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(54) **PRODRUGS OF HIV REVERSE TRANSCRIPTASE INHIBITORS**

PRODRUGS VON HIV-UMKEHRTRANSKRIPTASEHEMMERN

PROMÉDICAMENTS D'INHIBITEURS DE TRANSCRIPTASE INVERSE DE VIH

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- **LI, A ET AL.: 'Novel Pyridinone Derivatives As Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) with High Potency against NNRTI-Resistant HIV-1 Strains' J. MED. CHEM., [Online] vol. 56, 2013, pages 3593 - 3608, XP055229212 Retrieved from the Internet: <URL:http://www.researchgate.net/profile/Yabo_Ouyang/publicabon/236092079_Novel_pyridi none_derivatives_as_non_nucleoside_reverse_transcriptase_inhibitors_(NNRTIs)_with_high_potency_against_NNRTI_resistant_HIV-1_strains/links/00b4951c1b1ac1a542 000000.pdf> [retrieved on 2015-05-20]**

EP 3 125 894 B1

Description

[0001] The sequence listing of the present application is submitted electronically via EFS-Web as an ASCII formatted sequence listing with a file name "23744-US-PSP-SEQLIST-01APR2014", having a creation date of April 1, 2014, and a size of 1.92kb. This sequence listing submitted via EFS-Web is part of the specification and is herein incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] The retrovirus designated human immunodeficiency virus (HIV), particularly the strains known as HIV type-1 (HIV-1) and type-2 (HIV-2), have been etiologically linked to the immunosuppressive disease known as acquired immunodeficiency syndrome (AIDS). HIV seropositive individuals are initially asymptomatic but typically develop AIDS related complex (ARC) followed by AIDS. Affected individuals exhibit severe immunosuppression which makes them highly susceptible to debilitating and ultimately fatal opportunistic infections. Replication of HIV by a host cell requires integration of the viral genome into the host cell's DNA. Since HIV is a retrovirus, the HIV replication cycle requires transcription of the viral RNA genome into DNA via an enzyme known as reverse transcriptase (RT).

[0003] Reverse transcriptase has three known enzymatic functions: The enzyme acts as an RNA-dependent DNA polymerase, as a ribonuclease, and as a DNA-dependent DNA polymerase. In its role as an RNA-dependent DNA polymerase, RT transcribes a single-stranded DNA copy of the viral RNA. As a ribonuclease, RT destroys the original viral RNA and frees the DNA just produced from the original RNA. And as a DNA-dependent DNA polymerase, RT makes a second, complementary DNA strand using the first DNA strand as a template. The two strands form double-stranded DNA, which is integrated into the host cell's genome by the integrase enzyme.

[0004] It is known that compounds that inhibit enzymatic functions of HIV RT will inhibit HIV replication in infected cells. These compounds are useful in the prophylaxis or treatment of HIV infection in humans. Among the compounds approved for use in treating HIV infection and AIDS are the RT inhibitors 3'-azido- 3'-deoxythymidine (AZT), 2',3'-dideoxyinosine (ddI), 2',3'- dideoxycytidine (ddC), d4T, 3TC, nevirapine, delavirdine, efavirenz, abacavir, emtricitabine, and tenofovir. Current standard of care is to employ highly active anti-retroviral therapy (HAART). HAART therapy is defined as the combination of 3 agents from at least 2 different mechanistic classes . While HAART based treatment regimens employing RT inhibitors are effective in treating HIV infection and AIDS, there remains a need to develop additional HIV antiviral drugs including additional RT inhibitors. A particular problem is the development of mutant HIV strains that are resistant to the known inhibitors. The use of RT inhibitors to treat AIDS often leads to viruses that are less sensitive to the inhibitors. This resistance is typically the result of mutations that occur in the reverse transcriptase segment of the pol gene. The continued use of antiviral compounds to treat HIV infection will inevitably result in the emergence of new resistant strains of HIV. Accordingly, there is a particular need for new RT inhibitors that are effective against mutant HIV strains.

[0005] WO 2009/067166 and WO 2011/126969 disclose certain RT inhibitors prodrugs. Clemo et al., J. Chem. Soc. 1954, pp. 2693-2702 discloses certain derivatives of the 4-oxo-3-(2-pyridyl)pyridocoline system and in particular discloses 6-methyl-6'-phenoxy-2,2'-methylenedipyridine. Sweeney et al., Bioorganic & Medicinal Chem. Letters 2008, vol. 18, pp. 4348-4351 discloses a series of triazolinones that were found to be non-nucleoside inhibitors of HIV reverse transcriptase. WO 2001/034578 discloses certain substituted azoles (including, for example, certain imidazoles and benzimidazoles) having *anti-Helicobacter pylori* activity. In particular, WO '578 discloses 1-[(3-methyl-4-phenoxy-2-pyridinyl)methyl]-1*H*-benzimidazole (see Compound 91 on page 40). WO 2004/085406 and corresponding US 7189718 disclose certain benzyl pyridazinones as reverse transcriptase inhibitors. WO 2005/102989 and corresponding US 7166738 disclose certain N-phenyl 2-phenylacetamides to be non-nucleoside reverse transcriptase inhibitors. WO 2006/067587 discloses certain biaryl ether derivatives to be modulators of the reverse transcriptase enzyme. WO 2007/045572 and WO 2007/045573 disclose certain 2-(2-phenoxyphenyl) N-phenyl acetamides as non-nucleoside reverse transcriptase inhibitors. WO 2008/076225 discloses certain indazoles, benzotriazoles and related bicyclic compounds as HIV reverse transcriptase inhibitors. WO 2009/067166 discloses certain aryloxy-, cycloalkyloxy-, and heterocyclyloxy-pyridines and related compounds. The compounds are HIV reverse transcriptase inhibitors suitable, for example, for the treatment of infection by HIV. Among the compounds disclosed are certain 3-(3,5-disubstituted phenoxy)-1-(1*H*-pyrazolo[3,4-*b*]pyridin-3-ylmethyl)-4-(substituted)pyridin-2(1*H*)-ones. US 2004/0192704 discloses certain 3-(phenoxy)benzyl substituted 5-membered triazolones, oxadiazolones, and thiadiazolones. The compounds are disclosed to be non-nucleoside reverse transcriptase inhibitors useful for the treatment or prophylaxis of HIV mediated diseases. US 2007/0021442 and WO 2007/015812 disclose certain substituted aromatic compounds. The compounds are HIV reverse transcriptase inhibitors suitable, for example, for the treatment of infection by HIV. WO 2009/067166 and WO2011/120133 discloses HIV non-nucleoside reverse transcriptase inhibitors. WO 2011/126969 discloses prodrugs of HIV non-nucleoside reverse transcriptase inhibitors

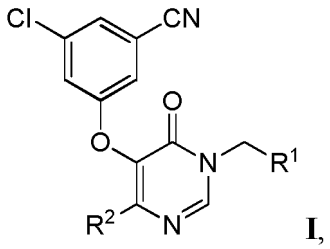
SUMMARY OF THE INVENTION

[0006] The present invention is directed to certain derivatives of 4-pyrimidinones. The compounds of Formula I are believed to be pro-drugs which can be metabolized *in vivo* to compounds of Formula I' (defined below) which are inhibitors of HIV reverse transcriptase. The compounds of Formula I' inhibit the polymerase function of HIV-1 reverse transcriptase, and more particularly inhibit the RNA-dependent DNA polymerase activity of HIV-1 reverse transcriptase. The compounds of Formula I' also exhibit activity against drug resistant forms of HIV (e.g., mutant strains of HIV-1 in which reverse transcriptase has a mutation at lysine 103 → asparagine (K103N) and/or tyrosine 181 → cysteine (Y181C)). Thus compounds of Formula I, which can be used to facilitate administration of compounds of Formula I', can exhibit decreased cross-resistance against currently approved antiviral therapies. Therefore, the compounds of Formula I (including hydrates and solvates thereof) are useful, for example, in the inhibition of HIV reverse transcriptase, the prophylaxis of infection by HIV, the treatment of infection by HIV and in the prophylaxis, treatment, and delay in the onset or progression of AIDS and/or ARC, either as compounds per se, or as pharmaceutical composition ingredients, whether or not in combination with other HIV antivirals, anti-infectives, immunomodulators, antibiotics or vaccines.

[0007] International Patent Application publication number WO 00/03998 (Noviro Pharmaceuticals Limited) discloses certain substituted 6-benzyl-4-oxopyrimidines, process for their preparation and pharmaceutical compositions containing them. United States Patent Application publication number US 2005/0065145 (Syrrx Inc.) discloses certain dipeptidyl peptidase inhibitors.

DETAILED DESCRIPTION OF THE INVENTION

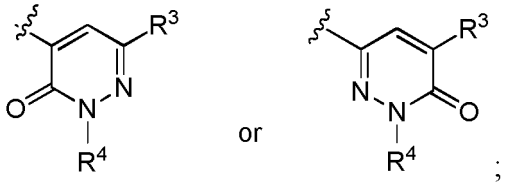
[0008] The invention encompasses compounds of structural Formula I or a pharmaceutically acceptable salt thereof:



I,

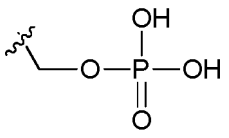
wherein

R^1 is



;

R^2 is halo or -C_{1-3}alkyl substituted with 1 to 3 of -F;
R^3 is (a) halo, (b) -C_{1-3}alkyl substituted with 1 to 3 of -F, or (3) phenyl substituted with halo; and
R^4 is



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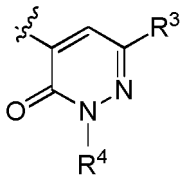
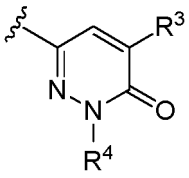
[0009] In Embodiment A of this invention are compounds of Formula I or a pharmaceutically acceptable salt thereof wherein **R^1** is



[0010] In Embodiment B of this invention are compounds of Formula I or a pharmaceutically acceptable salt thereof wherein **R1** is

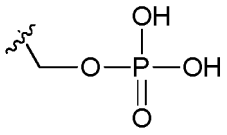


[0011] In another embodiment of this invention are compounds of Formula I or Embodiment A or Embodiment B, or a pharmaceutically acceptable salt thereof, wherein **R2** is methyl substituted with 1, 2 or 3 of -F; or ethyl substituted with 1, 2 or 3 of -F; and more particularly **R2** is $-CHF_2$, $-CF_3$, or $-CF_2CH_3$.

[0012] In another embodiment of this invention are compounds of Formula I or Embodiment A or Embodiment B, or a pharmaceutically acceptable salt thereof, wherein **R3** is -F; -Cl; methyl substituted with 1, 2 or 3 of -F; ethyl substituted with 1, 2 or 3 of -F; or phenyl substituted with -F; and more particularly **R3** is -Cl, $-CHF_2$, $-CF_3$, $-CF_2CH_3$, or phenyl substituted with -F.

[0013] In another embodiment of this invention are compounds of Formula I, Embodiment A or Embodiment B, or a pharmaceutically acceptable salt thereof, wherein:

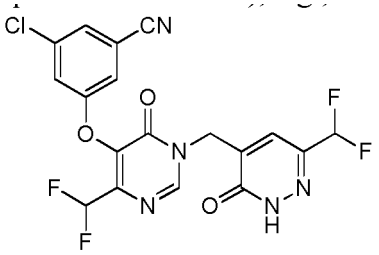
R2 is methyl substituted with 1, 2 or 3 of -F; or ethyl substituted with 1, 2 or 3 of -F; and more particularly **R2** is $-CHF_2$, $-CF_3$, or $-CF_2CH_3$;
R3 is -F, -Cl, methyl substituted with 1, 2 or 3 of -F; ethyl substituted with 1, 2 or 3 of -F; or phenyl substituted with -F; and more particularly **R3** is -Cl, $-CHF_2$, $-CF_3$, $-CF_2CH_3$, or phenyl substituted with -F; and
R4 is



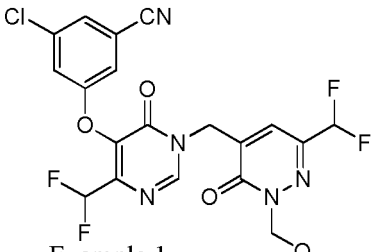
[0014] As used herein, the term "alkyl" refers to a straight or branched chain, saturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range. Thus, for example, "$-C_{1-3}$ alkyl" means linear or branched chain alkyl groups, including all isomers, having the specified number of carbon atoms, i.e., *n*- and *i*-propyl (Pr = propyl), ethyl (Et) and methyl (Me).

[0015] The term "halogen" (or "halo") refers to fluorine, chlorine, bromine or iodine (alternatively referred to as fluoro, chloro, bromo, and iodo). Fluoro or chloro are preferred.

[0016] The compounds of Formula I are believed to act as pro-drugs which are converted *in vivo* into their pharmaceutically active counterparts of Formula I', wherein Formula I' is identical to Formula I except that R^4 is replaced with -H. For a specific compound of Formula I, the corresponding compound of Formula I' may be referred to herein as the "Parent" compound (whether or not either or both of the corresponding compounds are in a salt form, unless specified otherwise), e.g.,



Parent compound of Example 1
(within scope of Formula I')



Example 1
(within scope of Formula I)

[0017] The compounds of Formula I' are HIV reverse transcriptase inhibitors. Rat AUC data for the compounds of Examples 1-8 are provided in Table 3, *infra.*

[0018] All structural Formulas, embodiments and classes thereof described herein include the pharmaceutically acceptable salts of the compounds defined therein. Reference to the compounds of Formula I herein encompasses the compounds of Formulas I and all embodiments and classes thereof. Reference to the compounds of this invention as those of a specific formula or embodiment, e.g., Formula I, or embodiments thereof, or any other generic structural formula or specific compound described or claimed herein, is intended to encompass the specific compound or compounds falling within the scope of the Formula or embodiment, including salts thereof, particularly pharmaceutically acceptable salts, solvates (including hydrates) of such compounds and solvated salt forms thereof, where such forms are possible, unless specified otherwise

[0019] The present invention includes each of the Examples described herein, and pharmaceutically acceptable salts thereof. The invention also encompasses pharmaceutical compositions comprising an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0020] Unless expressly stated to the contrary, substitution by a named substituent is permitted on any atom in a chain or ring provided such substitution is chemically allowed and results in a stable compound. A "stable" compound is a compound which can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (e.g., therapeutic or prophylactic administration to a subject). The compounds of the present invention are limited to stable compounds embraced by Formula I and its embodiments.

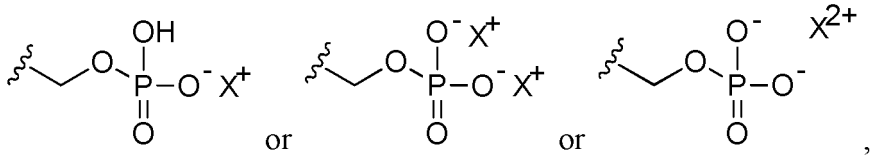
[0021] To the extent substituents and substituent patterns provide for the existence of tautomers (e.g., keto-enol tautomers) in the compounds of the invention, all tautomeric forms of these compounds, whether present individually or in mixtures, are within the scope of the present invention. It is understood that a reference to a compound capable of tautomerism includes within its scope a reference to each individual tautomer and combinations thereof, e.g., keto and enol forms.

[0022] In the compounds of Formula I, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of Formula I. For example, different isotopic forms of hydrogen (H) include protium (^{1}H) and deuterium (^{2}H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within Formula I can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

[0023] The compounds can be administered in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to a salt which is not biologically or otherwise undesirable (e.g., is neither toxic nor otherwise deleterious to the recipient thereof). When the compounds of Formula I contain one or more acidic or basic groups the invention also includes the corresponding pharmaceutically acceptable salts. Thus, the compounds of Formula I which contain acidic groups can be used according to the invention as, for example but not limited to, alkali metal salts, alkaline earth metal salts or as ammonium salts. Examples of such salts include but are not limited to sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. Compounds of Formula I which contain one or more basic groups, i.e. groups which can be protonated, can be used according to the invention in the form of their acid addition salts with inorganic or organic acids as, for example but not limited to, salts with hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, benzenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids,

oxalic acid, acetic acid, trifluoroacetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfaminic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid, etc. If the compounds of Formula I simultaneously contain acidic and basic groups in the molecule the invention also includes, in addition to the salt forms mentioned, pharmaceutically acceptable inner salts or betaines (zwitterions). Salts can be obtained from the compounds of Formula I by customary methods which are known to the person skilled in the art, for example by combination with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange from other salts. The present invention also includes all salts of the compounds of Formula I which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

[0024] As an example, the compounds of Formula I include, but are not limited to, such compounds wherein the alkyl-phosphate of R^4 may be a base salt, which refers to a pharmaceutically acceptable salt which is represented by the loss of at least one proton from the group balanced by one or more positive counter-ions (e.g., an alkali metal cation). A base salt of R^4 can be represented as:



wherein X^+ and X^{2+} are positive counter-ions. The base salt can be formed by treating the free form of the compound of Formula I with a suitable inorganic or organic base. Suitable inorganic bases include but are not limited to ammonium hydroxide, alkali metal hydroxides (e.g., NaOH or KOH), alkaline earth metal hydroxides and the like. Suitable organic bases include alkali metal alkylcarboxylates (e.g., potassium acetate or sodium acetate), alkyl ammonium hydroxides and the like.

[0025] Another embodiment of the present invention is a compound of Formula I wherein the compound or its salt is in a substantially pure form. As used herein "substantially pure" means suitably at least about 60 wt.%, typically at least about 70 wt.%, preferably at least about 80 wt.%, more preferably at least about 90 wt.% (e.g., from about 90 wt.% to about 99 wt.%), even more preferably at least about 95 wt.% (e.g., from about 95 wt.% to about 99 wt.%, or from about 98 wt. % to 100 wt. %), and most preferably at least about 99 wt.% (e.g., 100 wt.%) of a product containing a compound of Formula I or its salt (e.g., the product isolated from a reaction mixture affording the compound or salt) consists of the compound or salt. The level of purity of the compounds and salts can be determined using a standard method of analysis such as thin layer chromatography, gel electrophoresis, high performance liquid chromatography, and/or mass spectrometry. If more than one method of analysis is employed and the methods provide experimentally significant differences in the level of purity determined, then the method providing the highest purity level governs. A compound or salt of 100% purity is one which is free of detectable impurities as determined by a standard method of analysis.

[0026] Furthermore, compounds of the present invention may exist in amorphous form and/or one or more crystalline forms, and as such all amorphous and crystalline forms and mixtures thereof of the compounds of Formula I are intended to be included within the scope of the present invention. In addition, compounds of the instant invention may form solvates with water (i.e., a hydrate) or common organic solvents. The solvates include both stoichiometric and non-stoichiometric solvates. Such solvates and hydrates, particularly the pharmaceutically acceptable solvates and hydrates, of the instant compounds are likewise encompassed within the scope of this invention, along with un-solvated and anhydrous forms.

[0027] Accordingly, the compounds within the generic structural formulas, embodiments and specific compounds described and claimed herein encompass salts, all possible stereoisomers and tautomers, physical forms (e.g., amorphous and crystalline forms), solvate and hydrate forms thereof and any combination of these forms, as well as the salts thereof, where such forms are possible unless specified otherwise.

[0028] The invention discloses methods for the treatment or prophylaxis of infection by HIV, for the inhibition of HIV reverse transcriptase, or for the treatment, prophylaxis, or delay in the onset of AIDS in a subject in need thereof, which comprises administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof.

[0029] The invention also encompasses a compound of the invention, or a pharmaceutically acceptable salt thereof, for use in the preparation of a medicament for the treatment or prophylaxis of infection by HIV, for the inhibition of HIV reverse transcriptase, or for the treatment, prophylaxis, or delay in the onset of AIDS in a subject in need thereof.

[0030] The invention also encompasses a pharmaceutical composition comprising an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier and further comprising an effective amount of an anti-HIV agent selected from the group consisting of HIV antiviral agents, immu-

nomodulators, and anti-infective agents. Within this embodiment, the anti-HIV agent is an antiviral selected from the group consisting of HIV protease inhibitors, HIV reverse transcriptase inhibitors, HIV integrase inhibitors, HIV fusion inhibitors, HIV entry inhibitors, and HIV maturation inhibitors.

[0031] Other embodiments of the present invention include the following:

(a) A pharmaceutical composition comprising an effective amount of a compound of Formula I or Embodiment A or B as defined above, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

(b) A pharmaceutical composition which comprises the product prepared by combining (e.g., mixing) an effective amount of a compound of Formula I or Embodiment A or B as defined above, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

(c) The pharmaceutical composition of (a) or (b), further comprising an effective amount of an anti-HIV agent selected from the group consisting of HIV antiviral agents, immunomodulators, and anti-infective agents.

(d) The pharmaceutical composition of (c), wherein the anti-HIV agent is an antiviral selected from the group consisting of HIV protease inhibitors, nucleoside HIV reverse transcriptase inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, HIV integrase inhibitors, HIV fusion inhibitors, and HIV entry inhibitors.

(e) A combination which is (i) a compound of Formula I or Embodiment A or B as defined above, or pharmaceutically acceptable salt thereof, and (ii) an anti-HIV agent selected from the group consisting of HIV antiviral agents, immunomodulators, and anti-infective agents; wherein the compound and the anti-HIV agent are each employed in an amount that renders the combination effective for inhibition of HIV reverse transcriptase, for treatment or prophylaxis of infection by HIV, or for treatment, prophylaxis of, or delay in the onset or progression of AIDS.

(f) The combination of (e), wherein the anti-HIV agent is an antiviral selected from the group consisting of HIV protease inhibitors, nucleoside HIV reverse transcriptase inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, HIV integrase inhibitors, HIV fusion inhibitors, and HIV entry inhibitors.

(g) A compound of Formula I or Embodiment A or B or pharmaceutically acceptable salt thereof for use in the inhibition of HIV reverse transcriptase in a subject in need thereof which comprises administering to the subject an effective amount of a compound of Formula I or Embodiment A or B or pharmaceutically acceptable salt thereof.

(h) A compound of Formula I or Embodiment A or B or pharmaceutically acceptable salt thereof for use in the prophylaxis or treatment of infection by HIV (e.g., HIV-1) in a subject in need thereof which comprises administering to the subject an effective amount of a compound of Formula I or Embodiment A or B or pharmaceutically acceptable salt thereof.

(i) The compound for use of (h), wherein the compound of Formula I or Embodiment A or B is administered in combination with an effective amount of at least one other HIV antiviral selected from the group consisting of HIV protease inhibitors, HIV integrase inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, nucleoside HIV reverse transcriptase inhibitors, HIV fusion inhibitors, and HIV entry inhibitors.

(j) A compound of Formula I or Embodiment A or B or pharmaceutically acceptable salt thereof for use in the prophylaxis, treatment or delay in the onset or progression of AIDS in a subject in need thereof which comprises administering to the subject an effective amount of a compound of Formula I or Embodiment A or B or pharmaceutically acceptable salt thereof.

(k) The compound for use of (j), wherein the compound is administered in combination with an effective amount of at least one other HIV antiviral selected from the group consisting of HIV protease inhibitors, HIV integrase inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, nucleoside HIV reverse transcriptase inhibitors, HIV fusion inhibitors, and HIV entry inhibitors.

(l) The pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f) for use in the inhibition of HIV reverse transcriptase in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

(m) The pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f) for use in the prophylaxis or treatment of infection by HIV (e.g., HIV-1) in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

(n) The pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f) for use in the prophylaxis, treatment, or delay in the onset or progression of AIDS in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

[0032] The present invention also includes a compound of Formula I or Embodiment A or B, or a pharmaceutically acceptable salt thereof, (i) for use in, (ii) for use as a medicament for, or (iii) for use in the manufacture/preparation of a medicament for: (a) therapy (e.g., of the human body), (b) medicine, (c) inhibition of HIV reverse transcriptase, (d) treatment or prophylaxis of infection by HIV, or (e) treatment, prophylaxis of, or delay in the onset or progression of AIDS. In these uses, the compounds of the present invention can optionally be employed in combination with one or more other anti-HIV agents selected from HIV antiviral agents, anti-infective agents, and immunomodulators.

[0033] Additional embodiments of the invention include the pharmaceutical compositions, combinations and uses set forth in (a)-(n) above and the uses (i)(a)-(e) through (iii)(a)-(e) set forth in the preceding paragraph, wherein the compound of the present invention employed therein is a compound of one of the embodiments, aspects, classes, sub-classes, or features described above. In all of these embodiments etc., the compound can optionally be used in the form of a pharmaceutically acceptable salt.

[0034] Additional embodiments of the present invention include each of the pharmaceutical compositions, combinations, and uses set forth in the preceding paragraphs, wherein the compound of the present invention or its salt employed therein is substantially pure. With respect to a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable carrier and optionally one or more excipients, it is understood that the term "substantially pure" is in reference to a compound of Formula I or its salt per se.

[0035] Still additional embodiments of the present invention include the pharmaceutical compositions, combinations and uses set forth in (a)-(n) above and the uses (i)(a)-(e) through (iii)(a)-(e) set forth above, wherein the HIV of interest is HIV-1. Thus, for example, in the pharmaceutical composition (d), the compound of Formula I is employed in an amount effective against HIV-1 and the anti-HIV agent is an HIV-1 antiviral selected from the group consisting of HIV-1 protease inhibitors, HIV-1 reverse transcriptase inhibitors, HIV-1 integrase inhibitors, HIV-1 fusion inhibitors and HIV-1 entry inhibitors.

[0036] Unless expressly stated to the contrary, all ranges cited herein are inclusive. It is also understood that any range cited herein includes within its scope all of the sub-ranges within that range. For example, a moiety described as optionally substituted with "from 1 to 3 substituents" is intended to include as aspects thereof, such moiety substituted with 1 to 3 substituents, 2 or 3 substituents, 3 substituents, 1 or 2 substituents, 2 substituents, or 1 substituent. As another example, a dosage in a range of 1 to 500 milligrams means the dosage can be 1 mg or 500 mg or any amount therebetween.

[0037] The uses of the present invention involve the use of compounds of the present invention in the inhibition of HIV reverse transcriptase (e.g., wild type HIV-1 and other strains), the prophylaxis or treatment of infection by HIV and the prophylaxis, treatment or delay in the onset or progression of consequent pathological conditions such as AIDS. Preventing AIDS, treating AIDS, delaying the onset or progression of AIDS, or treating or preventing infection by HIV is defined as including, but not limited to, treatment of a wide range of states of HIV infection: AIDS, ARC, both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the present invention can be employed to treat infection by HIV after suspected past exposure to HIV by such means as blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery. As another example, the present invention can also be employed to inhibit transmission of HIV from a pregnant female infected with HIV to her unborn child or from an HIV-infected female who is nursing (i.e., breast feeding) a child to the child via administration of an effective amount of a compound of Formula I.

