhydrous THF (80 ml) at 0 °C was added $Ti(O^iPr)_4$ (4.1 ml, 0.0141 mol). The reaction was heated at 60 °C for 48 h. The reaction mixture was poured over crushed ice and extracted with DCM. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography, eluted with a mixture of EtOAc:hexanes (50:50) providing (*R,E*)-2-methyl-N-(1-(4-phenoxyphenyl)ethylidene)propane-2-sulfinamide as a colourless liquid (0.920 g, 28%); Mass: 316 $[M+H]^+$.

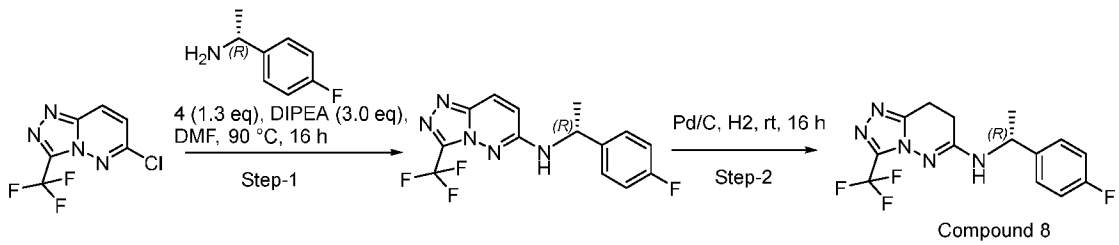
[0095] Step 2: To the solution of ((*R*)-2-methyl-N-(1-(4-phenoxyphenyl)ethylidene)propane-2-sulfinamide (0.9g, 0.004 mol) in THF (10 ml) was added DIBAL-H (8 ml, 0.008 mol) at -78 °C and stirred for 6 h. The reaction mixture was quenched with ammonium chloride, poured over crushed ice and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was then purified by silica gel chromatography, eluted with a gradient of 0 to 5% MeOH in DCM providing (*R*)-2-methyl-N-((R)-1-(4-phenoxyphenyl)ethyl)propane-2-sulfinamide as a colourless liquid (0.9 g, 90%). ; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36 (m, 4H), 7.11 (s, 1H), 7.02-6.96 (m, 4H), 4.56-4.51 (m, 1H), 1.50 (d, J = 8 Hz, 3H) ,1.23 (s, 9H).

[0096] Step 3: To the solution of (*R*)-2-methyl-N-((*R*)-1-(4-phenoxyphenyl)ethyl)propane-2-sulfinamide (0.9 g, 0.002 mol) in DCM (20 ml) was added 4M HCl in dioxane (15 ml) at 0 °C and stirred at RT for overnight. The reaction mixture was concentrated and co-precipitated with MeOH:ether as co-solvent to provide (*R*)-1-(4-phenoxyphenyl)ethanamine hydrochloride as a white solid (0.630 g, 54%).

[0097] Step 4: To the solution of (*R*)-1-(4-phenoxyphenyl)ethanamine hydrochloride (0.600 g, 0.0024 mol) in DMF (10 ml) was added DIPEA (0.936 ml, 0.007 mol) followed by addition of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.590 g, 0.003 mol). The reaction was heated at 80 °C for 16 h. The reaction mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography, eluted with a gradient of 0 to 5% MeOH in DCM providing (*R*)-N-(1-(4-phenoxyphenyl)ethyl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-amine as a cream coloured solid (0. 07 g, 8%).

[0098] ^{1}H-NMR (400 MHz, DMSO-d6): δ (ppm) 8.23 (d, J = 7.2 Hz, 1H), 8.08 (d, J = 10 Hz, 1H), 7.41-7.35 (m, 4H), 7.12 (t, J = 7.2 Hz, 1H), 7.03 (d, J = 10 Hz ,1H), 6.97-6.94 (m, 4H), 4.88-4.81 (m, 1H) ,1.51 (d, J = 6.8 Hz, 3H); Mass: 400.39 $[M+H]^+$. LCMS: 98.24% ; SOR: $[\alpha]_\lambda^T$ = + 373.80.

[0099] Example 8: Synthesis of (*R*)-N-(1-(4-fluorophenyl)ethyl)-3-(trifluoromethyl)-7,8-dihydro-[1,2,4]triazolo[4,3-b]pyridazin-6-amine (*Compound 8*)



[0100] Step 1: To the solution of (6-chloro-3-trifluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine) (11.00 g, 0.049 mol) in DMF (220 ml) was added DIPEA (19 ml, 0.1486 mol) followed (*R*)-1-(4-fluorophenyl)ethanamine (7.23 g, 0.052 mol). The reaction mixture

was placed in a seal tube and heated at 90 °C for 16 h. The reaction was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography, eluted with a gradient of 0 to 5% MeOH in DCM providing (*R*)-N-(1-(4-fluorophenyl)ethyl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-amine as a cream coloured solid (7.76 g, 47%). ;

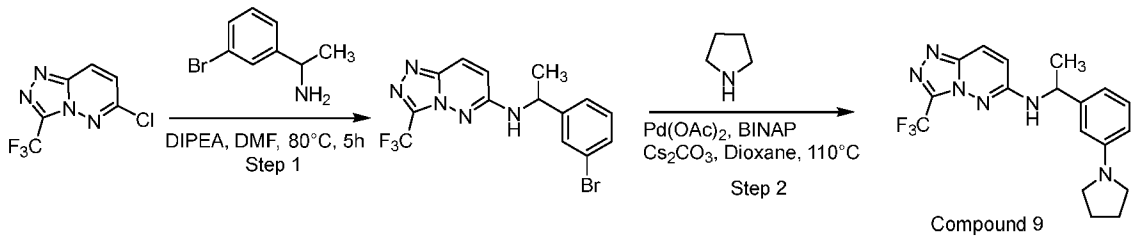
[0101] ^{1}H-NMR (400 MHz, DMSO-d6): δ (ppm) 8.26 (d, J = 8 Hz, 1H), 8.08 (d, J = 8 Hz, 1H), 7.44-7.40 (m, 2H), 7.16-7.11 (m, 2H), 7.02 (d, J = 8 Hz 1H), 4.85-4.80 (m, 1H), 1.50 (d, J = 8 Hz, 3H); Mass: 326 $[M+H]^+$; SOR: $[\alpha]_\lambda^T$ = + 303.16.

[0102] Step 2: To the solution of (*R*)-N-(1-(4-fluorophenyl)ethyl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-amine (0.250 g, 0.76 mol) in MeOH (5 ml) in a reaction vial was added Pd/C (0.25 g) and reaction was stirred in hydrogen atmosphere for 16 h. Reaction mixture was filtered through celite to get the crude compound. The crude was then purified by silica gel chromatography, eluted with a gradient of 0 to 5% MeOH in DCM providing (*R*)-N-(1-(4-fluorophenyl)ethyl)-3-(trifluoromethyl)-7,8-dihydro-[1,2,4]triazolo[4,3-b]pyridazin-6-amine as an off-white colour solid (0.2 g, 80%).

[0103] ^{1}H-NMR (400 MHz, DMSO-d6): δ (ppm) 7.96 (d, J = 6.8 Hz, 1H), 7.39-7.35 (m, 2H), 7.15-7.11 (m, 2H), 4.87-4.84 (m, 1H), 3.08-3.04 (m, 2H), 2.73-2.66 (m, 2H), 1.43 (d, J = 7.2 Hz, 3H); Mass: 328.25 $[M+H]^+$; LCMS: 99.17%; SOR: $[\alpha]_\lambda^T$ = + 159.24.

Synthesis of compounds of Series B

[0104] Example 9: N-(1-(3-(pyrrolidin-1-yl)phenyl)ethyl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-amine (*Compound 9*)



[0105] Step 1: N-(1-(3-bromophenyl)ethyl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-amine

[0106] A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.3 g, 1.347 mmol), DMF (4 mL), 1-(3-bromophenyl)ethan-1-amine (0.27 g, 1.347 mmol) and DIPEA (3.37 mL, 4.043 mmol) was heated at 90°C for 5h. The reaction mixture was evaporated to dryness and, after an aqueous/ethyl acetate extraction work up, the crude product was purified by column chromatography to give N-(1-(3-bromophenyl)ethyl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-amine an off-white solid (0.35g, 67%).

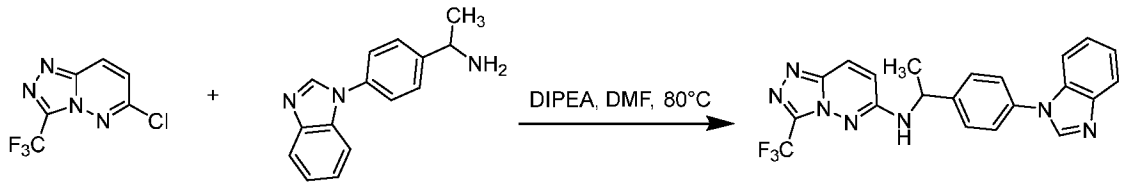
[0107] Step 2: N-(1-(3-(pyrrolidin-1-yl)phenyl)ethyl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-amine

[0108] A suspension of the product of Step 1 (0.15 g, 0.39 mmol), cesium carbonate (0.38 g, 1.17 mmol) in 1,4-dioxane (5 mL) and pyrrolidine (0.16 mL), 1.9 mmol) was purged with Argon gas for 15 minutes. After adding $Pd(OAc)_2$ (9 mg, 0.034 mmol) and X-Phos (37 mg, 0.078 mmol), the reaction mass was irradiated by microwave at 100oC for 1h. The reaction mass was diluted with water (7 mL) and after an aqueous/ethyl acetate extraction work up, the crude product was purified by column chromatography (Davisil) using 5% methanol in DCM to give N-(1-(3-(pyrrolidin-1-yl)phenyl)ethyl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-amine (50mg, 47%).

[0109] ^{1}H-NMR (400 MHz, DMSO-d6): δ (ppm) 8.16 (d, J = 7.60 Hz, 1H), 8.06 (d, J = 10.00 Hz, 1H), 7.10 (t, J = 7.60 Hz, 1H), 7.02 (d, J = 10.00 Hz, 1H), 6.63 (d, J = 7.60 Hz, 1H), 6.56 (s, 1H), 6.39 (dd, J = 1.60, 8.00 Hz, 1H), 4.84-4.75 (m, 1H), 3.19 (t, J

= 6.40 Hz, 4H), 1.93 (t, J = 6.40 Hz, 4H), 1.48 (d, J = 6.80 Hz, 3H). LCMS: 99.05 % (m/z = 377.25 $[M+H]^+$)

[0110] Example 10: Synthesis of N-(1-(4-(1H-benzo[d]imidazol-1-yl)phenyl)ethyl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-amine (*Compound 10*)



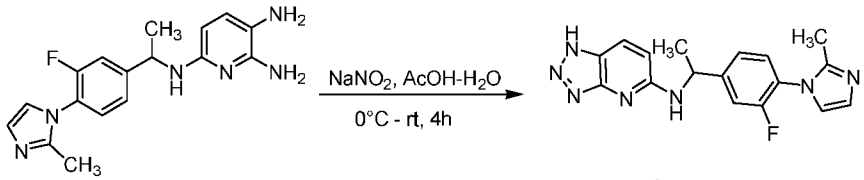
Compound 10

[0111] A solution of 1-(4-(1H-benzo[d]imidazol-1-yl)phenyl)ethan-1-amine (70mg, 0.3mmol) and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (66mg, 0.3mmol) in DMF (0.7mL) and DIPEA (0.15mL, 0.9mmol) was stirred at 80°C for 4h. The reaction was cooled and, after an aqueous/organic work up, purified by column chromatography to give N-(1-(4-(1H-benzo[d]imidazol-1-yl)phenyl)ethyl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-amine off-white solid (22mg, 19% yield.

