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(54) Benævnelse: **Forbindelser som ROR-gamma-modulatorer**

Fortsættes ...

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PASHA M. KHAN ET AL: "Small molecule amides as potent ROR-[gamma] selective modulators", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 23, no. 2, 1 January 2013 (2013-01-01), pages 532-536, XP055073469, ISSN: 0960-894X, DOI: 10.1016/j.bmcl.2012.11.025
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DESCRIPTION

BACKGROUND OF THE INVENTION

1. TECHNICAL FIELD

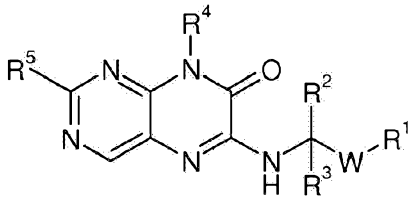
[0001] The present invention relates to novel compounds which modulate the activity of RORγ and their use as medicaments.

2. BACKGROUND INFORMATION

[0002] RORγ (retinoic acid receptor related orphan receptor gamma) (also referred to as "RORγt") is a transcription factor belonging to the steroid hormone receptor superfamily (reviewed in Jetten 2006. Adv. Dev Biol. 16 : 313-355.). RORγ has been identified as a transcriptional factor that is required for the differentiation of T cells and secretion of Interleukin 17 (IL-17) from a subset of T cells termed Th_{17} cells (Ivanov, Cell 2006, 126, 1121-1133). The rationale for the use of a RORγ targeted therapy for the treatment of chronic inflammatory diseases is based on the emerging evidence that Th_{17} cells and the cytokine IL-17 contribute to the initiation and progression of the pathogenesis of several autoimmune diseases including psoriasis, ankylosing spondylitis, rheumatoid arthritis, multiple sclerosis and Crohn's disease (reviewed in Miossec, Nature Drug Discovery 2012, 11, 763-776; see also Khan et al., Bioorganic & Medicinal Chemistry Letters 23 (2013), 532-536). The outcome of recent clinical trials with neutralizing antibodies to IL-17 and its receptor IL-17RA (Leonardi 2012, New England Journal of Medicine, 366, 1190-1199; Papp 2012, New England Journal of Medicine 366, 1181-1189) in psoriasis highlight the role of IL-17 in the pathogenesis of this disease. As such, attenuation of IL-17 secretion from activated Th_{17} T cells via inhibition of RORγ may offer similar therapeutic benefit.

SUMMARY OF THE INVENTION

[0003] The invention comprises a novel class of heteroaromatic compounds and methods for making and using the same, said compounds having the general structure of formula (I), wherein the substituent groups are as herein defined:



(I)

[0004] These compounds are useful for the treatment of autoimmune and allergic disorders in that they exhibit good modulatory effect upon RORγ.

DETAILED DESCRIPTION OF THE INVENTION

Definitions and Conventions Used

[0005] Terms that are not specifically defined here have the meanings that would be apparent to a person skilled in the art, in the light of the overall disclosure and the context as a whole.

[0006] As used herein, the following definitions apply, unless stated otherwise:
The use of the prefix C_{x-y}, wherein x and y each represent a natural number, indicates that the chain or ring structure or combination of chain and ring structure as a whole, specified and mentioned in direct association, may consist of a maximum of y and a minimum of x number of carbon atoms.

[0007] In general, for groups comprising two or more subgroups, unless otherwise indicated the last named subgroup is the radical attachment point, for example, the substituent "aryl-C_{1-3}-alkyl" means an aryl group which is bound to a C_{1-3}-alkyl-group, the latter of which is bound to the core or to the group to which the substituent is attached. However, if a bond is depicted just prior to the first named subgroup, then that first named subgroup is the radical attachment point, for example, the substituent "-$S(O)_nC_{1-6}$alkyl" means a C_{1-6}-alkyl-group which is bound to an $S(O)_n$ group, the latter of which is bound to the core or to the group to which the substituent is attached.

[0008] Alkyl denotes monovalent, saturated hydrocarbon chains, which may be present in both straight-chain (unbranched) and branched form. If an alkyl is substituted, the substitution may take place independently of one another, by mono- or polysubstitution in each case, on all the hydrogen-carrying carbon atoms.

[0009] For example, the term "C_{1-5}alkyl" includes for example H_3C-, H_3C-CH_2-, H_3C-CH_2-CH_2-, H_3C-$CH(CH_3)$-, H_3C-CH_2-CH_2-CH_2-, H_3C-CH_2-$CH(CH_3)$-, H_3C-$CH(CH_3)$-CH_2-, H_3C-$C(CH_3)_2$-, H_3C-CH_2-CH_2-CH_2-CH_2-, H_3C-CH_2-CH_2-$CH(CH_3)$-, H_3C-CH_2-$CH(CH_3)$-CH_2-, H_3C-$CH(CH_3)$-CH_2-CH_2-, H_3C-CH_2-$C(CH_3)_2$-, H_3C-$C(CH_3)_2$-CH_2-, H_3C-$CH(CH_3)$-$CH(CH_3)$- and H_3C-CH_2-$CH(CH_2CH_3)$-.

[0010] Further examples of alkyl are methyl (Me; -CH_3), ethyl (Et; -CH_2CH_3), 1-propyl (*n*-

propyl; *n*-Pr; -$CH_2CH_2CH_3$), 2-propyl (*i*-Pr; *iso*-propyl; -$CH(CH_3)_2$), 1-butyl (*n*-butyl; *n*-Bu; -$CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (*iso*-butyl; *i*-Bu; -$CH_2CH(CH_3)_2$), 2-butyl (*sec*-butyl; *sec*-Bu; -$CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (*tert*-butyl; *t*-Bu; -$C(CH_3)_3$),1-pentyl *n*-pentyl; -$CH_2CH_2CH_2CH_2CH_3$), 2-pentyl (-$CH(CH_3)CH_2CH_2CH_3$), 3-pentyl (-$CH(CH_2CH_3)_2$), 3-methyl-1-butyl (*iso*-pentyl; -$CH_2CH_2CH(CH_3)_2$), 2-methyl-2-butyl (-$C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl (-$CH(CH_3)CH(CH_3)_2$), 2,2-dimethyl-1-propyl(*neo*-pentyl;-$CH_2C(CH_3)_3$),2-methyl-1-butyl (-$CH_2CH(CH_3)CH_2CH_3$), 1-hexyl (*n*-hexyl; -$CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl (-$CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl (-$CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl (-$C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl (-$CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl (-$CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl (-$C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl (-$CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl (-$C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl (-$CH(CH_3)C(CH_3)_3$), 2,3-dimethyl-1-butyl (-$CH_2CH(CH_3)CH(CH_3)CH_3$), 2,2-dimethyl-1-butyl (-$CH_2C(CH_3)_2CH_2CH_3$), 3,3-dimethyl-1-butyl (-$CH_2CH_2C(CH_3)_3$), 2-methyl-1-pentyl (-$CH_2CH(CH_3)CH_2CH_2CH_3$), 3-methyl-1-pentyl (-$CH_2CH_2CH(CH_3)CH_2CH_3$), 1-heptyl (*n*-heptyl), 2-methyl-1-hexyl, 3-methyl-1-hexyl, 2,2-dimethyl-1-pentyl, 2,3-dimethyl-1-pentyl, 2,4-dimethyl-1-pentyl, 3,3-dimethyl-1-pentyl, 2,2,3-trimethyl-1-butyl, 3-ethyl-1-pentyl, 1-octyl (*n*-octyl), 1-nonyl (*n*-nonyl); 1-decyl (*n*-decyl) etc.

[0011] By the terms propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl etc. without any further definition are meant saturated hydrocarbon groups with the corresponding number of carbon atoms, wherein all isomeric forms are included.

[0012] The above definition for alkyl also applies if alkyl is a part of another (combined) group such as for example C_{x-y}alkylamino or C_{x-y}alkoxy.

[0013] Unlike alkyl, alkenyl, when used alone or in combination, consists of at least two carbon atoms, wherein at least two adjacent carbon atoms are joined together by a C-C double bond and a carbon atom can only be part of one C-C double bond. If in an alkyl as hereinbefore defined having at least two carbon atoms, two hydrogen atoms on adjacent carbon atoms are formally removed and the free valencies are saturated to form a second bond, the corresponding alkenyl is formed.

[0014] Alkenyl may optionally be present in the *cis* or *trans* or *E* or *Z* orientation with regard to the double bond(s).

[0015] Unlike alkyl, alkynyl, when used alone or in combination, consists of at least two carbon atoms, wherein at least two adjacent carbon atoms are joined together by a C-C triple bond. If in an alkyl as hereinbefore defined having at least two carbon atoms, two hydrogen atoms in each case at adjacent carbon atoms are formally removed and the free valencies are saturated to form two further bonds, the corresponding alkynyl is formed.

[0016] Haloalkyl (haloalkenyl, haloalkynyl), when used alone or in combination, is derived from

the previously defined alkyl (alkenyl, alkynyl) by replacing one or more hydrogen atoms of the hydrocarbon chain independently of one another by halogen atoms, which may be identical or different. If a haloalkyl (haloalkenyl, haloalkynyl) is to be further substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon atoms.

[0017] Examples of haloalkyl (haloalkenyl, haloalkynyl) are $-CF_3$, $-CHF_2$, $-CH_2F$,$-CF_2CF_3$, $-CHFCF_3$, $-CH_2CF_3$, $-CF_2CH_3$, $-CHFCH_3$, $-CF_2CF_2CF_3$, $-CF_2CH_2CH_3$, $-CF=CF_2$,$-CCl=CH_2$, $-CBr=CH_2$, $-C\equiv C-CF_3$, $-CHFCH_2CH_3$, $-CHFCH_2CF_3$ etc.

[0018] Halogen relates to fluorine, chlorine, bromine and/or iodine atoms.

[0019] The term "cycloalkyl", when used alone or in combination, refers to a nonaromatic 3 to 12-membered (but preferably, 3 to 6-membered) monocyclic carbocyclic radical or a nonaromatic 6 to 10-membered fused bicyclic, bridged bicyclic, propellane or spirocyclic carbocyclic radical. The C_{3-12} cycloalkyl may be either saturated or partially unsaturated, and the carbocycle may be attached by any atom of the cycle which results in the creation of a stable structure. Non-limiting examples of 3 to 10-membered monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptanyl, cycloheptenyl, and cyclohexanone. Non-limiting examples of 6 to 10-membered fused bicyclic carbocyclic radicals include bicyclo[1.1.1]pentane, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, and bicyclo[4.4.0]decanyl (decahydronaphthalenyl). Non-limiting examples of 6 to 10-membered bridged bicyclic carbocyclic radicals include bicyclo[2.2.2]heptanyl, bicyclo[2.2.2]octanyl, and bicyclo[3.2.1]octanyl. Non-limiting examples of 6 to 10-membered propellane carbocyclic radicals include but are not limited to [1.1.1.]propellane, [3.3.3]propellane and [3.3.1]propellane. Non-limiting examples of 6 to 10-membered spirocyclic carbocyclic radicals include but are not limited to spiro[3,3]heptanyl, spiro[3,4]octanyl and spiro [4,4] heptanyl.

[0020] The term "heterocyclyl", when used alone or in combination, refers to a heterocyclic ring system that contains 2-10 carbon atoms and one to four heteroatom ring atoms chosen from NH, NR', oxygen and sulfur wherein R' is C_{1-6} alkyl and includes stable nonaromatic 4-8 membered monocyclic heterocyclic radical or a stable nonaromatic 6 to 11-membered fused bicyclic, bridged bicyclic or spirocyclic heterocyclic radical. The heterocycle may be either completely saturated or partially unsaturated. In one embodiment the heterocycle is a C_{3-6} heterocycle, i.e., containing 3 to 6 ring carbon atoms. Non-limiting examples of nonaromatic monocyclic heterocyclic radicals include tetrahydrofuranyl, azetidinyl, pyrrolidinyl, pyranyl, tetrahydropyranyl, dioxanyl, thiomorpholinyl, 1,1-dioxo-1.lamda$_6$-thiomorpholinyl, morpholinyl, piperidinyl, piperazinyl, and azepinyl. Non-limiting examples of nonaromatic 6 to 11-membered fused bicyclic radicals include octahydroindolyl, octahydrobenzofuranyl, and octahydrobenzothiophenyl. Non-limiting examples of nonaromatic 6 to 11-membered bridged bicyclic radicals include 2-azabicyclo[2.2.1]heptanyl, 3-azabicyclo[3.1.0]hexanyl, and 3-azabicyclo[3.2.1]octanyl. Non-limiting examples of nonaromatic 6 to 11-membered spirocyclic

heterocyclic radicals include 7-aza-spiro[3,3]heptanyl, 7-spiro[3,4]octanyl, and 7-aza-spiro[3,4]octanyl. Sulfur and nitrogen may optionally be present in all the possible oxidation stages (sulphur → sulphoxide -SO-, sulphone -SO_2-; nitrogen → N-oxide).

[0021] The term "aryl", when used alone or in combination, refers to an aromatic hydrocarbon ring containing from six to fourteen carbon ring atoms (e.g., a C_{6-14} aryl, preferably C_{6-10} aryl). The term C_{6-14} aryl includes monocyclic rings, fused rings and bicyclic rings where at least one of the rings is aromatic. Non-limiting examples of C_{6-14} aryls include phenyl, indanyl, indenyl, benzocyclobutanyl, dihydronaphthyl, tetrahydronaphthyl, naphthyl, benzocycloheptanyl and benzocycloheptenyl.

[0022] As used herein, the term "heteroaryl", when used alone or in combination, refers to a heteroaromatic ring system that contains 2-10 carbon atoms and 1-4 heteroatom ring atoms selected from N, NH, NR', O and S wherein R' is C_{1-6} alkyl and includes aromatic 5 to 6-membered monocyclic heteroaryls and aromatic 7 to 11-membered heteroaryl bicyclic or fused rings where at least one of the rings is aromatic. Non-limiting examples of 5 to 6-membered monocyclic heteroaryl rings include furanyl, oxazolyl, isoxazolyl, oxadiazolyl, pyranyl, thiazolyl, pyrazolyl, pyrrolyl, imidazolyl, tetrazolyl, triazolyl, thienyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, and purinyl. Non-limiting examples of 7 to 11-membered heteroaryl bicyclic or fused rings include benzimidazolyl, 1,3-dihydrobenzoimidazol-2-one, quinolinyl, dihydro-2H-quinolinyl, isoquinolinyl, quinazolinyl, indazolyl, thieno[2,3-d]pyrimidinyl, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzofuranyl, benzopyranyl, benzodioxolyl, benzoxazolyl, benzothiazolyl, pyrrolo[2,3-b]pyridinyl, and imidazo[4,5-b]pyridinyl. Sulfur and nitrogen may optionally be present in all the possible oxidation stages (sulphur → sulphoxide -SO-, sulphone -SO_2-; nitrogen → N-oxide).

[0023] The compounds of the invention are only those which are contemplated to be chemically stable as will be appreciated by those skilled in the art. For example, a compound which would have a "dangling valency", or a carbanion are not compounds contemplated by the inventive methods disclosed herein.

[0024] Unless specifically indicated, throughout the specification and appended claims, a given chemical formula or name shall encompass tautomers and all stereo, optical and geometrical isomers (e.g. enantiomers, diastereomers, E/Z isomers, etc.) and racemates thereof as well as mixtures in different proportions of the separate enantiomers, mixtures of diastereomers, or mixtures of any of the foregoing forms where such isomers and enantiomers exist, as well as salts, including pharmaceutically acceptable salts thereof, and their corresponding unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like.

[0025] Compounds of the invention also include their isotopically-labelled forms. An isotopically-labelled form of an active agent of a combination of the present invention is identical to said active agent but for the fact that one or more atoms of said active agent have

been replaced by an atom or atoms having an atomic mass or mass number different from the atomic mass or mass number of said atom which is usually found in nature. Examples of isotopes which are readily available commercially and which can be incorporated into an active agent of a combination of the present invention in accordance with well established procedures, include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, *e.g.*, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. An active agent of a combination of the present invention, a prodrug thereof, or a pharmaceutically acceptable salt of either which contains one or more of the above-mentioned isotopes and/or other isotopes of other atoms is contemplated to be within the scope of the present invention.

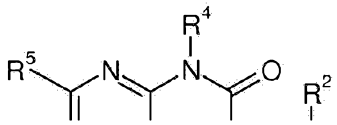
[0026] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, and commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfuric, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfuric and benzenesulfonic acids. Other acids, such as oxalic acid, while not themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds and their pharmaceutically acceptable acid addition salts. Further pharmaceutically acceptable salts can be formed with cations from metals like aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and the like (also see Pharmaceutical salts, Birge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19).

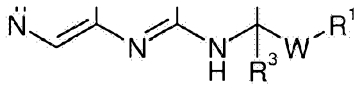
[0027] The pharmaceutically acceptable salts of the present invention can be synthesised from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base form of these compounds with a sufficient amount of the appropriate base or acid in water or in an organic diluent like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, or a mixture thereof.

[0028] By a therapeutically effective amount for the purposes of this invention is meant a quantity of substance that is capable of obviating symptoms of illness or alleviating these symptoms, or which prolong the survival of a treated patient.

Embodiments of the Invention

[0029] A general embodiment of the invention is directed to a compound of formula (I) below:





(I)

wherein:

R^1 is:

-CN;

$-S(O)_nR^6$;

$-S(O)_nNR^7R^8$;

$-S(O)(NR^9)R^6$,

$-N(R^9)C(O)R^6$;

$-N(R^9)C(O)OR^6$;

$-N(R^9)S(O)_nR^6$;

$-C(O)OR^9$;

$-C(O)NR^7R^8$; or

$-C(O)R^9$; or

R^6, R^7, R^8 or R^9 of R^1 may be cyclized onto W to form a ring; and

R^2 and R^3 are each independently:

1. (A) -H;
2. (B) C_{1-3} alkyl optionally substituted with one, two or three groups selected from:
    1. a) C_{3-6} cycloalkyl;
    2. b) $-OR^9$;
    3. c) -CN;
    4. d) $-CF_3$;
    5. e) -halo;
    6. f) $-C(O)OR^9$;
    7. g) $-C(O)N(R^9)_2$;
    8. h) $-S(O)_nR^9$; and
    9. i) $-S(O)_nNR^7R^8$; or

3. (C) C_{3-6} cycloalkyl;
4. (D) C_{3-6} heterocyclyl; or

R^2 and R^3 are taken together with the carbon to which they are attached to form a C_{3-6} carbocyclic ring; or

R^2 and R^3 are taken together with the carbon to which they are attached to form a C_{3-6} heterocyclic ring; or

R^2 or R^3 may be cyclized onto W to form a ring;

R^4 is:

1. (A) C_{1-6} alkyl optionally substituted with one, two or three groups selected from:
    1. a) C_{3-6} cycloalkyl;
    2. b) C_{3-6} heterocyclyl;
    3. c) $-OR^9$;
    4. d) -CN;
    5. e) $-S(O)_nR^9$;
    6. f) -halo; and
    7. g) $-CF_3$; or
2. (B) C_{3-12} cycloalkyl optionally substituted with one, two or three groups selected from:
    1. a) C_{1-6} alkyl;
    2. b) $-OR^9$;
    3. c) -CN;
    4. d) $-S(O)_nR^9$;
    5. e) -halo; and
    6. f) $-CF_3$; or
3. (C) aryl, heteroaryl or heterocyclyl each optionally substituted with one, two or three groups selected from:
    1. a) C_{1-6} alkyl;
    2. b) C_{3-6}cycloalkyl;
    3. c) $-OR^9$;
    4. d) -CN;
    5. e) $-S(O)_nR^9$;
    6. f) -halo; and
    7. g) $-CF_3$;

R^5 is aryl, heteroaryl, heterocyclyl or C_{3-12} cycloalkyl each optionally substituted with one, two or three groups selected from:

1. (A) C_{1-6} alkyl, C_{3-6} cycloalkyl or C_{3-6} heterocyclyl each optionally substituted with one, two or three groups selected from:
    1. a) C_{3-6} cycloalkyl;
    2. b) C_{3-6} heterocyclyl;
    3. c) $-OR^9$;
    4. d) -CN;
    5. e) $-S(O)_nNR^7R^8$
    6. f) $-S(O)_nR^9$;
    7. g) -halo; and
    8. h) $-CF_3$; or
2. (B) $-OR^9$;
3. (C) -CN;
4. (D) $-CF_3$;
5. (E) -halo;
6. (F) $-S(O)_nNR^7R^8$;
7. (G) $-S(O)_nR^9$; and
8. (H) $-NR^7R^8$;

W is aryl, heteroaryl, heterocyclyl, C_{3-12} cycloalkyl, or alkynyl each optionally substituted with one or two groups selected from:

1. a) C_{1-6} alkyl;
2. b) C_{3-6} cycloalkyl;
3. c) $-OR^9$;
4. d) -CN;
5. e) $-CF_3$;
6. f) -halo;
7. g) $-NR^7R^8$;
8. h) $-C(O)OR^9$; and
9. i) $-C(O)N(R^9)_2$;

R^6 is selected from:

1. (A) -OH;
2. (B) C_{1-6} alkyl optionally substituted with one or two groups selected from:
    1. a) C_{3-6}cycloalkyl;
    2. b) $-OR^9$;
    3. c) -CN;
    4. d) $-CF_3$; and
    5. e) -halo;

3. (C) C_{3-6} cycloalkyl; and
4. (D) $-CF_3$;

R^7 and R^8 are independently selected from:

1. (A) -H;
2. (B) C_{1-3} alkyl optionally substituted with one or two groups selected from:
    1. a) C_{3-6}cycloalkyl;
    2. b) $-OR^9$;
    3. c) -CN;
    4. d) -halo; and
3. (C) C_{3-6}cycloalkyl; or

R^7 and R^8, together with the nitrogen to which they are bonded, form a saturated ring with 3-6 carbon atoms wherein one carbon atom in said saturated ring may be optionally replaced by -O-, $-NR^9-$ or $-S(O)_n-$;

R^9 is selected from;

1. (A) -H;
2. (B) C_{1-3} alkyl optionally substituted with one or two groups selected from:

    a) C_{3-6}cycloalkyl;

    c) -CN;

    d) $-CF_3$; and

    e) -halo; or

3. (C) C_{3-6}cycloalkyl; and

n is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

[0030] Additional sub-embodiments within the various substituent definitions include the following:

R^1 Group Embodiments

1. (1) R^1 is:

    -CN,

    $-S(O)_nR^6$,

$-S(O)_nNR^7R^8$;

$-N(H)S(O)_nR^6$; or

$-S(O)(NH)R^6$; and

wherein:

R^6 is:

1. (A) C_{1-3} alkyl optionally substituted with one or two groups selected from:
    1. a) C_{3-6}cycloalkyl;
    2. b) $-OR^9$; and
    3. c) -CN; or
2. (B) C_{3-6}cycloalkyl;

R^7 and R^8 are each independently:

1. (A) -H; or
2. (B) C_{1-3} alkyl; and

R^9 is selected from;

(A) -H;

(B) C_{1-3} alkyl; or

(C) C_{3-6}cycloalkyl; and

n is 1 or 2.

2. (2) R^1 is:

$-S(O)_nR^6$,

$-S(O)_nNR^7R^8$, or

- $S(O)(NH)R^6$; and

wherein:

R^6 is:

1. (A) C_{1-3} alkyl optionally substituted with one or two groups selected from:
    1. a) C_{3-6}cycloalkyl;

2. b) -OR^9; and
3. c) -CN; or

2. (B) C_{3-6}cycloalkyl;

R^7 and R^8 are each independently:

1. (A) -H; or
2. (B) C_{1-3} alkyl; and

R^9 is selected from;

1. (A) -H;
2. (B) C_{1-3} alkyl; or
3. (C) C_{3-6}cycloalkyl; and

n is 1 or 2.

3. (3) R^1 is $-S(O)_nR^6$, $-S(O)_nNR^7R^8$ or $-S(O)(NH)R^6$; and

R^6 is C_{1-3} alkyl; and

R^7 and R^8 are each independently:

1. (A) -H; or
2. (B) C_{1-3} alkyl; and

n is 2.

R^2 and R^3 Group Embodiments

1. (1) R^2 and R^3 are each independently selected from:
   1. (A) -H;
   2. (B) C_{1-3} alkyl optionally substituted with one, two or three groups selected from:
      1. a) C_{3-6} cycloalkyl;
      2. b) -OR^9; or
      3. c) -halo; and

   R^2 and R^3 are taken together with the carbon to which they are attached to form a C_{3-6} carbocyclic ring; or

   R^2 and R^3 are taken together with the carbon to which they are attached to form a C_{3-6} heterocyclic ring; and

   R^9 is selected from:
   1. (A) -H; and
   2. (B) C_{1-3} alkyl.

2. (2) R^2 and R^3 are each independently selected from:
    1. (A) -H; and
    2. (B) C_{1-3} alkyl;
3. (3) R^2 and R^3 are H.

R^4 Group Embodiments

1. (1) R^4 is:
    1. (A) C_{1-6} alkyl optionally substituted with one, two or three groups selected from:
        1. a) C_{3-6} cycloalkyl;
        2. b) a 4, 5 or 6-memberedheterocyclyl;
        3. c) $-OR_9$;
        4. d) -CN;
        5. e) -halo; and
        6. f) $-CF_3$; or
    2. (B) C_{3-6} cycloalkyl optionally substituted with one, two or three groups selected from:
        1. a) C_{1-6} alkyl;
        2. b) $-OR^9$;
        3. c) -CN;
        4. d) -halo; and
        5. e) $-CF_3$; and

        wherein one carbon in said C_{3-6} cycloalkyl may be optionally replaced by -O-;
    3. (C) Phenyl; or
    4. (D) a 4, 5 or 6-membered heterocyclyl;

    R^9 is selected from:
    1. (A) -H; and
    2. (B) C_{1-3} alkyl.
2. (2) R^4 is:
    1. (A) C_{1-6} alkyl optionally substituted with one or two groups selected from:
        1. a) C_{3-6}cycloalkyl;
        2. b) a 4, 5, or 6-membered heterocyclyl;
        3. c) $-OR^9$;
        4. d) -CN;
        5. e) -halo; and
        6. f) $-CF_3$; or
    2. (B) C_{3-6} cycloalkyl optionally substituted with one, two or three groups selected from:
        1. a) C_{1-6} alkyl;
        2. b) $-OR^9$;
        3. c) -CN;

4. d) -halo; and
5. e) $-CF_3$; or

3. (C) Phenyl; or
4. (D) a 5 or 6-membered heterocyclyl; and

R^9 is C_{1-3} alkyl.

3. (3) R^4 is:
   1. (A) C_{1-6} alkyl optionally substituted with one or two groups selected from C_{3-6}cycloalkyl, halo, $-CF_3$, and C_{1-3} alkoxy; or
   2. (B) C_{3-6} cycloalkyl optionally substituted with one or two groups selected from C_{1-6} alkyl, $-CF_3$, and halo; or
   3. (C) a 5-membered heterocyclyl.

R^5 Group Embodiments

1. (1) R^5 is aryl, heteroaryl or heterocyclyl, each optionally substituted with one, two or three groups selected from:
   1. a) C_{1-6} alkyl;
   2. b) C_{3-6}cycloalkyl;
   3. c) $-OR^9$;
   4. d) -CN;
   5. e) $-CF_3$;
   6. f) -halo; and
   7. g) $-NR^7R^8$; and

   R^7, R^8 and R^9 are each independently selected from:
   1. (A) -H; and
   2. (B) C_{1-3} alkyl.

2. (2) R^5 is:
   1. (A) phenyl optionally substituted with one, two or three groups selected from:
      1. a) C_{1-6} alkyl;
      2. b) C_{3-6}cycloalkyl;
      3. c) $-OR^9$;
      4. d) -CN;
      5. e) $-CF_3$; and
      6. f) -halo; or
   2. (B) a 5 or 6-membered heteroaryl optionally substituted with one, two or three groups selected from:
      1. a) C_{1-6} alkyl;
      2. b) C_{3-6} cycloalkyl;
      3. c) $-OR^9$;
      4. d) -CN;

5. e) -CF_3;
6. f) -halo; and
7. g) -NR^7R^8; and

R^7, R^8 and R^9 are each independently selected from:

1. (A) -H; and
2. (B) C_{1-3} alkyl.

3. (3) R^5 is pyridinyl or pyrimidinyl each optionally substituted with one, two or three groups selected from:
    1. a) C_{1-6} alkyl;
    2. b) C_{3-6}cycloalkyl;
    3. c) -OR^9;
    4. d) -CF_3; and
    5. e) -NR^7R^8; and

    R^7 and R^8 are each independently selected from:
    1. (A) -H;
    2. (B) C_{1-3} alkyl; and

    R^9 is C_{1-3} alkyl.
4. (4) R^5 is pyrimidinyl optionally substituted with one or two groups selected from:
    1. a) C_{1-3} alkyl;
    2. b) C_{3-5} cycloalkyl;
    3. c) C_{1-3} alkoxy; and
    4. d) -CF_3.

W Group Embodiments

1. (1) W is phenyl, pyridinyl, pyrimidinyl, piperidinyl, piperizinyl, pyrazinyl or C_{3-12} cycloalkyl, each optionally substituted with one or two groups selected from:
    1. a) C_{1-6} alkyl;
    2. b) C_{3-6}cycloalkyl;
    3. c) -OR^9;
    4. d) -CN;
    5. e) -CF_3;
    6. f) -halo;
    7. g) -NR^7R^8
    8. h) -$C(O)OR^9$; and
    9. i) -$C(O)N(R^9)_2$;

    R^7, R^8 and R^9 are each selected from:
    1. (A) -H; and
    2. (B) C_{1-3} alkyl.

2. (2) W is phenyl, pyridinyl, pyrimidinyl or piperidinyl.

[0031] Additional embodiments include any possible combinations of the above sub-embodiments for R^1, R^2, R^3, R^4, R^5, R^6, and W.

Additional Subgeneric Embodiments of Formula (I)

[0032] Additional subgeneric embodiments of the compounds of formula (I) above include:

1. (1) A compound of formula (I) as described above, or a pharmaceutically acceptable salt thereof, wherein:

   R^1 is:

   $-S(O)nR^6$,

   $-S(O)nNR^7R^8$, or

   $-S(O)(NH)R^6$,

   R^2 and R^3 are each independently selected from:

   1. (A) -H; and
   2. (B) C_{1-3} alkyl;

   R^4 is:

   1. (A) C_{1-6} alkyl optionally substituted with one or two groups selected from:
      1. a) C_{3-6} cycloalkyl;
      2. b) a 4, 5, or 6-membered heterocyclyl;
      3. c) $-OR^9$;
      4. d) -CN;
      5. e) -halo; and
      6. f) $-CF_3$;
   2. (B) C_{3-6} cycloalkyl optionally substituted with one, two or three groups selected from:
      1. a) C_{1-6} alkyl;
      2. b) $-OR_9$;
      3. c) -CN;
      4. d) -halo; and
      5. e) $-CF_3$;

3. (C) Phenyl; or
4. (D) a 5 or 6-membered heterocyclyl;

R^5 is:

1. (A) phenyl optionally substituted with one or two groups selected from:
    1. a) C_{1-6} alkyl;
    2. b) C_{3-6} cycloalkyl;
    3. c) $-OR^9$;
    4. d) -CN;
    5. e) $-CF_3$; and
    6. f) -halo; or
2. (B) Pyridinyl or pyrimidinyl each optionally substituted with one, two or three groups selected from:
    1. a) C_{1-6} alkyl;
    2. b) C_{3-6}cycloalkyl;
    3. c) $-OR^9$;
    4. d) -CN;
    5. e) $-CF_3$;
    6. f) -halo; and
    7. g) $-NR^7R^8$; and

W is phenyl, pyridinyl, pyrimidinyl, piperidinyl or C_{3-12} cycloalkyl, each optionally substituted with one or two groups selected from:

1. a) C_{1-6} alkyl;
2. b) C_{3-6} cycloalkyl;
3. c) $-OR^9$;
4. d) -CN;
5. e) $-CF_3$;
6. f) -halo;
7. g) $-NR^7R^8$
8. h) $-C(O)OR^9$; and
9. i) $-C(O)N(R^9)_2$;

R^6 is:

1. (A) C_{1-3} alkyl optionally substituted with one or two groups selected from:

    a) C_{3-6} cycloalkyl;

    b) $-OR^9$ and

b) -CN; or

2. (B) C_{3-6}cycloalkyl;

R^7, R^8 and R^9 are each independently:

1. (A) -H; or
2. (B) C_{1-3} alkyl; and

n is 2.

2. (2) A compound of formula (I) as described above, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is $-S(O)_nR^6$ or $-S(O)_nNR^7R^8$; and

R^2 and R^3 are H;

R^4 is:

1. (A) C_{1-6} alkyl optionally substituted with one or two groups selected from C_{3-6} cycloalkyl, $-CF_3$, and C_{1-3} alkoxy; or
2. (B) C_{3-6} cycloalkyl optionally substituted with one or two groups selected from C_{1-6} alkyl, -CN, and halo; or
3. (C) 5-membered heterocyclyl;

R^5 is pyrimidinyl optionally substituted with one, two or three groups selected from:

1. a) C_{1-6} alkyl;
2. b) C_{3-6} cycloalkyl;
3. c) $-OR^9$;
4. d) $-CF_3$; and
5. e) $-NR^7R^8$;

W is phenyl, pyridinyl, pyrimidinyl or piperidinyl;

R^6 is C_{1-3} alkyl;

R^7, R^8 R^9 are each independently:

1. (A) -H; or
2. (B) C_{1-3} alkyl; and

n is 2.

3. (3) A compound of formula (I) as described immediately above in (2), or a

pharmaceutically acceptable salt thereof, wherein:

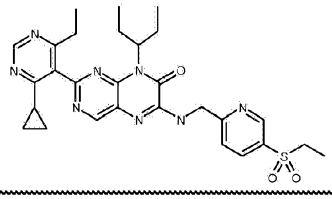
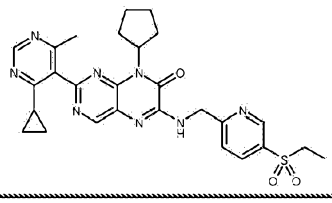
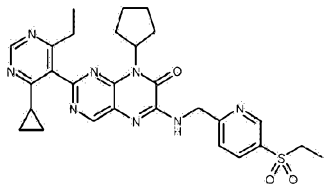
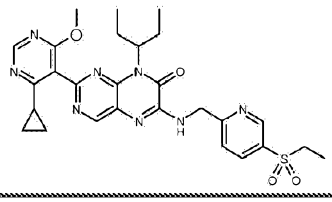
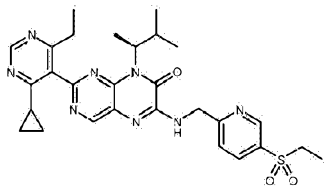
R^5 is pyrimidinyl optionally substituted with one or two groups selected from:

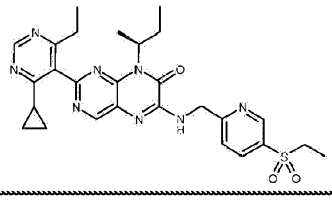
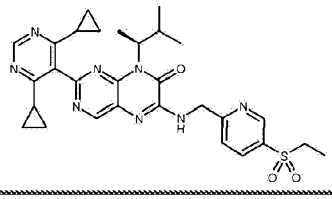
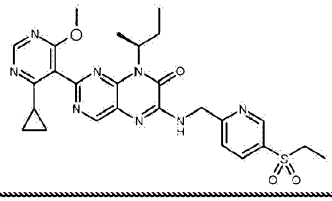
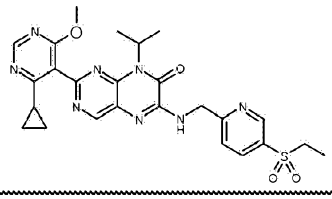
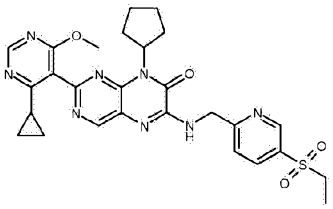
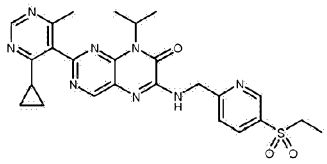
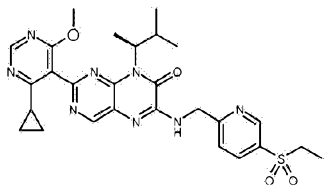
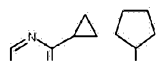
1. a) C_{1-3} alkyl;
2. b) C_{3-5} cycloalkyl; and
3. c) C_{1-3} alkoxy; and

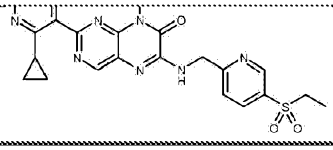
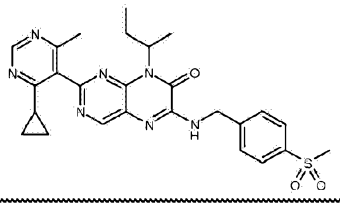
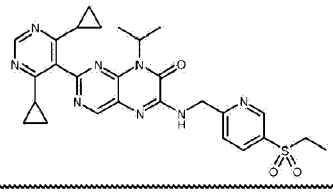
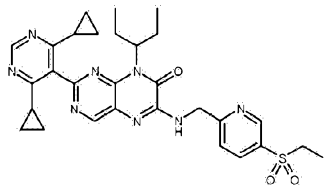
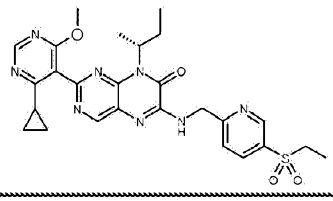
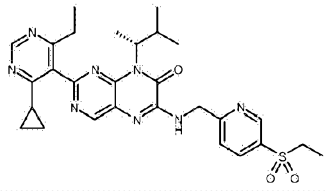
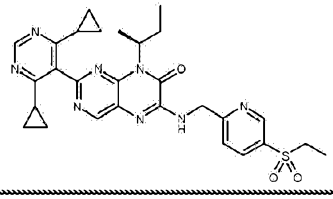
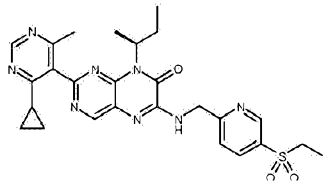
W is phenyl, pyridinyl, pyrimidinyl or piperidinyl.

