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(54) **SUBSTITUTED BRIDGED UREA ANALOGS AS SIRTUIN MODULATORS**

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(57) **ABSTRACT**

The present invention relates to novel substituted bridged urea analog compounds of Formula (I) or pharmaceutically acceptable salts thereof, corresponding pharmaceutical compositions, processes for making and use of such compounds, alone or in combination with other therapeutic agents, as Sirtuin Modulators useful for increasing lifespan of a cell, and in treating and/or preventing a wide variety of diseases and disorders, which include, but are not limited to, for example, diseases or disorders related to aging or stress, diabetes, obesity, neurodegenerative diseases, cardiovascular disease, blood clotting disorders, inflammation, cancer, and/or flushing as well as diseases or disorders that would benefit from increased mitochondrial activity.

SUBSTITUTED BRIDGED UREA ANALOGS AS SIRTUIN MODULATORS

FIELD OF THE INVENTION

[0001] In general, the present invention relates to substituted bridged urea analog compounds of Formulas (I) to (VI), corresponding analogs or derivatives thereof, or pharmaceutically acceptable salts thereof, corresponding pharmaceutical compositions, processes for making and use of such compounds, alone or in combination with other therapeutic agents, as Sirtuin Modulators useful for increasing lifespan of a cell, and in treating and/or preventing a wide variety of diseases and disorders, which include, but are not limited to, for example, diseases or disorders related to aging or stress, diabetes, obesity, neurodegenerative diseases, cardiovascular disease, blood clotting disorders, inflammation, cancer, and/or flushing as well as diseases or disorders that would benefit from increased mitochondrial activity.

BACKGROUND

[0002] The Silent Information Regulator (SIR) family of genes represents a highly conserved group of genes present in the genomes of organisms ranging from archaebacteria to eukaryotes. The encoded SIR proteins are involved in diverse processes from regulation of gene silencing to DNA repair. A well-characterized gene in this family is *S. cerevisiae* SIR2, which is involved in silencing HM loci that contain information specifying yeast mating type, telomere position effects and cell aging. The yeast Sir2 protein belongs to a family of histone deacetylases. The proteins encoded by members of the SIR gene family show high sequence conservation in a 250 amino acid core domain. The Sir2 homolog, CobB, in *Salmonella typhimurium*, functions as an NAD (nicotinamide adenine dinucleotide)-dependent ADP-ribosyl transferase.

[0003] The Sir2 protein is a class III deacetylase which uses NAD as a cosubstrate. Unlike other deacetylases, many of which are involved in gene silencing, Sir2 is insensitive to class I and II histone deacetylase inhibitors like trichostatin A (TSA).

[0004] Deacetylation of acetyl-lysine by Sir2 is tightly coupled to NAD hydrolysis, producing nicotinamide and a novel acetyl-ADP ribose compound. The NAD-dependent deacetylase activity of Sir2 is essential for its functions, which can connect its biological role with cellular metabolism in yeast. Mammalian Sir2 homologs have NAD-dependent histone deacetylase activity.

[0005] Biochemical studies have shown that Sir2 can readily deacetylate the amino-terminal tails of histones H3 and H4, resulting in the formation of 2'/3'-O-acetyl-ADP-ribose (OAADPR) and nicotinamide. Strains with additional copies of SIR2 display increased rDNA silencing and a 30% longer life span. It has also been shown that additional copies of the *C. elegans* SIR2 homolog, sir-2.1, and the *D. melanogaster* dSir2 gene extend life span in those organisms. This implies that the SIR2-dependent regulatory pathway for aging arose early in evolution and has been well conserved. Today, Sir2 genes are believed to have evolved to enhance an organism's health and stress resistance to increase its chance of surviving adversity.

[0006] In humans, there are seven Sir2-like genes (SIRT1-SIRT7) that share the conserved catalytic domain of Sir2. SIRT1 is a nuclear protein with the highest degree of sequence similarity to Sir2. SIRT1 regulates multiple cellular targets by deacetylation including the tumor suppressor p53, the cellular signaling factor NF-κB, and the FOXO transcription factor.

[0007] SIRT3 is a homolog of SIRT1 that is conserved in prokaryotes and eukaryotes. The SIRT3 protein is targeted to the mitochondrial cristae by a unique domain located at the N-terminus. SIRT3 has NAD^+-dependent protein deacetylase activity and is ubiquitously expressed, particularly in metabolically active tissues. Upon transfer to the mitochondria, SIRT3 is believed to be cleaved into a smaller, active form by a mitochondrial matrix processing peptidase (MPP).

[0008] Caloric restriction has been known for over 70 years to improve the health and extend the lifespan of mammals. Yeast life span, like that of metazoans, is also extended by interventions that resemble caloric restriction, such as low glucose. The discovery that both yeast and flies lacking the SIR2 gene do not live longer when calorically restricted provides evidence that SIR2 genes mediate the beneficial health effects of a restricted calorie diet. Moreover, mutations that reduce the activity of the yeast glucose-responsive cAMP (adenosine 3',5'-monophosphate)-dependent (PKA) pathway extend life span in wild type cells but not in mutant sir2 strains, demonstrating that SIR2 is likely to be a key downstream component of the caloric restriction pathway.

[0009] In addition to therapeutic potential, structural and biophysical studies of SIRT1 activity and activation by small molecule sirtuin modulators would be useful to advance understanding of the biological function of sirtuins, to further the understanding of the mechanism of action of sirtuin activation and to aid in the development of assays that identify novel sirtuin modulators.

[0010] The present invention is directed to overcoming these and other problems encountered in the art.

SUMMARY OF THE INVENTION

[0011] In general, the present invention relates to substituted bridged urea analog compounds of Formulas (I) to (VI), corresponding anlogs or derivatives thereof, or pharmaceutically acceptable salts thereof, corresponding pharmaceutical compositions, processes for making and use of such compounds, alone or in combination with other therapeutic agents, as Sirtuin Modulators useful for increasing lifespan of a cell, and in treating and/or preventing a wide variety of diseases and disorders, which include, but are not limited to, for example, diseases or disorders related to aging or stress, diabetes, obesity, neurodegenerative diseases, cardiovascular disease, blood clotting disorders, inflammation, cancer, and/or flushing as well as diseases or disorders that would benefit from increased mitochondrial activity.

[0012] In particular, the present invention relates to novel compounds of Formulas (I) to (VI)), corresponding analogs (i.e., with hydrogen substitution at the R^2 position) and corresponding pharmaceutical compositions comprising compounds of Formulas (I) to (VI) respectively.

[0013] The present invention also relates to processes for making compounds of Formulas (I) to (VI), and corresponding analogs (i.e., with hydrogen substitution at the R^2 position), respectively.

[0014] The present invention also relates to methods or uses for using Sirtuin Modulator compounds as defined herein in treating and/or preventing a wide variety of diseases and disorders, which include, but are not limited to, for example, diseases or disorders related to aging or stress, diabetes, obesity, neurodegenerative diseases, cardiovascular disease, blood clotting disorders, inflammation, cancer, and/or flushing as well as diseases or disorders that would benefit from increased mitochondrial activity, further which may be selected from or include, but are not limited to psoriasis, atopic dermatitis, acne, rosacea, inflammatory bowel disease, osteoporosis, sepsis, arthritis, COPD, systemic lupus erythematosus and ophthalmic inflammation.

DETAILED DESCRIPTION OF THE INVENTION

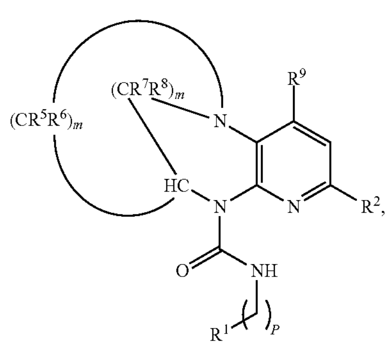
[0015] In general, the present invention relates to substituted bridged urea analog compounds of Formulas (I) to (VI), corresponding anlogs or derivatives thereof, or pharmaceutically acceptable salts thereof, corresponding pharmaceutical compositions, processes for making and use of such compounds, alone or in combination with other therapeutic agents, as Sirtuin Modulators useful for increasing lifespan of a cell, and in treating and/or preventing a wide variety of diseases and disorders, which include, but are not limited to, for example, diseases or disorders related to aging or stress, diabetes, obesity, neurodegenerative diseases, cardiovascular disease, blood clotting disorders, inflammation, cancer, and/or flushing as well as diseases or disorders that would benefit from increased mitochondrial activity.

Compounds

[0016] In particular, the present invention relates to novel compounds of Formulas (I) to (VI), corresponding analogs (i.e., with hydrogen substitution at the R^2 position) and corresponding pharmaceutical compositions comprising compounds of Formulas (I) to (VI), respectively.

[0017] International Patent Application No. WO09/061879, International Filing Date: 13 May 2014 discloses novel sirtuin-modulating substituted bridged urea and related analogs compounds of Formula (I):

(I)



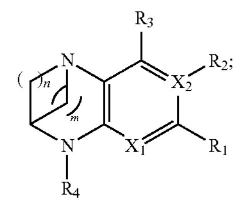
or

a pharmaceutically acceptable salt thereof, corresponding pharmaceutical compositions, combinations with other therapeutic agents, methods for making and methods or uses for increasing the lifespan of a cell, and treating and/or preventing a wide variety of diseases and disorders including, for example, diseases or disorders related to aging or stress, diabetes, obesity, neurodegenerative diseases, cardiovascular disease, blood clotting disorders, inflammation, cancer, and/or flushing as well as diseases or disorders that would benefit from increased mitochondrial activity.

[0018] In one aspect, the present invention provides novel sirtuin-modulating compounds of Structural Formulas (I) to (VI), respectively corresponding analogs (i.e., with hydrogen substitution at the R^2 position) as are described in detail below.

[0019] In one aspect, the present invention relates to a compound of Formula (I):

(I)



where:

[0020] X_1 or X_2 independently is selected from —N or —C;

[0021] R^1 is hydrogen, halogen, —CN, carbocyclyl, heterocyclyl, —N-substituted heterocyclyl, aryl, heteroaryl, —C(O)R_a or —C(O)—NR_bR_c; R^2 is halogen, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, or —C(O)—NR_bR_c;

[0022] R^3 is hydrogen, halogen, -hydroxy, -straight or branched C_1-C_6 alkyl, or -straight or branched-C_1-C_6 haloalkyl;

[0023] R^4 is hydrogen or —C(O)NR_bR_c;

[0024] where:

[0025] when X_2 is —N, R_2 is non-existent; or

[0026] when X_2 is —C, R_2 is as defined above;

[0027] each R^1, R^2, R^3 or R^4 as defined above optionally is further substituted with one or more substituents selected from hydrogen, halogen, —OH, —$(CH_2)_x$OH, —C≡N, —NR_dR_e, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, -straight or branched C_1-C_6 alkoxy, -straight or branched C_1-C_6 haloalkoxy, —O-straight or branched-C_1-C_6 haloalkyl, —C_1-C_6 cycloalkyl, —$(CH_2)_x$-cycloalkyl, heterocyclyl, aryl, -heteroaryl, —$(CH_2)_x$-heteroaryl, —O—$(CH_2)_x$CH(OH)CH_2(OH), or —C(O)OR_f;

[0028] each R_a, R_b, R_c, R_d, R_e, or R_f as defined above independently is selected from hydrogen, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, —C_1-C_6-cycloalkyl, —$(CH_2)_x C_1$-C_6-cycloalkyl, heterocyclyl, —N— heterocyclyl, aryl, heteroaryl, or —$(CH_2)_x$heteroaryl, —$(CHR_g)_x$heteroaryl;

[0029] where:

[0030] R_g is -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl;

[0031] each R_a, R_b, R_c R_d, R_e, or R_f as defined above optionally is further substituted with one or more substituents selected from hydrogen, halogen, —OH, —C≡N, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, -straight or branched C_1-C_6 alkoxy, —O-straight or branched-C_1-C_6 haloalkyl, —C_1-C_6 cycloalkyl, carbocyclyl, —$(CH_2)_x$-carbocyclyl, -heterocyclyl, —O-heterocyclyl aryl, -heteroaryl, —$(CH_2)_x$-heteroaryl, —O—$(CH_2)_x CH(OH)CH_2(OH)$, —$(CH_2)_x$—OH, or —C(O)—OH;

[0032] m is an integer from 1 to 3;
[0033] n is an integer selected from 1 to 3;
[0034] x is 0 or an integer from 1 to 6; or

a pharmaceutically salt thereof.

[0035] In another aspect, the present invention relates to a compound of the present invention as defined above (i.e., compounds of Formulas (I) to (VI), respectively corresponding analogs (i.e., with hydrogen substitution at the R^2 position) and throughout the instant application, where it is provided that:

[0036] when n=1, m≠1; and
[0037] when n=3, m≠3.

[0038] In another aspect, the present invention relates to a compound of the present invention, where R^2 is C(O)—NR_bR_c; wherein R_b and R_c are as defined above and throughout the present application.

[0039] In another aspect, the present invention relates to a compound of Formulas (I) to (VI) where:

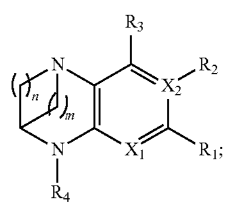
[0040] m is 1;
[0041] n is 2 or 3; and
[0042] R^4 is hydrogen.

[0043] In another aspect, the present invention relates to a compound of Formula (I), where:

[0044] m is 1;
[0045] n is 2 or 3; and
[0046] R^4 is —$C(O)NR_bR_c$, wherein each R_b and R_c is as defined above.

[0047] In one aspect, the present invention relates to a compound of Formula (II):

(II)



where:

[0048] X_1 or X_2 independently is selected from —N or —C;

[0049] R^1 is hydrogen, halogen, —CN, carbocyclyl, heterocyclyl, —N-substituted heterocyclyl, aryl, -heteroaryl, —$C(O)R_a$ or —C(O)—NR_bR_c;

[0050] R^2 is halogen, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, or —C(O)—NR_bR_c;

[0051] R^3 is hydrogen, halogen, -hydroxy, -straight or branched C_1-C_6 alkyl, or -straight or branched-C_1-C_6 haloalkyl;

[0052] R^4 is hydrogen or —$C(O)NR_bR_c$;

[0053] where:

[0054] when X_2 is —N, R_2 is non-existent; or

[0055] when X_2 is —C, R_2 is as defined above;

[0056] each R^1, R^2, R^3 or R^4 as defined above optionally is further substituted with one or more substituents selected from hydrogen, halogen, —OH, —$(CH_2)_x$OH, —C≡N, —NR_dR_e, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, -straight or branched C_1-C_6 alkoxy, -straight or branched C_1-C_6 haloalkoxy, —O-straight or branched-C_1-C_6 haloalkyl, —C_1-C_6 cycloalkyl, —$(CH_2)_x$-cycloalkyl, heterocyclyl, aryl, -heteroaryl, —$(CH_2)_x$-heteroaryl, —O—$(CH_2)_x CH(OH)CH_2(OH)$, or —$C(O)OR_f$;

[0057] each R_a, R_b, R_c, R_d, R_e, or R_f as defined above independently is selected from hydrogen, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, —C_1-C_6-cycloalkyl, —$(CH_2)_x C_1$-C_6-cycloalkyl, heterocyclyl, —N— heterocyclyl, aryl, heteroaryl, or —$(CH_2)_x$heteroaryl, —$(CHR_g)_x$heteroaryl;

[0058] where:

[0059] R_g is -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl;

[0060] each R_a, R_b, R_c R_d, R_e, or R_f as defined above optionally is further substituted with one or more substituents selected from hydrogen, halogen, —OH, —C≡N, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, -straight or branched C_1-C_6 alkoxy, —O-straight or branched-C_1-C_6 haloalkyl, —C_1-C_6 cycloalkyl, carbocyclyl, —$(CH_2)_x$-carbocyclyl, -heterocyclyl, —O-heterocyclyl aryl, -heteroaryl, —$(CH_2)_x$-heteroaryl, —O—$(CH_2)_x CH(OH)CH_2(OH)$, —$(CH_2)_x$—OH, or —C(O)—OH;

[0061] m is an integer from 1 to 3;

[0062] n is an integer selected from 1 to 3;

[0063] x is 0 or an integer from 1 to 6; or

a pharmaceutically salt thereof.

[0064] In another aspect, the present invention relates to a compound of the present invention as defined above (i.e., compounds of Structural Formulas (I) to (VI), respectively corresponding analogs (i.e., with hydrogen substitution at the R^2 position) and throughout the instant application, where it is provided that:

[0065] when n=1, m≠1; and

[0066] when n=3, m≠3.

[0067] In another aspect, the present invention relates to a compound of the present invention, where R^2 is C(O)—NR_bR_c; wherein R_b and R_c are as defined above and throughout the present application.

[0068] In another aspect, the present invention relates to a compound of Formulas (I) to (VI), where:

[0069] m is 1;

[0070] n is 2 or 3; and

[0071] R^4 is hydrogen.

[0072] In another aspect, the present invention relates to a compound of Formula (I), where:

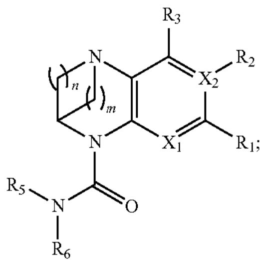
[0073] m is 1;

[0074] n is 2 or 3; and

[0075] R^4 is —$C(O)NR_bR_c$, wherein each R_b and R_c is as defined above.

[0076] In another aspect, the present invention relates to a compound of Formula (III):

(III)



where:

[0077] X_1 or X_2 independently is selected from —N or —C;

[0078] where:

[0079] when X_2 is —N, R_2 is non-existent; or

[0080] when X_2 is —C, R_2 is as defined above;

[0081] R^1 is hydrogen, halogen, —CN, carbocyclyl, heterocyclyl, —N-substituted heterocyclyl, aryl, heteroaryl, —C(O)R_a or —C(O)—NR_bR_c;

[0082] R^2 is halogen, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, or —C(O)—NR_bR_c;

[0083] R^3 is hydrogen, halogen, -hydroxy, -straight or branched C_1-C_6 alkyl, or -straight or branched-C_1-C_6 haloalkyl;

[0084] each R^5 and R^6 independently is selected from hydrogen, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, —C_1-C_6cycloalkyl, —$(CH_2)_x C_1$-C_6cycloalkyl, heterocyclyl, —N-heterocyclyl, aryl, heteroaryl, or —$(CH_2)_x$heteroaryl, —$(CHR_g)_x$heteroaryl;

[0085] wherein:

[0086] each R^1, R^2, R^3, R^5 and R^6 as defined above optionally is further substituted with one or more substituents selected from hydrogen, halogen, —OH, —$(CH_2)_x$OH, —C≡N, —NR_dR_e, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, -straight or branched C_1-C_6 alkoxy, -straight or branched C_1-C_6 haloalkoxy, —O-straight or branched-C_1-C_6 haloalkyl, —C_1-C_6 cycloalkyl, —$(CH_2)_x$-cycloalkyl, heterocyclyl, aryl, -heteroaryl, —$(CH_2)_x$-heteroaryl, —O—$(CH_2)_x$CH(OH)CH_2(OH), or —C(O)OR_f;

[0087] each R_a, R_b, R_c, R_d, R_e, R_f or R_g as defined above independently is selected from hydrogen, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, —C_1-C_6-cycloalkyl, —$(CH_2)_x C_1$-C_6-cycloalkyl, heterocyclyl, —N— heterocyclyl, aryl, heteroaryl, or —$(CH_2)_x$heteroaryl;

[0088] where:

[0089] each R_a, R_b, R_c R_d, R_e, R_f or R_g as defined above optionally is further substituted with one or more substituents selected from hydrogen, halogen, —OH, —$(CH_2)_x$OH, —C≡N, NR_hR_j, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, -straight or branched C_1-C_6 alkoxy, -straight or branched-C_1-C_6 haloalkoxy, —C_1-C_6 cycloalkyl, —$(CH_2)_x$-cycloalkyl, heterocyclyl, -heterocyclyl, —O-heterocyclyl, aryl, -heteroaryl, —$(CH_2)_x$-heteroaryl, —O—$(CH_2)_x$CH(OH)CH_2(OH), —$(CH_2)_x$—OH, or —C(O)OR_j;

[0090] where:

[0091] each Rh, Ri and Rj independently is selected from hydrogen, -straight or branched C_1-C_6 alkyl or -straight or branched-C_1-C_6 haloalkyl;

[0092] m is an integer from 1 to 3;

[0093] n is an integer selected from 2 to 3;

[0094] x is 0 or an integer from 1 to 6; or

a pharmaceutically salt thereof.

[0095] In another aspect, the present invention relates to a compound of the present invention, where n is 2 or 3 and m is 1.

[0096] In another aspect, the present invention relates to a compound of the present invention of Formula (I), where:

[0097] m is 1;

[0098] n is 2; and

[0099] R^4 is —C(O)NR_bR_c, wherein R_b and R_e is as defined above.

[0100] In another aspect, the present invention relates to a compound of the present invention of Formula (I), where:

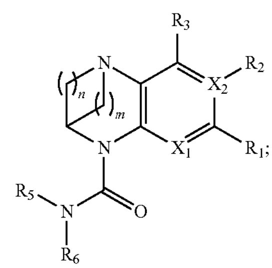
[0101] m is 1;

[0102] n is 3; and

[0103] R^4 is —C(O)NR_bR_c, wherein R_b and R_e is as defined above.

[0104] In another aspect, the present invention relates to a compound of Formula (IV):

(IV)



where:

[0105] X_1 or X_2 independently is —N;

[0106] where:

[0107] when X_2 is —N, R_2 is non-existent;

[0108] R^1 is hydrogen, halogen, —CN, carbocyclyl, heterocyclyl, —N-substituted heterocyclyl, aryl, heteroaryl, —C(O)R_a or —C(O)—NR_bR_c;

[0109] R^2 is hydrogen, halogen, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, or —C(O)—NR_bR_c;

[0110] R^3 is hydrogen, halogen, -hydroxy, -straight or branched C_1-C_6 alkyl, or -straight or branched-C_1-C_6 haloalkyl;

[0111] each R^5 and R^6 independently is selected from hydrogen, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, —C_1-C_6cycloalkyl, —$(CH_2)_x C_1$-C_6cycloalkyl, heterocyclyl, —N-heterocyclyl, aryl, heteroaryl, or —$(CH_2)_x$heteroaryl, —$(CHR_g)_x$heteroaryl;

[0112] where:

[0113] each R^1, R^2, R^3, R^5 and R^6 as defined above optionally is further substituted with one or more substituents selected from hydrogen, halogen, —OH, —$(CH_2)_x$OH, —C≡N, —NR_dR_e, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, -straight or branched C_1-C_6 alkoxy, -straight or branched C_1-C_6 haloalkoxy, —O-straight or branched-C_1-C_6 haloalkyl, —C_1-C_6 cycloalkyl, —$(CH_2)_x$-cycloalkyl, heterocyclyl, aryl, -heteroaryl, —$(CH_2)_x$-heteroaryl, —O—$(CH_2)_x$CH(OH)CH_2(OH), or —C(O)OR_f;

[0114] each R_a, R_b, R_c, R_d, R_e, R_f or R_g as defined above independently is selected from hydrogen, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, —C_1-C_6-cycloalkyl, —$(CH_2)_x C_1$-C_6-cycloalkyl, heterocyclyl, —N-heterocyclyl, aryl, heteroaryl, or —$(CH_2)_x$heteroaryl;

[0115] where:

[0116] each R_a, R_b, R_c R_d, R_e, R_f or R_g as defined above optionally is further substituted with one or more substituents selected from hydrogen, halogen, —OH, —$(CH_2)_x$OH, —C≡N, —NR_hR_i, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, -straight or branched C_1-C_6 alkoxy, -straight or branched-C_1-C_6 haloalkoxy, —C_1-C_6 cycloalkyl, —$(CH_2)_x$-cycloalkyl, heterocyclyl, -heterocyclyl, —O-heterocyclyl, aryl, -heteroaryl, —$(CH_2)_x$-heteroaryl, —O—$(CH_2)_x$CH(OH)CH_2(OH), —$(CH_2)_x$—OH, or —C(O)OR_j;

[0117] where:

[0118] each Rh, Ri and Rj independently is selected from hydrogen, -straight or branched C_1-C_6 alkyl or -straight or branched-C_1-C_6 haloalkyl;

[0119] m is an integer from 1 to 3;

[0120] n is an integer selected from 2 to 3;

[0121] x is 0 or an integer from 1 to 6; or

a pharmaceutically salt thereof.

[0122] In another aspect, the present invention relates to a compound of the present invention of Formula (I), where:

[0123] m is 1;

[0124] n is 2 or 3; and

[0125] R^1 is hydrogen, halogen, —CN, carbocyclyl, heterocyclyl, —N-substituted heterocyclyl, aryl, heteroaryl, —C(O)R_a or —C(O)—NR_bR_c;

[0126] R^4 is —C(O)NR_bR_c, wherein R_b and R_c is as defined above.

[0127] In another aspect, the present invention relates to a compound of the present invention of Formula (I), where:

[0128] m is 1;

[0129] n is 2; and

[0130] R^1 is hydrogen, halogen, —CN, carbocyclyl, heterocyclyl, —N-substituted heterocyclyl, aryl, heteroaryl, —C(O)R_a or —C(O)—NR_bR_c;

[0131] R^4 is —C(O)NR_bR_c, wherein R_b and R_c is as defined above in claim **1**.

[0132] In another aspect, the present invention relates to a compound of the present invention of Formula (I), where:

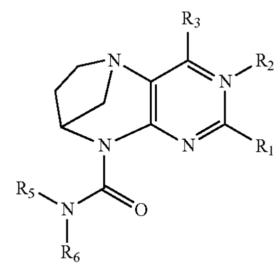
[0133] m is 1;

[0134] n is 3; and

[0135] R^4 is —C(O)NR_bR_c, wherein R_b and R_c is as defined above in claim **1**.

[0136] In another aspect, the present invention relates to a compound of Formula (V):

(V)



where:

[0137] R^1 is hydrogen, halogen, —CN, carbocyclyl, heterocyclyl, —N-substituted heterocyclyl, aryl, heteroaryl, —C(O)R_a or —C(O)—NR_bR_c;

[0138] R^2 is hydrogen, halogen, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, or —C(O)—NR_bR_c;

[0139] R^3 is hydrogen, halogen, -hydroxy, -straight or branched C_1-C_6 alkyl, or -straight or branched-C_1-C_6 haloalkyl;

[0140] each R^5 and R^6 independently is selected from hydrogen, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, —C_1-C_6cycloalkyl, —$(CH_2)_x C_1$-C_6cycloalkyl, heterocyclyl, —N-heterocyclyl, aryl, heteroaryl, or —$(CH_2)_x$heteroaryl, —$(CHR_g)_x$heteroaryl;

[0141] where:

[0142] each R^1, R^2, R^3, R^5 and R^6 as defined above optionally is further substituted with one or more substituents selected from hydrogen, halogen, —OH, —$(CH_2)_x$OH, —C≡N, —NR_dR_e, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, -straight or branched C_1-C_6 alkoxy, -straight or branched C_1-C_6 haloalkoxy, —O-straight or branched-C_1-C_6 haloalkyl, —C_1-C_6 cycloalkyl, —$(CH_2)_x$-cycloalkyl, heterocyclyl, aryl, -heteroaryl, —$(CH_2)_x$-heteroaryl, —O—$(CH_2)_x$CH(OH)CH_2(OH), or —C(O)OR_f;

[0143] each R_a, R_b, R_c, R_d, R_e, R_f or R_g as defined above independently is selected from hydrogen, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, —C_1-C_6-cycloalkyl, —$(CH_2)_x C_1$-C_6-cycloalkyl, heterocyclyl, —N-heterocyclyl, aryl, heteroaryl, or —$(CH_2)_x$heteroaryl;

[0144] where:

[0145] each R_a, R_b, R_c, R_d, R_e, R_f or R_g as defined above optionally is further substituted with one or more substituents selected from hydrogen, halogen, —OH, —$(CH_2)_x$OH, —C≡N, —NR_hR_i, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, -straight or branched C_1-C_6 alkoxy, -straight or branched-C_1-C_6 haloalkoxy, —C_1-C_6 cycloalkyl, —$(CH_2)_x$—cycloalkyl, heterocyclyl, -heterocyclyl, —O-heterocyclyl, aryl, -heteroaryl, —$(CH_2)_x$-heteroaryl, —O—$(CH_2)_x$CH(OH)CH_2(OH), —$(CH_2)_x$—OH, or —C(O)OR_j;

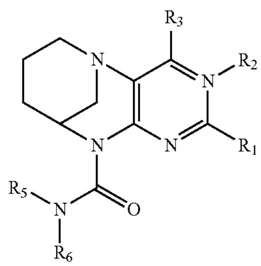
[0146] where:

[0147] each Rh, Ri and Rj independently is selected from hydrogen, -straight or branched C_1-C_6 alkyl or -straight or branched-C_1-C_6 haloalkyl;

[0148] x is 0 or an integer from 1 to 6; or
a pharmaceutically salt thereof;

[0149] In another aspect, the present invention relates to a compound of Formula (VI):

(VI)



wherein:

[0150] R^1 is hydrogen, halogen, —CN, carbocyclyl, heterocyclyl, —N-substituted heterocyclyl, aryl, heteroaryl, —C(O)R_a or —C(O)—NR_bR_c;

[0151] R^2 is hydrogen, halogen, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, or —C(O)—NR_bR_c;

[0152] R^3 is hydrogen, halogen, -hydroxy, -straight or branched C_1-C_6 alkyl, or -straight or branched-C_1-C_6 haloalkyl;

[0153] each R^5 and R^6 independently is selected from hydrogen, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, —C_1-C_6cycloalkyl, —$(CH_2)_x$$C_1$-$C_6$cycloalkyl, heterocyclyl, —N-heterocyclyl, aryl, heteroaryl, $(CH_2)_x$heteroaryl, or —$(CHR_g)_x$heteroaryl;

[0154] wherein:

[0155] each R^1, R^2, R^3, R^5 and R^6 as defined above optionally is further substituted with one or more substituents selected from hydrogen, halogen, —OH, —$(CH_2)_x$OH, —C≡N, —NR_dR_e, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, -straight or branched C_1-C_6 alkoxy, -straight or branched C_1-C_6 haloalkoxy, —O-straight or branched-C_1-C_6 haloalkyl, —C_1-C_6 cycloalkyl, —$(CH_2)_x$— cycloalkyl, heterocyclyl, aryl, -heteroaryl, —$(CH_2)_x$-heteroaryl, —O—$(CH_2)_x$CH(OH)CH_2(OH), or —C(O)OR_f;

[0156] each R_a, R_b, R_c, R_d, R_e, R_f or R_g as defined above independently is selected from hydrogen, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, —C_1-C_6-cycloalkyl, —$(CH_2)_x$$C_1$-$C_6$-cycloalkyl, heterocyclyl, —N-heterocyclyl, aryl, heteroaryl, or —$(CH_2)_x$heteroaryl;

[0157] wherein:

[0158] each R_a, R_b, R_c, R_d, R_e, R_f or R_g as defined above optionally is further substituted with one or more substituents selected from hydrogen, halogen, —OH, —$(CH_2)_x$OH, —C≡N, —NR_hR_i, -straight or branched C_1-C_6 alkyl, -straight or branched-C_1-C_6 haloalkyl, -straight or branched C_1-C_6 alkoxy, -straight or branched-C_1-C_6 haloalkoxy, —C_1-C_6 cycloalkyl, —$(CH_2)_x$— cycloalkyl, heterocyclyl, -heterocyclyl, —O-heterocyclyl, aryl, -heteroaryl, —$(CH_2)_x$-heteroaryl, —O—$(CH_2)_x$CH(OH)CH_2(OH), —$(CH_2)_x$—OH, or —C(O)OR_j;

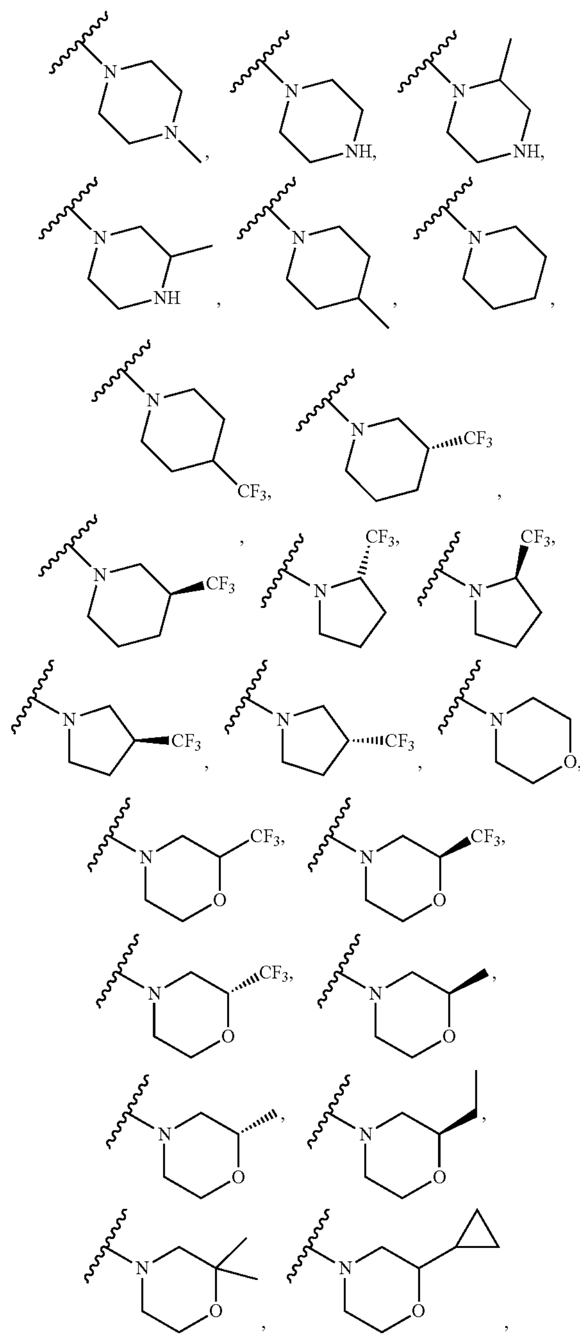
[0159] wherein:

[0160] each R_h, R_i and R_j independently is selected from hydrogen, -straight or branched C_1-C_6 alkyl or -straight or branched-C_1-C_6 haloalkyl;

[0161] x is 0 or an integer from 1 to 6; or

a pharmaceutically salt thereof;

[0162] In another aspect, the present invention relates to compounds of Formulas (I) to (IV), respectively, wherein R^1 is selected from:



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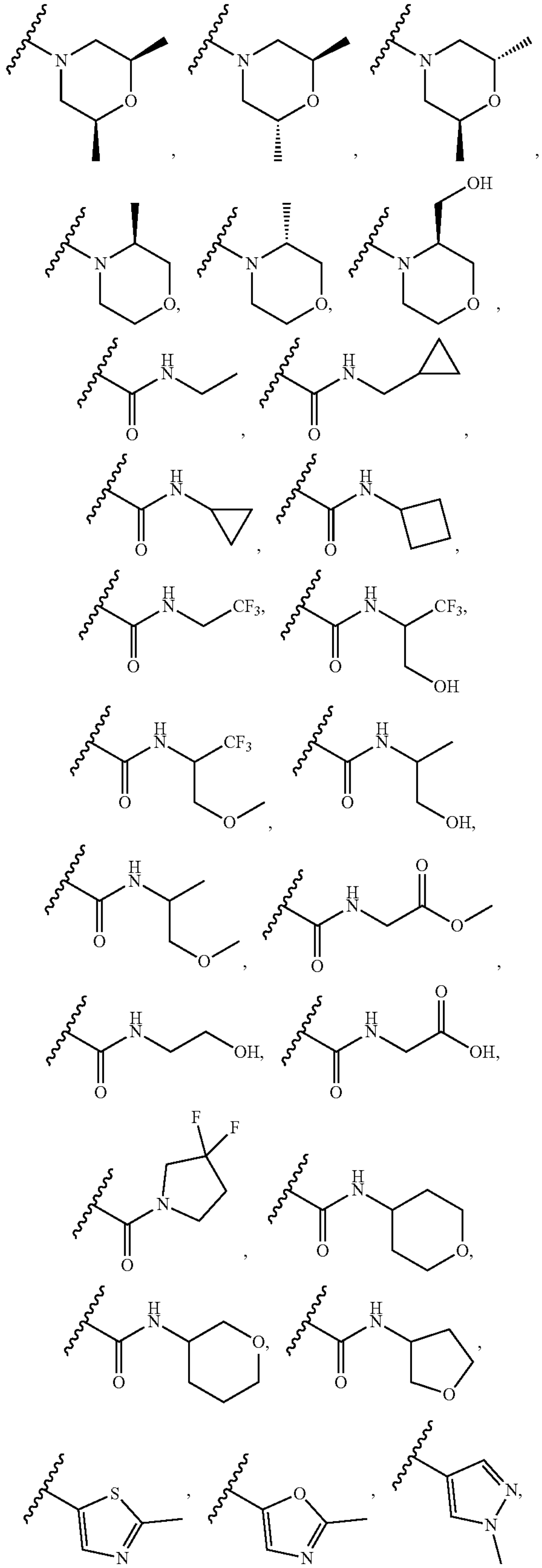

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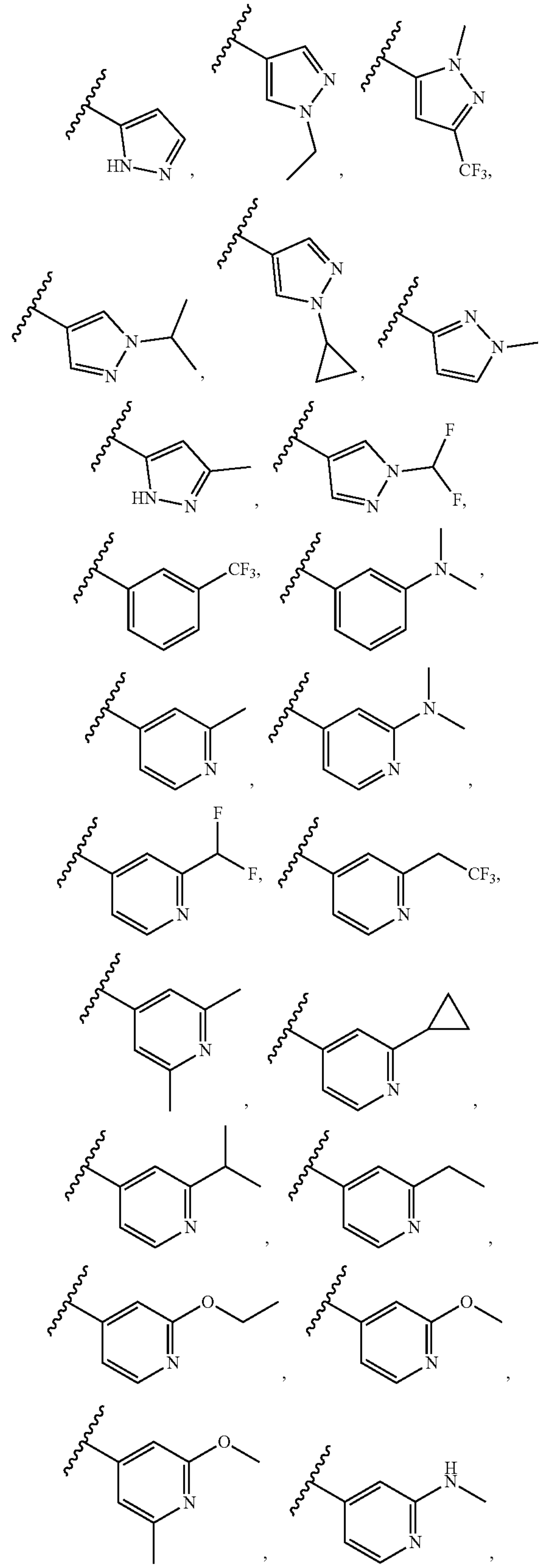

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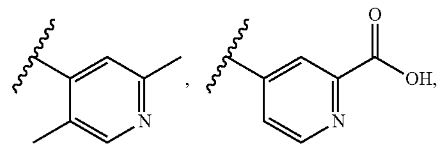
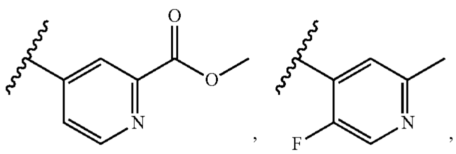
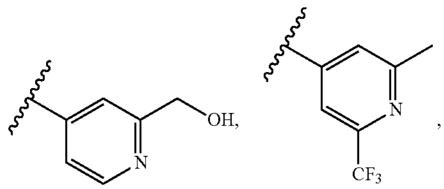
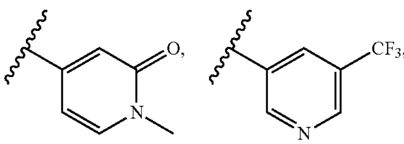
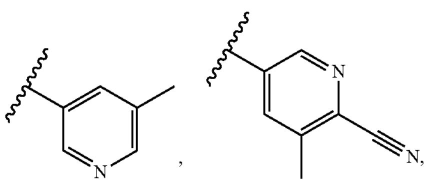
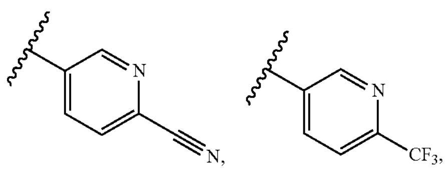
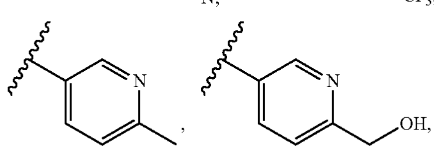
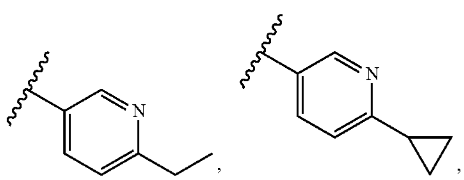
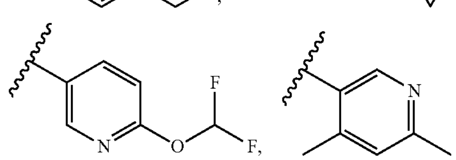
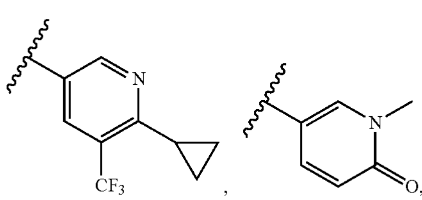

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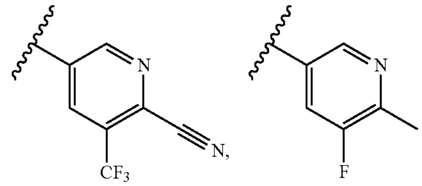
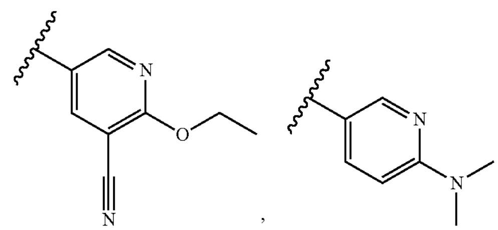
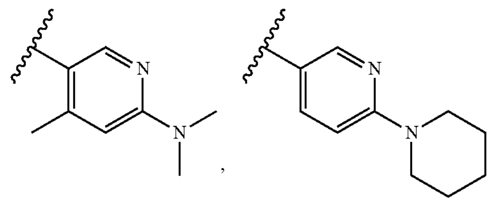
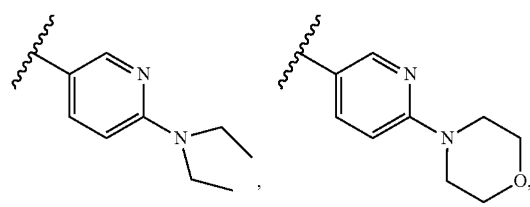
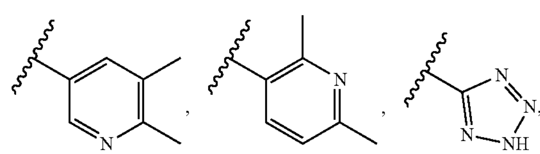
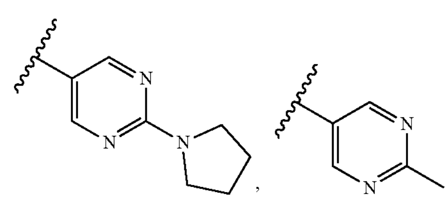
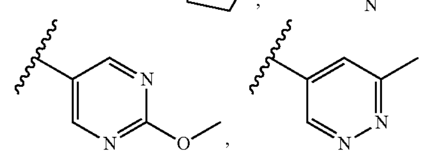

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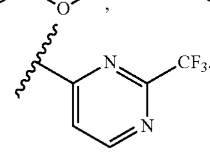
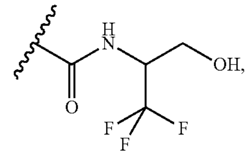
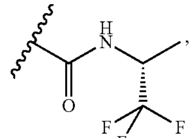
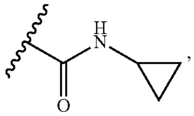
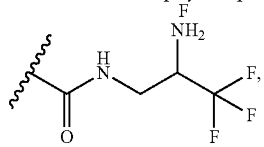
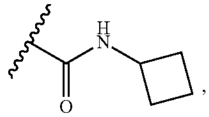
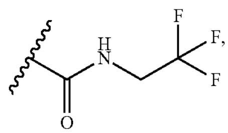
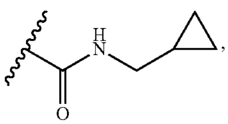
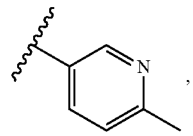
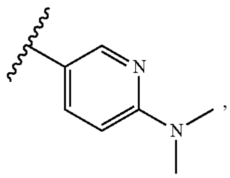
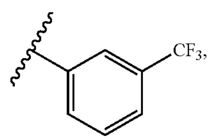
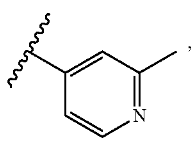
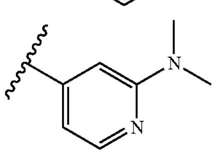
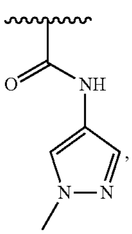
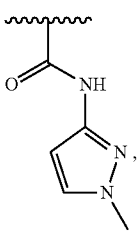
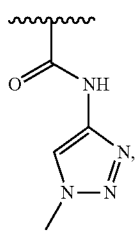
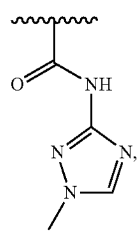
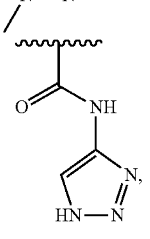
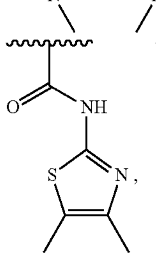
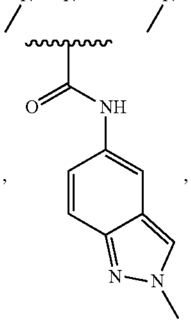


[0163] In another aspect, the present invention relates to compounds of Formulas (I) to (VI), respectively, wherein R^1 is selected from:

[0164] In another aspect, the present invention relates to compound(s) of Formulas (I) to (VI), respectively, where R^4 is selected from:

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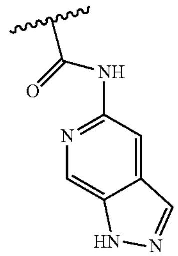
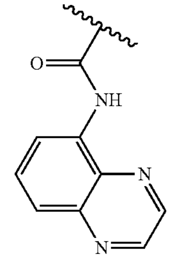
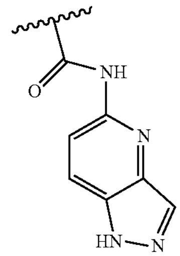
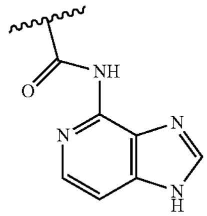
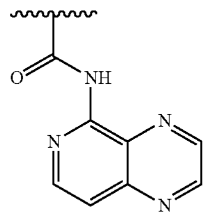
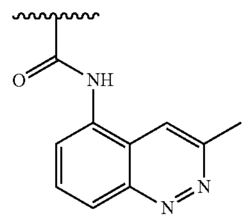
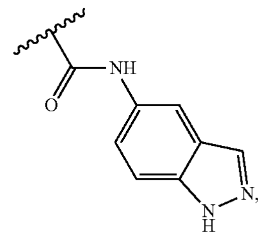
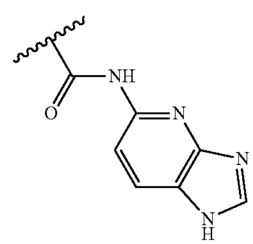
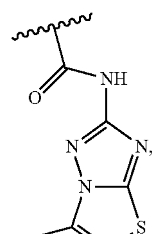
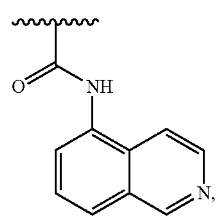
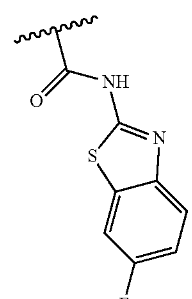
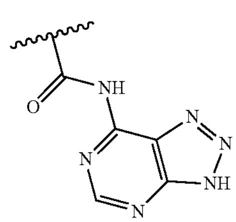
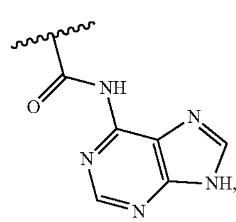

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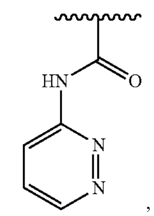
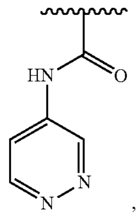
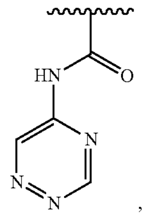
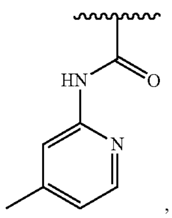
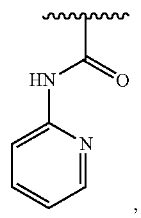
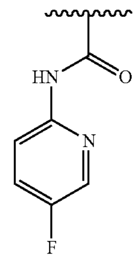
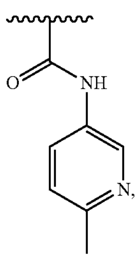
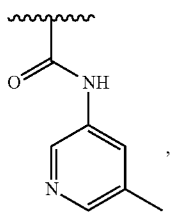
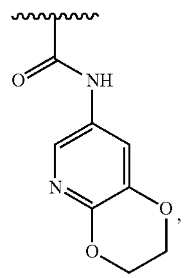
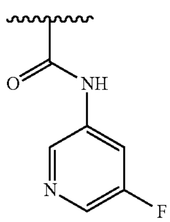
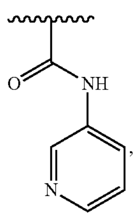
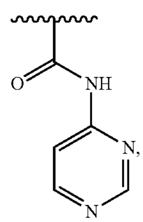
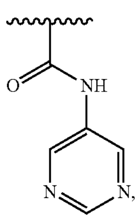
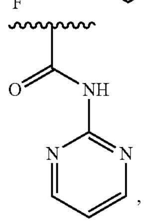
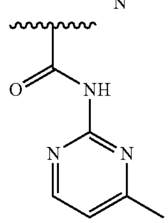
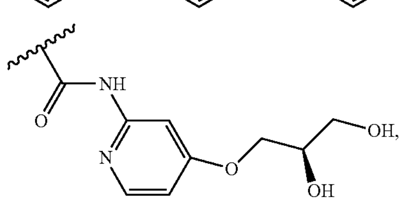
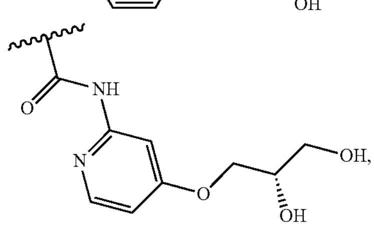

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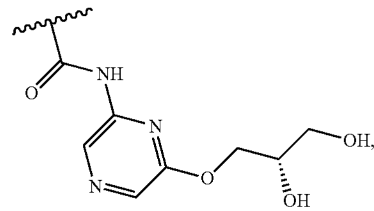
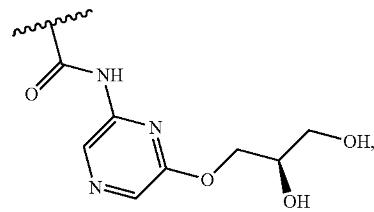
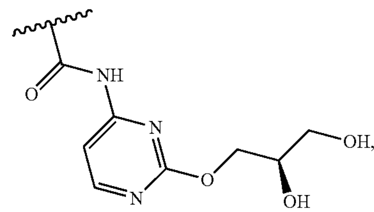
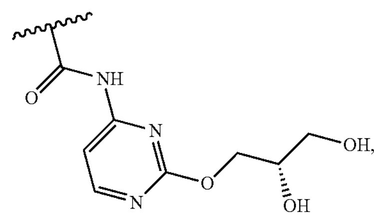
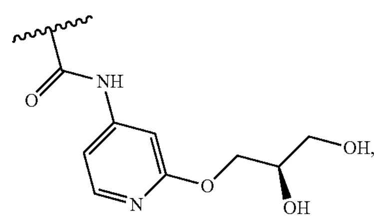
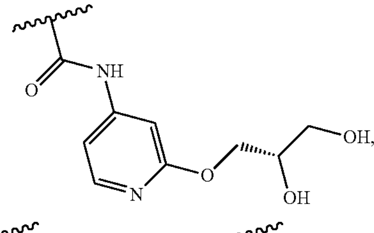
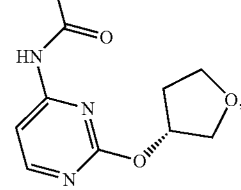
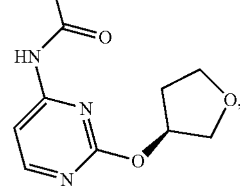

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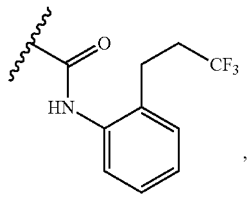
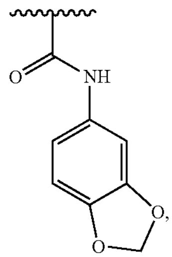
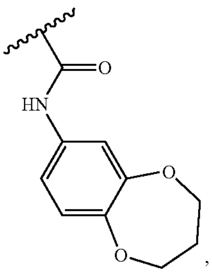
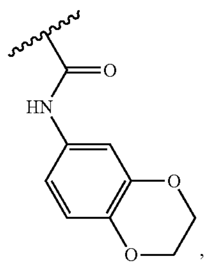
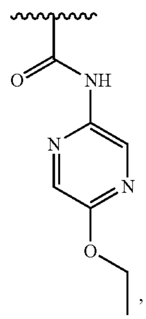
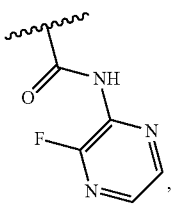
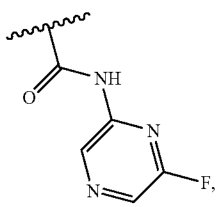
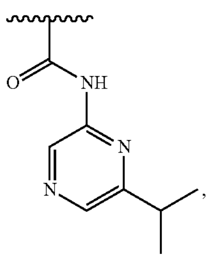
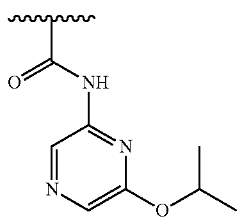
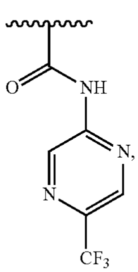
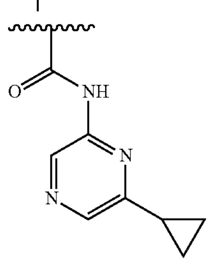
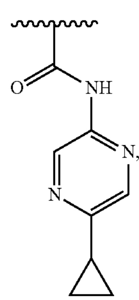
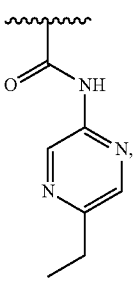
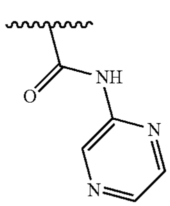
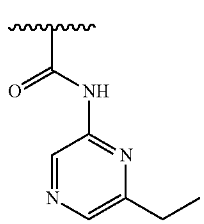

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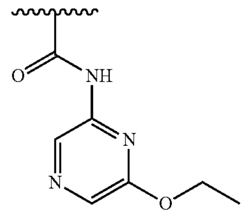
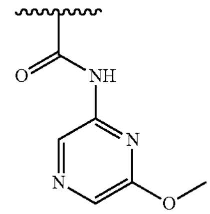
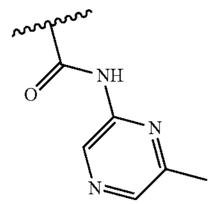
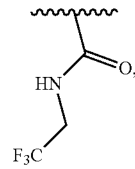
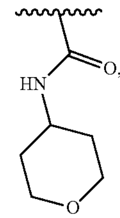
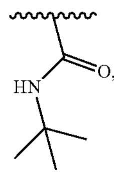
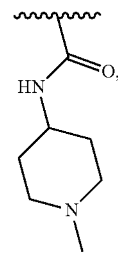
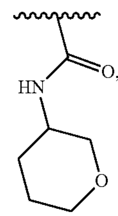
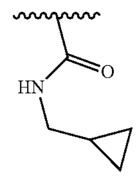
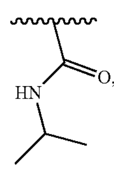
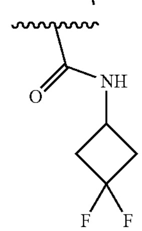
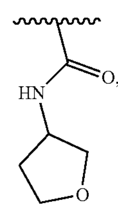
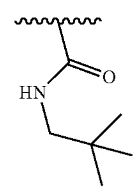
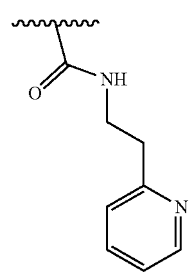
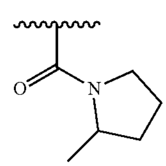
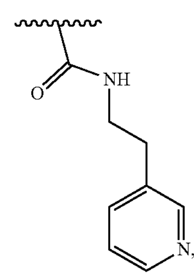
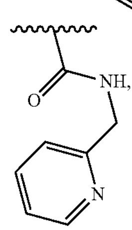
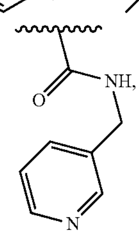
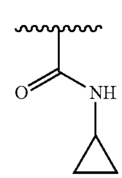
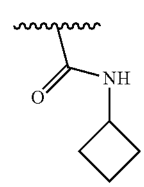
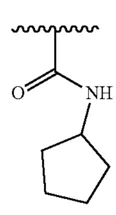
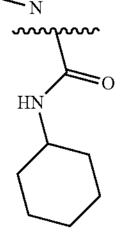
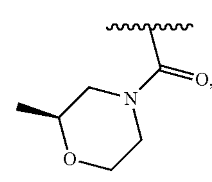

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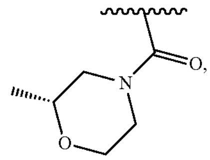
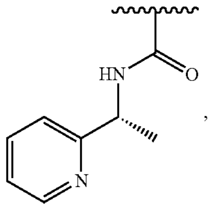
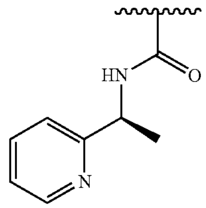
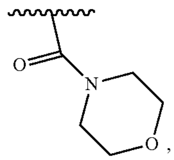
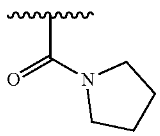
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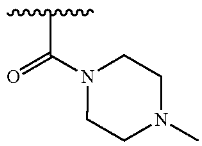
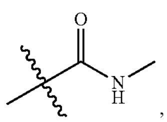
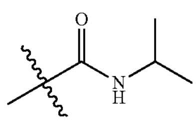
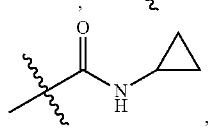
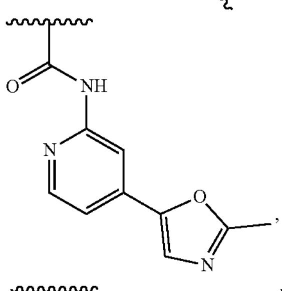
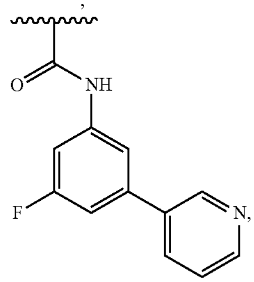
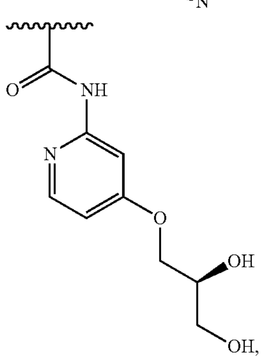
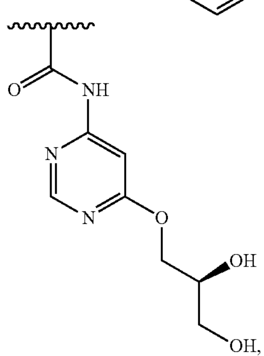


[0165] In another aspect, the present invention relates to compound(s) of Formulas (I) to (VI), respectively, where R^4 is selected from:

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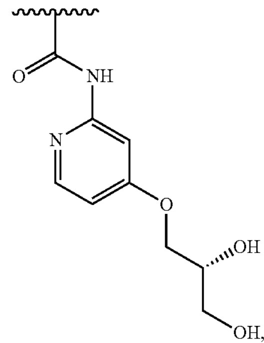
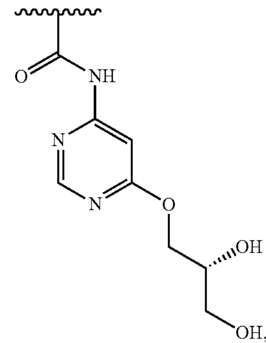
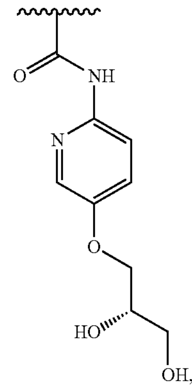
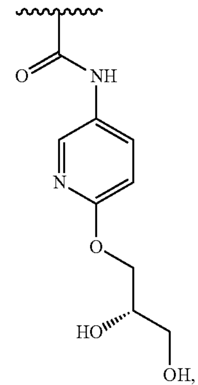
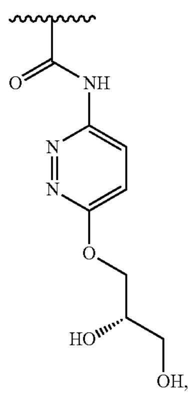
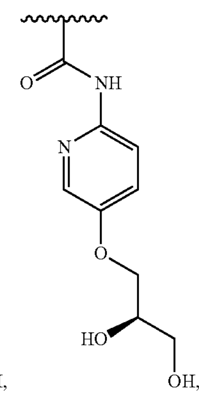
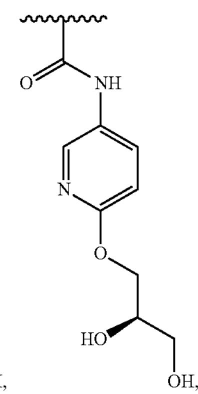
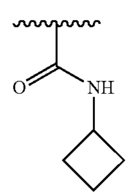
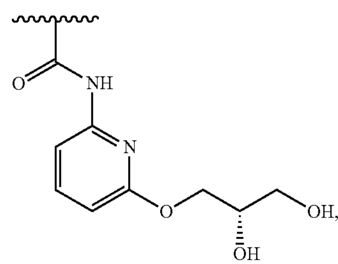
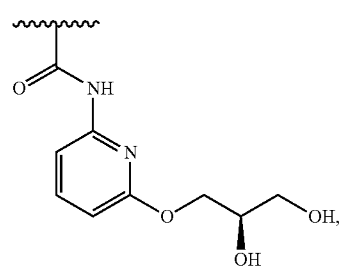
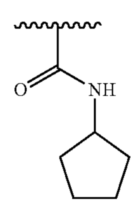

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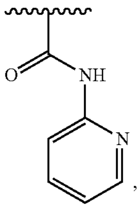
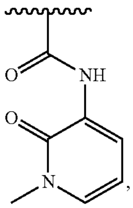
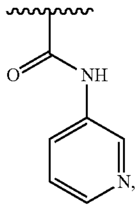
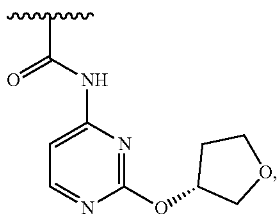
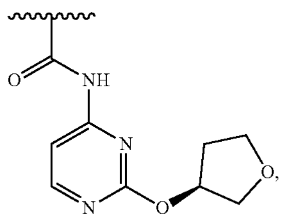
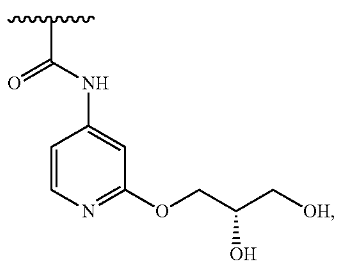
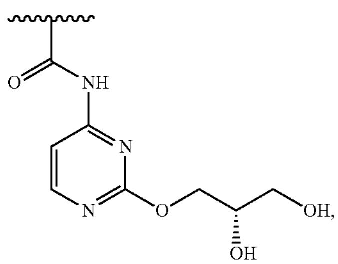
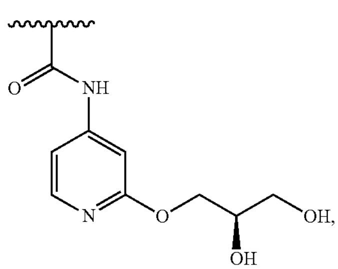
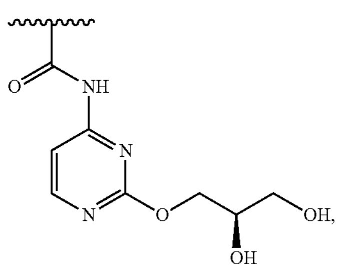

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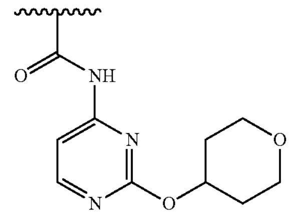
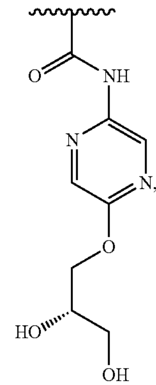
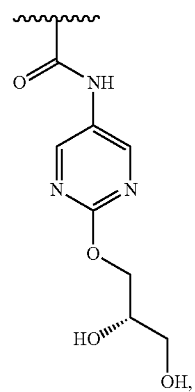
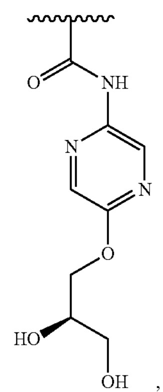
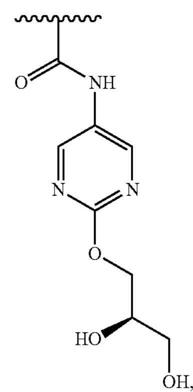
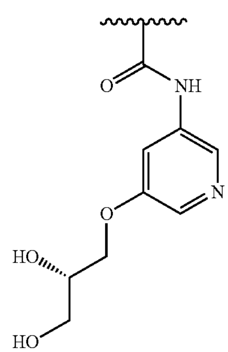
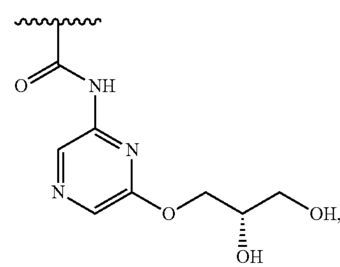
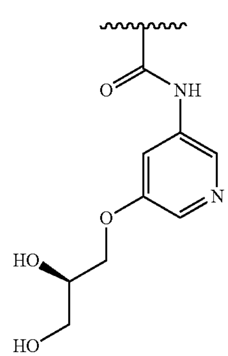
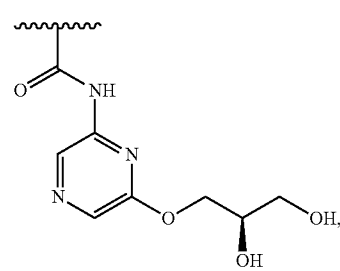

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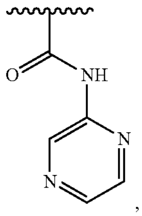

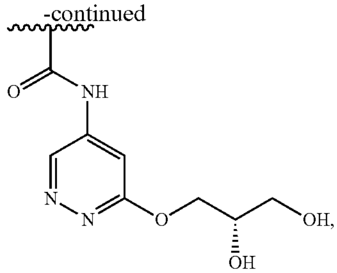

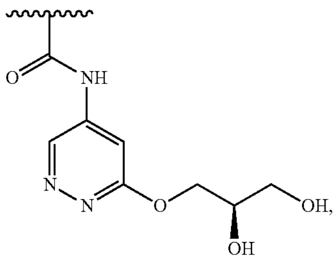

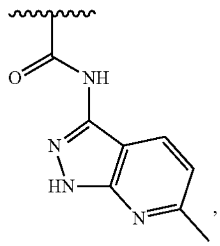

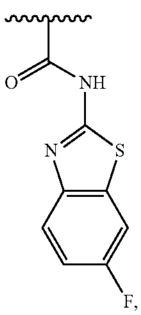

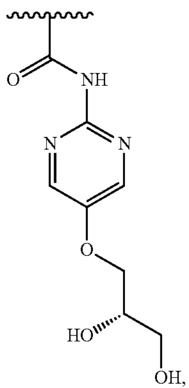

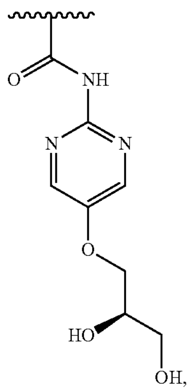

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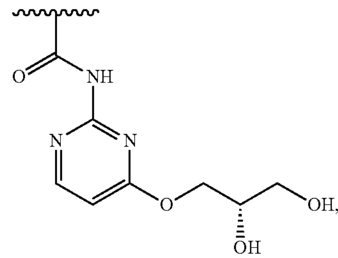
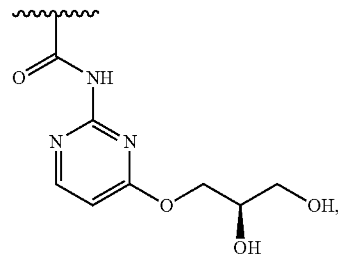
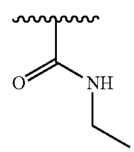
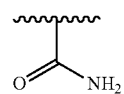








[0166] In another aspect, the present invention relates to a compound which is as defined in Table 1 of the instant specification starting at page 353:

[0167] In another aspect, the present invention relates to a compound which is a corresponding analog or derivative of the present invention s (i.e., with hydrogen substitution at the R^2 position):

Chart 5 - 2 Bridge Carbon Unit Pyrimidine Compounds

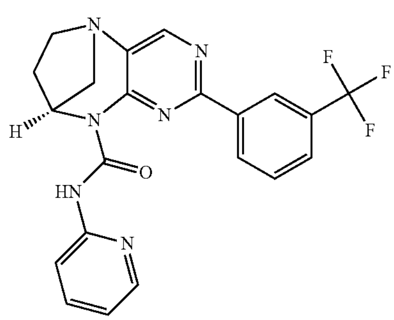
Structure	Chemical Name: Generated by ChemAxon
	(9S)-N-(pyridin-2-yl)-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide

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Chart 5 - 2 Bridge Carbon Unit Pyrimidine Compounds

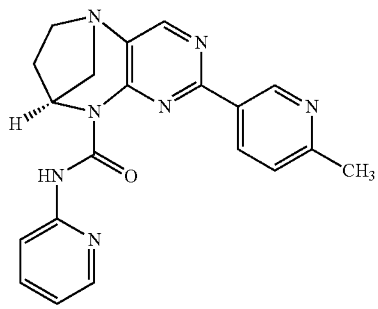
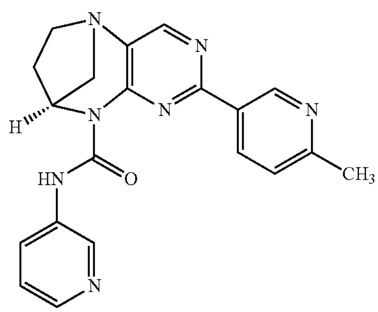
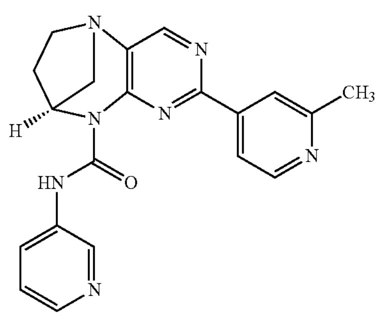
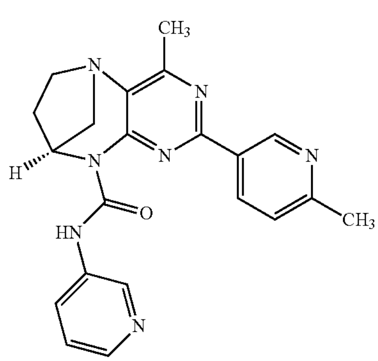
Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-(6-methylpyridin-3-yl)-N-(pyridin-2-yl)-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(6-methylpyridin-3-yl)-N-(pyridin-3-yl)-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-3-methyl-5-(6-methylpyridin-3-yl)-N-(pyridin-3-yl)-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide

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Chart 5 - 2 Bridge Carbon Unit Pyrimidine Compounds

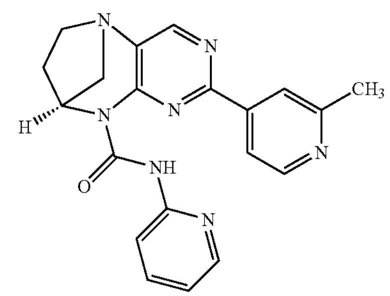
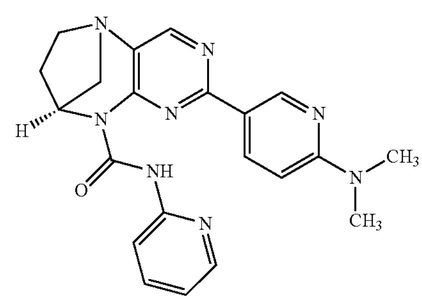
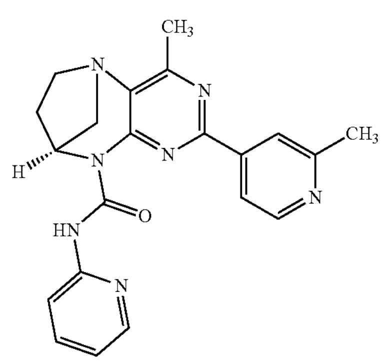
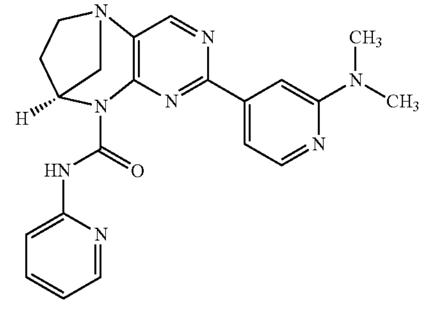
Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-(2-methylpyridin-4-yl)-N-(pyridin-2-yl)-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-[6-(dimethylamino)pyridin-3-yl]-N-(pyridin-2-yl)-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-3-methyl-5-(2-methylpyridin-4-yl)-N-(pyridin-2-yl)-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-5-[2-(dimethylamino)pyridin-4-yl]-N-(pyridin-2-yl)-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

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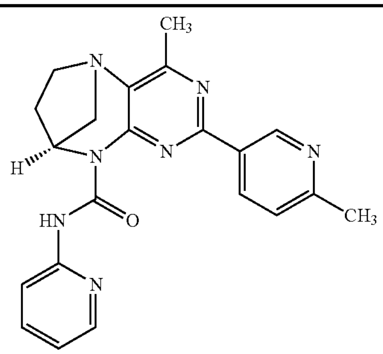
Chart 5 - 2 Bridge Carbon Unit Pyrimidine Compounds

Structure	Chemical Name: Generated by ChemAxon
	(9S)-3-methyl-5-(6-methylpyridin-3-yl)-N-(pyridin-2-yl)-1,4,6,8-tetraazatricyclo[7.2.1.$0^{2,7}$]dodeca-2,4,6-triene-8-carboxamide

Terms and Definitions

Section 1

[0168] Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including cis- and trans-isomers, (R)- and (S)-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

[0169] The compounds and salts thereof described herein can also be present as the corresponding hydrates (e.g., hemihydrate, monohydrate, dihydrate, trihydrate, tetrahydrate) or solvates. Suitable solvents for preparation of solvates and hydrates can generally be selected by a skilled artisan.

[0170] The compounds and salts thereof can be present in amorphous or crystalline (including co-crystalline and polymorph) forms.

[0171] Sirtuin-modulating compounds of the invention advantageously modulate the level and/or activity of a sirtuin protein, particularly the deacetylase activity of the sirtuin protein.

[0172] Separately or in addition to the above properties, certain sirtuin-modulating compounds of the invention do not substantially have one or more of the following activities: inhibition of PI3-kinase, inhibition of aldoreductase, inhibition of tyrosine kinase, transactivation of EGFR tyrosine kinase, coronary dilation, or spasmolytic activity, at concentrations of the compound that are effective for modulating the deacetylation activity of a sirtuin protein (e.g., such as a SIRT1 and/or a SIRT3 protein).

[0173] An "alkyl" group or "alkane" is a straight chained or branched non-aromatic hydrocarbon which is completely saturated. Typically, a straight chained or branched alkyl group has from 1 to about 20 carbon atoms, preferably from 1 to about 10 unless otherwise defined. Examples of straight chained and branched alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, pentyl, hexyl, pentyl and octyl. A C_1-C_4 straight chained or branched alkyl group is also referred to as a "lower alkyl" group.

[0174] In any of the preceding embodiments, a C_1-C_4 alkoxy-substituted group may include one or more alkoxy substituents such as one, two or three methoxy groups or a methoxy group and an ethoxy group, for example. Exemplary C_1-C_4 alkoxy substituents include methoxy, ethoxy, isopropoxy, and tert-butoxy.

[0175] In any of the preceding embodiments, a hydroxy-substituted group may include one or more hydroxy substituents, such as two or three hydroxy groups.

[0176] A "halogen" refers to F, Cl, Br or I.

[0177] A "halogen-substitution" or "halo" substitution designates replacement of one or more hydrogens with F, Cl, Br or I.

[0178] In one aspect, the term haloalkyl is defined as any alkyl radical having one or more hydrogen atoms replaced by a halogen atom. In any of the preceding embodiments, a "halo-substituted" group includes from one halo substituent up to perhalo substitution. Exemplary halo-substituted C_1-C_4 alkyl includes CFH_2, $CClH_2$, $CBrH_2$, CF_2H, CCl_2H, CBr_2H, CF_3, CCl_3, CBr_3, CH_2CH_2F, CH_2CH_2Cl, CH_2CH_2Br, CH_2CHF_2, $CHFCH_3$, $CHClCH_3$, $CHBrCH_3$, CF_2CHF_2, CF_2CHCl_2, CF_2CHBr_2, $CH(CF_3)_2$, and $C(CF_3)_3$. Perhalo-substituted C_1-C_4 alkyl, for example, includes CF_3, CCl_3, CBr_3, CF_2CF_3, CCl_2CF_3 and CBr_2CF_3.

[0179] The terms "alkenyl" ("alkene") and "alkynyl" ("alkyne") refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyl groups described above, but that contain at least one double or triple bond respectively.

[0180] In any of the preceding embodiments, a "carbocycle" group may refer to a monocyclic carbocycle embodiment and/or a polycyclic carbocycle embodiment, such as a fused, bridged or bicyclic carbocycle embodiment. "Carbocycle" groups of the invention may further refer to an aromatic carbocycle embodiment and/or a non-aromatic carbocycle embodiment, or, in the case of polycyclic embodiments, a carbocycle having both one or more aromatic rings and/or one or more non-aromatic rings. Polycyclic carbocycle embodiments may be a bicyclic ring, a fused ring or a bridged bicycle. Non-limiting exemplary carbocycles include phenyl, cyclohexane, cyclopentane, or cyclohexene, amantadine, cyclopentane, cyclohexane, bicyclo[2.2.1]heptane, 1,5-cyclooctadiene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]oct-3-ene, naphthalene, adamantane, decalin, naphthalene, 1,2,3,4-tetrahydronaphthalene, norbornane, decalin, spiropentane, memantine, biperiden, rimantadine, camphor, cholesterol, 4-phenylcyclcohexanol, bicyclo[4.2.0]octane, memantine and 4,5,6,7-tetrahydro-1H-indene and bicyclo[4.1.0]hept-3-ene.

[0181] In any of the preceding embodiments, a "heterocycle" group may refer to a monocyclic heterocycle embodiment and/or a polycyclic heterocyclic embodiment, such as a fused, bridged or bicyclic heterocycle embodiment. "Heterocycle" groups of the invention may further refer to an aromatic heterocycle embodiment and/or a non-aromatic heterocycle embodiment, or, in the case of polycyclic embodiments, a heterocycle having both one or more aromatic rings and/or one or more non-aromatic rings. Polycyclic heterocycle embodiments may be a bicyclic ring, a fused ring or a bridged bicycle. Non-limiting exemplary heterocycles include pyridyl, pyrrolidine, piperidine, piperazine, pyrrolidine, morpholine, pyrimidine, benzofuran, indole, quinoline, lactones, lactams, benzodiazepine, indole, quinoline, purine, adenine, guanine, 4,5,6,7-tetrahydrobenzo[d]thiazole, hexamine and methenamine.

[0182] "Alkenyl" refers to an unsaturated hydrocarbon chain having the specified number of member carbon atoms and having one or more carbon-carbon double bonds within the chain. For example, C_2-C_6 alkenyl refers to an alkenyl group having from 2 to 6 member carbon atoms. In certain embodiments, alkenyl groups have one carbon-carbon double bond within the chain. In other embodiments, alkenyl groups have more than one carbon-carbon double bond within the chain. Alkenyl groups may be optionally substituted with one or more substituents as defined herein. Alkenyl groups may be straight or branched. Representative branched alkenyl groups have one, two, or three branches. Alkenyl includes ethylenyl, propenyl, butenyl, pentenyl, and hexenyl.

[0183] "Alkoxy" refers to an alkyl moiety attached through an oxygen bridge (i.e. a —O—C_1-C_6 alkyl group wherein C_1-C_6 is defined herein). Examples of such groups include methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy.

[0184] "Alkynyl" refers to an unsaturated hydrocarbon chain having the specified number of member carbon atoms and having one or more carbon-carbon triple bonds within the chain. For example, C_2-C_6 alkynyl refers to an alkynyl group having from 2 to 6 member atoms. In certain embodiments alkynyl groups have one carbon-carbon triple bond within the chain. In other embodiments, alkynyl groups have more than one carbon-carbon triple bond within the chain. For the sake of clarity, unsaturated hydrocarbon chains having one or more carbon-carbon triple bond within the chain and one or more carbon-carbon double bond within the chain are referred to as alkynyl groups. Alkynyl groups may be optionally substituted with one or more substituents as defined herein. Representative branched alkynyl groups have one, two, or three branches. Alkynyl includes ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

[0185] The term "aromatic carbocycle" refers to an aromatic hydrocarbon ring system containing at least one aromatic ring. The ring may be fused or otherwise attached to other aromatic carbocyclic rings or non-aromatic carbocyclic rings. Examples of aromatic carbocycle groups include carbocyclic aromatic groups such as phenyl, naphthyl, and anthracyl.

[0186] "Azabicyclo" refers to a bicyclic molecule that contains a nitrogen atom in the ring skeleton. The two rings of the bicycle may be fused at two mutually bonded atoms, e.g., indole, across a sequence of atoms, e.g., azabicyclo[2.2.1]heptane, or joined at a single atom, e.g., spirocycle.

[0187] "Bicycle" or "bicyclic" refers to a two-ring system in which one, two or three or more atoms are shared between the two rings. Bicycle includes fused bicycles in which two adjacent atoms are shared by each of the two rings, e.g., decalin, indole. Bicycle also includes spiro bicycles in which two rings share a single atom, e.g., spiro[2.2]pentane, 1-oxa-6-azaspiro[3.4]octane. Bicycle further includes bridged bicycles in which at least three atoms are shared between two rings, e.g., norbornane.

[0188] "Bridged bicycle" compounds are bicyclic ring systems in which at least three atoms are shared by both rings of the system, i.e., they include at least one bridge of one or more atoms connecting two bridgehead atoms. Bridged azabicyclo refers to a bridged bicyclic molecule that contains a nitrogen atom in at least one of the rings.

[0189] The term "Boc" refers to a tert-butyloxycarbonyl group (a common amine protecting group).

[0190] The terms "carbocycle", and "carbocyclic", as used herein, refers to a saturated or unsaturated ring in which each atom of the ring is carbon. The term carbocycle includes both aromatic carbocycles and non-aromatic carbocycles. Non-aromatic carbocycles include both cycloalkane rings, in which all carbon atoms are saturated, and cycloalkene rings, which contain at least one double bond. "Carbocycle" includes 5-7 membered monocyclic and 8-12 membered bicyclic rings. Each ring of a bicyclic carbocycle may be selected from non-aromatic and aromatic rings. Carbocycle includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term "fused carbocycle" refers to a bicyclic carbocycle in which each of the rings shares two adjacent atoms with the other ring. Each ring of a fused carbocycle may be selected from non-aromaticaromatic rings. In an exemplary embodiment, an aromatic ring, e.g., phenyl, may be fused to a non-aromatic or aromatic ring, e.g., cyclohexane, cyclopentane, or cyclohexene. Any combination of non-aromtatic and aromatic bicyclic rings, as valence permits, is included in the definition of carbocyclic. Exemplary "carbocycles" include cyclopentane, cyclohexane, bicyclo[2.2.1]heptane, 1,5-cyclooctadiene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]oct-3-ene, naphthalene and adamantane. Exemplary fused carbocycles include decalin, naphthalene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]octane, 4,5,6,7-tetrahydro-1H-indene and bicyclo[4.1.0]hept-3-ene. "Carbocycles" may be substituted at any one or more positions capable of bearing a hydrogen atom.

[0191] A "cycloalkyl" group is a cyclic hydrocarbon ring having the specified number of member carbon atoms which is completely saturated (non-aromatic). Typically, a cycloalkyl group has from 3 to about 10 carbon atoms, more typically 3 to 8 carbon atoms unless otherwise defined. Cycloalkyl groups are monocyclic ring systems. For example, C_3-C_6 cycloalkyl refers to a cycloalkyl group having from 3 to 6 member atoms. Cycloalkyl groups may be optionally substituted with one or more substituents as defined herein. Cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0192] A "cycloalkenyl" group is a cyclic hydrocarbon ring containing one or more double bonds within the ring. For example, C_3-C_6 cycloalkenyl refers to a cycloalkenyl group having from 3 to 6 member carbon atoms. In certain embodiments, cycloalkenyl groups have one carbon-carbon double bond within the ring. In other embodiments, cycloalkenyl groups have more than one carbon-carbon double bonds within the ring. Cycloalkenyl rings are not aromatic. Cycloalkenyl groups are monocyclic ring systems. Cycloalkenyl groups may be optionally substituted with one or more substituents as defined herein. Cycloalkenyl includes cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, and cyclohexadienyl.

[0193] "Aryl" refers to an aromatic hydrocarbon ring system. Aryl groups are monocyclic ring systems or bicyclic ring systems. Monocyclic aryl ring refers to phenyl. Bicyclic aryl rings refer to napthyl and to rings wherein phenyl is fused to a cycloalkyl or cycloalkenyl ring having 5, 6, or 7 member carbon atoms. Aryl groups may be optionally substituted with one or more substituents as defined herein.

[0194] The term "heteroaryl" or "aromatic heterocycle" includes substituted or unsubstituted aromatic single ring structures, preferably 5- to 7-membered rings, more preferably 5- to 6-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The term "heteroaryl" also includes ring systems having one or two rings wherein at least one of the rings is heteroaromatic, e.g., the other cyclic rings can be cycloalkyl, cycloalkenyl, cycloalkynyl, aromatic carbocycle, heteroaryl, and/or heterocyclyl. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrazine, pyridazine, and pyrimidine.

[0195] The terms "heterocycle", and "heterocyclic", as used herein, refers to a non-aromatic or aromatic ring comprising one or more heteroatoms selected from, for example, N, O, B and S atoms, preferably N, O, or S. The term "heterocycle" includes both "aromatic heterocycles" and "non-aromatic heterocycles." Heterocycles include 4-7 membered monocyclic and 8-12 membered bicyclic rings. Heterocycle includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. Each ring of a bicyclic heterocycle may be selected from non-aromatic and aromatic rings. The term "fused heterocycle" refers to a bicyclic heterocycle in which each of the rings shares two adjacent atoms with the other ring. Each ring of a fused heterocycle may be selected from non-aromatic and aromatic rings. In an exemplary embodiment, an aromatic ring, e.g., pyridyl, may be fused to a non-aromatic or aromatic ring, e.g., cyclohexane, cyclopentane, pyrrolidine, 2,3-dihydrofuran or cyclohexene. "Heterocycle" groups include, for example, piperidine, piperazine, pyrrolidine, morpholine, pyrimidine, benzofuran, indole, quinoline, lactones, and lactams. Exemplary "fused heterocycles" include benzodiazepine, indole, quinoline, purine, and 4,5,6,7-tetrahydrobenzo[d]thiazole. "Heterocycles" may be substituted at any one or more positions capable of bearing a hydrogen atom.

[0196] "Monocyclic rings" include 5-7 membered aromatic carbocycle or heteroaryl, 3-7 membered cycloalkyl or cycloalkenyl, and 5-7 membered non-aromatic heterocyclyl. Exemplary monocyclic groups include substituted or unsubstituted heterocycles or carbocycles such as thiazolyl, oxazolyl, oxazinyl, thiazinyl, dithianyl, dioxanyl, isoxazolyl, isothiazolyl, triazolyl, furanyl, tetrahydrofuranyl, dihydrofuranyl, pyranyl, tetrazolyl, pyrazolyl, pyrazinyl, pyridazinyl, imidazolyl, pyridinyl, pyrrolyl, dihydropyrrolyl, pyrrolidinyl, piperidinyl, piperazinyl, pyrimidinyl, morpholinyl, tetrahydrothiophenyl, thiophenyl, cyclohexyl, cyclopentyl, cyclopropyl, cyclobutyl, cycloheptanyl, azetidinyl, oxetanyl, thiiranyl, oxiranyl, aziridinyl, and thiomorpholinyl.

[0197] "Member atoms" refers to the atom or atoms that form a chain or ring. Where more than one member atom is present in a chain and within a ring, each member atom is covalently bound to an adjacent member atom in the chain or ring. Atoms that make up a substituent group on a chain or ring are not member atoms in the chain or ring.

[0198] "Optionally substituted" indicates that a group, such as alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heteroaryl, may be unsubstituted, or the group may be substituted with one or more substituents as defined herein.

[0199] As used herein, "substituted" means substituting a hydrogen atom in a structure with an atom or molecule other than hydrogen. "Substituted" in reference to a group indicates that one or more hydrogen atoms attached to a member atom within the group is replaced with a substituent selected from the group of defined substituents. A substitutable atom such as a "substitutable nitrogen" is an atom that bears a hydrogen atom in at least one resonance form. The hydrogen atom may be substituted for another atom or group such as a CH_3 or an OH group. For example, the nitrogen in a piperidine molecule is substitutable if the nitrogen is bound to a hydrogen atom. If, for example, the nitrogen of a piperidine is bound to an atom other than hydrogen, the nitrogen is not substitutable. An atom that is not capable of bearing a hydrogen atom in any resonance form is not substitutable. It should be understood that the term "substituted" includes the implicit provision that such substitution be in accordance with the permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound (i.e. one that does not spontaneously undergo transformation such as by hydrolysis, rearrangement, cyclization, or elimination, and that is sufficiently robust to survive isolation from a reaction mixture). When it is stated that a group may contain one or more substituents, one or more (as appropriate) member atom within the group may be substituted. In addition, a single member atom within the group may be substituted with more than one substituent as long as such substitution is in accordance with the permitted valence of the atom. Suitable substituents are defined herein for each substituted or optionally substituted group.

[0200] Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. As used herein, the term "stable" refers to compounds that possess stability sufficient to allow manufacture and that maintain the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein.

Deutrated Compounds

[0201] The compounds disclosed herein also include partially and fully deuterated variants. In certain embodiments, deuterated variants may be used for kinetic studies. One of skill in the art can select the sites at which such deuterium atoms are present.

[0202] The invention also includes various deuterated forms of the compounds of Formulas (I) or pharmaceutically acceptable salts thereof. Each available hydrogen atom attached to a carbon atom may be independently replaced with a deuterium atom.

[0203] A person of ordinary skill in the art will know how to synthesize deuterated forms of the compounds of Formulas (I) to (II) of the present invention. For example, deuterated materials, such as alkyl groups may be prepared by conventional techniques (see for example: methyl-d_3-amine available from Aldrich Chemical Co., Milwaukee, Wis., Cat. No. 489,689-2).

Isotopes

[0204] The subject invention also includes isotopically-labeled compounds which are identical to those recited in Formulas (I) and (II) but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine, iodine and chlorine such as ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{123}I or ^{125}I.

[0205] Compounds of the present invention and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H or ^{14}C have been incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, ie. ^{3}H, and carbon-14, ie. ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. ^{11}C and ^{18}F isotopes are particularly useful in PET (positron emission tomography).

Purity

[0206] Because the compounds of the present invention are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions.

Salts

[0207] In certain embodiments, compounds according to Formula I or a pharmaceutically acceptable salt thereof may contain an acidic functional group. In certain other embodiments, compounds according to Formula I may contain a basic functional group. Thus, the skilled artisan will appreciate that salts of the compounds according to Formula I may be prepared. Indeed, in certain embodiments of the invention, salts of the compounds according to Formula I may be preferred over the respective free base or free acid because, for example, such salts may impart greater stability or solubility to the molecule thereby facilitating formulation into a dosage form.

[0208] Because of their potential use in medicine, the salts of the compounds of Formulas (I) are suitably pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse J. Pharm. Sci (1977) 66, pp 1-19.

[0209] Also included in the present invention are salts, particularly pharmaceutically acceptable salts, of the compounds described herein. The compounds of the present invention that possess a sufficiently acidic, a sufficiently basic, or both functional groups, can react with any of a number of inorganic bases, and inorganic and organic acids, to form a salt. Alternatively, compounds that are inherently charged, such as those with quaternary nitrogen, can form a salt with an appropriate counterion (e.g., a halide such as bromide, chloride, or fluoride, particularly bromide).

[0210] Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such salts include the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, gamma-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate, and the like.

[0211] Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, and the like. "Enantiomeric excess" or "ee" is the excess of one enantiomer over the other expressed as a percentage. As a result, since both enantiomers are present in equal amounts in a racemic mixture, the enantiomeric excess is zero (0% ee). However, if one enantiomer was enriched such that it constitutes 95% of the product, then the enantiomeric excess would be 90% ee (the amount of the enriched enantiomer, 95%, minus the amount of the other enantiomer, 5%).

[0212] "Enantiomerically enriched" refers to products whose enantiomeric excess is greater than zero. For example, enantiomerically enriched refers to products whose enantiomeric excess is greater than 50% ee, greater than 75% ee, or greater than 90% ee.

[0213] "Enantiomerically pure" refers to products whose enantiomeric excess is 99% ee or greater.

[0214] "Pharmaceutically acceptable" refers to those compounds, materials, compositions, and dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings or animals without excessive toxicity, irritation, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0215] The compounds according to Formula (I) or a pharmaceutically acceptable salt thereof, may contain one or more asymmetric centers (also referred to as a chiral center) and may, therefore, exist as individual enantiomers, diastereomers, or other stereoisomeric forms, or as mixtures thereof.

[0216] Chiral centers, such as chiral carbon atoms, may also be present in a substituent such as an alkyl group. Where the stereochemistry of a chiral center present in Formula I, or in any chemical structure illustrated herein, is not specified, the structure is intended to encompass all individual stereoisomers and all mixtures thereof.

[0217] Thus, compounds according to Formula (I) or pharmaceutically acceptable salts thereof, containing one or more chiral centers may be used as racemic mixtures, diastereomeric mixtures, enantiomerically enriched mixtures, diastereomerically enriched mixtures, or as enantiomerically and diastereomerically pure individual stereoisomers.

[0218] Individual stereoisomers of a compound according to Formula (I) or a pharmaceutically acceptable salt thereof which contain one or more asymmetric centers may be resolved by methods known to those skilled in the art. For example, such resolution may be carried out (1) by formation of diastereoisomeric salts, complexes or other derivatives; (2) by selective reaction with a stereoisomer-specific reagent, for example by enzymatic oxidation or reduction; or (3) by gas-liquid or liquid chromatography in a chiral environment, for example, on a chiral support such as silica with a bound chiral ligand or in the presence of a chiral solvent. The skilled artisan will appreciate that where the desired stereoisomer is converted into a diastereomeric salt, complex or derivative, a further step is required to liberate the desired form. Alternatively, specific stereoisomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation.

[0219] When a disclosed compound or its salt is named or depicted by structure, it is to be understood that the compound or salt, including solvates (particularly, hydrates) thereof, may exist in crystalline forms, non-crystalline forms or a mixture thereof. The compound or salt, or solvates (particularly, hydrates) thereof, may also exhibit polymorphism (i.e. the capacity to occur in different crystalline forms). These different crystalline forms are typically known as "polymorphs."

[0220] In light of this, salt forms of the present invention (i.e., which may include different polymorphs, anhydrous forms, solvates, or hydrates thereof) may exhibit characteristic polymorphism. As conventionally understood in the art, polymorphism is defined as an ability of a compound to crystallize as more than one distinct crystalline or "polymorphic" species. A polymorph is defined as a solid crystalline phase of a compound with at least two different arrangements or polymorphic forms of that compound molecule in the solid state.

[0221] Polymorphic forms of any given compound, including those of the present invention, are defined by the same chemical formula or composition and are as distinct in chemical structure as crystalline structures of two different chemical compounds. Such compounds may differ in packing, geometrical arrangement of respective crystalline lattices, etc.

[0222] It is to be understood that when named or depicted by structure, the disclosed compound, or solvates (particularly, hydrates) thereof, also include all polymorphs thereof. Polymorphs have the same chemical composition but differ in packing, geometrical arrangement, and other descriptive properties of the crystalline solid state.

[0223] In light of the foregoing, chemical and/or physical properties or characteristics vary with each distinct polymorphic form, which may include variations in solubility, melting point, density, hardness, crystal shape, optical and electrical properties, vapor pressure, stability, etc.

[0224] Solvates and/or hydrates of crystalline salt forms of the present invention also may be formed when solvent molecules are incorporated into the crystalline lattice structure of the compound molecule during the crystallization process. For example, solvate forms of the present invention may incorporate nonaqueous solvents such as methanol and the like as described herein below. Hydrate forms are solvate forms, which incorporate water as a solvent into a crystalline lattice.

[0225] Anhydrous with respect to solid state polymorphism refers to a crystalline structure that does not contain a repeating, crystalline solvent in the lattice. However, crystalline materials can be porous and may exhibit reversible surface adsorption of water.

Terms and Definitions

Section 2

1. Definitions

[0226] As used herein, the following terms and phrases shall have the meanings set forth below. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art.

[0227] The term "agent" is used herein to denote a chemical compound, a mixture of chemical compounds, a biological macromolecule (such as a nucleic acid, an antibody, a protein or portion thereof, e.g., a peptide), or an extract made from biological materials such as bacteria, plants, fungi, or animal (particularly mammalian) cells or tissues.

[0228] The term "bioavailable", when referring to a compound, is art-recognized and refers to a form of a compound that allows for all or a portion of the amount of compound administered to be absorbed by, incorporated into, or otherwise physiologically available to a subject or patient to whom it is administered.

[0229] "Biologically active portion of a sirtuin" refers to a portion of a sirtuin protein having a biological activity, such as the ability to deacetylate ("catalytically active"). Catalytically active portions of a sirtuin may comprise the core domain of sirtuins. Catalytically active portions of SIRT1 having GenBank Accession No. NP_036370 that encompass the NAD^+ binding domain and the substrate binding domain, for example, may include without limitation, amino acids 240-664 or 240-505 of GenBank Accession No. NP_036370, which are encoded by the polynucleotide of GenBank Accession No. NM_012238. Therefore, this region is sometimes referred to as the core domain. Other catalytically active portions of SIRT1, also sometimes referred to as core domains, include about amino acids 261 to 447 of GenBank Accession No. NP_036370, which are encoded by nucleotides 834 to 1394 of GenBank Accession No. NM_012238; about amino acids 242 to 493 of GenBank Accession No. NP_036370, which are encoded by nucleotides 777 to 1532 of GenBank Accession No. NM_012238; or about amino acids 254 to 495 of GenBank Accession No. NP_036370, which are encoded by nucleotides 813 to 1538 of GenBank Accession No. NM_012238. Another "biologically active" portion of SIRT1 is amino acids 62-293 or 183-225 of GenBank Acession No. NP_036370, which comprise a domain N-terminal to the core domain that is important to the compound binding site.

[0230] The term "companion animals" refers to cats and dogs. As used herein, the term "dog(s)" denotes any member of the species *Canis familiaris*, of which there are a large number of different breeds. The term "cat(s)" refers to a feline animal including domestic cats and other members of the family Felidae, genus *Felis*.

[0231] "Diabetes" refers to high blood sugar or ketoacidosis, as well as chronic, general metabolic abnormalities arising from a prolonged high blood sugar status or a decrease in glucose tolerance. "Diabetes" encompasses both the type I and type II (Non Insulin Dependent Diabetes Mellitus or NIDDM) forms of the disease. The risk factors for diabetes include the following factors: waistline of more than 40 inches for men or 35 inches for women, blood pressure of 130/85 mmHg or higher, triglycerides above 150 mg/dl, fasting blood glucose greater than 100 mg/dl or high-density lipoprotein of less than 40 mg/dl in men or 50 mg/dl in women.

[0232] The term "ED_{50}" refers to the art-recognized measure of effective dose. In certain embodiments, ED_{50} means the dose of a drug which produces 50% of its maximum response or effect, or alternatively, the dose which produces a pre-determined response in 50% of test subjects or preparations, such as isolated tissue or cells. The term "LD_{50}" refers to the art-recognized measure of lethal dose. In certain embodiments, LD_{50} means the dose of a drug which is lethal in 50% of test subjects. The term "therapeutic index" is an art-recognized term which refers to the therapeutic index of a drug, defined as LD_{50}/ED_{50}.

[0233] The term "hyperinsulinemia" refers to a state in an individual in which the level of insulin in the blood is higher than normal.

[0234] The term "insulin resistance" refers to a state in which a normal amount of insulin produces a subnormal biologic response relative to the biological response in a subject that does not have insulin resistance.

[0235] An "insulin resistance disorder," as discussed herein, refers to any disease or condition that is caused by or contributed to by insulin resistance. Examples include: diabetes, obesity, metabolic syndrome, insulin-resistance syndromes, syndrome X, insulin resistance, high blood pressure, hypertension, high blood cholesterol, dyslipidemia, hyperlipidemia, atherosclerotic disease including stroke, coronary artery disease or myocardial infarction, hyperglycemia, hyperinsulinemia and/or hyperproinsulinemia, impaired glucose tolerance, delayed insulin release, diabetic complications, including coronary heart disease, angina pectoris, congestive heart failure, stroke, cognitive functions in dementia, retinopathy, peripheral neuropathy, nephropathy, glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, some types of cancer (such as endometrial, breast, prostate, and colon), complications of pregnancy, poor female reproductive health (such as menstrual irregularities, infertility, irregular ovulation, polycystic ovarian syndrome (PCOS)), lipodystrophy, cholesterol-related disorders, such as gallstones, cholecystitis and cholelithiasis, gout, obstructive sleep apnea and respiratory problems, osteoarthritis, and bone loss, e.g., osteoporosis in particular.

[0236] The term "livestock animals" refers to domesticated quadrupeds, which includes those being raised for meat and various byproducts, e.g., a bovine animal including cattle and other members of the genus *Bos*, a porcine animal including domestic swine and other members of the genus *Sus*, an ovine animal including sheep and other members of the genus *Ovis*, domestic goats and other members of the genus *Capra*; domesticated quadrupeds being raised for specialized tasks such as use as a beast of burden, e.g., an equine animal including domestic horses and other members of the family Equidae, genus *Equus*.

[0237] The term "mammal" is known in the art, and exemplary mammals include humans, primates, livestock animals (including bovines, porcines, etc.), companion animals (e.g., canines, felines, etc.) and rodents (e.g., mice and rats).

[0238] "Obese" individuals or individuals suffering from obesity are generally individuals having a body mass index (BMI) of at least 25 or greater. Obesity may or may not be associated with insulin resistance.

[0239] The terms "parenteral administration" and "administered parenterally" are art-recognized and refer to modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intra-articular, subcapsular, subarachnoid, intraspinal, and intrasternal injection and infusion.

[0240] A "patient", "subject", "individual" or "host" refers to either a human or a non-human animal.

[0241] The term "pharmaceutically acceptable carrier" is art-recognized and refers to a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting any subject composition or component thereof. Each carrier must be "acceptable" in the sense of being compatible with the subject composition and its components and not injurious to the patient. Some examples of materials which may serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

[0242] The term "preventing" is art-recognized, and when used in relation to a condition, such as a local recurrence (e.g., pain), a disease such as cancer, a syndrome complex such as heart failure or any other medical condition, is well understood in the art, and includes administration of a composition which reduces the frequency of, or delays the onset of, symptoms of a medical condition in a subject relative to a subject which does not receive the composition. Thus, prevention of cancer includes, for example, reducing the number of detectable cancerous growths in a population of patients receiving a prophylactic treatment relative to an untreated control population, and/or delaying the appearance of detectable cancerous growths in a treated population versus an untreated control population, e.g., by a statistically and/or clinically significant amount. Prevention of an infection includes, for example, reducing the number of diagnoses of the infection in a treated population versus an untreated control population, and/or delaying the onset of symptoms of the infection in a treated population versus an untreated control population. Prevention of pain includes, for example, reducing the magnitude of, or alternatively delaying, pain sensations experienced by subjects in a treated population versus an untreated control population.

[0243] The term "prophylactic" or "therapeutic" treatment is art-recognized and refers to administration of a drug to a host. If it is administered prior to clinical manifestation of the unwanted condition (e.g., disease or other unwanted state of the host animal) then the treatment is prophylactic, i.e., it protects the host against developing the unwanted condition, whereas if administered after manifestation of the unwanted condition, the treatment is therapeutic (i.e., it is intended to diminish, ameliorate or maintain the existing unwanted condition or side effects therefrom).

[0244] The term "pyrogen-free", with reference to a composition, refers to a composition that does not contain a pyrogen in an amount that would lead to an adverse effect (e.g., irritation, fever, inflammation, diarrhea, respiratory distress, endotoxic shock, etc.) in a subject to which the composition has been administered. For example, the term is meant to encompass compositions that are free of, or substantially free of, an endotoxin such as, for example, a lipopolysaccharide (LPS).

[0245] "Replicative lifespan" of a cell refers to the number of daughter cells produced by an individual "mother cell." "Chronological aging" or "chronological lifespan," on the other hand, refers to the length of time a population of non-dividing cells remains viable when deprived of nutrients. "Increasing the lifespan of a cell" or "extending the lifespan of a cell," as applied to cells or organisms, refers to increasing the number of daughter cells produced by one cell; increasing the ability of cells or organisms to cope with stresses and combat damage, e.g., to DNA, proteins; and/or increasing the ability of cells or organisms to survive and exist in a living state for longer under a particular condition, e.g., stress (for example, heatshock, osmotic stress, high energy radiation, chemically-induced stress, DNA damage, inadequate salt level, inadequate nitrogen level, or inadequate nutrient level). Lifespan can be increased by at least about 10%, 20%, 30%, 40%, 50%, 60% or between 20% and 70%, 30% and 60%, 40% and 60% or more using methods or uses described herein.

[0246] "Sirtuin-modulating compound" refers to a compound that increases the level of a sirtuin protein and/or increases at least one activity of a sirtuin protein. In an exemplary embodiment, a sirtuin-modulating compound may increase at least one biological activity of a sirtuin protein by at least about 10%, 25%, 50%, 75%, 100%, or more. Exemplary biological activities of sirtuin proteins include deacetylation, e.g., of histones and p53; extending lifespan; increasing genomic stability; silencing transcription; and controlling the segregation of oxidized proteins between mother and daughter cells.

[0247] proteins include deacetylation, e.g., of an acetylated peptide substrate.

[0248] "Sirtuin protein" refers to a member of the sirtuin deacetylase protein family, or preferably to the sir2 family, which include yeast Sir2 (GenBank Accession No. P53685), *C. elegans* Sir-2.1 (GenBank Accession No. NP_501912), and human SIRT1 (GenBank Accession No. NM_012238 and NP_036370 (or AF083106)) and SIRT2 (GenBank Accession No. NM_012237, NM_030593, NP_036369, NP_085096, and AF083107) proteins. Other family members include the four additional yeast Sir2-like genes termed "HST genes" (homologues of Sir two) HST1, HST2, HST3 and HST4, and the five other human homologues hSIRT3, hSIRT4, hSIRT5, hSIRT6 and hSIRT7 (Brachmann et al. (1995) Genes Dev. 9:2888 and Frye et al. (1999) BBRC 260:273).

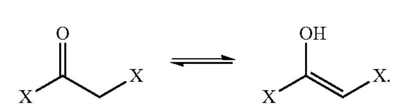
[0249] "SIRT1 protein" refers to a member of the sir2 family of sirtuin deacetylases. In certain embodiments, a SIRT1 protein includes yeast Sir2 (GenBank Accession No. P53685), *C. elegans* Sir-2.1 (GenBank Accession No. NP_501912), human SIRT1 (GenBank Accession No. NM_012238 or NP_036370 (or AF083106)), mouse SIRT1 (GenBank Accession No. NM_019812 or NP_062786), and equivalents and fragments thereof. In another embodiment, a SIRT1 protein includes a polypeptide comprising a sequence consisting of, or consisting essentially of, the amino acid sequence set forth in GenBank Accession Nos. NP 036370, NP 501912, NP 085096, NP 036369, or P53685. SIRT1 proteins include polypeptides comprising all or a portion of the amino acid sequence set forth in GenBank Accession Nos. NP_036370, NP_501912, NP_085096, NP_036369, or P53685; the amino acid sequence set forth in GenBank Accession Nos. NP_036370, NP_501912, NP_085096, NP_036369, or P53685 with 1 to about 2, 3, 5, 7, 10, 15, 20, 30, 50, 75 or more conservative amino acid substitutions; an amino acid sequence that is at least 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical to GenBank Accession Nos. NP_036370, NP_501912, NP_085096, NP_036369, or P53685, and functional fragments thereof. Polypeptides of the invention also include homologs (e.g., orthologs and paralogs), variants, or fragments, of GenBank Accession Nos. NP_036370, NP_501912, NP_085096, NP_036369, or P53685.

[0250] As used herein "SIRT2 protein", "SIRT3 protein", "SIRT4 protein", SIRT5 protein", "SIRT6 protein", and "SIRT7 protein" refer to other mammalian, e.g. human, sirtuin deacetylase proteins that are homologous to SIRT1 protein, particularly in the approximately 275 amino acid conserved catalytic domain. For example, "SIRT3 protein" refers to a member of the sirtuin deacetylase protein family that is homologous to SIRT1 protein. In certain embodiments, a SIRT3 protein includes human SIRT3 (GenBank Accession No. AAH01042, NP_036371, or NP_001017524) and mouse SIRT3 (GenBank Accession No. NP_071878) proteins, and equivalents and fragments thereof. In certain embodiments, a SIRT4 protein includes human SIRT4 (GenBank Accession No. NM_012240 or NP_036372). In certain embodiments, a SIRT5 protein includes human SIRT5 (GenBank Accession No. NM_012241 or NP_036373). In certain embodiments, a SIRT6 protein includes human SIRT6 (GenBank Accession No. NM_016539 or NP_057623). In another embodiment, a SIRT3 protein includes a polypeptide comprising a sequence consisting of, or consisting essentially of, the amino acid sequence set forth in GenBank Accession Nos. AAH01042, NP_036371, NP_001017524, or NP_071878. SIRT3 proteins include polypeptides comprising all or a portion of the amino acid sequence set forth in GenBank Accession AAH01042, NP_036371, NP_001017524, or NP_071878; the amino acid sequence set forth in GenBank Accession Nos. AAH01042, NP_036371, NP_001017524, or NP_071878 with 1 to about 2, 3, 5, 7, 10, 15, 20, 30, 50, 75 or more conservative amino acid substitutions; an amino acid sequence that is at least 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical to GenBank Accession Nos. AAH01042, NP_036371, NP_001017524, or NP_071878, and functional fragments thereof. Polypeptides of the invention also include homologs (e.g., orthologs and paralogs), variants, or fragments, of GenBank Accession Nos. AAH01042, NP_036371, NP_001017524, or NP_071878. In certain embodiments, a SIRT3 protein includes a fragment of SIRT3 protein that is produced by cleavage with a mitochondrial matrix processing peptidase (MPP) and/or a mitochondrial intermediate peptidase (MIP).

[0251] The term "steroisomer" as used herein is art-recognized and refers to any of two or more isomers that have the same molecular constitution and differ only in the three-dimensional arrangement of their atomic groupings in space. When used herein to describe a compounds or genus of compounds, stereoisomer includes any portion of the compound or the compound in its entirety. For example, diastereomers and enantiomers are stereoisomers.

[0252] The terms "systemic administration" and "administered systemically," are art-recognized and refer to the administration of a subject composition, therapeutic or other material enterally or parenterally.

[0253] The term "tautomer" as used herein is art-recognized and refers to any one of the possible alternative structures that may exist as a result of tautomerism, which refers to a form of constitutional isomerism in which a structure may exist in two or more constitutional arrangements, particularly with respect to the position of hydrogens bonded to oxygen. When used herein to describe a compound or genus of compounds, it is further understood that a "tautomer" is readily interconvertible and exists in equilibrium. For example, keto and enol tautomers exist in proportions determined by the equilibrium position for any given condition, or set of conditions:



[0254] The term "therapeutic agent" is art-recognized and refers to any biologically, physiologically, or pharmacologically active substance that acts locally or systemically in a subject. The term also means any substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease or in the enhancement of desirable physical or mental development and/or conditions in an animal or human.

[0255] The term "therapeutic effect" is art-recognized and refers to a beneficial local or systemic effect in animals, particularly mammals, and more particularly humans, caused by a pharmacologically active substance. The phrase "therapeutically-effective amount" means that amount of such a substance that produces some desired local or systemic effect at a reasonable benefit/risk ratio applicable to any treatment. The therapeutically effective amount of such substance will vary depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of skill in the art. For example, certain compositions described herein may be administered in a sufficient amount to produce a desired effect at a reasonable benefit/risk ratio applicable to such treatment.

[0256] "Treating" a condition or disease refers to curing as well as ameliorating at least one symptom of the condition or disease.

[0257] The term "vision impairment" refers to diminished vision, which is often only partially reversible or irreversible upon treatment (e.g., surgery). Particularly severe vision impairment is termed "blindness" or "vision loss", which refers to a complete loss of vision, vision worse than 20/200 that cannot be improved with corrective lenses, or a visual field of less than 20 degrees diameter (10 degrees radius).

Abbreviations and Symbols

[0258] In describing the present invention, chemical elements are identified in accordance with the Periodic Table of the Elements. Abbreviations and symbols utilized herein are in accordance with the common usage of such abbreviations and symbols by those skilled in the chemical and biological arts.

[0259] Specifically, the following abbreviations may be used in the examples and throughout the specification:

[0260] g (grams);

[0261] mg (milligrams);

[0262] kg (kilograms);

[0263] μg (micrograms);

[0264] L (liters);

[0265] mL (milliliters);

[0266] L (microliters);

[0267] psi (pounds per square inch);

[0268] M (molar);

[0269] mM (millimolar);

[0270] μM (micromolar);

[0271] nM (nanomolar);

[0272] pM (picomolar);

[0273] nm (nanometers);

[0274] mm (millimeters);

[0275] wt (weight);

[0276] N (Normal);

[0277] CFU (colony forming units);

[0278] I. V. (intravenous);

[0279] Hz (Hertz);

[0280] MHz (megahertz);

[0281] mol (moles);

[0282] mmol (millimoles);

[0283] RT (room temperature);
[0284] min (minutes);
[0285] h (hours);
[0286] b.p. (boiling point);
[0287] TLC (thin layer chromatography);
[0288] Tr (retention time);
[0289] RP (reverse phase);
[0290] MeOH (methanol);
[0291] i-PrOH (isopropanol);
[0292] TEA (triethylamine);
[0293] TFA (trifluoroacetic acid);
[0294] TFAA (trifluoroacetic anhydride);
[0295] THF (tetrahydrofuran);
[0296] DMSO (dimethylsulfoxide);
[0297] EtOAc (ethyl acetate);
[0298] DME (1,2-dimethoxyethane);
[0299] DCM (dichloromethane);
[0300] DCE (dichloroethane);
[0301] DMF (N,N-dimethylformamide);
[0302] DMPU (N,N'-dimethylpropyleneurea);
[0303] CDI (1,1-carbonyldiimidazole);
[0304] IBCF (isobutyl chloroformate);
[0305] AcOH (acetic acid);
[0306] HOAt (1-hydroxy-7-azabenzotriazole);
[0307] THP (tetrahydropyran);
[0308] NMM (N-methylmorpholine);
[0309] Pd/C (Palladium on Carbon);
[0310] MTBE (tert-butyl methyl ether);
[0311] HOBT (1-hydroxybenzotriazole);
[0312] mCPBA (meta-chloroperbenzoic acid;
[0313] EDC (1-[3-dimethylamino) propyl]-3-ethylcarbodiimide hydrochloride);
[0314] Boc (tert-butyloxycarbonyl);
[0315] FMOC (9-fluorenylmethoxycarbonyl);
[0316] DCC (dicyclohexylcarbodiimide);
[0317] CBZ (benzyloxycarbonyl);
[0318] Ac (acetyl);
[0319] atm (atmosphere);
[0320] TMSE (2-(trimethylsilyl)ethyl);
[0321] TMS (trimethylsilyl);
[0322] TIPS (triisopropylsilyl);
[0323] TBS (t-butyldimethylsilyl);
[0324] DMAP (4-dimethylaminopyridine);
[0325] BSA (bovine serum albumin)
[0326] NAD (nicotinamide adenine dinucleotide);
[0327] HPLC (high pressure liquid chromatography);
[0328] LC/MS (liquid chromatography/mass spectrometry);
[0329] BOP (bis(2-oxo-3-oxazolidinyl)phosphinic chloride);
[0330] TBAF (tetra-n-butylammonium fluoride);
[0331] HBTU(O-Benzotriazole-1-yl-N,N,N',N'-tetramethyluroniumhexafluoro phosphate).
[0332] HEPES (4-(2-hydroxyethyl)-1-piperazine ethane sulfonic acid);
[0333] DPPA (diphenylphosphoryl azide);
[0334] LAH (Lithium aluminum hydride);
[0335] $fHNO_3$ (fuming HNO_3);
[0336] NaOMe (sodium methoxide);
[0337] EDTA (ethylenediaminetetraacetic acid);
[0338] TMEDA (N,N,N',N'-tetramethyl-1,2-ethanediamine);
[0339] NBS (N-bromosuccinimide);
[0340] DIPEA (diisopropylethylamine);
[0341] dppf (1,1'-bis(diphenylphosphino)ferrocene); and
[0342] NIS (N-iodsuccinimide).

[0343] All references to ether are to diethyl ether and brine refers to a saturated aqueous solution of NaCl.

Synthetic Schemes and General Methods of Preparation

[0344] The present invention also relates to processes for making compounds of Formulas (I) to (IV), corresponding analogs (i.e., with hydrogen substitution at the R^2 position), and/or intermediate compounds thereof, respectively.

[0345] The compounds of Formulas (I) to (IV), corresponding analogs (i.e., with hydrogen substitution at the R^2 position) and/or intermediate compounds thereof, or pharmaceutically acceptable salts thereof, may be obtained by using synthetic procedures illustrated in the Schemes below or by drawing on the knowledge of a skilled organic chemist.

[0346] The synthesis provided in these Schemes (I) to (VI) are applicable for producing compounds of the invention having a variety of different functional groups employing appropriate precursors, which are suitably protected if needed, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, where needed, affords compounds of the nature generally disclosed. While the Schemes are shown with compounds, they are illustrative of processes that may be used to make the compounds of the invention.

[0347] Intermediates (compounds used in the preparation of the compounds of the invention) may also be present as salts. Thus, in reference to intermediates, the phrase "compound(s) of formula (number)" means a compound having that structural formula or a pharmaceutically acceptable salt thereof.

[0348] The present invention also relates to processes for making compounds of Formulas (I) to (IV), corresponding analogs (i.e., with hydrogen substitution at the R^2 position), and/or intermediate compounds thereof, respectively, or pharmaceutically acceptable salts thereof.

[0349] The compounds according to Formulas (I) to (II), respectively, The present invention also relates to processes for making compounds of Formulas (I) to (IV), corresponding analogs (i.e., with hydrogen substitution at the R^2 position), and/or intermediate compounds thereof, respectively, or pharmaceutically acceptable salts thereof are prepared using conventional organic syntheses.

[0350] The compounds of the present invention may be obtained by using synthetic procedures illustrated in Schemes below or by drawing on the knowledge of a skilled organic chemist.

[0351] Suitable synthetic routes are depicted below in the following general reaction schemes.

Compound Preparation

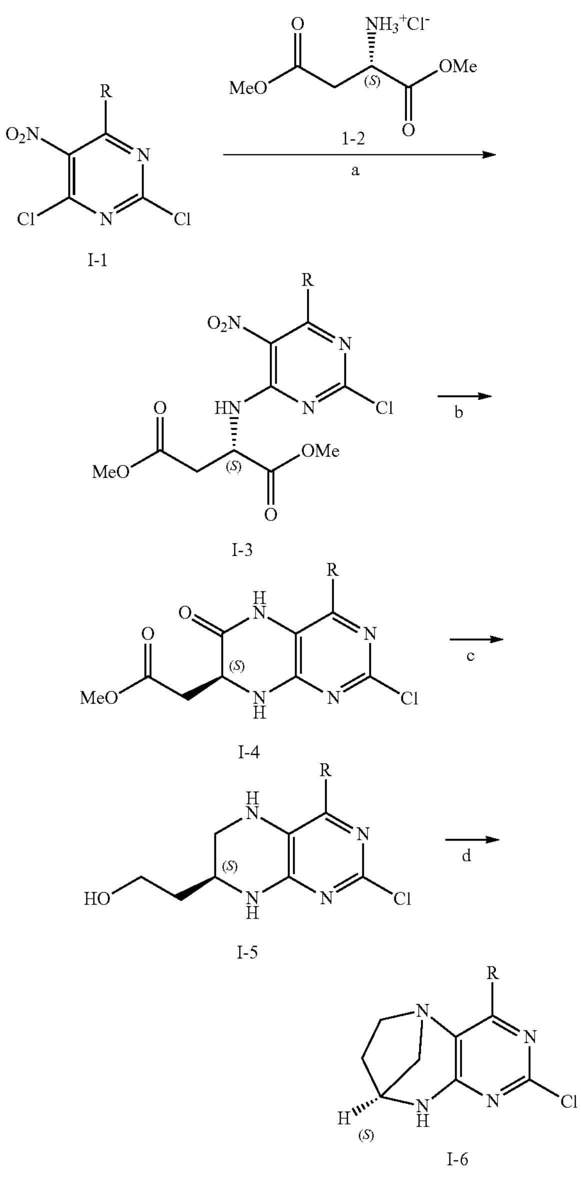
[0352] According to another embodiment, the present invention provides methods of producing the above-defined compounds. The compounds may be synthesized using conventional techniques. Advantageously, these compounds are conveniently synthesized from readily available starting materials.

[0353] Synthetic chemistry transformations and methodologies useful in synthesizing the compounds described herein are known in the art and include, for example, those

General Procedures

[0354]

Scheme I

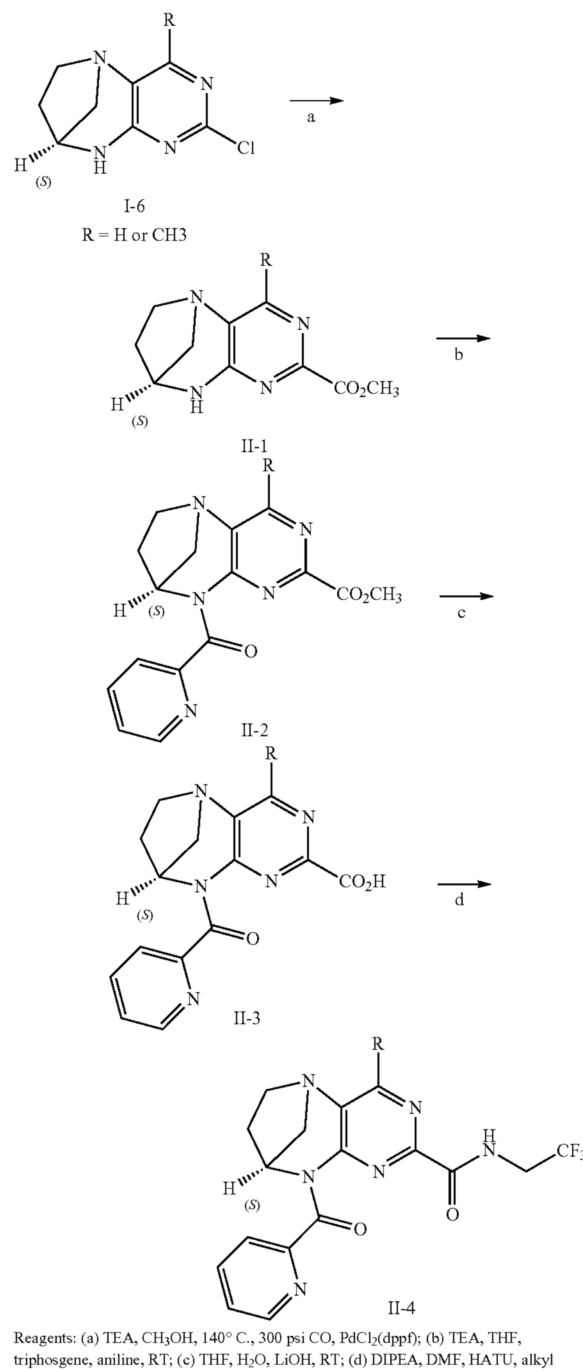


R = H or CH3

Reagents: (a) THF, $NaHCO_3$, 45° C.; (b) Fe, i-PrOH, HOAc, 70° C.; (c) $LiAlH_4$, THF, 0-25° C.; (d) DEA, DCM, $POCl_3$.

[0355] The commercial chloropyrimidine (I-1) was reacted with a nucleophilic amine (1-2) in the presence of a base (to scavenge HCl) in an aprotic solvent (eg., THF, DMF, dioxane) to provide the regioselective addition product (1-3). The nitro functionality of species (1-3) was reduced using Fe(0), (see, Bechamp reduction, *Org React.* 2, 428, 1944) in the presence of a Bronstead acid (HCl, HOAc) and a polar protic solvent. Other metals may be used such as Sn to effect this reduction. The resulting intermediate amine species formed in situ reacted with the ester functionality under elevated temperatures to form the cyclic amide 1-4. A strong hydride reducing agent, such as $LiAlH_4$, was reacted with compound I-4 resulting in the reduction of the ester to the corresponding alcohol and simultaneous reduction of the lactam to a cyclic amine (1-5). Reductions of this type are well-known to those instructed in the art, see H. C. Brown and S. Krishnamurthy, Tetrahedron, 1979, 35, 567. Reaction of the alcohol (I-5) with an activating group (such as $POCl_3$), capable of forming facile leaving group, provided the bicyclic amine compound (I-6).

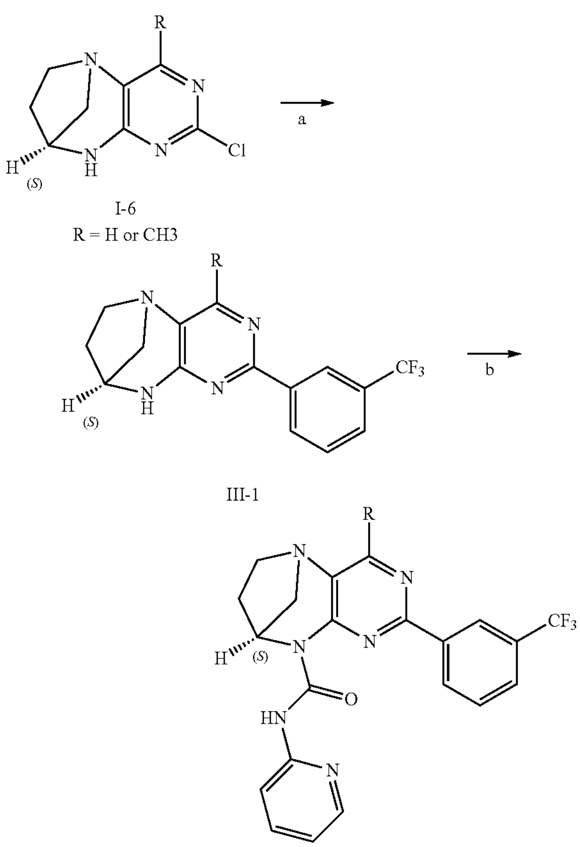
Scheme II



Reagents: (a) TEA, CH_3OH, 140° C., 300 psi CO, $PdCl_2$(dppf); (b) TEA, THF, triphosgene, aniline, RT; (c) THF, H_2O, LiOH, RT; (d) DIPEA, DMF, HATU, alkyl amine, RT.