[0112] ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.51 (s, 1H), 8.38 (d, J = 6.80 Hz, 1H), 8.11 (d, J = 10.00 Hz, 1H), 7.76 (dd, J = 2.00, 6.20 Hz, 1H), 7.64 (s, 4H), 7.58-7.56 (m, 1H), 7.35-7.25 (m, 2H), 7.07 (d, J = 10.00 Hz, 1H), 4.96 (t, J = 6.80 Hz, 1H), 1.58 (d, J = 6.80 Hz, 3H). LCMS: 99.68 %, m/z = 424.37 [M+H]))

[0113] Synthesis of compounds of Series C

[0114] Example 11: Synthesis of N-(1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethyl)-1H-[1,2,3]triazolo[4,5-b]pyridin-5-amine (*Compound 11*)

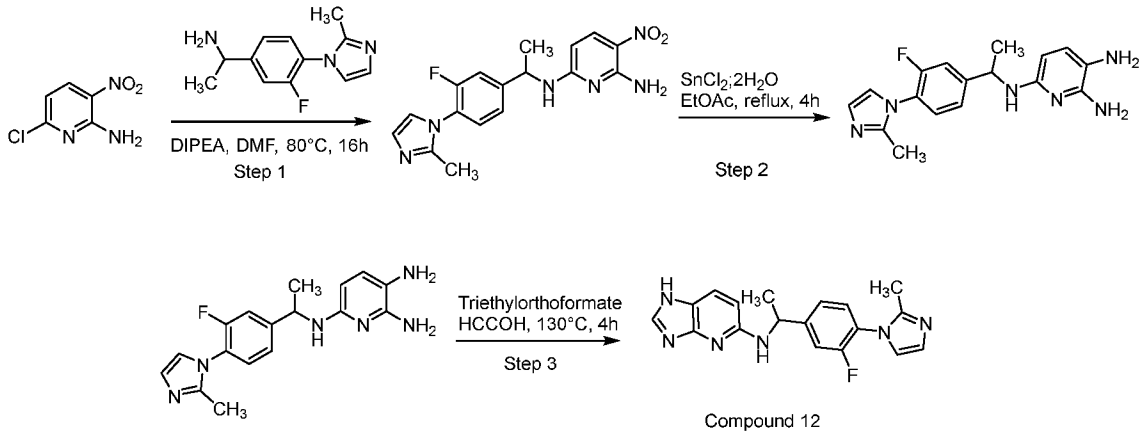


Compound 11

[0115] To a stirred solution of N6-(1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethyl)pyridine-2,3,6-triamine (0.16 g, 0.49 mmol) in a mixture of glacial acetic acid (0.4 mg, 0.008 mmol) and water (1.0 mL) at 5°C, was added a solution of sodium nitrite (51 mg, 0.73 mmol) in 1.5 mL of water. After 6hrs at RT, the reaction mass was diluted with ethyl acetate and the organic layer was washed with saturated NaHCO3 solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude was purified by column chromatography to give N-(1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethyl)-1H-[1,2,3]triazolo[4,5-b]pyridin-5-amine as a white solid (18 mg, 11% yield).

[0116] ^{1}H-NMR (400 MHz, DMSO-d6): δ (ppm) 15.25 (s, 1H), 7.99 (d, J = 8.80 Hz, 1H), 7.87 (d, J = 7.20 Hz, 1H), 7.36-7.35 (m, 3H), 7.21 (s, 1H), 6.91 (d, J = 1.60 Hz, 1H), 6.72 (d, J = 8.80 Hz, 1H), 5.24 (t, J = 7.20 Hz, 1H), 2.15 (s, 3H), 2.15 (d, J = 6.80 Hz, 3H). LCMS: 99.63% (m/z = 338.30 $[M+H]^+$).

[0117] Example 12: Synthesis of N-(1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethyl)-1H-imidazo[4,5-b]pyridin-5-amine (*Compound 12*)



Compound 12

[0118] Step 1: N2-(1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethyl)-5-nitropyridine-2,6-diamine

[0119] A stirred solution of 6-chloro-3-nitropyridin-2-amine, DIPEA (3mL) and 1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethan-1-amine (1.51g, 6.9mmol) in DMF (10mL), was heated at 80°C for 16h. The reaction mixture was diluted with ice-cold water and after an aqueous/ethyl acetate extraction work up, the crude product was purified by column chromatography to give N2-(1-(3-fluoro-4-(2-methyl-1H-

[0120] Step 2: N6-(1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethyl)pyridine-2,3,6-triamine

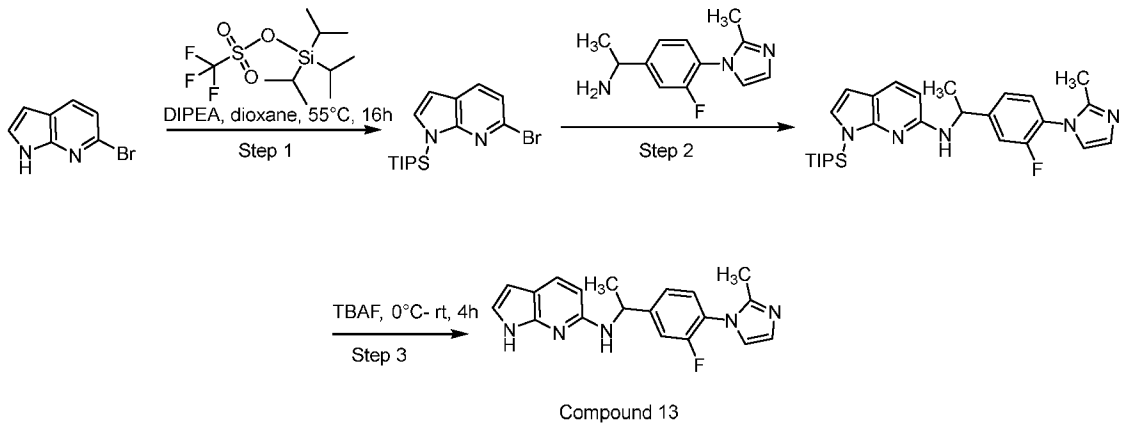
[0121] A stirred solution of the product of Step 1 and tin(II) chloride dihydrate in ethyl acetate (2.8mL) was stirred at 60°C for 6 h. The reaction mass was cooled, filtered through a celite bed and washed with sat. NaHCO3 solution, dried over Na2SO4 and concentrated to give a crude product (0.2g, 55%).

[0122] Step 3: N-(1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethyl)-1H-imidazo[4,5-b]pyridin-5-amine

[0123] Triethylorthoformate (132 mL) was added to a stirred solution of the product of Step 2 (6.53g, 26.3mmol) in formic acid (28mL) at 0°C. Reaction mixture was heated to 80°C for 3 hours. The reaction mixture was evaporated to dryness under reduced pressure and the crude product was purified by flash column chromatography (Davisil), eluted with 8% methanol in DCM to give N-(1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethyl)-1H-imidazo[4,5-b]pyridin-5-amine as white solid (0.042g).

[0124] ^{1}H-NMR (400 MHz, DMSO-d6): δ (ppm) 7.83 (s, 1H), 7.67 (d, J = 8.40 Hz, 1H), 7.42-7.44 (m, 3H), 7.21 (s, 1H), 7.12 (d, J = 7.60 Hz, 1H), 6.90 (d, J = 1.20 Hz, 1H), 6.50 (d, J = 8.80 Hz, 1H), 5.15 (t, J = 7.20 Hz, 1H), 0.00 (s, 3H), 0.00 (d, J = 6.80 Hz, 3H). LCMS: 99.5 % (m/z = 406.31 $[M+H]^+$ ion present)

[0125] Example 13: Synthesis of N-(1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (*Compound 13*)



[0126] Step 1: 6-bromo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine

[0127] A stirred solution of 6-bromo-1H-pyrrolo[2,3-b]pyridine (0.5 g, 2.53 mmol), DIPEA (1.36 g, 7.63 mmol) and triisopropylsilyl trifluoromethanesulfonate (1.94 g, 6.91 mmol) in 1,4-dioxane was heated at 80°C for 16h. The reaction was diluted with ethyl acetate, washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a crude product which was purified by column chromatography to give 6-bromo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine 3 as a yellow oil (0.6g, 67%).

[0128] Step 2: N-(1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethyl)-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridin-6-amine

[0129] A suspension of 1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethan-1-amine (0.3 g, 1.36 mmol), the product of Step 1 (0.48 g, 2.53 mmol) and cesium carbonate (1.34 g, 4.10 mmol) in dioxane was purged with nitrogen gas for 5 minutes. After adding $Pd_2(dba)_3$ (60 mg, 0.068 mmol) and racemic BINAP (64 mg, 0.103 mmol) the tube was sealed and the reaction mass was heated at 120°C for 1 h. The reaction mixture was filtered through celite, concentrated under reduced pressure and after an aqueous/ethyl

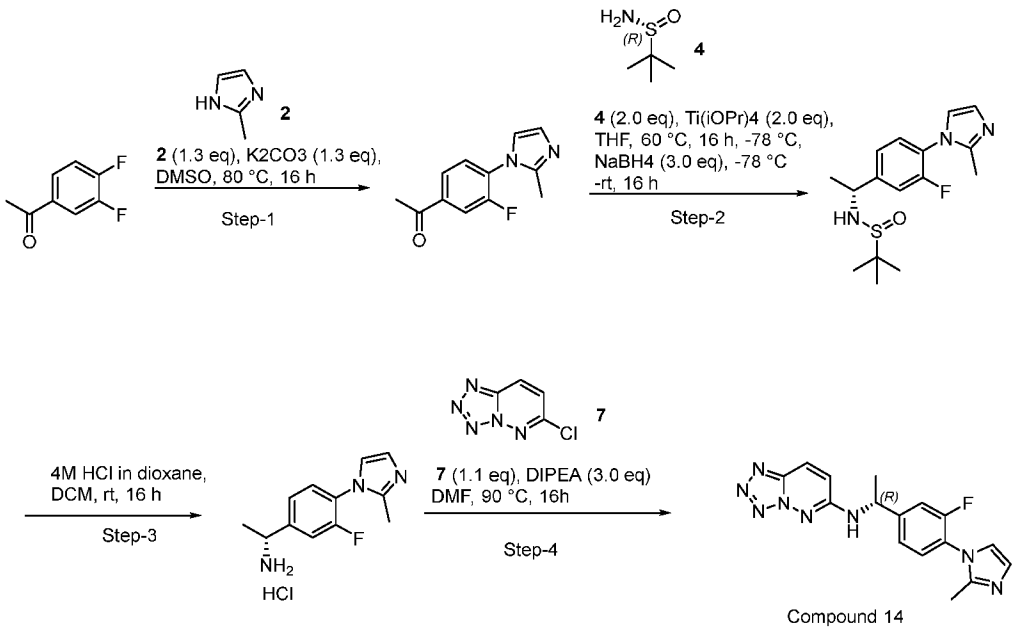
acetate extraction work up, the crude product was purified by silica gel column chromatography to give N-(1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethyl)-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridin-6-amine as a brown gum (0.2g, 29%).

[0130] Step 3: N-(1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethyl)-1H-pyrrolo[2,3-b]pyridin-6-amine

[0131] A stirred solution of the product of Step 2 (0.2 g, 0.47 mmol) and TBAF (0.47 g, 0.47 mmol) in THF (5 mL), was stirred at rt for 4h. The reaction was diluted with DCM and the organic layer was washed with saturated aqueous NH4Cl, dried over sodium sulfate, and evaporated to get crude product which was purified by column chromatography (Silica 100-200 mesh) to give N-(1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethyl)-1H-pyrrolo[2,3-b]pyridin-6-amine as white solid (0.02g, 15%).

[0132] ^{1}H-NMR (400 MHz, DMSO-d6): δ (ppm) 10.88 (s, 1H), 7.56 (d, J = 8.40 Hz, 1H), 7.48 (d, J = 1.20 Hz, 1H), 7.43 (t, J = 7.60 Hz, 1H), 7.38 (dd, J = 1.60, 8.20 Hz, 1H), 7.21 (s, 1H), 6.87-6.85 (m, 3H), 6.37 (d, J = 8.40 Hz, 1H), 6.15-6.14 (m, 1H), 6.13 (t, J = 7.20 Hz, 1H), 2.14 (s, 3H), 1.48 (d, J = 7.20 Hz, 3H). LCMS: 97.95% (m/z = 336.29 [M+H] +).

[0133] Example 14: Synthesis of (R)-N-(1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethyl)tetrazolo[1,5-b]pyridazin-6-amine (*Compound 14*)



[0134] Step-1: 1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethan-1-one

[0135] To the stirred solution of 1-(3,4-difluorophenyl)ethan-1-one (4.0 g, 0.256 mol, 1.0 eq) in DMSO (40 ml) was added K_2CO_3 (4.8 g, 0.033mol, 1.3 eq) followed by 2-methyl-1H-imidazole (2.8 g, 0.033 mol, 1.3 eq). The reaction mixture was heated at 80°C for 16 hours. The reaction mixture was diluted with EtOAc and washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethan-1-one as a brown solid (3.6 g, 64%).