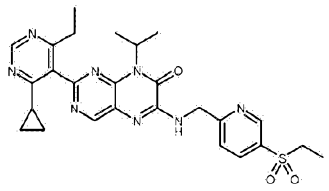
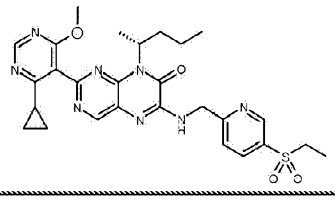
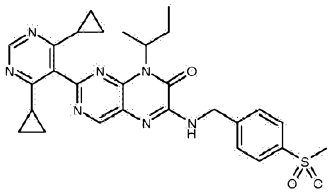
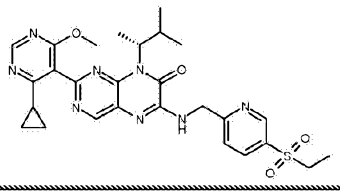
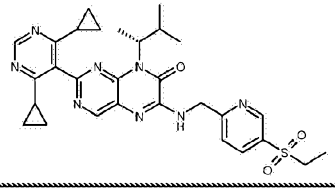
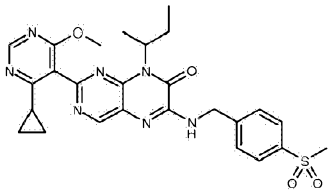
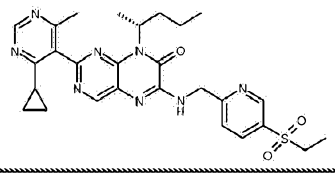
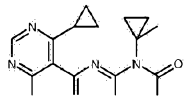
[0033] Specific compounds falling within the instant invention include the compounds in the following Table I, or their pharmaceutically acceptable salts:

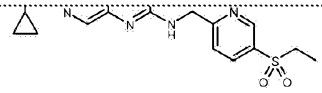
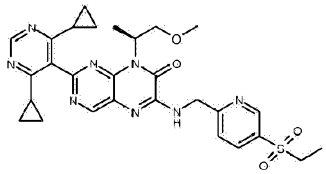
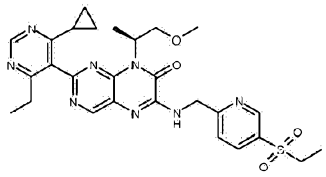
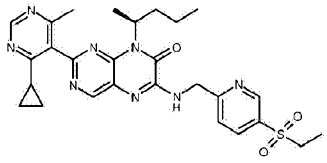
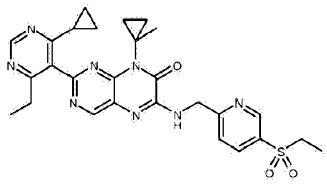
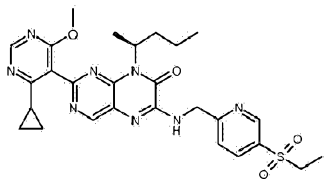
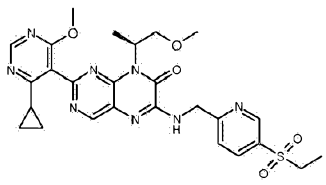
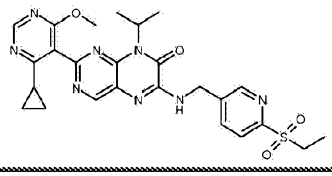
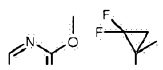
Table 1

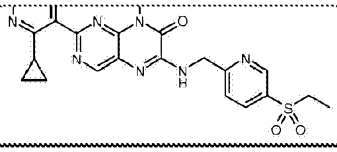
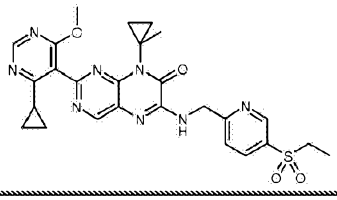
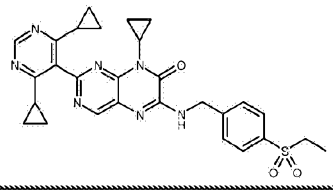
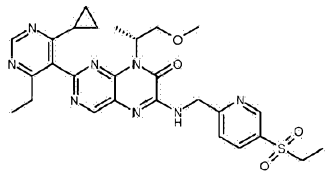
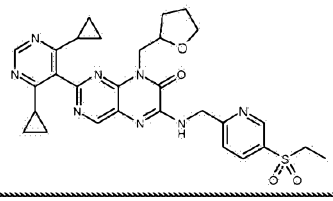
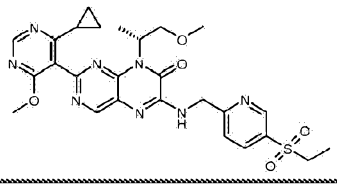
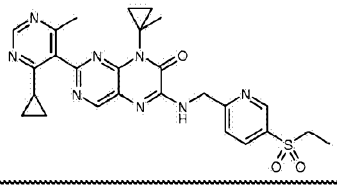
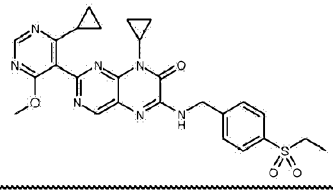
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
1		1.09	563.7		A
2		0.98	547.4		A
3		1.05	561.4		A
4		1.08	565.5		A
5		1.08	563.4		A

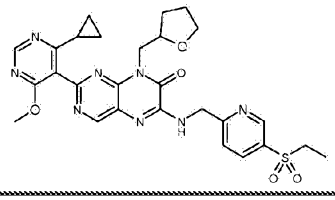
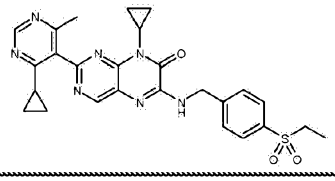
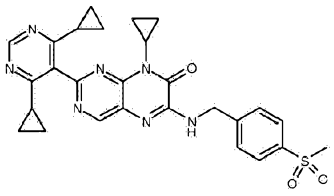
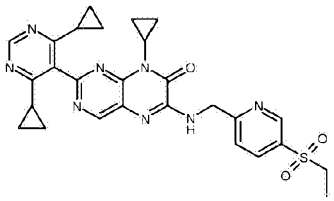
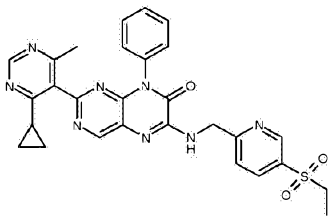
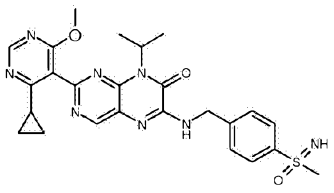
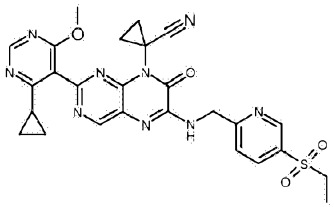
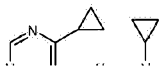
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
6		1.05	549.3		A
7		1.14	575.4		A
8		1.01	551.4		A
9		1.03	537.2		A
10		1.04	563.4		A
11		0.91	521.4		A
12		1.07	565.4		A
					

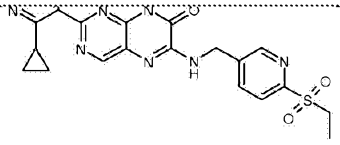
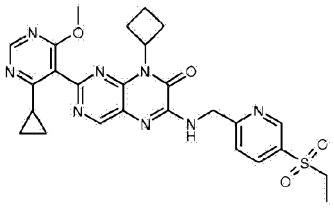
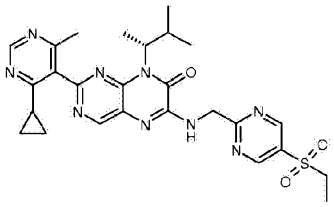
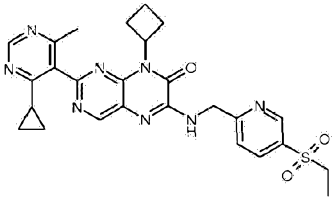
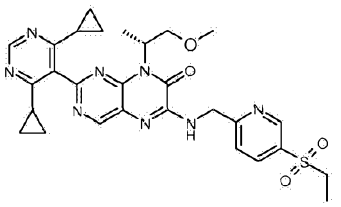
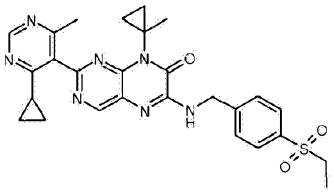
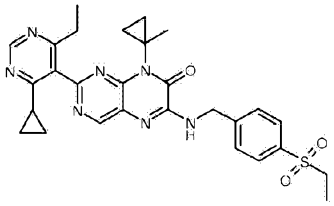
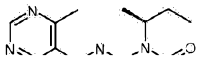
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
13		1.11	573.4		A
14		1.01	520.3		A
15		1.02	547.4		A
16		1.15	575.4		A
17		1.01	551.4		A
18		1.07	563.4		A
19		1.12	561.3		A
20		0.99	535.2		A

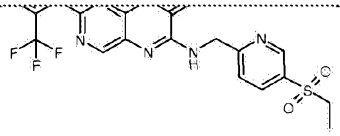
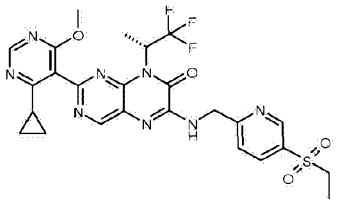
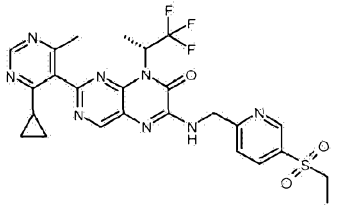
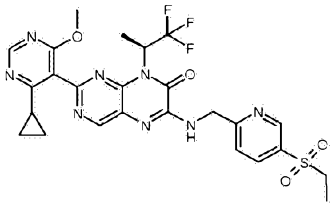
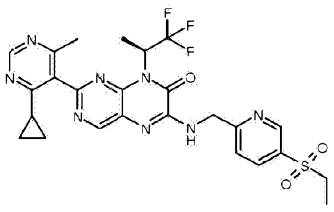
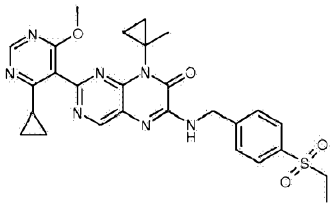
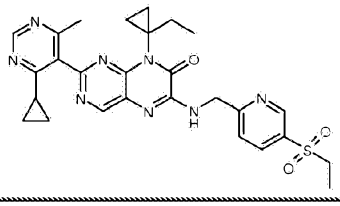
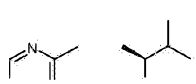
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
21		0.97	535.4		A
22		1.09	565.3	563.3	A
23		1.14	547.4		A
24		1.07	565.4		A
25		1.14	575.4		A
26		1.03	536.2		A
27		1.03	549.2	547.1	A
28		2.06	559.4	557.4	B

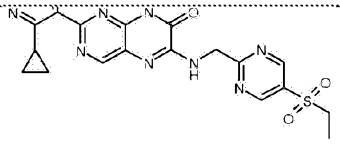
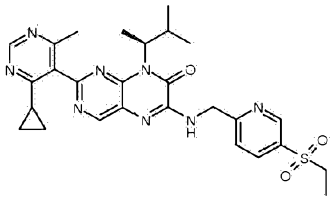
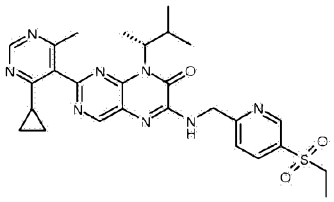
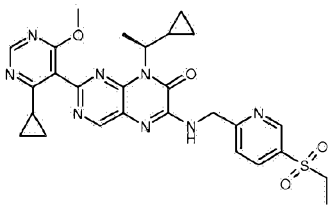
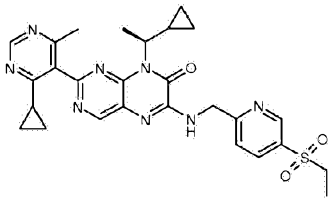
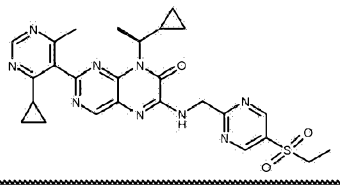
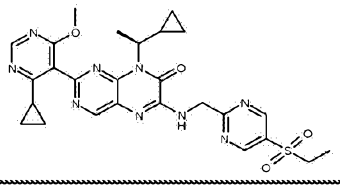
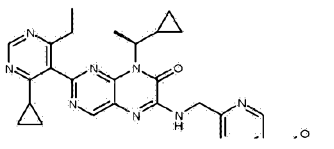
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
					
29		0.97	577.4		A
30		0.91	565.4		A
31		1.03	549.2	547.0	A
32		1.89	547.4	545.4	B
33		1.09	565.3	563.3	A
34		0.90	567.4		A
35		1.05	537.2		A
					

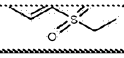
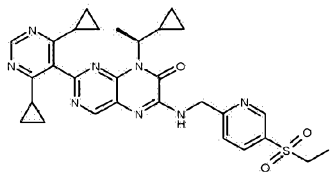
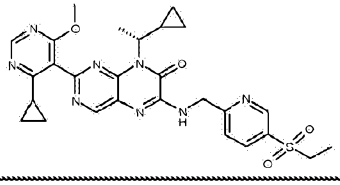
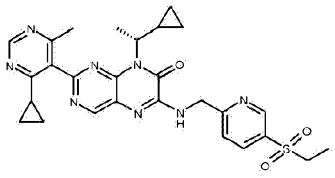
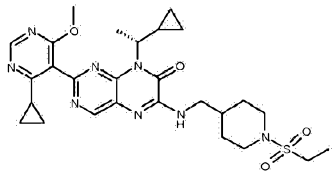
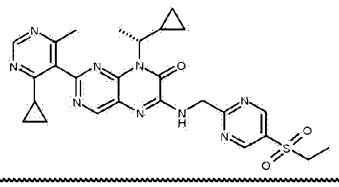
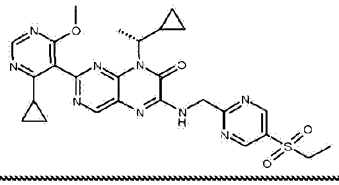
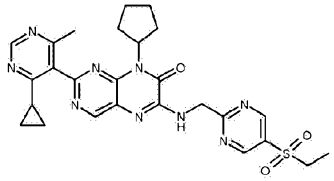
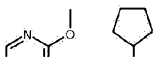
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
36		0.93	585.3	583.3	A
37		1.85	549.4	547.4	B
38		2.06	544.4	542.4	B
39		0.91	565.4		A
40		0.94	589.4		A
41		0.90	567.4		A
42		2.08	559.4	557.4	B
43		1.81	534.4	532.4	B

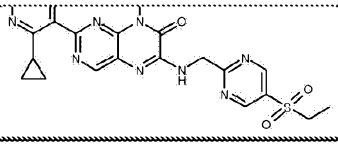
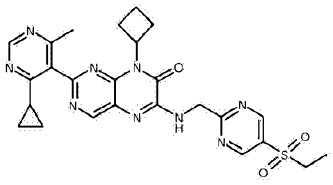
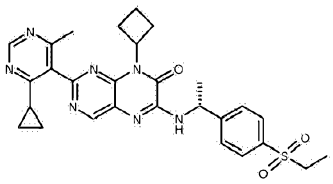
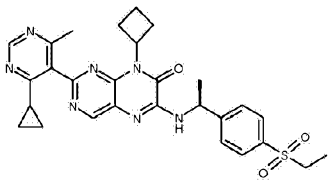
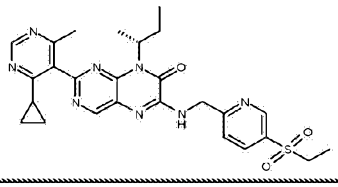
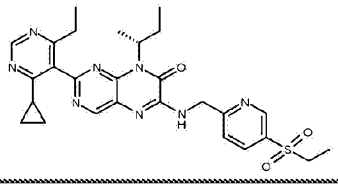
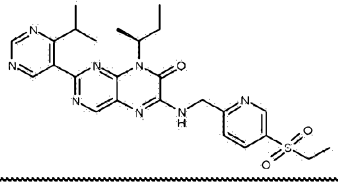
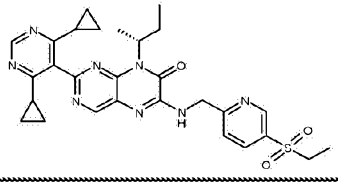
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
44		0.86	579.4		A
45		1.67	518.4	516.4	B
46		1.89	530.4	528.4	B
47		0.85	545.1	543.2	A
48		0.99	555.3		A
49		0.94	521.1		A
50		0.82	560.3	558.4	A
					

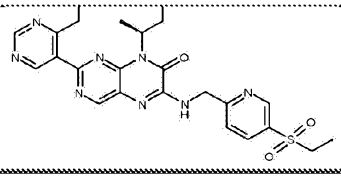
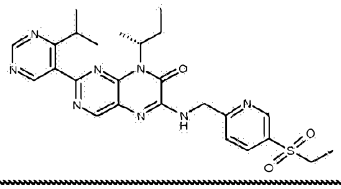
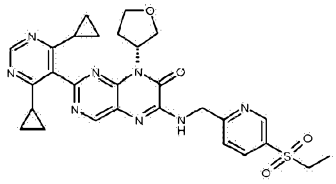
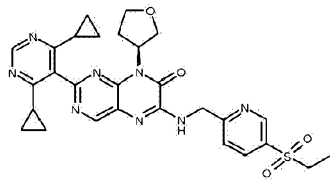
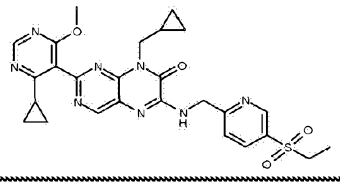
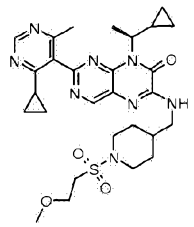
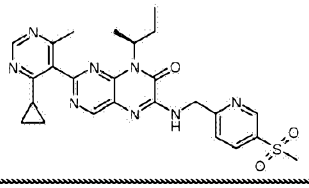
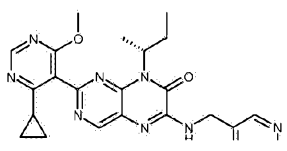
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
51		0.85	544.7	543.1	A
52		1.01	548.8		A
53		1.01	549.9		A
54		0.94	532.8		A
55		0.97	577.4		A
56		1.96	532.1	530.1	B
57		2.17	546.1	544.1	B
					

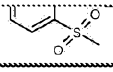
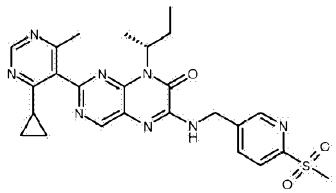
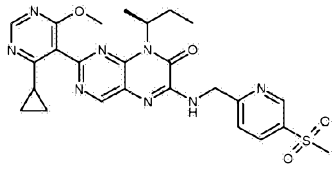
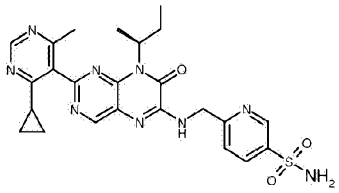
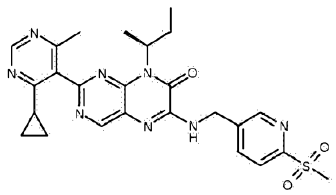
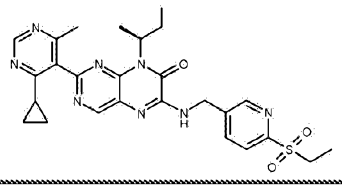
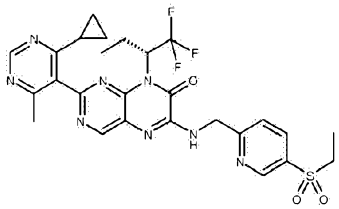
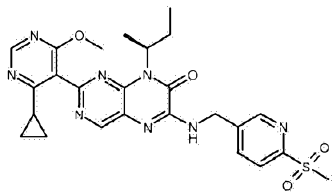
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
58		1.03	563.1		A
59		1.01	591.1	589	A
60		0.95	575.2	573	A
61		1.02	591.2	589	A
62		0.96	575.1	573	A
63		2.13	548.0	546.0	B
64		1.97	546.8	545.1	B
					

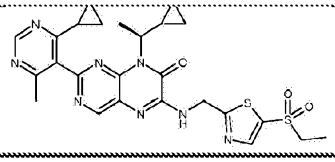
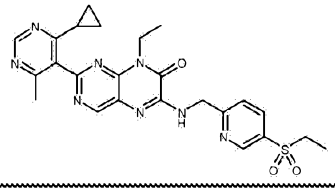
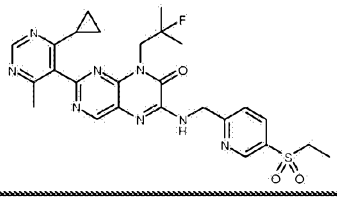
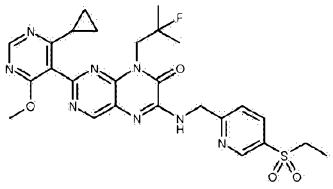
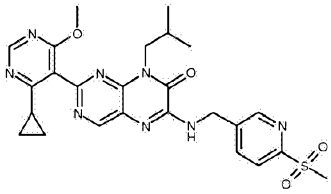
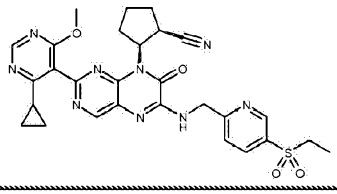
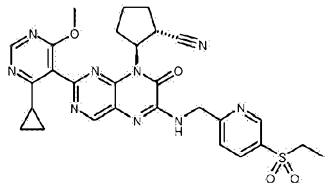
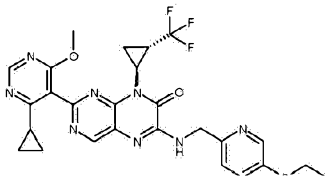
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
65		1.01	550.0		A
66		1.02	548.9		A
67		1.02	548.9		A
68		1.04	563.0		A
69		0.98	547.3		A
70		0.98	548.0		A
71		1.04	564.0		A
72		1.05	560.8		A

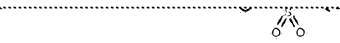
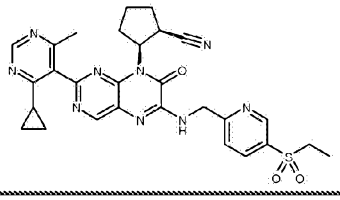
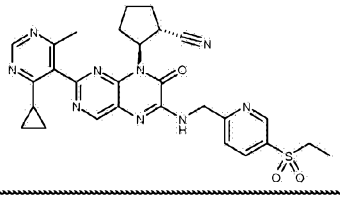
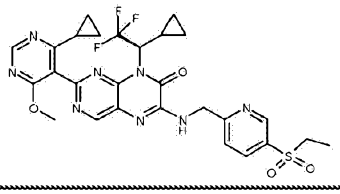
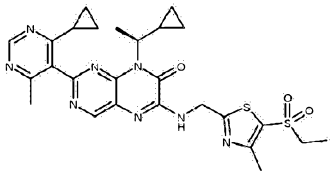
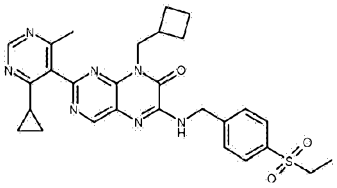
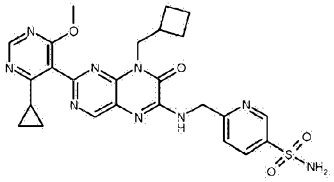
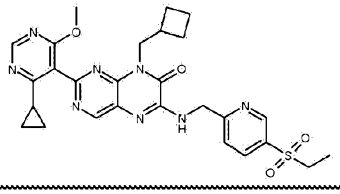
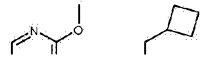
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
					
73		1.05	573.0		A
74		1.05	563.0		A
75		0.98	546.7		A
76		1.11	568.8		A
77		0.97	547.7		A
78		1.04	563.8		A
79		0.99	547.7		A
					

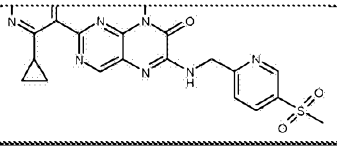
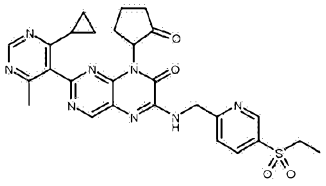
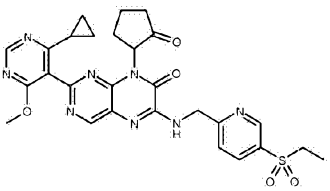
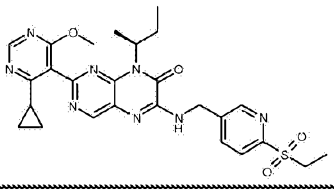
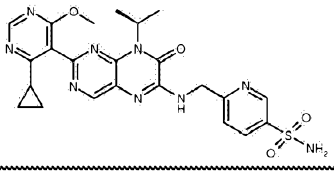
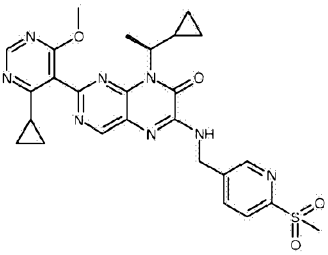
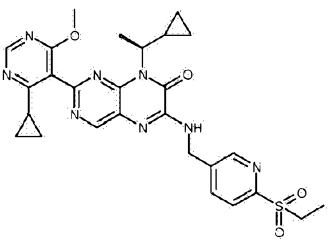
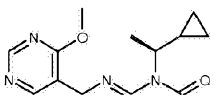
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
80		1.05	563.7		A
81		0.94	533.8		A
82		1.07	545.8		A
83		1.07	545.9		A
84		0.97	535.2		A
85		1.04	549.2		A
86		1.05	523.2		A
87		1.11	561.2		A

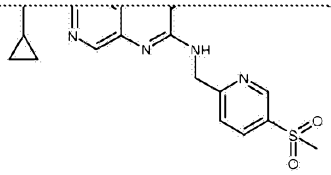
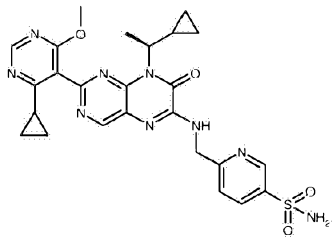
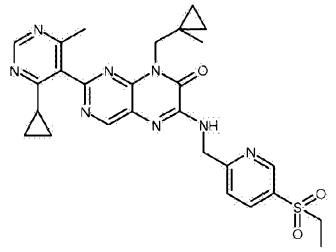
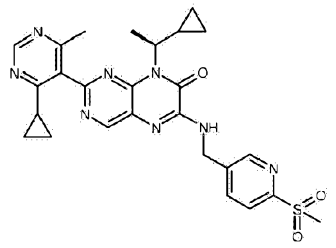
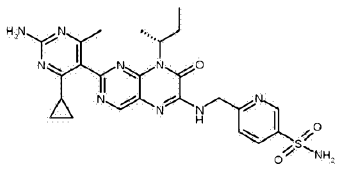
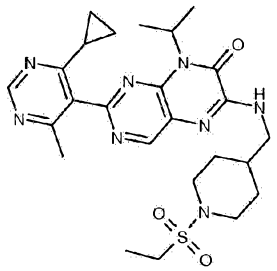
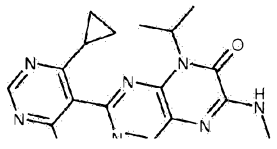
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
88		0.94	509.2		A
89		1.04	523.2		A
90		0.89	575.2		A
91		0.89	575.2		A
92		0.98	549.0		A
93		1.03	584.0		A
94		0.89	521.5		A
95		0.95	537.3		A

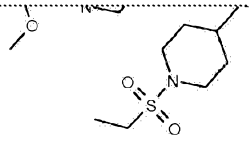
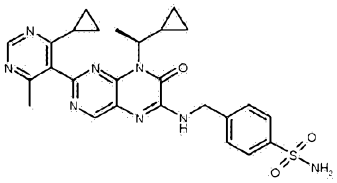
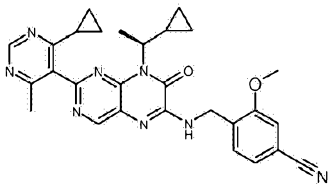
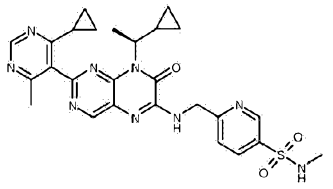
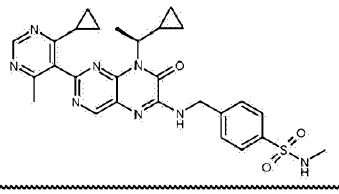
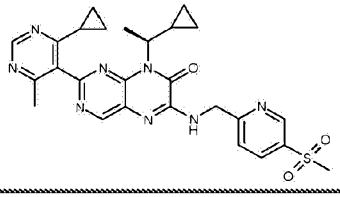
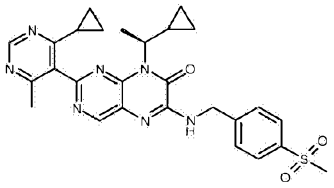
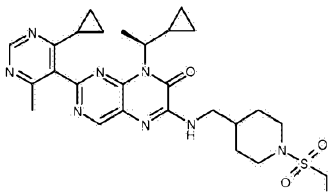
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
					
96		0.89	521.5		A
97		0.95	537.5		A
98		0.83	522.5		A
99		0.89	521.5		A
100		0.93	535.5		A
101		0.98	589.4		A
102		0.95	537.5		A

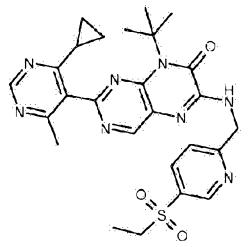
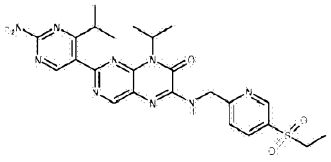
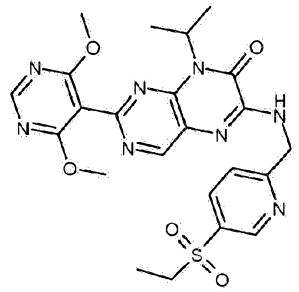
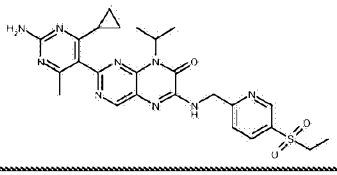
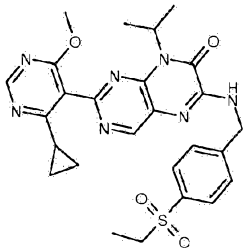
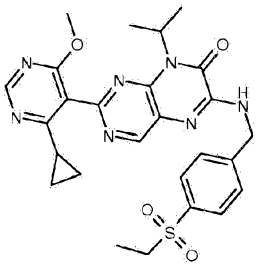
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
103		2.18	553.3		B
104		1.67	507.0		B
105		1.80	553.5		B
106		1.99	569.5		B
107		0.94	537.5		A
108		0.87	588.1		A
109		0.91	588.0		A
110		0.88	603.1		A

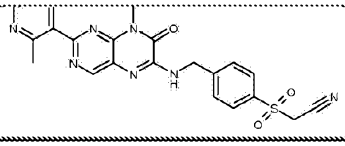
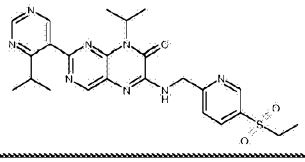
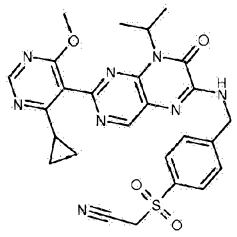
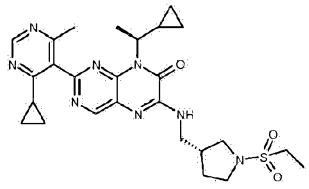
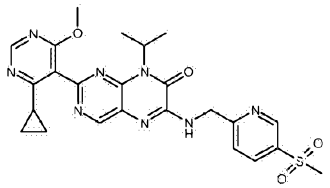
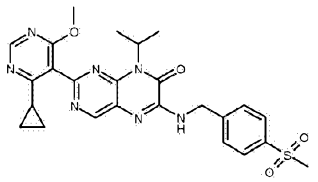
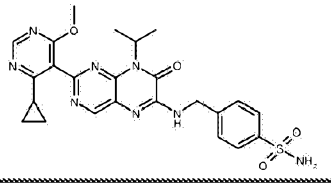
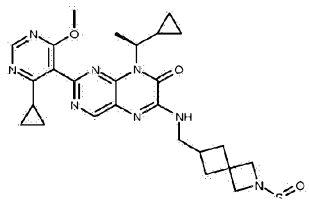
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
					
111		0.81	572.5		A
112		0.81	572.5		A
113		1.05	617.5		A
114		2.28	567.5		B
115		1.02	546.5		A
116		0.92	550.5		A
117		1.12	563.4		A
					

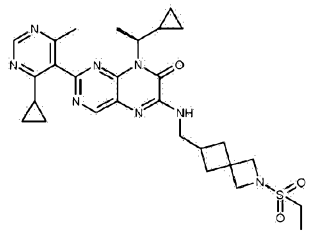
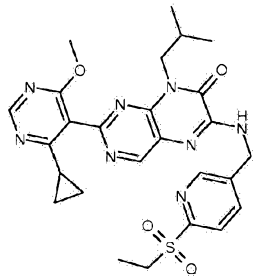
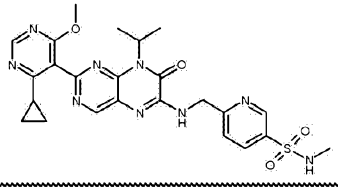
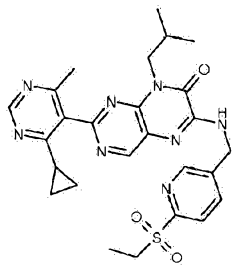
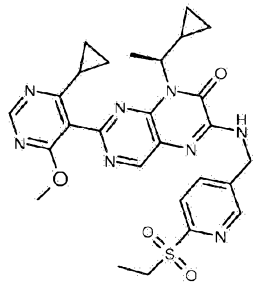
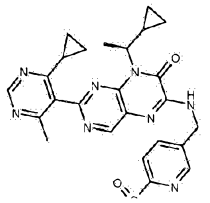
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
118		0.98	549.5		A
119		0.78	561.3		A
120		0.83	577.3		A
121		2.27	551.5		B
122		0.89	538.4		A
123		0.99	549.0		A
124		1.03	563.2		A
					

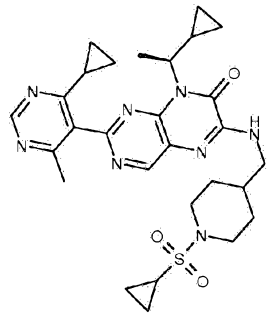
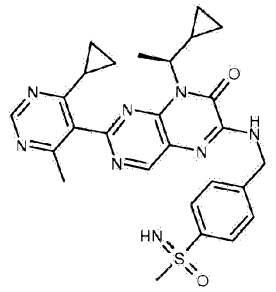
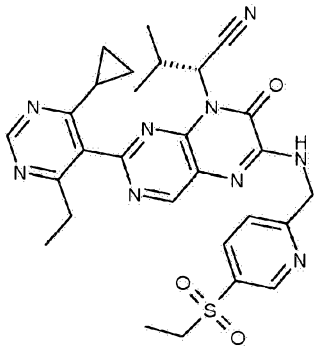
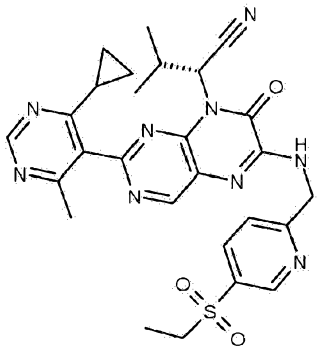
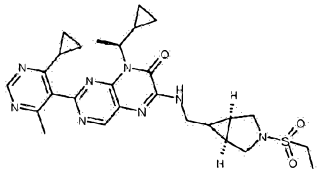
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
125		0.99	549.2		A
126		0.93	550.2		A
127		0.96	547.5		A
128		0.91	533.4		A
129		0.56	537.1		A
130		0.96	526.8		A
131		1.01	542.7		A

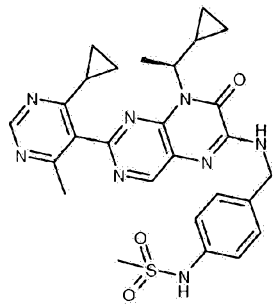
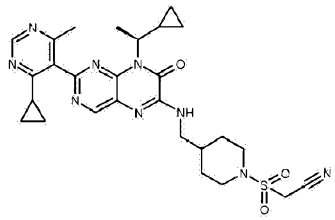
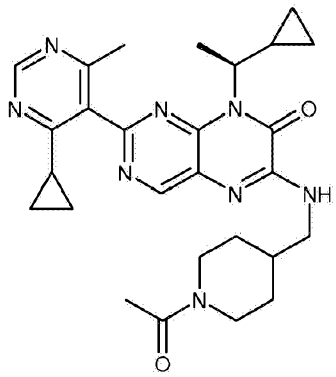
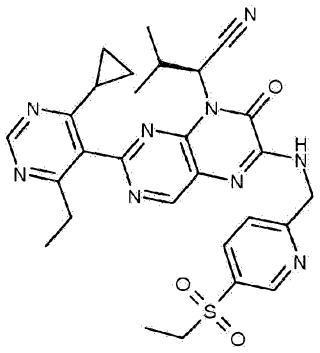
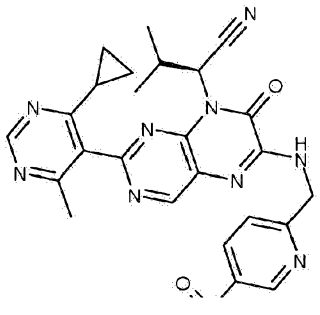
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
					
132		0.90	532.9		A
133		1.16	509.1		A
134		0.94	547.9		A
135		0.99	546.9		A
136		0.92	533.0		A
137		0.98	531.9		A
138		1.04	552.9		A

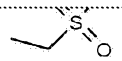
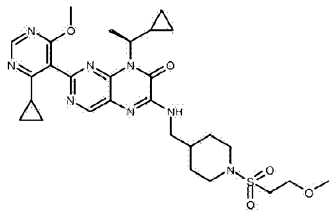
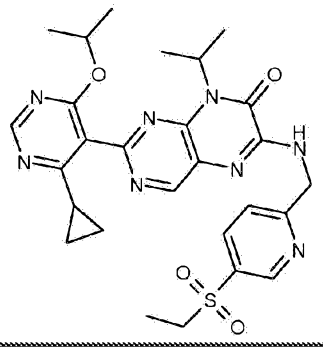
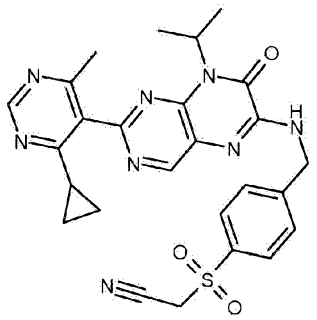
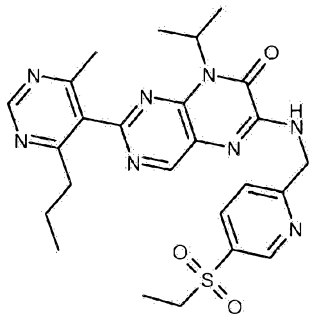
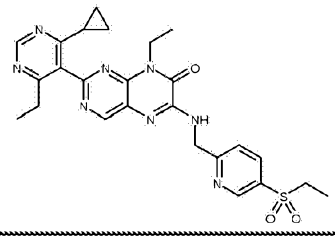
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
139		0.96	534.7		A
140		1.77	524.0		B
141		0.89	527.1		A
142		1.26	536.1		B
143		1.01	535.9		A
144		0.97	520.0		A
					