[0356] Aryl chloride (I-6) was reacted with CO under pressure and elevated temperature in the presence of an alcohol to produce the ester (II-1). Carbonylation reactions are described in the literature (see, Principles and Applications of Organotransition Metal Chemistry. Sausalito, Calif.: University Science Books; 1987) and are well known to those skilled in the art. The amine functionality of II-1 was reacted with an acylating reagent, such as triphosgene or carbonyl diimidazole in an aprotic solvent (DCM, $CHCl_3$, THF, etc.) followed by treatment in situ with an aniline compound or alkyl amine in the presence of a tertiary alkyl amine base providing ester (II-2). Hydrolysis of the ester functionality via aqueous LiOH afforded the acid species (II-3). Carboxylic acid (II-3) was reacted with an alkyl amine in the presence of a coupling reagent (HATU) in a polar aprotic solvent to give the corresponding amide (II-4). A variety of amide coupling reagents such as EDC, PyBrop, etc. are commercially available. Amide coupling reactions are generally run in solvents such as DCM or DMF, utilizing an organic base like Et_3N or $(i\text{-}Pr)_2NEt$.

Scheme III



I-6
R = H or CH3

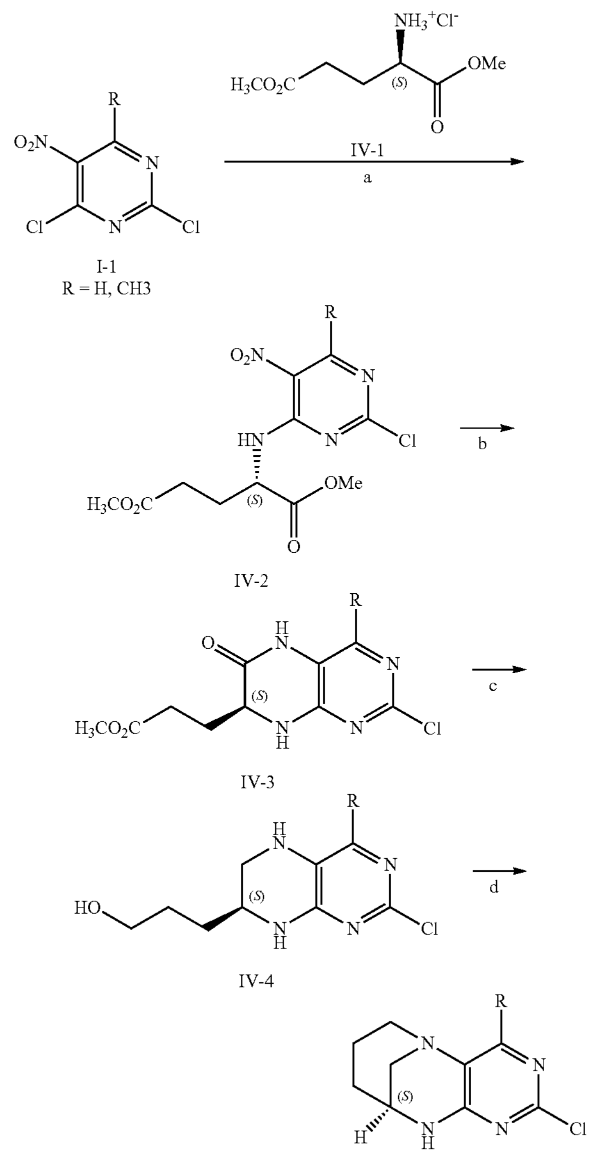
III-1

III-2

Reagents: (a) 3-Trifluoromethylphenylboronic acid, $Pd_2(dba)_3$, X—Phos, Cs_2CO_3, dioxane/H_2O, 90° C.; (b) TEA, triphosgene, THF; 2-aminopyridine, 65° C.

[0357] The chloro functionality of compound I-6 was coupled with a boronic acid using Suzuki coupling chemistry to give III-1. Suzuki-like couplings are typically run using a palladium(0) catalyst such as $Pd(PPh_3)_4$ with an inorganic base, for example K_2CO_3, Na_2CO_3 or K_3PO_4, in an aqueous mixture containing ethereal solvents such as DME, dioxane, or THF. Methods for palladium-mediated couplings are described in standard reference volumes, such as Schlosser "Organometallics in Synthesis" (published by Wiley and sons). Compound III-1 was reacted with an acylating reagent, such as triphosgene or carbonyl diimidazole in an aprotic solvent (DCM, $CHCl_3$, THF, etc.) to give a reactive acyl intermediate species which was treated in situ with an aniline compound or alkyl amine in the presence of a tertiary alkyl amine base to form the urea species (III-2).

Scheme IV



I-1
R = H, CH3

IV-1

IV-2

IV-3

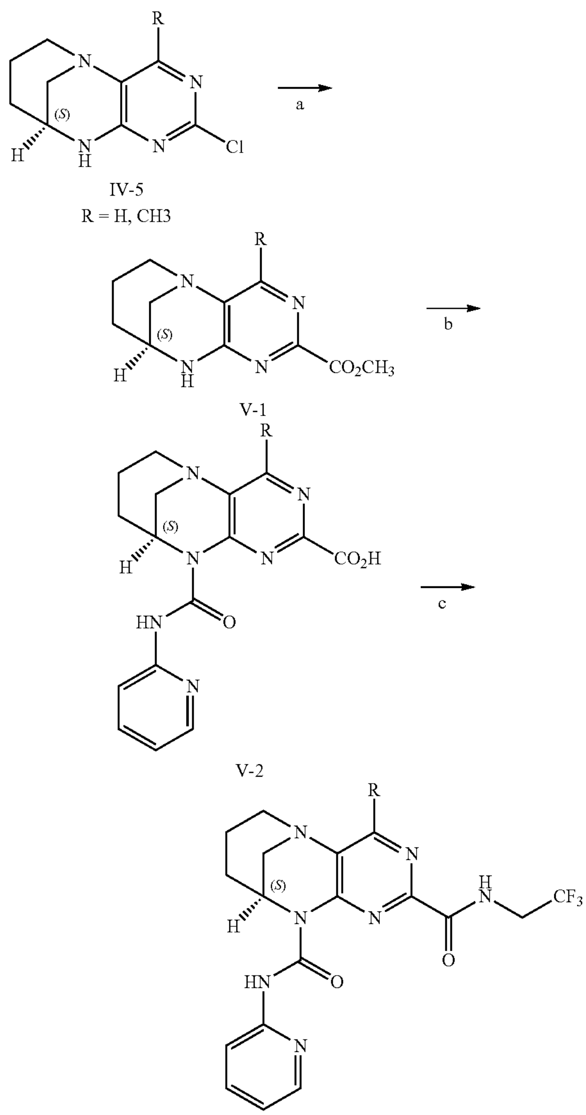
IV-4

IV-5

Reagents: (a) THF, $NaHCO_3$, 60° C.; (b) Fe, i-PrOH, HOAc, 80° C.; (c) $AlCl_3$, $LiAlH_4$, THF, RT; (d) $POCl_3$, DEA, DCM, 0° C.

[0358] The commercial chloropyridine (I-1) was reacted with a nucleophilic amine (IV-1) in the presence of a base (to scavenge HCl) in an aprotic solvent (eg., THF, DMF, dioxane) to provide the regioselective addition product (IV-2). The nitro functionality of species (IV-2) was reduced using Fe(0), (see, Bechamp reduction, *Org React.* 2, 428, 1944) in the presence of a Bronstead acid (HCl, HOAc) and a protic solvent. Other metals may be used such as Sn to effect this reduction. The resulting intermediate amine species formed in situ reacted with the ester functionality under elevated temperatures to form the cyclic amide IV-3. A strong hydride reducing agent, such as $LiAlH_4$, was reacted with compound IV-3 resulting in the reduction of the ester to the corresponding alcohol and simultaneous reduction of the lactam to a cyclic amine (IV-4). Reductions of this type are well-known to those instructed in the art, see H. C. Brown and S. Krishnamurthy, Tetrahedron, 1979, 35, 567. Reaction of the alcohol (IV-4) with an activating group (such as $POCl_3$), capable of forming facile leaving group, provided the bicyclic amine compound (IV-5).

Scheme V



IV-5
R = H, CH3

V-1

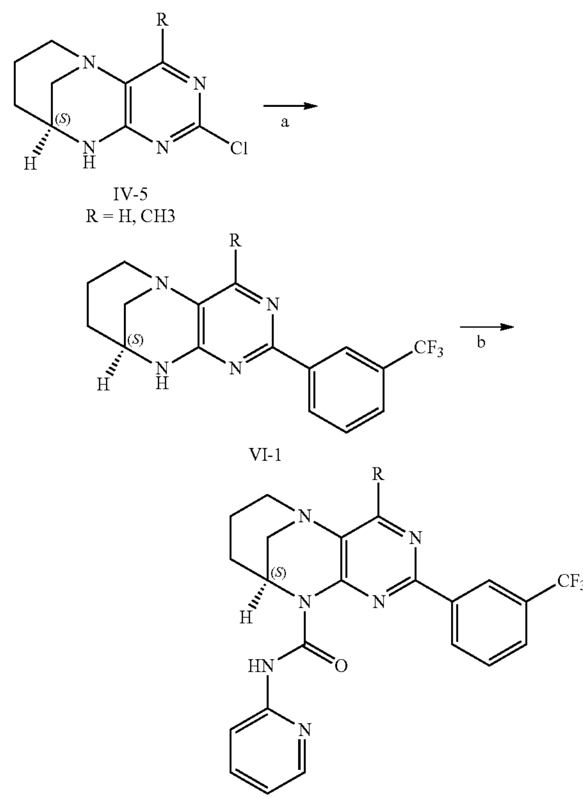
V-2

V-3

Reagents: (a) TEA, CH_3OH, 120° C., 300 psi CO, $PdCl_2$(dppf); (b) NaH, THF, 3-(pyridin-2-yl)-2H-pyrido[1,2a][1,3,5]triazine-2,4(3H)-dione, 65° C., then H_2O; (c) DIPEA, DMF, HATU, alkyl amine, RT.

[0359] Aryl chloride (IV-5) was reacted with CO under pressure and elevated temperature in the presence of an alcohol to produce the ester (V-1). Carbonylation reactions are described in the literature (see, Principles and Applications of Organotransition Metal Chemistry. Sausalito, Calif.: University Science Books; 1987) and are well known to those skilled in the art. The amine functionality of (V-1) was reacted with an acylating reagent, such as triphosgene or carbonyl diimidazole in an aprotic solvent (DCM, $CHCl_3$, THF, etc.) followed by treatment in situ with an aniline compound or alkyl amine in the presence of a tertiary alkyl amine base. Hydrolysis of the ester functionality via in situ formation of NaOH afforded the acid species V-2. Carboxylic acid (V-2) was reacted with an alkyl amine in the presence of a coupling reagent (HATU) in a polar aprotic solvent to give the corresponding amide (V-3). A variety of amide coupling reagents such as EDC, PyBrop, etc. are commercially available. Amide coupling reactions are generally run in solvents such as DCM or DMF, utilizing an organic base like Et3N or $(i\text{-}Pr)_2NEt$.

Scheme VI



IV-5
R = H, CH3

VI-1

VI-2

Reagents: (a) $Pd_2(dba)_3$, X-Phos, Cs_2CO_3, dioxane/H_2O, 90° C.; (b) TEA, triphosgene, THF; 2-aminopyridine, 65° C.

[0360] The chloro functionality of compound IV-5 was coupled with a boronic acid using Suzuki coupling chemistry to give VI-1. Suzuki-like couplings are typically run using a palladium(0) catalyst such as $Pd(PPh_3)_4$ with an inorganic base, for example K_2CO_3, Na_2CO_3 or K_3PO_4, in an aqueous mixture containing ethereal solvents such as DME, dioxane, or THF. Methods for palladium-mediated couplings are described in standard reference volumes, such as Schlosser "Organometallics in Synthesis" (published by

Wiley and sons). Compound VI-1 was reacted with an acylating reagent, such as triphosgene or carbonyl diimidazole in an aprotic solvent (DCM, $CHCl_3$, THF, etc.) to give a reactive acyl intermediate species which was treated in situ with an aniline compound or alkyl amine in the presence of a tertiary alkyl amine base to form the urea species (VI-2).

Compound Characteristics and Properties

[0361] In an exemplary embodiment, a therapeutic compound may traverse the cytoplasmic membrane of a cell. For example, a compound may have a cell-permeability of at least about 20%, 50%, 75%, 80%, 90% or 95%.

[0362] Compounds described herein may also have one or more of the following characteristics: the compound may be essentially non-toxic to a cell or subject; the compound may be an organic molecule or a small molecule of 2000 amu or less, 1000 amu or less; a compound may have a half-life under normal atmospheric conditions of at least about 30 days, 60 days, 120 days, 6 months or 1 year; the compound may have a half-life in solution of at least about 30 days, 60 days, 120 days, 6 months or 1 year; a compound may be more stable in solution than resveratrol by at least a factor of about 50%, 2 fold, 5 fold, 10 fold, 30 fold, 50 fold or 100 fold; a compound may promote deacetylation of the DNA repair factor Ku70; a compound may promote deacetylation of RelA/p65; a compound may increase general turnover rates and enhance the sensitivity of cells to TNF-induced apoptosis.

[0363] In certain embodiments, a sirtuin-modulating compound does not have any substantial ability to inhibit a histone deacetylase (HDAC) class I, and/or an HDAC class II at concentrations (e.g., in vivo) effective for modulating the deacetylase activity of the sirtuin. For instance, in preferred embodiments, the sirtuin-modulating compound is a sirtuin-modulating compound and is chosen to have an EC_{50} for activating sirtuin deacetylase activity that is at least 5 fold less than the EC_{50} for inhibition of an HDAC I and/or HDAC II, and even more preferably at least 10 fold, 100 fold or even 1000 fold less. Methods for assaying HDAC I and/or HDAC II activity are well known in the art and kits to perform such assays may be purchased commercially. See e.g., BioVision, Inc. (Mountain View, Calif.; world wide web at biovision.com) and Thomas Scientific (Swedesboro, N.J.; world wide web at tomassci.com).

[0364] In certain embodiments, a sirtuin-modulating compound does not have any substantial ability to modulate sirtuin homologs. In certain embodiments, an activator of a human sirtuin protein may not have any substantial ability to activate a sirtuin protein from lower eukaryotes, particularly yeast or human pathogens, at concentrations (e.g., in vivo) effective for activating the deacetylase activity of human sirtuin. For example, a sirtuin-modulating compound may be chosen to have an EC_{50} for activating a human sirtuin, such as SIRT1 and/or SIRT3, deacetylase activity that is at least 5 fold less than the EC_{50} for activating a yeast sirtuin, such as Sir2 (such as *Candida, S. cerevisiae*, etc.), and even more preferably at least 10 fold, 100 fold or even 1000 fold less. In another embodiment, an inhibitor of a sirtuin protein from lower eukaryotes, particularly yeast or human pathogens, does not have any substantial ability to inhibit a sirtuin protein from humans at concentrations (e.g., in vivo) effective for inhibiting the deacetylase activity of a sirtuin protein from a lower eukaryote. For example, a sirtuin-inhibiting compound may be chosen to have an IC50 for inhibiting a human sirtuin, such as SIRT1 and/or SIRT3, deacetylase activity that is at least 5 fold less than the IC_{50} for inhibiting a yeast sirtuin, such as Sir2 (such as *Candida, S. cerevisiae*, etc.), and even more preferably at least 10 fold, 100 fold or even 1000 fold less.

[0365] In certain embodiments, a sirtuin-modulating compound may have the ability to modulate one or more sirtuin protein homologs, such as, for example, one or more of human SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, or SIRT7. In some embodiments, a sirtuin-modulating compound has the ability to modulate both a SIRT1 and a SIRT3 protein.

[0366] In other embodiments, a SIRT1 modulator does not have any substantial ability to modulate other sirtuin protein homologs, such as, for example, one or more of human SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, or SIRT7, at concentrations (e.g., in vivo) effective for modulating the deacetylase activity of human SIRT1. For example, a sirtuin-modulating compound may be chosen to have an ED_{50} for modulating human SIRT1 deacetylase activity that is at least 5 fold less than the ED_{50} for modulating one or more of human SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, or SIRT7, and even more preferably at least 10 fold, 100 fold or even 1000 fold less. In some embodiments, a SIRT1 modulator does not have any substantial ability to modulate a SIRT3 protein.

[0367] In other embodiments, a SIRT3 modulator does not have any substantial ability to modulate other sirtuin protein homologs, such as, for example, one or more of human SIRT1, SIRT2, SIRT4, SIRT5, SIRT6, or SIRT7, at concentrations (e.g., in vivo) effective for modulating the deacetylase activity of human SIRT3. For example, a sirtuin-modulating compound may be chosen to have an ED_{50} for modulating human SIRT3 deacetylase activity that is at least 5 fold less than the ED_{50} for modulating one or more of human SIRT1, SIRT2, SIRT4, SIRT5, SIRT6, or SIRT7, and even more preferably at least 10 fold, 100 fold or even 1000 fold less. In some embodiments, a SIRT3 modulator does not have any substantial ability to modulate a SIRT1 protein.

[0368] In certain embodiments, a sirtuin-modulating compound may have a binding affinity for a sirtuin protein of about 10^{-9}M, 10^{-10}M, 10^{-11}M, 10^{-12}M or less. A sirtuin-modulating compound may reduce (activator) or increase (inhibitor) the apparent Km of a sirtuin protein for its substrate or NAD^+ (or other cofactor) by a factor of at least about 2, 3, 4, 5, 10, 20, 30, 50 or 100. In certain embodiments, Km values are determined using the mass spectrometry assay described herein. Preferred activating compounds reduce the Km of a sirtuin for its substrate or cofactor to a greater extent than caused by resveratrol at a similar concentration or reduce the Km of a sirtuin for its substrate or cofactor similar to that caused by resveratrol at a lower concentration. A sirtuin-modulating compound may increase the Vmax of a sirtuin protein by a factor of at least about 2, 3, 4, 5, 10, 20, 30, 50 or 100. A sirtuin-modulating compound may have an ED_{50} for modulating the deacetylase activity of a SIRT1 and/or SIRT3 protein of less than about 1 nM, less than about 10 nM, less than about 100 nM, less than about 1 μM, less than about 10 μM, less than about 100 μM, or from about 1-10 nM, from about 10-100 nM, from about 0.1-1 μM, from about 1-10 μM or from about 10-100 μM. A sirtuin-modulating compound may modulate the deacetylase activity of a SIRT1 and/or SIRT3 protein by a factor of at least about 5, 10, 20, 30, 50, or 100, as measured in a cellular assay or in a cell based assay. A sirtuin-modulating compound may cause at least about 10%, 30%, 50%, 80%, 2 fold, 5 fold, 10 fold, 50 fold or 100 fold greater induction of the deacetylase activity of a sirtuin protein relative to the same concentration of resveratrol. A sirtuin-modulating compound may have an ED_{50} for modulating SIRT5 that is at least about 10 fold, 20 fold, 30 fold, 50 fold greater than that for modulating SIRT1 and/or SIRT3.

Exemplary Uses

[0369] In certain aspects, the invention provides methods or uses for modulating the level and/or activity of a sirtuin protein and methods or uses thereof.

[0370] In certain embodiments, the invention provides methods or uses for using sirtuin-modulating compounds wherein the sirtuin-modulating compounds activate a sirtuin protein, e.g., increase the level and/or activity of a sirtuin protein. Sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be useful for a variety of therapeutic applications including, for example, increasing the lifespan of a cell, and treating and/or preventing a wide variety of diseases and disorders including, for example, diseases or disorders related to aging or stress, diabetes, obesity, neurodegenerative diseases, cardiovascular disease, blood clotting disorders, inflammation, cancer, and/or flushing, etc. The methods or uses comprise administering to a subject in need thereof a pharmaceutically effective amount of a sirtuin-modulating compound, e.g., a sirtuin-modulating compound.

[0371] Without wishing to be bound by theory, it is believed that activators of the instant invention may interact with a sirtuin at the same location within the sirtuin protein (e.g., active site or site affecting the Km or Vmax of the active site). It is believed that this is the reason why certain classes of sirtuin activators and inhibitors can have substantial structural similarity.

[0372] In certain embodiments, the sirtuin-modulating compounds described herein may be taken alone or in combination with other compounds. In certain embodiments, a mixture of two or more sirtuin-modulating compounds may be administered to a subject in need thereof. In another embodiment, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may be administered with one or more of the following compounds: resveratrol, butein, fisetin, piceatannol, or quercetin. In an exemplary embodiment, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may be administered in combination with nicotinic acid or nicotinamide riboside. In another embodiment, a sirtuin-modulating compound that decreases the level and/or activity of a sirtuin protein may be administered with one or more of the following compounds: nicotinamide (NAM), suramin; NF023 (a G-protein antagonist); NF279 (a purinergic receptor antagonist); Trolox (6-hydroxy-2,5,7,8,tetramethylchroman-2-carboxylic acid); (−)-epigallocatechin (hydroxy on sites 3,5,7,3',4',5'); (−)-epigallocatechin gallate (Hydroxy sites 5,7,3',4',5' and gallate ester on 3); cyanidin chloride (3,5,7,3',4'-pentahydroxyflavylium chloride); delphinidin chloride (3,5,7,3',4',5'-hexahydroxyflavylium chloride); myricetin (cannabiscetin; 3,5,7,3',4',5'-hexahydroxyflavone); 3,7,3',4',5'-pentahydroxyflavone; gossypetin (3,5,7,8,3',4'-hexahydroxyflavone), sirtinol; and splitomicin. In yet another embodiment, one or more sirtuin-modulating compounds may be administered with one or more therapeutic agents for the treatment or prevention of various diseases, including, for example, cancer, diabetes, neurodegenerative diseases, cardiovascular disease, blood clotting, inflammation, flushing, obesity, aging, stress, etc. In various embodiments, combination therapies comprising a sirtuin-modulating compound may refer to (1) pharmaceutical compositions that comprise one or more sirtuin-modulating compounds in combination with one or more therapeutic agents (e.g., one or more therapeutic agents described herein); and (2) co-administration of one or more sirtuin-modulating compounds with one or more therapeutic agents wherein the sirtuin-modulating compound and therapeutic agent have not been formulated in the same compositions (but may be present within the same kit or package, such as a blister pack or other multi-chamber package; connected, separately sealed containers (e.g., foil pouches) that can be separated by the user; or a kit where the compound(s) and other therapeutic agent(s) are in separate vessels). When using separate formulations, the sirtuin-modulating compound may be administered simultaneous with, intermittent with, staggered with, prior to, subsequent to, or combinations thereof, the administration of another therapeutic agent.

[0373] In certain embodiments, methods or uses for reducing, preventing or treating diseases or disorders using a compound described herein may also comprise increasing the protein level of a sirtuin, such as human SIRT1, SIRT2 and/or SIRT3, or homologs thereof. Increasing protein levels can be achieved by introducing into a cell one or more copies of a nucleic acid that encodes a sirtuin. For example, the level of a sirtuin can be increased in a mammalian cell by introducing into the mammalian cell a nucleic acid encoding the sirtuin, e.g., increasing the level of SIRT1 by introducing a nucleic acid encoding the amino acid sequence set forth in GenBank Accession No. NP_036370 and/or increasing the level of SIRT3 by introducing a nucleic acid encoding the amino acid sequence set forth in GenBank Accession No. AAH01042.

[0374] A nucleic acid that is introduced into a cell to increase the protein level of a sirtuin may encode a protein that is at least about 80%, 85%, 90%, 95%, 98%, or 99% identical to the sequence of a sirtuin, e.g., SIRT1 and/or SIRT3 protein. For example, the nucleic acid encoding the protein may be at least about 80%, 85%, 90%, 95%, 98%, or 99% identical to a nucleic acid encoding a SIRT1 (e.g. GenBank Accession No. NM_012238) and/or SIRT3 (e.g., GenBank Accession No. BC001042) protein. The nucleic acid may also be a nucleic acid that hybridizes, preferably under stringent hybridization conditions, to a nucleic acid encoding a wild-type sirtuin, e.g., SIRT1 and/or SIRT3 protein. Stringent hybridization conditions may include hybridization and a wash in 0.2×SSC at 65° C.

[0375] When using a nucleic acid that encodes a protein that is different from a wild-type sirtuin protein, such as a protein that is a fragment of a wild-type sirtuin, the protein is preferably biologically active, e.g., is capable of deacetylation. It is only necessary to express in a cell a portion of the sirtuin that is biologically active. For example, a protein that differs from wild-type SIRT1 having GenBank Accession No. NP_036370, preferably contains the core structure thereof. The core structure sometimes refers to amino acids 62-293 of GenBank Accession No. NP_036370, which are encoded by nucleotides 237 to 932 of GenBank Accession No. NM_012238, which encompasses the NAD binding as well as the substrate binding domains. The core domain of SIRT1 may also refer to about amino acids 261 to 447 of

GenBank Accession No. NP_036370, which are encoded by nucleotides 834 to 1394 of GenBank Accession No. NM_012238; to about amino acids 242 to 493 of GenBank Accession No. NP_036370, which are encoded by nucleotides 777 to 1532 of GenBank Accession No. NM 012238; or to about amino acids 254 to 495 of GenBank Accession No. NP_036370, which are encoded by nucleotides 813 to 1538 of GenBank Accession No. NM_012238. Whether a protein retains a biological function, e.g., deacetylation capabilities, can be determined according to methods known in the art.

[0376] In certain embodiments, methods or uses for reducing, preventing or treating diseases or disorders using a sirtuin-modulating compound may also comprise decreasing the protein level of a sirtuin, such as human SIRT1, SIRT2 and/or SIRT3, or homologs thereof. Decreasing a sirtuin protein level can be achieved according to methods known in the art. For example, an siRNA, an antisense nucleic acid, or a ribozyme targeted to the sirtuin can be expressed in the cell. A dominant negative sirtuin mutant, e.g., a mutant that is not capable of deacetylating, may also be used. For example, mutant H363Y of SIRT1, described, e.g., in Luo et al. (2001) Cell 107:137 can be used. Alternatively, agents that inhibit transcription can be used.

[0377] Methods or uses for modulating sirtuin protein levels also include methods or uses for modulating the transcription of genes encoding sirtuins, methods or uses for stabilizing/destabilizing the corresponding mRNAs, and other methods known in the art.

Aging/Stress

[0378] In one aspect, the invention provides a method extending the lifespan of a cell, extending the proliferative capacity of a cell, slowing aging of a cell, promoting the survival of a cell, delaying cellular senescence in a cell, mimicking the effects of calorie restriction, increasing the resistance of a cell to stress, or preventing apoptosis of a cell, by contacting the cell with a sirtuin-modulating compound of the invention that increases the level and/or activity of a sirtuin protein. In an exemplary embodiment, the methods or uses comprise contacting the cell with a sirtuin-modulating compound.

[0379] The methods or uses described herein may be used to increase the amount of time that cells, particularly primary cells (i.e., cells obtained from an organism, e.g., a human), may be kept alive in a cell culture. Embryonic stem (ES) cells and pluripotent cells, and cells differentiated therefrom, may also be treated with a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein to keep the cells, or progeny thereof, in culture for longer periods of time. Such cells can also be used for transplantation into a subject, e.g., after ex vivo modification.

[0380] In one aspect, cells that are intended to be preserved for long periods of time may be treated with a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein. The cells may be in suspension (e.g., blood cells, serum, biological growth media, etc.) or in tissues or organs. For example, blood collected from an individual for purposes of transfusion may be treated with a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein to preserve the blood cells for longer periods of time. Additionally, blood to be used for forensic purposes may also be preserved using a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein. Other cells that may be treated to extend their lifespan or protect against apoptosis include cells for consumption, e.g., cells from non-human mammals (such as meat) or plant cells (such as vegetables).

[0381] Sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may also be applied during developmental and growth phases in mammals, plants, insects or microorganisms, in order to, e.g., alter, retard or accelerate the developmental and/or growth process.

[0382] In another aspect, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used to treat cells useful for transplantation or cell therapy, including, for example, solid tissue grafts, organ transplants, cell suspensions, stem cells, bone marrow cells, etc. The cells or tissue may be an autograft, an allograft, a syngraft or a xenograft. The cells or tissue may be treated with the sirtuin-modulating compound prior to administration/implantation, concurrently with administration/implantation, and/or post administration/implantation into a subject. The cells or tissue may be treated prior to removal of the cells from the donor individual, ex vivo after removal of the cells or tissue from the donor individual, or post implantation into the recipient. For example, the donor or recipient individual may be treated systemically with a sirtuin-modulating compound or may have a subset of cells/tissue treated locally with a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein. In certain embodiments, the cells or tissue (or donor/recipient individuals) may additionally be treated with another therapeutic agent useful for prolonging graft survival, such as, for example, an immunosuppressive agent, a cytokine, an angiogenic factor, etc.

[0383] In yet other embodiments, cells may be treated with a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein in vivo, e.g., to increase their lifespan or prevent apoptosis. For example, skin can be protected from aging (e.g., developing wrinkles, loss of elasticity, etc.) by treating skin or epithelial cells with a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein. In an exemplary embodiment, skin is contacted with a pharmaceutical or cosmetic composition comprising a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein. Exemplary skin afflictions or skin conditions that may be treated in accordance with the methods or uses described herein include disorders or diseases associated with or caused by inflammation, sun damage or natural aging. For example, the compositions find utility in the prevention or treatment of contact dermatitis (including irritant contact dermatitis and allergic contact dermatitis), atopic dermatitis (also known as allergic eczema), actinic keratosis, keratinization disorders (including eczema), epidermolysis bullosa diseases (including pemphigus), exfoliative dermatitis, seborrheic dermatitis, erythemas (including erythema multiforme and erythema nodosum), damage caused by the sun or other light sources, discoid lupus erythematosus, dermatomyositis, psoriasis, skin cancer and the effects of natural aging. In another embodiment, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used for the treatment of wounds and/or burns to promote healing, including, for example, first-, second- or third-degree burns and/or thermal, chemical or electrical burns. The formulations may be administered topically, to the skin or mucosal tissue.

[0384] Topical formulations comprising one or more sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may also be used as preventive, e.g., chemopreventive, compositions. When used in a chemopreventive method, susceptible skin is treated prior to any visible condition in a particular individual.

[0385] Sirtuin-modulating compounds may be delivered locally or systemically to a subject. In certain embodiments, a sirtuin-modulating compound is delivered locally to a tissue or organ of a subject by injection, topical formulation, etc.

[0386] In another embodiment, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may be used for treating or preventing a disease or condition induced or exacerbated by cellular senescence in a subject; methods or uses for decreasing the rate of senescence of a subject, e.g., after onset of senescence; methods or uses for extending the lifespan of a subject; methods or uses for treating or preventing a disease or condition relating to lifespan; methods or uses for treating or preventing a disease or condition relating to the proliferative capacity of cells; and methods or uses for treating or preventing a disease or condition resulting from cell damage or death. In certain embodiments, the method does not act by decreasing the rate of occurrence of diseases that shorten the lifespan of a subject. In certain embodiments, a method does not act by reducing the lethality caused by a disease, such as cancer.

[0387] In yet another embodiment, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may be administered to a subject in order to generally increase the lifespan of its cells and to protect its cells against stress and/or against apoptosis. It is believed that treating a subject with a compound described herein is similar to subjecting the subject to hormesis, i.e., mild stress that is beneficial to organisms and may extend their lifespan.

[0388] Sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be administered to a subject to prevent aging and aging-related consequences or diseases, such as stroke, heart disease, heart failure, arthritis, high blood pressure, and Alzheimer's disease. Other conditions that can be treated include ocular disorders, e.g., associated with the aging of the eye, such as cataracts, glaucoma, and macular degeneration. Sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein can also be administered to subjects for treatment of diseases, e.g., chronic diseases, associated with cell death, in order to protect the cells from cell death. Exemplary diseases include those associated with neural cell death, neuronal dysfunction, or muscular cell death or dysfunction, such as Parkinson's disease, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, and muscular dystrophy; AIDS; fulminant hepatitis; diseases linked to degeneration of the brain, such as Creutzfeld-Jakob disease, retinitis pigmentosa and cerebellar degeneration; myelodysplasia such as aplastic anemia; ischemic diseases such as myocardial infarction and stroke; hepatic diseases such as alcoholic hepatitis, hepatitis B and hepatitis C; joint-diseases such as osteoarthritis; atherosclerosis; alopecia; damage to the skin due to UV light; lichen planus; atrophy of the skin; cataract; and graft rejections. Cell death can also be caused by surgery, drug therapy, chemical exposure or radiation exposure.

[0389] Sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein can also be administered to a subject suffering from an acute disease, e.g., damage to an organ or tissue, e.g., a subject suffering from stroke or myocardial infarction or a subject suffering from a spinal cord injury. Sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may also be used to repair an alcoholic's liver.

Cardiovascular Disease

[0390] In another embodiment, the invention provides a method for treating and/or preventing a cardiovascular disease by administering to a subject in need thereof a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein.

[0391] Cardiovascular diseases that can be treated or prevented using the sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein include cardiomyopathy or myocarditis; such as idiopathic cardiomyopathy, metabolic cardiomyopathy, alcoholic cardiomyopathy, drug-induced cardiomyopathy, ischemic cardiomyopathy, and hypertensive cardiomyopathy. Also treatable or preventable using compounds and methods or uses described herein are atheromatous disorders of the major blood vessels (macrovascular disease) such as the aorta, the coronary arteries, the carotid arteries, the cerebrovascular arteries, the renal arteries, the iliac arteries, the femoral arteries, and the popliteal arteries. Other vascular diseases that can be treated or prevented include those related to platelet aggregation, the retinal arterioles, the glomerular arterioles, the vasa nervorum, cardiac arterioles, and associated capillary beds of the eye, the kidney, the heart, and the central and peripheral nervous systems. The sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may also be used for increasing HDL levels in plasma of an individual.

[0392] Yet other disorders that may be treated with sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein include restenosis, e.g., following coronary intervention, and disorders relating to an abnormal level of high density and low density cholesterol.

[0393] In certain embodiments, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may be administered as part of a combination therapy with another cardiovascular agent. In certain embodiments, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may be administered as part of a combination therapy with an anti-arrhythmia agent. In another embodiment, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may be administered as part of a combination therapy with another cardiovascular agent.

Cell Death/Cancer

[0394] Sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be administered to subjects who have recently received or are likely to receive a dose of radiation or toxin. In certain embodiments, the dose of radiation or toxin is received as part of a work-related or medical procedure, e.g., administered as a prophylactic measure. In another embodiment, the radiation or toxin exposure is received unintentionally. In such a case, the compound is preferably administered as soon as possible after the exposure to inhibit apoptosis and the subsequent development of acute radiation syndrome.

[0395] Sirtuin-modulating compounds may also be used for treating and/or preventing cancer. In certain embodiments, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used for treating and/or preventing cancer. Calorie restriction has been linked to a reduction in the incidence of age-related disorders including cancer. Accordingly, an increase in the level and/or activity of a sirtuin protein may be useful for treating and/or preventing the incidence of age-related disorders, such as, for example, cancer. Exemplary cancers that may be treated using a sirtuin-modulating compound are those of the brain and kidney; hormone-dependent cancers including breast, prostate, testicular, and ovarian cancers; lymphomas, and leukemias. In cancers associated with solid tumors, a modulating compound may be administered directly into the tumor. Cancer of blood cells, e.g., leukemia, can be treated by administering a modulating compound into the blood stream or into the bone marrow. Benign cell growth, e.g., warts, can also be treated. Other diseases that can be treated include autoimmune diseases, e.g., systemic lupus erythematosus, scleroderma, and arthritis, in which autoimmune cells should be removed. Viral infections such as herpes, HIV, adenovirus, and HTLV-1 associated malignant and benign disorders can also be treated by administration of sirtuin-modulating compound. Alternatively, cells can be obtained from a subject, treated ex vivo to remove certain undesirable cells, e.g., cancer cells, and administered back to the same or a different subject.

[0396] Chemotherapeutic agents may be co-administered with modulating compounds described herein as having anti-cancer activity, e.g., compounds that induce apoptosis, compounds that reduce lifespan or compounds that render cells sensitive to stress. Chemotherapeutic agents may be used by themselves with a sirtuin-modulating compound described herein as inducing cell death or reducing lifespan or increasing sensitivity to stress and/or in combination with other chemotherapeutics agents. In addition to conventional chemotherapeutics, the sirtuin-modulating compounds described herein may also be used with antisense RNA, RNAi or other polynucleotides to inhibit the expression of the cellular components that contribute to unwanted cellular proliferation.

[0397] Combination therapies comprising sirtuin-modulating compounds and a conventional chemotherapeutic agent may be advantageous over combination therapies known in the art because the combination allows the conventional chemotherapeutic agent to exert greater effect at lower dosage. In a preferred embodiment, the effective dose (ED50) for a chemotherapeutic agent, or combination of conventional chemotherapeutic agents, when used in combination with a sirtuin-modulating compound is at least 2 fold less than the ED_{50} for the chemotherapeutic agent alone, and even more preferably at 5 fold, 10 fold or even 25 fold less. Conversely, the therapeutic index (TI) for such chemotherapeutic agent or combination of such chemotherapeutic agent when used in combination with a sirtuin-modulating compound described herein can be at least 2 fold greater than the TI for conventional chemotherapeutic regimen alone, and even more preferably at 5 fold, 10 fold or even 25 fold greater.

Neuronal Diseases/Disorders

[0398] In certain aspects, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein can be used to treat patients suffering from neurodegenerative diseases, and traumatic or mechanical injury to the central nervous system (CNS), spinal cord or peripheral nervous system (PNS). Neurodegenerative disease typically involves reductions in the mass and volume of the human brain, which may be due to the atrophy and/or death of brain cells, which are far more profound than those in a healthy person that are attributable to aging. Neurodegenerative diseases can evolve gradually, after a long period of normal brain function, due to progressive degeneration (e.g., nerve cell dysfunction and death) of specific brain regions. Alternatively, neurodegenerative diseases can have a quick onset, such as those associated with trauma or toxins. The actual onset of brain degeneration may precede clinical expression by many years. Examples of neurodegenerative diseases include, but are not limited to, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease), diffuse Lewy body disease, chorea-acanthocytosis, primary lateral sclerosis, ocular diseases (ocular neuritis), chemotherapy-induced neuropathies (e.g., from vincristine, paclitaxel, bortezomib), diabetes-induced neuropathies and Friedreich's ataxia. Sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein can be used to treat these disorders and others as described below.

[0399] AD is a CNS disorder that results in memory loss, unusual behavior, personality changes, and a decline in thinking abilities. These losses are related to the death of specific types of brain cells and the breakdown of connections and their supporting network (e.g. glial cells) between them. The earliest symptoms include loss of recent memory, faulty judgment, and changes in personality. PD is a CNS disorder that results in uncontrolled body movements, rigidity, tremor, and dyskinesia, and is associated with the death of brain cells in an area of the brain that produces dopamine. ALS (motor neuron disease) is a CNS disorder that attacks the motor neurons, components of the CNS that connect the brain to the skeletal muscles.

[0400] HD is another neurodegenerative disease that causes uncontrolled movements, loss of intellectual faculties, and emotional disturbance. Tay-Sachs disease and Sandhoff disease are glycolipid storage diseases where GM2 ganglioside and related glycolipids substrates for β-hexosaminidase accumulate in the nervous system and trigger acute neurodegeneration.

[0401] It is well-known that apoptosis plays a role in AIDS pathogenesis in the immune system. However, HIV-1 also induces neurological disease, which can be treated with sirtuin-modulating compounds of the invention.

[0402] Neuronal loss is also a salient feature of prion diseases, such as Creutzfeldt-Jakob disease in human, BSE in cattle (mad cow disease), Scrapie Disease in sheep and goats, and feline spongiform encephalopathy (FSE) in cats. Sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be useful for treating or preventing neuronal loss due to these prior diseases.

[0403] In another embodiment, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may be used to treat or prevent any disease or disorder involving axonopathy. Distal axonopathy is a type of peripheral neuropathy that results from some metabolic or toxic derangement of peripheral nervous system (PNS) neurons.

[0404] It is the most common response of nerves to metabolic or toxic disturbances, and as such may be caused by metabolic diseases such as diabetes, renal failure, deficiency syndromes such as malnutrition and alcoholism, or the effects of toxins or drugs. Those with distal axonopathies usually present with symmetrical glove-stocking sensori-motor disturbances.

[0405] Deep tendon reflexes and autonomic nervous system (ANS) functions are also lost or diminished in affected areas.

[0406] Diabetic neuropathies are neuropathic disorders that are associated with diabetes mellitus. Relatively common conditions which may be associated with diabetic neuropathy include third nerve palsy; mononeuropathy; mononeuritis multiplex; diabetic amyotrophy; a painful polyneuropathy; autonomic neuropathy; and thoracoabdominal neuropathy.

[0407] Peripheral neuropathy is the medical term for damage to nerves of the peripheral nervous system, which may be caused either by diseases of the nerve or from the side-effects of systemic illness. Major causes of peripheral neuropathy include seizures, nutritional deficiencies, and HIV, though diabetes is the most likely cause.

[0408] In an exemplary embodiment, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may be used to treat or prevent multiple sclerosis (MS), including relapsing MS and monosymptomatic MS, and other demyelinating conditions, such as, for example, chronic inflammatory demyelinating polyneuropathy (CIDP), or symptoms associated therewith.

[0409] In yet another embodiment, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may be used to treat trauma to the nerves, including, trauma due to disease, injury (including surgical intervention), or environmental trauma (e.g., neurotoxins, alcoholism, etc.).

[0410] Sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may also be useful to prevent, treat, and alleviate symptoms of various PNS disorders. The term "peripheral neuropathy" encompasses a wide range of disorders in which the nerves outside of the brain and spinal cord—peripheral nerves—have been damaged. Peripheral neuropathy may also be referred to as peripheral neuritis, or if many nerves are involved, the terms polyneuropathy or polyneuritis may be used.

[0411] PNS diseases treatable with sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein include: diabetes, leprosy, Charcot-Marie-Tooth disease, Guillain-Barré syndrome and Brachial Plexus Neuropathies (diseases of the cervical and first thoracic roots, nerve trunks, cords, and peripheral nerve components of the brachial plexus.

[0412] In another embodiment, a sirtuin-modulating compound may be used to treat or prevent a polyglutamine disease. Exemplary polyglutamine diseases include Spinobulbar muscular atrophy (Kennedy disease), Huntington's Disease (HD), Dentatorubral-pallidoluysian atrophy (Haw River syndrome), Spinocerebellar ataxia type 1, Spinocerebellar ataxia type 2, Spinocerebellar ataxia type 3 (Machado-Joseph disease), Spinocerebellar ataxia type 6, Spinocerebellar ataxia type 7, and Spinocerebellar ataxia type 17.

[0413] In certain embodiments, the invention provides a method to treat a central nervous system cell to prevent damage in response to a decrease in blood flow to the cell. Typically the severity of damage that may be prevented will depend in large part on the degree of reduction in blood flow to the cell and the duration of the reduction. In certain embodiments, apoptotic or necrotic cell death may be prevented. In still a further embodiment, ischemic-mediated damage, such as cytotoxic edema or central nervous system tissue anoxemia, may be prevented. In each embodiment, the central nervous system cell may be a spinal cell or a brain cell.

[0414] Another aspect encompasses administrating a sirtuin-modulating compound to a subject to treat a central nervous system ischemic condition. A number of central nervous system ischemic conditions may be treated by the sirtuin-modulating compounds described herein. In certain embodiments, the ischemic condition is a stroke that results in any type of ischemic central nervous system damage, such as apoptotic or necrotic cell death, cytotoxic edema or central nervous system tissue anoxia. The stroke may impact any area of the brain or be caused by any etiology commonly known to result in the occurrence of a stroke. In one alternative of this embodiment, the stroke is a brain stem stroke. In another alternative of this embodiment, the stroke is a cerebellar stroke. In still another embodiment, the stroke is an embolic stroke. In yet another alternative, the stroke may be a hemorrhagic stroke. In a further embodiment, the stroke is a thrombotic stroke.

[0415] In yet another aspect, a sirtuin-modulating compound may be administered to reduce infarct size of the ischemic core following a central nervous system ischemic condition. Moreover, a sirtuin-modulating compound may also be beneficially administered to reduce the size of the ischemic penumbra or transitional zone following a central nervous system ischemic condition.

[0416] In certain embodiments, a combination drug regimen may include drugs or compounds for the treatment or prevention of neurodegenerative disorders or secondary conditions associated with these conditions. Thus, a combination drug regimen may include one or more sirtuin activators and one or more anti-neurodegeneration agents.

Blood Coagulation Disorders

[0417] In other aspects, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein can be used to treat or prevent blood coagulation disorders (or hemostatic disorders). As used interchangeably herein, the terms "hemostasis", "blood coagulation," and "blood clotting" refer to the control of bleeding, including the physiological properties of vasoconstriction and coagulation. Blood coagulation assists in maintaining the integrity of mammalian circulation after injury, inflammation, disease, congenital defect, dysfunction or other disruption. Further, the formation of blood clots does not only limit bleeding in case of an injury (hemostasis), but may lead to serious organ damage and death in the context of atherosclerotic diseases by occlusion of an important artery or vein. Thrombosis is thus blood clot formation at the wrong time and place.

[0418] Accordingly, the present invention provides anti-coagulation and antithrombotic treatments aiming at inhibiting the formation of blood clots in order to prevent or treat blood coagulation disorders, such as myocardial infarction, stroke, loss of a limb by peripheral artery disease or pulmonary embolism.

[0419] As used interchangeably herein, "modulating or modulation of hemostasis" and "regulating or regulation of hemostasis" includes the induction (e.g., stimulation or increase) of hemostasis, as well as the inhibition (e.g., reduction or decrease) of hemostasis.

[0420] In one aspect, the invention provides a method for reducing or inhibiting hemostasis in a subject by administering a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein. The compositions and methods or uses disclosed herein are useful for the treatment or prevention of thrombotic disorders. As used herein, the term "thrombotic disorder" includes any disorder or condition characterized by excessive or unwanted coagulation or hemostatic activity, or a hypercoagulable state.

[0421] Thrombotic disorders include diseases or disorders involving platelet adhesion and thrombus formation, and may manifest as an increased propensity to form thromboses, e.g., an increased number of thromboses, thrombosis at an early age, a familial tendency towards thrombosis, and thrombosis at unusual sites.

[0422] In another embodiment, a combination drug regimen may include drugs or compounds for the treatment or prevention of blood coagulation disorders or secondary conditions associated with these conditions. Thus, a combination drug regimen may include one or more sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein and one or more anti-coagulation or anti-thrombosis agents.

Weight Control

[0423] In another aspect, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used for treating or preventing weight gain or obesity in a subject. For example, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used, for example, to treat or prevent hereditary obesity, dietary obesity, hormone related obesity, obesity related to the administration of medication, to reduce the weight of a subject, or to reduce or prevent weight gain in a subject. A subject in need of such a treatment may be a subject who is obese, likely to become obese, overweight, or likely to become overweight. Subjects who are likely to become obese or overweight can be identified, for example, based on family history, genetics, diet, activity level, medication intake, or various combinations thereof.

[0424] In yet other embodiments, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be administered to subjects suffering from a variety of other diseases and conditions that may be treated or prevented by promoting weight loss in the subject. Such diseases include, for example, high blood pressure, hypertension, high blood cholesterol, dyslipidemia, type 2 diabetes, insulin resistance, glucose intolerance, hyperinsulinemia, coronary heart disease, angina pectoris, congestive heart failure, stroke, gallstones, cholecystitis and cholelithiasis, gout, osteoarthritis, obstructive sleep apnea and respiratory problems, some types of cancer (such as endometrial, breast, prostate, and colon), complications of pregnancy, poor female reproductive health (such as menstrual irregularities, infertility, irregular ovulation), bladder control problems (such as stress incontinence); uric acid nephrolithiasis; psychological disorders (such as depression, eating disorders, distorted body image, and low self-esteem). Finally, patients with AIDS can develop lipodystrophy or insulin resistance in response to combination therapies for AIDS.

[0425] In another embodiment, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used for inhibiting adipogenesis or fat cell differentiation, whether in vitro or in vivo. Such methods or uses may be used for treating or preventing obesity.

[0426] In other embodiments, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used for reducing appetite and/or increasing satiety, thereby causing weight loss or avoidance of weight gain. A subject in need of such a treatment may be a subject who is overweight, obese or a subject likely to become overweight or obese. The method may comprise administering daily or, every other day, or once a week, a dose, e.g., in the form of a pill, to a subject. The dose may be an "appetite reducing dose."

[0427] In an exemplary embodiment, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be administered as a combination therapy for treating or preventing weight gain or obesity. For example, one or more sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be administered in combination with one or more anti-obesity agents.

[0428] In another embodiment, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be administered to reduce drug-induced weight gain. For example, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may be administered as a combination therapy with medications that may stimulate appetite or cause weight gain, in particular, weight gain due to factors other than water retention.

Metabolic Disorders/Diabetes

[0429] In another aspect, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used for treating or preventing a metabolic disorder, such as insulin-resistance, a pre-diabetic state, type II diabetes, and/or complications thereof. Administration of a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may increase insulin sensitivity and/or decrease insulin levels in a subject. A subject in need of such a treatment may be a subject who has insulin resistance or other precursor symptom of type II diabetes, who has type II diabetes, or who is likely to develop any of these conditions. For example, the subject may be a subject having insulin resistance, e.g., having high circulating levels of insulin and/or associated conditions, such as hyperlipidemia, dyslipogenesis, hypercholesterolemia, impaired glucose tolerance, high blood glucose sugar level, other manifestations of syndrome X, hypertension, atherosclerosis and lipodystrophy.

[0430] In an exemplary embodiment, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be administered as a combination therapy for treating or preventing a metabolic disorder. For example, one or more sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be administered in combination with one or more anti-diabetic agents.

Inflammatory Diseases

[0431] In other aspects, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein can be used to treat or prevent a disease or disorder associated with inflammation. Sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be administered prior to the onset of, at, or after the initiation of inflammation. When used prophylactically, the compounds are preferably provided in advance of any inflammatory response or symptom. Administration of the compounds may prevent or attenuate inflammatory responses or symptoms.

[0432] In another embodiment, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used to treat or prevent allergies and respiratory conditions, including asthma, bronchitis, pulmonary fibrosis, allergic rhinitis, oxygen toxicity, emphysema, chronic bronchitis, acute respiratory distress syndrome, and any chronic obstructive pulmonary disease (COPD). The compounds may be used to treat chronic hepatitis infection, including hepatitis B and hepatitis C.

[0433] Additionally, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used to treat autoimmune diseases, and/or inflammation associated with autoimmune diseases, such as arthritis, including rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, as well as organ-tissue autoimmune diseases (e.g., Raynaud's syndrome), ulcerative colitis, Crohn's disease, oral mucositis, scleroderma, myasthenia gravis, transplant rejection, endotoxin shock, sepsis, psoriasis, eczema, dermatitis, multiple sclerosis, autoimmune thyroiditis, uveitis, systemic lupus erythematosis, Addison's disease, autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome), and Grave's disease.

[0434] In certain embodiments, one or more sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be taken alone or in combination with other compounds useful for treating or preventing inflammation.

Flushing

[0435] In another aspect, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used for reducing the incidence or severity of flushing and/or hot flashes which are symptoms of a disorder. For instance, the subject method includes the use of sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein, alone or in combination with other agents, for reducing incidence or severity of flushing and/or hot flashes in cancer patients. In other embodiments, the method provides for the use of sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein to reduce the incidence or severity of flushing and/or hot flashes in menopausal and post-menopausal woman.

[0436] In another aspect, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used as a therapy for reducing the incidence or severity of flushing and/or hot flashes which are side-effects of another drug therapy, e.g., drug-induced flushing. In certain embodiments, a method for treating and/or preventing drug-induced flushing comprises administering to a patient in need thereof a formulation comprising at least one flushing inducing compound and at least one sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein. In other embodiments, a method for treating drug induced flushing comprises separately administering one or more compounds that induce flushing and one or more sirtuin-modulating compounds, e.g., wherein the sirtuin-modulating compound and flushing inducing agent have not been formulated in the same compositions. When using separate formulations, the sirtuin-modulating compound may be administered (1) at the same as administration of the flushing inducing agent, (2) intermittently with the flushing inducing agent, (3) staggered relative to administration of the flushing inducing agent, (4) prior to administration of the flushing inducing agent, (5) subsequent to administration of the flushing inducing agent, and (6) various combination thereof. Exemplary flushing inducing agents include, for example, niacin, raloxifene, antidepressants, anti-psychotics, chemotherapeutics, calcium channel blockers, and antibiotics.

[0437] In certain embodiments, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used to reduce flushing side effects of a vasodilator or an antilipemic agent (including anticholesteremic agents and lipotropic agents). In an exemplary embodiment, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may be used to reduce flushing associated with the administration of niacin.

[0438] In another embodiment, the invention provides a method for treating and/or preventing hyperlipidemia with reduced flushing side effects. In another representative embodiment, the method involves the use of sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein to reduce flushing side effects of raloxifene. In another representative embodiment, the method involves the use of sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein to reduce flushing side effects of antidepressants or anti-psychotic agent. For instance, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein can be used in conjunction (administered separately or together) with a serotonin reuptake inhibitor, or a 5HT2 receptor antagonist.

[0439] In certain embodiments, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used as part of a treatment with a serotonin reuptake inhibitor (SRI) to reduce flushing. In still another representative embodiment, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used to reduce flushing side effects of chemotherapeutic agents, such as cyclophosphamide and tamoxifen.

[0440] In another embodiment, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used to reduce flushing side effects of calcium channel blockers, such as amlodipine.

[0441] In another embodiment, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used to reduce flushing side effects of antibiotics. For example, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein can be used in combination with levofloxacin.

Ocular Disorders

[0442] One aspect of the present invention is a method for inhibiting, reducing or otherwise treating vision impairment by administering to a patient a therapeutic dosage of sirtuin modulator selected from a compound disclosed herein, or a pharmaceutically acceptable salt, prodrug or a metabolic derivative thereof.

[0443] In certain aspects of the invention, the vision impairment is caused by damage to the optic nerve or central nervous system. In particular embodiments, optic nerve damage is caused by high intraocular pressure, such as that created by glaucoma. In other particular embodiments, optic nerve damage is caused by swelling of the nerve, which is often associated with an infection or an immune (e.g., autoimmune) response such as in optic neuritis.

[0444] In certain aspects of the invention, the vision impairment is caused by retinal damage. In particular embodiments, retinal damage is caused by disturbances in blood flow to the eye (e.g., arteriosclerosis, vasculitis). In particular embodiments, retinal damage is caused by disruption of the macula (e.g., exudative or non-exudative macular degeneration).

[0445] Exemplary retinal diseases include Exudative Age Related Macular Degeneration, Nonexudative Age Related Macular Degeneration, Retinal Electronic Prosthesis and RPE Transplantation Age Related Macular Degeneration, Acute Multifocal Placoid Pigment Epitheliopathy, Acute Retinal Necrosis, Best Disease, Branch Retinal Artery Occlusion, Branch Retinal Vein Occlusion, Cancer Associated and Related Autoimmune Retinopathies, Central Retinal Artery Occlusion, Central Retinal Vein Occlusion, Central Serous Chorioretinopathy, Eales Disease, Epimacular Membrane, Lattice Degeneration, Macroaneurysm, Diabetic Macular Edema, Irvine-Gass Macular Edema, Macular Hole, Subretinal Neovascular Membranes, Diffuse Unilateral Subacute Neuroretinitis, Nonpseudophakic Cystoid Macular Edema, Presumed Ocular Histoplasmosis Syndrome, Exudative Retinal Detachment, Postoperative Retinal Detachment, Proliferative Retinal Detachment, Rhegmatogenous Retinal Detachment, Tractional Retinal Detachment, Retinitis Pigmentosa, CMV Retinitis, Retinoblastoma, Retinopathy of Prematurity, Birdshot Retinopathy, Background Diabetic Retinopathy, Proliferative Diabetic Retinopathy, Hemoglobinopathies Retinopathy, Purtscher Retinopathy, Valsalva Retinopathy, Juvenile Retinoschisis, Senile Retinoschisis, Terson Syndrome and White Dot Syndromes.

[0446] Other exemplary diseases include ocular bacterial infections (e.g. conjunctivitis, keratitis, tuberculosis, syphilis, gonorrhea), viral infections (e.g., Ocular Herpes Simplex Virus, Varicella Zoster Virus, Cytomegalovirus retinitis, Human Immunodeficiency Virus (HIV)) as well as progressive outer retinal necrosis secondary to HIV or other HIV-associated and other immunodeficiency-associated ocular diseases. In addition, ocular diseases include fungal infections (e.g., *Candida* choroiditis, histoplasmosis), protozoal infections (e.g., toxoplasmosis) and others such as ocular toxocariasis and sarcoidosis.

[0447] One aspect of the invention is a method for inhibiting, reducing or treating vision impairment in a subject undergoing treatment with a chemotherapeutic drug (e.g., a neurotoxic drug, or a drug that raises intraocular pressure, such as a steroid), by administering to the subject in need of such treatment a therapeutic dosage of a sirtuin modulator disclosed herein.

[0448] Another aspect of the invention is a method for inhibiting, reducing or treating vision impairment in a subject undergoing surgery, including ocular or other surgeries performed in the prone position such as spinal cord surgery, by administering to the subject in need of such treatment a therapeutic dosage of a sirtuin modulator disclosed herein. Ocular surgeries include cataract, iridotomy and lens replacements.

[0449] Another aspect of the invention is the treatment, including inhibition and prophylactic treatment, of age related ocular diseases include cataracts, dry eye, age-related macular degeneration (AMD), retinal damage and the like, by administering to the subject in need of such treatment a therapeutic dosage of a sirtuin modulator disclosed herein.

[0450] Another aspect of the invention is the prevention or treatment of damage to the eye caused by stress, chemical insult or radiation, by administering to the subject in need of such treatment a therapeutic dosage of a sirtuin modulator disclosed herein. Radiation or electromagnetic damage to the eye can include that caused by CRT's or exposure to sunlight or UV.

[0451] In certain embodiments, a combination drug regimen may include drugs or compounds for the treatment or prevention of ocular disorders or secondary conditions associated with these conditions. Thus, a combination drug regimen may include one or more sirtuin activators and one or more therapeutic agents for the treatment of an ocular disorder.

[0452] In certain embodiments, a sirtuin modulator can be administered in conjunction with a therapy for reducing intraocular pressure. In another embodiment, a sirtuin modulator can be administered in conjunction with a therapy for treating and/or preventing glaucoma. In yet another embodiment, a sirtuin modulator can be administered in conjunction with a therapy for treating and/or preventing optic neuritis. In certain embodiments, a sirtuin modulator can be administered in conjunction with a therapy for treating and/or preventing CMV Retinopathy. In another embodiment, a sirtuin modulator can be administered in conjunction with a therapy for treating and/or preventing multiple sclerosis.

Mitochondrial-Associated Diseases and Disorders

[0453] In certain embodiments, the invention provides methods or uses for treating diseases or disorders that would benefit from increased mitochondrial activity. The methods involve administering to a subject in need thereof a therapeutically effective amount of a sirtuin-modulating compound. Increased mitochondrial activity refers to increasing activity of the mitochondria while maintaining the overall numbers of mitochondria (e.g., mitochondrial mass), increasing the numbers of mitochondria thereby increasing mitochondrial activity (e.g., by stimulating mitochondrial biogenesis), or combinations thereof. In certain embodiments, diseases and disorders that would benefit from increased mitochondrial activity include diseases or disorders associated with mitochondrial dysfunction.

[0454] In certain embodiments, methods or uses for treating diseases or disorders that would benefit from increased mitochondrial activity may comprise identifying a subject suffering from a mitochondrial dysfunction. Methods or uses for diagnosing a mitochondrial dysfunction may involve molecular genetics, pathologic and/or biochemical analyses. Diseases and disorders associated with mitochondrial dysfunction include diseases and disorders in which deficits in mitochondrial respiratory chain activity contribute to the development of pathophysiology of such diseases or disorders in a mammal. Diseases or disorders that would benefit from increased mitochondrial activity generally include for example, diseases in which free radical mediated oxidative injury leads to tissue degeneration, diseases in which cells inappropriately undergo apoptosis, and diseases in which cells fail to undergo apoptosis.

[0455] In certain embodiments, the invention provides methods or uses for treating a disease or disorder that would benefit from increased mitochondrial activity that involves administering to a subject in need thereof one or more sirtuin-modulating compounds in combination with another therapeutic agent such as, for example, an agent useful for treating mitochondrial dysfunction or an agent useful for reducing a symptom associated with a disease or disorder involving mitochondrial dysfunction.

[0456] In exemplary embodiments, the invention provides methods or uses for treating diseases or disorders that would benefit from increased mitochondrial activity by administering to a subject a therapeutically effective amount of a sirtuin-modulating compound. Exemplary diseases or disorders include, for example, neuromuscular disorders (e.g., Friedreich's Ataxia, muscular dystrophy, multiple sclerosis, etc.), disorders of neuronal instability (e.g., seizure disorders, migraine, etc.), developmental delay, neurodegenerative disorders (e.g., Alzheimer's Disease, Parkinson's Disease, amyotrophic lateral sclerosis, etc.), ischemia, renal tubular acidosis, age-related neurodegeneration and cognitive decline, chemotherapy fatigue, age-related or chemotherapy-induced menopause or irregularities of menstrual cycling or ovulation, mitochondrial myopathies, mitochondrial damage (e.g., calcium accumulation, excitotoxicity, nitric oxide exposure, hypoxia, etc.), and mitochondrial deregulation.

[0457] Muscular dystrophy refers to a family of diseases involving deterioration of neuromuscular structure and function, often resulting in atrophy of skeletal muscle and myocardial dysfunction, such as Duchenne muscular dystrophy. In certain embodiments, sirtuin-modulating compounds may be used for reducing the rate of decline in muscular functional capacities and for improving muscular functional status in patients with muscular dystrophy.

[0458] In certain embodiments, sirtuin-modulating compounds may be useful for treatment mitochondrial myopathies. Mitochondrial myopathies range from mild, slowly progressive weakness of the extraocular muscles to severe, fatal infantile myopathies and multisystem encephalomyopathies. Some syndromes have been defined, with some overlap between them. Established syndromes affecting muscle include progressive external ophthalmoplegia, the Kearns-Sayre syndrome (with ophthalmoplegia, pigmentary retinopathy, cardiac conduction defects, cerebellar ataxia, and sensorineural deafness), the MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes), the MERFF syndrome (myoclonic epilepsy and ragged red fibers), limb-girdle distribution weakness, and infantile myopathy (benign or severe and fatal).

[0459] In certain embodiments, sirtuin-modulating compounds may be useful for treating patients suffering from toxic damage to mitochondria, such as, toxic damage due to calcium accumulation, excitotoxicity, nitric oxide exposure, drug induced toxic damage, or hypoxia.

[0460] In certain embodiments, sirtuin-modulating compounds may be useful for treating diseases or disorders associated with mitochondrial deregulation.

Muscle Performance

[0461] In other embodiments, the invention provides methods or uses for enhancing muscle performance by administering a therapeutically effective amount of a sirtuin-modulating compound. For example, sirtuin-modulating compounds may be useful for improving physical endurance (e.g., ability to perform a physical task such as exercise, physical labor, sports activities, etc.), inhibiting or retarding physical fatigues, enhancing blood oxygen levels, enhancing energy in healthy individuals, enhance working capacity and endurance, reducing muscle fatigue, reducing stress, enhancing cardiac and cardiovascular function, improving sexual ability, increasing muscle ATP levels, and/or reducing lactic acid in blood. In certain embodiments, the methods or uses involve administering an amount of a sirtuin-modulating compound that increase mitochondrial activity, increase mitochondrial biogenesis, and/or increase mitochondrial mass.

[0462] Sports performance refers to the ability of the athlete's muscles to perform when participating in sports activities. Enhanced sports performance, strength, speed and endurance are measured by an increase in muscular contraction strength, increase in amplitude of muscle contraction, shortening of muscle reaction time between stimulation and contraction. Athlete refers to an individual who participates in sports at any level and who seeks to achieve an improved level of strength, speed and endurance in their performance, such as, for example, body builders, bicyclists, long distance runners, short distance runners, etc. Enhanced sports performance in manifested by the ability to overcome muscle fatigue, ability to maintain activity for longer periods of time, and have a more effective workout.

[0463] In the arena of athlete muscle performance, it is desirable to create conditions that permit competition or training at higher levels of resistance for a prolonged period of time.

[0464] It is contemplated that the methods or uses of the present invention will also be effective in the treatment of muscle related pathological conditions, including acute sarcopenia, for example, muscle atrophy and/or cachexia associated with burns, bed rest, limb immobilization, or major thoracic, abdominal, and/or orthopedic surgery.

[0465] In certain embodiments, the invention provides novel dietary compositions comprising sirtuin modulators, a method for their preparation, and a method of using the compositions for improvement of sports performance. Accordingly, provided are therapeutic compositions, foods and beverages that have actions of improving physical endurance and/or inhibiting physical fatigues for those people involved in broadly-defined exercises including sports requiring endurance and labors requiring repeated muscle exertions. Such dietary compositions may additional comprise electrolytes, caffeine, vitamins, carbohydrates, etc.

Other Uses

[0466] Sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used for treating or preventing viral infections (such as infections by influenza, herpes or papilloma virus) or as antifungal agents. In certain embodiments, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be administered as part of a combination drug therapy with another therapeutic agent for the treatment of viral diseases.

In another embodiment, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be administered as part of a combination drug therapy with another anti-fungal agent.

[0467] Subjects that may be treated as described herein include eukaryotes, such as mammals, e.g., humans, ovines, bovines, equines, porcines, canines, felines, non-human primate, mice, and rats. Cells that may be treated include eukaryotic cells, e.g., from a subject described above, or plant cells, yeast cells and prokaryotic cells, e.g., bacterial cells. For example, modulating compounds may be administered to farm animals to improve their ability to withstand farming conditions longer.

[0468] Sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may also be used to increase lifespan, stress resistance, and resistance to apoptosis in plants. In certain embodiments, a compound is applied to plants, e.g., on a periodic basis, or to fungi. In another embodiment, plants are genetically modified to produce a compound. In another embodiment, plants and fruits are treated with a compound prior to picking and shipping to increase resistance to damage during shipping. Plant seeds may also be contacted with compounds described herein, e.g., to preserve them.

[0469] In other embodiments, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used for modulating lifespan in yeast cells. Situations in which it may be desirable to extend the lifespan of yeast cells include any process in which yeast is used, e.g., the making of beer, yogurt, and bakery items, e.g., bread. Use of yeast having an extended lifespan can result in using less yeast or in having the yeast be active for longer periods of time. Yeast or other mammalian cells used for recombinantly producing proteins may also be treated as described herein.

[0470] Sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may also be used to increase lifespan, stress resistance and resistance to apoptosis in insects. In this embodiment, compounds would be applied to useful insects, e.g., bees and other insects that are involved in pollination of plants. In a specific embodiment, a compound would be applied to bees involved in the production of honey. Generally, the methods or uses described herein may be applied to any organism, e.g., eukaryote, which may have commercial importance. For example, they can be applied to fish (aquaculture) and birds (e.g., chicken and fowl).

[0471] Higher doses of sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may also be used as a pesticide by interfering with the regulation of silenced genes and the regulation of apoptosis during development. In this embodiment, a compound may be applied to plants using a method known in the art that ensures the compound is bio-available to insect larvae, and not to plants.

[0472] At least in view of the link between reproduction and longevity, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein can be applied to affect the reproduction of organisms such as insects, animals and microorganisms.

Additional Embodiments

[0473] In one aspect, the present invention relates to a method of increasing sirtuin-1 activity in a cell comprising the step of contacting the cell with a compound of Formula (I) or a pharmaceutically acceptable salt or corresponding pharmaceutical composition, respectively, thereof.

[0474] In one aspect, the present invention relates to a method for treating insulin resistance, a metabolic syndrome, diabetes, or complications thereof, or for increasing insulin sensitivity, comprising administering a compound or a pharmaceutically acceptable salt or corresponding pharmaceutical composition, respectively, thereof, to a subject in need thereof.

[0475] In one aspect, the present invention relates to a method for treating metabolic dysfunctions comprising administering a compound or a pharmaceutically acceptable salt or corresponding pharmaceutical composition, respectively, thereof, to a subject in need thereof.

[0476] In one aspect, the present invention relates to a method for treating diseases or disorders resulting from diminished SIRT1 expression or activity, which comprises administering a compound or a pharmaceutically acceptable salt or corresponding pharmaceutical composition, respectively, thereof, to a subject in need thereof.

[0477] In one aspect, the present invention relates to a method where the diseases or disorders resulting from diminished SIRT1 expression or activity are selected from, but not limited to aging or stress, diabetes, metabolic dysfunctions, neurodegenerative diseases, cardiovascular disease, cancer or inflammatory disease.

[0478] In one aspect, the present invention relates to a method, where diseases related to aging or stress, diabetes, metabolic dysfunctions, neurodegenerative diseases, cardiovascular disease, cancer or inflammatory disease are selected from psoriasis, atopic dermatitis, acne, rosacea, inflammatory bowel disease, osteoporosis, sepsis, arthritis, COPD, systemic lupus erythematosus and ophthalmic inflammation.

[0479] In one aspect, the present invention relates to a method, where diseases related to aging or stress, diabetes, metabolic dysfunctions, neurodegenerative diseases, cardiovascular disease, cancer or inflammatory disease are selected from psoriasis, atopic dermatitis, acne, rosacea, inflammatory bowel disease, osteoporosis, sepsis, arthritis, COPD, systemic lupus erythematosus and ophthalmic inflammation.

[0480] In one aspect, the present invention relates to a method for treating psoriasis, which comprises administering a compound or a pharmaceutically acceptable salt or corresponding pharmaceutical composition, respectively, thereof, to a subject in need thereof.

[0481] In one aspect, the present invention relates to administering a compound or a pharmaceutically acceptable salt or corresponding pharmaceutical composition, respectively, thereof, for use in therapy in treating a subject suffering from or susceptible to insulin resistance, a metabolic syndrome, diabetes, or complications thereof, or for increasing insulin sensitivity in a subject.

[0482] In one aspect, the present invention relates to a use of administering a compound or a pharmaceutically acceptable salt or corresponding pharmaceutical composition, respectively, thereof, in the manufacture of a medicament for use in the treatment of insulin resistance, a metabolic syndrome, diabetes, or complications thereof, or for increasing insulin sensitivity in a subject.

Assays P Yet other methods or uses contemplated herein include screening methods or uses for identifying compounds or agents that modulate sirtuins. An agent may be a nucleic acid, such as an aptamer. Assays may be conducted in a cell based or cell free format. For example, an assay may comprise incubating (or contacting) a sirtuin with a test agent under conditions in which a sirtuin can be modulated by an agent known to modulate the sirtuin, and monitoring or determining the level of modulation of the sirtuin in the presence of the test agent relative to the absence of the test agent. The level of modulation of a sirtuin can be determined by determining its ability to deacetylate a substrate. Exemplary substrates are acetylated peptides which can be obtained from BIOMOL (Plymouth Meeting, Pa.). Preferred substrates include peptides of p53, such as those comprising an acetylated K382. A particularly preferred substrate is the Fluor de Lys-SIRT1 (BIOMOL), i.e., the acetylated peptide Arg-His-Lys-Lys. Other substrates are peptides from human histones H3 and H4 or an acetylated amino acid. Substrates may be fluorogenic. The sirtuin may be SIRT1, Sir2, SIRT3, or a portion thereof. For example, recombinant SIRT1 can be obtained from BIOMOL. The reaction may be conducted for about 30 minutes and stopped, e.g., with nicotinamide. The HDAC fluorescent activity assay/drug discovery kit (AK-500, BIOMOL Research Laboratories) may be used to determine the level of acetylation. Similar assays are described in Bitterman et al. (2002) J. Biol. Chem. 277: 45099. The level of modulation of the sirtuin in an assay may be compared to the level of modulation of the sirtuin in the presence of one or more (separately or simultaneously) compounds described herein, which may serve as positive or negative controls. Sirtuins for use in the assays may be full length sirtuin proteins or portions thereof. Since it has been shown herein that activating compounds appear to interact with the N-terminus of SIRT1, proteins for use in the assays include N-terminal portions of sirtuins, e.g., about amino acids 1-176 or 1-255 of SIRT1; about amino acids 1-174 or 1-252 of Sir2.

[0483] In certain embodiments, a screening assay comprises (i) contacting a sirtuin with a test agent and an acetylated substrate under conditions appropriate for the sirtuin to deacetylate the substrate in the absence of the test agent; and (ii) determining the level of acetylation of the substrate, wherein a lower level of acetylation of the substrate in the presence of the test agent relative to the absence of the test agent indicates that the test agent stimulates deacetylation by the sirtuin, whereas a higher level of acetylation of the substrate in the presence of the test agent relative to the absence of the test agent indicates that the test agent inhibits deacetylation by the sirtuin.

[0484] In another embodiment, the screening assay may detect the formation of a 2'/3'-O-acetyl-ADP-ribose product of sirtuin-mediated NAD-dependent deacetylation. This O-acetyl-ADP-ribose product is formed in equimolar quantities with the deacetylated peptide product of the sirtuin deacetylation reaction. Accordingly, the screening assay may include (i) contacting a sirtuin with a test agent and an acetylated substrate under conditions appropriate for the sirtuin to deacetylate the substrate in the absence of the test agent; and (ii) determining the amount of O-acetyl-ADP-ribose formation, wherein an increase in O-acetyl-ADP-ribose formation in the presence of the test agent relative to the absence of the test agent indicates that the test agent stimulates deacetylation by the sirtuin, while a decrease in O-acetyl-ADP-ribose formation in the presence of the test agent relative to the absence of the test agent indicates that the test agent inhibits deacetylation by the sirtuin.

[0485] Methods or uses for identifying an agent that modulates, e.g., stimulates, sirtuins in vivo may comprise (i) contacting a cell with a test agent and a substrate that is capable of entering a cell in the presence of an inhibitor of class I and class II HDACs under conditions appropriate for the sirtuin to deacetylate the substrate in the absence of the test agent; and (ii) determining the level of acetylation of the substrate, wherein a lower level of acetylation of the substrate in the presence of the test agent relative to the absence of the test agent indicates that the test agent stimulates deacetylation by the sirtuin, whereas a higher level of acetylation of the substrate in the presence of the test agent relative to the absence of the test agent indicates that the test agent inhibits deacetylation by the sirtuin. A preferred substrate is an acetylated peptide, which is also preferably fluorogenic, as further described herein. The method may further comprise lysing the cells to determine the level of acetylation of the substrate. Substrates may be added to cells at a concentration ranging from about 1 μM to about 10 mM, preferably from about 10 μM to 1 mM, even more preferably from about 100 μM to 1 mM, such as about 200 μM. A preferred substrate is an acetylated lysine, e.g., ε-acetyl lysine (Fluor de Lys, FdL) or Fluor de Lys-SIRT1. A preferred inhibitor of class I and class II HDACs is trichostatin A (TSA), which may be used at concentrations ranging from about 0.01 to 100M, preferably from about 0.1 to 10M, such as 1 μM. Incubation of cells with the test compound and the substrate may be conducted for about 10 minutes to 5 hours, preferably for about 1-3 hours. Since TSA inhibits all class I and class II HDACs, and that certain substrates, e.g., Fluor de Lys, is a poor substrate for SIRT2 and even less a substrate for SIRT3-7, such an assay may be used to identify modulators of SIRT1 in vivo.

Methods and Uses for Therapy or Medicament

[0486] The present invention also relates to methods or uses for using Sirtuin Modulator compounds as defined herein in treating and/or preventing a wide variety of diseases and disorders, which include, but are not limited to, for example, diseases or disorders related to aging or stress, diabetes, obesity, neurodegenerative diseases, cardiovascular disease, blood clotting disorders, inflammation, cancer, and/or flushing as well as diseases or disorders that would benefit from increased mitochondrial activity, further which may be selected from or include, but are not limited to psoriasis, atopic dermatitis, acne, rosacea, inflammatory bowel disease, osteoporosis, sepsis, arthritis, COPD, systemic lupus erythematosus and ophthalmic inflammation.

[0487] In another aspect, the invention provides methods or uses for using sirtuin-modulating compounds, or compositions comprising sirtuin-modulating compounds. In certain embodiments, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used for a variety of therapeutic applications including, for example, increasing the lifespan of a cell, and treating and/or preventing a wide variety of diseases and disorders including, for example, diseases or disorders related to aging or stress, diabetes, obesity, neurodegenerative diseases, chemotherapeutic-induced neuropathy, neuropathy associated with an ischemic event, ocular diseases and/or disorders, cardiovascular disease, blood clotting disorders, inflammation, and/or flushing, etc. Sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may also be used for treating a disease or disorder in a subject that would benefit from increased mitochondrial activity, for enhancing muscle performance, for increasing muscle ATP levels, or for treating or preventing muscle tissue damage associated with hypoxia or ischemia. In other embodiments, sirtuin-modulating compounds that decrease the level and/or activity of a sirtuin protein may be used for a variety of therapeutic applications including, for example, increasing cellular sensitivity to stress, increasing apoptosis, treatment of cancer, stimulation of appetite, and/or stimulation of weight gain, etc. As described further below, the methods or uses comprise administering to a subject in need thereof a pharmaceutically effective amount of a sirtuin-modulating compound.

[0488] In certain aspects, the sirtuin-modulating compounds may be administered alone or in combination with other compounds, including other sirtuin-modulating compounds, or other therapeutic agents.

[0489] In another aspect, the present invention relates to a method of increasing sirtuin-1 activity in a cell, which comprises the step of contacting the cell with a compound of Formulas (I) to (IV), corresponding anlogs or derivatives thereof (i.e., with hydrogen substitution at the R^2 position) or a pharmaceutical acceptable salt thereof of the present invention.

[0490] In another aspect, the present invention relates to a method of increasing sirtuin-1 activity in a cell comprising the step of contacting the cell with a pharmaceutical composition of the present invention as defined herein In another aspect, the present invention relates to a method for treating insulin resistance, a metabolic syndrome, diabetes, or complications thereof, or for increasing insulin sensitivity, which comprises administering a compound a compound of Formulas (I) to (IV), corresponding anlogs or derivatives thereof (i.e., with hydrogen substitution at the R^2 position) of the present invention to a subject in need thereof.

[0491] In another aspect, the present invention relates to a method for treating a subject suffering from or susceptible to insulin resistance, a metabolic syndrome, diabetes, or complications thereof, or for increasing insulin sensitivity in a subject, comprising administering a pharmaceutical composition of the present invention to the subject in need thereof.

[0492] In another aspect, the present invention relates to a method for treating insulin resistance, a metabolic syndrome, diabetes, or complications thereof, or for increasing insulin sensitivity, comprising administering a pharmaceutical composition of the present invention to a subject in need thereof.

[0493] In another aspect, the present invention relates to a method of increasing sirtuin-1 activity in a cell, which comprises the step of contacting a cell with a compound of Formulas (I) to (IV), corresponding anlogs or derivatives thereof (i.e., with hydrogen substitution at the R^2 position) or a pharmaceutical acceptable salt thereof.

[0494] In another aspect, the present invention relates to a method of increasing sirtuin-1 activity in a cell, which comprises the step of contacting a cell with a pharmaceutical composition of the present invention

[0495] In another aspect, the present invention relates to a method for treating metabolic dysfunctions, which comprises administering a compound of Formulas (I) to (IV), corresponding anlogs or derivatives thereof (i.e., with hydrogen substitution at the R^2 position) or a pharmaceutical acceptable salt thereof to a subject in need thereof.

[0496] In another aspect, the present invention relates to a method for treating metabolic dysfunctions comprising administering a pharmaceutical composition of the present invention to a subject in need thereof.

[0497] In another aspect, the present invention relates to a method for treating diseases or disorders resulting from diminished SIRT1 expression or activity, which comprises administering a compound of Formulas (I) to (IV), corresponding anlogs or derivatives thereof (i.e., with hydrogen substitution at the R^2 position) or a pharmaceutical acceptable salt thereof to a subject in need thereof.

[0498] In another aspect, the present invention relates to method where the diseases or disorders resulting from diminished SIRT1 expression or activity are selected from, but not limited to aging or stress, diabetes, metabolic dysfunctions, neurodegenerative diseases, cardiovascular disease, cancer or inflammatory disease.

[0499] In another aspect, the present invention relates to a method where diseases related to aging or stress, diabetes, metabolic dysfunctions, neurodegenerative diseases, cardiovascular disease, cancer or inflammatory disease are selected from psoriasis, atopic dermatitis, acne, rosacea, inflammatory bowel disease, osteoporosis, sepsis, arthritis, COPD, systemic lupus erythematosus and ophthalmic inflammation.

[0500] In another aspect, the present invention relates to a method for treating psoriasis, which comprises administering a compound of Formulas (I) to (VI), corresponding anlogs or derivatives thereof (i.e., with hydrogen substitution at the R^2 position) or a pharmaceutical acceptable salt thereof to a subject in need thereof.

[0501] In another aspect, the present invention relates to a method for treating psoriasis, which comprises administering a pharmaceutical composition of the present invention to a subject in need thereof

Pharmaceutical Compositions and Formulations

[0502] In general, the present invention relates to substituted bridged urea analog compounds of Formulas (I) to (VI), corresponding anlogs or derivatives thereof (i.e., with hydrogen substitution at the R^2 position), or pharmaceutically acceptable salts thereof, corresponding pharmaceutical compositions, processes for making and use of such compounds, alone or in combination with other therapeutic agents, as Sirtuin Modulators useful for increasing lifespan of a cell, and in treating and/or preventing a wide variety of diseases and disorders, which include, but are not limited to, for example, diseases or disorders related to aging or stress, diabetes, obesity, neurodegenerative diseases, cardiovascular disease, blood clotting disorders, inflammation, cancer, and/or flushing as well as diseases or disorders that would benefit from increased mitochondrial activity.

[0503] In particular, the present invention relates to novel compounds of Formulas (I) to (IV), corresponding anlogs or derivatives thereof (i.e., with hydrogen substitution at the R^2 position) or a pharmaceutical acceptable salt thereof and corresponding pharmaceutical compositions comprising compounds of Formulas (I) to (IV), respectively.

[0504] In another aspect, the present invention relates to a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound of Formulas (I) to (IV), corresponding anlogs or derivatives thereof (i.e., with hydrogen substitution at the R^2 position) or a pharmaceutical acceptable salt thereof.

[0505] In another aspect, the present invention relates to a pharmaceutical composition of the present invention, further comprising an additional active agent.

[0506] In another aspect, the present invention relates to a pharmaceutical composition comprising a compound of Formulas (I) to (IV), corresponding anlogs or derivatives thereof (i.e., with hydrogen substitution at the R^2 position) or a pharmaceutical acceptable salt thereof and at least one pharmaceutically acceptable carrier.

[0507] The compounds described herein may be formulated in a conventional manner using one or more physiologically or pharmaceutically acceptable carriers or excipients. For example, compounds and their pharmaceutically acceptable salts and solvates may be formulated for administration by, for example, injection (e.g. SubQ, IM, IP), inhalation or insufflation (either through the mouth or the nose) or oral, buccal, sublingual, transdermal, nasal, parenteral or rectal administration. In certain embodiments, a compound may be administered locally, at the site where the target cells are present, i.e., in a specific tissue, organ, or fluid (e.g., blood, cerebrospinal fluid, etc.).

[0508] The compounds can be formulated for a variety of modes of administration, including systemic and topical or localized administration. Techniques and formulations generally may be found in Remington's Pharmaceutical Sciences, Meade Publishing Co., Easton, Pa. For parenteral administration, injection is preferred, including intramuscular, intravenous, intraperitoneal, and subcutaneous. For injection, the compounds can be formulated in liquid solutions, preferably in physiologically compatible buffers such as Hank's solution or Ringer's solution. In addition, the compounds may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms are also included.

[0509] For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges, or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); nonaqueous vehicles (e.g., almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavoring, coloring and sweetening agents as appropriate. Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

[0510] For administration by inhalation (e.g., pulmonary delivery), the compounds may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin, for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0511] The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multidose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[0512] The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

[0513] In addition to the formulations described previously, compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt. Controlled release formula also includes patches.

[0514] In certain embodiments, the compounds described herein can be formulated for delivery to the central nervous system (CNS) (reviewed in Begley, Pharmacology & Therapeutics 104: 29-45 (2004)). Conventional approaches for drug delivery to the CNS include: neurosurgical strategies (e.g., intracerebral injection or intracerebroventricular infusion); molecular manipulation of the agent (e.g., production of a chimeric fusion protein that comprises a transport peptide that has an affinity for an endothelial cell surface molecule in combination with an agent that is itself incapable of crossing the BBB) in an attempt to exploit one of the endogenous transport pathways of the BBB; pharmacological strategies designed to increase the lipid solubility of an agent (e.g., conjugation of water-soluble agents to lipid or cholesterol carriers); and the transitory disruption of the integrity of the BBB by hyperosmotic disruption (resulting from the infusion of a mannitol solution into the carotid artery or the use of a biologically active agent such as an angiotensin peptide).

[0515] Liposomes are a further drug delivery system which is easily injectable. Accordingly, in the method of invention the active compounds can also be administered in the form of a liposome delivery system. Liposomes are well known by those skilled in the art. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine of phosphatidylcholines. Liposomes usable for the method of invention encompass all types of liposomes including, but not limited to, small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles.

[0516] Another way to produce a formulation, particularly a solution, of a compound described herein, is through the use of cyclodextrin. By cyclodextrin is meant α-, β-, or γ-cyclodextrin. Cyclodextrins are described in detail in Pitha et al., U.S. Pat. No. 4,727,064. Cyclodextrins are cyclic oligomers of glucose; these compounds form inclusion complexes with any drug whose molecule can fit into the lipophile-seeking cavities of the cyclodextrin molecule.

[0517] Rapidly disintegrating or dissolving dosage forms are useful for the rapid absorption, particularly buccal and sublingual absorption, of pharmaceutically active agents. Fast melt dosage forms are beneficial to patients, such as aged and pediatric patients, who have difficulty in swallowing typical solid dosage forms, such as caplets and tablets. Additionally, fast melt dosage forms circumvent drawbacks associated with, for example, chewable dosage forms, wherein the length of time an active agent remains in a patient's mouth plays an important role in determining the amount of taste masking and the extent to which a patient may object to throat grittiness of the active agent.

[0518] Pharmaceutical compositions (including cosmetic preparations) may comprise from about 0.00001 to 100% such as from 0.001 to 10% or from 0.1% to 5% by weight of one or more compounds described herein. In other embodiments, the pharmaceutical composition comprises: (i) 0.05 to 1000 mg of the compounds of the invention, or a pharmaceutically acceptable salt thereof, and (ii) 0.1 to 2 grams of one or more pharmaceutically acceptable excipients.

[0519] In some embodiments, a compound described herein is incorporated into a topical formulation containing a topical carrier that is generally suited to topical drug administration and comprising any such material known in the art. The topical carrier may be selected so as to provide the composition in the desired form, e.g., as an ointment, lotion, cream, microemulsion, gel, oil, solution, or the like, and may be comprised of a material of either naturally occurring or synthetic origin. It is preferable that the selected carrier not adversely affect the active agent or other components of the topical formulation. Examples of suitable topical carriers for use herein include water, alcohols and other nontoxic organic solvents, glycerin, mineral oil, silicone, petroleum jelly, lanolin, fatty acids, vegetable oils, parabens, waxes, and the like.

[0520] Formulations may be colorless, odorless ointments, lotions, creams, microemulsions and gels.

[0521] The compounds may be incorporated into ointments, which generally are semisolid preparations which are typically based on petrolatum or other petroleum derivatives. The specific ointment base to be used, as will be appreciated by those skilled in the art, is one that will provide for optimum drug delivery, and, preferably, will provide for other desired characteristics as well, e.g., emolliency or the like. As with other carriers or vehicles, an ointment base should be inert, stable, nonirritating and nonsensitizing.

[0522] The compounds may be incorporated into lotions, which generally are preparations to be applied to the skin surface without friction, and are typically liquid or semiliquid preparations in which solid particles, including the active agent, are present in a water or alcohol base. Lotions are usually suspensions of solids, and may comprise a liquid oily emulsion of the oil-in-water type.

[0523] The compounds may be incorporated into creams, which generally are viscous liquid or semisolid emulsions, either oil-in-water or water-in-oil. Cream bases are water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol; the aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation, as explained in Remington's, supra, is generally a nonionic, anionic, cationic or amphoteric surfactant.

[0524] The compounds may be incorporated into microemulsions, which generally are thermodynamically stable, isotropically clear dispersions of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant molecules (Encyclopedia of Pharmaceutical Technology (New York: Marcel Dekker, 1992), volume 9).

[0525] The compounds may be incorporated into gel formulations, which generally are semisolid systems consisting of either suspensions made up of small inorganic particles (two-phase systems) or large organic molecules distributed substantially uniformly throughout a carrier liquid (single phase gels). Although gels commonly employ aqueous carrier liquid, alcohols and oils can be used as the carrier liquid as well.

[0526] Other active agents may also be included in formulations, e.g., other anti-inflammatory agents, analgesics, antimicrobial agents, antifungal agents, antibiotics, vitamins, antioxidants, and sunblock agents commonly found in sunscreen formulations including, but not limited to, anthranilates, benzophenones (particularly benzophenone-3), camphor derivatives, cinnamates (e.g., octyl methoxycinnamate), dibenzoyl methanes (e.g., butyl methoxydibenzoyl methane), p-aminobenzoic acid (PABA) and derivatives thereof, and salicylates (e.g., octyl salicylate).

[0527] In certain topical formulations, the active agent is present in an amount in the range of approximately 0.25 wt. % to 75 wt. % of the formulation, preferably in the range of approximately 0.25 wt. % to 30 wt. % of the formulation, more preferably in the range of approximately 0.5 wt. % to 15 wt. % of the formulation, and most preferably in the range of approximately 1.0 wt. % to 10 wt. % of the formulation.

[0528] Conditions of the eye can be treated or prevented by, e.g., systemic, topical, intraocular injection of a compound, or by insertion of a sustained release device that releases a compound. A compound may be delivered in a pharmaceutically acceptable ophthalmic vehicle, such that the compound is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye, as for example the anterior chamber, posterior chamber, vitreous body, aqueous humor, vitreous humor, cornea, iris/ciliary, lens, choroid/retina and sclera. The pharmaceutically acceptable ophthalmic vehicle may, for example, be an ointment, vegetable oil or an encapsulating material. Alternatively, the compounds of the invention may be injected directly into the vitreous and aqueous humour. In a further alternative, the compounds may be administered systemically, such as by intravenous infusion or injection, for treatment of the eye.

[0529] The compounds described herein may be stored in oxygen free environment. For example, a composition can be prepared in an airtight capsule for oral administration, such as Capsugel from Pfizer, Inc.

[0530] Cells, e.g., treated ex vivo with a compound as described herein, can be administered according to methods or uses for administering a graft to a subject, which may be accompanied, e.g., by administration of an immunosuppressant drug, e.g., cyclosporin A. For general principles in medicinal formulation, the reader is referred to Cell Therapy: Stem Cell Transplantation, Gene Therapy, and Cellular Immunotherapy, by G. Morstyn & W. Sheridan eds, Cambridge University Press, 1996; and Hematopoietic Stem Cell Therapy, E. D. Ball, J. Lister & P. Law, Churchill Livingstone, 2000.

[0531] Toxicity and therapeutic efficacy of compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals. The LD_{50} is the dose lethal to 50% of the population. The ED_{50} is the dose therapeutically effective in 50% of the population. The dose ratio between toxic and therapeutic effects (LD_{50}/ED_{50}) is the therapeutic index. Compounds that exhibit large therapeutic indexes are preferred. While compounds that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

[0532] The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds may lie within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC_{50} (i.e., the concentration of the test compound that achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

Kits

[0533] Also provided herein are kits, e.g., kits for therapeutic purposes or kits for modulating the lifespan of cells or modulating apoptosis. A kit may comprise one or more compounds as described herein, e.g., in premeasured doses. A kit may optionally comprise devices for contacting cells with the compounds and instructions for use. Devices include syringes, stents and other devices for introducing a compound into a subject (e.g., the blood vessel of a subject) or applying it to the skin of a subject.

[0534] In yet another embodiment, the invention provides a composition of matter comprising a compound of this invention and another therapeutic agent (the same ones used in combination therapies and combination compositions) in separate dosage forms, but associated with one another. The term "associated with one another" as used herein means that the separate dosage forms are packaged together or otherwise attached to one another such that it is readily apparent that the separate dosage forms are intended to be sold and administered as part of the same regimen. The compound and the other agent are preferably packaged together in a blister pack or other multi-chamber package, or as connected, separately sealed containers (such as foil pouches or the like) that can be separated by the user (e.g., by tearing on score lines between the two containers).

[0535] In still another embodiment, the invention provides a kit comprising in separate vessels, a) a compound of this invention; and b) another therapeutic agent such as those described elsewhere in the specification.

[0536] The practice of the present methods or uses will employ, unless otherwise indicated, conventional techniques of cell biology, cell culture, molecular biology, transgenic biology, microbiology, recombinant DNA, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature. See, for example, Molecular Cloning A Laboratory Manual, 2[nd] Ed., ed. by Sambrook, Fritsch and Maniatis (Cold Spring Harbor Laboratory Press: 1989); DNA Cloning, Volumes I and II (D. N. Glover ed., 1985); Oligonucleotide Synthesis (M. J. Gait ed., 1984); Mullis et al. U.S. Pat. No. 4,683,195; Nucleic Acid Hybridization (B. D Hames & S. J. Higgins eds. 1984); Transcription And Translation (B. D. Hames & S. J. Higgins eds. 1984); Culture Of Animal Cells (R. I. Freshney, Alan R. Liss, Inc., 1987); Immobilized Cells And Enzymes (IRL Press, 1986); B. Perbal, A Practical Guide To Molecular Cloning (1984); the treatise, Methods In Enzymology (Academic Press, Inc., N.Y.); Gene Transfer Vectors For Mammalian Cells (J. H. Miller and M. P. Calos eds., 1987, Cold Spring Harbor Laboratory); Methods In Enzymology, Vols. 154 and 155 (Wu et al. eds.), Immunochemical Methods In Cell And Molecular Biology (Mayer and Walker, eds., Academic Press, London, 1987); Handbook Of Experimental Immunology, Volumes I-IV (D. M. Weir and C. C. Blackwell, eds., 1986); Manipulating the Mouse Embryo, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986).

[0537] The Examples set forth below are illustrative of the present invention and are not intended to limit, in any way, the scope of the present invention.

Examples

[0538] The Examples set forth below are illustrative of the present invention and are not intended to limit, in any way, the scope of the present invention, but rather to provide guidance to the skilled artisan to prepare and use the compounds, compositions, and methods or uses of the present invention.

[0539] While particular embodiments of the present invention are described, the skilled artisan will appreciate that various changes and modifications can be made without departing from the spirit and scope of the invention.

[0540] As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the *Journal of the American Chemical Society or the Journal of Biological Chemistry*. Standard single-letter or three-letter abbreviations are generally used to designate amino acid residues, which are assumed to be in the L-configuration unless otherwise noted. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification.

[0541] All references to ether are to diethyl ether; brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in ° C. (degrees Centigrade). All reactions are conducted under an inert atmosphere at room temperature unless otherwise noted, and all solvents are highest available purity unless otherwise indicated.

Instrumentation Used

[0542] LCMS with PDA:

Waters Allaince2695-2996/Quattromicro

Agilent-1200/SQD

[0543] Preparative LC with UV Detector (Prep HPLC):

Waters-2545/2998 PDA and 2487 UV

Shimadzu—LC-20AP/20AV-UV

Gilson-333,334/115-UV

Chiral HPLC:

Waters Alliance-2695/2998 &2996

SFC Purification Systems:

Thar—SFC-80

Waters SFC-200

NMR (400 MHz):

Varian-400 MHz

[0544] ^{1}H-NMR tabulation was generated with 2014 ACD labs software.

[0545] ^{1}H NMR (hereinafter also "NMR") spectra were recorded on a Varian-400 MHz spectromitor. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad).

LCMS Methods Used

[0546] Acq. Method Conditions: RND-ABC-6-MIN
Column: XBridge BEH C18 (50 mm×4.6 mm, 2.5 μm)
Mobile Phase: A: 5 mM Ammonium Bicarbonate in water (PH-10 with Ammonia): ACN
Time (min)/% ACN: 0/5, 0.5/5, 1/15, 3.3/98, 5.2/98, 5.5/5, 6.0/5
Column temp: 35° C., Flow Rate 1.3 ml/min

MS Parameters:

Mass Range: 100-1000

Scan Time: 0.5 Sec

[0547] Inter-Scan delay: 0.1 sec

Run Time: 6.0 min

Acq.Method Conditions: RND-FA-4.5-MIN

[0548] Column: Acquity BEH C18 (50 mm×2.1 mm, 1.7 um)
Mobile Phase: A: 0.1% FA in water; B: 0.1% FA in ACN

Time (min)/% B: 0/3, 0.4/3, 3.2/98, 3.8/98, 4.2/3, 4.5/3

Column Temp: 35° C., Flow Rate: 0.6 mL/min

MS Parameters:

Mass Range: 100-1000

Scan Time: 0.5 Sec

[0549] Inter-Scan delay: 0.1 sec

Run Time: 4.5 min

Acq.Method Conditions: RND-FA-4.5-MIN

[0550] Column: Acquity BEH C18 (50 mm×2.1 mm, 1.7 um)

Mobile Phase: A: 0.1% FA in water; B: 0.1% FA in ACN

Time (min)/% B: 0/3, 0.4/3, 3.2/98, 3.8/98, 4.2/3, 4.5/3

Column Temp: 35° C., Flow Rate: 0.6 mL/min

MS Parameters:

Mass Range: 100-1000

Fragmentor: 100

Step Size: 0.1

Run Time: 4.5 min

[0551] Acq. Method Conditions: RND-ABC-6.5-MIN

Column: XBridge BEH C18 (50 mm×4.6 mm, 2.5 μm)

Mobile Phase: A: 5 mM Ammonium Bicarbonate in water (PH-10 with Ammonia): ACN

Time (min)/% ACN: 0/5, 0.5/5, 1/15, 3.3/98, 6.0/98, 6.1/5, 6.5/5

Column temp: 35° C., Flow Rate 1.3 ml/min

MS Parameters:

Mass Range: 100-1000

Fragmentor: 100

Step Size: 0.1

Run Time: 6.5 min

[0552] Acq. Method Conditions: RND-ABC-10-MIN

Column: XBridge BEH C18 (50 mm×4.6 mm, 2.5 μm)

Mobile Phase: A: 5 mM Ammonium Bicarbonate in water (PH-10 with Ammonia): ACN

Time (min)/% ACN: 0/5, 0.5/5, 1.5/15, 7/98, 9.0/98, 9.5/5, 10/5

Column temp: 35° C., Flow Rate 1.3 ml/min

MS Parameters:

Mass Range: 100-1000

Fragmentor: 100

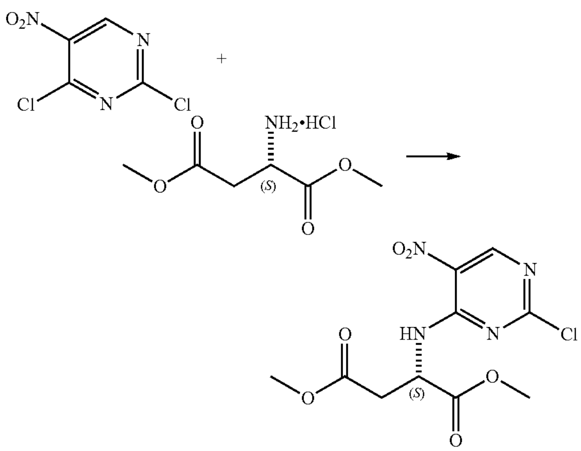
Step Size: 0.1

Run Time: 10.0 min

Intermediates

Synthesis of (S)-dimethyl 2-((2-chloro-5-nitropyrimidin-4-yl)amino)succinate

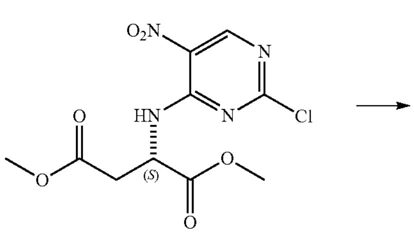
[0553]



[0554] To a stirred solution of 2, 4-dichloro-5-nitropyrimidine (225 g, 1160 mmol) in THF (2250 mL) was added sodium bicarbonate (292.29 g, 3479.74 mmol) at 25° C. and stirred for 10 min. Then (S)-dimethyl 2-aminosuccinate hydrochloride (344 g, 1739.7 mmol) was added and stirred under nitrogen atmosphere at 40° C. for 3 h. The reaction mixture was then filtered and concentrated under reduced pressure to remove all the THF solvent, the residue diluted with water (3.0 L). The mixture was extracted with ethyl acetate (2.5 L×2). The combined organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to obtain the crude compound. The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh, eluted with 20% to 40% ethyl acetate in pet ether) to afford (S)-dimethyl 2-((2-chloro-5-nitropyrimidin-4-yl)amino)succinate (125 g compound, yield: 25.9%, 76.73% purity by LCMS) as an off white solid (TLC: eluent: 30% Ethyl acetate in Pet ether, R_f 0.4), LCMS (m/z) 319.1 $[M+H]^+$.

Synthesis of (S)-methyl 2-(2-chloro-6-oxo-5,6,7,8-tetrahydropteridin-7-yl)acetate

[0555]



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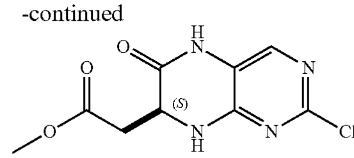
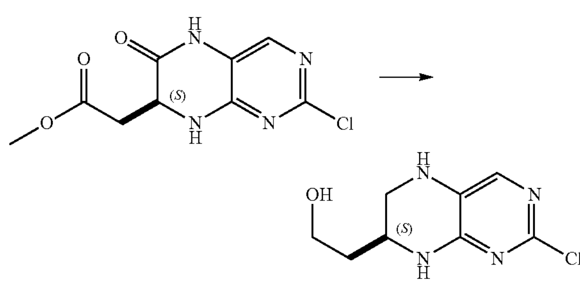


[0556] To a stirred solution of (S)-dimethyl 2-((2-chloro-5-nitropyrimidin-4-yl)amino)succinate (125 g, 393.05 mmol) in ethanol (750 mL), water (200 mL) and IPA (375 mL) was added Iron powder (109.76 g, 1965.4 mmol) at 25° C. and followed by glacial acetic acid (250 mL) was added. The reaction mixture was stirred under nitrogen atmosphere at 70° C. for 6 h. The reaction mixture was filtered through celite and washed thoroughly with ethyl acetate. The filtrate was evaporated under reduced pressure to obtain the residue which was diluted with water (500 mL) and extracted with ethyl acetate (5×750 mL). The combined organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to afford the crude compound. The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh, eluted with 2% to 5% methanol in dichloromethane) to yield (S)-methyl 2-(2-chloro-6-oxo-5,6,7,8-tetrahydropteridin-7-yl)acetate (80 g, 67.4% yield) as an off white solid (TLC: eluent: 60% Ethyl acetate in pet ether, R_f: 0.3), LCMS (m/z) 257.1 $[M+H]^+$.

Synthesis of (S)-2-(2-chloro-5,6,7,8-tetrahydropteridin-7-yl)ethanol

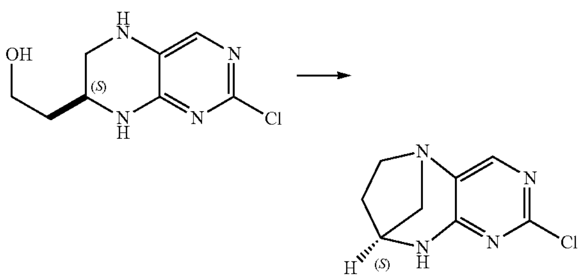
[0557]



[0558] To a stirred solution of (S)-methyl 2-(2-chloro-6-oxo-5,6,7,8-tetrahydropteridin-7-yl)acetate (160 g, 623 mmol) in THF (1600 mL) was added $LiAlH_4$ (118 g, 3117 mmol) in portions over a period of 1 h at 0° C. to −5° C. The reaction mixture was stirred under nitrogen atmosphere at 50° C. for 3 h. The reaction mixture was filtered through celite and washed thoroughly with ethyl acetate. Filtrate was evaporated under reduced pressure, then the residue diluted with water (500 mL) and extracted with ethyl acetate (10×750 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to obtain the crude compound. The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh, eluted with 5 to 10% methanol in dichloromethane) to afford (S)-2-(2-chloro-5,6,7,8-tetrahydropteridin-7-yl)ethanol (80 g, yield: 57.1%) as an off white solid (TLC: eluent: neat ethyl acetate, R_f: 0.3), LCMS (m/z) 215.1 $[M+H]^+$.

Synthesis of (8S)-2-chloro-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine

[0559]

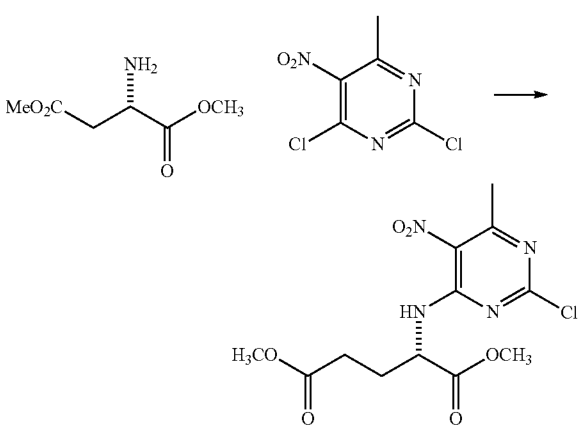


[0560] To a stirred solution of (S)-2-(2-chloro-5,6,7,8-tetrahydropteridin-7-yl)ethanol (80 g, 373.83 mmol) in DCM (1600 mL) was added DIPEA (145 g, 1118 mmol) followed by drop wise addition of $POCl_3$ (86 g, 559 mmol) over a period of 1 h at 0° C. to −5° C. The reaction mixture was stirred under nitrogen atmosphere at 25° C. for 30-40 min. The reaction mixture was evaporated under reduced pressure to remove excess $POCl_3$, then the residue diluted with water (500 mL) and extracted with ethyl acetate (10×250 mL). The combined organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to obtain the crude compound. The crude compound was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent 5 to 10% Methanol in DCM) to afford (8S)-2-chloro-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (50 g, 66.5% yield) as a yellow solid (TLC: eluent: 5% MeOH in Ethyl acetate, R_f: 0.3), LCMS (m/z) 197.1 [M+H]$^+$.

Synthesis of Substituted Bicyclic Pyrimidine Cores

Synthesis of (S)-dimethyl 2-((2-chloro-6-methyl-5-nitropyrimidin-4-yl)amino)pentanedioate

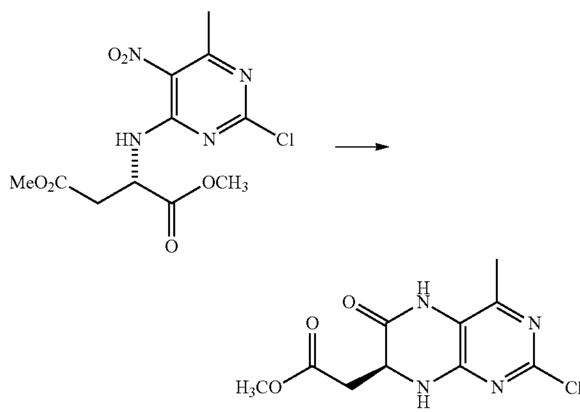
[0561]



[0562] To solid 2,4-dichloro-6-methyl-5-nitropyrimidine (10 g, 48.1 mmol) in Tetrahydrofuran (THF) (200 ml) stirred under nitrogen at room temp was added solid sodium bicarbonate (2.019 g, 24.04 mmol) and (S)-dimethyl 2-aminosuccinate hydrochloride (14.25 g, 72.1 mmol) portion wise during 15 min. The reaction mixture was stirred at room temperature for 48 hr. The reaction mixture was filtered and concentrated and the residue was taken up in ethyl acetate (200 mL). The solution was washed with water and brine, dried over Na_2SO_4, filtered and concentrated to give crude product compound. The crude compound added to a silica gel column and eluted with 20% EtOAc/pet ether to give pure compound (4.5 g, 2.318 mmol, 26.6% yield), LCMS (m/z) 331.1 [M+H]$^+$.

Synthesis of (S)-methyl 2-(2-chloro-4-methyl-6-oxo-5,6,7,8-tetrahydropteridin-7-yl)acetate

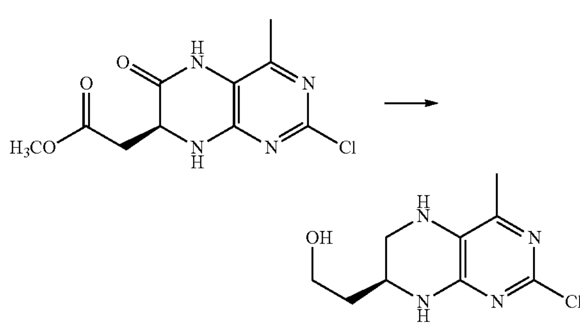
[0563]



[0564] To a solution of (S)-dimethyl 2-((2-chloro-6-methyl-5-nitropyrimidin-4-yl)amino)pentanedioate (4.5 g, 12.98 mmol), iron (3.62 g, 64.9 mmol) in isopropanol (150 mL) and water (50 ml) stirred at 40° C. was added a solution of AcOH (45 ml, 786 mmol). The reaction mixture was stirred at reflux for 16 hr. The organic phase was washed with saturated sodium bicarbonate solution (300 mL) and saturated brine (200 mL) and dried over sodium sulfate. The solution was evaporated in vacuo to give the product as an off-white solid (3.6 g, 11.76 mmol, 87% yield), LCMS (m/z) 271.1 [M+H]$^+$.

Synthesis of (S)-2-(2-chloro-4-methyl-5,6,7,8-tetrahydropteridin-7-yl)ethanol

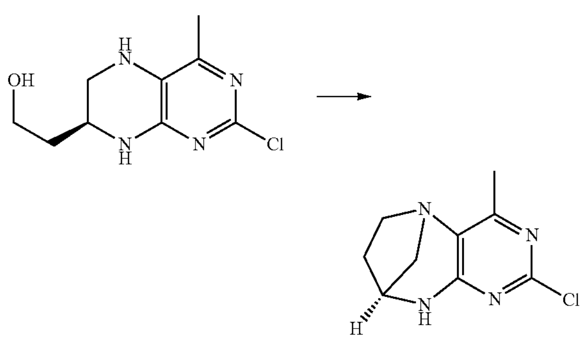
[0565]



[0566] To solid (S)-methyl 2-(2-chloro-4-methyl-6-oxo-5,6,7,8-tetrahydropteridin-7-yl)acetate (3.6 g, 13.30 mmol), in Tetrahydrofuran (THF) (360 mL) stirred under nitrogen at 0° C. was added solid LAH (0.505 g, 13.30 mmol) portion wise over 30 min. The reaction mixture was stirred at 25° C. for 36 hr. A solution of 8 g NaOH in 200 mL of water was added slowly to control the evolution of hydrogen gas. The reaction solution was extracted with ethyl acetate multiple times and the organic layer dried over sodium sulfate. The ethyl acetate solution was concentrated under vacuum to give the crude compound. The crude product was added to a silica gel column and was eluted with EtOAc to give pure compound (1.6 g, 6.54 mmol, 49% yield), LCMS (m/z) 228.9 $[M+H]^+$.

Synthesis of (8S)-2-chloro-4-methyl-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine

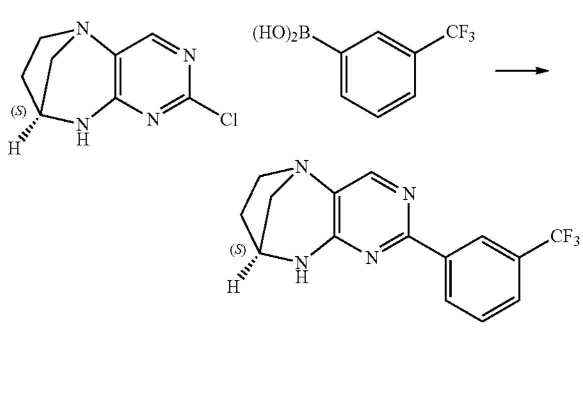
[0567]



[0568] To solid (S)-2-(2-chloro-4-methyl-5,6,7,8-tetrahydropteridin-7-yl)ethanol (1.6 g, 7.00 mmol) in Dichloromethane (DCM) (16 mL) stirred under nitrogen at 0° C. was added a solution of DIPEA (3.67 mL, 20.99 mmol) and $POCl_3$ (0.978 mL, 10.50 mmol) dropwise over 1 min. The reaction mixture was stirred at 0-25° C. for 1 hr. The reaction mixture was poured into saturated $NaHCO_3$ solution and the aqueous layer was extracted with Ethyl acetate (3×40 mL), washed with water. The organic layer was dried over Na_2SO_4 and concentrated to give the compound (810 mg, 3.74 mmol, 53% Yield), LCMS (m/z) 211.2 $[M+H]^+$.

Synthesis of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine

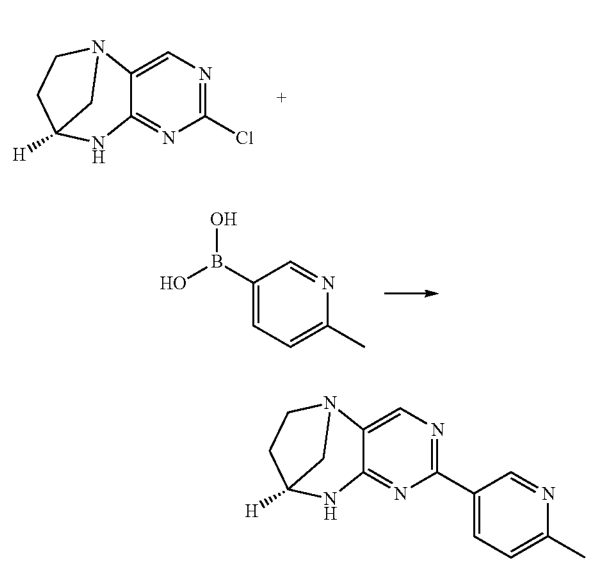
[0569]



[0570] To a solution of (8S)-2-chloro-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (600 mg, 3.05 mmol), (3-(trifluoromethyl)phenyl)boronic acid (869 mg, 4.58 mmol) and K_3PO_4 (2519 mg, 9.15 mmol) in 1,4-Dioxane (15 mL) and Water (5 mL). then purged with argon for 30 min at 27° C., then X-Phos (291 mg, 0.610 mmol) and Pd2(dba)$_3$ (279 mg, 0.305 mmol) under argon. The reaction mixture was stirred at 110° C. for 16 hr. The reaction mixture was diluted with water and extracted with ethyl acetate (250 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give semi pure compound. The crude product was added to a silica gel column and was eluted with DCM/EtOAc to give the desired product (500 mg, 1.80 mmol, 59%), LCMS (m/z): 306.9 $(M+H)^+$.

Synthesis of (8S)-2-(6-methylpyridin-3-yl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine

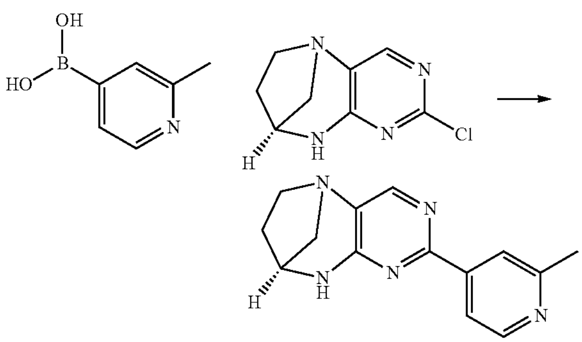
[0571]



[0572] To a degassed solution of (8S)-2-chloro-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (2 g, 10.17 mmol) and (6-methylpyridin-3-yl)boronic acid (2.089 g, 15.26 mmol) in 1,4-Dioxane (40 mL)/Water (10 mL) was added K_3PO_4 (6.48 g, 30.5 mmol), x-phos (0.970 g, 2.034 mmol) and Pd2(dba)$_3$ (0.931 g, 1.017 mmol). The reaction mixture was stirred at 110° C. for 3 hr. The reaction mixture was poured in to cold water (80 mL) and extracted with ethyl acetate (300 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude product. The crude product was added to a silica gel column and was eluted with 2% DCM/MeOH to give the pure product compound. (900 mg, 3.30 mmol, 33% yield), LCMS (m/z) 254.2 $[M+H]^+$.

Synthesis of (8S)-2-(2-methylpyridin-4-yl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine

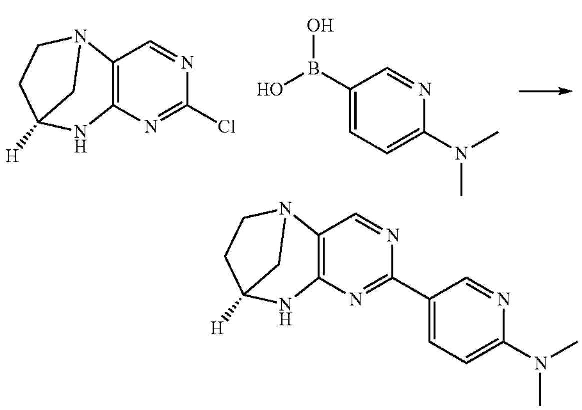
[0573]



[0574] To a degassed solution of (8S)-2-chloro-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (1 g, 5.09 mmol) and (2-methylpyridin-4-yl)boronic acid (1.045 g, 7.63 mmol) in 1,4-Dioxane (30 mL)/Water (7.5 mL) was added K_3PO_4 (3.24 g, 15.26 mmol) and X-phos (0.970 g, 2.034 mmol). The reaction mixture was stirred at 110° C. for 3 hrs. The reaction mixture was poured into cold water (100 mL) and extracted with ethyl acetate (300 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product. The crude product was added to a silica gel column and was eluted with 2% DCM/MeOH to give the pure product, (650 mg, 2.4 mmol, 47%), LCMS (m/z) 254.2 $[M+H]^+$.

Synthesis of N,N-dimethyl-5-((8S)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepin-2-yl)pyridin-2-amine

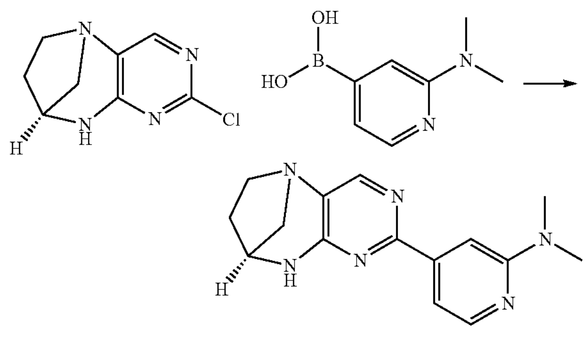
[0575]



[0576] To a degassed solution of (8S)-2-chloro-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (500 mg, 2.54 mmol) and (6-(dimethylamino)pyridin-3-yl)boronic acid (633 mg, 3.81 mmol) in 1,4-Dioxane (15 mL)/Water (3.75 mL) was added K_3PO_4 (1619 mg, 7.63 mmol) and X-phos (485 mg, 1.017 mmol). The reaction mixture was stirred at 110° C. for 3 hr. The reaction mixture was poured in to cold water (100 mL) and extracted with ethyl acetate (300 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product. The crude product was added to a silica gel column and was eluted with 2% DCM/MeOH to give the pure product compound, (400 mg, 1.36 mmol, 53%), LCMS (m/z) 283.2 $[M+H]^+$.

N,N-dimethyl-4-((8S)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepin-2-yl)pyridin-2-amine

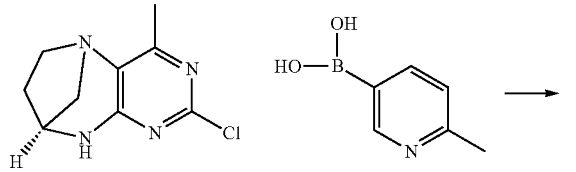
[0577]



[0578] To a degassed solution of (8S)-2-chloro-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (500 mg, 2.54 mmol) and (2-(dimethylamino)pyridin-4-yl)boronic acid (633 mg, 3.81 mmol) in 1,4-Dioxane (15 mL); water (3.75 mL) and was added K_3PO_4 (1619 mg, 7.63 mmol) and x-phos (485 mg, 1.017 mmol), K3PO4 (1619 mg, 7.63 mmol). The reaction mixture was stirred at 110° C. for 3 hr. The reaction was monitored by TLC (TLC System; 100% EtOAc, R_f=0.2). The reaction mixture was poured in to cold water (100 mL) and extracted with ethyl acetate (2×200 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (100-200 silica gel) using gradient mixture of 2% methanol in dichloromethane as eluent, to give N,N-dimethyl-4-((8S)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepin-2-yl)pyridin-2-amine (400 mg, 1.377 mmol, 54.1% yield), LCMS (m/z) 283.0 $(M+H)^+$.

Synthesis of (8S)-4-methyl-2-(6-methylpyridin-3-yl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine

[0579]



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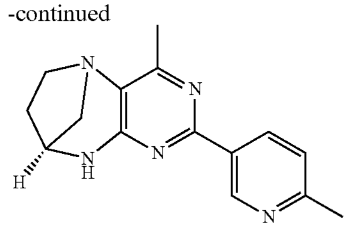
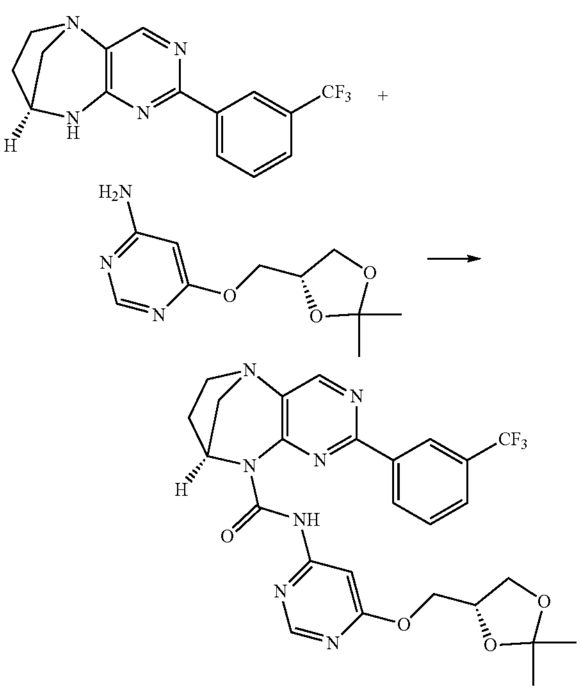


[0580] A solution of (8S)-2-chloro-4-methyl-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (500 mg, 2.373 mmol), (6-methylpyridin-3-yl)boronic acid (488 mg, 3.56 mmol) and potassium phosphate tri basic (1511 mg, 7.12 mmol) in 1,4-Dioxane (24 mL) and Water (6 mL) was stirred and degassed with argon for 10 minutes. X-phos (68.5 mg, 0.475 mmol) and $Pd_2(dba)_3$ (217 mg, 0.237 mmol) were added and the reaction mixture was degassed for 5 minutes and stirred at 90° C. for 16 hr. The reaction was monitored by TLC (5% MeOH/DCM). The organic phase was washed with water 50 mL, saturated brine (100 mL), dried over sodium sulfate and evaporated in vacuo to give the crude product as a brown solid. The crude product was washed with diethyl ether and pentane and triturated with diethyl ether to give the pure product compound, (200 mg, 0.59 mmol, 25%), LCMS (m/z) 268.0 $[M+H]^+$

Synthesis of (8S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

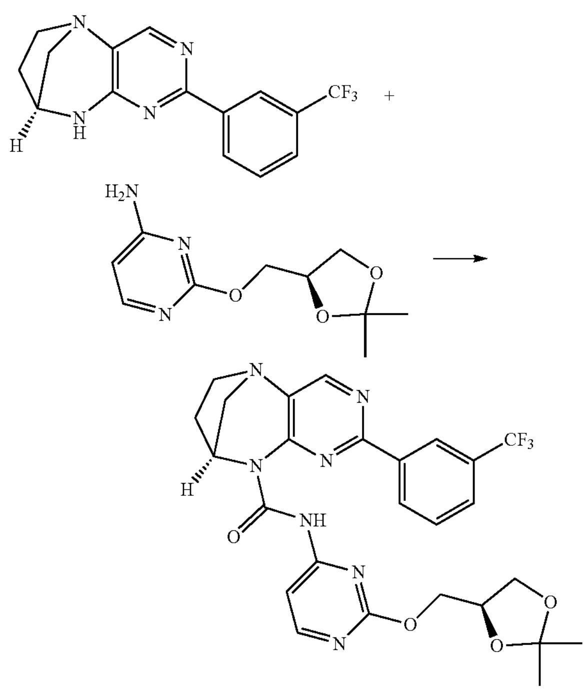
[0581]



[0582] (8 S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (500 mg, 1.632 mmol) was dissolved in tetrahydrofuran (THF) (5 mL) stirred under nitrogen at 0° C. triphosgene (242 mg, 0.816 mmol), DIPEA (1.426 mL, 8.16 mmol) were added. The reaction mixture was stirred for 30 min at room temperature. To this (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine (735 mg, 3.26 mmol) was added and stirred for 16 h at 80° C. The reaction mixture allowed to room temperature and quenched with 100 ml of water and extracted with 2×250 ml of ethyl acetate, The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain crude compound. The crude product was purified by Prep HPLC Column: XBridge C 18(75×4.6 mm, 3.5 t) Mobile Phase: A: 0.01 M Ammonium Bicarbonate B: ACN, Gradient: Time/% B: 0/5, 0.8/5, 5/50, 8/95, 12/95, 12.1/5, 15/5, Column Temp: Ambient, Flow Rate: 1.0 ml/min Diluent: ACN to afford (8S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (225 mg, 0.379 mmol, 23.24% yield) as an Off white solid, LCMS (m/z): 558.21 $[M+H]^+$.

Synthesis of (8S)—N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0583]

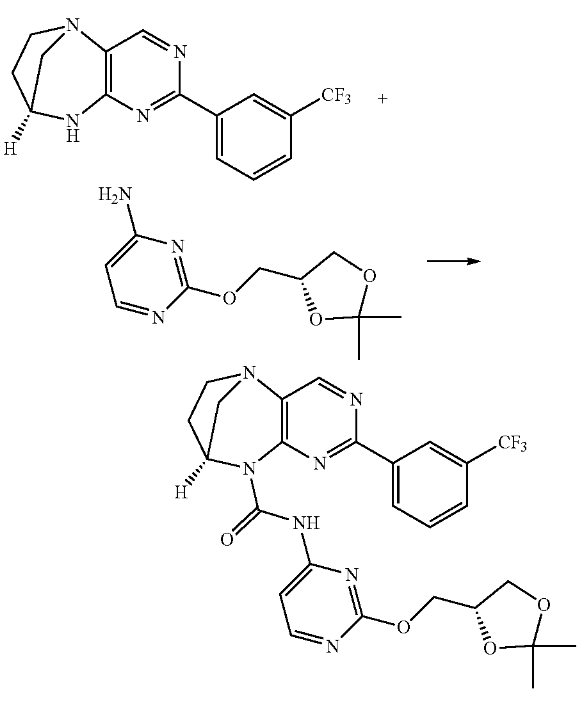


[0584] A solution of (S)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine (662 mg, 2.94 mmol), triphosgene (291 mg, 0.979 mmol) and triethylamine (0.819 mL, 5.88 mmol) in Tetrahydrofuran (THF) (10 mL) was stirred under nitrogen at room temp for 30 min. To this reaction mixture (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (300 mg, 0.979 mmol) was added. The reaction mixture was stirred at 70° C. for 16 h and progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature, poured in to water (10 mL) and extracted with EtOAc (3×20 mL). Then the combined organic layers was washed with water (10 mL), brine solution (10 mL), dried over Na_2SO_4, filtered and evaporated to get crude compound. The crude compound was purified by column chromatography using Neutral Alumina and eluted with 40% EtOAc in pet ether to get pure (8S)—N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (300 mg, 0.508 mmol, 51.9% yield).

[0585] LCMS (m/z): 558.21 [M+H]+.