[0136] ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.87-7.86 (m, 1H), 7.85-7.83 (m, 1H), 7.43 (t, J=12Hz, 1H), 7.09 (d, J=4Hz, 1H), 6.98 (d, J=4hz, 1H), 2.65 (s, 3H), 2.33 (s, 3H).

[0137] Step-2: N-((R)-1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide

[0138] To the solution of 1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethan-1-one (1.6 g, 0.0073 mol, 1.0 eq) and (R)-2-methylpropane-2-sulfinamide (1.78 g, 0.0147 mol, 2.0 eq) in anhydrous THF (30mL) at 0 °C, was added $Ti(iOPr)_4$ (2.51 g, 0.0110 mol, 1.5 eq). The reaction was heated at 60 °C for 16 h. The reaction was cooled to -50 °C and $NaBH_4$ (0.83 g, 0.022 mol, 3.0 eq) was added and allowed to stir overnight at room temp. The reaction was poured over crushed ice and aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography to give N-((R)-1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide as a white solid (2.0 g, 84%).

[0139] Step-3: (R)-1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethan-1-amine hydrochloride

[0140] To the solution of N-((R)-1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (1.0 g, 0.003 mol, 1.0 eq) in DCM (40 ml) in a reaction vial was added 4M HCl in dioxane (5 ml) at 0 °C and stirred at rt for overnight. The reaction was concentrated and co-precipitated with MeOH:ether as co-solvent to provide (R)-1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethan-1-amine hydrochloride as a white solid (0.6g, 89%).

[0141] ^{1}H-NMR (400 MHz, DMSO-d6): δ (ppm) 8.84 (bd, 3H), 7.92-7.82 (m, 4H), 7.66 (d, J=8Hz, 1H), 4.57 (m, 1H), 1.57 (d, J=8Hz, 3H).

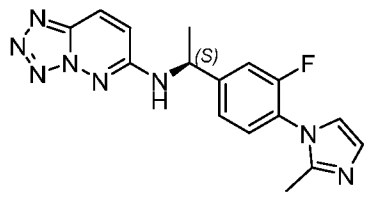
[0142] Step-4: (R)-N-(1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethyl)tetrazolo[1,5-b]pyridazin-6-amine

[0143] To the solution of 6-chlorotetrazolo[1,5-b]pyridazine (0.42 g, 0.0027, 1.1 eq) in DMF (10 ml) in a reaction vial was added DIPEA (1.8 ml, 0.0081 mol, 3 eq) followed by (R)-1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethan-1-amine hydrochloride (0.6 g, 0.002, 1.0 eq). The reaction mixture was heated at 90 °C for 16 h. The reaction was diluted with EtOAc and washed with brine, dried over Na2SO4, filtered, and concentrated.

The residue was purified by silica gel chromatography, to give ((R)-N-(1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethyl)tetrazolo[1,5-b]pyridazin-6-amine as a yellow solid (0.22 g, 27%).

[0144] ^{1}H-NMR (400 MHz, DMSO-d6): δ(ppm) 8.45 (d, J=8Hz, 1H), 8.26 (d, J=12Hz, 1H), 7.56-7.49 (m, 2H), 7.42 (d, J=8Hz, 1H) 7.24 (d, J=8Hz, 2H), 6.92 (d, J=4Hz, 1H), 5.15-5.11 (m, 1H), 2.15 (s, 3H), 1.55 (d, J=4Hz, 3H; LCMS = 338.97 $[M+H]^+$ HPLC = 97.29; SOR: $[\alpha]_\lambda^T$ = +272.3.

[0145] Example 15: Synthesis of (S)-N-(1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethyl)tetrazolo[1,5-b]pyridazin-6-amine (*Compound 15*)

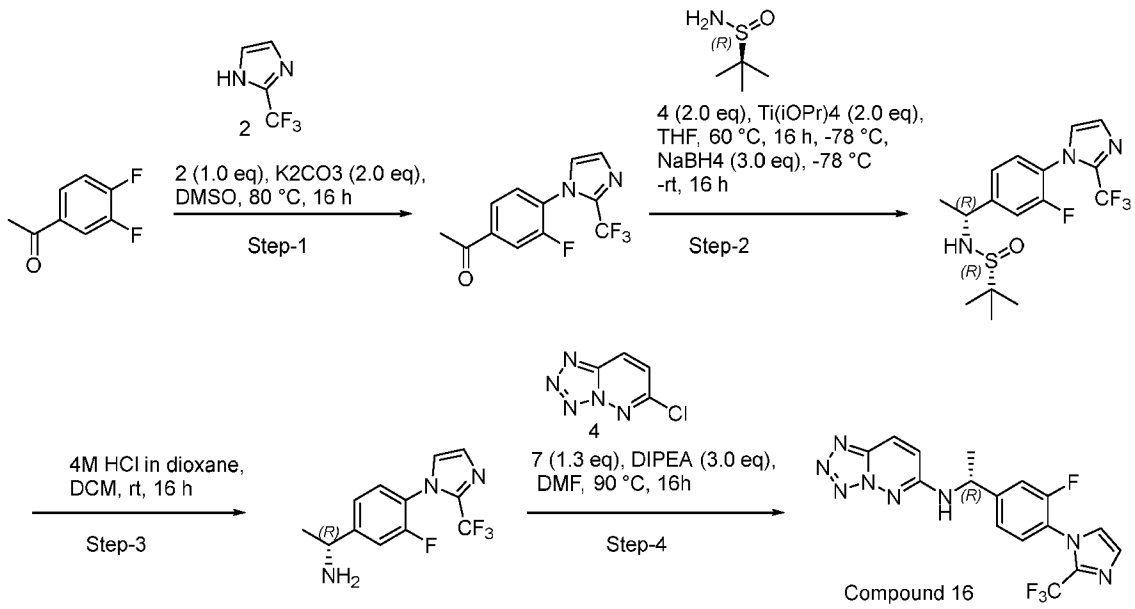


Compound 15

[0146] Compound 15 was prepared in a similar fashion as Example 14 to provide (S)-N-(1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethyl)tetrazolo[1,5-b]pyridazin-6-amine (0.1g, 32% yield).

[0147] ^{1}H-NMR (400 MHz, DMSO-d6): δ (ppm) 8.44 (d, J=8Hz, 1H), 8.28 (d, J=12Hz, 1H), 7.56-7.49 (m, 2H), 7.42 (d, J=8Hz, 1H), 7.24 (d, J=8Hz, 1H), 6.9 (s, 1H). 5.15-5.11 (m, 1H), 2.15 (s, 3H), 1.55 (d, J=4Hz, 3H); Mass: 337.03 $[M-H]^+$; HPLC: 97.64; SOR: $[\alpha]_\lambda^T$ = -202.26.

[0148] Example 16: Synthesis of (*R*)-N-(1-(3-fluoro-4-(2-(trifluoromethyl)-1H-imidazol-1-yl)phenyl)ethyl)tetrazolo[1,5-b]pyridazin-6-amine (*Compound 16*)



[0149] Step 1: 2-(Trifluoromethyl)-1H-imidazole (1.0 g, 0.0073 mol) in DMSO (20 mL) was taken in a sealed tube followed by 1-(3,4-difluorophenyl)ethanone (1.26 g, 0.0080 mol) and K_2CO_3 (2.01 g, 0.0146 mol) was added. The reaction mixture was heated at 80°C for 16 h. The reaction mass was dissolved in EtOAc and washed with brine solution. The organic layer was separated, and the aqueous layer was extracted two times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain 1-(3-fluoro-4-(2-(trifluoromethyl)-1H-imidazol-1-yl)phenyl)ethanone as an off white solid (1.31 g, 77%). . ^{1}H-NMR (400 MHz, DMSO-d6): δ (ppm) 8.07-8.03 (dd, J = 4 Hz, 12 Hz, 1H), 7.98-7.96 (dd, J = 4 Hz, 8 Hz, 1H), 7.87-7.82 (m, 2H), 7.38(s, 1H), 2.67 (s, 3H).

[0150] Step 2: To the solution of 1-(3-fluoro-4-(2-(trifluoromethyl)-1H-imidazol-1-yl)phenyl)ethanone (1.3 g, 0.0047 mol) and (*R*)-2-methylpropane-2-sulfinamide (1.04 g, 0.0086 mol) in anhydrous THF (30 ml) at 0 °C was added Ti(O^{i}Pr)$_4$ (5.9 ml, 0.0188). The reaction mixture was heated at 60 °C for 16 h. The reaction was cooled to -78 °C and $NaBH_4$ (0.715 g, 0.0188 mol) was added and allowed to stir for overnight at room temp. The reaction mixture was poured into crushed ice and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The

residue was purified by silica gel chromatography, eluted with a gradient of 0 to 50% EtOAc in hexanes providing (*R*)-N-((*R*)-1-(3-fluoro-4-(2-(trifluoromethyl)-1H-imidazol-1-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide as a colourless liquid (0.8 g, 44%). ; ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 7.75 (d, J = 4 Hz, 1H), 7.62-7.55 (m, 2H), 7.44-7.41(d, J =4 Hz , 8 Hz, 1H), 7.33 (d, J = 4 Hz , 1H), 5.90 (d, J= 8 Hz ,1H), 5.75 (s, 1H), 4.52-4.49 (m, 1H), 1.43 (d , J = 8 Hz, 3H) ,1.14 (s , 9H).

[0151] Step 3: To the solution of (R)-N-((R)-1-(3-fluoro-4-(2-(trifluoromethyl)-1H-imidazol-1-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (0.8 g, 0.0021 mol) in DCM (20 ml) was added 4M HCl in dioxane (5 ml) at 0 °C and stirred at RT for 16 h. The reaction mixture was concentrated and co-precipitated with a mixture of solvents MeOH and ether to provide (*R*)-1-(3-fluoro-4-(2-(trifluoromethyl)-1H-imidazol-1-yl)phenyl)ethanamine hydrochloride as a white solid (0.670 g, 99%). .

[0152] Step 4: To the solution of (*R*)-1-(3-fluoro-4-(2-(trifluoromethyl)-1H-imidazol-1-yl)phenyl)ethanamine hydrochloride (0.670 g, 0.0025 mol) in DMF (10 ml) was added DIPEA (1.3 ml, 0.0073 mol) followed by 6-chlorotetrazolo[1,5-b]pyridazine (0.418 g, 0.00269 mol). The reaction was heated in a seal tube at 90 °C for 16 h. The reaction was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography, eluted with a gradient of 0 to 5% MeOH in DCM providing (*R*)-N-(1-(4-fluorophenyl)propyl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-amine as an off-white colour solid (0. 38 g, 39%). /; ^{1}H-NMR (400 MHz, DMSO-d6): δ (ppm) 8.47 (d, J = 7.2 Hz, 1H), 8.29 (d, J = 9.6 Hz, 1H), 7.75 (s ,1H) 7.65-7.57 (m, 2H), 7.45 (d, J = 8 Hz, 1H), 7.31 (s, 1H), 7.25 (d, J = 10 Hz, 1H), 5.16-5.13 (m, 1H), 1.56 (d, J = 6.8 Hz, 3H); Mass: 393.39 $[M+H]^+$; LCMS: 95.32%. SOR: $[\alpha]_\lambda^T$ = +359.38.

Biological Studies

[0153] Indigo Biosciences Discovery Assay

[0154] The aim of this study was to evaluate compounds of the present invention

for antagonist activities against human AR. Reporter Cells used in these assays expressed a native receptor (AR). The reporter gene, firefly luciferase, is functionally linked to an upstream receptor-specific genetic response element (GRE). Reporter cells were treated with eight concentrations, starting at 50 uM and following with 3.17-fold dilutions. Single treatment concentration was performed (n=1). Assay performance was validated using the reference antagonist hydroxy flutamide

[0155] Step 1: A suspension of reporter cells was prepared in Cell Recovery Medium (CRM). Reporter cells were first supplemented with 2x-EC80 concentration of the reference agonist, 5α-dihydro-11-keto testosterone, then 100 ul of the Reporter Cell suspension was dispensed into wells of a white 96-well assay plate

[0156] Step 2: Test compound master stocks were diluted in DMSO to generate solutions at '500x-concentration' relative to the final treatment concentration and diluted directly into INDIGO's Compound Screening Medium (CSM; containing charcoal-stripped FBS) to generate '2x-concentration' treatment media. This was diluted into the wells to the final concentration. Assay plates were incubated at 37◦C, 5% CO2 and ~70% humidity for 24 hr.