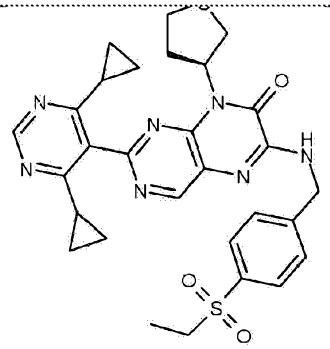
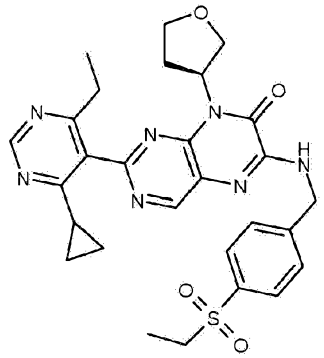
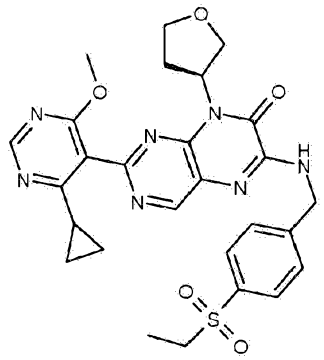
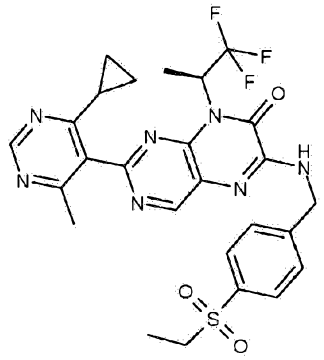
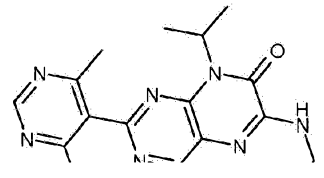
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
145		1.04	557.1		A
146		2.18	509.0		B
147		1.02	546.9		A
148		0.99	540.5		A
149		0.90	522.9		A
150		0.96	522.0		A
151		0.90	522.9		A
152		2.57	580.9		B

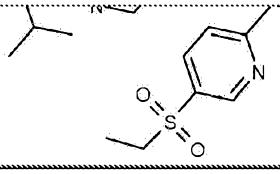
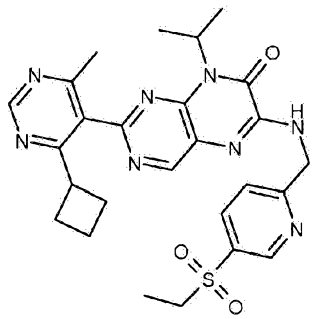
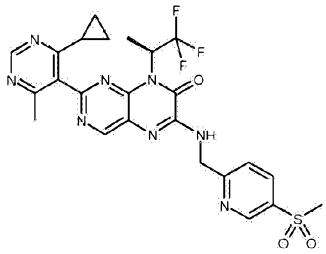
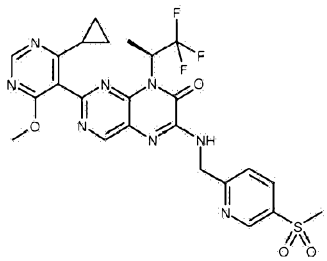
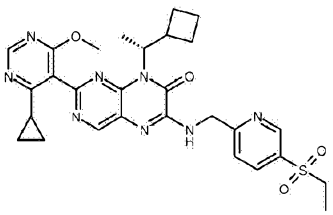
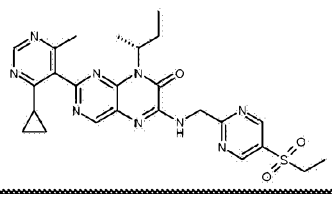
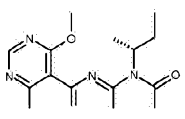
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
					
153		1.07	564.9		A
154		0.98	550.9		A
155		0.90	537.9		A
156		1.00	536.1		A
157		0.95	546.9		A
158		0.98	539.3		A

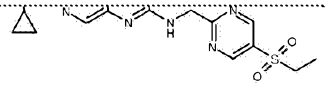
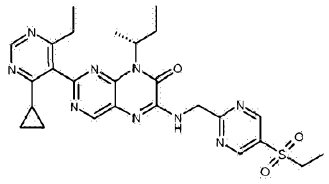
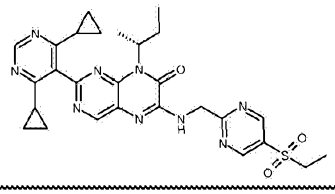
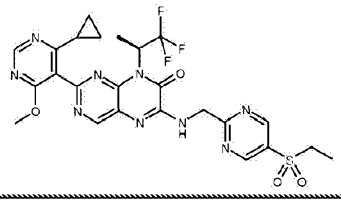
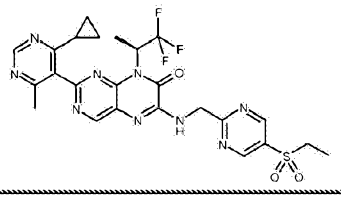
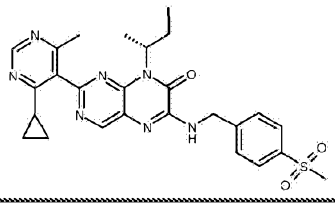
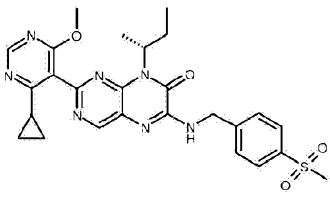
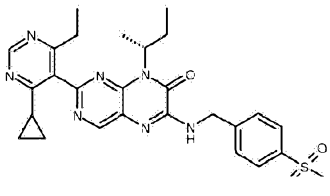
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
					
159		1.05	564.8		A
160		0.84	531.0		A
161		0.96	575.3		A
162		0.89	561.2		A
163		1.01	550.7		A

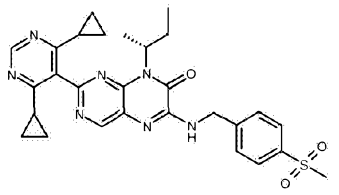
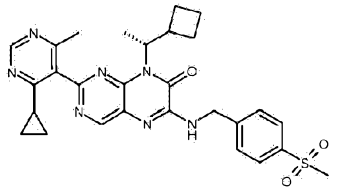
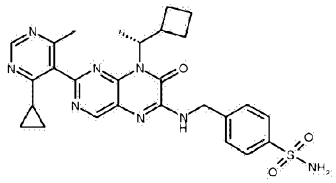
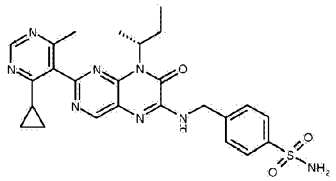
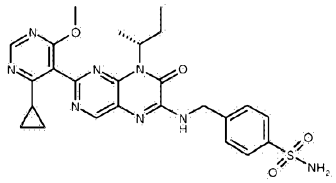
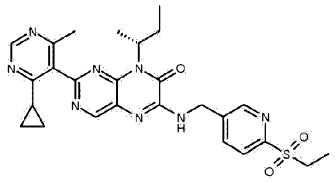
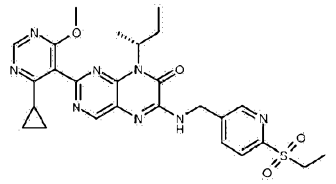
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
164		0.97	547.0		A
165		1.03	563.8		A
166		0.93	504.0		A
167		0.93	574.0		A
168		0.87	559.7		A

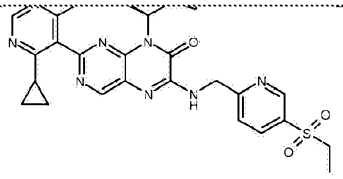
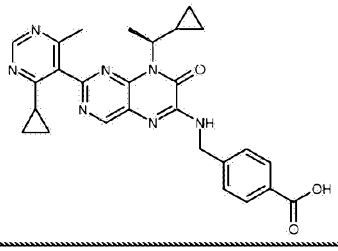
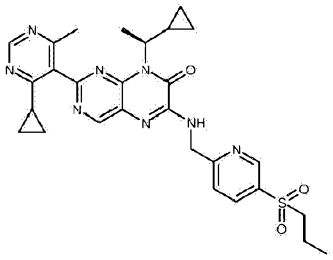
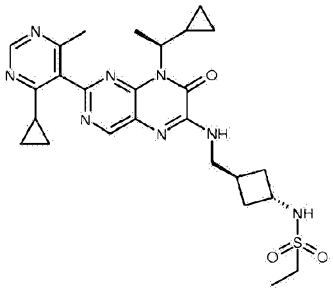
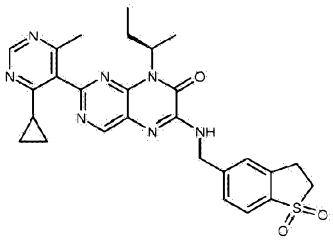
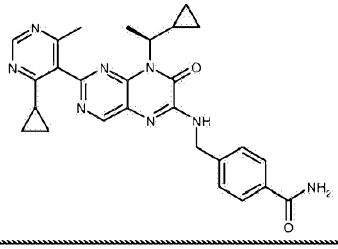
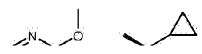
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
					
169		1.09	599.8		A
170		1.10	565.1		A
171		0.97	531.1		A
172		0.91	524		A
173		1.90	520.9		B

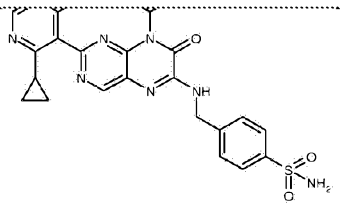
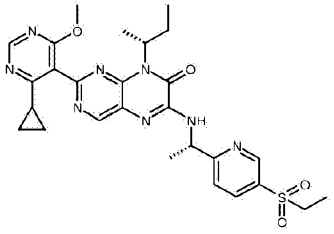
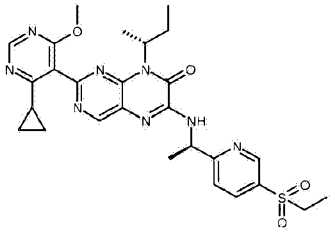
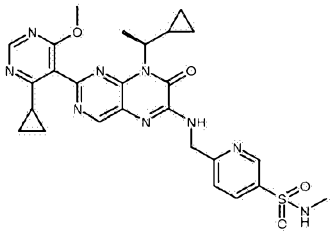
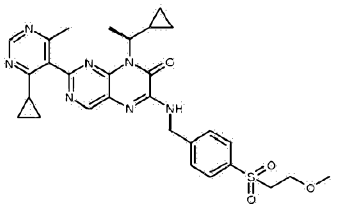
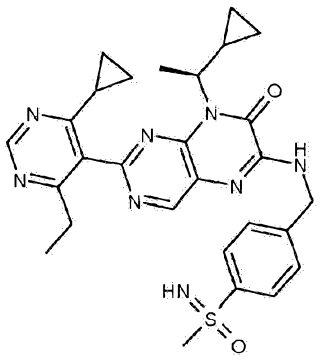
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
174		0.96	574		A
175		0.87	561.9		A
176		0.86	563.9		A
177		1.00	573.0		A
178		0.91	523.0		A

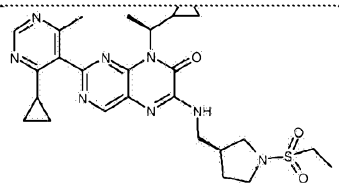
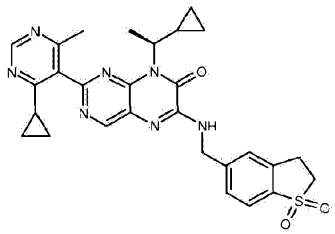
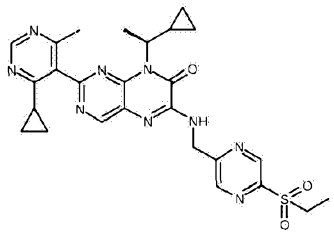
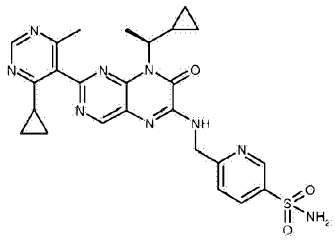
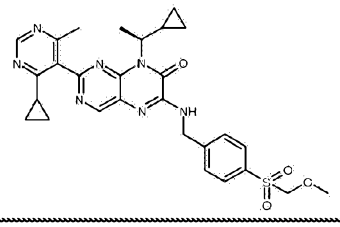
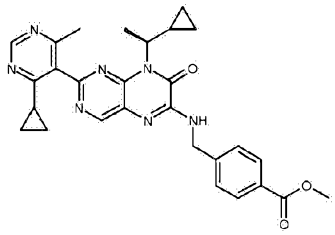
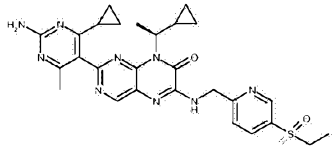
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
					
179		0.96	535.1		A
180		1.90	560.8		B
181		2.16	577.1		B
182		1.11	577.2		A
183		0.95	536.0		A
184		1.01	552.2		A

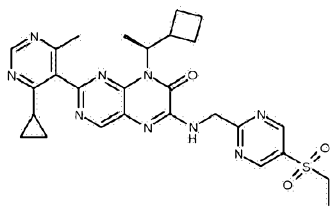
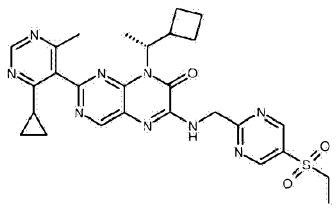
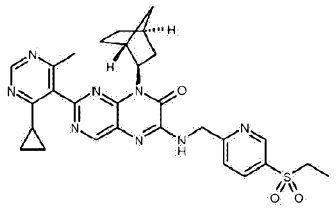
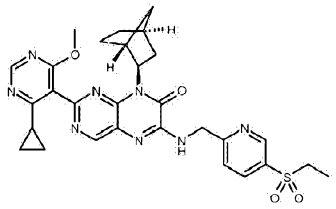
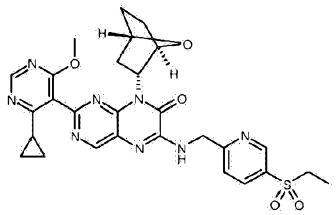
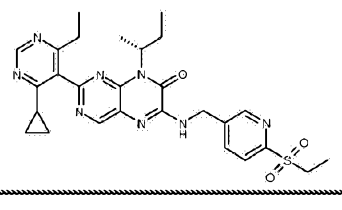
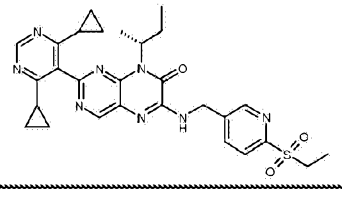
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
					
185		1.08	550.1		A
186		1.08	561.9		A
187		2.28	592.1		B
188		2.08	576.0		B
189		0.95	519.9		A
190		1.02	536.0		A
191		1.00	533.2		A

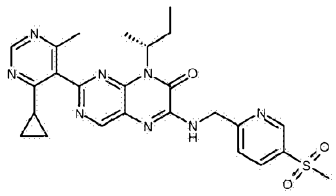
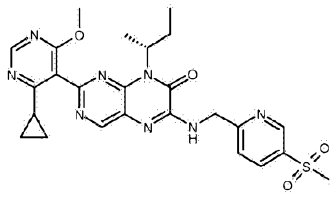
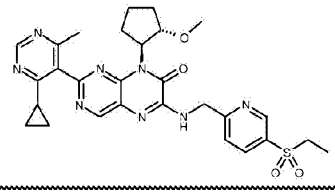
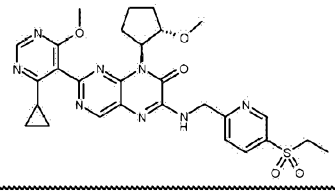
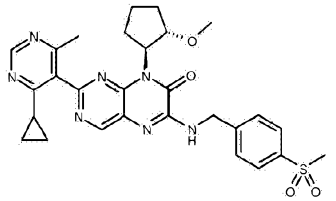
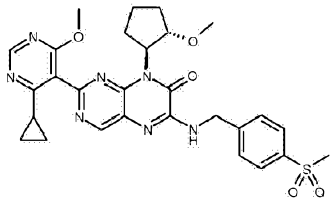
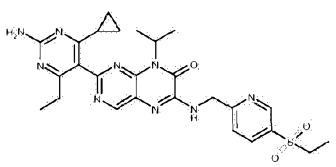
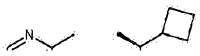
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
192		1.09	545.2		A
193		1.06	546.4		A
194		0.99	547.4		A
195		0.89	521.0		A
196		0.95	537.0		A
197		0.95	535.4		A
198		1.00	551.4		A
					

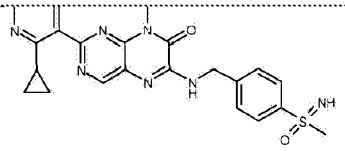
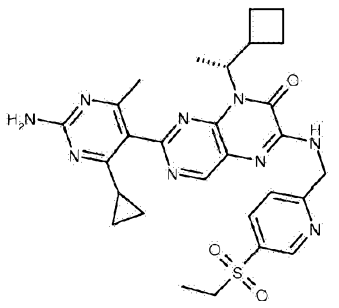
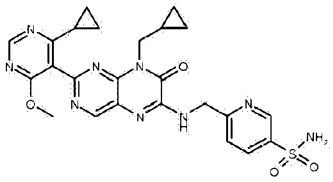
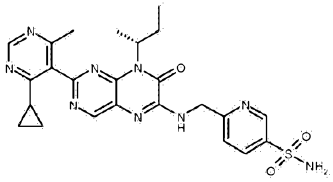
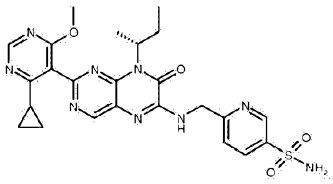
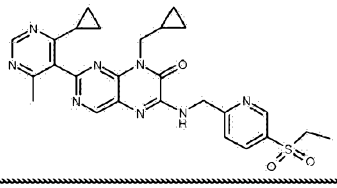
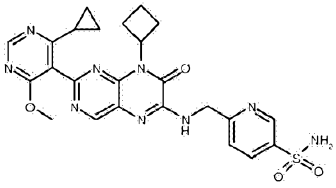
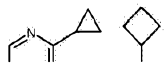
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
199		1.04	561.4		A
200		1.09	498.3		A
201		1.05	561.1		A
202		1.01	539.3		A
203		0.95	532.4		A
204		0.89	497.4		A
					

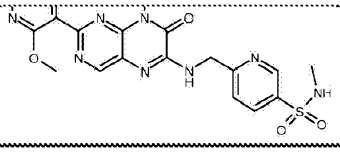
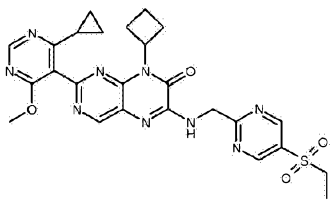
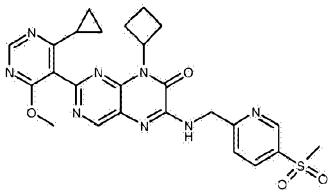
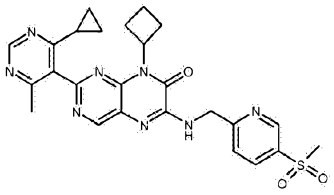
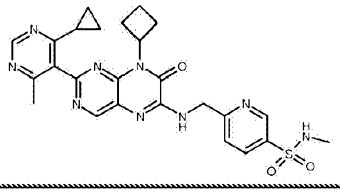
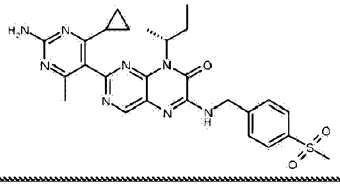
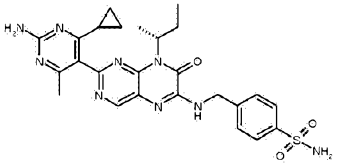
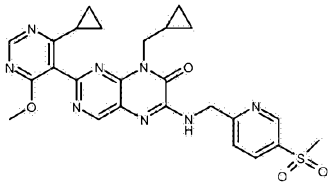
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
205		1.01	549.0		A
206		1.01	565.3		A
207		1.20	565.3		A
208		1.07	564		A
209		1.07	575.8		A
210		0.91	545.0		A
	^				

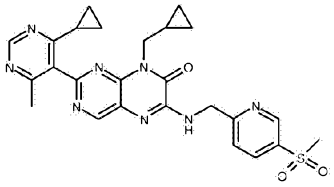
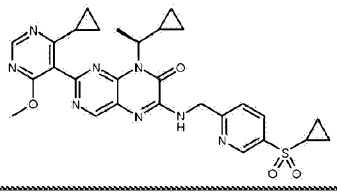
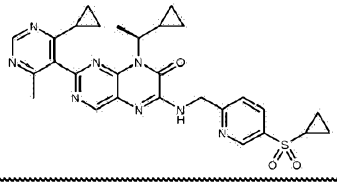
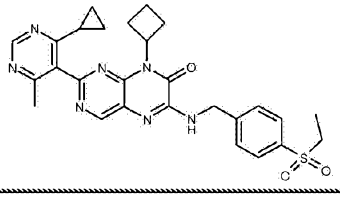
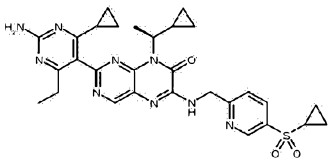
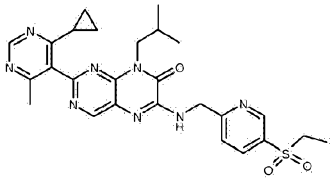
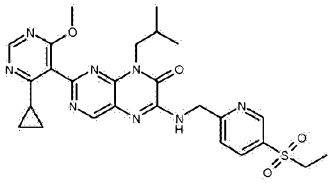
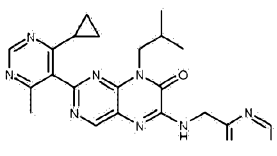
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
211		0.98	539.0		A
212		1.05	543.8		A
213		1.03	547.9		A
214		0.91	533.9		A
215		1.10	561.8		A
216		1.22	511.9		A
217		1.49	562.4		B

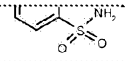
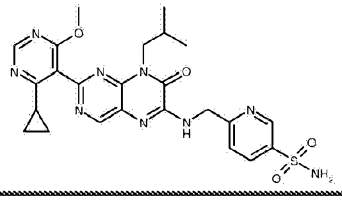
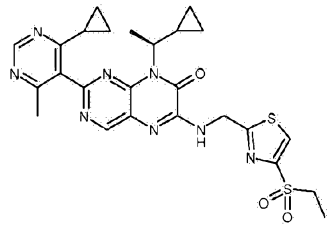
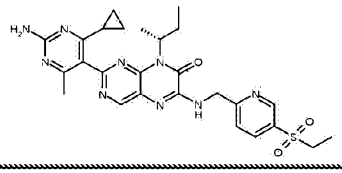
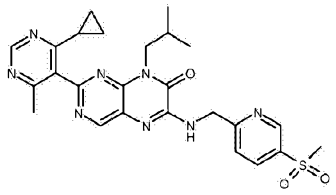
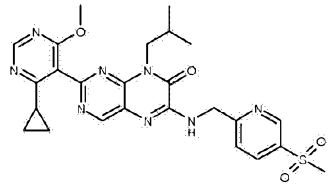
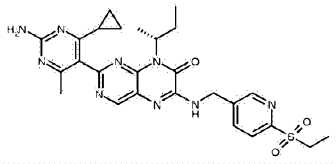
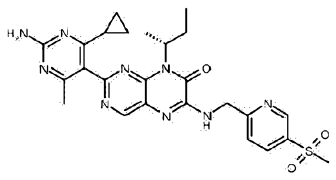
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
218		2.40	562.4		B
219		1.04	563.4		A
220		1.97	573.5		B
221		1.13	589.5		A
222		0.88	591.4		A
223		1.01	549.4		A
224		1.08	561.4		A

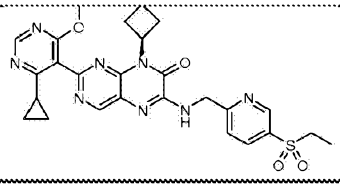
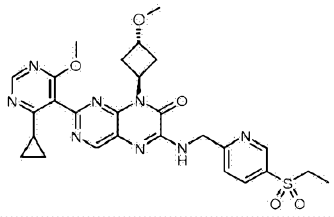
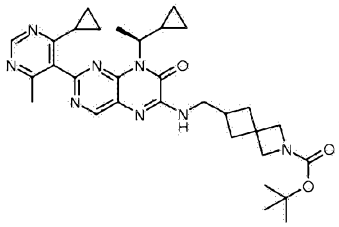
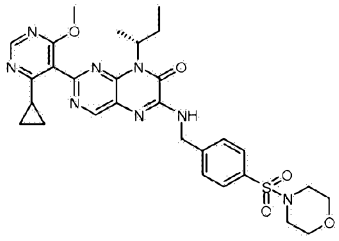
Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
225		0.90	521.1		A
226		0.96	537.2		A
227		0.88	577.3		A
228		0.95	593.4		A
229		0.91	562.2		A
230		0.96	578.1		A
231		1.41	550.2		B
					

Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
232		2.14	545		B
233		1.76	576		B
234		0.85	536.4		A
235		0.80	522.2		A
236		0.88	538.3		A
237		0.90	533.4		A
238		0.88	536.4		A
					

Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
239		0.96	550.4		A
240		0.98	550.5		A
241		0.94	535.4		A
242		0.88	519.4		A
243		0.89	534.5		A
244		0.70	535.3		A
245		0.65	536.3		A
246		0.91	535.5		A

Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
247		0.84	519.4		A
248		2.44	575.5		B
249		2.25	559.5		B
250		0.99	532.5		A
251		1.74	588.5		B
252		0.93	535.5		A
253		0.99	551.5		A
254		0.90	522.3		A

Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
					
255		0.97	538.3		A
256		2.13	553.4		B
257		1.42	550.5		B
258		1.92	521.5		B
259		0.95	537.5		A
260		0.69	550.3		A
261		0.64	536.2		A
					

Example	Structure	RT (min)	*m/z* $[M+H]^+$	*m/z* $[M-H]^-$	HPLC Method
262		0.86	579.3		A
263		0.86	579.3		A
264		0.89	607.3		A
265		0.89	521.5		A

[0034] Table I also provides physicochemical data (i.e., HPLC retention time and mass spec data) for all the prepared compounds. The HPLC methods are defined below in the Synthetic Examples section.

[0035] The present invention further relates to a pharmaceutically acceptable salt of a compound of the formula (I) with inorganic or organic acids or bases.

[0036] In another aspect, the invention relates to compounds of formula (I) - or the pharmaceutically acceptable salts thereof - as medicaments.

[0037] In another aspect, the invention relates to compounds of formula (I) - or the pharmaceutically acceptable salts thereof - for use in a method for treatment of a patient.

[0038] In another aspect, the invention relates to compounds of formula (I) - or the pharmaceutically acceptable salts thereof - for use in the treatment of autoimmune diseases and allergic disorders.

[0039] In another aspect, the invention relates to the use of compounds of formula (I) - or the pharmaceutically acceptable salts thereof - for preparing a pharmaceutical composition for the treatment of autoimmune diseases and allergic disorders.

[0040] In another aspect, the invention relates to a method for the treatment of autoimmune diseases and allergic disorders comprising administering a therapeutically effective amount of a compound of formula (I) - or one of the pharmaceutically acceptable salts thereof - to a patient.

[0041] In another aspect, the invention relates to a pharmaceutical composition containing as active substance one or more compounds of formula (I)- or the pharmaceutically acceptable salts thereof - optionally in combination with conventional excipients and/or carriers.

[0042] The compounds of formula (I) may be made using the general synthetic methods described below, which also constitute part of the invention.

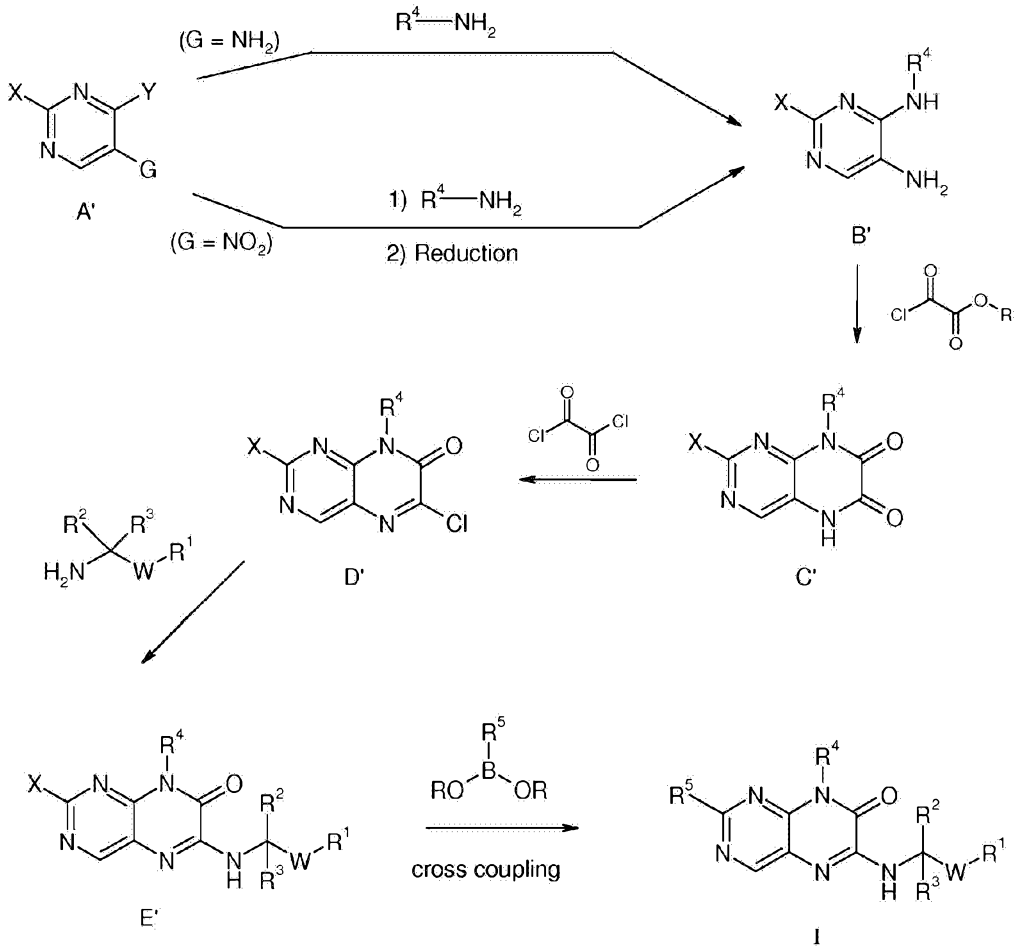
General Synthetic Methods

[0043] The compounds according to the invention may be prepared by the methods of synthesis, synthetic examples, methods known to those of ordinary skill in the art and methods reported in the chemical literature. In the methods of synthesis and examples described hereinafter, the substituents R^1, R^2, R^3, R^4, R^5, and W shall have the meanings defined hereinbefore in the detailed description of the compounds of formula I. These methods that are described here are intended as an illustration and for the enablement of the instant invention without restricting the scope of its subject matter, the claimed compounds, and the examples. Where the preparation of starting compounds is not described, they are commercially obtainable, may be prepared analogously to compounds or methods described herein, or are described in the chemical literature. Unless otherwise specified, solvents, temperatures, pressures, and other reaction conditions may be readily selected by one of ordinary skill in the art.

[0044] Amine intermediates of formula R^1-W-C(R^2)(R^3)-NH_2 are either commercially available, may be prepared according to the general procedures or references described in US 7,879,873 and WO 2011/049917, or may be prepared by one skilled in the art using methods described in the chemical literature.

[0045] Compounds of formula (I) may be prepared from intermediate A' according to Scheme I.

Scheme I



[0046] As illustrated in Scheme I, a suitable pyrimidine of formula A', wherein G is NH_2, X is a suitable group for palladium-mediated cross coupling reactions (e.g., I, Br, Cl, or OSO_2CF_3), and Y is a suitable leaving group (e.g., Cl), may be reacted with a suitable amine or amine salt (e.g., hydrochloride salt) of formula R^4NH_2 such as isopropyl amine in the presence of a suitable base (e.g., i-Pr_2EtN, or Et_3N) in a suitable solvent (e.g., *n*-butanol) and under a suitable reaction conditions such as an appropriate temperature (e.g., about 120 °C) to provide a compound of formula B'. Alternatively, the said pyrimidine of formula A' wherein G is a suitable synthetic precursor for NH_2 (e.g., a nitro group) may be reacted with a suitable amine or amine salt (e.g., hydrochloride salt) of formula R^4NH_2 such as 1-methyl cyclopropylamine in the presence of a suitable reagent and solvent (e.g., i-Pr_2EtN and THF, respectively), and under a suitable reaction conditions such as an appropriate temperature (e.g., about -78°C to about 25 °C) to afford an intermediate, which may be converted to a compound of formula B' upon further reaction with suitable reagents (e.g., a NO_2 group that may be reduced with a suitable reagent such as $SnCl_2$). The selection of a suitable amine of formula R^4NH_2 and pyrimidine of formula A' for the aforementioned reaction by a person skilled in the art may be based on criteria such as steric and electronic nature of the amine and the pyrimidine. A diaminopyrimidine of formula B' may be reacted with a suitable reagent such as chloro-oxo-

acetic acid ethyl ester in a suitable solvent (e.g., acetone) and in the presence of a suitable base (e.g., K_2CO_3) to furnish a compound of formula C'. A dicarbonyl compound of formula C' may be reacted with a suitable dehydrochlorinating reagent such as oxalyl chloride in the presence of a suitable additive (e.g., a catalytic amount of DMF) in a suitable solvent (e.g., CH_2Cl_2), and under a suitable reaction conditions such as an appropriate temperature (e.g., about ambient temperature) to provide a compound of formula D'. A chloro-pteridinone of formula D' may be reacted with a suitable amine or amine salt of formula R^1-W-C(R^2)(R^3)-NH_2 such as 4-ethanesulfonyl benzyl amine in the presence of a suitable base (e.g., Et_3N) in a suitable solvent (e.g., THF) and under a suitable reaction conditions such as an appropriate temperature (e.g., about ambient temperature) to yields a compound of formula E'. A pyrimidine of formula E' may be heated with a suitable cross-coupling partner (e.g., a boronic acid) and a suitable base (e.g., K_3PO_4), in a suitable solvent (e.g., 1,4-dioxane), in the presence of a suitable cross-coupling catalyst (e.g., Pd(dppf)Cl_2), under suitable reaction conditions such as a suitable atmosphere (e.g., argon) and at a suitable temperature (e.g., about 100 °C) to provide a compound of formula (I).

Synthetic Examples

[0047] Non-limiting examples demonstrating the preparation of the compounds of the invention are provided below. Optimum reaction conditions and reaction times may vary depending on the particular reactants used. Unless otherwise specified, solvents, temperatures, pressures and other reaction conditions may be readily selected by one of ordinary skill in the art. Specific procedures are provided in the Synthetic Examples section. Intermediates and products may be purified by chromatography on silica gel, recrystallization and/or reverse phase HPLC (RHPLC). Discrete enantiomers may be obtained by resolution of racemic products using chiral HPLC. RHPLC purification methods used anywhere from 0-100% acetonitrile in water containing 0.1% formic acid or 0.1% TFA and used one of the following columns:

1. a) Waters Sunfire OBD C18 5 µM 30x150 mm column
2. b) Waters XBridge OBD C18 5 µM 30x150 mm column
3. c) Waters ODB C8 5 µM 19x150 mm column.
4. d) Waters Atlantis ODB C18 5 µM 19x50 mm column.
5. e) Waters Atlantis T3 OBD 5 µM 30x100 mm column
6. f) Phenomenex Gemini Axia C18 5 µM 30x100 mm column

HPLC Methods:

Analytical LC/MS Analysis Method A:

[0048] Column: Waters BEH 2.1x50mm C18 1.7um column

Gradient:

[0049]

Time(min)	0.05% Formic Acid in Water	0.05% Formic Acid in ACN	Flow(mL/min)
0	90	10	0.8
1.19	0	100	0.8
1.77	0	100	0.8

Analytical LC/MS Analysis Method B:

[0050] Column: Waters BEH 2.1x50mm C18 1.7um column

Gradient:

[0051]

Time(min)	0.05% Formic Acid in Water	0.05% Formic Acid in ACN	Flow(mL/min)
0	90	10	0.8
4.45	0	100	0.8
4.58	0	100	0.8

List of abbreviations used in synthetic examples:

Ac	Acetyl
ACN	Acetonitrile
AcOH	Acetic acid
AIBN	Azobisisobutyronitrile
aq	Aqueous
Bu	Butyl
Boc_2O	Di-*tert*-butyl dicarbonate
dba	Dibenzylideneacetone
DCM	Dichloromethane

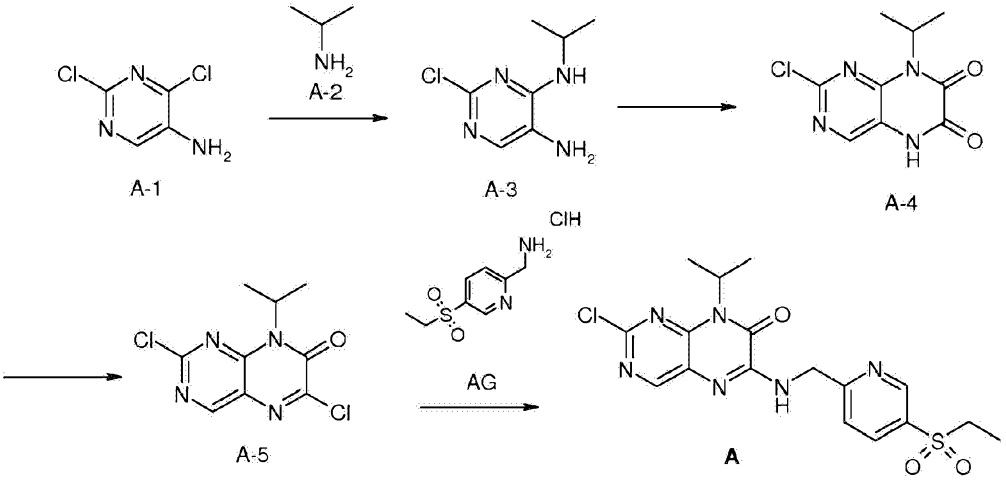
DMA	*N,N*-dimethylacetamide
DIEA	*N,N*-di*iso*propylethylamine
DME	1,2-Dimethoxyethane
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
dppe	(Diphenylphosphine)ethane
dppf	1.1'-bis(diphenylphosphino)ferrocene
ee	Enantiomeric excess
ES+	Electron spray positive ionization
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethanol
Josiphos	(S)-1-[(R_p)-2-(Dicyclohexylphosphino)ferroceyl]ethyl-di-t-butylphosphine
h	hour(s)
HPLC	High performance liquid chromatography
i	Iso
LC	Liquid chromatography
Me	Methyl
MeOH	Methanol
min	Minutes
MPLC	Medium Pressure Liquid Chromatography
MS	Mass spectrometry
NBS	*N*-Bromo-succinimide
NCS	*N*-Chloro-succinimide
NMP	*N*-Methylpyrrolidinone
Oxone	Potassium peroxymonosulfate
Pd/C	Palladium on carbon
Ph	Phenyl
PPh3	Triphenylphosphine
Pr	Propyl
RaNi	Raney Nickel
RT	Retention time (HPLC)
rt	Ambient temperature
SFC	Supercritical Fluid Chromatography
t	Tertiary

tert	Tertiary
Tf	Triflate
TBAF	Tetrabutylammonium fluoride
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Xanphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

Method 1:

Synthesis of Intermediate A

[0052]



[0053] To a stirred suspension of **A-1** (3.00 g, 18.18 mmol) in n-butanol (10 mL) is added **A-2** (10.80 g, 18.18 mmol) followed by DIEA (6.46 mL, 36.58 mmol). The mixture is stirred for 17 h at 120 °C. The reaction is cooled to rt and quenched by the addition of saturated aqueous NH_4Cl solution. The reaction is then diluted with EtOAc. The organic layer is separated and washed with water, followed by brine. The organic layer is dried (Na_2SO_4), decanted and concentrated. The resultant residue is purified by SiO_2 flash chromatography to yield **A-3**.