[0038] The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of Formula I means providing the compound to the individual in need of treatment or prophylaxis and includes both self-administration and administration to the patient by another person. When a compound is provided in combination with one or more other active agents (e.g., antiviral agents useful for treating or prophylaxis of HIV infection or AIDS), "administration" and its variants are each understood to include provision of the compound and other agents at the same time or at different times. When the agents of a combination are administered at the same time, they can be administered together in a single composition or they can be administered separately.

[0039] As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients, as well as any product which results from combining the specified ingredients.

[0040] By "pharmaceutically acceptable" is meant that the ingredients of the pharmaceutical composition must be compatible with each other and not deleterious to the recipient thereof.

[0041] The term "subject" or "patient" as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

[0042] The term "effective amount" as used herein means an amount sufficient to inhibit HIV reverse transcriptase, inhibit HIV replication, exert a prophylactic effect, and/or a exert a therapeutic effect after administration. One embodiment of "effective amount" is a "therapeutically effective amount" which is an amount of a compound that is effective for inhibiting HIV replication (which may also be referred to herein as an "inhibition effective amount"), treating HIV infection, treating AIDS, delaying the onset of AIDS, and/or slowing progression of AIDS in a patient. Another embodiment of "effective amount" is a "prophylactically effective amount" which is an amount of the compound that is effective for prophylaxis of HIV infection or prophylaxis of AIDS in a patient. It is understood that an effective amount can simultaneously be both a therapeutically effective amount, e.g., for treatment of HIV infection, and a prophylactically effective amount, e.g., for prevention or reduction of risk for developing AIDS. When the compound of Formula I is administered as a salt, reference to an amount of the compound is to the free form (i.e., the non-salt form) of the compound.

[0043] In the uses of the present invention (e.g., inhibiting HIV reverse transcriptase, treating or prophylaxis of HIV infection, inhibiting HIV replication, treating or prophylaxis of AIDS, delaying the onset of AIDS, or delaying or slowing progression of AIDS), the compounds of Formula I, optionally in the form of a salt, can be administered by means that

results in contact of the active agent with the agent's site of action. They can be administered by conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but typically are administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. The compounds of the invention can, for example, be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in the form of a unit dosage of a pharmaceutical composition containing an effective amount of the compound and conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. Liquid preparations suitable for oral administration (e.g., suspensions, syrups, elixirs and the like) can be prepared according to techniques known in the art and can employ any of the usual media such as water, glycols, oils, alcohols and the like. Solid preparations suitable for oral administration (e.g., powders, pills, capsules and tablets) can be prepared according to techniques known in the art and can employ such solid excipients as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like. Parenteral compositions can be prepared according to techniques known in the art and typically employ sterile water as a carrier and optionally other ingredients, such as a solubility aid. Injectable solutions can be prepared according to methods known in the art wherein the carrier comprises a saline solution, a glucose solution or a solution containing a mixture of saline and glucose. Further description of methods suitable for use in preparing pharmaceutical compositions for use in the present invention and of ingredients suitable for use in said compositions is provided in Remington's Pharmaceutical Sciences, 18th edition, edited by A. R. Gennaro, Mack Publishing Co., 1990 and in Remington - The Science and Practice of Pharmacy, 22nd Edition, published by Pharmaceutical Press and Philadelphia College of Pharmacy at University of the Sciences, 2012, ISBN 978 0 85711-062-6 and prior editions.

[0044] The compounds of Formula I can be administered orally in a dosage range of 0.001 to 1000 mg/kg of mammal (e.g., human) body weight per day in a single dose or in divided doses. One preferred dosage range is 0.01 to 500 mg/kg body weight per day orally in a single dose or in divided doses. Another preferred dosage range is 0.1 to 100 mg/kg body weight per day orally in single or divided doses. For oral administration, the compositions can be provided in the form of tablets or capsules containing 1 to 500 milligrams of a compound of the invention, particularly 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, and 500 milligrams for the symptomatic adjustment of the dosage to the patient to be treated. The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy. Compounds of the invention can be administered as a single dose, once-daily or less frequently.

[0045] Unless expressly stated to the contrary, references in the preceding paragraph or elsewhere herein to the administration of a quantity of a compound of the invention are references to the quantity (i.e., amount) of the corresponding salt-free compound of Formula I.

[0046] As noted above, the present invention is also directed to use of a compound of Formula I with one or more anti-HIV agents. An "anti-HIV agent" is any agent which is directly or indirectly effective in the inhibition of HIV reverse transcriptase or another enzyme or protein required for HIV replication or infection, the treatment or prophylaxis of HIV infection, and/or the treatment, prophylaxis or delay in the onset or progression of AIDS. It is understood that an anti-HIV agent is effective in treating, preventing, or delaying the onset or progression of HIV infection or AIDS and/or diseases or conditions arising therefrom or associated therewith. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of one or more anti-HIV agents selected from HIV antiviral agents, imunomodulators, anti-infectives, or vaccines useful for treating HIV infection or AIDS. Suitable HIV antivirals for use in combination with the compounds of the present invention include, for example, those listed in Table 1 as follows:

Table 1

Name	Type
abacavir, ABC, Ziagen®	nRTI
abacavir +lamivudine, Epzicom®	nRTI
abacavir + lamivudine + zidovudine, Trizivir®	nRTI
amprenavir, Agenerase®	PI
atazanavir, Reyataz®	PI
AZT, zidovudine, azidothymidine, Retrovir®	nRTI
capravirine	nnRTI

(continued)

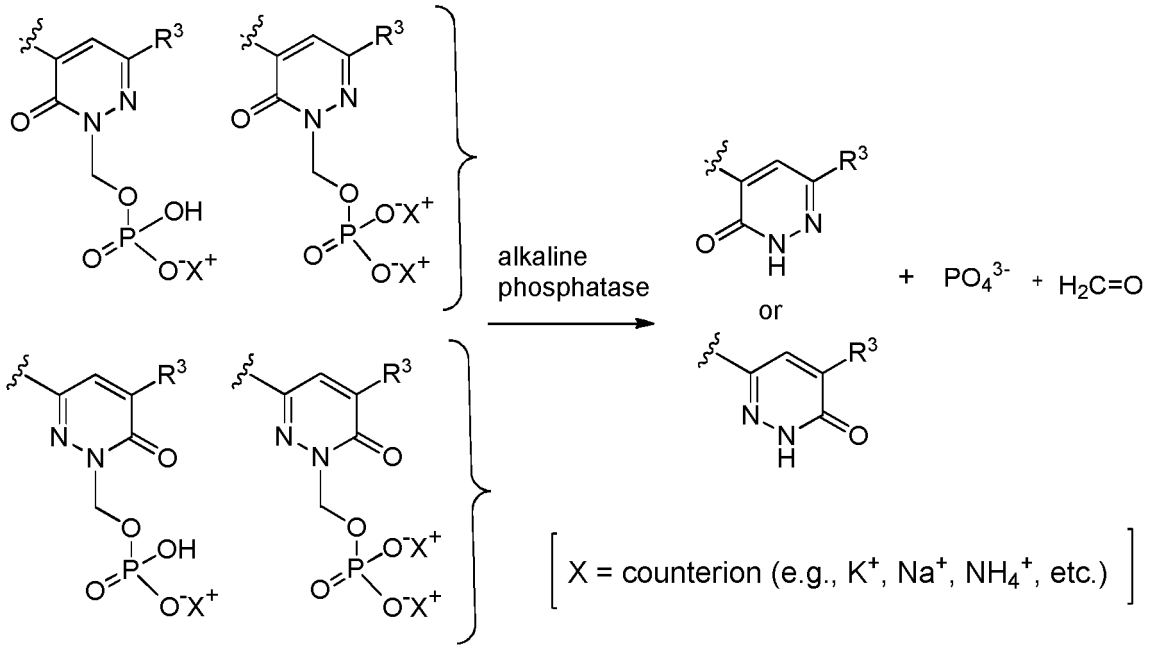
Name	Type
darunavir, Prezista®	PI
ddC, zalcitabine, dideoxycytidine, Hivid®	nRTI
ddI, didanosine, dideoxyinosine, Videx®	nRTI
ddI (enteric coated), Videx EC®	nRTI
delavirdine, DLV, Rescriptor®	nnRTI
dolutegravir, Tivicay®	InI
doravirine, MK-1439	nnRTI
efavirenz, EFV, Sustiva®, Stocrin®	nnRTI
efavirenz + emtricitabine + tenofovir DF, Atripla®	nnRTI + nRTI
EFdA (4'-ethynyl-2-fluoro-2'-deoxyadenosine)	nRTI
Elvitegravir	InI
emtricitabine, FTC, Emtriva®	nRTI
emtricitabine + tenofovir DF, Truvada®	nRTI
emvirine, Coactinon®	nnRTI
enfuvirtide, Fuzeon®	FI
enteric coated didanosine, Videx EC®	nRTI
etravirine, TMC-125, Intelence®	nnRTI
fosamprenavir calcium, Lexiva®	PI
indinavir, Crixivan®	PI
lamivudine, 3TC, Epivir®	nRTI
lamivudine + zidovudine, Combivir®	nRTI
lopinavir	PI
lopinavir + ritonavir, Kaletra®	PI
maraviroc, Selzentry®	EI
nelfinavir, Viracept®	PI
nevirapine, NVP, Viramune®	nnRTI
PPL-100 (also known as PL-462) (Ambrilia)	PI
raltegravir, MK-0518, Isentress™	InI
Rilpivirine	nnRTI
ritonavir, Norvir®	PI
saquinavir, Invirase®, Fortovase®	PI
stavudine, d4T,didehydrodeoxythymidine, Zerit®	nRTI
tenofovir DF (DF = disoproxil fumarate), TDF, Viread®	nRTI
Tenofovir, hexadecyloxypropyl (CMX-157)	nRTI
tipranavir, Aptivus®	PI

(continued)

Name	Type
vicriviroc	EI
EI = entry inhibitor; FI = fusion inhibitor; InI = integrase inhibitor; PI = protease inhibitor; nRTI = nucleoside reverse transcriptase inhibitor; nnRTI = non-nucleoside reverse transcriptase inhibitor. Some of the drugs listed in the table are used in a salt form; e.g., abacavir sulfate, delavirdine mesylate, indinavir sulfate, atazanavir sulfate, nelfinavir mesylate, saquinavir mesylate.	

[0047] It is understood that the scope of combinations of the compounds of this invention with anti-HIV agents is not limited to the HIV antivirals listed in Table A, but includes in principle any combination with any pharmaceutical composition useful for the treatment or prophylaxis of AIDS. The HIV antiviral agents and other agents will typically be employed in these combinations in their conventional dosage ranges and regimens as reported in the art, including, for example, the dosages described in the Physicians' Desk Reference, Thomson PDR, Thomson PDR, 57th edition (2003), the 58th edition (2004), or the 59th edition (2005) and the current Physicians' Desk Reference (68th ed.). (2014), Montvale, NJ: PDR Network. The dosage ranges for a compound of the invention in these combinations can be the same as those set forth above.

[0048] While not wishing to be bound by any particular theory, it is believed that the compounds of the present invention act as pro-drugs, wherein the compound is relatively stable at low pH (e.g., pH = 1 to 3) but will convert by hydrolysis or cyclization to its free base at physiological pH (e.g., a pH of about 7), thereby releasing the active substance *in vivo.* It is believed that the phosphate group of R^4 is cleaved primarily in the intestines by phosphatase enzymes in the lumen and secondarily at the brush border by phosphatases releasing the active substance *in vivo.* The conversion can be depicted as follows:



[0049] Abbreviations and acronyms employed herein include the following:

AcOH = acetic acid	mHz = megahertz
ACN = acetonitrile	min = minute
AIDS = acquired immunodeficiency syndrome	mL = milliliters
ARC = AIDS related complex;	mmol = millimoles
BSA = bovine serum albumin	Ms = SO_2CH_3

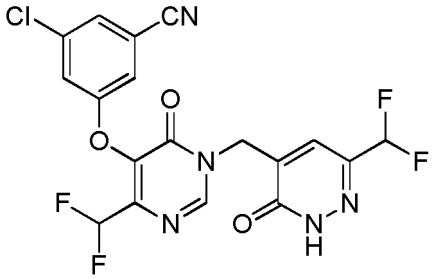
(continued)

CAN = ceric amonium nitrate	MS (ESI) = mass spectroscopy (electrospray ionization)
DAST = (diethylamino)sulfur trifluoride	NBS = *N*-bromosuccinimide
DCE = 1,2-dichloroethane	NHS = normal human serum
DCM = dichloromethane	nM = nanomolar
DEAD = diethyl azodicarboxylate	NMP = *N*-methyl-2-pyrrolidinone
Dess-Martin periodinane = 1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one	NMR = nuclear magnetic resonance
DHP = 3,4-dihydro-2*H*-pyran	PBS = phosphate buffered saline
DIPEA - diisopropylethylamine	PEG = polyethylene glycol
dppf = 1,1'-Bis(diphenylphosphino)ferrocene	PMB = 4-methyoxybenzyl
DMF = *N',N*-dimethylformamide	PMBC1 = 4-methoxybenzyl chloride
DMSO = dimethyl sulfoxide	PPTS = 4-toluenesulfonic acid
DNA = Deoxyribonucleic acid	RNA = ribonucleic acid
EDTA = ethylenediaminetetraacetic acid	r.t. = room temperature
EGTA = ethylene glycol tetracetic acid	TBAF = tetrabutylammonium fluoride
Et = ethyl	TBDPS = *tert*-Butyldiphenylsilyl
EtOAc = ethyl acetate	TBS = *tert*-Butyldimethylsilyl
EtOH = ethanol	TBS-Cl = *tert*-Butyldimethylsilyl chloride
FBS = fetal bovine serum	THP = tetrahydropyran
HIV = human immunodeficiency virus	t-Bu = *tert*-butyl
HPLC = high performance liquid chromatography	t-BuOH = *tert*-butanol
hr = hour	TEA = triethylamine
LCAP = liquid chromatography area percent	TGA = thermogravimetric analysis
LC-MS = liquid chromatography-mass spectroscopy	THF = tetrahydrofuran
LiHMDS = lithium bis(trimethylsilyl)amide	TFA = trifluoroacetic acid
m-CPBA = 3-chloroperbenzoic acid	TFAA = trifluoroacetic anhydride
Me = methyl	TLC = thin layer chromatography
MeOH = methanol	TMSC1 = trimethylsilyl chloride
Me-THF = 2-methyltetrahydrofuran	

[0050] The following examples serve only to illustrate the invention and its practice. The examples are not to be construed as limitations on the scope of the invention. In these examples, the term "room temperature" refers to a temperature in a range of from about 20°C to about 25°C.

Intermediate A

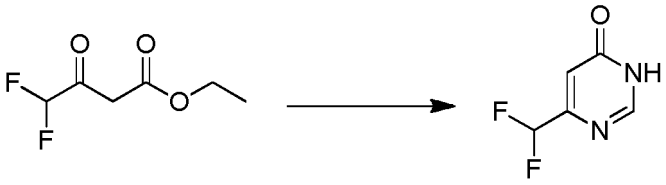
[0051]



3-chloro-5-((4-(1,1-difluoroethyl)-1-((6-(difluoroethyl)-3-oxo-2,3-dihydropyridazin-4-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

Step 1: *6-(difluoromethyl)pyrimidin-4(3H)-one*

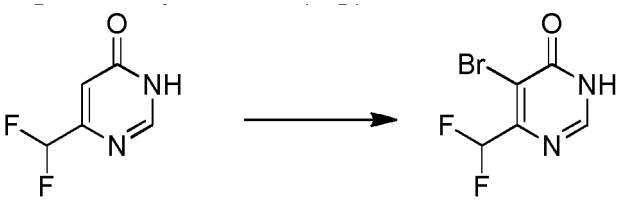
[0052]



[0053] A mixture of sodium (2.91 g, 126.5 mmol) in methanol (70 mL) was stirred at r.t. for 30 minutes then formamidine acetate (6.3 g, 60 mmol) and ethyl 4,4-difluoro-3-oxobutanoate (5.0 g, 30.1 mmol) were added. The mixture was stirred at 80 °C for 4 hr. After cooling to ambient temperature, the mixture was acidified with HCl to pH = 6 and extracted with ethyl acetate (200 mL×5). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to give 6-(difluoromethyl)pyrimidin-4(3*H*)-one. **MS (ESI): *m/z*** 147 **(M+H)** +

Step 2: *6-(difluoromethyl)pyrimidin-4(3H)-one*

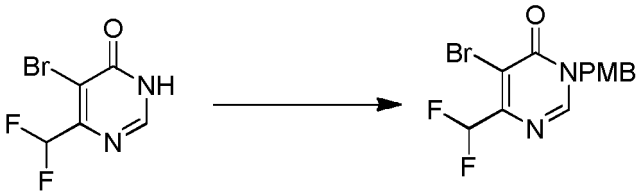
[0054]



[0055] To a mixture of compound 6-(difluoromethyl)pyrimidin-4(3*H*)-one (2.0 g, 13.7 mmol) and potassium acetate (4.0 g, 41.4 mmol) in acetic acid (20 mL), bromine (3.3 g, 20.5 mmol) was added under nitrogen atmosphere. The resulting mixture was stirred at 80 °C for 4 hr. Then the mixture was poured into ice water and the precipitate was collected by filtration to give 5-bromo-6-(difluoromethyl)pyrimidin-4(3*H*)-one. **MS (ESI): *m/z*** 225, 227 **(M+H)**$^+$

Step 3: 5-bromo-6-(difluoromethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one

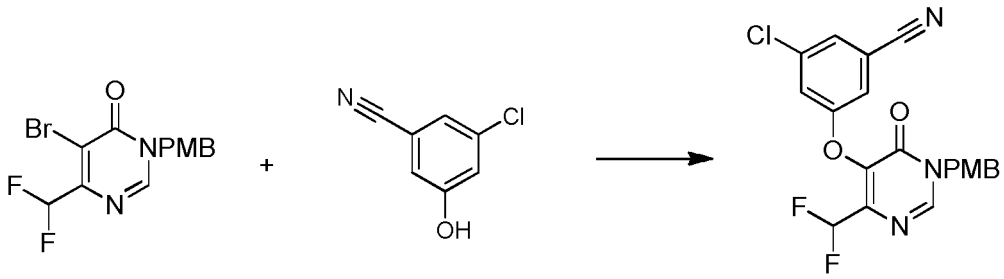
[0056]



[0057] A mixture of 5-bromo-6-(difluoromethyl)pyrimidin-4(3*H*)-one (1.01 g, 4.49 mmol), PMBC1 (735 mg, 4.71 mmol), potassium carbonate (1.24 g, 8.98 mmol) in DMF (10 mL) was stirred at ambient temperature for 4 hr under nitrogen atmosphere. 15 mL of water was added and the precipitate was collected by filtration to give 5-bromo-6-(difluoromethyl)-3-(4-methoxybenzyl) pyrimidin-4(3*H*)-one. **MS (ESI): *m/z*** 345, 347 **(M+H)**$^+$

Step 4: *3-chloro-5-((4-(difluoromethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile*

[0058]



[0059] A mixture of 3-chloro-5-hydroxybenzonitrile (1.57 g, 11.6 mmol), 5-bromo-6-(difluoromethyl)-3-(4-methoxybenzyl)pyrimidin-4(3*H*)-one (2.0 g, 5.81 mmol) and t-BuOK (1.43 g, 12.8 mmol) in NMP (10 mL) was stirred at 120 °C overnight. After cooling to ambient temperature, the mixture was diluted with 20 mL of water and extracted with ethyl acetate (100 mL×3). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. Then methanol (10 mL) was added and the precipitate was collected by filtration to afford 3-chloro-5-((4-(difluoromethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile. **MS (ESI): *m/z*** 418, 420 **(M+H)** +

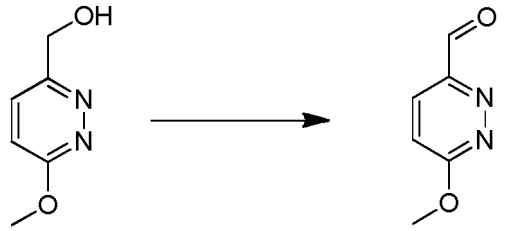
Step 5: *3-chloro-5-((4-(difluoromethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile*

[0060]

[0061] A solution of compound 3-chloro-5-((4-(difluoromethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (400 mg, 0.96 mmol) in TFA (5 mL) was stirred under microwave irradiation at 100 °C for 10 min. After cooling to ambient temperature, the mixture was concentrated under reduced pressure. Then methanol (10 mL) was added and the precipitate was collected by filtration to provide 3-chloro-5-((4-(difluoromethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy) benzonitrile. **MS (ESI): *m/z*** 298, 300 **(M+H)**$^+$

Step 6: *6-methoxypyridazine-3-carbaldehyde*

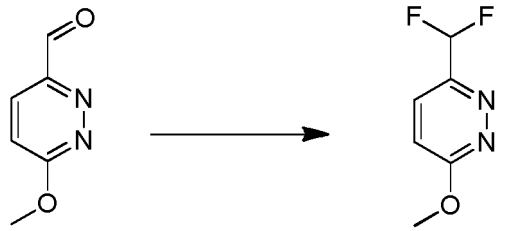
[0062]



[0063] To a stirred solution of (6-methoxypyridazin-3-yl)methanol (13 g, 93 mmol) in 500 mL of anhydrous dichloromethane was added Dess-Martin periodinane (59 g, 139 mmol). The mixture was stirred for 1 hr at room temperature. The mixture was diluted with dichloromethane, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate (15: 1 to 10: 1) as eluent) to afford 6-methoxypyridazine-3-carbaldehyde. **MS (ESI)** *m/z* 139 **$(M+H)^+$**

Step 7: *3-(difluoromethyl)-6-methoxypyridazine*

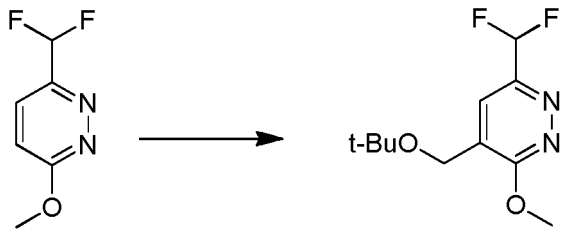
[0064]



[0065] To a stirred solution of 6-methoxypyridazine-3-carbaldehyde (6.0 g, 43.4 mmol) in 100 mL of anhydrous dichloromethane was added DAST (22.7 g, 141.3 mmol). The mixture was stirred for 1 hr at room temperature. The mixture was diluted with dichloromethane, washed with aqueous sodium bicarbonate (0.5 N, 100 mL), water and brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (petroleum ether/ethyl acetate (15:1 to 10: 1) as eluent) to afford 3-(difluoromethyl)-6-methoxypyridazine. **MS (ESI)** *m/z* 161 **$(M+H)^+$**

Step 8: *4-(tert-butoxymethyl)-6-(difluoromethyl)-3-methoxypyridazine*

[0066]

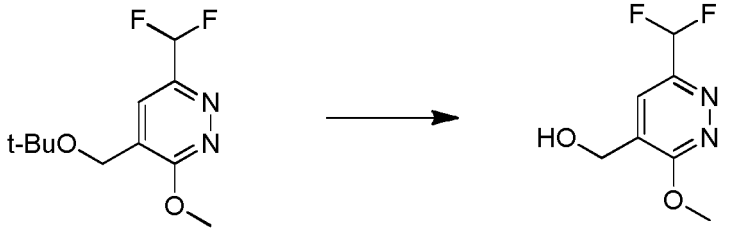


[0067] To a solution of tert-butoxy-acetic acid (0.92 g, 6.88 mmol) in THF/water (20 mol%, 7.76 mL) were added 3-(difluoromethyl)-6-methoxypyridazine (0.7 g, 4.3 mmol) and $AgNO_3$ (74 mg, 0.43 mmol). The mixture was degassed by N_2 with stirring at r.t. Then the mixture was heated to 70 °C, and then $(NH_4)_2S_2O_8$ (1.7 g, 7.31 mmol) in water (10 mL) was added dropwise. After addition, the mixture was stirred at 70-80 °C for 40 mins. After cooling to r.t., the mixture was extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate (15:1 to 10:1) as eluent) to afford 4-(tert-butoxymethyl)-6-(difluoromethyl) -3-methoxypyridazine.