[0157] Step 3: Following the incubation period, wells were rinsed once with Live Cell Multiplex (LCM) Buffer, then LCM substrate was added. Following incubation at room temperature for 15 min, LCM substrate was discarded and 100 µL/well of luciferase detection reagent was added. Subsequently, fluorescence was measured to determine the relative number of live cells per assay well. RLU values were quantified after a 10 min incubation period at room temperature to determine nuclear receptor activities

Mouse/Human Liver Microsome Stability

[0158] Procedure Summary

Test System	Liver Microsomes
Test compound concentration	1 µM
Time Points	0, 5, 10, 30 and 60 minutes
No of Replicates	Two
Final Protein Concentration	1 mg/mL

Final NADPH Concentration	1 mM
Potassium Phosphate Buffer pH 7.4	100 mM
Final DMSO Concentration	< 0.1%
Deliverables	% Remaining of test compound, Half life, CLint
Bioanalysis	LC-MS/MS

Assay Procedure

[0159] Preincubation mixture 2.5 µL Test Cpd. + 75 µL Liver microsomes (human or mouse source) @ 3.33 mg/mL + 85 µL of 100 mM potassium phosphate buffer (preincubate for 10 min @ 37°C). Incubation mixture 62 µL of cofactor (2.85 mM) + Remaining incubation mixture (Incubated for 60 min @ 37 °C). Sample preparation 25 µL incubation mixture + 200 µL of acetonitrile containing internal standard + Vortex 5 min @ 1200 rpm + Centrifuge 10 min @ 4000 rpm. Supernatant diluted 2-fold with water and injected on LC-MS/MS.

[0160] Table 1 shows the AR antagonist indigo cell based average IC50 (nM) values for example compounds of the present invention.

Table 1 IC50 (nM) values for compounds of the present invention

Compound #	AR-Antagonist_Indigo_Cell_Based: Avg IC50 (nM)*
Compound 1	+
Compound 2	+
Compound 3	+
Compound 4	+
Compound 5	+++
Compound 6	++
Compound 7	++
Compound 8	+++
Compound 9	+++
Compound 10	+
Compound 11	+
Compound 12	+
Compound 13	+++
Compound 14	+++

Compound 16	+++

*0-250 nm: “+++”; 251 nm-2000 nm: “++”, >2001 nm: “+”

[0161] Table 2 shows the *in vitro* microsome stability data for example compounds of the present description

Table 2 *In vitro* microsome stability data

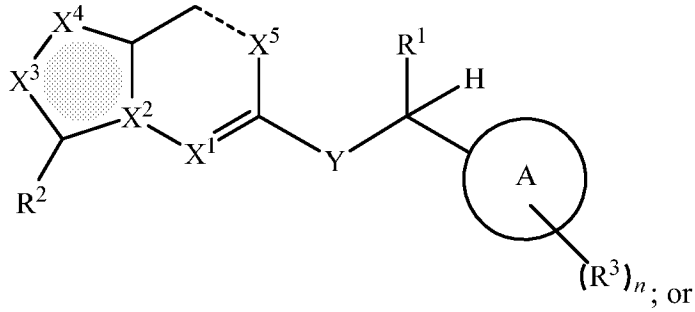
Compound #	Human LM: Rem @ 60 min (Percent)*	Mouse LM: Rem @ 60 min (Percent)*
Compound 5	+++	+
Compound 6	+	+
Compound 8	+++	+++
Compound 9	+	+
Compound 13	+	++
Compound 16	+++	+++

*0-30: “+”; 30.1-60: “++”, >60.1: “+++”

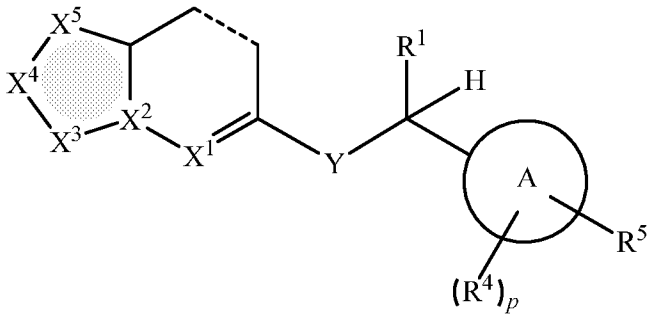
[0162] While only certain features of several embodiments have been illustrated and described herein, many modifications and changes will occur to those skilled in the art. It is, therefore, to be understood that the appended claims are intended to cover all such modifications and changes as fall within the scope of the invention and the appended claims.

CLAIMS

1. A compound having a formula (I) or (II) or a pharmaceutically acceptable salt thereof:



(I); or



(II);

wherein

dotted line "-----" is a single bond or a double bond;

"n" is an integer from 0 to 5; "p" is an integer from 0 to 4;

A is a C_3-C_9 cycloalkyl group, a C_3-C_{12} heterocycloalkyl group, a C_6-C_{12} aryl group, or a C_3-C_{12} heteroaryl group;

X^1, X^3, X^4 and X^5 are independently at each occurrence nitrogen, NH, CH or CH_2;

X^2 is independently at each occurrence carbon or nitrogen;

wherein in formula (I) at least one of X^1, X^2, X^3, X^4 and X^5 is carbon, CH or CH_2 and at least two of X^1, X^2, X^3, X^4 and X^5 are nitrogen or NH, and in formula (II) at least two of X^1, X^2, X^3, X^4 and X^5 are nitrogen or NH;

Y is O, S, or NR^6;

R^1 is a C_1-C_6 alkyl group optionally substituted with one or more fluorine or deuterium or a C_3-C_7 cycloalkyl group optionally substituted with one or more fluorine or deuterium;

R^2 is a C_1-C_6 alkyl group optionally substituted with one or more fluorine, a C_3-C_7 cycloalkyl group optionally substituted with one or more fluorine, —OR^7, or SF_5;

R^3 is independently at each occurrence halogen, —CN, —OR^7, —$NHC(=O)R^7$, —$C(–C_6H_5)R^7R^8$, —$C(=O)NR^7R^8$, —NR^7R^8, —$P(=O)R^7R^8$, a C_1-C_6 alkyl group optionally substituted with one or more fluorine or deuterium, a C_3-C_7 cycloalkyl group optionally substituted with one or more fluorine or deuterium, a C_1-C_{12} heterocycloalkyl group optionally substituted with one or more R^9, or a C_1-C_{12} heteroaryl group optionally substituted with one or more R^9;

R^4 is independently at each occurrence halogen, —CN, —OR^7, —$NHC(=O)R^7$, —$C(=O)NR^7R^8$, —NR^7R^8, —$P(=O)R^7R^8$, a C_1-C_6 alkyl group optionally substituted with one or more fluorine or deuterium, or a C_3-C_7 cycloalkyl group optionally substituted with one or more fluorine or deuterium;

R^5 is a C_1-C_{12} heterocycloalkyl group or a C_1-C_{12} heteroaryl group optionally substituted with one or more R^9;

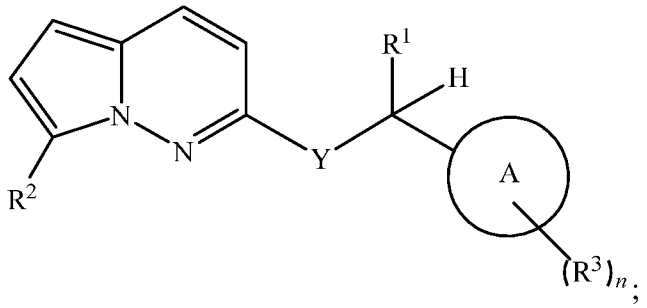
R^6 is hydrogen, a C_1-C_6 alkyl group, or a C_3-C_7 cycloalkyl group;

R^7 and R^8 are independently at each occurrence hydrogen, a C_1-C_6 alkyl group optionally substituted with one or more fluorine or an aminoalkyl group, a C_6-C_{10} aryl group optionally substituted with one or more fluorine, or R^7 and R^8 together with the carbon or nitrogen to which each is attached form a C_3-C_7 cycloalkyl optionally substituted with one or more fluorine or a C_3-C_{15} heterocycloalkyl group optionally substituted with one or more fluorine; and

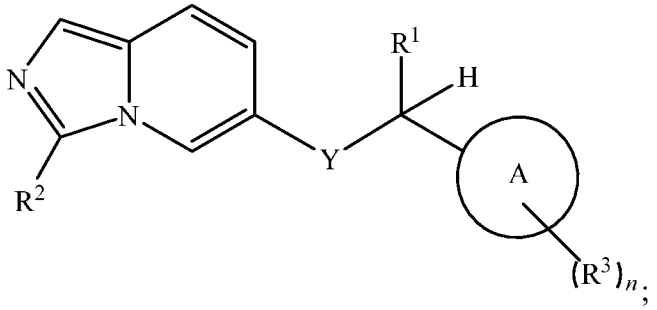
R^9 is independently at each occurrence halogen, —CN, —OR^7, —$NHC(=O)R^7$, —$C(=O)NR^7R^8$, —NR^7R^8, a C_1-C_6 alkyl group optionally substituted with one or more fluorine or a C_3-C_7 cycloalkyl group optionally substituted with one or more fluorine;

with the proviso that if in formula (I), A is an aryl group, Y is NH, X^1, X^2, X^3 and X^4, are all nitrogen, R^1 is a C_1-C_6 alkyl group, R^2 is a C_1-C_6 alkyl group optionally substituted with one or more fluorine, n is 1, then R^3 is not a halogen.

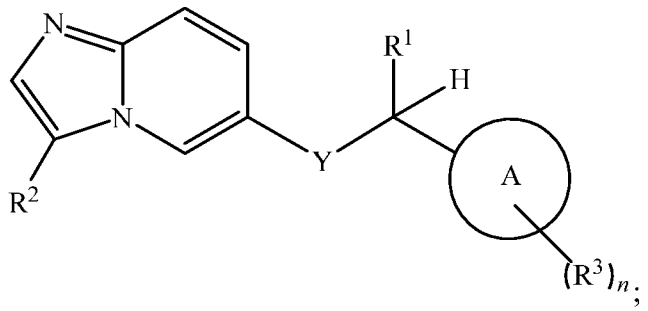
2. The compound of claim 1 selected from the group consisting of:



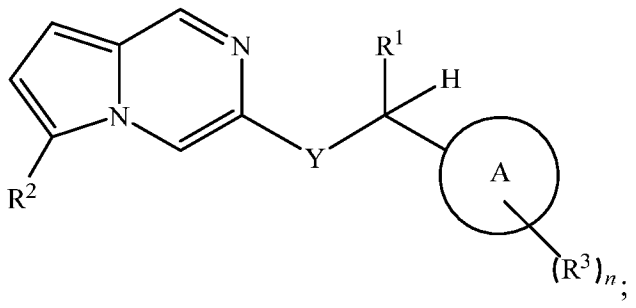
(III)



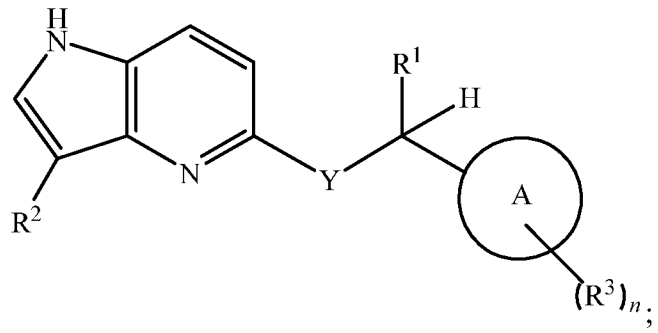
(IV)



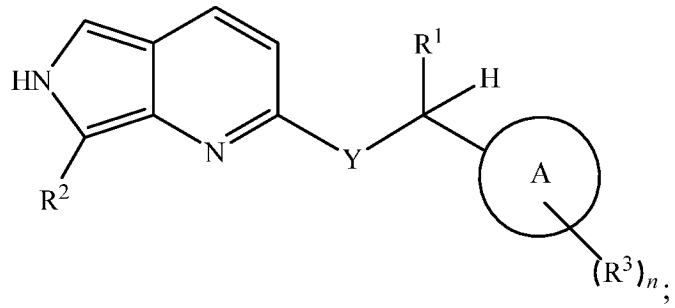
(V)



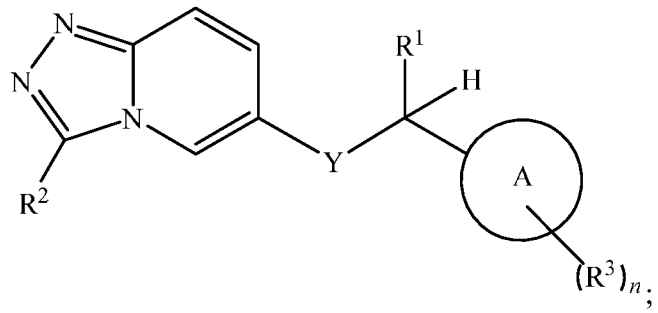
(VI)