Synthesis of (8S)—N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

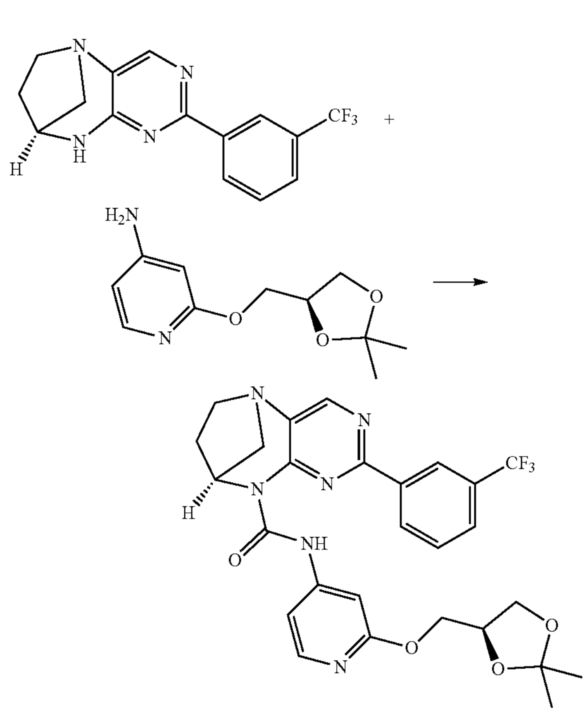
[0586]



[0587] To a solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (500 mg, 1.632 mmol) in Tetrahydrofuran (THF) (25 mL) was added triethylamine (1.365 mL, 9.79 mmol) and triphosgene (484 mg, 1.632 mmol) stirred under nitrogen at room temp for 30 minutes then to this solid (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine (1103 mg, 4.90 mmol) was added. The reaction mixture was stirred at 65° C. for 16 hr. Reaction was monitored by TLC. The solvent was removed under reduced pressure, diluted with water (20 mL) and extracted with ethyl acetate (2×50 mL). The combined organic layers were washed with water (30 mL), saturated brine solution (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude compound was dissolved in DCM (10 mL). Neutral alumina was added to the crude compound and purified by column chromatography. Product was eluted with 20-25% Ethyl acetate in Hexane. Collected fractions were evaporated under reduce pressure to afford pure (8S)—N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (350 mg, 0.622 mmol, 38.1% yield) as an off-white solid, LCMS (m/z): 558.31 [M+H]+.

Synthesis of (8S)—N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

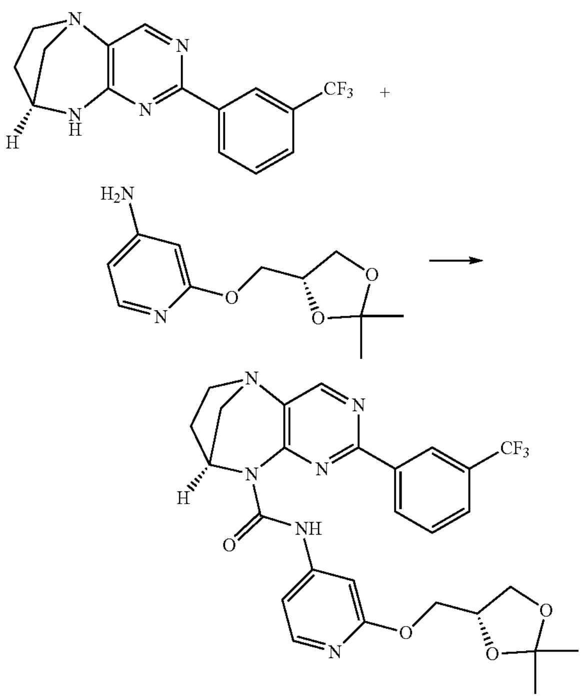
[0588]



[0589] Triphosgene (1.647 g, 5.55 mmol) was added to a stirred solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (1.7 g, 5.55 mmol), and TEA (3.87 mL, 27.8 mmol) in Tetrahydrofuran (THF) (50 mL) at 28° C. The reaction mixture was stirred for 30 min and was added (S)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (3.73 g, 16.65 mmol). The reaction mixture was stirred for 10 hr at 72° C. The reaction mixture was cooled to 25° C., and the precipitated solid was filtered and was washed with ethyl acetate (100 ml). The filtrate was washed with the water (50 ml) and brine solution (50 ml). The organic phase was separated, and was dried over anhydrous Na_2SO_4, filtered, and filtrate was evaporated to get the crude. This crude was purified by flash chromatography on neutral alumina, elected by 20-30% EtOAc/petether to get the (8S)—N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (1.5 g, 2.65 mmol, 47.8% yield) as a white solid, LCMS (m/z): 557.43 [M+H]+.

Synthesis of (8S)—N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

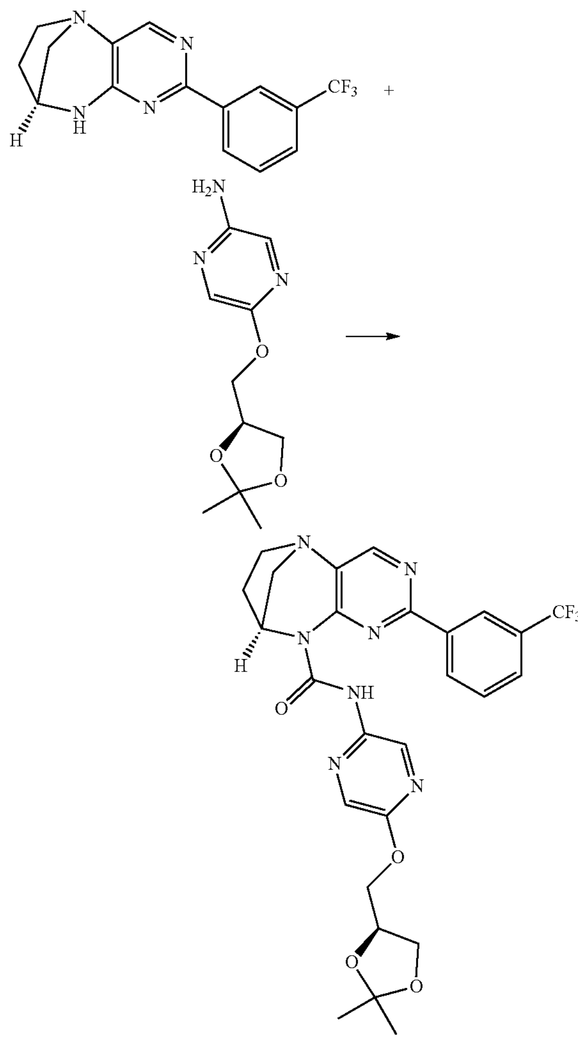
[0590]



[0591] To a solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (2 g, 6.53 mmol) in THF (80 ml) and triphosgene (0.969 g, 3.26 mmol) at 0° C. and stirred to RT for 1 h. Then triethylamine (4.55 mL, 32.6 mmol) and (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (2.197 g, 9.79 mmol) was added sub sequentially at 75° C. for 16 h. The reaction was monitored by TLC and LCMS. The reaction mixture was poured in saturated $NaHCO_3$ solution (50 mL) and extracted with ethyl acetate (2×150 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude. The crude was purified by column chromatography (100-200 silica gel) using gradient mixture of 80% EtOAc in Petether as eluent, to afford product. This compound was purified by Pd Scavenger resin process. To a stirred solution of (8S)—N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (2.5 g) in Ethanol (120 ml) at 50° C. was added Pd scavenger resin (1.5 g) and stirred for 5 h at 70° C. Then cooled to 30° C., the reaction mixture was filtered and concentrated under reduced pressure to afford (8S)—N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (2.5 g, 4.47 mmol, 68.5% yield) as a white solid LCMS (m/z): 557.13 $[M+H]^+$.

Synthesis of (8S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

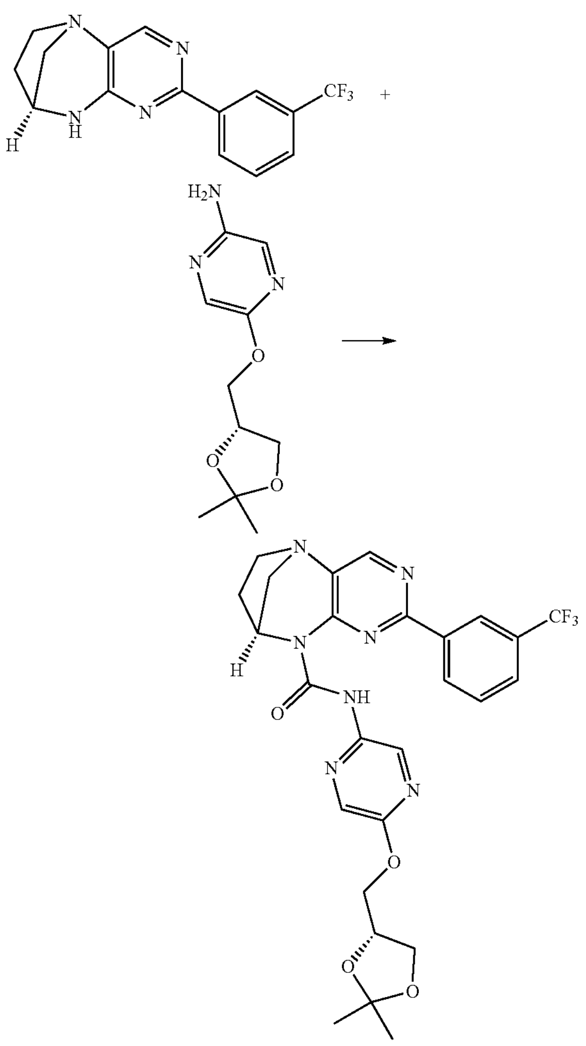
[0592]



[0593] To a stirred solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (500 mg, 1.632 mmol) in Tetrahydrofuran (THF) (10 mL), was added triphosgene (484 mg, 1.632 mmol) and followed by triethylamine (1.365 mL, 9.79 mmol) at RT. The reaction mixture was stirred for 30 min and added a solution of(S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine (735 mg, 3.26 mmol) in Tetrahydrofuran (THF) (5 mL). The reaction mixture was stirred at 65° C. for 16 hr. Progress of the reaction was monitored by TLC. TLC indicated starting material was consumed. Cooled the reaction mass to RT, diluted with water (50 mL) and extracted with ethyl acetate (50 mL×2). Combined the organic layers and dried over Na_2SO_4, filtered and concentrated to get crude as brown sticky compound. The crude product was purified in a combiflash silica gel column (40 g) and was eluted with Hex/EtOAc. Collected fractions: 50% EtOAc in pet ether, the product was eluted. Concentrated the product fractions to afford (8S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (130 mg, 0.214 mmol, 13.09% yield) as light yellow solid, LCMS (m/z): 558.44 $[M+H]^+$.

Synthesis of (8S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

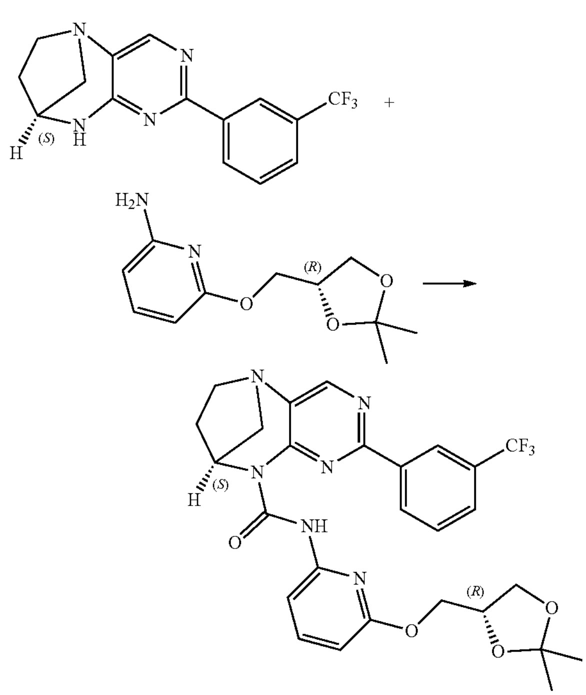
[0594]



[0595] To a stirred solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (500 mg, 1.632 mmol) in Tetrahydrofuran (THF) (20 mL) was added triphosgene (484 mg, 1.632 mmol) and TEA (1.138 mL, 8.16 mmol) at rt. Reaction mixture was stirred at rt for 30 min under Nitrogen atmosphere, then (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine (552 mg, 2.449 mmol) was added to the reaction mixture, reaction mixture was stirred at 70° C. for 18 hr. Progress of the reaction was monitored by TLC. Reaction mixture was diluted with water (30 mL) extracted with EtOAc (3×30 mL), organic layers were combined and washed with brine solution (20 mL), organic layer dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get crude compound, crude was purified by column chromatography using 100-200 mesh silica gel and eluted the compound in 40% EtOAc in Hexane to afford (8S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (550 mg, 0.968 mmol, 59.3% yield) as an Off-white solid, LCMS (m/z): 558.15 $(M+H)^+$.

Synthesis of (8S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

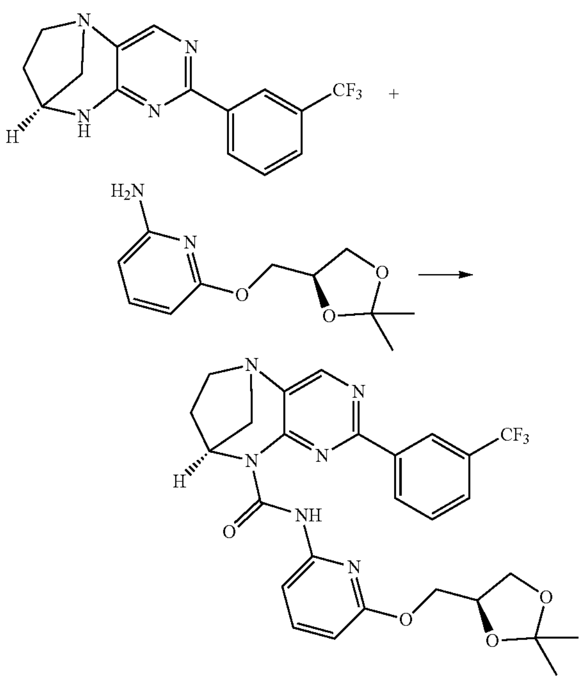
[0596]



[0597] Triphosgene (388 mg, 1.306 mmol) was added to a stirred solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (400 mg, 1.306 mmol) in Tetrahydrofuran (THF) (10 mL) at room temperature. The reaction mixture was stirred for 45 min at RT and then triethylamine (1.092 mL, 7.84 mmol) and (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (586 mg, 2.61 mmol) was added one by one. The reaction mixture was stirred at 65° C. for 6 hr. Reaction was monitored by TLC; TLC showed one polar spot and starting was consumed. Reaction was stopped. The reaction mixture was concentrated under reduced pressure to dryness. Residue was taken in DCM (100 ml) and organic layer was washed with water, followed by brine solution. Organic layer was dried over Na_2SO_4, filtered and concentrated to get crude product. The crude product was purified by column chromatography over silica gel (100-200 mesh) and column was eluted with 30% EtOAc/Hexane. Pure fraction were collected and evaporated to afford desired product (8S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (350 mg, 0.616 mmol, 47.2% yield) as a white solid, LCMS (m/z): 557.2 [M+H]+.

Synthesis of (8S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

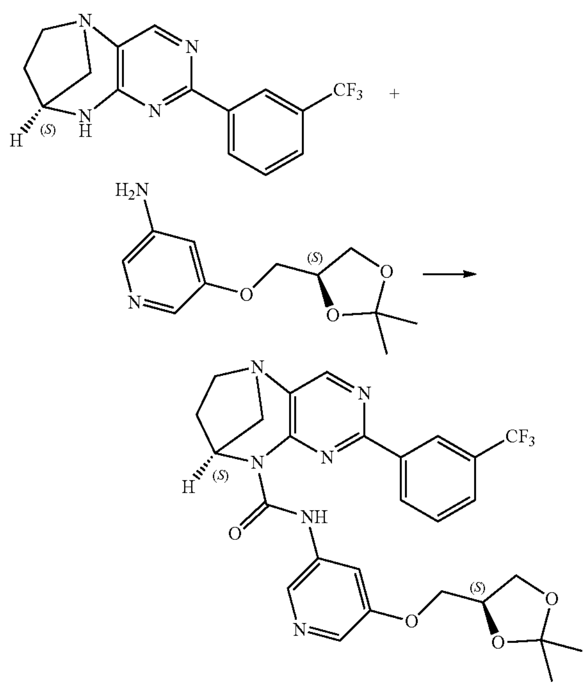
[0598]



[0599] To a stirred solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (500 mg, 1.632 mmol) in Tetrahydrofuran (THF) (20 mL), was added triphosgene (484 mg, 1.632 mmol) and followed by triethylamine (1.365 mL, 9.79 mmol) at RT. The reaction mixture was stirred for 45 min and added a solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (500 mg, 1.632 mmol) in Tetrahydrofuran (THF) (5 mL). The reaction mixture was stirred at 65° C. for 16 hr. TLC indicated that starting material was consumed and a new spot was formed. Water (25 mL) was added to the reaction mixture. The aqueous layer was extracted with EtOAc (2×25 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to obtain crude product. Crude product was purified by column chromatography using 100-200 silica gel (eluent 30-35% EtOAc in pet ether) to obtain the desired pure product (8S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (500 mg, 0.891 mmol, 54.6% yield) as light brown solid as light brown solid. LCMS (m/z): 557.11 [M+H]+.

Synthesis of (8S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0600]

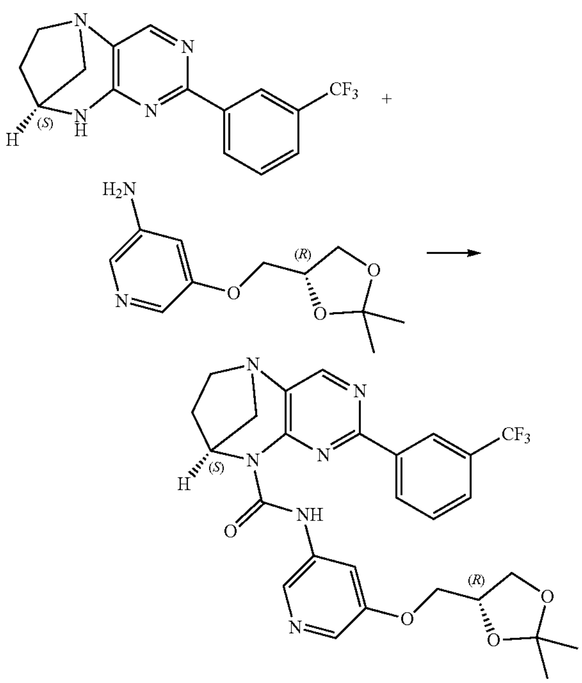


[0601] (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (500 mg, 1.632 mmol), triethylamine (1.365 mL, 9.79 mmol) were taken in Tetrahydrofuran (THF) (50 mL) at 0° C., the resulting yellow solution was stirred for 10 min. Then added triphosgene (484 mg, 1.632 mmol) in one portion at 0° C. The resulting yellow suspension was stirred for 45 min at room temperature. The THF (20 mL) solution of (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine (366 mg, 1.632 mmol) was added to the above yellow suspension at 0° C. over a period of 5 min. The resulting yellow suspension was heated to 70° C. for 24 hr. The reaction progress was monitored by TLC 10% MeOH in DCM, TLC indicated formation of multiple spots after 24 h. The reaction mass was cooled to room temperature, diluted with water (80 mL), ethyl acetate (60 mL*2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 filtered, concentrated under reduced pressure to afford yellow solid. The crude product was purified by combiflash chromatography over 230-400 mesh size silica gel. Column was eluted with a gradient of MeOH/DCM. Desired compound was eluted with 5% MeOH in DCM. Fractions containing pure compound were concentrated under reduced pressure to afford the (8S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido

[4,5-b][1,4]diazepine-9(6H)-carboxamide (500 mg, 0.483 mmol, 29.6% yield) as an off-white solid, LCMS (m/z): 557.13 [M+H]$^+$.

Synthesis of (8S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

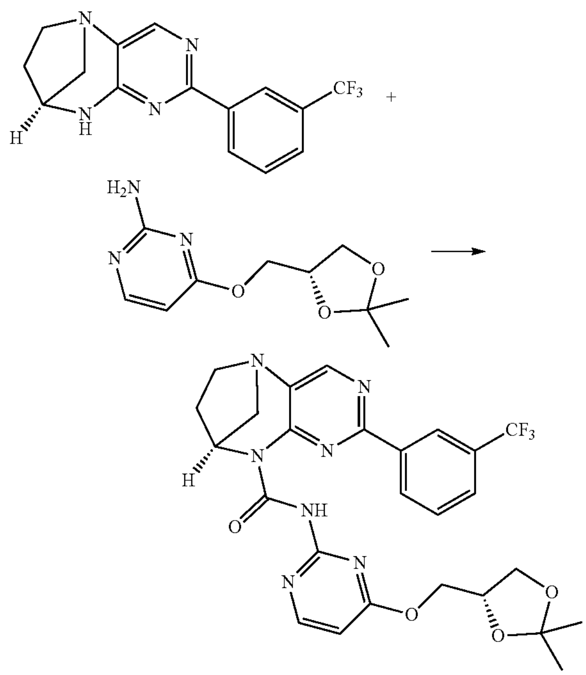
[0602]



[0603] (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (0.5 g, 1.632 mmol), triethylamine (1.365 mL, 9.79 mmol) were taken in Tetrahydrofuran (THF) (20 mL) at 0° C., the resulting yellow solution was stirred for 10 min. Then added triphosgene (0.484 g, 1.632 mmol) in one portion at 0° C. The resulting yellow suspension was stirred for 45 min at room temperature. The THF (4 mL) solution of (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine (0.366 g, 1.632 mmol) was added to the above yellow suspension at 0° C. over a period of 5 min. The resulting yellow suspension was heated to 70° C. for 24 hr. The reaction progress was monitored by TLC 10% MeOH in DCM, TLC indicated formation of multiple spots after 24 h. The reaction mass was cooled to room temperature, diluted with water (20 mL), ethyl acetate (30 mL*2). The combined organic layer was washed with brine (15 mL), dried over sodium sulphate filtered, concentrated under reduced pressure to afford brown solid. The crude product was purified by combiflash chromatography over 230-400 mesh size silica gel. This was combined with a previous batch of compound (350 mg) and purified by column, eluting with a gradient of MeOH/DCM. Desired compound was eluted with 7% MeOH in DCM. Fractions containing pure compound were concentrated under reduced pressure to afford (8S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (750 mg, 0.833 mmol, 51.0% yield) as off white solid, LCMS (m/z): 557.13 [M+H]$^+$.

Synthesis of (8S)—N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

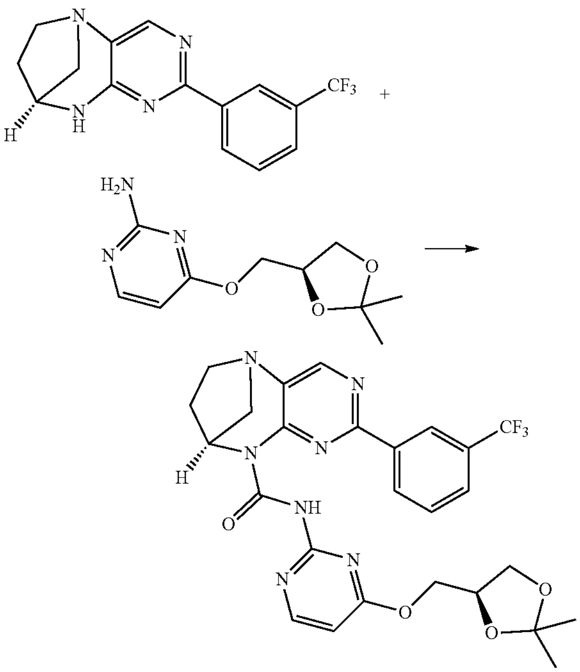
[0604]



[0605] To a stirred solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (350 mg, 1.143 mmol) in Tetrahydrofuran (THF) (15 mL) added triphosgene (203 mg, 0.686 mmol) stirred under nitrogen at 0° C. Then the reaction was stirred at 30° C. for 30 mins. Then added DIPEA (0.998 mL, 5.71 mmol) and (R)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-amine (386 mg, 1.714 mmol) and stirred at 75° C. for 16 hrs. The reaction progress was monitored by TLC and LCMS. The reaction mixture was poured into cold water (25 ml) and extracted with Ethyl Acetate (3×50 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give crude as yellow solid (TLC eluent: 100% EtOAc: R_f 0.2; UV active). The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 80% EtOAc in Pet ether) and obtained 220 mg with 96.22% purity by LCMS. The crude compound was washed with n-pentane to afford (8S)—N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (230 mg, 0.397 mmol, 34.7% yield) as white solid. LCMS (m/z) 550.00 [M+H

Synthesis of (8S)—N-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

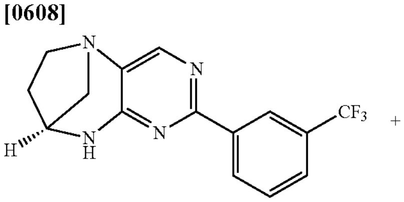
[0606]



[0607] DIPEA (886 mg, 6.86 mmol) followed by triphosgene (678 mg, 2.285 mmol) were added to a solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (700 mg, 2.285 mmol) in Tetrahydrofuran (THF) (15 mL) at 25° C., stirred for 1 h and (S)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-amine (1030 mg, 4.57 mmol) was added and heated at 70° C. for 17 h. The reaction mixture was cooled to 28° C. and was partitioned between water (20 mL) and EtOAc (50 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude (TLC eluent: 5% methanol in DCM R_f 0.3; UV active). The crude compound was purified by column chromatography (C-18: eluted with 90% methanol in 1% aq formic acid) to afford (8S)—N-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (200 mg, 0.349 mmol, 15.26% yield), as a yellow solid, LCMS (m/z) 558.15 $(M+H)^+$.

Synthesis of (8S)—N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0608]



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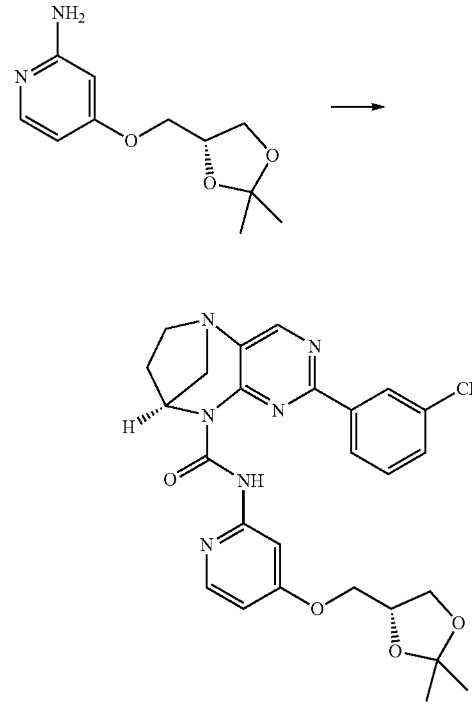
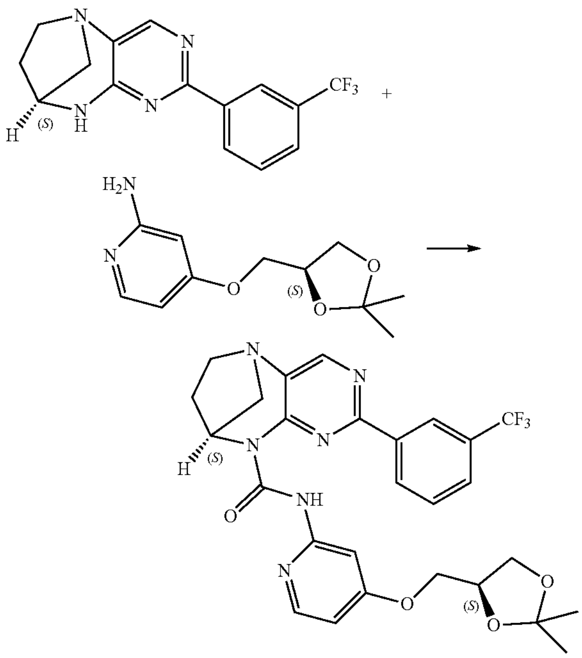


[0609] TEA (20.48 mL, 147 mmol) and triphosgene (7.27 g, 24.49 mmol) was added to a stirred solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (7.5 g, 24.49 mmol) in at room temp. The reaction mixture was stirred for 45 min and (R)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (8.24 g, 36.7 mmol) was added. The reaction mixture was stirred for 16 hr at 65° C. The reaction mixture was cooled to room temp, solvent evaporated under reduced pressure completely and was partitioned between water (100 mL) and EtOAc (500 mL). Organic layer was separated, dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford crude product. The crude product was purified by column chromatography using neutral alumina and was eluted with 20% EtOAc in Hexane (gradient system) to afford the desired product (8.50 g) as a white solid. The product (8.50 g) was diluted in ethanol (100 ml) and treated with Silicycle palladium scavenger (4.25 g) and stirred at 65° C. for 3 hr. The reaction mixture was filtered through pad of celite and the celite pad was washed with the hot ethanol (50 ml), the obtained filtrate was concentrated under reduced pressure to afford the desired product (8S)—N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (8 g, 14.33 mmol, 58.5% yield) as a white solid. (TLC eluent: 50% EtOAc in Hexane: R-0.3; UV active). LCMS (m/z): 557.12 $[M+H]^+$.

Synthesis of (8S)—N-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

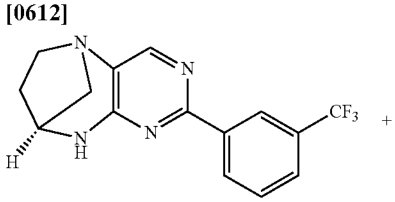
[0610]



[0611] To a solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (500 mg, 1.632 mmol) in THF (30 ml) and triphosgene (242 mg, 0.816 mmol) at 0° C. and stirred to RT for 1 h. Then triethylamine (1.138 mL, 8.16 mmol) and (S)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (549 mg, 2.449 mmol) was added sub sequentially under sealed tube condition at 75° C. for 16 h. The reaction was monitored by TLC and LCMS. The reaction mixture was poured in saturated $NaHCO_3$ solution (30 mL) and extracted with ethyl acetate (2×150 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (100-200 silica gel) using gradient mixture of 80% EtOAc in Petether as eluent, to afford the (8S)—N-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (400 mg, 0.713 mmol, 43.7% yield) as an off white solid LCMS (m/z) 557.05 $[M+H]^+$.

Synthesis of (8S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0612]



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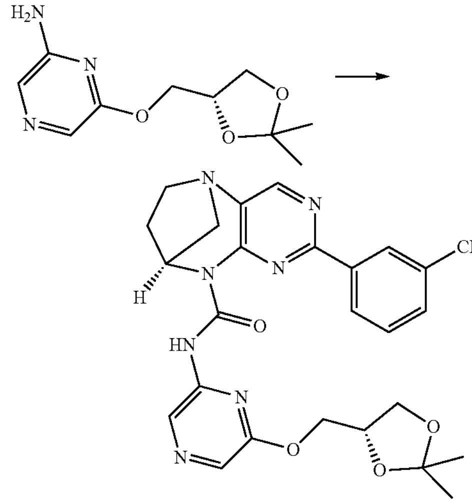
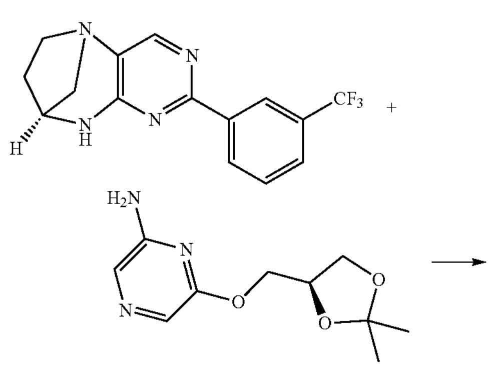


[0613] TEA (0.683 mL, 4.90 mmol) followed by triphosgene (484 mg, 1.632 mmol) were added to a solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (500 mg, 1.632 mmol) in Tetrahydrofuran (THF) (50 mL) at 25° C., stirred for 1 h and (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine (735 mg, 3.26 mmol) was added and heated at 70° C. for 15 h. The reaction mixture was cooled to 28° C. and was partitioned between water (20 mL) and EtOAc (50 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude (TLC eluent: Neat ethyl acetate R_f: 0.6; UV active). The crude compound was purified by (100-200 mesh) silica gel eluting with 60% Ethyl acetate in hexane to afford (8S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (290 mg, 0.512 mmol, 31.4% yield) LCMS (m/z) 557.9 $(M+H)^+$.

Synthesis of (8S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0614]



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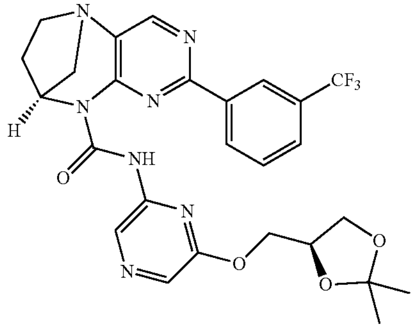
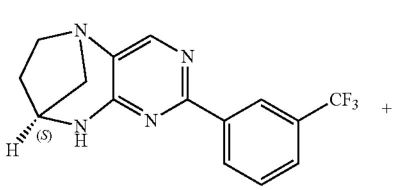


[0615] Triphosgene (7.27 g, 24.49 mmol) was added to a stirred solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (7.5 g, 24.49 mmol) and TEA (20.48 mL, 147 mmol) in Tetrahydrofuran (THF) (70 mL) at room temp. The reaction mixture was stirred for 4 h and (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine (11.03 g, 49.0 mmol) was added. The reaction mixture was stirred at 65° C. for 16 h. Reaction was monitored by TLC. The reaction mixture was diluted with water (250 mL) and extracted with 500 mL of Ethyl acetate. Organic layer washed with water (100 mL) followed by brine solution (100 mL), dried with anhydrous Na_2SO_4, filtered and concentrated to get crude product. The crude product was added to silica gel and was eluted with 60-70% EtOAc/Hexane. Collected fraction was evaporated under reduced pressure to afford a compound as a white solid. This compound (7.5 g) was dissolved in ethanol and treated with palladium scavenger (4.0 g) and stirred at 50° C. for 3 h. This was filtered through pad of celite and the obtained filtrate was evaporated under reduced pressure to get the (8S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (7.0 g, 12.48 mmol, 51.0% yield) as an off white solid, LCMS (m/z): 558.10 $[M+H]^+$.

Synthesis of (8S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0616]



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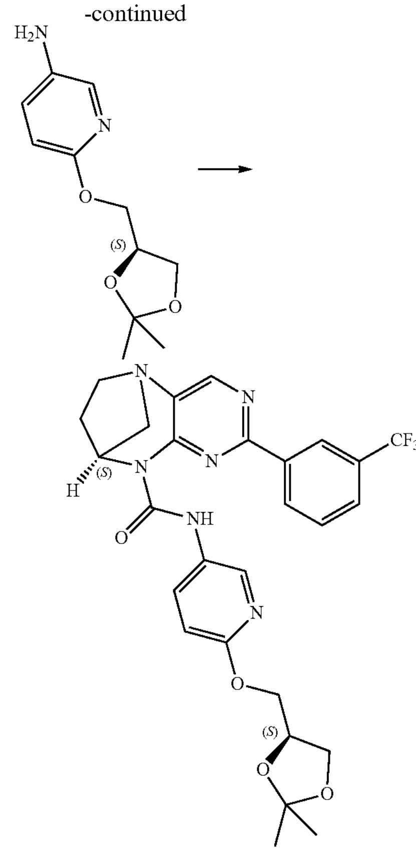
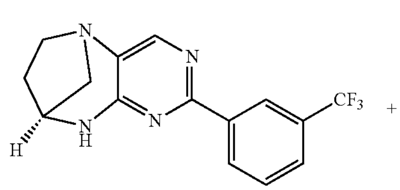


[0617] Triphosgene (174 mg, 0.588 mmol) and triethylamine (0.819 mL, 5.88 mmol) were added to a stirred solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (300 mg, 0.979 mmol) in Tetrahydrofuran (THF) (10 mL) at 0° C. and stirred for 1 h. Then (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine (439 mg, 1.959 mmol) was added to the reaction mixture at RT and stirred at 80° C. for 15 h. Reaction mixture was cooled to RT, diluted with water (20 mL), extracted with ethyl acetate (2×30 mL) and washed with brine solution (10 mL). Organic layer was separated, dried over Na_2SO_4, filtered and concentrated to get crude compound, LCMS (m/z): 557.37 $[M+H]^+$.

Synthesis of (8S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0618]



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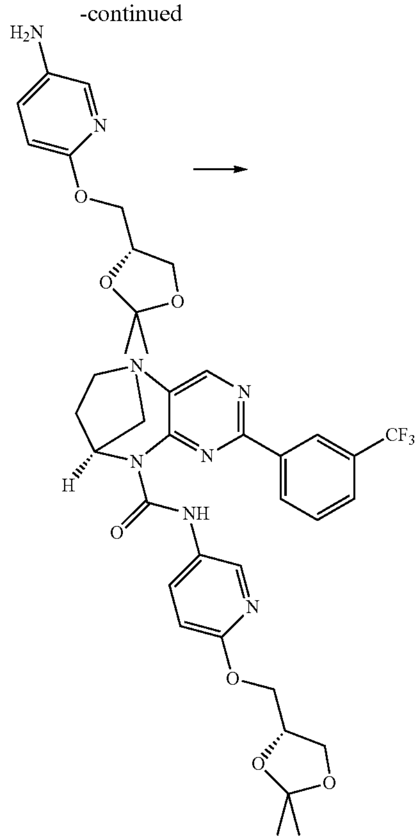
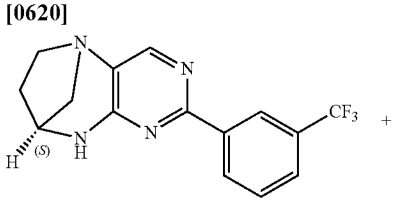


[0619] TEA (1.138 mL, 8.16 mmol) followed by triphosgene (484 mg, 1.632 mmol) were added to a solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (500 mg, 1.632 mmol) in Tetrahydrofuran (THF) (20 mL) at RT and stirred for 1 h then (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine (366 mg, 1.632 mmol) was added and heated at 80° C. for 15 h. The reaction mixture was cooled to 28° C. and was partitioned between water (25 mL) and EtOAc (35 mL×2). Organic layers were separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude compound, it was further purified by column chromatography (100-200 silica gel, column eluted at 80% ethyl acetate in hexane) to afford the (8S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (250 mg, 0.445 mmol, 27.2% yield) as an off white solid, LCMS (m/z): 557.15 $(M+H)^+$.

Synthesis of (8S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0620]



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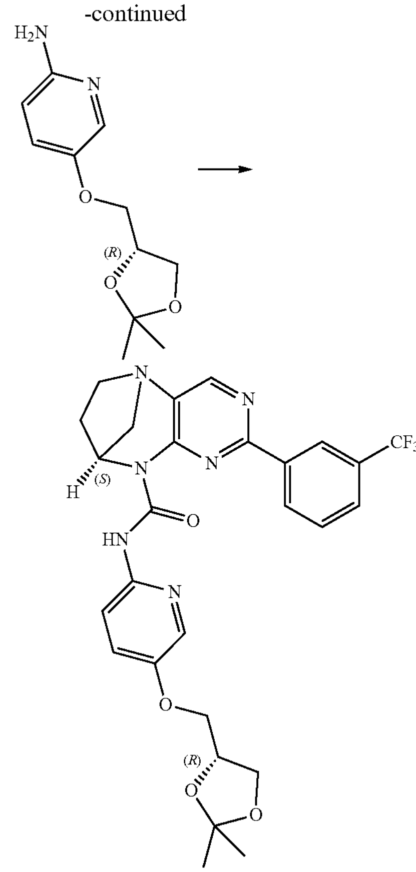
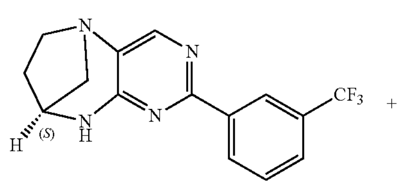


[0621] To a solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (300 mg, 0.979 mmol) in THF (30 ml) and triphosgene (145 mg, 0.490 mmol) at 0° C. Then triethylamine (0.683 mL, 4.90 mmol) was added stirred to RT for 1 h. Then (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (329 mg, 1.469 mmol) was added stirred at 75° C. for 16 h. The reaction was monitored by TLC and LCMS. The reaction mixture was poured in saturated $NaHCO_3$ solution (50 mL) and extracted with ethyl acetate (2×150 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude. The crude was purified by column chromatography (100-200 silica gel) using gradient mixture of 80% EtOAc in Petether as eluent, to afford the as a white solid LCMS (m/z): 557.18 $[M+H]^+$.

Synthesis of (8S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0622]



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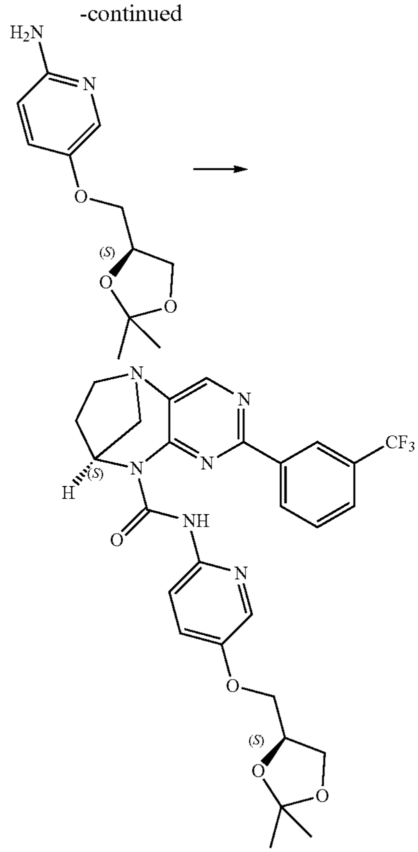
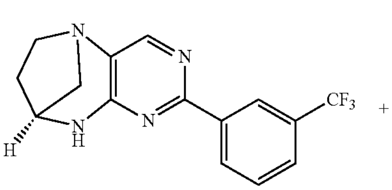


[0623] Triphosgene (174 mg, 0.588 mmol) and triethylamine (0.819 mL, 5.88 mmol) were added to a stirred solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (300 mg, 0.979 mmol) in Tetrahydrofuran (THF) (15 mL) at 0° C. and stirred for 1 h. Then (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (439 mg, 1.959 mmol) was added to the reaction mixture at RT and stirred at 80° C. for 15 h. Reaction mixture was cooled to RT, diluted with water (30 mL), extracted with ethyl acetate (2×50 mL) and washed with brine solution (50 mL). Organic layer was separated, dried over Na_2SO_4, filtered and concentrated to get crude compound, LCMS (m/z): 557.43 $[M+H]^+$.

Synthesis of (8S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido [4,5-b][1,4]diazepine-9(6H)-carboxamide

[0624]



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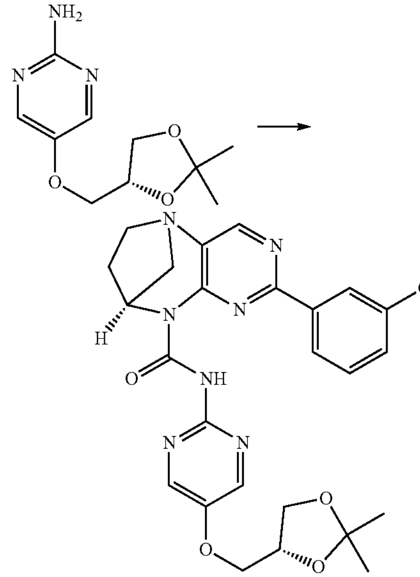
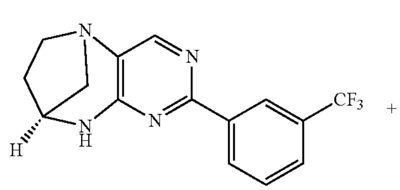


[0625] A solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (300 mg, 0.979 mmol), triphosgene (291 mg, 0.979 mmol) and triethylamine (0.683 mL, 4.90 mmol) in Tetrahydrofuran (THF) (20 mL) was stirred under nitrogen at room temp for 15 min. To this reaction mixture (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-amine (287 mg, 1.273 mmol) was added. The reaction mixture was stirred at 65° C. for 16 h and progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature, poured in to water (10 mL) and extracted with EtOAc (3×20 mL). The combined organic layer was washed with water (20 mL), brine solution (20 mL), dried over Na_2SO_4, filtered and evaporated to get crude compound. The crude compound was purified by column chromatography using Neutral Alumina and eluted with 80% EtOAc in Petether to afford pure (8S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido [4,5-b][1,4]diazepine-9(6H)-carboxamide (250 mg, 0.410 mmol, 41.9% yield) as off white solid, LCMS (m/z): 558.28 $[M+H]^+$.

Synthesis of (8S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido [4,5-b][1,4]diazepine-9(6H)-carboxamide

[0626]



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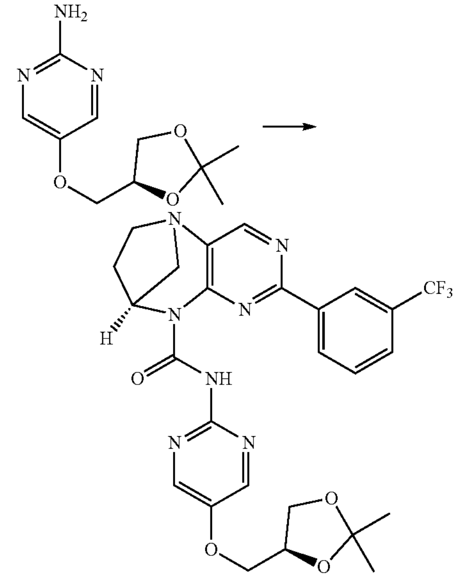
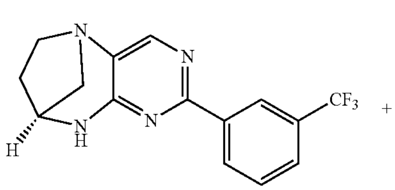


[0627] Triphosgene (484 mg, 1.632 mmol) was added to a stirred solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (500 mg, 1.632 mmol), and TEA (1.365 mL, 9.79 mmol) in Tetrahydrofuran (THF) (50 mL) under nitrogen at 28° C. The reaction mixture was stirred at rt for 30 min. and was added (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-amine (552 mg, 2.449 mmol). The reaction mixture was stirred 16 hr at 65° C. The reaction mixture was cooled to 28° C., the reaction mixture was partitioned between water (20 mL) and EtOAc (2×25 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude. The crude was purified by GRACE using C-18 reserval column, Mobile phase A: 0.1% Formic Acid in water; B: ACN, the product was eluted at 50% of ACN in 0.1% Formic Acid in water. The solvent was evaporated and was basified with saturated $NaHCO_3$. The precipitated solid was filtered, and was dried to afford (8S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (320 mg, 0.533 mmol, 32.7% yield) as brown solid, LCMS (m/z): 558.25 $[M+H]^+$.

Synthesis of (8S)—N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0628]



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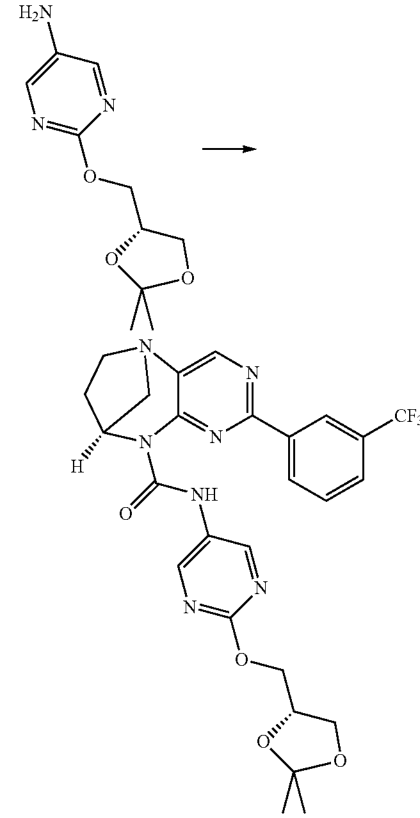
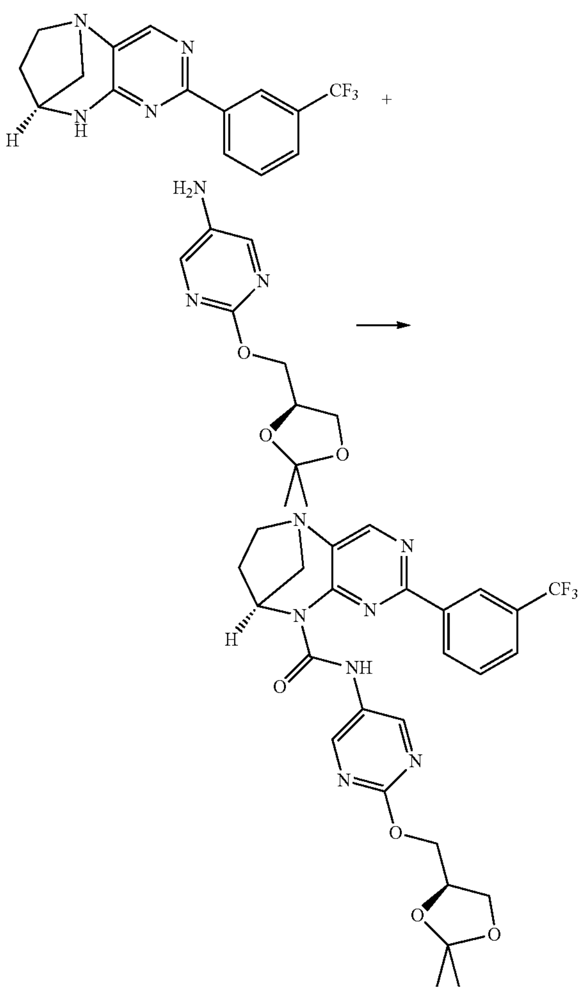


[0629] Triphosgene (484 mg, 1.632 mmol) was added to a stirred solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (500 mg, 1.632 mmol) and TEA (1.365 mL, 9.79 mmol) in Tetrahydrofuran (THF) (50 mL) at room temp. The reaction mixture was stirred for 4 h and (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-amine (919 mg, 4.08 mmol) was added. The reaction mixture was stirred at 65° C. for 16 h. Reaction was monitored by TLC. The reaction mixture was evaporated under reduced pressure and reconstituted in 150 mL of Ethyl acetate and diluted with water (100 mL). The Organic layer and wash with brine solution (50 mL) and separated the layer, dried with anhydrous Na_2SO_4, filtered and concentrated to get crude product. The crude product was determined by LCMS. The crude product was purified. The crude product was added to neutral alumina column and was eluted with 60% Ethyl acetate in hexane. The Collected fraction was evaporated under reduced pressure to get pure compound of (8S)—N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (700 mg, 1.201 mmol, 73.6% yield) as a off white solid, LCMS (m/z): 558.00 $[M+H]^+$.

Synthesis of (8S)—N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

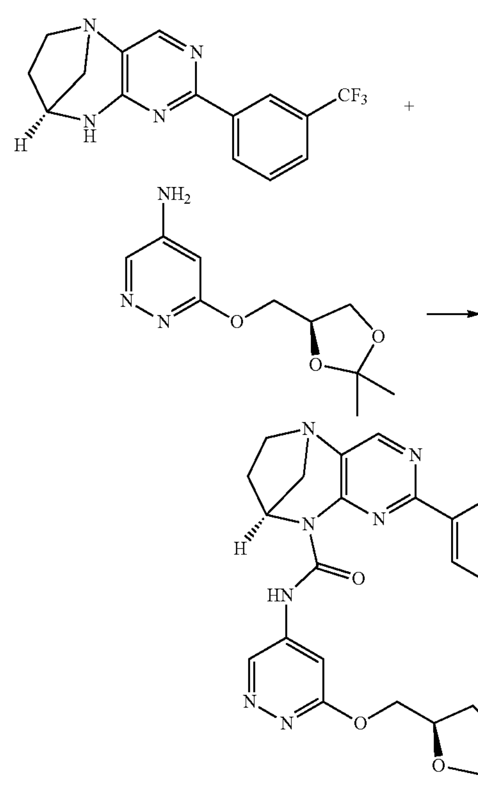
[0630]



[0631] Triphosgene (436 mg, 1.469 mmol) was added to a stirred solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (450.0 mg, 1.469 mmol), and TEA (1.229 mL, 8.82 mmol) in Tetrahydrofuran (THF) (20 mL) at 28° C. The reaction mixture was stirred for 30 min and was added (S)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-amine (993 mg, 4.41 mmol). The reaction mixture was stirred for 10 hr at 72° C. The reaction mixture was cooled to 25° C., and the precipitated solid was filtered and was washed with ethyl acetate (40 ml). The filtrate was washed with the water (10 ml) and brine solution (10 ml). The organic phase was separated, and was dried over anhydrous Na_2SO_4, filtered, and filtrate was evaporated to get the crude. This crude was purified by column on neutral alumina elute with 50% EtOAc in Pet ether to collect the fractions and evaporated to get the (8S)—N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (390.0 mg, 0.692 mmol, 47.1% yield) as white solid, LCMS (m/z): 558.25 $[M+H]^+$.

Synthesis of (8S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridazin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

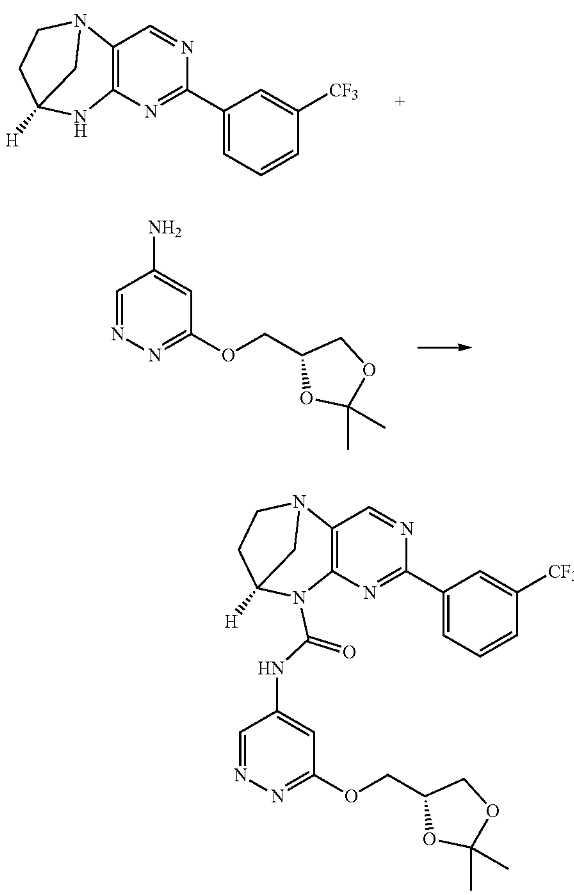
[0632]



[0633] To a solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (400 mg, 1.306 mmol) in THF (30 ml) and triphosgene (233 mg, 0.784 mmol) at 0° C. Then DIPEA (0.684 mL, 3.92 mmol) was added and stirred to RT for 1 h. and (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridazin-4-amine (441 mg, 1.959 mmol) was added sub sequentially at 75° C. for 16 h. The reaction was monitored by TLC and LCMS. The reaction mixture was poured in saturated $NaHCO_3$ solution (30 mL) and extracted with ethyl acetate (2×100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude. The crude was purified by column chromatography (100-200 silica gel) using gradient mixture of 2% Methanol in DCM as eluent, to afford the (8S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridazin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (150 mg, 0.265 mmol, 20.31% yield) as White solid, LCMS (m/z): 558.25 $[M+H]^+$.

Synthesis of (8S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridazin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

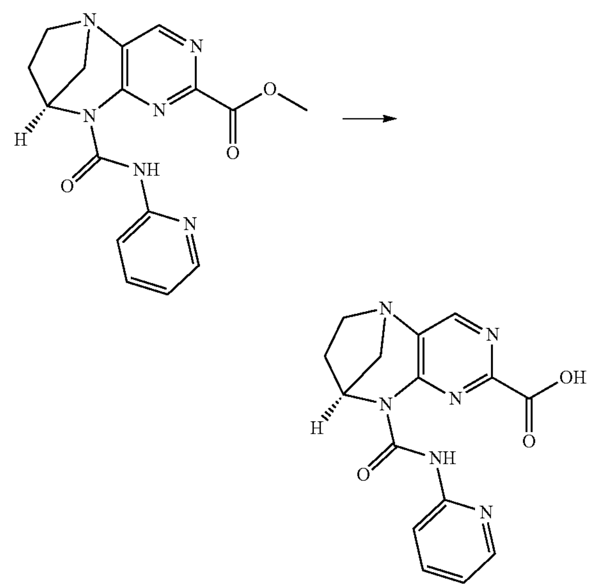
[0634]



[0635] To a solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (650 mg, 2.122 mmol) in THF (20 ml) and were added triphosgene (378 mg, 1.273 mmol), DIPEA (1.853 mL, 10.61 mmol) at 0° C. Then stirred to RT for 1 h. and (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridazin-4-amine (717 mg, 3.18 mmol) was added sub sequentially at 75° C. for 16 h. The reaction was monitored by TLC and LCMS. The reaction mixture was poured in saturated $NaHCO_3$ solution (10 mL) and extracted with ethyl acetate (2×50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude. The crude product was purified by flash column chromatography (100-200 silica gel, eluent: 80% ethyl acetate in hexane) to afford (8S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridazin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (140 mg, 0.238 mmol, 11.19% yield) as a brown solid, LCMS (m/z): 558.36 $[M+H]^+$.

Synthesis of (8S)-9-(pyridin-2-ylcarbamoyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylic acid

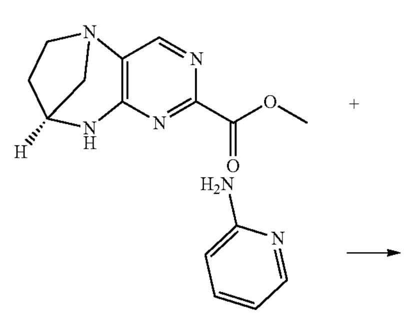
[0636]



[0637] To a solution of (8S)-methyl 9-(pyridin-2-ylcarbamoyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylate (750 mg, 2.204 mmol), in Tetrahydrofuran (THF) (10 mL) stirred under nitrogen at room temp, was added a solution of LiOH (106 mg, 4.41 mmol) in Water (10 mL) dropwise during 1 min. The reaction mixture was stirred at room temperature for 16 hr. Progress of the reaction was monitored by TLC. TLC indicated formation of a polar spot and complete consumption of SM. Reaction mixture was concentrated under reduced pressure, diluted with cold water (40 ml), washed with DCM (2×80 mL), aq layer was acidified with 1N HCl (10 mL) solid was not formed. Resulting crude was concentrated under reduced pressure to get (8S)-9-(pyridin-2-ylcarbamoyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylic acid (400 mg, 1.199 mmol, 54.4% yield) as off white solid, LCMS (m/z): 327.13 $[M+H]^+$.

Synthesis of (8S)-methyl 9-(pyridin-2-ylcarbamoyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylate

[0638]



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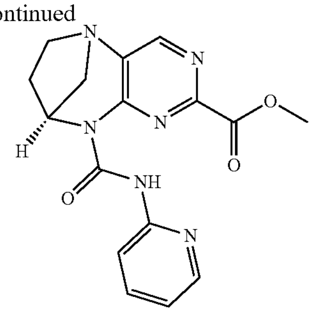
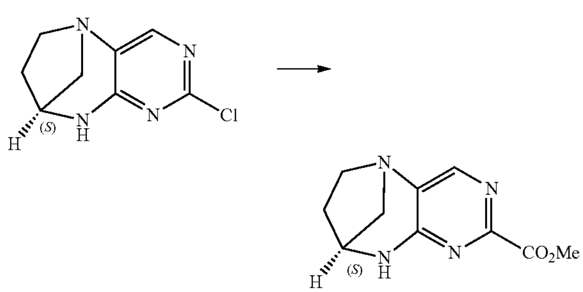


[0639] To a suspension of (8S)-methyl 6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylate (700 mg, 3.18 mmol) in Tetrahydrofuran (THF) (20 mL), added TEA (1.329 mL, 9.54 mmol) and triphosgene (566 mg, 1.907 mmol), reaction mixture was stirred under nitrogen at room temp for 1 hr, then added solid (8S)-methyl 6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylate (700 mg, 3.18 mmol). The resulting reaction mixture was stirred at Room temperature for 6 hr. Progress of the reaction was monitored by TLC. TLC indicated non polar spot and SM was consumed. Work-up: Reaction mass was diluted with (50 ml) of water, extracted with (2×100 ml) of EtOAc, and washed with saturated $NaHCO_3$ solution (50 mL), dried over Na_2SO_4, filtered and concentrated to get (8S)-methyl 9-(pyridin-2-ylcarbamoyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylate (850 mg, 1.405 mmol, 44.2% yield) as brown sticky mass. Crude compound was using next step without purification, LCMS (m/z): 341.13 $[M+H]^+$.

Synthesis of (8S)-methyl 6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylate

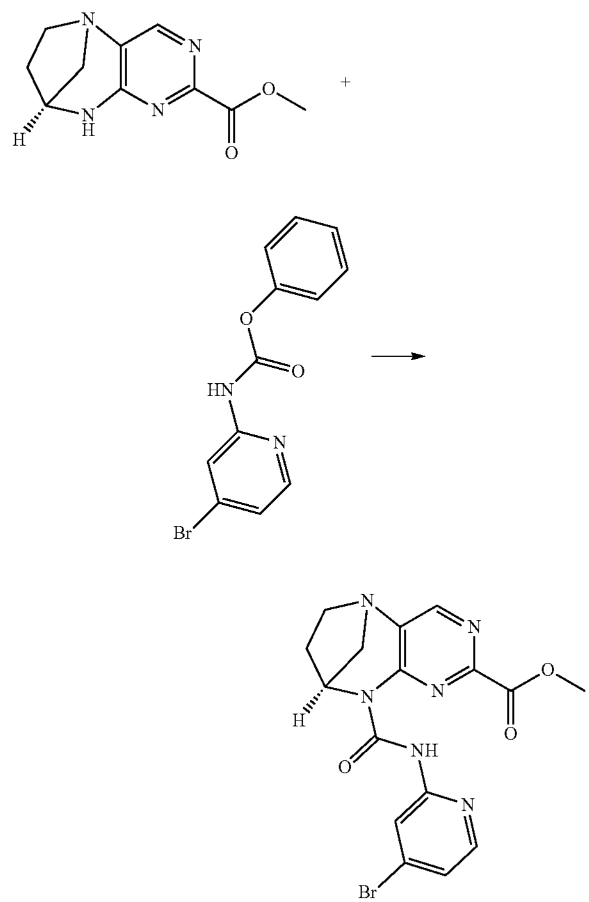
[0640]



[0641] To a solution of (8S)-2-chloro-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (50 g, 254 mmol) in Methanol (1200 mL) was degassed with argon gas for 30 min, then TEA (177 mL, 1271 mmol) and $PdCl_2$(dppf) (9.30 g, 12.71 mmol) were added and filled with 300 psi CO gas. The reaction mixture was stirred at 140° C. for 5 hr in steel bomb. Reaction mixture was concentrated under reduced pressure to afford crude compound. This was combined with another batch of this material and purified by column chromatography using neutral alumina to give (8S)-methyl 6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylate (40 g, 173 mmol, 67.9% yield), LCMS (m/z): 220.91 $[M+H]^+$.

Synthesis of (8S)-methyl 9-((4-bromopyridin-2-yl)carbamoyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylate

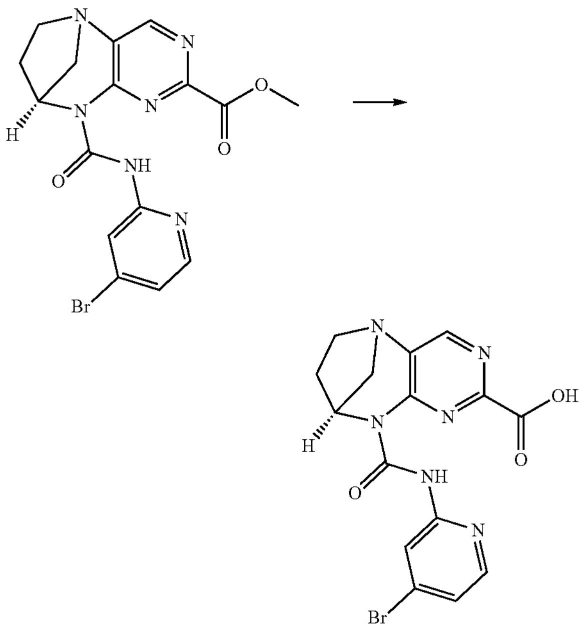
[0642]



[0643] A mixture of (8S)-methyl 6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylate (4 g, 18.16 mmol), phenyl (4-bromopyridin-2-yl)carbamate (10.65 g, 36.3 mmol) and Tetrahydrofuran (THF) (100 mL) were charged into 250 ml of sealed tube. DMAP (5.55 g, 45.4 mmol) was added to the mixture, resulting reaction mixture was stirred at 90° C. for 16 hr. Progress of the reaction was monitored by TLC. TLC indicated formation of two non polar spots and some amount of SM. Reaction mass was concentrated under reduced pressure to get crude. Crude material was purified by combiflash using silica gel column (80 g, 2% methanol in DCM). Fractions containing pure compound were combined and concentrated to afford the desired compound (8S)-methyl 9-((4-bromopyridin-2-yl)carbamoyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylate (3 g, 5.93 mmol, 32.7% yield) as off white solid, LCMS (m/z): 419.09 (M+H)+.

Synthesis of (8S)-9-((4-bromopyridin-2-yl)carbamoyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylic acid

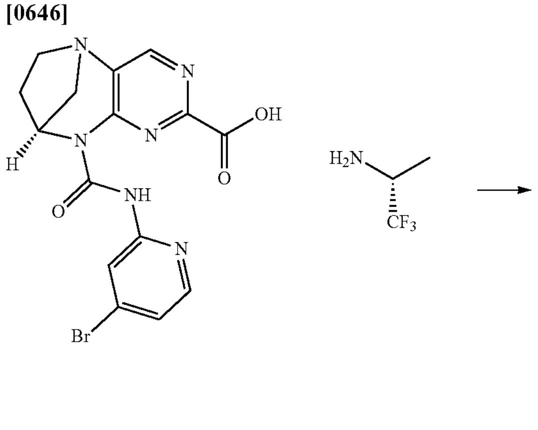
[0644]



[0645] To a suspension of (8S)-methyl 9-((4-bromopyridin-2-yl)carbamoyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylate (3 g, 7.16 mmol) in Tetrahydrofuran (THF) (30 mL), stirred at room temperature, was added a solution of lithium hydroxide hydrate (0.601 g, 14.31 mmol) in Water (15 mL). The reaction mixture was stirred at room temperature for 4 hr. Progress of the reaction was monitored by TLC. TLC indicated formation of polar spot and complete consumption of SM. Reaction mass was concentrated under reduced pressure, added 30 ml of water and washed with 50 ml of EtOAc. pH of aqueous layer was adjusted to 4 with 1N HCl at 0° C. Solid was formed, filtered and dried to get (8S)-9-((4-bromopyridin-2-yl)carbamoyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylic acid (2 g, 4.83 mmol, 67.6% yield) as off white solid, LCMS (m/z): 404.97 $(M+H)^+$.

Synthesis of (8S)—N9-(4-bromopyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2,9(6H)-dicarboxamide

[0646]



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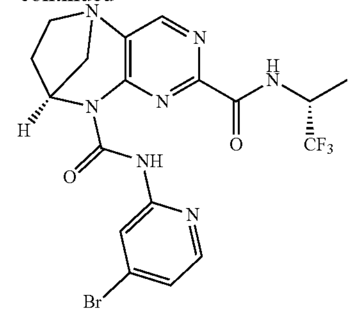
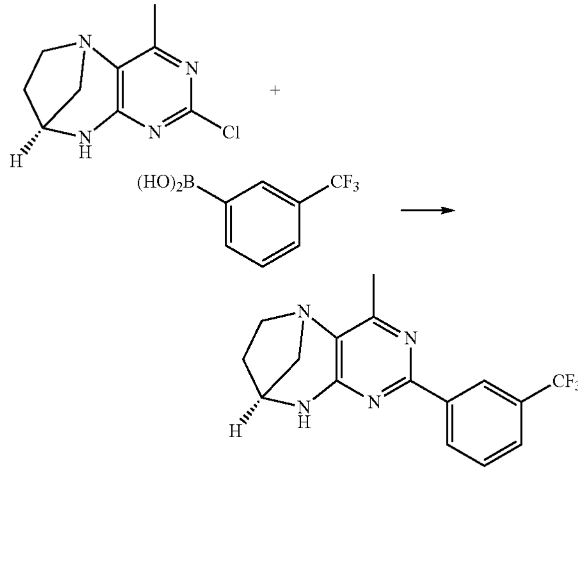


[0647] To a solution of (8S)-9-((4-bromopyridin-2-yl)carbamoyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylic acid (1.4 g, 3.46 mmol) in Dichloromethane (DCM) (100 mL) at room temperature, was added 1-methyl-1H-imidazole (1.135 g, 13.82 mmol) and MsCl (0.350 mL, 4.49 mmol). The resulting reaction mixture was stirred for 30 min at room temperature, then added (R)-1,1,1-trifluoropropan-2-amine (0.469 g, 4.15 mmol). The resulting reaction mixture was stirred at room temperature for 4 hr. Progress of the reaction was monitored by TLC. TLC indicated a non polar spot and SM was completely consumed. To the reaction mass was diluted 100 ml of water, extracted with DCM (2×200 ml), combined organic layer were washed with 100 ml of water, dried over Na_2SO_4, filtered and concentrated to get crude. Crude material was purified by combiflash using silica gel column (24 g, 3% methanol in DCM). Fractions containing pure compound were combined and concentrated to afford the desired (8 S)—N9-(4-bromopyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2,9(6H)-dicarboxamide (950 mg, 1.832 mmol, 53.0% yield) as off white solid, LCMS (m/z): 500.14 $(M+H)^+$.

Synthesis of (8S)-4-methyl-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine

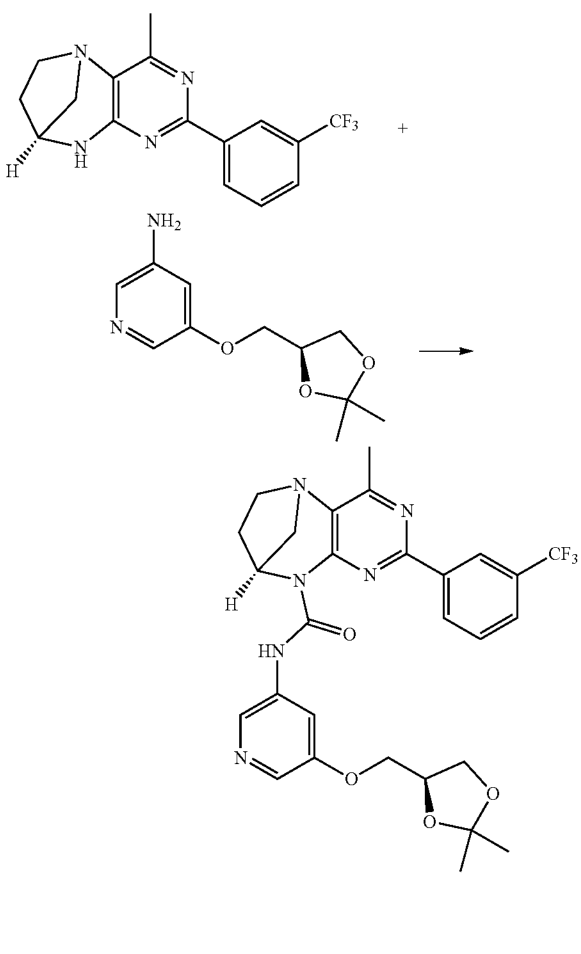
[0648]



[0649] A solid of (8S)-2-chloro-4-methyl-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (8 g, 38.0 mmol), (3-(trifluoromethyl)phenyl)boronic acid (10.82 g, 57.0 mmol) and Cs_2CO_3 (37.1 g, 114 mmol) in 1,4-Dioxane (160 mL) and Water (40 mL) was stirred and degassed with Argon for 15 min. To this reaction mixture X-PHOS (1.440 g, 3.80 mmol), palladium(II) acetate (0.853 g, 3.80 mmol) was added. Again degassed with Argon for 5 min. The reaction mixture was stirred at 110° C. for 4 hr and progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature filtered through celite and filtrate was concentrated and was diluted with water and Extracted with EtOAc (2×200 mL) and washed with water (100 mL) followed by brine solution (100 mL), dried over Na_2SO_4, filtered and evaporate to get crude compound. The crude product was added to a silica gel column and was eluted with 50% Hex/EtOAc. Collected fractions: washed with pentane and filtered to afforded pure solid (8S)-4-methyl-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (7.2 g, 21.94 mmol, 57.8% yield), LCMS (m/z): 321.02 $[M+H]^+$.

Synthesis of (8S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

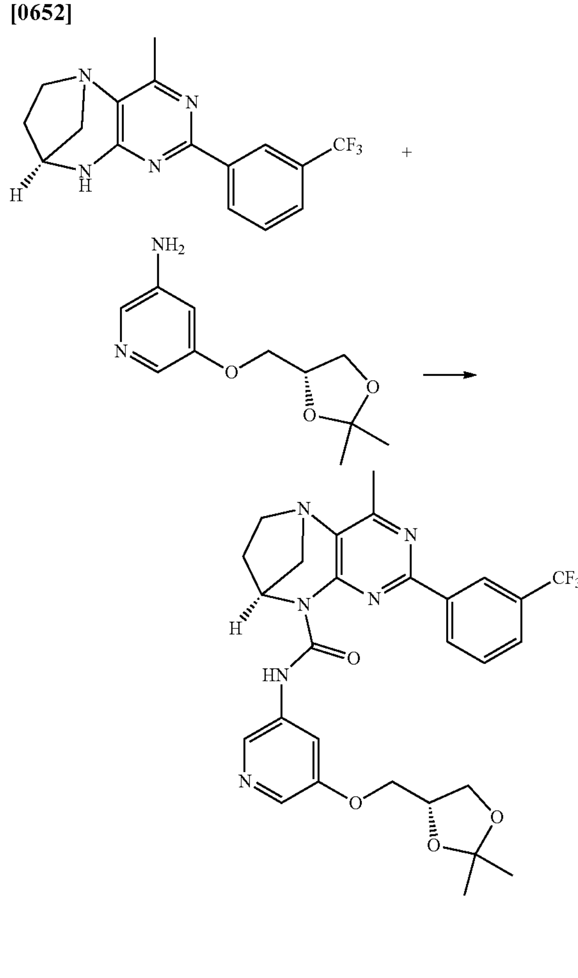
[0650]



[0651] Triphosgene (0.926 g, 3.12 mmol) was added slowly in portions to a stirred solution of (8S)-4-methyl-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (1 g, 3.12 mmol) and TEA (2.61 mL, 18.73 mmol) in Tetrahydrofuran (THF) (100 mL) at RT. This reaction mixture was stirred for 40 min (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine (1.400 g, 6.24 mmol) was added to the above reaction mixture and stirred at 65° C. for 16 hr. The reaction mixture was cooled to room temperature, concentrated in vacuo and the residue was partitioned between water (100 mL) and EtOAc (2×150 mL). Organic layer was separated and dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude compound. The crude compound was purified by combiflash chromatography by eluting 75% Acetonitrile in 0.1% formic acid in water. The collected fraction was evaporated under reduced pressure and basify with saturated sodium bi carbonate solution (50 mL) and extracted with DCM (2×75). The organic layer was evaporated under reduced pressure to afford (8S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (0.3 g, 0.498 mmol, 15.94% yield) as a white solid, LCMS (m/z): 571.29 $[M+H]^+$.

Synthesis of (8S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

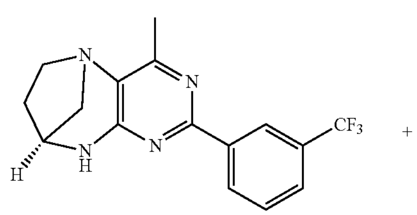
[0652]

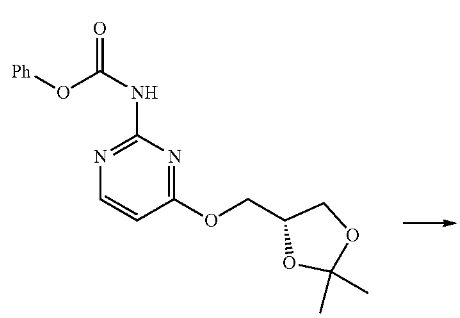


[0653] Triphosgene (556 mg, 1.873 mmol) was added slowly in portions to a stirred solution of (8S)-4-methyl-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (600 mg, 1.873 mmol) and TEA (1.566 mL, 11.24 mmol) in Tetrahydrofuran (THF) (50 mL) at RT. This reaction mixture was stirred for 40 min (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine (840 mg, 3.75 mmol) was added to the above reaction mixture and stirred at 65° C. for 16 hr. The reaction mixture was cooled to room temperature, concentrated in vacuo and the residue was partitioned between water (100 mL) and EtOAc (2×150 mL). Organic layer was separated and dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude compound. The crude compound was purified by combiflash chromatography by eluting 80% ACN in 0.1% formic acid in water. The collected fraction was evaporated under reduced pressure and basify with saturated sodium bi carbonate solution (30 mL) and extracted with DCM (2×50). The organic layer was evaporated under reduced pressure to afford (8S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (150 mg, 0.256 mmol, 13.66% yield) as a white solid, LCMS (m/z):571.14 $[M+H]^+$.

Synthesis of (8S)—N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0654]





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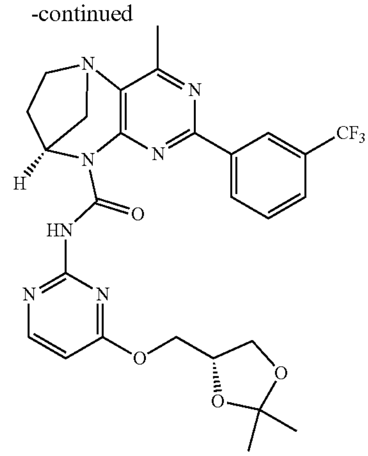
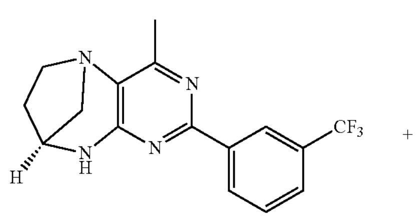


[0655] DMAP (0.915 g, 7.49 mmol) was added slowly in portions to a stirred solution of (8S)-4-methyl-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (0.8 g, 2.498 mmol) in Tetrahydrofuran (THF) (80 mL) at RT. This reaction mixture was stirred for 40 min (R)-phenyl (4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)carbamate (2.59 g, 7.49 mmol) was added to the above reaction mixture and stirred at 65° C. for 16 hr. The reaction mixture was cooled to room temperature, concentrated in vacuo and the residue was partitioned between water (100 mL) and EtOAc (2×150 mL). Organic layer was separated and dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude compound. The crude compound was purified by combiflash chromatography by eluting 94% ACN in 0.1% formic acid in water. The collected fraction was evaporated under reduced pressure and basify with saturated sodium bi carbonate solution (50 mL) and extracted with DCM (2×75). The organic layer was evaporated under reduced pressure to afford (8S)—N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (0.250 g, 0.429 mmol, 17.19% yield) as a white solid, LCMS (m/z): 572.14 $[M+H]^+$.

Synthesis of (8S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0656]



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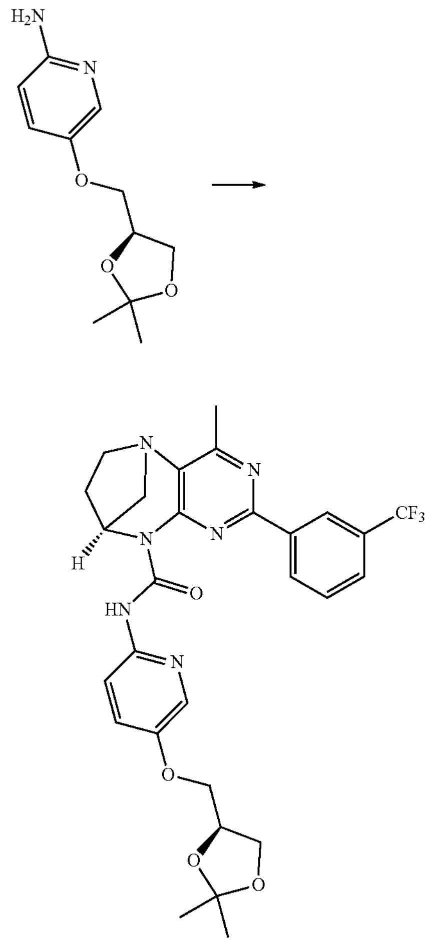
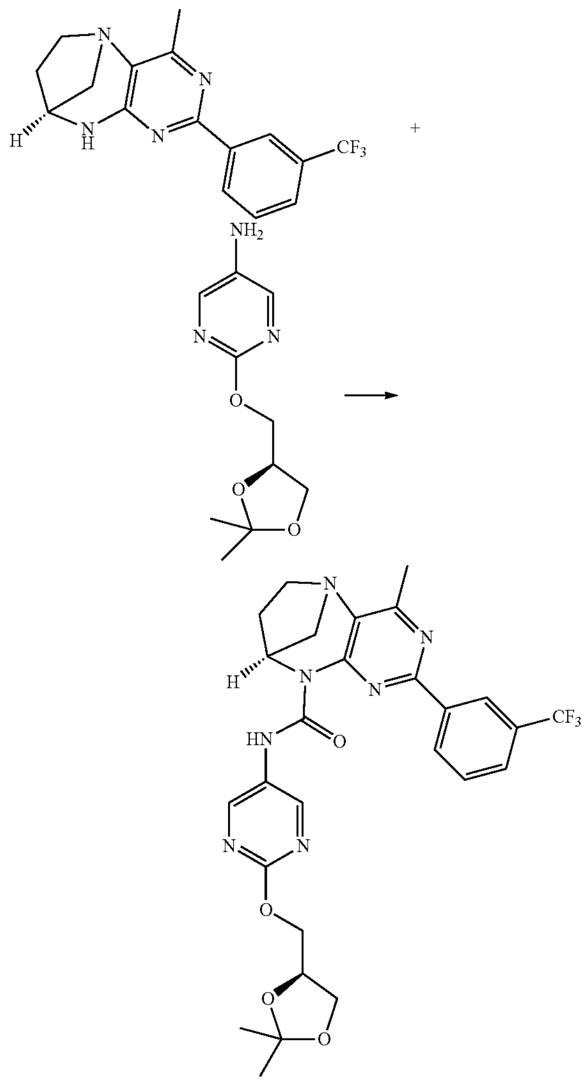


[0657] To a solution of (8S)-4-methyl-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (0.8 g, 2.498 mmol), in Tetrahydrofuran (THF) (10 mL) stirred under nitrogen at room temp, was added triphosgene (1.853 g, 6.24 mmol) and TEA (6.96 mL, 50.0 mmol). The reaction mixture was stirred for 30 min, was added (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (1.680 g, 7.49 mmol). The resulting reaction mixture was stirred at 75° C. for 16 hr. Progress of the reaction was monitored by TLC. TLC indicated formation of non polar spot and SM was not consumed. Reaction mass was diluted with 20 ml of water, extracted with (2×25 ml) of EtOAc. Combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to get crude compound which was purified by combi flash to afford (8S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (350 mg, 0.604 mmol, 24.19% yield) as a white solid, LCMS (m/z): 571.26 $[M+H]^+$.

Synthesis of (8S)—N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0658]

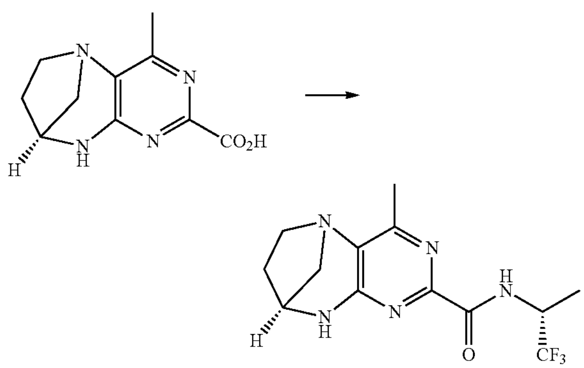


[0659] To a stirred solution of (8S)-4-methyl-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (500 mg, 1.561 mmol) and TEA (1.305 mL, 9.37 mmol) in Tetrahydrofuran (THF) (50 mL) at RT was added triphosgene (463 mg, 1.561 mmol). This reaction mixture was stirred for 30 min (S)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-amine (703 mg, 3.12 mmol) was added and the reaction mixture stirred at 65° C. for 16 hr. The reaction mixture was cooled to room temperature, concentrated in vacuo and the residue was partitioned between water (100 mL) and EtOAc (2×150 mL). Organic layer was separated and dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude compound. The crude compound was purified in Neutral

Alumina, 60% Ethylaceatae in pet ether as a eluent to afford (8S)—N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy) pyrimidin-5-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (350 mg, 0.607 mmol, 38.9% yield) as a white solid, LCMS (m/z): 572.1 $[M+H]^+$.

Synthesis of (8S)-4-methyl-N—((R)-1,1,1-trifluoropropan-2-yl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxamide

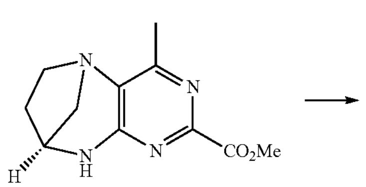
[0660]



[0661] To a stirred solution of (8S)-4-methyl-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylic acid (13 g, 59.0 mmol) in Tetrahydrofuran (THF) (30 mL), to this added HATU (33.7 g, 89 mmol) and DIPEA (30.9 mL, 177 mmol), reaction mixture was stirred for 15 min, then added (R)-1,1,1-trifluoropropan-2-amine (20.03 g, 177 mmol), reaction mixture was stirred at RT for 16 hr. Progress of the reaction was monitored by TLC. Reaction mixture was cooled to RT, Water (10 mL) was added to the reaction mixture and extracted with Ethyl acetate (10 mL), separated organic layer, dried over Na_2SO_4, concentrated under reduced pressure to obtain crude. Obtained crude was purified by column using silica gel (100-200 mesh; 1-50% of Ethyl acetate in Pet-ether as a eluent). Collected fractions were concentrated under reduced pressure to get (8S)-4-methyl-N—((R)-1,1,1-trifluoropropan-2-yl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxamide (2.3 g, 4.69 mmol, that was 64% pure by LCMS, 7.95% yield), LCMS (m/z): 316.22 $[M+H]^+$.

(8S)-4-methyl-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylic acid

[0662]



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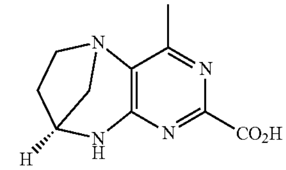
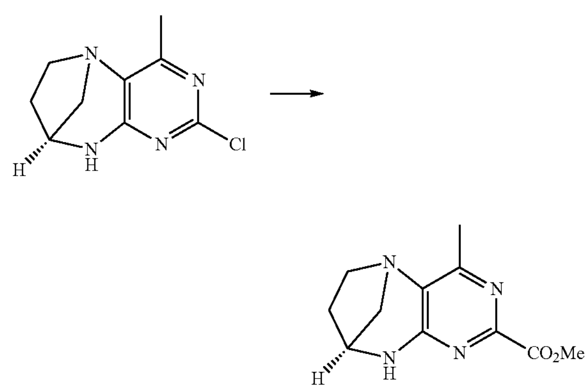


[0663] In a stirred solution of ((8S)-methyl 4-methyl-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylate (8 g, 34.2 mmol) in Tetrahydrofuran (THF) (30 mL) and Water (15 mL). To this LiOH (2.454 g, 102 mmol) was added at RT, reaction mixture was stirred at RT for 3 hr. Progress of the reaction was monitored by TLC. Distilled the solvent from the reaction mixture completely and acidified with 2M HCl (20 mL), concentrated under reduced pressure to obtain gummy liquid. The obtained product was directly used in the next step with out any father purification.

Synthesis of (8S)-methyl 4-methyl-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylate

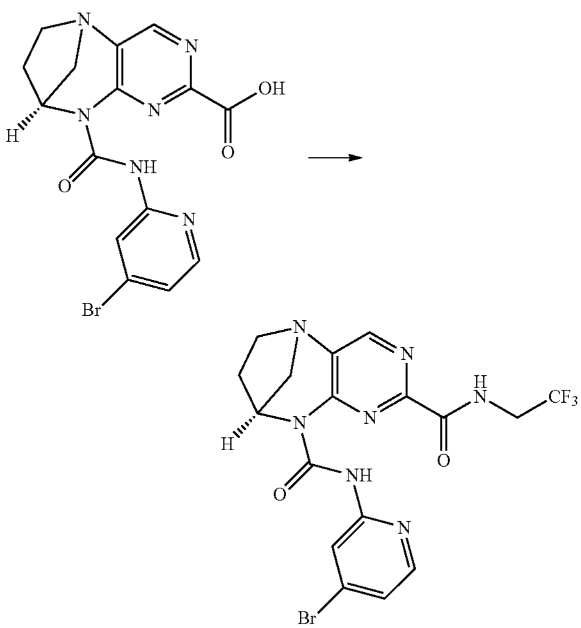
[0664]



[0665] To a solution of (8S)-2-chloro-4-methyl-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (8 g, 38.0 mmol) in Methanol (200 mL) was degassed with organ gas for 30 min, then TEA (10.59 mL, 76 mmol) and $PdCl_2(dppf)$ (0.556 g, 0.760 mmol) were added and filled with 300 psi CO gas. The reaction mixture was stirred at 140° C. for 4 hr in steel bomb. Reaction mixture was concentrated under reduced pressure to afford crude compound. The crude product was added to a 100-200 silica gel column and was eluted with 2% CH_2Cl_2/MeOH to afford pure compound (8S)-methyl 4-methyl-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylate (8 g, 30.2 mmol, 79% yield), LCMS (m/z): 235.26 $[M+H]^+$.

Synthesis of (8S)—N9-(4-bromopyridin-2-yl)-N2-(2,2,2-trifluoroethyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2,9(6H)-dicarboxamide

[0666]

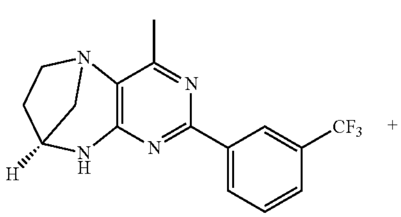


Procedure:

[0667] To a solution of (8S)-9-((4-bromopyridin-2-yl)carbamoyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylic acid (2.00 g, 4.94 mmol) and 2,2,2-trifluoroethanamine (0.733 g, 7.40 mmol) in N,N-Dimethylformamide (DMF) (30 mL) stirred under nitrogen at 28° C. was added HATU (2.252 g, 5.92 mmol) and DIPEA (1.724 mL, 9.87 mmol) and the reaction mixture was stirred at 28° C. for 16 hr. Reaction mixture was quenched with ice water and the solid precipitated filtered, washed thoroughly with water. The residue washed with Diethyl ether (2×50 mL) and dried under reduced pressure to afford (8S)—N9-(4-bromopyridin-2-yl)-N2-(2,2,2-trifluoroethyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2,9(6H)-dicarboxamide (750 mg, 1.278 mmol, 25.9% yield) as an Off white solid, LCMS (m/z): 487.84 $[M+H]^+$.

Synthesis of (8S)—N-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0668]



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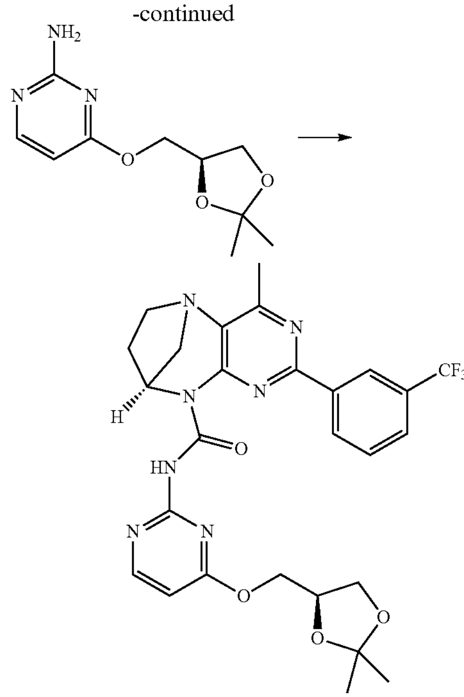
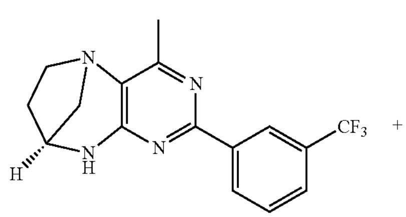


[0669] To a solution of (8S)-4-methyl-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (1 g, 3.12 mmol), in Tetrahydrofuran (THF) (100 mL) stirred under nitrogen at room temp, was added triphosgene (0.926 g, 3.12 mmol) and TEA (2.61 mL, 18.73 mmol) The reaction mixture was stirred for 24 hrs, was added (S)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-amine (1.406 g, 6.24 mmol) in Tetrahydrofuran (THF) (50 mL). The resulting reaction mixture was stirred at 75° C. for 16 hr. Progress of the reaction was monitored by TLC. TLC indicated formation of non polar spot and SM was intact. Reaction mass was diluted with 200 ml of water, extracted with (2×250 ml) of EtOAc. Combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to get crude compound which was purified by Prep HPLC to afford (8S)—N-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (200 mg, 0.343 mmol, 10.98% yield) as a brown gum, LCMS (m/z): 572.28 $[M+H]^+$.

Synthesis of (8S)—N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0670]



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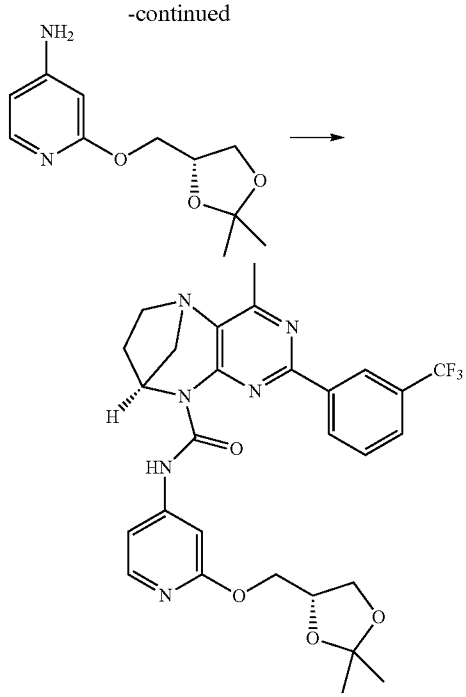

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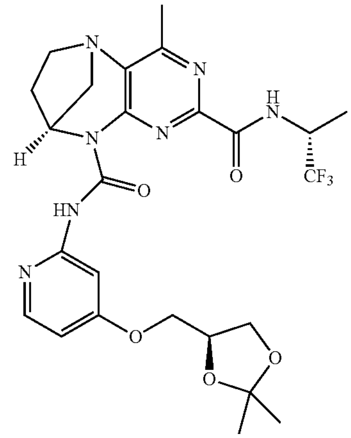
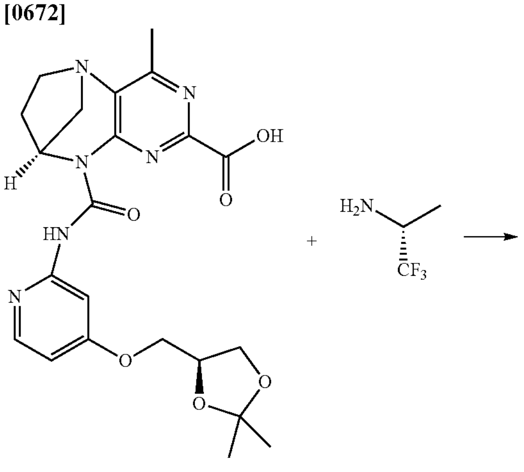


[0671] To a solution of (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (1120 mg, 5.00 mmol) in THF (10 ml) and triphosgene (1482 mg, 5.00 mmol) at 0° C. Then TEA (3.48 mL, 24.98 mmol) was added and stirred to RT for 1 h. and (8S)-4-methyl-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (800 mg, 2.498 mmol) was added sub sequentially at 75° C. for 16 h. The reaction was monitored by TLC and LCMS. The reaction mixture was poured in saturated $NaHCO_3$ solution (30 mL) and extracted with ethyl acetate (2×100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude of (8S)—N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (300 mg, 0.505 mmol, 20.21% yield), LCMS (m/z): 571.04 $[M+H]^+$.

Synthesis of (8S)—N9-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-4-methyl-N2-((R)-1,1,1-trifluoropropan-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2,9(6H)-dicarboxamide

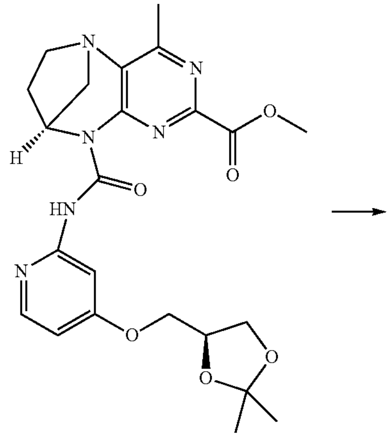
[0672]



[0673] To a stirred solution of (8S)-9-((4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-4-methyl-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylic acid (600 mg, 1.275 mmol) in Pyridine (10 mL) was added EDC (244 mg, 1.275 mmol) at 0° C. The resulting reaction mixture was stirred at 0° C. for 1 hr. (R)-1,1,1-trifluoropropan-2-amine hydrochloride (191 mg, 1.275 mmol) was added to the reaction mixture and stirred at room temperature for 16 hr. (TLC system: 10% MeOH in DCM, Rf: 0.5, UV active). Reaction mixture was diluted with ice cold water and extracted with EtOAc (3×40 mL). The combined organic layers were washed with water (30 mL), brine solution (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtained crude compound. The crude was purified by column chromatography (Silica gel: 100-200 mesh, Eluent: 3% MeOH in DCM), to afford (8S)—N9-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-4-methyl-N2-((R)-1,1,1-trifluoropropan-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2,9(6H)-dicarboxamide (350 mg, 0.568 mmol, 44.5% yield) as a Yellow solid. LCMS (m/z): 566.08 $[M+H]^+$.

(8S)-9-((4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-4-methyl-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylic acid

[0674]



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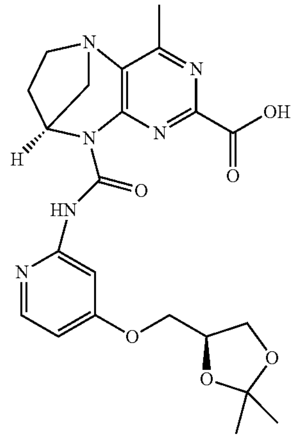
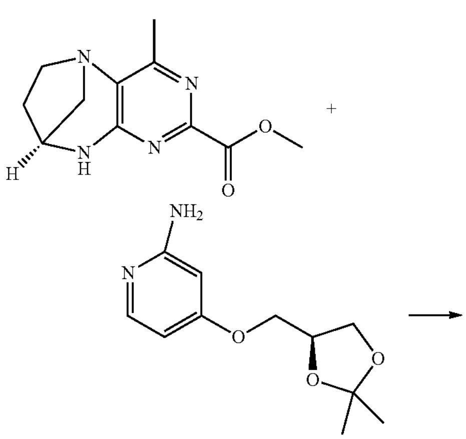


[0675] To a stirred solution of (8S)-methyl 9-((4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-4-methyl-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylate (850 mg, 1.754 mmol) in Tetrahydrofuran (THF) (20 mL) and Water (5 mL) was added lithium hydroxide hydrate (147 mg, 3.51 mmol). The resulting reaction mixture was stirred at Room temperature for 4 hr. Progress of the reaction was monitored by TLC. Reaction mixture was concentrated under vacuum to obtained crude compound. The Crude was neutralized with 1N HCl solution and extracted with 10% MeOH in DCM (3×40 mL). The combined organic layer was washed with brine solution (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford (8S)-9-((4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-4-methyl-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylic acid (600 mg, 0.743 mmol, 42.3% yield) as a brown sticky solid. LCMS (m/z): 471.27 $[M+H]^+$.

(8S)-methyl 9-((4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-4-methyl-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylate

[0676]



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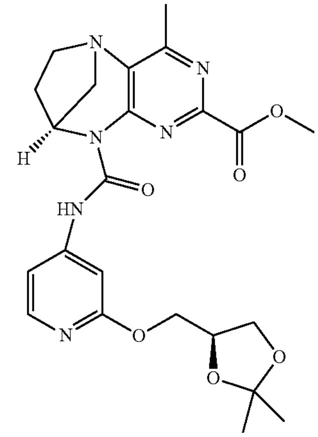
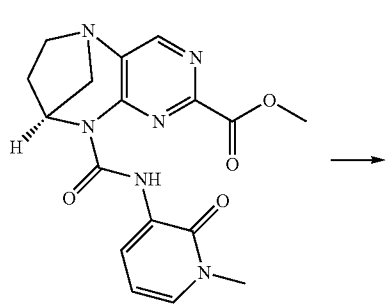


[0677] To a stirred solution of (8S)-methyl 4-methyl-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylate (1.0 g, 4.27 mmol) in Tetrahydrofuran (THF) (30 mL) was added triphosgene (1.013 g, 3.42 mmol) and TEA (1.785 mL, 12.81 mmol) at room temperature under Nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 1 hr. To the reaction mixture was added a solution of (S)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (0.957 g, 4.27 mmol) in Tetrahydrofuran (THF) (10 mL). The resulting reaction mixture was stirred at 70° C. for 16 hr. Progress of the reaction was monitored by TLC. Reaction mixture was diluted with water (30 mL), extracted with EtOAc (3×30 mL). Organic layers were combined and washed with brine solution (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtained crude compound. The crude was purified by column chromatography (100-200 mesh silica gel, eluent: 3% MeOH in DCM) to afford (8S)-methyl 9-((4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-4-methyl-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylate (950 mg, 1.606 mmol, 37.6% yield) as a brown sticky compound, LCMS (m/z): 485.32 $[M+H]^+$.

Synthesis of (8S)-9-((1-methyl-2-oxo-1,2-dihydropyridin-3-yl)carbamoyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylic acid N36502-35-A2

[0678]



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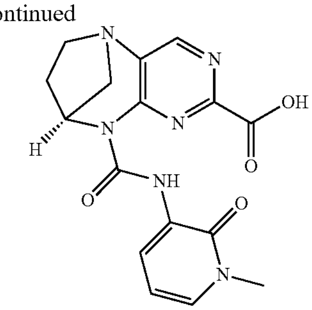
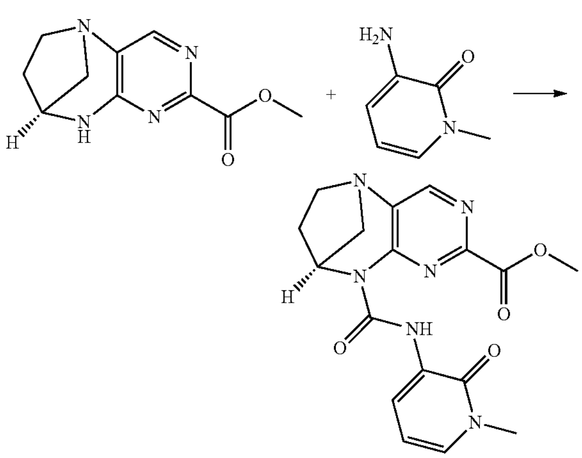


[0679] (8S)-methyl 9-((1-methyl-2-oxo-1,2-dihydropyridin-3-yl)carbamoyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylate (1.5 g, 4.05 mmol), LiOH (0.388 g, 16.20 mmol) were taken in Tetrahydrofuran (THF) (3 mL), Methanol (3.00 mL) and Water (3 mL) at 0° C., the resulting brown solution was stirred for 3 hr at room temperature. The reaction progress was monitored by TLC 10% MeOH in DCM, TLC indicated formation of polar spots. Reaction mixture was concentrated under reduced pressure, diluted with cold water (40 ml), washed with DCM (2×80 mL), aq layer was acidified with 1N HCl (10 mL) and filtered to get (8S)-9-((1-methyl-2-oxo-1,2-dihydropyridin-3-yl)carbamoyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylic acid (450 mg, 1.187 mmol, 29.3% yield) as pale yellow solid, LCMS (m/z): 357.05 $[M+H]^+$.

Synthesis of (8S)-methyl 9-((1-methyl-2-oxo-1,2-dihydropyridin-3-yl)carbamoyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylate

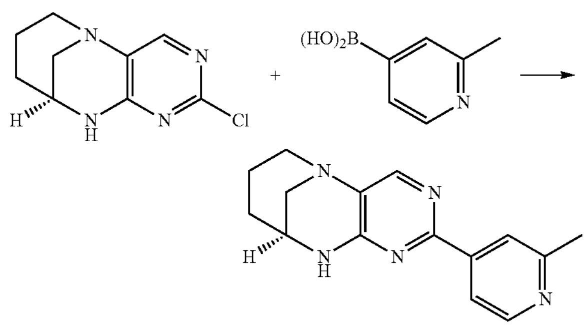
[0680]



[0681] Triphosgene (2.021 g, 6.81 mmol) was added to a solution of (8S)-methyl 6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylate (1.5 g, 6.81 mmol) in Tetrahydrofuran (THF) (10 mL) stirred under nitrogen at 28° C. was added TEA (0.949 mL, 6.81 mmol) at 28° C. The reaction mixture was stirred for 45 min at 28° C. To this 3-amino-1-methylpyridin-2(1H)-one (2.94 mL, 20.43 mmol) was added to the reaction mixture and stirred at 72° C. for 9 hr. The reaction mixture was cooled to room temperature and was partitioned between water (15 mL) and EtOAc (25 mL). EtOAc layer was separated and was dried over anhydrous Na_2SO_4, filtered. The filtrate was evaporated to get crude. The crude was purified by column chromatography using (100-200 mesh) silica gel (neutralized with TEA), and the product was eluted with 80% of EtOAc in pet ether. The collected fraction was evaporated to afford (8S)-methyl 9-((1-methyl-2-oxo-1,2-dihydropyridin-3-yl)carbamoyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylate (1.5 g, 2.025 mmol, 29.7% yield) as brown solid. LCMS (m/z): 371.19 $[M+H]^+$.

Synthesis of (9S)-2-(2-methylpyridin-4-yl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine

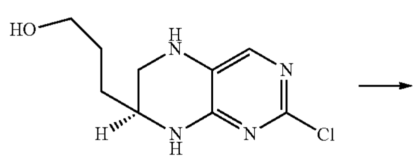
[0682]



[0683] To a suspension of (9S)-2-chloro-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (1 g, 4.75 mmol), (2-methylpyridin-4-yl)boronic acid (0.975 g, 7.12 mmol) in 1,4-Dioxane (15 mL) and Water (3 mL), K_3PO_4 (2.013 g, 9.49 mmol) was added. The reaction mixture was stirred and degassed with argon at room temp for 15 mins and $Pd_2(dba)_3$ (0.217 g, 0.237 mmol), X-PHOS (0.226 g, 0.475 mmol) added to the reaction mixture. Then the reaction mixture was stirred 16 hr at 100° C. The reaction was monitored by TLC. The reaction mass filtered through celite and distill out the solvent completely. Reaction mixture was diluted with EtOAc (150 mL) and washed with water (70 mL) followed by brine solution (20 mL) and dried out with Na_2SO_4, filtered and evaporated to get crude product. The crude product was purified. The crude product was washed with mixture of Et_2O and pentane (4:20 mL) stirred for 15 min and filtered. The solid was dried to afford a compound of (9S)-2-(2-methylpyridin-4-yl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (600 mg, 2.033 mmol, 42.8% yield) as a yellow solid, LCMS (m/z): 268.21 $[M+H]^+$.

Synthesis of (9S)-2-chloro-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine

[0684]



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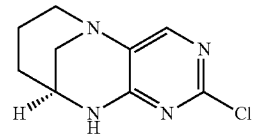
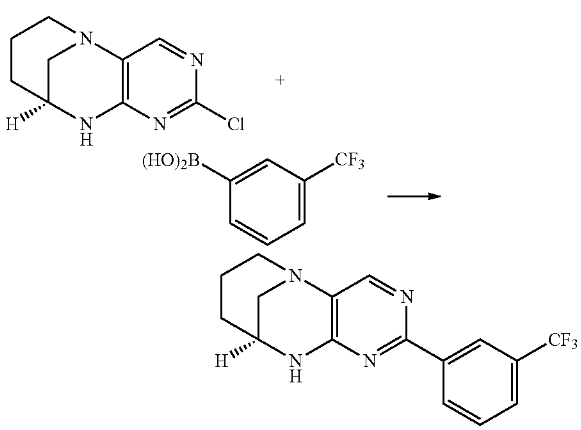


[0685] $POCl_3$ (23.85 mL, 256 mmol) was added to a stirred solution of (S)-3-(2-chloro-5,6,7,8-tetrahydropteridin-7-yl)propan-1-ol (39 g, 171 mmol) and DIPEA (89 mL, 512 mmol) in Dichloromethane (DCM) (600 mL) at 0° C. and stirred for 1 h at 0° C. saturated sodium bicarbonate solution was added slowly to reaction mixture at 0° C. and adjusted pH to basic condition and stirred for 1 h. The separated organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to get crude compound. Crude compound was triturated with diethyl ether 150 mL and resultant solid was filtered and dried to afford (9S)-2-chloro-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (20 g, 90 mmol, 52.9% yield) as pale yellow solid, LCMS (m/z): 211.08 $[M+H]^+$.

Synthesis of (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine

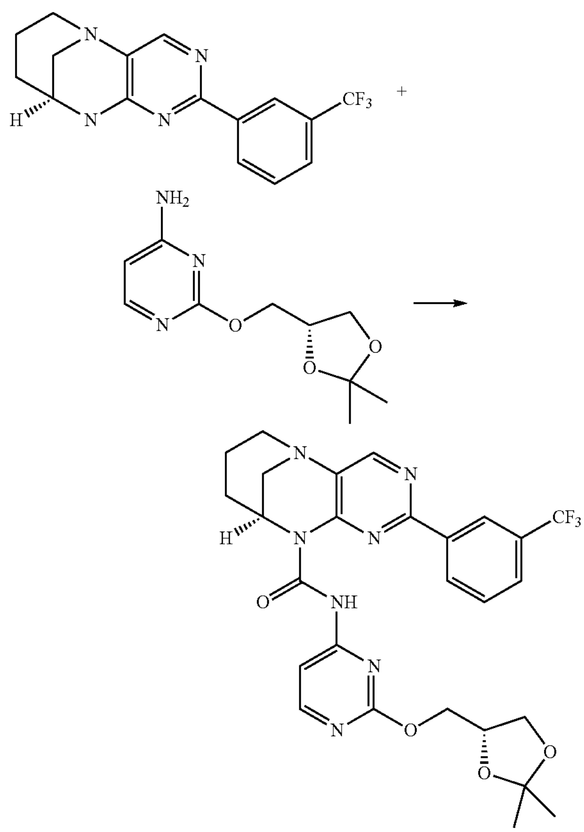
[0686]



[0687] A solution of (9S)-2-chloro-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (15 g, 71.2 mmol), (3-(trifluoromethyl)phenyl)boronic acid (20.29 g, 107 mmol) and Cs_2CO_3 (69.6 g, 214 mmol) in 1,4-Dioxane (120 mL), Water (12.00 mL) was stirred and degassed with Argon for 15 min. To this reaction mixture x-phos (0.849 g, 1.780 mmol), palladium(II) acetate (0.799 g, 3.56 mmol) was added. The reaction mixture was stirred at 90° C. for 16 hr and progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature filtered through celite and distilled the solvent completely. The reaction mixture was diluted with EtOAc (200 mL) and washed with water (50 mL) followed by brine solution (50 mL), dried over Na_2SO_4, filtered and evaporated to get crude compound. The crude compound was purified by column chromatography using Neutral Alumina and eluted with 20% EtOAc in petether to afford pure (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (15 g, 41.9 mmol, 58.9% yield) as off white solid, LCMS (m/z): 321.35 $[M+H]^+$.

Synthesis of (9S)—N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

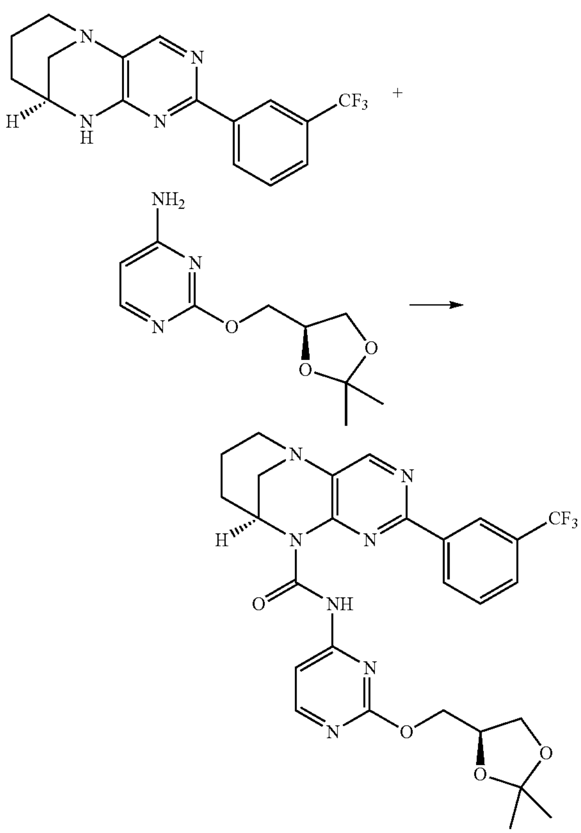
[0688]



[0689] Triethylamine (1.108 ml, 7.95 mmol) and triphosgene (417 mg, 1.405 mmol) was added to a stirred solution of (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (450 mg, 1.405 mmol) in Tetrahydrofuran (THF) (25 mL) under nitrogen at room temp. The reaction mixture was stirred at RT for 30 min. (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine (949 mg, 4.21 mmol) was added and the reaction mixture was stirred 8 hr at 65° C. The reaction mixture was cooled to room temp, solvent evaporated under reduced pressure completely and was partitioned between water (20 mL) and EtOAc (2×60 mL). Organic layer was separated, dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude as brown solid. The crude product was purified by column chromatography using neutral alumina and was eluted with 25-30% EtOAc in Hexane (gradient system) to afford the desired product (9S)—N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (300 mg, 0.521 mmol, 37.1% yield) as a white solid, LCMS (m/z): 572.55 [M+H]+.

Synthesis of (9S)—N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

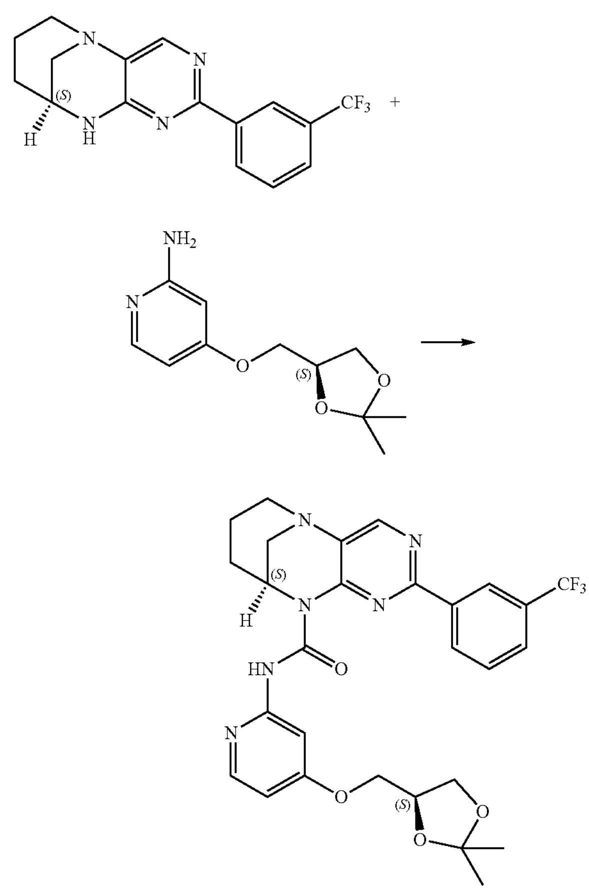
[0690]



[0691] A solution of (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (500 mg, 1.561 mmol), triphosgene (463 mg, 1.561 mmol) and triethylamine (1.088 mL, 7.80 mmol) in Tetrahydrofuran (THF) (15 mL) was stirred under nitrogen at room temp for 30 min. To this reaction mixture (S)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine (703 mg, 3.12 mmol) was added. The reaction mixture was stirred at 70° C. for 16 h and progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature, poured in to water (15 mL) and extracted with EtOAc (3×20 mL). The combined organic layer was washed with water (20 mL), brine solution (20 mL), dried over Na_2SO_4, filtered and evaporated to get crude compound. The crude compound was purified by Grace using C-18 reserval column, Mobile phase A: 0.1% Formic Acid in water; B: MeOH, the product was eluted at 90% MeOH/0.1% Formic Acid in water. The solvent was evaporated and was basified with saturated $NaHCO_3$. The aqueous layer was extracted with DCM. DCM layer was dried over anhydrous Na_2SO_4, filtered and evaporated to afford pure (9S)—N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (300 mg, 0.518 mmol, 33.2% yield) as off white solid, LCMS (m/z): 572.10 [M+H]+.

Synthesis of (9S)—N-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

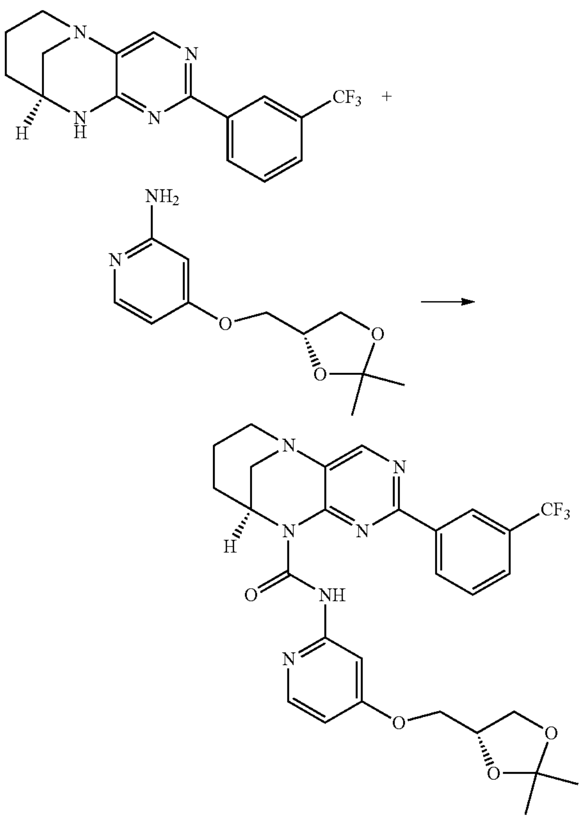
[0692]



[0693] To a solution of (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (500 mg, 1.561 mmol) in THF (10 ml) triphosgene (278 mg, 0.937 mmol), and TEA (0.218 mL, 1.561 mmol) were added at 0° C. and stirred to RT for 1 h. Then (S)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (700 mg, 3.12 mmol) was added sub sequentially under sealed tube condition at 75° C. for 16 h. The reaction was monitored by TLC and LCMS. The reaction mixture was poured in saturated $NaHCO_3$ solution (30 mL) and extracted with ethyl acetate (2×50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude compound, LCMS (m/z): 571.17 [M+H]+.

Synthesis of (8S)—N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

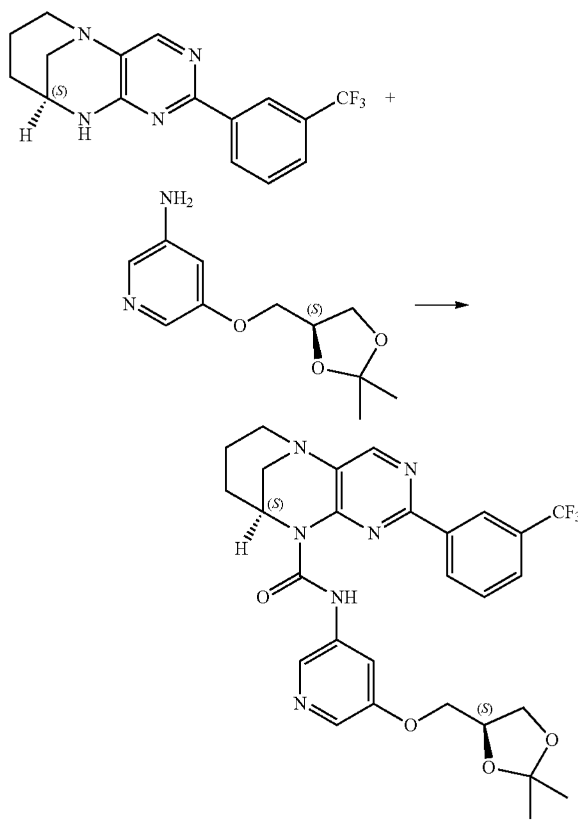
[0694]



[0695] TEA (20.48 mL, 147 mmol) and triphosgene (7.27 g, 24.49 mmol) was added to a stirred solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (7.5 g, 24.49 mmol) in at room temp. The reaction mixture was stirred for 45 min and (R)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (8.24 g, 36.7 mmol) was added. The reaction mixture was stirred for 16 hr at 65° C. The reaction mixture was cooled to room temp, solvent evaporated under reduced pressure completely and was partitioned between water (100 mL) and EtOAc (500 mL). Organic layer was separated, dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford crude product. The crude product was purified by column chromatography using neutral alumina and was eluted with 20% EtOAc in Hexane (gradient system) to afford the desired product (8.50 g) as a white solid. The product (8.50 g) was diluted in ethanol (100 ml) and treated with Silicycle palladium scavenger (4.25 g) and stirred at 65° C. for 3 hr. The reaction mixture was filtered through pad of celite and the celite pad was washed with the hot ethanol (50 ml), the obtained filtrate was concentrated under reduced pressure to afford the desired product (8S)—N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (8 g, 14.33 mmol, 58.5% yield) as a white solid, LCMS (m/z): 557.12 $[M+H]^+$.

Synthesis of (9S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

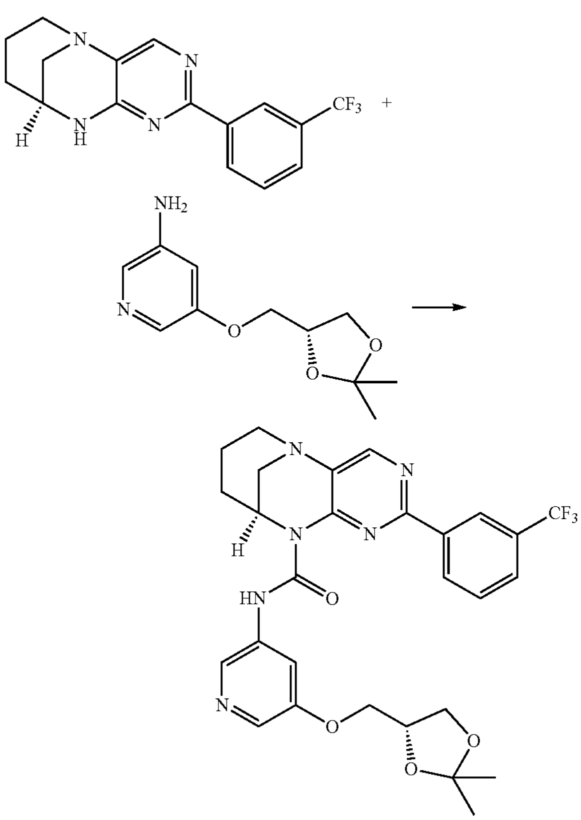
[0696]



[0697] Triphosgene (222 mg, 0.749 mmol) followed by triethylamine (1.044 mL, 7.49 mmol) was added to a stirred solution of (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (400 mg, 1.249 mmol) in Tetrahydrofuran (THF) (20 mL) at 10° C. and stirred for 30 min at 28° C. Then (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine (364 mg, 1.623 mmol) was added to the reaction mixture at 28° C. and stirred at 80° C. for 16 h. Reaction mixture was cooled to RT, diluted with water (40 mL), extracted with ethyl acetate (2×80 mL) and washed with brine solution (30 mL). Organic layer was separated, dried over Na_2SO_4, filtered and concentrated to get crude compound. The crude product was added to a silica gel (100:200 mesh) column and was eluted with 80% Ethyl acetate in Pet ether. Collected fractions with product to give (9S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (260 mg, 0.446 mmol, 35.7% yield), LCMS (m/z): 571.35 $[M+H]^+$.

Synthesis of (9S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

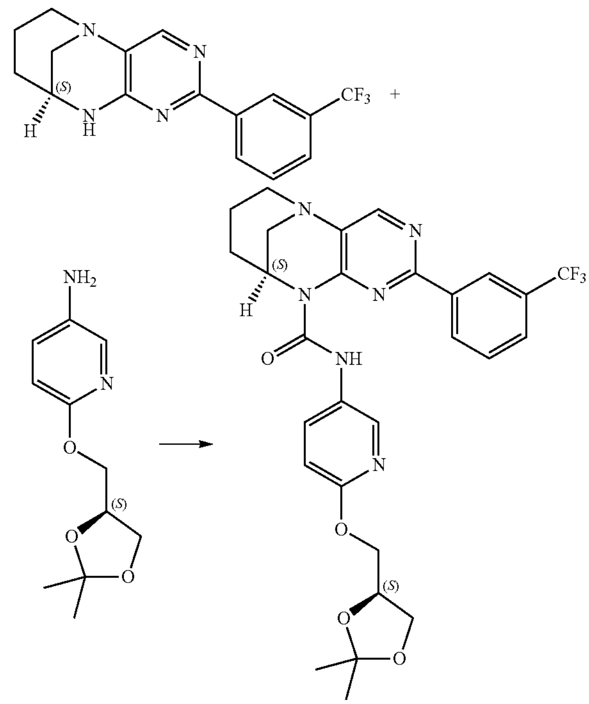
[0698]



[0699] Triphosgene (5.84 g, 19.67 mmol) was added to a solution of (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (6.3 g, 19.67 mmol), TEA (13.71 mL, 98 mmol) in Tetrahydrofuran (THF) (100 mL) was stirred under nitrogen at room temp for 1 h. To this reaction mixture (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine (9.92 g, 44.3 mmol) was added. The reaction mixture was stirred at 65° C. for 16 h and progress of the reaction was monitored by TLC and LCMS. The reaction mixture was cooled to room temperature, poured in to ice water (150 mL) and extracted with EtOAc (2×150 mL). The combined organic layer was washed with water (100 mL), brine solution (100 mL), dried over Na_2SO_4, filtered and evaporated to obtain crude compound. The crude compound was purified by column chromatography using neutral alumina and eluted in 50% ethyl acetate in hexane, the fractions were concentrated to get white solid and treated with Pd scavenger (3.75 g) in ethanol and heated to 80° C. for 4 h and filtered through celite pad in hot condition, filtrate was concentrated to afford (9S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (7.3 g, 12.67 mmol, 64.4% yield) as white solid, LCMS (m/z): 571.00 $[M+H]^+$.

Synthesis of (9S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

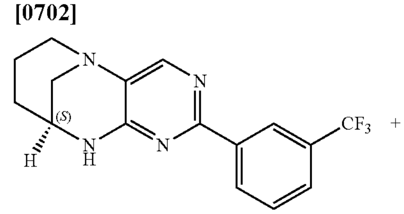
[0700]



[0701] TEA (1.305 mL, 9.37 mmol) followed by triphosgene (278 mg, 0.937 mmol) were added to a solution of (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (500 mg, 1.561 mmol) in Tetrahydrofuran (THF) (15 mL) at 10° C., stirred for 30 min and (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine (700 mg, 3.12 mmol) was added and stirred at 70° C. for 16 h. Reaction progress was monitored by TLC (Mobile phase: Ethyl acetate, 0.5 R_f, UV active) and LCMS. The reaction mixture was cooled to 28° C. and was partitioned between water (40 mL) and EtOAc (100 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude. The crude product was added to a silica gel (100:200 mesh) column and was eluted with 80% ethyl acetate in pet ether. Collected fractions: (9S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (250 mg, 0.434 mmol, 27.8% yield), LCMS (m/z): 571.22 $[M+H]^+$.