MS (ESI) *m/z* 247 **$(M+H)^+$**

Step 9: *(6-(difluoromethyl)-3-methoxypyridazin-4-yl)methanol*

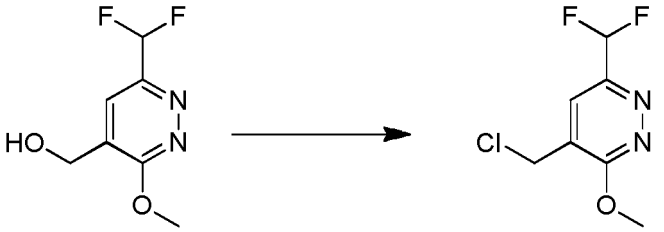
[0068]



[0069] To a solution of 4-(tert-butoxymethyl)-6-(difluoromethyl)-3-methoxypyridazine (480 mg, 1.95 mmol) in THF/DCE (1.3 mL/4.5 mL) was stirred at 60 °C for 1 hr. After cooling to r.t, the mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (petroleum ether/ethyl acetate (2:1) as eluent) to give (6-(difluoromethyl)-3-methoxy pyridazin-4-yl)methanol. **MS (ESI)** *m/z* 191 **(M+H)**$^+$

Step 10: *4-(chloromethyl)-6-(difluoromethyl)-3-methoxypyridazine*

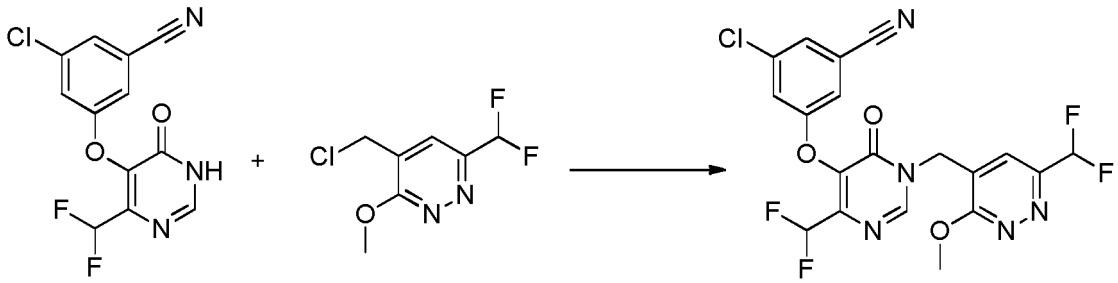
[0070]



[0071] To a solution of compound (6-(difluoromethyl)-3-methoxypyridazin-4-yl)methanol (600 mg, 3.1 mmol) in anhydrous dichloromethane (20 mL) was added dropwise methansulfonyl chloride (1.08 g, 9.4 mmol) and DIPEA (1.22 g, 9.4 mmol) respectively at 0 °C. The mixture was stirred at room temperature for 4 hr. Then the mixture was quenched with water and extracted with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 4-(chloromethyl)-6-(difluoromethyl)-3-methoxypyridazine. **MS (ESI)** *m/z* 209, 211 **(M+H)**$^+$

Step 11: *3-chloro-5-((4-(difluoromethyl)-1-((6-(difluoromethyl)-3-methoxypyridazin-4-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile*

[0072]

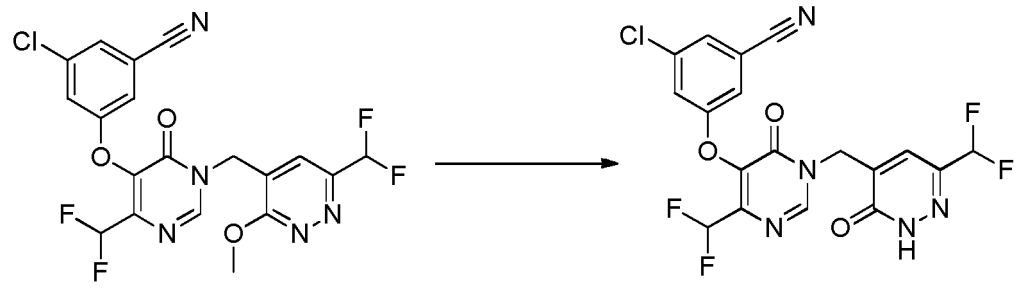


[0073] To a solution of 3-chloro-5-((4-(difluoromethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (150 mg, 0.5 mmol) in DMF (15 mL) were added K_2CO_3 (139 mg, 1.0 mmol), LiBr (88 mg, 1.0 mmol) and 4-(chloromethyl)-6-(difluoromethyl)-3-methoxypyridazine (105 mg, 0.5 mmol). The resulting mixture was stirred at room temperature overnight, diluted with water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, concentrated under reduced pressure to afford 3-chloro-5-((4-(difluoromethyl)-1-((6-(difluoromethyl)-3-methoxypyridazin-4-yl)methyl)-

6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile without further purification. **MS (ESI)** *m/z* 470, 472 **(M+H)**$^+$

Step 12: *3-chloro-5-((4-(1,1-difluoroethyl)-1-((6-(difluoroethyl)-3-oxo-2,3-dihydropyridazin-4-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile*

[0074]

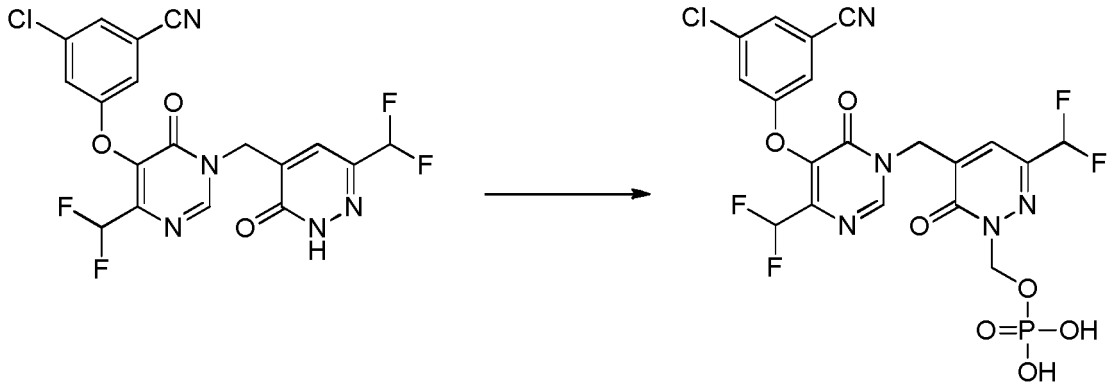


[0075] To a mixture of compound 3-chloro-5-((4-(difluoromethyl)-1-((6-(difluoromethyl)-3-methoxypyridazin-4-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (200 mg, 0.42 mmol) and KI (142 mg, 0.84 mmol) in acetonitrile (3 mL) was added TMSC1 (93 mg, 0.84 mmol) at room temperature. The resulting mixture was stirred at 70 °C for 1.5 hr. After cooled to r.t., the mixture was diluted with EtOAc and washed with aq. $Na_2S_2O_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative HPLC to afford the desired product 3-chloro-5-((4-(difluoromethyl)-1-((6-(difluoromethyl)-3-oxo-2,3-dihydropyridazin-4-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile. ^{1}**H NMR:** (Methanol-d_4, 400 MHz) δ13.60 (s, 1H), 8.66 (s, 1H), 7.71 (s, 1H), 7.62 (s, 2H), 7.59 (s, 1H), 6.98 (t, *J* = 52.0 Hz, 1H), 6.77 (t, *J* = 54.0 Hz, 1H), 4.97 (s, 2H). **MS (ESI)** *m/z* 456, 458 **(M+H)**$^+$

Example 1

(5-((5-(3-chloro-5-cyanophenoxy)-4-(difluoromethyl)-6-oxopyrimidin-1(6*H*)-yl)methyl)-3-(difluoromethyl)-6-oxopyridazin-1(6*H*)-yl)methyl dihydrogen phosphate

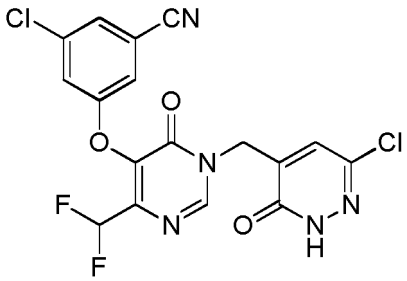
[0076]



[0077] The above compound was prepared by following similar procedures as described in Example 7 steps 1-2. ^{1}**H NMR** (500 MHz, DMSO-*d*6) δ 8.70 (s, 1H), 7.65 - 7.75 (m, 4H), 6.74 - 7.02 (m, 2H), 5.71 (d, *J* = 7.8 Hz, 2H), 5.06 (s, 2H). **MS:** 566 **(M+H)**$^+$

Intermediate B

[0078]



3-chloro-5-((1-((6-chloro-3-oxo-2,3-dihydropyridazin-4-yl)methyl)-4-(difluoromethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

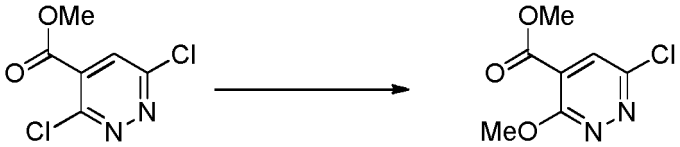
Step 1: *Methyl 3,6-dichloropyridazine-4-carboxylate*

[0079]

[0080] A suspension of 3,6-dichloropyridazine-4-carboxylic acid (5.5 g, 28.5 mmol) in DCM (50.0 ml) and MeOH (10 ml) was added trimethylsilyldiazomethane (2 M in hexane, 15 ml, 30.0 mmol) slowly at 0 °C. It became a clear solution after the addition. It was stirred for 30 min and was added another 15 mL of trimethylsilyldiazomethane and stirred for 30 min. It was quenched with 2 mL of acetic acid, concentrated and purified by ISCO (80g, 0-40% ethyl acetate in hexane) to give the title compound. **MS (ESI):** *m/z* 206 **(M+H)**$^+$

Step 2*: Methyl 6-chloro-3-methoxypyridazine-4-carboxylate*

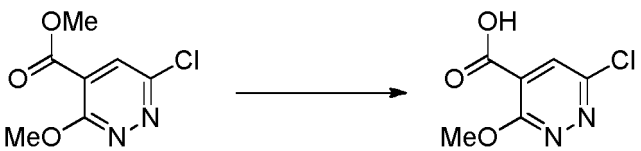
[0081]



[0082] Methyl 3,6-dichloropyridazine-4-carboxylate (2 g, 9.66 mmol) was weighted into a clean dry flask charged with a magnetic stirring bar. It was sealed and purged with nitrogen twice and dissolved in anhydrous THF (40 ml). The solution was cooled in an ice-water bath and added sodium methoxide (0.69 g, 12.77 mmol) in one portion. It was stirred for 30 min. LC-MS showed the completion of the reaction. It was quenched with saturated aqueous ammonium chloride (20 mL). The mixture was extracted with ethyl acetate (3x40 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by ISCO (80g, 0-30% ethyl acetate in hexane) to give the title compound.
MS (ESI): *m/z* 203 **(M+H)**$^+$

Step 3*: 6-Chloro-3-methoxypyridazine-4-carboxylic acid*

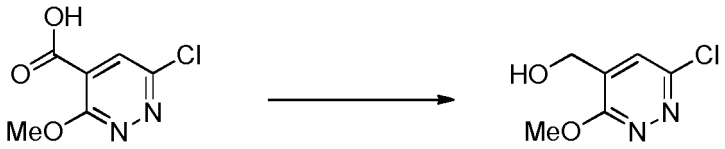
[0083]



[0084] A solution of methyl 6-chloro-3-methoxypyridazine-4-carboxylate (510 mg, 2.52 mmol) in tetrahydrofuran (5 ml) and methanol (5.00 mL) was treated with 4 M aqueous LiOH (5 mL, 20.00 mmol) for 15 min. It was neutralized by 1 N HCl and concentrated. The residue was dried under vacuum and used without purification. **MS (ESI):** *m*/*z* 189 **(M+H)**$^+$

Step 4: *(6-Chloro-3-methoxypyridazin-4-yl)methanol*

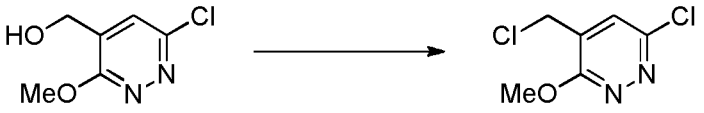
[0085]



[0086] A mixture of 6-chloro-3-methoxypyridazine-4-carboxylic acid (270 mg, 1.432 mmol) and carbonyldiimidazole (697 mg, 4.30 mmol) in THF (12 mL) was stirred for 1 h at rt. The solution was cooled to 0 °C and added sodium borohydride (271 mg, 7.16 mmol) followed by water (4 mL). It was stirred for 15 min and quenched with 5 mL of saturated aqueous ammonium chloride, extracted with ethyl acetate (4x20 mL). The combined organic layers were washed with brine (5 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by ISCO (40g, 0-50% ethyl acetate in hexane) to give the title compound. **MS (ESI):** *m*/*z* 175 **(M+H)**$^+$

Step 5: *6-Chloro-4-(chloromethyl)-3-methoxypyridazine*

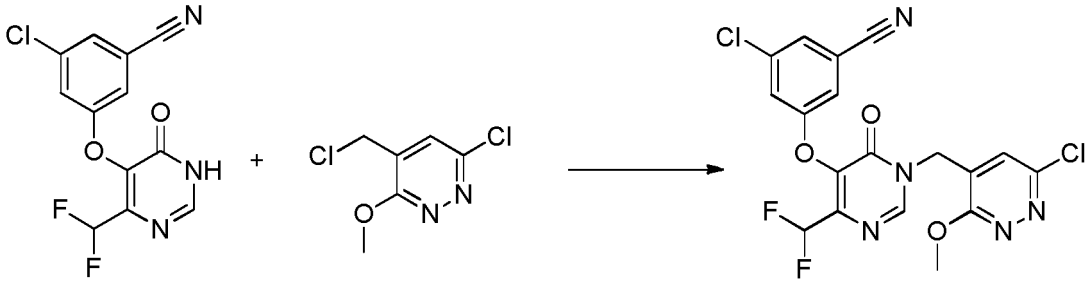
[0087]



[0088] To a solution of (6-chloro-3-methoxypyridazin-4-yl)methanol (100 mg, 0.573 mmol) in DCM (5 ml) at 0 °C was added methanesulfonyl chloride (0.134 ml, 1.718 mmol) and Hunig's Base (0.300 ml, 1.718 mmol). It was stirred at 0 °C for 15 min and allowed to warm to rt overnight. It was concentrated under reduced pressure. The residue was purified by ISCO (24g, 0-30% EtOAc/Hexanes gradient) to afford the title compound. **MS (ESI):** *m*/*z* 192 **(M+H)**

Step 6: *3-chloro-5-((1-((6-chloro-3-methoxypyridazin-4-yl)methyl)-4-(difluoromethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile*

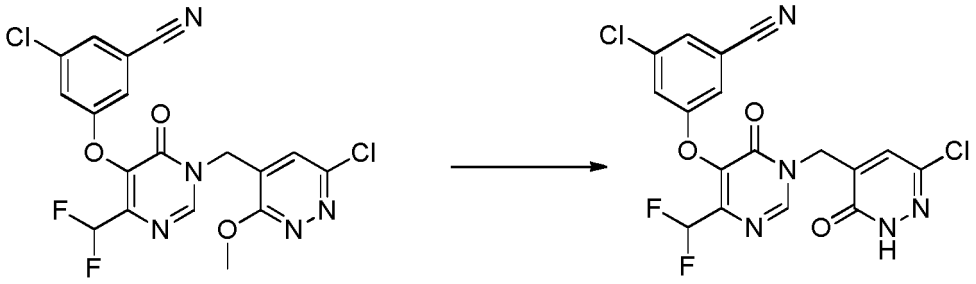
[0089]



[0090] Compound was prepared in the same as manner as Intermediate A, step 11.

Step 7*: 3-chloro-5-((1-((6-chloro-3-oxo-2,3-dihydropyridazin-4-yl)methyl)-4-(difluoromethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile*

[0091]

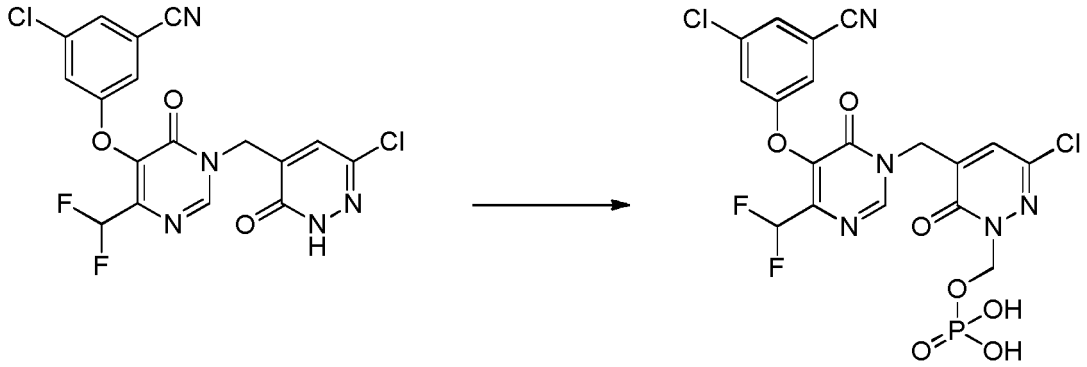


[0092] Compound was prepared in the same as manner as Intermediate A, step 12.
^{1}**H NMR:** (DMSO-d_6, 500 MHz) δ8.66 (s, 1H), 7.75 (s, 1H), 7.69 (s, 1H), 7.65 (m, 1H), 7.54 (s, 1H), 7.02 (t, *J* = 52.0 Hz, 1H), 4.96 (s, 2H). **MS (ESI)** *m*/*z* 440.1 **(M+H)**$^+$

Example 2

(3-chloro-5-((5-(3-chloro-5-cyanophenoxy)-4-(difluoromethyl)-6-oxopyrimidin-1(6*H*)-yl)methyl)-6-oxopyridazin-1(6*H*)-yl)methyl dihydrogen phosphate

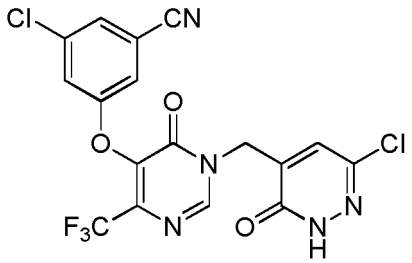
[0093]



[0094] The above compound was prepared by following similar procedures as described in Example 7 steps 1-2. ^{1}**H NMR** (500 MHz, DMSO-*d*6) δ 8.66 (s, 1H), 7.64 - 7.75 (m, 4H), 7.03 (t, *J* = 55 Hz, 1H), 5.63 (d, *J* = 8.05 Hz, 2H), 5.01 (s, 2H). **MS:** 550 **(M+H)**$^+$

Intermediate C

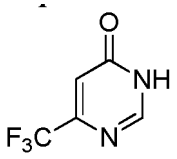
[0095]



3-chloro-5-((1-((6-chloro-3-oxo-2,3-dihydropyridazin-4-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

Step 1:

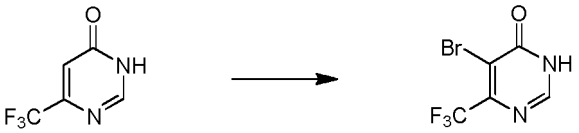
[0096]



[0097] Eur. J. Org. Chem. 2004, 3714-37188.

Step 2: *5-bromo-6-(trifluoromethyl)-4(3H)-pyrimidione*

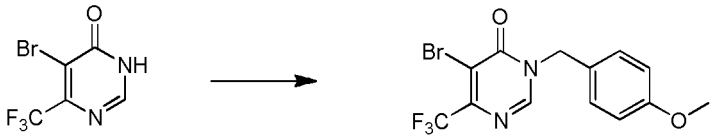
[0098]



[0099] To a solution of 6-(trifluoromethyl)pyrimidin-4(3H)-one (0.3 g, 1.8 mmol) in acetic acid (2 mL) was added CH_3COOK (0.54 g, 5.5 mmol). Then to the mixture was added a solution of Br_2 in acetic acid (1 mL) dropwise. The mixture was heated to 80°C and stirred overnight. After cooling to room temperature, the mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, and evaporated to afford 5-bromo-6-(trifluoromethyl)-4(3*H*)-pyrimidione.

Step 3: 5-bromo-3-(4-methoxybenzyl)-6-(trifluoromethyl)pyrimidin-4(3H)-one

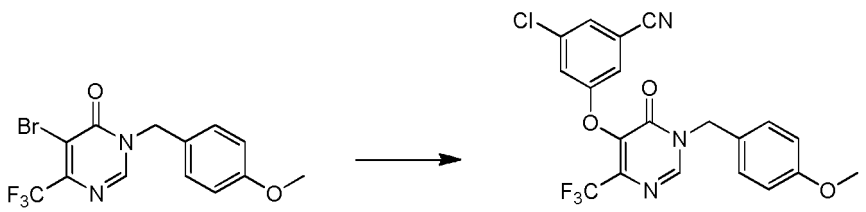
[0100]



[0101] To a solution of 5-bromo-6-(trifluoromethyl)pyrimidin-4(3*H*)-one (190 mg, 0.91 mmol) in DMF (2 mL) was added K_2CO_3 (250 mg, 1.82 mmol) and PMBC1 (210mg, 1.3 mmol). The mixture was stirred at room temperature for 5 hr. The mixture was poured into water, and extracted with EtOAc (40 mL × 3). The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate (5:1 to 1:1) as eluent) to afford 1 5-bromo-3-(4-methoxybenzyl)-6-(trifluoromethyl)pyrimidin-4(3*H*)-one. **^{1}H-NMR** J000159069 H11896-016-3 $CDCl_3$, 400 MHz δ 7.97 (s, 1H, ArH), 7.27 (d, *J*=8.8, 2H, ArH), 6.87 (d, *J*=8.8, 2H, ArH), 5.04 (s, 2H, CH), 3.78 (s, 3H, CH).

Step 4: *3-chloro-5-(1-(4-methoxybenzyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yloxy)benzonitrile*

[0102]

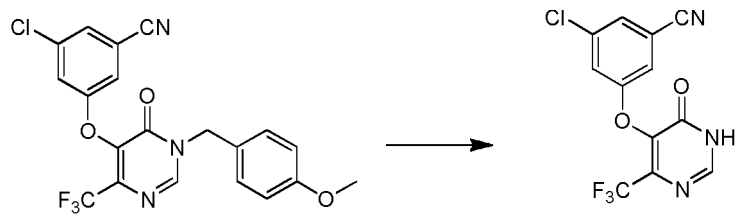


[0103] To a solution of 5-bromo-3-(4-methoxybenzyl)-6-(trifluoromethyl)pyrimidin-4(3H)-one (5 g, 13.8 mmol) in NMP (50 mL) was added K_2CO_3 (5.7 g, 41.3 mmol) and 3-chloro-5-hydroxybenzonitrile (3.2 g, 20.7 mmol). The mixture was stirred at 120 °C for 20 hr. The mixture was poured into water, and extracted with EtOAc (60 mL×3). The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column

chromatography (petroleum ether/ethyl acetate (5:1 to 1:1) as eluent) to afford 3-chloro-5-(1-(4-methoxybenzyl)-6-oxo-4-(trifluoromethyl)-1,6- dihydropyrimidin-5-yloxy)benzonitrile. ^{1}**H-NMR** J000169946 H11896-128-3 DMSO, 400 MHz δ 8.86 (s, 1H, ArH), 7.76 (s, 1H, ArH), 7.70 (s, 1H, ArH), 7.68 (s, 1H, ArH), 7.34 (d, *J*=8.6, 2H, ArH), 6.90 (d, *J*=8.6, 2H, ArH), 5.10 (s, 2H, CH), 3.72 (s, 3H, CH).

Step 5: *3-chloro-5-(6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yloxy)benzonitrile*

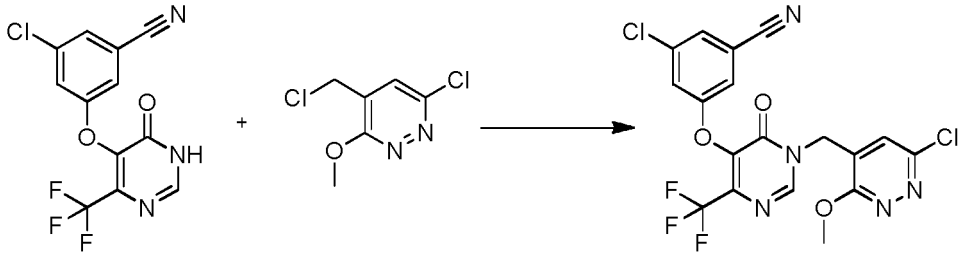
[0104]



[0105] To a solution of 3-chloro-5-(1-(4-methoxybenzyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yloxy)benzonitrile (2 g, 4.6 mmol) in CH_3CN (20 mL) and H_2O (8 mL) was added $Ce(NH_4)_2(NO_3)_6$ (10 g, 18.4 mmol) in portions. The mixture was stirred at room temperature overnight and then poured into water, and extracted with EtOAc (60 mL × 3). The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography on slica gel (petroleum ether/ethyl acetate (5:1 to 1:1) as eluent) to afford 3-chloro-5-(6-oxo-4-(trifluoro methyl)-1,6-dihydropyrimidin-5-yloxy)benzonitrile. ^{1}**H-NMR** J000170654 H11896-138-3 DMSO, 400 MHz δ 13.59 (s, 1H, NH), 8.36 (s, 1H, ArH), 7.76 (s, 1H, ArH), 7.73 (s, 1H, ArH), 7.70 (s, 1H, ArH).