[0054] To a stirred suspension of **A-3** (1.00 g, 5.00 mmol) in acetone (100 mL) is added ethyl chlorooxoacetate (0.88 g, 6.43 mmol) followed by K_2CO_3 (1.85g, 13.39 mmol). The mixture is stirred at rt for 18 h and the solid precipitate is isolated to yield **A-4**.

[0055] To a stirred suspension of **A-4** (1.14 g, 5.00 mmol) in CH_2Cl_2 (250 mL) is added oxalyl

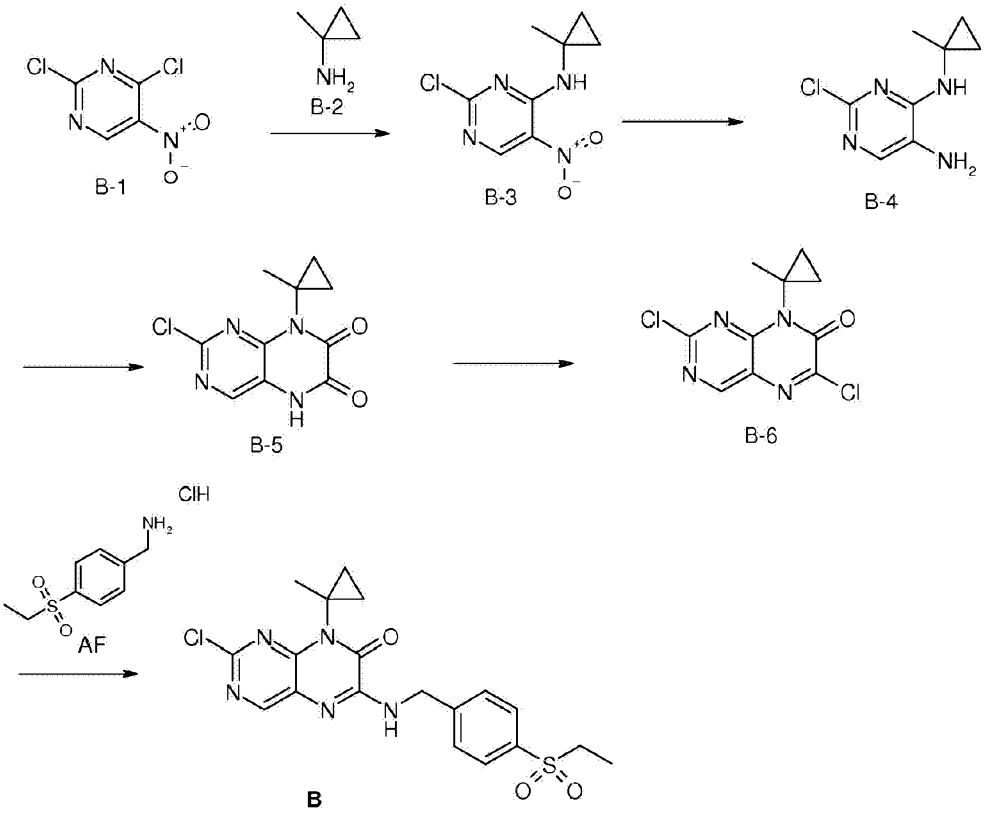
chloride (1 mL) followed by 5 drops of DMF. The mixture is stirred for 5 h at rt. The mixture is then concentrated at reduced pressure to yield **A-5**.

[0056] To a stirred suspension of **A-5** (0.1 g, 0.39 mmol) in THF (4 mL) is added TEA (0.16 mL, 1.16 mmol) (or DIEA), followed by **AG** (91 mg, 0.38 mmol). The reaction is allowed to stir for 18 h at rt. The reaction is quenched by the addition of saturated aqueous NH_4Cl solution and the organics are extracted with EtOAc. The organic layer is washed with water and brine, dried (Na_2SO_4), decanted and concentrated under vacuum. The resultant residue is purified by SiO_2 flash chromatography to yield **intermediate A.** MS (ES+): *m/z* 423.0 $[M+H]^+$.

Method 2:

Synthesis of Intermediate B

[0057]



[0058] To a stirred suspension of **B-1** (1.80 g, 9.30 mmol) and **B-2** (1.00 g, 9.30 mmol) in THF (10 mL) at -78 °C is added DIEA (3.29 mL, 18.59 mmol) and the reaction is allowed to slowly warm to 25 °C. The volatiles are removed under reduced pressure and the crude is redissolved in EtOAc and washed with H_2O. The organic layer is separated and washed two

more times with H_2O. The organic layer is washed with brine, dried (Na_2SO_4), decanted and concentrated. The resultant residue is purified by SiO_2 flash chromatography to yield **B-3**.

[0059] To a solution of **B-3** (1.78 g, 7.79 mmol) in EtOH (50 mL) is added $SnCl_2$ (1.48 g, 7.79 mmol) and heated to reflux for 4 h. The reaction is allowed to cool to rt then poured over ice. The solution is treated with 1N $NaOH_{(aq)}$ to bring the pH to ~9 then filtered through a pad of diatomaceous earth. The organic phase is separated and washed with H_2O followed by brine. The organic layer is dried ($Na_2SC>_4$), decanted and concentrated. The crude product is purified by SiO_2 flash chromatography to yield **B-4**.

[0060] As an alternative procedure for the reduction of nitropyrimidine to the corresponding amino pyrimidine the following general procedure has been utilized for analogous intermediates: To a solution of the nitropyrimidine in EtOH is added catalytic RaNi. The reaction vessel is evacuated and purged with $N_2(g)$, then evacuated and filled with $H_2(g)$. The reaction is maintained under $H_2(g)$ atmosphere for 15 h. The vessel is evacuated and purged with $N_2(g)$. The reaction is filtered through a pad of diatomaceous earth to remove the Ni catalyst and the filtrate is concentrated. The resultant residue is purified by SiO_2 flash chromatography to afford the corresponding aminopyrimidine.

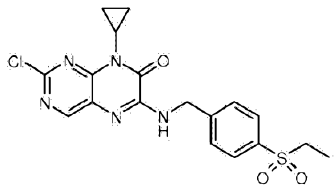
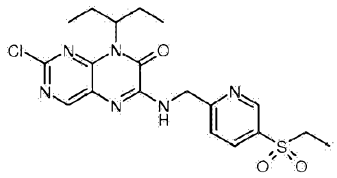
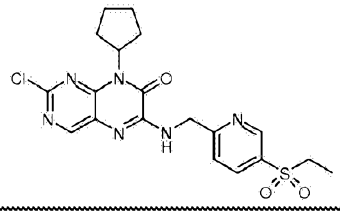
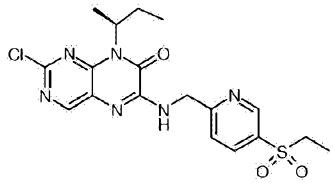
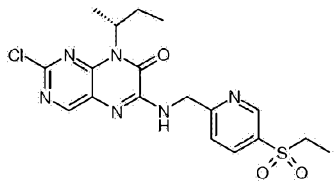
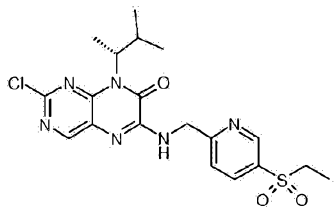
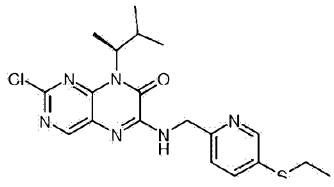
[0061] To a stirred solution of **B-4** (0.40 g, 2.01 mmol) in acetone (10 mL) is K_2CO_3 (0.70 g, 5.06 mmol) followed by ethyl chlorooxoacetate (0.27 mL, 2.43 mmol). The reaction is stirred at rt for 24 h. The reaction is then filtered, redissolved in H_2O and extracted with EtOAc. The aqueous phase is separated and extracted two more times with EtOAc. The organic layers are combined, dried (Na_2SO_4), decanted and concentrated to yield **B-5**.

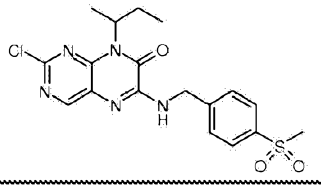
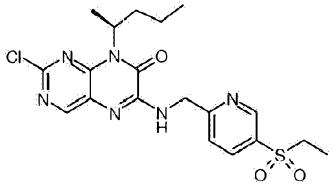
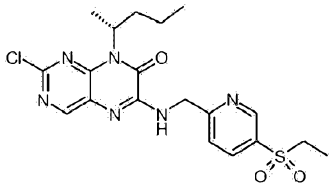
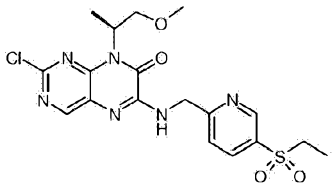
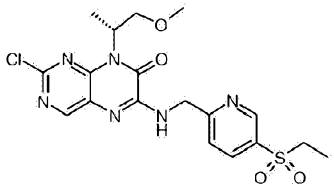
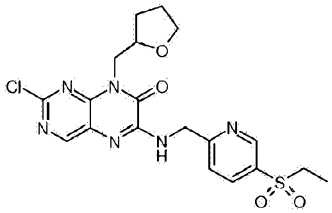
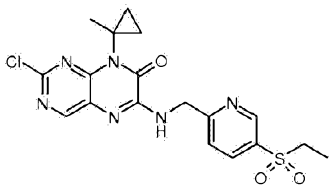
[0062] To a solution of **B-5** (0.70 g, 2.77 mmol) in CH_2Cl_2 (50 mL) is added oxalyl chloride (0.47 mL, 5.54 mmol) followed by 5 drops of DMF. The reaction is allowed to stir at rt for 18 h. The volatiles are removed in vacuo. The crude is redissolved in DCM and poured into H_2O. The organic layer is separated, washed with brine, dried (Na_2SO_4), decanted and concentrated. The resultant residue is purified by SiO_2 flash chromatography to yield **B-6**.

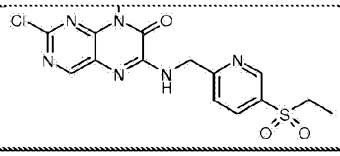
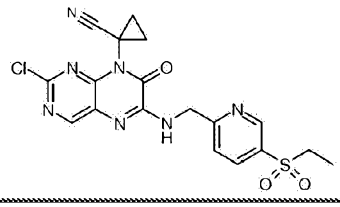
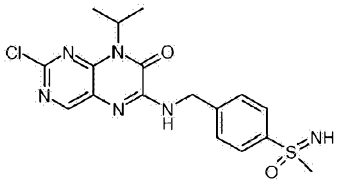
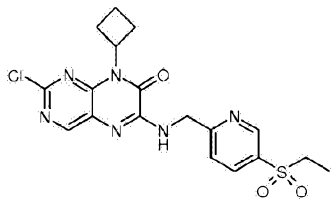
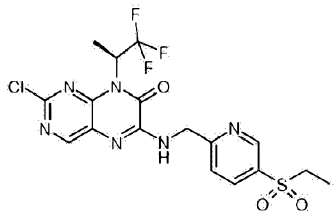
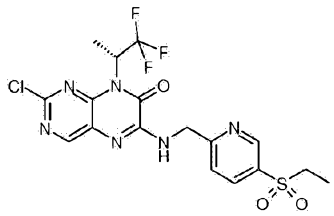
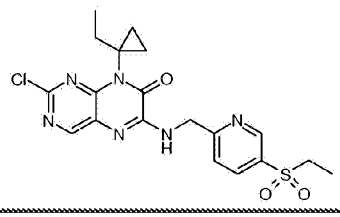
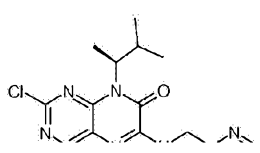
[0063] To a stirred solution of the **B-6** (0.83 g, 3.06 mmol) in THF (10 mL) is added DIEA (1.07 mL, 6.12 mmol) followed by **AF** (0.72 g, 3.06 mmol). The reaction is stirred at rt for 18 h. The volatiles are removed in vacuo, the crude residue is re-suspended in DCM and poured into H_2O. The aqueous phase is separated and extracted two more times with DCM. The organic layers are combined, washed with brine, dried (Na_2SO_4), decanted and concentrated. The resultant residue is purified by SiO_2 flash to yield **intermediate B.** MS (ES+): *m/z* 434.1 $[M+H]^+$.

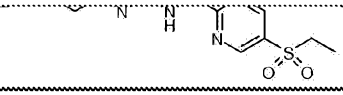
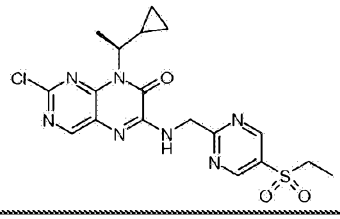
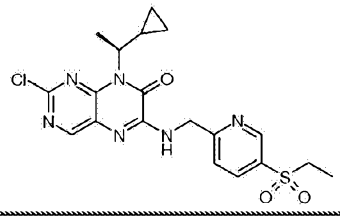
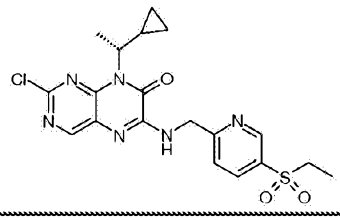
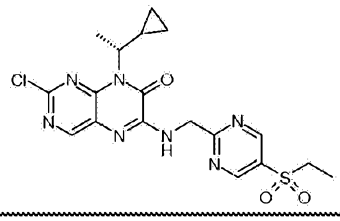
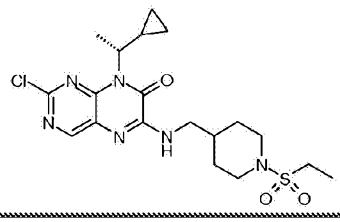
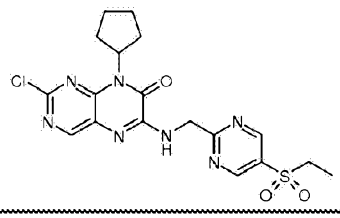
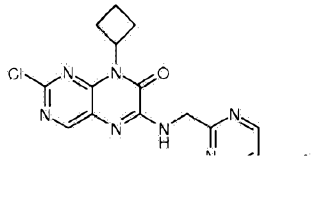
[0064] The following intermediates are prepared in analogous fashion:
(Note: As described in Method 34, the oxalamic acid ethyl ester intermediates generated from

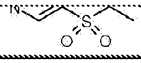
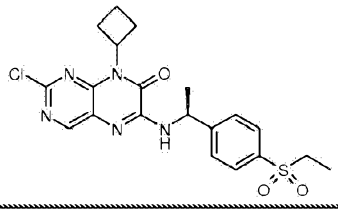
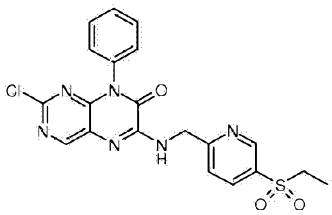
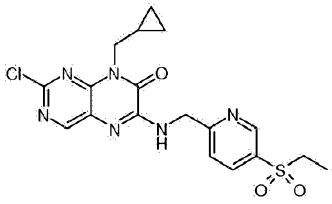
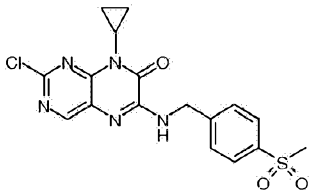
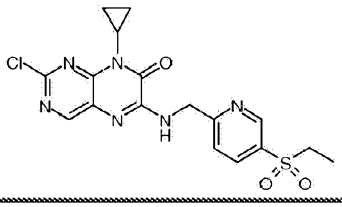
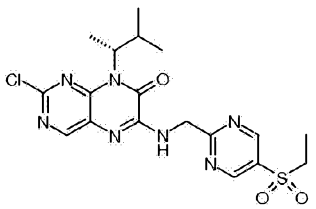
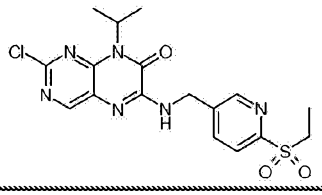
the reactions of A-3 (Method 1) and B-4 (Method 2) with ethyl chlorooxoacetate may be isolated and heated at a suitable temperature (e.g., 130 °C) with a suitable base, such as TEA, in a suitable solvent, such as EtOH, to afford the corresponding intermediates A-3 and B-5, respectively.)

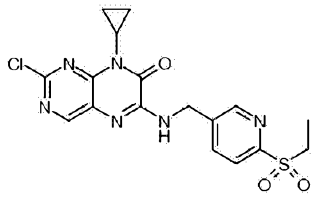
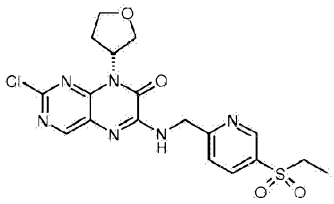
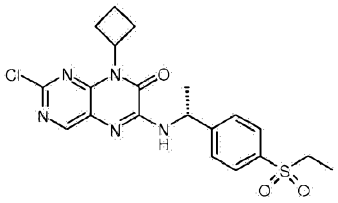
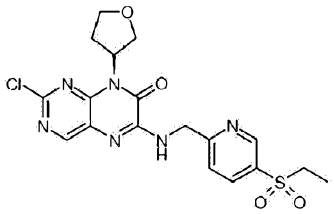
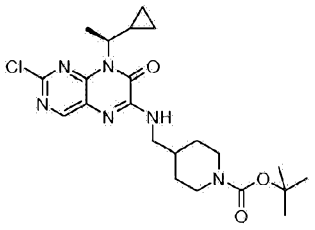
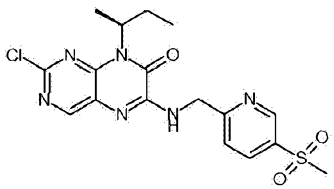
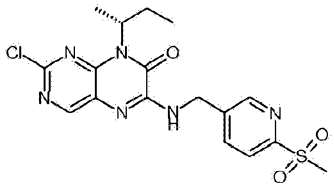
Intermediate	Structure	Synthetic Method	*m/z*[M+H]$^+$
C		1	420.1
D		1	451.2
E		2	449.3
F		1	437.2
G		1	437.2
H		1	451.2
I		1	451.2

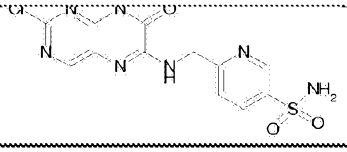
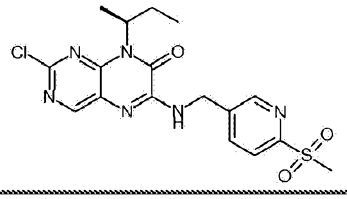
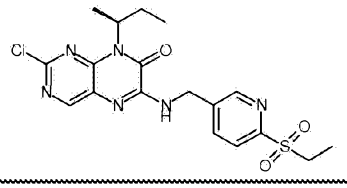
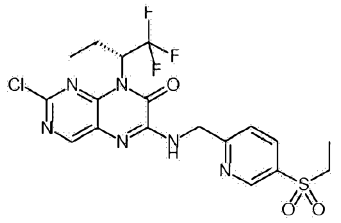
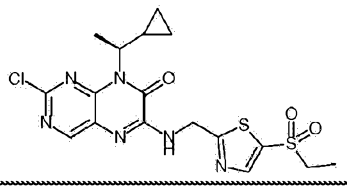
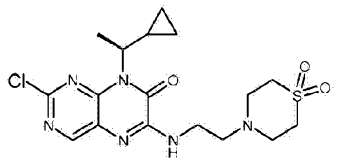
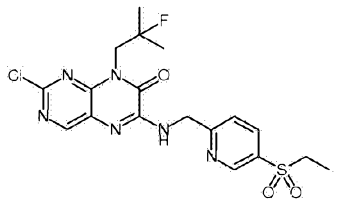
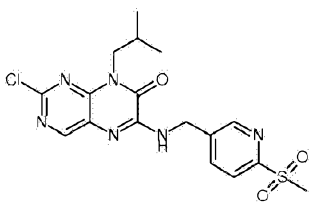
Intermediate	Structure	Synthetic Method	$m/z[M+H]^+$
J		1	422.5
K		2	451.1
L		2	451.1
M		1	453.2
N		1	453.2
O		1	465.2
P		2	435.2
			

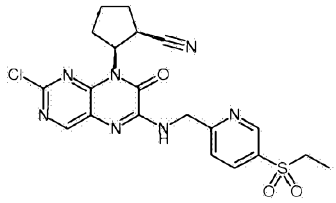
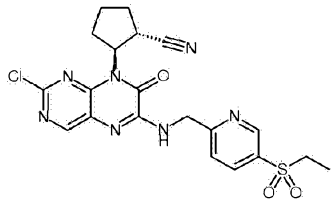
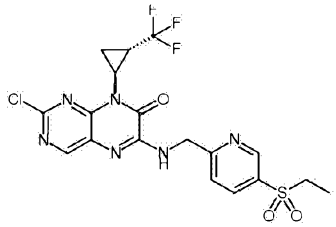
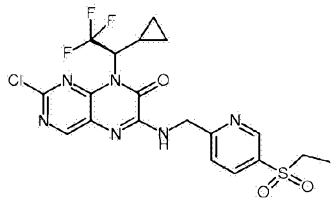
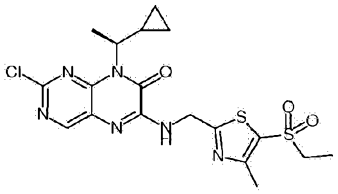
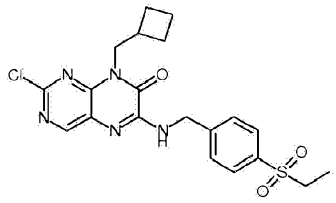
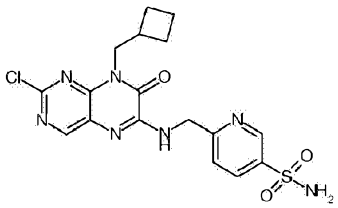
Intermediate	Structure	Synthetic Method	$m/z[M+H]^+$
Q		2	471.1
R		2	466.2
S		1	409.1
T		1	434.9
U		2	477.0
V		2	476.9
W		2	449.1
X		1	451.9

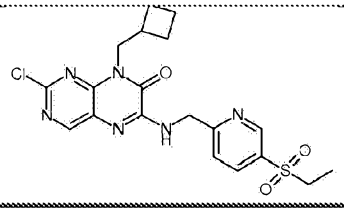
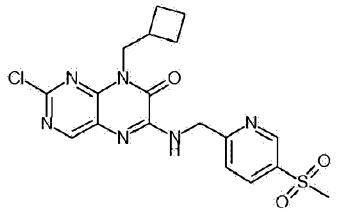
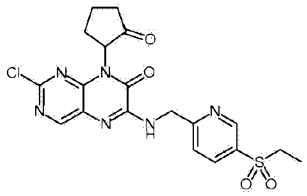
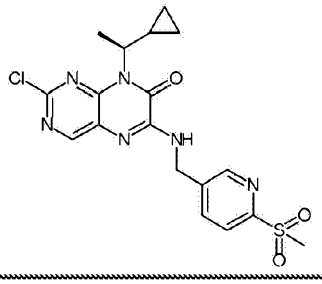
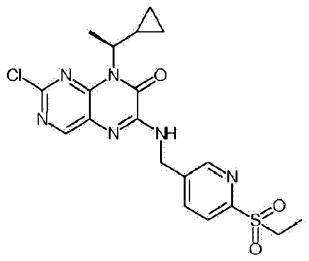
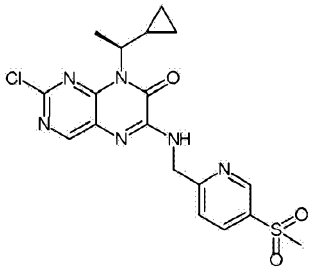
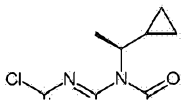
Intermediate	Structure	Synthetic Method	$m/z[M+H]^+$
			
Y		1	449.9
Z		1	448.9
AA		1	449.0
BB		1	449.9
CC		1	455.0
DD		1	449.9
EE		1	435.9

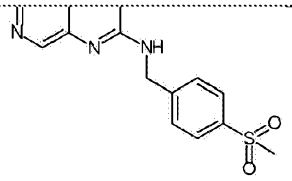
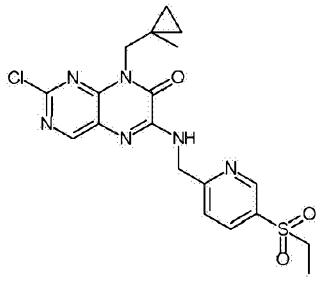
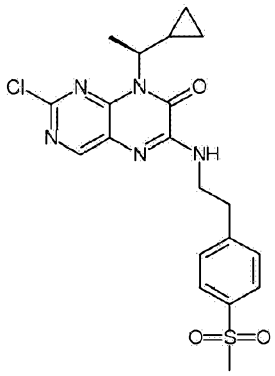
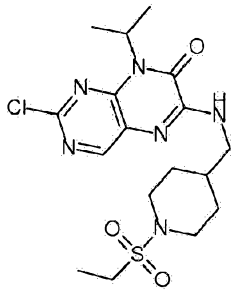
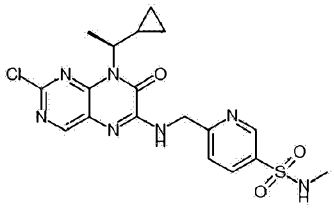
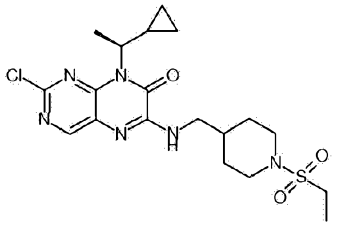
Intermediate	Structure	Synthetic Method	$m/z[M+H]^+$
			
FF		1	447.9
GG		1	457.1
HH		1	434.9
II		1	406.0
JJ		1	421.0
KK		1	451.2
LL		1	423.1

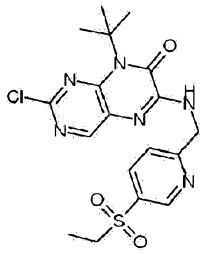
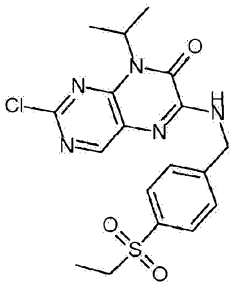
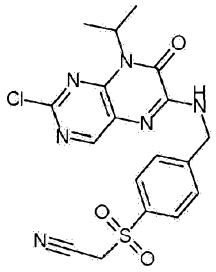
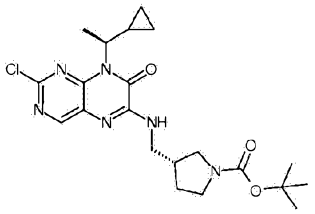
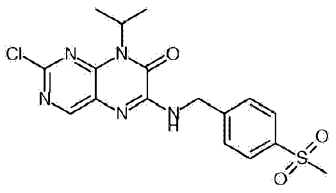
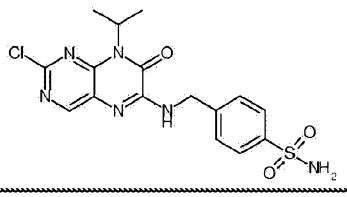
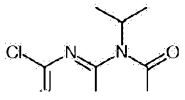
Intermediate	Structure	Synthetic Method	$m/z[M+H]^+$
MM		1	421.0
NN		1	451.0
OO		1	447.9
PP		1	451.0
QQ		1	463.0
RR		1	423.3
SS		1	423.3
			

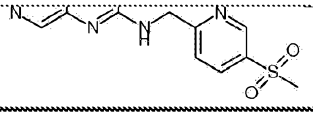
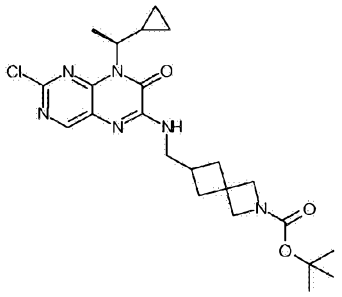
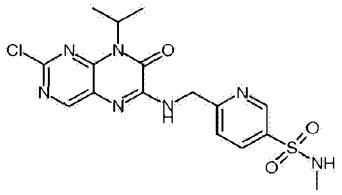
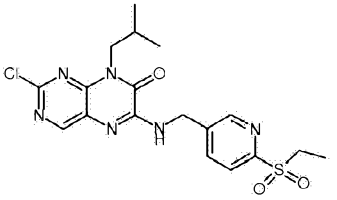
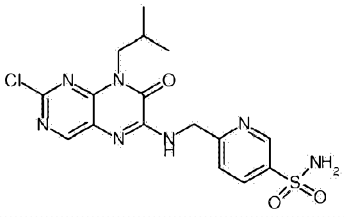
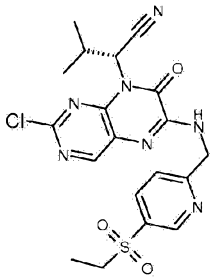
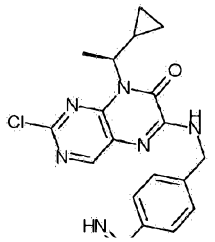
Intermediate	Structure	Synthetic Method	$m/z[M+H]^+$
TT		1	424.3
UU		1	423.3
VV		1	437.3
WW		2	491.3
XX		1	455.3
YY		2	427.3
ZZ		1	455.4
AAA		1	423.3

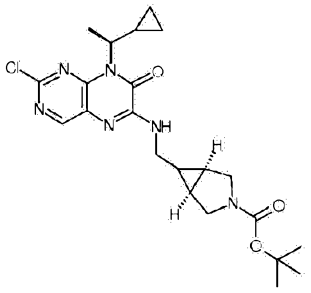
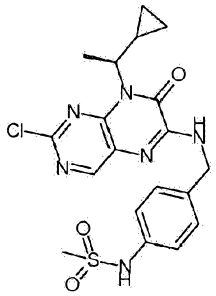
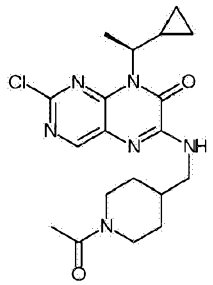
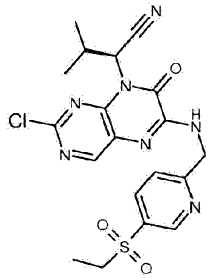
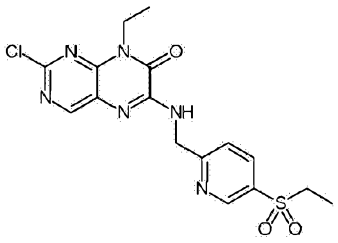
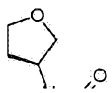
Intermediate	Structure	Synthetic Method	$m/z[M+H]^+$
BBB		1	474.1
CCC		1	474.1
DDD		2	489.1
EEE		2	503.3
FFF		1	469.3
GGG		1	448.1
HHH		1	436.3

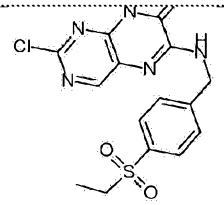
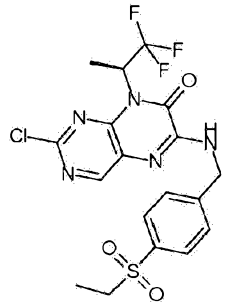
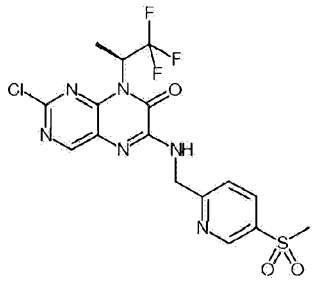
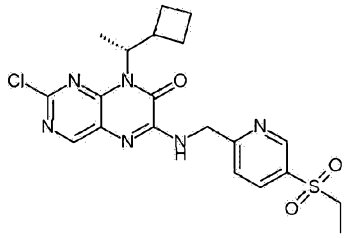
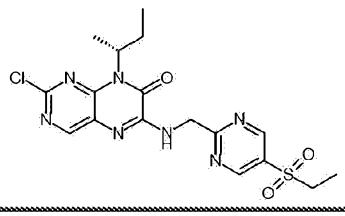
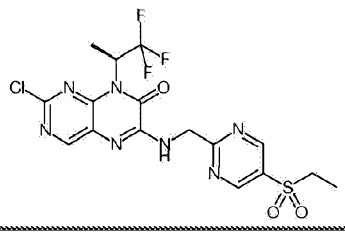
Intermediate	Structure	Synthetic Method	$m/z[M+H]^+$
III		1	449.3
JJJ		1	435.3
KKK		1	463.1
LLL		1	435.2
MMM		1	448.9
NNN		1	435.2
			

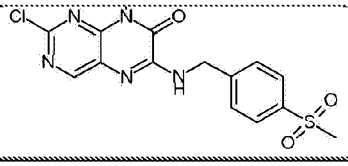
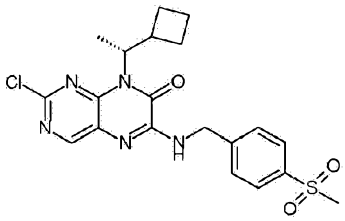
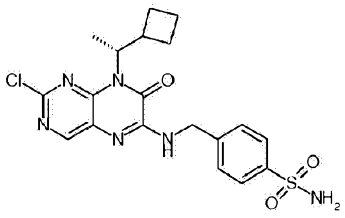
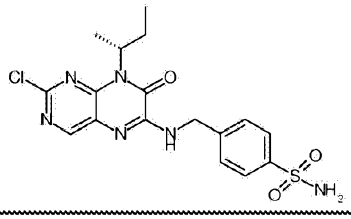
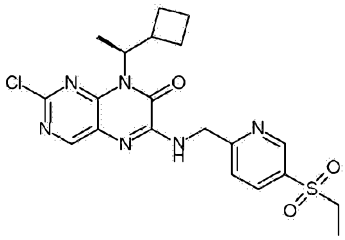
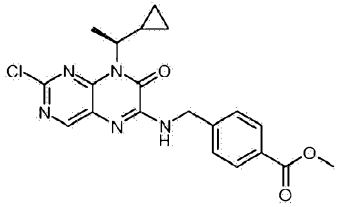
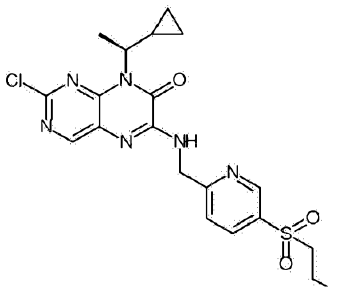
Intermediate	Structure	Synthetic Method	$m/z[M+H]^+$
OOO		1	434.9
PPP		1	449.2
QQQ		1	448.2
RRR		1	429.0
SSS		1	450.0
TTT		1	441.2

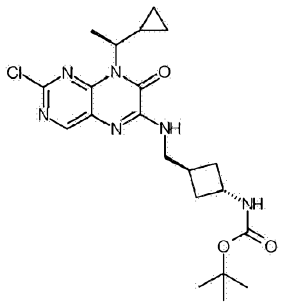
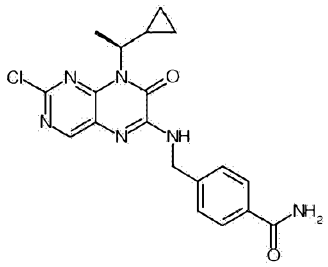
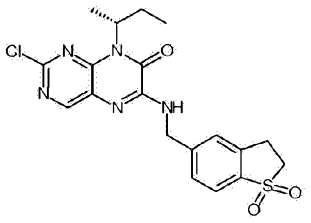
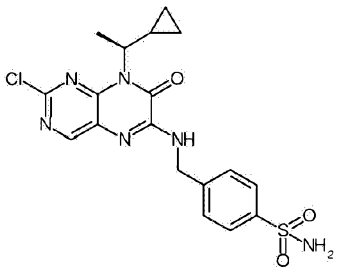
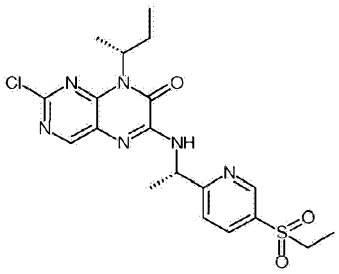
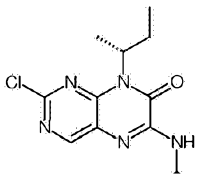
Intermediate	Structure	Synthetic Method	$m/z[M+H]^+$
UUU		1	436.9
VVV		1	422.0
WWW		1	432.9
XXX		1	449.0
YYY		1	407.8
ZZZ		1	408.8
AAAA		1	408.9

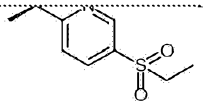
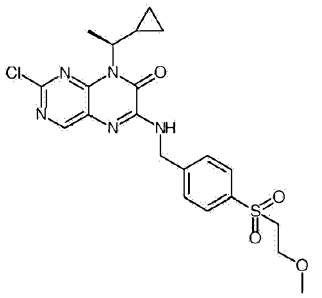
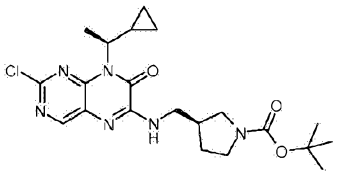
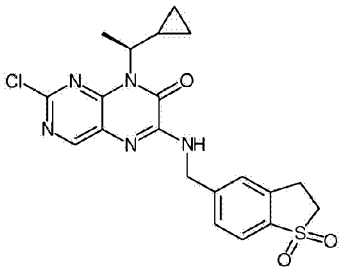
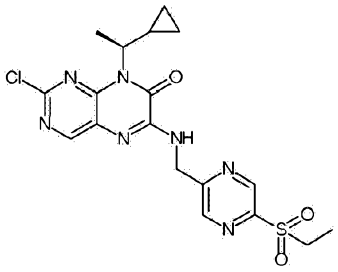
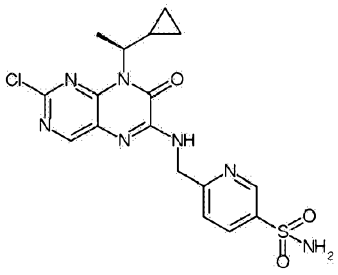
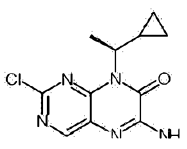
Intermediate	Structure	Synthetic Method	$m/z[M+H]^+$
			