Synthesis of (9S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[0702]



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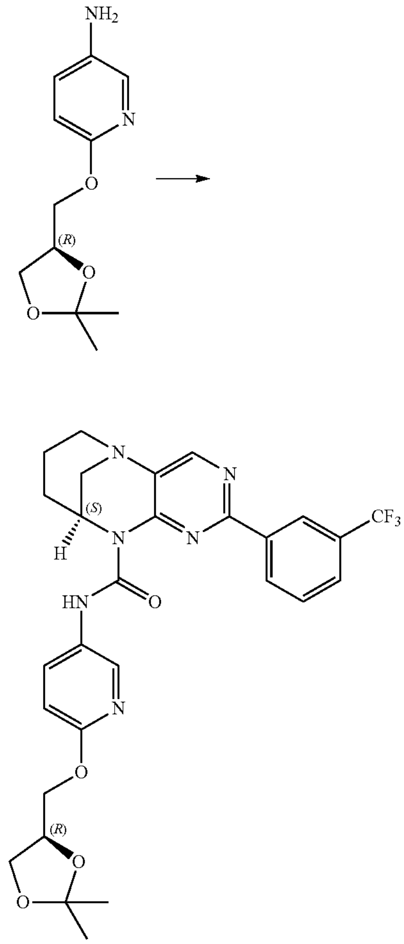
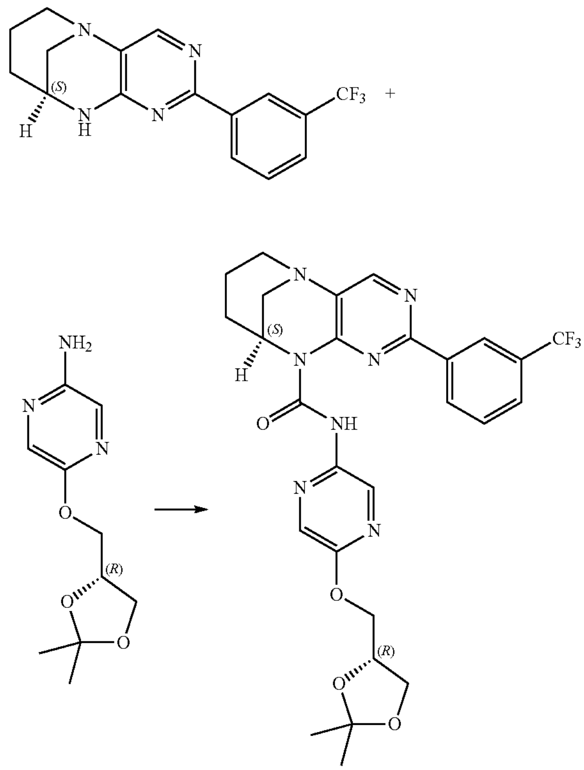


[0703] To a solution of (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (300 mg, 0.937 mmol), in Tetrahydrofuran (THF) (50 mL) stirred under nitrogen at 28° C. was added triphosgene (278 mg, 0.937 mmol) and DIPEA (605 mg, 4.68 mmol) the reaction mixture was stirred for 1 h, then added (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine (420 mg, 1.873 mmol). The reaction mixture was stirred at 70° C. for 16 hr. The reaction mixture was cooled to 28° C. and was partitioned between water (100 mL) and EtOAc (2×50 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude mass. The crude mass was purified by column chromatography (100-200) mesh silica gel eluted with 1% methanol in DCM to obtained (9S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (400 mg, 0.686 mmol, 73.3% yield) as a pale brown semi solid, LCMS (m/z): 571.47 $[M+H]^+$.

Synthesis of (9S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

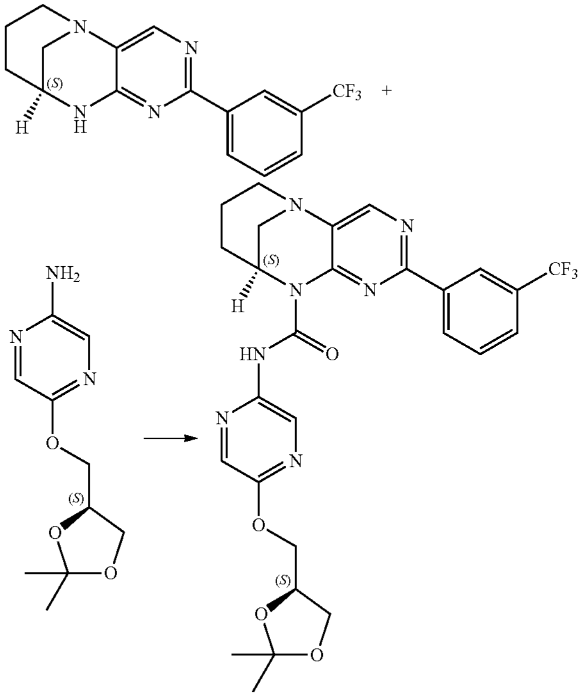
[0704]



[0705] Triphosgene (278 mg, 0.937 mmol) followed by triethylamine (1.305 mL, 9.37 mmol) was added to a stirred solution of (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (500 mg, 1.561 mmol) in Tetrahydrofuran (THF) (20 mL) at 10° C. and stirred for 30 min at 28° C. Then (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine (703 mg, 3.12 mmol) were added to the reaction mixture at 28° C. and stirred at 80° C. for 16 h. Reaction mixture was cooled to RT, diluted with water (40 mL), extracted with ethyl acetate (3×70 mL) and washed with brine solution (30 mL). Organic layer was separated, dried over Na_2SO_4, filtered and concentrated to get crude compound. The crude product was added to a silica gel (100:200 mesh) column and was eluted with 80% ethyl acetate in pet ether. Collected fractions: (9S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (250 mg, 0.434 mmol, 27.8% yield), LCMS (m/z): 572.48 $[M+H]^+$.

Synthesis of (9S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

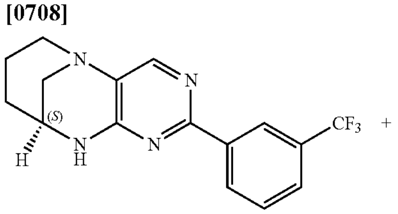
[0706]



[0707] To a solution of (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine (703 mg, 3.12 mmol) in Tetrahydrofuran (THF) (20 mL) stirred under nitrogen at room temp was added triphosgene (463 mg, 1.561 mmol) and triethylamine (1.305 mL, 9.37 mmol), To this (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine (703 mg, 3.12 mmol) was added and the reaction mixture was stirred at 65° C. for 16 hr. Reaction mixture was quenched with ice water and extracted with 2×25 ml of ethyl acetate, combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford crude compound. The crude product was purified by flash column chromatography (100-200 silica gel) eluting at 2% methanol in DCM to afford pure compound (9S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (250 mg, 0.423 mmol, 27.1% yield) as pale brown solid, LCMS (m/z): 572.42 $[M+H]^+$.

Synthesis of (9S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[0708]



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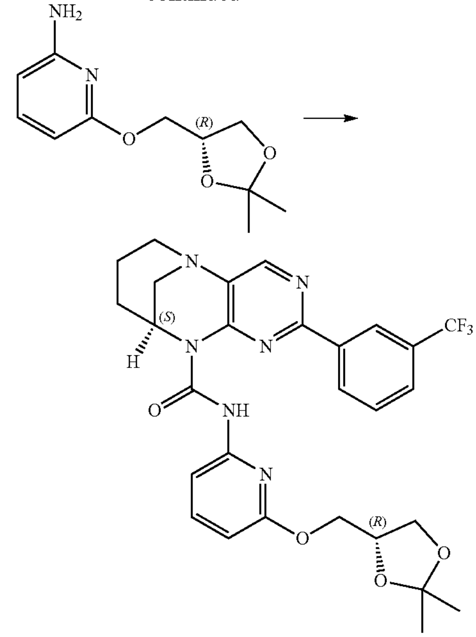
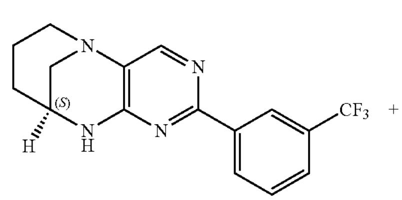


[0709] To a solution of (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (500 mg, 1.561 mmol) in THF (30 ml) and was added triphosgene (232 mg, 0.780 mmol), at 0° C. and stirred to RT for 1 h. Then DIPEA (0.818 mL, 4.68 mmol) and (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (700 mg, 3.12 mmol) was added sub sequentially under sealed tube condition at 75° C. for 16 h. The reaction was monitored by TLC and LCMS. The reaction mixture was poured in saturated $NaHCO_3$ solution (30 mL) and extracted with ethyl acetate (300 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product.

[0710] The crude was purified by column chromatography (100-200 silica gel) using gradient mixture of 80% EtOAc in Petether as eluent, to afford the (9S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (350 mg, 0.606 mmol, 38.8% yield), LCMS (m/z): 571.19 $[M+H]^+$.

Synthesis of (9S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[0711]



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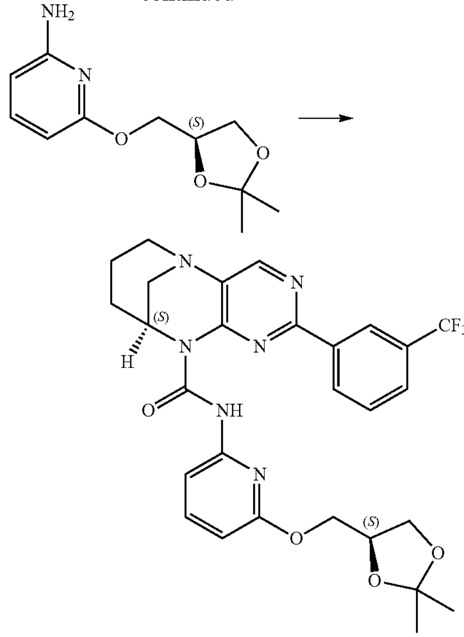
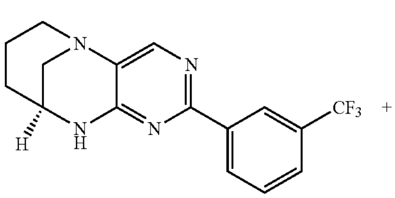


[0712] (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (500 mg, 1.561 mmol) was dissolved in Tetrahydrofuran (THF) (40 mL) stirred under nitrogen at 0° C. were added triphosgene (371 mg, 1.249 mmol), triethylamine (1.088 mL, 7.80 mmol). The reaction mixture was stirred for 30 min at room temperature. To this (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (525 mg, 2.341 mmol) was added and stirred for 16 h at 80° C. The reaction mixture allowed to room temperature and quenched with 60 ml of water and extracted with 3×100 ml of ethyl acetate, the combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain crude compound. The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh) to afford (9S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (355 mg, 0.619 mmol, 39.7% yield) as an Off white solid, LCMS (m/z): 571.11 $[M+H]^+$.

Synthesis of (9S)—N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[0713]



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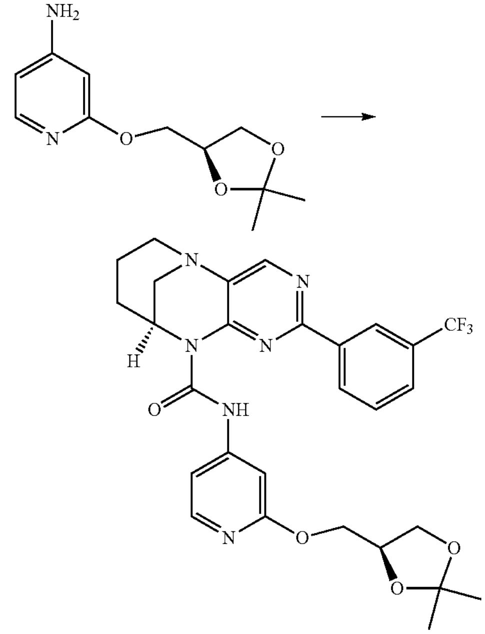
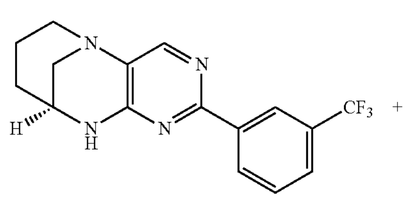


[0714] Triphosgene (417 mg, 1.405 mmol) was added to a stirred solution of (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (450.0 mg, 1.405 mmol), and triethylamine (1.175 mL, 8.43 mmol) in Tetrahydrofuran (THF) (20 mL) at 25° C. The reaction mixture was stirred for 60 min at ambient temperature and was added (S)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (945 mg, 4.21 mmol), then the reaction mixture was stirred for 16 hr at 65° C. The reaction mixture was cooled to 25° C., and the precipitated solid was filtered and was washed with ethyl acetate (40 ml). The filtrate was washed with the water (20 ml) and brine solution (20 ml). The organic phase was separated, and was dried over anhydrous Na_2SO_4, filtered it and filtrate was evaporated to get crude. This crude was purified by column on neutral alumina eluted with 20-30% EtOAc/petether to get the (9S)—N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (400.0 mg, 0.694 mmol, 49.4% yield) as off white solid. LCMS (m/z): 571.09 $[M+H]^+$.

Synthesis of (9S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[0715]



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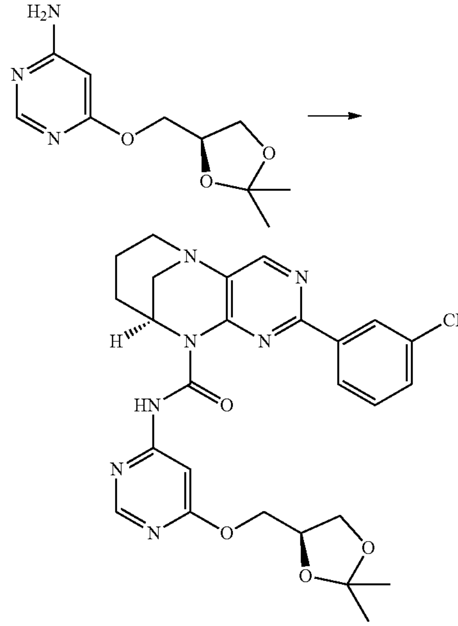
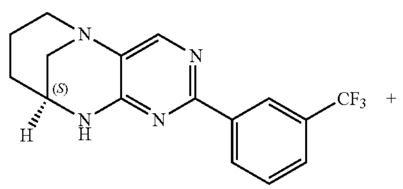


[0716] A solution of (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (0.5 g, 1.561 mmol), TEA (1.088 mL, 7.80 mmol), triphosgene (0.463 g, 1.561 mmol) in Tetrahydrofuran (THF) (50 mL) was stirred under nitrogen at room temp for 1 h. To this reaction mixture (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine (0.879 g, 3.90 mmol) was added. The reaction mixture was stirred at 65° C. for 16 h and progress of the reaction was monitored by TLC and LCMS. The reaction mixture was cooled to room temperature, poured in to ice water (50 mL) and extracted with EtOAc (2×100 mL). The combined organic layer was washed with water (50 mL), brine solution (50 mL), dried over Na_2SO_4, filtered and evaporated to obtain crude compound. The crude compound was purified by column chromatography using neutral alumina and eluted in 20% ethyl acetate in hexane to afford (9S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (0.35 g, 0.545 mmol, 34.9% yield) as white solid, LCMS (m/z): 572.42 $[M+H]^+$.

Synthesis of (9S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[0717]



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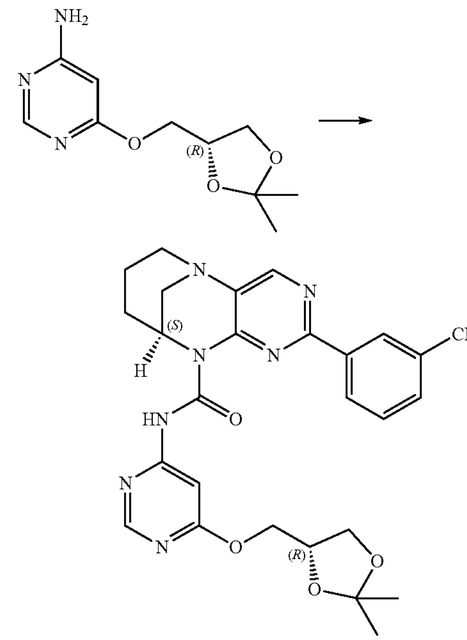
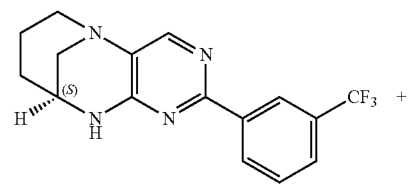


[0718] To a solution of (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine (703 mg, 3.12 mmol) in Tetrahydrofuran (THF) (20 mL) stirred under nitrogen at room temp was added triphosgene (463 mg, 1.561 mmol) and triethylamine (1.305 mL, 9.37 mmol), To this (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine (703 mg, 3.12 mmol) was added and the reaction mixture was stirred at 65° C. for 16 hr. Reaction mixture was quenched with ice water and extracted with 2×25 ml of ethyl acetate, combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford crude compound. The crude product was purified by flash column chromatography (100-200 silica gel) eluting at 2% methanol in DCM to afford pure compound (9S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (320 mg, 0.529 mmol, 33.9% yield) as off white solid, LCMS (m/z): 572.36 $[M+H]^+$.

Synthesis of (9S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[0719]



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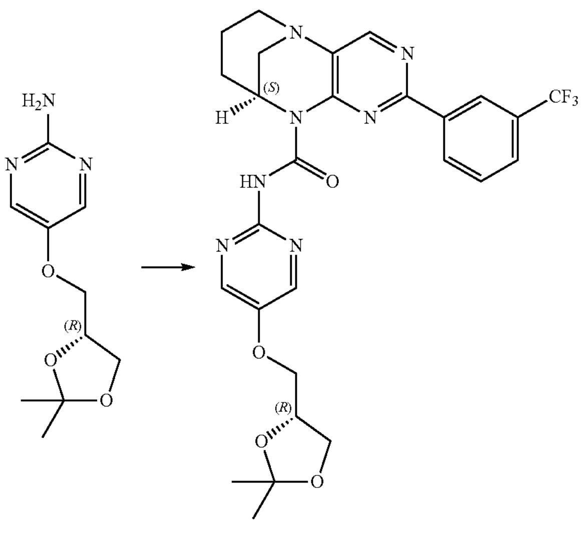
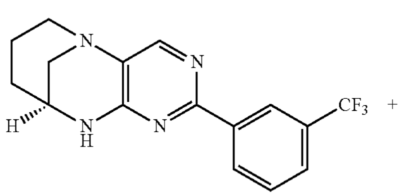


[0720] Triphosgene (0.463 g, 1.561 mmol) was added to a solution of (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (0.5 g, 1.561 mmol), TEA (1.088 mL, 7.80 mmol)) in Tetrahydrofuran (THF) (50 mL) was stirred under nitrogen at room temp for 1 h. To this reaction mixture benzo[d]isothiazol-3-amine (0.922 g, 6.14 mmol) was added. The reaction mixture was stirred at 65° C. for 16 h and progress of the reaction was monitored by TLC and LCMS. The reaction mixture was cooled to room temperature, poured in to ice water (50 mL) and extracted with EtOAc (2×100 mL). The combined organic layer was washed with water (50 mL), brine solution (50 mL), dried over Na_2SO_4, filtered and evaporated to obtain crude compound. The crude compound was purified by column chromatography using neutral alumina and eluted in 50% EtOAc in hexane to afford (9S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (0.3 g, 0.499 mmol, 31.9% yield) as white solid, LCMS (m/z): 572.29 $[M+H]^+$.

Synthesis of (9S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[0721]



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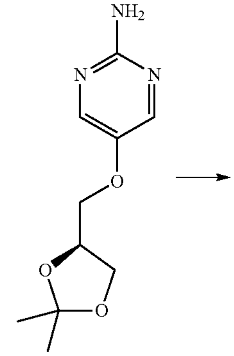
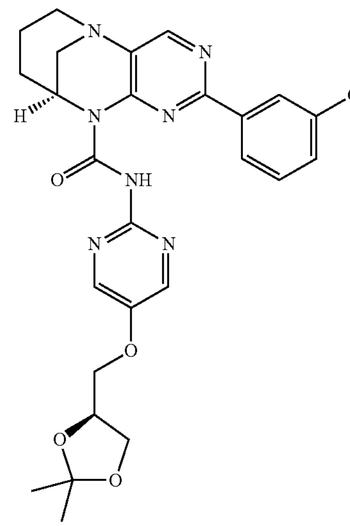
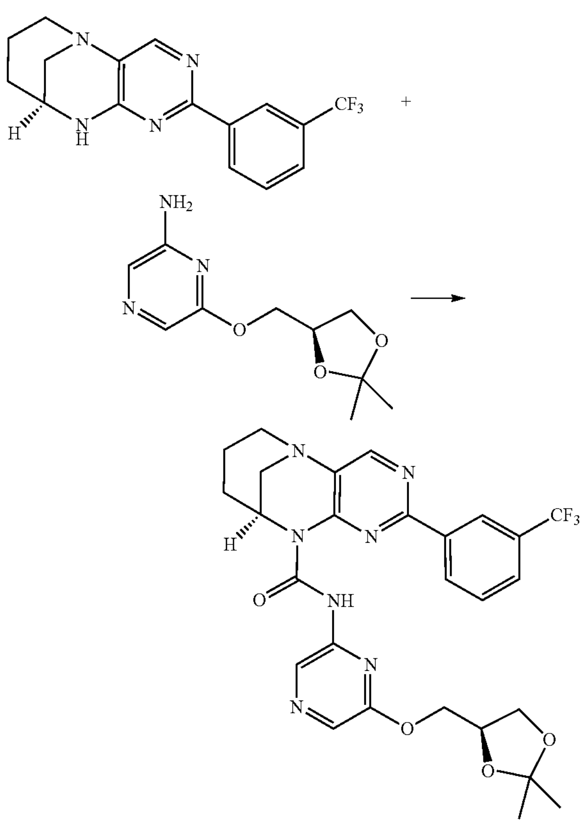




[0722] A solution of (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (400 mg, 1.249 mmol), triphosgene (371 mg, 1.249 mmol) and triethylamine (0.870 mL, 6.24 mmol) in Tetrahydrofuran (THF) (20 mL) was stirred under nitrogen at room temp for 30 min. To this reaction mixture (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-amine (563 mg, 2.498 mmol) was added. The reaction mixture was stirred at 70° C. for 16 h and progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature, poured in to water (10 mL) and extracted with EtOAc (3×20 mL). The combined organic layer was washed with water (20 mL), brine solution (20 mL), dried over Na_2SO_4 filtered and evaporated to get crude compound. The crude compound was purified by column chromatography using Neutral Alumina and eluted at 60% EtOAc in Petether. The solvent was evaporated to afford pure (9S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (350 mg, 0.611 mmol, 48.9% yield) as off white solid, LCMS (m/z): 572.25 $[M+H]^+$.

Synthesis of (9S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

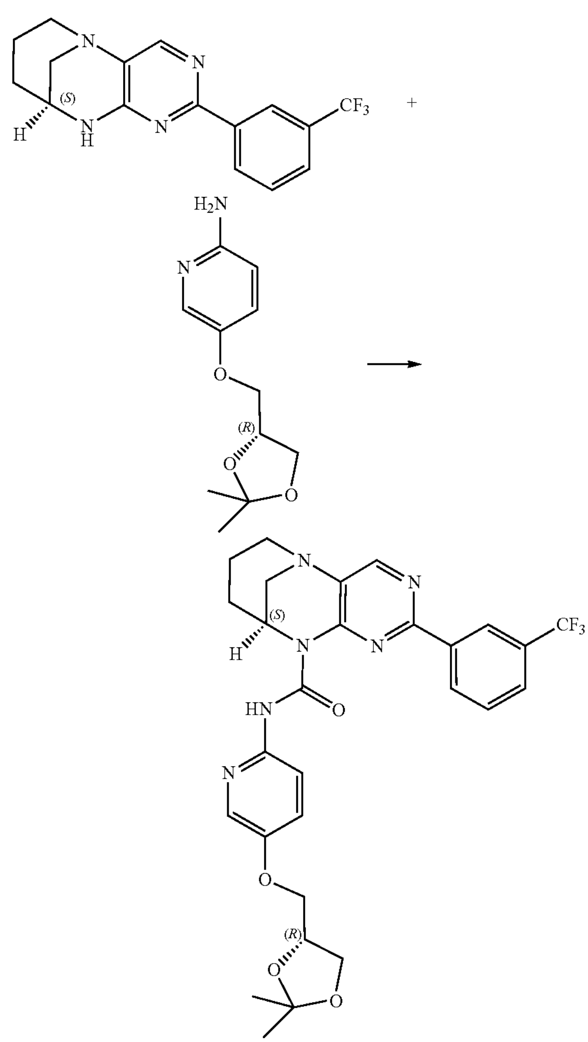
[0723]



[0724] Triphosgene (556 mg, 1.873 mmol) was added to a stirred solution of (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (600 mg, 1.873 mmol) and TEA (0.261 mL, 1.873 mmol) in Tetrahydrofuran (THF) (60 mL) at room temp. The reaction mixture was stirred for 4 h and (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine (1055 mg, 4.68 mmol) was added. The reaction mixture was stirred at 65° C. for 16 h. Reaction was monitored by TLC. The reaction mixture was diluted with water (250 mL) and extracted with 500 mL of EtOAc. Organic layer washed with water (100 mL) followed by brine solution (100 mL), dried with anhydrous Na_2SO_4, filtered and concentrated to get crude product. The crude product was added to Neutral alumina and was eluted with 60% EtOAc/Hexane. Collected fraction was evaporated under reduced pressure to afford a compound (9S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (200 mg, 0.330 mmol, 17.62% yield) as a White solid, LCMS (m/z): 572.42 $[M+H]^+$.

Synthesis of (9S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

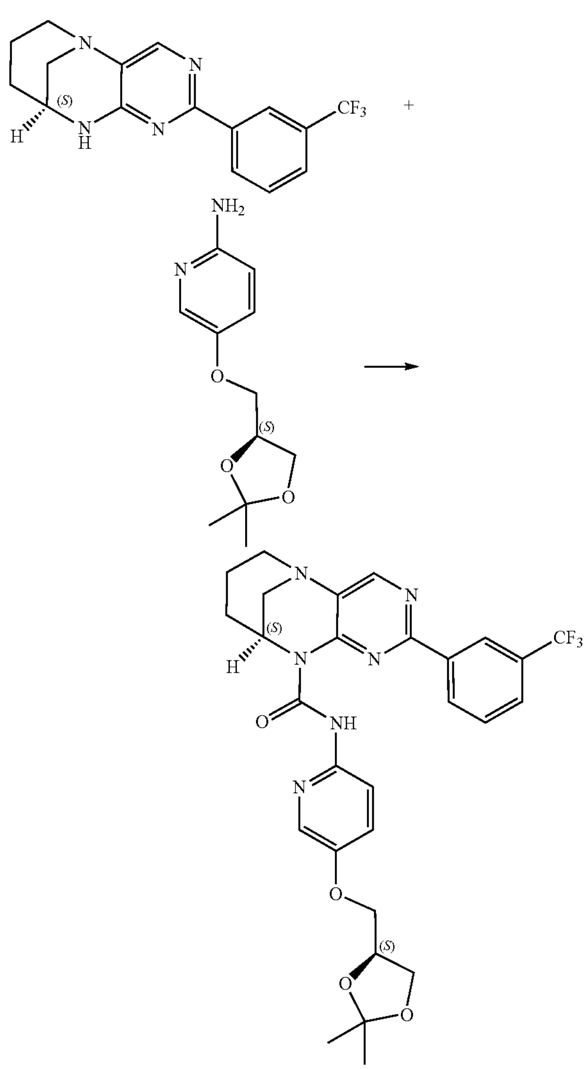
[0725]



[0726] TEA (1.088 mL, 7.80 mmol) followed by triphosgene (463 mg, 1.561 mmol) were added to a solution of (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (500 mg, 1.561 mmol) in Tetrahydrofuran (THF) (20 mL) at RT and stirred for 1 h and (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (350 mg, 1.561 mmol) was added then heated at 80° C. for 15 h. The reaction mixture was cooled to 28° C. and was partitioned between water (25 mL) and EtOAc (30 mL×3). Organic layers were separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude, then it was purified by column chromatography (using 100-200 silica gel, column eluted at 80% ethyl acetate in hexane) to afford (9S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (350 mg, 0.558 mmol, 35.8% yield) as an off white solid, LCMS (m/z): 571.00 $[M+H]^+$.

Synthesis of (9S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

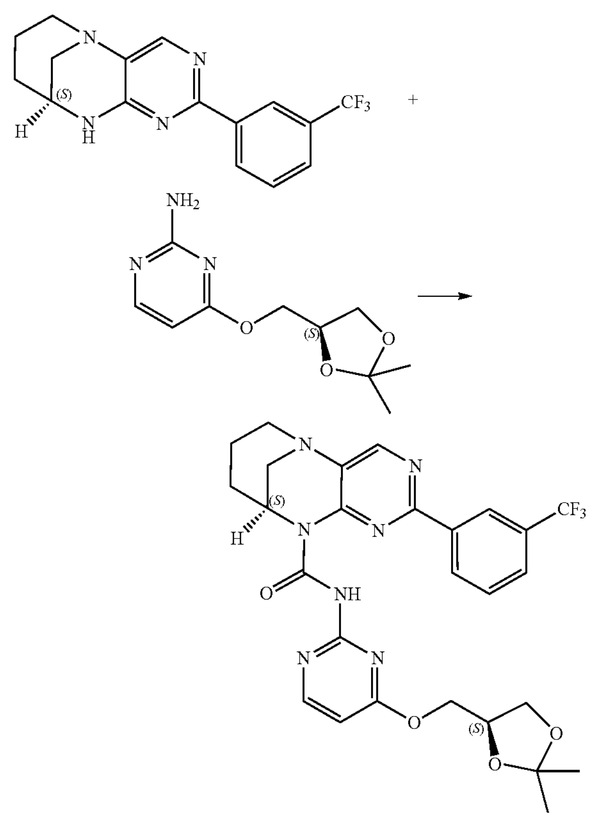
[0727]



[0728] DIPEA (726 mg, 5.62 mmol) followed by triphosgene (556 mg, 1.873 mmol) were added to a solution of (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (840 mg, 3.75 mmol) in Tetrahydrofuran (THF) (5 mL) at 25° C., stirred for 1 h and (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (600 mg, 1.873 mmol) was added and heated at 70° C. for 18 hr. The reaction mixture was cooled to 28° C. and was partitioned between water (20 mL) and EtOAc (50 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude. The crude compound was purified by column chromatography (C-18: eluted with 90% ACN in 1% aq formic acid) to afford (9S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (250 mg, 0.435 mmol, 23.23% yield), as an off white solid, LCMS (m/z) 571.28 (M+H)+.

Synthesis of (9S)—N-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[0729]

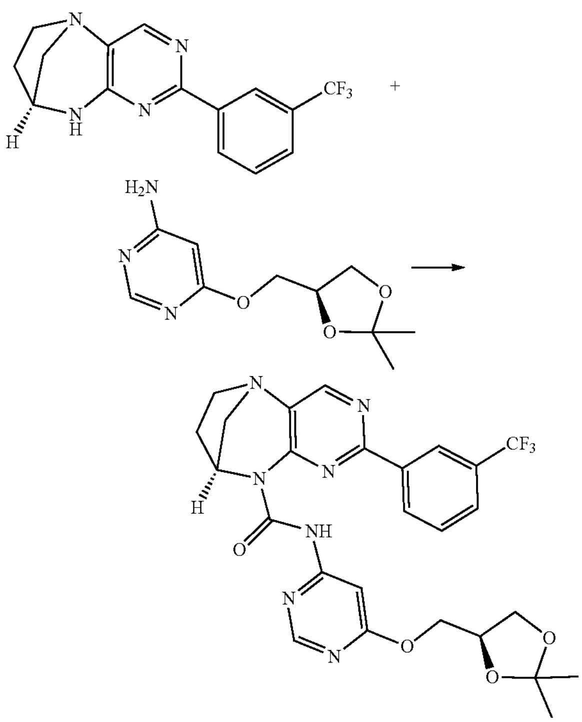


[0730] DIPEA (1.210 g, 9.37 mmol) followed by triphosgene (0.926 g, 3.12 mmol) were added to a solution of (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (1.0 g, 3.12 mmol) in Tetrahydrofuran (THF) (10 mL) at 25° C., stirred for 20 h and (S)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-amine (1.406 g, 6.24 mmol) was added and heated at 70° C. for 8 h. The reaction mixture was cooled to 28° C. and was partitioned between water (30 mL) and EtOAc (50 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude. Crude compound was purified by combi flash column chromatography (column: C_{18}, eluted with 90% methanol in 1% formic acid in water) to get (200 mg, LCMS: 91.20%). Further purified by column chromatography (silica-gel: 100-200 mesh, eluted with 3% methanol in DCM) to afford (9S)—N-(4-(((S)-2,2-dimethyl-1,3-

dioxolan-4-yl)methoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (160 mg, 0.276 mmol, 8.85% yield) as pale yellow solid, LCMS (m/z): 572.12 (M+H)+.

Synthesis of (8S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

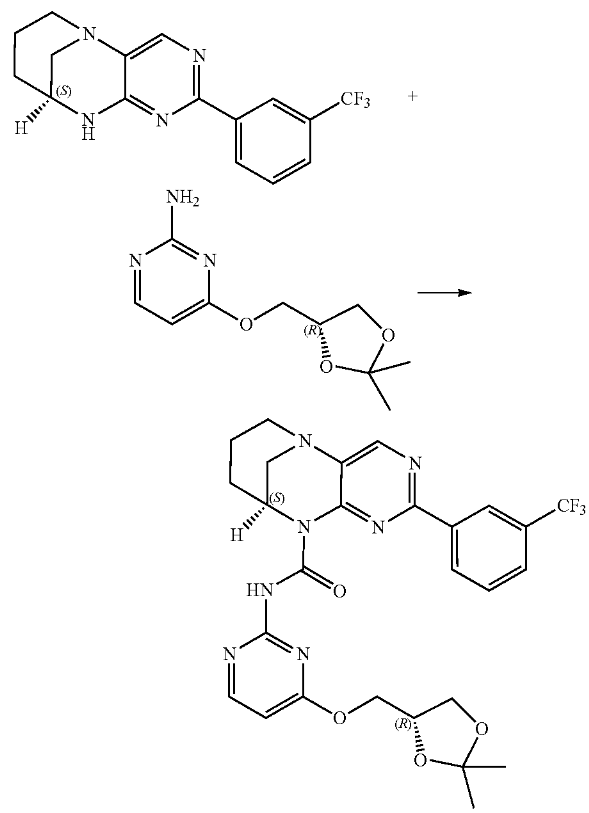
[0731]



[0732] TEA (0.910 mL, 6.53 mmol) was added to a stirred solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (0.4 g, 1.306 mmol) in Tetrahydrofuran (THF) (50 mL) at room temperature and followed by addition of triphosgene (0.388 g, 1.306 mmol) at same temperature and stirred for 1 h. (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine (0.882 g, 3.92 mmol) was added and stirred at 65° C. for 15 h. Cooled to room temperature and diluted with ethyl acetate (100 mL) and water (100 mL). The separated organic layer was washed with water (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain crude compound. Purified by column chromatography using neutral alumina and eluted 50% ethyl acetate in hexane to afford (8S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (0.22 g, 0.380 mmol, 29.1% yield) as white solid, LCMS (m/z): 558.25 [M+H]+.

Synthesis of (9S)—N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

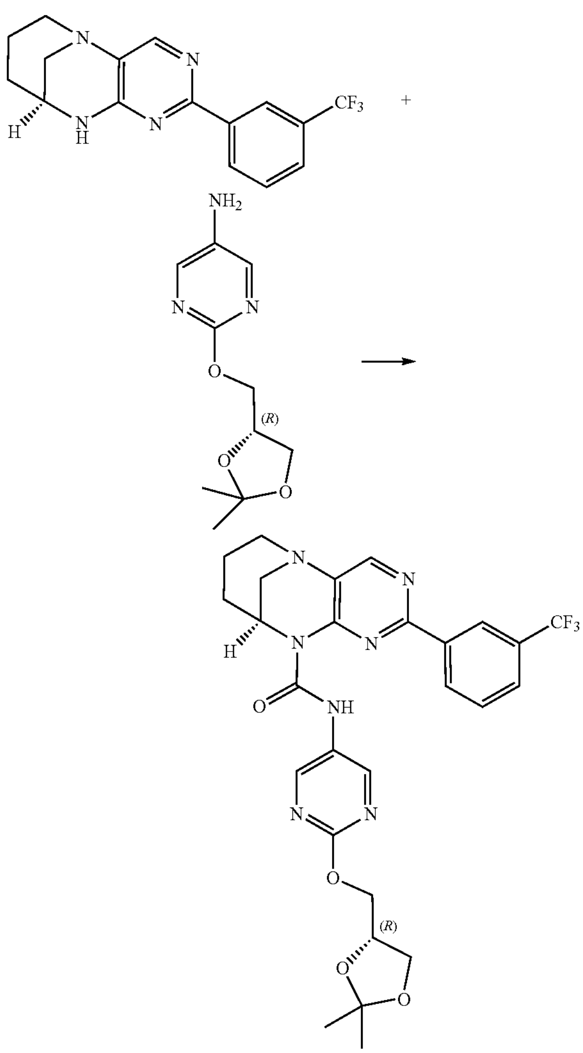
[0733]



[0734] To solid (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (1.6 g, 5.00 mmol), in Tetrahydrofuran (THF) (30 mL) stirred under nitrogen at room temp was added solid triphosgene (0.889 g, 3.00 mmol) and DIPEA (4.36 mL, 24.98 mmol) stirred under nitrogen at room temp for 16 hr To this (R)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-amine (1.688 g, 7.49 mmol) was added sub sequentially under sealed tube condition at 75° C. for 40 hr. The reaction was monitored by TLC and LCMS. The reaction mixture was concentrated and the residue was taken up in DCM (200 mL). The solution was washed with water and brine, dried over Na_2SO_4, filtered and concentrated to get crude compound. The crude product purified by combiflash chromatography by using methanol collected fractions and concentrated to get compound and washed with pentane to get pure compound (9S)—N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (405 mg, 0.675 mmol, 13.52% yield), LCMS (m/z): 572.48 [M+H]+.

Synthesis of (9S)—N-(2-((S)-2,3-dihydroxypropoxy)pyrimidin-5-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

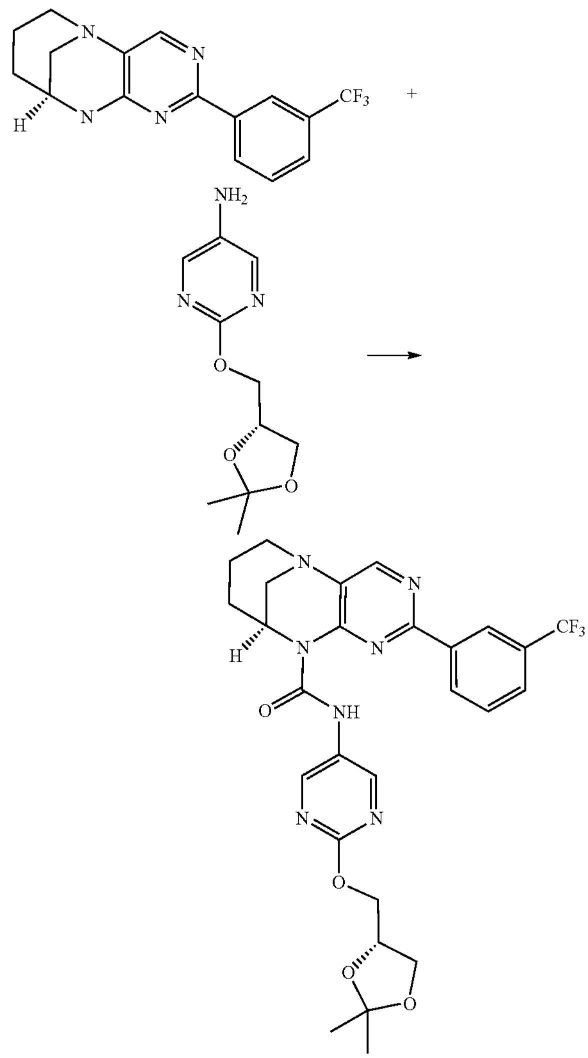
[0735]



[0736] Triphosgene (324 mg, 1.093 mmol) was added to a stirred solution of (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (350 mg, 1.093 mmol) and triethylamine (0.914 mL, 6.56 mmol) in Tetrahydrofuran (THF) (35 mL) at 28° C. The reaction mixture was stirred for 2 h and was added (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-amine (615 mg, 2.73 mmol). The reaction mixture was stirred for 7 hr at 65° C. The reaction mixture was cooled to room temp, solvent evaporated under reduced pressure completely and was partitioned between water (40 mL) and EtOAc (2×50 mL). Organic layer was separated, dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude as brown solid. Crude was diluted with DCM and absorbed with neutral alumina and eluted with 30-35% EtOAc in pet ether fractions were collected and concentrated to get (9S)—N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (420 mg, 0.734 mmol, 67.2% yield) as a Off white solid, LCMS (m/z): 572.29 $[M+H]^+$. R_t=2.74 min.

Synthesis of (9S)—N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

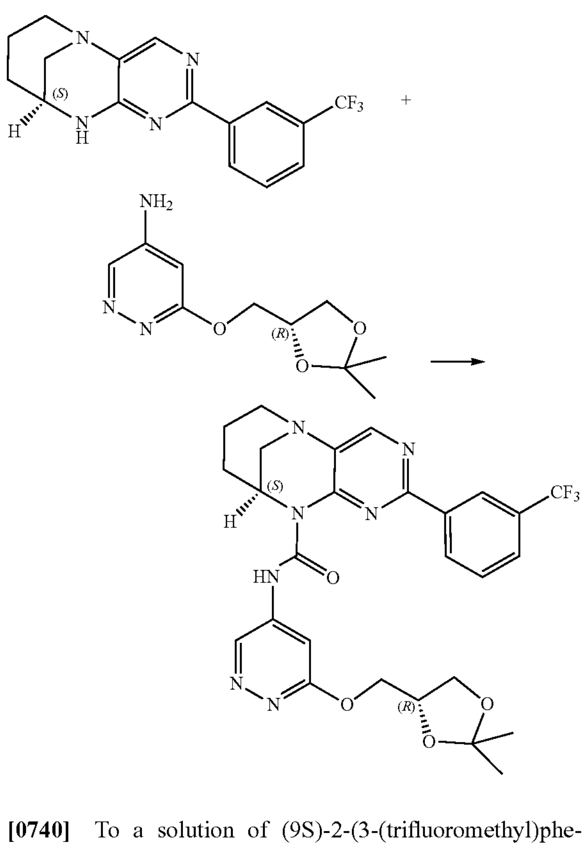
[0737]



[0738] Triphosgene (417 mg, 1.405 mmol) was added to a stirred solution of (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (450.0 mg, 1.405 mmol), and TEA (1.175 mL, 8.43 mmol) in Tetrahydrofuran (THF) (20.0 mL) at 0° C. The reaction mixture was stirred for 60 min and was added (S)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-amine (949 mg, 4.21 mmol). The reaction mixture was stirred for 8 hr at 72° C. After completion of the reaction mixture was cooled to 25° C., and the precipitated solid was filtered and was washed with ethyl acetate (60 ml). The filtrate was washed with the water (10 ml) and brine solution (10 ml). The organic phase was separated, and was dried over anhydrous Na_2SO_4, filtered it and the filtrate was evaporated to get the crude. This crude was purified by flash chromatography on neutral alumina eluted with the 40-50% Ethyl acetate in pet ether to collect the fractions and were evaporated to get the (9S)—N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (400.0 mg, 0.687 mmol, 48.9% yield) as an off white solid, LCMS (m/z): 572.18 $[M+H]^+$.

Synthesis of (9S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridazin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

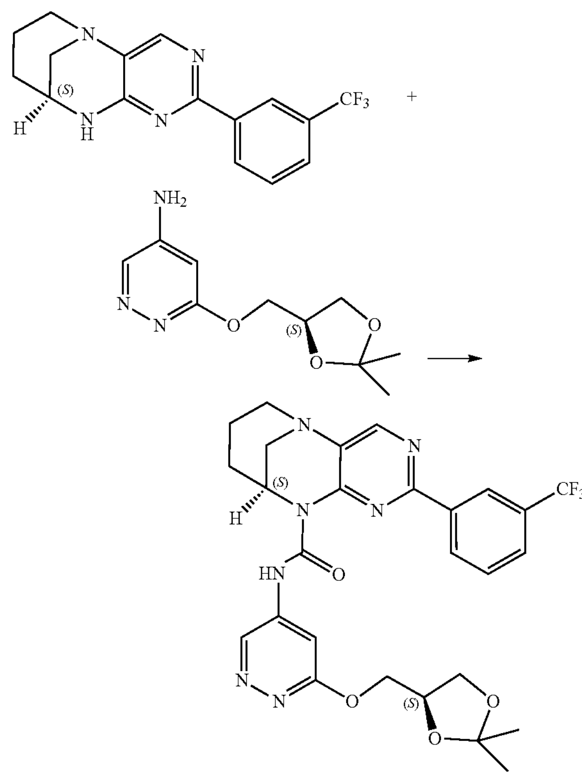
[0739]



[0740] To a solution of (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (700 mg, 2.185 mmol) in THF (25 ml) and triphosgene (649 mg, 2.185 mmol) at 0° C. Then TEA (1.828 mL, 13.11 mmol) was added and stirred to RT for 1 h and (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridazin-4-amine (984 mg, 4.37 mmol) was added sub sequentially and stirred at 75° C. for 16 h. The reaction was monitored by TLC and LCMS. The reaction mixture was poured in saturated $NaHCO_3$ solution (30 mL) and extracted with ethyl acetate (2×25 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude compound. The crude compound (400 mg) and a previous batch, (70 mg) were mixed together and purified by flash chromatography (100-200 mesh-90% EtOAc/petether) to afford compound (9S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridazin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (120 mg, 0.205 mmol, 9.38% yield) as Pale brown liquid, LCMS (m/z): 571.91 $[M+H]^+$.

Synthesis of (9S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridazin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

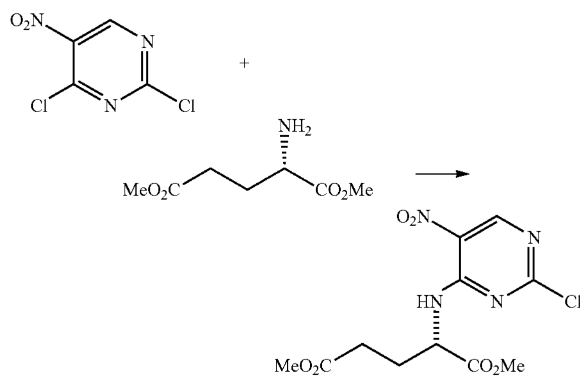
[0741]



[0742] To a solution of (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (800 mg, 2.498 mmol) in THF (5 ml) and triphosgene (741 mg, 2.498 mmol) at 0° C. Then TEA (2.089 mL, 14.99 mmol) was added and stirred to RT for 1 h and (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridazin-4-amine (1125 mg, 5.00 mmol) was added sub sequentially at 75° C. for 16 h. The reaction was monitored by TLC and LCMS. The reaction mixture was poured in saturated $NaHCO_3$ solution (25 mL) and extracted with ethyl acetate (2×25 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude compound. The crude compound was purified by flash chromatography (100-200 mesh-90% EtOAc/petether) to afford compound (9S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridazin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4] diazocine-10(7H)-carboxamide (120 mg, 0.189 mmol, 7.56% yield) as an off white solid, LCMS (m z): 572.33 $[M+H]^+$.

Synthesis of (S)-dimethyl 2-((2-chloro-5-nitropyrimidin-4-yl)amino)pentanedioate

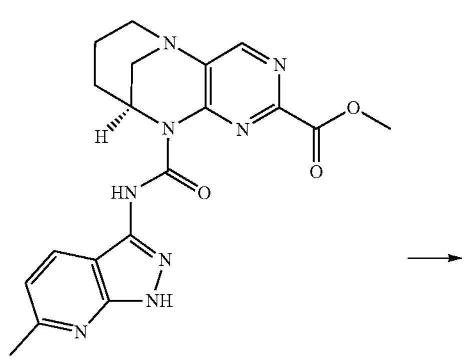
[0743]



[0744] Sodium bicarbonate (1083 g, 1.29E+04 mmol)) was added to a stirred solution of 2,4-dichloro-5-nitropyrimidine (500 g, 2578 mmol) and (S)-dimethyl 2-aminopentanedioate hydrochloride (546 g, 2578 mmol) in Tetrahydrofuran (THF) (5 L) at room temperature and heated to 15 h at 60° C. Reaction mixture was cooled to room temperature and filtered through celite bed. The filtrate was concentrated under reduced pressure and diluted with ethyl acetate (7 L) and water (2 L). The separated organic layer was washed with water (2 L) and brine (1 L). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain crude compound. The Crude compound was triturated with diethyl ether to afford (S)-dimethyl 2-((2-chloro-5-nitropyrimidin-4-yl)amino)pentanedioate (601 g, 1752 mmol, 68.0% yield) as pale yellow solid, LCMS (m/z): 334.93 $(M+H)^+$.

Synthesis of (9S)-10-((6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid

[0745]



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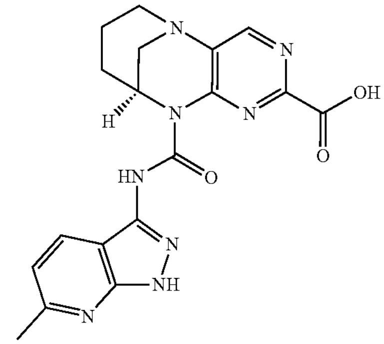
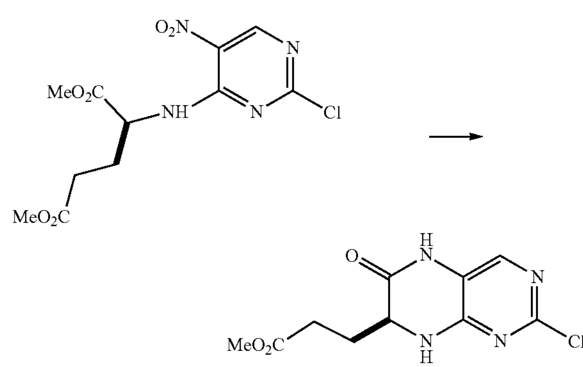


[0746] Lithium hydroxide (70.4 mg, 2.94 mmol) was added to a solution of (9S)-methyl 10-((6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (400 mg, 0.979 mmol) in Tetrahydrofuran (THF) (10 mL) & Water (3 mL) at 28° C. and stirred for 2 h at the same temperature. The reaction mixture solvent (THF) was removed by vacuum. It was washed with EtOAc (50 mL) to remove impurities and acidify with 2N HCl, then aqueous layer kept for lyophilization to remove water to afford the (9S)-10-((6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (250 mg, 0.634 mmol, 64.7% yield) as brown solid, LCMS (m/z): 395.02 $(M+H)^+$.

Synthesis of (S)-methyl 3-(2-chloro-6-oxo-5,6,7,8-tetrahydropteridin-7-yl)propanoate

[0747]

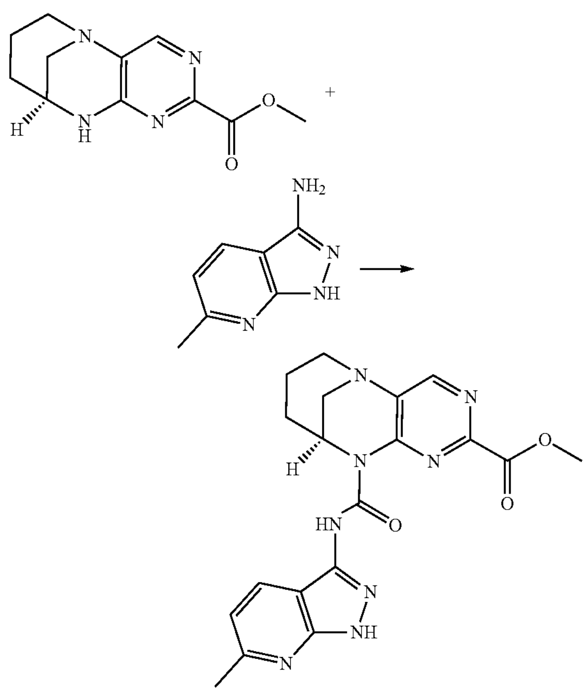


[0748] Acetic acid (0.344 L, 6011 mmol) was added to stirred solution of (S)-dimethyl 2-((2-chloro-5-nitropyrimidin-4-yl)amino)pentanedioate (400 g, 1202 mmol) and iron (201 g, 3607 mmol) in Isopropanol (3 L) and Water (700 mL) at room temperature and heated to 15 h at 80° C. Cooled to room temperature and filtered through celite bed. The filtrate was basified by adding sodium carbonate at 0° C. and diluted with 10% methanol in dichloromethane (7 L). The organic layer was separated and washed with water (2 L) and brine (1 L). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain crude compound. The Crude compound was triturated with dichloromethane (1 L) to afford (S)-methyl 3-(2-chloro-6-

oxo-5,6,7,8-tetrahydropteridin-7-yl)propanoate (165 g, 573 mmol, 47.7% yield) as light brown solid, LCMS (m/z): 271.0 $(M+H)^+$.

Synthesis of (9S)-methyl 10-((6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate

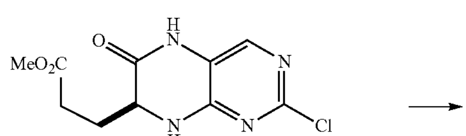
[0749]



[0750] To a solution of 6-methyl-1H-pyrazolo[3,4-b]pyridin-3-amine (664 mg, 4.48 mmol), triphosgene (532 mg, 1.793 mmol) in Tetrahydrofuran (THF) (5 mL) stirred under nitrogen at 0° C. and added (9S)-methyl 7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (700 mg, 2.99 mmol). Then the reaction mixture was stirred at 30° C. for 30 min and added (9S)-methyl 7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (700 mg, 2.99 mmol), then the reaction mixture was stirred at 80° C. for 15.5 hr. The reaction was monitored by LCMS and TLC. The reaction mixture was poured in to the cold water (200 mL) and extracted with ethyl acetate (2×100 mL). The organic layer was dried over anhydrous sodium Na_2SO_4 and concentrated under vacuum to give crude product, LCMS (m/z): 409.19 $(M+H)^+$.

Synthesis of (S)-3-(2-chloro-5,6,7,8-tetrahydropteridin-7-yl)propan-1-ol

[0751]



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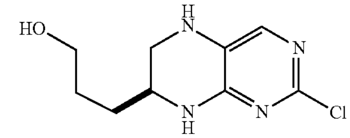
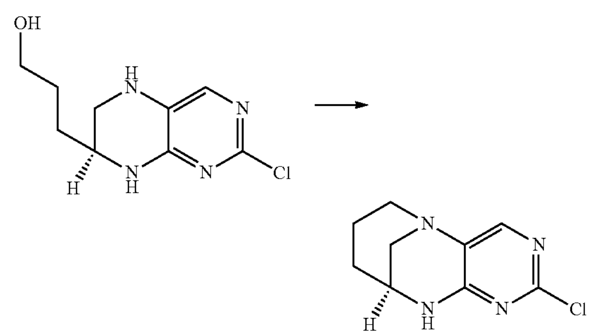


[0752] To a solution of aluminum chloride (69.0 g, 517 mmol), in Tetrahydrofuran (THF) (1 L) stirred under nitrogen was added 2M solution of lithium aluminum hydride (0.924 L, 1847 mmol) in THF dropwise at a rate to control gas evolution. This gave a solution of alane (AlH_3) in THF. In a separate flask, a solution of (S)-methyl 3-(2-chloro-6-oxo-5,6,7,8-tetrahydropteridin-7-yl)propanoate (100 g, 369 mmol) in Tetrahydrofuran (THF) (1.500 L) was prepared under nitrogen, to this was added the alane solution, dropwise at −78° C. over 2 hr. When the addition was complete, the cooling bath was removed, and the reaction was allowed to warm to ambient temperature for 16 hr. The reaction was monitored by TLC. The reaction mixture was quenched with 10% NaOH solution at 0° C. and stirred 16 hr and filtered through celite and washed with (100 ml) DCM. Take filtrate dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford the desired product (S)-3-(2-chloro-5,6,7,8-tetrahydropteridin-7-yl)propan-1-ol (52.0 g, 224 mmol, 60.5% yield) as a pale yellow solid, LCMS (m/z): 228.96 $(M+H)^+$.

Synthesis of (9S)-2-chloro-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine

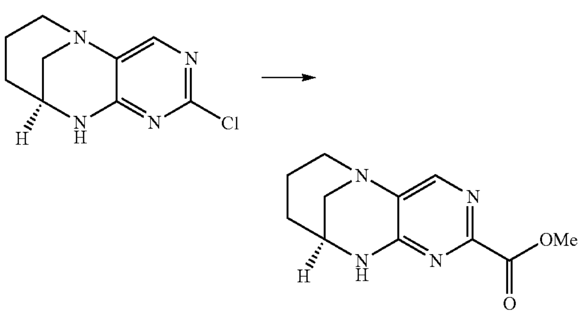
[0753]



[0754] $POCl_3$ (16.51 mL, 177 mmol) was added to a stirred solution of (S)-3-(2-chloro-5,6,7,8-tetrahydropteridin-7-yl)propan-1-ol (27 g, 118 mmol) and DIPEA (51.6 mL, 295 mmol) in Dichloromethane (DCM) (200 mL) at 0° C. and stirred for 1 h at 0° C. Saturated sodium bicarbonate solution was added slowly to reaction mixture at 0° C. and adjusted pH to basic condition and stirred for 1 h. The separated organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to get crude compound. Crude compound was triturated with diethyl ether 150 mL and resultant solid was filtered and dried to afford (9S)-2-chloro-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (15 g, 69.1 mmol, 58.5% yield) as pale yellow solid, LCMS (m/z): 210.99 $(M+H)^+$.

Synthesis of (9S)-methyl 7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate

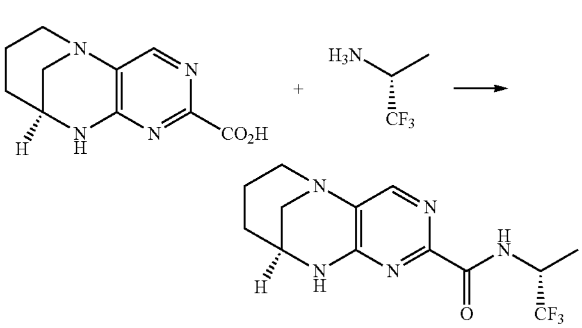
[0755]



[0756] To a solution of (9S)-2-chloro-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (6.0 g, 28.5 mmol) in Methanol (500 mL) was degassed for 30 min, then triethylamine (19.85 mL, 142 mmol) and $PdCl_2$(dppf)-CH_2Cl_2 adduct (1.163 g, 1.424 mmol) were added and filled with 300 psi CO gas. The reaction mixture was stirred at 120° C. for 12 hr in auto clave. The reaction was monitored by TLC. The reaction mixture was filtered through celite and washed with MeOH. Take filtrate and evaporated to afford crude product. The crude product was purified by column chromatography using neutral alumina and was eluted with DCM (gradient system) to afford the desired product (9S)-methyl 7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (4.0 g, 15.36 mmol, 53.9% yield) as an off-white solid, LCMS (m/z): 235.0 $[M+H]^+$.

Synthesis of (9S)—N—((R)-1,1,1-trifluoropropan-2-yl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxamide

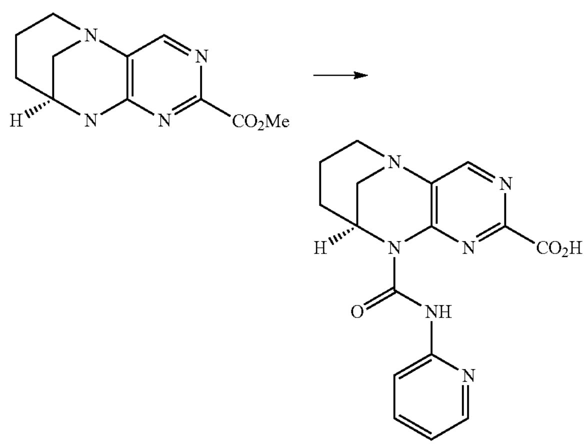
[0757]



[0758] DIPEA (3.17 mL, 18.16 mmol) was added to a stirred solution of (9S)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (0.8 g, 3.63 mmol), (R)-1,1,1-trifluoropropan-2-amine (0.616 g, 5.45 mmol) & HATU (2.072 g, 5.45 mmol) in N,N-Dimethylformamide (DMF) (15 mL) under nitrogen at 0° C. The reaction mixture was stirred at 26° C. for 16 hr. The reaction mixture was partitioned between ice cold water (10 mL) and DCM (10 mL). Organic layer was separated, dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford the crude product. The crude compound was purified by Grace using C-18 reserval column, Mobile phase A: 0.1% Formic Acid in water; B: ACN, the product was eluted at 42% ACN/0.1% Formic Acid in water. The solvent was evaporated and was basified with saturated $NaHCO_3$. The aqueous layer was extracted with DCM. DCM layer was dried over anhydrous Na_2SO_4, filtered and evaporated to afford pure (9S)—N—((R)-1,1,1-trifluoropropan-2-yl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxamide (0.570 g, 1.760 mmol, 48.4% yield) as an off-white solid, LCMS (m/z): 316.20 $(M+H)^+$.

Synthesis of (9S)-10-(pyridin-2-ylcarbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid

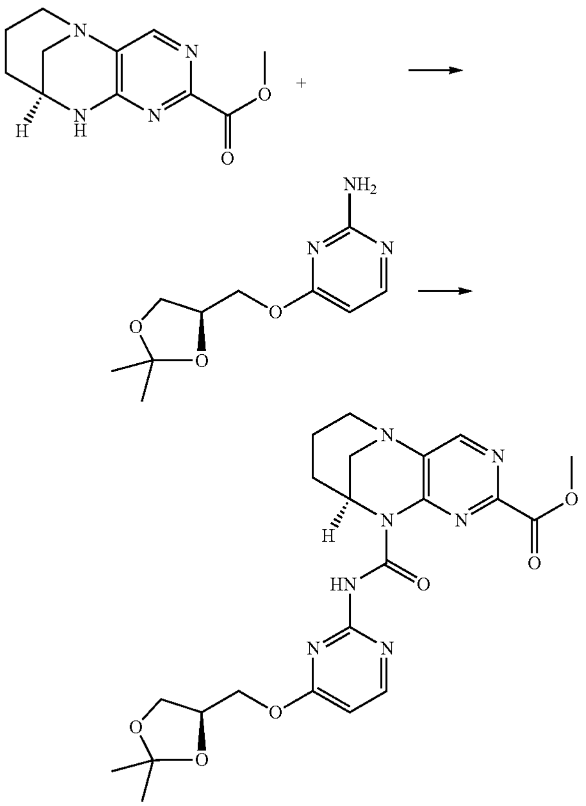
[0759]



[0760] NaH (3.79 g, 95 mmol) was added to a stirred solution of (9S)-methyl 7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (3.7 g, 15.79 mmol) in Tetrahydrofuran (THF) (50 mL) stirred under nitrogen at room temp° C. The reaction mixture was stirred at RT for 30 minutes. 3-(pyridin-2-yl)-2H-pyrido[1,2-a][1,3,5]triazine-2,4(3H)-dione (5.69 g, 23.69 mmol) was added at RT. Then the reaction mixture was stirred at 65° C. for 16 hr. Reaction was monitored by TLC. The reaction mixture was quenched with ice cold water (25 ml) and extracted with EtOAc (100 ml). Separated EtOAc layer and kept a side. Take aqueous layer and acidified with in HCl solution and distillout aqueous layer completely and added 10% MeOH in DCM (100 ml), stirred 10 min at room temp. Filtered the reaction mass through celite. Take filtrate and dried out with Na_2SO_4, filtered and concentrated in vacuo to afford product (9S)-10-(pyridin-2-ylcarbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (4.0 g, 9.15 mmol, 57.9% yield) as a pale yellow solid, LCMS (m/z): 341.0 [M+H

Synthesis of (9S)-methyl 10-((4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate

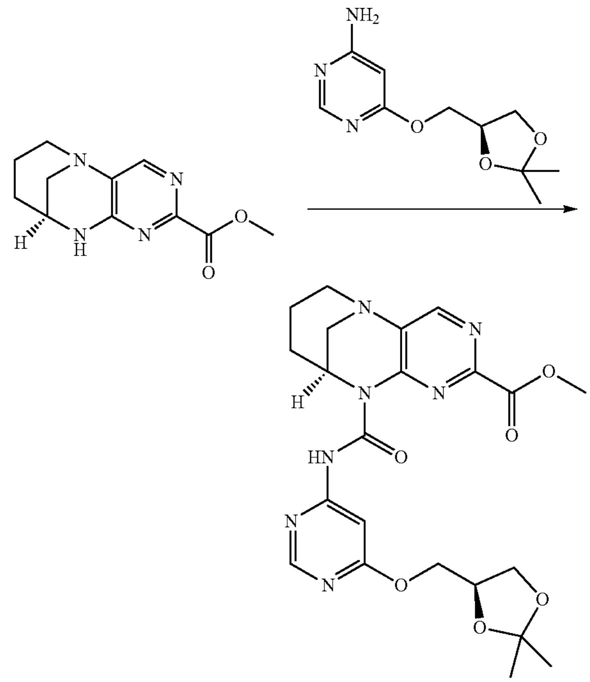
[0761]



[0762] To a stirred solution of (9S)-methyl 7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (1.5 g, 6.40 mmol), in Tetrahydrofuran (THF) (150 mL) was added triphosgene (1.710 g, 5.76 mmol) and TEA (4.46 mL, 32.0 mmol) at room temperature under Nitrogen atmosphere and stirred for 1 hr at room temperature. To the reaction mixture was added a solution of (R)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-amine (1.731 g, 7.68 mmol) in Tetrahydrofuran (THF) (50 mL). The resulting reaction mixture was stirred at 80° C. for 18 hr. Progress of the reaction was monitored by TLC. TLC indicated formation of non polar spot and SM was consumed. Reaction mass was diluted with water (100 mL), extracted with EtOAc (3×100 ml). Organic layers were combined and dried over Na_2SO_4, filtered and concentrated under reduced pressure to get crude. The crude material was purified by column chromatography (100-200 mesh silica gel, eluent: 4% MeOH in DCM) to afford (9S)-methyl 10-((4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (1.4 g, 1.903 mmol, 29.7% yield) as pale brown solid, LCMS (m/z):486.44 $[M+H]^+$.

Synthesis of (9S)-methyl 10-((6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate

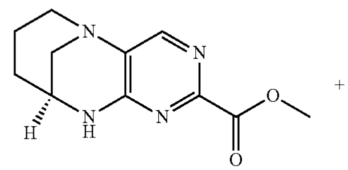
[0763]



[0764] To a stirred solution of (9S)-methyl 7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (2.0 g, 8.54 mmol) in Tetrahydrofuran (THF) (150 mL) was added triphosgene (2.280 g, 7.68 mmol) and TEA (5.95 mL, 42.7 mmol) at room temperature under Nitrogen atmosphere and stirred for 1 hr at room temperature. To the reaction mixture was added a solution of (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine (1.923 g, 8.54 mmol) in Tetrahydrofuran (THF) (50 mL). The resulting reaction mixture was stirred at 80° C. for 16 hr. Progress of the reaction was monitored by TLC. TLC indicated formation of non polar spot and SM was consumed. Reaction mass was diluted with water (100 mL), extracted with EtOAc (3×100 ml). Organic layers were combined and dried over Na_2SO_4, filtered and concentrated under reduced pressure to get crude. The crude material was purified by column chromatography (100-200 mesh silica gel, eluent: 4% MeOH in DCM) to afford (9S)-methyl 10-((6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (1.8 g, 1.801 mmol, 21.10% yield) as yellow solid, LCMS (m/z):486.21 [M+H]+; LCMS (m/z): 486.21 (M+H)

Synthesis of (9S)-methyl 10-((5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrido[2,3-b][1,4]diazocine-2-carboxylate

[0765]



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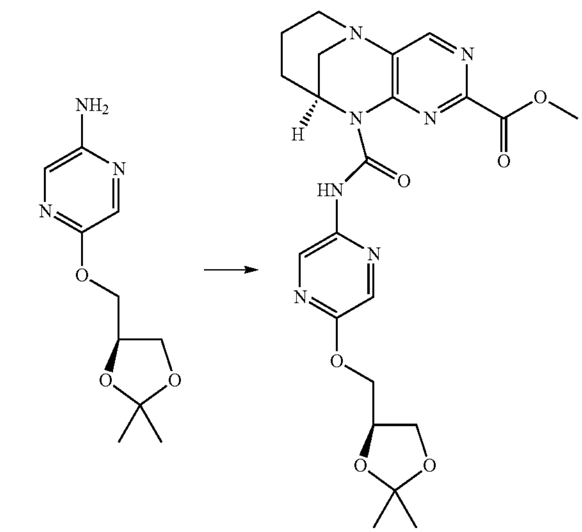
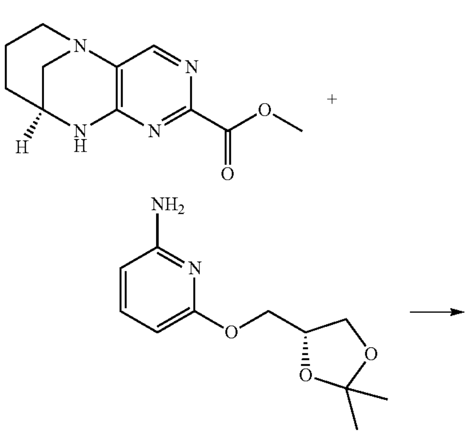


[0766] Triphosgene (0.763 g, 2.57 mmol) was added to a stirred solution of (9S)-methyl 10-((5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrido[2,3-b][1,4]diazocine-2-carboxylate (800 mg, 1.531 mmol, 35.7% yield) in Tetrahydrofuran (THF) (30 mL) at 10° C. and stirred for 30 min at 28° C. Then (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine (0.966 g, 4.29 mmol) was added to the reaction mixture at 28° C. and stirred at 80° C. for 16 h. Reaction mixture was cooled to RT, diluted with water (150 mL), extracted with ethyl acetate (3×100 mL) and washed with brine solution (100 mL). Organic layer was separated, dried over Na_2SO_4, filtered and concentrated to get crude compound, LCMS (m/z): 486.13 $(M+H)^+$.

Synthesis of (9S)-methyl 10-((6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate

[0767]



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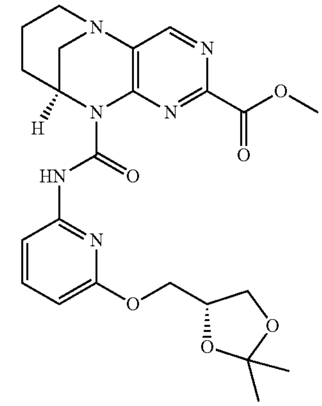
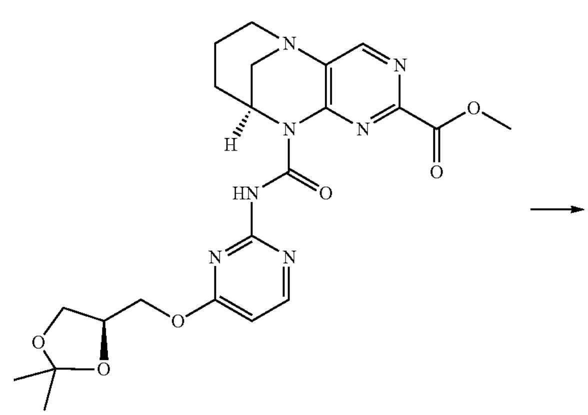


[0768] To a solution of (9S)-methyl 7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (1 g, 4.27 mmol) in Tetrahydrofuran (THF) (20 mL) was added triphosgene (1.267 g, 4.27 mmol) followed by triethylamine (3.57 mL, 25.6 mmol), the resulting suspension was stirred at RT for 20 min. (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (1.915 g, 8.54 mmol) was added to the reaction mass and the resulting suspension was heated to 70° C. for 16 hr. Reaction was monitored by TLC (starting material completely consumed and the new major spot observed at 0.4 R_f). Water (50 mL) was added to the reaction mass and the aqueous layer was extracted with ethyl acetate (2×50 mL). Organic layer was dried over Na_2SO_4 filtered and concentrated under reduced pressure to get crude compound. Resulting crude compound was washed with EtOAc (50 mL) filtered and dried under high vacuum to get (9S)-methyl 10-((6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (1 g, 1.666 mmol, 39.0% yield) as a pale brown solid, LCMS (m/z): 485.23 $(M+H)^+$.

Synthesis of (9S)-10-((4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid

[0769]



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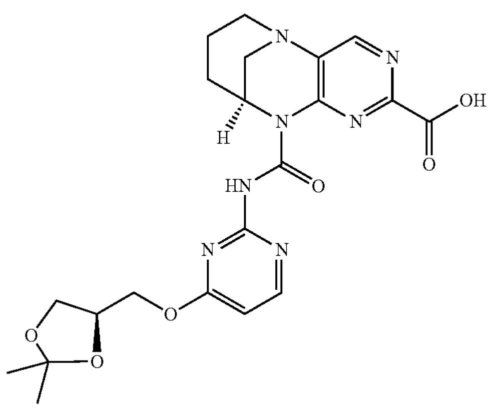
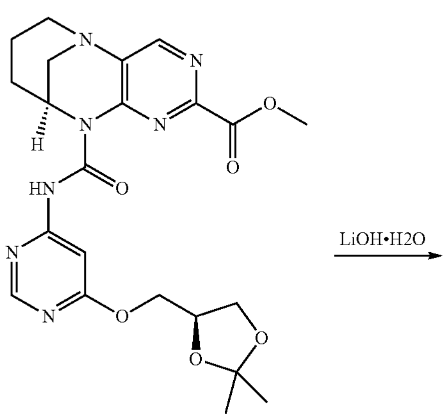


[0770] To a stirred solution of (9S)-methyl 10-((4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (1.4 g, 2.88 mmol) in Tetrahydrofuran (THF) (30 mL) and Water (10 mL) was added lithium hydroxide hydrate (0.242 g, 5.77 mmol). The resulting reaction mixture was stirred at room temperature for 6 hr. Progress of the reaction was monitored by TLC, TLC indicated SM was consumed and polar spot was formed. Reaction mixture was concentrated under vacuum to remove THF and neutralized with 1N HCl extracted with 10% MeOH in DCM (5×50 mL). Organic layers were combined and washed with brine solution (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford (9S)-10-((4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (550 mg, 0.794 mmol, 27.5% yield) as a pale brown solid, LCMS (m/z):472.21 $[M+H]^+$.

Synthesis of (9S)-10-((6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid

[0771]



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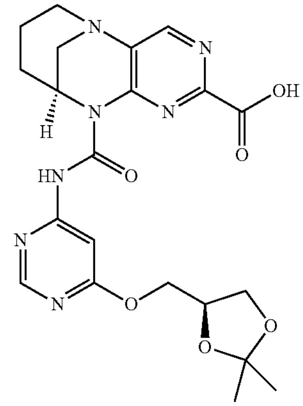
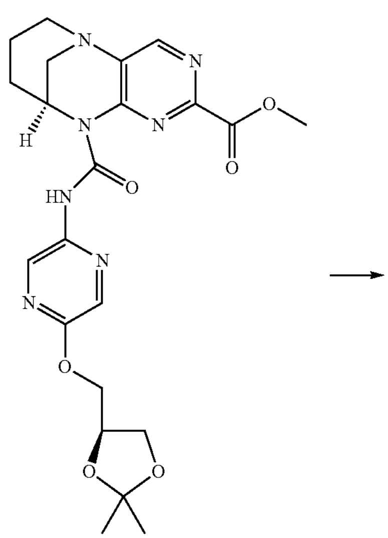


[0772] To a stirred solution of (9S)-methyl 10-((6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (1.8 g, 3.71 mmol) in Tetrahydrofuran (THF) (30 mL) and Water (10 mL) was added lithium hydroxide hydrate (0.156 g, 3.71 mmol). The resulting reaction mixture was stirred at room temperature for 6 hr. Progress of the reaction was monitored by TLC, TLC indicated SM was consumed and polar spot was formed. Reaction mixture was concentrated under vacuum to remove THF and neutralized with 1N HCl extracted with 10% MeOH in DCM (5×50 mL). Organic layers were combined and washed with brine solution (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford (9S)-10-((6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (800 mg, 1.511 mmol, 40.7% yield) as a brown solid. LCMS (m z):472.20[M+H]+.

Synthesis of lithium 10-((5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate

[0773]



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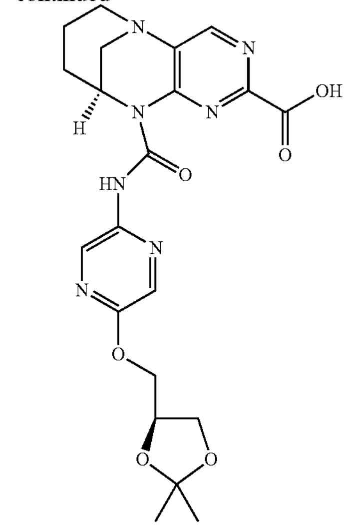
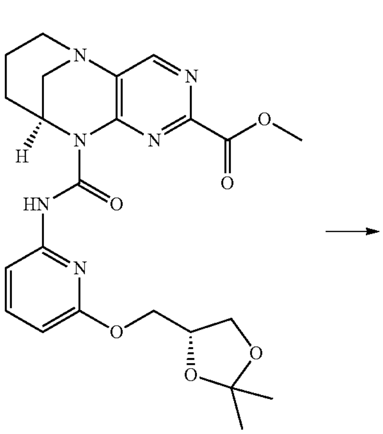


[0774] LiOH (79 mg, 3.30 mmol) was added to a solution of methyl 10-((5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (800 mg, 1.648 mmol) in Tetrahydrofuran (THF) (55 mL) & Water (44 mL) at 28° C. and stirred for 16 h at the same temperature. The reaction mixture solvents were removed by vacuum. It was washed with EtOAc (300 mL) to remove impurities then triturated with n-pentane (100 mL×2) to afford the lithium 10-((5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (800 mg, 1.493 mmol, 91% yield) as brown solid, LCMS (m/z): 477.98 $(M+H)^+$.

Synthesis of (9S)-10-((6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid

[0775]



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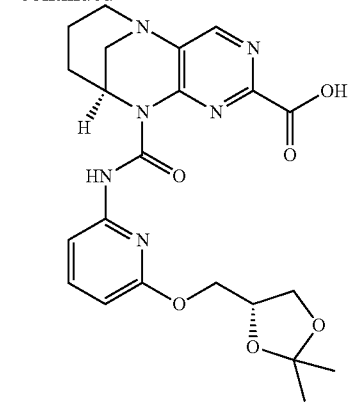
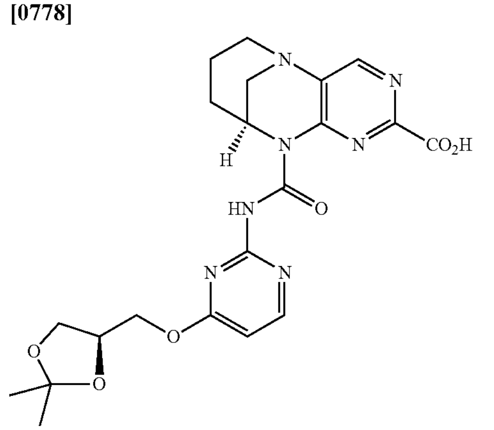


[0776] To a solution of (9S)-methyl 10-((6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (1 g, 2.064 mmol) in Tetrahydrofuran (THF) (10 mL) stirred under nitrogen at room temp, was added a solution of lithium hydroxide hydrate (0.173 g, 4.13 mmol) in Water (10.00 mL) dropwise during 1 min. The reaction mixture was stirred at room temperature for 16 hr. Progress of the reaction was monitored by TLC.

[0777] TLC indicated formation of a polar spot and complete consumption of SM. Reaction mixture was concentrated under reduced pressure, diluted with cold water (20 ml), washed with DCM (2×40 mL), aq layer was acidified with 1N HCl (25 mL) to not get solid, resulting aq layer was washed with DCM (2×50 mL). Separated DCM layer dried Na_2SO_4 filtered and concentrated under vacuum to get (9S)-10-((6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (800 mg, 1.670 mmol, 81% yield) as pale yellow solid, LCMS (m/z): 471.15 $[M+H]^+$.

Synthesis of (9S)—N10-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

[0778]



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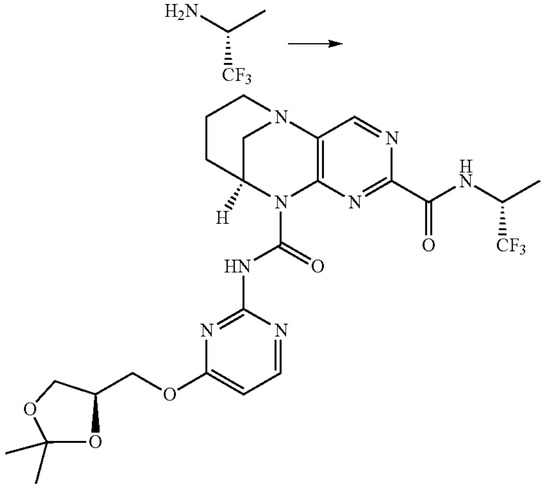
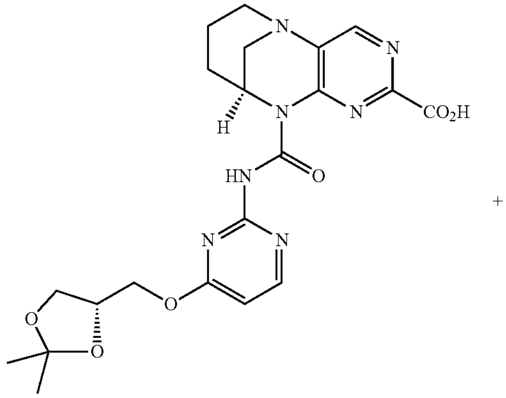


[0779] To a stirred solution of (9S)-10-((4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (500 mg, 1.061 mmol) in Pyridine (10 mL) was added EDC (407 mg, 2.121 mmol) at 0° C. The resulting reaction mixture was stirred at 0° C. for 30 min. To the reaction mixture was added (R)-1,1,1-trifluoropropan-2-amine (180 mg, 1.591 mmol) and stirred at room temperature for 18 hr. Progress of the reaction was monitored by TLC, TLC indicated SM was consumed and non-polar spot was formed. Reaction mixture was concentrated under vacuum to get crude compound, crude was diluted with water (50 mL), extracted with (3×50 mL). Organic layers were combined and washed with water (30 mL), brine solution (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to get crude compound which was purified by column chromatography using 100-200 mesh silica gel and eluted the desired compound with 3% MeOH in DCM, pure fractions were collected and evaporated under reduced pressure to afford (9S)—N10-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (180 mg, 0.313 mmol, 29.5% yield) as an Off-white solid, LCMS (m/z): 567.39[M+H]$^+$.

Synthesis of (9S)—N10-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

[0780]



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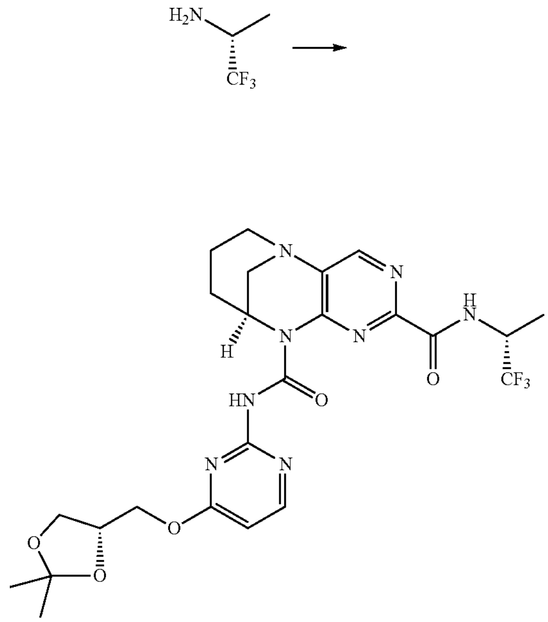
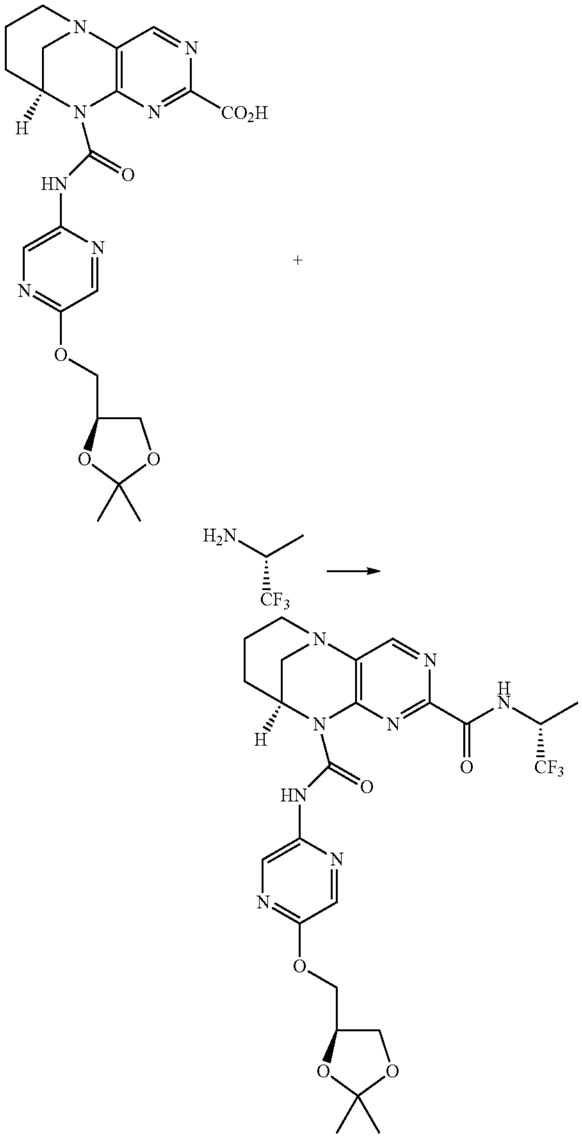


[0781] To a stirred solution of (9S)-10-((6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (700 mg, 1.485 mmol) in Pyridine (10 mL) was added EDC (569 mg, 2.97 mmol) at 0° C. The resulting reaction mixture was stirred at 0° C. for 30 min. To the reaction mixture was added (R)-1,1,1-trifluoropropan-2-amine (252 mg, 2.227 mmol) and stirred at room temperature for 18 hr. Progress of the reaction was monitored by TLC, TLC indicated SM was consumed and non-polar spot was formed. Reaction mixture was concentrated under vacuum to get crude compound, crude was diluted with water (30 mL), extracted with (3×30 mL). Organic layers were combined and washed with water (30 mL), brine solution (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to get crude compound which was purified by column chromatography using 100-200 mesh silica gel and eluted the desired compound with 3% MeOH in DCM, pure fractions were collected and evaporated under reduced pressure to afford (9S)—N10-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (400 mg, 0.684 mmol, 46.1% yield) as an Off-white solid, LCMS (m/z): 567.57 [M+H]$^+$.

Synthesis of (9S)—N10-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

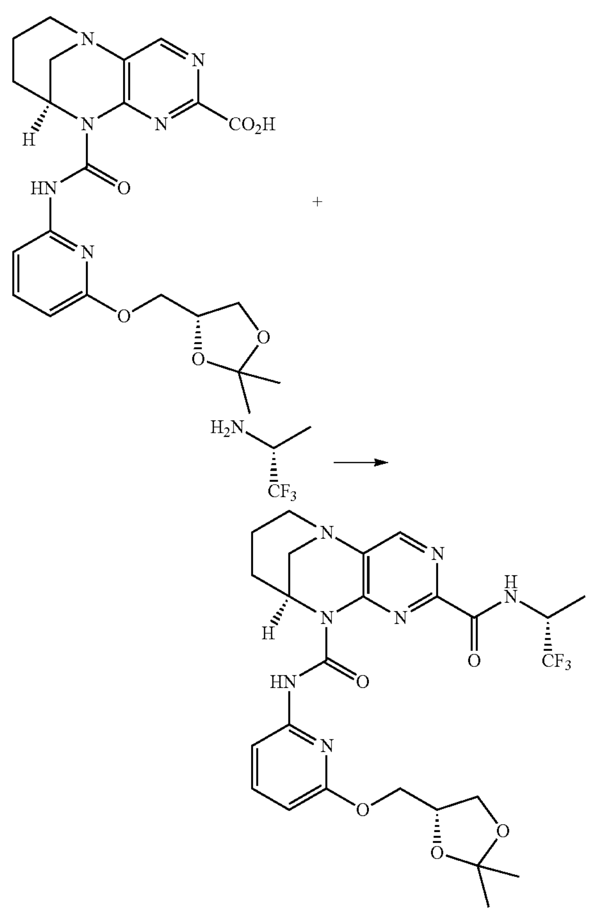
[0782]



[0783] To a solution of (9S)—N10-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido [4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (600 mg, 0.979 mmol, 58.4% yield) in N,N-Dimethylformamide N,N-Dimethylformamide (DMF) (40 mL) stirred under nitrogen at 28° C. was added HATU (637 mg, 1.676 mmol) and DIPEA (0.293 mL, 1.676 mmol) then reaction mixture was stirred for 30 min at 28° C., To this (S)-1,1,1-trifluoropropan-2-amine (189 mg, 1.676 mmol) was added and the reaction mixture was stirred at 28° C. for 16 hr. Reaction mixture was quenched with ice water and extracted with 2×150 ml of ethyl acetate, combined organic layers were washed with 2×50 ml of water and 50 ml of brine solution, organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford crude compound. The crude product was added to a silica gel (100:200 mesh) column and was eluted with ethyl acetate. Collected fractions: (9S)—N10-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl) methoxy)pyrazin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (600 mg, 0.979 mmol, 58.4% yield), LCMS (m/z): 567.01 $(M+H)^+$.

Synthesis of (9S)—N10-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

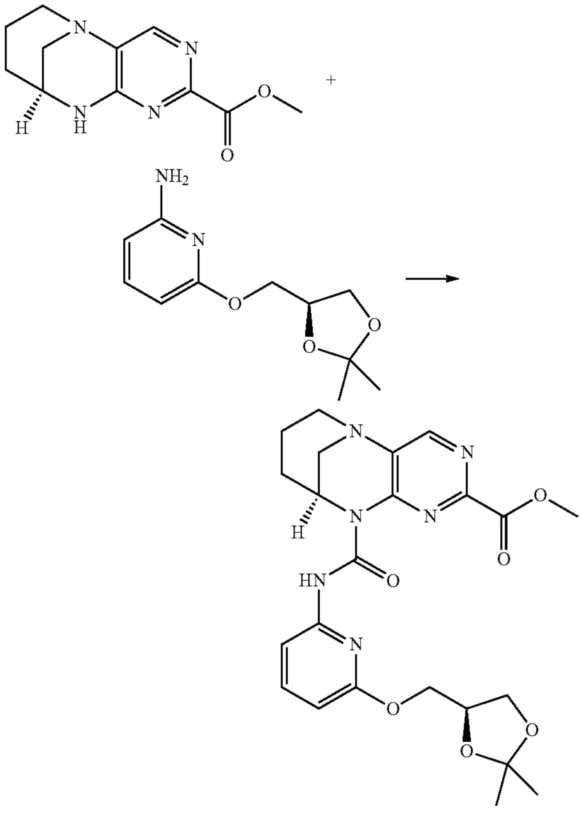
[0784]



[0785] To a solution of (9S)-10-((6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (600 mg, 1.275 mmol), in Pyridine (6 mL) stirred at 0° C. The reaction mixture was stirred at 0° C. for 30 min, then added (R)-1,1,1-trifluoropropan-2-amine (159 mg, 1.403 mmol). Resulting reaction mixture was stirred at room temperature for 16 hr. Progress of the reaction was monitored by TLC. TLC indicated formation of a polar spot and complete consumption of SM. Reaction mixture was concentrated under reduced pressure, diluted with cold water (50 ml) to get solid, solid formed was collected by filtration and dried to give (9S)—N10-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (400 mg, 0.663 mmol, 52.0% yield) as pale yellow solid, LCMS (m/z): 566.29 $[M+H]^+$.

Synthesis of (9S)-methyl 10-((6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate

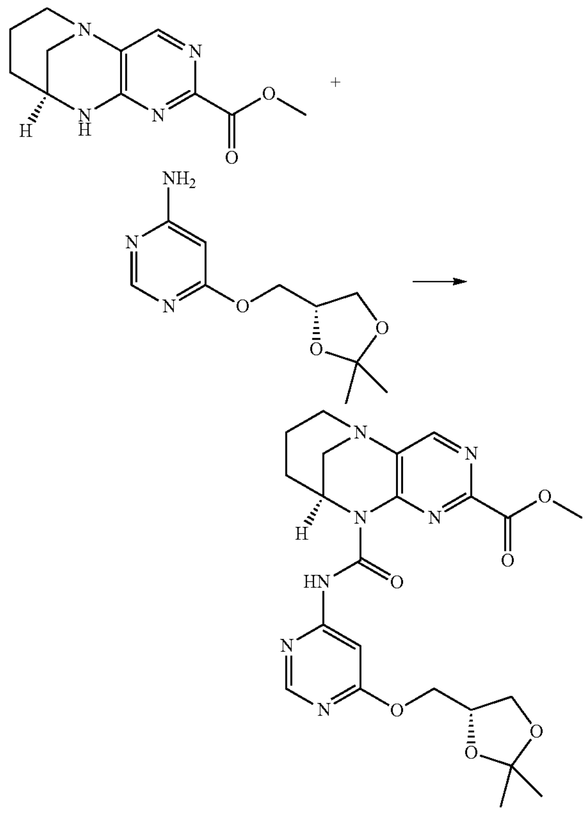
[0786]



[0787] To a stirred solution of (9S)-methyl 7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (1.0 g, 4.27 mmol), in Tetrahydrofuran (THF) (30 mL) was added triphosgene (1.267 g, 4.27 mmol) and TEA (2.97 mL, 21.34 mmol) under Nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1 hr. To the reaction mixture was added a solution of (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (1.436 g, 6.40 mmol) in Tetrahydrofuran (THF) (20 mL). The resulting reaction mixture was stirred at room temperature for 1 hr. Progress of the reaction was monitored by TLC. TLC indicated formation of non polar spot and SM was consumed. Reaction mixture was diluted with water (100 mL) extracted with EtOAc (3×50 ml). Organic layers were combined washed with brine solution (30 mL) dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get crude which was purified by column chromatography using 100-200 mesh silica gel and eluted the desired product with 3% MeOH in DCM, pure fractions were collected and evaporated under reduced pressure to afford (9S)-methyl 10-((6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (1.4 g, 2.82 mmol, 66.0% yield) as a pale brown solid, LCMS (m/z): 485.1 $[M+H]^+$.

Synthesis of (9S)-methyl 10-((6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate

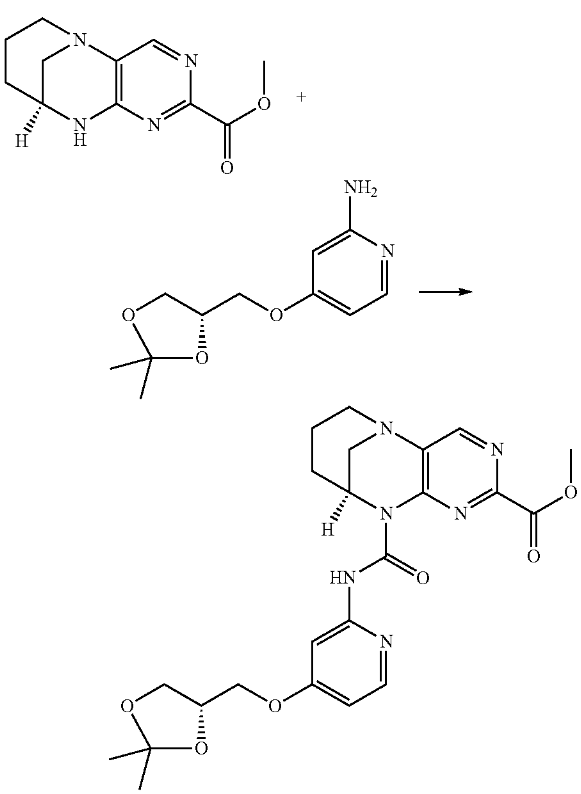
[0788]



[0789] To a solution of (9S)-methyl 7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (1.2 g, 5.12 mmol), in Tetrahydrofuran (THF) (20 mL) stirred under nitrogen at room temp, was added triphosgene (1.520 g, 5.12 mmol) and TEA (3.57 mL, 25.6 mmol). The reaction mixture was stirred for 30 min, was added (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine (1.731 g, 7.68 mmol) in Tetrahydrofuran (THF) (10 mL). The resulting reaction mixture was stirred at room temperature for 16 hr. Progress of the reaction was monitored by TLC. TLC indicated formation of non polar spot and SM was consumed. Reaction mass was diluted with 200 ml of water, extracted with (2×250 ml) of EtOAc. Combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to get crude compound (9S)-methyl 10-((6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl) methoxy)pyrimidin-4-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (1.4 g, 1.615 mmol, 31.5% yield) as pale brown solid, LCMS (m/z): 486.18 $(M+H)^+$.

Synthesis of (9S)-methyl 10-((4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate

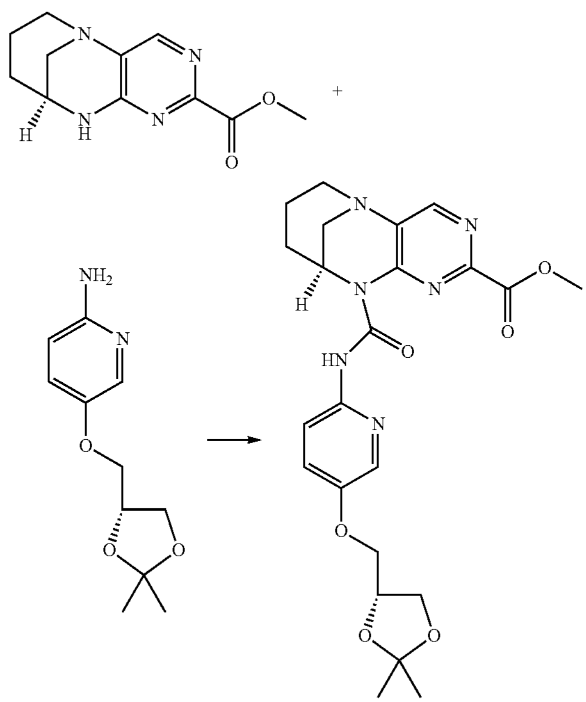
[0790]



[0791] To a solution of (9S)-methyl 7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (900 mg, 3.84 mmol), triphosgene (684 mg, 2.305 mmol) in Tetrahydrofuran (THF) (20 mL) stirred under nitrogen at 0° C. and added DIPEA (3.36 mL, 19.21 mmol). Then the reaction mixture was stirred at 28° C. for 30 min and added (S)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy) pyridin-2-amine (1723 mg, 7.68 mmol), then the reaction mixture was stirred at 80° C. for 15.5 hr. The reaction was monitored by LCMS and TLC. The reaction mixture was poured in to the cold water (50 mL) and extracted with ethyl acetate (2×50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum to give crude product. The crude compound was purified by column chromatography using 100-200 mesh size silica gel and 50% to 100% ethyl acetate and pet ether as an eluent. Collected fractions were evaporated in vacuum to afford (9S)-methyl 10-((4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (800 mg, 1.269 mmol, 33.0% yield) as a pale yellow solid, LCMS (m/z): 485.29 $(M+H)^+$.

Synthesis of (9S)-methyl 10-((5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate

[0792]

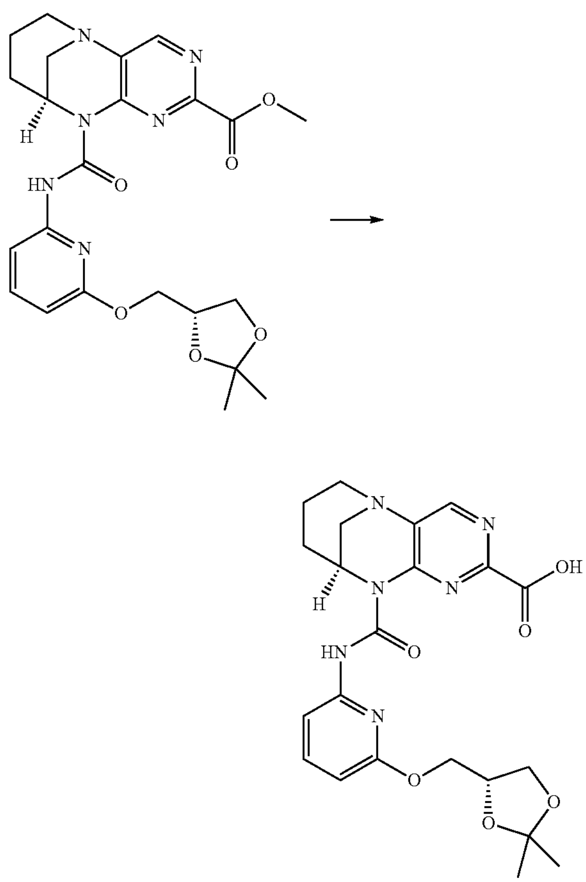


[0793] To a solution of (9S)-methyl 7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (1 g, 4.27 mmol), in Tetrahydrofuran (THF) (20 mL) stirred under nitrogen at room temp was added TEA (2.97 mL, 21.34 mmol), triphosgene (1.267 g, 4.27 mmol). The reaction mixture was stirred at RT for 30 min. To this added (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (0.957 g, 4.27 mmol) at room temperature. The reaction mixture was stirred at 80° C. for 16 hr. Progress of the reaction was monitored by TLC. TLC indicated starting material was consumed. Cooled the reaction mass to room temperature, diluted with water (50 mL), extracted with Ethyl acetate (100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to get crude as brown sticky compound. The crude product was added to a silica gel column and was eluted with 2% DCM/MeOH Collected fractions. Concentrated the product fractions to afford (9S)-methyl 10-((5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (1.1 g, 1.957 mmol, 45.9% yield) as Light brown solid.

[0794] LCMS (m/z): 485.54 $(M+H)^+$.

Synthesis of (9S)-10-((6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid

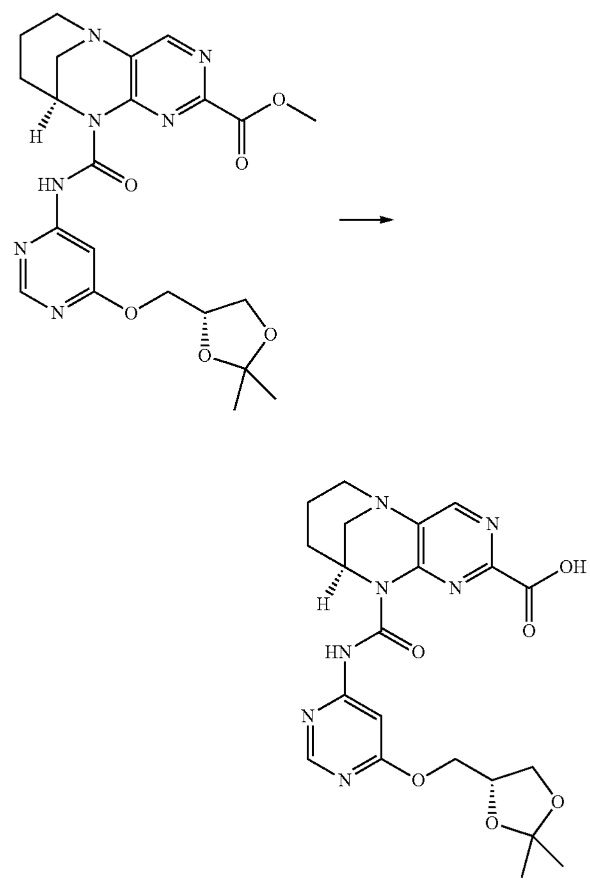
[0795]



[0796] To a solution of (9S)-methyl 10-((6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (1.4 g, 2.89 mmol) in Tetrahydrofuran (THF) (20 mL) and Water (5 mL) was added lithium hydroxide hydrate (0.243 g, 5.78 mmol). The resulting reaction mixture was stirred at room temperature for 4 hr. Progress of the reaction was monitored by TLC, TLC indicated SM was consumed and polar spot was formed. Reaction mixture was concentrated under vacuum to remove THF and neutralized with 1N HCl extracted with 10% MeOH in DCM (5×30 mL). Organic layers were combined and washed with brine solution (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford (9S)-10-((6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (800 mg, 1.278 mmol, 44.2% yield) as a brown solid, LCMS (m/z): 471.01 $[M+H]^+$.

Synthesis of (9S)-10-((6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid

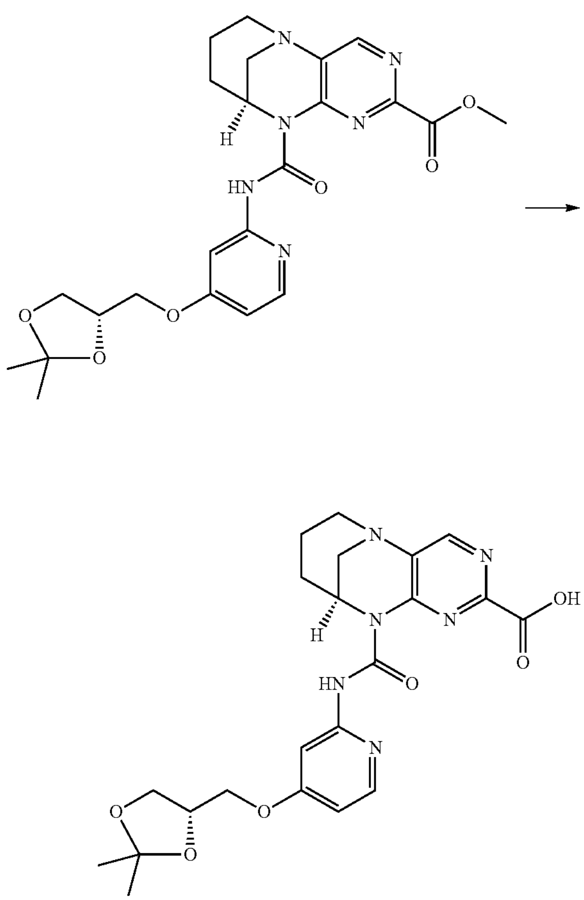
[0797]



[0798] To a solution of (9S)-methyl 10-((6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (1.2 g, 2.472 mmol) in Tetrahydrofuran (THF) (5 mL) and Water (5 mL) was added LiOH (0.178 g, 7.42 mmol) at 0° C. The resulting suspension was stirred at RT for 5 hr. After the completion of reaction (monitored by TLC, starting material completely consumed and the new spot observed at polar), concentrated the reaction mass and the obtained material was dissolved in water. The aqueous solution was adjusted pH to 5 with 2N HCl (aqueous) to get brown colored precipitation, which was filtered and dried in vacuum to get brown solid. Obtained solid was triturated with diethyl ether (20 mL) and dried to get (9S)-10-((6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (400 mg, 0.535 mmol, 21.62% yield) as light brown solid, LCMS (m/z): 472.08 $(M+H)^+$.

Synthesis of (9S)-10-((4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid

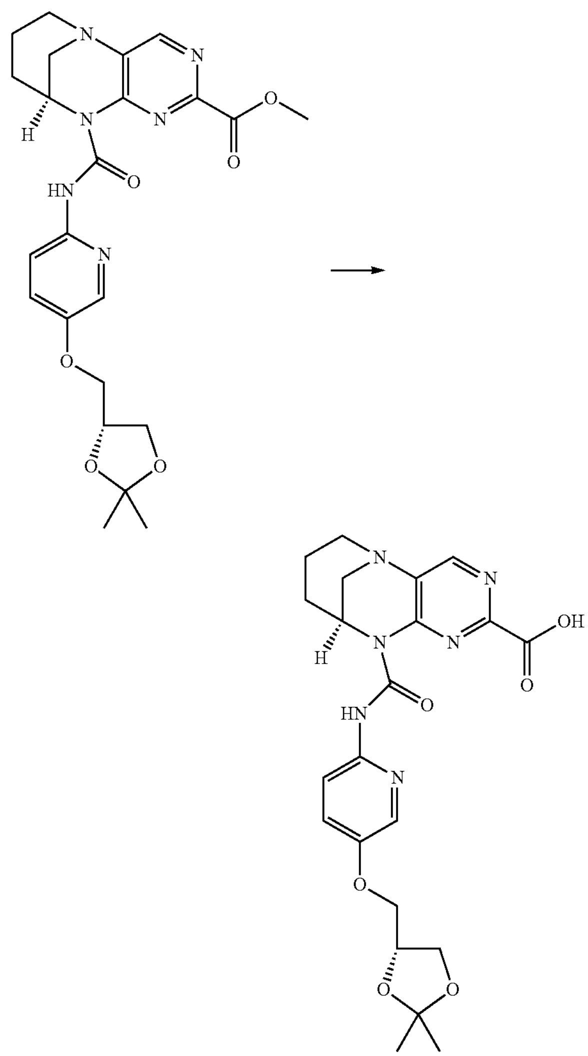
[0799]



[0800] To a solution of (9S)-methyl 10-((4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (0.800 g, 1.651 mmol) in Tetrahydrofuran (THF) (35 mL) and Water (35.0 mL) was added LiOH (0.059 g, 2.477 mmol). The reaction mixture was stirred at RT for 1 hr. Reaction mixture was concentrated under reduced pressure to afford compound (9S)-10-((4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (800 mg, 1.549 mmol, 94% yield) as Off white solid, LCMS (m/z): 471.13 $(M+H)^+$.

Synthesis of (9S)-10-((5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid

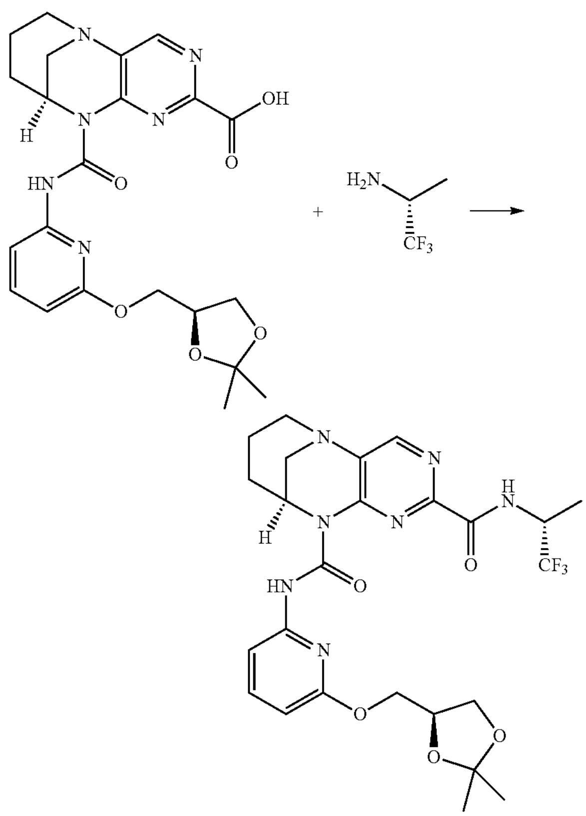
[0801]



[0802] To a solution of (9S)-methyl 10-((5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (1 g, 2.064 mmol), in Tetrahydrofuran (THF) (10 mL), Water (2.500 mL) at room temp was added LiOH (0.148 g, 6.19 mmol). The reaction mixture was stirred at room temperature for 4 hr. Progress of the reaction was monitored by TLC. TLC indicated starting material was consumed. Concentrated the reaction mass under vacuum to remove THF, diluted with water (10 mL), acidified with saturated citric acid solution. Water layer was extracted with DCM (50 mL×2), organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to afford (9S)-10-((5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (700 mg, 1.390 mmol, 67.3% yield) as Off-white solid, LCMS (m/z): 471.55 $(M+H)^+$.

Synthesis of (9S)—N10-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

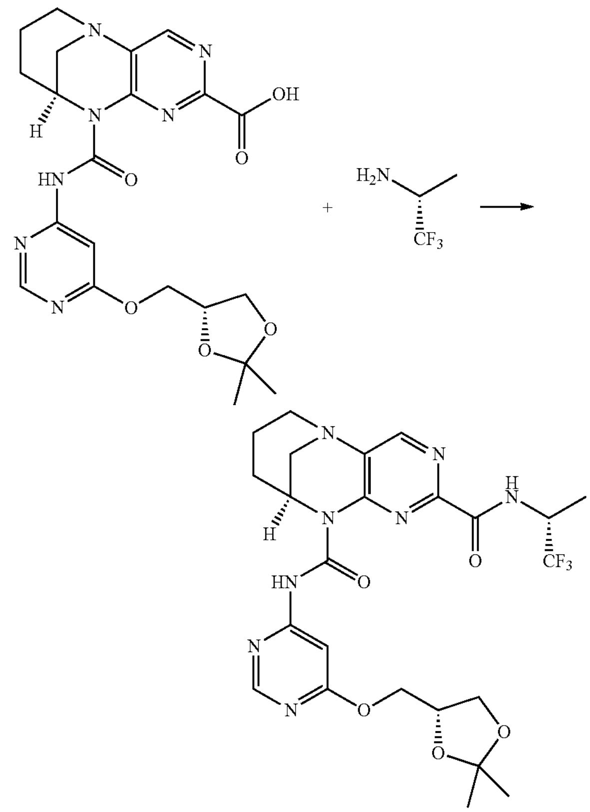
[0803]



[0804] To a stirred solution of (9S)-10-((6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (800 mg, 1.700 mmol) in Pyridine (10 mL) was added EDC (652 mg, 3.40 mmol) at 0° C. The resulting reaction mixture was stirred at 0° C. for 30 min. To the reaction mixture was added (R)-1,1,1-trifluoropropan-2-amine (288 mg, 2.55 mmol) and stirred at room temperature for 18 hr. Progress of the reaction was monitored by TLC, TLC indicated SM was consumed and non-polar spot was formed. Reaction mixture was concentrated under vacuum to get crude compound, crude was diluted with water (30 mL), extracted with (3×30 mL). Organic layers were combined and washed with water (30 mL), brine solution (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to get crude compound which was purified by column chromatography using 100-200 mesh silica gel and eluted the desired compound with 3% MeOH in DCM, pure fractions were collected and evaporated under reduced pressure to afford (9S)—N10-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (450 mg, 0.725 mmol, 42.6% yield) as a Off-white solid, LCMS (m/z): 566.29 $[M+H]^+$.

Synthesis of (9S)—N10-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

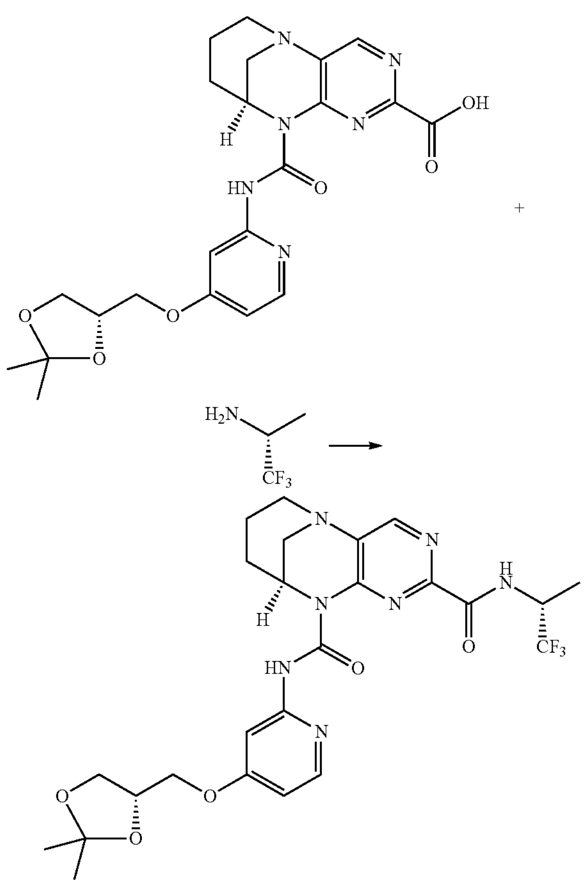
[0805]



[0806] To a stirred solution of (9S)-10-((6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (350 mg, 0.742 mmol) in Pyridine (3 mL), EDC (427 mg, 2.227 mmol) was added at 0° C. and the reaction was stirred for 30 min at 0° C. then (R)-1,1,1-trifluoropropan-2-amine (168 mg, 1.485 mmol) was added at 0° C. and the reaction was stirred at rt for 16 hr under Nitrogen condition. Reaction progress was monitored by TLC. Water (100 ml) was added to the reaction mixture and compound was extracted with Ethyl acetate (2×50 ml). Ethyl acetate layer was concentrated to get crude compound. which was washed with diethyl ether to afford (9S)—N10-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (200 mg, 0.335 mmol, 45.2% yield) as off white solid, LCMS (m/z): 566.94 $[M+H]^+$.

Synthesis of (9S)—N10-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

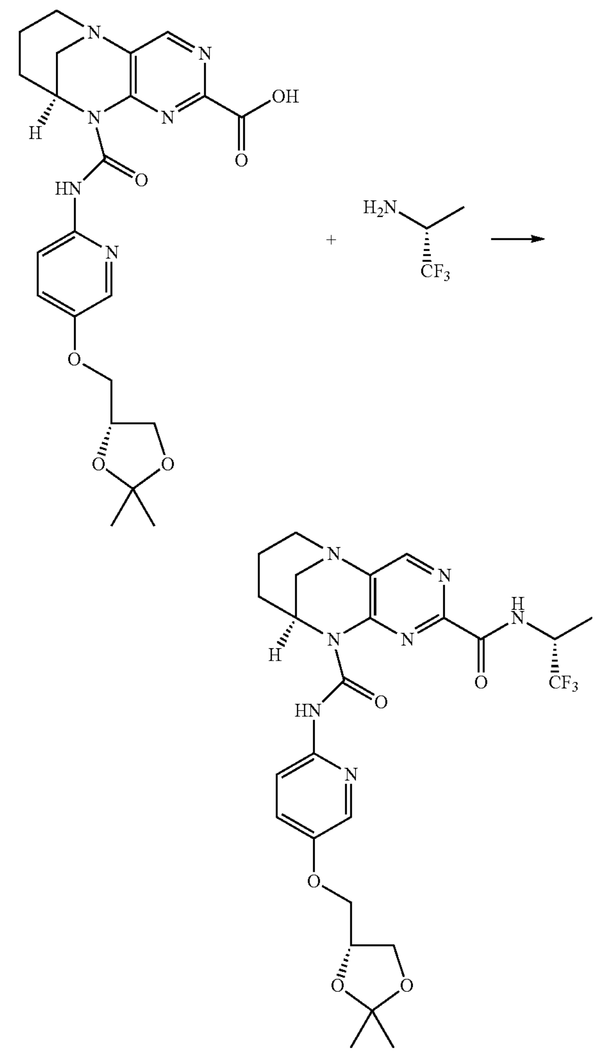
[0807]



[0808] To a solution of (9S)-10-((4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (500 mg, 1.063 mmol) and (R)-1,1,1-trifluoropropan-2-amine (180 mg, 1.594 mmol) in Tetrahydrofuran (THF) (20 mL) stirred under nitrogen at 28° C. was added HATU (485 mg, 1.275 mmol) and DIPEA (0.371 mL, 2.125 mmol) and the reaction mixture was stirred at 28° C. for 16 hr. Reaction mixture was quenched with ice water and extracted with 3×20 ml of ethyl acetate, combined organic layers were washed with 20 ml of brine solution and dried over Na_2SO_4 and concentrated under reduced pressure to afford crude compound. The sample was loaded in dichloromethane and purified on silica (Si) 5 g using a 0-15% methanol-dichloromethane. The appropriate fractions were combined and evaporated in vacuo to give the required product, LCMS (m/z): 566.10 $[M+H]^+$.

Synthesis of (9S)—N10-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

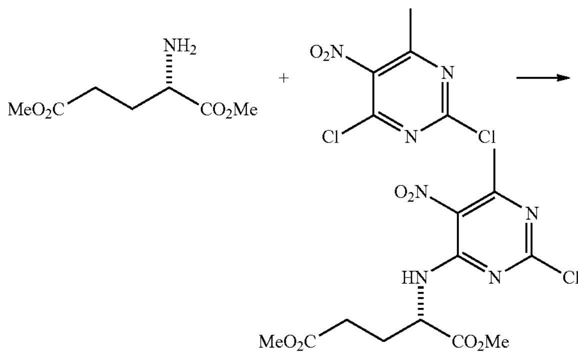
[0809]



[0810] To a solution of (9S)-10-((5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (700 mg, 1.488 mmol), in Tetrahydrofuran (THF) (5 mL) stirred under nitrogen at room temp was added DIPEA (0.780 mL, 4.46 mmol), HATU (849 mg, 2.232 mmol). The reaction mixture was stirred at room temperature for 15 min. To this added (R)-1,1,1-trifluoropropan-2-amine (252 mg, 2.232 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 hr. Progress of the reaction was monitored by TLC. TLC indicated starting material was consumed to form new spot with 0.4 R_f. The reaction mass was concentrated under vacuum, diluted with water (50 mL) and extracted with DCM (50 mL×2). Combined the organic layers and dried over anhydrous Na_2SO_4, filtered and concentrated to get crude as Off-white solid. The crude product was added to a combiflash silica gel (40 g) column and was eluted with 3% DCM/MeOH. Collected fractions: Concentrated the product fractions to afford (9S)—N10-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (450 mg, 0.775 mmol, 52.1% yield) as Off-white solid. LCMS (m/z): 566.43 $(M+H)^+$.

Synthesis of (S)-dimethyl 2-((2-chloro-6-methyl-5-nitropyrimidin-4-yl)amino)pentanedioate

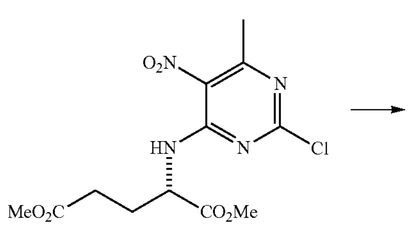
[0811]



[0812] 2,4-dichloro-6-methyl-5-nitropyrimidine (200 g, 962 mmol) was added to a stirred solution of (S)-dimethyl 2-aminopentanedioate hydrochloride (204 g, 962 mmol) and K_2CO_3 (266 g, 1923 mmol) in Acetone (2000 mL) stirred under nitrogen at 0° C. The reaction mixture was stirred at 26° C. for 16 hr. Reaction was monitored by TLC. Filtered the reaction mass through celite. Take filtrate and dried out with Na_2SO_4, filtered and concentrated in vacuo to afford crude product. The crude product was purified by column chromatography using neutral alumina and was eluted with 10% EtOAc in Hexane (gradient system) to afford the desired product (S)-dimethyl 2-((2-chloro-6-methyl-5-nitropyrimidin-4-yl)amino)pentanedioate (202 g, 573 mmol, 59.6% yield) as a pale yellow solid, LCMS (m/z): 347.11 $[M+H]^+$.

Synthesis of (S)-methyl 3-(2-chloro-4-methyl-6-oxo-5,6,7,8-tetrahydropteridin-7-yl)propanoate

[0813]



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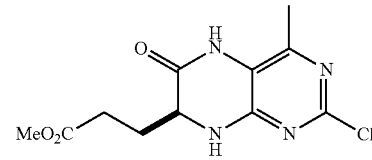
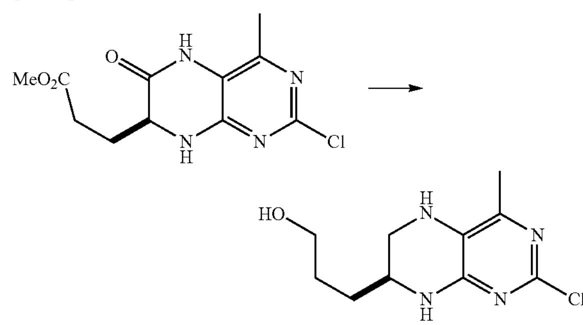


[0814] Iron (163 g, 2913 mmol) was added to a stirred solution of (S)-dimethyl 2-((2-chloro-6-methyl-5-nitropyrimidin-4-yl)amino)pentanedioate (202 g, 583 mmol) in IPA (450 mL) and Water (90 mL) at room temp. Reaction mixture was heated to 40° C. Glacialacetic acid (50.0 mL, 874 mmol) was added to reaction mixture at 40° C. The reaction mixture was stirred at 80° C. for 2 hr. Reaction was monitored by TLC. The reaction mixture was cooled to RT, and made basic with saturated $NaHCO_3$, filtered through celite and washed with DCM (3×1000 mL). Take filtrate separated DCM layer, washed with brine solution and dried out with Na_2SO_4, filtered and concentrated and dried to afford crude product. The crude product was purified by ether (1000 ml) washings to afford desired product (S)-methyl 3-(2-chloro-4-methyl-6-oxo-5,6,7,8-tetrahydropteridin-7-yl)propanoate (120 g, 415 mmol, 71.3% yield) as an off-white solid, LCMS (m/z): 285.0 $[M+H]^+$.

Synthesis of (S)-3-(2-chloro-4-methyl-5,6,7,8-tetrahydropteridin-7-yl)propan-1-ol

[0815]

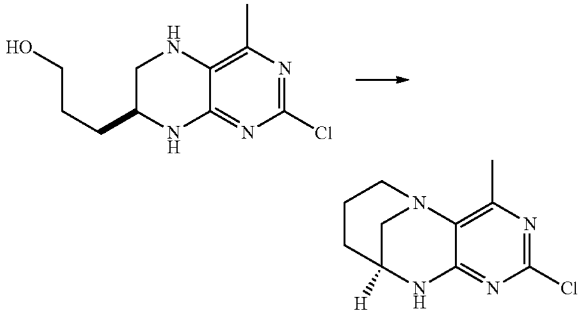


[0816] To a solution of aluminum chloride (79 g, 590 mmol), in Tetrahydrofuran (THF) (1200 mL) stirred under nitrogen was added 2M solution of lithium aluminum hydride (1054 mL, 2107 mmol) in THF dropwise at a rate to control gas evolution. This gave a solution of alane (AlH_3) in THF. In a separate flask, a solution of (S)-methyl 3-(2-chloro-4-methyl-6-oxo-5,6,7,8-tetrahydropteridin-7-yl)propanoate (120 g, 421 mmol) in Tetrahydrofuran (THF) (1800 mL) was prepared under nitrogen, to this was added the alane solution, dropwise at −78° C. over 30 minutes. When the addition was complete, the cooling bath was removed, and the reaction was allowed to warm to ambient temperature for 16 hr.

[0817] The reaction was monitored by TLC. The reaction mixture was quenched with 10% NaOH solution at 0° C. and stirred 6 hr and filtered through celite and washed with (2000 ml) DCM. Take filtrate dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford the crude product. The crude product was purified with ether (500 ml) washings to afford desired product (S)-3-(2-chloro-4-methyl-5,6,7,8-tetrahydropteridin-7-yl)propan-1-ol (67 g, 275 mmol, 65.2% yield) as an off-white solid (TLC eluent: 100% EtOAc in Hexane: R-0.3; UV active). LCMS (m/z): 243.19 $[M+H]^+$.

Synthesis of (9S)-2-chloro-4-methyl-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine

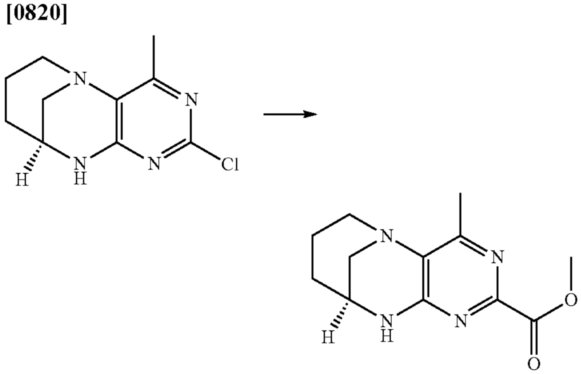
[0818]



[0819] $POCl_3$ (38.6 mL, 414 mmol) was added to a stirred solution of (S)-3-(2-chloro-4-methyl-5,6,7,8-tetrahydropteridin-7-yl)propan-1-ol (67 g, 276 mmol) and DIPEA (121 mL, 690 mmol) in Dichloromethane (DCM) (670 mL) at 0° C. and stirred for 2 hr at 0° C. The reaction was monitored by TLC. The reaction mass was partitioned between saturated $NaHCO_3$ solution. Take DCM layer dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford the crude product. The crude product was purified with pentane & ether (200 ml & 50 ml) washings to afford pure product (9S)-2-chloro-4-methyl-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (42 g, 183 mmol, 66.2% yield) as an off-white solid, LCMS (m/z): 225.03 $[M+H]^+$.

Synthesis of (9S)-methyl 4-methyl-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate

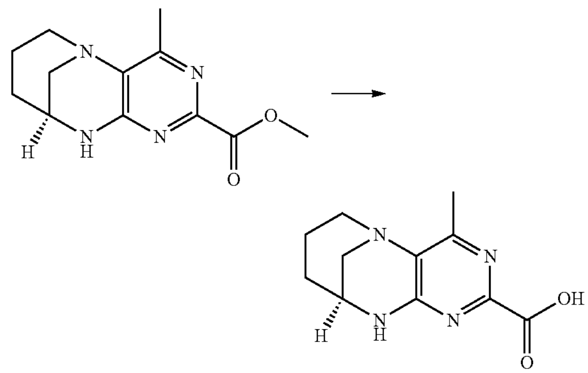
[0820]



[0821] To a solution of (9S)-2-chloro-4-methyl-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (5.0 g, 22.25 mmol) in Methanol (20 mL) was degassed for 30 min, then triethylamine (15.51 mL, 111 mmol) and $PdCl_2(dppf)\text{-}CH_2Cl_2$ adduct (0.909 g, 1.113 mmol) were added and filled with 300 psi CO gas. The reaction mixture was stirred at 130° C. for 5 hr in auto clave. The reaction was monitored by TLC. The reaction mixture was filtered through celite and washed with MeOH. Take filtrate and evaporated to afford crude product. The crude product was purified by column chromatography using neutral alumina and was eluted with DCM (gradient system) to afford the desired product (9S)-methyl 4-methyl-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (3.7 g, 9.32 mmol, 41.9% yield) as an off-white solid, LCMS (m/z): 249.05 $[M+H]^+$.