Step 6*: 3-chloro-5-((1-((6-chloro-3-methoxypyridazin-4-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile*

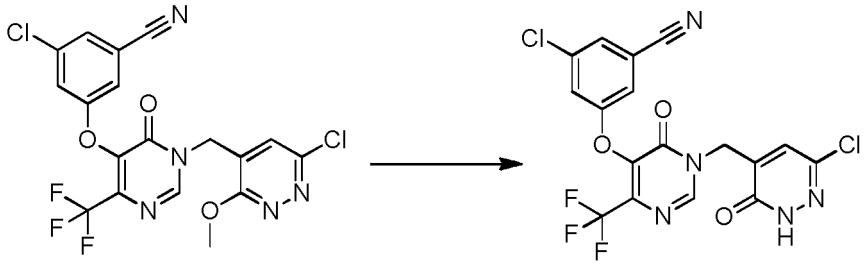
[0106]



[0107] To a soution of 3-chloro-5-((6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (100 mg, 0.32 mmol) in DMF (5 mL) were added 6-chloro-4-(chloromethyl)-3-methoxypyridazine (55 mg, 0.29 mmol, Example 2, step 5) and K_2CO_3 (80 mg, 0.58 mmol). The resulting mixture was stirred was stirred at 80°C for 2 hours. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to give the desired product 3-chloro-5-((1-((6-chloro-3-methoxy-2,3-dihydropyridazin-4-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile, which was used for the next step without further purification. **MS (ESI)** *m/z* 472, 474, 476 **(M+H)$^+$**

Step 7*: 3-chloro-5-((1-((6-chloro-3-oxo-2,3-dihydropyridazin-4-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile*

[0108]

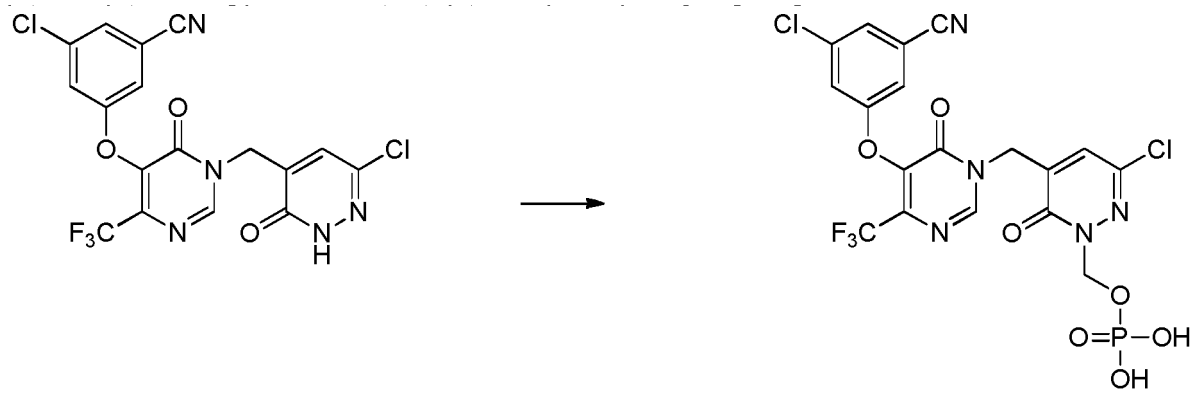


[0109] To a mixture of compound 3-chloro-5-((1-((6-chloro-3-methoxypyridazin-4-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (110 mg, 0.23 mmol) and KI (77 mg, 0.46 mmol) in acetonitrile (10 mL) was added TMSC1 (50 mg, 0.46 mmol) at room temperature. The resulting mixture was stirred for 1 hour at 70 °C. After cooling to r.t., the mixture was diluted with EtOAc and washed with aq. $Na_2S_2O_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by Prep-HPLC to afford 3-chloro-5-((1-((6-chloro-3-oxo-2,3-dihydropyridazin-4-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile. **^{1}H NMR** (**Methanol-d_4, 400 MHz)** : δ 8.60 (s, 1H), 7.68 (s, 1H), 7.47 (s, 1H), 7.28 (s, 1H), 7.24 (s, 1H), 5.07 (s, 2H), 1.92 (t, *J*=18.4 Hz, 6H). **MS (ESI)** *m/z* 458, 460, 462 **(M+H)$^+$**

Example 3

(3-chloro-5-((5-(3-chloro-5-cyanophenoxy)-6-oxo-4-(trifluoromethyl)pyrimidin-1(6*H*)-yl)methyl)-6-oxopyridazin-1(6*H*)-yl)methyl dihydrogen phosphate

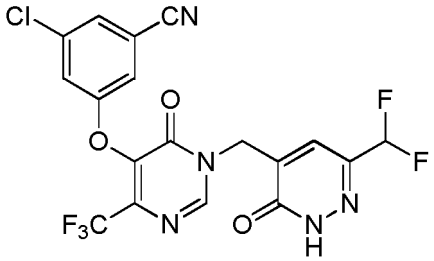
[0110]



[0111] The above compound was prepared by following similar procedures as described in Example 7 steps 1-2. **^{1}H NMR** (500 MHz, DMSO-*d*6) 8.79 (s, 1H), 7.80-7.70 (m, 3H), 7.70 (s, 1H), 5.60 (d, 2H), 5.00 (s, 2H). **MS:** 568 **(M+H)$^+$**

Intermediate D

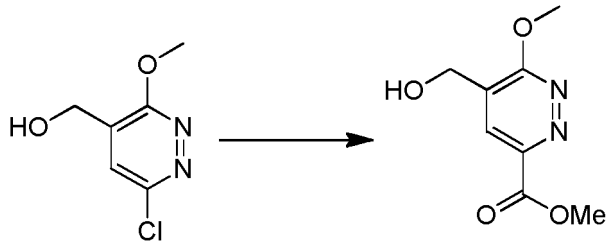
[0112]



3-chloro-5-((1-((6-(difluoromethyl)-3-oxo-2,3-dihydropyridazin -4-yl)methyl) -6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

Step 1: *methyl 5-(hydroxymethyl)-6-methoxypyridazine-3-carboxylate*

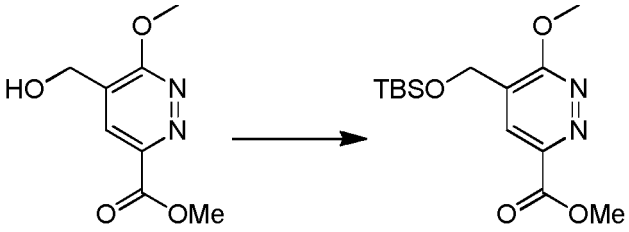
[0113]



[0114] To a solution of (6-chloro-3-methoxypyridazin-4-yl)methanol (4.6 g, 26.4 mmol), triethyl amine (7.4 mL) and $Pd(dppf)_2Cl_2$ (0.5 g, 1mmol) in 30 mL of methanol and ethyl acetate (10 mL) was stirred under carbon monoxide (50 psi) at 70 °C overnight. Then the reaction mixture was poured into water, extracted with ethyl acetate (15 mL × 3). The organic extracts were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column (petroleum ether/ethyl acetate (5:1 to 2:1) as eluent) to give methyl 5-(hydroxymethyl) -6-methoxypyridazine-3-carboxylate. **MS (ESI)** *m/z* 199 **$(M+H)^+$**

Step 2: *methyl 5-(((tert-butyldimethylsilyl)oxy)methyl)-6-methoxypyridazine-3-carboxylate*

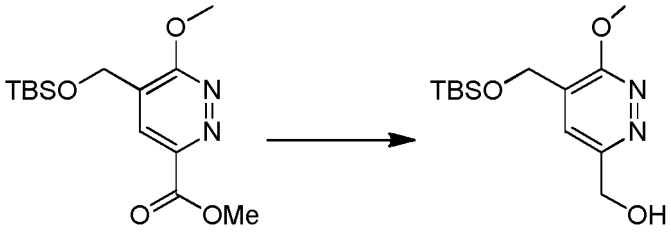
[0115]



[0116] To a solution of methyl 5-(hydroxymethyl)-6-methoxypyridazine-3-carboxylate (2.1 g, 10.6 mmol) in THF (150 mL) was added TBSC1 (4.55 g, 30.2 mmol) and imidazole (2.05 g, 30.2 mmol) at r.t. Then the resulting reaction was stirred at room temperature overnight. The reaction mixture was filtered and the filtrate was washed with water. The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford methyl 5-(((tert-butyldimethylsilyl)oxy)methyl)-6-methoxypyridazine-3-carboxylate. **MS (ESI)** *m/z* 313 **$(M+H)^+$**

Step 3: *(5-(((tert-butyldimethylsilyl)oxy)methyl)-6-methoxypyridazin-3-yl)methanol*

[0117]

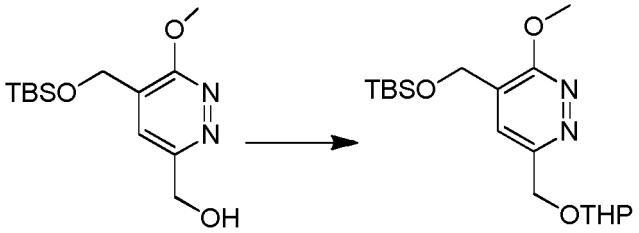


[0118] To a solution of methyl 5-(((tert-butyldimethylsilyl)oxy)methyl)-6- methoxypyridazine-3-carboxylate (2.1 g, 6.7 mmol) in ethanol (15 mL) was added $NaBH_4$ (0.38 g, 10.0 mmol) and $CaCl_2$ (0.37 g, 3.4 mmol) at 0 °C. The mixture was stirred for 1 hr at room temperature, then quenched by addition of water (20 mL), acidified to pH = 8 using HCl solution

(2 M) and extracted with ethyl acetate (15 mL × 3). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure to give (5-(((tert-butyldimethylsilyl) oxy)methyl)-6-methoxypyridazin-3-yl)methanol. **MS (ESI)** *m/z* 285 **(M+H)**$^+$

Step 4: *4-(((tert-butyldimethylsilyl)oxy)methyl)-3-methoxy-6-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridazine*

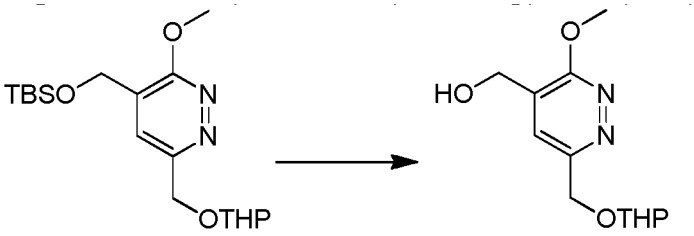
[0119]



[0120] To a solution of (5-(((tert-butyldimethylsilyl)oxy)methyl)-6-methoxypyridazin-3-yl)methanol (1.5 g, 5.3 mmol) in acetonitrile (10 mL) was added DHP (0.53 g, 6.3 mmol) and PPTS (126 mg, 0.5 mmol) at r.t. The mixture was stirred at at 80 °C for 16 hr. After cooling to r.t., the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on a silica gel (petroleum ether/ethyl acetate (10:1) as eluent) to give 4-(((tert-butyldimethylsilyl)oxy)methyl)-3-methoxy-6-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridazine. **MS (ESI)** ***m/z*** 369 **(M+H)**$^+$

Step 5*: (3-methoxy-6-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridazin-4-yl)methanol*

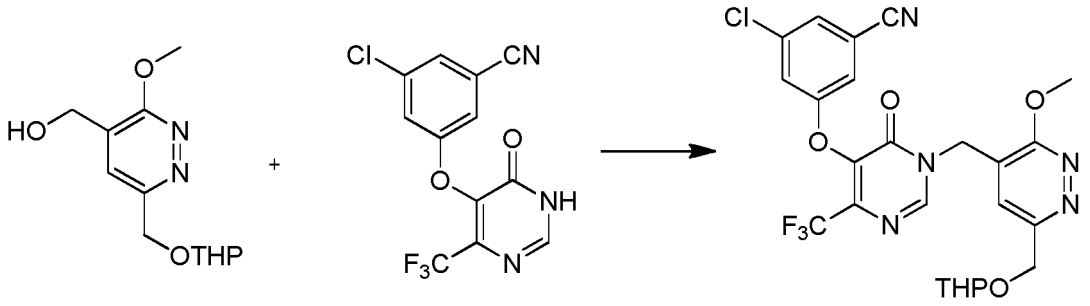
[0121]



[0122] A solution of 4-(((tert-butyldimethylsilyl)oxy)methyl)-3-methoxy -6-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridazine (0.9 g, 2.4 mmol) and TBAF (3.2 g, 12.2 mmol) in THF (20.0 mL) was stirred for 1.0 h at r.t. Water was added and the resulting mixture was extracted with ethyl acetate. The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (petroleum ether/ethyl acetate (1:2) as eluent) to give the (3-methoxy-6-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridazin-4-yl)methanol. **MS (ESI)** *m/z* 255 **(M+H)**$^+$

Step 6*: 3-chloro-5-((1-((3-methoxy-6-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridazin-4-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile*

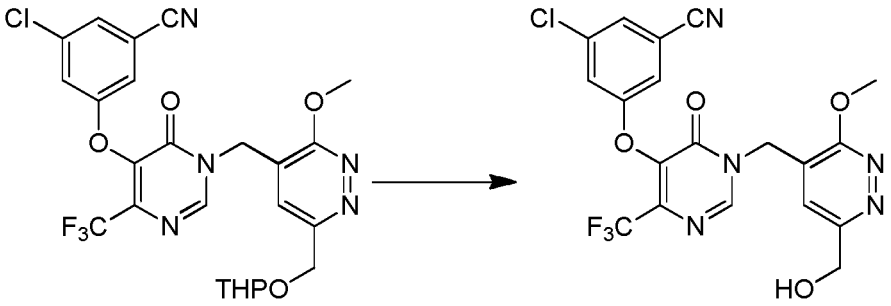
[0123]



[0124] To a solution of (3-methoxy-6-(((tetrahydro-2H-pyran-2-yl)oxy)methyl) pyridazin-4-yl)methanol (0.6 g, 2.4 mmol), 3-chloro-5-((6-oxo-4-(trifluoromethyl) -1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (0.76 g, 2.4 mmol, Example 3, step 5) and triphenylphosphine (1.3 g, 4.8 mmol) in dichloromethane (10.0 mL) was added DEAD (0.84 g, 4.8 mmol) at 0 °C under a nitrogen atmosphere. The mixture was stirred at r.t for 1 h, quenched with water (10 mL) and extracted with dichloromethane (20 mL × 3). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by preparative TLC (petroleum ether/ethyl acetate (1:1) as eluent) to give 3-chloro-5-((1-((3-methoxy-6-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridazin-4-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile. **MS (ESI)** *m/z* 552, 554 **(M+H)**$^+$

Step 7: *3-chloro-5-((1-((6-(hydroxymethyl)-3-methoxypyridazin-4-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile*

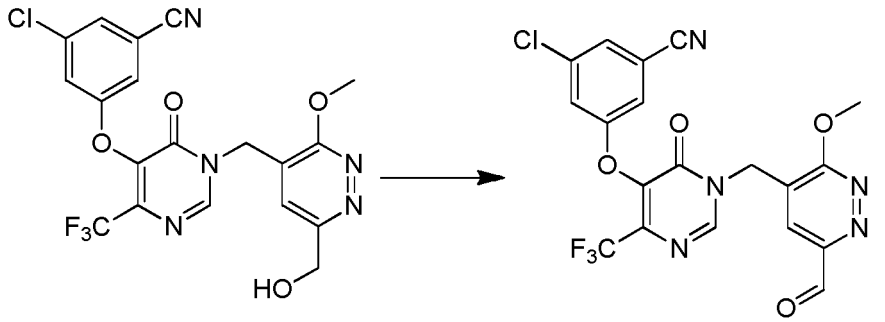
[0125]



[0126] To a solution of 3-chloro-5-((1-((3-methoxy-6-(((tetrahydro-2H-pyran-2-yl)oxy)methyl) pyridazin-4-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (1.2 g, 2.2 mmol) in methanol (10 mL) was added HCl/methanol (1 N, 10 mL) at r.t. The resulting mixture was stirred at room temperature for 1 hr and concentrated under reduced pressure to give 3-chloro-5-((1-((6-(hydroxymethyl)-3-methoxypyridazin-4-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile. **MS (ESI)** *m/z* 468, 470 **(M+H)**$^+$

Step 8: *3-chloro-5-((1-((6-formyl-3-methoxypyridazin-4-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile*

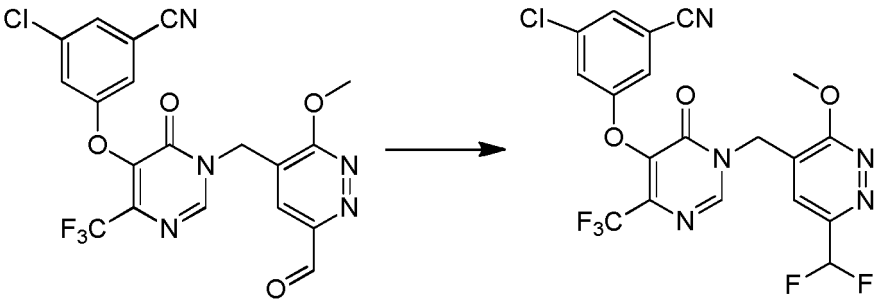
[0127]



[0128] To a solution of 3-chloro-5-((1-((6-(hydroxymethyl)-3-methoxypyridazin-4-yl) methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (1.0 g, 2.1 mmol) in dichloromethane (20 mL) was added Dess-Martin periodinane (1.36 g, 3.2 mmol) at 0 °C under a nitrogen atmosphere. The mixture was stirred at r.t for 1 hr, quenched with water (10 mL) and extracted with dichloromethane (20 mL × 3). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by preparative TLC (petroleum ether/ethyl acetate (1:1) as eluent) to give 3-chloro-5-((1-((6-formyl-3-methoxypyridazin-4-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy) benzonitrile. **MS (ESI)** *m/z* 466, 468 **(M+H)**$^+$

Step 9: *3-chloro-5-((1-((6-(difluoromethyl)-3-methoxypyridazin-4-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile*

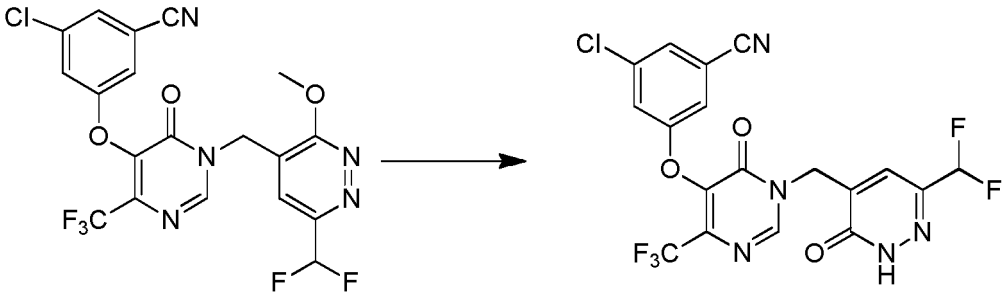
[0129]



[0130] To a stirred mixture of 3-chloro-5-((1-((6-formyl-3-methoxypyridazin-4-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (0.14 g, 0.3 mmol) in dichloromethane (5 mL) was added DAST (0.43 g, 1.6 mmol) at r.t., and the mixture was stirred under a nitrogen atmosphere for 16 hr. The mixture was quenched with H_2O and extracted with dichloromethane. The organic layer was washed with water , dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate (2:1) as eluent) to give 3-chloro-5-((1-((6-(difluoromethyl)-3-methoxypyridazin-4-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile. **MS (ESI)** *m/z* 488, 490 **(M+H)**$^+$

Step 10: *3-chloro-5-((1-((6-(difluoromethyl)-3-oxo-2,3-dihydropyridazin-4-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile*

[0131]

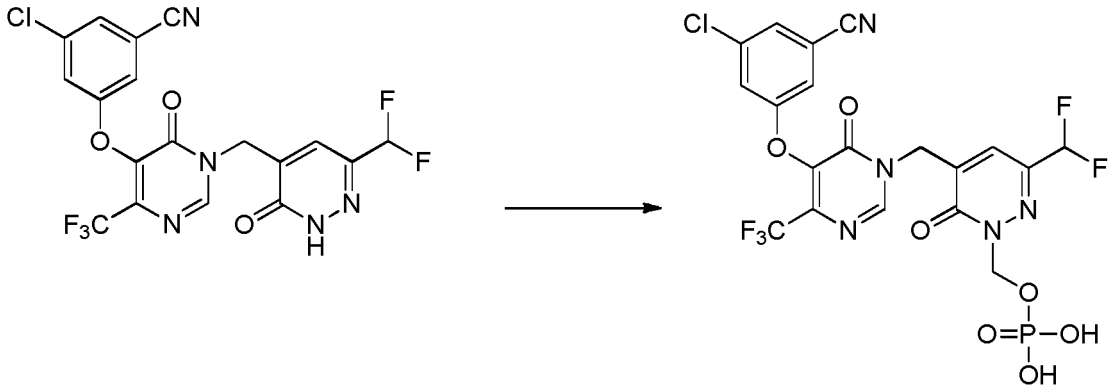


[0132] To a mixture of 3-chloro-5-((1-((6-(difluoromethyl)-3-methoxypyridazin-4-yl) methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (90 mg, 0.2 mmol) and KI (100 mg, 0.6 mmol) in acetonitrile (3 mL) was added TMSC1 (33 mg, 0.3 mmol). The mixture was stirred at r.t for 1 hr, quenched with water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to afford 3-chloro-5-((1-((6-(difluoromethyl)-3-oxo-2,3-dihydropyridazin-4-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile. **^{1}HNMR** (Methanol-*d4*, 400 MHz) δ 13.62 (s, 1H), 8.72 (s, 1H), 7.73 (s, 1H), 7.71 (s, 1H), 7.68 (s, 1H), 7.66 (s, 1H), 6.78 (t, *J* = 56.0 Hz, 1H), 4.99 (s, 2H). **MS (ESI)** *m/z* 474, 476 **(M+H)**$^+$

Example 4

(5-((5-(3-chloro-5-cyanophenoxy)-6-oxo-4-(trifluoromethyl)pyrimidin-1(6*H*)-yl)methyl)-3-(difluoromethyl)-6-oxopyridazin-1(6*H*)-yl)methyl dihydrogen phosphate

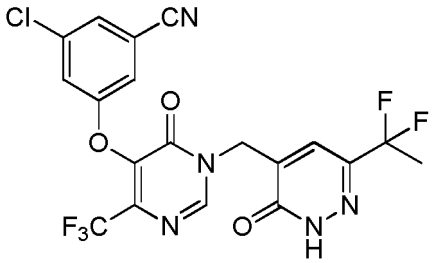
[0133]



[0134] The above compound was prepared by following similar procedures as described in Example 7 steps 1-2. ^{1}**H NMR** (500 MHz, DMSO-*d6*) δ 8.76 (s, 1H), 7.72 - 7.78 (m, 4H), 6.85 (t, *J*= 53 Hz, 1H), 5.71 (d, *J*= 7.81 Hz, 2H), 5.08 (s, 2H). **MS:** 584 **(M+H)**$^+$

Intermediate E

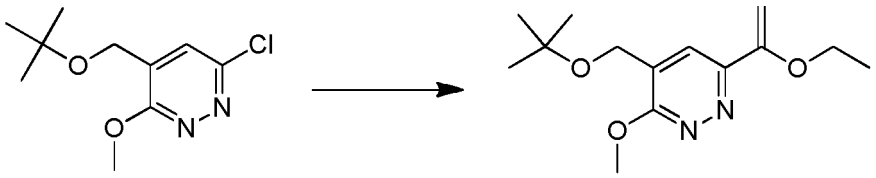
[0135]



3-chloro-5-((1-((6-(1,1-difluoroethyl)-3-oxo-2,3-dihydropyridazin-4-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

Step 1: *4-(tert-butoxymethyl)-6-(1-ethoxyvinyl)-3-methoxypyridazine*

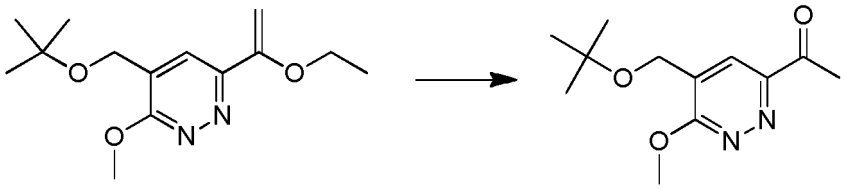
[0136]



[0137] To a mixture of 4-(tert-butoxymethyl)-6-chloro-3-methoxypyridazine (1 g, 5.7 mmol), tributyl(1-ethoxyvinyl)stannane (6.2 g, 17.2 mmol) in toluene (10 mL) was added $Pd(PPh_3)_4$ (0.6 g, 0.57 mmol) under N_2. The resulting suspension was stirred at 120 °C overnight under a nitrogen atmosphere. After cooling to r.t., the mixture was poured into ice-water, extracted with ethyl acetate, and the combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate (5:1 to 2:1) as eluent) to afford 4-(tert-butoxymethyl)-6-(1-ethoxyvinyl)-3-methoxypyridazine. **MS (ESI):** ***m/z*** 267 **(M+H)**$^+$

Step 2: *1-(5-(tert-butoxymethyl)-6-methoxypyridazin-3-yl)ethanone*

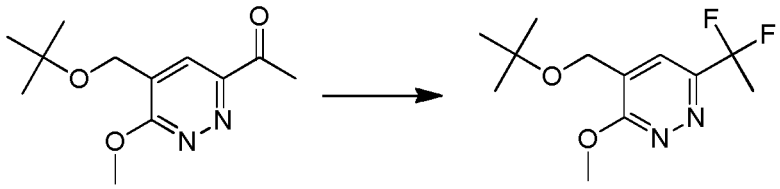
[0138]



[0139] To a solution of 4-(tert-butoxymethyl)-6-(1-ethoxyvinyl)-3-methoxypyridazine (400 mg, 1.5 mmol) in 1,4-dioxane (6 mL) was added HCl/1,4-dioxane (3N, 6 mL), the solution was stirred at room temperature overnight. The mixture was diluted with water and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prepreative TLC (petroleum ether/ethyl acetate (1:1) as eluent) to give 1-(5-(tert-butoxymethyl)-6-methoxy pyridazin-3-yl) ethanone. **MS (ESI)** *m/z* 239 **(M+H)**$^+$

Step 3: *4-(tert-butoxymethyl)-6-(1,1-difluoroethyl)-3-methoxypyridazine*

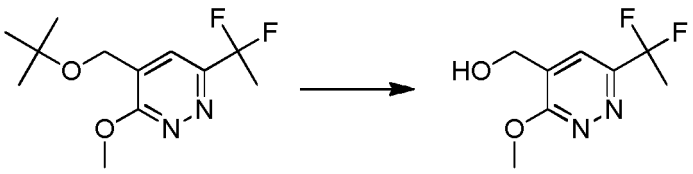
[0140]



[0141] To a solution of 1-(5-(tert-butoxymethyl)-6-methoxypyridazin-3-yl)ethanone (240 mg, 1.0 mmol) in dichloromethane (8 mL) was added DAST (0.8 mL, 6.1 mmol). The mixture was stirred at r.t. for 4 hr. LCMS showed that the reaction was completed. The mixture was quenched with water and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 4-(tert-butoxymethyl)-6-(1,1-difluoroethyl)-3-methoxypyridazine. **MS (ESI)** *m/z* 261 **(M+H)**$^+$

Step 4: *(6-(1,1-difluoroethyl)-3-methoxypyridazin-4-yl)methanol*

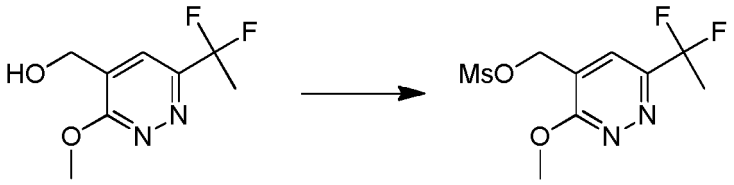
[0142]



[0143] To a solution of 4-(tert-butoxymethyl)-6-(1,1-difluoroethyl)-3-methoxypyridazine (150 mg, 0.58 mmol) in dichloromethane (8 mL) was added 4N HCl/methanol (3 mL). The mixture was stirred at room temperature for 3 hr, then quenched with water and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure and purified by preparative TLC (petroleum ether/ethyl acetate (1:1.5) as eluent) to give (6-(1,1-difluoroethyl)-3-methoxypyridazin-4-yl)methanol. **MS (ESI)** *m/z* 205 **(M+H)**$^+$

Step 5: *(6-(1,1-difluoroethyl)-3-methoxypyridazin-4-yl)methyl methanesulfonate*

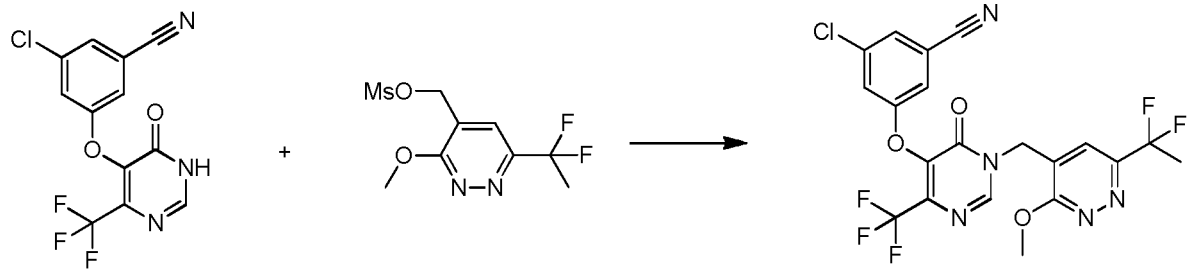
[0144]