BBBB		1	475.0
CCCC		1	423.9
DDDD		1	436.9
EEEE		1	424.3
FFFF		2	461.9
GGGG		1	433.0

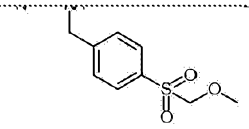
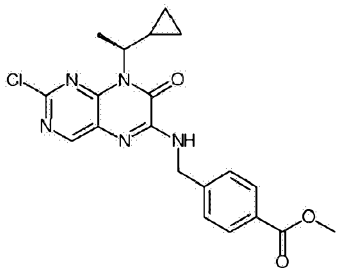
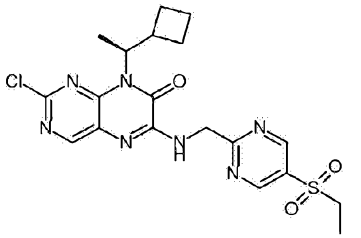
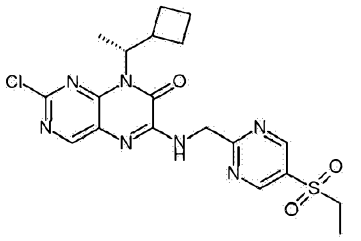
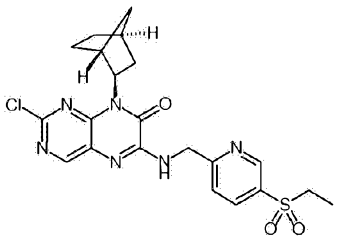
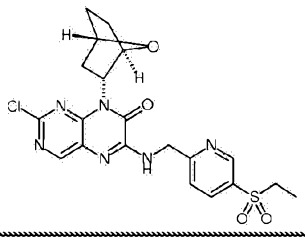
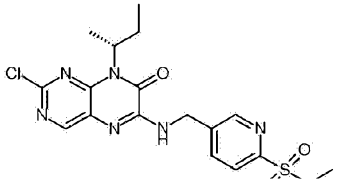
Intermediate	Structure	Synthetic Method	$m/z[M+H]^+$
			
HHHH		1	461.0
IIII		1	448.9
JJJJ		1	405.0
KKKK		2	461.9
LLLL		1	409.2
			

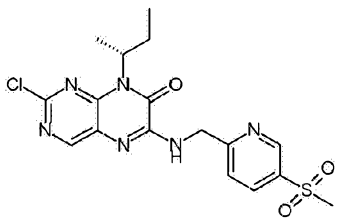
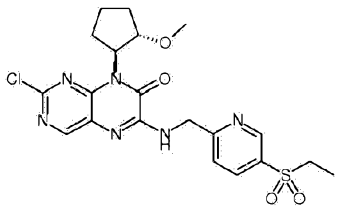
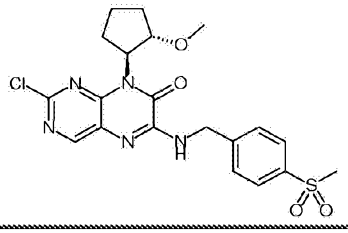
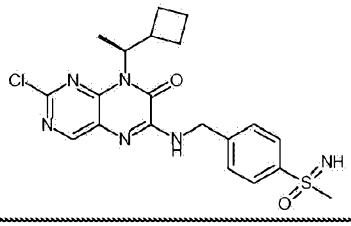
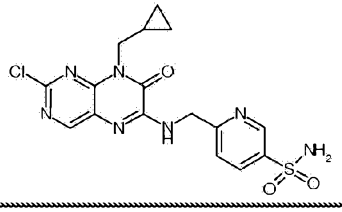
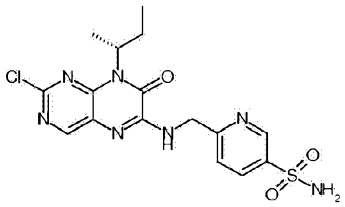
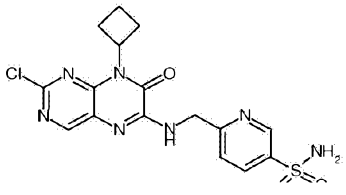
Intermediate	Structure	Synthetic Method	$m/z[M+H]^+$
MMMM		1	449.9
NNNN		2	475.9
OOOO		2	463.2
PPPP		1	463.2
QQQQ		1	438.1
RRRR		2	477.9
			

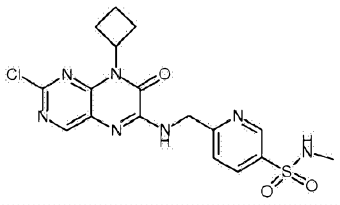
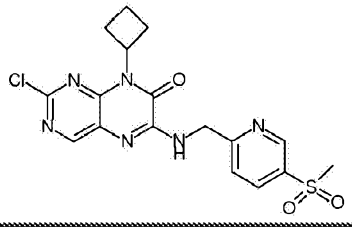
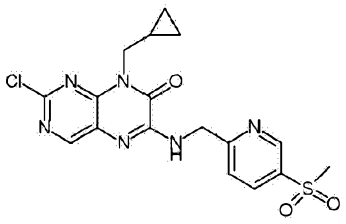
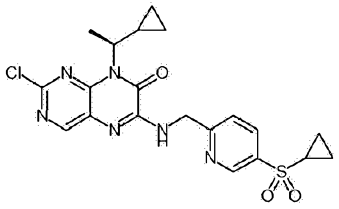
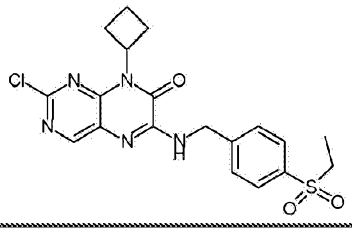
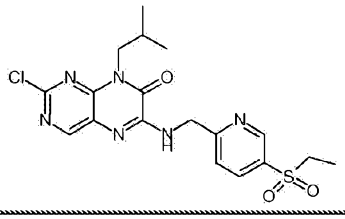
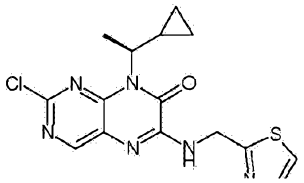
Intermediate	Structure	Synthetic Method	$m/z[M+H]^+$
SSSS		1	422.1
TTTT		1	448.2
UUUU		1	449.2
VVVV		1	423.1
WWWW		1	463.2
XXXX		1	414.0
YYYY		1	463.2

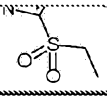
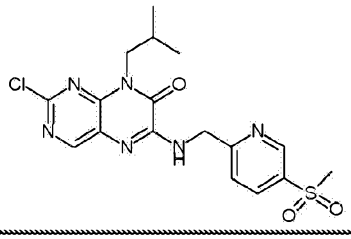
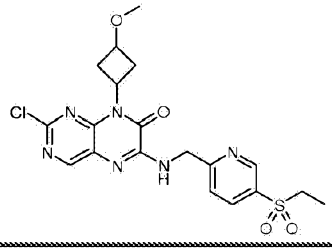
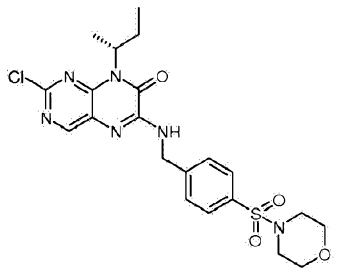
Intermediate	Structure	Synthetic Method	$m/z[M+H]^+$
ZZZZ		1	449.3
AAAAA		1	399.3
BBBBB		1	433.9
CCCCC		1	435.9
DDDDD		1	451.0
EEEEE		1	451.0

Intermediate	Structure	Synthetic Method	$m/z[M+H]^+$
			
FFFFF		1	477.9
GGGGG		1	449.0
HHHHH		1	446.0
IIIII		1	450.0
JJJJJ		1	435.9
KKKKK		1	464.0

Intermediate	Structure	Synthetic Method	$m/z[M+H]^+$
			
LLLLL		1	414.0
MMMMM		1	464.3
NNNNN		1	464.3
OOOOO		1	475.2
PPPPP		1	477.3
QQQQQ		1	437.2

Intermediate	Structure	Synthetic Method	$m/z[M+H]^+$
RRRRR		1	423.2
SSSSS		1	479.3
TTTTT		1	464.1
UUUUU		1	447.3
VVVVV		1	422.2
WWWWW		1	424.1
XXXXX		1	422.2

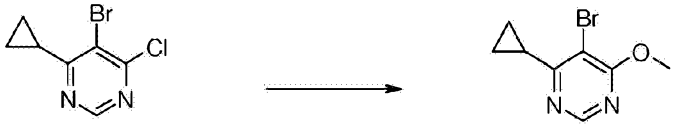
Intermediate	Structure	Synthetic Method	$m/z[M+H]^+$
YYYYY		1	436.3
ZZZZZ		1	421.2
AAAAAA		1	421.2
BBBBBB		1	461.3
CCCCC		1	434.3
DDDDDD		1	437.3
EEEEEE		1	455.3

Intermediate	Structure	Synthetic Method	$m/z[M+H]^+$
			
FFFFFF		1	423.3
GGGGGG		1	465.1
HHHHHH		1	493.2

Method 3:

Synthesis of Intermediate AB

[0065]



AB-1

AB

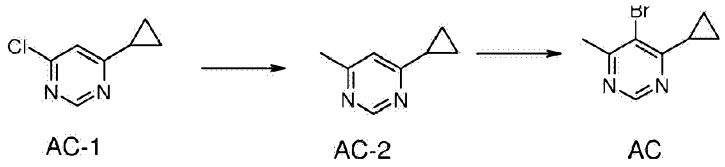
[0066] To a solution of **AB-1** (300 mg, 1.29 mmol) in anhydrous MeOH (15 mL) is added NaOMe (208 mg, 3.86 mmol). The mixture is stirred at rt for 1 h. The solution is filtered and concentrated. The residue is purified by SiO_2 flash chromatography to yield **intermediate AB.**

MS (ES+): *m/z* 230.8 $[M+H]^+$.

Method 4:

Synthesis of Intermediate AC

[0067]



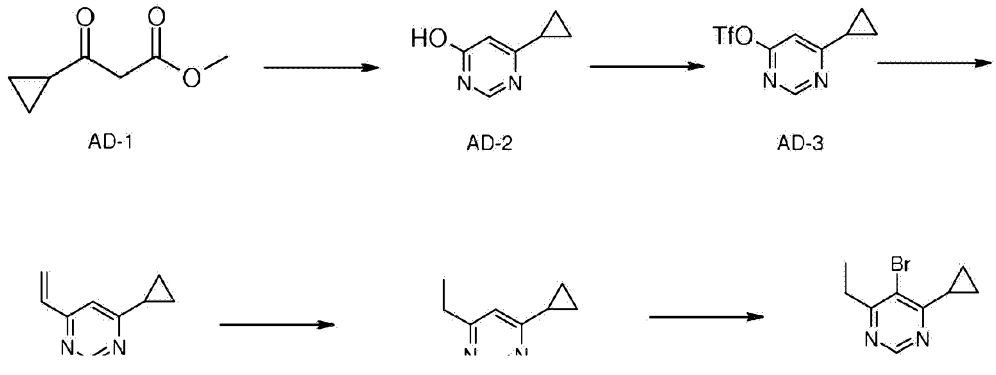
[0068] To a solution of **AC-1** (320 mg, 2.07 mmol), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (520 mg, 4.14 mmol), and aq Na_2CO_3 (2M, 3.1 mL, 6.21 mmol) in dioxane (10 mL) is added dichloropalladium 4-ditert-butylphosphanyl-N,N-dimethyl-aniline (73 mg, 0.10 mmol). The mixture is heated to 130 °C for 40 min in a microwave reactor. The mixture is diluted with MeOH (5 mL), filtered and concentrated. The residue is purified by SiO_2 flash chromatography to yield **AC-2.**

[0069] To a solution of **AC-2** (363 mg, 2.71 mmol) in EtOH (10 mL) at -10 °C is added Br_2 (432 mg, 2.71 mmol). The reaction mixture is stirred at rt for 18 h. The solution is concentrated and the residue is purified by SiO_2 flash chromatography to yield **intermediate AC.** MS (ES+): *m/z* 214.3 $[M+H]^+$.

Method 5:

Synthesis of Intermediate AD

[0070]



AD-4

AD-5

AD

[0071] A mixture of **AD-1** (100.0 g, 0.70 mol), formamidine acetate (146 g, 1.4 mol) and NaOMe (266.0 g, 4.9 mol) in MeOH (2 L) is stirred at 16 °C for 2 days. The reaction mixture is neutralized to pH 7 with acetic acid and filtered. The filtrate is concentrated under reduced pressure and the crude product is purified by SiO_2 flash chromatography to yield **AD-2.**

[0072] To a stirred solution of **AD-2** (66.0 g, 0.48 mol) and TEA (145.1 g, 1.44 mol) in DCM (1.5 L) at 0 °C is added, dropwise, a solution of Tf_2O (164.2 g, 0.58 mol) in DCM (500 mL) and stirred for 3 h. The reaction mixture is quenched by the addition of H_2O (200 mL) and extracted with DCM (3 x 500 mL). The combined organic phase is washed with saturated aq $NaHCO_3$, dried (Na_2SO_4), decanted and concentrated. The resultant residue is purified by SiO_2 flash chromatography to yield **AD-3.**

[0073] A mixture of **AD-3** (17.0 g, 0.06 mol), vinylboronic acid pinacolester (29.3 g, 0.09 mol), K_2CO_3 (26.3 g, 0.19 mol), Ag_2O (1.7 g, 10%wt) and $Pd(dppf)Cl_2$ (1.7 g, 10% wt) in anhydrous THF (400 mL) is stirred at reflux under N_2 atmosphere for 18 h. The mixture is cooled to rt and filtered. The filtrate is concentrated under reduced pressure and the resultant residue is purified by SiO_2 flash chromatography to yield **AD-4.**

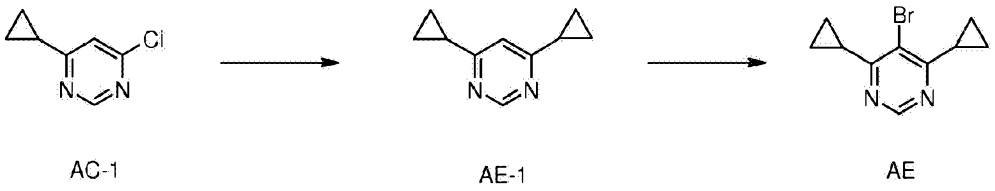
[0074] A mixture of **AD-4** (27.3 g, 0.28 mol) and RaNi (30.0 g, 10% wt) in EtOH (500 mL) is stirred under an H_2 atmosphere for 16 h. The vessel is purged with N_2 and the contents filtered. The filtrate is concentrated under reduced pressure and the resultant **AD-5** (19.6 g) is used directly.

[0075] To a stirred solution of **AD-5** (19.6 g, 0.13 mol) in EtOH (300 mL) at -10 °C is added Br_2 (52.9 g, 0.33 mol). Following the addition, the mixture is stirred at rt for 30 min. The reaction mixture is quenched by the addition of 10% $Na_2S_2O_{3(aq)}$ solution and basified by the addition of 10% $Na_2CO_{3(aq)}$ solution to adjust to ~pH 8. The mixture is extracted with EtOAc (3 x 200 mL). The organic layers are combined, dried (Na_2SO_4), decanted and concentrated. The resultant residue is purified by SiO_2 flash chromatography to yield **intermediate AD.** MS (ES+): *m/z* 228.9 $[M+H]^+$.

Method 6:

Synthesis of Intermediate AE

[0076]



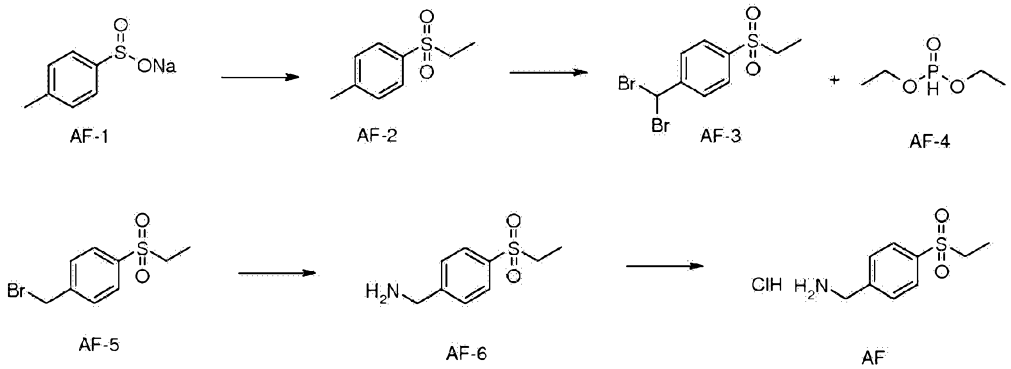
[0077] To a solution of **AC-1** (2.50 g, 16.17 mmol), cyclopropylboronic acid (4.17 g, 48.51 mmol) and Na_2CO_3 (aq) (2M, 24.26 mL, 48.51 mmol) in dioxane (30 mL) is added bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (572.5 mg, 0.81 mmol). The vessel is sealed and heated to 130 °C for 2 h. The vessel is cooled to rt, diluted with MeOH and filtered. The filtrate is concentrated and purified by SiO_2 flash chromatography to yield **AE-1.**

[0078] To a solution of **AE-1** (660 mg, 4.12 mmol) in EtOH (15 mL) at -10 °C is added Br_2 (658 mg, 4.12 mmol). The reaction is stirred at rt for 3h. NH_3 in MeOH solution (2N, 1 mL) is added to neutralize. The mixture is concentrated and purified by SiO_2 flash chromatography to yield **intermediate AE.** MS (ES+): *m/z* 240.9 $[M+H]^+$.

Method 7:

Synthesis of Intermediate AF

[0079]



[0080] A mixture of **AF-1** (100 g, 561 mmol), EtI (131 g, 842 mmol) and TBAB (18 g, 56 mmol) in H_2O (200 mL), acetone (150 mL) and toluene (150 mL) is stirred in a sealed vessel at 80 °C for 18 h. The mixture is partitioned between H_2O and EtOAc. The organic layer is dried and concentrated. The residue is purified by SiO_2 flash chromatography to yield **AF-2.**

[0081] A mixture of **AF-2** (200 g, 1.09 mol), NBS (425.02 g, 2.39 mol) and AIBN (17.82 g,

108.54 mmol) in CCl_4 (1.40 L) is refluxed for 18 h. The mixture is partitioned between H_2O and DCM. The organic layer is dried (Na_2SO_4), decanted and concentrated to yield **AF-3.**

[0082] To a solution of **AF-3** (333 g, 974 mmol) and DIEA (129 g, 1 mol) in ACN (500 mL) at 0 °C is added **AF-4** (138 g, 1 mol) in ACN (150 mL) dropwise. The mixture is stirred for 5 h then concentrated. The resultant residue is crystallized from MeOH to yield **AF-5.**

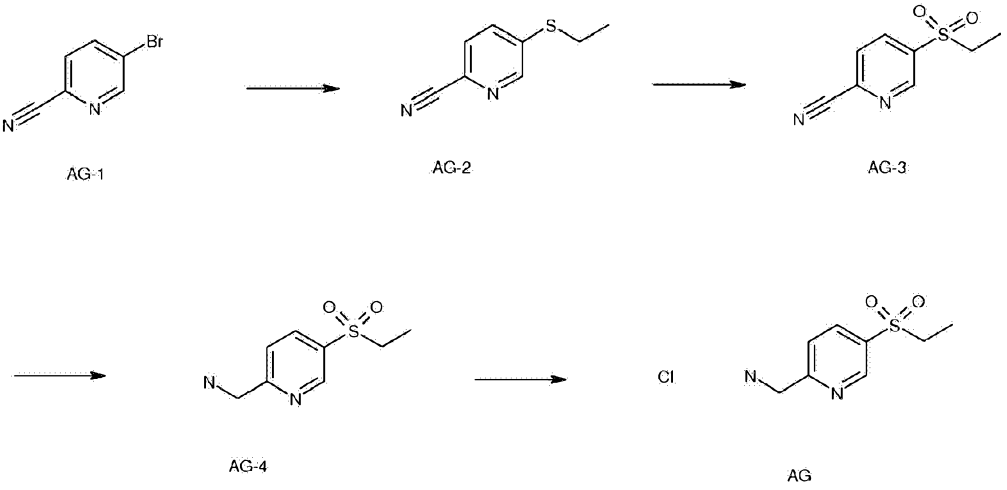
[0083] A solution of **AF-5** (50 g, 190 mmol) in MeOH (200 mL) is added into a solution of NH_3 in MeOH (2N, 800 mL) at -78°C. The reaction mixture is stirred at rt for 18 h then concentrated. The resultant residue is crystallized from EtOAc to afford **AF-6.**

[0084] A solution of **AF-6** (50 g, 250 mmol) in HCl in MeOH (1N, 250 mL) is stirred at rt for 12h then concentrated to yield **intermediate AF** as the HCl salt. MS (ES+): *m/z* 200.4 $[M+H]^+$.

Method 8:

Synthesis of Intermediate AG

[0085]



[0086] A mixture of **AG-1** (8.0 g, 43.96 mmol), K_2CO_3 (7.88 g, 57.1 mmol) and sodium ethanethiolate (4.06 g, 48.3 mmol) in NMP (60.0 mL) under N_2 is stirred at rt for 18 h. The reaction mixture is poured into H_2O and filtered. The solids are washed with H_2O and dried under vacuum to yield **AG-2.**

[0087] To a suspension of **AG-2** (6.0 g, 36.6 mmol) in AcOH (2.63 g, 43.8 mmol) is added a solution of $KMnO_4$ (5.78 g, 36.6 mmol) in H_2O (20.0 mL) dropwise. The reaction mixture is stirred at rt for 15 h. The mixture is diluted with water and extracted with EtOAc. The organic

layer is dried (Na_2SO_4), decanted and concentrated. The resultant residue is purified by SiO_2 flash chromatography to yield **AG-3.**

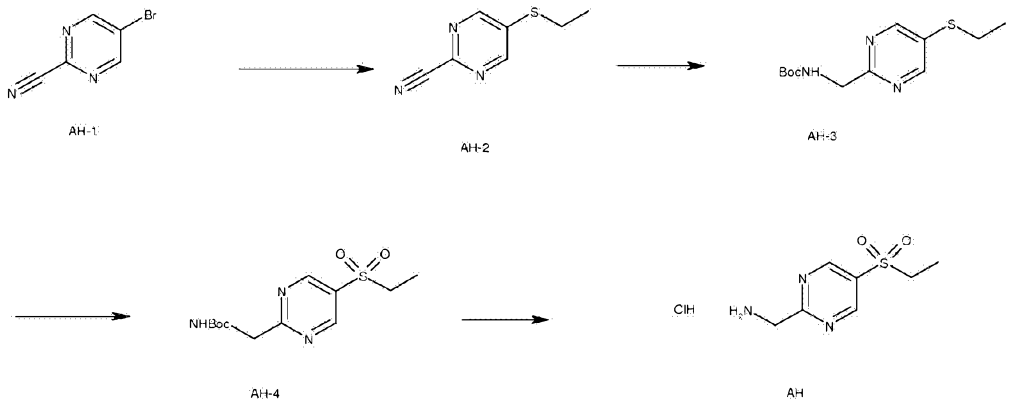
[0088] A solution of **AG-3** (3.3 g, 16.8 mmol) and Pd/C (500 mg, 10% on carbon catalyst) in MeOH (30 mL) is stirred at rt under H_2 (50 psi) for 8 h. The vessel is purged with N_2, filtered and the filtrate concentrated to yield **AG-4.**

[0089] To a stirred solution of **AG-4** (2.5 g, 12.5 mmol) in EtOAc (30 mL) is added HCl in EtOAc (2N, 20.0 mL). The solution is stirred at rt for 5 h and then filtered to yield **intermediate AG.** MS (ES+): m/z 201.2 $[M+H]^+$.

Method 9:

Synthesis of Intermediate AH

[0090]



[0091] A mixture of **AH-1** (113 g, 0.62 mol), K_2CO_3 (171 g, 1.24 mol) and sodium ethanethiolate (67 g, 0.80 mol) in DMF (2 L) is stirred at rt under N_2 for 18 h. The mixture is diluted with H_2O and extracted with EtOAc. The organic layers are dried (Na_2SO_4), decanted and concentrated. The resultant residue is purified by SiO_2 flash chromatography to yield **AH-2.**

[0092] A solution of **AH-2** (20.0 g, 0.12 mol), RaNi (40 g), Boc_2O (31.7g, 0.14 mol) and TEA (24.5 g, 0.24 mol) in THF (600 mL) is stirred at rt under H_2 (50 psi) for 12 h. The mixture is filtered and the filtrate concentrated under reduced pressure. The resultant residue is purified by SiO_2 flash chromatography to yield **AH-3.**

[0093] To a suspension of **AH-3** (65 g, 0.24 mol) in AcOH (200 mL) at -10 °C is added

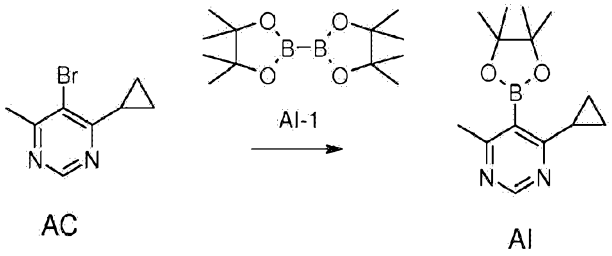
dropwise a solution of $KMnO_4$ (45.8 g, 0.29 mL) in water (500 mL). Following complete addition, the reaction mixture is stirred at rt for 30 min. The mixture is diluted with H_2O and basified by addition of aqueous Na_2CO_3 to ~pH 8 and extracted with EtOAc. The combined organic layers are dried (Na_2SO_4), decanted, and concentrated. The resultant residue is purified by crystallization to yield **AH-4.**

[0094] To a stirred solution of compound **AH-4** (46.5 g, 0.15 mol) in MeOH (300 mL) is added 4M HCl in MeOH (300 mL) at rt and stirred for 15 h. The mixture is concentrated under reduced pressure. The resultant residue is purified by crystallization to yield **intermediate AH.** MS (ES+): *m/z* 202.1 $[M+H]^+$.

Method 10:

Synthesis of Intermediate AI

[0095]

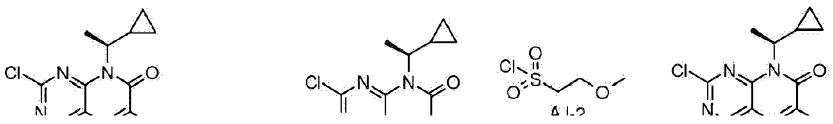


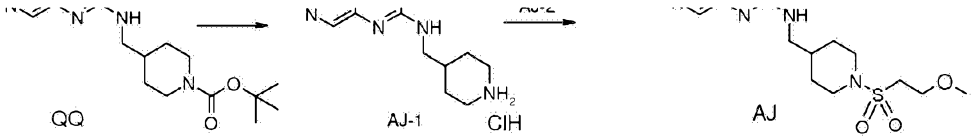
[0096] A suspension of **AC** (2 g, 9.4 mmol), **AI-1** (4.8 g, 18.8 mmol), KOAc (2.8 g, 28.2 mmol), and Pd(dppf)Cl_2 (1.15 g, 0.15 mmol) in 1,4-dioxane (40 mL) is stirred at 100 °C for 18 h. After cooling to rt, the mixture is diluted with water (10 mL) and extracted with EtOAc (2x50 mL). The combined organic phase is dried (Na_2SO_4), decanted and concentrated. The resultant residue is purified by SiO_2 flash chromatography to yield **AI.** MS (ES+): *m/z* 262.2 $[M+H]^+$.

Method 11:

Synthesis of Intermediate AJ

[0097]





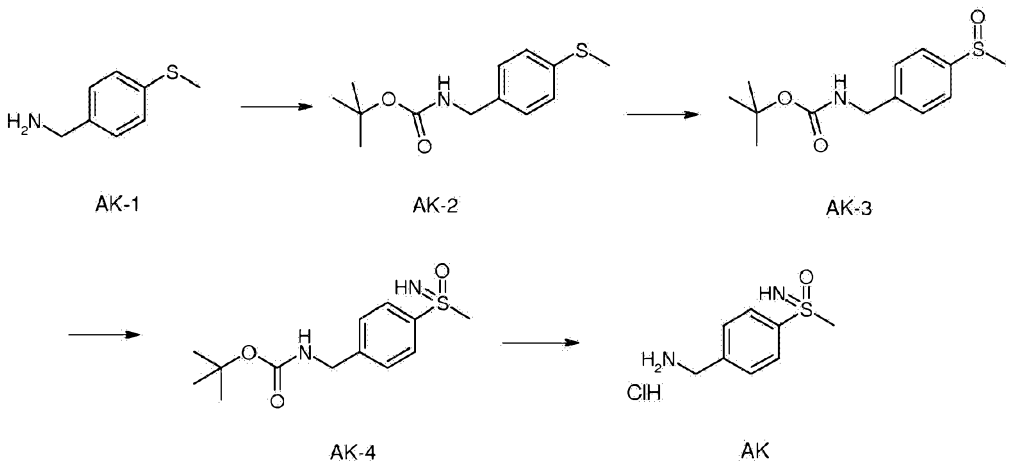
[0098] To a solution of **QQ** (509 mg, 1.1 mmol) in MeOH (4 mL) is added HCl in dioxane (4N, 1.1 mL, 4.4 mmol). The reaction mixture is stirred at rt for 18 h. The mixture is concentrated under reduced pressure. The resultant residue is triturated with diethyl ether and filtered to yield intermediate **AJ-1.**

[0099] To a solution of **AJ-1** (200 mg, 0.55 mmol) in DCM (3 mL) is added TEA (0.77 mL, 5.51 mmol), followed by **AJ-2** (175 mg, 1.10 mmol). The reaction mixture is stirred at rt for 1 h, then diluted with water (5 mL) and extracted with EtOAc (20 mL). The organic layer is dried (Na_2SO_4), decanted and concentrated. The resultant residue is purified by SiO_2 flash chromatography to yield **intermediate AJ.** MS (ES+): m/z 485.0 $[M+H]^+$.

Method 12:

Synthesis of Intermediate AK

[0100]



[0101] To a solution of **AK-1** (2.00 g, 13.1 mmol) in THF (25 mL) is added Boc_2O (3.45 mL, 15.0 mmol) and TEA (3.64 mL, 26.1 mmol). The reaction mixture is stirred at rt for 18 h and then diluted with H_2O and extracted with EtOAc. The organic layers are concentrated to yield **AK-2**.

[0102] To solution of **AK-2** (3.3 g, 13.1 mmol) in AcOH (10 mL) is slowly added H_2O_2 (1.37 mL, 13.7 mmol) The reaction mixture is stirred at rt for 3 h and is then quenched with saturated

$Na_2SO_{3(aq)}$ and neutralized with IN $NaOH_{(aq)}$. The mixture is extracted with EtOAc and concentrated to yield **AK-3.**

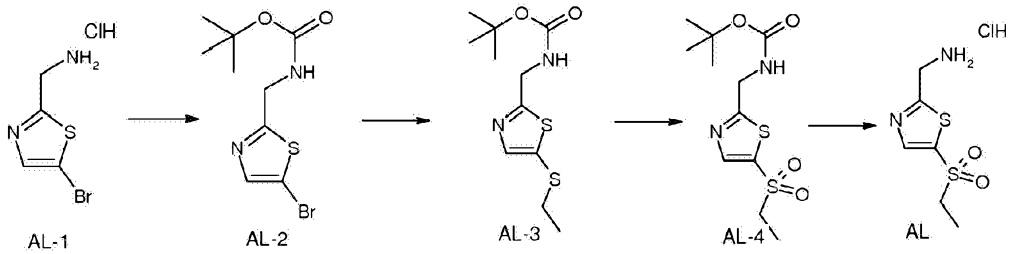
[0103] A mixture of **AK-3** (1.0 g, 3.7 mmol), MgO (600 mg, 14.9 mmol), trifluoroacetamide (839 mg, 7.4 mmol), and Rh(II) acetate dimer (115 mg, 0.26 mmol) in DCM (10 mL) is added (diacetoxyiodo)benzene (1.79 g, 5.6 mmol). The mixture is stirred at rt for 18 h and then concentrated under reduced pressure. The resultant residue is dissolved in MeOH, filtered through a pad of diatomaceous earth and to it, K_2CO_3 (2.55 g, 18.6 mmol) is added. The mixture is stirred at rt for 18 h and is concentrated under reduced pressure. The resultant residue is purified by SiO_2 flash chromatography to yield **AK-4.**

[0104] To a stirred solution of compound **AK-4** (585 mg, 2.1 mmol) in DCM (2 mL) is added HCl in dioxane (4N, 2 mL). The reaction mixture is stirred at rt for 15 h and then concentrated under reduced pressure to yield **intermediate AK**. MS (ES+): *m/z* 185.0 $[M+H]^+$.

Method 13:

Synthesis of Intermediate AL

[0105]



[0106] To a solution of **AL-1** (500 mg, 2.18 mmol) in ACN (12 mL) is added DIEA (0.46 mL, 2.61 mmol), Boc_2O (1.02 g, 4.68 mmol), followed by DMAP (13.3 mg, 0.11 mmol). The reaction mixture is stirred at rt for 2.5 h. The reaction mixture is concentrated and the residue is diluted with EtOAc and washed with H_2O then brine, dried over Na_2SO_4, filtered and concentrated. The residue is purified by SiO_2 flash chromatography to yield **AL-2.**

[0107] A mixture of **AL-2** (250 mg, 0.85 mmol), $Pd_2(dba)_3$ (39 mg, 0.043 mmol) Xanphos (41 mg, 0.071 mmol), Josiphos (13 mg, 0.024 mmol) and TEA (0.83 mL, 0.97 mmol) in toluene (17 mL) is degassed and heated to 115 °C for 1 h. The reaction mixture is then cooled to rt and ethanethiol (0.076 mL, 1.02 mmol) is added. The reaction mixture is heated to 115 °C for 3 h. The reaction mixture is concentrated and the residue is purified by SiO_2 flash chromatography to yield **AL-3.**

[0108] To a solution of **AL-3** (200 mg, 0.71 mmol) in acetone (14 mL) is added a solution of oxone (961 mg, 1.56 mmol) in water (7 mL). The reaction mixture is stirred at rt of or 18 h.

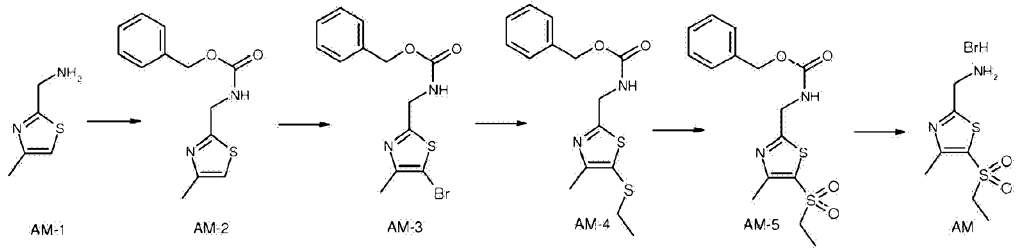
[0109] The mixture is concentrated then diluted with H_2O and extracted with DCM twice. The organics are combined and washed with brine, dried over Na_2SO_4, filtered and concentrated to yield **AL-4.**

[0110] To a solution of **AL-4** (206 mg, 0.67 mmol) in DCM (4 mL) is added HCl in dioxane (4N, 1.68 mL, 6.73 mmol). The reaction mixture is stirred at rt for 2 h. The reaction mixture is concentrated to yield **AL** as the HCl salt. MS (ES+): m/z 207.1 $[M+H]^+$.

Method 14:

Synthesis of Intermediate AM

[0111]



[0112] To a solution of **AM-1** (1 g, 7.80 mmol) in THF (40 mL) at 0 °C is added DIEA (4.08 mL, 23.40 mmol) followed by dropwise addition of benzylchloroformate (1.52 mL, 10.14 mmol). The reaction mixture is warmed to rt and stirred overnight. The reaction mixture is then concentrated, diluted with water and then extracted with EtOAc. The organic layer is then washed with sat. aq $NaHCO_3$ (2X), H_2O (2X), and brine, dried over $MgSO_4$, filtered and concentrated. The residue is purified by SiO_2 flash chromatography to yield **AM-2.**

[0113] To a solution of **AM-2** (1 g, 3.81 mmol) in THF (20 mL) at 0 °C is added dropwise Br_2 (0.30 mL, 5.91 mmol). The reaction mixture is warmed to rt and stirred overnight. The reaction mixture is diluted with water then extracted with EtOAc. The organic layer is then washed with sat. aq $NaHCO_3$ (2X), water (2X) and brine, dried over $MgSO_4$, filtered and concentrated. The residue is purified by SiO_2 flash chromatography to yield **AM-3.**

[0114] AM-4 is synthesized in a fashion analogous to **intermediate AL-3.**

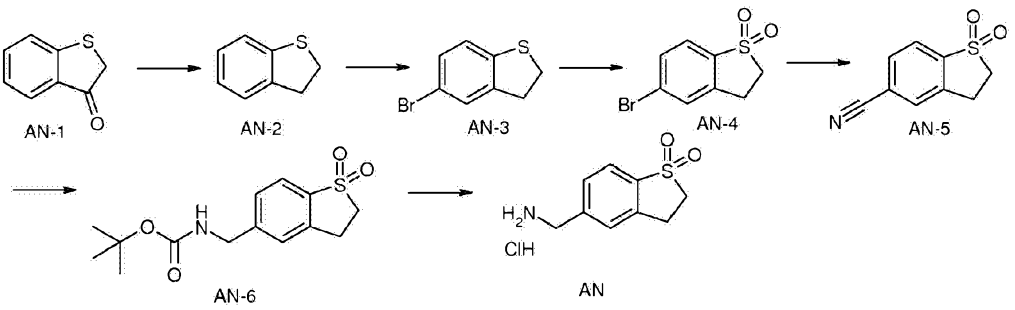
[0115] AM-5 is synthesized in a fashion analogous to **intermediate AL-4.**

[0116] To a solution of **AM-5** (146 mg, 0.41 mmol) in EtOH (10 mL) is added 10% Pd/C (150 mg) and the mixture is stirred at rt under an H_2 atmosphere for 18 h. The reaction mixture is filtered through celite and washed with EtOAc. The filtrate is concentrated then HBr in acetic acid (1.5 mL, 33wt%) is added. The mixture is stirred at rt for 2.5 h then filtered to yield **AM** as the HCl salt. MS (ES+): m/z 221.1 $[M+H]^+$.

Method 15:

Synthesis of Intermediate AN

[0117]



[0118] To a solution of **AN-1** (6 g, 3.99 mmol) in EtOH (60 mL) is added N_2H_4 hydrate (31.1 ml). The mixture is heated to reflux for 45 min. The mixture is cooled to rt and then concentrated. The residue is dissolved in diethylene glycol (20 mL) and KOH (6.72 g, 120 mmol) is added. The mixture is stirred at 120 °C for 18 h. The mixture is cooled to rt, diluted with EtOAc and the pH is adjusted with IN HCl to pH < 4. The organic layers are washed with brine, dried over Na_2SO_4 and concentrated. The residue is purified by SiO_2 flash chromatography to yield **AN-2.**

[0119] To a solution of **AN-2** (1.3 g, 9.54 mmol) in DCM (20 mL) is added dropwise Br_2 (1.53 g, 9.57 mmol) at 0 °C. The mixture is stirred at rt for 12 h. The mixture is quenched with aq $NaHSO_3$ and extracted with DCM twice. The organic layers are combined and washed with brine, dried over Na_2SO_4 and concentrated. The residue is purified by SiO_2 flash chromatography to yield **AN-3.**

[0120] AN-4 is synthesized in a fashion analogous to **intermediate AH-4.**

[0121] To a solution of **AN-4** (800 mg, 3.24 mmol) in NMP (10 mL) is added CuI (920 mg, 4.83 mmol) and CuCN (397 mg, 4.43 mmol). The microwave reaction is heated at 200 °C for 3 h.