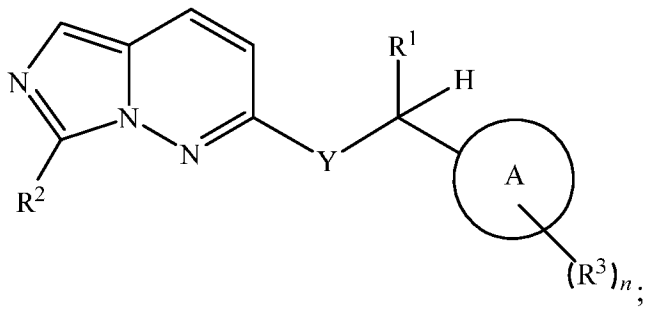
(VII)



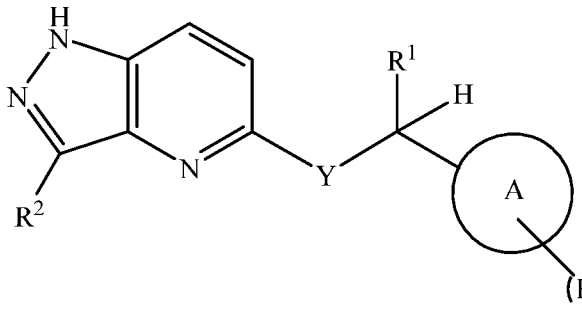
(VIII)



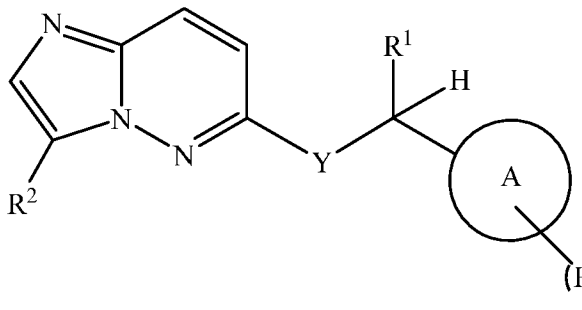
(IX)



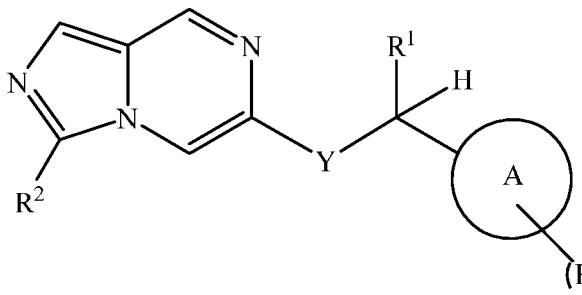
(X)



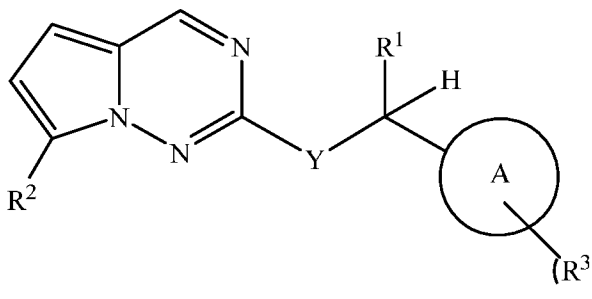
(XI);



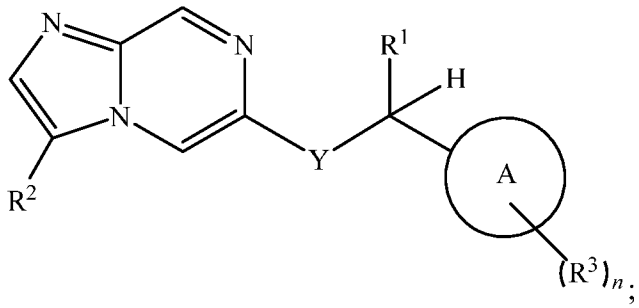
(XII);



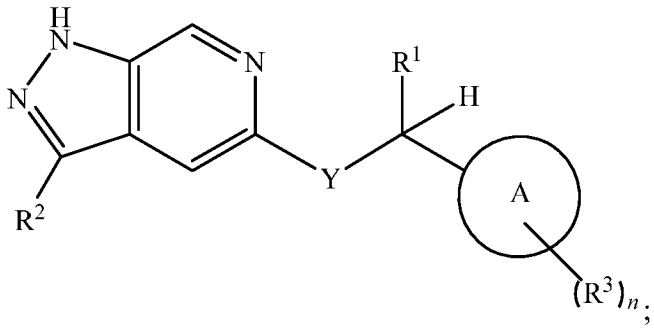
(XIII);



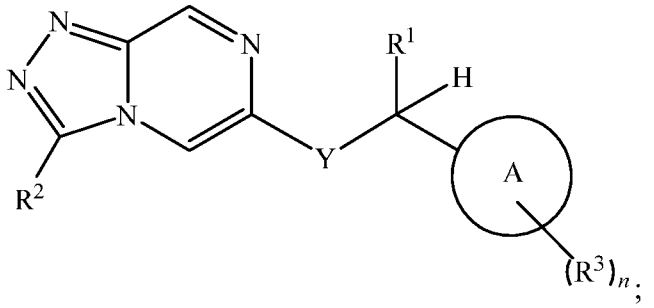
(XIV);



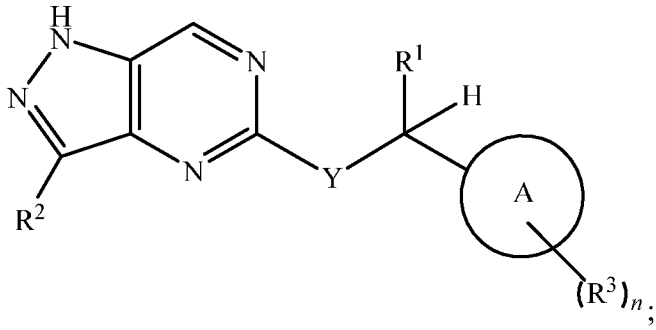
(XV);



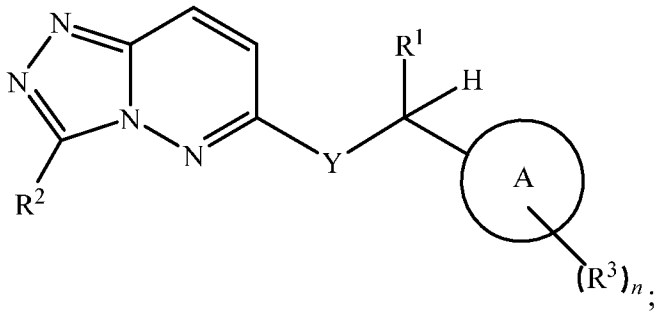
(XVI);



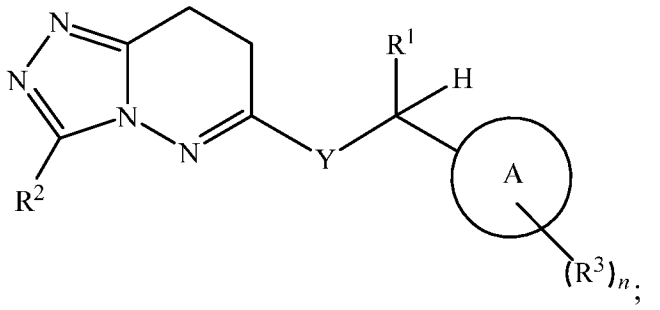
(XVII);



(XVIII);



(XIX);



(XX);

and any pharmaceutically acceptable salts thereof.

3. The compound of claim 1, wherein Y is O, S, or NR^6, R^1 is a C_1-C_3 alkyl group optionally substituted with one or more fluorine, R^2 is a C_1-C_3 alkyl group substituted with one or more fluorine, and R^6 is hydrogen, a C_1-C_6 alkyl group, or a C_3-C_7 cycloalkyl group.

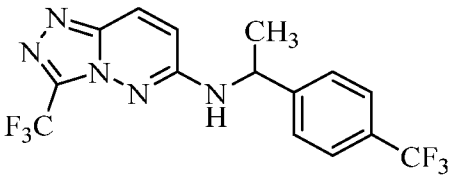
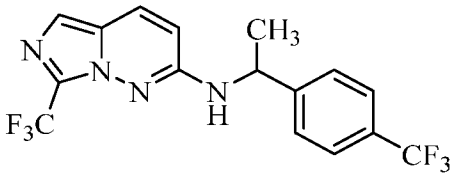
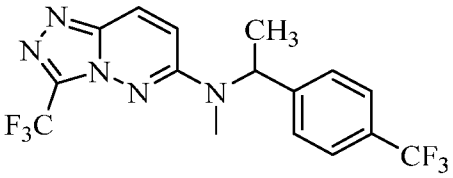
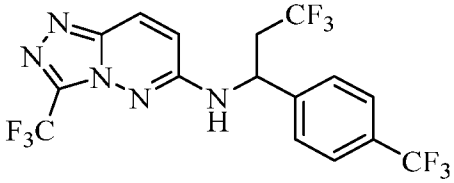
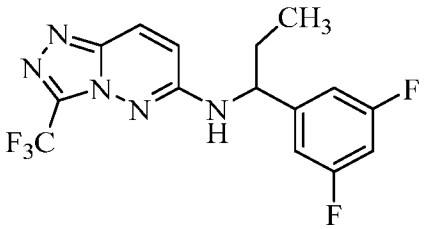
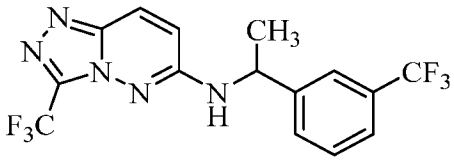
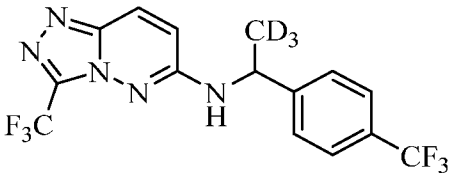
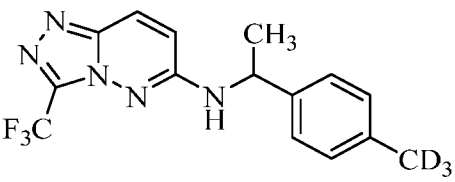
4. The compound of claim 1, wherein Y is O, S, or NR^6, R^1 is a C_1-C_3 alkyl group optionally substituted with one or more fluorine, R^2 is a C_1-C_3 alkyl group substituted with one or more fluorine, R^3 is independently at each occurrence halogen, —CN, —OR^7, or a C_1-C_3 alkyl group substituted with one or more fluorine, and R^6 is hydrogen, a C_1-C_6 alkyl group, or a C_3-C_7 cycloalkyl group.

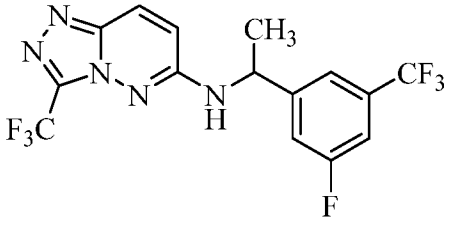
5. The compound of claim 1, wherein Y is O, S, or NR^6, R^1 is a C_1-C_3 alkyl group optionally substituted with one or more fluorine, R^2 is a C_1-C_3 alkyl group substituted with one or more fluorine, R^3 is independently at each occurrence a C_1-C_3 alkyl group

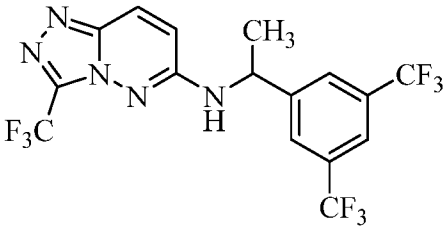
substituted with one or more fluorine, and R^6 is hydrogen, a C_1-C_6 alkyl group, or a C_3-C_7 cycloalkyl group.

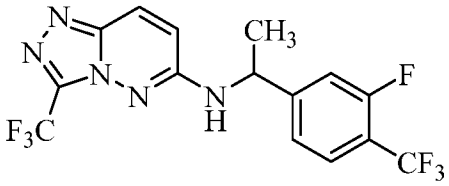
6. The compound of claim 1, wherein Y is NR^6, R^1 is a C_1-C_3 alkyl group optionally substituted with one or more fluorine, R^2 is a C_1-C_3 alkyl group substituted with one or more fluorine, R^3 is independently at each occurrence a C_1-C_3 alkyl group substituted with one or more fluorine, and R^6 is a C_1-C_3 alkyl group.