[0145] To a solution of (6-(1,1-difluoroethyl)-3-methoxypyridazin-4-yl)methanol (110 mg, 0.54 mmol) in dichloromethane (6 mL) was added DIPEA (209 mg, 1.6 mmol) and methanesulfonyl chloride (75 mg, 0.62 mmol) dropwise. The mixture was stirred at room temperature for 2 hr. The mixture was diluted with water and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give (6-(1,1-difluoroethyl)-3-methoxypyridazin -4-yl)methyl methanesulfonate. **MS (ESI)** *m/z* 283 **(M+H)**$^+$

Step 6: *3-chloro-5-((1-((6-(1,1-difluoroethyl)-3-methoxypyridazin-4-yl)methyl)-6-oxo -4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile*

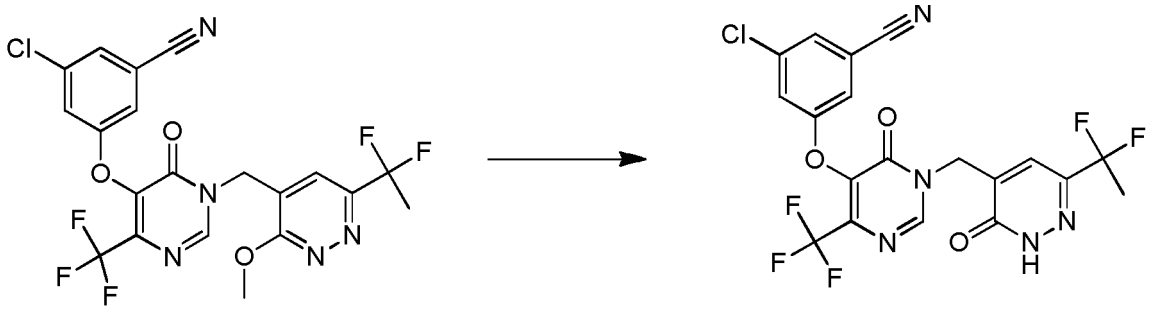
[0146]



[0147] To a solution of (6-(1,1-difluoroethyl)-3-methoxypyridazin-4-yl)methyl methanesulfonate (120 mg, 0.54 mmol) in DMF (5 mL) was added 3-chloro-5-((6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (187 mg, 0.59 mmol, Example 3, step 5), TEA (0.23 mL, 1.6 mmol). The mixture was stirred at 30 °C for 2 hr. After cooling to r.t., the mixture was diluted with water, extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under redcued pressure to give 3-chloro-5-((1-((6-(1,1-difluoroethyl)-3-methoxypyridazin-4-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile. **MS (ESI)** *m/z* 502, 504 **(M+H)**$^+$

Step 7: *3-chloro-5-((1-((6-(1,1-difluoroethyl)-3-oxo-2,3-dihydropyridazin-4-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile*

[0148]

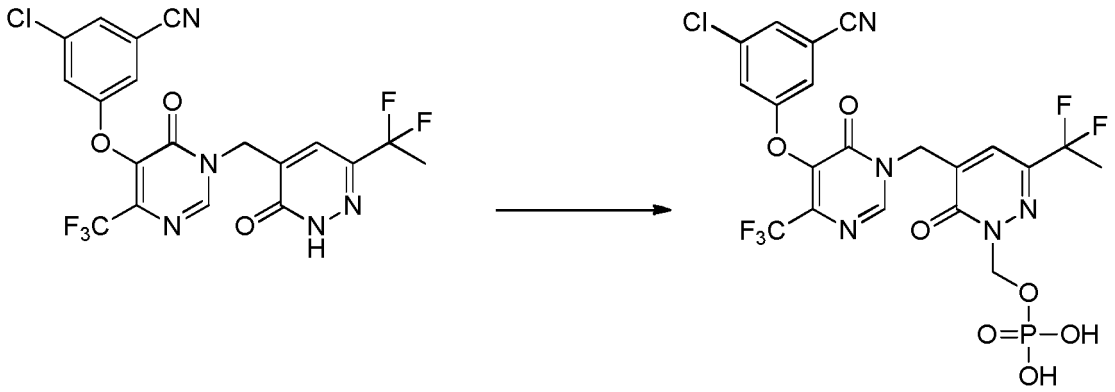


[0149] To a mixture of 3-chloro-5-((1-((6-(1,1-difluoroethyl)-3-methoxypyridazin-4-yl)methyl) -6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (120 mg, 0.24 mmol) and KI (79.5 mg, 0.48 mmol) in acetonitrile (4 mL) was added TMSC1 (51.7 mg, 0.48 mmol) dropwise at r.t. After addition, the mixture was stirred at 30 °C for 3 hr. After cooling to r.t., the mixture was quenched with MeOH and concentrated under reduce pressure. The residue was purified by preparative HPLC to afford 3-chloro-5- ((1-((6-(1,1-difluoroethyl)-3-oxo-2,3-dihydropyridazin-4-yl)methyl)-6-oxo-4-(trifluoromethyl) -1,6-dihydropyrimidin-5-yl)oxy)benzonitrile. ^{1}**H NMR** (DMSO-*d6*, 400MHz): δ 13.53 (s, 1H), 8.72 (s, 1H), 7.67-7.72 (m, 4H), 5.10 (s, 2H), 1.85-1.90 (m, 3H). **MS (ESI):** *m/z* 488, 490 **(M+H)$^+$**

Example 5

(5-((5-(3-chloro-5-cyanophenoxy)-6-oxo-4-(trifluoromethyl)pyrimidin-1(6*H*)-yl)methyl)-3-(1,1-difluoroethyl)-6-oxopyridazin-1(6*H*)-yl)methyl dihydrogen phosphate

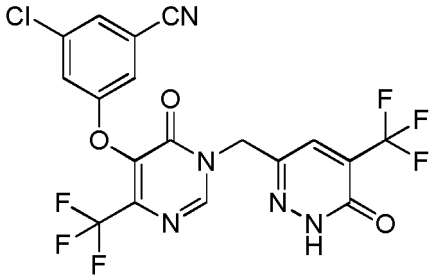
[0150]



[0151] The above compound was prepared by following similar procedures as described in Example 7 steps 1-2. ^{1}**H NMR** (500 MHz, DMSO-*d6*) 8.90 (s, 1H), 7.80-7.70 (m, 4H), 5.70 (d, 2H), 5.05 (s, 2H), 2.0-1.95 (t, 3H). **MS:** 598 **(M+H)**$^+$

Intermediate F

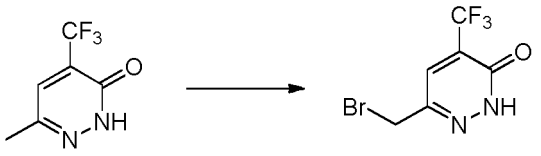
[0152]



3-**chloro-5-((6-oxo-1-((6-oxo-5-(trifluoromethyl)-1,6-dihydropyridazin-3-yl)methyl)-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile**

Step 1: 6-(bromomethyl)-4-(trifluoromethyl)pyridazin-3(2H)-one

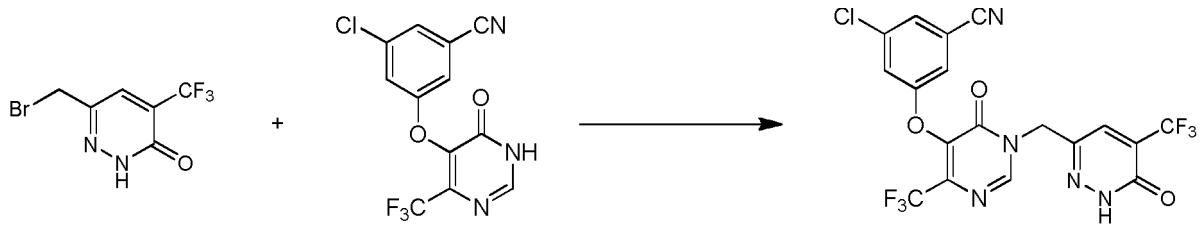
[0153]



[0154] To a mixture of 6-methyl-4-(trifluoromethyl)pyridazin-3(2H)-one (2 g, 11.2 mmol) in 20 mL of CCl_4 was added NBS (3 g, 17.2 mmol) and benzoyl peroxide (100 mg) at r.t. The resulting mixture was heated at reflux for 18 hr. LCMS showed the reaction completed, the mixture was poured into ice-water and extracted with dichloromethane. The combined extracts were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate (5: 1) as eluent) to afford 6-(bromomethyl)-4-(trifluoromethyl) pyridazin-3(2H)-one.

Step 2: *3-chloro-5-((6-oxo-1-((6-oxo-5-(trifluoromethyl)-1,6-dihydropyridazin-3-yl)methyl)-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile*

[0155]



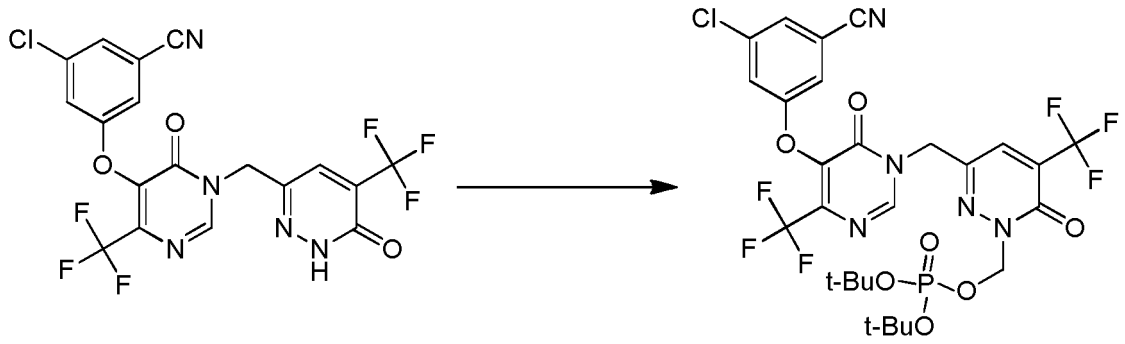
[0156] A mixture of 3-chloro-5-(6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yloxy) benzonitrile (400 mg, 1.27 mmol, Example 3, step 5), 6-(bromomethyl)-4-(trifluoromethyl)pyridazin-3(2H)-one (260 mg, 1.0 mmol) and potassium carbonate (170 mg, 1.23 mmol) in DMF (6 mL) was stirred at room temperature for 18 hr. The mixture was diluted with water, extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over sodium sulfate, filtered and under reduced pressure. The residue was purified by preparative HPLC to afford 3-chloro-5-((6-oxo-1-((6-oxo-5-(trifluoromethyl)-1,6-dihydropyridazin-3-yl)methyl)-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile. ^{1}**H NMR** (DMSO-d_6, 400 MHz): δ 13.72 (s, 1H), 8.77 (s, 1H), 8.02(s, 1H), 7.78 (s, 1H), 7.71 (s, 1H), 7.68 (s, 1H), 5.19 (s, 2H). **MS (ESI)** *m/z* 492, 494 **(M+H)**$^+$

Example 6

Sodium (3-((5-(3-chloro-5-cyanophenoxy)-6-oxo-4-(trifluoromethyl)pyrimidin-1(6*H*)-yl)methyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)methyl phosphate

Step 1: *di-tert-butyl ((3-((5-(3-chloro-5-cyanophenoxy)-6-oxo-4-(trifluoromethyl)pyrimidin-1(6H)-yl)methyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6H)-yl)methyl) phosphate*

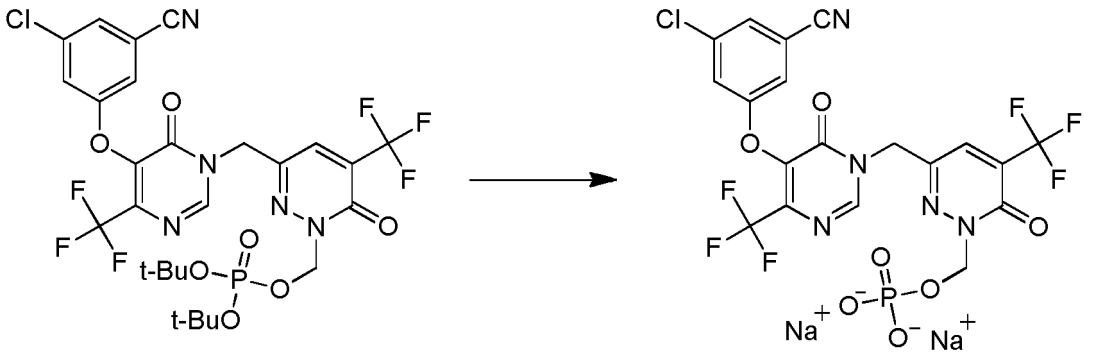
[0157]



[0158] To a solution of 3-chloro-5-((6-oxo-1-((6-oxo-5-(trifluoromethyl)-1,6-dihydro yridazin-3-yl)methyl)-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (1.5 g, 3.05 mmol) in Dioxane:DMF (5:1, 25 mL) was added potassium carbonate (0.843 g, 6.1 mol). The reaction mixture was stirred at room temperature for 0.5 h. Phosphoric acid di-tert-butyl ester chloromethyl ester (1.19 g, 4.58 mmol) was added at -30 °C. The resulting mixture was stirred at 40 °C for 2.5 h under microwave. After cooled to r.t., the reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate and concentrated in vacuum. The residue was purified by prep. HPLC to afford the desired product di-tert-butyl ((3-((5-(3-chloro-5-cyanophenoxy)-6- oxo-4-(trifluoromethyl)pyrimidin-1(6H)-yl)methyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6H)-yl)methyl) phosphate. **MS (ESI): *m/z*** 736 (M+Na)$^+$. ^{1}**H NMR** (400 MHz, DMSO-*d6*) δ 8.75 (s, 1H), 8.13 (s, 1H), 7.63-7.74 (m, 3H), 5.59 (d, *J*= 8.0 Hz, 2H), 5.21 (s, 2H).

Step 2: *sodium (3-((5-(3-chloro-5-cyanophenoxy)-6-oxo-4-(trifluoromethyl)pyrimidin-1(6H)-yl)methyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6H)-yl)methylphosphate*

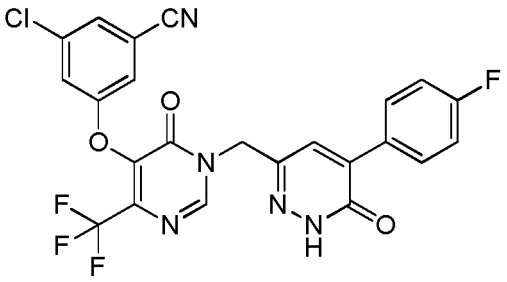
[0159]



[0160] To a solution of di-tert-butyl ((3-((5-(3-chloro-5-cyanophenoxy)-6-oxo-4-(trifluoromethyl)pyrimidin-1(6H)-yl)methyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6H)-yl)methyl) phosphate (260 mg, 0.36 mmol) in dichloromethane (7 mL) was added a solution of CF_3COOH (0.14 mL) in dichloromethane (0.5 mL). After stirred at room temperature for 2h, the mixture was concentrated in vacuum. The residue was dissolved in methanol (5 mL), then sodium acetate (59.8 mg, 0.73 mmol) in methanol (0.6 mL) was added. The resulting mixture was stirred overnight at room temperature. The mixture was lyophilized and the solid was washed with methanol and dried in vacuum to afford sodium (3-((5-(3-chloro-5-cyanophenoxy)-6-oxo-4-(trifluoromethyl)pyrimidin-1(6H)-yl)methyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6H)-yl)methyl phosphate. ^{1}**H NMR** (DMSO&D_2O, 400 MHz) δ 8.65 (s, 1H), 7.95 (s, 1H), 7.60-7.69 (m, 3H), 5.59 (d, *J*= 8.4 Hz, 2H), 5.14 (s, 2H).

Intermdiate G

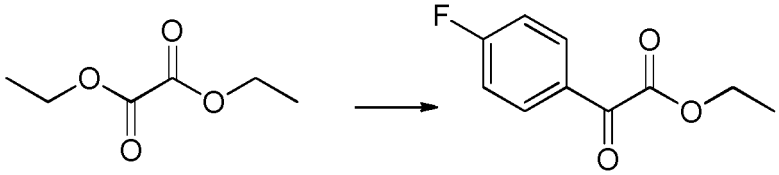
[0161]



3-chloro-5-((1-((5-(4-fluorophenyl)-6-oxo-1,6-dihydropyridazin-3-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

Step1: *ethyl 2-(4-fluorophenyl)-2-oxoacetate*

[0162]

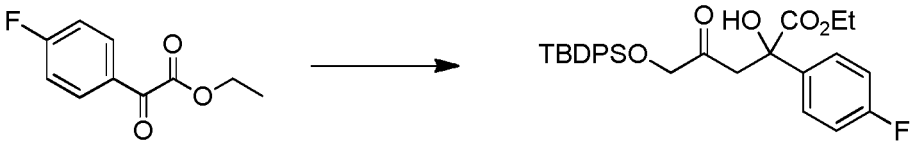


[0163] Into a 10-L round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of diethyl oxalate (360 g, 2.46 mol, 1.00 equiv) in tetrahydrofuran (3000 mL). This was followed by the addition

of a solution of 4-fluorophenylmagnesium bromide in tetrahydrofuran (1.9 L, 1 N 0.78 equiv) dropwise with stirring at -78 °C in 2.5 hr. The resulting solution was stirred for 30 min at -78 °C, then slowly warmed to -20 °C. The reaction was then quenched by the addition of 500 mL of 2 M HCl. The resulting solution was extracted with 2 × 500 mL of ethyl acetate and the organic layers combined.The resulting mixture was washed with 2 × 200 mL of brine. The mixture was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was purified by distillation under reduced pressure (5 mm Hg) and the fraction was collected at 106 °C to provide ethyl 2-(4-fluorophenyl)-2-oxoacetate.

Step 2: *ethyl 5-((tert-butyldiphenylsilyl)oxy)-2-(4-fluorophenyl)-2-hydroxy-4-oxopentanoate*

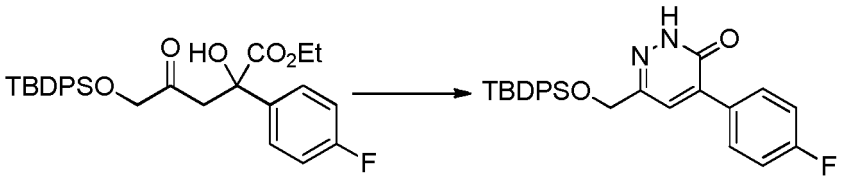
[0164]



[0165] Into a 250-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed ethyl 2-(4-fluorophenyl)-2-oxoacetate (55 g, 280 mmol, 1.00 equiv), 1-[(tert-butyldiphenylsilyl)oxy]propan-2-one (110 g, 352 mmol, 1.26 equiv), acetic acid (33 g, 550 mmol, 1.96 equiv), pyrrolidine (7.8 g, 93 mmol, 0.33 equiv). The resulting solution was stirred overnight at 85 °C and then applied onto a silica gel column with ethyl acetate/petroleum ether (1:60-1:10) to obtain ethyl 5-[(tert-butyldiphenylsilyl)oxy]-2-(4-fluorophenyl)-2-hydroxy-4-oxopentanoate.

Step 3: *6-[[(tert-butyldiphenylsilyl)oxy]methyl]-4-(4-fluorophenyl)-2,3-dihydropyridazin -3-one*

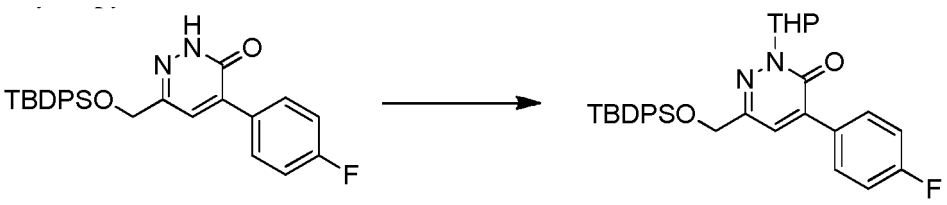
[0166]



[0167] Into a 1000-mL 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of ethyl 5-[(tert-butyldiphenylsilyl) oxy]-2-(4-fluorophenyl)-2-hydroxy-4-oxopentanoate (292 g, 574 mmol) in acetic acid (520 mL). This was followed by the addition of hydrazine hydrate (115 g, 2.30 mol) dropwise with stirring below 30 °C in 30 min. The resulting solution was stirred for 3 h at r.t., then, heated to 80 °C for 2 hr. The reaction mixture was then poured into 2000 mL of water/ice. The resulting solution was extracted with 3 × 1000 of ethyl acetate and the organic layers combined. The resulting mixture was washed with 2000 mL of 5%$NaHCO_3$ and 1000 mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by recrystallization from n-hexane to afford 6-[[(tert-butyldiphenylsilyl)oxy]methyl]-4-(4-fluorophenyl)-2,3- dihydro pyridazin-3-one.

Step 4: *6-[[(tert-butyldiphenylsilyl)oxy]methyl]-4-(4-fluorophenyl)-2-(oxan-2-yl)- 2,3-dihydropyridazin-3-one*

[0168]

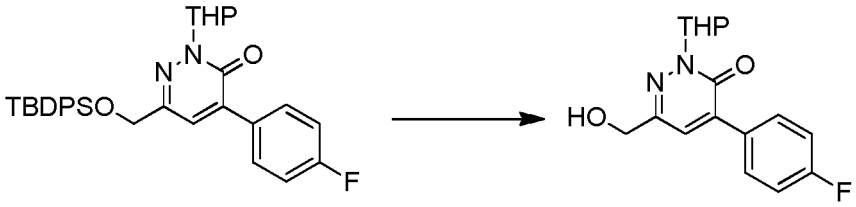


[0169] Into a 2000-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a

solution of 6-[[(tert-butyldiphenylsilyl)oxy]methyl] -4-(4-fluorophenyl)-2,3-dihydropyridazin-3-one (150 g, 327 mmol, 1.00 equiv) in toluene (1.2 L), 3,4-dihydro-2H-pyran (80 g, 951 mmol, 2.91 equiv), PPTS (15 g, 59.8 mmol, 0.18 equiv). The resulting solution was stirred for 5 h at 90 °C. To this added additional DHP (55 g, 654 mmol), and the mixture was stirred overnight at 90 °C. The reaction mixture was cooled to room temperature and then poured into 1000 mL of 5% $NaHCO_3$. The resulting solution was extracted with 2×500 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 500 mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. This afforded (crude) 6-[[(tert-butyldiphenylsilyl)oxy]methyl]-4-(4-fluorophenyl)-2-(oxan-2-yl)-2,3 -dihydropyridazin-3 -one.

Step 5: *4-(4-fluorophenyl)-6-(hydroxymethyl)-2-(oxan-2-yl)-2,3-dihydropyridazin-3-one*

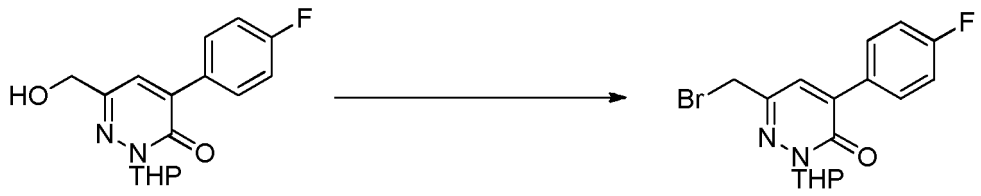
[0170]



[0171] Into a 2000-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 6-[[(tert-butyldiphenylsilyl)oxy]methyl]-4- (4-fluorophenyl)-2-(oxan-2-yl)-2,3-dihydropyridazin-3-one (220 g, 324 mmol, 1.00 equiv, 80%) in tetrahydrofuran (1.1 L). This was followed by the addition of TBAF (87 g, 333 mmol, 1.03 equiv) in several batches at 20 °C in 5 min. The resulting solution was stirred for 30 min at room temperature and then poured into 1000 mL of 5% $NaHCO_3$. The resulting solution was extracted with 2×500 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 1000 mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10-1:1) to afford 4-(4-fluorophenyl)-6-(hydroxymethyl)-2-(oxan-2-yl)-2,3-dihydro pyridazin-3-one. **MS (ESI)** m/z 305 **$(M+H)^+$**

Step 6: *6-(bromomethyl)-4-(4-fluorophenyl)-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one*

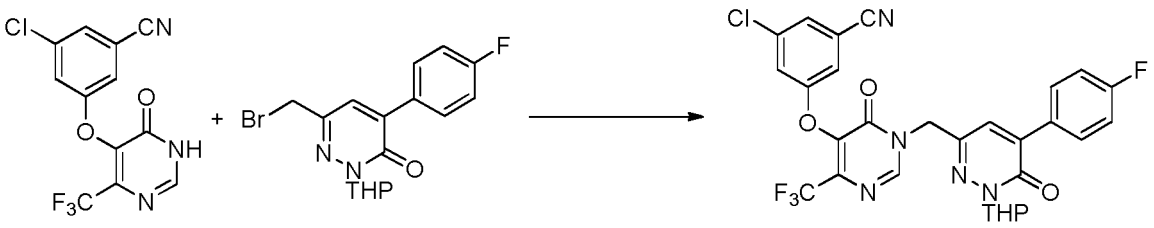
[0172]



[0173] To a stirring solution of 4-(4-fluorophenyl)-6-(hydroxymethyl)-2-(tetrahydro-2H- pyran-2-yl)pyridazin-3(2H)-one (10 g, 32.9 mmol) in DCM (40 mL) at 0 °C was added carbon tetrabromide (13.08 g, 39.4 mmol) followed by a slow addition of a solution of triphenylphosphine (10.34 g, 39.4 mmol) in DCM (10 mL). The resulting mixture was allowed to stir at 0 °C for 1 hr and then concentrated under reduced pressure. Diethyl ether (500 mL) was added to the crude mixture and solids were filtered out. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography on slica gel (ethyl acetate/hexane (0% - 60%) as eluent) to afford 6-(bromomethyl)-4-(4-fluorophenyl)- 2-(tetrahydro-2H-pyran- 2-yl)pyridazin-3(2H)-one. **MS (ESI)** m/z 367, 369 **$(M+H)^+$**

Step 7: *3-chloro-5-((1-((5-(4-fluorophenyl)-6-oxo-1-(tetrahydro-2H-pyran-2-yl)-1,6-dihydropyridazin-3-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile*