Synthesis of (9S)-4-methyl-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid

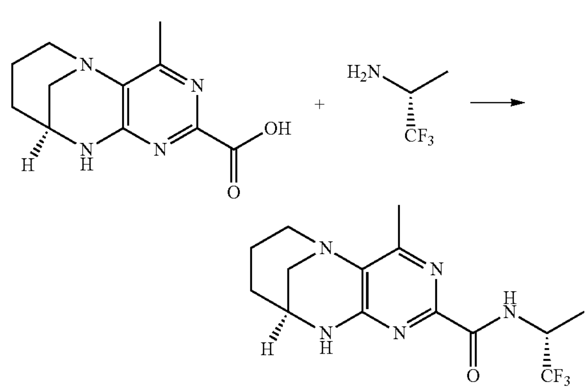
[0822]



[0823] Lithium hydroxide mono hydrate (0.676 g, 16.11 mmol) in Water (4 mL) was added to a stirred solution of (9S)-methyl 4-methyl-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylate (2.0 g, 8.06 mmol) in Tetrahydrofuran (THF) (20 mL) at room temp. The reaction mixture was stirred at 26° C. for 2 hr. The reaction mixture solvent evaporated under reduced pressure completely and was acidified with 1N HCl solution. The reaction mixture was evaporated under reduced pressure completely, added 20% MeOH in DCM (50 ml) and stirred 15 min. Filtered the reaction mass through celite and washed with celite by 20% MeOH in DCM (10 ml). Take filtrate was evaporated to afford crude product. The crude product was purified with ether washings to afford desired product (9S)-4-methyl-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (1.5 g, 5.49 mmol, 68.1% yield) as a brown solid LCMS (m/z): 235.00 $[M+H]^+$.

Synthesis of (9S)-4-methyl-N—((R)-1,1,1-trifluoropropan-2-yl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxamide

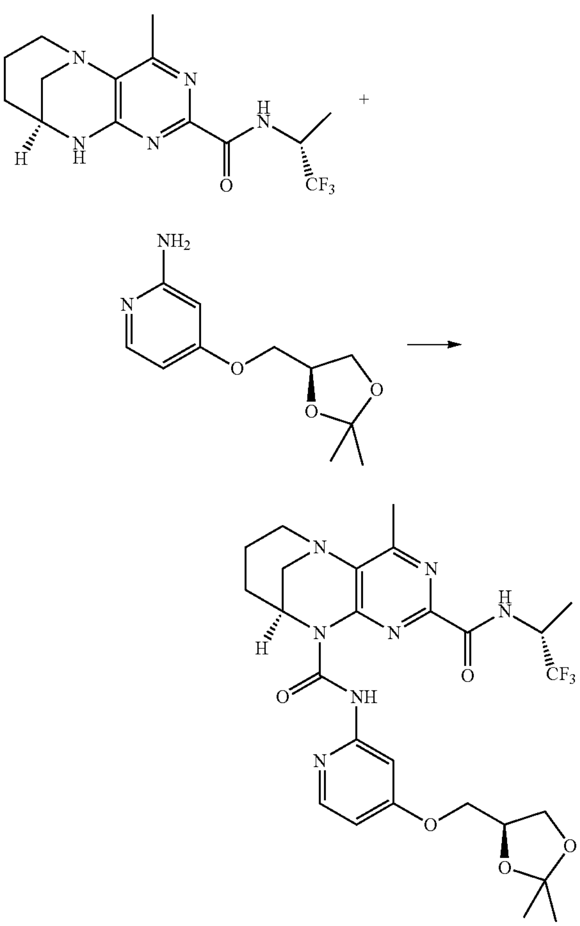
[0824]



[0825] DIPEA (5.41 mL, 30.9 mmol) was added to a stirred solution of (9S)-4-methyl-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (1.45 g, 6.19 mmol), (R)-1,1,1-trifluoropropan-2-amine (1.050 g, 9.28 mmol) & HATU (3.53 g, 9.28 mmol) in N,N-Dimethylformamide (DMF) (10 mL) under nitrogen at 0° C. The reaction mixture was stirred at 26° C. for 16 hr. The reaction mixture was partitioned between ice cold water (10 mL) and DCM (10 mL). Organic layer was separated, dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford the product (9S)-4-methyl-N—((R)-1,1,1-trifluoropropan-2-yl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxamide (1.0 g, 2.96 mmol, 47.8% yield) as an off-white solid, LCMS (m/z): 330.03 $[M+H]^+$.

Synthesis of (9S)—N10-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-4-methyl-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

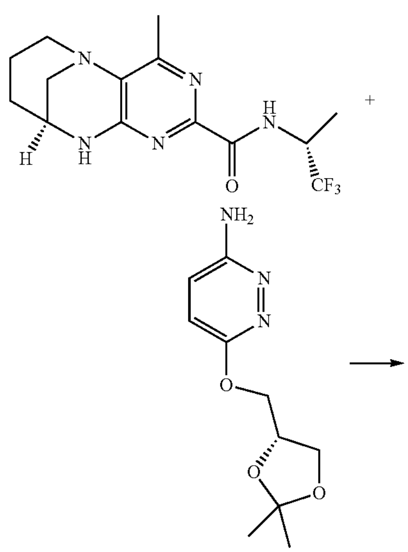
[0826]



[0827] TEA (2.158 mL, 15.49 mmol) and triphosgene (0.766 g, 2.58 mmol) was added to a stirred solution of (9S)-4-methyl-N—((R)-1,1,1-trifluoropropan-2-yl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxamide (0.850 g, 2.58 mmol) in Tetrahydrofuran (THF) (40 mL) under nitrogen at room temp. The reaction mixture was stirred at RT for 30 min. (S)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (1.736 g, 7.74 mmol) was added and the reaction mixture was stirred 16 hr at 65° C. The reaction mixture was cooled to room temp, solvent evaporated under reduced pressure completely and was partitioned between water (30 mL) and EtOAc (100 mL). Organic layer was separated, dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford crude product. The crude compound was purified by Grace using C-18 reserval column, Mobile phase A: 0.1% Formic Acid in water; B: ACN, the product was eluted at 74% ACN/0.1% Formic Acid in water. The solvent was evaporated and was basified with saturated $NaHCO_3$. The aqueous layer was extracted with DCM. DCM layer was dried over anhydrous Na_2SO_4, filtered and evaporated to afford pure (9S)—N10-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-4-methyl-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (0.750 g, 1.240 mmol, 48.1% yield) as an off-white solid, LCMS (m/z): 579.88 $[M+H]^+$.

Synthesis of (9S)—N10-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridazin-3-yl)-4-methyl-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

[0828]



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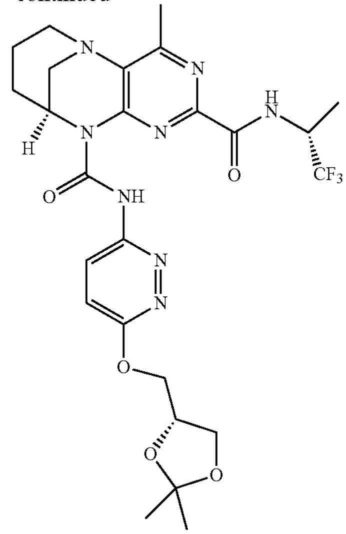
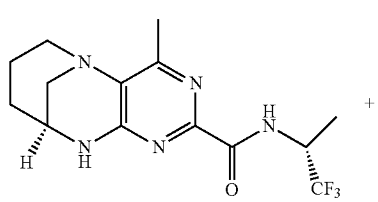


[0829] To a stirred solution of (9S)-4-methyl-N—((R)-1,1,1-trifluoropropan-2-yl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxamide (600 mg, 1.822 mmol) in Tetrahydrofuran (THF) (40 mL) were added TEA (1.524 mL, 10.93 mmol) and triphosgene (541 mg, 1.822 mmol) at 25° C. and stirred for 1 hr then (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridazin-3-amine (821 mg, 3.64 mmol) was added and heated at 65° C. for 15 hr. The reaction mixture was cooled to room temperature, concentrated in vacuo and the residue was partitioned between water (30 mL) and DCM (2×50 mL).

[0830] Organic layer was separated and dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude product. The crude product was purified by Grace using C-18 reserval column, Mobile phase A: 0.1% Formic Acid in water; B: ACN, the product was eluted at 64% ACN in 0.1% Formic Acid in water. The solvent was evaporated and was basified with saturated $NaHCO_3$. The aqueous layer was extracted with DCM. DCM layer was dried over anhydrous Na_2SO_4, filtered and evaporated to afford pure (9S)—N10-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridazin-3-yl)-4-methyl-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (350 mg, 0.519 mmol, 28.5% yield) as a brown colour solid, LCMS (m/z): 581.55 $[M+H]^+$.

Synthesis of (9S)—N10-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-4-methyl-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

[0831]



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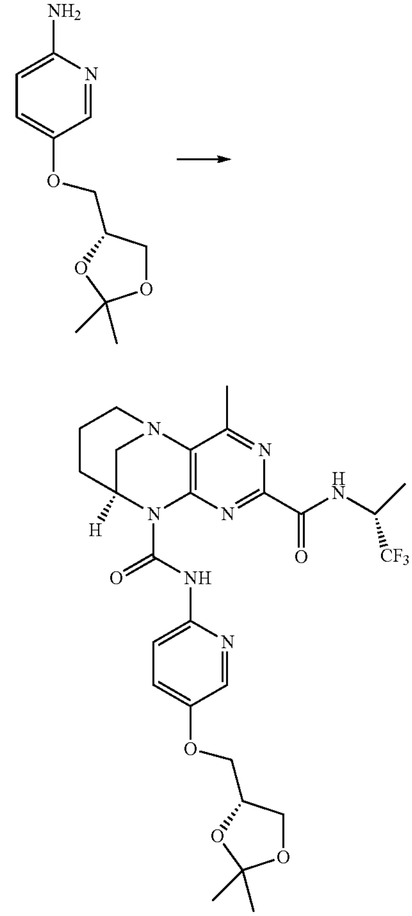
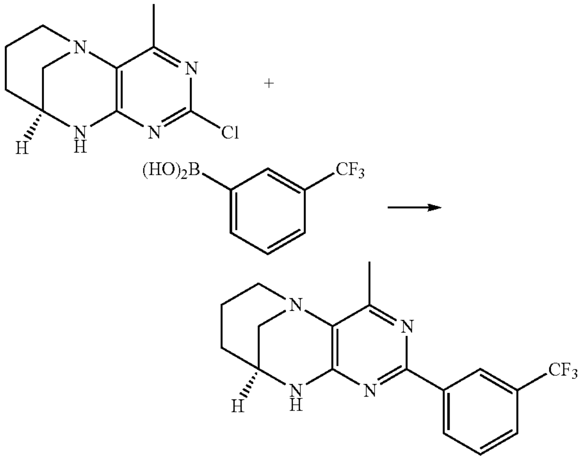


[0832] To a solution (9S)-4-methyl-N—((R)-1,1,1-trifluoropropan-2-yl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxamide (900 mg, 2.73 mmol) in Tetrahydrofuran (THF) (20 mL) was added TEA (2.285 mL, 16.40 mmol), triphosgene (811 mg, 2.73 mmol) at 26° C. Stirred the reaction mixture for 1 h at room temp and (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (919 mg, 4.10 mmol) was added, stirred the reaction mixture at 80° C. for 16 hr. Reaction mixture was cooled to RT, diluted with water and extracted with ethyl acetate (2×200 mL). Combined organics were washed with brine solution (100 mL), dried over Na_2SO_4, filtered and concentrated to get the crude compound. Crude directly submitted to LC-MS. The residue was purified via grace (1:1 MeCN/FA 0.1%; 40 gm reverse phase column). Collected fractions and evaporated to get pure compound (9S)—N10-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-4-methyl-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (540 mg, 0.889 mmol, 32.5% yield), LCMS (m/z): 580.22 $[M+H]^+$.

Synthesis of (9S)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine

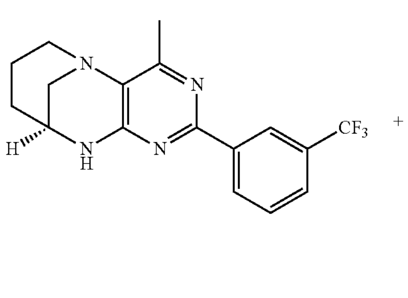
[0833]



[0834] A solution of (9S)-2-chloro-4-methyl-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (7.0 g, 31.2 mmol), (3-(trifluoromethyl)phenyl)boronic acid (8.88 g, 46.7 mmol) and Cs_2CO_3 (30.5 g, 93 mmol) in 1,4-Dioxane (70 mL), Water (14 mL) was stirred and degassed with Argon for 15 min. To this reaction mixture X-PHOS (1.181 g, 3.12 mmol), palladium(II) acetate (0.699 g, 3.12 mmol) was added. The reaction mixture was stirred at 90° C. for 3 hr and progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature filtered through celite and filtrate was concentrated and was diluted with EtOAc (100 mL) and washed with water (50 mL) followed by brine solution (50 mL), dried over Na_2SO_4, filtered and evaporate to get crude compound. The crude product was purified by column chromatography using neutral alumina and was eluted with 20% EtOAc in Hexane (gradient system) to afford the desired product (9S)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (8.0 g, 23.93 mmol, 77% yield) as a white solid, LCMS (m/z): 335.09 $[M+H]^+$.

Synthesis of (9S)—N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[0835]



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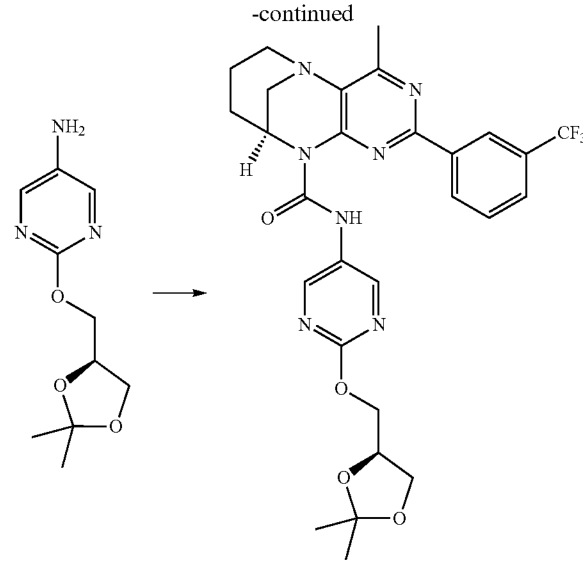
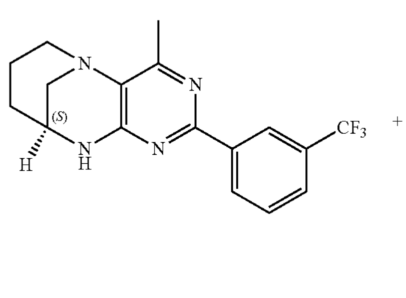


[0836] TEA (2.501 mL, 17.95 mmol) and triphosgene (0.888 g, 2.99 mmol) was added to a stirred solution of (9S)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (1.0 g, 2.99 mmol) in Tetrahydrofuran (THF) (40 mL) under nitrogen at room temp. The reaction mixture was stirred at rt for 30 min. (S)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-amine (2.021 g, 8.97 mmol) was added and the reaction mixture was stirred 16 hr at 65° C. The reaction mixture was cooled to room temp, solvent evaporated under reduced pressure completely and was partitioned between water (20 mL) and EtOAc (50 mL). Organic layer was separated, dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford crude product. The crude compound was purified by Grace using C-18 reserval column, Mobile phase A: 0.1% Formic Acid in water; B: ACN, the product was eluted at 96% ACN/0.1% Formic Acid in water. The solvent was evaporated and was basified with saturated $NaHCO_3$. The aqueous layer was extracted with DCM. DCM layer was dried over anhydrous Na_2SO_4, filtered and evaporated to afford pure (9S)—N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (0.400 g, 0.670 mmol, 22.40% yield) as an off-white solid, LCMS (m/z): 586.1 $[M+H]^+$.

Synthesis of (9S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[0837]



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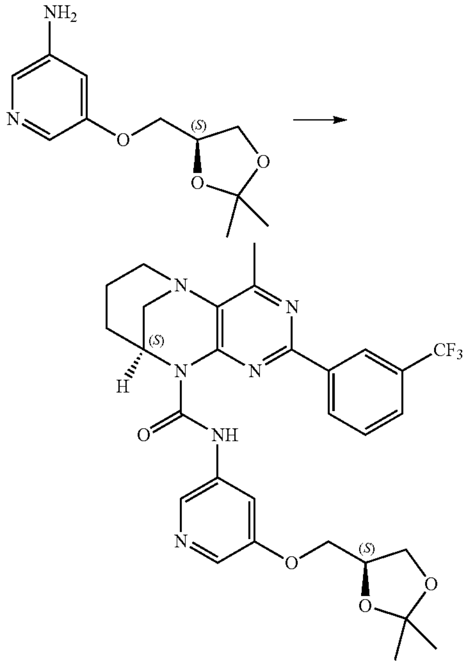
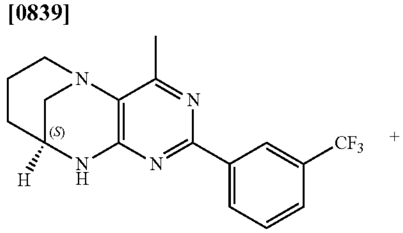


[0838] Triphosgene (0.888 g, 2.99 mmol) was added to a stirred solution of (9S)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (1 g, 2.99 mmol) and triethylamine (2.501 mL, 17.95 mmol) in Tetrahydrofuran (THF) (40 mL) at 28° C. The reaction mixture was stirred for 30 min and was added (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine (2.012 g, 8.97 mmol). The reaction mixture was stirred for 16 hr at 65° C. Reaction mixture was partitioned between water (30 mL) and dichloromethane (2×60 mL). Organic layer was separated, dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford crude. The crude compound was dissolved in dichloromethane (30 mL). Neutral alumina was added to the crude compound and purified by column chromatography. Product was eluted with 30-35% ethyl acetate in hexane. Collected fractions were evaporated under reduce pressure to get (9S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (160 mg, 0.241 mmol, 8.05% yield) as a white gummy, LCMS (m/z): 585.26 $[M+H]^+$.

Synthesis of (9S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[0839]



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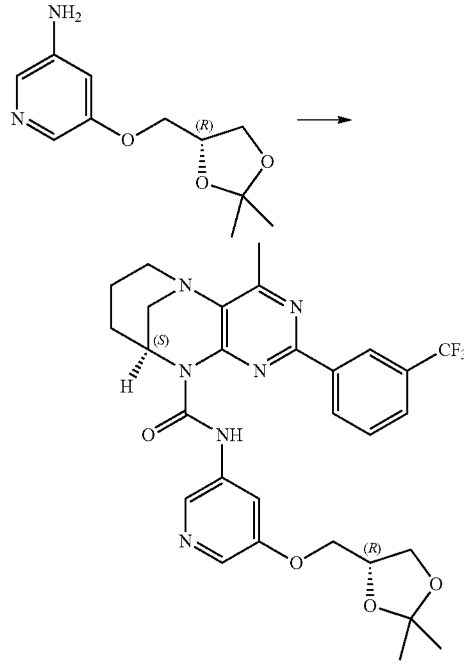
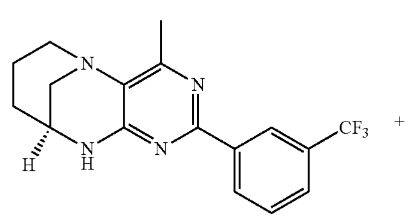


[0840] To a solution (9S)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (500 mg, 1.495 mmol) in Tetrahydrofuran (THF) (20 mL) was added TEA (1.251 mL, 8.97 mmol), triphosgene (444 mg, 1.495 mmol) at 0° C. Stirred the reaction mixture for 1 h at room temp and (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine (503 mg, 2.243 mmol) was added, stirred the reaction mixture at 80° C. for 16 hr. Reaction mixture was cooled to RT, diluted with water and extracted with ethyl acetate (2×100 mL). Combined organics were washed with brine solution (10 mL), dried over Na_2SO_4, filtered and concentrated to get the crude compound. The crude product was added to a silica gel column and was eluted with 50% Hex/EtOAc. Collected fractions evaporated to get pure compound (9S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (220 mg, 0.337 mmol, 22.50% yield), LCMS (m/z): 585.13 $[M+H]^+$.

Synthesis of (9S)—N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[0841]



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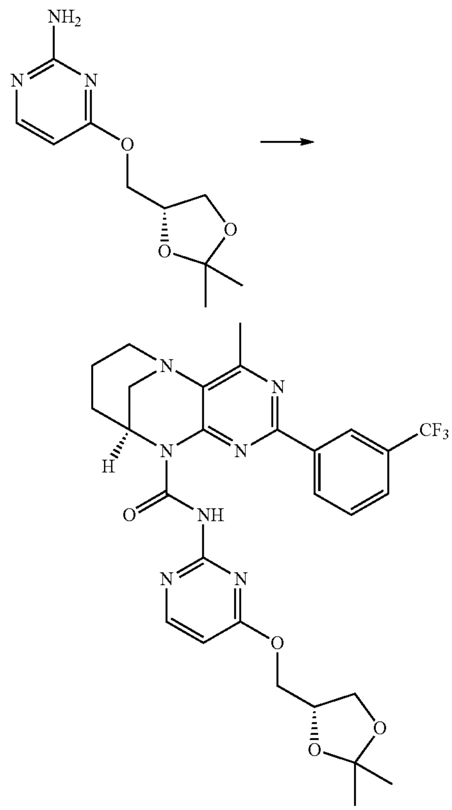
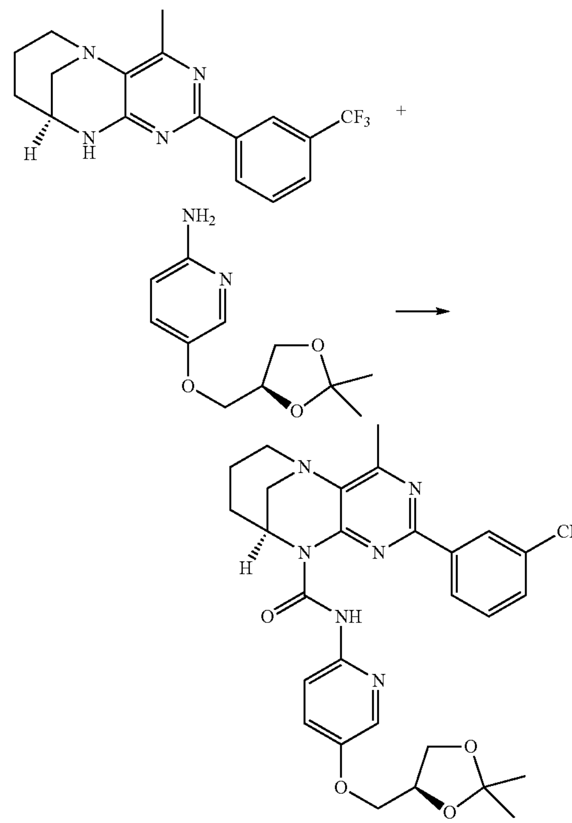


[0842] To a stirred solution of (9S)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (900 mg, 2.69 mmol) in Tetrahydrofuran (THF) (30 mL) were added TEA (2.251 mL, 16.15 mmol) and triphosgene (799 mg, 2.69 mmol) at 25° C. and stirred for 1 hr then (R)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-amine (1213 mg, 5.38 mmol) was added and heated at 65° C. for 15 hr. The reaction mixture was cooled to room temperature, concentrated in vacuo and the residue was partitioned between water (20 mL) and DCM (2×60 mL). Organic layer was separated and dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude compound. The crude compound was purified by Grace using C-18 reserval column, Mobile phase A: 0.1% Formic Acid in water; B: ACN, the product was eluted at 100% ACN. The solvent was evaporated and was basified with saturated $NaHCO_3$. The aqueous layer was extracted with DCM. DCM layer was dried over anhydrous Na_2SO_4, filtered and evaporated to afford pure (9S)—N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (160 mg, 0.265 mmol, 9.85% yield) as an off-white solid, LCMS (m/z): 585.81 $[M+H]^+$.

Synthesis of (9S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

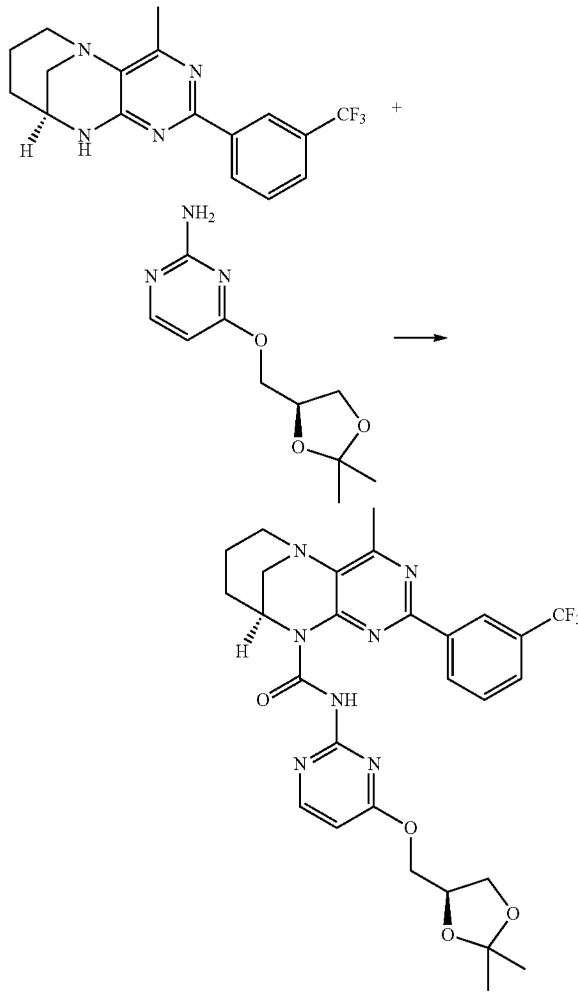
[0843]



[0844] To a stirred solution of (9S)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (900 mg, 2.69 mmol) in Tetrahydrofuran (THF) (40 mL) were added TEA (2.251 mL, 16.15 mmol) and triphosgene (799 mg, 2.69 mmol) at 25° C. and stirred for 1 hr then (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (1207 mg, 5.38 mmol) was added and heated at 65° C. for 15 hr. The reaction mixture was cooled to room temperature, concentrated in vacuo and the residue was partitioned between water (20 mL) and DCM (2×30 mL). Organic layer was separated and dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude compound. The crude compound was purified by Grace using C-18 reserval column, Mobile phase A: 0.1% Formic Acid in water; B: ACN, the product was eluted at 100% ACN. The solvent was evaporated and was basified with saturated $NaHCO_3$. The aqueous layer was extracted with DCM. DCM layer was dried over anhydrous Na_2SO_4, filtered and evaporated to afford pure (9S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (300 mg, 0.459 mmol, 17.05% yield) as an off-white solid, LCMS (m/z): 585.35 $[M+H]^+$.

Synthesis of (9S)—N-(4-(((S)-2,2-dim ethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

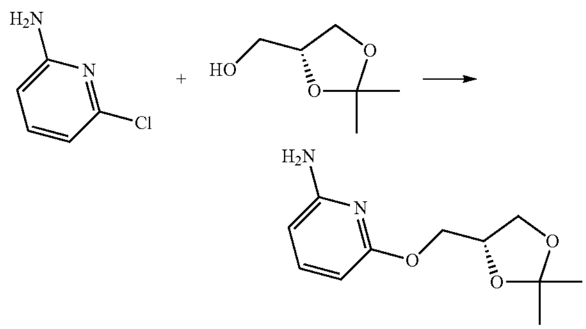
[0845]



[0846] To a stirred solution of (9S)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (900 mg, 2.69 mmol) in Tetrahydrofuran (THF) (40 mL) were added TEA (2.251 mL, 16.15 mmol) and triphosgene (799 mg, 2.69 mmol) at 25° C. and stirred for 1 hr then (S)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-amine (909 mg, 4.04 mmol) was added and heated at 65° C. for 15 hr. The reaction mixture was cooled to room temperature, concentrated in vacuo and the residue was partitioned between water (5 mL) and DCM (2×10 mL). Organic layer was separated and dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude compound. The crude compound was purified by Grace using C-18 reserval column, Mobile phase A: 0.1% Formic Acid in water; B: ACN, the product was eluted at 100% ACN. The solvent was evaporated and was basified with saturated $NaHCO_3$. The aqueous layer was extracted with DCM. DCM layer was dried over anhydrous Na_2SO_4, filtered and evaporated to afford pure (9S)—N-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (150 mg, 0.243 mmol, 9.02% yield) as a pale yellow color solid, LCMS (m/z): 585.86 $[M+H]^+$.

Synthesis of (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine

[0847]

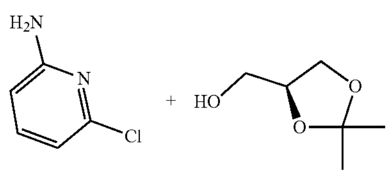


[0848] To a stirred suspension of NaH (11.67 g, 292 mmol) in N-Methyl-2-pyrrolidone (NMP) (100 mL) under nitrogen at 0° C. was added a solution of (R)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (25.7 g, 194 mmol) in N-Methyl-2-pyrrolidone (NMP) (100 mL) dropwise during 10 min at 0° C. After 10 min added a solution of 6-chloropyridin-2-amine (25 g, 194 mmol) in N-Methyl-2-pyrrolidone (NMP) (100 mL) dropwise during 10 min at 0° C. The reaction mixture was heated at 100° C. for 36 hr. TLC indicates small amount starting material along with product.

[0849] Reaction mixture was poured into ice cold water (600 mL), aqueous layer was extracted with EtOAc (2×500 mL). The organic layer was washed with water (3×300 mL) to remove excess NMP. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain crude product. Crude product was purified by column chromatography using 100-200 silica gel as a eluent (12-15% EtOAc in petether) to obtain (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (10 g, 44.6 mmol, 22.93% yield) as a yellow thick liquid.

Synthesis of (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine

[0850]



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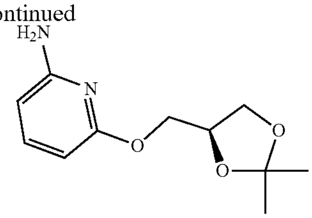
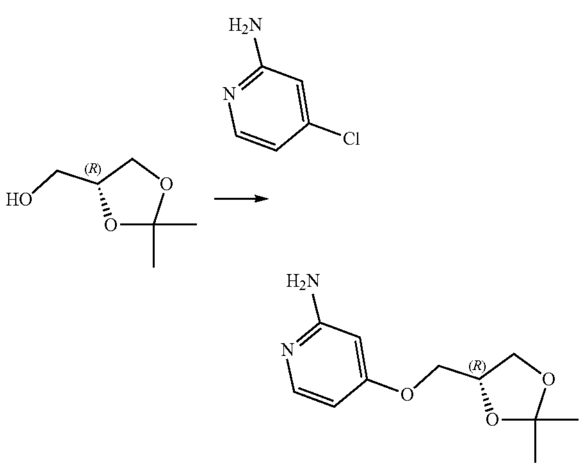


[0851] To a stirred suspension of NaH (62.2 g, 1556 mmol) in N-Methyl-2-pyrrolidone (NMP) (800 mL), under nitrogen at 0° C., was added a solution of (S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (206 g, 1556 mmol) in N-Methyl-2-pyrrolidone (NMP) (300 mL) dropwise during 2 h. After stirring for another 10 min added a solution of 6-chloropyridin-2-amine (200 g, 1556 mmol) in N-Methyl-2-pyrrolidone (NMP) (300 mL) dropwise during 30 min at 0° C. The reaction mixture was stirred at 120° C. for 48 hr. TLC indicated that starting material was. Reaction mixture was poured into ice cold water (2000 mL), aqueous layer was extracted with EtOAc (3×1000 mL). The combined organic layer was washed with water (3×1000 mL) to remove excess NMP. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain crude product. Crude product was purified by column chromatography using 100-200 silica gel (eluent 12-15% EtOAc in pet ether) to obtain the desired pure product (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (75 g, 325 mmol, 20.92% yield) as a yellow viscous liquid.

[0852] LCMS (m/z): 225 $[M+H]^+$.

Synthesis of (R)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine

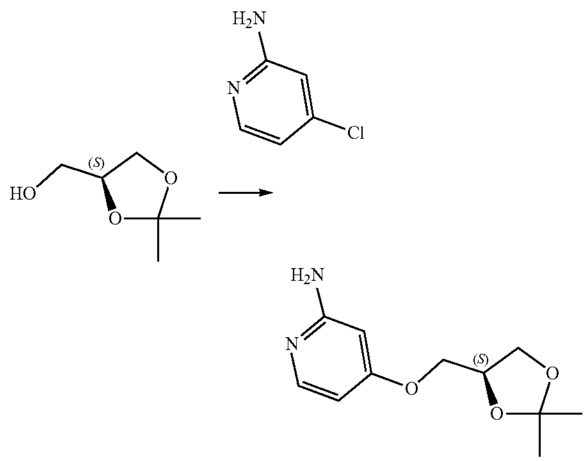
[0853]



[0854] To a suspension of (R)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (3.000 g, 22.70 mmol), 4-chloropyridin-2-amine (1.459 g, 11.35 mmol) and sodium (0.522 g, 22.70 mmol) in a sealed tube. The reaction mixture was stirred at 140° C. for 16 h. Next, the reaction mixture was cooled to room temperature, dissolved in MeOH and poured in to ice water and extracted with EtOAc. The organic phase was washed with brine solution and dried over sodium sulfate, filtered and evaporated to get crude compound. The crude compound was purified by column chromatography using silica gel and eluted with 2-3% MeOH/DCM to get pure compound (1.1 g, 21%), LCMS (m/z) 225.2 $[M+H]^+$.

Synthesis of (S)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine

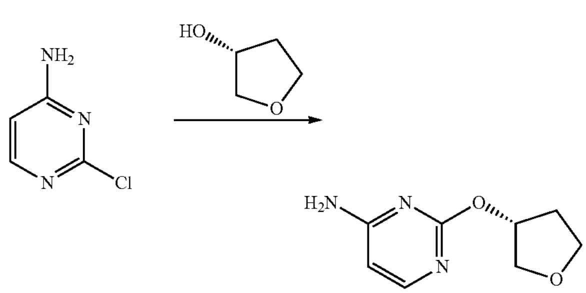
[0855]



[0856] To a suspension of (S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (3.000 g, 22.70 mmol), 4-chloropyridin-2-amine (1.459 g, 11.35 mmol) and sodium (0.522 g, 22.70 mmol) in a sealed tube. The reaction mixture was stirred at 140° C. for 16 h before being cooled to room temperature, dissolved in MeOH and poured in to ice water and extracted with EtOAc. The organic phase was washed with brine solution and dried over sodium sulfate, filtered and evaporated. The crude material was purified by silica gel column chromatography eluting with 2-3% MeOH/DCM to give the desired product (1.2 g, 22%), LCMS (m/z) 225.2 $[M+H]^+$.

Synthesis of (R)-2-(tetrahydrofuran-3-yloxy)pyrimidin-4-amine

[0857]

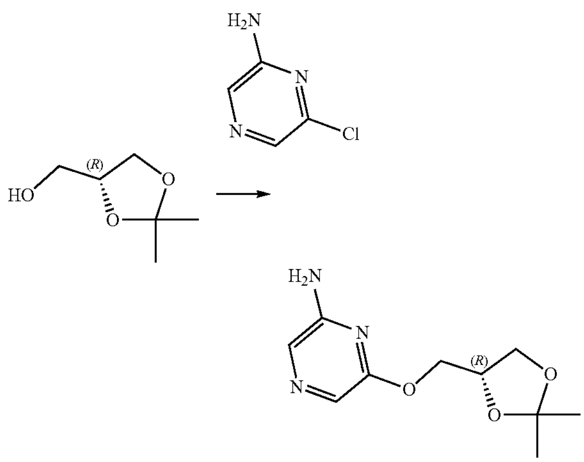


[0858] To a stirred solution of (R)-tetrahydrofuran-3-ol (2.72 g, 30.9 mmol) in THF (30 mL) was added NaH (0.926 g, 23.16 mmol) and stirred for 30 min at room temperature. To this 2-chloropyrimidin-4-amine (2.0 g, 15.44 mmol) was added in portions for about 15 min and heated at 70° C. for

16 h. The reaction mixture was allowed to room temperature and subsequently cooled to 0° C., quenched with ice cold water and extracted with ethyl acetate (3×50 ml). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude compound. The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh) to afford (R)-2-(tetrahydrofuran-3-yloxy)pyrimidin-4-amine (1.6 g, 8.839 mmol, 51.5% yield) as an off white solid.

Synthesis of (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine

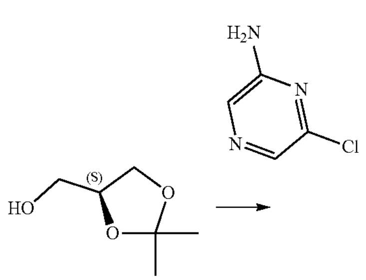
[0859]



[0860] To a solution of 6-chloropyrazin-2-amine (5 g, 38.6 mmol), sodium hydride (2.316 g, 57.9 mmol) and (R)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (5.61 g, 42.5 mmol) in Tetrahydrofuran (THF) (50 mL) stirred under nitrogen at 0° C. was added reaction mixture was stirred at 80° C. for 16 h. Reaction mixture was quenched with ice cold water and extracted into ethyl acetate. Organic layer dried over Na_2SO_4. Solvent evaporated under reduced pressure to afford the crude product. The crude product was added to a silica gel column and was eluted with DCM/MeOH. Fractions with product were combined and evaporated under reduced pressure to give the required product (2.8 g, 11.9 mmol, 31%), LCMS (m/z) 225.9 $[M+H]^+$.

Synthesis of (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine

[0861]



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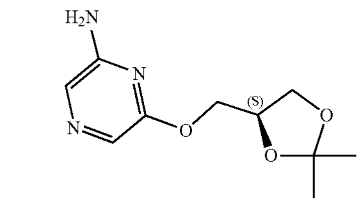
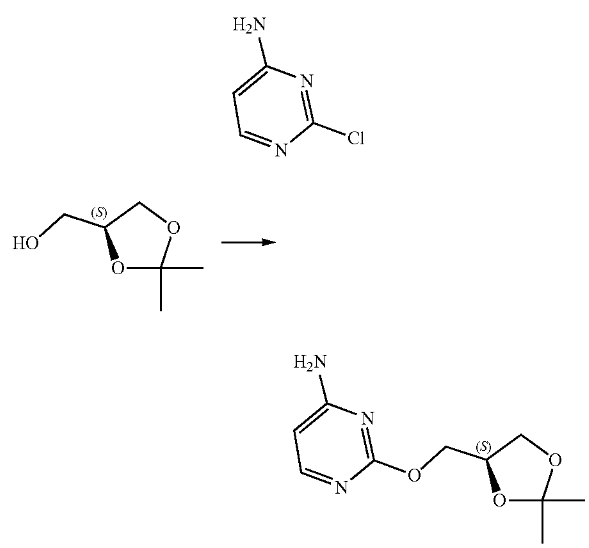


[0862] 6-chloropyrazin-2-amine (0.980 g, 7.57 mmol), (S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (2 g, 15.13 mmol) and sodium (0.348 g, 15.13 mmol) were taken in a seal tube and heated at 130° C. for 16 hr and then the reaction mixture was quenched with methanol and ice cold water (100 mL) and extracted with ethyl acetate (5×50 mL). The combined organic layers were washed with water, saturated brine solution, dried over anhydrous sodium sulfate, filtered and concentrated to give the product (1 g, 4.26 mmol, 28.2% yield), LCMS (m/z) 265.1 $[M+H]^+$.

Synthesis of (S)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine

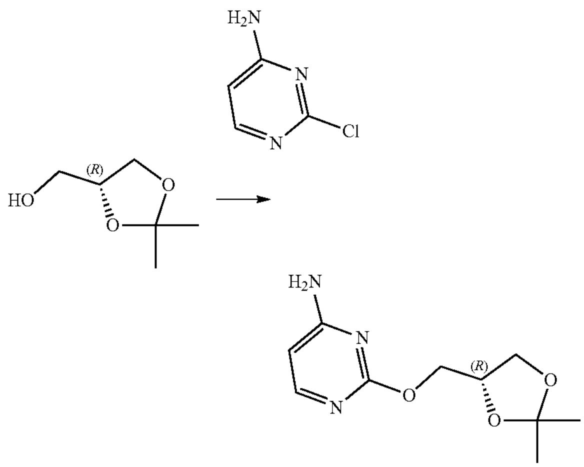
[0863]



[0864] To suspension of (S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (10.20 g, 77 mmol), and NaH (4.63 g, 116 mmol) in tetrahydrofuran (THF) (50 mL) stirred under nitrogen at room temperature was added 2-chloropyrimidin-4-amine (5 g, 38.6 mmol) portion wise over 15 min. The reaction mixture was stirred at 70° C. for 16 hr. Next, the reaction mixture was quenched with solution of aq. $NaHCO_3$ and then extracted with EtOAc, dried Na_2SO_4 and evaporated. The crude product was added to a silica gel column and was eluted with 50% Hex/EtOAc. Collected fractions were evaporated to give the desired product (3 g, 11.84 mmol, 30.7% yield) as off white solid, LCMS (m/z) 226.2 $[M+H]^+$.

Synthesis of (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl) methoxy)pyrimidin-4-amine

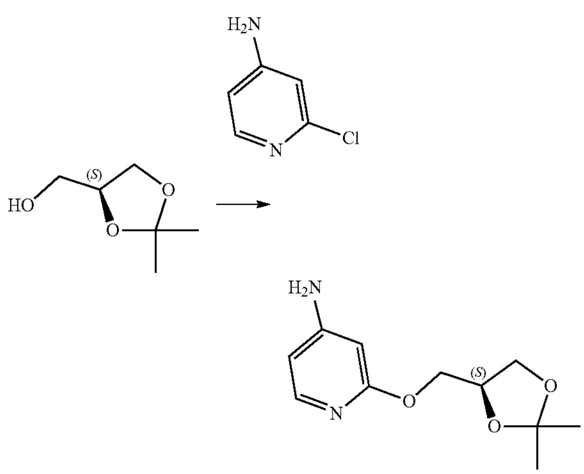
[0865]



[0866] To a solution of sodium hydride (0.817 g, 34.1 mmol) in Tetrahydrofuran (THF) (30 mL) at room temperature was added a solution of (R)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (3 g, 22.70 mmol) in THF (5 mL) over 1 min and stirred at room temperature for 15 min then add 2-chloropyrimidin-4-amine (2.059 g, 15.89 mmol) portion wise at room temperature. The reaction mixture was stirred at 65° C. for 16 h. The reaction mixture was poured in to water and extracted with EtOAc (3×100 mL). Then the combined organic layer was washed with water, brine solution, dried over sodium sulfate and evaporated to get 4.0 g of crude compound. The crude compound was purified by column chromatography using 100-200 silica gel mesh and eluted with 2-3% MeOH/DCM to get pure compound (2.5 g, 10.42 mmol, 46%), LCMS (m/z) 226.2 $[M+H]^+$.

Synthesis of (S)-2-((2,2-dimethyl-1,3-dioxolan-4-yl) methoxy)pyridin-4-amine

[0867]

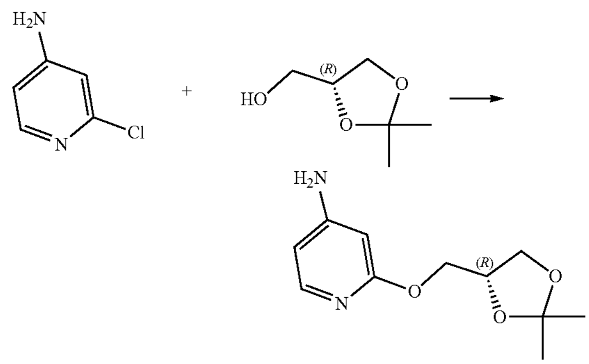


[0868] To a suspension of 2-chloropyridin-4-amine (1.459 g, 11.35 mmol), (S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (3.0 g, 22.70 mmol) was added sodium (0.522 g, 22.70 mmol). The reaction mixture was stirred at 140° C. for 16 hr and progress of the reaction was monitored by

[0869] The reaction mixture was dissolved in MeOH, poured in to ice water and extracted with EtOAc (3×100 mL). Then the combined organic layer was washed with water, brine solution, dried over sodium sulfate and evaporated to get 4.0 g of crude compound. The crude compound was purified by column chromatography using 100-200 silica gel mesh and eluted with 2-3% MeOH/DCM to get (S)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (2.5 g, 10.73 mmol, 47.3% yield), LCMS (m/z) 225.3 $[M+H]^+$.

Synthesis of (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl) methoxy)pyridin-4-amine

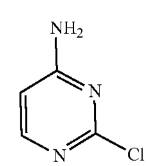
[0870]



[0871] To a solution of 2-chloropyridin-4-amine (4 g, 31.1 mmol), (R)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (2.056 g, 15.56 mmol) and sodium (0.715 g, 31.1 mmol) in sealed tube at room temperature. The reaction mixture was stirred at 140° C. for 48 hr. The reaction mixture was cooled to room temp and quenched with MeOH followed by water. Then reaction mass was extracted with the EtOAc. Then organic layer washed with water followed by brine solution and dried out with sodium sulfate and filtered and distill out completely. The crude product was added to a silica gel column and was eluted with Hex/EtOAc (1:1) collected fractions were evaporated to give the desired product (2.250 g, 9.93 mmol, 31.9% yield), LCMS (m/z) 225.0 $[M+H]^+$.

Synthesis of (S)-2-((tetrahydrofuran-3-yl)oxy)pyrimidin-4-amine

[0872]



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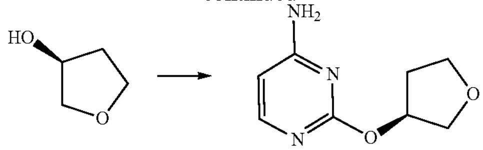
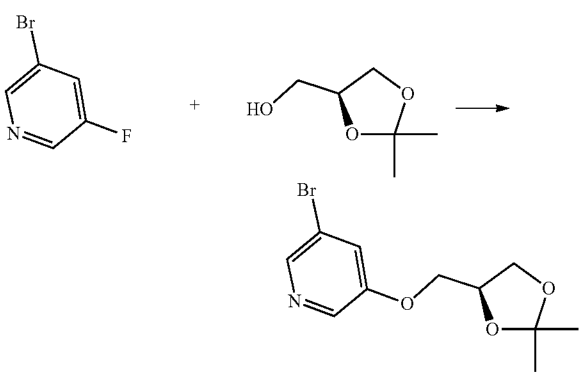


[0873] To a stirred solution of 2-chloropyrimidin-4-amine (2 g, 15.44 mmol) in Tetrahydrofuran (THF) (20 mL) was added NaH (0.741 g, 30.9 mmol) portion wise over a period of 5 min at room temperature. Then the reaction was stirred at 30° C. for about 10 min. To the above reaction added (S)-tetrahydrofuran-3-ol (1.088 g, 12.35 mmol) at 30° C. and stirred at 80° C. for 8 hrs. The reaction mixture was quenched with ice cold water at 0° C. and extracted with ethyl acetate. The organic layer was washed thoroughly with water and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the product. The crude product was triturated with pet ether, LCMS (m/z) 182.2 $[M+H]^+$.

Synthesis of (S)-3-bromo-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridine

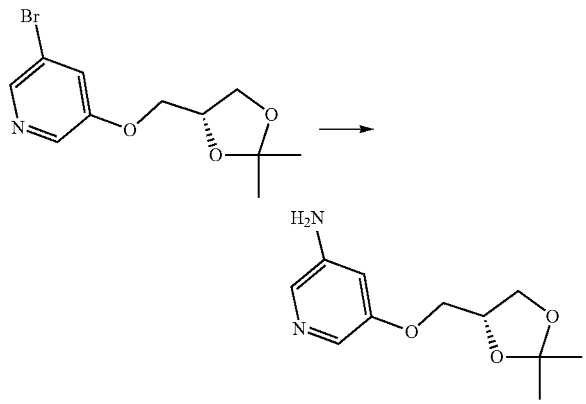
[0874]



[0875] Cesium carbonate (37.0 g, 114 mmol) was taken into multi-neck RB. Then flask was cooled to 0° C. and N-Methyl-2-pyrrolidone (NMP) (100 mL) was added slowly over a period of 3 minutes. The resulting reaction mixture was stirred under nitrogen for 15 min. Then (S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (10 g, 76 mmol) was added dropwise over a period of 5 min at 0° C. This suspension was stirred at room temperature ° C. for 1 h. Suspension became pale yellow solution after added 3-bromo-5-fluoropyridine (7.62 mL, 73.9 mmol). The resulting solution was stirred at 75° C. for 24 hr. Reaction progress was monitored by TLC 40% EtOAc in Hexane. TLC indicated consumption of SM and formation of new spot after 24 h. The reaction mass was cooled to room temperature, diluted with water (500 mL). The aqueous layer was extracted with ethyl acetate (2×300 mL). The organic layer was washed with brine (250 mL), dried over Na_2SO_4 filtered, concentrated under reduced pressure to afford brown oil. The crude product was purified by column chromatography over 100-200 mesh size silica gel. Column was eluted with a gradient of EtOAc/Hexane. Desired compound was eluted with 20% EtOAc in Hexane. Compound fractions containing pure compound were concentrated under reduced pressure to afford (S)-3-bromo-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridine (10 g, 34.0 mmol, 44.9% yield) as pale yellow viscous oil, LCMS (m/z): 289.99 $[M+H]^+$.

Synthesis of (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine

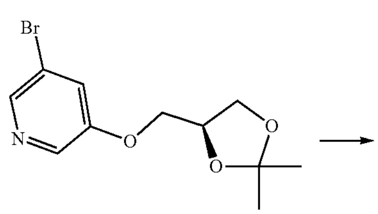
[0876]



[0877] (R)-3-bromo-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridine (50 g, 174 mmol), liquor ammonia (25 mL, 1155 mmol) were taken in a sealed tube. Then added copper(II) sulfate (5.54 g, 34.7 mmol) at 0° C. The resulting blue solution was heated to 120° C. for 2 hr. The reaction progress was monitored by TLC 10% MeOH in DCM, TLC indicated formation of new spot and consumption of SM after 24 h. After completion, The reaction mass was cooled to room temperature. The reaction mass was brought to pH 10 with 20% NaOH, saturated with NaCl, extracted with ethyl acetate (30 mL*2). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude brown solid, which was triturated with diethyl ether and stirred for 4 hours then filtered to afford (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine (35.4 g, 146 mmol, 84% yield) as pale brown solid, LCMS (m/z): 225.29 $[M+H]^+$.

Synthesis of (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine

[0878]



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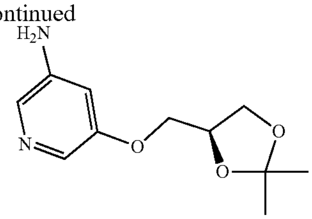
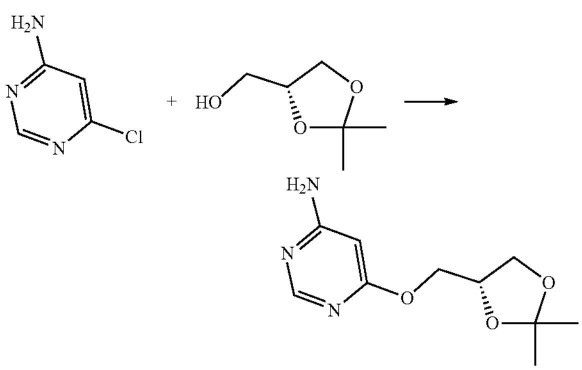


[0879] (S)-3-bromo-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridine (10 g, 34.7 mmol), liquor ammonia (100 mL, 4621 mmol) were taken in a sealed tube. The resulting brown solution was heated to 120° C. for 24 hr. The reaction progress was monitored by TLC 10% MeOH in DCM, TLC indicated formation of new spot and consumption of SM after 24 h. After completion, The reaction mass was cooled to room temperature. The reaction mass was brought to pH 10 with 20% NaOH, saturated with NaCl, extracted with ethyl acetate (30 mL*2). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine (6 g, 25.8 mmol, 74.2% yield) as an pale brown solid, LCMS (m/z): 225.10 $[M+H]^+$.

Synthesis of (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine

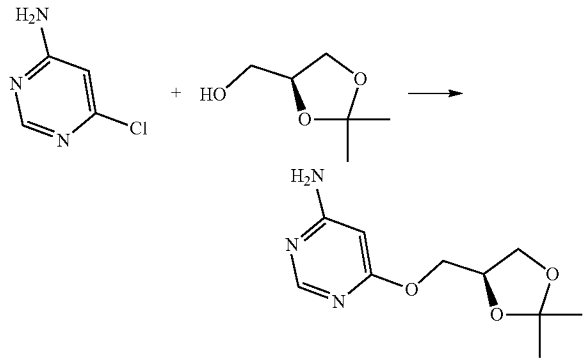
[0880]



[0881] To a suspension of NaH (11.35 g, 473 mmol) in THF (100 mL) was added dropwise a solution of (R)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (25 g, 189 mmol) in THF (150 mL) under Nitrogen at 0° C. The resulting suspension was stirred at rt for 1 h. 6-chloropyrimidin-4-amine (19.61 g, 151 mmol) was added to the reaction mixture portion wise at rt and the resulting suspension was heated to 90° C. for 48 hr. After the completion of reaction (monitored by TLC, it shows little bit of starting and new spot observed at polar), reaction mixture was poured into ice water (500 mL) and aqueous layer was extracted with EtOAc (2×1000 mL). Combined organics dried over Na_2SO_4, filtered and concentrated under reduced pressure to get light brown solid (crude). Crude material was purified by silica gel column (100-200, 3% MeOH in DCM). Fractions containing pure compound were combined and concentrated to afford the desired product (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine (13 g, 53.9 mmol, 28.5% yield) as an off-white solid and also get the impure compound (10 g). LCMS (m/z):226.17 $(M+H)^+$.

Synthesis of (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine

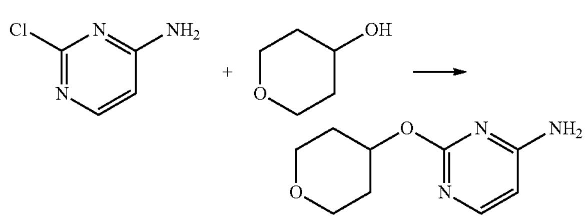
[0882]



[0883] To a suspension of NaH (9.08 g, 378 mmol) in THF (150 mL) was added drop wise a solution of (S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (20 g, 151 mmol) in THF (200 mL) under Nitrogen at 0° C., and the resulting suspension was stirred at rt for 1 h. 6-chloropyrimidin-4-amine (15.68 g, 121 mmol) was added to the reaction mass portion wise at rt and the resulting suspension was heated to 90° C. for 48 hr. After the completion of reaction (monitored by TLC, starting material completely consumed and new spot observed at polar), reaction mass was poured into ice water (200 mL) and extracted with ethyl acetate (2×400 ml). Combined organics dried over Na_2SO_4, filtered and concentrated under reduced pressure to get light brown solid. The obtained solid was stirred in diethyl ether (200 ml) for 30 min filtered and dried under vacuum to get (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine (13 g, 57.3 mmol, 37.9% yield) as a light brown solid, LCMS (m/z): 225.96 $[M+H]^+$.

Synthesis of 2-((tetrahydro-2H-pyran-4-yl)oxy)pyrimidin-4-amine

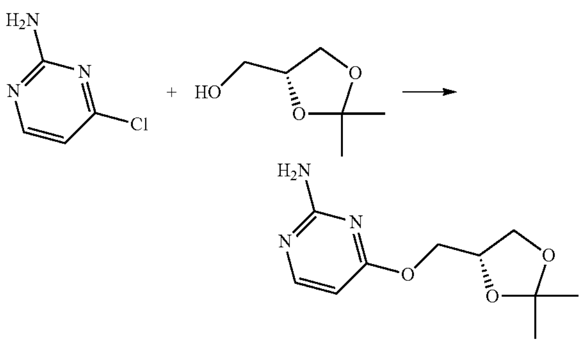
[0884]



[0885] To a solution of tetrahydro-2H-pyran-4-ol (25 g, 245 mmol) in Tetrahydrofuran (THF) (500 mL) stirred under nitrogen, was added NaH (22.52 g, 563 mmol) at 27° C. in 10 mints, after 1 hr was added 2-chloropyrimidin-4-amine (22.20 g, 171 mmol) at 27° C. The reaction mixture was stirred at 85° C. for 36 hr. The progress of reaction was monitored by TLC. TLC indicated a polar spot along with SM. Reaction mass was poured in 200 ml ice cool water, extracted with EtOAc (3×200 ml), combined organic layers dried over Na_2SO_4 filtered and concentrated under reduced pressure and was purified using column chromatography with (60-120) silica mesh SM was eluted at 50% EtOAc in Hexane and required compound was eluted at 90% EtOAc in Hexane, combined compound fractions concentrated to get 2-((tetrahydro-2H-pyran-4-yl)oxy)pyrimidin-4-amine (9 g, 39.9 mmol, 16.31% yield), LCMS (m/z): 196.00 $[M+H]^+$.

Synthesis of (R)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-amine

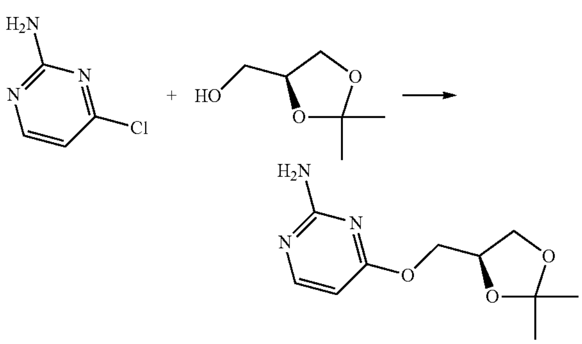
[0886]



[0887] To a suspension of NaH (9.08 g, 378 mmol) in THF (150 mL) was added dropwise a solution of (R)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (20 g, 151 mmol) in THF (250 mL) under Nitrogen at 0° C. The resulting suspension was stirred at rt for 1 h. 4-chloropyrimidin-2-amine (15.68 g, 121 mmol) was added to the reaction mixture portion wise at rt and the resulting suspension was heated to 90° C. for 48 hr. After the completion of reaction (monitored by TLC, starting completely consumed and new spot observed at polar), reaction mixture was poured into ice water (250 mL) and aqueous layer was extracted with EtOAc (2×300 mL). Combined organics dried over Na_2SO_4, filtered and concentrated under reduced pressure to get pale yellow liquid (crude). Obtained crude material was purified by column (100-200 silica gel) by using 0-50% EtOAc-petether to get (R)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-amine (13 g, 57.0 mmol, 37.7% yield) as pale yellow solid, LCMS (m/z): 226.20 $[M+H]^+$.

Synthesis of (S)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-amine

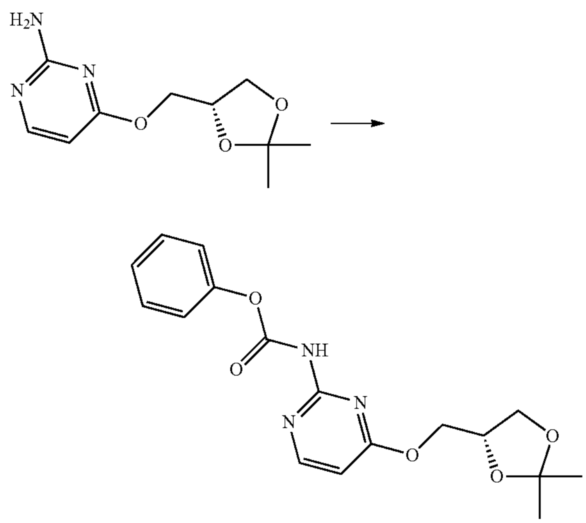
[0888]



[0889] To a suspension of NaH (8.25 g, 189 mmol) in 1,4-Dioxane (200 mL) was added dropwise a solution of (S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (10 g, 76 mmol) in 1,4-Dioxane (50 mL) under Nitrogen at 0° C. The resulting suspension was stirred at rt for 1 h. 4-chloropyrimidin-2-amine (7.84 g, 60.5 mmol) was added to the reaction mixture portion wise at rt and the resulting suspension was heated to 90° C. for 48 hr. The reaction mixture was cooled to 28° C. and was partitioned between water (200 mL) and EtOAc (200 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude (TLC eluent: Neat ethyl acetate R_f 0.3; UV active). The crude compound was purified by column chromatography (100-200 mesh silica gel, eluted at 60% Ethyl acetate in hexane) to afford (S)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-amine (8.0 g, 35.4 mmol, 46.8% yield) as pale yellow solid LCMS (m/z) 226.30 $(M+H)^+$.

Synthesis of (R)-phenyl (4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)carbamate

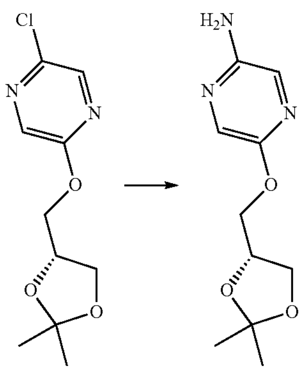
[0890]



[0891] To a solution of phenyl carbonochloridate (2.71 g, 17.31 mmol) and pyridine (1.724 mL, 21.31 mmol) in Dichloromethane (DCM) (50 mL) stirred under nitrogen at room temp was added (R)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-amine (3.0 g, 13.32 mmol). The reaction mixture was stirred at 28° C. for 2 hr. The Reaction was monitored by TLC. The reaction mixture was diluted with water (75 mL) extracted with DCM (2×75 mL). The organic layer was separated and dried out with Na_2SO_4, filtered and concentrated under high vacuum to get crude product. To the Crude product the mixture of Diethyl ether and pentane (3:1) was added and stirred for 10 min and filtered to afford a compound of (R)-phenyl (4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)carbamate (2.5 g, 2.375 mmol, 17.83% yield), LCMS (m/z): 346.21 $[M+H]^+$.

Synthesis of (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl) methoxy)pyrazin-2-amine

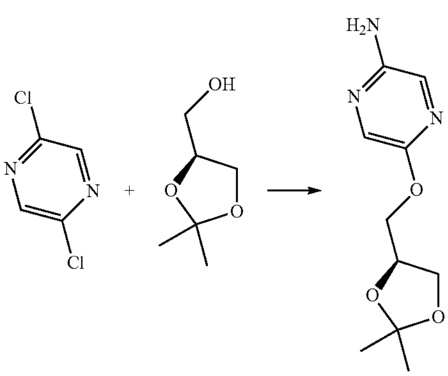
[0892]



[0893] To a stirred solution of (R)-2-chloro-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazine (12 g, 49.0 mmol) in Tetrahydrofuran (THF) (20 mL) was added ammonium hydroxide (300 mL, 1926 mmol) and copper(II) sulfate (1.566 g, 9.81 mmol) in a sealed tube. Reaction mixture was stirred at 120° C. for 18 hr. Progress of the reaction was monitored by TLC, TLC indicates formation of polar spot along with un-reacted SM. Reaction mixture was diluted with water (300 mL), extracted with EtOAc (3×200 mL), organic layers were combined and washed with water (100 mL), brine solution (100 mL), organic layer dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl) methoxy)pyrazin-2-amine (10 g, 3.97 mmol, 8.09% yield) as a yellow oily crude compound, LCMS (m/z): 226.13 $(M+H)^+$.

Synthesis of (S)-2-chloro-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazine

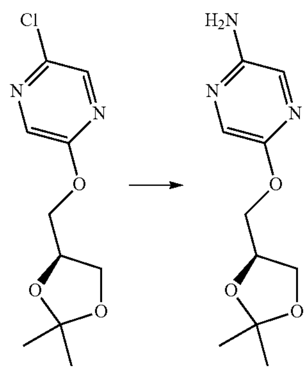
[0894]



[0895] To a suspension of (S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (8.87 g, 67.1 mmol), in N,N-Dimethylformamide (DMF) (50 mL) stirred under nitrogen at 0° C. was added cesium carbonate (32.8 g, 101 mmol), the resulting reaction mixture was stirred at 0° C. for 1 hr. To this added 2,5-dichloropyrazine (10 g, 67.1 mmol). The resulting reaction mixture was stirred at 100° C. for 6 hr. Progress of the reaction was monitored by TLC. TLC indicated starting material was consumed to form new polar spot with 0.3 Rf. The reaction mass was cooled to rt, added water (100 mL) and extracted with Ethyl acetate (100 mL). The organic layer was washed with water (100 mL×2). The organic layer was dried over Na_2SO_4 and filtered and concentrated to get crude as light brown liquid. The crude product was added to a silica gel (60-120) column and was eluted with Hex/EtOAc. Collected fractions: 30% EtOAc in Hexane the product was eluted. Concentrated the product fractions to afford (S)-2-chloro-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazine (12 g, 47.7 mmol, 71.0% yield) as light brown liquid, LCMS (m/z): 244.90 $[M+H]^+$.

Synthesis of (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl) methoxy)pyrazin-2-amine

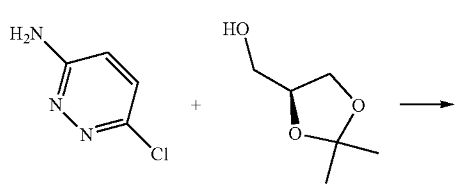
[0896]



[0897] To a solution of (S)-2-chloro-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazine (10 g, 40.9 mmol), in Tetrahydrofuran (THF) (10 mL) stirred at room temp was added ammonium hydroxide (63.7 mL, 409 mmol) and copper(II) sulfate (3.26 g, 20.44 mmol) at rt. The reaction mixture was stirred in sealed tube at 130° C. for 2 days. Progress of the reaction was monitored by TLC. TLC indicated starting material was consumed. Cooled the reaction mass to rt, diluted with water (100 mL), Extracted with ethyl acetate (250 mL×2). The organic layer was dried over Na_2SO_4, filtered and concentrated to get crude compound as brown sticky compound. The crude product was added to a silica gel column and was eluted with DCM/EtOAc. Collected fractions: 50% EtOAc in petether the product was eluted. Concentrated the product fractions to afford (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine (2 g, 8.77 mmol, 21.46% yield)(N35119-51-A2) as light brown solid. NMR: in CDCl3 consistent with, LCMS (m/z): 226.09 $[M+H]^+$.

Synthesis of (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl) methoxy)pyridazin-3-amine

[0898]



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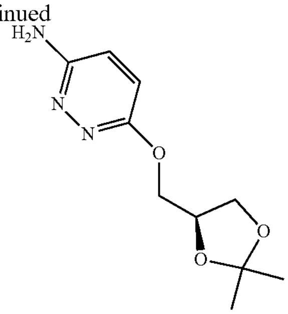
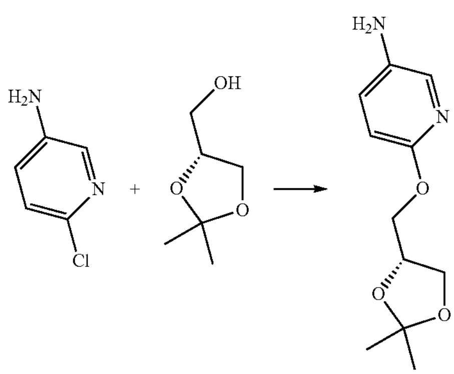


[0899] To a suspension of KOtBu (12.99 g, 116 mmol) in 1,4-Dioxane (300 mL) was added dropwise a solution of (S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (4.08 g, 30.9 mmol) in 20 ml under Nitrogen at 0° C. The resulting suspension was stirred at rt for 1 h. 6-chloropyridazin-3-amine (5 g, 38.6 mmol) was added to the reaction mixture portion wise at rt and the resulting suspension was heated to 110° C. for 16 hr. After the completion of reaction (monitored by TLC, it shows little bit of starting and new spot observed at polar), reaction mixture was poured into ice water (50 mL) and aqueous layer was extracted with EtOAc (2×50 mL). Combined organics dried over Na_2SO_4. LCMS (m/z): 226.19 $[M+H]^+$.

Synthesis of (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine

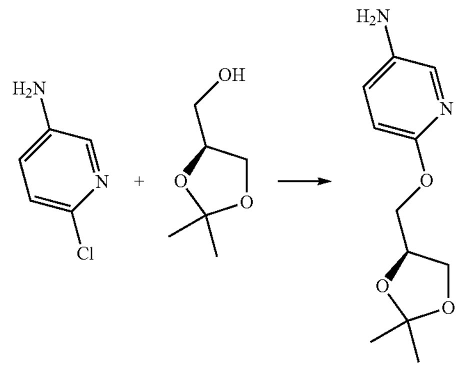
[0900]



(R)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (27.8 g, 210 mmol) was added to a stirred solution of KOtBu (45.8 g, 408 mmol) in NMP (200 mL) at 0° C. then stirred at RT for 1 h and cooled to 0° C., 6-chloropyridin-3-amine (15 g, 117 mmol) was added and heated to 110° C. for 144 h. The reaction mixture cooled to RT and partitioned between water (500 mL×2) and EtOAc (200 mL×4). Organic layers were separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude and purified by column chromatography (using 100-200 silica gel, column eluted at 50% ethyl acetate in hexane) to afford the (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine (8 g, 35.1 mmol, 30.1% yield) as brown oil, LCMS (m/z): 225.16 $[M+H]^+$.

Synthesis of (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine

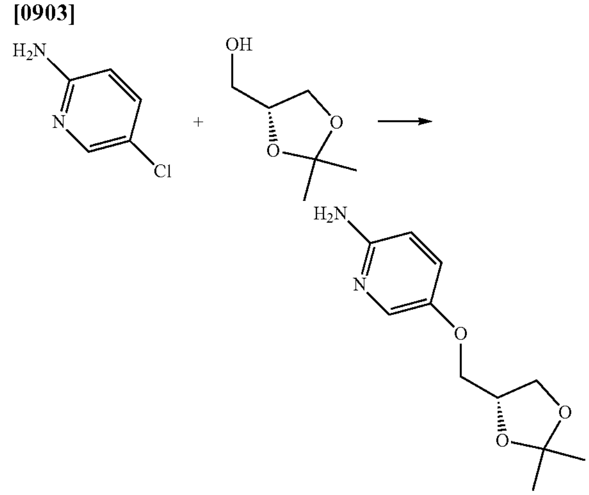
[0901]



[0902] (S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (18.50 g, 140 mmol) was added to a stirred solution of KOtBu (30.5 g, 272 mmol) in NMP (600 mL) at 0° C. then stirred at RT for 1 h and cooled to 0° C., 6-chloropyridin-3-amine (10.0 g, 78 mmol) was added and heated to 110° C. for 88 h. The reaction mixture cooled to RT and partitioned between water (50 mL×2) and EtOAc (100 mL×2). Organic layers were separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude compound as a gum. (TLC: Eluent: 100% ethyl acetate, R_f 0.5; UV active:). The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh) eluted with 50% EtOAc in hexane to afford (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine (10.0 g, 41.7 mmol, 53.6% yield) as a dark sticky mass, LCMS (m/z) 225.0 $(M+H)^+$.

Synthesis of (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine

[0903]

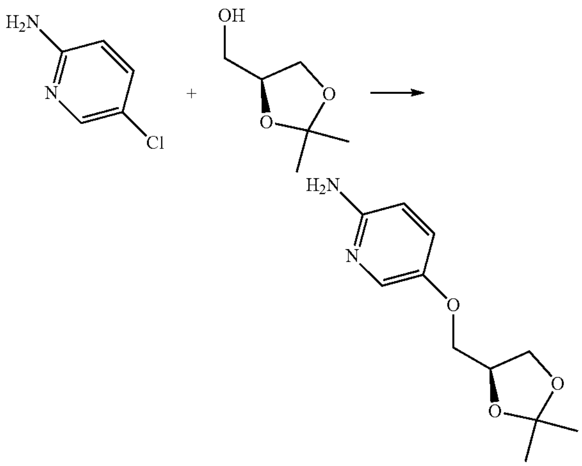


[0904] (R)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (30.7 g, 232 mmol) was added to a stirred solution of KOtBu (70.1 g, 624 mmol) in NMP (800 mL) at 0° C. then stirred at RT for 1 h and cooled to 0° C. then 5-fluoropyridin-2-amine (20 g, 178 mmol) was added and heated to 110° C. for 114 h. The reaction mixture cooled to RT and partitioned between water (500 mL×2) and EtOAc (500 mL×4). Organic layers were separated and was dried over anhydrous

Na_2SO_4, filtered and filtrate was evaporated to get crude compound, then it was purified by column chromatography (using 100-200 silica gel, column eluted at 80% ethyl acetate in hexane) to afford the (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (10 g, 40.1 mmol, 22.50% yield) as a brown oil, LCMS: 225.0 (M+H).

Synthesis of (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl) methoxy)pyridin-2-amine

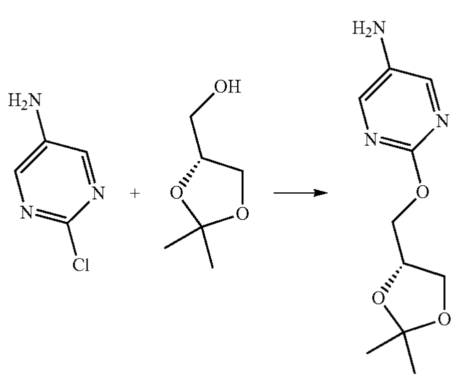
[0905]



[0906] NaH (12.84 g, 268 mmol) was added to a stirred solution of (S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (31.8 g, 241 mmol) in Dimethyl Sulfoxide (DMSO) (100 mL) at 0° C. then stirred at RT for 1 h and cooled to 0° C., 5-fluoropyridin-2-amine (15.0 g, 134 mmol) was added and heated to 110° C. for 60 h. The reaction mixture cooled to RT and partitioned between water (50 mL) and EtOAc (100 mL). Organic layers were separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude compound (TLC: Eluent: 100% ethyl acetate, R_f 0.5; UV active), The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh) eluted with 50% EtOAc in hexane to afford (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (7.2 g, 32.1 mmol, 23.99% yield) as a pale yellow sticky, LCMS (m/z): 225.1 $(M+H)^+$.

Synthesis of (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl) methoxy)pyrimidin-5-amine

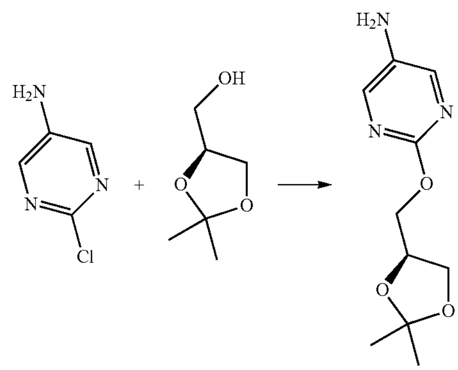
[0907]



[0908] Tetrahydrofuran (75 mL) was added to NaH (5.56 g, 232 mmol) at 0° C., (R)-(2,2-dimethyl-1,3-dioxolan-4-yl) methanol (12.46 mL, 100 mmol) in Tetrahydrofuran (50 mL was added to the reaction mixture at 0° C., and the reaction mixture was stirred for 1 h at 28° C. 2-chloropyrimidin-5-amine (10 g, 77 mmol) in Tetrahydrofuran (25 mL) was added and stirred for 16 hr at 70° C. The reaction mixture was quenched with cold water (30 mL) and extracted with ethyl acetate (3×80 mL). The organic layer was washed with water (2×50 mL) and saturated brine solution (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude compound was purified by column chromatography (Neutral alumina) product was eluted with 40-45% Ethyl acetate in Hexane to afford (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-amine (6.5 g, 28.3 mmol, 36.6% yield) as pale yellow solid, LCMS (m/z): 226.0 $[M+H]^+$.

Synthesis of (S)-2-((2,2-dimethyl-1,3-dioxolan-4-yl) methoxy)pyrimidin-5-amine

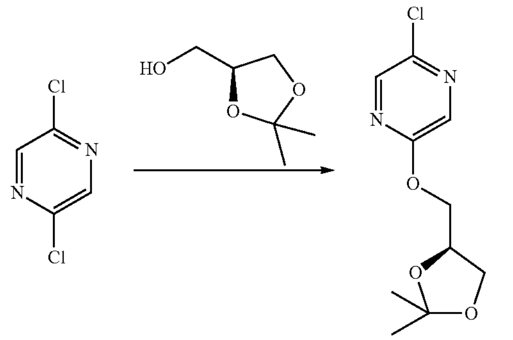
[0909]



[0910] To a suspension of NaH (6.17 g, 154 mmol) in THF (100 ml) was added (S)-(2,2-dimethyl-1,3-dioxolan-4-yl) methanol (13.26 g, 100 mmol) in THF (50 ml) was added to the reaction mixture at 0° C., and the reaction mixture was stirred for 1 h at 25° C. to this 2-chloropyrimidin-5-amine (10 g, 77 mmol) in THF (50 ml) and was added at 0° C. and slowly heated to 80° C. and stirred for 16 hr at 80° C. After completion of the reaction, reaction mixture was quenched with the ammonium chloride (10 ml) and extracted with the ethyl acetate (3×20 ml). The organic layer was separated and washed with the brine and dried over Na_2SO_4, filtered it and concentrated under reduced pressure to get the crude. This crude was triturated with the diethyl ether to get (S)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-amine (5.0 g, 19.77 mmol, 25.6% yield) as a brown solid, LCMS (m/z): 226.1 $[M+H]^+$.

Synthesis of (S)-2-chloro-5-((2,2-dimethyl-1,3-dioxolan-4-yl) methyl) pyrazine

[0911]

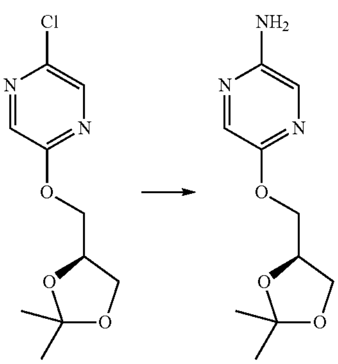


[0912] To a stirred solution of cesium carbonate (492 g, 1510 mmol) in DMF (1000 mL) was added (S)-(2,2-dimethyl-1,3-dioxolan-4-yl) methanol (133 g, 1007 mmol) at 0° C. The resulting reaction mixture was stirred at room temperature for 30 min. Then a solution of 2,5-dichloropyrazine (150 g, 1007 mmol) in DMF (500 mL) was added at 0° C. and the resulted reaction mixture was stirred at 100° C. for 4 h. (TLC System: 20% Ethyl acetate in Petether, R_f: 0.5, UV active). The reaction mixture was diluted with ice cold water (500 mL), extracted with EtOAc (3×300 mL). The combined organic layer was washed with water (2×200 mL) and brine solution (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain crude compound. The crude compound was purified by flash column chromatography (silica gel: 100-200 mesh, eluent: 10% EtOAc in Hexane) to afford the desired product (S)-2-chloro-5-((2,2-dimethyl-1,3-dioxolan-4-yl) methoxy) pyrazine (200 g, 768 mmol, 76% yield) as a yellow liquid.

[0913] LCMS (m/z): 245.1 $[M+H]^+$.

Synthesis of (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl) methoxy)pyrazin-2-amine

[0914]

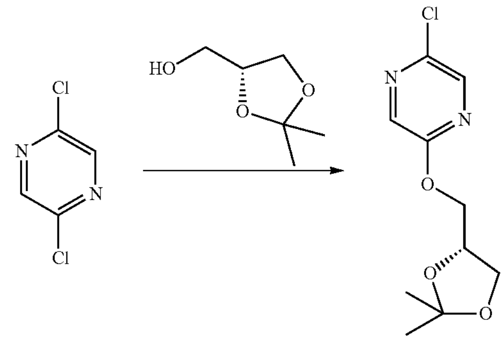


[0915] To a stirred solution of (S)-2-chloro-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazine (120 g, 490 mmol) in THF (30 mL) were added ammonium hydroxide (1000 mL, 6420 mmol) and copper(II) sulfate (15.66 g, 98 mmol) in a sealed tube and the resulted reaction mixture was stirred at 120° C. for 48 h (TLC System: 50% Ethyl acetate in Petether, R_f 0.4, UV active). The reaction mixture was diluted with water (300 mL), extracted with EtOAc (3×500 mL). The combined organic layer was washed with water (200 mL) and brine solution (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get crude compound. The crude was purified by flash column chromatography (using 100-200 mesh silicagel and eluted the compound with 40% EtOAc in Hexane) to afford the desired product (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl) methoxy)pyrazin-2-amine (65 g, 280 mmol, 57.2% yield) as a yellow crystal solid.

[0916] LCMS (m/z): 226.13 $[M+H]^+$.

Synthesis of (R)-2-chloro-5-((2,2-dimethyl-1,3-dioxolan-4-yl) methoxy)pyrazine

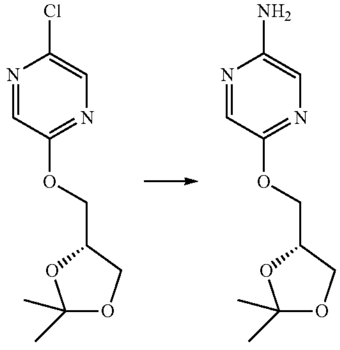
[0917]



[0918] To a stirred suspension of cesium carbonate (32.8 g, 101 mmol) in DMF (100 mL) was added (R)-(2,2-dimethyl-1,3-dioxolan-4-yl) methanol (8.87 g, 67.1 mmol) at 0° C. and stirred at room temperature for 30 min. Then 2,5-dichloropyrazine (10 g, 67.1 mmol) was added and the resulting reaction mixture was stirred at 100° C. for 4 h. (TLC System: 20% Ethyl acetate in Hexane, R 0.5, UV active). The reaction mixture was diluted with ice cold water (200 mL), extracted with EtOAc (3×100 mL). The combined organic layer was washed with water (2×50 mL) and brine solution (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford (R)-2-chloro-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazine (12 g, 43.8 mmol, 65.3% yield) as a yellow oily compound. LCMS (m/z): 244.99 $[M+H]^+$.

Synthesis of (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl) methoxy) pyrazin-2-amine

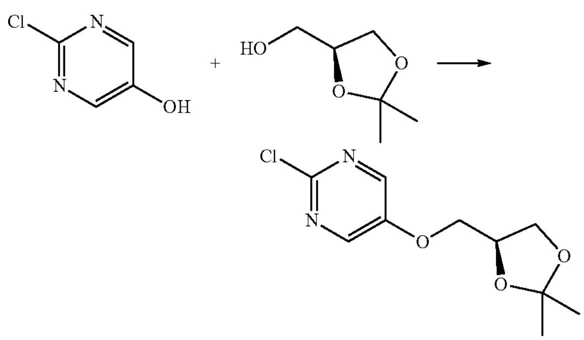
[0919]



[0920] To a stirred solution of (R)-2-chloro-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazine (8 g, 32.7 mmol) in Tetrahydrofuran (10 mL) was added ammonium hydroxide (400 mL, 2568 mmol) and copper(II) sulfate (1.044 g, 6.54 mmol) in a sealed tube and the reaction mixture was stirred at 120° C. for 48 h. (TLC System: 50% Ethyl acetate in Hexane, R_1 0.4, UV active). The reaction mixture was diluted with water (200 mL), extracted with EtOAc (3×50 mL). The combined organic layer was washed with water (50 mL), brine solution (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get crude compound. The crude was purified by flash column chromatography (using 100-200 mesh silicagel and eluted the compound with 40% EtOAc in Hexane), pure fraction were collected and concentrated under reduced pressure to afford (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine (2 g, 8.65 mmol, 26.4% yield) as a yellow crystal solid. LCMS (m/z): 226.10 $[M+H]^+$.

Synthesis of (S)-2-chloro-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidine

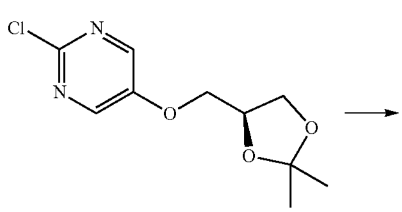
[0921]



[0922] To a stirred solution of 2-chloropyrimidin-5-ol (13 g, 100 mmol) in THF (100 mL) at 0° C. was added (S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (13.16 g, 100 mmol), triphenylphosphine (32.7 g, 124 mmol) followed by DEAD (19.71 mL, 124 mmol) and reaction was stirred at RT for 4 h. (TLC eluting system: 30% EtOAc in pet ether; R_f-0.5; UV active). The reaction mixture was quenched with water (50 mL) and extracted into EtOAc (2×75 mL). Organic layer was separated and dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude product. The crude was purified by chromatography (Silicagel, eluent: 20% EtOAc in hexane) to afford (S)-2-chloro-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidine (20 g, 79 mmol, 79% yield) as an off white solid. LCMS (m/z): 245.10; $[M+H]^+$.

Synthesis of (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-amine

[0923]



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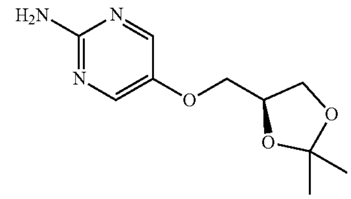
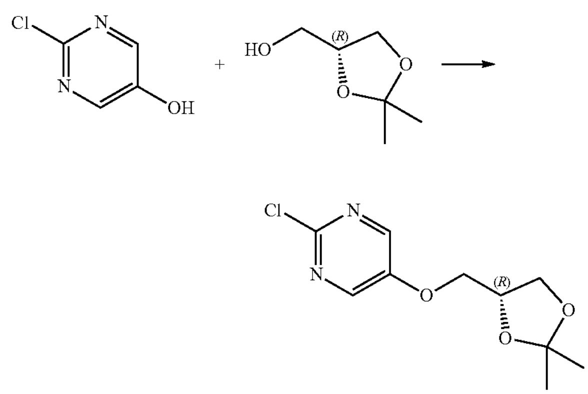


[0924] A mixture of (S)-2-chloro-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidine (10 g, 40.9 mmol) and aq. ammonia (66.3 ml, 1226 mmol) in a sealed tube was heated at 120° C. for 24 h. (TLC eluting system: 100% EtOAc; R_f-0.2; UV active). The reaction mixture was cooled to RT, quenched with water (50 mL) and extracted into EtOAc (2×75 mL). Organic layer was separated, dried over anhydrous sodiumsulphate, filtered and filtrate was evaporated to give crude product as yellow solid. The crude compound was triturated with n-pentane (50 mL) to afford (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-amine (6.6 g, 28.6 mmol, 70.0% yield) as an off white solid.

[0925] LCMS (m/z): 226.17; $[M+H]^+$.

Synthesis of (R)-2-chloro-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidine

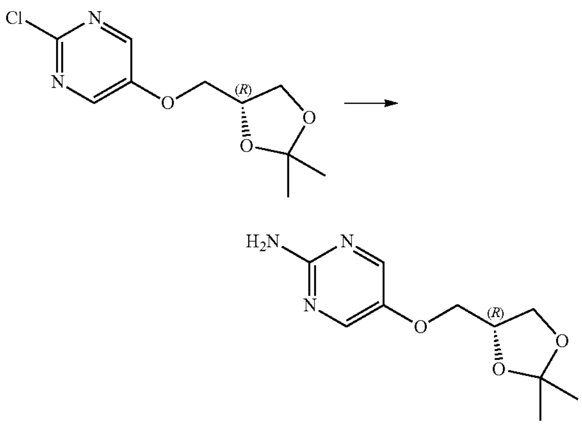
[0926]



[0927] To a stirred solution of 2-chloropyrimidin-5-ol (20 g, 153 mmol) in THF (100 mL) at 0° C. was added (R)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (24.30 g, 184 mmol), triphenylphosphine (50.2 g, 192 mmol) followed by DEAD (30.3 mL, 192 mmol) and the reaction was stirred at RT for 12 h. (TLC eluting system: 70% EtOAc in pet ether; R_f-0.5; UV active). The reaction mixture was quenched with water (100 mL) and extracted into EtOAc (200 mL). Organic layer was separated and dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude product. The crude was purified by chromatography (Silicagel, eluent: 35% EtOAc in hexane) to afford (R)-2-chloro-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidine (23 g, 91 mmol, 59.5% yield) as a white solid. LCMS (m/z): 245.06; $[M+H]^+$.

Synthesis of (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl) methoxy)pyrimidin-2-amine

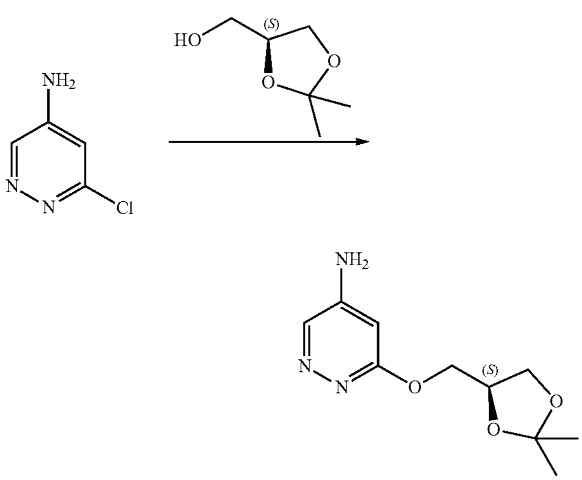
[0928]



[0929] A mixture of (R)-2-chloro-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidine (5 g, 20.44 mmol) and aq. ammonia (50 ml, 924 mmol) in a sealed tube was heated 120° C. for 48 h. (TLC eluting system: 100% EtOAc; R_f-0.2; UV active). The reaction mixture was cooled to RT, quenched with water (50 mL) and extracted into DCM (2×75 mL). Organic layer was separated, dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-amine (2.7 g, 11.5 mmol, 57.5% yield) as a pale yellow solid. LCMS (m/z): 226.02; $[M+H]^+$.

Synthesis of (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl) methoxy)pyridazin-4-amine

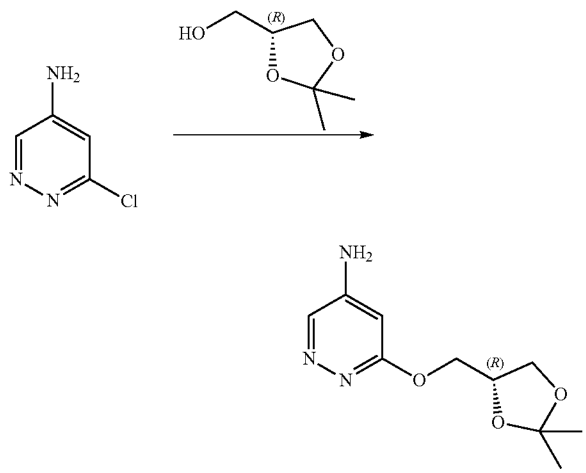
[0930]



[0931] To a stirred suspension of potassium tert-butoxide (3.90 g, 34.7 mmol) in 1,4-Dioxane (50 mL) was added a mixture of (S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (2.75 g, 20.84 mmol) at 0° C. and the reaction mixture was stirred at 25° C. for 1 h. under Nitrogen atmosphere, then 6-chloropyridazin-4-amine (1.5 g, 11.58 mmol) was added to the reaction mixture and the resulted reaction mixture was stirred at 110° C. for 16 h. (TLC System: Neat Ethyl acetate, Rf: 0.3). The reaction mixture was poured in to ice cold water (40 ml) and extracted with EtOAc (2×80 mL). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get crude compound. The crude material was purified by flash column chromatography (Neutral alumina, Eluent: 65% Ethyl acetate in Pet ether) to afford the desired product (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridazin-4-amine (1.0 g, 4.28 mmol, 37.0% yield) as a white solid. LCMS (m/z): 226.20 $[M+H]^+$.

Synthesis of (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl) methoxy)pyridazin-4-amine

[0932]



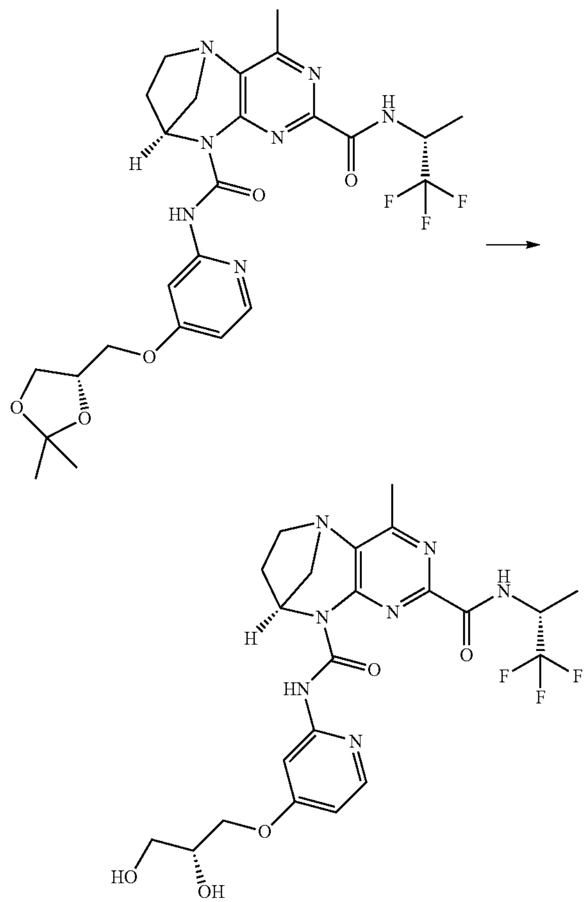
[0933] To a stirred suspension of potassium tert-butoxide (7.80 g, 69.5 mmol) in 1,4-Dioxane (50 mL) was added (R)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (5.20 mL, 41.7 mmol) at 0° C. and the reaction mixture was stirred at 25° C. for 1 h. under Nitrogen atmosphere. Then 6-chloropyridazin-4-amine (3 g, 23.16 mmol) was added to the reaction mixture and the resulting reaction mixture was stirred at 110° C. for 16 h. (TLC System Ethyl acetate, Rf: 0.3). The reaction mixture was poured into ice cold water (40 ml) and extracted with EtOAc (2×80 mL). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get crude compound. The crude product was purified by flash column chromatography (Neutral alumina, Eluent: 65% Ethyl acetate in Pet ether) to afford the desired product (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridazin-4-amine (2.2 g, 9.66 mmol, 41.7% yield) as an off white solid. LCMS (m/z): 226.05 $[M+H]^+$, Rt=1.00 min.

Compound Examples

Example 1

Synthesis of (8S)—N9-(4-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-4-methyl-N2-((R)-1,1,1-trifluoropropan-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2,9(6H)-dicarboxamide

[0934]

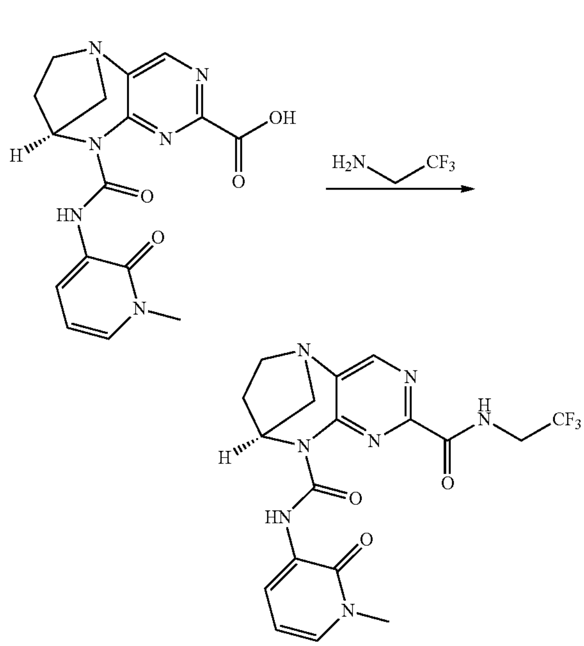


[0935] To a stirred solution of (8S)—N9-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-4-methyl-N2-((R)-1,1,1-trifluoropropan-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2,9(6H)-dicarboxamide (350 mg, 0.619 mmol) in Methanol (5 mL) was added aqueous HCl (1.5 mL, 18.00 mmol) at 0° C. and the reaction mixture was stirred at 28° C. for 2 h. (TLC eluent:5% MeOH in DCM, Rf: 0.3) then evaporated the solvent and the resulted residue was neutralized with $NaHCO_3$ solution, filtered the obtain solid and triturated with pentane (20 mL), dried under reduced pressure to afford the desired product (8S)—N9-(4-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-4-methyl-N2-((R)-1,1,1-trifluoropropan-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2,9(6H)-dicarboxamide (117 mg, 0.219 mmol, 35.4% yield) as an off white solid. LCMS (m/z): 526.26 $[M+H]^+$, Rt=1.55 min.

[0936] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.99 (br s, 1H), 8.19 (d, J=5.70 Hz, 1H), 8.03 (d, J=9.87 Hz, 1H), 7.70 (d, J=1.97 Hz, 1H), 6.60 (dd, J=5.59, 2.30 Hz, 1H), 5.61 (dd, J=5.70, 2.41 Hz, 1H), 5.05-4.94 (m, 1H), 4.19-4.10 (m, 3H), 3.88-3.80 (m, 1H), 3.78-3.71 (m, 1H), 3.23-3.13 (m, 2H), 3.10-2.99 (m, 2H), 2.67 (s, 4H), 2.35 (td, J=14.14, 5.70 Hz, 1H), 2.12-2.00 (m, 2H), 1.50 (d, J=7.02 Hz, 3H).

Example 2 Synthesis of (8S)—N9-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-N2-(2,2,2-trifluoroethyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2,9(6H)-dicarboxamide

[0937]



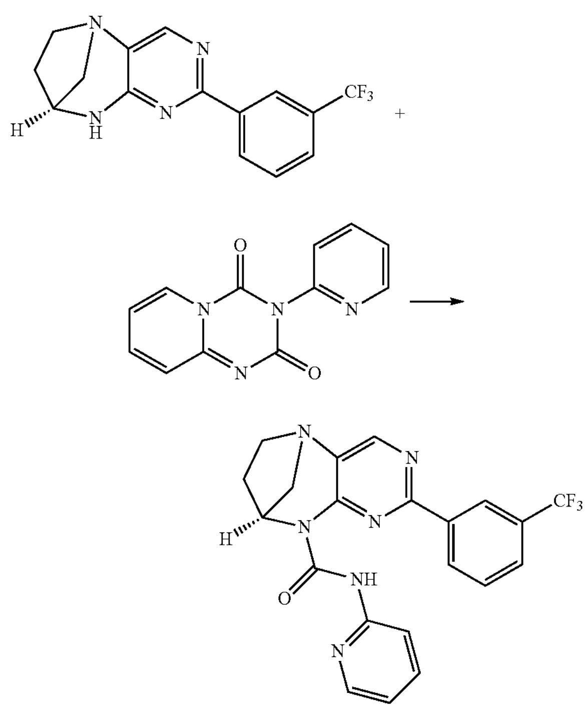
[0938] To a stirred solution of (8S)-9-((1-methyl-2-oxo-1,2-dihydropyridin-3-yl)carbamoyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylic acid (200 mg, 0.561 mmol) in DMF (2 mL) were added DIPEA (0.490 mL, 2.81 mmol), HATU (46.8 mg, 0.123 mmol) and 2,2,2-trifluoroethanamine (55.6 mg, 0.561 mmol) at RT in one charge. The reaction mixture was stirred at RT for 16 h. (TLC eluent: 5% MeOH in DCM: R_f-0.5; UV active). Reaction mixture was diluted with cold water and extracted with ethyl acetate (2×50 ml). The combined organic layer was washed with brine solution (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get crude product. The crude product was purified by combi flash chromatography (using silica gel column 12 g, elutent: 5% methanol in DCM) to afford the desired compound (8S)—N9-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-N2-(2,2,2-trifluoroethyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2,9(6H)-dicarboxamide (53 mg, 0.120 mmol, 21.40% yield) as an off white solid. LCMS (m/z): 438.05 $[M+H]^+$, R_t=1.81 min.

[0939] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.04 (s, 1H), 10.10 (br s, 1H), 8.63 (s, 1H), 8.38 (dd, J=7.67, 1.75 Hz, 1H), 7.25-6.99 (m, 1H), 6.34 (t, J=7.13 Hz, 1H), 5.69 (d, J=5.92 Hz, 1H), 4.37-4.10 (m, 2H), 3.64 (s, 3H), 3.35-3.13 (m, 2H), 3.06 (s, 2H), 2.44-2.22 (m, 1H), 2.21-1.97 (m, 1H).

Example 3

Synthesis of (8S)—N-(pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methano pyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0940]



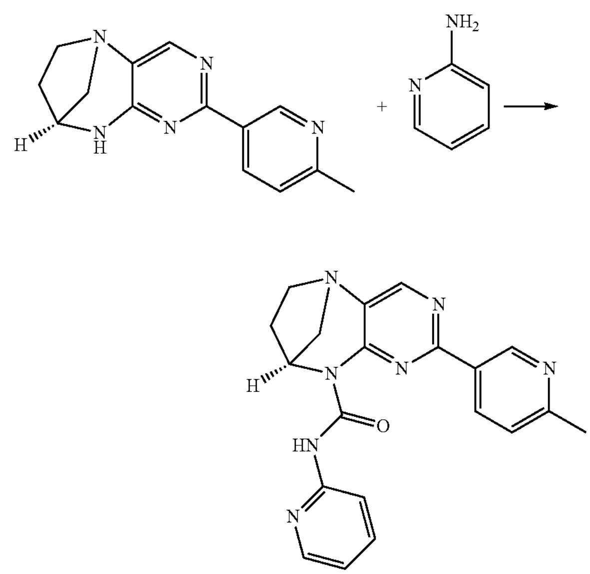
[0941] To a solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (550 mg, 1.796 mmol), 3-(pyridin-2-yl)-2H-pyrido[1,2-a][1,3,5]triazine-2,4(3H)-dione (863 mg, 3.59 mmol) in THF (15 mL) was added sodium hydride (359 mg, 8.98 mmol) at 0° C. The reaction mixture was heated to 60° C. for 16 h. Allowed to room temperature and the reaction mixture was poured in to cold water (100 mL) and extracted with ethyl acetate (2×200 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure to obtain the crude product. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, using gradient mixture of 70 to 100% ethyl acetate in pet ether) to obtain 400 mg of semi pure compound with 91% purity, it was triturated with diethyl ether to afford (8S)—N-(pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methano pyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (260 mg, 33.6% yield) (TLC: 100% ethyl acetate, R_f=0.5), LCMS (m/z): 472.24 $[M+H]^+$.

[0942] ^1H NMR (400 MHz, DMSO-d6): δ ppm 13.15 (s, 1H), 8.82 (d, J=7.77 Hz, 2H), 8.65-8.46 (m, 1H), 8.45-8.28 (m, 1H), 8.11 (dt, J=8.33, 0.88 Hz, 1H), 7.98-7.77 (m, 3H), 7.16 (ddd, J=7.34, 4.82, 0.99 Hz, 1H), 5.48 (dd, J=5.92, 3.07 Hz, 1H), 3.28-3.20 (m, 1H), 3.16-2.99 (m, 3H), 2.35-2.16 (m, 1H), 2.13-1.97 (m, 1H).

Example 4

Synthesis of (8S)-2-(6-methylpyridin-3-yl)-N-(pyridin-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0943]



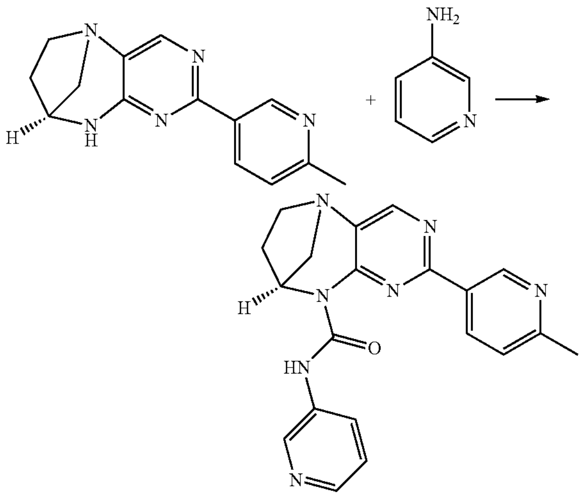
[0944] To a solution of (8S)-2-(6-methylpyridin-3-yl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (300 mg, 1.184 mmol) in THF (15 ml) was added triphosgene (176 mg, 0.592 mmol) at 0° C. and stirred at RT for 1 h. Then pyridin-2-amine (167 mg, 1.777 mmol) and triethylamine (0.825 mL, 5.92 mmol) were added sequentially at RT and heated the reaction mixture at 75° C. for 16 h in sealed tube. The reaction mixture was poured in saturated $NaHCO_3$ solution (50 mL) and extracted with Ethyl acetate (3×50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, using gradient mixture of 1% MeOH in CH_2Cl_2 as eluent) to afford (8S)-2-(6-methylpyridin-3-yl)-N-(pyridin-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (150 mg, 0.402 mmol, 42% yield) as pale yellow solid (TLC: 5% MeOH in CH_2Cl_2), LCMS (m/z): 374.21 $[M+H]^+$.

[0945] ^1H NMR (400 MHz, $CDCl_3$): δ ppm 13.20 (s, 1H), 9.62 (d, J=2.41 Hz, 1H) 8.83 (dd, J=8.11, 2.41 Hz, 1H) 8.45 (s, 1H) 8.42 (d, J=6.5 Hz 1H) 8.15 (d, J=8.33 Hz, 1H) 7.72 (td, J=7.89, 1.97 Hz, 1H) 7.33 (d, J=8.11 Hz, 1H) 7.04 (ddd, J=7.34, 4.93, 1.10 Hz, 1H) 5.67 (dd, J=5.92, 3.07 Hz, 1H) 3.34-3.19 (m, 2H) 3.18-2.98 (m, 2H) 2.66 (s, 3H) 2.41-2.25 (m, 1H) 2.23-2.00 (m, 1H).

Example 5

Synthesis of (8S)-2-(6-methylpyridin-3-yl)-N-(pyridin-3-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0946]



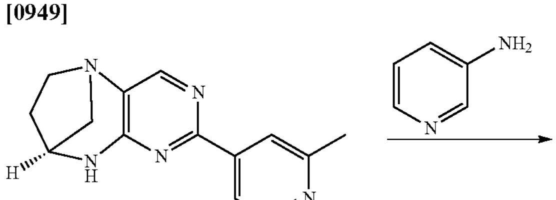
[0947] To a solution of (8S)-2-(6-methylpyridin-3-yl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (300 mg, 1.184 mmol) in THF (15 ml) was added triphosgene (176 mg, 0.592 mmol) at 0° C. and stirred to RT for 1 h. Then pyridin-3-amine (167 mg, 1.777 mmol) and triethylamine (0.825 mL, 5.92 mmol) were added sequentially at RT and heated the reaction mixture at 75° C. for 16 h. The reaction mixture was poured in saturated $NaHCO_3$ solution (50 mL) and extracted with ethyl acetate (3×50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product and it was purified by flash column chromatography (silica-gel: 100-200 mesh, using gradient mixture of 1% MeOH in DCM as eluent) to afford (8S)-2-(6-methylpyridin-3-yl)-N-(pyridin-3-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (160 mg, 0.428 mmol, 35.2% yield) as pale yellow solid (TLC: 5% MeOH in DCM, R_f=0.3), LCMS (m/z): 374.21 $[M+H]^+$.

[0948] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.52 (s, 1H), 9.32 (d, J=1.97 Hz, 1H), 8.72 (d, J=2.63 Hz, 1H), 8.50 (s, 1H), 8.45-8.28 (m, 2H), 8.01-8.28 (m, 1H), 7.27-7.36 (m, 2H), 5.67 (dd, J=6.03, 2.96 Hz, 1H), 3.18-3.35 (m, 2H), 3.00-3.18 (m, 2H), 2.66 (s, 3H), 2.26-2.44 (m, 1H), 2.12 (dt, J=14.25, 7.13 Hz, 1H).

Example 6

Synthesis of (8S)-2-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-7,8-dihydro-5,8-methano pyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0949]



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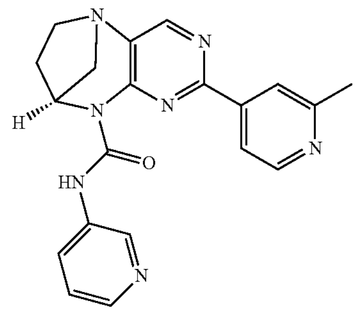


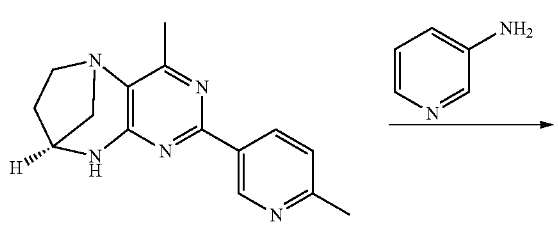
[0950] To a stirred solution of (8S)-2-(2-methylpyridin-4-yl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (300 mg, 1.184 mmol) in THF (15 ml, in sealed tube) was added triphosgene (176 mg, 0.592 mmol) at 0° C. and stirred to RT for 1 h. Then pyridin-3-amine (167 mg, 1.777 mmol) and triethylamine (0.825 mL, 5.92 mmol) were added sub sequentially and heated the reaction mixture at 75° C. for 16 h. The reaction mixture was poured in to saturated $NaHCO_3$ solution (50 mL) and extracted with ethyl acetate (2×50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluted with 1 to 2% methanol in dichloromethane) to afford (8S)-2-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)Carboxamide (85 mg, 0.216 m mol, 18.26% yield) as a yellow solid (TLC system: eluent: 5% Methanol in dichloromethane, R_f: 0.3), LCMS (m/z): 373.9 $[M+H]^+$.

[0951] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.48 (s, 1H), 8.73 (d, J=5.48 Hz, 2H), 8.56 (s, 1H), 8.40 (s, 1H), 8.18 (d, J=7.24 Hz, 1H), 8.00 (s, 1H), 7.92 (d, J=4.60 Hz, 1H), 7.35 (s, 1H), 5.69 (d, J=3.07 Hz, 1H), 3.33-3.24 (m, 2H), 3.17-3.08 (m, 2H), 2.74 (s, 3H), 2.40 (d, J=5.48 Hz, 1H), 2.14 (dd, J=14.14, 7.56 Hz, 1H).

Example 7

Synthesis of (8S)-4-methyl-2-(6-methylpyridin-3-yl)-N-(pyridin-3-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0952]



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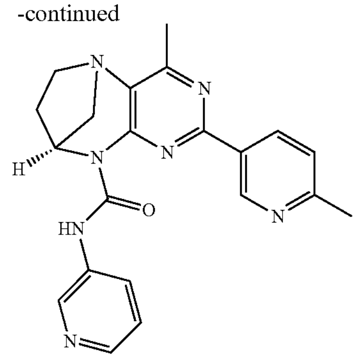


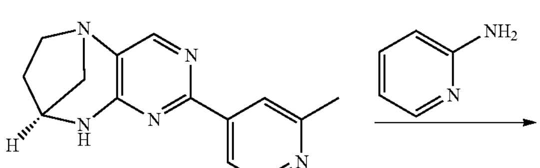
[0953] To a stirred solution of (8S)-4-methyl-2-(6-methylpyridin-3-yl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (200 mg, 0.748 mmol) in THF (10 mL) were added DIPEA (0.653 mL, 3.74 mmol) and triphosgene (133 mg, 0.449 mmol) at 0° C. and stirred the reaction mixture at RT for 30 min. Then pyridin-3-amine (106 mg, 1.122 mmol) was added. The reaction mixture was stirred at 60° C. for 16 h. The reaction mixture was allowed to RT and organic solvent was evaporated under reduced pressure to obtain crude residue. The crude residue was dissolved in CH_2Cl_2 (100 mL) and washed with water, brine and dried over anhydrous Na_2SO_4, filtered and concentrated to obtain the crude compound. The crude product was purified by flash chromatography (silica-gel: 100-200 mesh, eluted with 5% MeOH/CH_2Cl_2) to afford (8S)-4-methyl-2-(6-methylpyridin-3-yl)-N-(pyridin-3-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diaze pine-9(6H)-carboxamide (165 mg, 0.425 mmol, 56.8% yield) as a pale yellow solid (TLC: 10% MeOH/CH_2Cl_2, R_f: 0.4), LCMS (m/z): 388.32 $[M+H]^+$.

[0954] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.71 (s, 1H), 9.31 (d, J=2.19 Hz, 1H), 8.71 (d, J=2.41 Hz, 1H), 8.39-8.32 (m, 2H), 8.17-8.10 (m, 1H), 7.36-7.28 (m, 2H), 5.66 (dd, J=5.92, 2.19 Hz, 1H), 3.25-3.16 (m, 2H), 3.06 (d, J=2.85 Hz, 2H), 2.66 (d, J=8.11 Hz, 6H), 2.36 (ddt, J=14.14, 8.61, 5.73, 5.73 Hz, 1H), 2.15-2.03 (m, 1H).

Example 8

(8S)-2-(2-methylpyridin-4-yl)-N-(pyridin-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0955]



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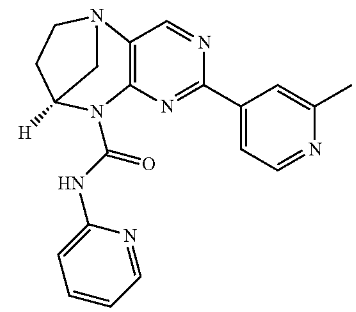


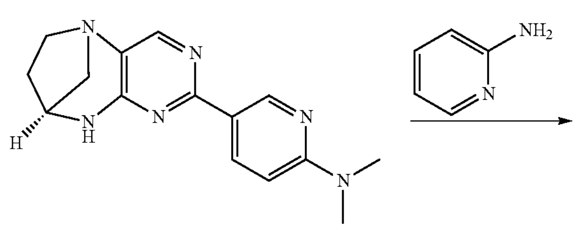
[0956] To a stirred solution of (8S)-2-(2-methylpyridin-4-yl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (200 mg, 0.790 mmol) in THF (15 ml, sealed tube) was added triphosgene (117 mg, 0.395 mmol) at 0° C. and stirred to RT for 1 h. Then pyridin-2-amine (111 mg, 1.184 mmol) and triethylamine (0.550 mL, 3.95 mmol) were added sub sequentially and heated the reaction mixture at 75° C. for 16 h. The reaction mixture was poured in to saturated $NaHCO_3$ solution (60 mL) and extracted with ethyl acetate (2×50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluted with 1 to 2% methanol in dichloromethane) to afford (8S)-2-(2-methylpyridin-4-yl)-N-(pyridin-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4] diazepine-9 (6H)-carboxamide (140 mg, 0.373 mmol, 47.2% yield) as a pale yellow solid (TLC: eluent: 5% Methanol in dichloromethane, R_f: 0.3), LCMS (m/z): 374.28 $[M+H]^+$.

[0957] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.24 (s, 1H), 8.68 (d, J=5.26 Hz, 1H), 8.53 (s, 1H), 8.48 (s, 1H), 8.43-8.39 (m, 1H), 8.23-8.17 (m, 2H), 7.77-7.70 (m, 1H), 7.07 (ddd, J=7.23, 4.82, 0.88 Hz, 1H), 5.68 (dd, J=5.92, 2.85 Hz, 1H), 3.34-3.21 (m, 2H), 3.16-3.05 (m, 2H), 2.75 (s, 3H), 2.44-2.33 (m, 1H), 2.12 (dt, J=14.25, 7.13 Hz, 1H).

Example 9

(8S)-2-(6-(dimethylamino)pyridin-3-yl)-N-(pyridin-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0958]



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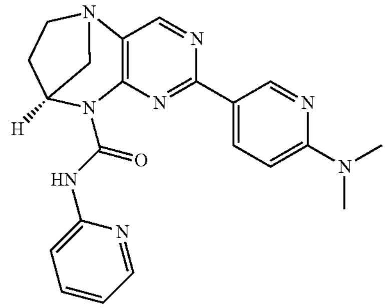


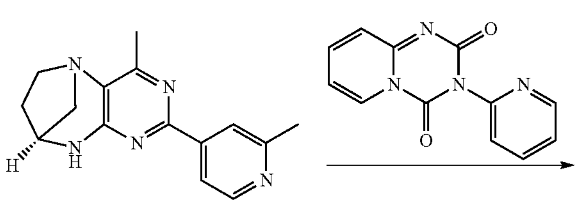
[0959] To a stirred solution of N,N-dimethyl-5-((8S)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepin-2-yl)pyridin-2-amine (200 mg, 0.708 mmol) in THF (15 ml, sealed tube) was added triphosgene (105 mg, 0.354 mmol) at 0° C. and stirred to RT for 1 h. Then pyridin-2-amine (100 mg, 1.063 mmol) and triethylamine (0.494 mL, 3.54 mmol) were added sub sequentially and heated the reaction mixture at 75° C. for 16 h. The reaction mixture was poured in saturated $NaHCO_3$ solution (50 mL) and extracted with ethyl acetate (2×50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluted with 1 to 2% methanol in dichloromethane) to afford (8S)-2-(6-(dimethylamino)pyridin-3-yl)-N-(pyridin-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (130 mg, 0.320 mmol, 45.2% yield) as a white solid (TLC: eluent: ethylacetate, R_f: 0.3), LCMS (m/z): 403.36 $[M+H]^+$.

[0960] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.35 (s, 1H), 9.33 (dd, J=2.41, 0.66 Hz, 1H), 8.68 (dd, J=9.10, 2.52 Hz, 1H), 8.48-8.38 (m, 2H), 8.20-8.14 (m, 1H), 7.77-7.64 (m, 1H), 7.02 (ddd, J=7.34, 4.93, 0.88 Hz, 1H), 6.62 (d, J=8.99 Hz, 1H), 5.64 (dd, J=5.92, 3.07 Hz, 1H), 3.21 (s, 8H), 3.15-3.00 (m, 2H), 2.40-2.28 (m, 1H), 2.15-2.04 (m, 1H).

Example 10

Synthesis of (8S)-4-methyl-2-(2-methylpyridin-4-yl)-N-(pyridin-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0961]



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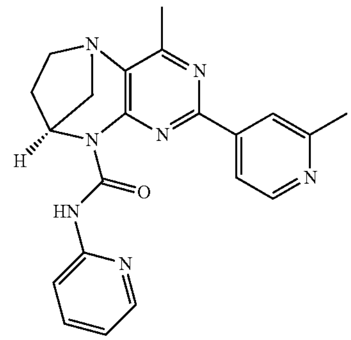
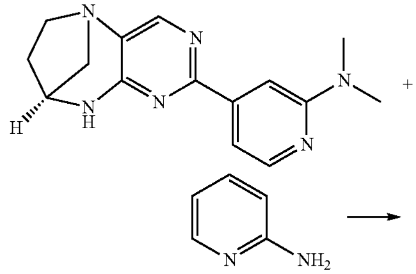


[0962] To a stirred solution of (8S)-4-methyl-2-(2-methylpyridin-4-yl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (200 mg, 0.748 mmol) in THF (8 mL) was added sodium hydride (163 mg, 3.74 mmol) at 0° C. and stirred for 30 min. Then 3-(pyridin-2-yl)-2H-pyrido[1,2-a][1,3,5]triazine-2,4(3H)-dione (270 mg, 1.122 mmol) was added and the reaction mixture was stirred at 60° C. for 16 h. The reaction mixture was allowed to RT and quenched it with water followed by extracted with ethyl acetate (2×50 mL). The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and the organic layer was concentrated under reduced pressure to obtain the crude product. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluted with 5% $MeOH/CH_2Cl_2$) to afford (4(8S)-4-methyl-2-(2-methylpyridin-4-yl)-N-(pyridin-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (165 mg, 0.425 mmol, 56.8% yield) as a pale yellow solid (TLC: 10% $MeOH/CH_2Cl_2$, R_f: 0.3), LCMS (m/z): 388.28 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$): δ ppm 13.42 (s, 1H), 8.66 (d, J=5.26 Hz, 1H), 8.47 (s, 1H), 8.43-8.40 (m, 1H), 8.27-8.15 (m, 2H), 7.73 (td, J=7.95, 1.86 Hz, 1H), 7.05 (ddd, J=7.29, 4.88, 0.99 Hz, 1H), 5.72-5.63 (m, 1H), 3.26-3.14 (m, 2H), 3.11-3.04 (m, 2H), 2.75 (s, 3H), 2.68 (s, 3H), 2.42-2.29 (m, 1H), 2.08 (dt, J=14.52, 7.54 Hz, 1H).

Example 11

Synthesis of (8S)-2-(2-(dimethylamino)pyridin-4-yl)-N-(pyridin-2-yl)-7,8-dihydro-5,8-methano pyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0963]



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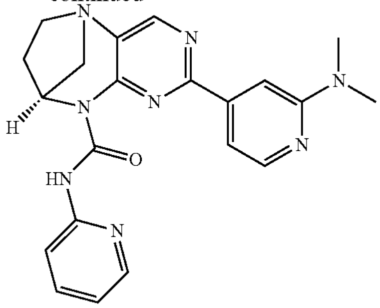


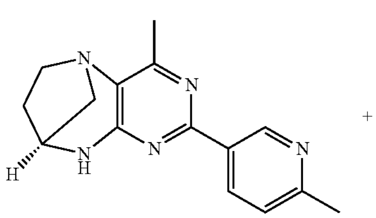
[0964] To a solution of N,N-dimethyl-4-((8S)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepin-2-yl)pyridin-2-amine (200 mg, 0.708 mmol) in THF (15 ml) triphosgene (105 mg, 0.354 mmol) was added at 0° C. and stirred at RT for 1 h. Then pyridin-2-amine (100 mg, 1.063 mmol) and triethylamine (0.494 mL, 3.54 mmol) was added sequentially under sealed tube condition at 75° C. and stirred for 16 h. The reaction was monitored by TLC and LCMS. The reaction mixture was poured in saturated $NaHCO_3$ solution (50 mL) and extracted with ethyl acetate (2×80 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude product. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluted with 1 to 2% methanol in dichloromethane) to afford (8S)-2-(2-(dimethylamino)pyridin-4-yl)-N-(pyridin-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (160 mg, 0.393 mmol, 55.4% yield) as a yellow solid (TLC: eluted ethyl acetate, R_f 0.3), LCMS (m/z): 403.35 $[M+H]^+$.

[0965] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 12.96 (s, 1H), 8.52 (s, 1H), 8.36-8.28 (m, 2H), 8.17 (d, J=8.55 Hz, 1H), 7.76-7.65 (m, 2H), 7.59 (s, 1H), 7.03-6.99 (m, 1H), 5.69 (dd, J=5.92, 3.07 Hz, 1H), 3.31-3.20 (m, 8H), 3.16-3.00 (m, 2H), 2.46-2.28 (m, 1H), 2.19-2.04 (m, 1H).

Example 12

Synthesis of (8S)-4-methyl-2-(6-methylpyridin-3-yl)-N-(pyridin-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0966]



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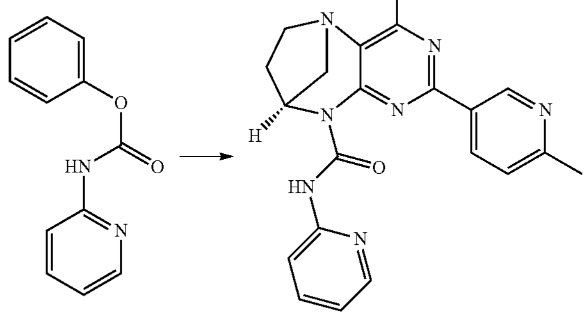
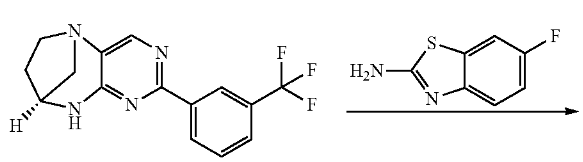


[0967] To a stirred solution of (8S)-4-methyl-2-(6-methylpyridin-3-yl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (200 mg, 0.748 mmol) in Tetrahydrofuran (THF) (15 mL) was added NaH (71.8 mg, 1.496 mmol) at 0° C. and stirred at RT for 30 min. Then phenyl pyridin-2-ylcarbamate (481 mg, 2.244 mmol) was added. The reaction mixture was heated at 65° C. for 16 h. The reaction mixture was cooled to 0° C. and quenched with ice water (50 ml). The aqueous layer was extracted with ethyl acetate (2×50 ml). The combined organic layer was washed with water (50 mL) and dried over anhydrous sodium sulfate. The organic layer was evaporated in vacuo to obtain the crude product. The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 2% of MeOH in CH_2Cl_2) to afford (8S)-4-methyl-2-(6-methylpyridin-3-yl)-N-(pyridin-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (139 mg, 0.341 mmol, 45.6% yield) as a white solid (TLC: 10% MeOH in DCM, R_f=0.4), LCMS (m/z): 388.28 $[M+H]^+$.

[0968] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.37 (s, 1H), 9.61 (d, J=2.41 Hz, 1H), 8.81 (dd, J=8.22, 2.30 Hz, 1H), 8.46-8.40 (m, 1H), 8.15 (d, J=8.33 Hz, 1H), 7.76-7.67 (m, 1H), 7.31 (d, J=8.11 Hz, 1H), 7.02 (ddd, J=7.29, 4.88, 0.99 Hz, 1H), 5.66 (dd, J=5.92, 2.63 Hz, 1H), 3.27-3.15 (m, 2H), 3.10-2.99 (m, 2H), 2.66 (d, J=3.51 Hz, 6H), 2.35 (ddt, J=14.31, 8.93, 5.37, 5.37 Hz, 1H), 2.07 (dt, J=14.25, 6.91 Hz, 1H).

Example 13 Synthesis of (8S)—N-(6-fluorobenzo[d]thiazol-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0969]



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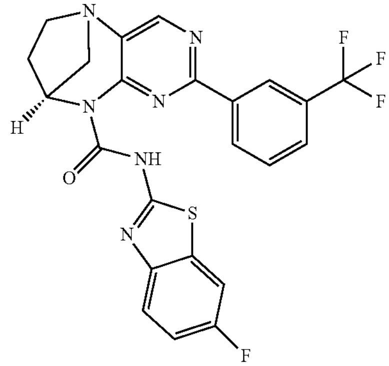


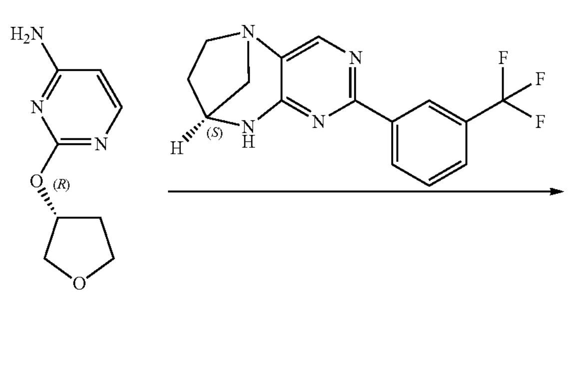
[0970] To a stirred solution of (8S)-2-(3-(trifluoromethyl) phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (300 mg, 0.979 mmol) in THF (15 mL, in sealed tube) was added triphosgene (145 mg, 0.490 mmol) at RT, and stirred for 30 min, then TEA (0.683 mL, 4.90 mmol) and 6-fluorobenzo[d]thiazol-2-amine (214 mg, 1.273 mmol) were added and stirred at 80° C. for 16 h. (TLC eluent: 5% MeOH in EtOAc, R_f: 0.6). The reaction mixture was cooled to room temperature; THF was distilled off and was partitioned between water (25 mL) and EtOAc (40 mL). The organic layer was separated and dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to obtain the crude compound. The crude compound was purified by flash column chromatography (silica gel: 100-200 mesh, eluent: 1% methanol in Ethyl acetate) to afford the desired product (8S)—N-(6-fluorobenzo[d]thiazol-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (160 mg, 0.310 mmol, 31.7% yield) as an off white solid. LCMS (m/z): 500.90 $[M+H]^+$, Rt=3.12 min.

[0971] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 14.24 (s, 1H), 8.77 (s, 1H), 8.71 (d, J=8.11 Hz, 1H), 8.58 (s, 1H), 7.85-7.78 (m, 2H), 7.75-7.68 (m, 1H), 7.51 (dd, J=8.22, 2.52 Hz, 1H), 7.18 (td, J=8.99, 2.63 Hz, 1H), 5.68 (dd, J=5.92, 2.85 Hz, 1H), 3.35-3.23 (m, 2H), 3.20-3.05 (m, 2H), 2.47-2.34 (m, 1H), 2.23-2.08 (m, 1H).