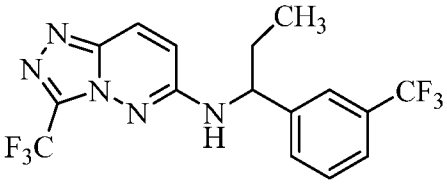
7. The compound of claim 1 selected from the consisting of:

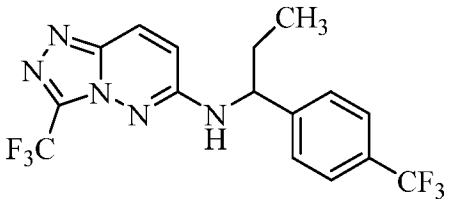









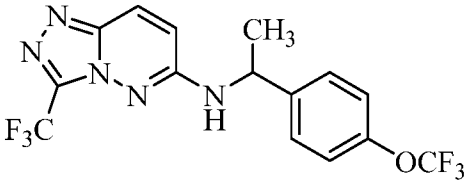


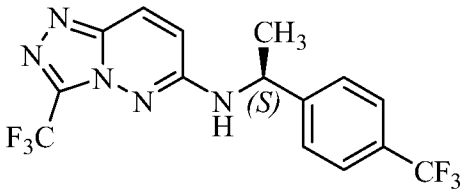


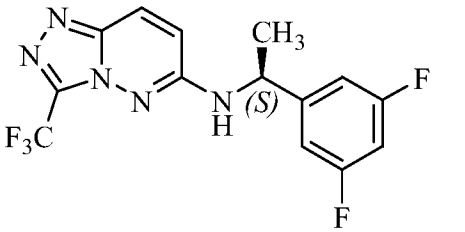


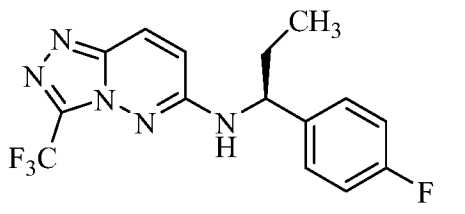


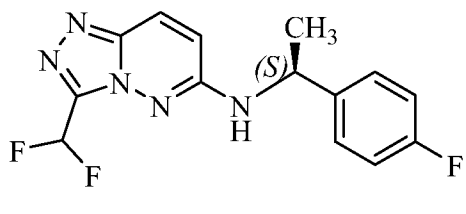


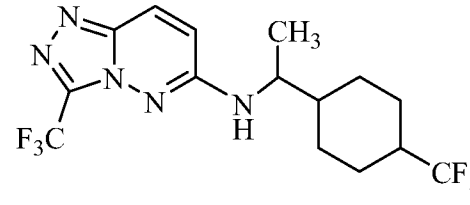


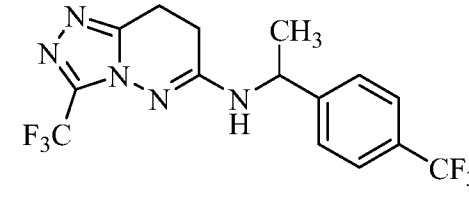


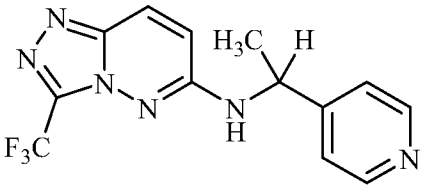


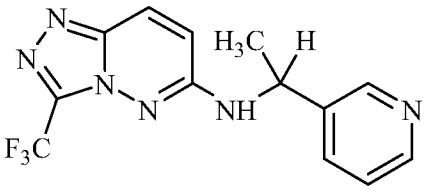


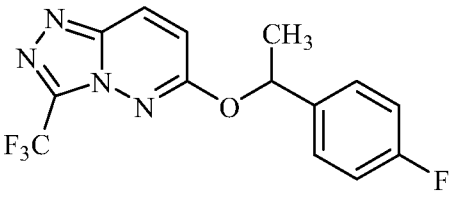


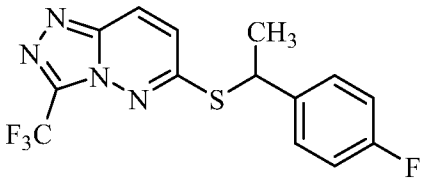


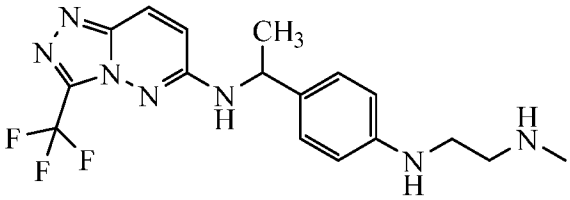


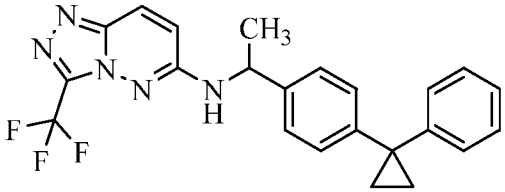


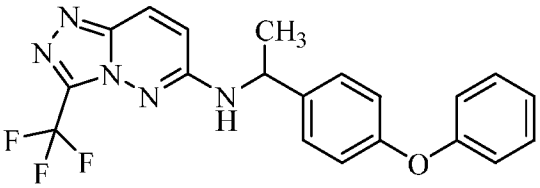


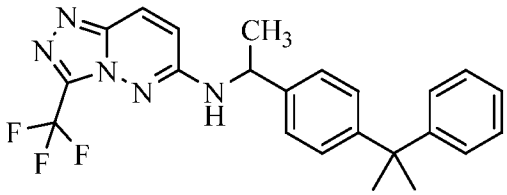


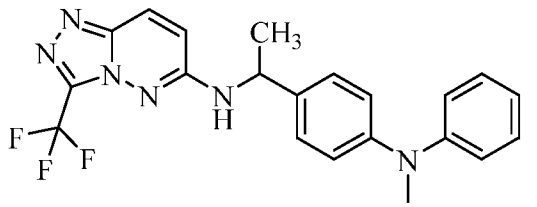


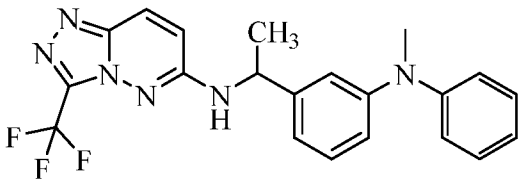


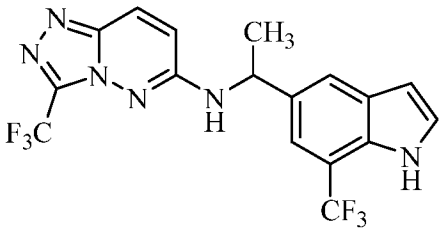


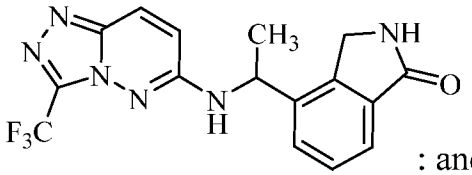




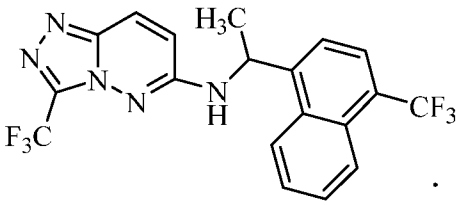






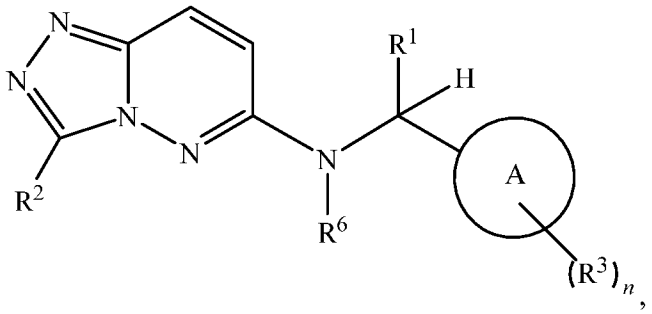


: and



.

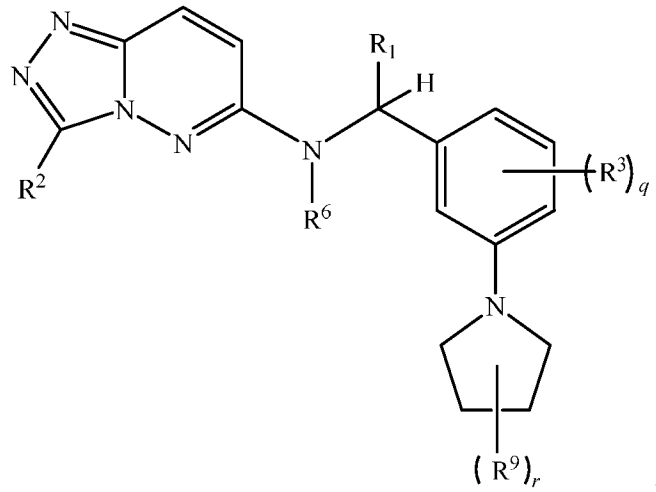
8. The compound of claim 1 having a formula (XXI) or any pharmaceutically acceptable salts thereof:



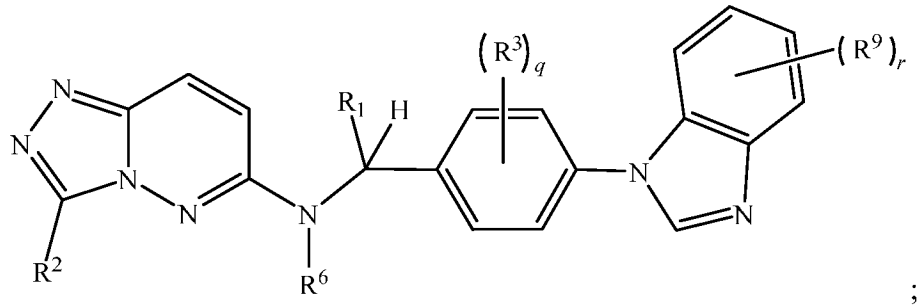
(XXI)

wherein "n" is an integer from 1 to 5, and at least one R^3 is a C_1-C_{12}heterocycloalkyl group optionally substituted with one or more R^9 or a C_1-C_{12} heteroaryl group optionally substituted with one or more R^9.

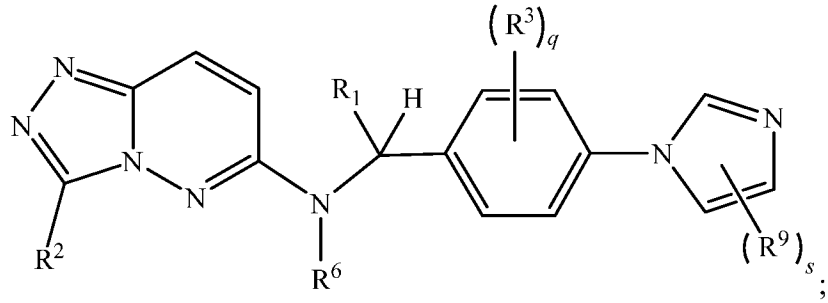
9. The compound of claim 8 selected from the group consisting of:



(XXII) ;



(XXIII) ;

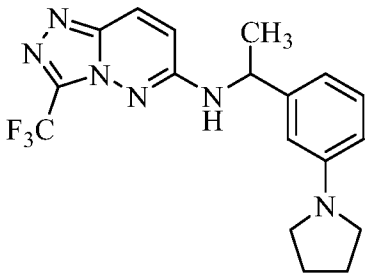


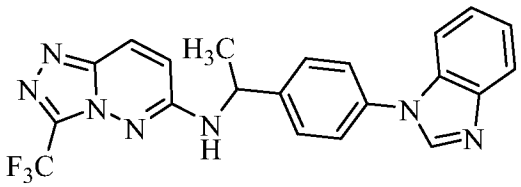
(XXIV) ; and

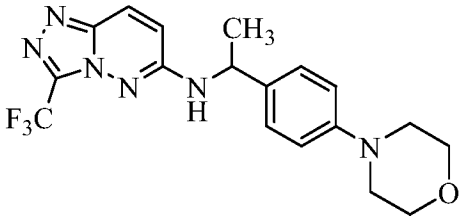
any pharmaceutically acceptable salts thereof, wherein "q" is an integer from 0 to 4; "r" is an integer from 0 to 4, and "s" is an integer from 0 to 3.