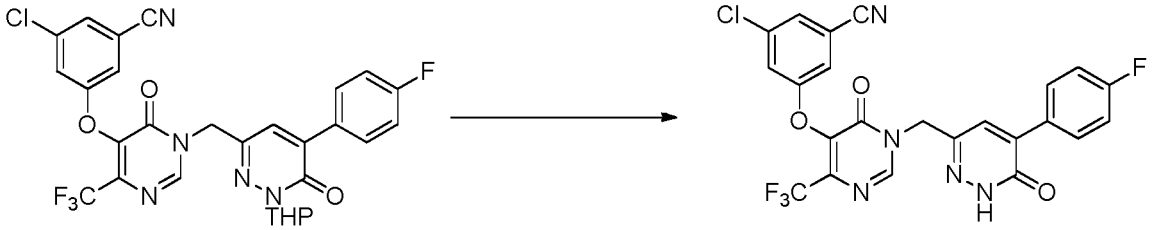
[0174]



[0175] To a mixture of 6-(bromomethyl)-4-(4-fluorophenyl)-2-(tetrahydro-2H-pyran-2-yl) pyridazin-3(2H)-one (10.59 g, 28.8 mmol), and 3-chloro-5-((6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (9.10 g, 28.8 mmol, Example 3, step 5) in DMF (35 mL) was added DIPEA (6.55 mL, 37.5 mmol) at 0 °C. After 30 min the reaction mixture was warmed up to room temperature and stirring was continued for an additional 1 hr. The mixture was concentrated under reduced pressure and water (200 mL) was added. The resulting precipitate was collected by filtration and washed with water (2 × 50 mL) followed by diethyl ether (3 × 50 mL) to afford 3-chloro-5-((1-((5-(4-fluorophenyl)-6-oxo-1-(tetrahydro-2H-pyran-2-yl)-1,6-dihydropyridazin-3-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile. **MS (ESI)** m/z 601, 602 **(M+H)**$^+$

Step 8: *3-chloro-5-((1-((5-(4-fluorophenyl)-6-oxo-1,6-dihydropyridazin-3-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile*

[0176]



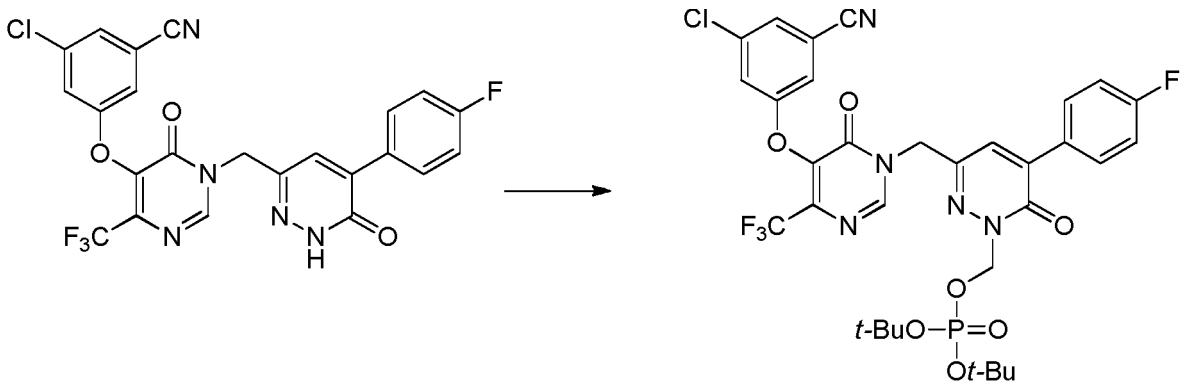
[0177] A solution of 3-chloro-5-((1-((5-(4-fluorophenyl)-6-oxo-1-(tetrahydro-2H-pyran-2-yl) -1,6-dihydropyridazin-3-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy) benzonitrile (15.78 g, 26.2 mmol) in TFA (40.4 mL, 524 mmol) was stirred at r.t. for 1 hr. TFA was removed under reduced pressure and diethyl ether (250 mL) was added. The resulting solid was collected by filtration and washed with diethyl ether (2 × 125 mL) to afford 3-chloro-5-((1-((5-(4-fluorophenyl)-6-oxo-1,6-dihydropyridazin-3-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile. **MS (ESI)** m/z 518, 520 **(M+H)**$^+$; ^{1}**H NMR: (DMSO-*d6*, 400 MHz)** δ 13.13 (s, 1H), 8.74 (s, 1H), 7.87 (t, *J* =6.8 Hz, 2H), 7.62-7.72 (m, 4H), 7.26 (t, *J* = 6.8 Hz, 2H), 5.14 (s, 2H).

Example 7

(3-((5-(3-chloro-5-cyanophenoxy)-6-oxo-4-(trifluoromethyl)pyrimidin-1(6*H*)-yl)methyl)-5-(4-fluorophenyl)-6-oxopyridazin-1(6*H*)-yl)methyl dihydrogen phosphate

Step 1: *di-tert-butyl ((3-((5-(3-chloro-5-cyanophenoxy)-6-oxo-4-(trifluoromethyl)pyrimidin-1(6H)-yl)methyl)-5-(4-fluorophenyl)-6-oxopyridazin-1(6H)-yl)methyl)phosphate*

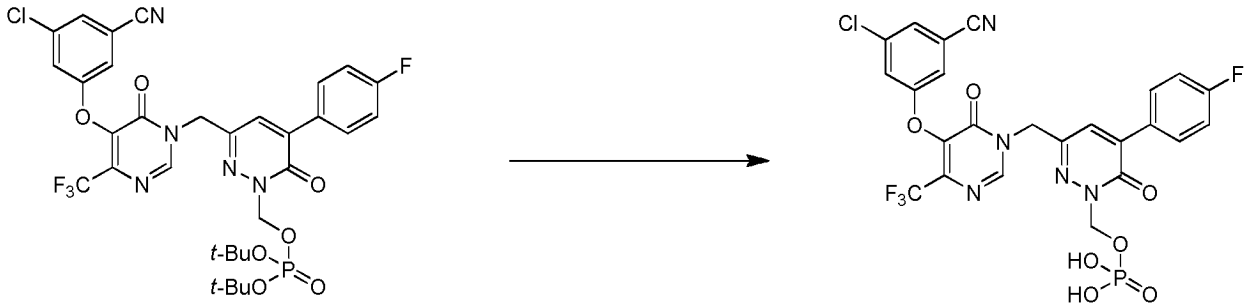
[0178]



[0179] To a slurry of 3-chloro-5-((1-((5-(4-fluorophenyl)-6-oxo-1,6-dihydropyridazin-3-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (250 mg, 0.48 mmol) and sodium iodide (94 mg, 0.63 mmol) in THF (3.8 mL) at 0 °C was added lithium tert-butoxide (1M in THF) (0.56 mLl, 0.56 mmol) followed by di-tert-butyl chloromethyl phosphate (0.13 mL 0.63 mmol). Reaction mixture was warmed up to room temperature and stirred further for 16 h. Upon reaction completion, it was cooled to 0 °C and quenched with a few drops of water. The solvent was removed by rotary evaporation keeping the temperature of water bath not to exceed 25 °C. The residue was dissolved in DCM (25 mL) and washed with sat. $NaHCO_3$ (1 x 5 ml), brine (1 x 5 ml,) dried over anhydrous MgSO4, filtered and concentrated by rotary evaporation keeping the temperature of water bath not to exceed 25 °C to afford di-tert-butyl ((3-((5-(3-chloro-5-cyanophenoxy)-6-oxo-4-(trifluoromethyl)pyrimidin-1(6*H*)-yl)methyl)-5-(4-fluorophenyl)-6-oxopyridazin-1(6H)-yl)methyl) phosphate, which was used in the next step without purification.

Step 2: *(3-((5-(3-chloro-5-cyanophenoxy)-6-oxo-4-(trifluoromethyl)pyrimidin-1(6H)-yl)methyl)-5-(4-fluorophenyl)-6-oxopyridazin-1(6H)-yl)methyldihydrogenphosphate*

[0180]

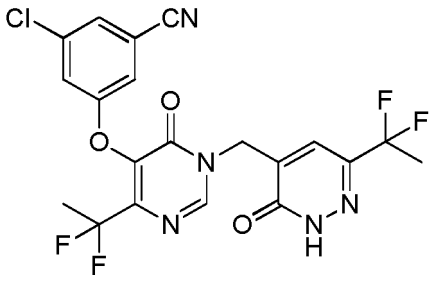


[0181] To a crude solution of di-tert-butyl ((3-((5-(3-chloro-5-cyanophenoxy)-6-oxo-4-(trifluoromethyl)pyrimidin-1(6H)-yl)methyl)-5-(4-fluorophenyl)-6-oxopyridazin-1(6H)-yl)methyl) phosphate (357 mg, 0.48 mmol) in dichloromethane (5.8 mL) at 0 °C was added trifluoroacetic acid (149 μl, 1.932 mmol). The reaction mixture was allowed to warm up to ambient temperature and stirred further for 16 h. Upon reaction completion, the mixture was filtered and purified by reverse phase HPLC (ACN/water with 0.1% TFA modifier) to afford (3-((5-(3-chloro-5-cyanophenoxy)-6-oxo-4-(trifluoromethyl)pyrimidin-1(6H)-yl)methyl)-5-(4-fluorophenyl)-6-oxopyridazin-1(6H)-yl)methyl dihydrogen phosphate. **MS:** 628 **$(M+H)^+$**

^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.76 (s, 1H), 7.71 - 7.86 (m, 6H), 7.33 (t, *J*= 8.7 Hz, 2H), 5.7 1(d, *J*= 7.7 Hz, 2H), 5.19 (s, 2H).

Intermediate H

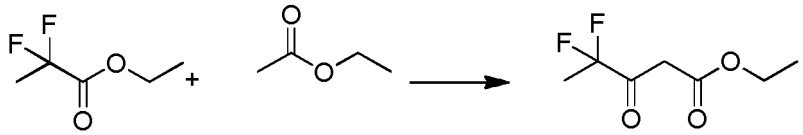
[0182]



3-chloro-5-((4-(1,1-difluoroethyl)-1-((6-(1,1-difluoroethyl)-3-oxo-2,3-dihydropyridazin-4-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

Step 1: *ethyl 4,4-difluoro-3-oxopentanoate*

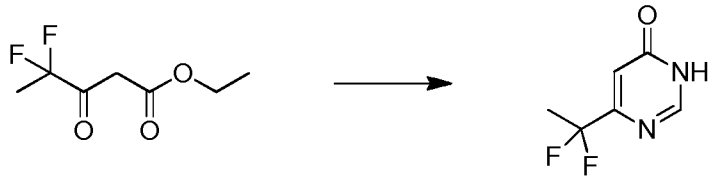
[0183]



[0184] To a solution of compound ethyl 2,2-difluoropropanoate (10.6 g, 76.8 mmol) and ethyl acetate (8.11 g, 92.1 mmol, dried over $MgSO_4$) in THF (100 mL) was added LiHMDS (92 mL, 92.1 mmol) at -78 °C under N_2 protection. The mixture was stirred at -78°C for 1 hour. Then the mixture was stirred at 20°C for another 1.5 hours. The reaction was quenched with HCl solution (1 N) slowly. The mixture was extracted with EtOAc (100 mL x 3), washed with brine (200 mL), dried over MgSO4, filtered and concentrated under reduced pressure to give the desired product. The residue was used directly without further purification.

Step 2: *6-(1,1-difluoroethyl)pyrimidin-4(3H)-one*

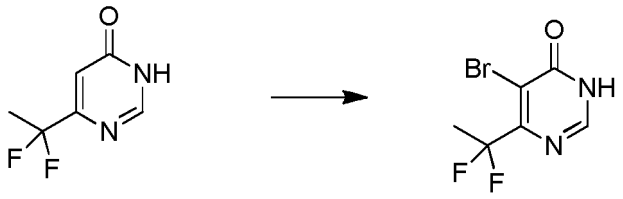
[0185]



[0186] A solution of formimidamide acetate (16.0 g, 153.6 mmol) and sodium methoxide (16.6 g, 307 mmol) in methanol (140 mL) was stirred at r.t. for 20 min, then ethyl 4,4-difluoro-3-oxopentanoate (14 g crude, 76.8 mmol) was added. The resulting mixture was stirred at 70°C for 14 hours. After cooling to room temperature, the mixture was diluted with water (200 mL), extracted with EtOAc (200 mL x 3). The combined organic layers were dried over MgSO4, filtered and concentrated under reduced pressure to afford the desired product. **^{1}HNMR:** (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 6.77 (s, 1H), 1.90 (t, *J*= 18.8 Hz, 3H). **MS (ESI)** *m/z* 161.21 **(M+H)$^+$**

Step 3: *5-bromo-6-(1,1-difluoroethyl)pyrimidin-4(3H)-one*

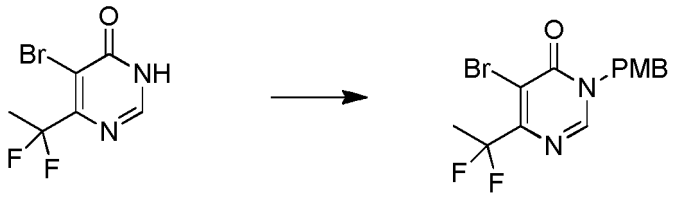
[0187]



[0188] A solution of compound 6-(1,1-difluoroethyl)pyrimidin-4(3H)-one (9.5 g, 59 mmol) and potassium acetate (11.6 g, 119 mmol) in acetic acid (100 mL) was stirred at r.t. for 30 min, then Br_2 (11.2 g, 71 mmol) was added dropwise at r.t.. The resulting mixture was stirred at reflux for 2 hours. After cooling to r.t., the mixture was quenched with Na_2SO_3 (sat.) till the color turned to light yellow, and extracted with EA (200 mL x 3). The combined organic layers were dried over MgSO4, filtered and concentrated under reduced pressure to afford the desired product. **MS (ESI)** *m/z* 238.8, 240.8 **(M+H)$^+$.**

Step 4: *5-bromo-6-(1,1-difluoroethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one*

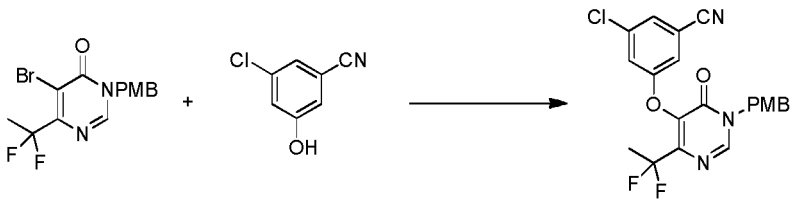
[0189]



[0190] To a solution of compound 5-bromo-6-(1,1-difluoroethyl)pyrimidin-4(3H)-one (15.0 g, 59 mmol) in DMF (150 mL) was added K_2CO_3 (17.4 g,126 mmol) and PMBC1 (108. g, 69 mmol). The reaction mixture was stirred at 80°C for 3 hours. After cooling to room temperature, the mixture was diluted with H_2O (100 mL) and extracted with EtOAc (200 mL x 3). The combined organic layers were dried over MgSO4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE/EA=10/1 to 5/1) to afford the desired product. **^{1}HNMR:** (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.96 (s, 1H), 7.28 (d, 2H, J=8.4 Hz), 6.85 (s, 2H, J=8.4 Hz), 5.04 (s, 2H), 3.75 (s, 2H), 1.92 (t, *J*=18.4 Hz, 3H). **MS (ESI)** *m/z* 359.1, 361.1 **(M+H)$^+$**

Step 5: *3-chloro-5-((4-(1,1-difluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile*

[0191]

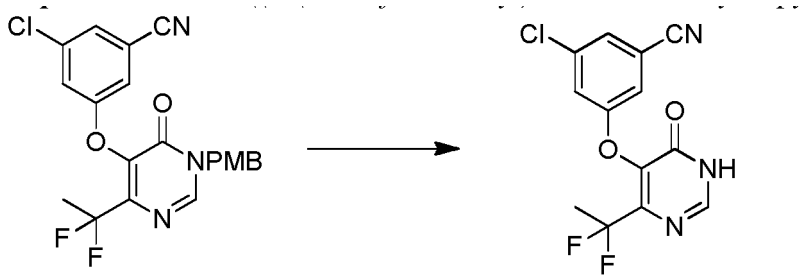


[0192] To a solution of compound 5-bromo-6-(1,1-difluoroethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one (3.0 g, 8.56 mmol) in NMP (50 mL) was added potassium carbonate (2.31 g, 16.70 mmol) and 3-chloro-5-hydroxybenzonitrile (3.86 g, 25.07 mmol). The mixture was heated to 140°C for 6 hr, and then cooled down to 130°C, the mixture was stirred at 130°C overnight. After cooling, the mixture was diluted with water (200 mL) and extracted with ethyl acetate (100 mL×3). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether: ethyl acetate (20:1 to 8:1) as eluent) to give 3-chloro-5-((4-(1,1-difluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydro pyrimidin-5-yl)oxy) benzonitrile.

MS (ESI) *m/z* 432, 434 **(M+H)$^+$**

Step 6: *3-chloro-5-((4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile*

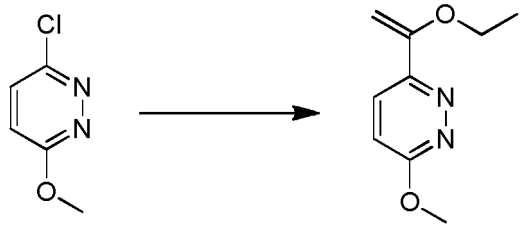
[0193]



[0194] A solution of 3-chloro-5-((4-(1,1-difluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (10 g, 23.2 mmol) in mixed solvent (TFA/TFAA = 48 mL/24 mL) was stirred at 100°C for 4 hr. After cooling to room temperature, the mixture was concentrated under reduced pressure to give crude product 3-chloro-5-((4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile which was used without further purification.
MS (ESI) *m/z* 312, 314 **(M+H)**$^+$

Step 7: *3-(1-ethoxyvinyl)-6-methoxypyridazine*

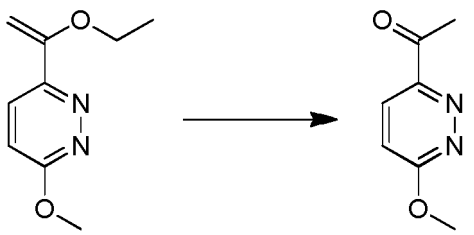
[0195]



[0196] To a mixture of 3-chloro-6-methoxypyridazine (15 g, 103.8 mmol), tributyl(1-ethoxyvinyl)stannane (82.44 g, 228.3 mmol) in toluene (200 mL) was added $Pd(PPh_3)_4$ (6 g, 5.19 mmol) under nitrogen atmosphere. The resulting suspension was flushed three times with nitrogen and then stirred at 110 °C for 36 hr. After cooling to room temperature, the mixture was poured into ice-water, filtered through a pad of Celite®. The filtrate was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate (15:1 to 10:1) as eluent) to afford the desired product 3-(1-ethoxyvinyl)-6-methoxypyridazine. **MS (ESI)** *m/z* 181 **(M+H)**$^+$

Step 8: *1-(6-methoxypyridazin-3-yl)ethanone*

[0197]

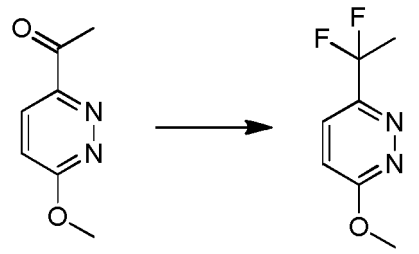


[0198] To a solution of 3-(1-ethoxyvinyl)-6-methoxypyridazine (12 g, 66.59 mmol) in 1,4-dioxane (120 mL) was added HCl/1,4-dioxane (24 mL, 4 M) dropwise at 0 °C. The mixture was stirred at room temperature for 1 hr. The mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica

gel (petroleum ether/ethyl acetate (10:1 to 8:1) as eluent) to afford 1-(6-methoxypyridazin-3-yl)ethanone. **MS (ESI)** *m/z* 153 **(M+H)$^+$**

Step 9: *3-(1,1-difluoroethyl)-6-methoxypyridazine*

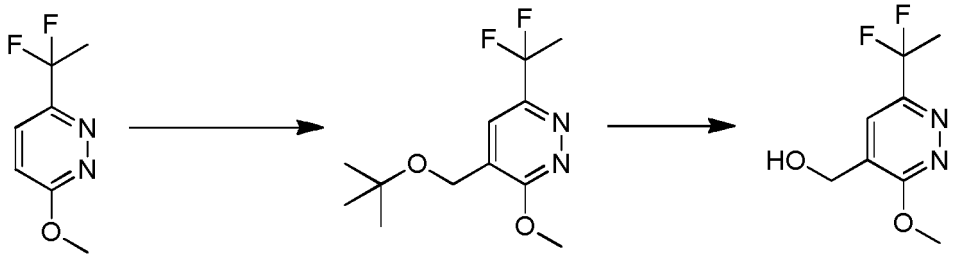
[0199]



[0200] To a solution of 1-(6-methoxypyridazin-3-yl)ethanone (4.2 g, 27.6 mmol) in dichloromethane (45 mL) was added DAST (13.35 mg, 82.81 mmol) dropwise at 0 °C. The mixture was stirred at 40 °C for 24 hr. After cooling to r.t., the mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate (15:1 to 10:1) as eluent) to afford 3-(1,1-difluoroethyl)-6-methoxypyridazine. **MS (ESI)** *m/z* 175 **(M+H)$^+$**

Step 10: *(6-(1,1-difluoroethyl)-3-methoxypyridazin-4-yl)methanol*

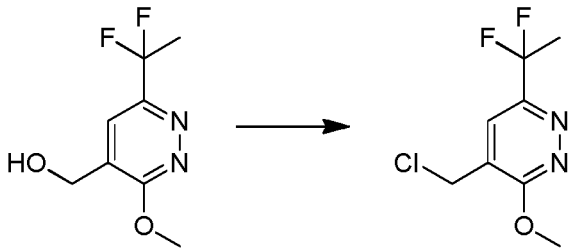
[0201]



[0202] To a mixture of tert-butoxy-acetic acid (4.23 g, 32.04 mmol) in TFA/water (20 mol%, 30 mL) were added 3-(1,1-difluoroethyl)-6-methoxypyridazine (3.1 g, 17.8 mmol) and $AgNO_3$ (303 mg, 1.78 mmol). The mixture was flushed with nitrogen with stirring at room temperature, then the mixture was heated to 70 °C, and $(NH_4)_2S_2O_8$ (8.12 g, 35.6 mmol) in water (40 mL) was added dropwise. After addition the mixture was stirred at 75 °C for 40 min. After cooling to room temperature, the mixture was extracted with ethyl acetate (20 mL × 3), the combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to afford crude product. A solution of 4-(tert-butoxymethyl)-6-(1,1-difluoroethyl)-3-methoxypyridazine in TFA/DCE (10 mL/40 mL) was stirred at 60 °C for 1 hr. After cooling to r.t., the mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (20 mL), washed with aqueous potassium carbonate, brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate (8:1 to 5:1) as eluent) to afford (6-(1,1-difluoroethyl)-3-methoxy pyridazin-4-yl)methanol. **MS (ESI)** *m/z* 205 **(M+H)$^+$**

Step 11: *4-(chloromethyl)-6-(1,1-difluoroethyl)-3-methoxypyridazine*

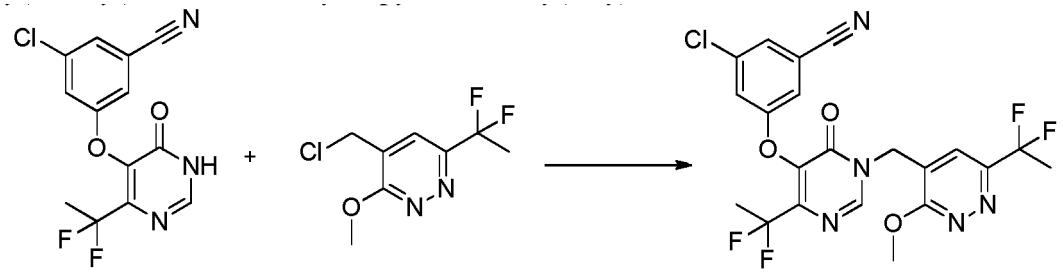
[0203]



[0204] To a solution of (6-(1,1-difluoroethyl)-3-methoxypyridazin-4-yl)methanol (180 mg, 0.88 mmol) in dichloromethane (3 mL) was added triethylamine (268 mg, 2.64 mmol) and methanesulfonyl chloride (303 mg, 2.64 mmol) at 0 °C. The mixture was stirred at room temperature for 24 hr, quenched with water and extracted with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (petroleum ether/ethyl acetate (2:1) as eluent) to afford 4-(chloromethyl)-6-(1,1-difluoroethyl)-3-methoxypyridazine. **MS (ESI)** *m/z* 223 **$(M+H)^+$**

Step 12: *3-chloro-5-((4-(1,1-difluoroethyl)-1-((6-(1,1-difluoroethyl)-3-methoxypyridazin-4-yl)methyl)-6-oxo-1, 6-dihydropyrimidin-5-yl) oxy) benzonitrile*

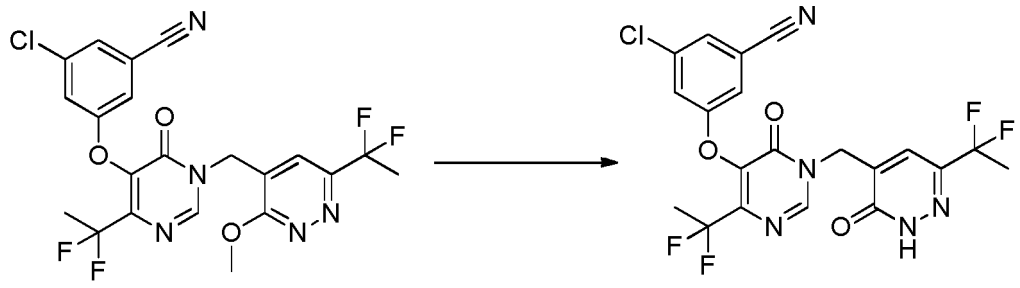
[0205]



[0206] To a solution of 3-chloro-5-((4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (500 mg, 1.60 mmol) in DMF (2 mL) was added potassium carbonate (443 mg, 3.21 mmol) and 4-(chloromethyl)-6-(1,1-difluoroethyl)-3-methoxypyridazine (as described in Steps 1-5 of Example 178) (82 mg, 0.27 mmol). The resulting mixture was stirred at 80 °C for 3 h. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over sodium sulfate, filtered, concentrated under reduced pressure. The residue was purified by preparative TLC (petroleum ether/EtOAc =1:1) to afford the desired product 3-chloro-5-((4-(1,1-difluoroethyl)-1-((6-(1,1-difluoroethyl)-3-methoxypyridazin-4-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile. **MS (ESI)** *m/z* 498, 500 **$(M+H)^+$**