Example 14

Synthesis of (8S)—N-(2-(((R)-tetrahydrofuran-3-yl)oxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0972]



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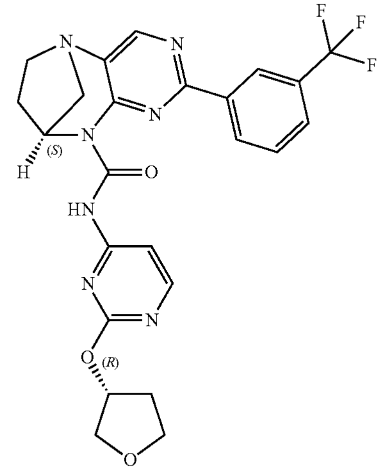


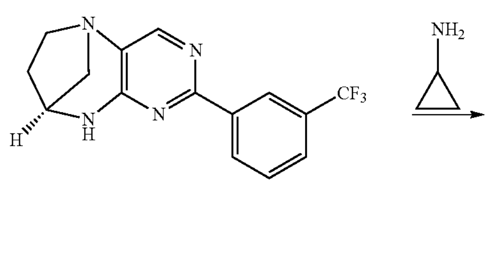
[0973] To a stirred solution of (R)-2-((tetrahydrofuran-3-yl)oxy)pyrimidin-4-amine (213 mg, 1.175 mmol) in THF (15 mL, in sealed tube) was added triphosgene (174 mg, 0.588 mmol) at RT, and stirred for 30 min, then TEA (0.683 mL, 4.90 mmol) and (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (300 mg, 0.979 mmol) were added and heated at 80° C. for 16 h. (TLC eluent: 5% MeOH in EtOAc, R_f: 0.6). The reaction mixture was cooled to room temperature; THF was distilled off and was partitioned between water (25 mL) and EtOAc (2×30 mL). The organic layer was separated and dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to obtain the crude compound. The crude compound was purified by flash column chromatography (silica gel: 100-200 mesh, eluent: 1% methanol in Ethyl acetate) to afford the desired product (8S)—N-(2-(((R)-tetrahydrofuran-3-yl)oxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (120 mg, 0.227 mmol, 23.14% yield) as an off white solid. LCMS (m/z): 514.07 $[M+H]^+$, Rt=2.55 min.

[0974] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.23 (s, 1H), 8.81 (d, J=7.89 Hz, 1H), 8.71 (s, 1H), 8.55 (s, 1H), 8.41 (d, J=5.48 Hz, 1H), 7.79 (d, J=5.70 Hz, 2H), 7.70-7.62 (m, 1H), 5.64 (dd, J=5.92, 2.85 Hz, 1H), 5.58-5.53 (m, 1H), 4.11-3.99 (m, 2H), 3.97-3.90 (m, 2H), 3.32-3.22 (m, 2H), 3.16-3.04 (m, 2H), 2.44-2.34 (m, 1H), 2.24-2.17 (m, 2H), 2.10 (dt, J=14.20, 7.04 Hz, 1H).

Example 15

Synthesis of (8S)—N-cyclopropyl-2-(3-(trifluoromethyl) phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0975]



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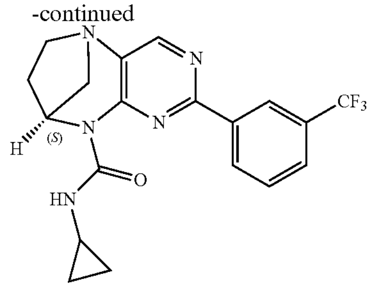


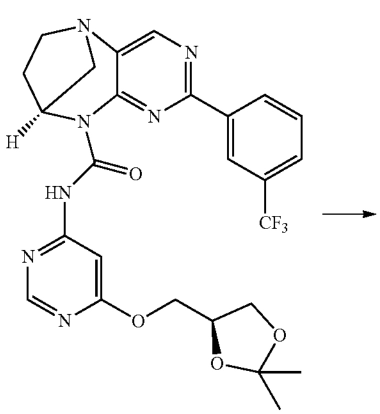
[0976] To a stirred solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (6 g, 19.59 mmol) in THF (120 mL) under nitrogen at 20° C. was added solid Triphosgene (3.49 g, 11.75 mmol) and stirred for 30 min at room temperature. Then Triethylamine (13.65 mL, 98 mmol) and cyclopropanamine (1.342 g, 23.51 mmol) were added to the reaction mixture and stirred at 80° C. for 2.5 h. (TLC system:5% Methanol in Ethyl acetae. R_f value: 0.5.). The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3×100 ml). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain crude compound. The crude product was purified by flash column chromatography (100-200 silicagel eluted with 50% of Ethyl acetate in Pet ether) to afford the desired product (8S)—N-cyclopropyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (5.2 g, 13.30 mmol, 67.9% yield) as a white solid. LCMS (m/z): 390.10 $[M+H]^+$, Rt=2.43 min.

[0977] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 10.19 (s, 1H), 8.44 (s, 1H), 8.42-8.36 (m, 2H), 7.76 (d, J=7.89 Hz, 1H), 7.66-7.59 (m, 1H), 5.64 (dd, J=5.92, 2.63 Hz, 1H), 3.29-3.15 (m, 2H), 3.08-2.98 (m, 2H), 2.89 (qd, J=7.02, 3.95 Hz, 1H), 2.38-2.27 (m, 1H), 2.19-2.02 (m, 1H), 0.94-0.84 (m, 2H), 0.71-0.63 (m, 2H).

Example 16

Synthesis of (8S)—N-(6-((R)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0978]



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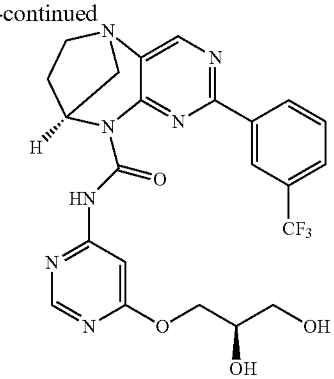


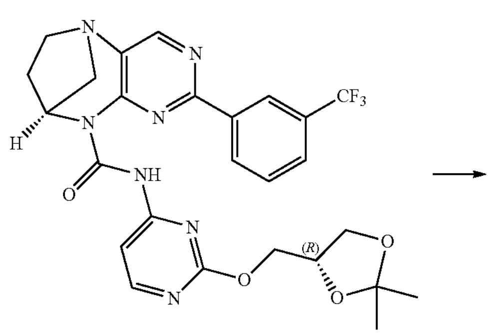
[0979] To a stirred solution (8S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (0.220 g, 0.395 mmol) in DCM (5 mL) and methanol (10 mL) at 0° C. was added 4M HCl in dioxane (1.586 mL, 6.35 mmol) and stirred at 0° C. for 4 h. (TLC eluent: 10% MeOH in EtOAc: R_f-0.25; UV active). Reaction mixture was basified by adding saturated sodium bicarbonate solution (till pH-8-9) then volatiles were concentrated. The residue was diluted with water (10 mL) and extracted into ethyl acetate (2×25 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude product. The crude was purified by column chromatography (neutral alumina, eluent: 50% ethyl acetate in hexane) to afford desired product (8S)—N-(6-((R)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (0.1 g, 0.185 mmol, 46.9% yield) as white solid. LCMS (m/z): 518.08 $[M+H]^+$, R_t=2.16 min.

[0980] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.41 (s, 1H), 8.87 (s, 1H), 8.76 (br d, J=7.89 Hz, 1H), 8.62-8.41 (m, 2H), 7.78 (br d, J=7.67 Hz, 1H), 7.70-7.59 (m, 1H), 7.56 (d, J=0.88 Hz, 1H), 5.64 (dd, J=5.92, 2.85 Hz, 1H), 4.59-4.46 (m, 2H), 4.07 (dq, J=10.08, 5.12 Hz, 1H), 3.81-3.61 (m, 2H), 3.48-3.38 (m, 1H), 3.33-3.17 (m, 2H), 3.15-3.03 (m, 2H), 2.49 (t, J=6.36 Hz, 1H), 2.43-2.34 (m, 1H), 2.09 (dt, J=14.85, 7.59 Hz, 1H).

Example 17

Synthesis of (8S)—N-(2-((S)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0981]



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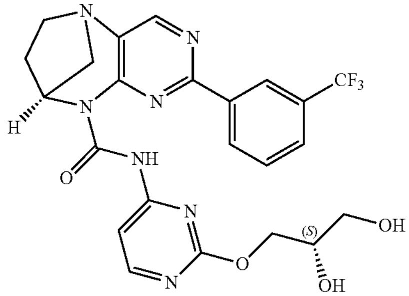


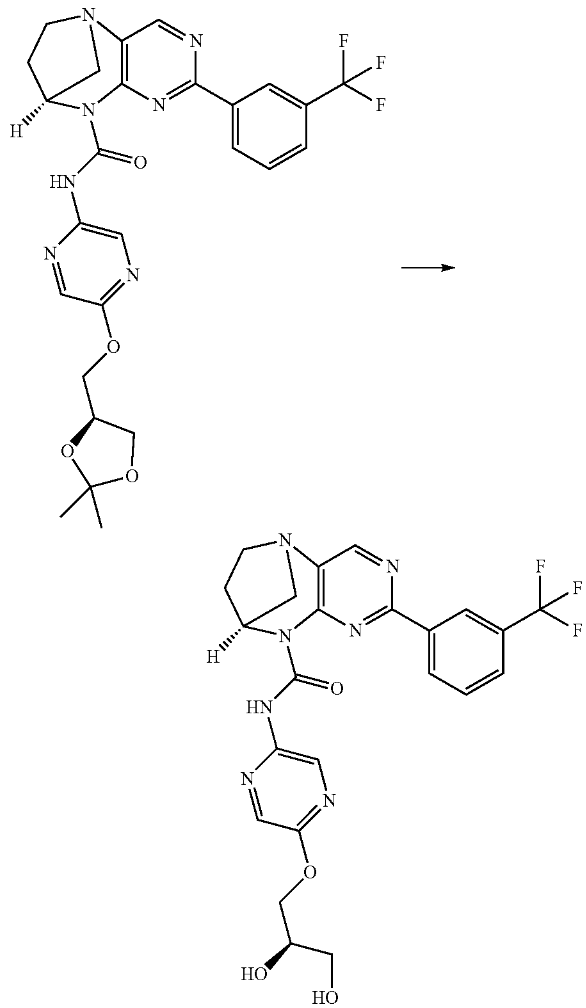
[0982] To a solution of (8S)—N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (200 mg, 0.359 mmol) in 1,4-Dioxane (5 mL) at 0° C. was added 4M HCl in 1,4-dioxane (2 mL, 8.00 mmol,) and stirred at RT for 16 h. (TLC eluent:10% Methanol in DCM, R_f=0.3; UV active). The reaction mixture was basified with saturated sodium bicarbonate solution (till pH-8-9) at 0° C. and concentrated. The residue was diluted with water (10 mL) and extracted into dichloromethane (2×40 mL). Combined organic extracts were dried over anhydrous sodium sulphate, filtered and filtrate was evaporated in vacuo to give crude product. The crude compound was purified by prep HPLC (Conditions—Column: XBridge C18(150×30 mm, 5); Mobile Phase-A: 5 mM Ammonium Bicarbonate B: Acetionitrile; Gradient-Time/% B: 0/10, 1/10, 10/45, 12/45, 12.5/100, 17/100; Column Temp: Ambient; Flow Rate: 30 ml/min: Diluent: THF+MEOH+ACN) to obtain desired product (110 mg) as a diastereomeric mixtures in 86:13 ratio. This was further purified by Chiral SFC (Conditions-Column: Chiralpak AD-H (250×30 mm); % CO_2:75.0; % Co-solvent:25.0 (0.5% DEA in MeOH); Total Flow:70.0 g/min; Back Pressure: 100.0 bar; Stack time:6.3 min; Load/inj:7.6 mg; Diluent: MeOH) and SFC solvent was evaporated under reduced pressure, diluted with water (10 mL) and the resultant solid was filtered through Buckner funnel and dried to obtained (8S)—N-(2-((S)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (50 mg, 0.095 mmol, 26.6% yield) as an off white solid. LCMS (m/z): 518.08 $[M+H]^+$, R_t=2.01 min.

[0983] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.26 (s, 1H), 8.76 (d, J=7.67 Hz, 1H), 8.71 (s, 1H), 8.56 (s, 1H), 8.41 (d, J=5.70 Hz, 1H), 7.84 (d, J=5.70 Hz, 1H), 7.81-7.77 (m, 1H), 7.75-7.69 (m, 1H), 5.65 (dd, J=5.92, 2.85 Hz, 1H), 4.50 (dd, J=5.26, 2.19 Hz, 2H), 4.15-4.09 (m, 1H), 3.81-3.69 (m, 2H), 3.31-3.20 (m, 3H), 3.16-3.02 (m, 2H), 2.44-2.34 (m, 2H), 2.10 (dt, J=14.14, 6.96 Hz, 1H).

Example 18

Synthesis of (8S)—N-(5-((R)-2,3-dihydroxypropoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0984]



[0985] To a solution of (8S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (100 mg, 0.179 mmol) in methanol (5 mL) at RT was added aq. HCl (3 mL, 6.00 mmol) and stirred for 3 h. (TLC system 5% Methanol in DCM, Rf value: 0.1). Methanol was concentrated under vacuum and the residue was basified with saturated $NaHCO_3$ solution, then the aqueous layer was extracted with DCM (2×20 mL). Combined DCM extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give crude product. The crude was triturated with diethylether (5 mL) to afford (8S)—N-(5-((R)-2,3-dihydroxypropoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-

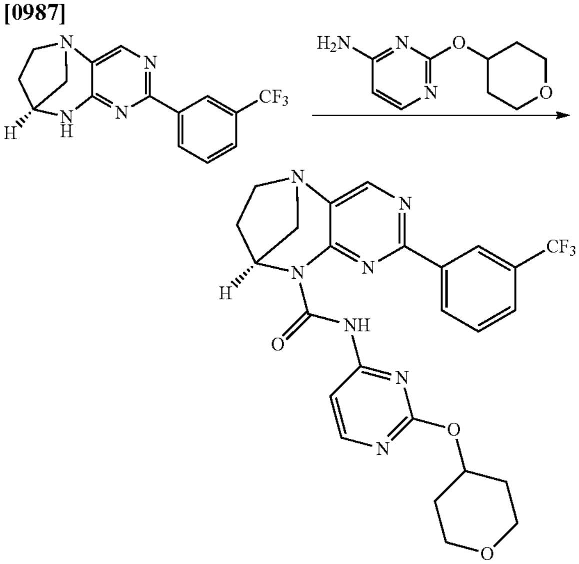
carboxamide (90 mg, 0.170 mmol, 95% yield) as Off-white solid. LCMS (m/z): 518.12 $[M+H]^+$, Rt=2.14 min.

[0986] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.12-13.37 (m, 1H), 8.97 (d, J=1.54 Hz, 1H), 8.82 (s, 1H), 8.70 (br d, J=7.89 Hz, 1H), 8.53 (s, 1H), 8.10 (d, J=1.32 Hz, 1H), 7.78 (br d, J=7.89 Hz, 1H), 7.64 (t, J=7.89 Hz, 1H), 5.61-5.74 (m, 1H), 4.38-4.55 (m, 2H), 4.06-4.20 (m, 1H), 3.67-3.84 (m, 2H), 3.20-3.38 (m, 2H), 3.01-3.18 (m, 3H), 2.25-2.44 (m, 2H), 2.05-2.18 (m, 1H).

Example 19

Synthesis of (8S)—N-(2-((tetrahydro-2H-pyran-4-yl)oxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0987]



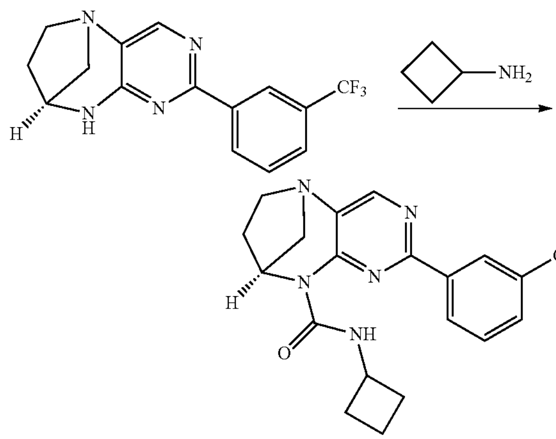
[0988] To a stirred solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (300 mg, 0.979 mmol) in THF (20 mL, in sealed tube) were added triphosgene (145 mg, 0.490 mmol), triethylamine (0.683 mL, 4.90 mmol) at RT, and stirred for 30 min. Then 2-((tetrahydro-2H-pyran-4-yl)oxy)pyrimidin-4-amine (287 mg, 1.469 mmol) was added and stirred at 80° C. for 16 h. (TLC eluent: 5% MeOH in DCM, R_f: 0.5). The reaction mixture was allowed to cool to room temperature; THF was distilled off and was partitioned between water (30 mL) and EtOAc (2×40 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to obtain the crude compound. The crude compound was purified by flash column chromatography (Neutral alumina, Eluent: 50% ethylacetate in Pet ether) to afford the desired product (8S)—N-(2-((tetrahydro-2H-pyran-4-yl)oxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (196 mg, 0.370 mmol, 37.8% yield) as an off white solid. LCMS (m/z): 528.09 $[M+H]^+$, R_t=2.62 min.

[0989] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.22 (s, 1H), 8.79-8.89 (m, 1H), 8.71 (s, 1H), 8.55 (s, 1H), 8.41 (d, J=5.70 Hz, 1H), 7.59-7.84 (m, 3H), 5.64 (dd, J=5.81, 2.74 Hz, 1H), 5.23 (tt, J=8.11, 3.95 Hz, 1H), 3.92-4.09 (m, 2H), 3.51-3.63 (m, 2H), 3.22-3.34 (m, 2H), 2.99-3.16 (m, 2H), 2.39 (qd, J=9.72, 5.04 Hz, 1H), 2.00-2.13 (m, 3H), 1.80-1.95 (m, 2H).

Example 20

Synthesis of (8S)—N-cyclobutyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0990]



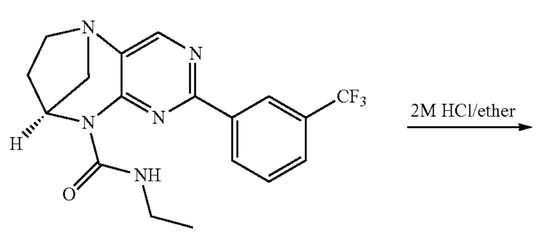
[0991] To a stirred solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (300 mg, 0.979 mmol) in THF (20 mL, in sealed tube) were added triphosgene (174 mg, 0.588 mmol) and DIPEA (0.855 mL, 4.90 mmol) at RT, and stirred for 30 min. Then cyclobutanamine (104 mg, 1.469 mmol) was added and stirred at 80° C. for 16 h. (TLC eluent: Neat Ethyl acetate, R_f: 0.5). The reaction mixture was allowed to cool to room temperature; THF was distilled off and was partitioned between water (30 mL) and EtOAc (2×40 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to obtain the crude compound. The crude compound was purified by flash column chromatography (Neutral alumina, Eluent: 50% ethylacetate in Pet ether) to afford the desired product (8S)—N-cyclobutyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (227 mg, 0.561 mmol, 57.3% yield) as an off white solid. LCMS (m/z): 404.14 $[M+H]^+$, R_t=2.66 min.

[0992] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 10.23 (d, J=7.02 Hz, 1H), 8.49-8.43 (m, 3H), 7.79-7.73 (m, 1H), 7.67-7.58 (m, 1H), 5.60 (dd, J=5.92, 2.85 Hz, 1H), 4.51-4.38 (m, 1H), 3.28-3.12 (m, 2H), 3.08-2.93 (m, 2H), 2.51-2.41 (m, 2H), 2.36-2.24 (m, 1H), 2.12-1.96 (m, 3H), 1.88-1.67 (m, 2H).

Example 21

Synthesis of (8S)—N-ethyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methano pyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide, Hydrochloride

[0993]



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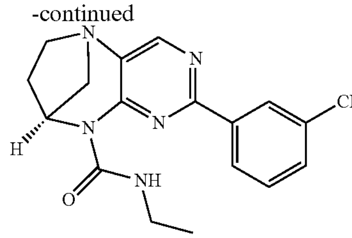


[0994] To a stirred solution of (8S)—N-ethyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (360 mg, 0.954 mmol) in Diethyl ether (10 mL) was added 2M HCl in ether (5 mL, 10.00 mmol) at 0° C. over a period of 5 min. Then the reaction mixture was stirred at 30° C. for 2 h. (TLC eluent: 10% MeOH in DCM: R_1-0.5; UV active) and the solvent was evaporated, washed with n-pentane (2×20 mL) to afford the desired product (8S)—N-ethyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide, Hydrochloride (267 mg, 0.614 mmol, 64.4% yield) as an off white solid.

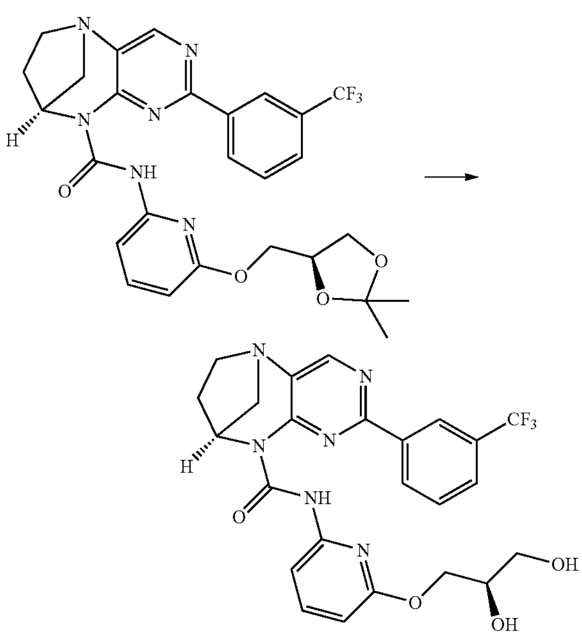
[0995] LCMS (m/z): 378.08 $[M+H]^+$, Rt=2.41 min.

[0996] ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.66 (t, J=5.04 Hz, 1H), 8.57 (s, 1H), 8.46 (d, J=7.89 Hz, 1H), 8.40 (s, 1H), 7.94 (d, J=7.67 Hz, 1H), 7.87-7.76 (m, 1H), 5.41 (dd, J=5.81, 2.52 Hz, 1H), 3.42-3.32 (m, 3H), 3.30-3.13 (m, 3H), 2.37-2.22 (m, 1H), 2.00 (dt, J=14.03, 7.23 Hz, 1H), 1.25 (t, J=7.23 Hz, 3H).

Example 22

Synthesis of (8S)—N-(6-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[0997]



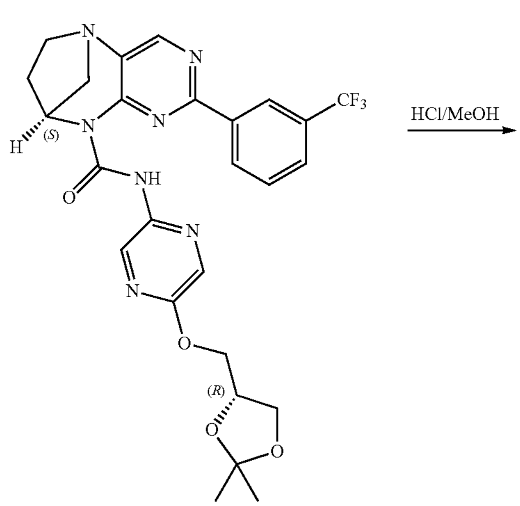
[0998] To a stirred solution of (8S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (500 mg, 0.898 mmol) in methanol (10 mL), art RT was added a solution of 2 M aq HCl (5 ml, 165 mmol) and stirred for 1 h. (TLC system:70% EtOAc in petether. Rf value: 0.2). Reaction mixture was concentrated to remove methanol and the residue was basified the with saturated $NaHCO_3$ (10 mL) solution at 10° C., the obtained solid was filtered, washed with water (10 mL) and dried under high vacuum to obtain desired pure product (8S)—N-(6-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (250 mg, 0.480 mmol, 53.5% yield) as an off-white solid. LCMS (m/z): 517.11$[M+H]^+$, Rt=2.20 min.

[0999] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.58 (br s, 1H), 8.68 (s, 1H), 8.61 (br d, J=7.67 Hz, 1H), 8.53 (s, 1H), 7.59-7.80 (m, 4H), 6.54 (d, J=7.67 Hz, 1H), 5.69 (br d, J=3.07 Hz, 1H), 4.19-4.44 (m, 2H), 3.90-4.15 (m, 1H), 3.48-3.75 (m, 2H), 3.17-3.40 (m, 2H), 2.95-3.17 (m, 2H), 2.81 (br d, J=5.26 Hz, 1H), 2.37 (ddd, J=14.20, 9.37, 4.93 Hz, 1H), 1.98-2.23 (m, 2H).

Example 23

Synthesis of (8S)—N-(5-((S)-2,3-dihydroxypropoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl) phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4] diazepine-9(6H)-carboxamide

[1000]



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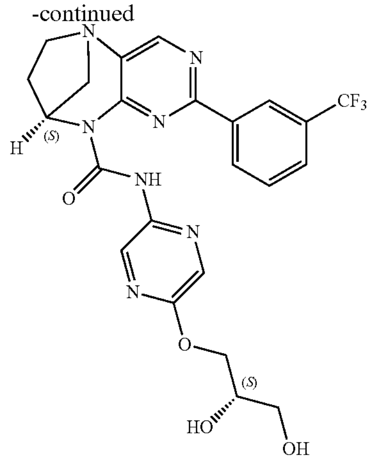


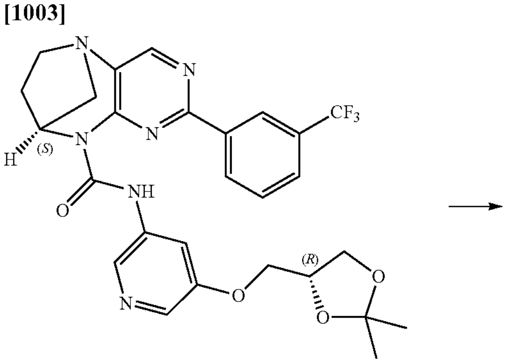
[1001] To a stirred solution (8S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (550 mg, 0.987 mmol) in Methanol (20 mL) was added 2.0 M HCl (5 mL, 10.00 mmol) at room temperature. The resulting reaction mixture was stirred at RT for 1 h. (TLC System: 10% MeOH in DCM, R_f: 0.4). Then the reaction mixture was concentrated under vacuum to remove Methanol and basified with saturated sodium bicarbonate solution (20 mL), extracted with DCM (3×30 mL). The combined organic layer was washed with water (20 mL), brine solution (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure, the obtained semi solid was washed with diethyl ether to afford the desire product (8S)—N-(5-((S)-2,3-dihydroxypropoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (390 mg, 0.751 mmol, 76% yield) as an off-white solid. LCMS (m/z): 518.31 $[M+H]^+$. R_t=2.15 min.

[1002] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.24 (s, 1H), 8.96 (d, J=1.32 Hz, 1H), 8.81 (s, 1H), 8.69 (d, J=8.11 Hz, 1H), 8.53 (s, 1H), 8.10 (d, J=1.32 Hz, 1H), 7.78 (d, J=7.67 Hz, 1H), 7.68-7.58 (m, 1H), 5.68 (dd, J=5.81, 2.74 Hz, 1H), 4.53-4.38 (m, 2H), 4.16-4.06 (m, 1H), 3.83-3.68 (m, 2H), 3.36-3.23 (m, 2H), 3.21 (d, J=5.26 Hz, 1H), 3.16-3.02 (m, 2H), 2.49-2.32 (m, 2H), 2.13 (td, J=14.69, 7.02 Hz, 1H).

Example 24

Synthesis of (8S)—N-(5-((S)-2,3-dihydroxypropoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1003]



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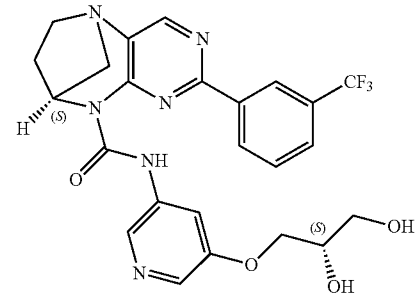


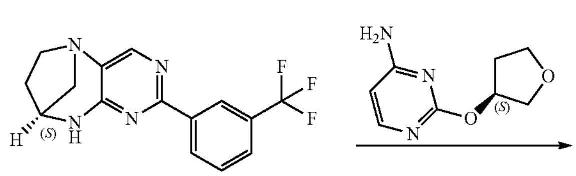
[1004] To a stirred solution of (8S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (0.750 g, 1.348 mmol) in methanol (6 mL) at 0° C. was added aq. HCl (5 mL, 165 mmol) over a period of 10 min. and the resulting yellow solution was stirred for 5 h. (TLC system: 10% Methanol in DCM. R_f: 0.2). The reaction mixture was concentrated in vacuo to afford yellow viscous oil and neutralized with saturated sodium bicarbonate solution, then extracted with EtOAc (2×30 mL). The combined organic layer was washed with brine solution (10 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure to afford crude product. The crude product was purified by column chromatography (silica gel eluted with 12% of MeOH in CH_2Cl_2) to afford (8S)—N-(5-((S)-2,3-dihydroxypropoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (475 mg, 0.916 mmol, 68.0% yield) as off white solid. LC-MS (m/z): 517.08 $[M+H]^+$, Rt=1.82 min.

[1005] ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.13 (s, 1H), 8.52-8.60 (s, 1H), 8.42-8.54 (m, 2H), 8.22-8.32 (m, 1H), 8.02 (s, 1H), 7.90 (br d, J=7.67 Hz, 1H), 7.70-7.85 (m, 2H), 5.39 (dd, J=5.81, 2.96 Hz, 1H), 4.95 (br d, J=4.60 Hz, 1H), 4.64-4.74 (m, 1H), 4.05 (dd, J=9.87, 3.95 Hz, 1H), 3.91 (dd, J=9.76, 6.25 Hz, 1H), 3.79 (br d, J=4.17 Hz, 1H), 3.29-3.52 (m, 2H), 3.19 (br d, J=8.11 Hz, 1H), 2.88-3.15 (m, 3H), 2.17-2.32 (m, 1H), 1.98-2.10 (m, 1H).

Example 25

Synthesis of (8S)—N-(2-(((S)-tetrahydrofuran-3-yl)oxy)pyrimidin-4-yl)-2-(3-(trifluoro-methyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1006]



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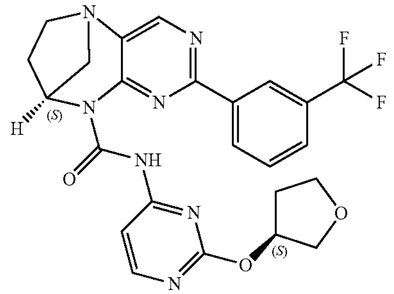


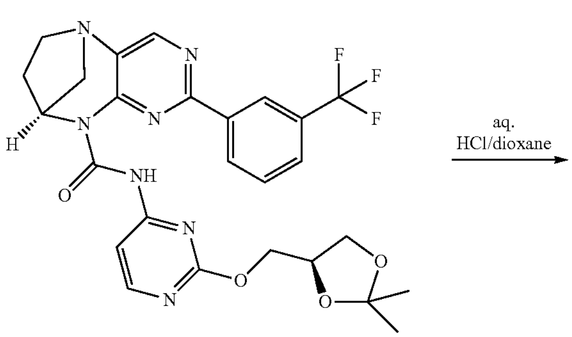
[1007] To a stirred solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (300 mg, 0.979 mmol) in THF (20 mL, in sealed tube) were added triethylamine (0.819 mL, 5.88 mmol) and triphosgene (291 mg, 0.979 mmol) at RT, and stirred for 30 min. Then (S)-2-((tetrahydrofuran-3-yl)oxy)pyrimidin-4-amine (355 mg, 1.959 mmol) was added and stirred at 80° C. for 16 h. (TLC eluent: 5% MeOH in DCM, R_f: 0.4). The reaction mixture was allowed to cool to room temperature. THF was distilled off and added water (30 mL), extracted with EtOAc (2×40 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to obtain the crude compound. The crude compound was purified by Prep HPLC (conditions: 5 Mm ammonium bicarbonate (Aq) MP-B: Acetonitrile Column: KROMOSIL C18 (21.2×250)mm 10μ Method: 30:70 Flow: 19 ml/min Solubility: Exess THF+ACN+MEOH) to afford the desired product (8S)—N-(2-(((S)-tetrahydrofuran-3-yl)oxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (160 mg, 0.312 mmol, 31.8% yield) as an off white solid. LCMS (m/z): 514.1 $[M+H]^+$, Rt=2.53 min.

[1008] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.23 (s, 1H), 8.81 (d, J=7.89 Hz, 1H), 8.71 (s, 1H), 8.55 (s, 1H), 8.41 (d, J=5.70 Hz, 1H), 7.79 (d, J=5.70 Hz, 2H), 7.59-7.70 (m, 1H), 5.64 (dd, J=5.92, 2.85 Hz, 1H), 5.59-5.52 (m, 1H), 4.13-4.01 (m, 2H), 3.98-3.86 (m, 2H), 3.34-3.20 (m, 2H), 3.17-3.02 (m, 2H), 2.47-2.31 (m, 1H), 2.27-2.16 (m, 2H), 2.13-2.02 (m, 1H).

Example 26

Synthesis of (8S)—N-(4-((R)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1009]



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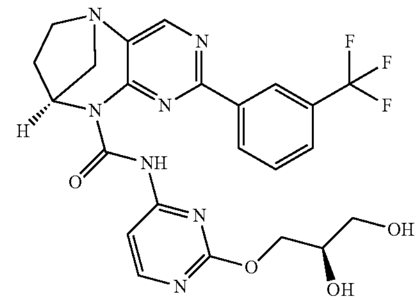


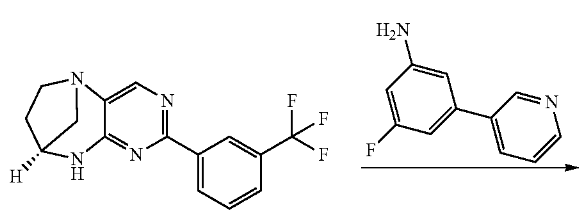
[1010] To a stirred solution of (8S)—N-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (200 mg, 0.359 mmol) in 1,4-Dioxane (5.0 mL) was added 4M HCl in dioxane (0.897 mL, 3.59 mmol) at room temperature and was stirred for 4 h at the same temperature (TLC system: 100% ethylacetate, Rf value: 0.2). The reaction mixture was quenched with saturated $NaHCO_3$ solution (10 mL) and extracted with EtOAc (30 mL). The combined organic layer was separated and dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to obtain crude compound. The crude compound was purified by flash column chromatography (silicagel, 100-200 mesh Eluent: 70% Ethylacetate in hexane) to afford the desired product (8S)—N-(4-((R)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (145 mg, 0.273 mmol, 76% yield) as a brown solid. LCMS (m/z): 518.19 $[M+H]^+$, R_t=1.96 min.

[1011] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.67 (s, 1H), 8.89 (s, 1H), 8.75 (d, J=7.89 Hz, 1H), 8.54 (s, 1H), 8.37 (d, J=5.70 Hz, 1H), 7.77 (d, J=7.67 Hz, 1H), 7.68-7.60 (m, 1H), 6.53 (d, J=5.70 Hz, 1H), 5.74 (dd, J=5.92, 2.85 Hz, 1H), 4.74-4.66 (m, 1H), 4.59 (dd, J=12.17, 4.49 Hz, 1H), 4.36 (d, J=5.70 Hz, 1H), 3.98 (d, J=4.60 Hz, 1H), 3.67 (brs, 2H), 3.36-3.19 (m, 3H), 3.13-2.99 (m, 2H), 2.43-2.31 (m, 1H), 2.13-2.03 (m, 1H).

Example 27

Synthesis of (8S)—N-(3-fluoro-5-(pyridin-3-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1012]



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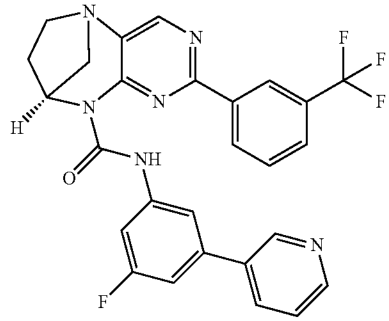


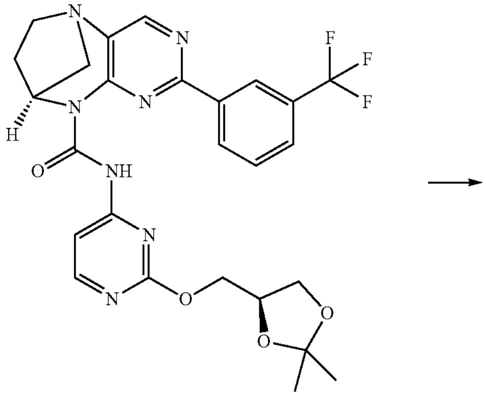
[1013] In a sealed tube to a stirred solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (300 mg, 0.979 mmol) in THF (15 mL) were added triphosgene (145 mg, 0.490 mmol) and triethylamine (0.683 mL, 4.90 mmol) at room temperature and stirred for 30 min. Then, 3-fluoro-5-(pyridin-3-yl)aniline (240 mg, 1.273 mmol) was added and stirred at 80° C. for 15 h. (TLC System: Rf—0.3, 5% MeOH/EtOAc). The reaction mixture was allowed to cool to room temperature and diluted with water (25 mL), extracted with EtOAc (2×40 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to obtain the crude compound. The crude compound was purified by flash column chromatography (silica-gel: 100-200 mesh, Eluent: 0.5% methanol in ethylacetate) to afford the desired product (8S)—N-(3-fluoro-5-(pyridin-3-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (140 mg, 0.268 mmol, 27.3% yield) as an off white solid. LCMS (m/z): 521.11 [M+H]$^+$, R_t=2.50 min.

[1014] ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.28 (s, 1H), 8.62 (dd, J=4.82, 1.53 Hz, 1H), 8.59-8.53 (m, 1H), 8.52-8.34 (m, 1H), 8.06 (dt, J=7.89, 1.97 Hz, 1H), 7.92 (d, J=7.89 Hz, 1H), 7.78 (t, J=7.78 Hz, 2H), 7.66 (s, 1H), 7.59 (dd, J=10.96, 1.97 Hz, 2H), 7.56-7.45 (m, 1H), 7.45-7.21 (m, 1H), 5.43 (dd, J=5.70, 2.85 Hz, 1H), 3.20-3.08 (m, 3H), 3.08-2.82 (m, 1H), 2.35-2.22 (m, 1H), 2.09 (m, 1H).

Example 28

Synthesis of (8S)—N-(2-((R)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1015]



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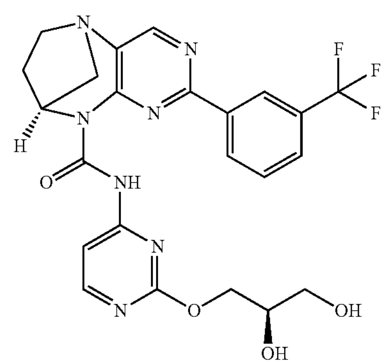
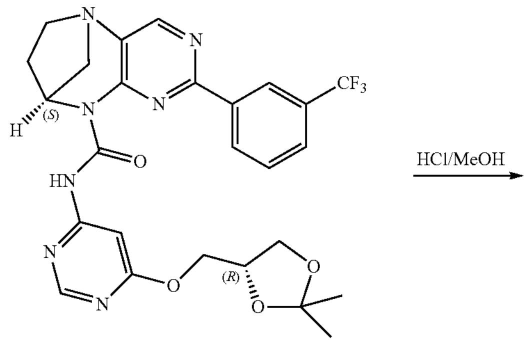


[1016] To a stirred solution of (8S)—N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (250 mg, 0.448 mmol) in methanol (10 mL) under nitrogen at 0° C. was added aq. HCl (1 ml, 4.00 mmol, 36%) and stirred at RT for 1 h. (TLC eluent: 5% Methanol in DCM, R_f: 0.3, UV active). To the reaction mixture was added saturated $NaHCO_3$ solution (till pH-8-9) and extracted with DCM (3×15 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated to obtain crude compound. The crude was triturated with diethylether (3×5 mL) to afford pure (8S)—N-(2-((R)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (210 mg, 0.399 mmol, 89% yield) as an off white solid. LCMS (m/z): 518.08 [M+H]$^+$, R_t=2.02 min.

[1017] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.25 (s, 1H), 8.76 (d, J=7.67 Hz, 1H), 8.71 (s, 1H), 8.56 (s, 1H), 8.41 (d, J=5.70 Hz, 1H), 7.83 (d, J=5.70 Hz, 1H), 7.81-7.77 (m, 1H), 7.75-7.68 (m, 1H), 5.64 (dd, J=5.92, 2.85 Hz, 1H), 4.55-4.44 (m, 2H), 4.12 (m, 1H), 3.82-3.68 (m, 2H), 3.34-3.20 (m, 3H), 3.16-3.03 (m, 2H), 2.45-2.32 (m, 2H), 2.10 (m, 1H).

Example 29 Synthesis of (8S)—N-(6-((S)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-2-(3-(trifluoro methyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1018]



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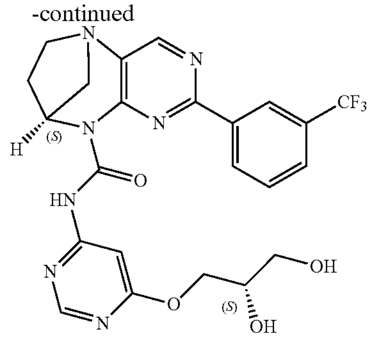


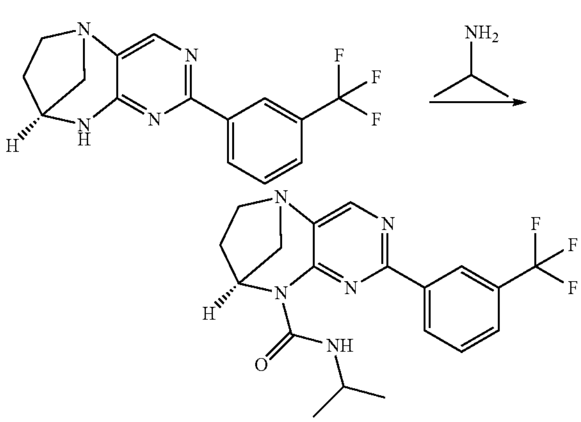
[1019] To a stirred solution of (8S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (200 mg, 0.359 mmol) in Methanol (5 mL) was added hydrochloric acid (0.054 mL, 1.794 mmol) at 0° C. then stirred at RT for 2 h. (TLC System: R_f-0.4, 5% MeOH/DCM). The reaction concentrated in vacuo and the residue was neutralized with aq $NaHCO_3$ solution and obtained solid was filtered then washed with n-pentane (10 mL×2) to afford the desired product (8S)—N-(6-((S)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (150 mg, 0.285 mmol, 80% yield) as an off white solid. LCMS (m/z): 518.0 $[M+H]^+$, Rt=2.15 min.

[1020] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.41 (s, 1H), 8.87 (s, 1H), 8.76 (d, J=8.11 Hz, 1H), 8.57-8.51 (m, 2H), 7.78 (d, J=7.67 Hz, 1H), 7.70-7.63 (m, 1H), 7.57 (d, J=0.66 Hz, 1H), 5.64 (dd, J=5.92, 2.63 Hz, 1H), 4.60-4.48 (m, 2H), 4.07 (dq, J=10.00, 5.14 Hz, 1H), 3.77-3.64 (m, 2H), 3.41 (d, J=5.26 Hz, 1H), 3.33-3.20 (m, 2H), 3.14-3.04 (m, 2H), 2.48 (t, J=6.36 Hz, 1H), 2.37 (td, J=9.87, 3.95 Hz, 1H), 2.09 (dt, J=14.85, 7.59 Hz, 1H).

Example 30

Synthesis of (8S)—N-isopropyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1021]



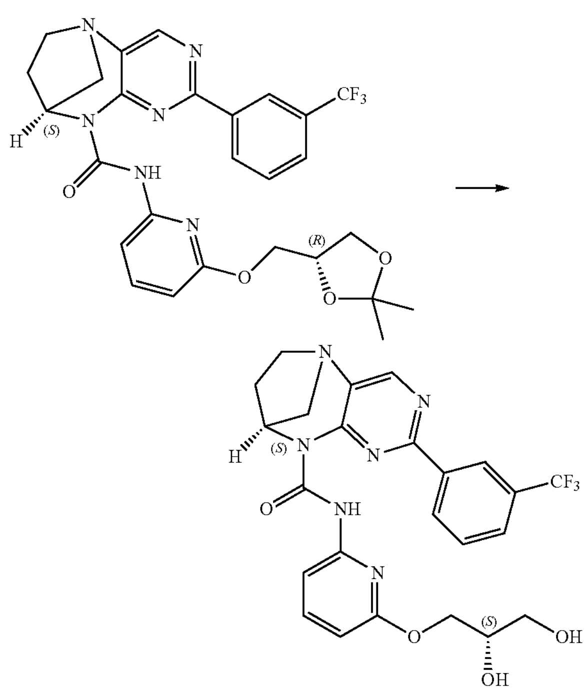
[1022] To a stirred solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (300 mg, 0.979 mmol) in THF (10 mL, in sealed tube) were added triphosgene (145 mg, 0.490 mmol) and DIPEA (0.855 mL, 4.90 mmol) at RT and stirred for 30 min. Then propan-2-amine (0.126 mL, 1.469 mmol) was added and stirred at 80° C. for 16 h. (TLC System: R_f—0.4, Neat EtOAc). The reaction mixture allowed to cool to room temperature and diluted it with water (100 ml) and extracted with ethylacetate (2×200 ml). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain crude compound. The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 60% ethyl acetate in hexane) and it was again purified by Prep HPLC (Conditions: MP-A: 5 mM Ammonium Bicarbonate (Aq) MP-B: Acetonitrile+METHONOL(1:1) Column: Xbridge C18 (250×30) mm 5μ Method: 0/15, 1/15, 10/33, 10.5/100 Flow: 28 ml/min Solubility: ACN+MeOH+THF) to afford the desired product (8S)—N-isopropyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (201 mg, 0.513 mmol, 52.4% yield) as an off white solid. LCMS (m/z): 392.0 $[M+H]^+$, Rt=2.58 min.

[1023] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 9.92 (d, J=6.80 Hz, 1H), 8.46-8.39 (m, 3H), 7.74 (d, J=7.45 Hz, 1H), 7.65-7.58 (m, 1H), 5.62 (dd, J=6.14, 2.85 Hz, 1H), 4.19-4.07 (m, 1H), 3.29-3.16 (m, 2H), 3.07-2.96 (m, 2H), 2.37-2.25 (m, 1H), 2.12-2.00 (m, 1H), 1.33 (d, J=6.58 Hz, 6H).

Example 31

Synthesis of (8S)—N-(6-((S)-2,3-dihydroxypropoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1024]



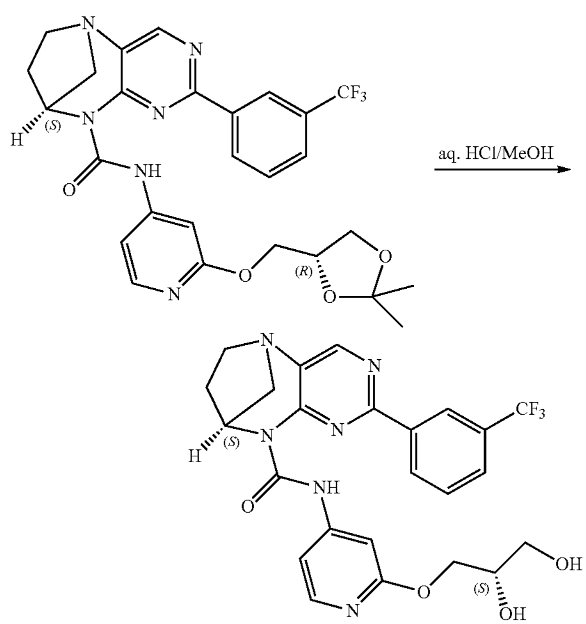
[1025] To a stirred solution of (8S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (300 mg, 0.539 mmol) in Methanol (10 mL) was added 3M HCl (10 mL, 30.0 mmol) at RT. The resulting mixture was stirred at RT for 1 h. (TLC System: Neat EtOAC, R_f: 0.3) and the reaction mass was basified with saturated sodium bicarbonate solution (10 mL), extracted with DCM (2×20 mL). the combined organic layer was washed with brine solution (10 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford (8S)—N-(6-((S)-2,3-dihydroxypropoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (240 mg, 0.463 mmol, 86% yield) as a white solid. LCMS (m/z): 517.18 $[M+H]^+$, R_t=2.19 min.

[1026] ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.51 (s, 1H), 8.77-8.62 (m, 2H), 8.57 (s, 1H), 8.02-7.84 (m, 2H), 7.83-7.63 (m, 2H), 6.58 (dd, J=7.67, 0.88 Hz, 1H), 5.50 (dd, J=5.81, 2.96 Hz, 1H), 4.31-4.06 (m, 2H), 3.94 (br s, 1H), 3.81 (dt, J=10.80, 5.45 Hz, 2H), 3.43 (d, J=5.70 Hz, 1H), 3.24 (d, J=8.99 Hz, 2H), 3.19-2.97 (m, 3H), 2.47-2.21 (m, 1H), 2.16-1.97 (m, 1H).

Example 32

Synthesis of (8S)—N-(2-((S)-2,3-dihydroxypropoxy)pyridin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1027]



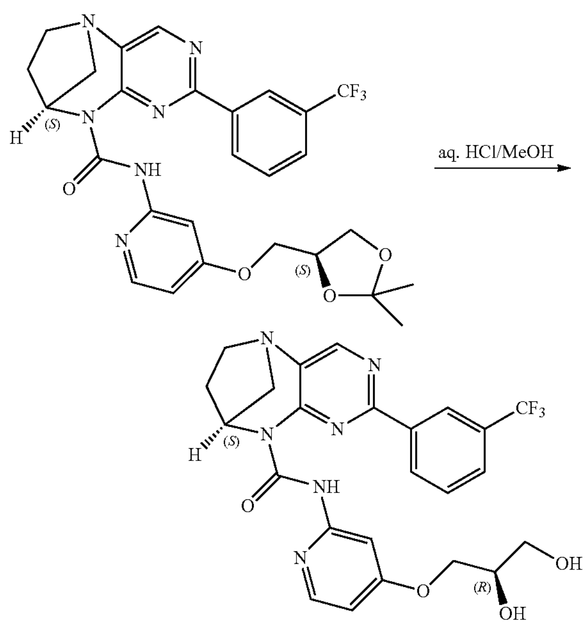
[1028] To a stirred solution of (8S)—N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (2.5 g, 4.49 mmol) in Methanol (50 mL) was added hydrochloric acid (10 mL, 118 mmol) at 0° C. then stirred at RT for 1 h. (TLC system: Neat Ethyl acetate, R_f: 0.2) and the reaction mixture was concentrated in vacuo, and the residue was neutralized with aq $NaHCO_3$ solution and obtained solid was filtered then washed with n-Pentane (2×10 mL), Diethy ether (2×10 mL) to afford the desired product (8S)—N-(2-((S)-2,3-dihydroxypropoxy)pyridin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (1.1 g, 2.129 mmol, 47.4% yield) as a white solid. LCMS (m/z): 517.08 $[M+H]^+$, R_t=1.98 min.

[1029] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.64 (s, 1H), 8.59-8.55 (m, 1H), 8.48-8.40 (m, 2H), 8.00 (d, J=5.92 Hz, 1H), 7.81 (d, J=7.89 Hz, 1H), 7.73-7.65 (m, 1H), 7.22 (d, J=1.53 Hz, 1H), 7.04 (dd, J=5.81, 1.86 Hz, 1H), 5.66 (dd, J=5.92, 2.63 Hz, 1H), 4.57-4.44 (m, 2H), 4.19 (d, J=5.70 Hz, 1H), 4.01 (dq, J=9.95, 4.94 Hz, 1H), 3.80-3.61 (m, 2H), 3.39-3.21 (m, 2H), 3.18-3.02 (m, 2H), 2.84 (t, J=6.47 Hz, 1H), 2.47-2.30 (m, 1H), 2.11 (dt, J=14.52, 7.32 Hz, 1H).

Example 33

Synthesis of (8S)—N-(4-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1030]



[1031] To a stirred solution of (8S)—N-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (350 mg, 0.629 mmol) in Methanol (10 mL) was added hydrochloric acid (2 ml, 23.70 mmol) at 0° C. then stirred at RT for 1 h. (TLC system: Neat Ethyl acetate, R_f: 0.2). The reaction mixture was concentrated in vacuo and the resulted residue was neutralized with saturated $NaHCO_3$ solution and obtained solid was filtered then washed with n-Pentane (2×10 mL), Diethy ether (2×10 mL) to afford the desired compound (8S)—N-(4-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-2-(3-

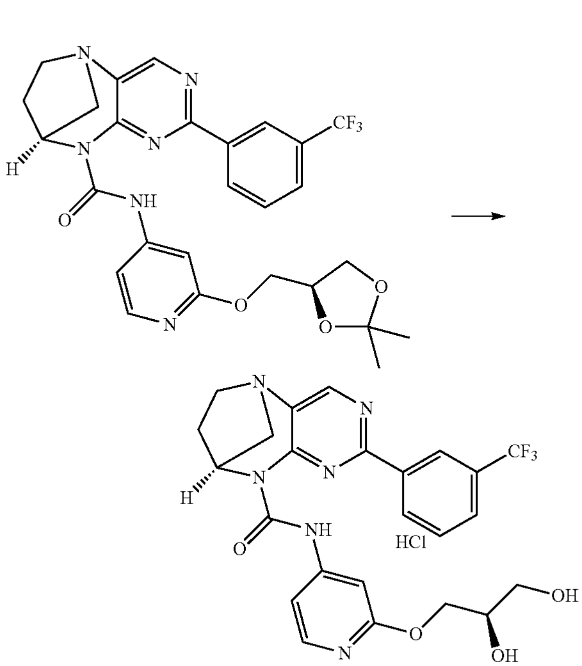
(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (160 mg, 0.309 mmol, 49.1% yield) as an off white solid. LCMS (m/z): 517.11 [M+H]$^+$, R_t=2.07 min.

[1032] ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.13 (s, 1H), 8.92-8.76 (m, 2H), 8.55 (s, 1H), 8.18 (d, J=5.70 Hz, 1H), 7.93 (s, 1H), 7.83 (t, J=7.67 Hz, 1H), 7.72 (d, J=1.75 Hz, 1H), 6.80-6.72 (m, 1H), 5.47 (br s, 1H), 4.13 (dd, J=9.76, 4.06 Hz, 1H), 4.03-3.93 (m, 1H), 3.84 (d, J=3.73 Hz, 1H), 3.47 (d, J=4.60 Hz, 2H), 3.13 (d, J=12.50 Hz, 3H), 3.01 (dd, J=12.06, 2.63 Hz, 1H), 2.33-2.18 (m, 2H), 2.10-1.99 (m, 2H).

Example 34

Synthesis of (8S)—N-(2-((R)-2,3-dihydroxypropoxy)pyridin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide hydrochloride

[1033]



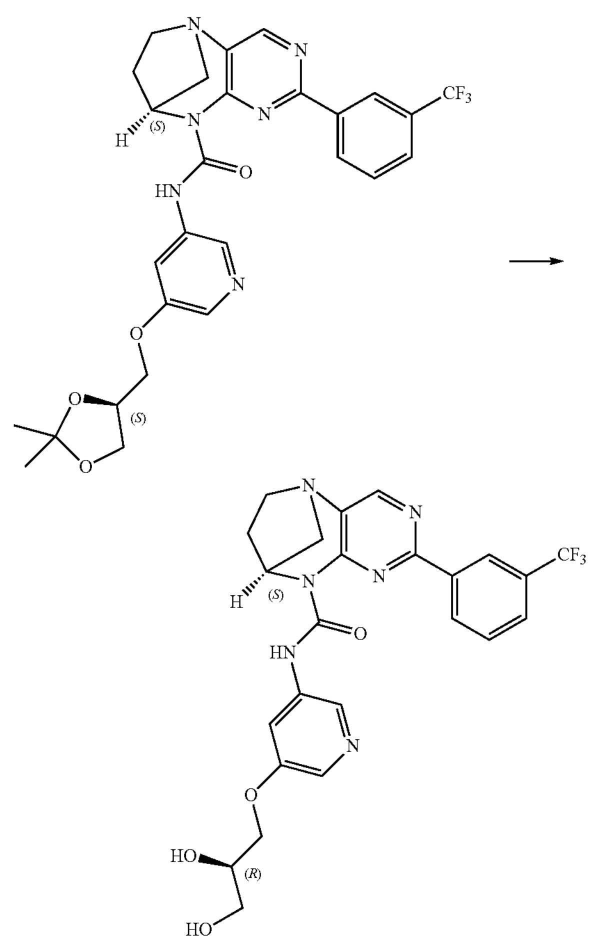
[1034] To a stirred solution of (8S)—N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (1.5 g, 2.70 mmol) in methanol (15.0 mL) was added aqueous HCl (1.638 mL, 53.9 mmol) at 0° C. and stirred at RT for 4 h. The reaction mixture was basified with saturated sodium bicarbonate solution (till pH-8-9) at 0° C. and concentrated. The residue was diluted with water (8 mL) and extracted into EtOAc (3×10 mL). Combined organic extracts were dried over anhydrous sodium sulphate, filtered and filtrate was evaporated under reduced pressure and the crude was triturated with ethyl acetate (2×10 ml), diethyl ether (10 ml) and pentane (3×10 ml) to afford the desired product (8S)—N-(2-((R)-2,3-dihydroxypropoxy)pyridin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide hydrochloride (1.086 g, 1.905 mmol, 70.7% yield) as a white solid. LCMS (m/z): 517.11 [M+H]$^+$, R_t=2.00 min.

[1035] ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.28 (s, 1H), 8.68 (s, 1H), 8.52 (d, J=7.89 Hz, 1H), 8.47 (s, 1H), 8.14 (d, J=6.14 Hz, 1H), 7.97 (d, J=7.89 Hz, 1H), 7.89-7.83 (m, 1H), 7.38 (d, J=1.75 Hz, 1H), 7.16 (dd, J=6.14, 1.75 Hz, 1H), 5.41 (dd, J=5.92, 2.85 Hz, 1H), 5.01-5.39 (br s, 2H) 4.33 (dd, J=10.52, 4.17 Hz, 1H), 4.21 (dd, J=10.63, 6.25 Hz, 1H), 3.87-3.81 (m, 1H), 3.46 (d, J=5.92 Hz, 2H), 3.40-3.32 (m, 1H), 3.29-3.16 (m, 3H), 2.39-2.29 (m, 1H), 2.16-2.07 (m, 1H).

Example 35

Synthesis of (8S)—N-(5-((R)-2,3-dihydroxypropoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1036]



[1037] To a stirred solution of (8S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (450 mg, 0.809 mmol) in methanol (10 mL) under nitrogen at 0° C. was added aq. HCl (2 mL, 65.8 mmol) and the suspension was stirred at 0° C. for 1 h. (TLC eluent: 10% Methanol in DCM

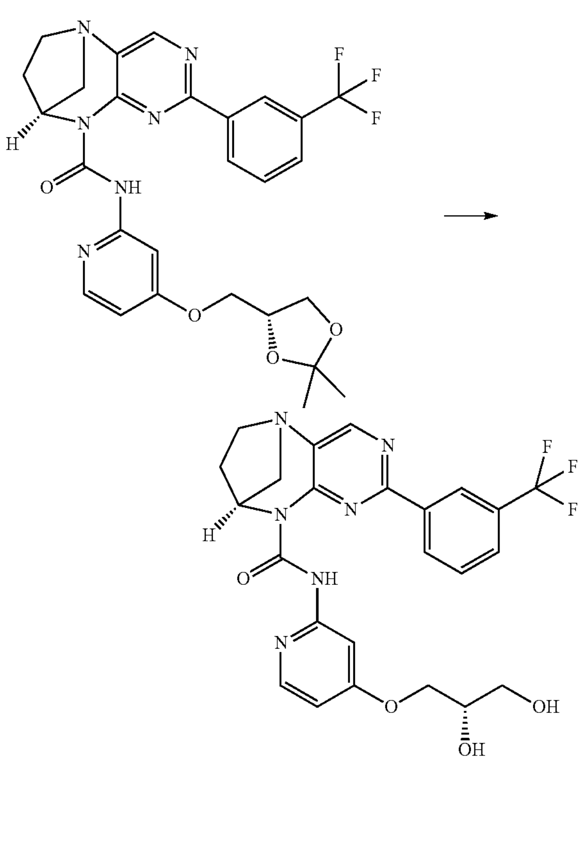
Rf: 0.1; UV active). The reaction mass was concentrated under reduced pressure and the resultant brown viscous oil was dissolved in water, basified with saturated aqueous sodium bicarbonate solution (10 mL), then extracted with 10% methanol in DCM (100 mL). Organic layer was washed with brine (50 mL), dried over sodium sulphate and filtered and concentrated. The crude material was purified by combiflash chromatography (using Silica gel column, 5% Methanol in DCM) to afford (8S)—N-(5-((R)-2,3-dihydroxypropoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (160 mg, 0.309 mmol, 38.3% yield) (HPLC:99.5%, LCMS: 99.85% and Chiral HPLC ee:99%) as an off-white solid. LC-MS (m/z): 517.08 $[M+H]^+$, Rt=1.82 min.

[1038] ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.16 (s, 1H), 8.40-8.62 (m, 3H), 8.26 (d, J=1.75 Hz, 1H), 8.06 (d, J=2.41 Hz, 1H), 7.94 (br d, J=7.67 Hz, 1H), 7.74-7.89 (m, 2H), 5.32-5.54 (m, 1H), 4.99 (br d, J=4.17 Hz, 1H), 4.69 (br s, 1H), 4.09 (dd, J=9.65, 3.95 Hz, 1H), 3.94 (dd, J=9.65, 6.36 Hz, 1H), 3.74-3.88 (m, 1H), 3.47 (br s, 2H), 3.23 (br d, J=7.45 Hz, 1H), 2.93-3.19 (m, 3H), 2.21-2.36 (m, 1H), 2.03 (dt, J=13.81, 7.13 Hz, 1H).

Example 36

Synthesis of (8S)—N-(4-((S)-2,3-dihydroxypropoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1039]



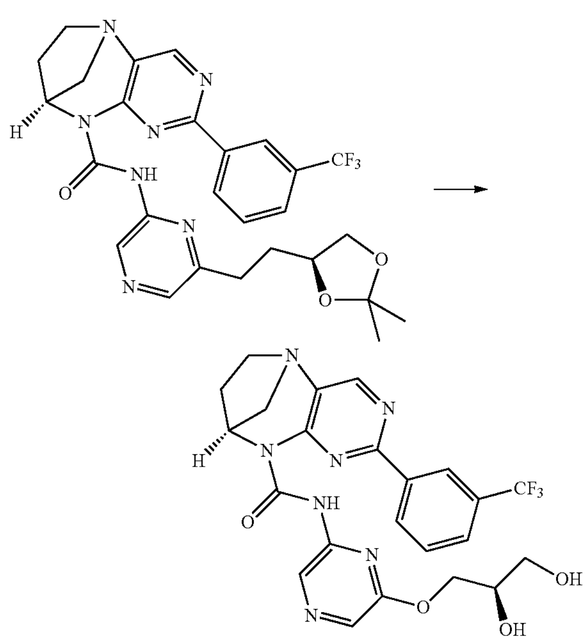
[1040] To a stirred solution of (8S)—N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (8.0 g, 14.37 mmol) in methanol (80 mL) under nitrogen at 0° C. was added aq HCl (8.74 mL, 287 mmol, 36%) and stirred for 2 h. (TLC eluent: 100% EtOAc: R_f-0.2; UV active). The reaction mixture was basified with saturated sodium bicarbonate solution (till pH-8-9) and solvent was evaporated under reduced pressure. The residue was diluted with water (100 mL) and extracted into dichloromethane (5×50 mL). Combined organic extracts were dried over anhydrous sodium sulphate, filtered and filtrate was evaporated in vacuo and the crude was triturated with diethyl ether (50 mL) to afford (8S)—N-(4-((S)-2,3-dihydroxypropoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (5.4 g, 10.45 mmol, 72.7% yield) as a white solid LCMS (m/z): 517.11 $[M+H]^+$, R_t=2.07 min

[1041] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 13.21 (s, 1H) 8.90 (s, 1H) 8.80 (d, J=8.11 Hz, 1H) 8.51 (s, 1H) 8.21 (d, J=5.70 Hz, 1H) 7.86-7.72 (m, 2H) 7.70-7.57 (m, 1H) 6.61 (dd, J=5.70, 2.41 Hz, 1H) 5.64 (dd, J=5.92, 3.07 Hz, 1H) 4.24-4.04 (m, 3H) 3.89-3.82 (m, 1H) 3.80-3.73 (m, 1H) 3.33-3.20 (m, 2H) 3.17-3.10 (m, 1H) 3.09-3.03 (m, 1H) 2.64 (d, J=3.95 Hz, 1H) 2.42-2.31 (m, 1H) 2.16-2.03 (m, 2H).

Example 37

Synthesis of (8S)—N-(6-((R)-2,3-dihydroxypropoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1042]



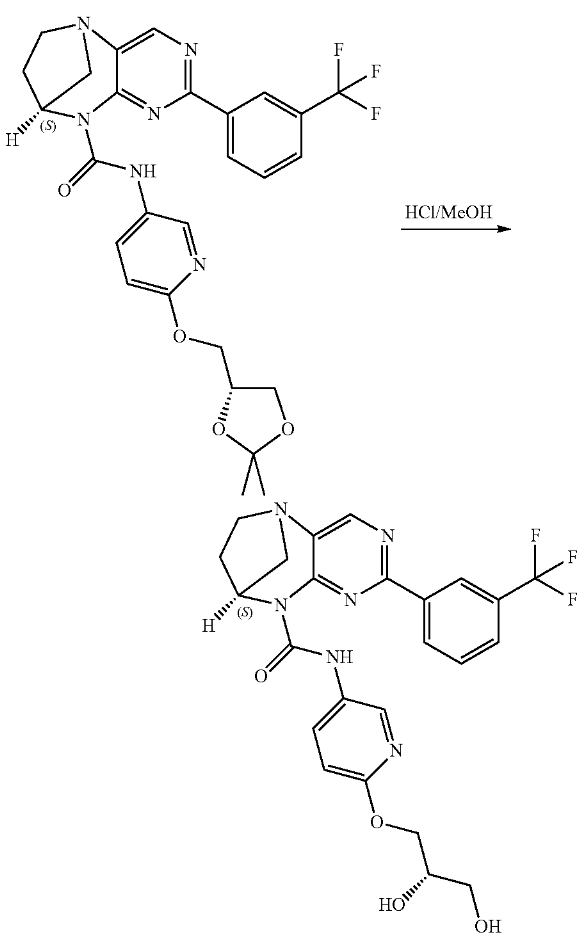
[1043] To a stirred solution of (8S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4, 5-b][1,4]diazepine-9(6H)-carboxamide (7.0 g, 12.56 mmol) in methanol (100 mL) at 0° C. under nitrogen was added aq. HCl (25 mL, 823 mmol) and the reaction mixture was stirred at 30° C. for 4 h. (TLC eluent:5% MeOH in DCM, Rf: 0.3). The reaction mixture was concentrated in vacuo and the residue was basified with saturated $NaHCO_3$ solution (75 mL). The resultant solid was filtered, triturated with pentane (100 mL) dried under reduced pressure to afford the desired product (8S)—N-(6-((R)-2,3-dihydroxypropoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (5.5 g, 10.59 mmol, 84% yield) as an off white solid. LCMS (m/z): 518.12 [M+H]+; Rt=2.03 min

[1044] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.76 (s, 1H), 9.07 (s, 1H), 8.69 (s, 1H), 8.64-8.47 (m, 2H), 8.05 (d, J=0.66 Hz, 1H), 7.83-7.65 (m, 2H), 5.70 (dd, J=5.81, 2.74 Hz, 1H), 4.50-4.27 (m, 2H), 4.10 (dq, J=10.00, 5.14 Hz, 1H), 3.84-3.71 (m, 1H), 3.71-3.60 (m, 1H), 3.45-3.21 (m, 2H), 3.21-2.92 (m, 2H), 2.66 (d, J=4.82 Hz, 1H), 2.51-2.29 (m, 1H), 2.27-2.08 (m, 1H), 2.05 (t, J=5.92 Hz, 1H).

Example 38

Synthesis of (8S)—N-(6-((S)-2,3-dihydroxypropoxy)pyridin-3-yl)-2-(3-(trifluoromethyl) phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4] diazepine-9(6H)-carboxamide

[1045]



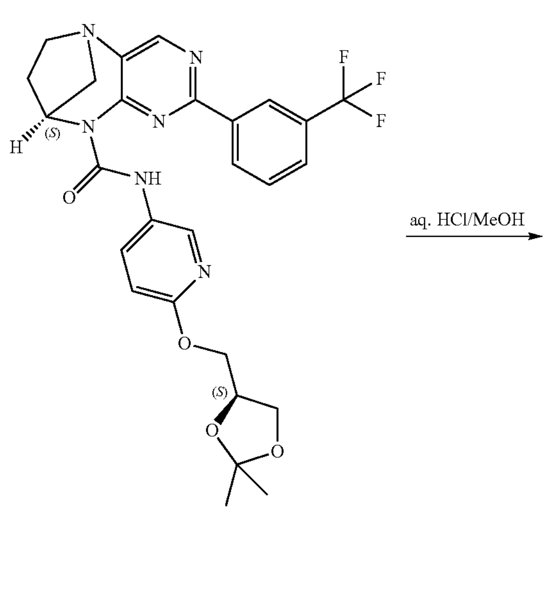
[1046] To a stirred solution of (8S)—N-(6-(((R)-2,2-dimethyl-1,3-di oxolan-4-yl)methoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (170 mg, 0.305 mmol) in Methanol (10 mL) was added HC (0.2 mL, 6.58 mmol) at 0° C. and stirred at RT for 2 h. (TLC system: neat ethyl acetate, R_f: 0.2). The reaction mixture was concentrated in vacuo and the residue was neutralized with saturated $NaHCO_3$ solution and extracted with ethyl acetate (20 mL×2). The combined organic layer was washed with water (15 mL×2) and brine (10 mL), dried over anhydrous Na_2SO_4 filtered and concentrated under reduced pressure to obtain the crude. The crude material was purified by flash column chromatography (100-200 silicagel eluent: 80% ethyl acetate in hexane) to afford the desired product (8S)—N-(6-((S)-2,3-dihydroxypropoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6N)-carboxamide (125 mg, 0.241 mmol, 79% yield) as a light yellow solid. LCMS (m/z): 517.15 $[M+H]^+$, Rt=2.01 min.

[1047] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.35 (s, 1H), 8.52 (s, 1H), 8.46 (s, 1H), 8.41 (d, J=8.11 Hz, 1H), 8.34 (d, J=2.63 Hz, 1H), 7.92 (dd, J=8.88, 2.74 Hz, 1H), 7.78 (d, J=7.89 Hz, 1H), 7.69-7.64 (i, 1H), 6.84 (d, J=8.99 Hz, 1H), 5.67 (dd, J=5.92, 2.63 Hz, 1H), 4.47 (dd, J=4.82, 2.41 Hz, 2H), 4.06-4.01 (i, 1H), 3.86 (d, J=5.48 Hz, 1H), 3.75-3.65 (m, 2H), 3.31-3.22 (m, 2H), 3.14-3.05 (m, 2H), 2.63 (t, J=6.47 Hz, 1H), 2.42-2.32 (m, 1H), 2.17-2.08 (m, 1H).

Example 39

Synthesis of (8S)—N-(6-((R)-2,3-dihydroxypropoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1048]



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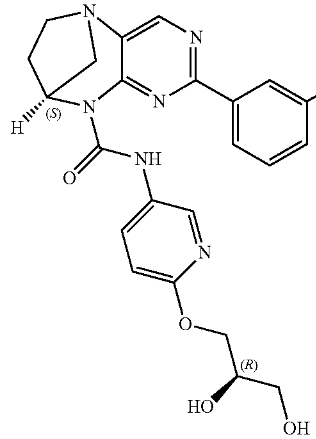


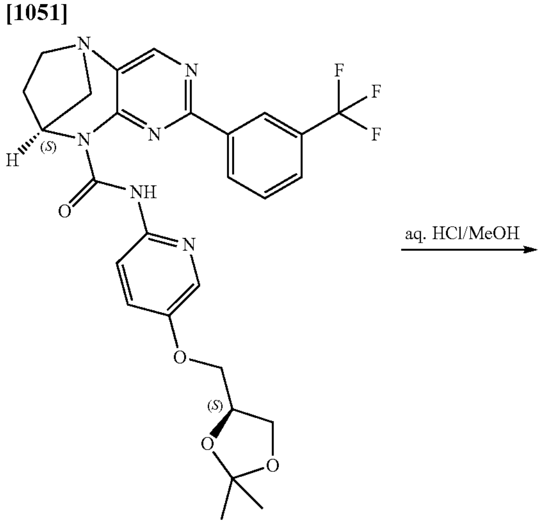
[1049] To a stirred solution of (8S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (200 mg, 0.359 mmol) in Methanol (10 mL) was added HCl (5 mL, 165 mmol)) at 0° C. then stirred at RT for 2 h. (TLC system: 10% MeOH in DCM, R 0.3). The reaction mixture was concentrated in vacuo and the residue was neutralized with aq $NaHCO_3$ solution and obtained solid was filtered then washed with Water (2×10 mL) to afford the desired product (8S)—N-(6-((R)-2,3-dihydroxypropoxy)pyridin-3-yl)-2-(3-(trifluoromethyl) phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (180 mg, 0.348 mmol, 97% yield) as an off white solid. LCMS (m/z): 517.18 $[M+H]^+$, Rt: 1.99 min.

[1050] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.35 (s, 1H), 8.52 (s, 1H), 8.47-8.38 (m, 2H), 8.34 (d, J=2.41 Hz, 1H), 7.92 (dd, J=8.88, 2.52 Hz, 1H), 7.78 (d, J=7.67 Hz, 1H), 7.70-7.61 (m, 1H), 6.84 (d, J=8.77 Hz, 1H), 5.67 (dd, J=5.48, 2.41 Hz, 1H), 4.52-4.42 (m, 2H), 4.04 (s, 1H), 3.88 (s, 1H), 3.69 (d, J=5.48 Hz, 2H), 3.34-3.21 (m, 2H), 3.15-3.03 (m, 2H), 2.67 (s, 1H), 2.44-2.30 (m, 1H), 2.12 (dt, J=14.36, 7.29 Hz, 1H).

Example 40

Synthesis of (8S)—N-(5-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-2-(3-(trifluoromethyl) phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1051]



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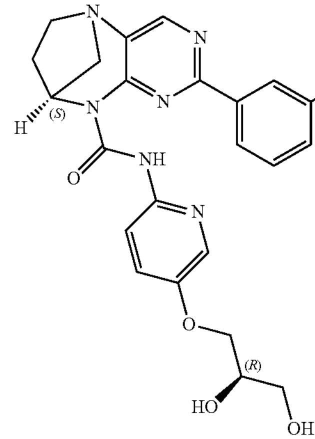


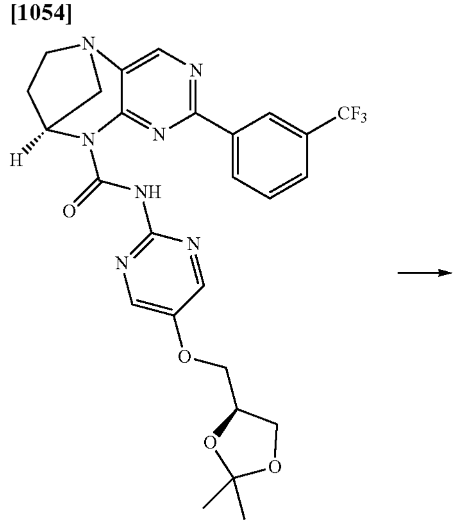
[1052] To a stirred solution of (8S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (200 mg, 0.359 mmol) in Methanol (10 mL) was added hydrochloric acid (5 mL, 165 mmol)) at 0° C. then stirred at RT for 2 h. (TLC system: 10% MeOH in DCM, R_f: 0.3). The reaction mixture was concentrated in vacuo and the residue was neutralized with aq $NaHCO_3$ solution and obtained solid was filtered then washed with Water (2×10 mL) to afford the desired product (8S)—N-(5-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (150 mg, 0.286 mmol, 80% yield) as an off white solid. LCMS (m/z): 517.18 $[M+H]^+$, Rt: 2.09 min.

[1053] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.12 (s, 1H), 8.88 (s, 1H), 8.77 (d, J=7.89 Hz, 1H), 8.51 (s, 1H), 8.15-8.07 (m, 2H), 7.77 (d, J=7.89 Hz, 1H), 7.68-7.61 (m, 1H), 7.31 (dd, J=8.99, 3.07 Hz, 1H), 5.67 (dd, J=5.81, 2.74 Hz, 1H), 4.21-4.04 (m, 3H), 3.92-3.85 (m, 1H), 3.82-3.76 (m, 1H), 3.32-3.20 (m, 2H), 3.14-3.02 (m, 2H), 2.56 (d, J=4.38 Hz, 1H), 2.37 (qd, J=9.87, 4.60 Hz, 1H), 2.16-2.04 (m, 1H), 1.95 (t, J=5.92 Hz, 1H).

Example 41

Synthesis of (8S)—N-(5-((R)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1054]



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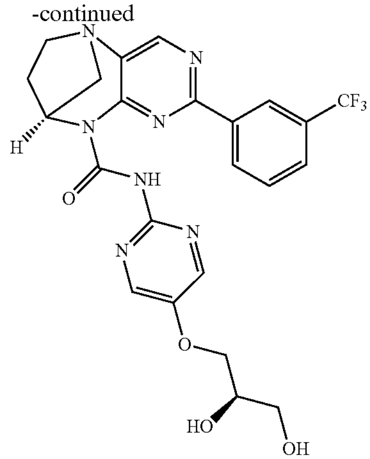


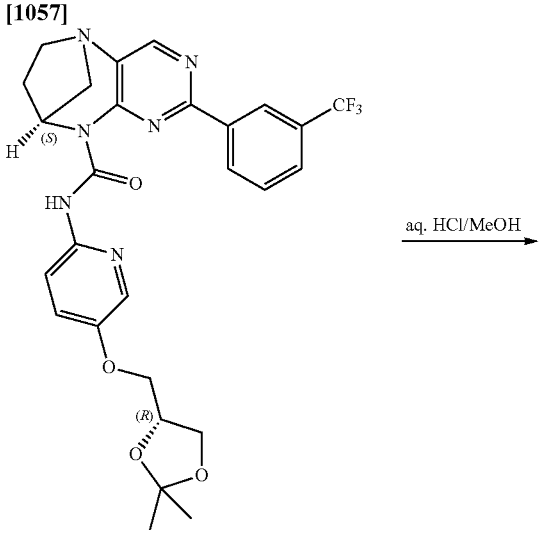
[1055] To a stirred solution of (8S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (320 mg, 0.574 mmol) in methanol (25 mL) was added aq. HCl (0.017 mL, 0.574 mmol, 36%) at 0° C. and stirred at RT for 1 h. (TLC eluent: 10% MeOH in EtOAc: R-0.1; UV active). The reaction mixture was basified with saturated sodium bicarbonate solution (till pH-8-9) at 0° C. and concentrated. The residue was diluted with water (8 mL) and extracted into DCM (2×25 mL). Combined organic extracts were dried over anhydrous sodium sulphate, filtered and filtrate was evaporated under reduced pressure to afford (8S)—N-(5-((R)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (245 mg, 0.469 mmol, 82% yield) as an off white solid. LCMS (m/z): 518.19 $[M+H]^+$, R_t=1.90 min.

[1056] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.50 (s, 1H), 8.85 (s, 1H), 8.71 (br d, J=7.89 Hz, 1H), 8.52 (s, 1H), 8.33-8.46 (m, 2H), 7.76 (br d, J=7.89 Hz, 1H), 7.44-7.69 (m, 1H), 5.73 (dd, J=5.70, 2.85 Hz, 1H), 4.16 (s, 3H), 3.70-3.99 (m, 2H), 3.18-3.34 (m, 2H), 2.94-3.18 (m, 2H), 2.66 (br s, 1H), 2.37 (dt, J=9.48, 4.58 Hz, 1H), 1.96-2.21 (m, 2H).

Example 42

Synthesis of (8S)—N-(5-((S)-2,3-dihydroxypropoxy)pyridin-2-yl)-2-(3-(trifluoro methyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1057]



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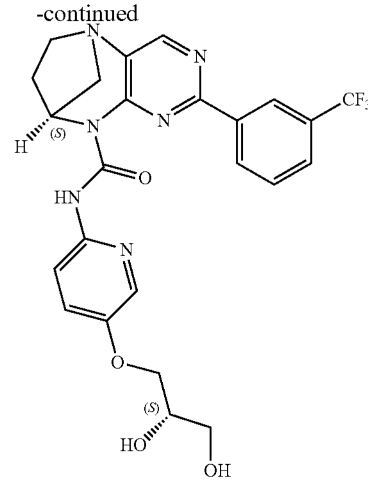


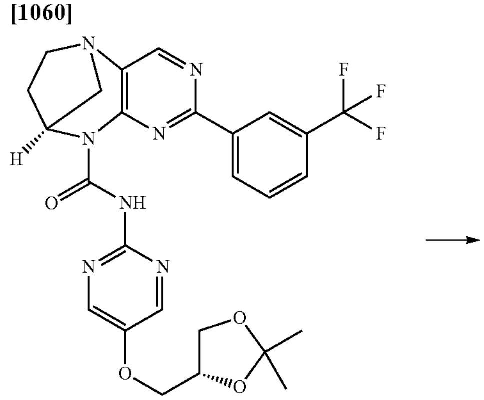
[1058] To a stirred solution of (8S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (250 mg, 0.449 mmol) in Methanol (20 mL) was added hydrochloric acid (1 ml, 11.85 mmol) at 0° C. then stirred at RT for 1 h. (TLC system: Neat Ethyl acetate, R_f 0.2). The reaction mixture was concentrated in vacuo and the residue was neutralized with saturated $NaHCO_3$ solution and obtained solid was filtered then washed with n-Pentane (2×10 mL) to afford the desired product (8S)—N-(5-((S)-2,3-dihydroxypropoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (146 mg, 0.282 mmol, 62.9% yield) as an off white solid. LCMS (m/z): 517.18 $[M+H]^+$, R_t=2.18 min.

[1059] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.12 (s, 1H), 8.88 (s, 1H), 8.77 (d, J=7.89 Hz, 1H), 8.51 (s, 1H), 8.10 (d, J=9.65 Hz, 2H), 7.77 (d, J=7.67 Hz, 1H), 7.68-7.59 (m, 1H), 7.31 (dd, J=8.99, 3.07 Hz, 1H), 5.67 (dd, J=5.81, 2.96 Hz, 1H), 4.19-4.07 (m, 3H), 3.91-3.84 (m, 1H), 3.83-3.74 (m, 1H), 3.34-3.19 (m, 2H), 3.15-3.02 (m, 2H), 2.60 (d, J=4.38 Hz, 1H), 2.42-2.30 (m, 1H), 2.11 (dt, J=14.69, 7.56 Hz, 1H), 2.00 (t, J=5.92 Hz, 1H).

Example 43

Synthesis of (8S)—N-(5-((S)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1060]



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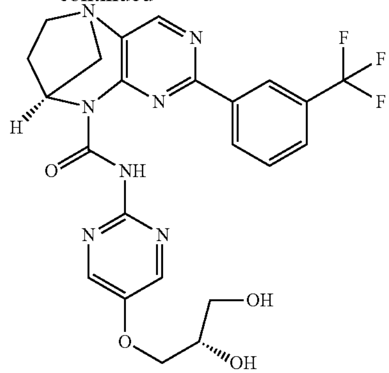


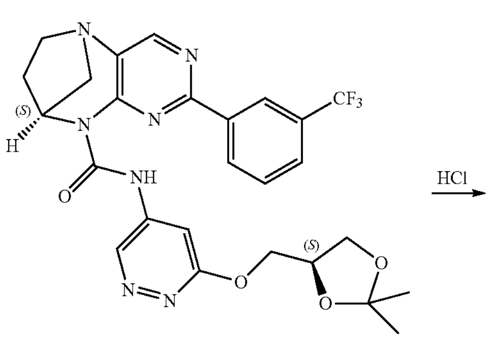
[1061] To a stirred solution of (8S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (200 mg, 0.359 mmol) in methanol (10 mL) under nitrogen at 0° C. was added aq. HCl (1.0 mL, 4.00 mmol, 36%) and stirred at RT for 1 h. (TLC eluent: 5% Methanol in DCM, R_f:0.3, UV active). To the reaction mixture was added saturated $NaHCO_3$ solution (till pH-8-9) and extracted into EtOAc (3×10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to obtain crude product. The crude was triturated with diethylether (2×10 mL) to afford (8S)—N-(5-((S)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (120 mg, 0.231 mmol, 64.3% yield) as an off white solid LCMS (m/z): 518.16 $[M+H]^+$, R_t=1.89 min.

[1062] ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.26 (s, 1H), 8.81-8.70 (m, 2H), 8.54 (s, 1H), 8.47 (s, 2H), 7.93 (br d, J=7.45 Hz, 1H), 7.87-7.79 (m, 1H), 5.45 (br d, J=2.63 Hz, 1H), 5.05 (br s, 1H), 4.71 (br s, 1H), 4.18 (dd, J=10.08, 3.95 Hz, 1H), 4.04 (dd, J=9.98, 6.25 Hz, 1H), 3.86-3.78 (m, 1H), 3.47 (br d, J=5.48 Hz, 2H), 3.30 (m, 1H), 3.17-2.94 (m, 3H), 2.34-2.20 (m, 1H), 2.08-1.96 (m, 1H).

Example 44

Synthesis of (8S)—N-(6-((R)-2,3-dihydroxypropoxy)pyridazin-4-yl)-2-(3-(trifluoromethyl) phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4] diazepine-9(6H)-carboxamide

[1063]



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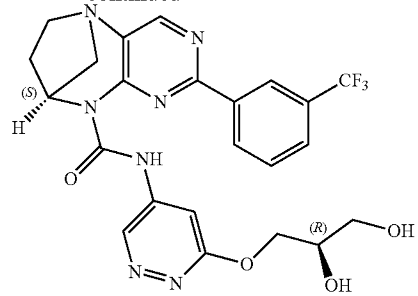


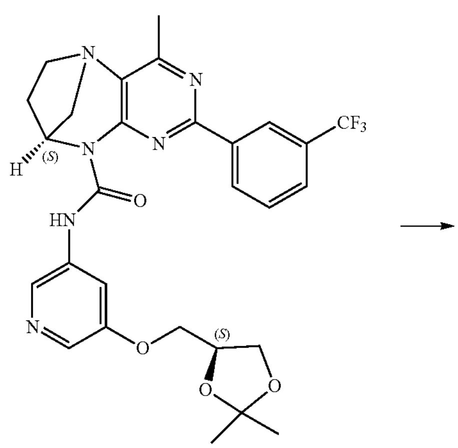
[1064] To a stirred solution of (8S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridazin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (140 mg, 0.251 mmol) in methanol (30 mL) was added hydrochloric acid (0.6 ml, 7.11 mmol) drop wise over a period of 5 min. at room temperature. Then the reaction mixture was stirred at 28° C. for 1 h. (TLC system: 10% MeOH in EtOAc, Rf: 0.3). and concentrated under reduced pressure to obtain the crude compound, diluted with water and neutralized with saturated $NaHCO_3$ solution (30 mL), filtered the obtain solid and washed with diethyl ether (30 mL), dried to afford the desired product (8S)—N-(6-((R)-2,3-dihydroxypropoxy) pyridazin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (106 mg, 0.203 mmol, 81% yield) as an off white solid. LCMS (m/z): 518.19 $[M+H]^+$, R_t=1.86 min.

[1065] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.87 (s, 1H), 8.85 (d, J=2.19 Hz, 1H), 8.58 (s, 1H), 8.47 (s, 1H), 8.39 (d, J=7.67 Hz, 1H), 7.83 (d, J=7.67 Hz, 1H), 7.76-7.69 (m, 1H), 7.58 (d, J=2.19 Hz, 1H), 5.65 (dd, J=5.70, 2.41 Hz, 1H), 4.73-4.60 (m, 2H), 4.11 (dq, J=9.70, 5.02 Hz, 1H), 3.81-3.63 (m, 3H), 3.35-3.23 (m, 2H), 3.17-3.05 (m, 2H), 2.57 (t, J=6.36 Hz, 1H), 2.46-2.35 (m, 1H), 2.11 (dt, J=14.63, 7.26 Hz, 1H).

Example 45

Synthesis of (8S)—N-(5-((R)-2,3-dihydroxypropoxy)pyridin-3-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1066]



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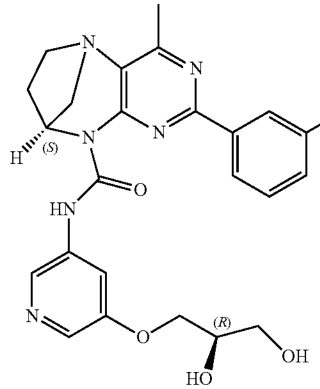


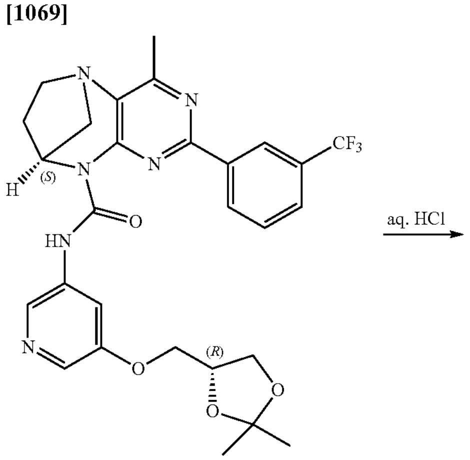
[1067] To a stirred solution of (8S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (300 mg, 0.526 mmol) in Methanol (15 mL) was added aqueous HCl (2.0 mL, 24.00 mmol) under nitrogen at 0° C. and the reaction mixture was stirred for 2 h. at 28° C. (TLC eluent: 100% Ethylacetate, Rf value:0.2, UV active) and the reaction mixture was concentrated in vacuo and diluted with water followed by quenched it with saturated $NaHCO_3$ solution (25 mL) at 0° C. and extracted with DCM (2×50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude compound. This compound was triturated with n-pentane (30 mL) to afford the desired product (8S)—N-(5-((R)-2,3-dihydroxypropoxy)pyridin-3-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (210 mg, 0.391 mmol, 74.3% yield) as a pale brown solid. (TLC eluent: 100% Ethylacetate, Rf value: 0.2, UV active). LCMS (m/z): 531.23 $[M+H]^+$, Rt=2.11 min.

[1068] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.76 (s, 1H), 8.56-8.35 (m, 2H), 8.26-8.05 (m, 2H), 7.96 (t, J=2.30 Hz, 1H), 7.77 (d, J=7.89 Hz, 1H), 7.73-7.62 (m, 1H), 5.65 (br d, J=5.92 Hz, 1H), 4.24-4.08 (m, 3H), 3.93-3.81 (m, 2H), 3.33-3.15 (m, 2H), 3.07 (s, 2H), 2.69 (s, 3H), 2.61 (br d, J=3.51 Hz, 1H), 2.43-2.32 (m, 1H), 2.14-1.98 (m, 2H).

Example 46

Synthesis of (8S)—N-(5-((S)-2,3-dihydroxypropoxy)pyridin-3-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1069]



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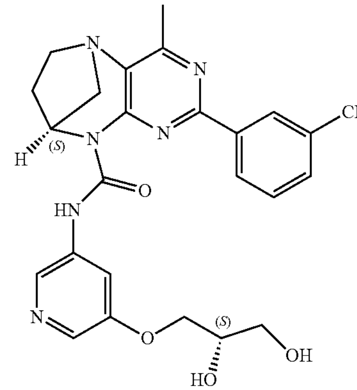


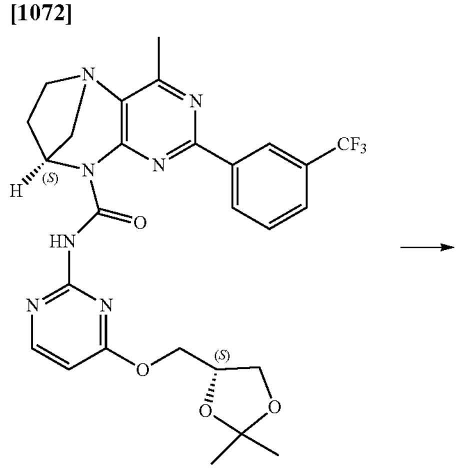
[1070] To a stirred solution of (8S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (150 mg, 0.263 mmol) in Methanol (10 mL) was added aqueous HCl (2.0 mL, 24.00 mmol) under nitrogen at 0° C. and the reaction mixture was stirred for 2 h at 28° C. (TLC eluent: 100% Ethylacetate, Rf value: 0.2, UV active). Then the reaction mixture was concentrated in vacuo and added water followed by quenched with saturated $NaHCO_3$ solution (20 mL) at 0° C. and extracted with DCM (2×40 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated and triturated with n-pentane (30 mL) to afford the desired product (8S)—N-(5-((S)-2,3-dihydroxypropoxy)pyridin-3-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (71 mg, 0.131 mmol, 49.8% yield) as an off white solid. LCMS (m/z): 531.23 $[M+H]^+$, Rt=2.11 min.

[1071] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.76 (s, 1H), 8.53-8.37 (m, 2H), 8.24 (d, J=1.75 Hz, 1H), 8.09 (d, J=2.63 Hz, 1H), 8.03-7.96 (m, 1H), 7.77 (br d, J=7.67 Hz, 1H), 7.73-7.62 (m, 1H), 5.65 (br d, J=5.70 Hz, 1H), 4.20-4.08 (m, 3H), 3.97-3.67 (m, 2H), 3.28-3.14 (m, 2H), 3.07 (s, 2H), 2.69 (s, 3H), 2.37 (td, J=14.09, 5.59 Hz, 1H), 2.14-1.98 (m, 1H), 1.55 (s, 2H).

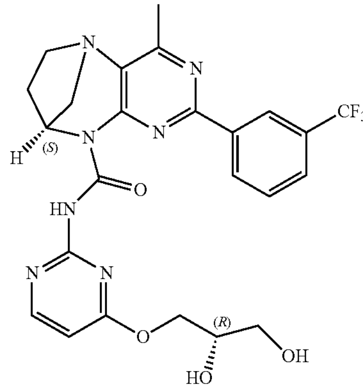
Example 47

Synthesis of (8S)—N-(4-((S)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1072]



-continued



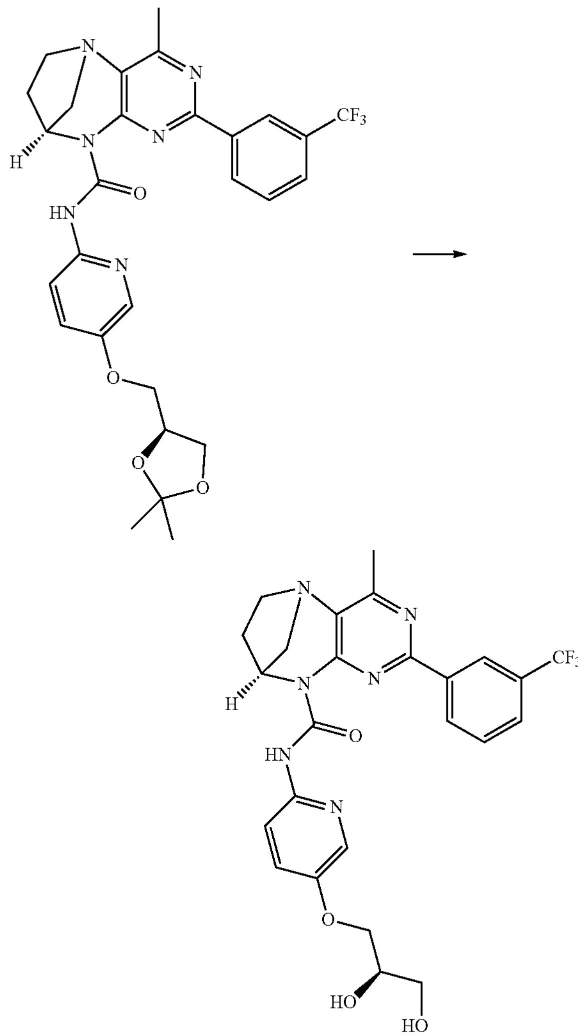
[1073] To a stirred solution of (8S)—N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (250 mg, 0.437 mmol) in Tetrahydrofuran (THF) (10 mL) was added aqueous HCl (0.036 mL, 0.437 mmol) under nitrogen at 0° C. and the reaction mixture was stirred for 2 h at 0° C. (TLC system: Neat ethyl acetate. R_f value: 0.2.). The reaction mixture was concentrated in vacuo and diluted with water, followed by quenched with saturated $NaHCO_3$ solution (20 mL) at 0° C. and extracted with DCM (2×40 mL). The combined organic layer was separated and dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude compound. This compound was triturated with n-pentane (30 mL) to afford the desired product (8S)—N-(4-((S)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (170 mg, 0.316 mmol, 72.2% yield) as a white solid. LCMS (m/z): 532.27 [M+H]+; Rt=2.26 min.

[10754] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.88 (s, 1H), 8.88 (s, 1H), 8.76 (d, J=7.89 Hz, 1H), 8.36 (d, J=5.70 Hz, 1H), 7.75 (d, J=7.67 Hz, 1H), 7.59-7.66 (m, 1H), 6.50 (d, J=5.70 Hz, 1H), 5.73 (dd, J=6.14, 2.41 Hz, 1H), 4.74 (dd, J=12.06, 5.04 Hz, 1H), 4.55 (dd, J=12.17, 4.49 Hz, 1H), 4.34 (d, J=6.36 Hz, 1H), 3.92-4.02 (m, 1H), 3.62-3.71 (m, 2H), 3.42 (br t, J=6.91 Hz, 1H), 3.12-3.23 (m, 2H), 2.99-3.07 (m, 2H), 2.68 (s, 3H), 2.27-2.41 (m, 1H), 1.98-2.13 (m, 1H).

Example 48

Synthesis of (8S)—N-(5-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1075]



[1076] To a stirred solution of (8S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (300 mg, 0.526 mmol) in Methanol (5 mL) was added HCl (1 mL, 11.52 mmol) at room temperature. The resulting mixture was stirred at RT for 1 h. (TLC 5% MeOH/DCM R_f: 0.3; UV active). Reaction mass was concentrated under reduced pressure to get crude compound which was basified with saturated bicarbonate solution (10 mL) and filtered the obtain solid to afford the desired product (8S)—N-(5-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b]

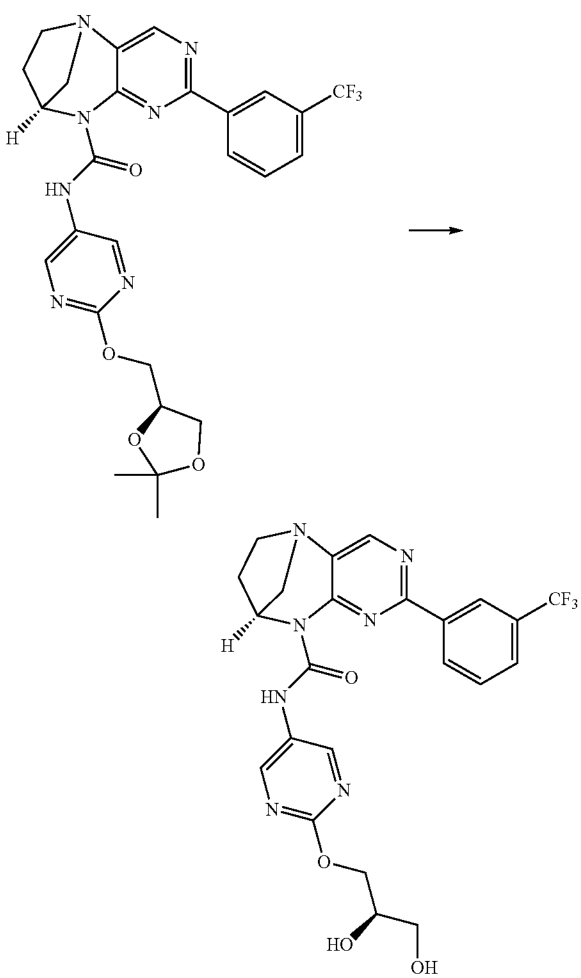
[1,4]diazepine-9(6H)-carboxamide (242 mg, 0.449 mmol, 85% yield) as an off white solid. LCMS (m z): 531.19 $[M+H]^+$, R_t=2.46 min.

[1077] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.30 (s, 1H), 8.87 (s, 1H), 8.78 (d, J=7.7 Hz, 1H), 8.21-8.01 (m, 2H), 7.75 (d, J=7.7 Hz, 1H), 7.63 (t, J=7.9 Hz, 1H), 7.45-7.27 (m, 1H), 5.67 (d, J=4.2 Hz, 1H), 4.24-4.01 (m, 3H), 3.98-3.72 (m, 2H), 3.29-3.13 (m, 2H), 3.13-2.95 (m, 2H), 2.67 (s, 3H), 2.57 (d, J=4.6 Hz, 1H), 2.47-2.21 (m, 1H), 2.07 (td, J=7.1, 14.4 Hz, 1H), 1.96 (t, J=5.9 Hz, 1H).

Example 49

Synthesis of (8S)—N-(2-((R)-2,3-dihydroxypropoxy)pyrimidin-5-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1078]



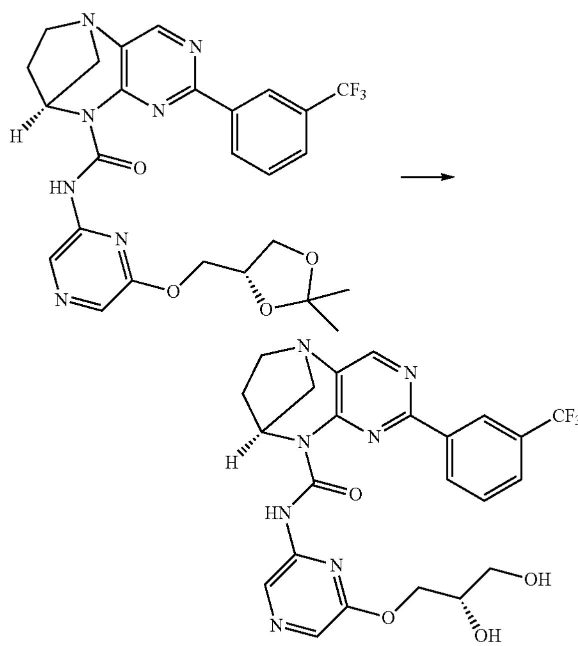
[1079] To a stirred solution of (8S)—N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (200 mg, 0.359 mmol) in methanol (10 mL) at 0° C. was added aq. HCl (0.448 mL, 5.38 mmol) and stirred at 0° C. for 1 h. (TLC eluent: 100% Ethyl acetate, R_f=0.2; UV active). The reaction mixture was basified with saturated sodium bicarbonate solution (till pH-8-9) at 0° C. and methanol was concentrated. The residue was diluted with water and stirred for 10 min. The resultant solid was filtered through Buchner Funnel, dried under reduced pressure and to afford (8S)—N-(2-((R)-2,3-dihydroxypropoxy)pyrimidin-5-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (140 mg, 0.269 mmol, 74.9% yield) as off white solid. LCMS (m/z): 518.19 $[M+H]^+$, R_t=1.91 min.

[1080] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.62-12.36 (m, 1H), 8.79 (s, 2H), 8.55 (s, 1H), 8.45 (s, 1H), 8.38 (d, J=7.89 Hz, 1H), 7.79 (d, J=7.89 Hz, 1H), 7.70-7.63 (m, 1H), 5.66 (dd, J=5.92, 2.63 Hz, 1H), 4.56-4.45 (m, 2H), 4.14 (dq, J=10.14, 5.02 Hz, 1H), 3.85-3.70 (m, 2H), 3.33-3.22 (m, 2H), 3.16-3.04 (m, 3H), 2.44-2.30 (m, 2H), 2.12 (dt, J=14.31, 7.21 Hz, 1H).

Example 50

Synthesis of (8S)—N-(6-((S)-2,3-dihydroxypropoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1081]



[1082] To a stirred solution of (8S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (240 mg, 0.430 mmol) in 1,4-Dioxane (5.0 mL) was added 4M HCl in dioxane (1.076 mL, 4.30 mmol) at RT and was stirred for 4 h at the same temperature (TLC Eluent: Neat ethylacetate, R_f: 0.2) The reaction mixture was partitioned between saturated Aq $NaHCO_3$ solution (10 mL) and EtOAc (30 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude.

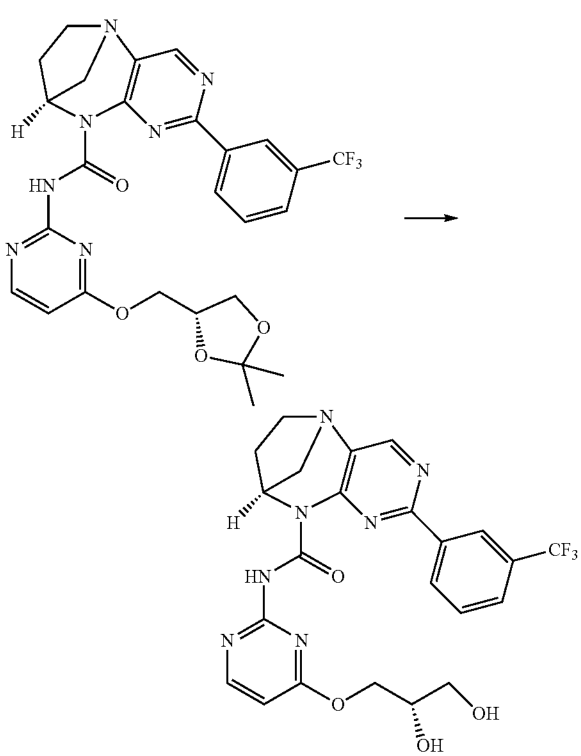
The crude compound was purified by flash column chromatography (silicagel: 100-200 mesh, Eluent: 70% Ethylacetate in hexane) to afford the desired product (8S)—N-(6-((S)-2,3-dihydroxypropoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (155 mg, 0.296 mmol, 68.7% yield) as a brown solid. LCMS (m/z): 518.05 $[M+H]^+$, Rt=2.02 min.

[1083] ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.74 (s, 1H), 8.97 (s, 1H), 8.67-8.61 (m, 2H), 8.59 (s, 1H), 8.07 (s, 1H), 7.94-7.88 (m, 2H), 5.50 (dd, J=6.03, 2.96 Hz, 1H), 5.04 (d, J=5.04 Hz, 1H), 4.70 (t, J=5.48 Hz, 1H), 4.34-4.23 (m, 2H), 3.86 (dq, J=10.47, 5.43 Hz, 1H), 3.49-3.41 (m, 2H), 3.23 (br d, J=8.55 Hz, 1H), 3.17-3.10 (m, 2H), 3.02 (dd, J=12.06, 3.07 Hz, 1H), 2.33-2.23 (m, 1H), 2.11-2.00 (m, 1H).

Example 51

Synthesis of (8S)—N-(4-((S)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1084]



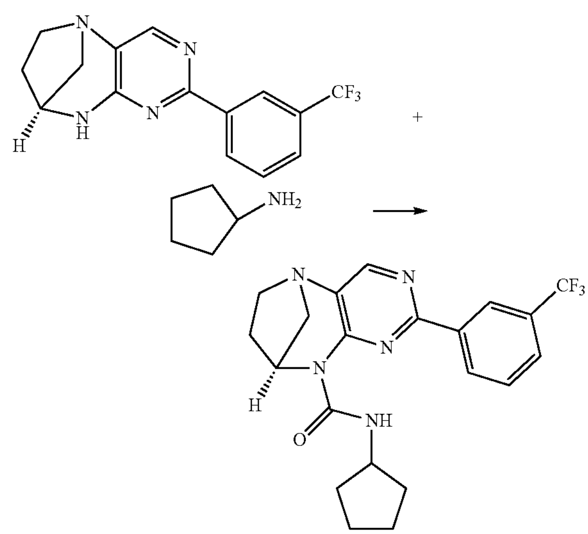
[1085] To a stirred solution of (8S)—N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (200 mg, 0.359 mmol) in methanol (5 mL) at 0° C. was added HCl (10.90 μL, 0.359 mmol) drop wise over a period of 5 min. Then the reaction mixture was stirred at 30° C. for 2 h. (TLC eluent: 5% MeOH in DCM: R_f-0.4; UV active). After 2 h, methanol was evaporated and neutralized with saturated $NaHCO_3$ solution (5 ml), filtered the obtain solid and washed with diethylether (2×20 ml) to afforded the desired product (8S)—N-(4-((S)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (135 mg, 0.257 mmol, 71.5% yield) as an off white solid. LCMS (m/z): 518.12 $[M+H]^+$, Rt=1.97 min.

[1086] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.68 (s, 1H), 8.89 (s, 1H), 8.75 (d, J=7.89 Hz, 1H), 8.54 (s, 1H), 8.37 (d, J=5.70 Hz, 1H), 7.77 (d, J=7.67 Hz, 1H), 7.68-7.61 (m, 1H), 6.52 (d, J=5.70 Hz, 1H), 5.74 (dd, J=6.03, 2.96 Hz, 1H), 4.74 (dd, J=12.06, 4.82 Hz, 1H), 4.56 (dd, J=12.06, 4.60 Hz, 1H), 4.32 (br s, 1H), 3.97 (br s, 1H), 3.71-3.63 (m, 2H), 3.43-3.21 (m, 3H), 3.13-2.99 (m, 2H), 2.46-2.30 (m, 1H), 2.18-2.02 (m, 1H).

Example 52

Synthesis of (8S)—N-cyclopentyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1087]



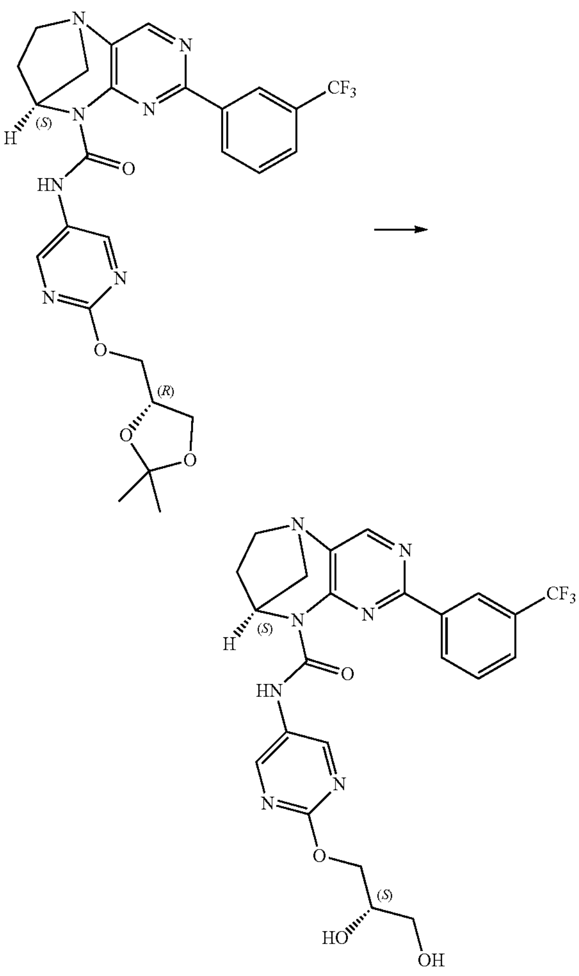
[1088] To a stirred solution of (8S)-2-(3-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine (300 mg, 0.979 mmol) in THF (30 mL) under nitrogen at RT, was added solid triphosgene (174 mg, 0.588 mmol) and stirred for 30 min. then added triethylamine (0.683 mL, 4.90 mmol) and cyclopentanamine (125 mg, 1.469 mmol) and the reaction was heated at 75° C. for 16 h. (TLC eluent: EtOAc: R_f-0.5; UV active). The reaction mixture was cooled to RT, concentrated and the residue partitioned between water (30 mL) and DCM (2×100 mL). Organic layer was separated, dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude compound. The crude product was purified by chromatography (neutral alumina, eluted with EtOAc) to afford pure (8S)—N-cyclopentyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (101 mg, 0.241 mmol, 24.62% yield) as an off white solid. LCMS (m/z): 418.18 $[M+H]^+$, R_t=2.77 min

[1089] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 9.97 (d, J=6.58 Hz, 1H), 8.36-8.44 (m, 3H), 7.74 (d, J=7.67 Hz, 1H), 7.57-7.64 (m, 1H), 5.63 (dd, J=5.92, 2.85 Hz, 1H), 4.25 (m, J=6.84 Hz, 1H), 3.15-3.29 (m, 2H), 2.97-3.08 (m, 2H), 2.26-2.36 (m, 1H), 2.01-2.18 (m, 3H), 1.57-1.80 (m, 6H).

Example 53

Synthesis of (8S)—N-(2-((S)-2,3-dihydroxy-propoxy)pyrimidin-5-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1090]



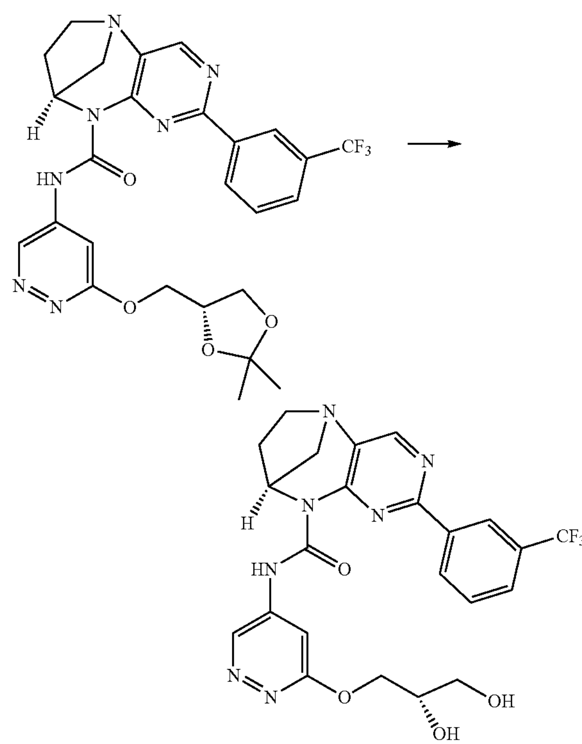
[1091] To a stirred solution of (8S)—N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (0.4 g, 0.717 mmol) in Methanol (15 mL) was added aq HCl (1.5 mL, 18.00 mmol) at 0° C. and the reaction mixture was stirred at 0° C. for 4 h. (TLC system: 5% MeOH in DCM. R_f value: 0.3). The reaction mixture was neutralized with saturated $NaHCO_3$ solution (25 mL) at 0° C. and filtered the obtain solid, which was triturated with n-pentane (25 mL) to afford the desired product (8S)—N-(2-((S)-2,3-dihydroxypropoxy)pyrimidin-5-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (0.193 g, 0.372 mmol, 51.9% yield) as an off white solid. LCMS (m/z):518.12 [M+H]$^+$, Rt=1.89 min.

[1092] ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 11.95 (s, 1H), 8.90-8.40 (m, 5H), 8.05-7.67 (m, 2H), 5.42 (br s, 1H), 4.95 (d, J=5.04 Hz, 1H), 4.65 (t, J=5.59 Hz, 1H), 4.44-4.28 (m, 1H), 4.20 (dd, J=10.85, 6.47 Hz, 1H), 3.83 (dd, J=10.19, 5.15 Hz, 1H), 3.58-3.39 (m, 2H), 3.21-2.95 (m, 4H), 2.28 (br s, 1H), 2.13-1.92 (m, 1H).

Example 54

Synthesis of (8S)—N-(6-((S)-2,3-dihydroxy-propoxy)pyridazin-4-yl)-2-(3-(trifluoro methyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1093]



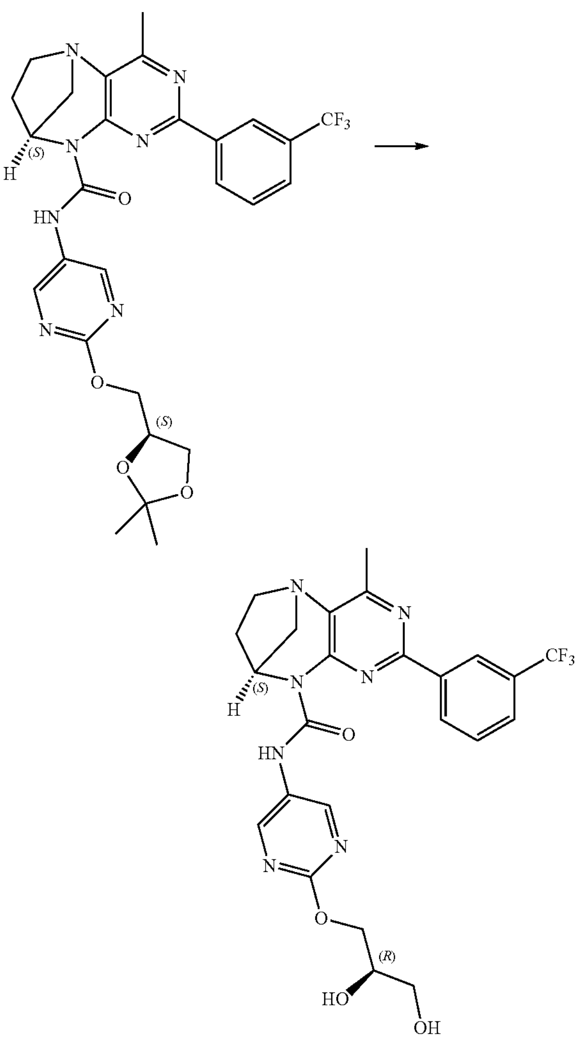
[1094] To a stirred solution of (8S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridazin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (135 mg, 0.242 mmol) in methanol (50 mL) at 0° C. was added HCl (0.074 mL, 2.421 mmol), drop wise over a period of 5 min. Then the reaction mixture was stirred at 30° C. for 2 h. (TLC eluent: 5% MeOH in DCM: R_f-0.5; UV active) and evaporated the solvent from the reaction mixture to obtain residue, it was neutralized with sodium bicarbonate solution and filtered the obtain solid, followed by washed with ether (2×50 ml) and n-pentane (2×50 ml) to afford the desired product (8S)—N-(6-((S)-2,3-dihydroxypropoxy)pyridazin-4-yl)-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (115 mg, 0.220 mmol, 91% yield) as a pale yellow solid. LCMS (m/z): 518.30 $[M+H]^+$, Rt=1.93 min.

[1095] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.87 (br s, 1H), 8.85 (s, 1H), 8.58 (s, 1H), 8.47 (s, 1H), 8.39 (d, J=7.67 Hz, 1H), 7.84 d, J=7.45 Hz, 1H), 7.75-7.69 (m, 1H), 7.58 (s, 1H), 5.66 (s, 1H), 4.73-4.58 (m, 2H), 4.11 (d, J=3.95 Hz, 1H), 3.82-3.56 (m, 3H), 3.34-3.22 (m, 2H), 3.17-3.03 (m, 2H), 2.56 (br s, 1H), 2.41 (d, J=5.70 Hz, 1H), 2.18-2.03 (m, 1H).

Example 55

Synthesis of (8S)—N-(2-((R)-2,3-dihydroxypropoxy)pyrimidin-5-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1096]



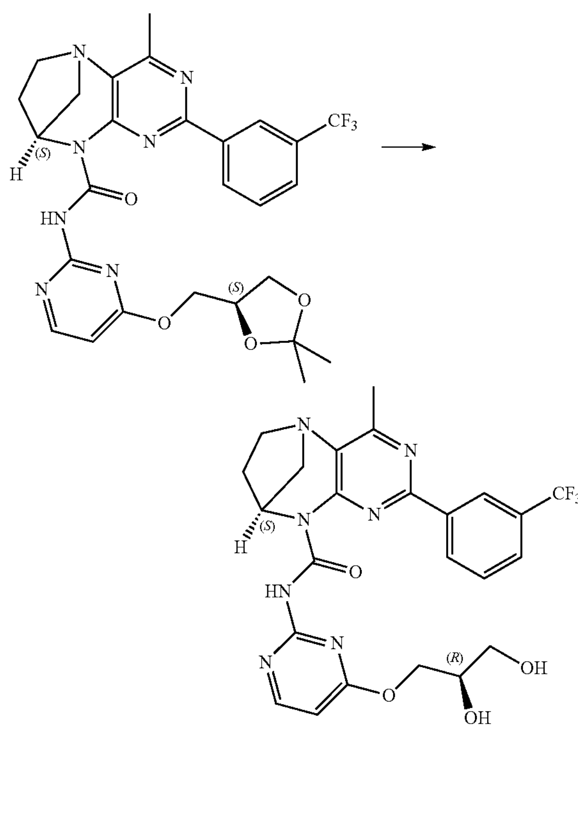
[1097] To a stirred solution of (8S)—N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (350 mg, 0.612 mmol) in Methanol (5 mL) was added HCl (1.5 mL, 9.00 mmol) at 0° C. and the reaction mixture was stirred for 2 h. at 28° C. (TLC eluent: 5% MeOH/DCM, Rf value: 0.3, UV active). The reaction mixture was evaporated and neutralized with $NaHCO_3$ solution and filtered the obtain solid. This compound (230 mg) was purified by prep HPLC (conditions: MP-A: 10 Mm Ammonium Acetate (Aq) MP-B: Acetonitrile Column: Kromasil C18 (250×21.2) mm, 5u Flow: 20 ml/min Method: 60:40 Solubility: THF+CAN). The Collected fractions were evaporated under reduced pressure and the residue was partitioned between water and extracted with DCM (2×25 mL). The organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure to afford the desired product (8S)—N-(2-((R)-2,3-dihydroxypropoxy)pyrimidin-5-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (40 mg, 0.074 mmol, 12.12% yield) as an off white solid. LCMS (m/z): 532.27 $[M+H]^+$, Rt=2.17 min.

[1098] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.78-12.58 (m, 1H), 8.79 (s, 2H), 8.44 (s, 1H), 8.37 (d, J=7.45 Hz, 1H), 7.77 (d, J=7.67 Hz, 1H), 7.69-7.61 (m, 1H), 5.76-5.55 (m, 1H), 4.56-4.44 (m, 2H), 4.13 (t, J=4.93 Hz, 1H), 3.84-3.69 (m, 3H), 3.21 (t, J=7.78 Hz, 2H), 3.07 (s, 2H), 2.69 (s, 3H), 2.37 (td, J=13.87, 5.59 Hz, 1H), 2.24 (br s, 1H), 2.14-2.02 (m, 1H).

Example 56

Synthesis of (8S)—N-(4-((R)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1099]



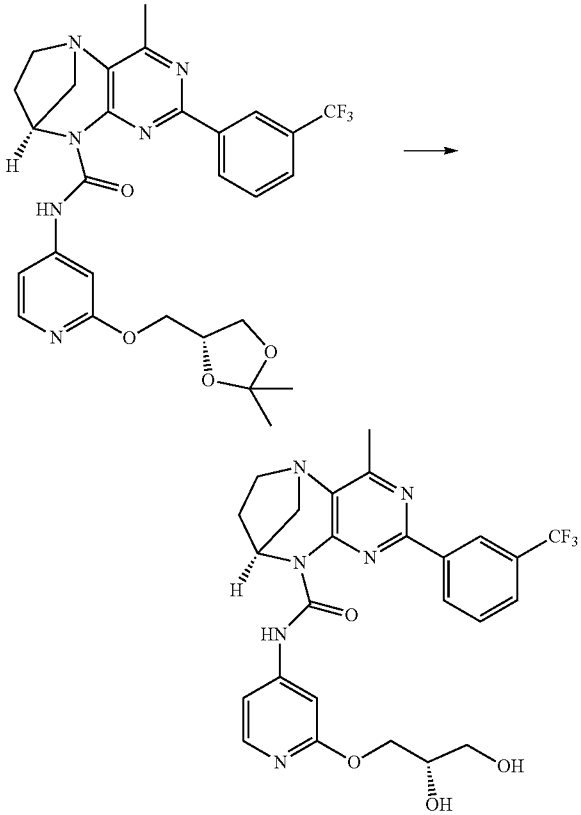
[1100] To a stirred solution of (8S)—N-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (200 mg, 0.350 mmol) in Methanol (5 mL) was added HCl (1 mL, 11.52 mmol) at room temp. The resulting mixture was stirred at rt for 1 h. (TLC eluent: Neat Ethyl acetate, Rf value: 0.2, UV active) then evaporated the solvent. The reaction mixture was neutralized with $NaHCO_3$ solution and filtered the obtain solid, which was dried to afford pure compound (8S)—N-(4-((R)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (170 mg, 0.312 mmol, 89% yield) as an off white solid. LCMS (m/z): 532.34 $[M+H]^+$, Rt=2.22 min.

[1101] ^1H NMR (400 MHz, $CDCl_3$): δ ppm 13.88 (s, 1H), 8.87 (s, 1H), 8.76 (br d, J=7.67 Hz, 1H), 8.36 (d, J=5.70 Hz, 1H), 7.75 (d, J=7.67 Hz, 1H), 7.67-7.56 (m, 1H), 6.51 (d, J=5.70 Hz, 1H), 5.73 (d, J=4.38 Hz, 1H), 4.71 (dd, J=12.06, 4.60 Hz, 1H), 4.58 (dd, J=12.06, 4.38 Hz, 1H), 4.40 (d, J=5.92 Hz, 1H), 4.02-3.91 (m, 1H), 3.74-3.59 (m, 2H), 3.38 (t, J=6.80 Hz, 1H), 3.24-3.10 (m, 2H), 3.07-2.99 (m, 2H), 2.68 (s, 3H), 2.42-2.26 (m, 1H), 2.05 (dt, J=14.47, 7.45 Hz, 1H).

Example 57

Synthesis of (8S)—N-(2-((S)-2,3-dihydroxypropoxy)pyridin-4-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide

[1102]

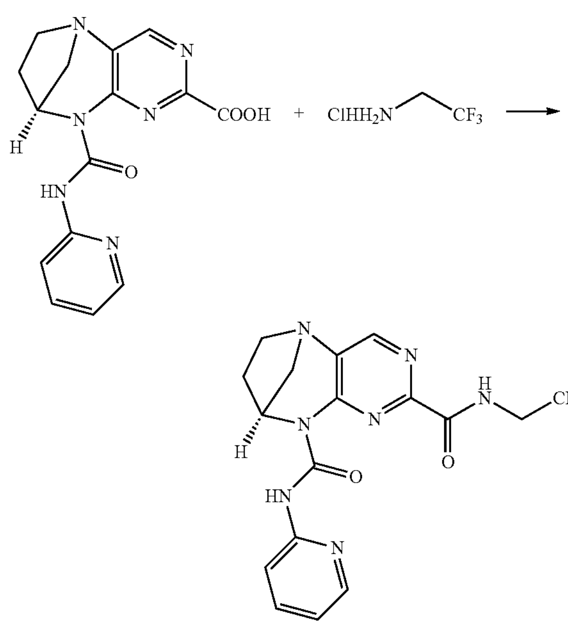


[1103] To a stirred solution of (8S)—N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (300 mg, 0.526 mmol) in Methanol (5 mL) was added HCl (0.5 mL, 5.76 mmol) at rt and the resulting mixture was stirred at rt for 1 h. (TLC eluent: Neat ethyl acetate: R_f: 0.3; UV active) then evaporated the solvent. The reaction mixture was neutralized with $NaHCO_3$ solution and filtered the obtain solid, which was dried to afford pure compound (8S)—N-(2-((S)-2,3-dihydroxypropoxy)pyridin-4-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-9(6H)-carboxamide (276 mg, 0.515 mmol, 98% yield) as an off white solid. LCMS (m/z): 531.3 $[M+H]^+$, Rt=2.28 min.

[1104] ^1H NMR (400 MHz, $CDCl_3$): δ ppm 12.85 (s, 1H), 8.49-8.36 (m, 2H), 7.98 (d, J=5.92 Hz, 1H), 7.79 (d, J=7.67 Hz, 1H), 7.74-7.52 (m, 1H), 7.27-7.20 (m, 1H), 7.20-6.97 (m, 1H), 5.65 (d, J=5.92 Hz, 1H), 4.47 (d, J=5.04 Hz, 2H), 4.22 (d, J=3.95 Hz, 1H), 4.00 (d, J=3.95 Hz, 1H), 3.73-3.58 (m, 2H), 3.2-3.01 (m, 2H), 3.06 (s, 2H), 3.01-2.77 (m, 1H), 2.68 (s, 3H), 2.37 (td, J=13.98, 6.03 Hz, 1H), 2.24-1.96 (m, 1H).