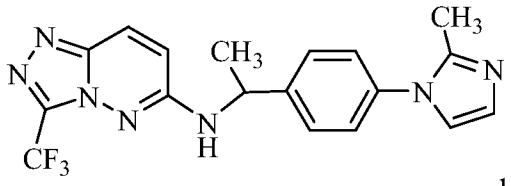
10. The compound of claim 9, wherein R^1 is a C_1-C_3 alkyl group optionally substituted with one or more fluorine, R^2 is a C_1-C_3 alkyl group substituted with one or more fluorine, and R^6 is hydrogen.

11. The compound of claim selected from the group consisting of:

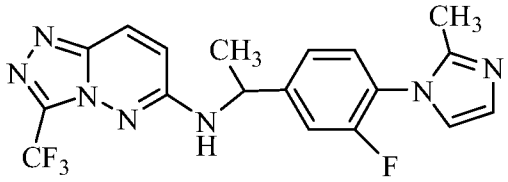


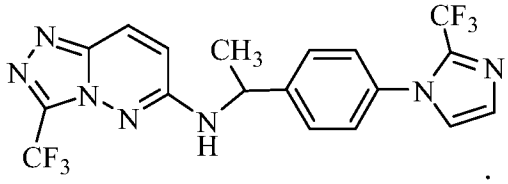






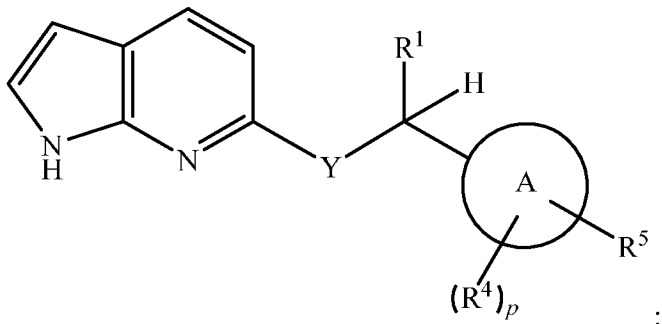
; and



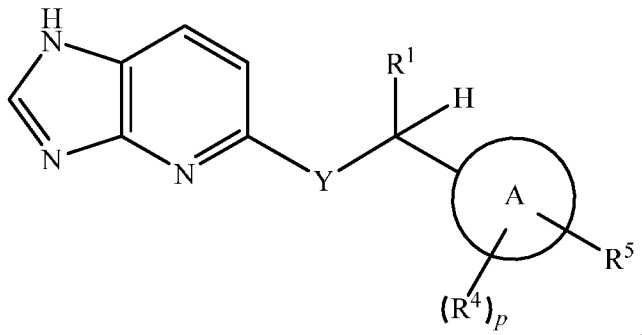


.

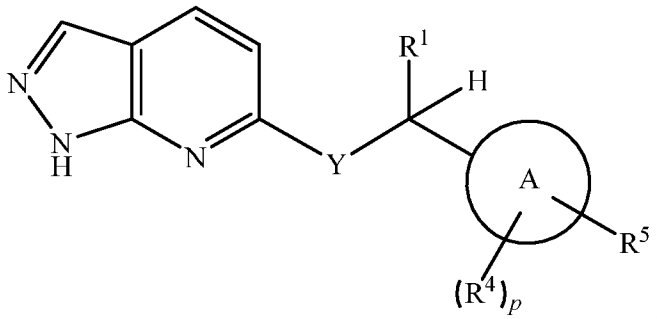
12. The compound of claim 1 having a formula (II) selected from the group consisting of:



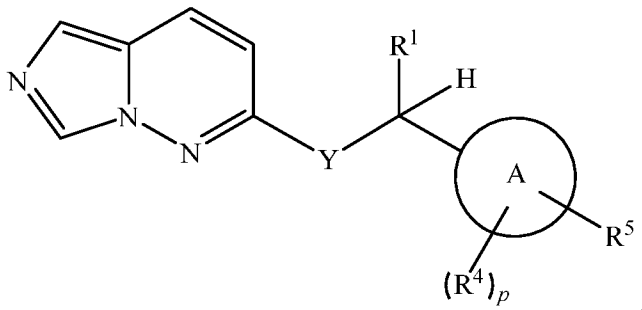
(XXV) ;



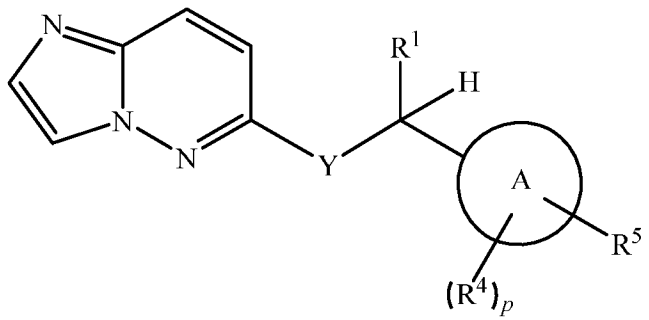
(XXVI) ;



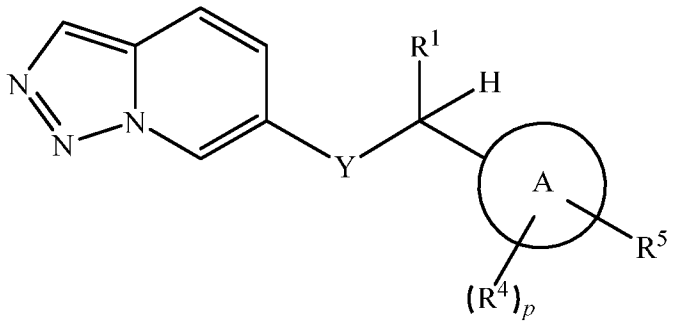
(XXVII) ;



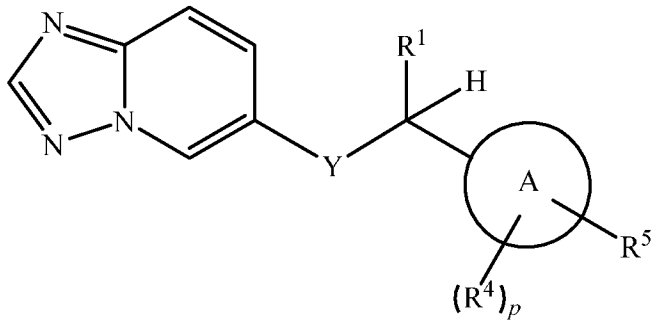
(XXVIII) ;



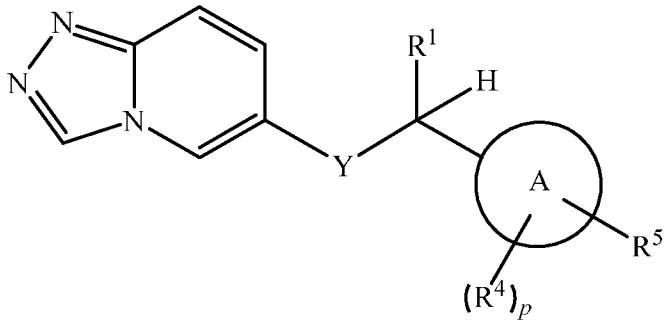
(XXIX) ;



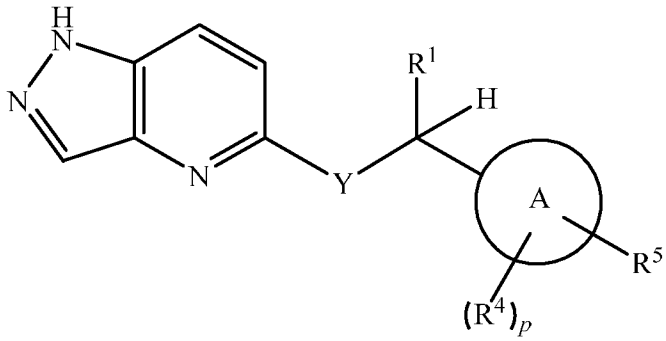
(XXX) ;



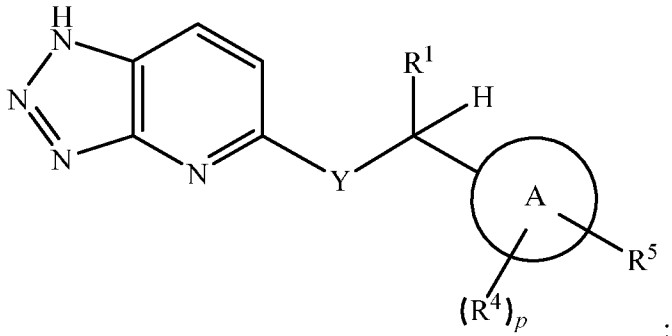
(XXXI) ;



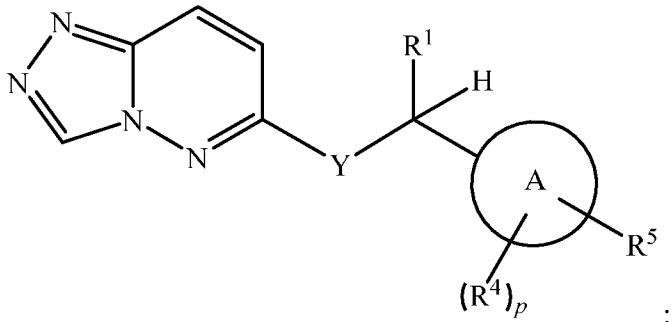
(XXXII) ;



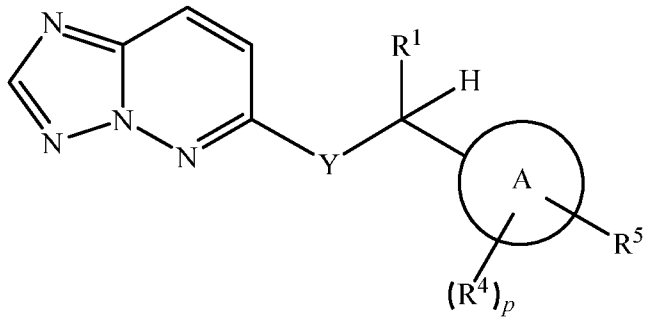
(XXXIII) ;



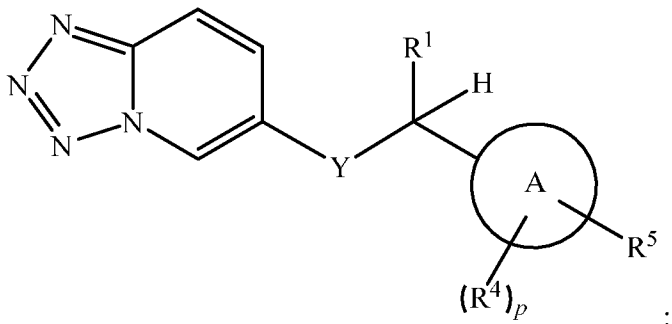
(XXXIV) ;



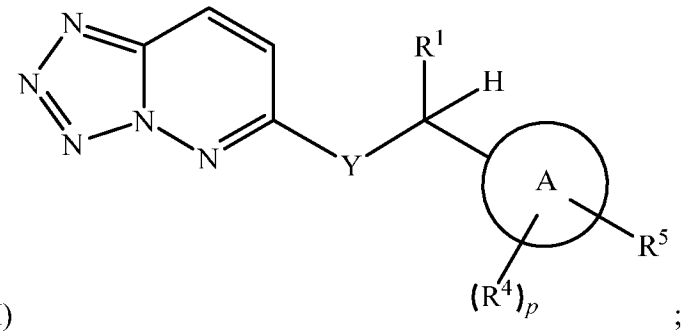
(XXXV) ;



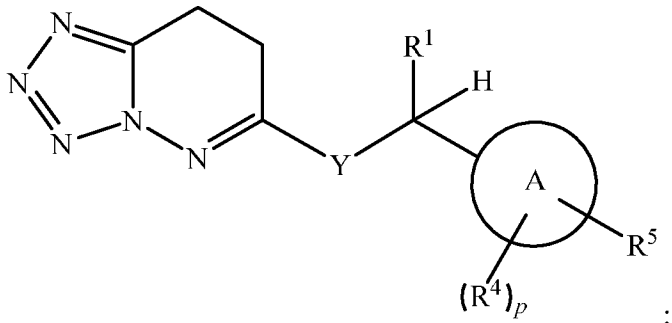
(XXXVI) ;



(XXXVII) ;



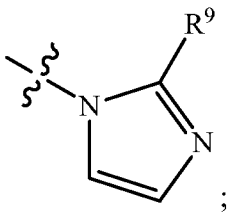
(XXXVIII) ;

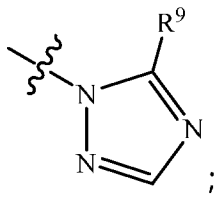


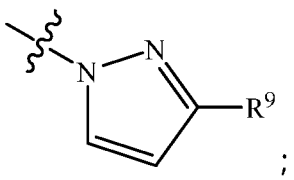
(XXXIX) ;

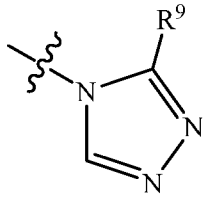
and any pharmaceutically acceptable salts thereof.