The mixture is poured into H_2O, extracted with EtOAc. The organic layer is washed with brine, dried over Na_2SO_4 and concentrated. The residue is purified by recrystallization to yield **AN-5.**

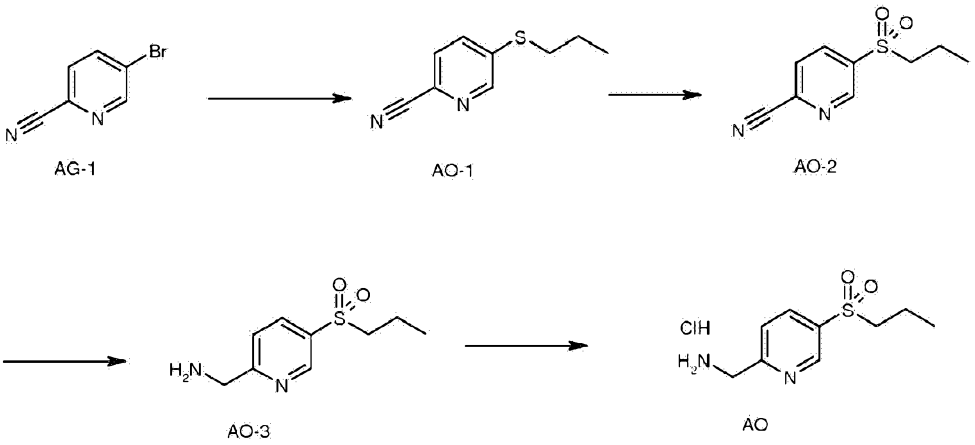
[0122] **AN-6** is synthesized in a fashion analogous to **intermediate AH-3.**

[0123] **AN** is synthesized in a fashion analogous to **intermediate AH.** MS (ES+): m/z 198.0 $[M+H]^+$.

Method 16:

Synthesis of Intermediate AO

[0124]



[0125] To a solution of sodium 1-propanethiolate (12.8 g, 130 mmol) in ACN (150 mL) kept below 20 °C is added portion-wise **AG-1** (19.8 g, 108 mmol). The mixture is then stirred at rt for 16 h, poured into water (300 mL) and extracted with EtOAc (300 mL). The combined organic phase is dried (Na_2SO_4), filtered and concentrated. The residue is purified by SiO_2 flash chromatography to yield **AO-1.**

[0126] To a stirred solution of **AO-1** (16.5 g, 83.0 mmol) in AcOH (150 mL) kept below 10 °C is added a solution of $KMnO_4$ (14.5 g, 92.0 mmol) in H_2O (150 mL) dropwise. The reaction mixture is stirred for 30 min. The mixture is diluted with water, basified by addition of saturated aq Na_2CO_3 and extracted with EtOAc. The solution is concentrated and the residue is purified by SFC to yield **AO-2.**

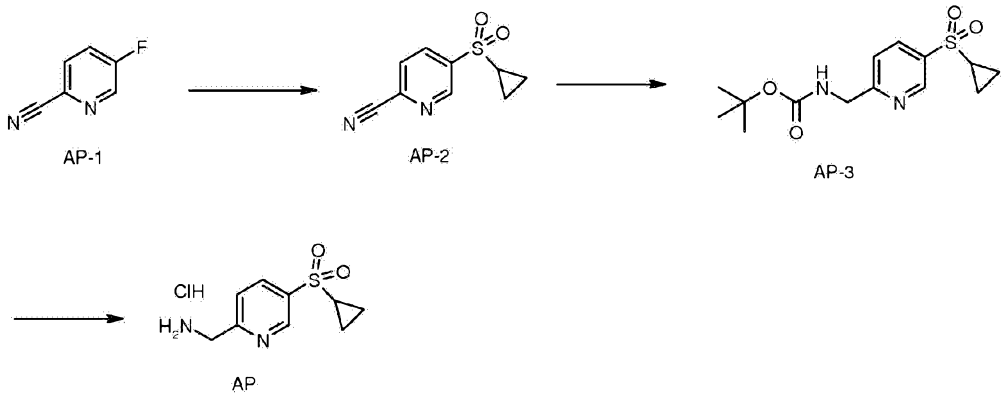
[0127] A mixture of **AO-2** (7.80 g, 37.0 mmol) and Ra Ni (8.00 g) in MeOH (100 mL) is stirred at rt under H_2 for 18 h. After filtration and concentration the residue is purified by MPLC to yield **AO-3.**

[0128] To solid **AO-3** (7.40 g, 35.0 mmol) is added acetic acid ethyl ester (2 mL) and HCl in EtOAc (100 mL). The solution is stirred at rt for 5h and the solids are filtered to yield **intermediate AO.**

Method 17:

Synthesis of Intermediate AP

[0129]



[0130] A mixture of **AP-1** (12.8 g, 130 mmol), sodium cyclopropanesulfonate (53.1 g, 369 mmol) and CuI (23.3 g, 123 mmol) in DMSO (150 mL) is stirred at 110 °C for 2 h. After cooling to rt, the solution is poured into water and extracted with EtOAc. The combined organic phase is dried over Na_2SO_4, filtered and concentrated. The resulting residue is purified by MPLC to yield **AP-2.**

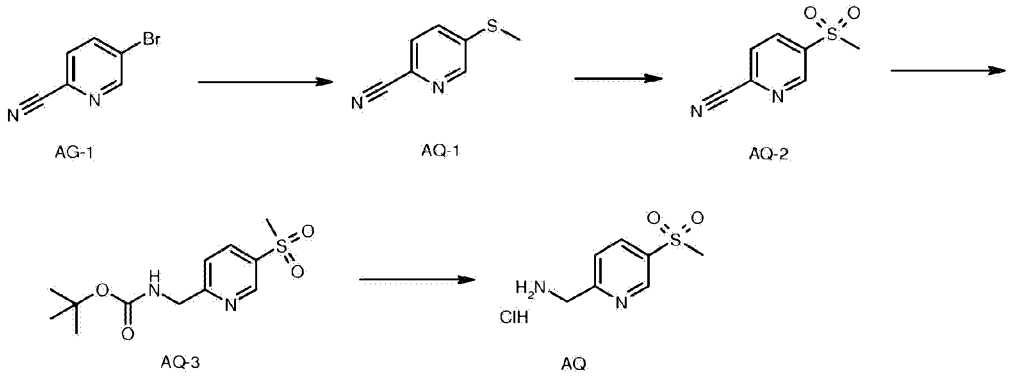
[0131] A mixture of **AP-2** (10.3 g, 49 mmol), Ra Ni (25.0 g), Boc_2O (16.2 g, 74 mmol) and TEA (10.0 g, 99 mmol) in MeOH (250 mL) is stirred under a H_2 atmosphere at rt for 18 h. After filtration and concentration the residue is purified by MPLC to AP-3.

[0132] To a solution of **AP-3** (6.90 g, 22 mmol) in MeOH (60 mL) is added HCl in EtOH (60 mL). The solution is stirred at rt for 3 h and is concentrated and recrystallized to yield **intermediate AP.**

Method 18:

Synthesis of Intermediate AQ

[0133]



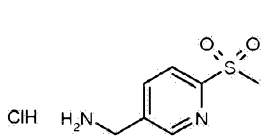
[0134] To a solution of **AG-1** (82.0 g, 448 mmol) in ACN (1.0 L) is added sodium t-butoxide (64.5 g). The mixture is cooled to 0 °C and sodium methanethiolate (172.5 g, 20% in H_2O) is added dropwise. The reaction mixture is then allowed to stir at rt for 16 h. Water (800 mL) is added and the mixture is extracted with DCM. The combined organic phases are washed with brine, dried (Na_2SO_4) and concentrated. The residue is purified by SiO_2 flash chromatography to yield **AQ-1.**

[0135] To a suspension of **AQ-1** (51.5 g, 343 mmol) in AcOH (500 mL) is added a solution of $KMnO_4$ (59.7 g, 36.6 mmol) in H_2O (500.0 mL) dropwise at 5 °C. The reaction mixture is then stirred at rt for 1 h. The mixture is extracted with EtOAc, washed with aq. $NaHCO_3$, dried (Na_2SO_4) and concentrated. The resultant residue is purified by recrystallization to yield **AQ-2.**

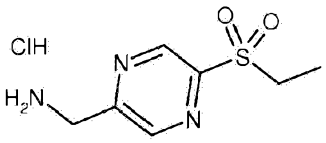
[0136] To a solution of **AQ-2** (15.0 g, 82 mmol) in MeOH (200 mL) is added Ra Ni (10.0 g), TEA (34.4 mL) and Boc_2O (17.8 g). The mixture is stirred at rt under H_2 (50 psi) for 12 h. The vessel is purged with N_2, filtered and the filtrate concentrated. The residue is purified by SiO_2 flash chromatography to yield **AQ-3.**

[0137] A solution of **AQ-3** (30.0 g, 105 mmol) in HCl in MeOH (500 mL) is stirred at rt for 12 h. The mixture is concentrated and recrystallized to yield **intermediate AQ.** MS (ES+): m/z 187 $[M+H]^+$.

[0138] Intermediate AR and **Intermediate AS** (as the HCl salt. MS (ES+): m/z 202.1 $[M+H]^+$) is synthesized in a fashion analogous to **intermediate AQ.**



AR

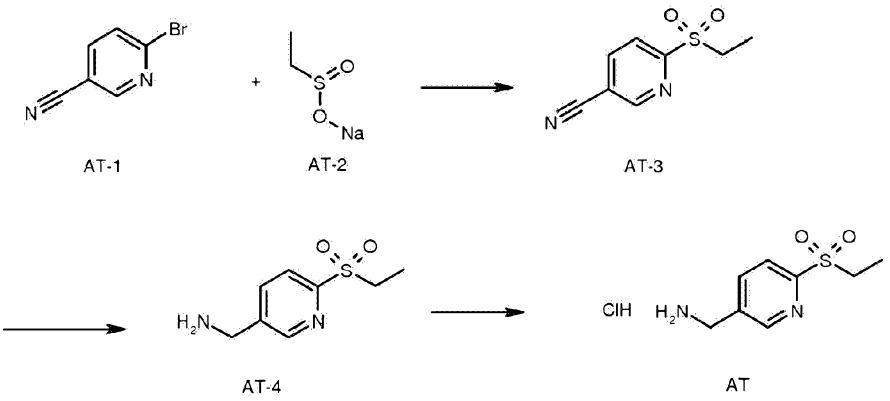


AS

Method 19:

Synthesis of Intermediate AT

[0139]



[0140] To a mixture of **AT-1** (10.0 g, 55 mmol), N,N-dimethyl-ethane-1,2-diamine (0.96 g, 11 mmol) and Copper(II) trifluoromethanesulfonate (1.98, 5 mmol) in DMSO (100 mL) is added **AT-2** (8.27 g, 98 mmol) at rt. The mixture is then heated to 120 °C for 30 min, quenched with H_2O and extracted with EtOAc. The organic layer is dried, concentrated and purified by SiO_2 flash chromatography to yield **AT-3.**

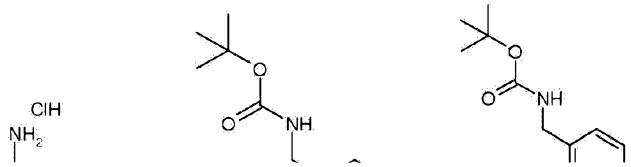
[0141] A mixture of **AT-3** (32.3 g, 165 mmol) and Pd (3.50 g, 33 mmol) in NH_4OH (30 mL)/EtOH (200 mL) is stirred at rt under H_2 (15 psi) for 15 h. The mixture is filtered, concentrated and purified by SiO_2 flash chromatography to yield **AT-4.**

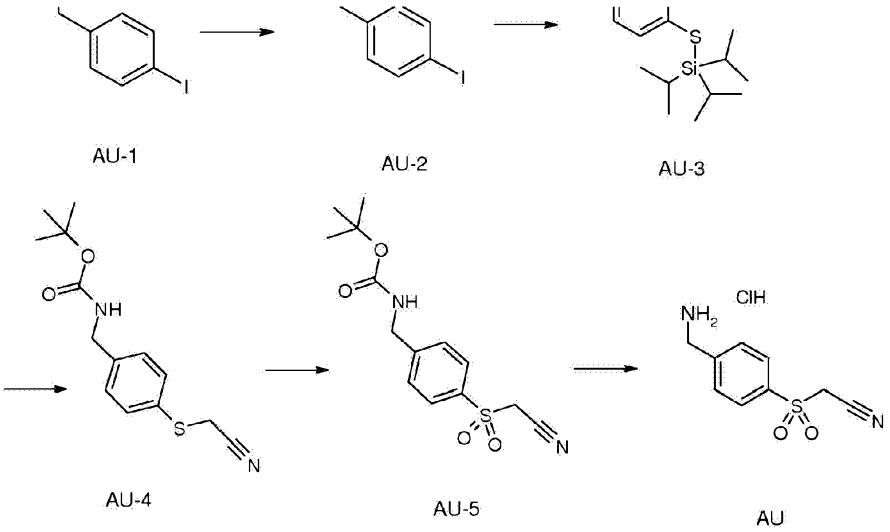
[0142] To a stirred solution of **AT-4** (17.5 g, 87 mmol) in EtOH (100 mL) is added HCl in EtOH (100 mL). The solution is stirred at rt for 3 h and then concentrated and recrystallized to yield **intermediate AT.** MS (ES+): m/z 201 $[M+H]^+$.

Method 20:

Synthesis of Intermediate AU

[0143]





[0144] To a solution of **AU-1** (7.15 g, 26.5 mmol) in THF (50 mL) is added Boc_2O (6.70 mL, 29.2 mmol) and TEA (7.40 mL, 53.1 mmol). The reaction is allowed to stir at rt for 72 h. The solution is concentrated to yield **AU-2.**

[0145] A mixture of **AU-2** (5.25 g, 15.8 mmol), sodium t-butoxide (1.82 g, 18.9 mmol), $Pd(OAc)_2$ (177 mg, 0.79 mmol), and 1,1'-Bis(diisopropylphosphino)ferrocene (396 mg, 0.95 mmol) are added to a sealed vessel which is purged with argon. Dioxane (35 mL) is added and the mixture is stirred at rt for 1h. Triisopropylsilanethiol (3.72 mL, 17.3 mmol) is added and the solution is heated to 100 °C for 1 h. The reaction is then poured into EtOAc and water. The organic layer is concentrated and the residue is purified by SiO_2 flash chromatography to yield **AU-3.**

[0146] A solution of **AU-3** (2.50 g, 6.32 mmol) in THF (25 mL) is cooled to 0 °C and degassed with argon. Terabutylammoniumbromide (2.12 g, 7.58 mmol) is then added and the solution is stirred at 0 °C for 1 h. Bromoacetonitrile (660 uL, 9.48 mmol) is then added and the solution is stirred at 0 °C for 5 min. The solution is concentrated and partitioned between diethyl ether and water. The organic layer is concentrated to yield **AU-4** which is carried forward without further manipulation.

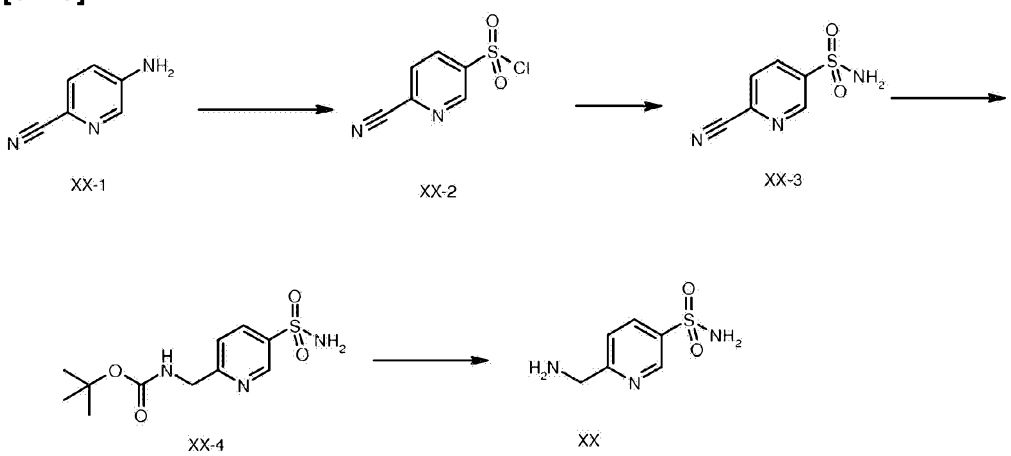
[0147] To a solution of **AU-4** (1.80 g, 6.47 mmol) in ACN/H_2O (10 mL) is added sodium periodate (4.18 g, 19.5 mmol) followed by ruthenium(III) chloride (7.87 mg, 0.038 mmol). The reaction mixture is stirred at rt for 30 min and is then concentrated. The residue is purified by SiO_2 flash chromatography to yield **AU-5.**

[0148] To a stirred solution of **AU-5** (470 mg, 1.51 mmol) in DCM (3 mL) is added HCl in dioxane (2.00 mL, 8.00 mmol). The solution is stirred at rt for 1 h and concentrated to yield **intermediate AU.** MS (ES+): m/z 211.1 $[M+H]^+$.

Method 21:

Synthesis of Intermediate AV

[0149]



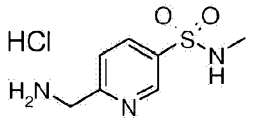
[0150] AV-1 (20.0 g, 168 mmol) is added to conc. HCl (200 mL) at 0 °C followed by dropwise addition of aq $NaNO_2$ (25.5 g in 25 mL H2O) maintaining an internal temperature of < 5 °C. The solution is allowed to stir at 0 °C for 15 min and then is slowly added to a mixture of SO_2 (108 g) and CuCl (84 mg) in AcOH (200 mL, > 5eq) at 5 °C. The solution is stirred 90 min at 5 °C. The reaction mixture is extracted with DCM (2 x 500 mL), dried (Na_2SO_4), and the organic solution of **AV-2** used directly in the next step.

[0151] To a solution of **AV-2** (20.0 g, 99 mmol) in DCM (200 mL) is added a solution of ammonia in MeOH (100 mL) at 0 C and stirred at rt for 30 min. The mixture is concentrated to dryness and the resultant residue is purified by SiO_2 flash chromatography to yield **AV-3.**

[0152] To a solution of **AV-3** (15.0 g, 82 mmol) in MeOH (200 mL) is added Ra Ni (10.0 g), TEA (34.4 mL) and Boc_2O (17.8 g). The mixture is stirred at rt under H_2 (50 psi) for 12 h. The vessel is purged with N_2, filtered and the filtrate concentrated. The residue is purified by SiO_2 flash chromatography to yield **AV-4.**

[0153] A solution of **AV-4** (30.0 g, 105 mmol) in HCl in MeOH (500 mL) is stirred at rt for 12 h. The mixture is concentrated and recrystallized to yield **intermediate AV.** MS (ES+): m/z 188.1 $[M+H]^+$.

[0154] Intermediate AW is synthesized in a fashion analogous to **Intermediate AV.**

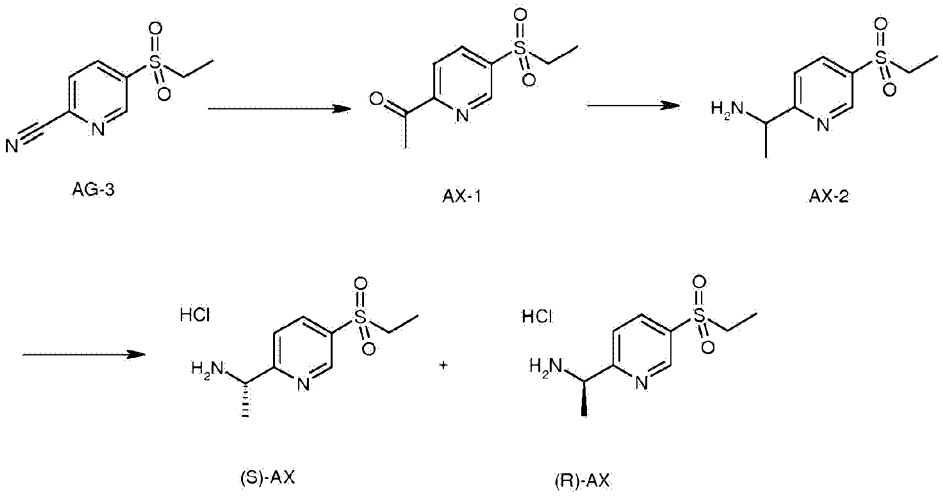


AW

Method 22:

Synthesis of Intermediates (S)- AX and (R)-AX

[0155]



[0156] To a solution of **AG-3** (2.40g, 12 mmol) in THF (30 mL) is added dropwise MeMgBr (30 mL) at -30 °C. After the addition, the mixture is stirred at rt for 4 h.The reaction mixture is quenched by addition of sat. aq NH_4Cl (100 mL) and extracted with EtOAc (3 x 100 mL). The organic phase is washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue is purified by SiO_2 flash chromatography to yield **AX-1.**

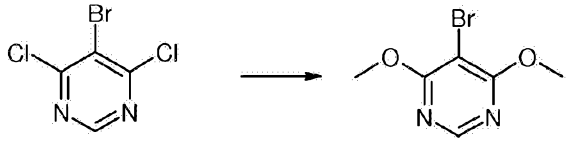
[0157] To a solution of **AX-1** (200 mg, 1.0 mmol) in MeOH (2 mL) is added NH_4OAc (723 mg) and $NaBH_3CN$ (41 mg) at 0 °C. The mixture is stirred at rt for 16 h. The solvent is removed under reduced pressure, water (50 mL) is added and the mixture is adjusted to pH > 12 and then extracted with DCM (50 mL). The organic phase is dried over Na_2SO_4 and concentrated. The residue is purified by prep-TLC to yield **AX-2.**

[0158] AX-2 is separated by SFC to give **(S)-AX** (67.9%ee) and **(R)-AX** (95.5%ee).

Method 23:

Synthesis of Intermediates AY

[0159]



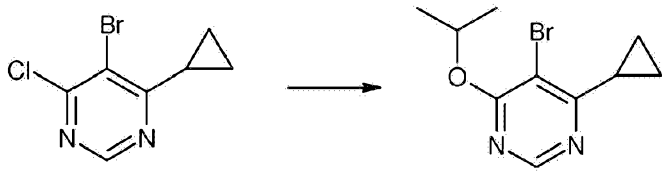
AY-1 AY

[0160] To a solution of **AY-1** (1.25g, 5.49 mmol) in anhydrous MeOH (15 mL) is added NaOMe (2.37g, 43.89 mmol). The mixture is stirred at rt for 1 h. The solution is filtered and concentrated. The residue is purified by SiO_2 flash chromatography to yield **intermediate AY.** MS (ES+): *m/z* 218.9 $[M+H]^+$.

Method 24:

Synthesis of Intermediates AZ

[0161]



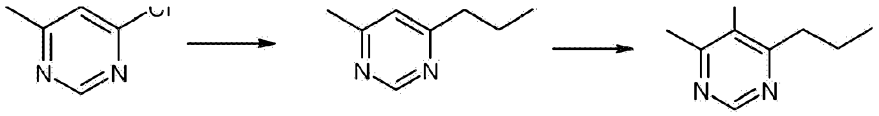
AB-1 AZ

[0162] To a solution of sodium hydride (342 mg, (60%), 8.57 mmol) in DMF (10 mL) is added anhydrous isopropanol (360 uL, 4.71 mmol). The mixture is stirred at rt for 1 h. **AB-1** (1.00 g, 4.28 mmol) is then added and the mixture is stirred for an additional 1 h before being poured onto ice. The mixture is then extracted with EtOAc and concentrated. The residue is purified by SiO_2 flash chromatography to yield **intermediate** AZ. MS (ES+): *m/z* 258.8 $[M+H]^+$.

Method 25:

Synthesis of Intermediates BA

[0163]



BA-1 BA-2 BA

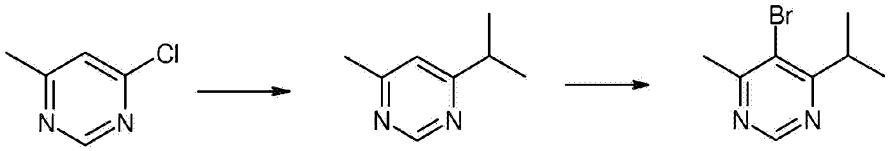
[0164] A solution of **BA-1** (1.00 g, 7.78 mmol), and $Ni(dppe)Cl_2$ (82 mg, 0.16 mmol) in anhydrous Et_2O (5 mL) is cooled to -10 °C. Then, n-propyl magnesium bromide is added dropwise and the mixture is stirred for 2 h at -10 °C. The mixture is quenched with saturated NH_4Cl, extracted with DCM and concentrated. The crude **BA-2** is carried forward without further manipulation.

[0165] To a solution of **BA-2** (1.0 g, 7.34 mmol) in EtOH (10 mL) at 0 °C is added Br_2 (379 uL, 7.34 mmol). The reaction mixture is stirred at rt for 2 h. The solution is concentrated and the residue is purified by SiO_2 flash chromatography to yield **intermediate BA.** MS (ES+): *m/z* 217.4 $[M+H]^+$.

Method 26:

Synthesis of Intermediates BC

[0166]



BA-1 BC-1 BC

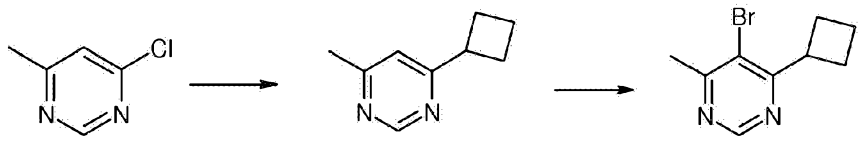
[0167] A solution of **BA-1** (1.00 g, 7.78 mmol), and $Ni(dppe)Cl_2$ (82 mg, 0.16 mmol) in anhydrous Et_2O (5 mL) is cooled to -10 °C. A solution of isopropyl magnesium bromide (3.22 mL, 9.33 mmol) is added dropwise and the mixture is stirred for 1 h at -10 °C. The mixture is quenched with sat. NH_4Cl, extracted with DCM and concentrated. The crude **BC-1** is carried on as is.

[0168] To a solution of **BC-1** (1.0 g, 7.34 mmol) in EtOH (10 mL) at 0 °C is added Br_2 (378 uL, 7.34 mmol). The reaction mixture is stirred at rt for 2 h. The solution is concentrated and the residue is purified by SiO_2 flash chromatography to yield **intermediate BC.** MS (ES+): *m/z* 216.4 $[M+H]^+$.

Method 27:

Synthesis of Intermediates BD

[0169]



BA-1 BD-1 BD

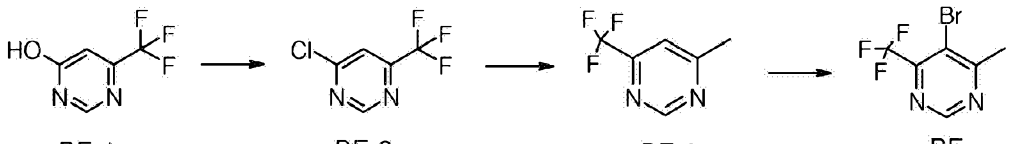
[0170] A solution of **BA-1** (1.00 g, 7.78 mmol), and $Ni(dppe)Cl_2$ (82 mg, 0.16 mmol) in anhydrous Et_2O (5 mL) is cooled to -10 °C. A solution of cyclopropyl magnesium bromide (1.36 g, 8.56 mmol) is added dropwise and the mixture is stirred for 2 h at -10 °C. The mixture is quenched with saturated aqueous NH_4Cl, extracted with DCM and concentrated. The crude **BD-1** is carried forward without further manipulation.

[0171] To a solution of **BD-1** (1.0 g, 6.74 mmol) in EtOH (10 mL) at 0 °C is added Br_2 (347 uL, 6.74 mmol). The reaction mixture is stirred at rt for 18 h. The solution is concentrated and the residue is purified by SiO_2 flash chromatography to yield **intermediate BD.** MS (ES+): *m/z* 229.2 $[M+H]^+$.

Method 28:

Synthesis of Intermediate BE

[0172]



BE-1 BE-2 BE-3 BE

[0173] To a solution of **BE-1** (40.0 g, 244 mmol) in THF (800 mL) is added PPh_3 (98.0 g) and NCS (160.0 g). The reaction mixture is stirred at 80 °C for 10 h. The mixture is then quenched with water and extracted with EtOAc. The solution is concentrated and the residue is purified by SiO_2 flash chromatography to yield **BE-2.**

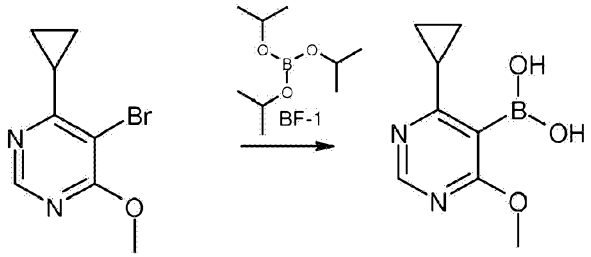
[0174] To a stirred solution of **BE-2** (3.00 g, 14.79 mmol) in toluene and DMF is added $Pd(PPh_3)_4$ (600 mg), $Pd(dppf)Cl_2$ (600 mg) and Na_2CO_3 (6.27 g, 59.17 mmol). The mixture is stirred at 90 °C for 5 h. The mixture is quenched with water, extracted with EtOAc. The solution is concentrated and the residue is purified by SiO_2 flash chromatography to yield **BE-3.**

[0175] To a solution of **BE-3** (860 mg, 5.0 mmol) in EtOH (5 mL) at-10 °C is added Br_2 (347 uL, 6.74 mmol). The reaction mixture is stirred at rt for 18 h. The solution is concentrated and the residue is purified by SiO_2 flash chromatography to yield **intermediate BE.** MS (ES+): *m/z* 267 $[M+H]^+$.

Method 29:

Synthesis of Intermediate BF

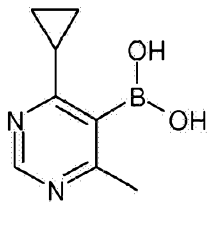
[0176]



AB BF

[0177] To a solution of **AB** (6.00 g, 26.2 mmol) and **BF-1** (7.86 mL, 34.1 mmol) in toluene (60 mL) and THF (18 mL) at -78 °C is added n-butyl lithium (12.6 mL, 31.4 mmol), dropwise, over 30 min. The solution is the stirred at -78 °C for 30 min and is then slowly warmed to - 20 °C. The solution is the quenched with 1 N HCl (40 mL). The layers are then separated and the aqueous layer is adjusted to pH ~8 with 2M NaOH. A white solid begins to precipitate and the mixture is cooled in the refrigerator for 1 h. The solids are filtered to yield **intermediate BF.** The aqueous layer is extracted with MeTHF and concentrated to give additional **intermediate BF.** MS (ES+): *m/z* 195.1 $[M+H]^+$.

[0178] Intermediate BG is synthesized in a fashion analogous to **Intermediate BF.**

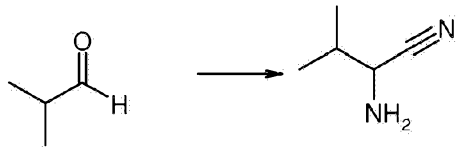


BG

Method 30:

Synthesis of Intermediate BH

[0179]



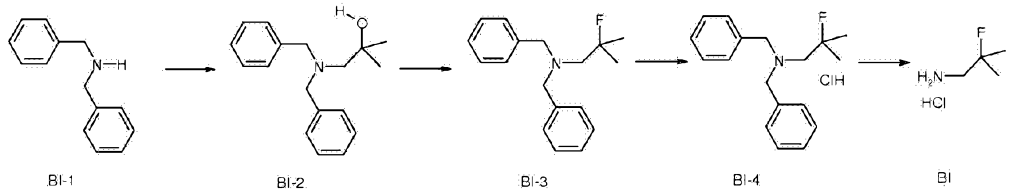
BH

[0180] To a mixture of 2-methyl-propionaldehyde (5 g, 69.34 mmol) and NH_4Cl (7.42 g, 138.69 mmol) in water (50 mL) is added NaCN (4.08 g, 83.2 mmol). The mixture is stirred at rt for 18 h. The mixture is extracted with EtOAc (3x). The organics are combined, dried over Na_2SO_4, concentrated to give crude **intermediate BH,** which is carried forward without further manipulation.

Method 31:

Synthesis of Intermediate BI

[0181]



BI-1 BI-2 BI-3 BI-4 BI

[0182] To a mixture of **BI-1** (20 mL, 104 mmol) and 2,2-dimethyl oxirane (15 mL, 17 mmol) is added LiBr (1.86 g, 21.4 mmol) in one portion. The reaction mixture is stirred at rt for 16 h. Additional 2,2-dimethyl oxirane (2.0 mL, 23 mmol) is added and the mixture is heated at 60 °C for 2 h. The reaction mixture is quenched with water then extracted with EtOAc twice. The organics are combined and washed with brine, dried over Na_2SO_4, filtered and concentrated to yield **BI-2.**

[0183] To a solution of **BI-2** (2.0 g, 7.4 mmol) in DCM (20 mL) at -21 °C is added Deoxo-Fluor (1.51 mL, 8.17 mmol). After the addition, the reaction mixture is stirred at -21 °C for 5 mins then quenched with sat. aq $NaHCO_3$ until pH ~ 8. The layers are separated and the aq layer is extracted with DCM. The combined organics are washed with sat. aq $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated to yield **BI-3.**

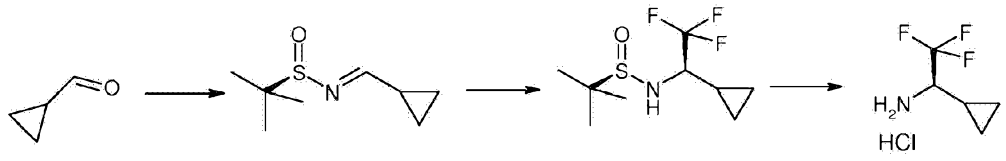
[0184] To a solution of **BI-3** (1.5 g, 5.5 mmol) in toluene (30 mL) is added dropwise HCl in dioxane (4N, 1.45 mL, 5.80 mmol). The reaction mixture is stirred at rt for 2 h then filtered to yield **BI-4.**

[0185] A mixture of **BI-4** (500 mg, 1.62 mmol), 5% Pd/C (103 mg) and MeOH (3 mL) is hydrogenated on Endeavor (60 °C, 400 psi) for 5 h. The reaction mixture is filtered through celite and rinsed with MeOH. The filtrate is concentrated to yield **intermediate BI** as the HCl salt. MS (ES+): m/z 92.3 $[M+H]^+$.

Method 32:

Synthesis of Intermediate BJ

[0186]



BJ-1 BJ-2 BJ-3 BJ

[0187] To a solution of **BJ-1** (7.40 mL, 99.0 mmol) in DCM (100 mL) is added (R)-2-methyl-2-propanesulfinamide (10.0 g, 82.5 mmol), $MgSO_4$ (49.66 g, 412 mmol) and pyridinium p-toluenesulfonate (1.04 g, 4.13 mmol). The reaction mixture is allowed to stir at rt for 72 h. The reaction mixture is then filtered and the residue is purified by SiO_2 flash chromatography to yield **BJ-2.**

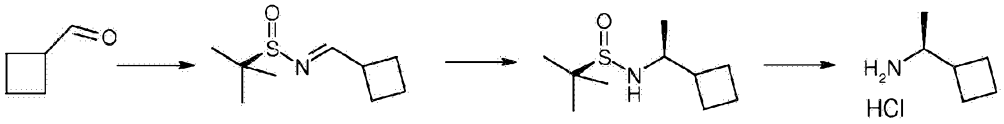
[0188] To a solution of **BJ-2** (9.72 g, 56.1 mmol) in THF (200 mL) is added tetramethylammonium fluoride (6.27 g, 67.3 mmol). The solution is degassed with argon and is then cooled to -55 °C. A solution of trifluoromethyltrimethylsilane (12.4 mL, 84.1 mmol) in THF (250 mL) is added dropwise with an additional funnel and the reaction is allowed to stir at -55 °C for 2 h. The reaction mixture is then slowly allowed to warm to - 10 °C and is quenched with sat. aqueous NH_4Cl. The aqueous layer is extracted with EtOAc and the combined organic layers are concentrated to yield **BJ-3,** which is carried forward without further manipulation.

[0189] To a solution of **BJ-3** (9.00 g, 37.0 mmol) in MeOH (30 mL) is added 4M HCl in dioxane (18.5 mL, 74.0 mmol). The solution is allowed to stir at rt for 1 h. The reaction mixture is then concentrated to half volume and diluted with diethyl ether until a white precipitate is formed. The solid is then filtered to yield **intermediate BJ.**

Method 33:

Synthesis of Intermediate BK

[0190]



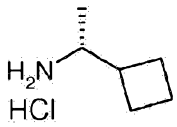
BK-1 BK-2 BK-3 BK

[0191] To a solution of **BK-1** (9.47 g, 113 mmol) in DCM (100 mL) is added (R)-2-methyl-2-propanesulfinamide (10.5 g, 86.6 mmol), $MgSO_4$ (52.1 g, 433 mmol) and pyridinium p-toluenesulfonate (1.09 g, 4.33 mmol). The reaction mixture is allowed to stir at rt for 18 h. The reaction mixture is then filtered and the residue is purified by SiO_2 flash chromatography to yield **BK-2.**

[0192] To a solution of **BK-2** (8.60 g, 45.9 mmol) in DCM (350 mL) at -50 °C, is added methylmagnesium bromide (36.0 mL, 108 mmol). The solution is stirred at -50 °C for 3h. The reaction is then allowed to warm to rt and stirred for 18 h. The solution is quenched with sat. aqueous NH_4Cl and extracted with EtOAc (2X). The organic layer is concentrated to yield **BK-3,** which is carried forward without further manipulation.