Example 58 Synthesis of (8S)—N9-(pyridin-2-yl)-N2-(2,2,2-trifluoroethyl)-7,8-dihydro-5,8-methano pyrimido[4,5-b][1,4]diazepine-2,9(6H)-dicarboxamide

[1105]



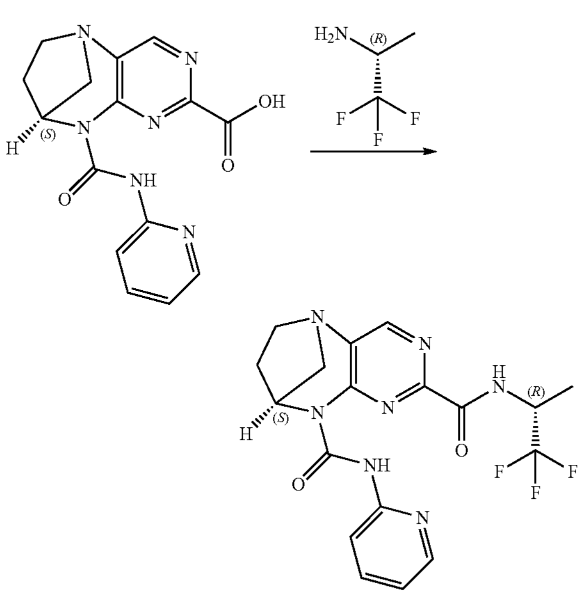
[1106] To a stirred solution of (8S)-9-(pyridin-2-ylcarbamoyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylic acid (1 g, 3.06 mmol) and 2,2,2-trifluoroethanamine hydrochloride (0.831 g, 6.13 mmol) in Dichloromethane (DCM) (20 mL) was added DIEA (2.141 mL, 12.26 mmol) followed by HATU (2.330 g, 6.13 mmol) at RT then stirred at the same temperature for 16 h. (TLC eluent: 10% MeOH in DCM R_f:0.3, UV active). The reaction mixture was partitioned between water (10 mL) and DCM (20 mL×2). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude, then it was purified by flash column chromatography (silica gel: 100-200 Mesh, Eluent: 3% MeOH in DCM) to afford the desired product (8S)—N9-(pyridin-2-yl)-N2-(2,2,2-trifluoroethyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2,9(6H)-dicarboxamide (135 mg, 0.331 mmol, 10.81% yield) as an off white solid. LCMS (m/z): 408.27 $[M+H]^+$. Rt=1.70 min.

[1107] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.92 (s, 1H), 8.49 (s, 1H), 8.40-8.37 (m, 1H), 8.29 (t, J=6.47 Hz, 1H), 8.05 (dt, J=8.33, 0.88 Hz, 1H), 7.75-7.69 (m, 1H), 7.04 (ddd, J=7.34, 4.93, 1.10 Hz, 1H), 5.67-5.62 (m, 1H), 4.21 (qd, J=9.03, 6.69 Hz, 2H), 3.36-3.17 (m, 2H), 3.10-3.04 (m, 2H), 2.43-2.31 (m, 1H), 2.09 (dt, J=14.74, 7.65 Hz, 1H).

Example 59

Synthesis of (8S)—N9-(pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2,9(6H)-dicarboxamide

[1108]



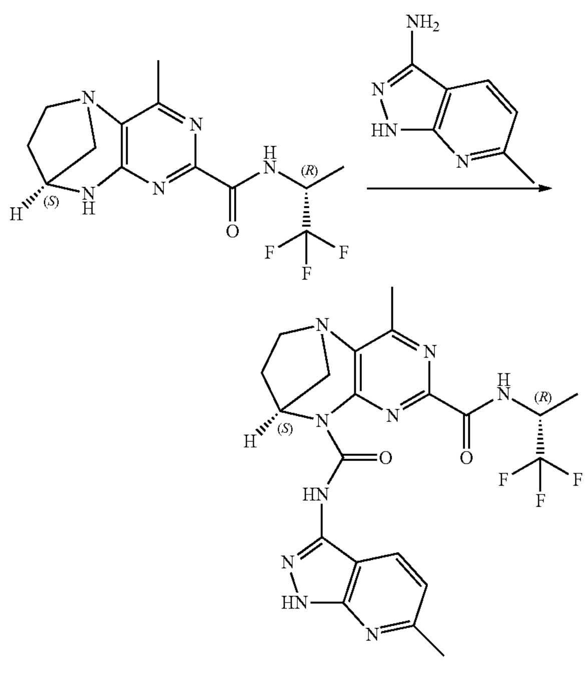
[1109] To a stirred solution of (8S)-9-(pyridin-2-ylcarbamoyl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxylic acid (400 mg, 1.226 mmol) in DMF (4 mL), under nitrogen at 0° C. was added DIPEA (0.642 mL, 3.68 mmol), HATU (932 mg, 2.452 mmol) and (R)-1,1,1-trifluoropropan-2-amine (139 mg, 1.226 mmol) and stirred at RT for 16 h. (TLC system: 5% Methanol in DCM. Rf value: 0.3). The reaction mixture was quenched with cold water (50 mL) and extracted with EtOAc (2×100 mL). Combined organic layer was washed with brine (50 mL), dried over sodium sulphate and concentrated under reduced pressure to get crude compound. The crude material was purified by prep HPLC (Column: XBRIDGE C-18 (150×19) mm; Mobilile Phase-A: 5 mM Ammonium bicarbonate, B: Acetonitrile; Method (% B/Time): 0/10-2/25/10/55; Solubility: MeOH+THF) to afford (8S)—N9-(pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2,9(6H)-dicarboxamide (53 mg, 0.126 mmol, 10.25% yield) as a pale yellow solid. LCMS (m/z): 422.14 $[M+H]^+$, Rt=1.83 min.

[1110] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.82 (s, 1H), 8.49 (s, 1H), 8.25-8.44 (m, 1H), 7.93-8.15 (m, 2H), 7.61-7.86 (m, 1H), 6.99-7.14 (m, 1H), 5.57-5.81 (m, 1H), 4.94-5.11 (m, 1H), 3.19-3.32 (m, 2H), 3.00-3.16 (m, 2H), 2.26-2.44 (m, 1H), 2.04-2.25 (m, 1H), 1.49-1.60 (s, 3H).

Example 60

Synthesis of (8S)-4-methyl-N9-(6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2,9(6H)-dicarboxamide

[1111]



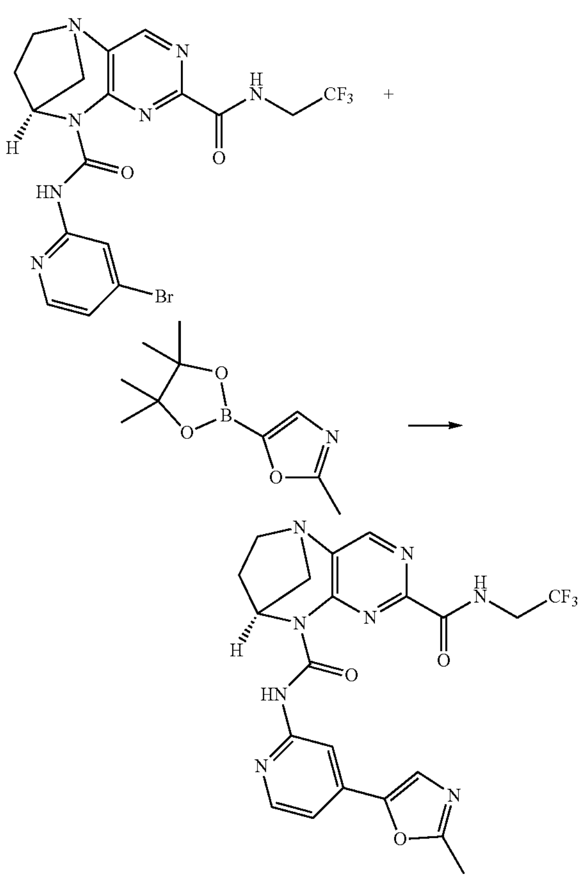
[1112] To a stirred solution of (8S)-4-methyl-N—((R)-1,1,1-trifluoropropan-2-yl)-6,7,8,9-tetrahydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2-carboxamide (600 mg, 1.903 mmol) in THF (10 mL) were added triphosgene (565 mg, 1.903 mmol) and DIPEA (1.662 mL, 9.51 mmol) at 0° C. and stirred at room temp for 4 h. To this 6-methyl-1H-pyrazolo[3,4-b]pyridin-3-amine (423 mg, 2.85 mmol) was added and stirred at 80° C. for 16 h. (TLC eluent: Neat Ethyl acetate, Rf value:0.2, UV active). The reaction mixture was poured in saturated $NaHCO_3$ solution (50 mL) and extracted with ethyl acetate (2×100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude compound. The crude product was purified by Prep-HPLC (condition: MP-A: 0.1% formic acid in water MP-B: Acetonitrile Column: Xbridge C_{18}(250*30 mm) 5 Method: A:B 0/42, 14/42, 14.1/100, 17/100, 17.1/42, 20/42. Flow: 25 ml/min Solubility: THF+ACN+MeOH). Fractions were concentrated under reduced pressure to afford desired product (8S)-4-methyl-N9-(6-methyl-1Hpyrazolo[3,4-b]pyridin-3-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2,9(6H)-dicarboxamide (64 mg, 0.129 mmol, 6.77% yield) as a brown color solid. LCMS (m/z): 490.26 $[M+H]^+$, Rt=2.08 min

[1113] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.36 (s, 1H), 9.94 (br s, 1H), 8.64 (d, J=8.33 Hz, 1H), 8.01 (d, J=9.65 Hz, 1H), 7.04 (d, J=8.33 Hz, 1H), 5.70 (dd, J=5.59, 2.74 Hz, 1H), 4.94 (dq, J=16.94, 7.22 Hz, 1H), 3.26-3.14 (m, 2H), 3.12-3.00 (m, 2H), 2.66 (d, J=4.82 Hz, 6H), 2.43-2.29 (m, 1H), 2.08 (dt, J=14.63, 7.26 Hz, 1H), 1.46 (d, J=7.02 Hz, 3H).

Example 61

Synthesis of (8S)—N9-(4-(2-methyloxazol-5-yl)-pyridin-2-yl)-N2-(2,2,2-trifluoroethyl)-7,8-dihydro-5,8-methanopyrimido-[4,5-b][1,4]-diazepine-2,9(6H)-dicarboxamide

[1114]



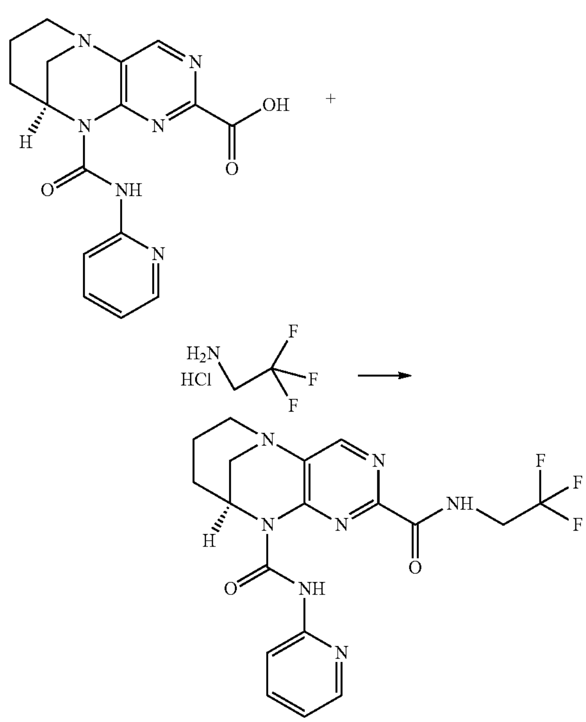
[1115] To a degassed solution of (8S)—N9-(4-bromopyridin-2-yl)-N2-(2,2,2-trifluoroethyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2,9(6H)-dicarboxamide (500 mg, 1.028 mmol) and 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (322 mg, 1.542 mmol) in 1,4-Dioxane (20.0 mL) and Water (3.0 mL), at RT was added K_3PO_4 (655 mg, 3.08 mmol) followed by $PdCl_2$(dppf)-CH_2Cl_2 adduct (42.0 mg, 0.051 mmol) and stirred at 110° C. for 2 h. (TLC eluent: 100% ethyl acetate R_f: 0.5; UV active). Reaction mixture was cooled to RT and diluted with water (50 mL), extracted with ethylacetate (2×50 mL). The organic layer was dried over anhydrous sodiumsulphate, filtered and concentrated to afford crude product. The crude product was purified by preparative HPLC. (Column: kinetex 5u phenyl hexyl (150×30) mm; MP-A: 10 Mm Ammonium Bicarbonate (aq), MP-B: Acetonitrile; Method % of B: 0/10, 1/10, 10/50, 10.1/100, 15/100, 15.1/10; Flow: 30 ml/min; Solubility: ACN+MeOH+THF) to afford (8S)—N9-(4-(2-methyloxazol-5-yl)pyridin-2-yl)-N2-(2,2,2-trifluoroethyl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2,9(6H)-dicarboxamide (50 mg, 0.102 mmol, 9.94% yield) as an off white solid. LCMS (m/z): 489.14 $[M+H]^+$, Rt=1.87.

[1116] ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.73 (s, 1H), 9.34 (br t, J=6.47 Hz, 1H), 8.51 (s, 1H), 8.41 (d, J=5.04 Hz, 1H), 8.31 (s, 1H), 7.82 (s, 1H), 7.42 (dd, J=5.26, 1.32 Hz, 1H), 5.48 (dd, J=5.81, 2.96 Hz, 1H), 4.20-4.03 (m, 2H), 3.23 (br d, J=8.77 Hz, 1H), 3.15-2.98 (m, 3H), 2.54 (s, 3H), 2.33-2.20 (m, 1H), 2.11-2.01 (m, 1H)

Example 62

Synthesis of (9S)—N10-(pyridin-2-yl)-N2-(2,2,2-trifluoroethyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

[1117]



[1118] To a stirred solution of (9S)-10-(pyridin-2-ylcarbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylicacid (2.0 g, 5.88 mmol) in DMF (20 mL) under nitrogen at 0° C. was added 2,2,2-trifluoroethanamine hydrochloride (1.195 g, 8.81 mmol), HATU (3.35 g, 8.81 mmol) and DIPEA (4.11 mL, 23.51 mmol) and stirred at RT for 16 h. (TLC eluent:100% EtOAc:

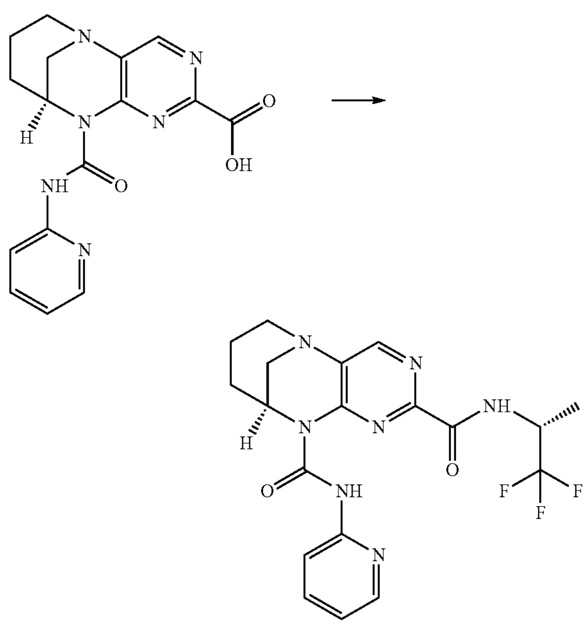
R_f-0.5.; UV active). The reaction mixture was diluted with water (50 mL) and extracted into DCM (3×30 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford crude product. The crude product was purified by column chromatography (neutral alumina, eluent: 100% ethyl acetate in hexane) to afford the desired product (9S)—N10-(pyridin-2-yl)-N2-(2,2,2-trifluoroethyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (1.2590 g, 2.98 mmol, 50.7% yield) as a white solid. LCMS (m/z): 422.21 $[M+H]^+$, Rt=1.77 min.

[1119] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.45 (s, 1H), 8.44 (s, 1H), 8.41-8.31 (m, 2H), 8.07 (dd, J=8.33, 0.88 Hz, 1H), 7.72 (td, J=7.84, 1.86 Hz, 1H), 7.04 (ddd, J=7.34, 4.93, 0.88 Hz, 1H), 5.00 (br s, 1H), 4.23 (qd, J=8.99, 6.80 Hz, 2H), 3.45-3.25 (m, 3H), 2.90 (br d, J=13.59 Hz, 1H), 2.23 (br d, J=13.81 Hz, 1H), 2.06-1.88 (m, 1H), 1.51-1.23 (m, 2H)

Example 63

Synthesis of (9S)—N10-(pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

[1120]



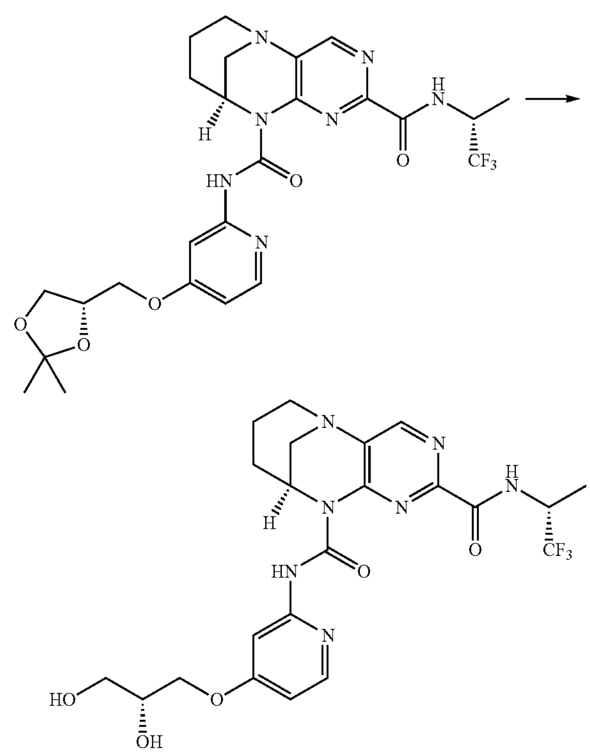
[1121] To a stirred solution of (9S)-10-(pyridin-2-ylcarbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (2.0 g, 5.88 mmol) in DMF (10 mL) under nitrogen at 0° C. was added HATU (2.234 g, 5.88 mmol), DIPEA (2.57 mL, 14.69 mmol) followed by (R)-1,1,1-trifluoropropan-2-amine (1.329 g, 11.75 mmol) and stirred at RT for 12 h. (TLC eluent: 100% Ethylacetate in Hexane: R_f=0.5; UV active). The reaction mixture was quenched with water (50 mL) and extracted into EtOAc (3×30 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford crude product. The crude product was purified by column chromatography (neutral alumina, eluent: 50% ethyl acetate in hexane) to afford (9S)—N10-(pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9 methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (0.560 g, 1.282 mmol, 21.82% yield) as an off white solid. LCMS (m/z): 436.11 $[M+H]^+$, Rt=1.91 min.

[1122] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.33 (s, 1H), 8.35-8.48 (m, 2H), 8.09 (br d, J=8.33 Hz, 2H), 7.75-7.65 (m, 1H) 7.05 (ddd, J=7.29, 4.88, 0.99 Hz, 1H), 5.13-4.96 (m, 2H), 3.45-3.26 (m, 3H), 2.90 (br d, J=14.03 Hz, 1H), 2.21 (br s, 1H), 1.95 (br dd, J=5.37, 2.96 Hz, 1H), 1.60 (s, 3H), 1.52 (d, J=7.02 Hz, 2H).

Example 64

Synthesis of (9S)—N10-(4-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

[1123]



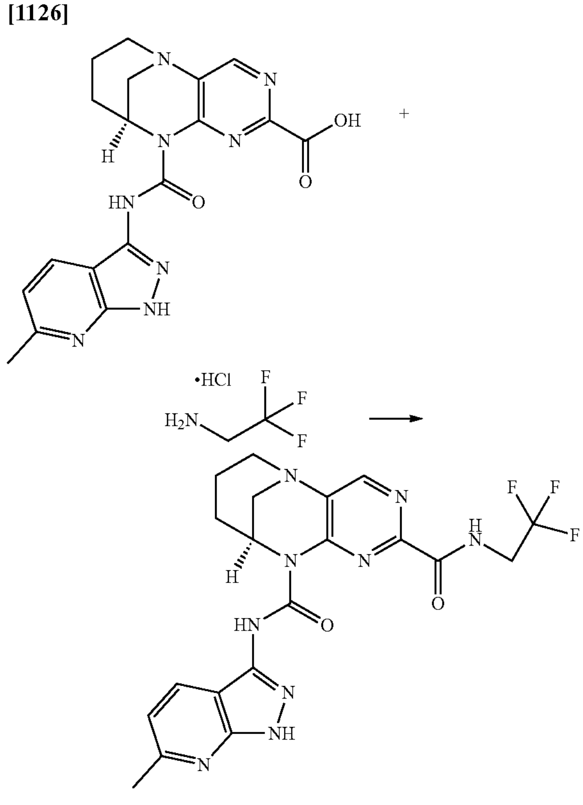
[1124] To a stirred solution of (9S)—N10-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (170 mg, 0.301 mmol) in methanol (10 mL) under nitrogen at 0° C. was added HCL (0.522 mL, 6.01 mmol) and stirred for 1 h. (TLC system: 100% Ethyl acetate, R_f value: 0.3). The reaction mixture was diluted with Aq $NaHCO_3$ solution (20 mL) and extracted with DCM (30 mL). The combined organic layer was washed with brine solution (30 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain crude compound. The product was triturated with pentane and diethylether (1:1) to afford (9S)—N10-(4-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (92 mg, 0.169 mmol, 56.4% yield) as an off white solid. LCMS (m/z): 526.19[M+H]$^+$, Rt=1.45 min.

[1125] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.00 (s, 1H), 9.04 (br d, J=8.99 Hz, 1H), 8.52 (s, 1H), 8.15 (d, J=5.92 Hz, 1H), 7.68 (d, J=2.19 Hz, 1H), 6.75 (dd, J=5.70, 2.19 Hz, 1H), 5.01 (d, J=5.26 Hz, 1H), 4.79-4.95 (m, 2H), 4.70 (br t, J=5.70 Hz, 1H), 4.11 (dd, J=9.76, 3.84 Hz, 1H), 3.95 (dd, J=9.87, 6.58 Hz, 1H), 3.82 (brdd, J=9.98, 5.59 Hz, 1H), 3.40-3.49 (m, 2H), 3.29 (s, 5H), 2.85 (br d, J=13.37 Hz, 1H), 1.97 (br s, 1H), 1.44 (d, J=7.02 Hz, 2H), 1.32 (s, 2H).

Example 65

Synthesis of (9S)—N10-(6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-N2-(2,2,2-trifluoroethyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

[1126]



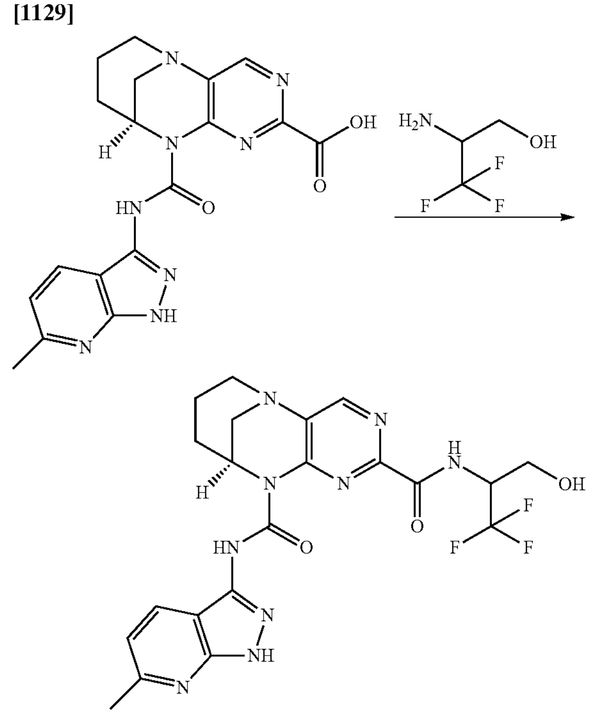
[1127] To a stirred solution of (9S)-10-((6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (180 mg, 0.456 mmol) in N,N-Dimethylformamide (10 mL) were added HATU (174 mg, 0.456 mmol) and DIPEA (0.080 mL, 0.456 mmol) 2,2,2-trifluoroethanamine hydrochloride (93 mg, 0.685 mmol) at 28° C. The reaction mixture was stirred at room temperature for 16 h. (TLC System: 10% MeOH in DCM: R-0.3; UV active) and quenched with ice cold water (30 mL), extracted with Ethyl acetate (2×30 mL). The combined organic layer was washed with brine solution then dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure to obtain crude material. The crude was purified by GRACE (C-18 reserval column, Eluent: 70% of MeOH and 0.1% Formic Acid in water) to afford the desired product (9S)—N10-(6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-N2-(2,2,2-trifluoroethyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (105 mg, 0.216 mmol, 47.4% yield) as an off white solid. LCMS (m/z): 476.22 [M+H]$^+$, Rt=1.88 min.

[1128] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.67 (s, 1H), 10.20 (br s, 1H), 8.63 (d, J=8.33 Hz, 1H), 8.37 (s, 1H), 8.20 (t, J=6.25 Hz, 1H), 7.04 (d, J=8.33 Hz, 1H), 5.07 (br s, 1H), 4.28-4.11 (m, 2H), 3.49-3.26 (m, 3H), 2.92 (br d, J=14.03 Hz, 1H), 2.68 (s, 3H), 2.28 (d, J=14.25 Hz, 1H), 2.04-1.89 (m, 1H), 1.51-1.31 (m, 2H).

Example 66

Synthesis of (9S)—N10-(6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-N2-(1,1,1-trifluoro-3-hydroxypropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

[1129]



[1130] To a stirred suspension of (9S)-10-((6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (4.5 g, 11.41 mmol) in pyridine (100 mL) under nitrogen at 0° C. was added EDC (4.37 g, 22.82 mmol) followed by 2-amino-3,3,3-trifluoropropan-1-ol (2.209 g, 17.12 mmol) and stirred at Room temperature for 16 h. (TLC system 5% Methanol in DCM. Rf value:0.4). The reaction mixture was concentrated and the residue was dissolved in EtOAc (200 mL) and washed with water (2×100 mL). Combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to get crude as brown solid. The solid was triturated with diethylether (50 mL) filtered and dried to get the desired compound as diastereomeric mixture. The diastereomers were separated by preparative chiral SFC (Column/dimensions: Chiralpak AD-H (250×30) mm, 5 i; % CO_2: 50.0; % Co-solvent: 40.0 (0.5% DEA in Ethanol); Total Flow: 70.0 g/min, Back Pressure: 100.0 bar; UV: 220 nm, Stack time: 4 min, Load/inj: 15.0 mg, Solubility: EtOH+DCM, Total No of injections: 700, Instrument details: Make/Model: Thar SFC-200 NEW-1).

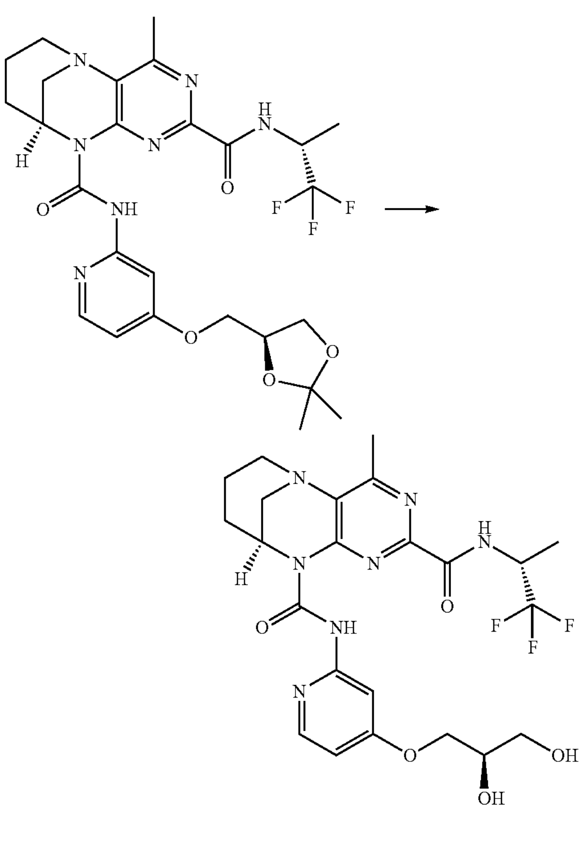
[1131] Peak-1: Collected fraction from SFC was concentrated and washed with diethylether (20 mL), dried and grounded in mortar to afford (9S)—N10-(6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-N2-(1,1,1-trifluoro-3-hydroxypropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (780 mg, 1.490 mmol, 13.06% yield) as an off white solid. LCMS (m/z): 506.17[M+H]$^+$, Rt=1.78 min.

[1132] ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.24 (s, 1H), 13.05 (s, 1H), 8.55 (s, 1H), 8.31 (d, J=8.33 Hz, 1H), 7.60-7.85 (m, 2H), 7.05 (d, J=8.55 Hz, 1H), 5.28 (t, J=5.70 Hz, 1 H), 4.88 (br s, 2H), 3.85 (m, 2H), 3.44 (br d, J=13.59 Hz, 2H), 2.89 (br d, J=13.59 Hz, 1H), 2.58 (s, 3H), 1.91-2.09 (m, 2H), 1.28-1.41 (m, 2H).

Example 67

Synthesis of (9S)—N10-(4-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-4-methyl-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

[1133]



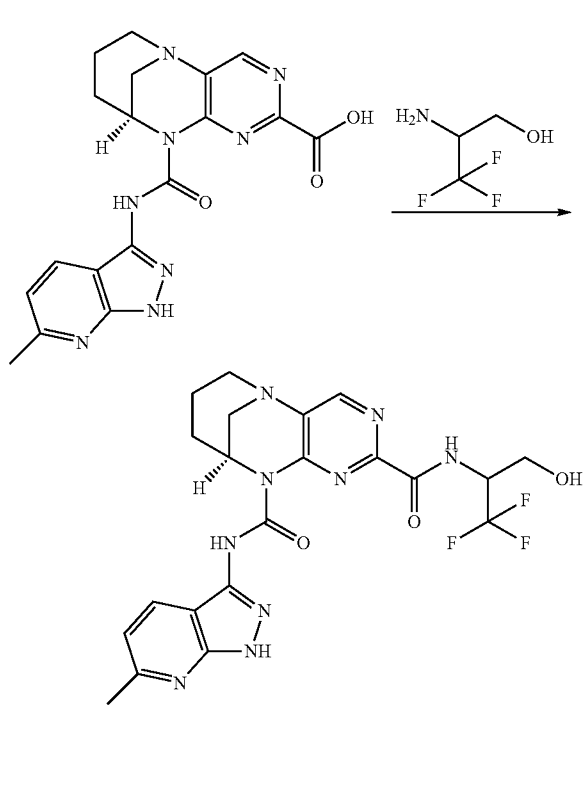
[1134] To a stirred solution of (9S)—N10-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-4-methyl-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (700 mg, 1.208 mmol) in methanol (10 mL) at 0° C. was added aq. HCl (1.019 mL, 12.08 mmol) and stirred for 2 h. (TLC eluent: 100% EtOAc: R_1-0.2; UV active). The reaction mixture was basified with saturated sodium bicarbonate solution (till pH-8-9) and solvent was evaporated under reduced pressure. The residue was diluted with water (10 mL) and extracted into dichloromethane (2×20 mL). Combined organic extracts were dried over anhydrous sodium sulphate, filtered and filtrate was evaporated in vacuo and the crude was triturated with pentane (2×20 mL) to afford the desired product (9S)—N10-(4-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-4-methyl-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (562 mg, 1.030 mmol, 85% yield) as an off-white solid. LCMS (m/z): 540.26 [M+H]$^+$, R_t=1.74 min.

[1135] ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.14 (s, 1H), 8.89 (d, J=9.21 Hz, 1H), 8.13 (d, J=5.70 Hz, 1H), 7.68 (d, J=2.19 Hz, 1H), 6.74 (dd, J=5.81, 2.30 Hz, 1H), 5.00 (d, J=5.26 Hz, 1H), 4.94-4.79 (m, 2H), 4.70 (t, J=5.70 Hz, 1H), 4.09-4.14 (m, 1H), 3.95 (dd, J=9.87, 6.36 Hz, 1H), 3.85-3.80 (m, 1H), 3.50-3.38 (m, 3H), 3.20 (br d, J=7.45 Hz, 2 H), 2.85 (br d, J=13.59 Hz, 1H), 2.57-2.47 (m, 3H), 2.04-1.91 (m, 2H), 1.45 (d, J=7.02 Hz, 3H), 1.38-1.22 (m, 2H)

Example 68

Synthesis of (9S)—N10-(6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-N2-(1,1,1-trifluoro-3-hydroxypropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

[1136]



[1137] To a stirred suspension of (9S)-10-((6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (4.5 g, 11.41 mmol) in pyridine (100 mL) under nitrogen at 0° C. was added EDC (4.37 g, 22.82 mmol) followed by 2-amino-3,3,3-trifluoropropan-1-ol (2.209 g, 17.12 mmol) and stirred at Room temperature for 16 h. (TLC system 5% Methanol in DCM. Rf value:0.4).

[1138] The reaction mixture was concentrated and the residue was dissolved in EtOAc (200 mL) and washed with water (2×100 mL). Combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to get crude as brown solid. The solid was triturated with diethylether (50 mL) filtered and dried to get the desired compound as diastereomeric mixture. The diastereomers were separated by preparative chiral SFC (Column/dimensions: Chiralpak AD-H (250×30) mm, 5 i; % CO_2: 50.0%; % Co-solvent: 40.0% (0.5% DEA in Ethanol); Total Flow: 70.0 g/min, Back Pressure: 100.0 bar; UV: 220 nm, Stack time: 4 min, Load/inj: 15.0 mg, Solubility: EtOH+DCM, Total No of injections: 700, Instrument details: Make/Model: Thar SFC-200 NEW-1).

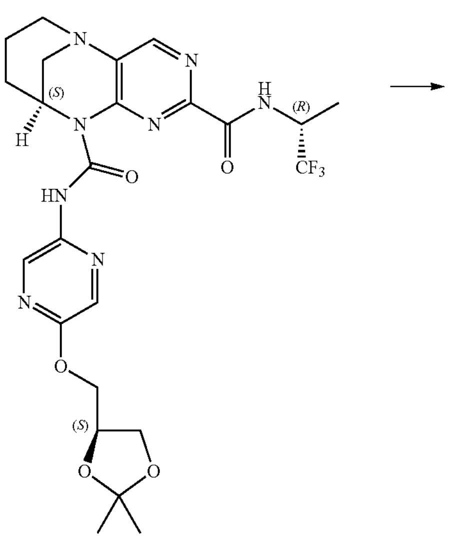
[1139] Peak-2: Collected fraction from SFC was concentrated and washed with diethylether (20 mL), dried and grinded in mortor to afford (9S)—N10-(6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-N2-(1,1,1-trifluoro-3-hydroxypropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (470 mg, 0.885 mmol, 7.75% yield) as Pale yellow solid. LCMS (m/z): 506.20[M+H]$^+$, Rt=1.82 min.

[1140] ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm 13.24 (s, 1H), 12.93-13.15 (m, 1H), 9.07 (br d, J=9.65 Hz, 1H), 8.55 (s, 1H), 8.31 (d, J=8.33 Hz, 1H), 7.05 (d, J=8.33 Hz, 1H), 5.29 (t, J=5.70 Hz, 1H), 4.88 (br s, 2H), 3.67-3.93 (m, 2H), 3.44 (br d, J=12.50 Hz, 1H), 3.33 (br s, 2H) 2.89 (br d, J=13.37 Hz, 1H), 2.58 (s, 3H), 2.01 (br s, 2H), 1.35 (br s, 2H).

Example 69

Synthesis of (9S)—N10-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazo cine-2,10(7H)-dicarboxamide

[1141]



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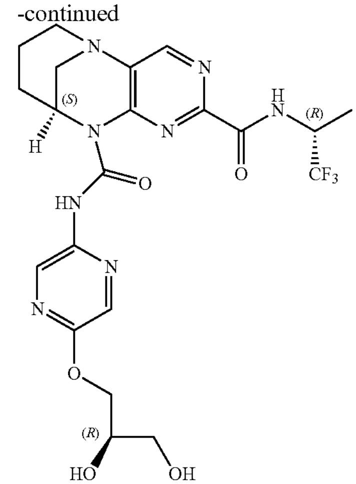


[1142] To a stirred solution of (9S)—N10-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (600 mg, 1.059 mmol) in Methanol (10 mL) at 0° C. was added HCl (2 ml, 395 mmol) drop wise over a period of 5 min. Then the reaction mixture was stirred at 30° C. for 1 h. (TLC: ethyl acetate, R_f=0.3, UV) and evaporated the solvent. The reaction mixture was neutralised with sodium bicarbonate solution and extracted with ethyl acetate (3×50 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain a crude product. The crude was triturated with n-pentane (2×20 mL) to afford the desired product (9S)—N10-(5-((R)-2,3-dihydroxypropoxy)pyrazin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (130 mg, 0.240 mmol, 22.70% yield) as an off white solid.

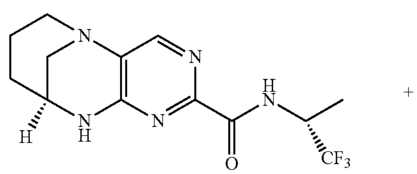
[1143] LCMS (m/z): 527.23 [M+H]$^+$, Rt=1.7 min.

[1144] ^{1}H NMR (400 MHz, DMSO-d$_6$): δ ppm 13.12 (s, 1H), 9.19 (d, J=9.43 Hz, 1H), 8.82 (d, J=1.32 Hz, 1H), 8.53 (s, 1H), 8.13 (d, J=1.10 Hz, 1H), 4.97-4.76 (m, 3H), 4.65 (t, J=5.59 Hz, 1H), 4.33 (dd, J=10.85, 4.06 Hz, 1H), 4.19 (dd, J=10.63, 6.47 Hz, 1H), 3.83 (dd, J=10.19, 5.59 Hz, 1H), 3.50-3.37 (m, 3H), 2.86 (d, J=13.37 Hz, 1H), 1.98 (m, 3H), 1.42 (d, J=7.02 Hz, 3H), 1.32 (m, 3H).

Example 70

Synthesis of (9S)—N-(2-((R)-2,3-dihydroxypropoxy)pyrimidin-5-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1145]



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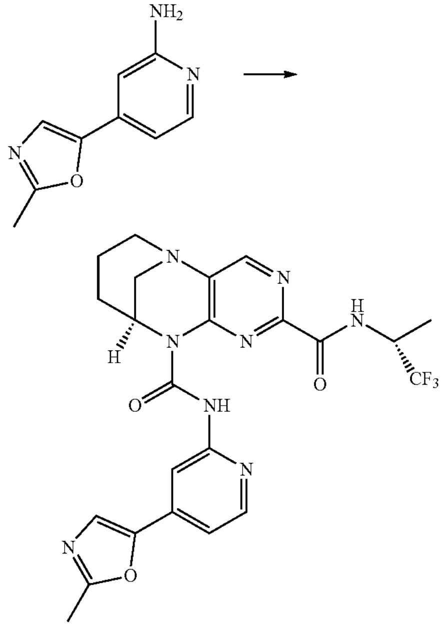


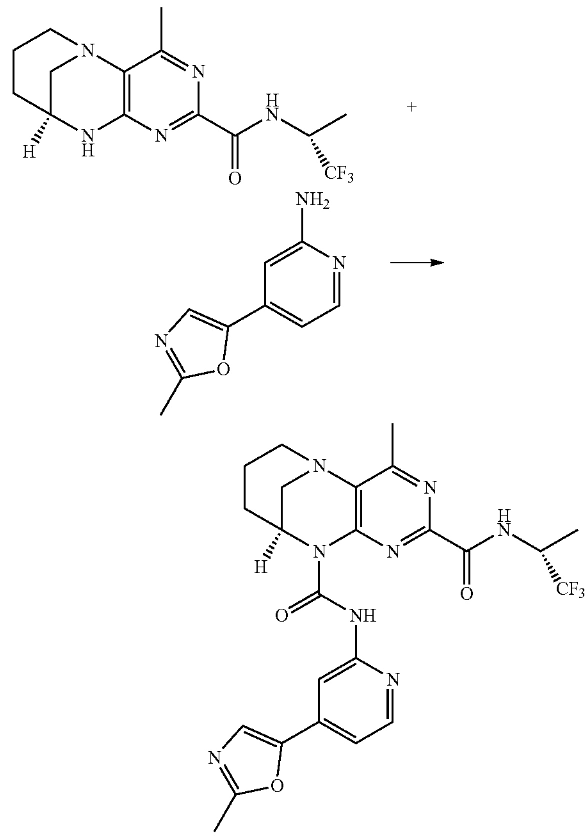
[1146] To a stirred solution of (9S)—N—((R)-1,1,1-trifluoropropan-2-yl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxamide (450 mg, 1.427 mmol) in THF (30 mL) at RT was added TEA (1.194 mL, 8.56 mmol), triphosgene (424 mg, 1.427 mmol) and stirred for 1 h. then added 4-(2-methyloxazol-5-yl)pyridin-2-amine (375 mg, 2.141 mmol) and the reaction was heated at 65° C. for 15 h. (TLC eluent: 100% EtOAc: R_f-0.2; UV active). The reaction mixture was cooled to RT, concentrated in vacuo and the residue was partitioned between water (20 mL) and DCM (2×30 mL). Organic layer was separated and dried over anhydrous sodium sulphate, filtered and filtrate was evaporated to get crude compound. The crude product was purified by flash column chromatography (neutral alumina, eluent: 100% ethylacetate) followed by preparative HPLC (Column: kinetex 5u phenyl hexyl (150×30) mm; MP-A: 10 mM Ammonium Bicarbonate (aq), MP-B: Acetonitrile, Method: 0/20, 8/60, 10/65, 10.5/100, 13/100, 13.1/20, 16/20; Flow: 28 ml/min Solubility: THF+H_2O) fractions containing the compound was concentrated and the resulting solid was suspended in millique water (10 mL) and stirred for 1 h, filtered and dried under vacuum to afford desired product (9S)—N10-(4-(2-methyloxazol-5-yl)pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (165 mg, 0.317 mmol, 22.21% yield) as an off-white solid. LCMS (m/z): 517.26 $[M+H]^+$, R_t=2.13 min.

[1147] ^1H NMR (400 MHz, $CDCl_3$): δ ppm 13.47 (s, 1H), 8.49-8.43 (m, 2H), 8.36 (s, 1H), 8.05 (br d, J=10.08 Hz, 1H), 7.46 (s, 1H), 7.28-7.19 (m, 1H), 5.09-4.94 (m, 2H), 3.46-3.32 (m, 3H), 2.91 (br d, J=14.47 Hz, 1H), 2.56 (s, 3H), 2.25 (br d, J=13.81 Hz, 1H), 2.00-1.93 (m, 1H), 1.51 (d, J=7.02 Hz, 3H), 1.46-1.29 (m, 2H).

Example 71

Synthesis of (9S)-4-methyl-N10-(4-(2-methyloxazol-5-yl)pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

[1148]



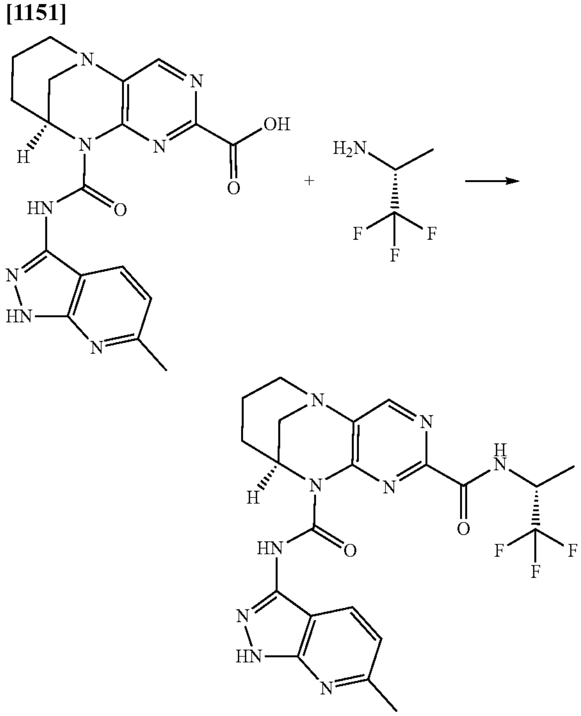
[1149] To a stirred solution of (9S)-4-methyl-N—((R)-1,1,1-trifluoropropan-2-yl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxamide (500 mg, 1.518 mmol) in THF (30 mL) at RT was added TEA (1.270 mL, 9.11 mmol), triphosgene (451 mg, 1.518 mmol) and stirred for 1 h. then added 4-(2-methyloxazol-5-yl)pyridin-2-amine (399 mg, 2.277 mmol) and the reaction was heated at 65° C. for 15 h. (TLC eluent: 100% EtOAc: R-0.3; UV active). The reaction mixture was cooled to RT, concentrated in vacuo and the residue was partitioned between water (20 mL) and DCM (2×30 mL). Organic layer was separated and dried over anhydrous sodium sulphate, filtered and filtrate was evaporated to get crude compound. The crude product was purified by preparative HPLC. (Column: AtlantiesT3 (250×19 mm, 10u); MP-A: 10 mM Ammonium Bicarbonate (aq), MP-B: Acetonitrile; Method: 0/60, 10.5/60, 11/100, 15/100, 15.1/60, 20/60; Flow: 16 ml/min; Solubility: Acetonitrile+MeOH+THF), collected fractions were concentrated and the resulting solid was suspended in millique water (10 mL) and stirred for 1 h, filtered and dried under vacuum to afford desired product (9S)-4-methyl-N10-(4-(2-methyloxazol-5-yl)pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (229 mg, 0.429 mmol, 28.2% yield) as an off-white solid. LCMS (m/z): 531.26 $[M+H]^+$, R_t=2.32 min.

[1150] ^{1}H NMR (400 MHz, $CCCl_3$): δ ppm 13.66 (s, 1H), 8.44 (d, J=5.26 Hz, 1H), 8.37 (s, 1H), 8.07 (br d, J=10.08 Hz, 1H), 7.46 (s, 1H), 7.23-7.21 (m, 1H), 5.07-4.97 (m, 2H), 3.41 (dd, J=13.81, 1.75 Hz, 1H), 3.28-3.19 (m, 2H), 2.90 (br d, J=13.81 Hz, 1H), 2.59 (s, 3H), 2.55 (s, 3H), 2.28 (br d, J=12.72 Hz, 1H), 3.02-1.91 (m, 1H), 1.51 (d, J=7.02 Hz, 3H), 1.45 (br d, J=2.41 Hz, 2H)

Example 72

Synthesis of (9S)—N10-(6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-N2-(2,2,2-trifluoroethyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

[1151]



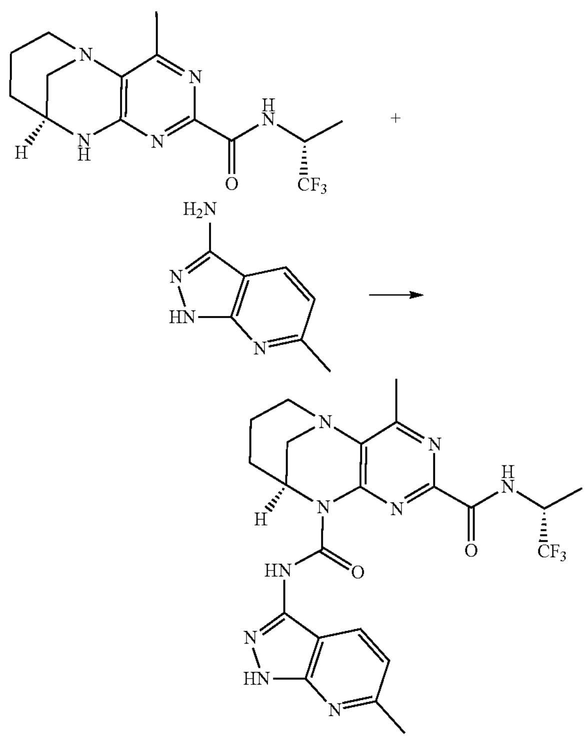
[1152] To a stirred solution of (9S)-10-((6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)carbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (400 mg, 1.014 mmol) in Tetrahydrofuran (20 mL) were added HOBT (466 mg, 3.04 mmol), EDC (583 mg, 3.04 mmol) and DIPEA (0.354 mL, 2.028 mmol) at 0° C. and stirred at rt for 1 h. Then (R)-1,1,1-trifluoropropan-2-amine (115 mg, 1.014 mmol) was added at 0° C. and the reaction mixture was stirred at room temperature for 16 h. (TLC System: 5% MeOH in DCM: R_f-0.3; UV active). The reaction mixture was partitioned between ice cold water (20 ml) and ethylacetate (3×15 mL). The combined organic layer was washed with water, brine solution then dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude compound. The crude compound was purified by GRACE (C-18 reserval column, Eluent: 80% of MeOH and 0.1% Formic Acid in water) to afford the desired product (9S)—N10-(6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (240 mg, 0.489 mmol, 48.2% yield) as an off-white solid. LCMS (m/z): 490.18[M+H]+; Rt=2.03 min.

[1153] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.71 (s, 1H), 10.10 (br s, 1H), 8.63 (d, J=8.33 Hz, 1H), 8.36 (s, 1H), 8.02 (d, J=9.65 Hz, 1H), 7.04 (d, J=8.33 Hz, 1H), 5.06 (br s, 1H), 5.02-4.91 (m, 1H), 3.46-3.26 (m, 3H), 2.92 (d, J=14.03 Hz, 1H), 2.67 (s, 3H), 2.28 (d, J=14.69 Hz, 1H), 2.03-1.90 (m, 1H), 1.53-1.30 (m, 5H).

Example 73

Synthesis of (9S)-4-methyl-N10-(6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

[1154]



[1155] To a stirred solution of (9S)-4-methyl-N—((R)-1,1,1-trifluoropropan-2-yl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxamide (450 mg, 1.366 mmol) in THF (30 mL) at RT was added TEA (1.143 mL, 8.20 mmol) and triphosgene (405 mg, 1.366 mmol) and stirred for 1 h. then 6-methyl-1H-pyrazolo[3,4-b]pyridin-3-amine (405 mg, 2.73 mmol) was added to the above reaction mixture and heated at 65° C. for 15 h. (TLC eluent: 100% EtOAc: R_f-0.4; UV active). The reaction mixture was cooled to RT, concentrated in vacuo and the residue was partitioned between water (20 mL) and DCM (2×35 mL). Organic layer was separated and dried over anhydrous sodium sulphate, filtered and filtrate was evaporated to get crude compound. The crude compound was purified by chromatography (Grace using C-18 reserval column, Mobile phase A: 0.1% Formic Acid in water; B: ACN, the product was eluted at 67% ACN in 0.1% Formic

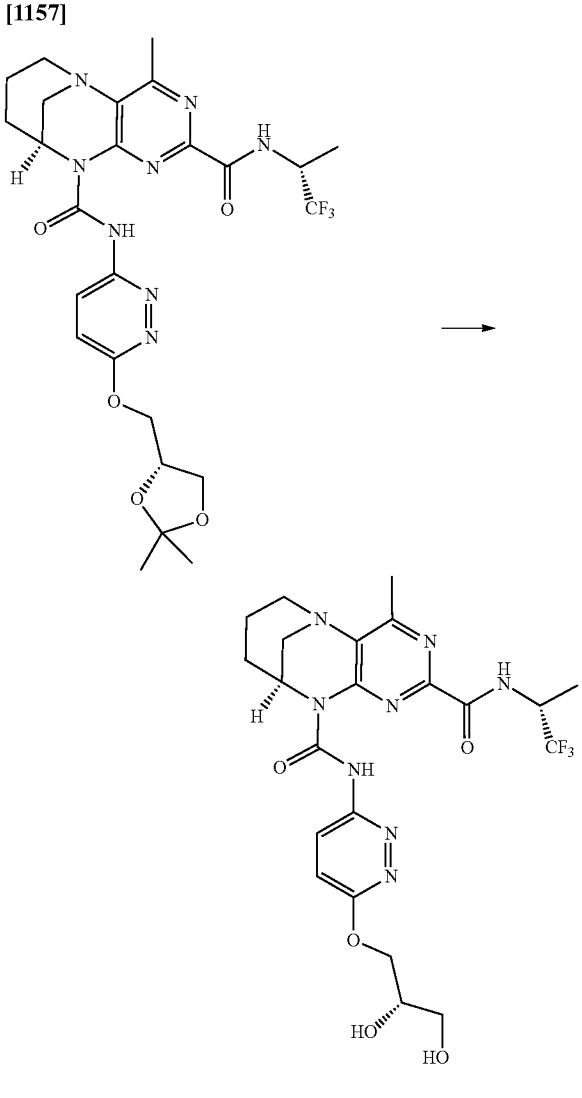
Acid in water). The combined fractions were concentrated and was basified with saturated $NaHCO_3$. The aqueous layer was extracted with DCM. DCM layer was dried over anhydrous Na_2SO_4, filtered and evaporated to afford pure (9S)-4-methyl-N10-(6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (196 mg, 0.387 mmol, 28.3% yield) as an off-white solid. LCMS (m/z): 504.26 $[M+H]^+$, Rt=2.26 min.

[1156] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.91 (s, 1H), 9.96 (br s, 1H), 8.64 (d, J=8.33 Hz, 1H), 8.05 (br d, J=10.08 Hz, 1H), 7.03 (d, J=8.33 Hz, 1H), 5.09-4.93 (m, 2H), 3.41 (dd, J=13.59, 1.75 Hz, 1H), 3.23 (br d, J=6.80 Hz, 2H), 2.91 (br d, J=14.03 Hz, 1H), 2.66 (s, 3H), 2.57 (s, 3H), 2.31 (br d, J=12.28 Hz, 1H), 2.01-1.90 (m, 1H), 1.47 (d, J=7.02 Hz, 4H), 1.36-1.26 (m, 1H).

Example 74

Synthesis of (9S)—N10-(6-((S)-2,3-dihydroxypropoxy)pyridazin-3-yl)-4-methyl-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

[1157]



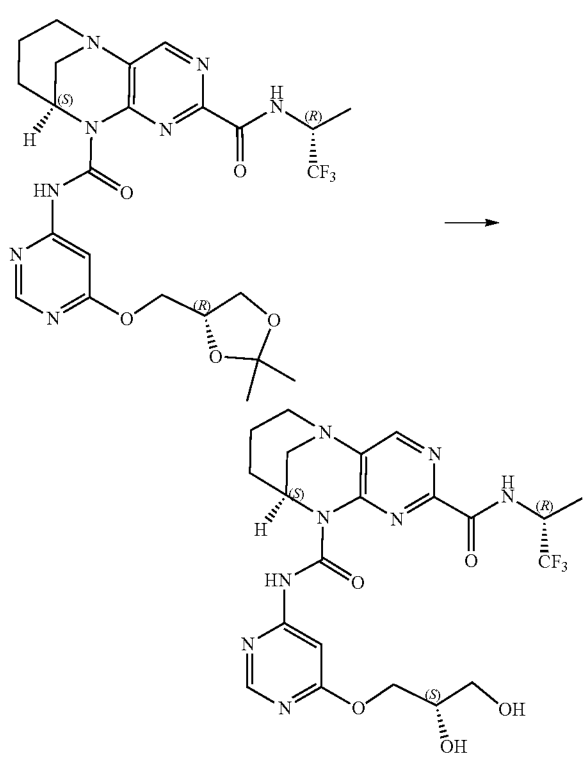
[1158] To a stirred solution of (9S)—N10-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridazin-3-yl)-4-methyl-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (300 mg, 0.517 mmol) in methanol (5 mL) at 0° C. was added aq. HCl (0.436 mL, 5.17 mmol) and the reaction mixture was stirred at 0° C. for 2 h. (TLC eluent: 100% EtOAc: R_f-0.2; UV active) The reaction mixture was basified with saturated sodiumbicarbonate solution (till pH-8-9) and solvent was evaporated under reduced pressure. The residue was diluted with water (5 mL) and extracted into dichloromethane (2×5 mL). Combined organic extracts were dried over anhydrous sodiumsulphate, filtered and filtrate was evaporated in vacuo to afford desired product (9S)—N10-(6-((S)-2,3-dihydroxypropoxy)pyridazin-3-yl)-4-methyl-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (240 mg, 0.443 mmol, 86% yield) as an off-white solid. LCMS (m/z): 541.23 $[M+H]^+$, R_t=1.91 min.

[1159] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 14.00 (s, 1H), 8.29 (br d, J=9.4 Hz, 1H), 8.02 (br d, J=9.6 Hz, 1H), 7.07 (br d, J=9.4 Hz, 1H), 5.07-4.86 (m, 2H), 4.71-4.46 (m, 2H), 4.12 (br d, J=5.3 Hz, 1H), 3.88-3.57 (m, 3H), 3.39 (br d, J=13.2 Hz, 1H), 3.23 (br d, J=7.9 Hz, 2H), 2.89 (br d, J=13.8 Hz, 1H), 2.65-2.48 (m, 4H), 2.23 (br d, J=13.4 Hz, 1H), 1.95 (br t, J=12.8 Hz, 1H), 1.56-1.41 (m, 4H), 1.31 (br d, J=9.6 Hz, 1H).

Example 75

Synthesis of (9S)—N10-(6-((S)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

[1160]



[1161] To a stirred solution of (9S)—N10-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]di azocine-2,10(7H)-dicarboxamide (150 mg, 0.265 mmol) in Methanol (10 mL) was added HCl (1 mL, 11.52 mmol) at RT. The resulting mixture was stirred at room temperature for 1 h. (TLC system: Neat EtOAC, R_f: 0.1; UV active) and the reaction mass was concentrated under reduced pressure to get crude compound, which was basified with saturated bicarbonate solution (10 mL) and filtered the obtain solid to afford the desired product (9S)—N10-(6-((S)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (130 mg, 0.237 mmol, 89% yield) as a brown solid.

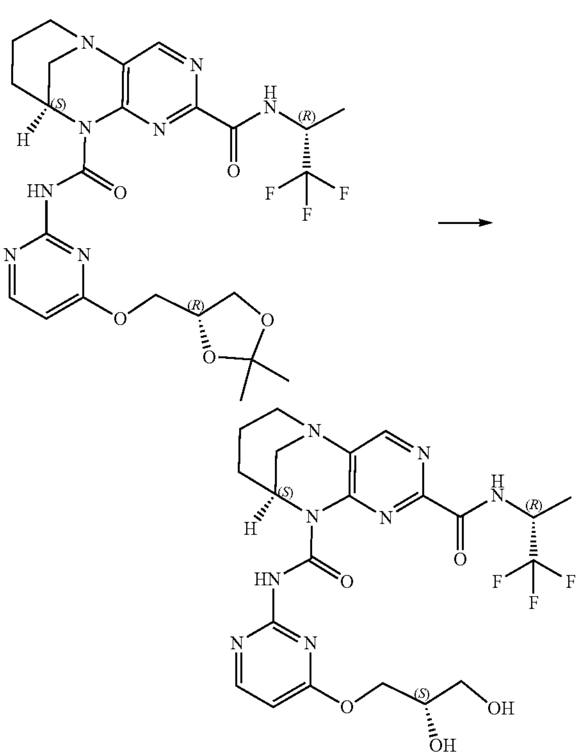
[1162] LCMS (m/z): 527.2 $[M+H]^+$, Rt=3.66 min.

[1163] ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.26 (br s, 1H), 9.2 (m, 1H), 8.54 (br s, 2H), 7.44 (br s, 1H), 4.90 (br s, 2H), 4.43-4.30 (m, 4H), 4.21 (d, J=10.52 Hz, 1H), 3.86-3.62 (m, 1H), 3.60-3.32 (m, 4H), 2.86 (d, J=12.28 Hz, 1H), 1.97 (br s, 2H), 1.43 (d, J=6.80 Hz, 3H), 1.31 (m, 2H).

Example 76

Synthesis of (9S)—N10-(4-((S)-2,3-dihydroxy-propoxy)pyrimidin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

[1164]



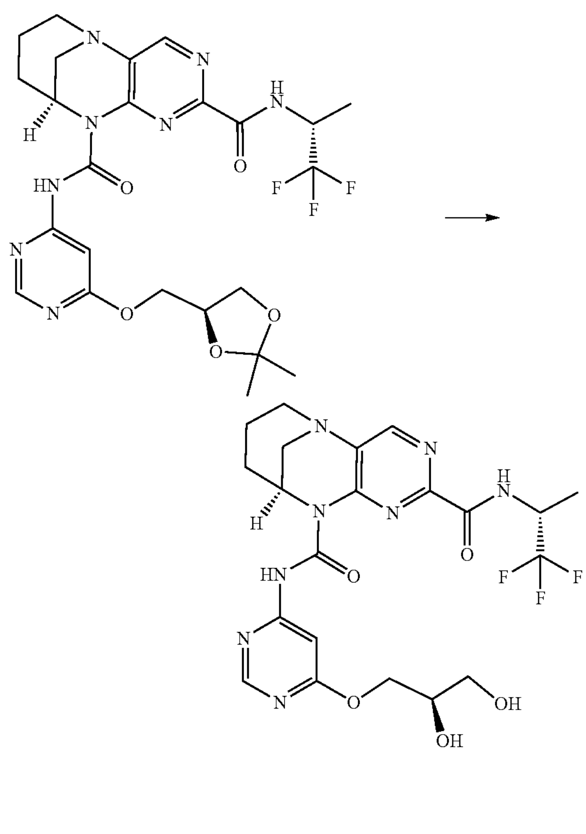
[1165] To a stirred solution of (9S)—N10-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazo cine-2,10(7H)-dicarboxamide (200 mg, 0.353 mmol) in Methanol (2 mL) was added 2.0 M HCl (0.353 mL, 0.706 mmol) in water at 0° C. The resulting reaction mixture was stirred at 0° C. for 1 h. (TLC System: 10% MeOH in DCM, R_f: 0.4). The reaction mixture was concentrated under reduced pressure to obtain crude material. The crude was basified with saturated sodium bicarbonate solution (20 mL) and extracted with DCM (3×30 mL). The combined organic layer was washed with water (20 mL), brine solution (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain solid, which was washed with diethyl ether (5 mL) and n-pentane (10 mL), filtered and dried well to afford the desired product (9S)—N10-(4-((S)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (85 mg, 0.161 mmol, 45.7% yield) as an off-white solid. LCMS (m/z): 527.23 $[M+H]^+$, R_t=1.55 min.

[1166] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.75 (s, 1H), 8.45-8.36 (m, 2H), 8.14 (d, J=9.87 Hz, 1H), 6.50 (d, J=5.92 Hz, 1H), 5.05 (br s, 1H), 4.92-4.81 (m, 1H), 4.76 (dd, J=11.73, 5.15 Hz, 1H), 4.58 (dd, J=11.62, 5.92 Hz, 1H), 4.18-4.05 (m, 2H), 3.80-3.60 (m, 2H), 3.44-3.25 (m, 3H), 2.99-2.81 (m, 2H), 2.26 (d, J=14.91 Hz, 1H), 1.94 (t, J=11.29 Hz, 1H), 1.50-1.21 (m, 5H).

Example 77

Synthesis of (9S)—N10-(6-((R)-2,3-dihydroxy-propoxy)pyrimidin-4-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

[1167]



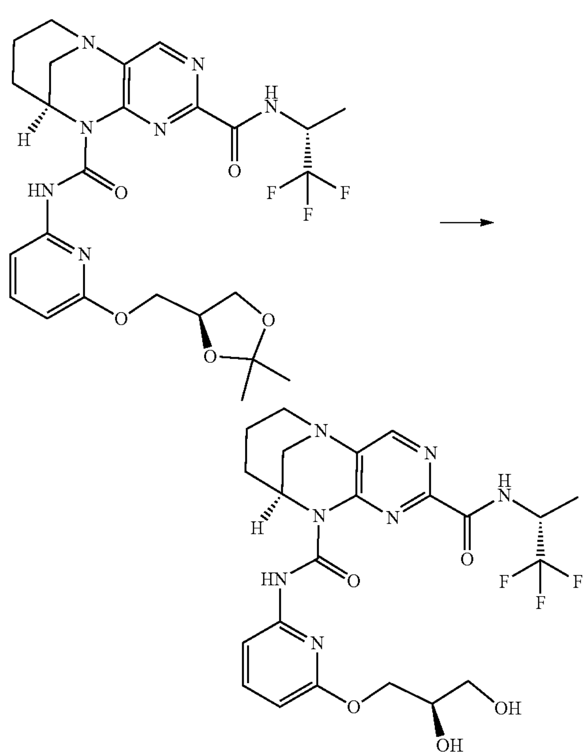
[1168] To a stirred solution of (9S)—N10-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazo cine-2,10(7H)-dicarboxamide (400 mg, 0.706 mmol) in Methanol (4 mL) was added 2.0 M HCl (1.765 mL, 3.53 mmol) in water at 0° C. The resulting reaction mixture was stirred at 0° C. for 1 h. (TLC system: 10% MeOH in DCM, R_f: 0.4). Reaction mixture was concentrated under reduced pressure to obtain crude compound. The crude was basified with saturated sodium bicarbonate solution (20 mL), stirred for 10 min. and filtered the obtain solid, dried well to afford the desired product (9S)—N10-(6-((R)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (180 mg, 0.340 mmol, 48.2% yield) as an off-white solid. LCMS (m/z): 527.23 $[M+H]^+$, R_t=1.73 min.

[1169] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.57 (s, 1H), 8.61 (s, 1H), 8.42 (s, 1H), 8.01 (d, J=10.52 Hz, 1H), 7.66-7.48 (m, 1H), 5.08-4.89 (m, 2H), 4.62-4.44 (m, 2H), 4.16-3.95 (m, 1H), 3.77-3.59 (m, 2H), 3.41-3.23 (m, 4H), 2.90 (d, J=13.81 Hz, 1H), 2.42 (t, J=6.36 Hz, 1H), 2.20 (d, J=13.81 Hz, 1H), 2.04-1.95 (m, 1H), 1.48 (d, J=7.02 Hz, 3H), 1.46-1.29 (m, 2H).

Example 78

Synthesis of (9S)—N10-(6-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

[1170]



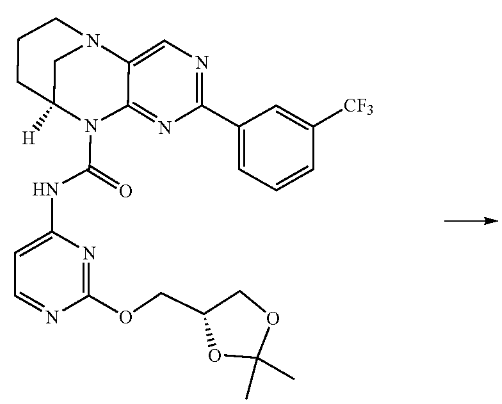
[1171] To a stirred solution of (9S)—N10-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (450 mg, 0.796 mmol) in Methanol (5 mL) was added 2M HCl (2.0 mL, 4.00 mmol) in water at 0° C. The resulting reaction mixture was stirred at 0° C. for 1 h. (TLC system: 10% MeOH in DCM, Rf: 0.4). Reaction mixture was concentrated under reduced pressure to obtain crude compound. The crude compound was basified with saturated sodium bicarbonate solution (20 mL), extracted with DCM (3×20 mL). The combined organic layer was washed with water (20 mL), brine solution (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain crude compound. The crude was purified by flash column chromatography (Silicagel: 100-200 mesh, Eutent: 4% MeOH in DCM) to obtain gummy solid. The gummy solid was washed with n-pentane (20 mL) and dried well to afford (9S)—N10-(6-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (250 mg, 0.457 mmol, 57.4% yield) as an off-white solid. LCMS (m/z): 526.22 $[M+H]^+$, R_t=1.97 min.

[1172] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.30 (s, 1H), 8.34 (s, 1H), 8.19 (d, J=9.65 Hz, 1H), 7.74-7.68 (m, 1H), 7.64-7.60 (m, 1H), 6.59-6.44 (m, 1H), 5.03 (br s, 1H), 4.66-4.95 (m, 2H), 4.41 (dd, J=11.51, 6.25 Hz, 1H), 4.14-4.26 (m, 2H), 3.66-3.88 (m, 2H), 3.24-3.50 (m, 3H), 2.72-2.92 (m, 2H), 2.22 (d, J=14.47 Hz, 1H), 1.95 (tdd, J=13.92, 13.92, 5.26, 3.29 Hz, 1H) 1.22-1.52 (m, 5H).

Example 79

Synthesis of (9S)—N-(2-((S)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1173]



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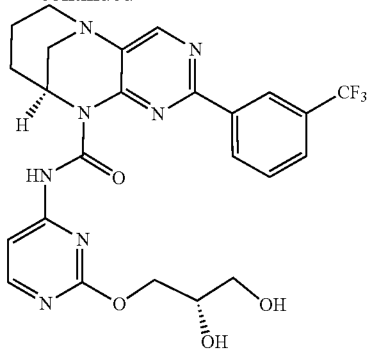


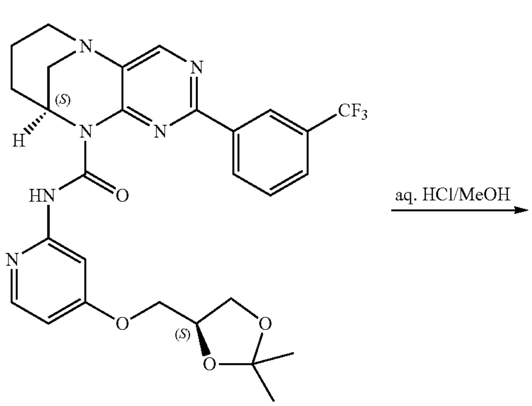
[1174] To a solution of (9S)—N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (275 mg, 0.481 mmol) in methanol (10 mL) at 0° C. was added aq. HCl (2 mL, 65.8 mmol, 36%) and stirred at RT for 2 h. (TLC eluent: 10% MeOH in DCM: R_f-0.2; UV active). To the reaction mixture at 0° C. was added saturated sodium bicarbonate solution (till pH-8-9) and solvent was evaporated under reduced pressure. The residue was diluted with water (10 mL) and extracted into DCM (2×30 mL). Combined organic extracts were dried over anhydrous sodium sulphate, filtered and filtrate was evaporated to give the desired product (9S)—N-(2-((S)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (200 mg, 0.370 mmol, 77% yield) as an off white solid. LCMS (m/z): 532.16 $[M+H]^+$, Rt=2.18 min.

[1175] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.78 (s, 1H), 8.82 (d, J=7.67 Hz, 1H), 8.73 (s, 1H), 8.51 (s, 1H), 8.40 (d, J=5.70 Hz, 1H), 7.85 (d, J=5.70 Hz, 1H), 7.81-7.70 (m, 2H), 4.96 (br s, 1H), 4.55-4.44 (m, 2H), 4.12 (dq, J=9.92, 5.10 Hz, 1H), 3.83-3.67 (m, 2H), 3.45-3.24 (m, 4H), 2.97 (br d, J=14.03 Hz, 1H), 2.42 (t, J=6.25 Hz, 1H), 2.24 (br d, J=13.81 Hz, 1H), 2.02-1.89 (m, 1H), 1.50-1.40 (m, 2H).

Example 80

Synthesis of (9S)—N-(4-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1176]



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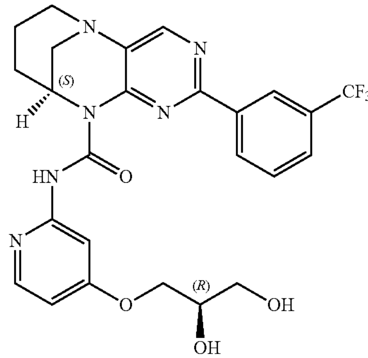


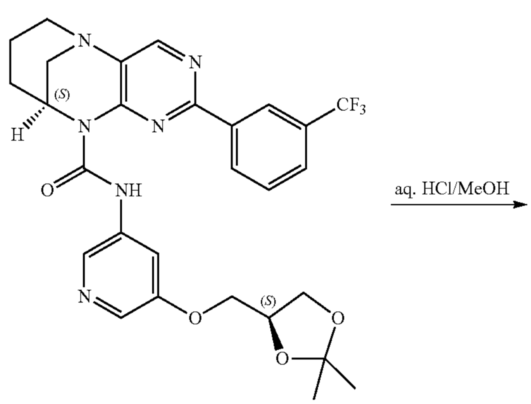
[1177] To a stirred solution of (9S)—N-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (300 mg, 0.526 mmol) in Methanol (10 mL), Hydrochloric acid (4 mL, 132 mmol) was added drop wise over a period of 5 min at 0° C. Then the reaction mixture was stirred at 30° C. for 30 min. (TLC: 5% MeOH in DCM: R_f-0.5; UV), and evaporated the solvent. The obtained residue was neutralization with sodium bicarbonate solution and filtered the obtained solid, washed with n-Pentane (20 mL) to afford the desired product (9S)—N-(4-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (135 mg, 0.254 mmol, 48.4% yield) as an off-white solid. LCMS (m/z): 531.15 $[M+H]^+$, R_t=2.17 min.

[1178] ^{1}H NMR (400 MHz, DMSO): δ ppm 13.59 (s, 1H), 8.92-8.85 (m, 2H), 8.58 (s, 1H), 8.20 (d, J=5.92 Hz, 1H), 7.93 (d J=7.67 Hz, 1H), 7.87-7.80 (m, 1H), 7.74 (d, J=2.19 Hz, 1H), 6.78 (dd, J=5.81, 2.30 Hz, 1H), 4.84 (s, 3H), 4.13 (dd, J=9.87, 3.95 Hz, 1H), 3.97 (dd, J=9.76, 6.25 Hz, 1H), 3.86-3.79 (m, 1H), 3.50-3.36 (m, 5H), 2.90 (d, J=13.81 Hz, 1H), 2.03-1.90 (m, 2H), 1.42-1.24 (m, 2H).

Example 81

Synthesis of (9S)—N-(5-((R)-2,3-dihydroxypropoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1179]



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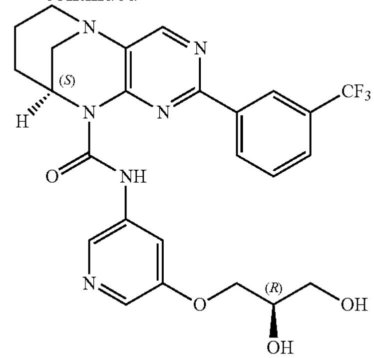


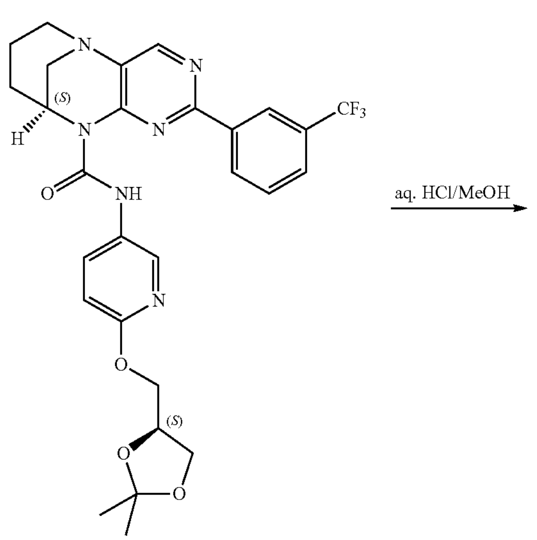
[1180] To a stirred solution of (9S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (260 mg, 0.456 mmol) in Methanol (10 mL), Hydrochloric acid (4 mL, 132 mmol) was added drop wise over a period of 5 min. at 0° C. Then the reaction mixture was stirred at 30° C. for 30 min. (TLC: 10% MeOH in DCM: R-0.3; UV) and evaporated the solvent, neutralized the obtained residue with saturated sodium bicarbonate solution, filtered the obtained solid and washed with n-pentane (2×20 mL) to afford the desired product (9S)—N-(5-((R)-2,3-dihydroxypropoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (160 mg, 0.300 mmol, 65.8% yield) as an off-white solid. LCMS (m/z): 531.19 [M+H]$^+$, R_t=1.91 min.

[1181] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.08 (s, 1H), 8.60-8.46 (m, 2H), 8.42 (d, J=7.89 Hz, 1H), 8.27 (d, J=1.97 Hz, 1H), 8.11 (d, J=2.41 Hz, 1H), 7.98 (t, J=2.19 Hz, 1H), 7.80 (d, J=7.89 Hz, 1H), 7.75-7.66 (m, 1H), 5.00 (s, 1H), 4.21-4.02 (m, 3H), 3.91-3.71 (m, 2H), 3.47-3.21 (m, 3H), 2.96 (d, J=13.59 Hz, 1H), 2.66 (s, 1H), 2.25 (d, J=14.25 Hz, 1H), 2.08 (s, 1H), 2.02-1.91 (m, 1H), 1.53-1.40 (m, 2H).

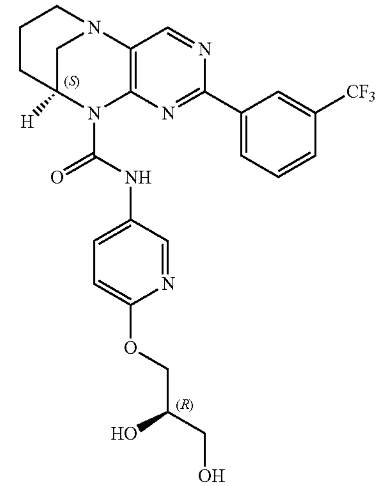
Example 82

Synthesis of (9S)—N-(6-((R)-2,3-dihydroxypropoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1182]



-continued



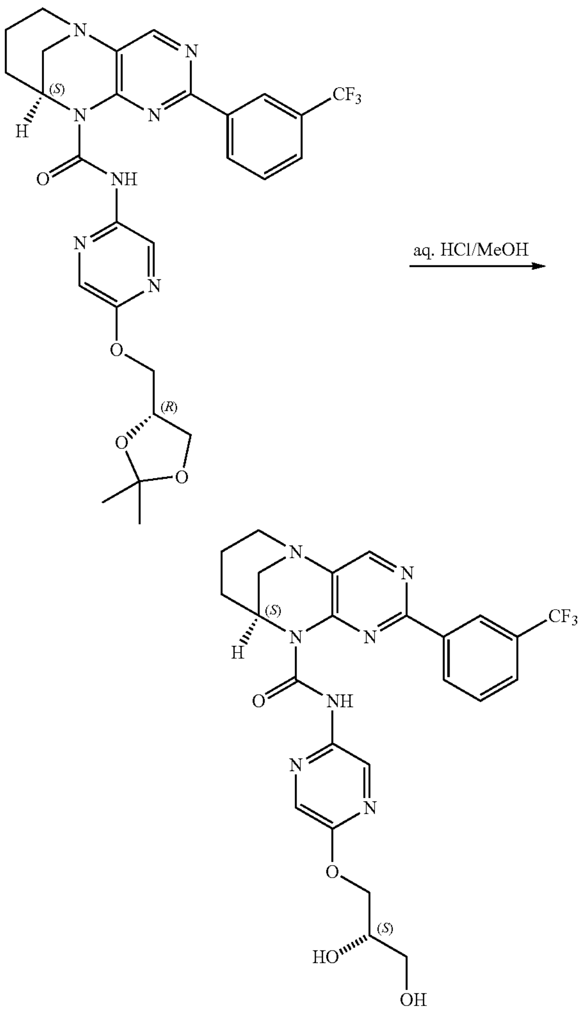
[1183] To a stirred solution of (9S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (240 mg, 0.421 mmol) in Methanol (10 mL), aq. Hydrochloric acid (4 mL, 132 mmol) was added drop wise over a period of 5 min. at 0° C. Then the reaction mixture was stirred at 30° C. for 30 min (TLC: 10% MeOH in DCM; R_f: 0.2; UV active) and evaporated the solvent. The obtained residue was neutralized with saturated sodium bicarbonate solution and filtered the obtained solid, washed with n-Pentane (2×20 mL) to afford the desired product (9S)—N-(6-((R)-2,3-dihydroxypropoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (170 mg, 0.316 mmol, 75% yield) as an off-white solid. LCMS (m/z): 531.15 [M+H]$^+$, R_t=3.81 min.

[1184] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.87 (s, 1H), 8.65-8.39 (m, 3H), 8.36 (d, J=2.63 Hz, 1H), 7.95 (dd, J=8.77, 2.63 Hz, 1H), 7.79 (d, J=7.45 Hz, 1H), 7.71-7.62 (m, 1H), 6.84 (d, J=8.99 Hz, 1H), 5.00 (s, 1H), 4.52-4.38 (m, 2H), 4.09-3.99 (m, 1H), 3.90 (d, J=4.82 Hz, 1H), 3.77-3.63 (m, 2H), 3.47-3.19 (m, 3H), 2.96 (d, J=14.03 Hz, 1H), 2.67 (s, 1H), 2.25 (d, J=14.25 Hz, 1H), 2.04-1.87 (m, 1H), 1.52-1.35 (m, 2H).

Example 83

Synthesis of (9S)—N-(5-((S)-2,3-dihydroxypropoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1185]



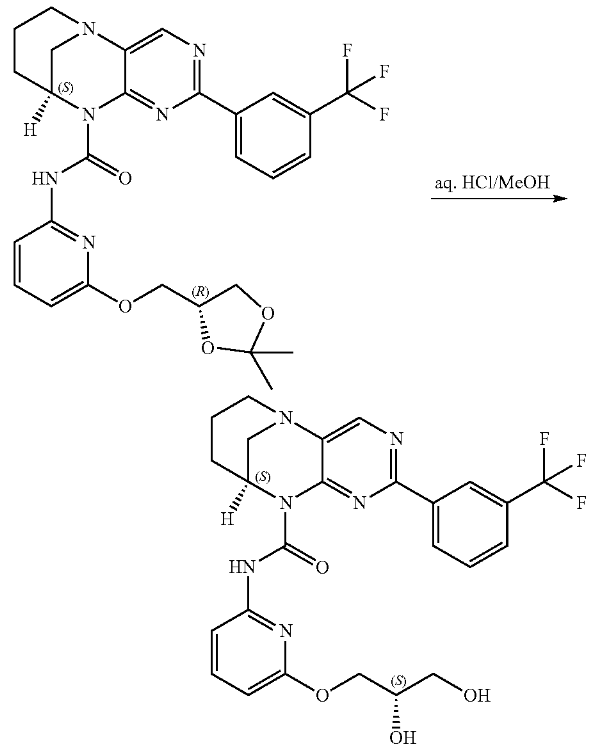
[1186] To a stirred solution of (9S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (240 mg, 0.420 mmol) in Methanol (10 mL), Hydrochloric acid (4 mL, 132 mmol) was added drop wise over a period of 5 min. at 0° C. Then the reaction mixture was stirred at 30° C. for 30 min (TLC: 10% MeOH in DCM: R_f-0.3; UV active). and evaporated the solvent. The reaction mixture was neutralized with saturated sodium bicarbonate solution, obtained solid was filtered and washed with n-pentane (2×20 mL) to afford the desired product (9S)—N-(5-((S)-2,3-dihydroxypropoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (130 mg, 0.237 mmol, 56.3% yield) as an off-white solid. LCMS (m/z): 532.1 $[M+H]^+$, Rt=2.29 min.

[1187] ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.60 (s, 1H), 8.90 (s, 1H), 8.81-8.69 (m, 2H), 8.58 (s, 1H), 8.09 (s, 1H), 7.93 (d, J=7.67 Hz, 1H), 7.79-7.89 (m, 1H), 4.98 (s, 1H), 4.84 (s, 1H), 4.69 (s, 1H), 4.34 (dd, J=10.63, 3.84 Hz, 1H), 4.20 (dd, J=10.63, 6.47 Hz, 1H), 3.84 (s, 1H), 3.60-3.36 (m, 3H), 3.30 (s, 2H), 2.90 (d, J=13.37 Hz, 1H), 2.00 (s, 2H), 1.45-1.20 (m, 2H).

Example 84

Synthesis of (9S)—N-(6-((S)-2,3-dihydroxypropoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1188]



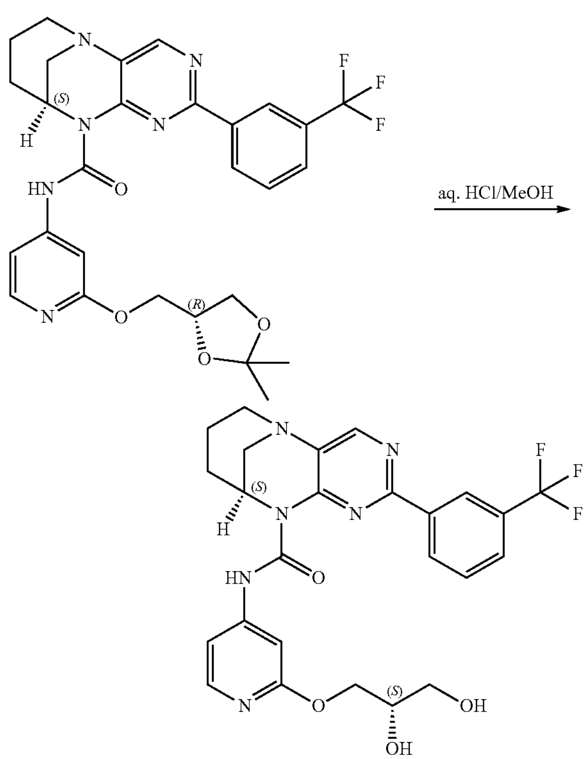
[1189] To a stirred solution of (9S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (350 mg, 0.613 mmol) in Methanol (8 mL) was added HCl (0.023 mL, 0.767 mmol), at 0° C. and stirred to RT for 1 h. (TLC system: 10% MeOH/DCM, R_f: 0.3). The reaction mixture was poured in saturated $NaHCO_3$ solution (30 mL) and extracted with DCM (2×50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give semi pure compound and washed with pentane (2×10 ml) to afford the desired product (9S)—N-(6-((S)-2,3-dihydroxypropoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methano pyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (250 mg, 0.469 mmol, 76% yield), LCMS (m/z): 531.15 $[M+H]^+$, Rt=2.37 min.

[1190] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.08 (s, 1H), 8.76-8.57 (m, 2H), 8.48 (s, 1H), 7.82-7.57 (m, 4H), 6.55 (d, J=7.67 Hz, 1H), 5.01 (s, 1H), 4.25-4.45 (m, 2H), 4.05-3.94 (m, 1H), 3.75-3.53 (m, 2H), 3.29-3.45 (m, 3H), 2.96 (d, J=13.37 Hz, 1H), 2.77 (d, J=5.26 Hz, 1H), 2.26 (d, J=14.69 Hz, 1H), 2.10 (t, J=6.14 Hz, 1H), 2.02-1.87 (m, 1H), 1.46 (m, 2H).

Example 85

Synthesis of (9S)—N-(2-((S)-2,3-dihydroxypropoxy)pyridin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1191]



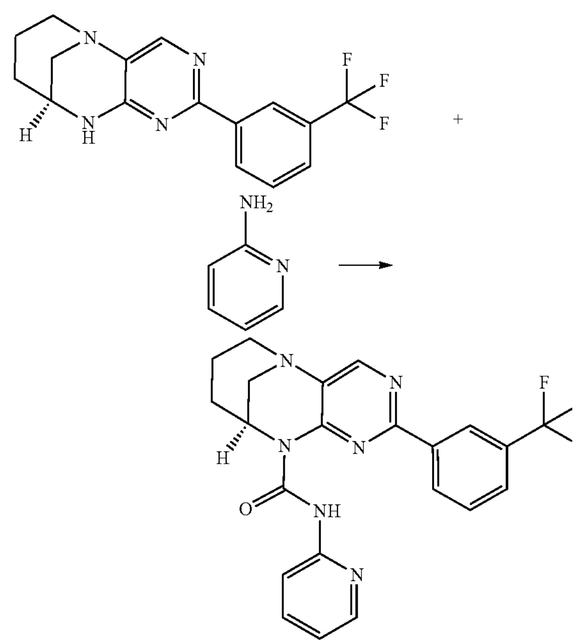
[1192] To a stirred solution of (9S)—N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (220 mg, 0.386 mmol) in methanol (8 mL) at 0° C. was added aq HCl (1.172 µL, 0.039 mmol) dropwise over a period of 5 min. Then the reaction mixture was stirred at 30° C. for 2 h. (TLC eluent: 5% MeOH in DCM: R_f—0.6). and evaporated the solvent. The reaction mixture was neutralized with sodium bicarbonate solution (20 ml) and formed solid was washed by ether (2×10 ml), pentane (2×5 ml) to afford the desired product (9S)—N-(2-((S)-2,3-dihydroxypropoxy)pyridin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (182 mg, 0.341 mmol, 88% yield) as an off white solid. LCMS (m/z): 531.19 $[M+H]^+$, Rt=2.10 min.

[1193] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.16 (s, 1H), 8.50 (s, 1H), 8.49-8.44 (m, 2H), 8.00 (d, J=5.92 Hz, 1H), 7.82 (d, J=7.67 Hz, 1H), 7.73-7.67 (m, 1H), 7.25 (d, J=1.75 Hz, 1H), 7.06 (dd, J=5.70, 1.75 Hz, 1H), 4.99 (s, 1H), 4.50-4.47 (m, 2H), 4.19 (d, J=5.48 Hz, 1H), 4.04-3.98 (m, 1H), 3.72-3.63 (m, 2H), 3.44-3.32 (m, 3H), 2.95 (d, J=13.81 Hz, 1H), 2.81 (t, J=6.58 Hz, 1H), 2.24 (d, J=13.81 Hz, 1H), 2.02-1.91 (m, 1H), 1.58-1.43 (m, 2H).

Example 86

Synthesis of (9S)—N-(pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1194]



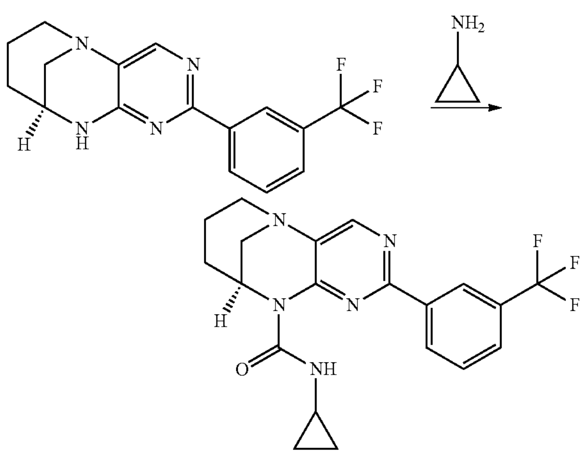
[1195] To a solution of (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (300 mg, 0.937 mmol) in THF (15 mL) under nitrogen was added triethylamine (0.783 mL, 5.62 mmol), triphosgene (278 mg, 0.937 mmol) and stirred at RT for 30 min. To this reaction mixture pyridin-2-amine (264 mg, 2.81 mmol) was added and heated at 70° C. for 16 h. (TLC Eluent: 100% EtOAc in Hexane, R_f: 0.4). The reaction mixture was cooled to RT, quenched with water (10 mL) and extracted in to EtOAc (3×20 mL). The combined organic extracts were dried over anhydrous sodiumsulfate, filtered and evaporated under reduced pressure to get crude compound. The crude was purified by column chromatography (neutral alumina, eluent: 15% ethyl acetate in hexane) to afford (9S)—N-(pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (227 mg, 0.513 mmol, 54.8% yield) as an off white solid. LCMS (m/z): 441.04 $[M+H]^+$, Rt=2.97 min.

[1196] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.68 (s, 1H), 8.94 (d, J=0.66 Hz, 1H), 8.87 (d, J=7.89 Hz, 1H), 8.47 (s, 1H), 8.40-8.44 (m, 1H), 8.18 (dt, J=8.39, 0.96 Hz, 1H), 7.63-7.81 (m, 3H), 7.05 (ddd, J=7.34, 4.82, 0.99 Hz, 1H), 5.01 (br s, 1H), 3.29-3.44 (m, 3H), 2.97 (br d, J=13.15 Hz, 1H), 2.20-2.31 (m, 1H), 1.87-2.02 (m, 1H), 1.40-1.47 (m, 2H).

Example 87

Synthesis of (9S)—N-cyclopropyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1197]



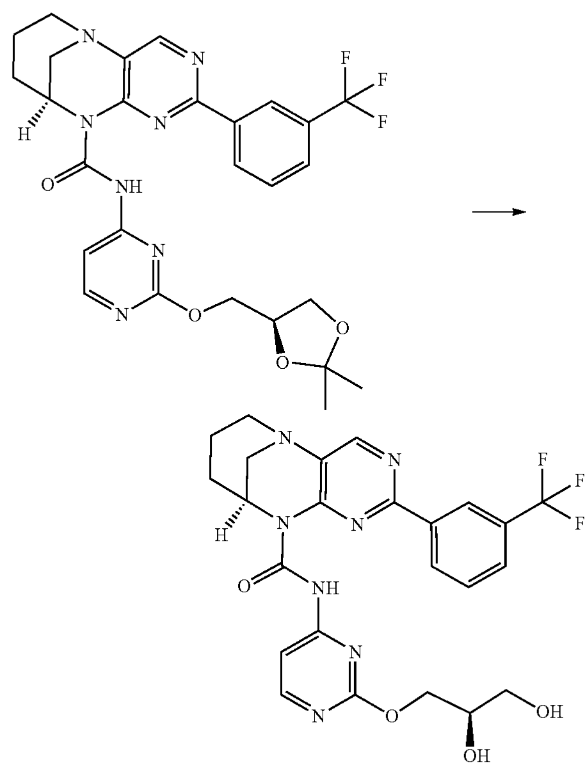
[1198] To a solution of (9S)-2-(3-(trifluoromethyl)phenyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (7.0 g, 21.85 mmol) in THF (70 mL) under nitrogen was added triethylamine (18.28 mL, 131 mmol), triphosgene (6.49 g, 21.85 mmol) and stirred at RT for 1 h. To this reaction mixture cyclopropanamine (3.74 g, 65.6 mmol) was added and stirred at 70° C. for 16 h. (TLC eluent: 100% EtOAc/Hexane, R_f: 0.4, UV active). The reaction mixture was cooled to RT diluted with water (70 mL) and extracted in to EtOAc (3×100 mL). The combined organic extracts were dried over anhydrous sodiumsulfate, filtered and evaporated to get crude compound. The crude compound was purified by chromatography (Grace instrument using C-18 column, Mobile phase A: 0.1% Formic Acid in water; B: MeOH, the product was eluted at 65% MeOH/0.1% Formic Acid in water) to afford the desired compound (5.6 g). This was taken in ethanol (100 mL) and treated with Silicycle palladium scavenger (2.8 g) and stirred at 50° C. for 3 h. The mixture was filtered through celite pad and washed with hot ethanol (50 ml), the obtained filtrate was concentrated under reduced pressure to afford (9S)—N-cyclopropyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (5.2 g, 12.79 mmol, 58.5% yield) as an off white solid. LCMS (m/z): 404.08 [M+H]+; Rt=2.60 min.

[1199] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 10.65 (br s, 1H), 8.48-8.35 (m, 3H), 7.77-7.72 (m, 1H), 7.68-7.60 (m, 1H), 4.96 (t, J=2.30 Hz, 1H), 3.38-3.23 (m, 3H), 2.97-2.82 (m, 2H), 2.27-2.15 (m, 1H), 1.97-1.83 (m, 1H), 1.48-1.35 (m, 2H), 0.94-0.85 (m, 2H), 0.73-0.64 (m, 2H).

Example 88

Synthesis of (9S)—N-(2-((R)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1200]



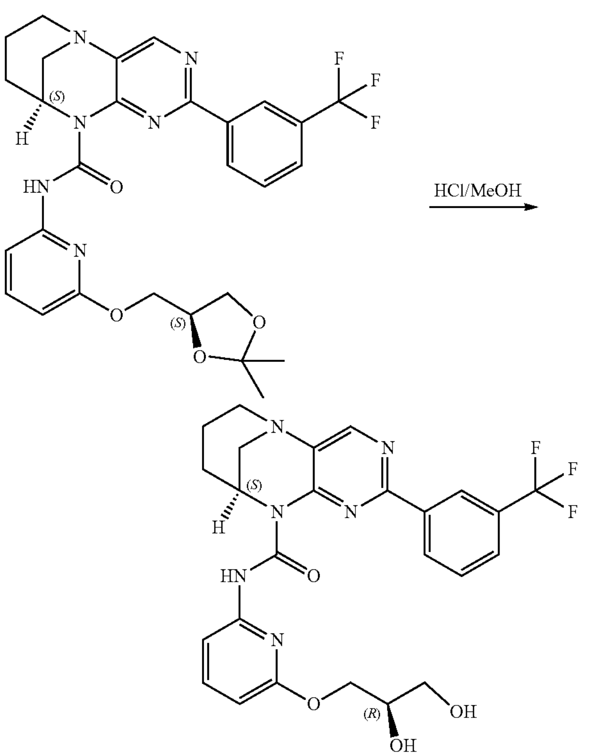
[1201] To a stirred solution of (9S)—N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (250 mg, 0.437 mmol) in methanol (10 mL) under nitrogen at 0° C. was added aq. HCl (1 ml, 4.00 mmol, 36%) and stirred at RT for 1 h. (TLC eluent: 5% Methanol in DCM, R_f:0.2, UV active). To the reaction mixture was added saturated $NaHCO_3$ solution (till pH-8-9) and extracted with DCM (3×15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to obtain crude compound. The crude compound was triturated with diethylether (3×5 mL) to afford (9S)—N-(2-((R)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (210 mg, 0.384 mmol, 88% yield) as an off-white solid. LCMS (m/z): 532.16 $[M+H]^+$, R_t=2.18 min.

[1202] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.78 (s, 1H), 8.83 (br d, J=7.45 Hz, 1H), 8.73 (s, 1H), 8.51 (s, 1H), 8.40 (d, J=5.70 Hz, 1H), 7.85 (d, J=5.70 Hz, 1H), 7.72-7.81 (m, 2H), 4.96 (br s, 1H), 4.45-4.57 (m, 2H), 4.09-4.18 (m, 1H), 3.69-3.82 (m, 2H), 3.26-3.47 (m, 4H), 2.97 (br d, J=14.25 Hz, 1H), 2.40 (br t, J=6.14 Hz, 1H), 2.24 (br d, J=14.69 Hz, 1H), 1.91-2.06 (m, 1H), 1.41-1.51 (m, 2H).

Example 89

Synthesis of (9S)—N-(6-((R)-2,3-dihydroxy-propoxy)pyridin-2-yl)-2-(3-(trifluoro-meth yl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1203]



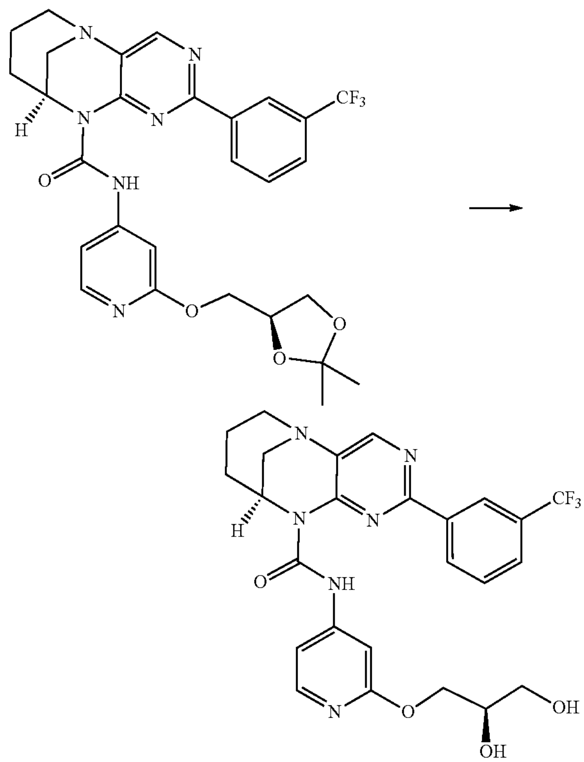
[1204] To a stirred solution of (9S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido [4,5-b][1,4]di azocine-10(7H)-carboxamide (300 mg, 0.526 mmol) in Methanol (15 mL) was added HCl (0.128 mL, 4.21 mmol) at 0° C. The reaction mixture was stirred for 1 h. (TLC System: R_f-0.4, 50% EtOAc-Pet ether), at room temperature and concentrated under reduced pressure to obtain residue. The residue was neutralized with saturated sodium bicarbonate solution to afford solid product, filtered and dried to afford the desired product (9S)—N-(6-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (175 mg, 0.329 mmol, 62.6% yield) as an off white solid. LCMS (m/z): 531 $[M+H]^+$, Rt=2.36 min.

[1205] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.07 (s, 1H), 8.69 (s, 1H), 8.64 (d, J=7.45 Hz, 1H), 8.48 (s, 1H), 7.79-7.62 (m, 4H), 6.55 (d, J=7.67 Hz, 1H), 5.01 (s, 1H), 5.06-4.96 (m, 1H), 4.44-4.35 (m, 1H), 4.33-4.26 (m, 1H), 4.00 (dq, J=10.06, 5.20 Hz, 1H), 3.71-3.55 (m, 2H), 3.45-3.29 (m, 3H), 2.96 (d, J=14.03 Hz, 1H), 2.80 (d, J=5.04 Hz, 1H), 2.26 (d, J=14.47 Hz, 1H), 2.12 (s, 1H), 2.03-1.90 (m, 1H), 1.60-1.51 (m, 1H).

Example 90

Synthesis of (9S)—N-(2-((R)-2,3-dihydroxy-propoxy)pyridin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1206]



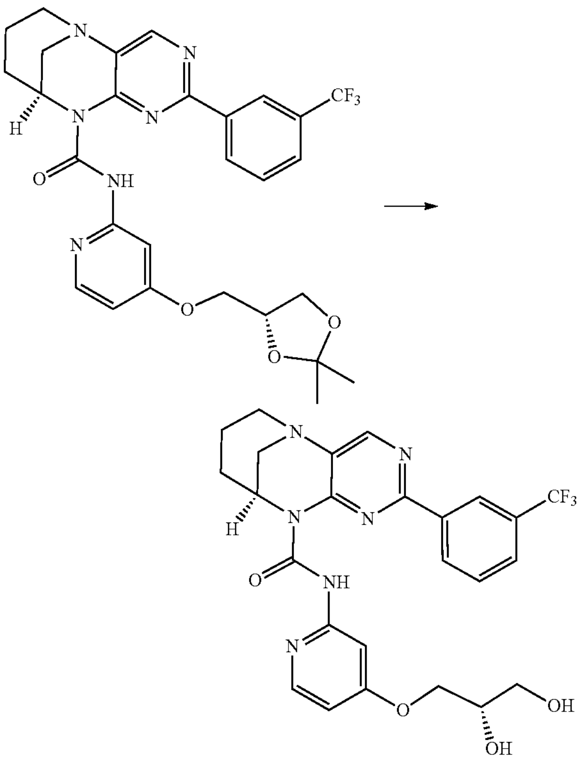
[1207] To a stirred solution of (9S)—N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido [4,5-b][1,4]diazocine-10(7H)-carboxamide (350.0 mg, 0.613 mmol) in methanol (10 mL) was added aqueous HCl (0.5 mL, 16.46 mmol) at 0° C. and stirred at RT for 4 h. The reaction mixture was evaporated under reduced pressure to get the crude (TLC: eluent 100% EtOAc, R_f-0.2, UV active). The crude was diluted with the water (5 ml) and basified with the 10% sodium bicarbonate solution. The precipitated solid was filtered and was washed with the water and dried over vacuum to afford (9S)—N-(2-((R)-2,3-dihydroxypropoxy)pyridin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10 (7H)-carboxamide (233.6 mg, 0.440 mmol, 71.7% yield) as an off white solid. LCMS (m/z): 531.15$[M+H]^+$, R_t=2.13 min.

[1208] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.16 (br s, 1H), 8.52-8.42 (m, 3H), 8.00 (br d, J=5.48 Hz, 1H), 7.82 (br d, J=7.67 Hz, 1H), 7.74-7.66 (m, 1H), 7.25 (br s, 1H), 7.06 (br d, J=5.04 Hz, 1H), 4.99 (br s, 1H), 4.48 (br d, J=2.63 Hz, 2H), 4.20 (br s, 1H), 4.01 (br s, 1H), 3.68 (br s, 2H), 3.45-3.27 (m, 3H), 3.00-2.79 (m, 2H), 2.24 (br d, J=12.72 Hz, 1H), 2.02-1.90 (m, 1H), 1.50-1.49 (m, 1H), 1.46 (br d, J=0.88 Hz, 1H).

Example 91

Synthesis of (9S)—N-(4-((S)-2,3-dihydroxy-propoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1209]



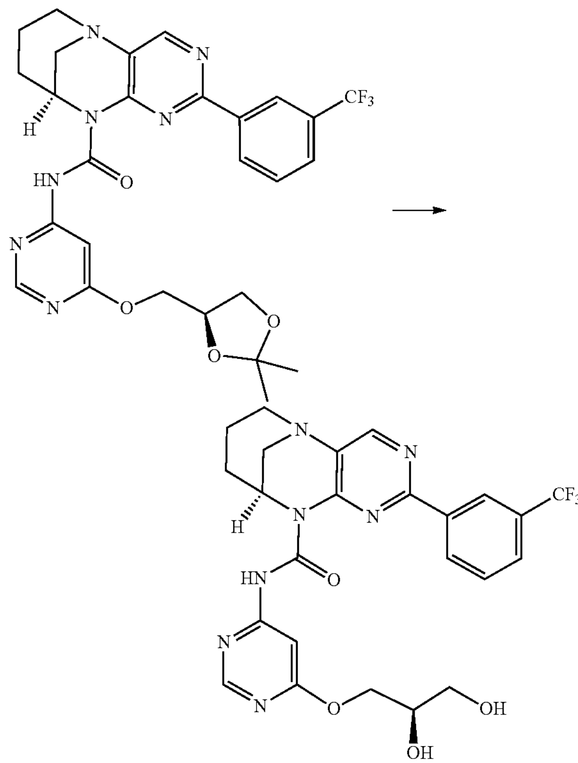
[1210] To a stirred solution of (9S)—N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (300 mg, 0.526 mmol) in methanol (10 mL) under nitrogen at 0° C. was added aq HCl (0.320 mL, 10.52 mmol, 36%) and stirred for 2 h. (TLC eluent: 100% EtOAc: R_f-0.2; UV active). The reaction mixture was basified with saturated sodium bicarbonate solution (till pH-8-9) and solvent was evaporated under reduced pressure. The residue was diluted with water (20 mL) and extracted into DCM (2×25 mL). Combined organic extracts were dried over anhydrous sodium sulphate, filtered and filtrate was evaporated in vacuo and the crude was triturated with diethyl ether (10 mL) to afford (9S)—N-(4-((S)-2,3-dihydroxypropoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (200 mg, 0.377 mmol, 71.7% yield) as a white solid. LCMS (m/z): 531.12 $[M+H]^+$, Rt=2.20 min

[1211] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.70 (s, 1H), 8.93 (s, 1H), 8.86 (d, J=7.89 Hz, 1H), 8.47 (s, 1H), 8.22 (d, J=5.70 Hz, 1H), 7.82 (d, J=2.19 Hz, 1H), 7.77 (d, J=7.67 Hz, 1H), 7.69-7.62 (m, 1H), 6.61 (dd, J=5.70, 2.41 Hz, 1H), 4.98 (br s, 1H), 4.12-4.19 (m, 3H), 3.89-3.81 (m, 1H), 3.80-3.72 (m, 1H), 3.44-3.27 (m, 3H), 2.98 (br d, J=13.81 Hz, 1H), 2.60 (d, J=3.73 Hz, 1H), 2.24 (br d, J=14.03 Hz, 1H), 2.05-1.87 (m, 2H), 1.49-1.41 (m, 2H).

Example 92

Synthesis of (9S)—N-(6-((R)-2,3-dihydroxy-propoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1212]



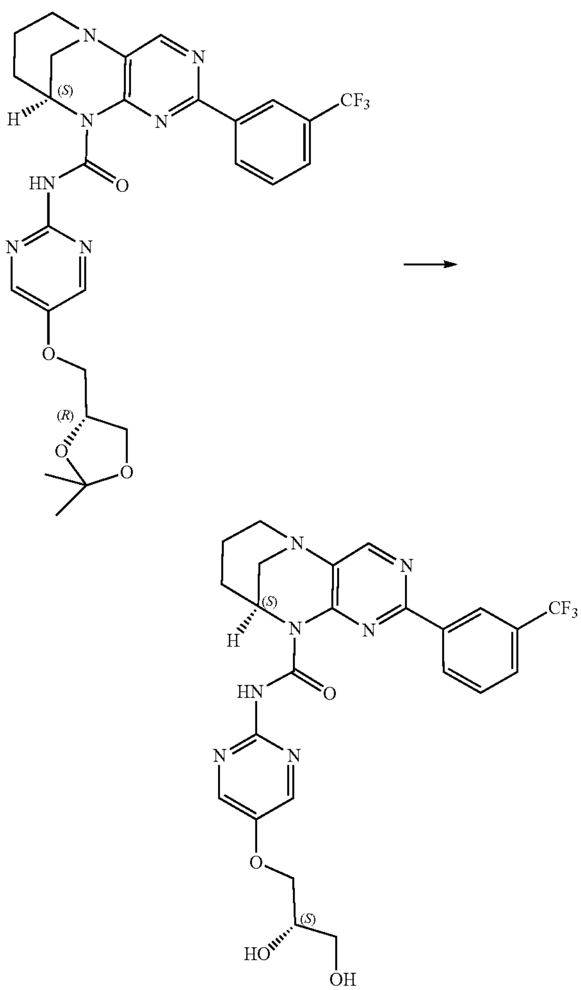
[1213] To a stirred solution (9S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (0.35 g, 0.612 mmol) in methanol (10 mL) at 0° C. was added aq HCl (0.5 mL, 6.00 mmol, 36%) and stirred for 2 h. (TLC eluent: 100% EtOAc: R-0.3; UV active). Reaction mixture was basified by adding saturated sodium bicarbonate solution (till pH-8-9) then concentrated. The residue was diluted with water (10 mL) and extracted into EtOAc (2×25 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude product. The crude was triturated with diethyl ether (10 mL) to afford desired product (9S)—N-(6-((R)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (0.135 g, 0.251 mmol, 41.0% yield) as an off-white solid LCMS (m/z): 532.13 $[M+H]^+$, R_t=2.33 min.

[1214] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.90 (s, 1H), 8.90 (s, 1H), 8.81 (br d, J=8.11 Hz, 1H), 8.41-8.59 (m, 2H), 7.79 (d, J=7.89 Hz, 1H), 7.61-7.71 (m, 1H), 7.60 (d, J=0.88 Hz, 1H), 4.97 (br s, 1H), 4.59-4.44 (m, 2H), 4.06 (dq, J=9.89, 5.11 Hz, 1H), 3.81-3.62 (m, 2H), 3.52-3.18 (m, 4H), 2.97 (br d, J=13.37 Hz, 1H), 2.48 (t, J=6.36 Hz, 1H), 2.33-2.17 (m, 1H), 2.06-1.89 (m, 1H), 1.51-1.33 (m, 2H).

Example 93

Synthesis of (9S)—N-(5-((S)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1215]



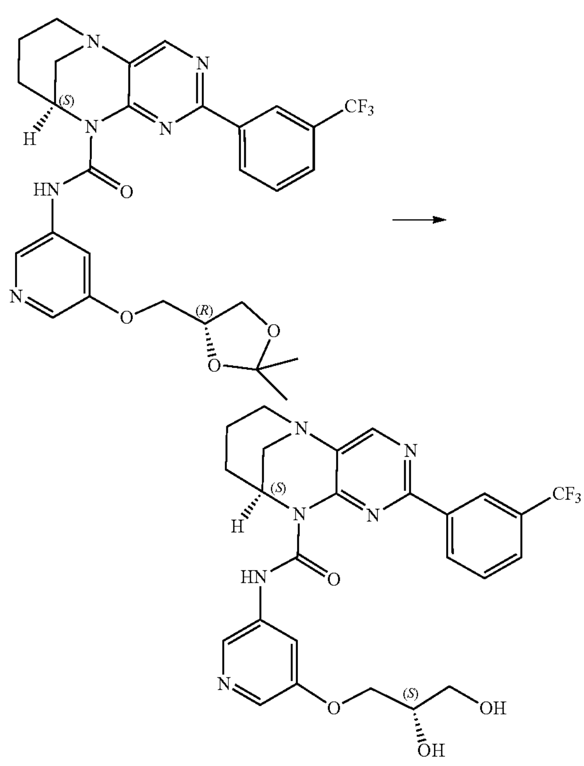
[1216] To a stirred solution of (9S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-2-(3 (trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido [4,5 b][1,4]diazocine-10(7H)-carboxamide (0.3 g, 0.525 mmol) in methanol (10 mL) at 0° C. was added aq. HCl (0.5 mL, 6.00 mmol, 12 M) and stirred at RT for 1 h. (TLC eluent: 100% Ethyl acetate, R_f=0.2; UV active). Reaction mixture was basified by adding saturated sodium bicarbonate (till pH-8-9) and solvent was evaporated under reduced pressure. The residue was diluted with water (10 mL) and extracted into EtOAc (20 mL). Combined organic extracts were dried over anhydrous sodium sulphate, filtered and filtrate was evaporated in vacuo and the crude was triturated with diethylether (10 mL) to afford the desired product (9S)—N-(5-((S)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5b][1,4]diazocine-10(7H)-carboxamide (0.185 g, 0.345 mmol, 65.8% yield) as off-White solid. LCMS (m/z): 532.20 $[M+H]^+$, R_t=4.48 min.

[1217] ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.71 (s, 1H), 8.82 (br d, J=7.67 Hz, 1H), 8.75 (br s, 1H), 8.56 (s, 1H), 8.48 (s, 2H), 7.93 (br d, J=8.11 Hz, 1H), 7.88-7.82 (m, 1H), 5.04 (br s, 1H), 4.81 (br s, 1H), 4.71 (br s, 1H), 4.18 (br dd, J=9.87, 3.51 Hz, 1H), 4.08-4.02 (m, 1H), 3.83 (br s, 1H), 3.50-3.39 (m, 5H), 2.89 (br d, J=12.93 Hz, 1H), 1.98 (br s, 2H), 1.34 (br s, 2H).

Example 94

Synthesis of (9S)—N-(5-((S)-2,3-dihydroxypropoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1218]



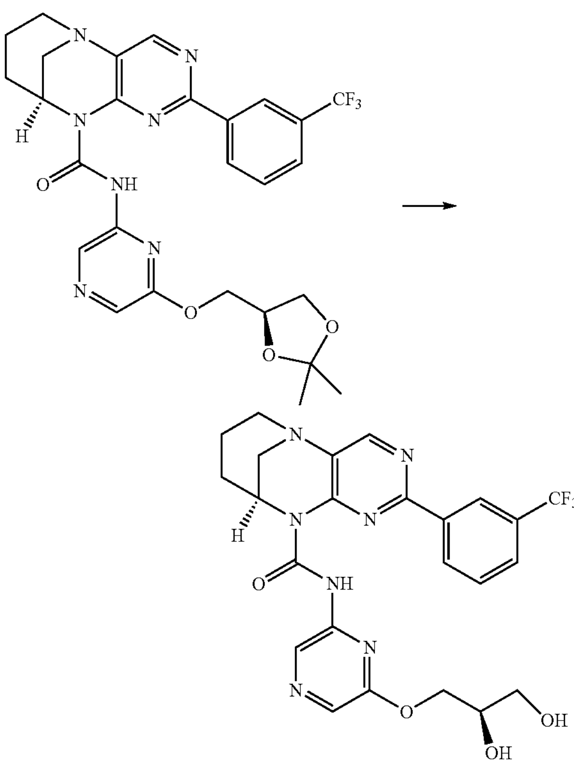
[1219] To a stirred solution of ((9S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido [4,5b][1,4]diazocine-10(7H)-carboxamide (7.0 g, 12.27 mmol) in methanol (25 mL) at 0° C. was added aq. HCl (0.5 mL, 6.00 mmol, 12M) and stirred at RT for 1 h. (TLC eluent: 100% Ethylacetate: R=0.1; UV active). Reaction mixture was basified by adding saturated sodium bicarbonate solution (till pH-8-9) and then concentrated under reduced pressure. The residue was diluted with water (5 mL) and extracted into ethyl acetate (2×10 mL). Combined organic extracts were dried over anhydrous sodium sulphate, filtered and filtrate was evaporated in vacuo and the crude was triturated with diethylether (10 mL) to afford solid compound. The obtained product was grinded in glass mortar to afford fine powder of desired product (9S)—N-(5-((S)-2,3-dihydroxypropoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (6.0 g, 11.31 mmol, 92% yield) as an off-white solid. LCMS (m/z): 531.23 $[M+H]^+$, R_t=2.25 min.

[1220] ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.59 (s, 1H), 8.61-8.39 (m, 3H), 8.28 (d, J=1.53 Hz, 1H), 8.07 (d, J=2.41 Hz, 1H), 7.92 (br d, J=7.89 Hz, 1H), 7.86-7.72 (m, 2H), 5.01 (d, J=5.04 Hz, 1H), 4.81 (br s, 1H), 4.70 (t, J=5.59 Hz, 1H), 4.09 (dd, J=9.65, 3.95 Hz, 1H), 3.96 (dd, J=9.65, 6.36 Hz, 1H), 3.84 (dq, J=10.17, 5.31 Hz, 1H), 3.54-3.38 (m, 3H), 3.32 (s, 2H), 2.88 (br d, J=13.59 Hz, 1H), 2.17-1.90 (m, 2H), 1.35 (br s, 2H).

Example 95

Synthesis of (9S)—N-(6-((R)-2,3-dihydroxypropoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1221]



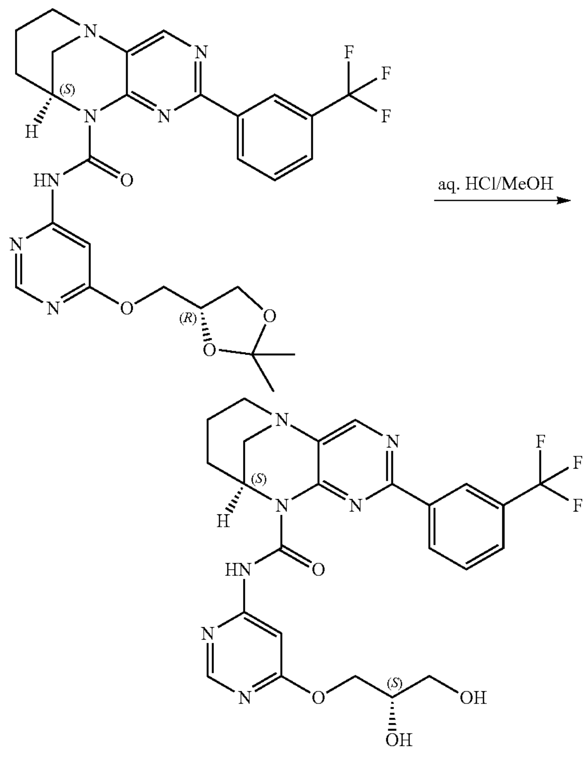
[1222] To a stirred solution of (9S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (150 mg, 0.262 mmol) in methanol (15 mL) at 0° C. was added aqueous HCl (1 mL, 32.9 mmol) and stirred for 2 h. (TLC eluent: 5% MeOH in DCM, R_f: 0.3). The reaction mixture was concentrated in vacuo and the residue was basified with saturated $NaHCO_3$ solution (15 mL). The resultant solid was filtered, triturated with pentane (25 mL) dried under reduced pressure to afford the desired product (9S)—N-(6-((R)-2,3-dihydroxypropoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (88 mg, 0.165 mmol, 63.0% yield) as an off white solid. LCMS (m/z): 532.16 $[M+H]^+$, Rt=2.18 min.

[1223] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.25 (s, 1H), 9.08 (s, 1H), 8.70 (s, 1H), 8.59 (d, J=7.23 Hz, 1H), 8.51 (s, 1H), 8.06 (s, 1H), 7.85-7.65 (m, 2H), 5.02 (br s, 1H), 4.50-4.29 (m, 2H), 4.19-4.05 (m, 1H), 3.89-3.73 (m, 1H), 3.67 (dt, J=11.35, 5.62 Hz, 1H), 3.50-3.29 (m, 3H), 2.97 (br d, J=14.47 Hz, 1H), 2.58 (d, J=4.82 Hz, 1H), 2.27 (br d, J=13.59 Hz, 1H), 2.08-1.89 (m, 2H), 1.53-1.36 (m, 2H).

Example 96

Synthesis of (9S)—N-(6-((S)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1224]



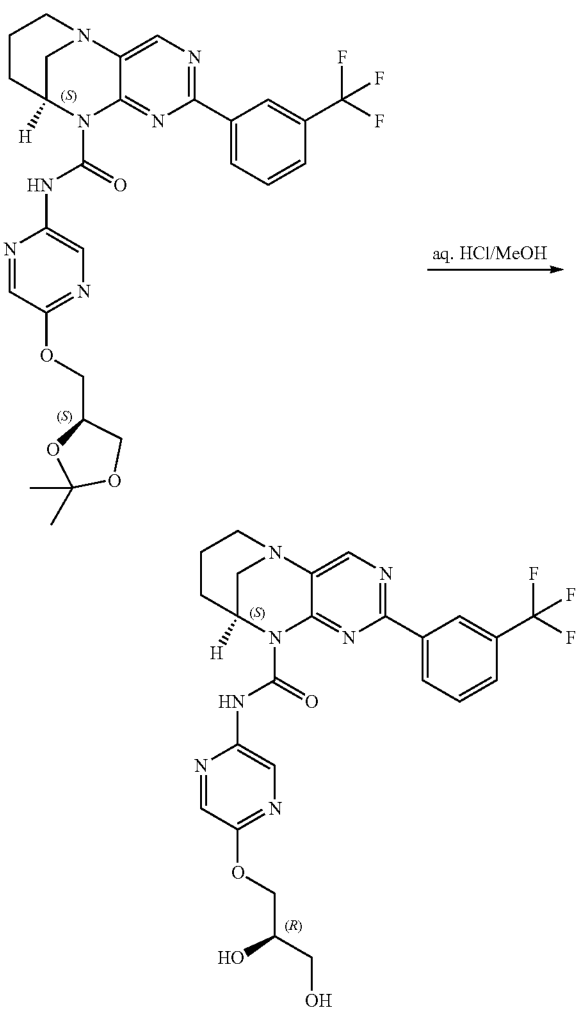
[1225] To a stirred solution of (9S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazo cine-10(7H)-carboxamide (300 mg, 0.525 mmol) in Methanol (5 mL) was added hydrochloric acid (0.016 mL, 0.525 mmol) drop wise over a period of 5 min at 0° C. Then the reaction mixture was stirred at room temperature for 2 h. (TLC eluent: 10% MeOH in DCM: R_f-0.3). and evaporated the solvent, neutralized with sodium bicarbonate solution and filtered the obtain solid, washed with water and dried to get crude compound. The crude compound was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 4% methanol in DCM) to afford the desired compound (9S)—N-(6-((S)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (110 mg, 0.205 mmol, 39.1% yield) as a white solid. LCMS (m/z): 532.13 $[M+H]^+$, Rt=2.32 min.

[1226] ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.80 (s, 1H), 8.92-8.76 (m, 2H), 8.61 (s, 1H), 8.55 (d, J=0.88 Hz, 1H), 7.95 (d, J=7.89 Hz, 1H), 7.88-7.82 (m, 1H), 7.45 (s, 1H), 4.98 (s, 1H), 4.82 (br s, 1H), 4.67 (t, J=5.70 Hz, 1H), 4.40 (dd, J=10.85, 4.06 Hz, 1H), 4.31-4.15 (m, 1H), 3.89-3.73 (m, 1H), 3.89-3.73 (m, 1H), 3.52-3.35 (m, 3H), 2.95-2.87 (m, 1H), 2.91 (d, J=13.59 Hz, 1H), 2.54-2.46 (m, 2H), 2.03-1.92 (m, 2H).

Example 97

Synthesis of (9S)—N-(5-((R)-2,3-dihydroxypropoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1227]



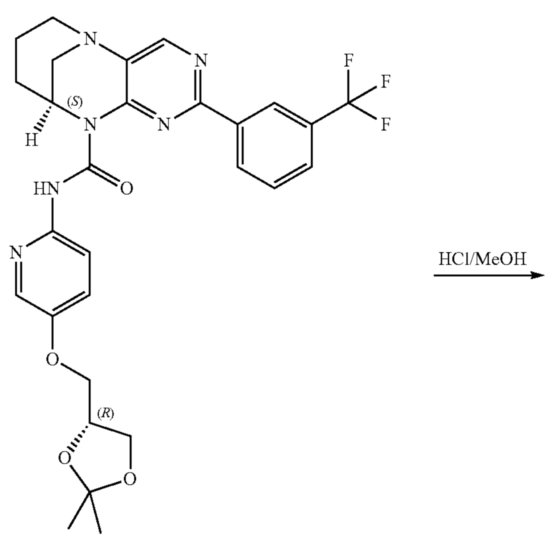
[1228] To a stirred solution of (9S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (250 mg, 0.437 mmol) in Methanol (10 mL) was added hydrochloric acid (2 mL, 65.8 mmol) drop wise over a period of 5 min at 0° C. Then the reaction mixture was stirred at room temperature for 2 h. (TLC eluent: 10% MeOH in DCM: R_f—0.3) and evaporated the solvent. The reaction mixture was neutralized with sodium bicarbonate solution and filtered the obtained solid compound, washed with water and dried to afford the desired compound (9S)—N-(5-((R)-2,3-dihydroxypropoxy)pyrazin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methano pyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (225 mg, 0.413 mmol, 94% yield) as a pale brown solid. LC-MS (m/z): 532.16 $[M+H]^+$, Rt=2.28 min.

[1229] ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.60 (s, 1H), 8.90 (d, J=1.53 Hz, 1H), 8.83-8.73 (m, 2H), 8.09 (d, J=1.53 Hz, 1H), 7.94 (d, J=7.67 Hz, 1H), 7.88-7.79 (m, 2H), 4.97 (brs, 1H), 4.85 (brs, 1H), 4.77-4.58 (m, 2H), 4.34 (dd, J=10.85, 4.06 Hz, 1H), 4.27-4.11 (m, 2H), 3.93-3.73 (m, 1H), 3.58-3.36 (m, 3H), 2.90 (d, J=13.59 Hz, 1H), 2.11-1.85 (m, 2H), 1.47-1.27 (m, 2H).

Example 98

Synthesis of (9S)—N-(5-((S)-2,3-dihydroxypropoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1230]



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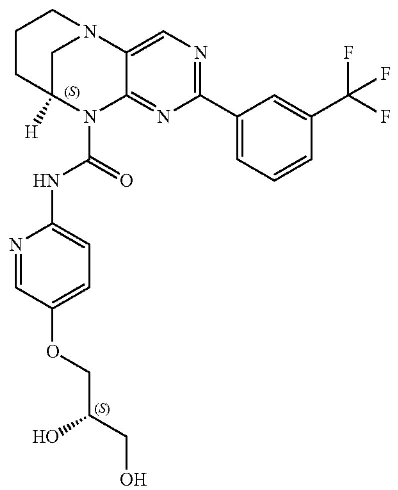


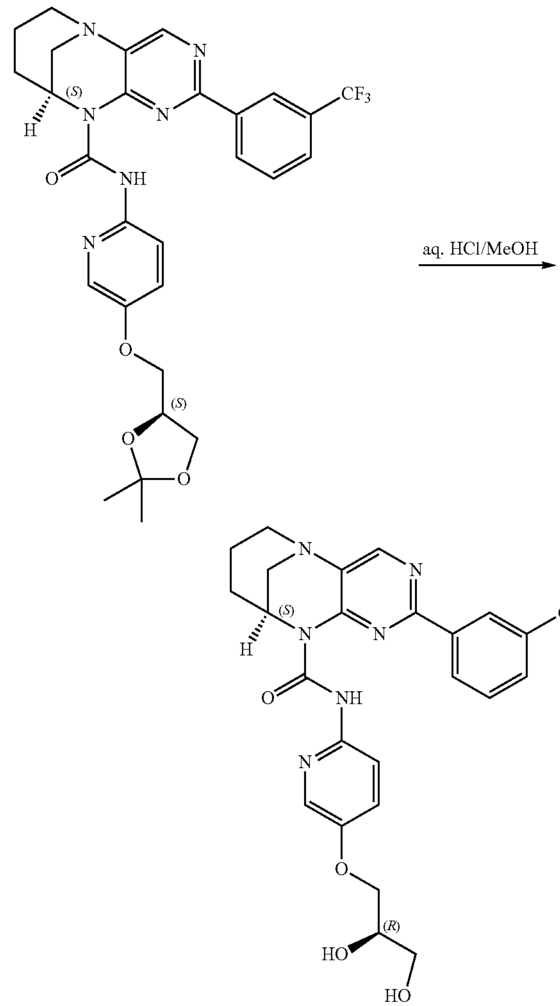
[1231] To a stirred solution of (9S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (250 mg, 0.438 mmol) in Methanol (4 mL) and Tetrahydrofuran (THF) (4 mL) was added HCl (0.3 mL, 9.87 mmol) at 0° C. then stirred at RT for 2 h. (TLC system: neat ethyl acetate; R_f: 0.2). The reaction mixture was concentrated in vacuo and the residue was neutralized with saturated $NaHCO_3$ solution and filtered the obtained solid, washed with n-pentane (10 mL×2) to afford the desired product (9S)—N-(5-((S)-2,3-dihydroxypropoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (175 mg, 0.323 mmol, 73.7% yield) as a pale yellow solid. LCMS (m/z): 531.23 $[M+H]^+$, Rt=2.26 min.