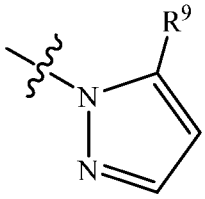
13. The compound of claim 12, wherein R^5 is selected from the group consisting of:

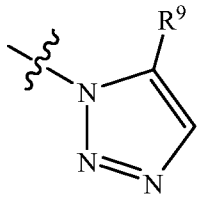
 ;

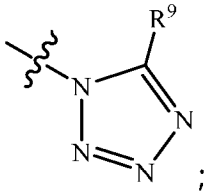
 ;

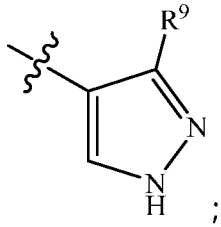
 ;

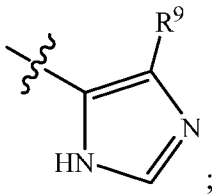


 ;

 ;


;


;

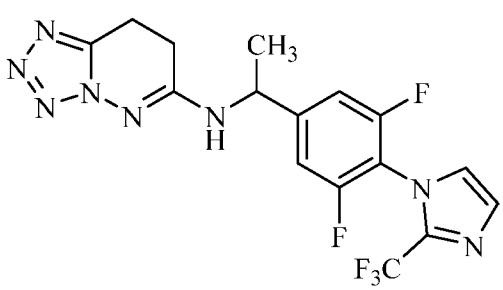

; and

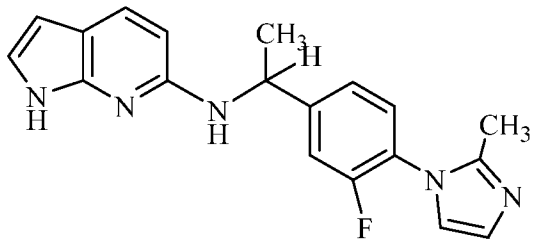
wherein R^9 is halogen or a C_1-C_3 alkyl group optionally substituted with one or more fluorine.

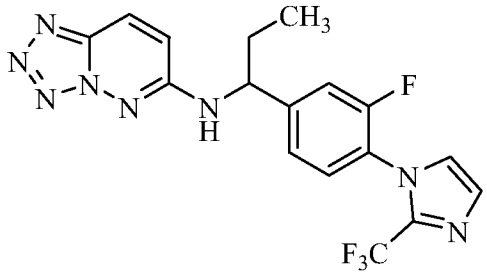
14. The compound of claim 12, wherein Y is O, S, or NR^6, R^1 is a C_1-C_3 alkyl group optionally substituted with one or more fluorine, R^4 is independently at each occurrence halogen, and R^6 is hydrogen, a C_1-C_6 alkyl group, or a C_3-C_7 cycloalkyl group.

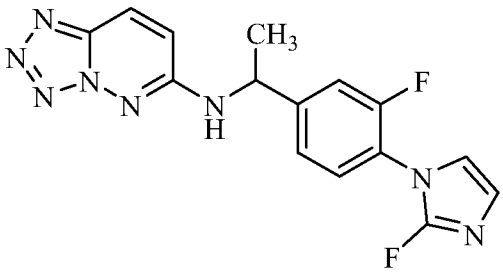
15. The compound of claim 12, wherein Y is NR^6, R^1 is a C_1-C_3 alkyl group optionally substituted with one or more fluorine, R^4 is independently at each occurrence halogen, and R^6 is a C_1-C_3 alkyl group.

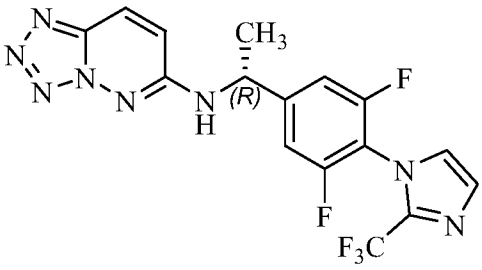
16. The compound of claim 12 selected from the group consisting of:

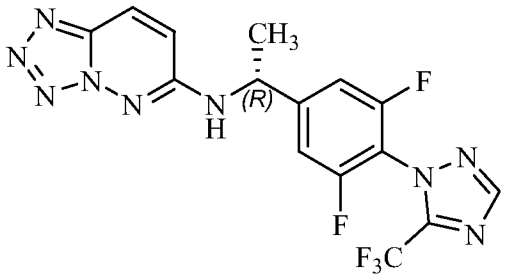


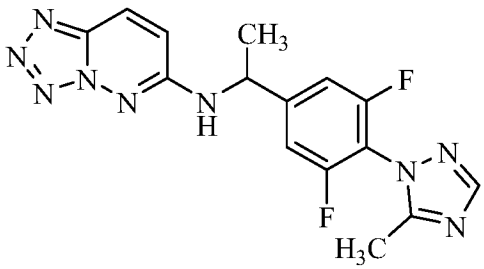


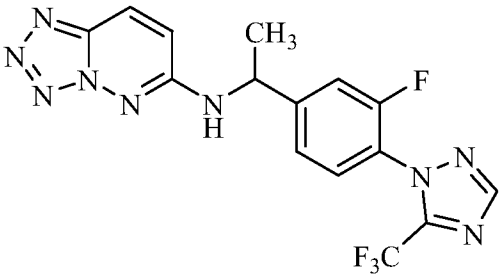


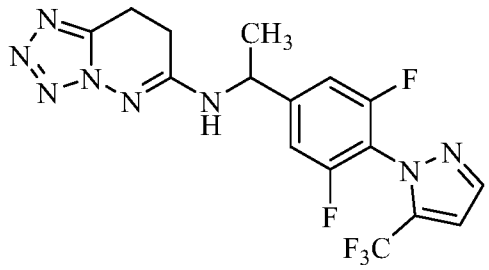


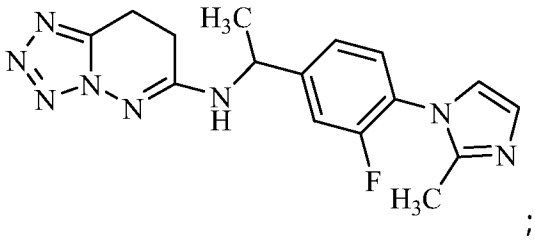












;

and any pharmaceutically acceptable salts thereof.

17. A pharmaceutical composition comprising:

the compound of claim 1 or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, or co-crystal thereof, and

a pharmaceutically carrier, diluent, or excipient.

18. A method for modulation of androgen receptor activity for treatment of prostate cancer, breast cancer, ovarian cancer, or melanoma, the method comprising administering to a patient a therapeutically effective amount of a pharmaceutical composition comprising a compound of claim 1.

19. The method of claim 18, wherein the method comprises modulation of androgen receptor activity for treatment of metastatic castration-resistant prostate cancer.

20. The method of claim 19, wherein the method comprises modulation of N-terminal domain of an androgen receptor for treatment of metastatic castration-resistant prostate cancer.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/027412

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***C07D 237/26*** (2024.01); ***C07D 487/04*** (2024.01); ***C07D 235/02*** (2024.01); *A61K 31/5025* (2024.01); *A61P 35/00* (2024.01)

CPC: ***C07D 237/26; C07D 235/02; C07D 487/04;*** *A61P 35/00; A61K 31/5025*

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)

See Search History Document

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

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2020/0325123 A1 (ONCOSTELLAE S.L.) 15 October 2020 (15.10.2020) entire document	1-5, 7, 17-20
A	US 2010/0022550 A1 (FALES et al.) 28 January 2010 (28.01.2010) entire document	1-5, 7, 17-20
A	PUBCHEM, SID 335426188, Modify Date: 25 April 2023 [retrieved on 15 June 2024]., Retrieved from the Internet <URL: https://pubchem.ncbi.nlm.nih.gov/substance/335426188> entire document	1-5, 7, 17-20
A	PUBCHEM, SID 124688335, Modify Date: 02 August 2011 [retrieved on 11 June 2024]., Retrieved from the Internet <URL: https://pubchem.ncbi.nlm.nih.gov/substance/124688335> entire document	1-5, 7, 17-20

☐ Further documents are listed in the continuation of Box C. ☐ 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
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 June 2024 (19.06.2024)	**13 August 2024 (13.08.2024)**

Name and mailing address of the ISA/US	Authorized officer
Mail Stop PCT, Attn: ISA/US **Commissioner for Patents** **P.O. Box 1450, Alexandria, VA 22313-1450**	**MATOS** **TAINA**
Facsimile No. **571-273-8300**	Telephone No. **571-272-4300**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/027412

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-20 are drawn to compounds having a formula (I) or (II) or a pharmaceutically acceptable salt thereof, pharmaceutical compositions, and methods for modulation of androgen receptor activity for treatment of prostate cancer, breast cancer, ovarian cancer, or melanoma.

The first invention of Group I+ is restricted to a compound having a formula (I) or (II) or a pharmaceutically acceptable salt thereof, specifically the first shown compound in instant claim 7, pharmaceutical compositions comprising the same, and methods for modulation of androgen receptor activity for treatment of prostate cancer, breast cancer, ovarian cancer, or melanoma comprising the same. The first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Specifically, the first named invention was selected based on the first listed compound species presented in the claims (see claim 7). It is believed that claims 1-5, 7, and 17-20 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound having a formula (I) or (II) or a pharmaceutically acceptable salt thereof, specifically the second shown compound in instant claim 7, pharmaceutical compositions comprising the same, and methods for modulation of androgen receptor activity for treatment of prostate cancer, breast cancer, ovarian cancer, or melanoma comprising the same. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables, dotted line, A, X1, X2, X3, X4, X5, Y, R1, R3, R4, R5, n, p, and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features of a compound having the core structure of formula (I) or (II) or a pharmaceutically acceptable salt thereof; a pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, or co-crystal thereof, and a pharmaceutically carrier, diluent, or excipient; and a method for modulation of androgen receptor activity for treatment of prostate cancer, breast cancer, ovarian cancer, or melanoma, the method comprising administering to a patient a therapeutically effective amount of a pharmaceutical composition comprising a compound, these shared technical features do not represent a contribution over the prior art as disclosed by Substance Record for SID 124688335 to PubChem (hereinafter, "PubChem") and US 2020/0325123 A1 to Oncostellae, S.L. (hereinafter, "Oncostellae").

PubChem teaches a compound having the core structure of formula (I) or (II) or a pharmaceutically acceptable salt thereof (Pg. 2, compound as shown).

Oncostellae teaches a pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, or co-crystal thereof, and a pharmaceutically carrier, diluent, or excipient (Para. [0523], present invention also provides pharmaceutical compositions which comprise, as an active ingredient, at least a dihydropyridine derivative of formula (I) or a pharmaceutically acceptable salt thereof in association with other therapeutics agents, as have been mentioned above, and with a pharmaceutically

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

acceptable excipient such as a carrier or diluent); and a method for modulation of androgen receptor activity for treatment of prostate cancer, breast cancer, ovarian cancer, or melanoma, the method comprising administering to a patient a therapeutically effective amount of a pharmaceutical composition comprising a compound (Para. [0078], the present invention relates to methods for the treatment of diseases that can be ameliorated by modulation of nuclear receptors, in particular by antagonism of androgen receptor and/or glucocorticoid receptor, by administration of the compounds defined in the first aspect or the pharmaceutical compositions of the third aspect or the combination product of the fourth aspect to a subject in need of said treatment; Para. [0080], the present invention relates to a compound as defined in the first aspect for use in the treatment of a disease or pathological condition selected from the group consisting of cancer, prostate cancer).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☑ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1-5, 7, 17-20**

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.