[0193] To a solution of **BK-3** (5.00 g, 24.6 mmol) in MeOH (20 mL) is added 4M HCl in dioxane (12.3 mL, 49.2 mmol). The solution is allowed to stir at rt for 1 h. The reaction mixture is then concentrated and the residue is purified by SiO_2 flash chromatography to yield **intermediate BK.**

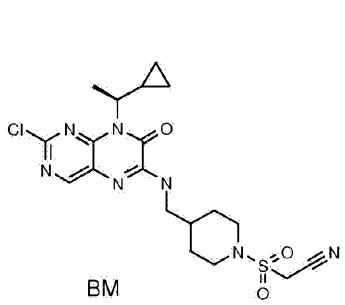
[0194] Intermediate BL is synthesized in a fashion analogous to **Intermediate BK**



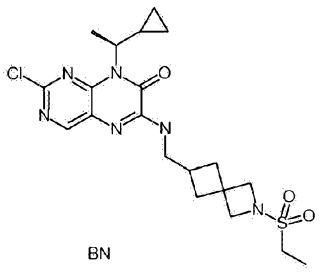
BL

Intermediates BM, BN, BO, BP, BQ, BR, BS are synthesized in a fashion analogous to Intermediate AJ

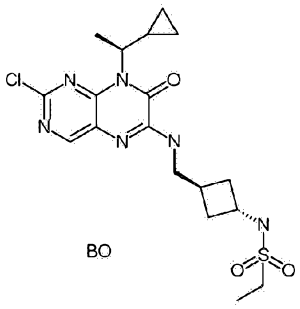
[0195]



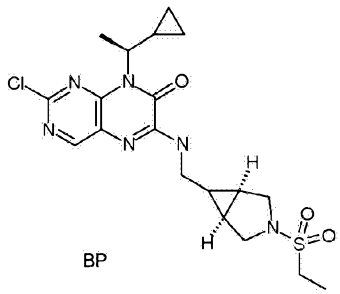
BM



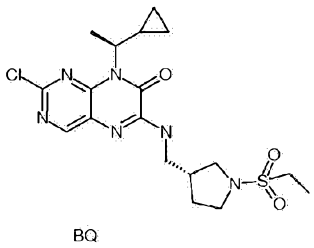
BN



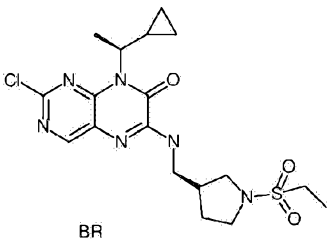
BO



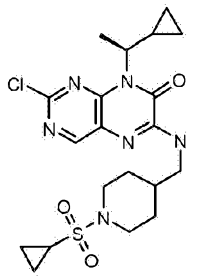
BP



BQ



BR

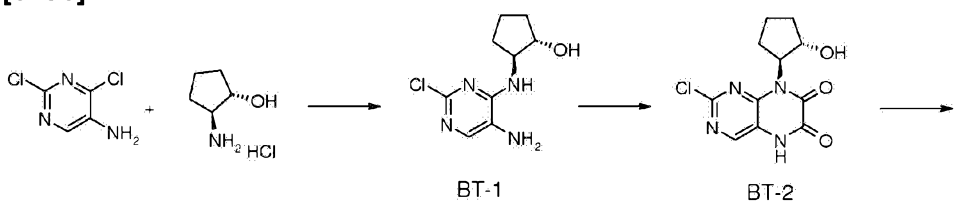


BS

Method 34:

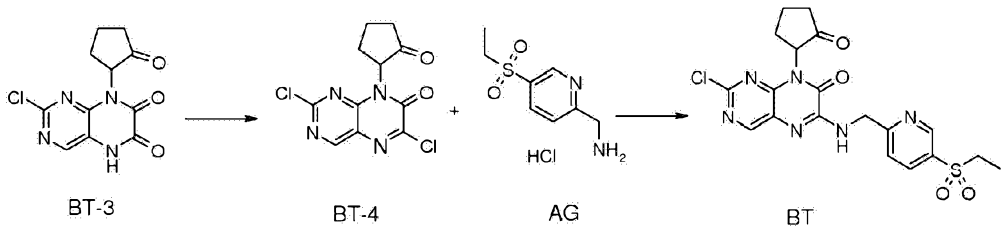
Synthesis of Intermediates BT

[0196]



BT-1

BT-2



[0197] To a stirring suspension of 2,4-Dichloro-pyrimidin-5-ylamine (3.03 g, 18.1 mmol) in n-BuOH (40 mL) is added (1S,2S)-2-Amino-cyclopentanol hydrochloride (2.50 g, 17.2 mmol) and DIEA (9.20 ml, 51.8 mmol). The mixture is stirred at 130 °C for 4 h. The reaction mixture is then concentrated under reduced pressure and the crude product is triturated to a solid in EtOAc and heptane and filtered to yield **BT-1.**

[0198] To a stirred solution of **BT-1** (3.61 g, 15.5 mol) in acetone (200 mL) is added K_2CO_3 (5.34 g, 38.6 mmol) and chloro-oxo-acetic acid ethyl ester (1.94 mL, 17.0 mmol). The mixture is stirred at rt for 1h. The reaction mixture is filtered and the filtrate is concentrated under reduced pressure. The crude ketoester is dissolved in absolute EtOH (50 mL), placed in a pressure flask, and TEA (5.43 mL, 38.6 mmol) is added. This is heated to 130 °C for 1 h. The reaction mixture is concentrated under reduced pressure and dissolved in EtOAc (100 mL). The organic layer is washed with water (2 x 20 mL) then brine (20 mL) and dried (Na_2SO_4), decanted and concentrated. The resultant residue is triturated to a solid in EtOAc and heptane to yield **BT-2.**

[0199] To a mixture of **BT-2** (500 mg, 1.73 mmol) in DCM (100 mL) is added Dess-Martin periodinane (2.25 g, 5.20 mmol) and the mixture is stirred at rt for 96 h. The mixture is washed with sat. $NaHCO_3$ (50 mL) and the organic layer dried (Na_2SO_4) and concentrated under reduced pressure. The solid residue is twice suspended in DCM (50 mL), sonicated, and filtered. The resulting solid is re-suspended in EtOAc (20 mL) and sonicated. The solid product is filtered to yield **BT-3.**

[0200] To a mixture of **BT-3** (124 mg, 0.442 mmol) in DCM (6 mL) at rt is added oxalyl chloride (0.076 mL, 0.88 mmol) followed dropwise by dry DMF (0.30 mL, 3.9 mmol) until dissolution of the solid. The mixture is stirred at rt for 30 min, whereupon LCMS indicates unreacted starting material. To the mixture is added more oxalyl chloride (0.048 mL, 0.55 mmol) and the mixture stirred an additional 10 min. The reaction is concentrated under a stream of nitrogen at 35 °C for 1h and the resultant residue **BT-4** is used directly.

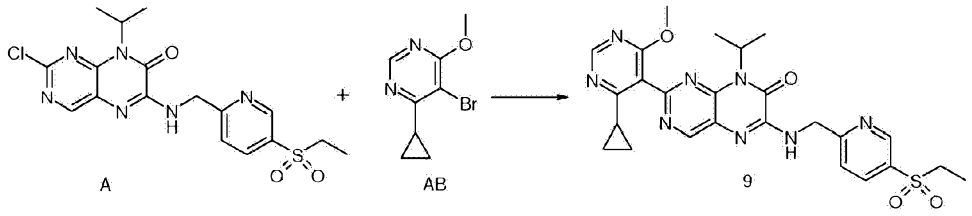
[0201] To a stirred solution of **BT-4** (132 mg, 0.442 mmol) and **AG** (105 mg, 0.442 mmol) in DMF (2 mL) at rt is added TEA (0.311 mL, 2.21 mmol) and the mixture is stirred at rt for 15 min. To the reaction mixture is added water (50 mL) and this is extracted with EtOAc (3 x 50 mL). The organic layers are combined, dried (Na_2SO_4), decanted and concentrated. The resultant residue is purified by SiO_2 flash chromatography to yield **intermediate BT.** MS (ES+):

m/z 463.1 $[M+H]^+$.

Method 35:

Synthesis of Example 9.

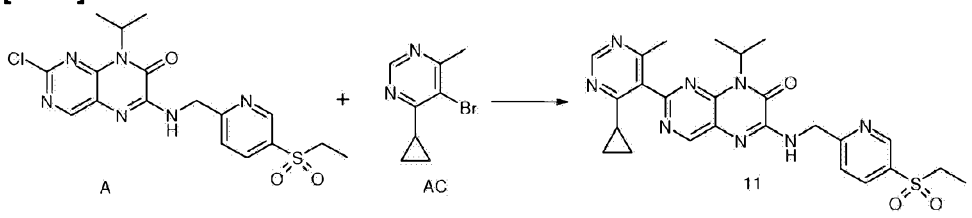
[0202]



[0203] Intermediate **AB** (27 mg, 0.12 mmol), bis(pinacolato)diboron (30 mg, 0.12 mmol), potassium acetate (35 mg, 0.36 mmol) and [1,1'-bisdiphenylphosphinoferrocene]-palladium(II) dichloride (9 mg, 0.011 mmol) are combined in a solution of degassed toluene/DME/ethanol/water (3:2:2:1, 3 mL). The vessel is heated to 90 °C for 20 min in a microwave reactor. In a separate vessel, intermediate **A** (50 mg, 0.12 mmol), bis(pinacolato)diboron (30 mg, 0.12 mmol), KOAc (35 mg, 0.36 mmol) and bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (8 mg, 0.011 mmol) are combined in degassed 1,4 dioxane (3 mL). The reaction is heated to 90 °C for 20 min in a microwave reactor. The contents of the two vessels are combined and $Na_2CO_{3(aq)}$ (2M, 1 mL) is added. The reaction is heated to 120 °C for 30 min in a microwave reactor. The vessel is cooled to rt and the contents filtered and concentrated. The resultant residue is purified by SiO_2 flash chromatography to yield **Example 9**. MS (ES+): *m/z* 537.2 $[M+H]^+$.

Synthesis of Example 11.

[0204]



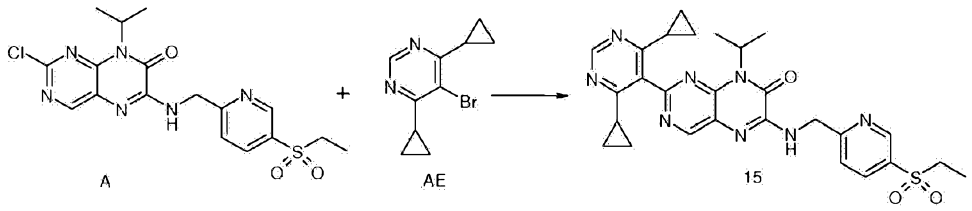
[0205] Intermediate **AC** (252 mg, 1.18 mmol), bis(pinacolato)diboron (600 mg, 2.36 mmol), potassium acetate (348 mg, 2.36 mmol) and [1,1'-bisdiphenylphosphinoferrocene]-palladium(II) dichloride (95 mg, 0.118 mmol) are combined in a solution of degassed

toluene/DME/ethanol/water (3:2:2:1, 3 mL). The vessel is heated to 90 °C for 20 min in a microwave reactor. In a separate vessel, intermediate **A** (500 mg, 1.18 mmol), bis(pinacolato)diboron (600 mg, 2.36 mmol), potassium acetate (348 mg, 2.36 mmol) and bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (84 mg, 0.118 mmol) are combined in degassed 1,4 dioxane (3 mL). The reaction is heated to 90 °C for 20 min in a microwave reactor. The contents of the two vessels are combined and $Na_2CO_{3(aq)}$ (2M, 1 mL) is added. The reaction is heated to 120 °C for 30 min in a microwave reactor. The vessel is cooled to rt and the contents filtered and concentrated.

[0206] The resultant residue is purified by SiO_2 flash chromatography to yield **Example 11.** MS (ES+): *m/z* 521.4 $[M+H]^+$.

Synthesis of Example 15.

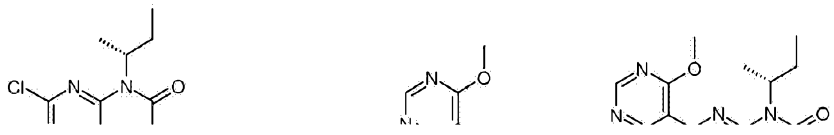
[0207]

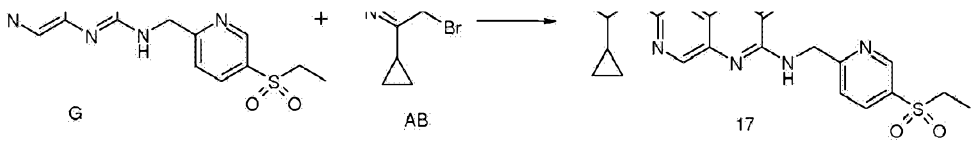


[0208] Intermediate **AE** (283 mg, 1.18 mmol), bis(pinacolato)diboron (600 mg, 2.36 mmol), potassium acetate (348mg, 3.54 mmol) and [1,1'-bisdiphenylphosphinoferrocene]-palladium(II) dichloride (95 mg, 0.12 mmol) are combined in a solution of degassed toluene/DME/ethanol/water (3:2:2:1, 3 mL). The vessel is heated to 90 °C for 20 min in a microwave reactor. In a separate vessel, intermediate **A** (500 mg, 1.18 mmol), bis(pinacolato)diboron (600 mg, 2.36 mmol), potassium acetate (348 mg, 3.54 mmol) and bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (84 mg, 0.12 mmol) are combined in degassed 1,4 dioxane (3 mL). The reaction is heated to 90 °C for 20 min in a microwave reactor. The contents of the two vessels are combined and 2M sodium bicarbonate (1 mL) is added. The reaction is heated to 120 °C for 30 min in a microwave reactor. The vessel is cooled to rt and the contents filtered and concentrated. The resultant residue is purified by SiO_2 flash chromatography to yield **Example 15.** MS (ES+): *m/z* 547.4 $[M+H]^+$.

Synthesis of Example 17.

[0209]

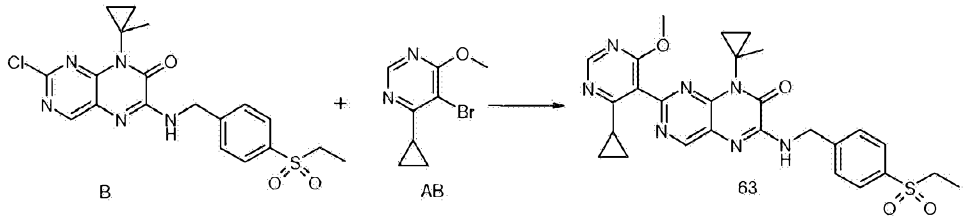




[0210] Intermediate **AB** (52 mg, 0.23 mmol), bis(pinacolato)diboron (58 mg, 0.23 mmol), KOAc (67mg, 0.23 mmol) and [1,1'-bisdiphenylphosphinoferrocene]-palladium(II) dichloride (18 mg, 0.23 mmol) are combined in a solution of degassed toluene/DME/ethanol/water (3:2:2:1, 3 mL). The vessel is heated to 90 °C for 20 min in a microwave reactor. In a separate vessel, intermediate **G** (100 mg, 0.23 mmol), bis(pinacolato)diboron (58 mg, 0.23 mmol), KOAc (67 mg, 0.69 mmol) and bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (16 mg, 0.023 mmol) are combined in degassed 1,4 dioxane (3 mL). The reaction is heated to 90 °C for 20 min in a microwave reactor. The contents of the two vessels are combined and $Na_2CO_{3(aq)}$ (2M, 1 mL) is added. The reaction is heated to 120 °C for 30 min in a microwave reactor. The vessel is cooled to rt and the contents filtered and concentrated. The resultant residue is purified by SiO_2 flash chromatography to yield **Example 17**. MS (ES+): *m/z* 551.4 $[M+H]^+$.

Synthesis of Example 63.

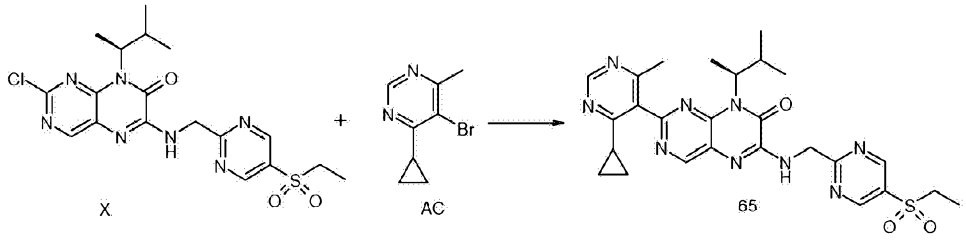
[0211]



[0212] Intermediate **AB** (105 mg, 0.46 mmol), bis(pinacolato)diboron (175 mg, 0.69 mmol), potassium acetate (67mg, 0.69 mmol) and [1,1'-bisdiphenylphosphinoferrocene]-palladium(II) dichloride (18 mg, 0.045 mmol) are combined in a solution of degassed toluene/DME/ethanol/water (3:2:2:1, 3 mL). The vessel is heated to 90 °C for 20 min in a microwave reactor. In a separate vessel, intermediate **B** (100 mg, 0.23 mmol), bis(pinacolato)diboron (175 mg, 0.69 mmol), KOAc (67 mg, 0.69 mmol) and bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (16 mg, 0.045 mmol) are combined in degassed 1,4 dioxane (3 mL). The reaction is heated to 90 °C for 20 min in a microwave reactor. The contents of the two vessels are combined and 2M sodium bicarbonate (1 mL) is added. The reaction is heated to 120 °C for 30 min in a microwave reactor. The vessel is cooled to rt and the contents filtered and concentrated. The resultant residue is purified by SiO_2 flash chromatography to yield **Example 63**. MS (ES+): *m/z* 548.0 $[M+H]^+$.

Synthesis of Example 65.

[0213]



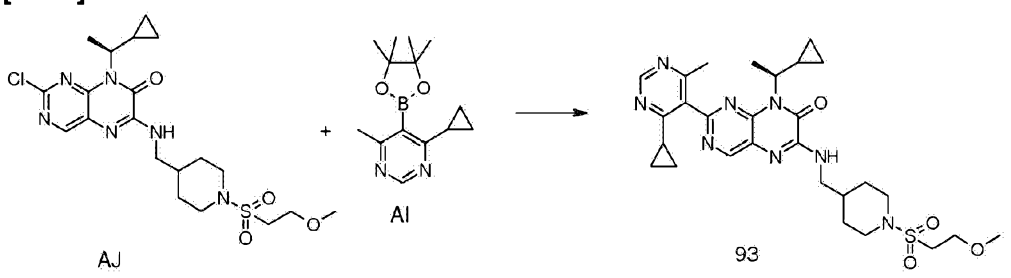
[0214] Intermediate **AC**(174 mg, 0.820 mmol), bis(pinacolato)diboron (277 mg, 1.093 mmol), potassium acetate (161mg, 1.64 mmol) and [1,1'-bisdiphenylphosphinoferrocene]-palladium(II) dichloride (43 mg, 0.055 mmol) are combined in a solution of degassed toluene/DME/ethanol/water (3:2:2:1, 3 mL). The vessel is heated to 90 °C for 20 min in a microwave reactor. In a separate vessel, intermediate **X** (247 mg, 0.547 mmol), bis(pinacolato)diboron (277 mg, 0.820 mmol), potassium acetate (161 mg, 1.64 mmol) and bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (43 mg, 0.055 mmol) are combined in degassed 1,4 dioxane (3 mL). The reaction is heated to 90 °C for 20 min in a microwave reactor. The contents of the two vessels are combined and $Na_2CO_{3(aq)}$ (2M, 1 mL) is added. The reaction is heated to 120 °C for 30 min in a microwave reactor. The vessel is cooled to rt and the contents filtered and concentrated. The resultant residue is purified by SiO_2 flash chromatography to yield **Example 65**. MS (ES+): *m/z* 550.0 $[M+H]^+$.

[0215] The following compounds are prepared in an analogous manner:
Examples **1-8, 10, 12-14, 16, 18-62, 64, 66-92, 129.**

Method 14:

Synthesis of Example 93.

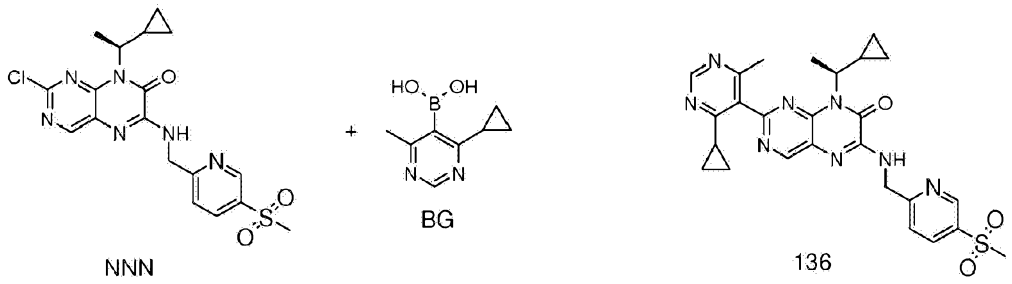
[0216]



[0217] A mixture of **AJ** (100 mg, 0.21 mmol), intermediate **AI** (83.7 mg, 0.32 mmol), K_3PO_4 (91 mg, 0.43 mmol), and $Pd(dppf)Cl_2$ (26 mg, 0.03 mmol) in 1,4-dioxane (2 mL) is purged with argon, and then H_2O (0.25 mL) is added. The mixture is stirred at 100 °C for 18h. After cooling to rt, the mixture is diluted with water (2 mL) and extracted with EtOAc (2x5 mL). The combined organic phase is dried (Na_2SO_4), decanted and concentrated. The resultant residue is purified by reversed HPLC to yield **Example 93**. MS (ES+): m/z 584.0 $[M+H]^+$.

Synthesis of Example 136.

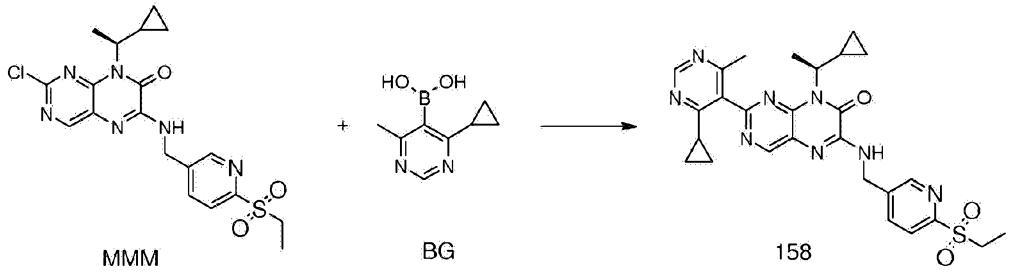
[0218]



[0219] A mixture of **NNN** (3500 mg, 8.05 mmol), intermediate **BG** (2149 mg, 12.07 mmol), K_3PO_4 (3417 mg, 16.09 mmol), and $Pd(dppf)Cl_2$ (986 mg, 1.21 mmol) in 1,4-dioxane (60 mL) is purged with argon, and then H_2O (6 mL) is added. The mixture is stirred at 100 °C for 18h. After cooling to rt, the mixture is diluted with water (2 mL) and extracted with EtOAc (2x5 mL). The combined organic phase is dried (Na_2SO_4), decanted and concentrated. The resultant residue is purified by reversed HPLC to yield **Example 136**. MS (ES+): m/z 533.0 $[M+H]^+$.

Synthesis of Example 158

[0220]



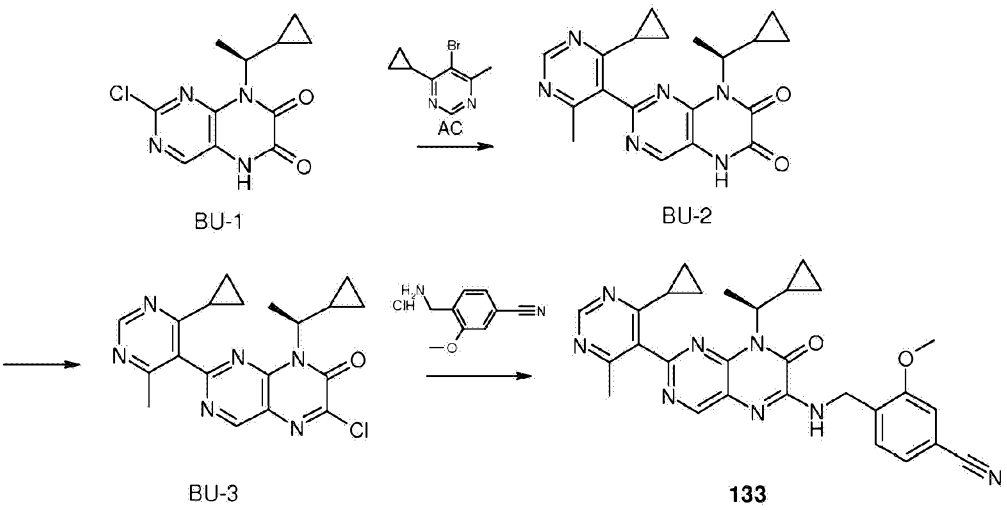
[0221] A mixture of **MMM** (3360 mg, 7.49 mmol), intermediate **BG** (2664 mg,14.97 mmol), K_3PO_4 (3177 mg, 14.97 mmol), and $Pd(dppf)Cl_2$ (916 mg, 1.12 mmol) in 1,4-dioxane (60 mL) is purged with argon, and then H_2O (6 mL) is added. The mixture is stirred at 100 °C for 18h.

After cooling to rt, the mixture is diluted with water (2 mL) and extracted with EtOAc (2x5 mL). The combined organic phase is dried (Na_2SO_4), decanted and concentrated. The resultant residue is purified by reversed HPLC to yield **Example 158**. MS (ES+): m/z 539.3.0 $[M+H]^+$.

[0222] The following compounds are prepared in an analogous manner:
Examples **94-128, 130-132, 134, 137-144, 146-157, 159-199, 201-265.**

Synthesis of Example 133:

[0223]

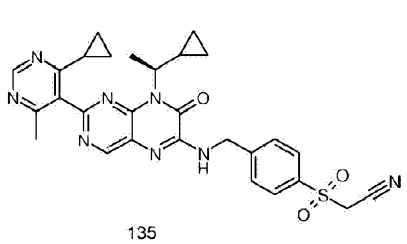


[0224] A mixture of **AC** (5.39 g, 25.3 mmol), bis(pinacolato) diboron (10.4 g, 40.5 mmol), potassium acetate (3.98 g, 40.5 mmol), and Pd(dppf)Cl_2 DCM complex (0.83 g, 1.01 mmol) in DME/Tol/EtOH/H_2O (10:6:3:1) is purged with argon, sealed, and stirred at 80 °C for 30 min. This is added to an argon purged mixture of **BU-1** (2.70 g, 10.1 mmol) and Pd(amphos)Cl_2 (0.71 g, 1.01 mmol) and the sealed mixture is heated to 110°C for 2h. The mixture is then concentrated, diluted with EtOAc, filtered and then concentrated again. The crude is purified by SiO_2 flash chromatography to yield **BU-2**.

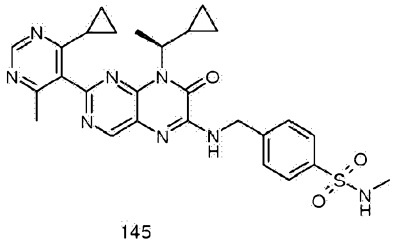
[0225] To a solution of the **BU-2** (856 mg, 2.35 mmol) in DCM (15 ml) is added oxalyl chloride (596 mg, 4.70 mmol) followed by 5 drops of DMF. The reaction is allowed to stir for 18 h. The reaction is then concentrated and the residue yields **BU-3** which is carried on as is.

[0226] To a stirred solution of the **BU-3** (150 mg, 0.36 mmol) in DMF is added DIEA (196 uL, 1.41 mmol) at rt. After 10 minutes **BU-4** (84.1 mg, 0.42 mmol) is added and the reaction is stirred at rt for 10min. The mixture is then concentrated and purified by reversed HPLC (NH_4CO_3) to yield **Example 133**. MS (ES+): m/z 509.1 $[M+H]^+$.

[0227] Example 135 and 145 are synthesized in a fashion analogous to **Example 133.**



135

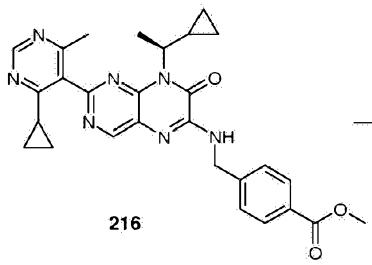


145

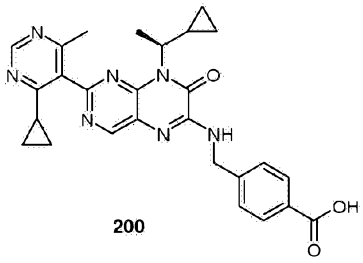
Method XX:

Synthesis of Example 200:

[0228]



216



200

[0229] To a solution of **216** (100 mg, 0.195 mmol) in dioxane (2 mL)/water (1 mL) is added LiOH (28.0 mg, 1.17 mmol). The reaction is stirred at rt for 16 h. The mixture is concentrated and dissolved in water, acidified with IN HCl to pH~5, filtered, washed with water, and dried in vacuum oven to yield **200**. MS (ES+): *m/z* 498.1 $[M+H]^+$

Biological Activity

[0230] The compounds of the present invention have activity as modulators of RORγ (retinoid acid receptor-related orphan receptor γ).

Reporter Gene Assay (RGA)

[0231] A nuclear receptor transactivation assay is performed to quantitate the ability of test compounds to inhibit RORγ transactivation of a luciferase reporter. A similar assay is described in: Khan et al., Bioorganic & Medicinal Chemistry Letters 23 (2013), 532-536. The system uses transiently transfected HEK 293 cells cotransfected with two plasmids (pGL4.3,

luc2P/GAL4UAS/Hygro, and pBIND, Gal4DBD hRORC LBD1-3). The positive control is co-transiently transfected with both plasmids, and the negative control contains the pGL4.3 promoter sequence. Assays are assembled in 384 well plates where transiently transfected cells and test compound at varying concentrations are incubated for 20-24 h. The next day, assays plates are taken out and equilibrated at RT for 20-30 minutes. Bright-Glo™ Luciferase Assay System is used to detect Luciferase production. After addition of Bright GLO detection reagent, the plates are incubated at RT for 20 minutes. The plates are read on an Envision plate reader to measure luminescence signal. The RLU signal is converted to POC relative to control and blank wells.

Cell Seeding Media:

[0232] RPMI 1640-Invitrogen #11875135), 2.5% FBS-Invitrogen # 26140, 1xPenicillin-Streptomycin-Gibco # 15140

Compound dilution buffer:

[0233] IX HBSS-Invitrogen #14025126
Assay Plates: Greiner #781080-020
Bright Glo Luciferase Assay System: Promega #E2620
Thaw lysis buffer provided in kit, add 100 mL lysis buffer to substrate powder.

[0234] The below table presents the results obtained when the compounds of the present invention were tested in the above assay, demonstrating their activity as modulators of RORγ:
Table II: Table of Biological Activity in Reporter Gene Assay

Example	RGA IC_{50} (nM)	Example	RGA IC_{50} (nM)	Example	RGA IC_{50} (nM)
1	210	101	115	201	75
2	230	102	250	202	455
3	230	103	82	203	800
4	250	104	3000	204	665
5	260	105	1600	205	80
6	260	106	1150	206	777
7	280	107	560	207	1400
8	290	108	300	208	125
9	300	109	790	209	75
10	300	110	1350	210	150
11	300	111	460	211	225
12	300	112	920	212	120

Example	RGA IC_{50} (nM)	Example	RGA IC_{50} (nM)	Example	RGA IC_{50} (nM)
13	300	113	108	213	155
14	310	114	107	214	220
15	310	115	67	215	330
16	320	116	300	216	1385
17	330	117	155	217	160
18	330	118	225	218	170
19	330	119	720	219	280
20	330	120	420	220	390
21	360	121	130	221	350
22	360	122	150	222	1250
23	390	123	135	223	135
24	390	124	97	224	120
25	410	125	175	225	230
26	420	126	119	226	155
27	420	127	570	227	455
28	440	128	160	228	595
29	470	129	2500	229	530
30	550	130	285	230	270
31	560	131	205	231	195
32	640	132	243	232	180
33	670	133	1035	233	155
34	730	134	400	234	590
35	870	135	240	235	425
36	880	136	255	236	185
37	930	137	278	237	265
38	1100	138	160	238	400
39	1100	139	700	239	205
40	1400	140	730	240	600
41	1400	141	925	241	310
42	1500	142	333	242	395
43	2600	143	134	243	230
44	2800	144	162	244	475
45	2900	145	95	245	1700
46	3000	146	435	246	645

Example	RGA IC_{50} (nM)	Example	RGA IC_{50} (nM)	Example	RGA IC_{50} (nM)
47	3200	147	250	247	385
48	3800	148	505	248	540
49	4300	149	305	249	530
50	4400	150	230	250	190
51	7600	151	255	251	158
52	420	152	470	252	325
53	680	153	375	253	340
54	420	154	295	254	455
55	1400	155	185	255	285
56	1400	156	275	256	1900
57	560	157	92	257	155
58	420	158	106	258	210
59	850	159	91	259	190
60	750	160	285	260	515
61	470	161	375	261	470
62	990	162	795	262	4000
63	930	163	160	263	4300
64	920	164	410	264	5900
65	590	165	157	265	4800
66	410	166	1600		
67	370	167	270		
68	330	168	435		
69	320	169	145		
70	630	170	235		
71	480	171	200		
72	250	172	440		
73	290	173	690		
74	410	174	275		
75	590	175	380		
76	1600	176	550		
77	1600	177	73		
78	2400	178	240		
79	610	179	675		
80	1100	180	235		

Example	RGA IC_{50} (nM)	Example	RGA IC_{50} (nM)	Example	RGA IC_{50} (nM)
81	1700	181	175		
82	380	182	130		
83	2200	183	325		
84	400	184	295		
85	290	185	175		
86	550	186	150		
87	310	187	255		
88	3400	188	315		
89	750	189	120		
90	4100	190	130		
91	1800	191	86		
92	850	192	83		
93	110	193	99		
94	125	194	180		
95	355	195	183		
96	320	196	157		
97	101	197	225		
98	195	198	225		
99	265	199	120		
100	130	200	855		

Methods of Therapeutic Use

[0235] On the basis of their biological properties the compounds of formula (I) according to the invention, or their tautomers, racemates, enantiomers, diastereomers, mixtures thereof and the salts of all the above-mentioned forms are suitable for treating autoimmune and allergic disorders in that they exhibit good modulatory effect upon RORγ.

[0236] The present invention is therefore directed to compounds of general formula (I), and the pharmaceutically acceptable salts thereof, and all tautomers, racemates, enantiomers, diastereomers, mixtures thereof, which are useful in the treatment of a disease and/or condition wherein the activity of RORγ modulators is of therapeutic benefit, including but not limited to the treatment of autoimmune or allergic disorders.

[0237] Such disorders that may be treated by the compounds of the invention include for example: rheumatoid arthritis, psoriasis, systemic lupus erythromatosis, lupus nephritis,

systemic sclerosis, vasculitis, scleroderma, asthma, allergic rhinitis, allergic eczema, multiple sclerosis, juvenile rheumatoid arthritis, juvenile idiopathic arthritis, type I diabetes, Crohn's disease, ulcerative colitis, graft versus host disease, psoriatic arthritis, reactive arthritis, ankylosing spondylitis, atherosclerosis, uveitis and non-radiographic spondyloarthropathy.

[0238] For treatment of the above-described diseases and conditions, a therapeutically effective dose will generally be in the range of approximately 0.01 mg to about 10 mg/kg of body weight per dosage of a compound of the invention; preferably, from about 0.1 mg to about 5 mg/kg of body weight per dosage. For example, for administration to a 70 kg person, the dosage range would be approximately 0.7 mg to about 750 mg per dosage of a compound of the invention, preferably from about 7.0 mg to about 350 mg per dosage. Some degree of routine dose optimization may be required to determine an optimal dosing level and pattern. The active ingredient may be administered from 1 to 6 times a day.

General Administration and Pharmaceutical Compositions

[0239] When used as pharmaceuticals, the compounds of the invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared using procedures well known in the pharmaceutical art and generally comprise at least one compound of the invention and at least one pharmaceutically acceptable carrier. The compounds of the invention may also be administered alone or in combination with adjuvants that enhance stability of the compounds of the invention, facilitate administration of pharmaceutical compositions containing them in certain embodiments, provide increased dissolution or dispersion, increased antagonist activity, provide adjunct therapy, and the like. The compounds according to the invention may be used on their own or in conjunction with other active substances according to the invention, optionally also in conjunction with other pharmacologically active substances. In general, the compounds of this invention are administered in a therapeutically or pharmaceutically effective amount, but may be administered in lower amounts for diagnostic or other purposes.

[0240] Administration of the compounds of the invention, in pure form or in an appropriate pharmaceutical composition, can be carried out using any of the accepted modes of administration of pharmaceutical compositions. Thus, administration can be, for example, orally, buccally (e.g., sublingually), nasally, parenterally, topically, transdermally, vaginally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as, for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. The pharmaceutical compositions will generally include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, diluents, vehicles, or combinations thereof. Such pharmaceutically acceptable excipients, carriers, or additives as well as methods of making pharmaceutical compositions for various modes or administration are well-known to those of skill in the art. The

state of the art is evidenced, e.g., by Remington: The Science and Practice of Pharmacy, 20th Edition, A. Gennaro (ed.), Lippincott Williams & Wilkins, 2000; Handbook of Pharmaceutical Additives, Michael & Irene Ash (eds.), Gower, 1995; Handbook of Pharmaceutical Excipients, A. H. Kibbe (ed.), American Pharmaceutical Ass'n, 2000; H. C. Ansel and N. G. Popovish, Pharmaceutical Dosage Forms and Drug Delivery Systems, 5th ed., Lea and Febiger, 1990; each of which is incorporated herein by reference in their entireties to better describe the state of the art. As one of skill in the art would expect, the forms of the compounds of the invention utilized in a particular pharmaceutical formulation will be selected (e.g., salts) that possess suitable physical characteristics (e.g., water solubility) that are required for the formulation to be efficacious.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US7879873B [0044]
- WO2011049917A [0044]

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- **IVANOV**Cell, 2006, vol. 126, 1121-1133 [0002]
- **MIOSSEC**Nature Drug Discovery, 2012, vol. 11, 763-776 [0002]
- **KHAN et al.**Bioorganic & Medicinal Chemistry Letters, 2013, vol. 23, 532-536 [0002] [0231]
- **LEONARDI**New England Journal of Medicine, 2012, vol. 366, 1190-1199 [0002]
- **PAPP**New England Journal of Medicine, 2012, vol. 366, 1181-1189 [0002]
- **BIRGE, S.M. et al.**Pharmaceutical saltsJ. Pharm. Sci., 1977, vol. 66, 1-19 [0026]
- Remington: The Science and Practice of PharmacyLippincott Williams & Wilkins20000000 [0240]
- Handbook of Pharmaceutical AdditivesGower19950000 [0240]

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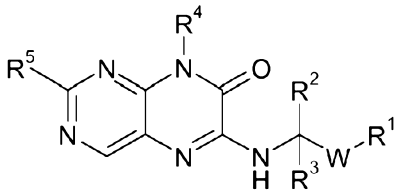
- **H. C. ANSELN. G. POPOVISH**Pharmaceutical Dosage Forms and Drug Delivery SystemsLea and Febiger19900000 [0240]

P A T E N T K R A V

1. Forbindelse med formlen (I)



(I)

hvor:

R^1 er:

-CN;

$-S(O)_nR^6$;

$-S(O)_nNR^7R^8$;

$-S(O)(NR^9)R^6$;

$-N(R^9)C(O)R^6$;

$-N(R^9)C(O)OR^6$;

$-N(R^9)S(O)_nR^6$;

$-C(O)OR^9$;

$-C(O)NR^7R^8$; eller

$-C(O)R^9$; eller

R^6, R^7, R^8 eller R^9 i R^1 kan være cykliserede på W til dannelse af en ring; og

R^2 og R^3 er hver især uafhængigt:

(A) -H;

(B) C_{1-3}-alkyl eventuelt substitueret med en, to eller tre grupper udvalgt blandt:

a) C_{3-6}-cykloalkyl;

b) $-OR^9$;

c) -CN;

d) $-CF_3$;

e) -halo;

f) $-C(O)OR^9$;

g) $-C(O)N(R^9)_2$;

h) $-S(O)_nR^9$; og

i) $-S(O)_nNR^7R^8$; eller

(C) C_{3-6}-cykloalkyl;

(D) C_{3-6}-heterocyklyl; eller

R^2 og R^3 danner sammen med carbonatomet, hvortil de er forbundne, en C_{3-6}-carbocyklisk ring; eller

R^2 og R^3 danner sammen med carbonatomet, hvortil de er forbundne, en C_{3-6}-heterocyklisk ring; eller

R^2 eller R^3 kan være cykliserede på W til dannelse af en ring;

R^4 er:

(A) C_{1-6}-alkyl eventuelt substitueret med en, to eller tre grupper udvalgt blandt:

a) C_{3-6}-cykloalkyl;

b) C_{3-6}-heterocyklyl;

c) $-OR^9$;

d) -CN;

e) $-S(O)_nR^9$;

f) -halo; og

g) $-CF_3$; eller

(B) C_{3-12}-cykloalkyl eventuelt substitueret med en, to eller tre grupper udvalgt blandt:

a) C_{1-6}-alkyl;

b) $-OR^9$;

c) -CN;

d) $-S(O)_nR^9$;

e) -halo; og

f) $-CF_3$; eller

(C) aryl, heteroaryl eller heterocyklyl, hver eventuelt substitueret med en, to eller tre grupper udvalgt blandt:

a) C_{1-6}-alkyl;

b) C_{3-6}-cykloalkyl;

c) $-OR^9$;

d) -CN;

e) $-S(O)_nR^9$;

f) -halo; og

g) $-CF_3$;

R^5 er aryl, heteroaryl, heterocyklyl eller C_{3-12}-cykloalkyl, hver eventuelt substitueret med en, to eller tre grupper udvalgt blandt:

(A) C_{1-6}-alkyl, C_{3-6}-cykloalkyl eller C_{3-6}-heterocyklyl, hver eventuelt substitueret med en, to eller tre grupper udvalgt blandt:

a) C_{3-6}-cykloalkyl;

b) C_{3-6} heterocyklyl;

c) $-OR^9$;

d) -CN;

e) $-S(O)_nNR^7R^8$

f) $-S(O)_nR^9$;

g) -halo; og

h) $-CF_3$; eller

(B) $-OR^9$;

(C) -CN;

(D) -CF_3;

(E) -halo;

(F) -$S(O)_nNR^7R^8$;

(G) -$S(O)_nR^9$; og

(H) -NR^7R^8;

W er aryl, heteroaryl, heterocyklyl, C_{3-12}-cykloalkyl eller alkynyl, hver eventuelt substitueret med en eller to grupper udvalgt blandt:

a) C_{1-6}-alkyl;

b) C_{3-6}-cykloalkyl;

c) -OR^9;

d) -CN;

e) -CF_3;

f) -halo;

g) -NR^7R^8;

h) -$C(O)OR^9$; og

i) -$C(O)N(R^9)_2$;

R^6 er udvalgt blandt:

(A) -OH;

(B) C_{1-6}-alkyl, eventuelt substitueret med en eller to grupper udvalgt blandt:

a) C_{3-6}-cykloalkyl;

b) -OR^9;

c) -CN;

d) -CF_3; og

e) -halo;

(C) C_{3-6}-cykloalkyl; og

(D) -CF_3;

R^7 og R^8 er uafhængigt udvalgt blandt:

(A) -H;

(B) C_{1-3}-alkyl, eventuelt substitueret med en eller to grupper udvalgt blandt:

a) C_{3-6}-cykloalkyl;

b) -OR^9;

c) -CN; og

d) -halo; og

(C) C_{3-6}-cykloalkyl; eller

R^7 og R^8 danner sammen med nitrogenatomet, hvortil de er bundne, en mættet ring med 3-6 carbonatomer, hvor ét carbonatom i den mættede ring eventuelt kan være erstattet med -O-, -NR^9- eller -$S(O)_n$-;

R^9 er udvalgt blandt;

(A) -H;

(B) C_{1-3}-alkyl eventuelt substitueret med en eller to grupper udvalgt blandt:

a) C_{3-6}-cykloalkyl;

c) -CN;

d) $-CF_3$

e) -halo; eller

(C) C_{3-6}-cykloalkyl; og

n er 0, 1 eller 2;

eller et farmaceutisk acceptabelt salt deraf.