Step 13: *3-chloro-5-((4-(1,1-difluoroethyl)-1-((6-(1,1-difluoroethyl)-3-oxo-2,3-dihydropyridazin-4-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile*

[0207]



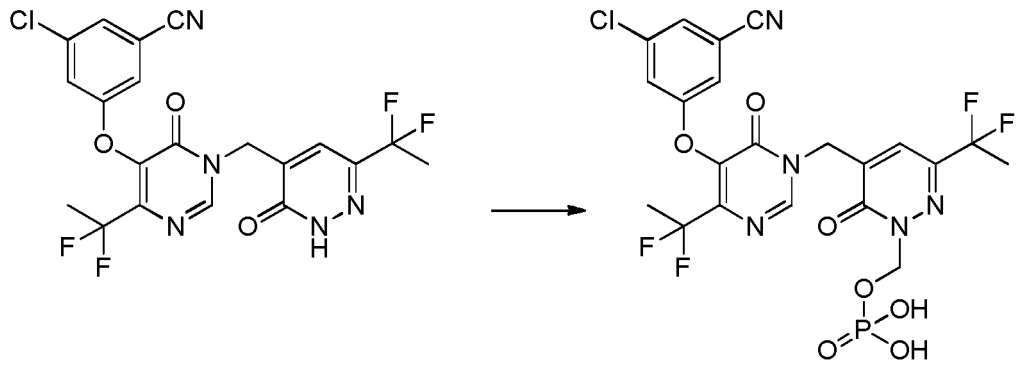
[0208] To a mixture of compound 3-chloro-5-((4-(1,1-difluoroethyl)-1-((6-(1,1-difluoroethyl)-3-methoxypyridazin-4-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (250 mg, 0.50 mmol) and KI (166 mg, 1.0 mmol) in acetonitrile (3 mL) was added TMSCl (109 mg, 1 mmol) at room temperature. The resulting mixture was heated and stirred at 70°C

for 1 hr. After cooling to room temperature, the mixture was diluted with EtOAc and washed with aq. $Na_2S_2O_3$ and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by preparative HPLC to afford 3-chloro-5-((4-(1,1-difluoroethyl)-1-((6-(1,1-difluoroethyl)-3-oxo-2,3-dihydropyridazin-4-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile . **^{1}H NMR** (Methanol-d_4, 400 MHz) : δ 8.60 (s, 1H), 7.68 (s, 1H), 7.47 (s, 1H), 7.28 (s, 1H), 7.24 (s, 1H), 5.07 (s, 2H), 1.92 (m, 6H). **MS (ESI)** *m/z* 484, 486 **$(M+H)^+$**

Example 8

(5-((5-(3-chloro-5-cyanophenoxy)-4-(1,1-difluoroethyl)-6-oxopyrimidin-1(6*H*)-yl)methyl)-3-(1,1-difluoroethyl)-6-oxopyridazin-1(6*H*)-yl)methyl dihydrogen phosphate

[0209]



[0210] The above compound was prepared by following similar procedures as described in Example 7 steps 1-2. **^{1}H NMR** (500 MHz, DMSO-*d6*) δ 8.68 (s, 1H), 7.61 - 7.75 (m, 4H), 5.70 (d, *J* = 8.2 Hz, 2H), 5.06 (s, 2H), 1.90 - 1.99 (m, 6H). **MS:** 594 **$(M+H)^+$**

Determination of HIV-1 reverse transcriptase inhibitory activity

[0211] The heterodimeric nucleic acid substrate used in the HIV-1 RT polymerase reactions was generated by annealing the DNA primer, biotinylated pD500 (Sigma Aldrich, USA, 5'-biotin-ttg aaa tga ctg cgg tac ggc-3'), (SEQ ID NO: 1) to the nucleotide RNA template t500 (derived from hepatitis C virus [HCV] sequence, IBA, Germany, 5' - GAG GUU CAG GUG GUU UCC ACC GCA ACA CAA UCC UUC CUG GCG ACC UGC GUC AAC GGC GUG UGU UGG ACC GUU UAC CAU GGU GCU GGC UCA AAG ACC UUA GCC GGC CCA AAG GGG CCA AUC ACC CAG AUG UAC ACU AAU GUG GAC CAG GAC CUC GUC GGC UGG CAG GCG CCC CCC GGG GCG CGU UCC UUG ACA CCA UGC ACC UGU GGC AGC UCA GAC CUU UAC UUG GUC ACG AGA CAU GCU GAC GUC AUU CCG GUG CGC CGG CGG GGC GAC AGU AGG GGG AGC CUG CUC UCC CCC AGG CCU GUC UCC UAC UUG AAG GGC UCU UCG GGU GGU CCA CUG CUC UGC CCU UCG GGG CAC GCU GUG GGC AUC UUC CGG GCU GCC GUA UGC ACC CGG GGG GUU GCG AAG GCG GUG GAC UUU GUG CCC GUA GAG UCC AUG GAA ACU ACU AUG CGG UCU CCG GUC UUC ACG GAC AAC UCA UCC CCC CCG GCC GUA CCG CAG UCA UUU CAA-3'), (SEQ ID NO: 2). The HIV-1 RT wild-type enzyme (final concentration of 83 pM) was combined with an inhibitor or dimethyl sulfoxide (DMSO, 10% in the final reaction mixture) in assay buffer (62.5 mM Tris-HCl [pH 7.8], 1.25 mM dithiothreitol, 7.5 mM $MgCl_2$, 100 mM KCl, 0.03% CHAPS, and 125 μM EGTA). The mixture was then preincubated on an orbital shaker for 30 min at room temperature in microtiter plates (Costar 3365, Corning, USA). A polymerization reaction was initiated by the addition of RNA template / pD500 DNA primer hybrid (16.6 nM final of RNA/DNA hybrid) and dNTPs (2 μM dATP, dGTP, dCTP and 66.6 nM Ru-dUTP (Meso Scale Discovery, USA)). Plate was sealed and incubated for 5-10 min at room temperature on an orbital shaker. Plate was then incubated for 90 min at 37°C and reactions quenched with 60 μl quenching buffer (50 mM EDTA, 0.7 % BSA, 0.7% Tween-20, 0.017% sodium azide in PBS). The resulting solution was incubated at room temperature for an additional 5 min and then 50 μL was transferred to pre-blocked Avidin plates (L15AA, Meso Scale Discovery). Each well of Avidin plate was blocked for 1 h at room temperature with 100 μL 5% BSA in PBS. Blocking solution was removed by tapping vigorously on filter paper to remove all excess liquid. Reaction on pre-blocked avidin plate proceeded for 60 min at room temperature and then contents removed by tapping vigorously on filter paper to remove all excess liquid. After washing plate 3 times with 150 μL IX PBS and blotting dry between cycles, 150 μL IX Read Buffer T (4X Read Buffer T, Meso Scale Discovery) was added and incubated for 5 min at room temperature before counting on a Sector Imager S6000 (Meso Scale Discovery). Titration curves and IC_{50} values were

calculated using a four parameter logisitc fit according to standard procedures. Briefly, % Inhibition= 100 x ((sample raw value) - (mean value of the low control or 0% inhibition)) / ((mean value of wells representing 100% inhbition) - (mean value of 0% inhbition)). In this assay, low control wells contain DMSO (0% inhbition) and 100% inhibition wells contain 1 μM efavirenz.

[0212] The results of compounds of the invention tested in the above assay are shown in the following Table 2.

Table 2

Parent Compound of:	IC_{50} (nM)
Example No 1	6.0
Example No 2	3.3
Example No 3	2.7
Example No 4	3.2
Example No 5	4.6
Example No 6	7.9
Example No 7	3.7
Example No 8	4.7

Pharmacokinetic Studies

[0213] All animal studies were carried out under Good Laboratory Practice regulations for nonclinical laboratory studies. All animal housing and care procedures were in compliance with the Federal Animal Welfare Act and the Institute for Laboratory Animal Resources. All procedures carried out on the animals were reviewed and approved by the Institutional Animal Care and Use Committee. The animal facility was fully accredited with the Association for Assessment and Accreditation of Laboratory Animal Care International.

[0214] Two or three male Wistar-Hannover rats weighing 250 to 350 grams with vendor-placed carotid artery catheters were obtained from Charles River (Raleigh, North Carolina, U.S.A.). Animals were acclimated on a 12-hour light:dark cycle for a minimum of three days in ventilated plastic cages with food and water ad libitum. Blood samples were automatically collected using the Instech Automated Blood sampler (ABS, Plymouth Meeting, PA) at designated intervals up to 24 hr and were manually collected post 24 hr.

[0215] Animals were fasted overnight before either the Parent compounds of Examples 1-8 (Formula I') or compounds of Examples 1 to 8 (Formula I) were administered to rats via an oral gavage at the doses and in vehicles specified in Table 3. The animals were allowed access to water ad libitum, while food was returned 4 hours after dosing.

[0216] Blood was drawn from catheters placed in the carotid vein at pre-dose, and 0.25, 0.5, 1, 2, 4, 8, 12, 18, 24, 30, and 48 hr after dosing for all compounds and additionally at 72 hr for compounds of example 1, 3, 4, 5, and 7. The plasma was separated by centrifugation (2 minutes at 10000 rpm) and stored at -70°C until further analysis.

[0217] The quantitative analysis of the compounds was performed using a liquid chromatography and tandem mass spectrometry method (LC-MS/MS). The plasma samples were stabilized as needed prior to extraction. Fifty microliter of each unknown together with the standards and quality control samples were extracted using an automated protein precipitation procedure on a Hamilton workstation. The extract was centrifuged and the supernatant was transferred for analysis. The separation was enabled by a Thermo Aria LX-2 LC system on a reversed phase column e.g. Waters XSelect HSS T3 XP (50 x 2.1mm x 2.5u) or Phenomenex Beta Test Column (50 x 2.1 mm). The compounds were detected using selected reaction monitoring (SRM) methods by an AB Sciex API5000 mass spectrometer in the positive or negative ionization mode. In addition, chromatographic peaks for Parent compounds of Examples 1-8 (Formula I')and compounds of Examples 1 to 8 (Formula I) were resolved chromatographically with baseline to baseline separation.

[0218] Pharmacokinetic parameters were obtained using noncompartmental methods (Watson®). The area under the plasma concentration-time curve (AUC_{0-t}) was calculated from the first time point (0 minutes) up to the last time point with measurable drug concentration (i.e., concentration of Parent (Formula I' compound) resulting after administration of each of the Parent and Example compounds) using the linear trapezoidal or linear/log-linear trapezoidal rule. The remaining area under the plasma concentration-time curve ($AUC_{t-\infty}$) was estimated by dividing the observed concentration at the last time point by the elimination rate constant. This value was added to AUC_{0-t} to estimate the $AUC_{0-\infty}$. The maximum plasma concentration (C_{max}) and the time at which maximum concentration occurred (T_{max}) were obtained by inspection of the plasma concentration-time data.

[0219] Table 3 provides AUC values obtained in these studies. In Table 3, the Parent of each Example number refers

to the Parent counterpart compound of said Example number compound wherein R^4 is replaced with -H.

Table 3 - Results of PK Studies

	Dose	Rat AUC $_{(0-\infty)}$	Vehicle
Ex. 1	6.2 mg/kg PO	14.3 μM•hr	0.5% methylcellulose
Parent of Ex. 2	5 mg/kg PO	15.3 μM•hr	40% PEG400/10% Tween-80/50% water
Ex. 2	6.25 mg/kg PO	16.0 μM•hr	0.5% methylcellulose
Parent of Ex. 3	5 mg/kg PO	10.2 μM•hr	40% PEG400/10% Tween-80/50% water
Ex. 3	6.2 mg/kg PO	14.0 μM•hr	0.5% methylcellulose
Parent of Ex. 4	5 mg/kg PO	21.0 μM•hr	40% PEG400/10% Tween-80/50% water
Ex. 4	6.2 mg/kg PO	15.0 μM•hr	0.5% methylcellulose
Parent of Ex. 5	5 mg/kg PO	29.1 μM•hr	40% PEG400/10% Tween-80/50% water
Ex. 5	6.2 mg/kg PO	28.2 μM•hr	0.5% methylcellulose
Parent of Ex. 6	5 mg/kg PO	2.0 μM•hr	40% PEG400/10% Tween-80/50% water
Ex. 6	6.6 mg/kg PO	5.7 μM•hr	40% PEG400/10% Tween-80/50% water
Parent of Ex. 7	5 mg/kg PO	8.2 μM•hr	40% PEG400/10% Tween-80/50% water
Ex. 7	6.2 mg/kg PO	11.6 μM•hr	0.5% methylcellulose
Parent of Ex. 8	5 mg/kg PO	13.9 μM•hr	40% PEG400/10% Tween-80/50% water
Ex. 8	5 mg/kg PO	21.6 μM•hr	0.5% methylcellulose

SEQUENCE LISTING

[0220]

<110> Merck Sharp & Dohme Corp.
Burgey, Christopher S.
Fritzen, Jeffrey F., Jr.
Balsells, Jaume
Patel, Mehul

<120> PRODRUGS OF HIV REVERSE TRANSCRIPTASE INHIBITORS

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<150> 61/973,689
<151> April 1, 2014

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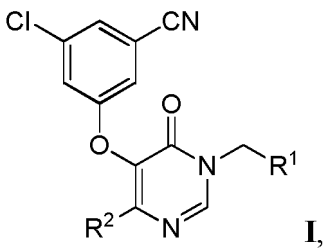
Claims

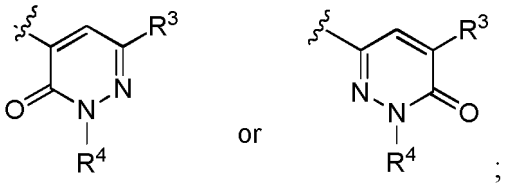
1. A compound of structural Formula I or a pharmaceutically acceptable salt thereof:



I,

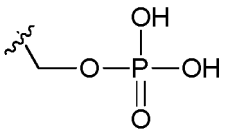
wherein

R^1 is



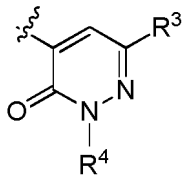
;

R2 is halo or -C_{1-3}alkyl substituted with 1 to 3 of -F;
R3 is (a) halo, (b) -C_{1-3}alkyl substituted with 1 to 3 of -F, or (3) phenyl substituted with halo; and;
R4 is



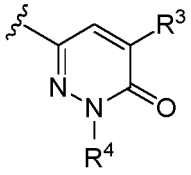
.

2. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein **R1** is



.

3. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein **R1** is



.

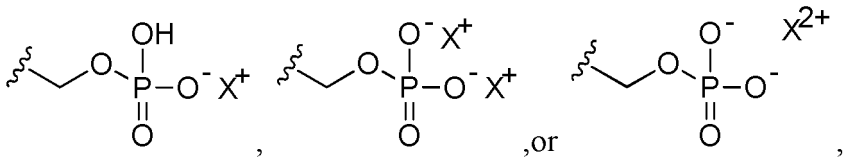
4. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein **R2** is methyl substituted with 1, 2 or 3 of -F; or ethyl substituted with 1, 2 or 3 of-F.

5. The compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein **R2** is -CHF_2, -CF_3, or -CF_2CH_3.

6. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein **R3** is -F; -Cl; methyl substituted with 1, 2 or 3 of -F; ethyl substituted with 1, 2 or 3 of -F; or phenyl substituted with -F.

7. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein **R3** is - Cl, -CHF_2, -CF_3, -CF_2CH_3, or phenyl substituted with -F.

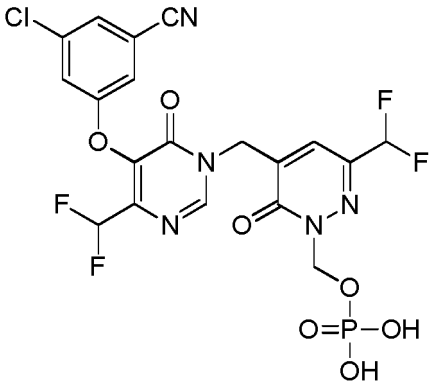
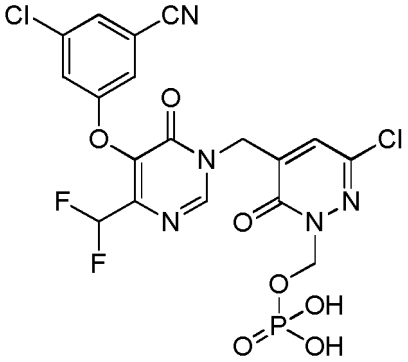
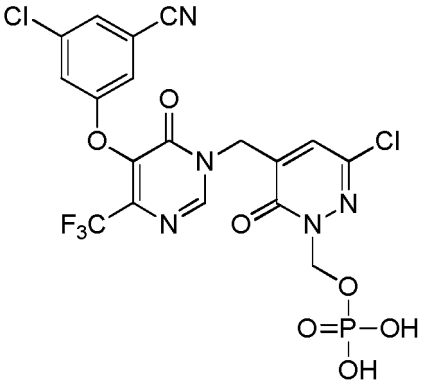
8. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein **R4** is:



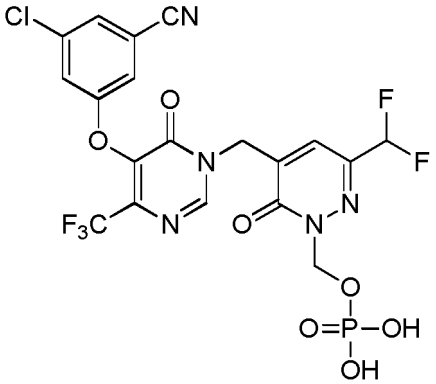
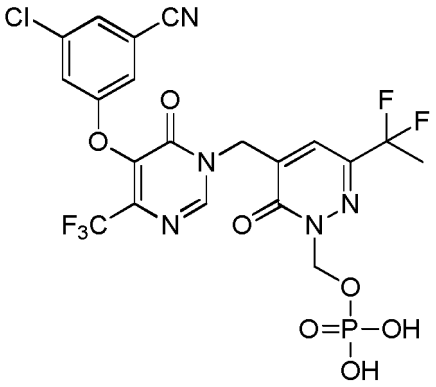
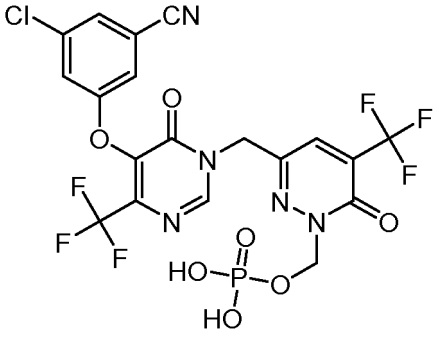
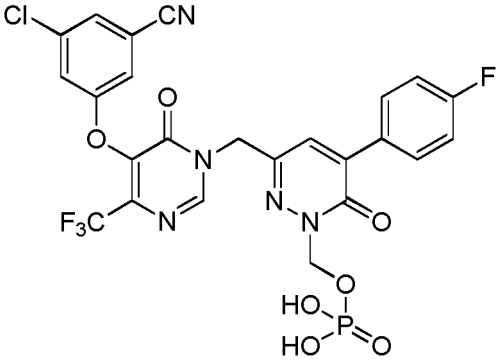
wherein X^+ and X^{2+} are positive counter-ions.

9. The compound of claim 8, wherein the positive counter ions are K^+, Na^+ or NH_4^+.

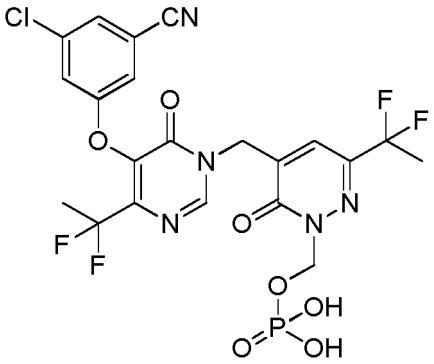
10. The compound of claim 1 that is:

1)	(5-((5-(3-chloro-5-cyanophenoxy)-4-(difluoromethyl)-6-oxopyrimidin-1(6*H*)-yl)methyl)-3-(difluoromethyl)-6-oxopyridazin-1(6*H*)-yl)methyl dihydrogen phosphate; 
2)	(3-chloro-5-((5-(3-chloro-5-cyanophenoxy)-4-(difluoromethyl)-6-oxopyrimidin-1(6*H*)-yl)methyl)-6-oxopyridazin-1(6*H*)-yl)methyl dihydrogen phosphate;
	
3)	3-chloro-5-((5-(3-chloro-5-cyanophenoxy)-6-oxo-4-(trifluorornethyl)pyrimidin-1(6*H*)-yl)methyl)-6-oxopyridazin-1(6*H*)-yl)methyl dihydrogen phosphate; 
4)	(5-((5-(3-chloro-5-cyanophenoxy)-6-oxo-4-(trifluoromethyl)pyrimidin-1(6*H*)-yl)methyl)-3-(difluoromethyl)-6-oxopyridazin-1(6*H*)-yl)methyldihydrogen phosphate;

(continued)

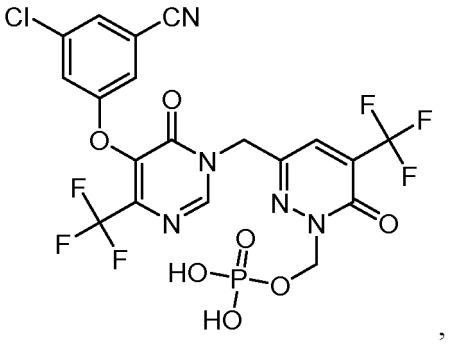
	
5)	(5-((5-(3-chloro-5-cyanophenoxy)-6-oxo-4-(trifluoromethyl)pyrimidin-1(6*H*)-yl)methyl)-3-(1,1-difluoroethyl)-6-oxopyridazin-1(6*H*)-yl)methyldihydrogen phosphate;
	
6)	(3-((5-(3-chloro-5-cyanophenoxy)-6-oxo-4-(trifluoromethyl)pyrimidin-1(6*H*)-yl)methyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)methyl phosphate; 
7)	(3-((5-(3-chloro-5-cyanophenoxy)-6-oxo-4-(trifluoromethyl)pyrimidin-1(6*H*)-yl)methyl)-5-(4-fluorophenyl)-6-oxopyridazin-1(1*H*)-yl)methyl dihydrogen phosphate; 

(continued)

	or
8)	(5-((5-(3-chloro-5-cyanophenoxy)-4-(1,1-difluoroethyl)-6-oxopyrimidin-1(6*H*)-yl)methyl)-3-(1,1-difluoroethyl)-6-oxopyridazin-1(6*H*)-yl)methyl dihydrogen phosphate; 

or a pharmaceutically acceptable salt thereof.

11. The compound of claim 1 that is:
(3-((5-(3-chloro-5-cyanophenoxy)-6-oxo-4-(trifluoromethyl)pyrimidin-1(6*H*)-yl)methyl)-6-oxo-5-(trifluoromethyl)pyridazin-1(6*H*)-yl)methyl phosphate



or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising a compound of any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

13. A pharmaceutical composition comprising a compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier and further comprising an effective amount of an anti-HIV agent selected from an anti-HIV antiviral agent, an immunomodulator, or anti-infective agent.

14. The pharmaceutical composition of claim 13, wherein the anti-HIV antiviral agent is an HIV protease inhibitor, HIV reverse transcriptase inhibitor, HIV integrase inhibitor, HIV fusion inhibitor, HIV entry inhibitor, or HIV maturation inhibitor.

15. A compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof for use in therapy.

16. A compound of any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof for use in inhibiting HIV replication.

17. A compound of any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof for use in the treatment or prophylaxis of infection by HIV or for use in the treatment, prophylaxis or delay in the onset of AIDS.

18. The pharmaceutical composition of claim 12 further comprising one or more anti-HIV agents selected from the following table:

abacavir, ABC
abacavir +lamivudine
abacavir + lamivudine + zidovudine
amprenavir
atazanavir
AZT, zidovudine, azidothymidine
capravirine
darunavir
ddC, zalcitabine, dideoxycytidine
ddI, didanosine, dideoxyinosine
ddI (enteric coated)
delavirdine, DLV
dolutegravir
doravirine, MK-1439
efavirenz, EFV
efavirenz + emtricitabine + tenofovir DF
EFdA (4'-ethyny1-2-fluoro-2'-deoxyadenosine)
Elvitegravir
emtricitabine, FTC
emtricitabine + tenofovir DF
emvirine
enfuvirtide
enteric coated didanosine
etravirine, TMC-125
fosamprenavir calcium
indinavir
lamivudine, 3TC
lamivudine + zidovudine
lopinavir
lopinavir + ritonavir
maraviroc
nelfinavir
nevirapine, NVP
PPL-100 (also known as PL-462) (Ambrilia)
raltegravir, MK-0518
Rilpivirine
ritonavir

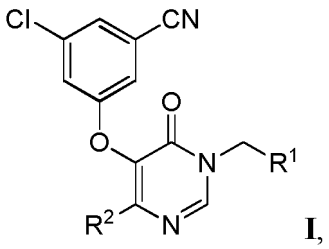
(continued)

saquinavir
stavudine, d4T, di dehydrodeoxythymi dine
tenofovir DF (DF = disoproxil fumarate), TDF
Tenofovir, hexadecyloxypropyl (CMX-157)
tipranavir
vicriviroc

19. A combination comprising a compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof and one or more anti-HIV agents selected from the table in claim 18.

Patentansprüche

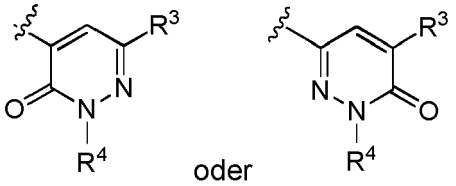
1. Eine Verbindung der Strukturformel I oder ein pharmazeutisch annehmbares Salz davon:



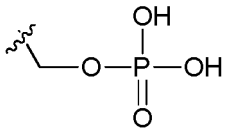
I,

wobei

R1

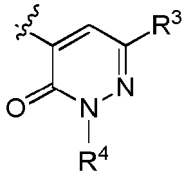


ist,
R2 Halogen oder -C_{1-3}-Alkyl, das mit 1 bis 3 -F substituiert ist, ist,
R3 (a) Halogen, (b) -C_{1-3}-Alkyl, das mit 1 bis 3 -F substituiert ist, oder (3) Phenyl, das mit Halogen substituiert ist, ist, und
R4



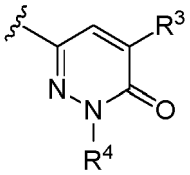
ist.

2. Die Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon, wobei **R1**



ist.

3. Die Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon, wobei $\mathbf{R^1}$



ist.