2. Forbindelse med formlen (I) ifølge krav 1, eller et farmaceutisk acceptabelt salt deraf, hvor:

R^1 er:

- CN,

- $S(O)_nR^6$,

- $S(O)_nNR^7R^8$;

- $N(H)S(O)_nR^6$; eller

- $S(O)(NH)R^6$; og

hvor:

R^6 er:

(A) C_{1-3}-alkyl eventuelt substitueret med en eller to grupper udvalgt blandt:

a) C_{3-6}-cykloalkyl;

b) $-OR^9$; og

c) -CN; eller

(B) C_{3-6}-cykloalkyl;

R^7 og R^8 er hver især uafhængigt:

(A) -H; eller

(B) C_{1-3}-alkyl; og

R^9 er udvalgt blandt;

(A) -H;

(B) C_{1-3}-alkyl; eller

(C) C_{3-6}-cykloalkyl; og

n er 1 eller 2.

3. Forbindelse med formlen (I) ifølge et hvilket som helst af de foregående krav, eller et farmaceutisk acceptabelt salt deraf, hvor:

R^2 og R^3 hver især uafhængigt er udvalgt blandt:

(A) -H;

(B) C_{1-3}-alkyl, eventuelt substitueret med en, to eller tre grupper udvalgt blandt:

a) C_{3-6}-cykloalkyl;

b) $-OR^9$; eller

c) -halo; og

R^2 og R^3 danner sammen med carbonatomet, hvortil de er forbundne, en C_{3-6}-carbocyklisk ring; eller

R^2 og R^3 danner sammen med carbonatomet, hvortil de er forbundne, en C_{3-6}-heterocyklisk ring; og

R^9 er udvalgt blandt:

(A) -H; og

(B) C_{1-3}-alkyl.

4. Forbindelse med formlen (I) ifølge et hvilket som helst af de foregående krav, eller et farmaceutisk acceptabelt salt deraf, hvor:

R^4 er:

(A) C_{1-6}-alkyl, eventuelt substitueret med en, to eller tre grupper udvalgt blandt:

a) C_{3-6}-cykloalkyl;

b) en 4-, 5- eller 6-leddet heterocyklyl;

c) -OR^9;

d) -CN;

e) -halo; og

f) -CF_3; eller

(B) C_{3-6}-cykloalkyl, eventuelt substitueret med en, to eller tre grupper udvalgt blandt:

a) C_{1-6}-alkyl;

b) -OR^9;

c) -CN;

d) -halo; og

e) -CF_3; og

hvor ét carbonatom i nævnte C_{3-6}-cykloalkyl eventuelt kan være erstattet af -O-;

(C) phenyl; eller

(D) en 4-, 5- eller 6-leddet heterocyklyl; og

R^9 er udvalgt blandt:

(A) -H; og

(B) C_{1-3}-alkyl.

5. Forbindelse med formlen (I) ifølge et hvilket som helst af de foregående krav, eller et farmaceutisk acceptabelt salt deraf, hvor:

R^5 er aryl, heteroaryl eller heterocyklyl, hver eventuelt substitueret med en, to eller tre grupper udvalgt blandt:

a) C_{1-6}-alkyl;

b) C_{3-6}-cykloalkyl;

c) -OR^9;

d) -CN;

e) -CF_3;

f) -halo; og

g) -NR^7R^8; og

R^7, R^8 og R^9 er hver især uafhængigt udvalgt blandt:

(A) -H; og

(B) C_{1-3}-alkyl.

6. Forbindelse med formlen (I) ifølge et hvilket som helst af de foregående krav, eller et farmaceutisk acceptabelt salt deraf, hvor:

W er phenyl, pyridinyl, pyrimidinyl, piperidinyl, piperizinyl, pyrazinyl eller C_{3-12}-cykloalkyl, hver eventuelt substitueret med en eller to grupper udvalgt blandt:

a) C_{1-6}-alkyl;

b) C_{3-6}-cykloalkyl;

c) -OR^9;

d) -CN;

e) -CF_3;

f) -halo;

g) -NR^7R^8

h) -$C(O)OR^9$; og

i) -$C(O)N(R^9)_2$;

R^7, R^8 og R^9 er hver især udvalgt blandt:

(A) -H; og

(B) C_{1-3}-alkyl.

7. Forbindelse med formlen (I) ifølge krav 1, eller et farmaceutisk acceptabelt salt deraf, hvor:

R^1 er:

-S(O)nR^6,

-S(O)nNR^7R^8, eller

-S(O)(NH)R^6;

R^2 og R^3 er hver især uafhængigt udvalgt blandt:

(A) -H; og

(B) C_{1-3}-alkyl;

R^4 er:

(A) C_{1-6}-alkyl, eventuelt substitueret med en eller to grupper udvalgt blandt:

a) C_{3-6}-cykloalkyl;

b) en 4-, 5-, eller 6-leddet heterocyklyl;

c) -OR^9;

d) -CN;

e) -halo; og

f) -CF_3;

(B) C_{3-6}-cykloalkyl, eventuelt substitueret med en, to eller tre grupper udvalgt blandt:

a) C_{1-6}-alkyl;

b) -OR^9;

c) -CN;

d) -halo; og

e) -CF_3;

(C) phenyl; eller

(D) en 5- eller 6-leddet heterocyklyl;

R^5 er:

(A) phenyl, eventuelt substitueret med en eller to grupper udvalgt blandt:

a) C_{1-6}-alkyl;

b) C_{3-6}-cykloalkyl;

c) -OR^9;

d) -CN;

e) -CF_3; og

f) -halo; eller

(B) pyridinyl eller pyrimidinyl, hver eventuelt substitueret med en, to eller tre grupper udvalgt blandt:

a) C_{1-6}-alkyl;

b) C_{3-6}-cykloalkyl;

c) -OR^9;

d) -CN;

e) -CF_3;

f) -halo; og

g) -NR^7R^8; og

W er phenyl, pyridinyl, pyrimidinyl, piperidinyl eller C_{3-12}-cykloalkyl, hver eventuelt substitueret med en eller to grupper udvalgt blandt:

a) C_{1-6}-alkyl;

b) C_{3-6}-cykloalkyl;

c) -OR^9;

d) -CN;

e) -CF_3;

f) -halo;

g) -NR^7R^8

h) -$C(O)OR^9$; og

i) -$C(O)N(R^9)_2$;

R^6 er:

(A) C_{1-3}-alkyl, eventuelt substitueret med en eller to grupper udvalgt blandt:

a) C_{3-6}-cykloalkyl;

b) -OR^9 og

b) -CN; eller

(B) C_{3-6}-cykloalkyl;

R^7, R^8 og R^9 er hver især uafhængigt:

(A) -H; eller

(B) C_{1-3}-alkyl; og

n er 2.

8. Forbindelse med formlen (I) ifølge krav 1, eller et farmaceutisk acceptabelt salt deraf, hvor:

R^1 er $-S(O)_nR^6$ eller $-S(O)_nNR^7R^8$; og

R^2 og R^3 er H;

R^4 er:

(A) C_{1-6}-alkyl, eventuelt substitueret med en eller to grupper udvalgt blandt C_{3-6}-cykloalkyl, $-CF_3$, og C_{1-3}-alkoxy; eller

(B) C_{3-6}-cykloalkyl, eventuelt substitueret med en eller to grupper udvalgt blandt C_{1-6}-alkyl, -CN, og halo; eller

(C) 5-leddet heterocyklyl;

R^5 er pyrimidinyl, eventuelt substitueret med en, to eller tre grupper udvalgt blandt:

a) C_{1-6}-alkyl;

b) C_{3-6}-cykloalkyl;

c) $-OR^9$;

d) $-CF_3$; og

e) $-NR^7R^8$;

W er phenyl, pyridinyl, pyrimidinyl eller piperidinyl;

R^6 er C_{1-3}-alkyl;

R^7, R^8 R^9 er hver især uafhængigt:

(A) -H; eller

(B) C_{1-3}-alkyl; og

n er 2.

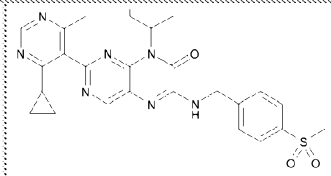
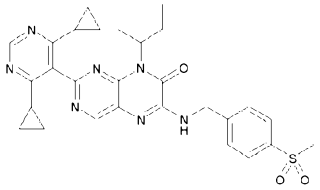
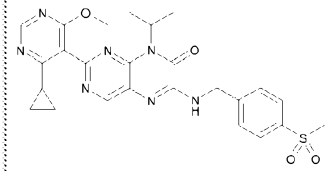
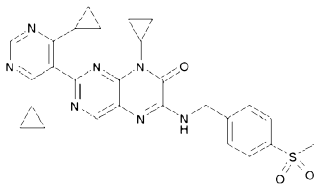
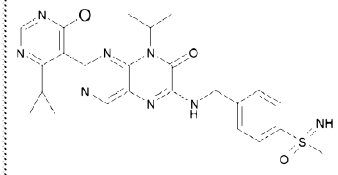
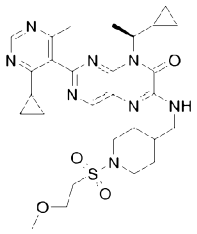
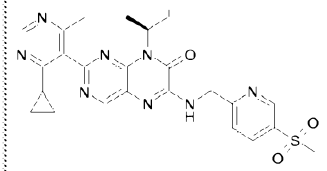
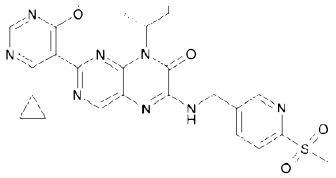
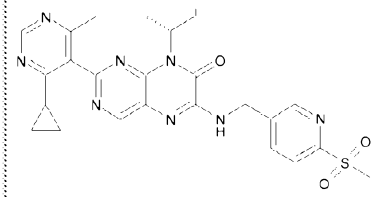
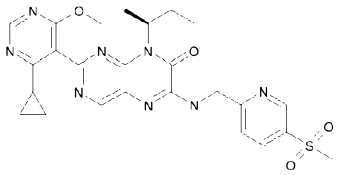
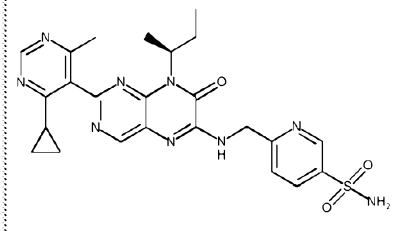
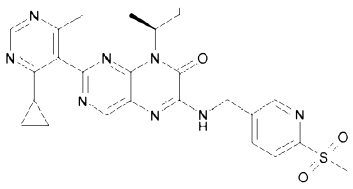
9. Forbindelse med formlen (I) ifølge krav 1, eller et farmaceutisk acceptabelt salt deraf, hvor:

R^1 er $-S(O)_2Me$ eller $-S(O)_2NR^7R^8$, og

R^7 og R^8 er hver især uafhængigt -H eller Me.

10. Forbindelse ifølge krav 1 udvalgt blandt forbindelserne i følgende tabel:

Eksempel	Struktur	Eksempel	Struktur
14		23	

Eksempel	Struktur	Eksempel	Struktur
			
26		46	
49		93	
94		95	
96		97	
98		99	
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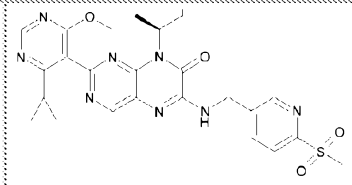
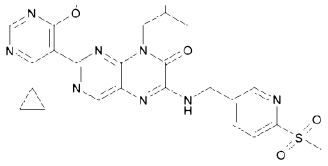
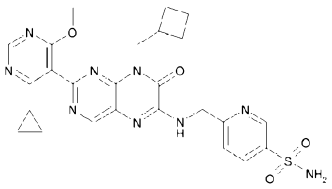
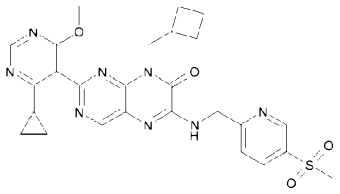
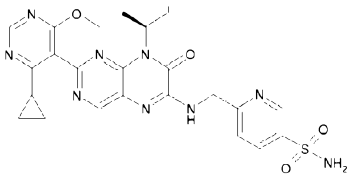
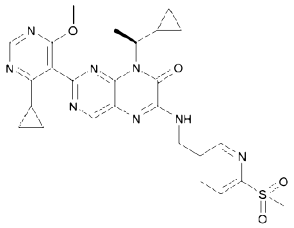
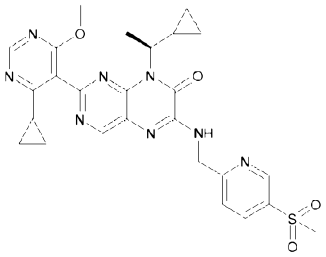
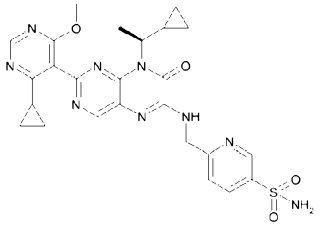
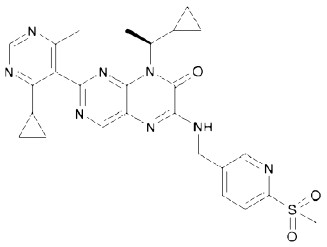
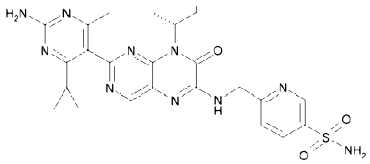
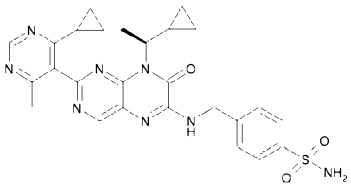
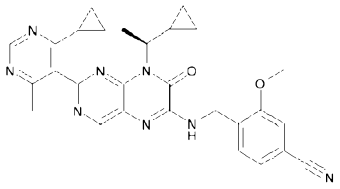
Eksempel	Struktur	Eksempel	Struktur
			
116		118	
122		123	
125		126	
128		129	
132		133	
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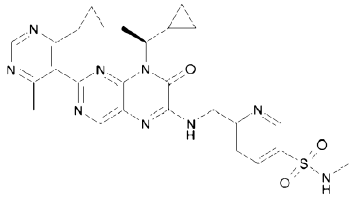
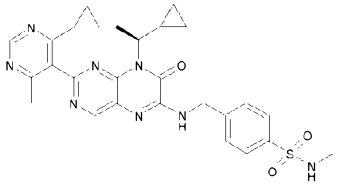
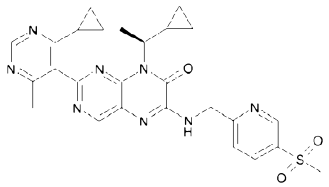
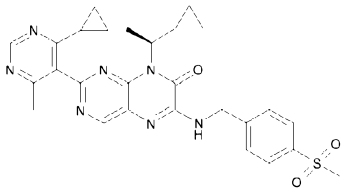
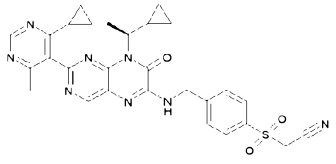
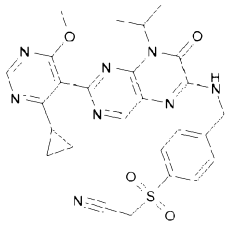
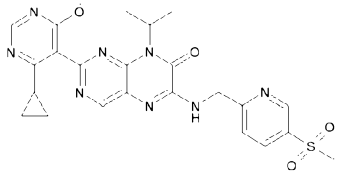
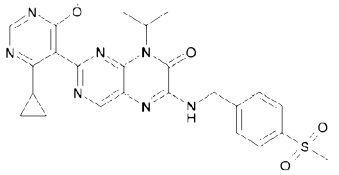
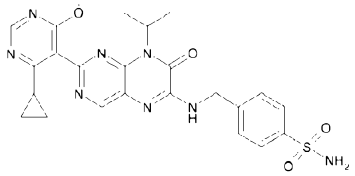
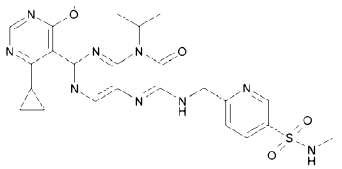
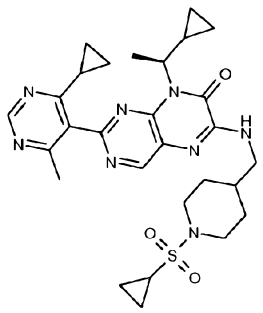
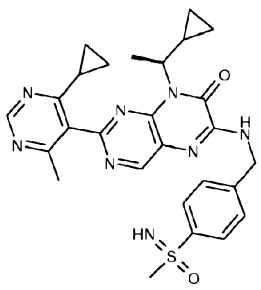
Eksempel	Struktur	Eksempel	Struktur
			
136		137	
145		147	
149		150	
151		155	
159		160	
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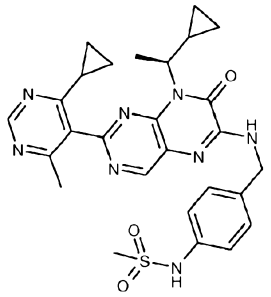
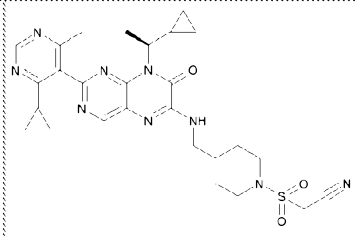
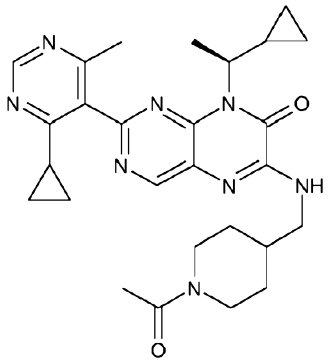
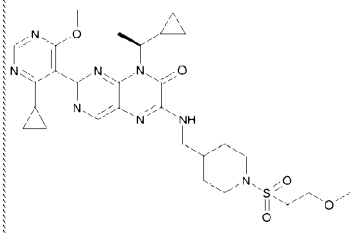
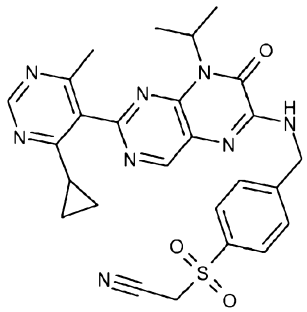
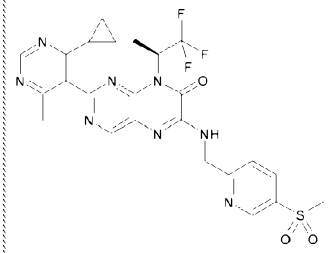
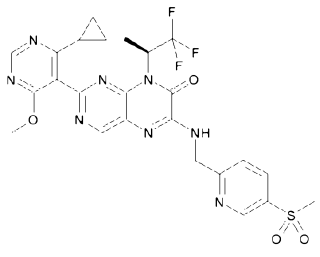
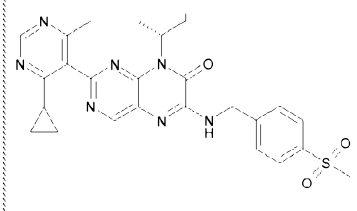
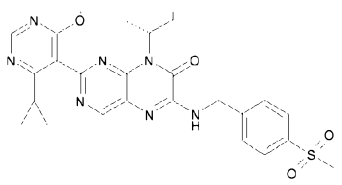
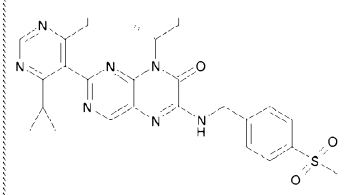
Eksempel	Struktur	Eksempel	Struktur
			
166		169	
171		180	
181		189	
190		191	

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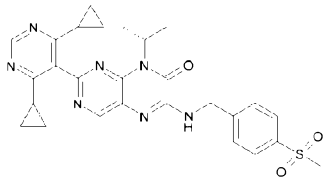
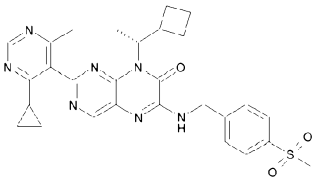
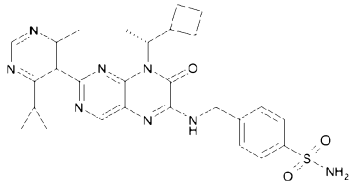
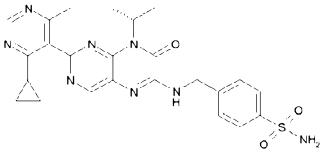
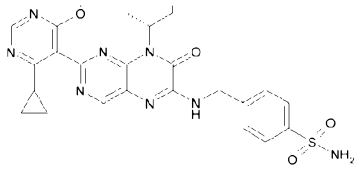
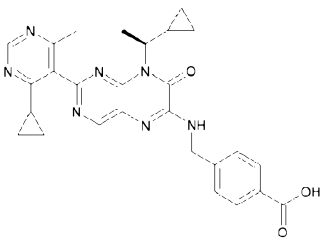
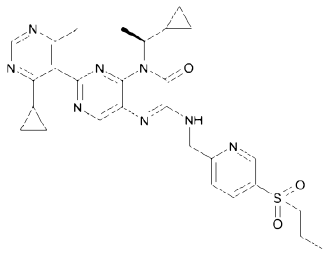
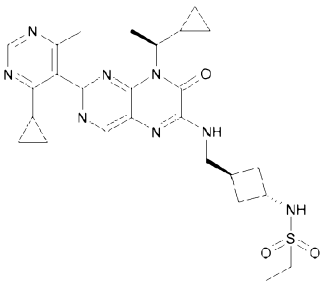
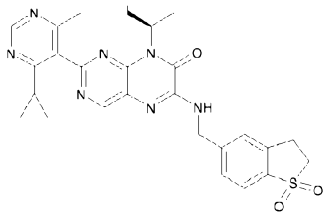
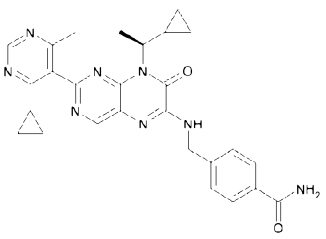
192		193	
194		195	
196		200	
201		202	
203		204	
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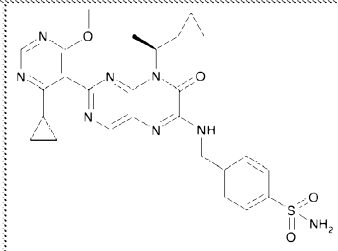
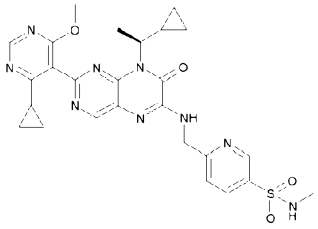
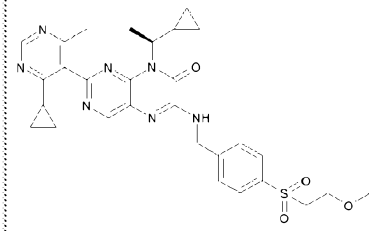
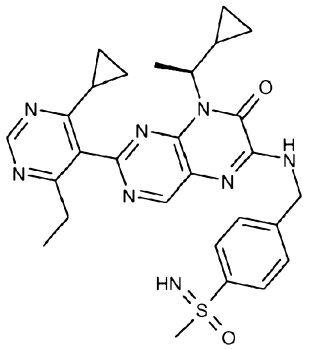
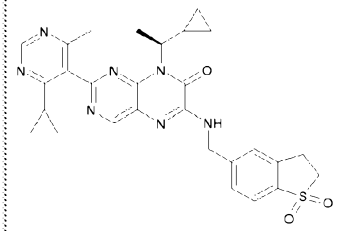
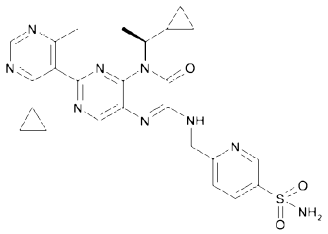
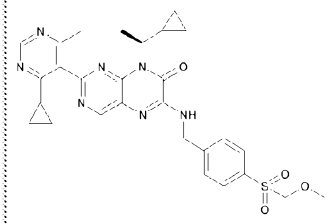
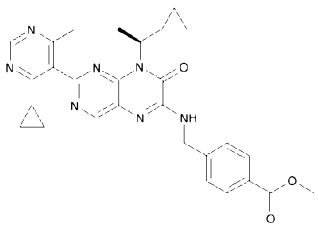
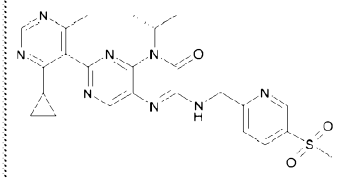
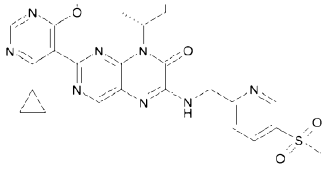
			
209		210	
212		214	
215		216	
225		226	
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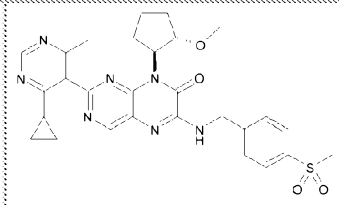
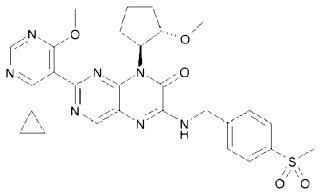
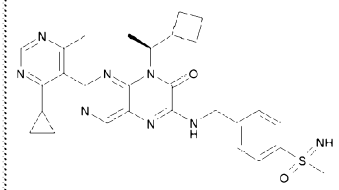
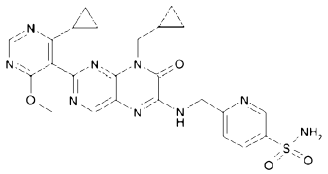
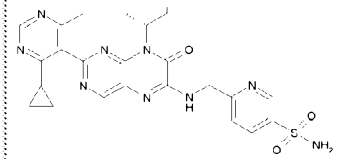
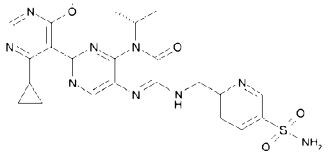
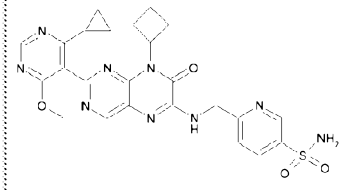
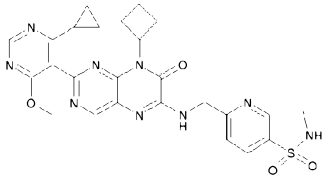
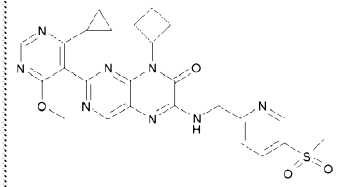
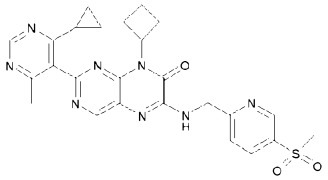
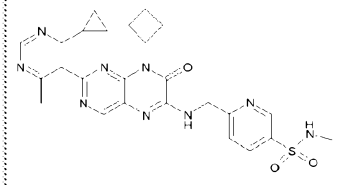
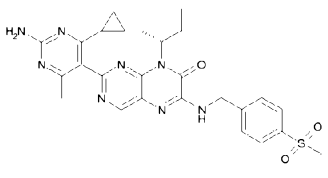
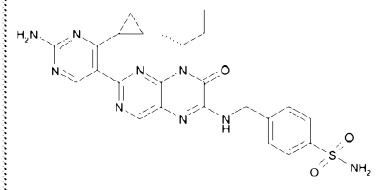
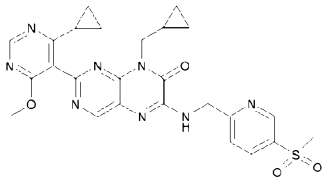
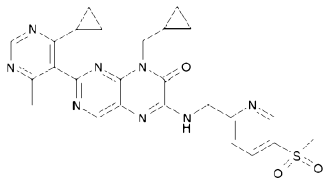
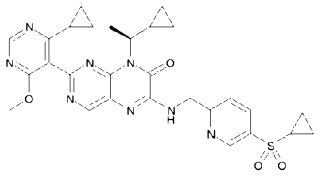
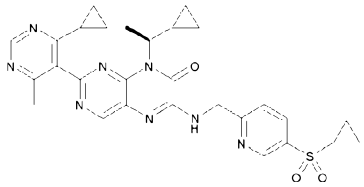
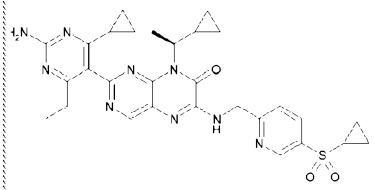
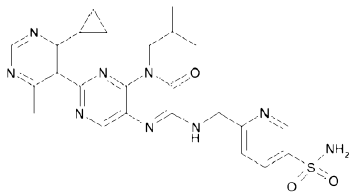
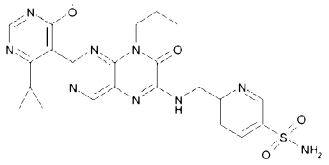
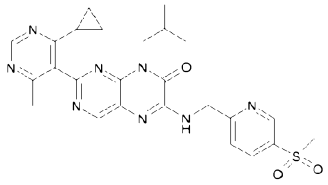
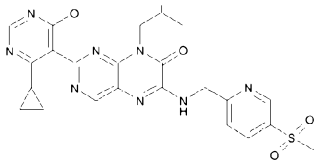
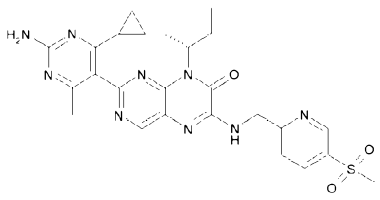
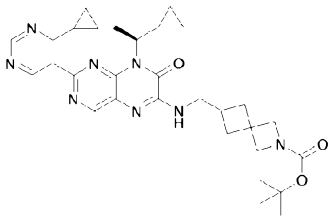
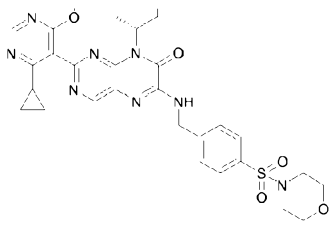
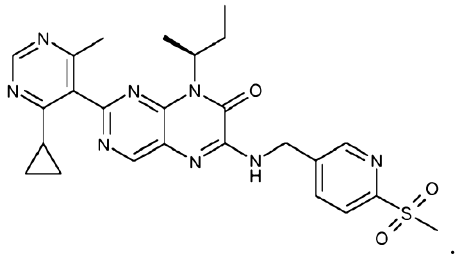
			
232		234	
235		236	
238		239	
241		242	
243		244	
245		246	

Eksempel	Struktur	Eksempel	Struktur
247		248	
249		251	
254		255	
258		259	
261		264	
265			

eller et farmaceutisk acceptabelt salt deraf.

11. Forbindelse ifølge krav 1, hvor forbindelsen er



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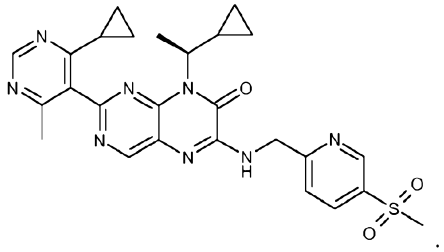

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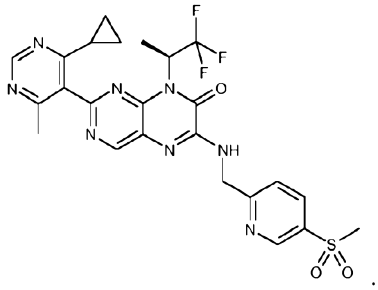

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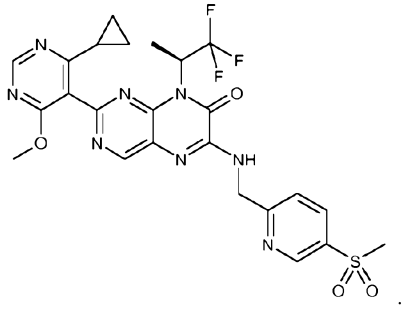

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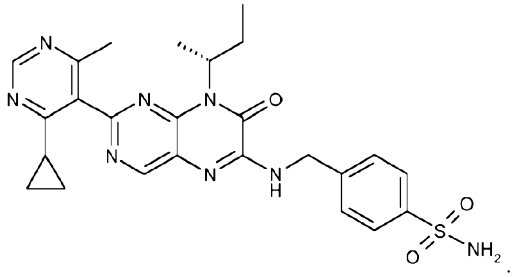

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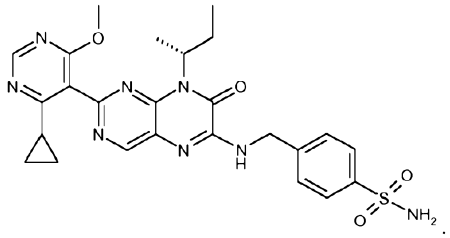

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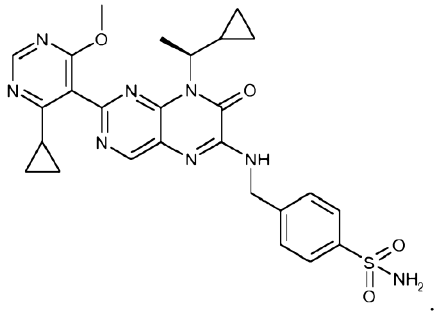

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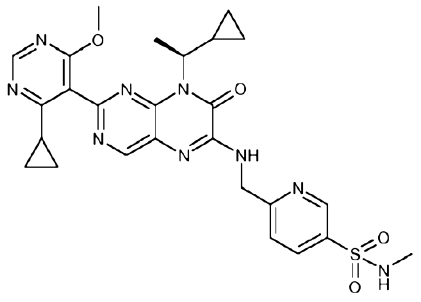

19. Farmaceutisk acceptabelt salt af forbindelsen ifølge et hvilket som helst af kravene 11 til 18.

20. Farmaceutisk sammensætning omfattende en forbindelse med formlen (I) ifølge et hvilket som helst af de foregående krav, eller et farmaceutisk acceptabelt salt deraf, og mindst ét farmaceutisk acceptabelt bærestof.

21. Forbindelse med formlen (I) ifølge et hvilket som helst af kravene 1 til 18, eller et farmaceutisk acceptabelt salt deraf, til anvendelse som lægemiddel.

22. Forbindelse med formlen (I) ifølge et hvilket som helst af kravene 1 til 18, eller et farmaceutisk acceptabelt salt deraf, til anvendelse som lægemiddel til behandling af en autoimmunsygdom eller allergisk lidelse hos en patient.

23. Forbindelse med formlen (I) ifølge et hvilket som helst af kravene 1 til 18, eller et farmaceutisk acceptabelt salt deraf, til anvendelse ifølge krav 22, hvor autoimmunsygdommen eller den allergiske lidelse er udvalgt blandt rheumatoid arthrit, psoriasis, systemisk lupus erythomatosis, lupus nephritis, bruskbold, astma, allergisk rhinitis, allergisk eksem, dissemineret sklerose, Stills sygdom, børneleddegigt, type 1-diabetes, kronisk tarmbetændelse, implantat-modtager-sygdom, psoriatisk arthrit, Reiters syndrom, ankyloserende spondylitis, Chrohns sygdom, ulcerøs colit, årehindebetændelse og ikke-radiografisk spondyloartrose.