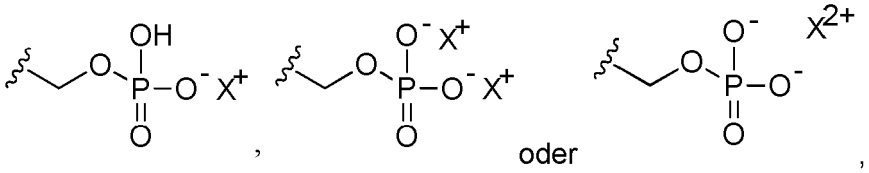
4. Die Verbindung nach einem der Ansprüche 1 bis 3 oder ein pharmazeutisch annehmbares Salz davon, wobei $\mathbf{R^2}$ Methyl, das mit 1, 2 oder 3 -F substituiert ist, oder Ethyl, das mit 1, 2 oder 3 -F substituiert ist, ist.

5. Die Verbindung nach Anspruch 4 oder ein pharmazeutisch annehmbares Salz davon, wobei $\mathbf{R^2}$ $-CHF_2$, $-CF_3$ oder $-CF_2CH_3$ ist.

6. Die Verbindung nach einem der Ansprüche 1 bis 5 oder ein pharmazeutisch annehmbares Salz davon, wobei $\mathbf{R^3}$ -F, -Cl, Methyl, das mit 1, 2 oder 3 -F substituiert ist, Ethyl, das mit 1, 2 oder 3 -F substituiert ist, oder Phenyl, das mit -F substituiert ist, ist.

7. Die Verbindung nach Anspruch 6 oder ein pharmazeutisch annehmbares Salz davon, wobei $\mathbf{R^3}$ -Cl, $-CHF_2$, $-CF_3$, $-CF_2CH_3$ oder Phenyl, das mit -F substituiert ist, ist.

8. Die Verbindung nach einem der Ansprüche 1 bis 7 oder ein pharmazeutisch annehmbares Salz davon, wobei $\mathbf{R^4}$ ist:



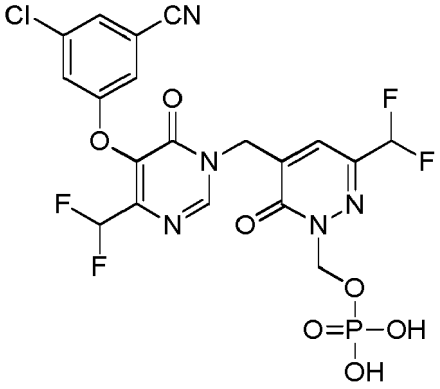
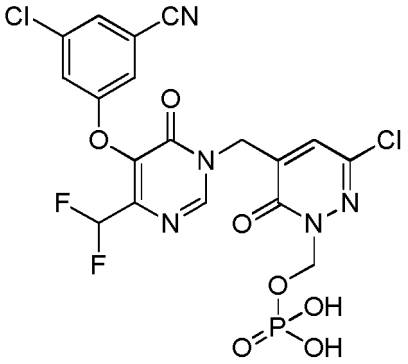
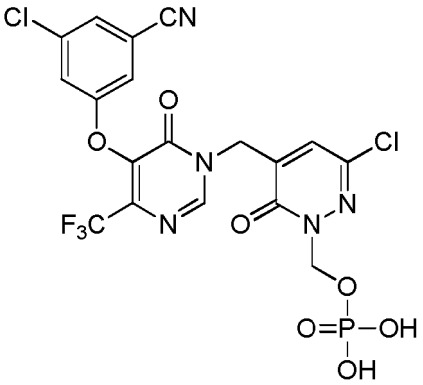
wobei X^+ und X^{2+} positive Gegenionen sind.

9. Die Verbindung nach Anspruch 8, wobei die positiven Gegenionen K^+, Na^+ oder NH_4^+ sind.

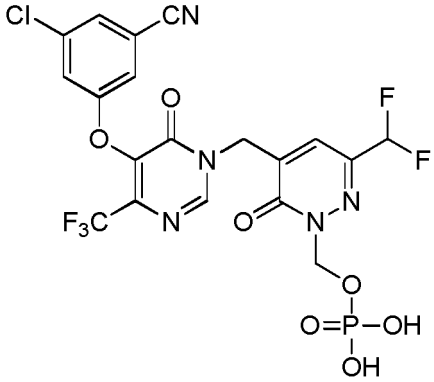
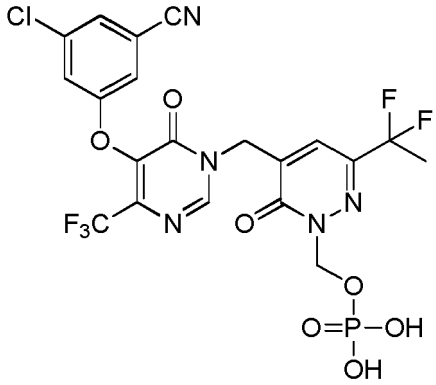
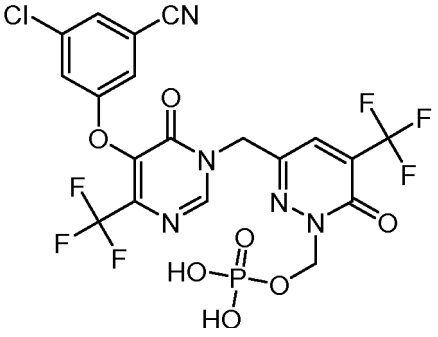
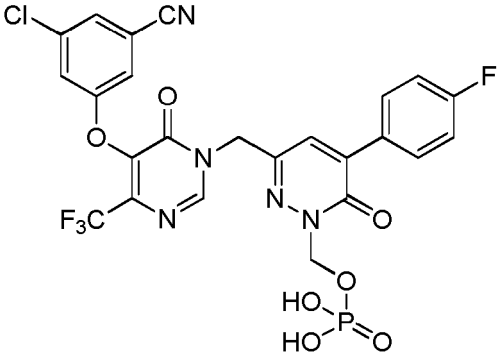
10. Die Verbindung nach Anspruch 1, die ist:

1)	(5-((5-(3-Chlor-5-cyanophenoxy)-4-(difluormethyl)-6-oxopyrimidin-1(6*H*)-yl)methyl)-3-(difluormethyl)-6-oxopyridazin-1(6*H*)-yl)methyldihydrogenphosphat,

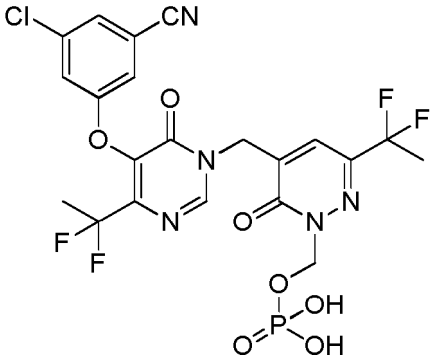
(fortgesetzt)

	
2)	(3-Chlor-5-((5-(3-chlor-5-cyanophenoxy)-4-(difluormethyl)-6-oxopyrimidin-1(6*H*)-yl)methyl)-6-oxopyridazin-1(6*H*)-yl)methyldihydrogenphosphat, 
3)	3-Chlor-5-(((5-(3-chlor-5-cyanophenoxy)-6-oxo-4-(trifluormethyl)pyrimidin-1(6*H*)-yl)methyl)-6-oxopyridazin-1(6*H*)-yl)methyldihydrogenphosphat, 
4)	(5-((5-(3-Chlor-5-cyanophenoxy)-6-oxo-4-(trifluormethyl)pyrimidin-1(6*H*)-yl)methyl)-3-(difluormethyl)-6-oxopyridazin-1(6*H*)-yl)methyldihydrogenphosphat,

(fortgesetzt)

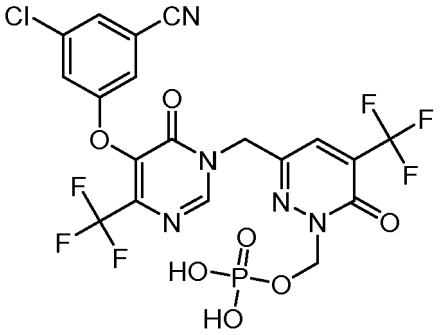
	
5)	(5-((5-(3-Chlor-5-cyanophenoxy)-6-oxo-4-(trifluormethyl)pyrimidin-1(6*H*)-yl)methyl)-3-(1,1-difluorethyl)-6-oxopyridazin-1(6*H*)-yl)methyldihydrogenphosphat, 
6)	(3-((5-(3-Chlor-5-cyanophenoxy)-6-oxo-4-(thrifluormethyl)pyrimidin-1(6*H*)-yl)methyl)-6-oxo-5-(trifluormethyl) pyridazin-1(6*H*)-yl)methylphosphat, 
7)	(3-((5-(3-Chlor-5-cyanophenoxy)-6-oxo-4-(trifluormethyl)pyrimidin-1(6*H*)-yl)methyl)-5-(4-fluorphenyl)-6-oxopyridazin-1(6*H*)-yl)methyl-dihydrogenphosphat, 

(fortgesetzt)

	oder
8)	(5-((5-(3-Chlor-5-cyanophenoxy)-4-(1,1-difluorethyl)-6-oxopyrimidin-1(6*H*)-yl)methyl)-3-(1,1-difluorethyl)-6-oxopyridazin-1(6*H*)-yl)methyl-dihydrogenphosphat, 

oder ein pharmazeutisch annehmbares Salz davon.

11. Die Verbindung nach Anspruch 1, die ist:
(3-((5-(3-Chlor-5-cyanophenoxy)-6-oxo-4-(trifluormethyl)pyrimidin-1(6*H*)-yl)methyl)-6-oxo-5-(trifluormethyl)pyridazin-1(6*H*)-yl)methylphosphat



oder ein pharmazeutisch annehmbares Salz davon.

12. Eine pharmazeutische Zusammensetzung, die eine Verbindung nach einem der Ansprüche 1 bis 11 oder ein pharmazeutisch annehmbares Salz davon und einen pharmazeutisch annehmbaren Träger umfasst.

13. Eine pharmazeutische Zusammensetzung, die eine Verbindung nach einem der Ansprüche 1 bis 11 oder ein pharmazeutisch annehmbares Salz davon und einen pharmazeutisch annehmbaren Träger umfasst und ferner eine wirksame Menge eines Anti-HIV-Mittels, ausgewählt aus einem Anti-HIV-Virostatikum, einem Immunmodulator oder einem Antiinfektivum, umfasst.

14. Die pharmazeutische Zusammensetzung nach Anspruch 13, wobei das Anti-HIV-Virostatikum ein HIV-Protease-Inhibitor, HIV-Reverse-Transkriptase-Inhibitor, HIV-Integrase-Inhibitor, HIV-Fusionsinhibitor, HIV-Entry-Inhibitor oder HIV-Maturationsinhibitor ist.

15. Eine Verbindung nach einem der Ansprüche 1 bis 11 oder ein pharmazeutisch annehmbares Salz davon zur Verwendung in der Therapie.

16. Eine Verbindung nach einem der Ansprüche 1 bis 11 oder ein pharmazeutisch annehmbares Salz davon zur Verwendung bei der Inhibierung der HIV-Replikation.

17. Eine Verbindung nach einem der Ansprüche 1 bis 11 oder ein pharmazeutisch annehmbares Salz davon zur Ver-

wendung bei der Behandlung oder Prophylaxe einer HIV-Infektion oder zur Verwendung bei der Behandlung, Prophylaxe oder Verzögerung des Ausbruchs von AIDS.

18. Die pharmazeutische Zusammensetzung nach Anspruch 12, die ferner ein oder mehrere Anti-HIV-Mittel umfasst, ausgewählt aus der folgenden Tabelle:

Abacavir, ABC
Abacavir + Lamivudin
Abacavir + Lamivudin + Zidovudin
Amprenavir
Atazanavir
AZT, Zidovudin, Azidothymidin
Capravirin
Darunavir
ddC, Zalcitabin, Didesoxycytidin
ddI, Didanosin, Didesoxyinosin
ddI (magensaftresistent beschichtet)
Delavirdin, DLV
Dolutegravir
Doravirin, MK-1439
Efavirenz, EFV
Efavirenz + Emtricitabin + Tenofovir DF
EFdA (4'-Ethinyl-2-fluor-2'-desoxyadenosin)
Elvitegravir
Emtricitabin, FTC
Emtricitabin + Tenofovir DF
Emvirin
Enfuvirtid
magensaftresistent beschichtetes Didanosin
Etravirin, TMC-125
Fosamprenavir-Calcium
Indinavir
Lamivudin, 3TC
Lamivudin + Zidovudin
Lopinavir
Lopinavir + Ritonavir
Maraviroc
Nelfinavir
Nevirapin, NVP
PPL-100 (auch bekannt als PL-462) (Ambrilia)
Raltegravir, MK-0518

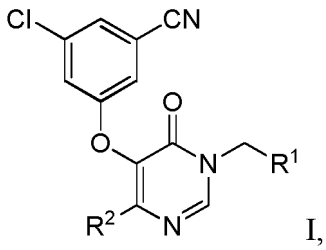
(fortgesetzt)

Rilpivirin
Ritonavir
Saquinavir
Stavudin, d4T, Didehydrodesoxythymidin
Tenofovir DF (DF = Disoproxilfumarat), TDF
Tenofovir, Hexadecyloxypropyl (CMX-157)
Tipranavir
Vicriviroc

19. Eine Kombination, die eine Verbindung nach einem der Ansprüche 1-11 oder ein pharmazeutisch annehmbares Salz davon und ein oder mehrere Anti-HIV-Mittel, ausgewählt aus der Tabelle in Anspruch 18, umfasst.

Revendications

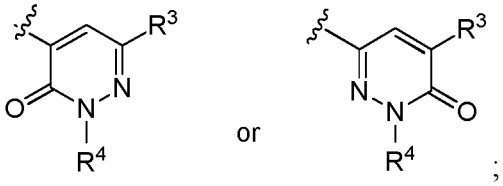
1. Composé de la Formule structurale I ou un sel pharmaceutiquement acceptable de celui-ci:



I,

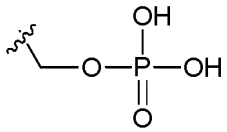
où

R^1 est



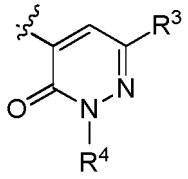
;

R^2 est un halo ou un -C_{1-3} alkyle substitué par 1 à 3 de -F;
R^3 est (a) un halo, (b) un -C_{1-3} alkyle substitué par 1 à 3 de -F, ou (3) un phényle substitué par un halo; et;
R^4 est



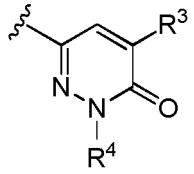
.

2. Composé selon la revendication 1 ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel R^1 est:



.

3. Composé selon la revendication 1 ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel R^1 est:



.

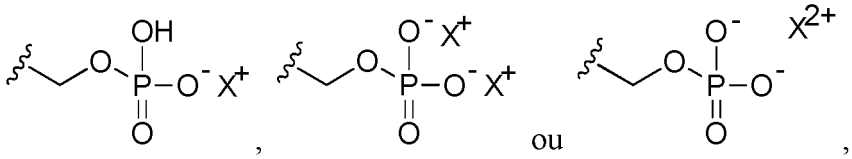
4. Composé selon l'une quelconque des revendications 1 à 3, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel R^2 est un méthyle substitué par 1, 2 ou 3 de -F; ou un éthyle substitué par 1, 2 ou 3 de -F.

5. Composé selon la revendication 4, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel R^2 est $-CHF_2$, $-CF_3$ ou $-CF_2CH_3$.

6. Composé selon l'une quelconque des revendications 1 à 5, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel R^3 est -F; -Cl; un méthyle substitué par 1, 2 ou 3 de -F; un éthyle substitué par 1, 2 ou 3 de -F; ou un phényle substitué par -F.

7. Composé selon la revendication 6, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel R^3 est -Cl, $-CHF_2$, $-CF_3$, $-CF_2CH_3$ ou un phényle substitué par -F.

8. Composé selon l'une quelconque des revendications 1 à 7, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel R^4 est:



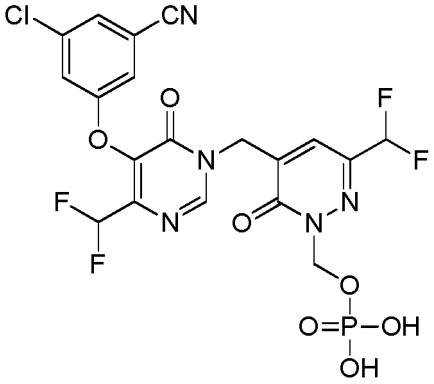
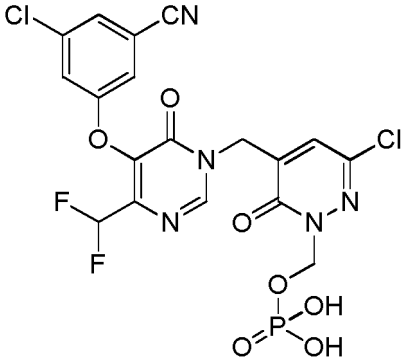
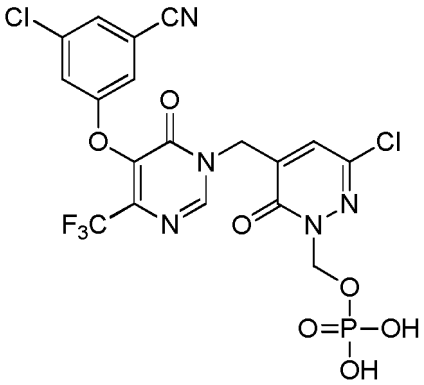
dans lequel X^+ et X^{2+} sont des contre-ions positifs.

9. Composé selon la revendication 8, dans lequel les contre-ions positifs sont K^+, Na^+ ou NH_4^+.

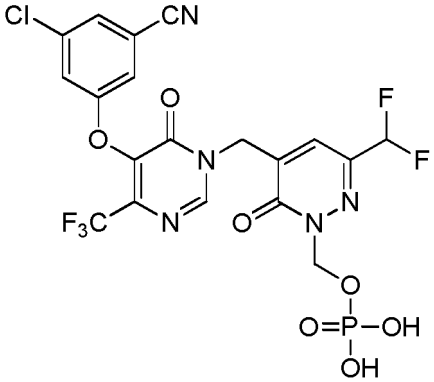
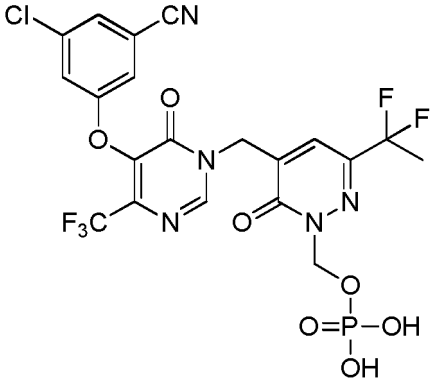
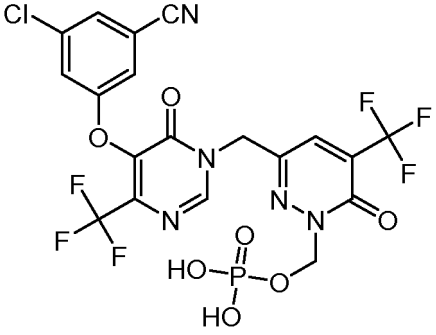
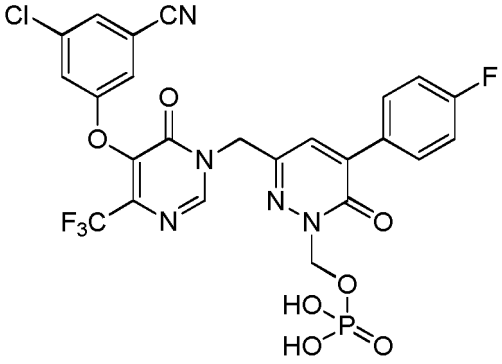
10. Composé selon la revendication 1 qui est:

1)	(5-((5-(3-chloro-5-cyanophénoxy)-4-(difluorométhyl)-6-oxopyrimidin-1(6H)-yl)méthyl)-3-(difluorométhyl)-6-oxopyridazin-1(6H)-yl)méthyl-dihydrogénophosphate;

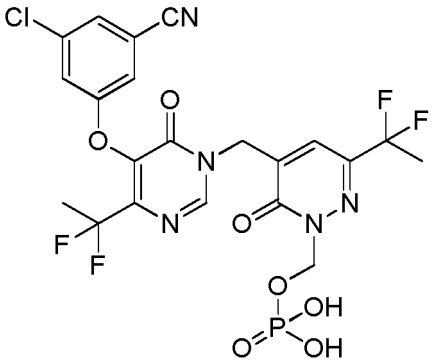
(suite)

	
2)	(3-chloro-5-((5-(3-chloro-5-cyanophénoxy)-4-(difluorométhyl)-6-oxopyrimidin-1(6H)-yl)méthyl)-6-oxopyridazin-1(6H)-yl)méthyl-dihydrogénophosphate; 
3)	3-chloro-5-((5-(3-chloro-5-cyanophénoxy)-6-oxo-4-(trifluorométhyl)pyrimidin-1(6H)-yl)méthyl)-6-oxopyridazin-1(6H)-yl)méthyl-dihydrogénophosphate;
	
4)	(5-((5-(3-chloro-5-cyanophénoxy)-6-oxo-4-(trifluorométhyl)pyrimidin-1(6H)-yl)méthyl)-3(difluorométhyl)-6-oxopyridazin-1 (6H)-yl)méthyl-dihydrogénophosphate;

(suite)

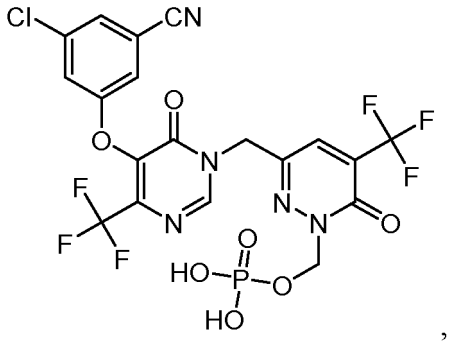
	
5)	(5-((5-(3-chloro-5-cyanophénoxy)-6-oxo-4-(trifluorométhyl)pyrimidin-1(6H)-yl)méthyl)-3-(1,1-difluoroéthyl)-6-oxopyridazin-1(6H)-yl)méthyl-dihydrogénophosphate; 
6)	(3-((5-(3-chloro-5-cyanophénoxy)-6-oxo-4-(trifluorométhyl)pyrimidin-1(6H)-yl)méthyl)-6-oxo-5-(trifluorométhyl)pyridazin-1(6H)-yl)méthyl-phosphate;
	
7)	(3-((5-(3-chloro-5-cyanophénoxy)-6-oxo-4-(trifluorométhyl)pyrimidin-1(6H)-yl)méthyl)-5-(4-fluorophényl)-6-oxopyridazin-1(6H)-yl)méthyl-dihydrogénophosphate; 

(suite)

	ou
8)	(5-((5-(3-chloro-5-cyanophénoxy)-4-(1,1-difluoroéthyl)-6-oxopyrimidin-1(6H)-yl)méthyl)-3-(1,1-difluoroéthyl)-6-oxopyridazin-1(6H)-yl)méthyl-dihydrogénophosphate; 

ou un sel pharmaceutiquement acceptable de ceux-ci.

11. Composé selon la revendication 1 qui est:
(3-((5-(3-chloro-5-cyanophénoxy)-6-oxo-4-(trifluorométhyl)pyrimidin-1(6H)-yl)méthyl)-6-oxo-5-(trifluorométhyl)pyridazin-1 (6H)-yl)méthyl-phosphate



,

ou un sel pharmaceutiquement acceptable de celui-ci.

12. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 11 ou un sel pharmaceutiquement acceptable de celui-ci et un véhicule pharmaceutiquement acceptable.

13. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 11, ou un sel pharmaceutiquement acceptable de celui-ci, et un véhicule pharmaceutiquement acceptable et comprenant en outre une quantité efficace d'un agent anti-VIH choisi parmi un agent antiviral anti-VIH, un immuno-modulateur ou un agent anti-infectieux.

14. Composition pharmaceutique selon la revendication 13, dans lequel l'agent antiviral anti-VIH est un inhibiteur de protéase de VIH, un inhibiteur de transcriptase inverse de VIH, un inhibiteur d'intégrase de VIH, un inhibiteur de fusion de VIH, un inhibiteur d'entrée de VIH ou un inhibiteur de maturation de VIH.

15. Composé selon l'une quelconque des revendications 1 à 11, ou un sel pharmaceutiquement acceptable de celui-ci pour une utilisation en thérapie.

16. Composé selon l'une quelconque des revendications 1 à 11 ou un sel pharmaceutiquement acceptable de celui-ci pour une utilisation dans l'inhibition d'une réplication de VIH.

17. Composé selon l'une quelconque des revendications 1 à 11 ou un sel pharmaceutiquement acceptable de celui-ci

pour une utilisation dans le traitement ou la prophylaxie d'une infection par VIH ou pour une utilisation dans le traitement, la prophylaxie ou le retardement dans l'apparition du SIDA.

18. Composition pharmaceutique selon la revendication 12 comprenant en outre un ou plusieurs agents anti-VIH choisis dans le tableau suivant:

abacavir, ABC
abacavir + lamivudine
abacavir + lamivudine + zidovudine
amprénavir
atazanavir
AZT, zidovudine, azidothymidine
capravirine
darunavir
ddC, zalcitabine, didésoxycytidine
ddI, didanosine, didésoxyinosine
ddI (avec enrobage entérique)
delavirdine, DLV
dolutégravir
doravirine, MK-1439
éfavirenz, EFV
éfavirenz + emtricitabine + ténofovir DF
EFdA (4'-éthynyl-2-fluoro-2'-désoxyadénosine)
Elvitégravir
emtricitabine, FTC
emtricitabine + ténofovir DF
emvirine
enfuvirtide
didanosine avec enrobage entérique
étravirine, TMC-125
fosamprénavir calcium
indinavir
lamivudine, 3TC
lamivudine + zidovudine
lopinavir
lopinavir + ritonavir
maraviroc
nelfinavir
névirapine, NVP
PPL-100 (aussi connu comme PL-462) (Ambrilia)
raltégravir, MK-0518

(suite)

Rilpivirine
ritonavir
saquinavir
stavudine, d4T, didéhydrodésoxythymidine
ténofovir DF (DF = disoproxil fumarate), TDF
Ténofovir, hexadécyloxypropyle (CMX-157)
tipranavir
vicriviroc

19. Combinaison comprenant un composé selon l'une quelconque des revendications 1-11, ou un sel pharmaceutiquement acceptable de celui-ci et un ou plusieurs agents anti-VIH choisis dans le tableau dans la revendication 18.

REFERENCES CITED IN THE DESCRIPTION

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