[1232] ^1H NMR (400 MHz, $CDCl_3$): δ ppm 13.60 (s, 1H), 8.91 (s, 1H), 8.81 (d, J=7.89 Hz, 1H), 8.46 (s, 1H), 8.14-8.10 (m, 2H), 7.77 (d, J=7.67 Hz, 1H), 7.68-7.63 (m, 1H), 7.33-7.28 (m, 1H), 5.00 (br s, 1H), 4.14-4.09 (m, 3H), 3.91-3.85 (m, 1H), 3.82-3.76 (m, 1H), 3.43-3.29 (m, 3H), 2.96 (d, J=13.81 Hz, 1H), 2.64 (d, J=3.95 Hz, 1H), 2.24 (d, J=13.81 Hz, 1H), 2.06 (t, J=5.48 Hz, 1H), 1.98-1.89 (m, 1H), 1.44 (d, J=4.38 Hz, 2H).

Example 99

Synthesis of (9S)—N-(5-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-2-(3-(trifluoro-methyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1233]



[1234] To a stirred solution of (9S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (250 mg, 0.438 mmol) in Methanol (10 mL) was added HCl (0.133 mL, 4.38 mmol) at 0° C. then stirred at room temperature for 2 h. (TLC system: 100% ethylacetate, R_f value: 0.2). The reaction mixture was quenched with saturated $NaHCO_3$ solution (10 mL) and extracted with DCM (2×30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to obtain residue. The residue was triturated with n-pentane (3×10 mL) to afford the desired product (9S)—N-(5-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (130 mg, 0.244 mmol, 55.8% yield) as a white solid. LCMS (m/z): 531.19 $[M+H]^+$, R_t=2.25 min.

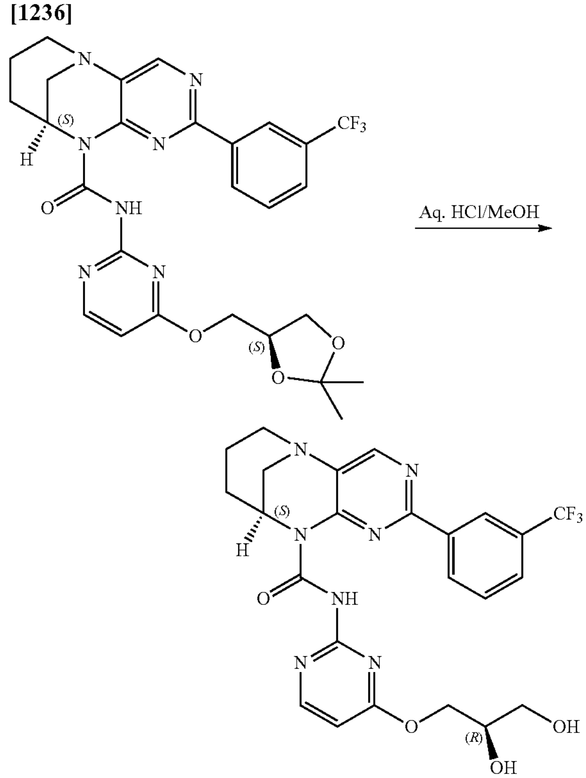
[1235] ^1H NMR (400 MHz, $CDCl_3$): δ ppm 13.61 (s, 1H), 8.91 (s, 1H), 8.82 (d, J=7.89 Hz, 1H), 8.46 (s, 1H), 8.15-8.10

(m, 2H), 7.77 (d, J=7.89 Hz, 1H), 7.69-7.63 (m, 1H), 7.34-7.29 (m, 1H), 5.00 (brs, 1H), 4.18-4.09 (m, 3H), 3.92-3.85 (m, 1H), 3.82-3.76 (m, 1H), 3.43-3.29 (m, 3H), 2.96 (d, J=13.81 Hz, 1H), 2.57 (br s, 1H), 2.25 (br d, J=13.59 Hz, 1H), 2.01-1.88 (m, 2H), 1.47-1.38 (m, 2H).

Example 100

Synthesis of (9S)—N-(4-((R)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1236]



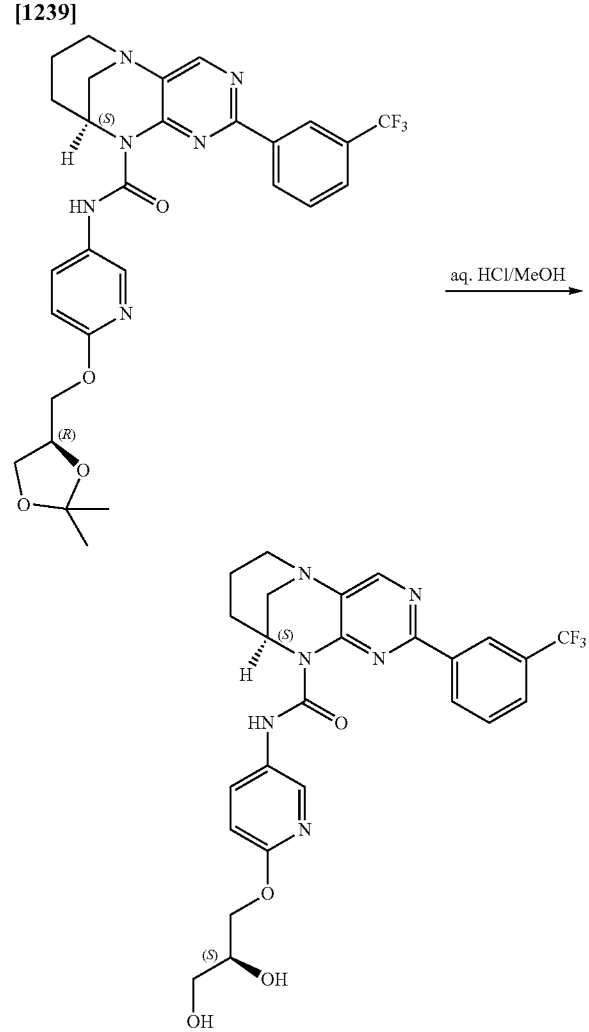
[1237] To a stirred solution of (9S)—N-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (160 mg, 0.280 mmol) in Methanol (5 mL) was added HCl (0.243 mL, 2.80 mmol) at 25° C. and stirred for 2 h. (TLC system: 100% ethylacetate, Rf value: 0.3). Then the reaction mixture was neutralized with saturated aq $NaHCO_3$ solution (10 mL) and extracted with DCM (2×30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford the desired product (9S)—N-(4-((R)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (120 mg, 0.222 mmol, 79% yield) as an off white solid. LCMS (m/z): 532.13 $[M+H]^+$, Rt=2.10 min.

[1238] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 14.17 (s, 1H), 8.91 (s, 1H), 8.79 (d, J=7.89 Hz, 1H), 8.50 (s, 1H), 8.39 (d, J=5.70 Hz, 1H), 7.77 (d, J=7.45 Hz, 1H), 7.69-7.62 (m, 1H), 6.53 (d, J=5.70 Hz, 1H), 5.04 (brs, 1H), 4.73 (dd, J=12.06, 4.82 Hz, 1H), 4.58 (dd, J=12.17, 4.28 Hz, 1H), 4.24 (brs, 1H), 3.96 (d, J=4.60 Hz, 1H), 3.66 (brs, 2H), 3.41-3.30 (m, 4H), 2.94 (d, J=13.59 Hz, 1H), 2.27 (d, J=14.25 Hz, 1H), 2.00-1.89 (m, 1H), 1.43 (d, J=8.77 Hz, 2H).

Example 101

Synthesis of (9S)—N-(6-((S)-2,3-dihydroxypropoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1239]



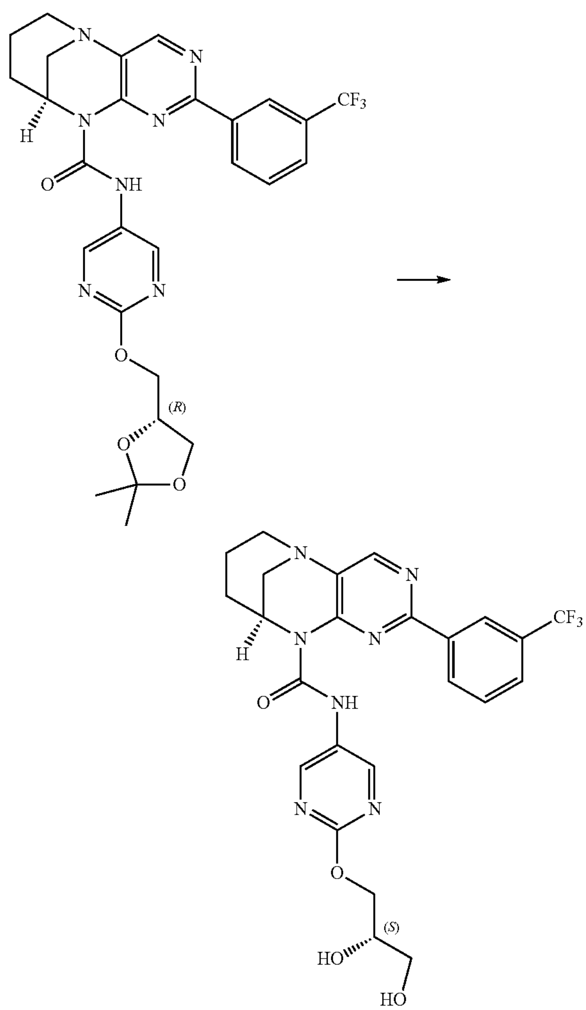
[1240] To a stirred solution of (9S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (300 mg, 0.526 mmol), in Methanol (15 mL), was added aq HCl (3.0 mL, 99 mmol) over a period of 5 min at 5° C. The reaction mixture was stirred at room temperature for 1 h. (TLC: 5% MeOH in DCM Rf: 0.3; UV active) and poured into ice cold water (20 mL), adjusted the PH of the reaction mixture to neutral with saturated $NaHCO_3$ solution, extracted with DCM (2×10 mL). The combined organic layer was washed with water (10 mL), brine solution (10 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain crude compound. The crude compound was purified by flash column chromatography (silicagel: 100-200 mesh, Eluent: 1% MeOH in DCM) to afford the desired product (9S)—N-(6-((S)-2,3-dihydroxypropoxy)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (150 mg, 0.277 mmol, 52.7% yield) as an off green solid. LCMS (m/z): 531.23 $[M+H]^+$, R_t=2.13 min.

[1241] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm: 12.87 (s, 1H), 8.48 (s, 2H), 8.43 (d, J=7.89 Hz, 1H), 8.36 (d, J=2.63 Hz, 1H), 7.95 (dd, J=8.88, 2.74 Hz, 1H), 7.78 (d, J=7.67 Hz, 1H), 7.71-7.64 (m, 1H), 6.84 (d, J=8.77 Hz, 1H), 5.00 (br s, 1H), 4.48 (dd, J=4.71, 2.08 Hz, 2H), 4.03 (br s, 1H), 3.91 (br s, 1H), 3.75-3.67 (m, 2H), 3.44-3.32 (m, 3H), 2.96 (d, J=13.59 Hz, 1H), 2.69 (br s, 1H), 2.25 (d, J=14.03 Hz, 1H), 2.01-1.90 (m, 1H), 1.49-1.41 (m, 2H).

Example 102

Synthesis of (9S)—N-(2-((S)-2,3-dihydroxypropoxy)pyrimidin-5-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1242]



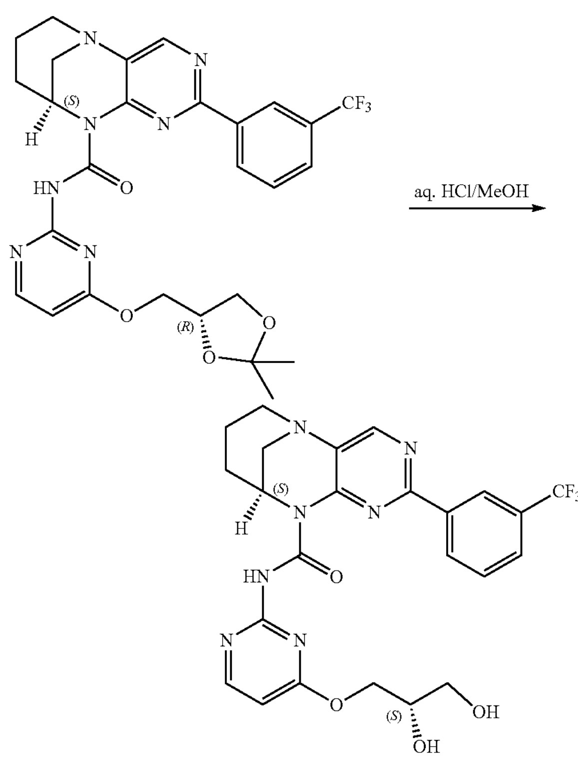
[1243] To a solution of (9S)—N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (300 mg, 0.525 mmol) in methanol (10 mL) at 0° C. was added aq. HCl (1.5 mL, 18.00 mmol, 36%) and stirred for 1 h. (TLC eluent:100% Ethyl acetate R-0.2; UV active). The reaction mixture was cooled to 0° C. and basified with saturated sodium bicarbonate solution (till pH-8-9), then concentrated. The residue was stirred in water for 15 min. to result the solid and was filtered through Buchner funnel followed by drying to afford (9S)—N-(2-((S)-2,3-dihydroxypropoxy)pyrimidin-5-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (200 mg, 0.373 mmol, 71.1% yield) as off white solid. LCMS (m/z): 532.23 $[M+H]^+$, Rt=2.02 min.

[1244] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.01 (s, 1H), 8.81 (s, 2H), 8.50 (s, 1H), 8.47 (s, 1H), 8.39 (d, J=7.89 Hz, 1H), 7.79 (d, J=7.89 Hz, 1H), 7.72-7.64 (m, 1H), 5.00 (br s, 1H), 4.57-4.44 (m, 2H), 4.14 (dq, J=9.98, 5.01 Hz, 1H), 3.84-3.69 (m, 2H), 3.45-3.29 (m, 3H), 3.19 (d, J=5.26 Hz, 1H), 2.97 (br d, J=13.81 Hz, 1H), 2.38 (t, J=6.25 Hz, 1H), 2.24 (br d, J=14.69 Hz, 1H), 2.04-1.90 (m, 1H), 1.53-1.40 (m, 2H).

Example 103

Synthesis of (9S)—N-(4-((S)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1245]



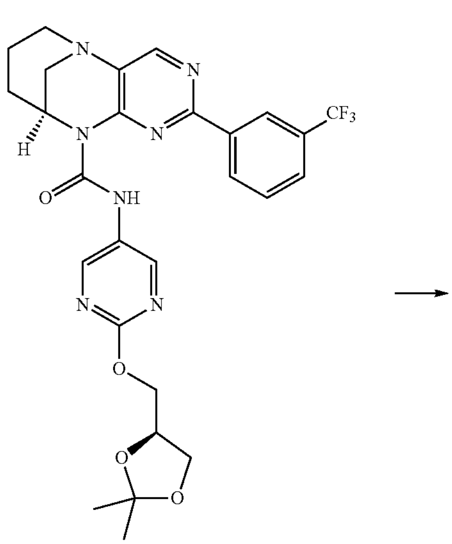
[1246] To a stirred solution of (9S)—N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido [4,5-b][1,4]diazo cine-10(7H)-carboxamide (360 mg, 0.630 mmol) in Methanol was added hydrochloric acid (5 mL, 165 mmol) over a period of 5 min. at 0° C. Then the reaction mixture was stirred at 30° C. for 2 h. (TLC System: 5% MeOH in DCM: R_f-0.5; UV active). The solvent was evaporated and the reaction mixture was neutralized with sodium bicarbonate solution and extracted with DCM, dried over anhydrous sodium sulphate and evaporated to obtain solid compound. The solid compound was washed with n-pentane (2×20 mL) to afford the desired product (9S)—N-(4-((S)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido [4,5-b][1,4]diazocine-10(7H)-carboxamide (250 mg, 0.466 mmol, 74.0% yield) as an off-white solid. LCMS (m/z): 532.16 $[M+H]^+$, R_t=2.08 min.

[1247] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 14.17 (s, 1H), 8.91 (s, 1H), 8.79 (d, J=7.89 Hz, 1H), 8.50 (s, 1H), 8.39 (d, J=5.48 Hz, 1H), 7.77 (d, J=7.67 Hz, 1H), 7.69-7.61 (m, 1H), 6.52 (d, J=5.70 Hz, 1H), 5.04 (s, 1H), 4.74 (dd, J=12.06, 5.04 Hz, 1H), 4.56 (dd, J=12.06, 4.60 Hz, 1H), 4.19 (d, J=5.48 Hz, 1H), 3.96 (d, J=4.17 Hz, 1H), 3.65 (s, 2H), 3.47-3.26 (m, 4H), 2.95 (d, J=13.81 Hz, 1H), 2.26 (d, J=14.69 Hz, 1H), 2.02-1.85 (m, 1H), 1.49-1.39 (m, 2H).

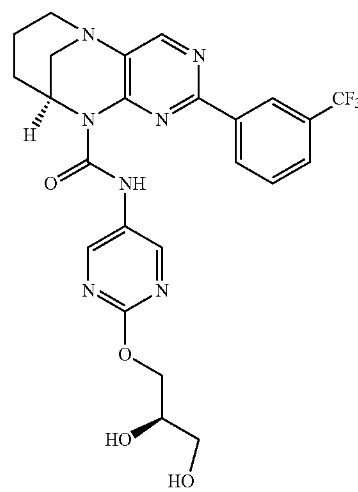
Example 104

Synthesis of (9S)—N-(2-((R)-2,3-dihydroxypropoxy)pyrimidin-5-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1248]



-continued



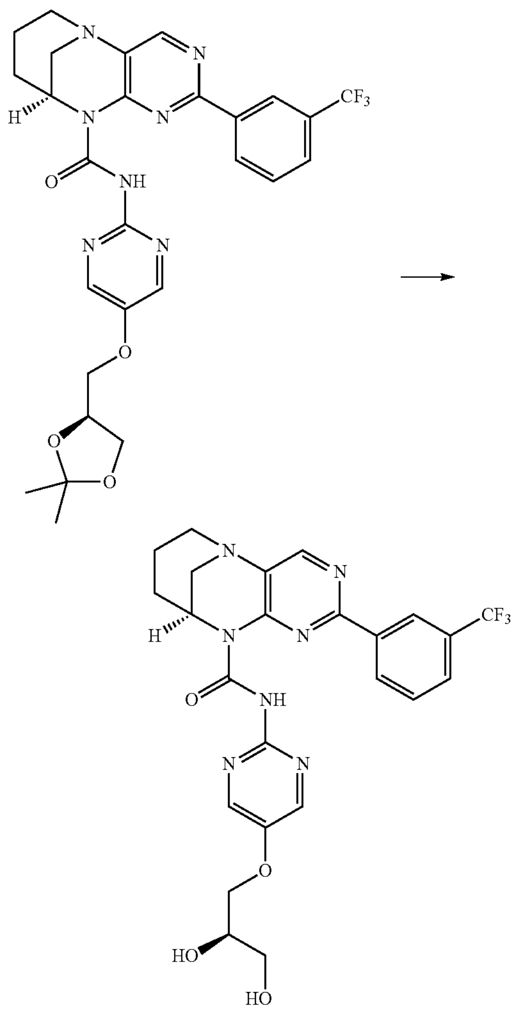
[1249] To a stirred solution of (9S)—N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido [4,5-b][1,4]diazocine-10(7H)-carboxamide (350.0 mg, 0.612 mmol) in methanol (10 mL) at 0° C. was added aq. HCl (2.041 mL, 24.49 mmol) and stirred for 1 h. The reaction mixture was basified with saturated sodium bicarbonate solution (till pH-8-9) at 0° C. and the precipitated solid was filtered, dried and triturated with diethylether (10 mL) to afford (9S)—N-(2-((R)-2,3-dihydroxypropoxy)pyrimidin-5-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (284.5 mg, 0.531 mmol, 87% yield) as an off white. LCMS (m/z): 532.16 $[M+H]^+$, Rt: 2.02 min.

[1250] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.02 (s, 1H), 8.81 (s, 2H), 8.50 (s, 1H), 8.47 (s, 1H), 8.39 (br d, J=7.67 Hz, 1H), 7.79 (br d, J=7.89 Hz, 1H), 7.71-7.65 (m, 1H), 5.00 (br s, 1H), 4.56-4.46 (m, 2H), 4.18-4.10 (m, 1H), 3.85-3.70 (m, 2H), 3.46-3.30 (m, 3H), 3.14 (br d, J=4.60 Hz, 1H), 2.96 (br d, J=14.25 Hz, 1H), 2.35-2.20 (m, 2H), 2.02-1.92 (m, 1H), 1.50-1.47 (m, 2H).

Example 105

Synthesis of (9S)—N-(5-((R)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1251]



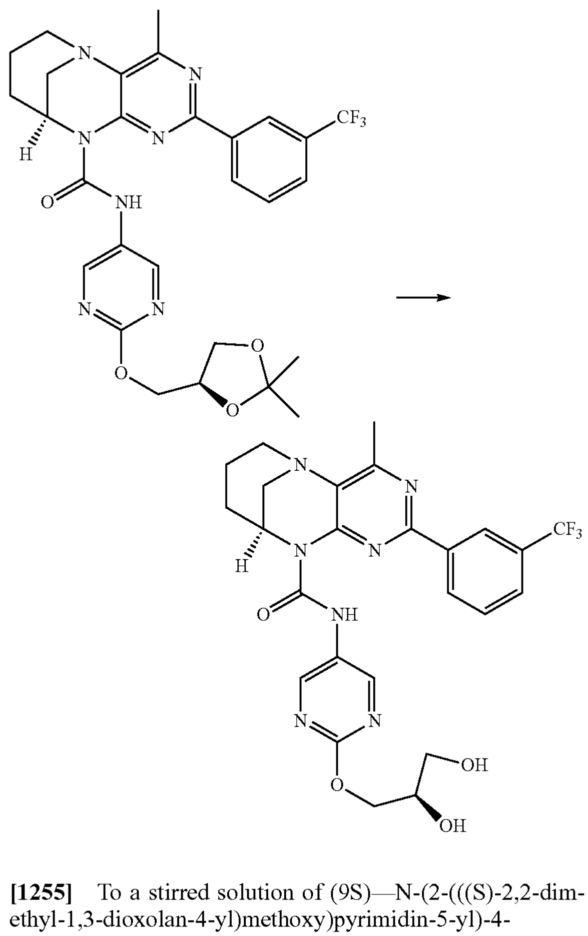
[1252] To a stirred solution of (9S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (300 mg, 0.525 mmol) in methanol (10 mL) under nitrogen at 0° C. was added aq. HCl (1 mL, 32.9 mmol, 36%) and stirred at RT for 1 h. (TLC eluent: 5% Methanol in DCM, R_f: 0.2, UV active). To the reaction mixture was added saturated $NaHCO_3$ solution (till pH-8-9) and extracted into EtOAc (3×10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to obtain crude product. The crude was triturated with diethylether (3×10 mL) to afford (9S)—N-(5-((R)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (250 mg, 0.468 mmol, 89% yield) as an off-white solid. LCMS (m/z): 532.20 $[M+H]^+$, Rt=2.02 min.

[1253] ^1H NMR (400 MHz, $CDCl_3$): δ ppm 14.01 (s, 1H), 8.88 (s, 1H), 8.75 (br d, J=7.89 Hz, 1H), 8.47 (s, 1H), 8.41 (s, 2H), 7.77 (br d, J=7.89 Hz, 1H), 7.68-7.60 (m, 1H), 5.04 (br s, 1H), 4.16 (s, 3H), 3.94-3.75 (m, 2H), 3.44-3.27 (m, 3H), 2.96 (br d, J=14.03 Hz, 1H), 2.68 (br s, 1H), 2.31 (br d, J=14.03 Hz, 1H), 2.10 (br s, 1H), 2.00-1.89 (m, 1H), 1.54-1.39 (m, 2H).

Example 106

Synthesis of (9S)—N-(2-((R)-2,3-dihydroxypropoxy)pyrimidin-5-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1254]



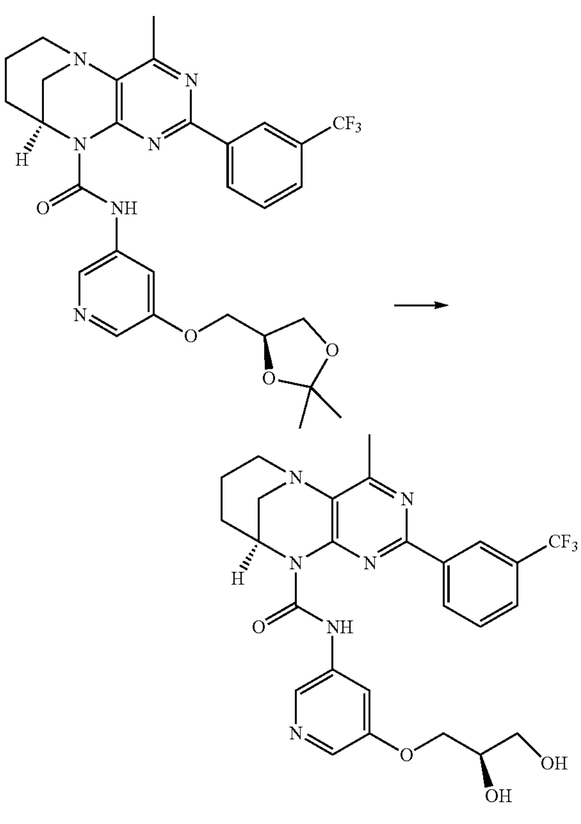
[1255] To a stirred solution of (9S)—N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (0.350 g, 0.598 mmol) in methanol (10 mL) at 0° C. was added Aq HCl (0.504 mL, 5.98 mmol) and stirred for 2 h. (TLC eluent: 100% EtOAc: R-0.3; UV active). The reaction mixture was basified with saturated sodium bicarbonate solution (till pH-8-9) and solvent was evaporated under reduced pressure. The residue was diluted with water (10 mL) and extracted into dichloromethane (2×20 mL). Combined organic extracts were dried over anhydrous sodium sulphate, filtered and filtrate was evaporated in vacuo and the crude was triturated with pentane (20 mL) to afford the desired product (9S)—N-(2-((R)-2,3-dihydroxypropoxy)pyrimidin-5-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (140 mg, 0.255 mmol, 42.7% yield) as an off-white solid. LCMS (m/z): 546.31 $[M+H]^+$, R_t=2.34 min.

[1256] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.37-12.90 (m, 1H), 8.81 (s, 2H), 8.46 (s, 1H), 8.38 (d, J=7.89 Hz, 1H), 7.77 (d, J=7.89 Hz, 1H), 7.61-7.69 (m, 1H), 4.96 (br s, 1H), 4.57-4.44 (m, 2H), 4.13 (br s, 1H), 3.84-3.68 (m, 2H), 3.40 (dd, J=13.70, 1.86 Hz, 1H), 3.28-3.11 (m, 3H), 2.95 (br d, J=13.59 Hz, 1H), 2.61 (s, 3H), 2.27 (br d, J=16.66 Hz, 2H), 1.89-2.02 (m, 1H), 1.49-1.40 (m, 2H).

Example 107

Synthesis of (9S)—N-(5-((R)-2,3-dihydroxypropoxy)pyridin-3-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1257]



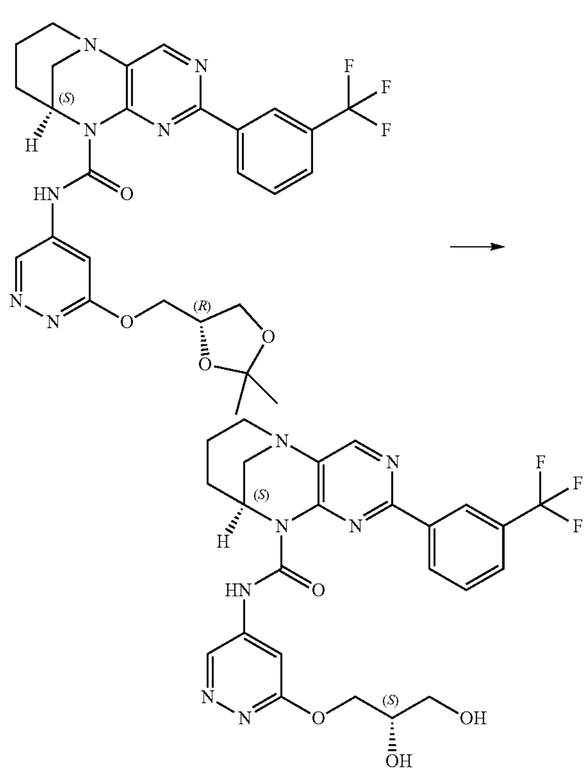
[1258] To a stirred solution of (9S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (240 mg, 0.411 mmol) in methanol (10 mL) at 0° C. was added Aq. HCl (1 mL, 12.00 mmol) and stirred under nitrogen at 0° C.-RT for 2 h. (TLC eluent: 10% Methanol in DCM, R_f=0.2; UV active). The reaction mixture was basified with saturated sodium bicarbonate solution (pH-8-9) at 0° C. and solvent was evaporated under reduced pressure. The residue was diluted with water (20 mL) and stirred for 15 min. The resultant solid was filtered through Buckner funnel and dried to obtained (9S)—N-(5-((R)-2,3-dihydroxypropoxy)pyridin-3-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (150 mg, 0.274 mmol, 66.8% yield). LCMS (m/z): 545.26 [M+H]+; R_t=2.25 min.

[1259] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.31 (s, 1H), 8.52 (s, 1H), 8.41 (d, J=7.67 Hz, 1H), 8.25 (d, J=1.97 Hz, 1H), 8.09 (d, J=2.63 Hz, 1H), 7.98 (t, J=2.30 Hz, 1H), 7.77 (br d, J=7.89 Hz, 1H), 7.71-7.65 (m, 1H), 4.96 (br s, 1H), 4.19-4.08 (m, 3H), 3.89-3.72 (m, 2H), 3.40 (dd, J=13.70, 1.64 Hz, 1H), 3.26-3.16 (m, 2H), 2.95 (br d, J=13.81 Hz, 1H), 2.69 (br d, J=2.85 Hz, 1H), 2.61 (s, 3H), 2.27 (br d, J=14.03 Hz, 1H), 2.13 (t, J=5.81 Hz, 1H), 2.01-1.90 (m, 1H), 1.48-1.36 (m, 2H).

Example 108

Synthesis of (9S)—N-(6-((S)-2,3-dihydroxypropoxy)pyridazin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1260]



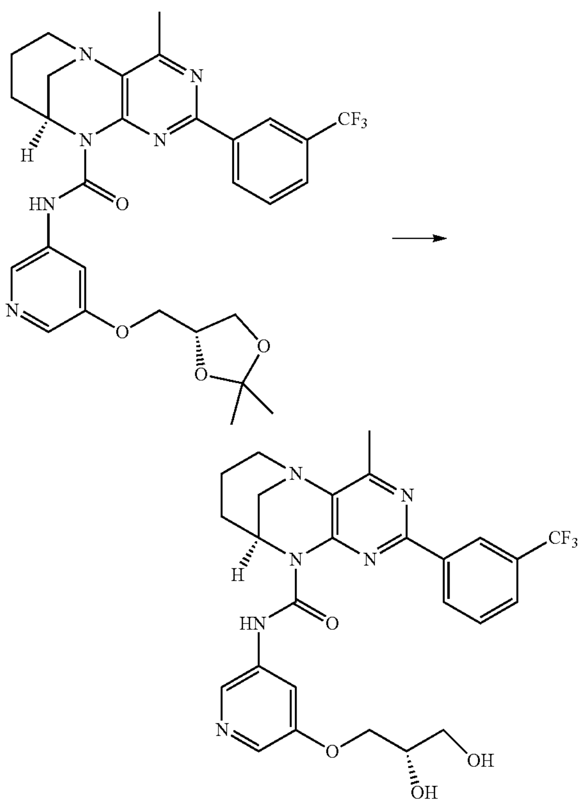
[1261] To a stirred solution of (9S)—N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridazin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (120 mg, 0.210 mmol) in Methanol (2 mL) was added aq hydrogen chloric acid (1 ml, 32.9 mmol), drop wise over a period of 5 min at 0° C. and stirred for 2 h. (TLC system:5% Methanol in DCM. R_f-value: 0.3.). Then evaporated the solvent, neutralized with saturated $NaHCO_3$ solution and filtered the obtain solid, washed with water and triturated with 1:1 ratio of n-pentane and diethyl ether, dried to afford the desired product (9S)—N-(6-((S)-2,3-dihydroxypropoxy)pyridazin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (98 mg, 0.181 mmol, 86% yield) as a pale brown solid. LCMS (m/z): 532.23 $[M+H]^+$, Rt=2.02 min.

[1262] ^1H NMR (400 MHz, DMSO-d_6): δ ppm 12.63 (s, 1H), 8.86 (s, 1H), 8.65-8.45 (m, 3H), 7.95 (br s, 1H), 7.90-7.80 (m, 1H), 7.50 (d, J=1.97 Hz, 1H), 4.96 (d, J=5.04 Hz, 1H), 4.78 (br s, 1H), 4.66 (d, J=11.18 Hz, 1H), 4.52-4.40 (m, 1H), 4.38-4.25 (m, 1H), 3.95-3.79 (m, 1H), 3.56-3.38 (m, 2H), 3.33 (br s, 2H), 2.88 (d, J=13.59 Hz, 1H), 2.07-1.98 (m, 2H), 1.36 (br s, 2H).

Example 109

Synthesis of Synthesis of (9S)—N-(5-((S)-2,3-dihydroxypropoxy)pyridin-3-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1263]



[1264] To a stirred solution of (9S)—N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (200 mg, 0.342 mmol) in methanol (10 mL) at 0° C. was added HCL (4 mL, 132 mmol) and the reaction mixture was stirred at RT for 3 h. (TLC eluent: 100% EtOAc, R_f:0.2, UV active). The reaction mixture was basified with saturated sodium bicarbonate solution (till pH-8-9) and solvent was evaporated under reduced pressure. The residue was diluted with water (20 mL) and extracted into dichloromethane (2×50 mL). Combined organic extracts were dried over anhydrous sodium sulphate, filtered and filtrate was evaporated in vacuo to give crude compound.

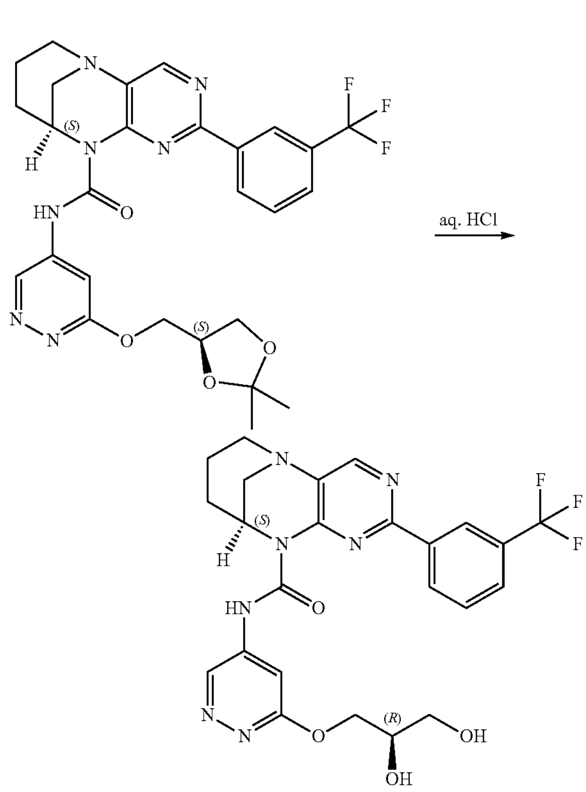
[1265] The crude was triturated with pentane (2×20 mL) to afford desired product (9S)—N-(5-((S)-2,3-dihydroxypropoxy)pyridin-3-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (137 mg, 0.251 mmol, 73.5% yield) as a white solid LCMS (m/z): 545.1 $[M+H]^+$, R_t=4.13 min.

[1266] ^1H NMR (400 MHz, $CDCl_3$): δ ppm 13.31 (s, 1H), 8.52 (s, 1H), 8.41 (d, J=7.89 Hz, 1H), 8.25 (d, J=2.19 Hz, 1H), 8.09 (d, J=2.63 Hz, 1H), 7.98 (t, J=2.30 Hz, 1H), 7.75-7.83 (m, 1H), 7.64-7.72 (m, 1H), 4.96 (br s, 1H), 4.08-4.20 (m, 3H), 3.74-3.90 (m, 2H), 3.40 (dd, J=13.70, 1.86 Hz, 1H), 3.16-3.29 (m, 2H), 2.95 (br d, J=13.37 Hz, 1H), 2.61 (s, 4H), 2.28 (br d, J=14.47 Hz, 1H), 1.91-2.04 (m, 2H), 1.40-1.49 (m, 2H).

Example 110

Synthesis of (9S)—N-(6-((R)-2,3-dihydroxypropoxy)pyridazin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1267]



[1268] To a stirred solution of (9S)—N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridazin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido

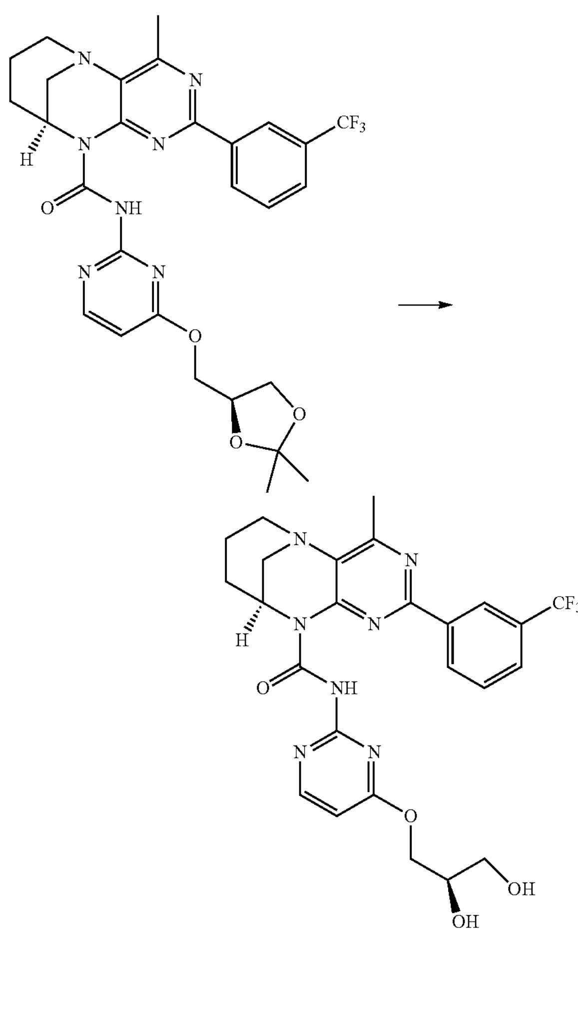
[4,5-b][1,4]diazocine-10(7H)-carboxamide (120 mg, 0.210 mmol) in Methanol (2 mL) was added aq HCl (1 ml, 32.9 mmol), drop wise over a period of 5 min at 0° C. and stirred for 2 h. at room temperature, evaporated the solvent, neutralized with saturated $NaHCO_3$ solution and filtered the obtained solid, washed with water and triturated with 1:1 ratio of n-pentane and diethyl ether and dried to afford product the desired product (9S)—N-(6-((R)-2,3-dihydroxypropoxy)pyridazin-4-yl)-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (50 mg, 0.093 mmol, 44.1% yield) as an off white solid (TLC system:5% Methanol in DCM. R_f value: 0.3.). LCMS (m/z): 532.27 $[M+H]^+$, Rt=2.03 min.

[1269] ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.69 (s, 1H), 8.85 (d, J=1.97 Hz, 1H), 8.66-8.46 (m, 3H), 8.00-7.91 (m, 1H), 7.89-7.80 (m, 1H), 7.50 (d, J=1.97 Hz, 1H), 4.96 (d, J=5.04 Hz, 1H), 4.78 (br s, 1H), 4.66 (t, J=5.70 Hz, 1H), 4.46 (dd, J=10.96, 4.17 Hz, 1H), 4.33 (dd, J=10.74, 6.36 Hz, 1H), 3.91-3.81 (m, 1H), 3.53-3.39 (m, 3H), 2.88 (d, J=13.81 Hz, 1H), 2.16-1.88 (m, 2H), 1.66-1.58 (m, 2H), 1.36 (s, 2H).

Example 111

Synthesis of (9S)—N-(4-((R)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1270]



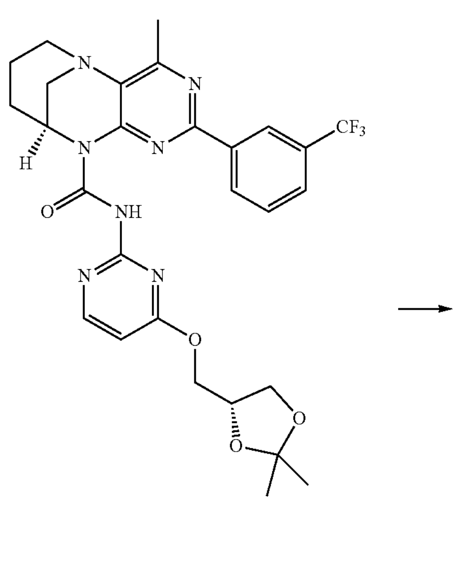
[1271] To a stirred solution of (9S)—N-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (130 mg, 0.222 mmol) in methanol (2 mL) at 0° C. was added aq. HCL (0.187 mL, 2.220 mmol) and stirred for 2 h. (TLC eluent: 100% EtOAc: R-0.2; UV active). The reaction mixture was basified with saturated sodium bicarbonate solution (till pH-8-9) and solvent was evaporated under reduced pressure. The residue was diluted with water (5 mL) and extracted into dichloromethane (2×50 mL). Combined organic extracts were dried over anhydrous sodiumsulphate, filtered and filtrate was evaporated in vacuo and the crude compound was triturated with pentane (2×10 ml) to afford desired product (9S)—N-(4-((R)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (112 mg, 0.203 mmol, 91% yield) as an off-white solid. LCMS (m/z): 546.20 $[M+H]^+$, R_t=2.39 min

[1272] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 14.39 (s, 1H), 8.90 (s, 1H), 8.80 (d, J=7.9 Hz, 1H), 8.38 (d, J=5.7 Hz, 1H), 7.75 (d, J=7.7 Hz, 1H), 7.68-7.58 (m, 1H), 6.51 (d, J=5.7 Hz, 1H), 5.01 (br s, 1H), 4.72 (dd, J=5.0, 12.1 Hz, 1H), 4.58 (dd, J=4.4, 12.1 Hz, 1H), 4.25 (d, J=6.4 Hz, 1H), 4.02-3.85 (m, 1H), 3.71-3.58 (m, 2H), 3.48-3.39 (m, 2H), 3.26-3.13 (m, 2H), 2.93 (br d, J=13.8 Hz, 1H), 2.60 (s, 3H), 2.29 (br d, J=14.0 Hz, 1H), 1.93 (ddt, J=3.0, 5.6, 13.6 Hz, 1H), 1.48-1.30 (m, 2H).

Example 112

Synthesis of (9S)—N-(4-((S)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1273]



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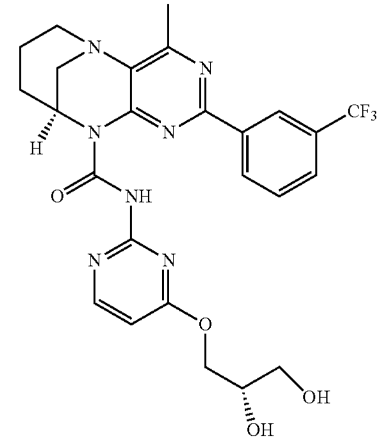


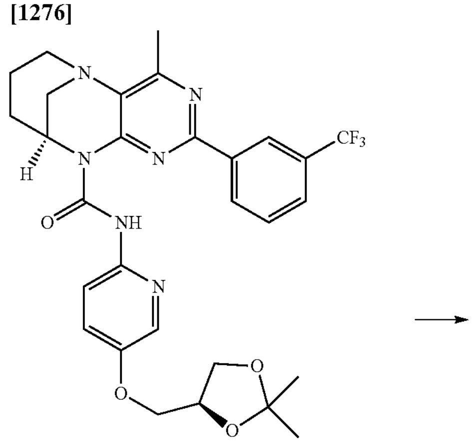
[1274] To a stirred solution of (9S)—N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (150 mg, 0.256 mmol) in methanol (5 mL) at 0° C. was added aq. HCl (0.216 mL, 2.56 mmol) and the reaction mixture was stirred for 2 h. (TLC eluent: 100% EtOAc, R_f-0.2; UV active). The reaction mixture was basified with saturated sodium bicarbonate solution (till pH-8-9) and solvent was evaporated under reduced pressure. The residue was diluted with water (10 mL) and extracted into dichloromethane (2×20 mL). Combined organic extracts were dried over anhydrous sodium sulphate, filtered and filtrate was evaporated in vacuo and the crude was triturated with pentane (2×10 ml) to afford desired product (9S)—N-(4-((S)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (101 mg, 0.179 mmol, 70.0% yield) as a pale brown color solid. LCMS (m/z): 546.27 $[M+H]^+$, R_t=2.45 min

[1275] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 14.40 (s, 1H), 8.90 (s, 1H), 8.80 (br d, J=7.67 Hz, 1H), 8.38 (d, J=5.70 Hz, 1H), 7.75 (br d, J=7.89 Hz, 1H), 7.67-7.60 (m, 1H), 6.51 (d, J=5.70 Hz, 1H), 5.01 (br s, 1H), 4.74 (dd, J=12.06, 5.04 Hz, 1H), 4.55 (dd, J=12.06, 4.38 Hz, 1H), 4.19 (d, J=6.80 Hz, 1H), 4.00-3.92 (m, 1H), 3.69-3.63 (m, 2H), 3.52-3.45 (m, 1H), 3.37 (br d, J=12.50 Hz, 1H), 3.25-3.16 (m, 2H), 2.93 (br d, J=14.25 Hz, 1H), 2.60 (s, 3H), 2.29 (br d, J=14.47 Hz, 1H), 1.99-1.87 (m, 1H), 1.44 (br s, 2H).

Example 113

Synthesis of (9S)—N-(5-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1276]



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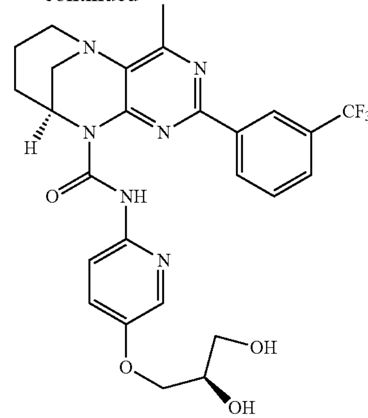
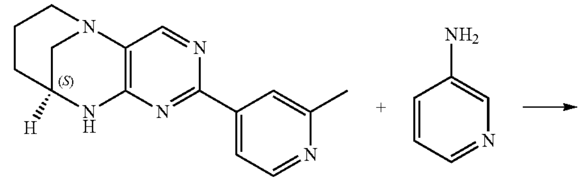


[1277] To a stirred solution of (9S)—N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (250 mg, 0.428 mmol) in methanol (5 mL) at 0° C. was added aq. HCl (0.361 mL, 4.28 mmol) and the reaction mixture was stirred for 2 h. (TLC eluent: 100% EtOAc, R_f-0.2, UV active). The reaction mixture was basified with saturated sodium bicarbonate solution (till pH-8-9) and solvent was evaporated under reduced pressure. The residue was diluted with water (10 mL) and extracted into dichloromethane (2×20 mL). Combined organic extracts were dried over anhydrous sodium sulphate, filtered and filtrate was evaporated in vacuo and the crude was triturated with diethyl ether (2×10 mL) and pentane (10 ml) to afford desired product (9S)—N-(5-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-4-methyl-2-(3-(trifluoromethyl)phenyl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (230 mg, 0.422 mmol, 99% yield) as a white solid. LCMS (m/z): 545.26 $[M+H]^+$, R_t=2.64 min

[1278] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.81 (s, 1H), 8.90 (s, 1H), 8.83 (d, J=8.11 Hz, 1H), 8.16-8.09 (m, 2H), 7.75 (d, J=7.67 Hz, 1H), 7.69-7.60 (m, 1H), 7.35-7.29 (m, 1H), 4.97 (br s, 1H), 4.18-4.08 (m, 3H), 3.92-3.86 (m, 2H), 3.38 (dd, J=13.59, 1.53 Hz, 1H), 3.26-3.17 (m, 2H), 2.94 (br d, J=13.37 Hz, 1H), 2.60 (s, 3H), 2.56 (d, J=4.38 Hz, 1H), 2.27 (br d, J=14.25 Hz, 1H), 1.98-1.89 (m, 2H), 1.48-1.39 (m, 2H).

Example 114 Synthesis of (9S)-2-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide

[1279]



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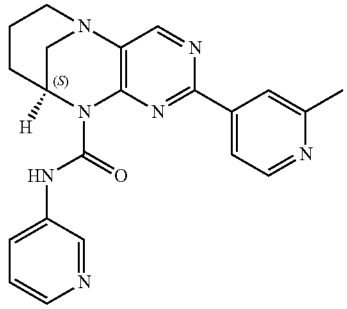


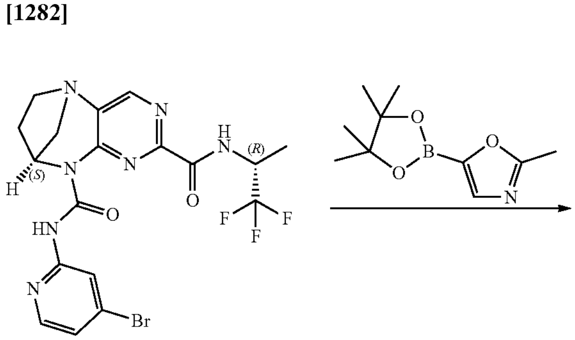
[1280] To a stirred solution of (9S)-2-(2-methylpyridin-4-yl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine (550 mg, 2.057 mmol) in Tetrahydrofuran (40 mL) were added triphosgene (611 mg, 2.057 mmol) and TEA (1.721 mL, 12.34 mmol) at room temperature for 30 min. Then pyridin-3-amine (387 mg, 4.11 mmol) was added and stirred at 65° C. for 16 h. (TLC system: Neat ethyl acetate. R_f value: 0.4: Detection: UV active). The reaction mixture was allowed to room temperature diluted with water (100 mL) and extracted with ethylacetate (2×125 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain crude compound. The crude compound was purified by flash column chromatography (Neutral Allumina, Eluent 40% Ethylacetate in peteher) to afford the desired product (9S)-2-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-10(7H)-carboxamide (231 mg, 0.592 mmol, 28.8% yield) as a white solid. LCMS (m/z): 388.12 $[M+H]^+$, Rt=1.28 min.

[1281] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.06 (s, 1H), 8.77 (d, J=2.41 Hz, 1H), 8.72 (d, J=4.82 Hz, 1H), 8.51-8.48 (m, 1H), 8.39 (dd, J=4.71, 1.42 Hz, 1H), 8.22-8.17 (m, 1H), 7.97 (s, 1H), 7.88 (dd, J=5.26, 1.10 Hz, 1H), 7.33 (dd, J=8.33, 4.60 Hz, 1H), 5.02 (br s, 1H), 3.45-3.29 (m, 3H), 2.96 (d, J=13.59 Hz, 1H), 2.71 (s, 3H), 2.32-2.20 (m, 1H), 2.02-1.91 (m, 2H), 1.53-1.42 (m, 1H).

Example 115

Synthesis of (8S)—N9-(4-(2-methyloxazol-5-yl)pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2,9(6H)-dicarboxamide

[1282]



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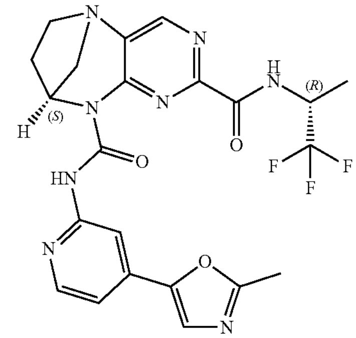


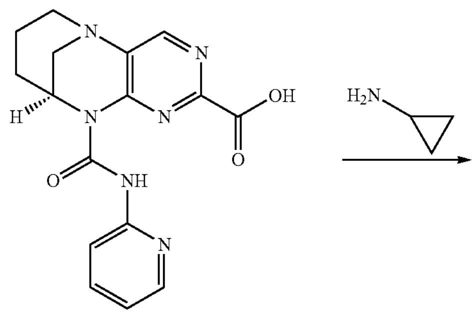
[1283] To a stirred solution of (8S)—N9-(4-bromopyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2,9(6H)-dicarboxamide (900 mg, 1.799 mmol) in 1,4-Dioxane (10 mL) and Water (2.5 mL) at RT was added potassium acetate (353 mg, 3.60 mmol) and 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (564 mg, 2.70 mmol) and the mixture was degassed for 30 min, then added $PdCl_2$(dppf)-CH_2Cl_2 (118 mg, 0.144 mmol) and the resulting reaction mixture was stirred at 70° C. for 5 h. (TLC eluent: 5% MeOH in DCM: R-0.2; UV active). Reaction mixture was diluted with water (100 mL), the aqueous layer was extracted with EtOAc (2×150 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to get crude compound. Crude material was purified by combiflash chromatography (using silica gel column, 2% methanol in DCM). Fractions containing pure compound were combined and concentrated to get the solid compound, this was grounded in mortar to afford (8S)—N9-(4-(2-methyloxazol-5-yl)pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-7,8-dihydro-5,8-methanopyrimido[4,5-b][1,4]diazepine-2,9-(6H)-dicarboxamide (330 mg, 0.652 mmol, 36.3% yield) as an off-white solid. LCMS (m/z): 503.22 $[M+H]^+$, R_t=1.97 min.

[1284] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.95 (s, 1H), 8.49 (s, 1H), 8.41 (d, J=5.04 Hz, 1H), 8.35 (s, 1H), 7.99 (br d, J=10.08 Hz, 1H), 7.46 (s, 1H), 7.23 (dd, J=5.26, 1.53 Hz, 1H), 5.67 (br d, J=5.92 Hz, 1H), 5.02 (dt, J=9.76, 7.07 Hz, 1H), 3.26 (t, J=7.45 Hz, 2H), 3.10 (d, J=2.41 Hz, 2H), 2.46 (br, 3H) 2.39 (br dd, J=14.03, 7.45 Hz, 1H), 2.06-2.16 (m, 1H), 1.50 (d, J=7.02 Hz, 3H).

Example 116

Synthesis of (9S)—N2-cyclopropyl-N10-(pyridin-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

[1285]



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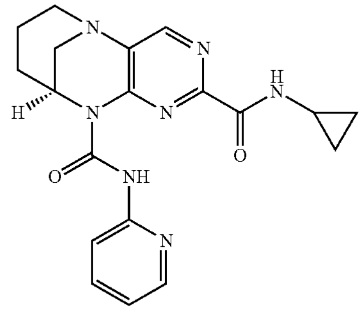


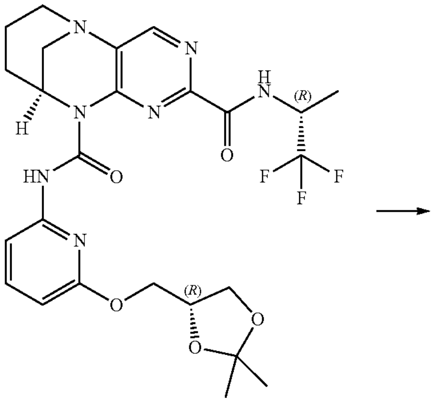
[1286] To a stirred suspension of (9S)-10-(pyridin-2-ylcarbamoyl)-7,8,9,10-tetrahydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2-carboxylic acid (500 mg, 1.469 mmol) in acetonitrile (5 mL), under nitrogen at RT was added $POCl_3$ (0.274 mL, 2.94 mmol) and cyclopropanamine (126 mg, 2.204 mmol) and stirred for 2 h. (TLC system: 5% Methanol in DCM, Rf value: 0.3). The reaction mixture was basified with saturated $NaHCO_3$ solution (20 mL) and extracted with Ethylacetate (50 mL). Combined organic extracts were dried over anhydrous sodiumsulfate, filtered and concentrated to get crude compound. The crude product was purified by combifish chromatography (using silicagel column and was eluted with 3% Methaol in DCM.) to afford (9S)—N2-cyclopropyl-N10-(pyridin-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (105 mg, 0.266 mmol, 18.13% yield) as an off-white solid. LCMS (m/z): 380.13 $[M+H]^+$, RT=1.60 min.

[1287] ^1H NMR (400 MHz, DMSO-d_6): δ ppm 13.04-13.23 (m, 1H), 8.65 (br d, J=4.17 Hz, 1H), 8.47 (s, 1H), 8.23-8.43 (m, 1H), 8.05 (d, J=8.33 Hz, 1H), 7.71-7.88 (m, 1H), 7.15 (ddd, J=6.74, 5.54, 0.88 Hz, 1H), 4.83 (br s, 1H), 3.41 (dd, J=13.70, 1.64 Hz, 1H), 3.23-3.33 (m, 2H), 2.89-3.04 (m, 1H), 2.84 (br d, J=13.59 Hz, 1H), 1.88-2.04 (m, 2H), 1.13-1.39 (m, 3H), 0.65-0.81 (m, 4H).

Example 117

Synthesis of (9S)—N10-(6-((S)-2,3-dihydroxypropoxy)pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

[1288]



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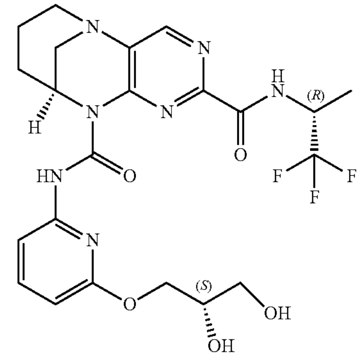


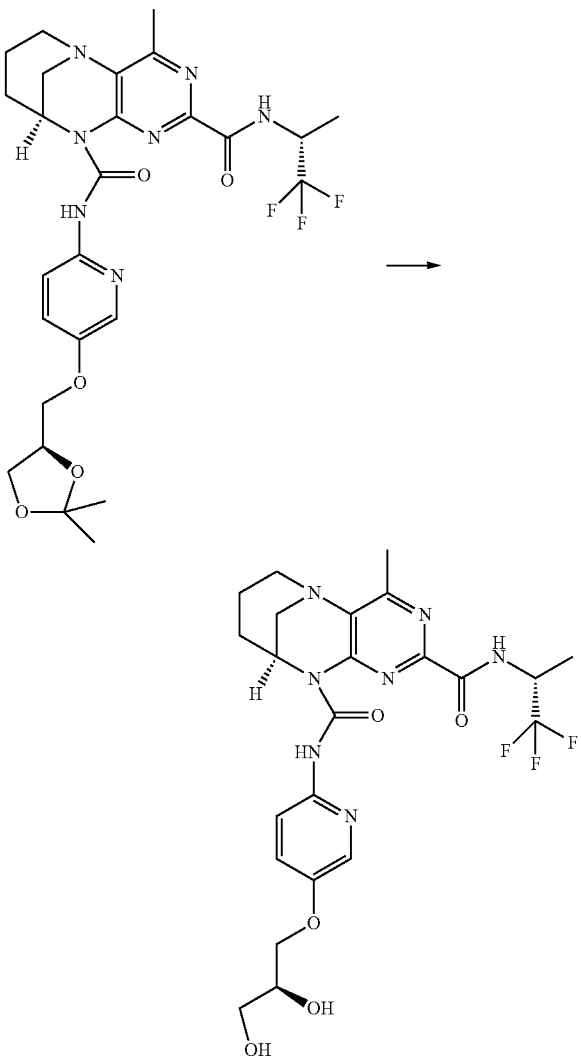
[1289] To a stirred solution of (9S)—N10-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazo cine-2,10(7H)-dicarboxamide (370 mg, 0.654 mmol) in Methanol (5 mL) was added 2M HCl (2 mL, 4.00 mmol) in water at 0° C. The resulting reaction mixture was stirred at 0° C. for 1 h. (TLC system: 10% MeOH in DCM, Rf: 0.4). The reaction mixture was concentrated under reduced pressure to obtain crude compound. The crude was basified with saturated sodium bicarbonate solution (20 mL) and extracted with DCM (3×20 mL). The combined organic layer was washed with water (20 mL), brine solution (20 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain crude compound. The crude was purified by column chromatography (silicagel: 100-200 mesh, Eluent: 4% MeOH in DCM), obtained sticky solid. The sticky solid was washed with a mixture of Ethanol (1 mL) and n-Pentane (20 mL), filtered and dried well to afford the desired product (9S)—N10-(6-((S)-2,3-dihydroxypropoxy)pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (130 mg, 0.246 mmol, 37.7% yield) as an off-white solid. LCMS (m/z): 526.26 $[M+H]^+$, R_t=1.96 min.

[1290] ^1H NMR (400 MHz, $CDCl_3$): δ ppm 13.31 (s, 1H), 8.34 (s, 1H), 8.20 (d, J=9.65 Hz, 1H), 7.74-7.68 (m, 1H), 7.64-7.60 (m, 1H), 6.51 (d, J=7.45 Hz, 1H), 5.03 (br s, 1H), 4.86-4.73 (m, 2H), 4.49-4.43 (m, 1H), 4.23-4.15 (m, 2H), 3.83-3.77 (m, 1H), 3.74-3.67 (m, 1H), 3.44-3.26 (m, 3H), 2.92-2.78 (m, 2H), 2.21 (d, J=13.37 Hz, 1H), 1.95 (tdd, J=13.92, 13.92, 5.26, 3.29 Hz, 1H), 1.52-1.26 (m, 5H).

Example 118

Synthesis of (9S)—N10-(5-((S)-2,3-dihydroxypropoxy)pyridin-2-yl)-4-methyl-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

[1291]



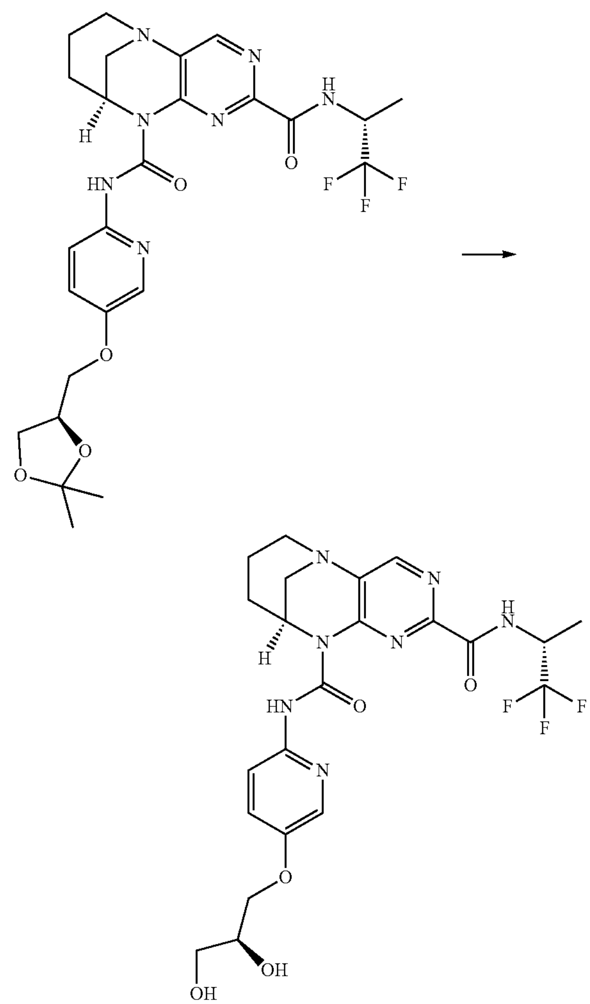
[1292] To a stirred solution of (9S)—N10-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-4-methyl-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (450 mg, 0.776 mmol) in methanol (10 mL) at RT was added aq. HCl (4 mL, 132 mmol) and stirred for 3 h. (TLC eluent:10% MeOH & DCM: R_f-0.2; UV active). The reaction mixture was basified with saturated sodium bicarbonate solution (till pH-8-9) and solvent was evaporated under reduced pressure. The residue was partitioned between water (20 mL) and dichloromethane (2×60 mL). Organic layer separated dried over anhydrous sodium sulphate, filtered and filtrate was evaporated in vacuo to give crude compound. The crude compound was triturated with pentane (2×20 mL) to afford desired product (9S)—N10-(5-((S)-2,3-dihydroxypropoxy)pyridin-2-yl)-4-methyl-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (272 mg, 0.504 mmol, 64.9% yield) as a white solid. LCMS (m/z): 540.22[M+H]$^+$, R_t=1.89 min

[1293] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.42 (s, 1H), 8.14 (br s, 1H), 8.04 (br d, J=10.08 Hz, 2H), 7.33-7.23 (m, 1H), 5.07-4.92 (m, 2H), 4.17-4.03 (m, 3H), 3.90-3.71 (m, 2H), 3.38 (dd, J=13.81, 1.53 Hz, 1H), 3.25-3.16 (m, 2H), 2.87 (br d, J=13.81 Hz, 1H), 2.58 (s, 4H), 2.25 (br d, J=14.91 Hz, 1H), 2.06-1.86 (m, 2H), 1.52-1.40 (m, 4H), 1.38-1.22 (m, 1H)

Example 119

Synthesis of (9S)—N10-(5-((S)-2,3-dihydroxypropoxy)pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide

[1294]



[1295] To a solution of (9S)—N10-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (350 mg, 0.619 mmol) in methanol (10 mL) under nitrogen at RT, was added aq. HCl (1 mL, 32.9 mmol) and the reaction mixture was stirred for 2 h. (TLC system 5% Methanol in DCM. Rf value: 0.1). The reaction mixture was concentrated, the residue basified with saturated $NaHCO_3$ solution. The resultant solid was filtered, dried and triturated with diethylether (10 mL) to afford (9S)—N10-(5-((S)-2,3-dihydroxypropoxy)pyridin-2-yl)-N2-((R)-1,1,1-trifluoropropan-2-yl)-8,9-dihydro-6H-5,9-methanopyrimido[4,5-b][1,4]diazocine-2,10(7H)-dicarboxamide (230 mg, 0.435 mmol, 70.3% yield) as an off-white solid. LCMS (m/z): 526.22$[M+H]^+$, Rt=1.70 min.

[1296] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.25 (s, 1H), 8.40 (s, 1H), 8.14 (d, J=2.8 Hz, 1H), 8.08-7.85 (m, 2H), 7.30 (brdd, J=2.9, 8.8 Hz, 1H), 5.10-4.89 (m, 2H), 4.21-4.00 (m, 3H), 3.96-3.72 (m, 2H), 3.50-3.26 (m, 3H), 2.89 (br d, J=13.8 Hz, 1H), 2.58 (br d, J=4.4 Hz, 1H), 2.22 (br d, J=14.5 Hz, 1H), 2.02-1.85 (m, 2H), 1.50 (br d, J=7.0 Hz, 3H), 1.46-1.21 (m, 2H).

Example 120. Biochemical Activity

[1297] Mass spectrometry based assays were used to identify modulators of SIRT1 activity. The TAMRA based assay utilized a peptide having 20 amino acid residues as follows: Ac-EE-K(biotin)-GQSTSSHSK(Ac)NleSTEG-K(5TMR)-EE-NH_2 (SEQ ID NO: 1), wherein K(Ac) is an acetylated lysine residue and Nle is a norleucine. The peptide was labeled with the fluorophore 5TMR (excitation 540 nm/emission 580 nm) at the C-terminus. The sequence of the peptide substrate was based on p53 with several modifications. In addition, the methionine residue naturally present in the sequence was replaced with the norleucine because the methionine may be susceptible to oxidation during synthesis and purification. The Trp based assay utilized a peptide having an amino acid residues as follows: Ac-R—H—K-K(Ac)—W—NH2 (SEQ ID NO: 2).

[1298] The TAMRA based mass spectrometry assay was conducted as follows: 0.5 μM peptide substrate and 120 μM βNAD^+ was incubated with 10 nM SIRT1 for 25 minutes at 25° C. in a reaction buffer (50 mM Tris-acetate pH 8, 137 mM NaCl, 2.7 mM KCl, 1 mM $MgCl_2$, 5 mM DTT, 0.05% BSA). The SIRT1 protein was obtained by cloning the SirT1 gene into a T7-promoter containing vector, which was then transformed and expressed in BL21(DE3) bacterial cells. Test compound was added at varying concentrations to this reaction mixture and the resulting reactions were monitored. After the 25 minute incubation with SIRT1, 10 μL of 10% formic acid was added to stop the reaction. The resulting reactions were sealed and frozen for later mass spec analysis. Determination of the amount of deacetylated substrate peptide formed (or, alternatively, the amount of O-acetyl-ADP-ribose (OAADPR) generated) by the sirtuin-mediated NAD-dependent deacetylation reaction allowed for the precise measurement of relative SIRT1 activity in the presence of varying concentrations of the test compound versus control reactions lacking the test compound.

[1299] The Trp mass spectrometry assay was conducted as follows. 0.5 μM peptide substrate and 120 μM βNAD^+ were incubated with 10 nM SIRT1 for 25 minutes at 25° C. in a reaction buffer (50 mM HEPES pH 7.5, 1500 mM NaCl. 1 mM DTT, 0.05% BSA). The SIRT1 protein was obtained by cloning the SirT1 gene into a T7-promoter containing vector, which was then expressed in BL21(DE3) bacterial cells and purified as described in further detail below. Test compound was added at varying concentrations to this reaction mixture and the resulting reactions were monitored. After the 25 minute incubation with SIRT1, 10 μL of 10% formic acid was added to stop the reaction. The resulting reactions were sealed and frozen for later mass spec analysis. The relative SIRT1 activity was then determined by measuring the amount of O-acetyl-ADP-ribose (OAADPR) formed (or, alternatively, the amount of deacetylated Trp peptide generated) by the NAD-dependent sirtuin deacetylation reaction in the presence of varying concentrations of the test compound versus control reactions lacking the test compound.

[1300] The degree to which the test agent activated deacetylation by SIRT1 was expressed as $EC_{1.5}$ (i.e., the concentration of compound required to increase SIRT1 activity by 50% over the control lacking test compound), and Percent Maximum Activation (i.e., the maximum activity relative to control (100%) obtained for the test compound).

[1301] A control for inhibition of sirtuin activity was conducted by adding 1 μL of 500 mM nicotinamide as a negative control at the start of the reaction (e.g., permits determination of maximum sirtuin inhibition). A control for activation of sirtuin activity was conducted using 10 nM of sirtuin protein, with 1 μL of DMSO in place of compound, to determine the amount of deacetylation of the substrate at a given time point within the linear range of the assay. This time point was the same as that used for test compounds and, within the linear range, the endpoint represents a change in velocity.

[1302] For the above assay, SIRT1 protein was expressed and purified as follows. The SirT1 gene was cloned into a T7-promoter containing vector and transformed into BL21 (DE3). The protein was expressed by induction with 1 mM IPTG as an N-terminal His-tag fusion protein at 18° C. overnight and harvested at 30,000×g. Cells were lysed with lysozyme in lysis buffer (50 mM Tris-HCl, 2 mM Tris[2-carboxyethyl]phosphine (TCEP), 10 μM $ZnCl_2$, 200 mM NaCl) and further treated with sonication for 10 min for complete lysis. The protein was purified over a Ni-NTA column (Amersham) and fractions containing pure protein were pooled, concentrated and run over a sizing column (Sephadex S200 26/60 global). The peak containing soluble protein was collected and run on an Ion-exchange column (MonoQ). Gradient elution (200 mM-500 mM NaCl) yielded pure protein. This protein was concentrated and dialyzed against dialysis buffer (20 mM Tris-HCl, 2 mM TCEP) overnight. The protein was aliquoted and frozen at −80° C. until further use.

[1303] Sirtuin-modulating compounds of Formula (I) that activated SIRT1 were identified using the assay described above and are shown below in Table 1. The $EC_{1.5}$ values represent the concentration of test compounds that result in 150% activation of SIRT1. The $EC_{1.5}$ values for the activating compounds of Formula (I) are represented by A ($EC_{1.5}$<1 μM), B ($EC_{1.5}$ 1-25 μM), C ($EC_{1.5}$>25 μM). The percent maximum fold activation is represented by A (Fold activation ≥150%) or B (Fold Activation <150%). "NT" means not tested; "ND" means not determinable. The compound numbering in the table starts with compound number 10, and parenthetic numbering (#) corresponding to the STAC numbering system in FIG. 4 and Examples 90-106 (i.e., compound no. 68 is also STAC 1, so it is shown as 68(1), and further STACs: 546(3), 444(4), 314(5), 816(7), 76(8), and 81(9)).

[1304] It is noted that compounds of the present invention have been named by two different chemical nomenclature conventions as generated by two different chemical drawing and/or chemical naming computer programs, i.e., generated by Chem Axon (JChem-Excel) and Cambridge Soft (ChemDraw®), respective companies.

TABLE 1

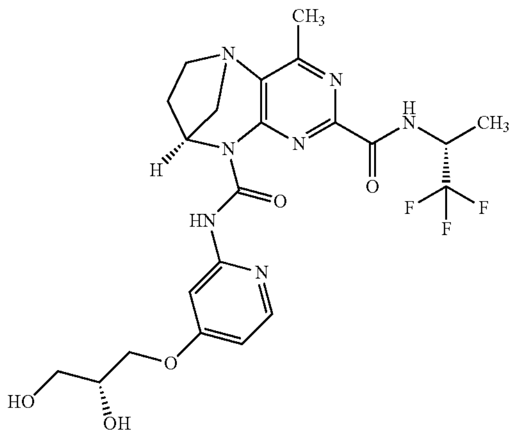
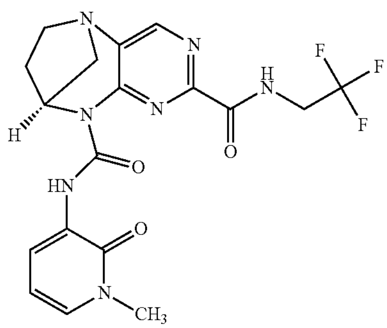
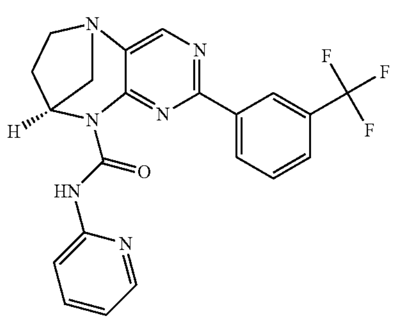
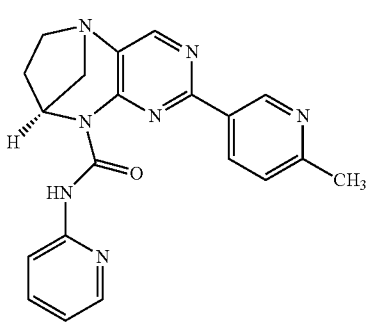
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
1		(9S)-8-N-{4-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-3-methyl-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-5,8-dicarboxamide	A	A
2		(9S)-8-N-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-5-N-(2,2,2-trifluoroethyl)-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2,4,6-triene-5,8-dicarboxamide	B	A
3		(9S)-N-(pyridin-2-yl)-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2,4,6-triene-8-carboxamide	A	A
4		(9S)-5-(6-methylpyridin-3-yl)-N-(pyridin-2-yl)-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

TABLE 1-continued

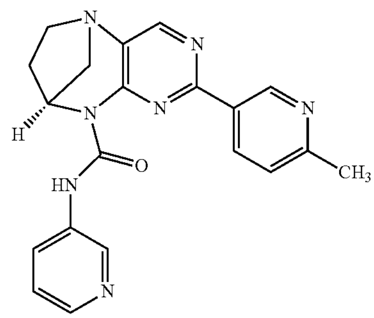
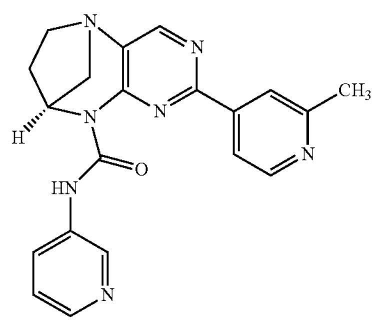
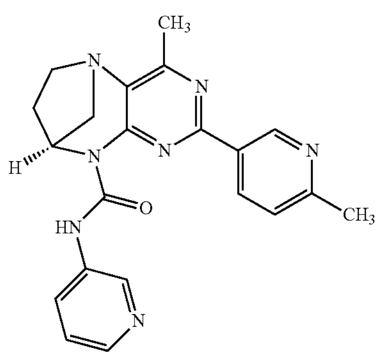
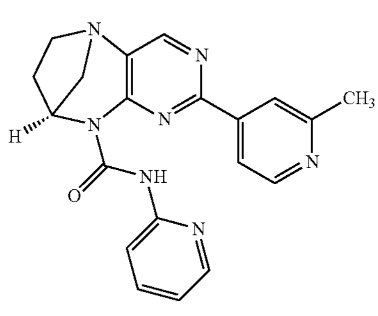
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
5		(9S)-5-(6-methylpyridin-3-yl)-N-(pyridin-3-yl)-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
6		(9S)-5-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
7		(9S)-3-methyl-5-(6-methylpyridin-3-yl)-N-(pyridin-3-yl)-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
8		(9S)-5-(2-methylpyridin-4-yl)-N-(pyridin-2-yl)-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

TABLE 1-continued

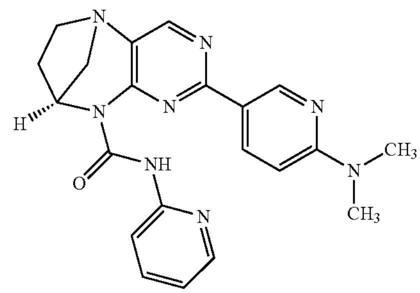
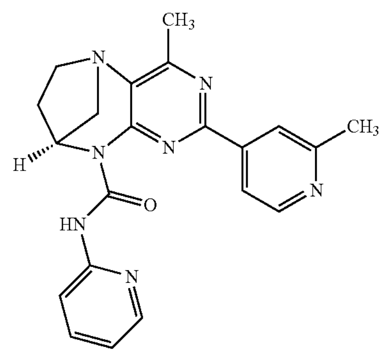
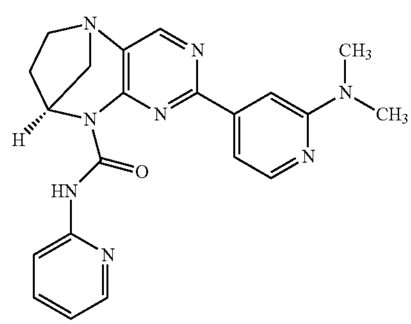
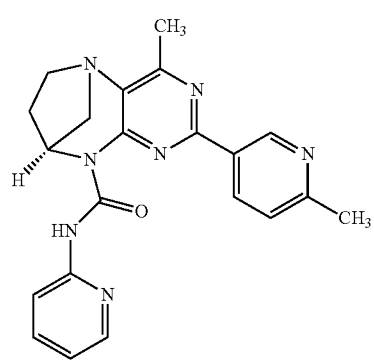
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
9		(9S)-5-[6-(dimethylamino)pyridin-3-yl]-N-(pyridin-2-yl)-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
10		(9S)-3-methyl-5-(2-methylpyridin-4-yl)-N-(pyridin-2-yl)-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
11		(9S)-5-[2-(dimethylamino) pyridin-4-yl]-N-(pyridin-2-yl)-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
12		(9S)-3-methyl-5-(6-methylpyridin-3-yl)-N-(pyridin-2-yl)-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A

TABLE 1-continued

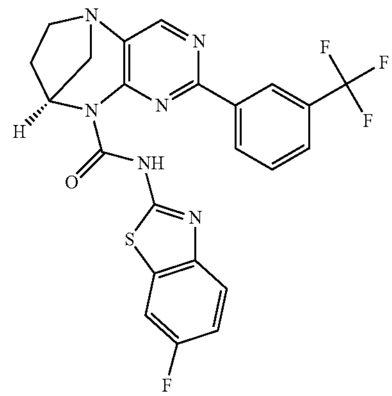
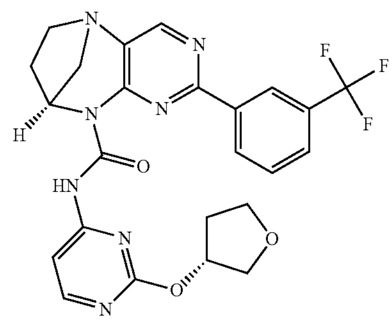
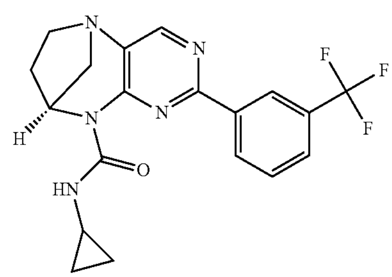
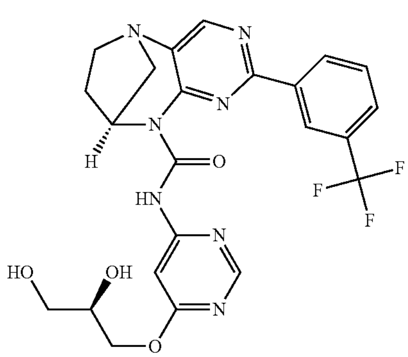
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
13		(9S)-N-(6-fluoro-1,3-benzothiazol-2-yl)-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-8-carboxamide		B
14		(9S)-N-{2-[(3R)-oxolan-3-yloxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
15		(9S)-N-cyclopropyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
16		(9S)-N-{6-[(2R)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2,4,6-triene-8-carboxamide	B	A

TABLE 1-continued

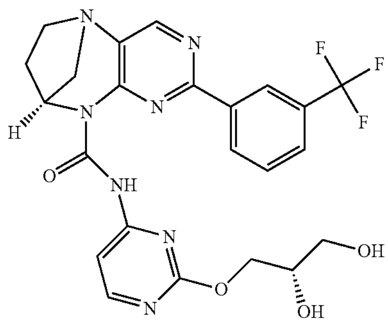
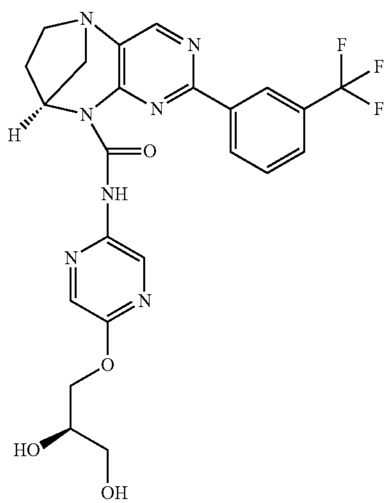
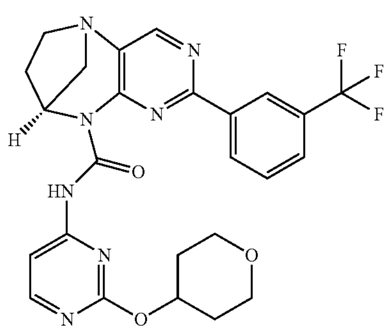
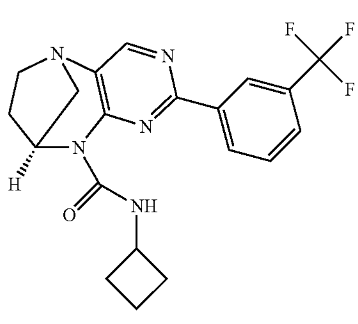
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
17		(9S)-N-{2-[(2S)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
18		(9S)-N-{5-[(2R)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo [7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
19		(9S)-N-[2-(oxan-4-yloxy)pyrimidin-4-yl]-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
20		(9S)-N-cyclobutyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A

TABLE 1-continued

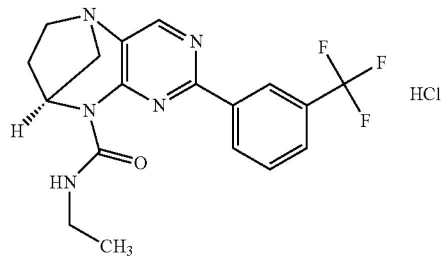
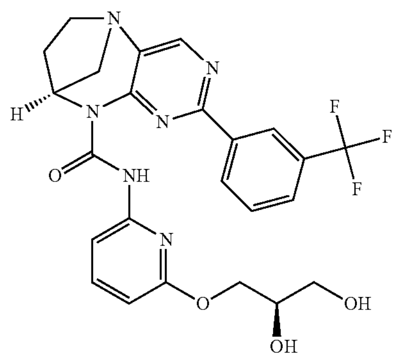
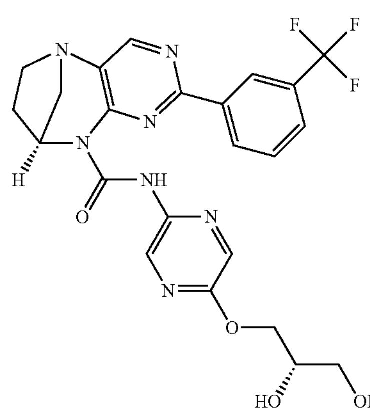
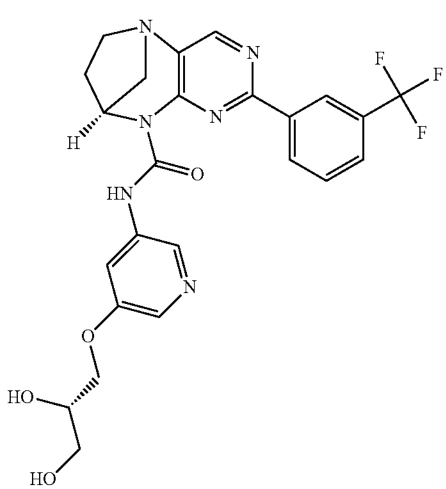
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
21		(9S)-N-ethyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-8-carboxamide hydrochloride	A	A
22		(9S)-N-{6-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2,4,6-triene-8-carboxamide	A	A
23		(9S)-N-{5-[(2S)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
24		(9S)-N-{5-[(2S)-2,3-dihydroxypropoxy]pyridin-3-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

TABLE 1-continued

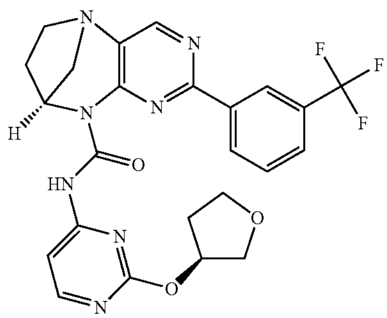
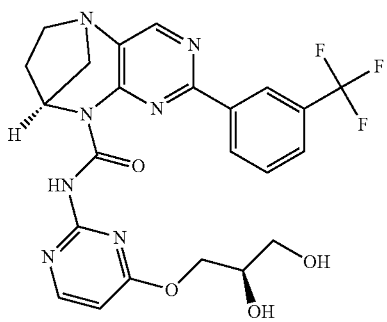
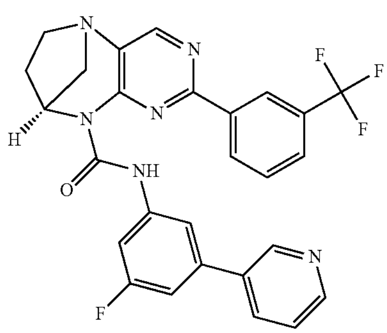
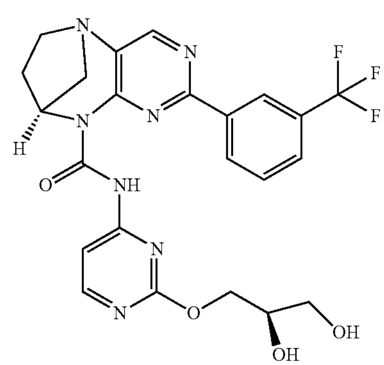
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
25		(9S)-N-{2-[(3S)-oxolan-3-yloxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
26		(9S)-N-{4-[(2R)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
27		(9S)-N-[3-fluoro-5-(pyridin-3-yl)phenyl]-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
28		(9S)-N-{2-[(2R)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

TABLE 1-continued

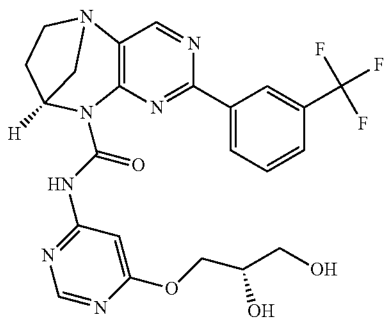
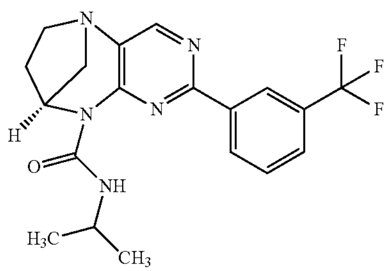
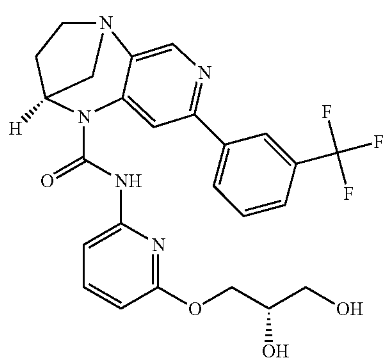
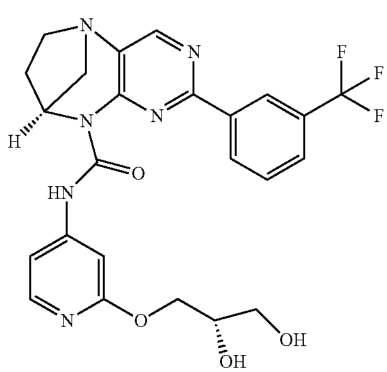
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
29		(9S)-N-{6-[(2S)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
30		(9S)-N-(propan-2-yl)-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
31		(9S)-N-{6-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo [7.2.1.0^{2},^{7}]dodeca-2,4,6-triene-8-carboxamide	A	A
32		(9S)-N-{2-[(2S)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-[3-(trifluoromethyl) phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A

TABLE 1-continued

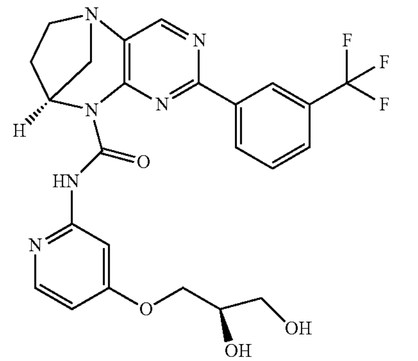
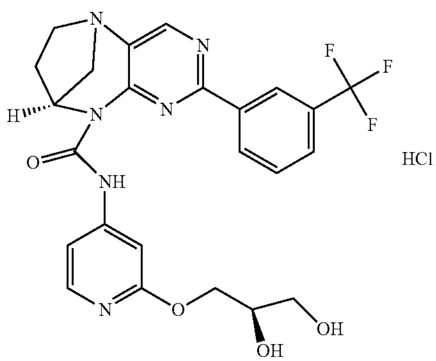
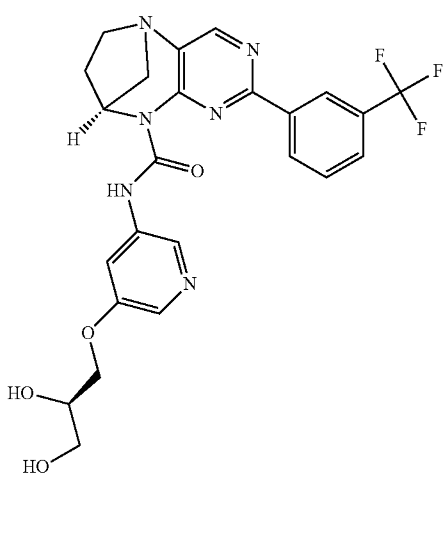
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
33		(9S)-N-{4-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo [7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
34		(9S)-N-{2-[(2R)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo [7.2.1.0^{2},^{7}]dodeca-2,4,6-triene-8-carboxamide hydrochloride	A	A
35		(9S)-N-{5-[(2R)-2,3-dihydroxypropoxy]pyridin-3-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo [7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

TABLE 1-continued

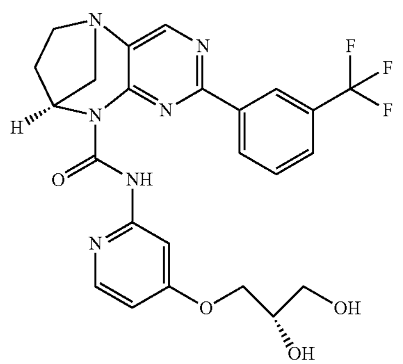
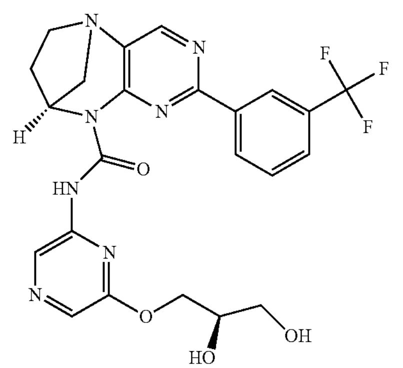
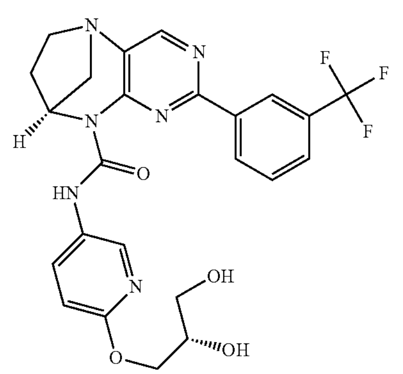
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
36		(9S)-N-{4-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2,4,6-triene-8-carboxamide	B	A
37		(9S)-N-{6-[(2R)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
38		(9S)-N-{6-[(2S)-2,3-dihydroxypropoxy]pyridin-3-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A

TABLE 1-continued

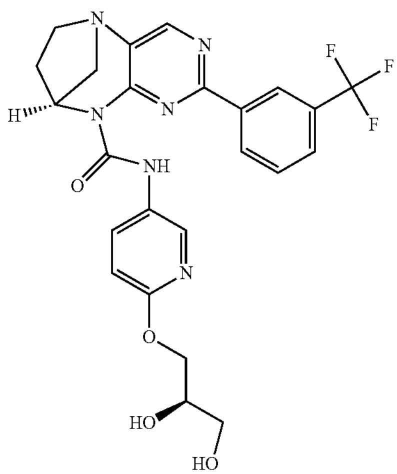
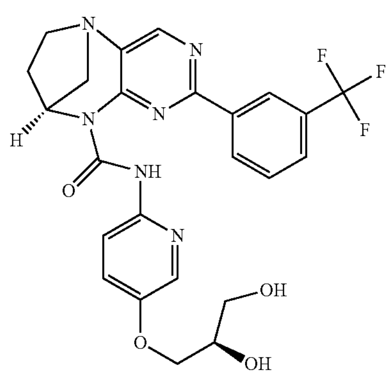
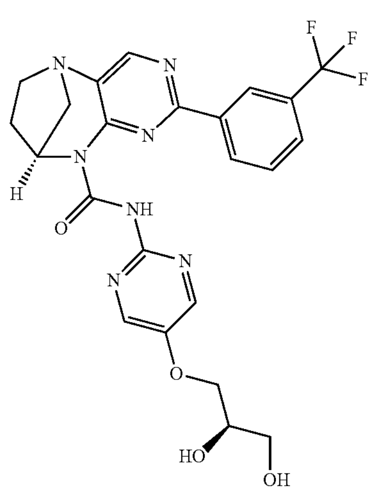
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
39		(9S)-N-{6-[(2R)-2,3-dihydroxypropoxy]pyridin-3-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo [7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A
40		(9S)-N-{5-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A
41		(9S)-N-{5-[(2R)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-5-[3-(trifluoromethyl) phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A

TABLE 1-continued

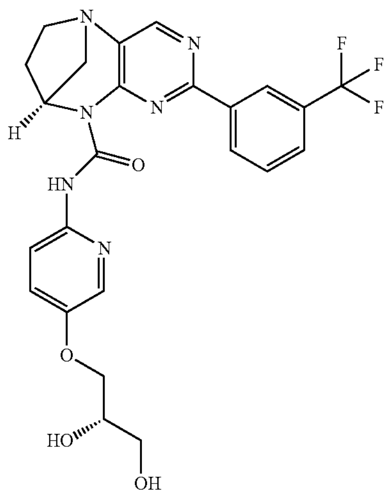
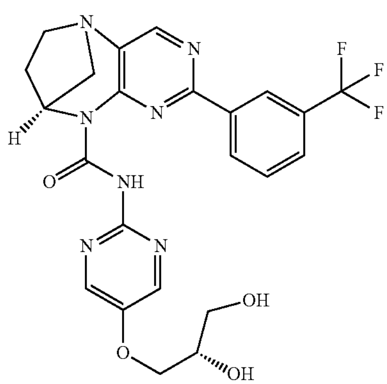
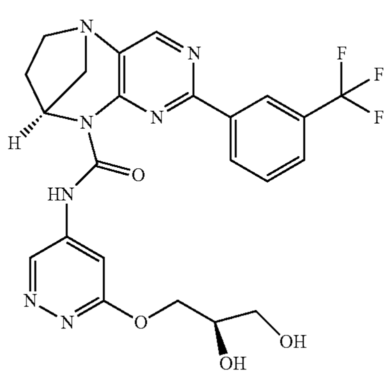
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
42		(9S)-N-{5-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo [7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
43		(9S)-N-{5-[(2S)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-5-[3-(trifluoromethyl) phenyl]-1,4,6,8-tetraazatricyclo [7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
44		(9S)-N-{6-[(2R)-2,3-dihydroxypropoxy]pyridazin-4-yl}-5-[3-(trifluoromethyl) phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

TABLE 1-continued

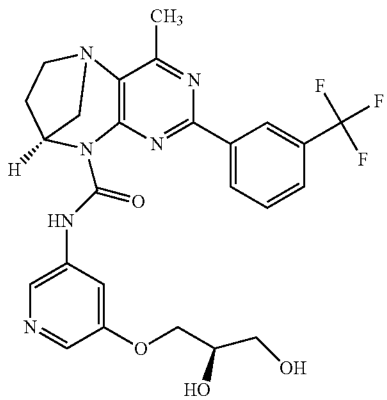
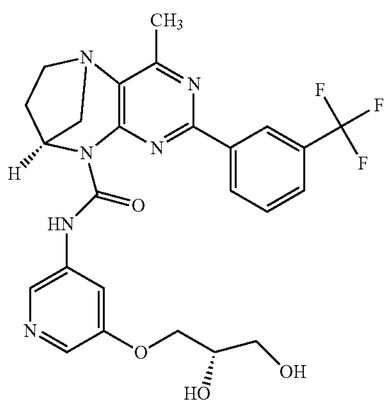
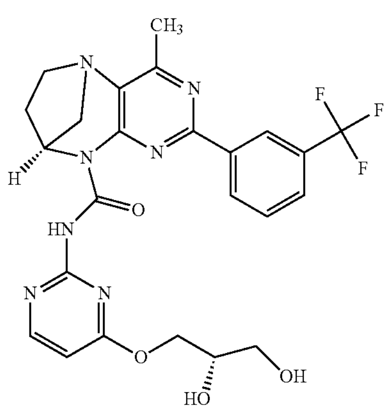
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
45		(9S)-N-{5-[(2R)-2,3-dihydroxypropoxy]pyridin-3-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
46		(9S)-N-{5-[(2S)-2,3-dihydroxypropoxy]pyridin-3-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
47		(9S)-N-{4-[(2S)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

TABLE 1-continued

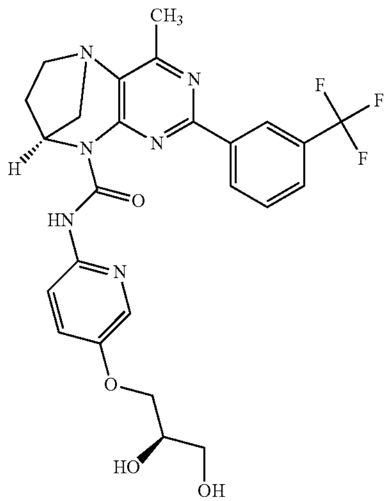
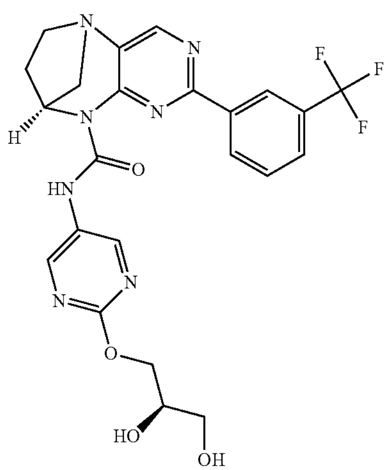
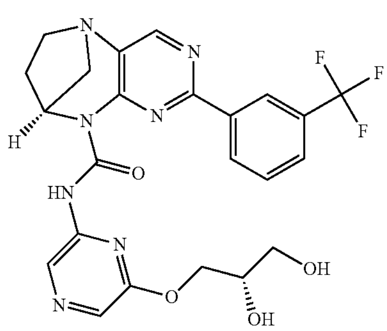
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
48		(9S)-N-{5-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
49		(9S)-N-{2-[(2R)-2,3-dihydroxypropoxy]pyrimidin-5-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2,4,6-triene-8-carboxamide	B	A
50		(9S)-N-{6-[(2S)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

TABLE 1-continued

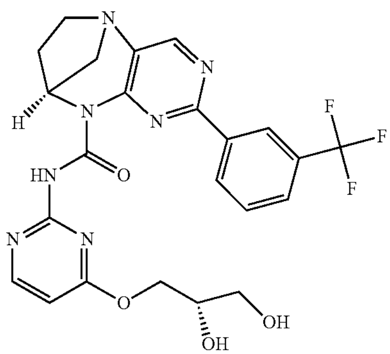
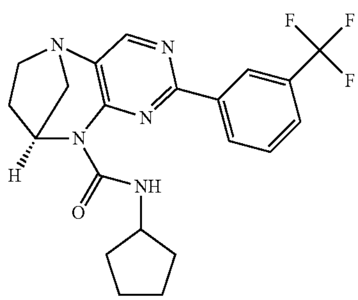
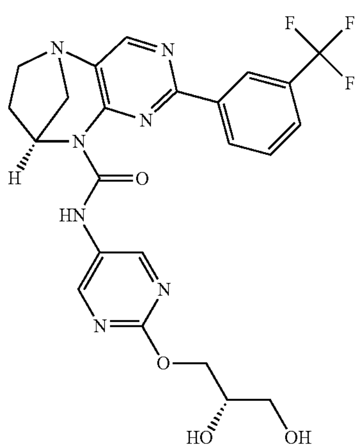
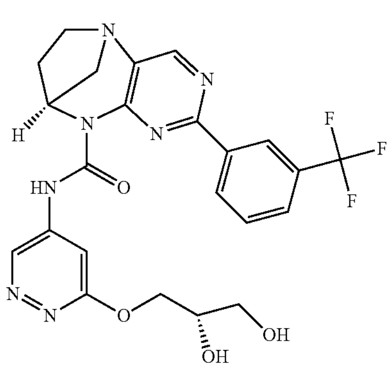
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
51		(9S)-N-{4-[(2S)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-5-[3-(trifluoromethyl) phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
52		(9S)-N-cyclopentyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
53		(9S)-N-{2-[(2S)-2,3-dihydroxypropoxy]pyrimidin-5-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
54		(9S)-N-{6-[(2S)-2,3-dihydroxypropoxy]pyridazin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

TABLE 1-continued

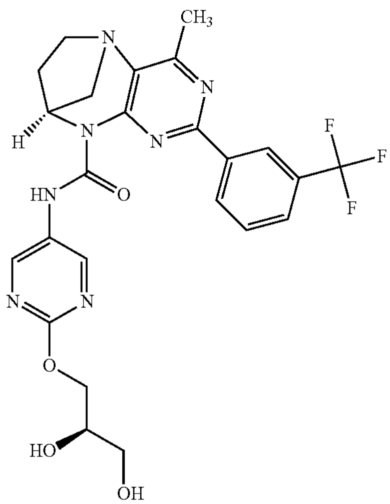
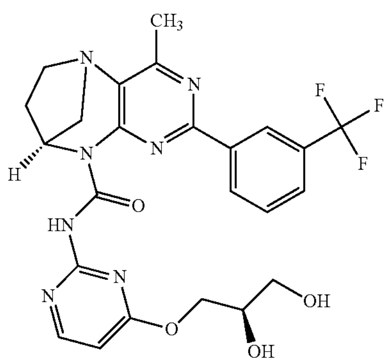
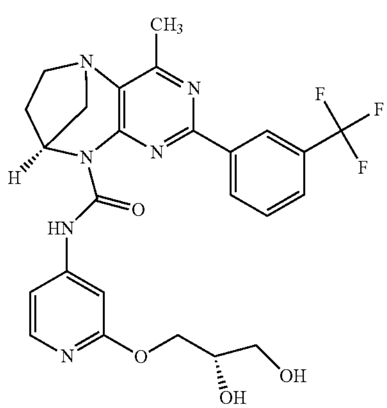
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
55		(9S)-N-{2-[(2R)-2,3-dihydroxypropoxy]pyrimidin-5-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
56		(9S)-N-{4-[(2R)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
57		(9S)-N-{2-[(2S)-2,3-dihydroxypropoxy]pyridin-4-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

TABLE 1-continued

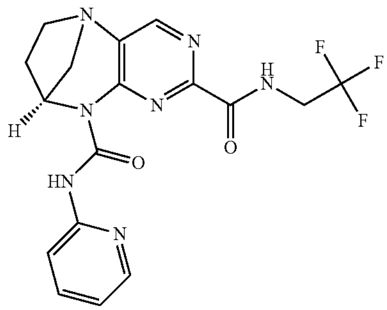
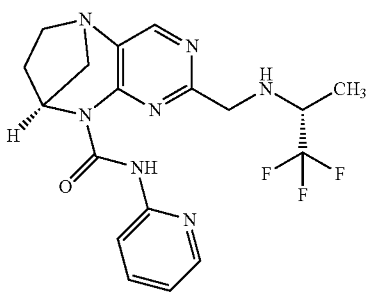
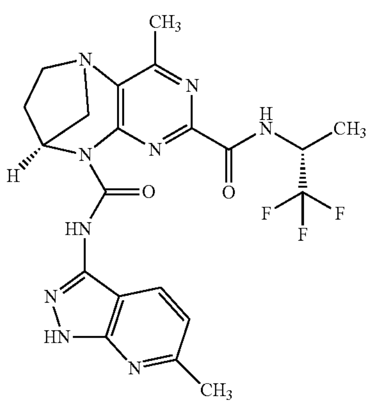
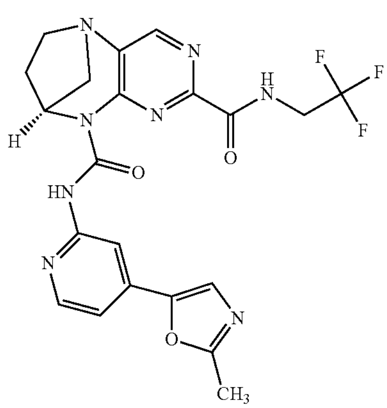
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
58		(9S)-8-N-(pyridin-2-yl)-5-N-(2,2,2-trifluoroethyl)-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-5,8-dicarboxamide	B	A
59		(9S)-8-N-(pyridin-2-yl)-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-5,8-dicarboxamide	A	A
60		(9S)-3-methyl-8-N-{6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl}-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-5,8-dicarboxamide	B	A
61		(9S)-8-N-[4-(2-methyl-1,3-oxazol-5-yl)pyridin-2-yl]-5-N-(2,2,2-trifluoroethyl)-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-5,8-dicarboxamide	B	A

TABLE 1-continued

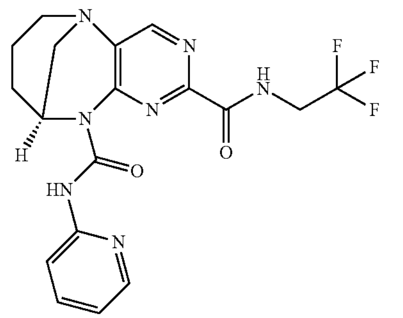
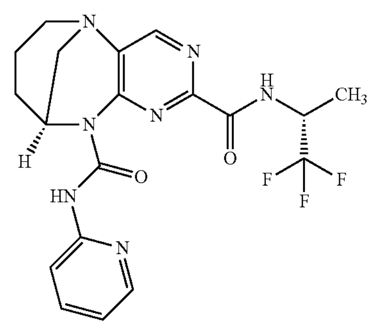
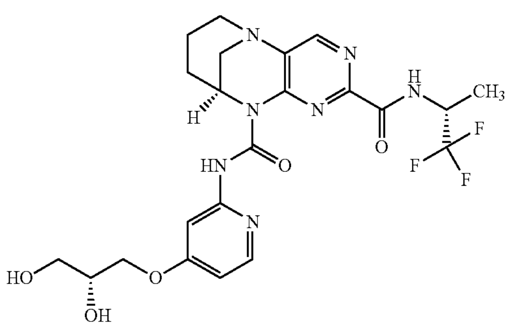
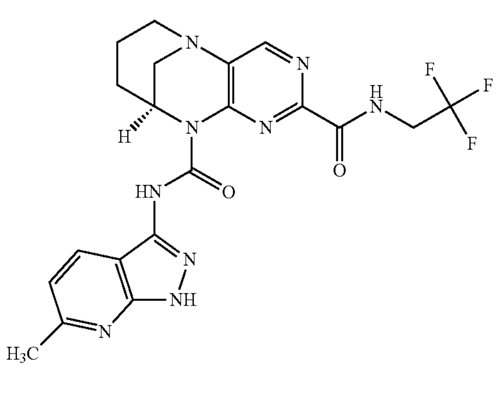
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
62		(9S)-8-N-(pyridin-2-yl)-5-N-(2,2,2-trifluoroethyl)-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-5,8-dicarboxamide	A	A
63		(9S)-8-N-(pyridin-2-yl)-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo [7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-5,8-dicarboxamide	A	A
64		(9S)-8-N-{4-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}] trideca-2(7),3,5-triene-5,8-dicarboxamide	A	A
65		(9S)-8-N-{6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl}-5-N-(2,2,2-trifluoroethyl)-1,4,6,8-tetraazatricyclo [7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-5,8-dicarboxamide	B	A

TABLE 1-continued

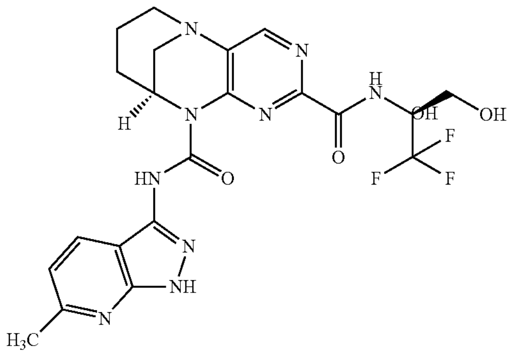
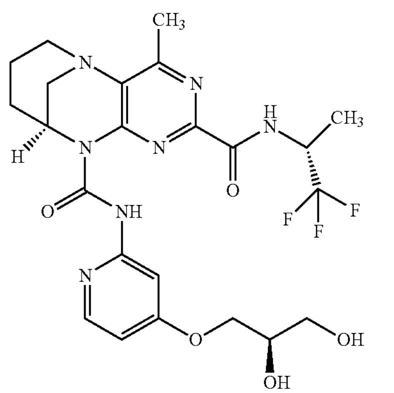
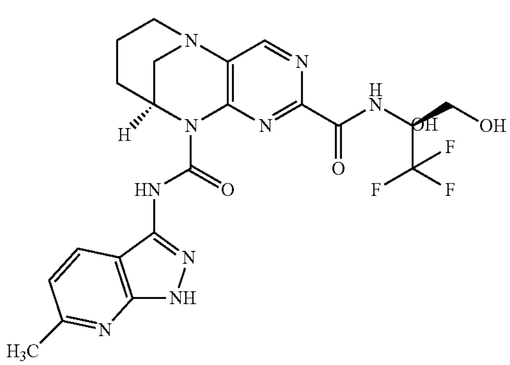
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
66	 ISOMER 1	(9S)-8-N-{6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl}-5-N-[(2S)-1,1,1-trifluoro-3-hydroxypropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-5,8-dicarboxamide	A	A
67		(9S)-8-N-{4-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-3-methyl-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-5,8-dicarboxamide	A	A
68	 ISOMER 2	(9S)-8-N-{6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl}-5-N-[(2S)-1,1,1-trifluoro-3-hydroxypropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-5,8-dicarboxamide	B	A

TABLE 1-continued

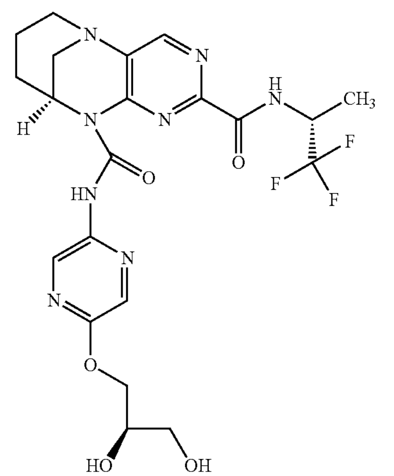
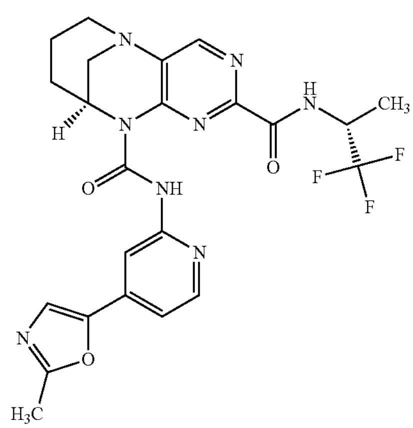
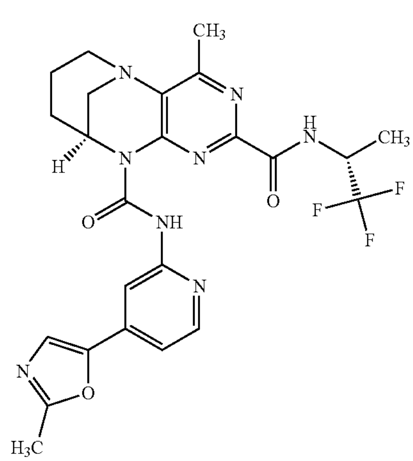
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
69		(9S)-8-N-{5-[(2R)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5,8-dicarboxamide	B	A
70		(9S)-8-N-[4-(2-methyl-1,3-oxazol-5-yl)pyridin-2-yl]-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5,8-dicarboxamide	A	A
71		(9S)-3-methyl-8-N-[4-(2-methyl-1,3-oxazol-5-yl)pyridin-2-yl]-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5,8-dicarboxamide	A	A

TABLE 1-continued

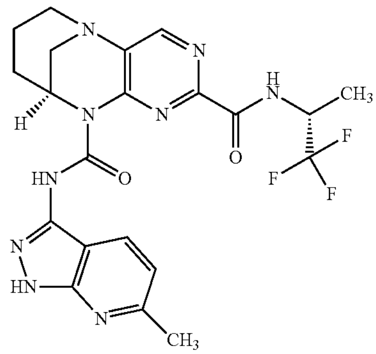
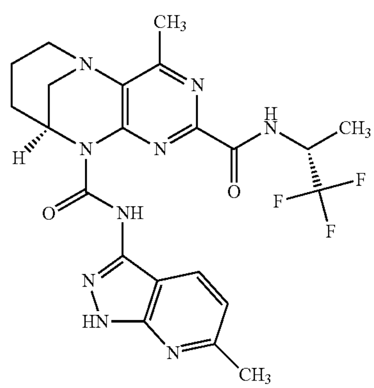
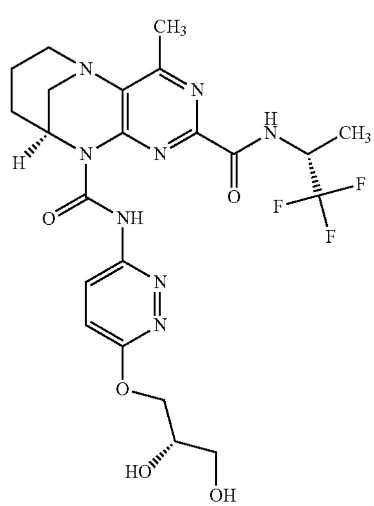
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
72		(9S)-8-N-{6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl}-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-5,8-dicarboxamide	A	A
73		(9S)-3-methyl-8-N-{6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl}-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-5,8-dicarboxamide	A	A
74		(9S)-8-N-{6-[(2S)-2,3-dihydroxypropoxy]pyridazin-3-yl}-3-methyl-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-5,8-dicarboxamide	B	A

TABLE 1-continued

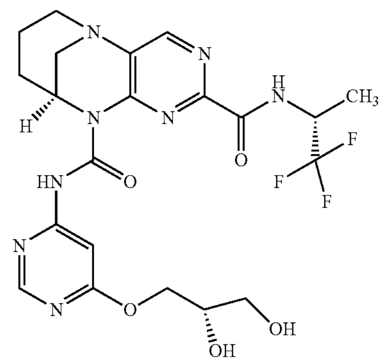
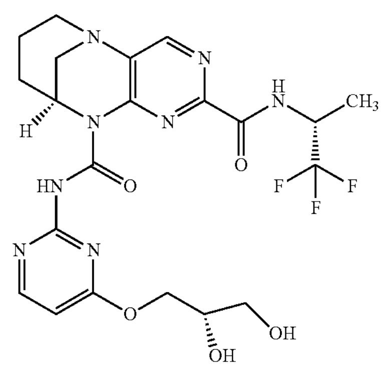
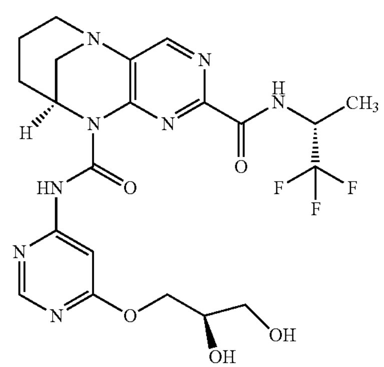
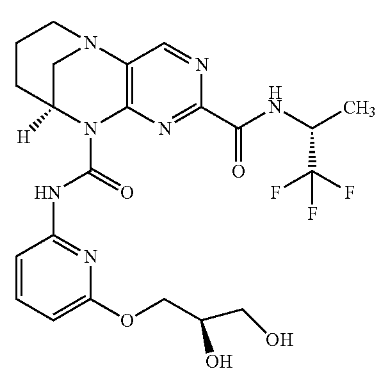
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
75		(9S)-8-N-{6-[(2S)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-5,8-dicarboxamide	B	A
76		(9S)-8-N-{4-[(2S)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-5,8-dicarboxamide	B	A
77		(9S)-8-N-{6-[(2R)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-5,8-dicarboxamide	B	A
78		(9S)-8-N-{6-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-5,8-dicarboxamide	B	A

TABLE 1-continued

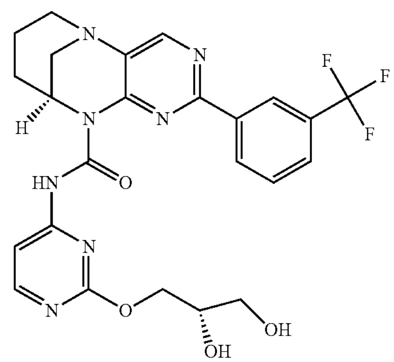
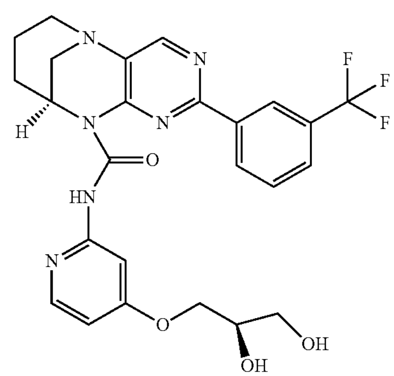
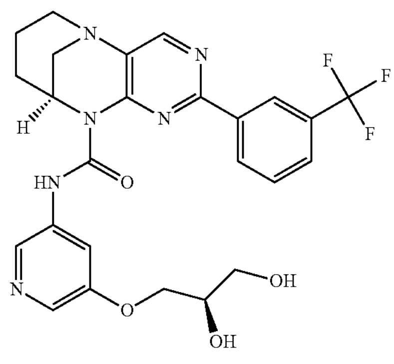
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
79		(9S)-N-{2-[(2S)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl) phenyl]-1,4,6,8-tetraazatricyclo [7.3.1.$0^{2,7}$]trideca-2,4,6-triene-8-carboxamide	A	A
80		(9S)-N-{4-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo [7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-8-carboxamide	A	A
81		(9S)-N-{5-[(2R)-2,3-dihydroxypropoxy]pyridin-3-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo [7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-8-carboxamide	A	A

TABLE 1-continued

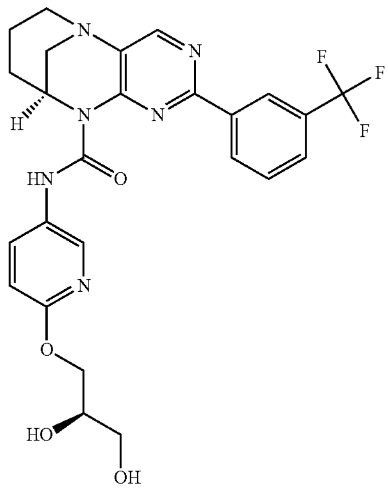
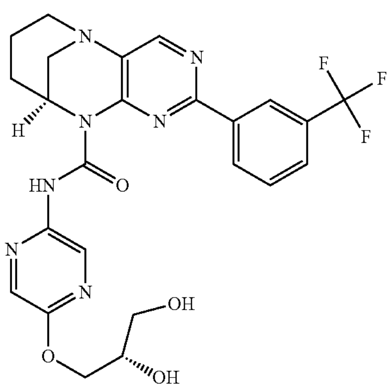
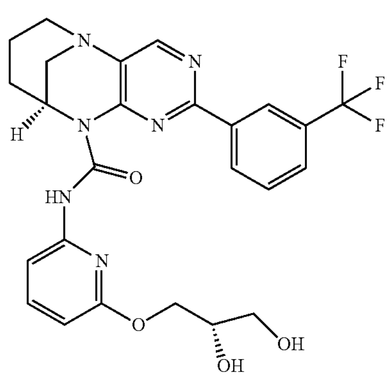
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
82		(9S)-N-{6-[(2R)-2,3-dihydroxypropoxy]pyridin-3-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo [7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-8-carboxamide	A	A
83		(9S)-N-{5-[(2S)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo [7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-8-carboxamide	A	A
84		(9S)-N-{6-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo [7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-8-carboxamide	A	A

TABLE 1-continued

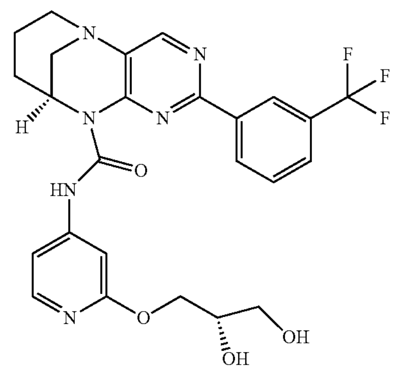
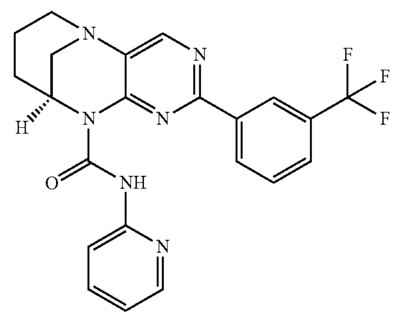
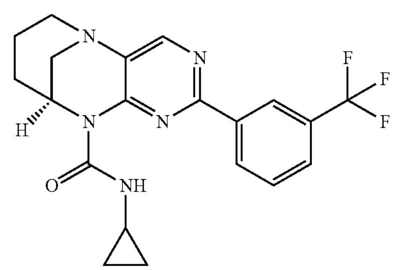
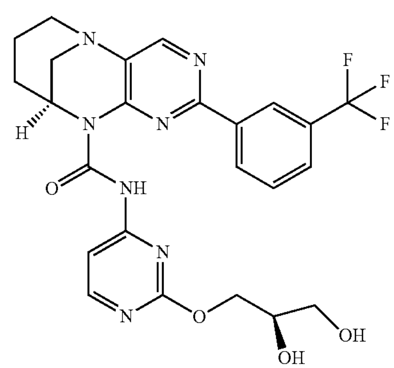
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
85		(9S)-N-{2-[(2S)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-8-carboxamide	A	A
86		(9S)-N-(pyridin-2-yl)-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene-8-carboxamide	A	A
87		(9S)-N-cyclopropyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene-8-carboxamide	A	A
88		(9S)-N-{2-[(2R)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-8-carboxamide	A	A

TABLE 1-continued

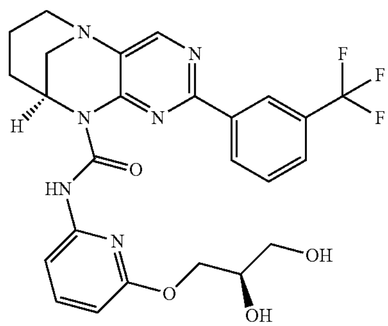
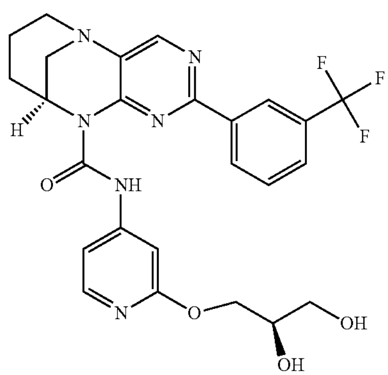
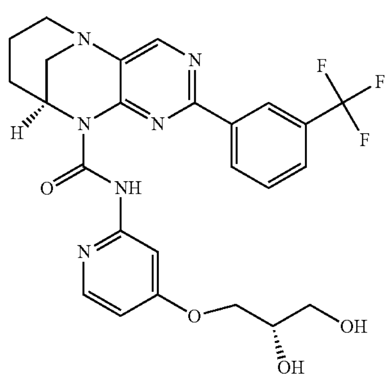
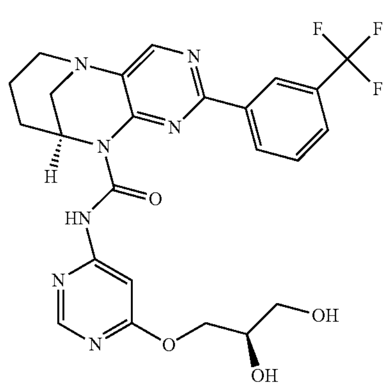
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
89		(9S)-N-{6-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-8-carboxamide	A	A
90		(9S)-N-{2-[(2R)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-8-carboxamide	A	A
91		(9S)-N-{4-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-8-carboxamide	A	A
92		(9S)-N-{6-[(2R)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-8-carboxamide	A	A

TABLE 1-continued

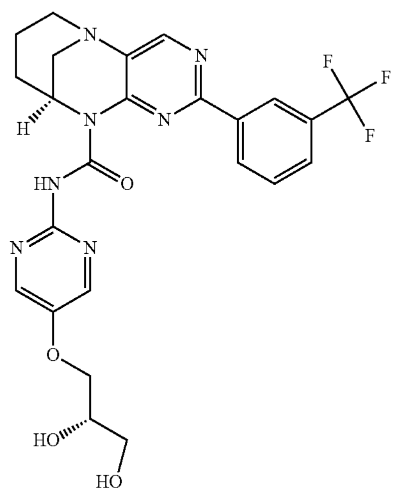
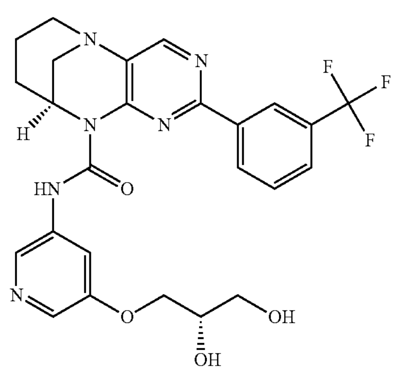
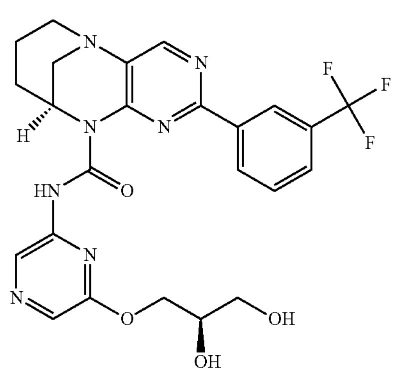
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
93		(9S)-N-{5-[(2S)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2,4,6-triene-8-carboxamide	B	A
94		(9S)-N-{5-[(2S)-2,3-dihydroxypropoxy]pyridin-3-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-8-carboxamide	A	A
95		(9S)-N-{6-[(2R)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-8-carboxamide	A	A

TABLE 1-continued

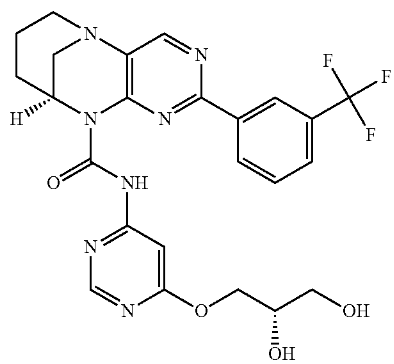
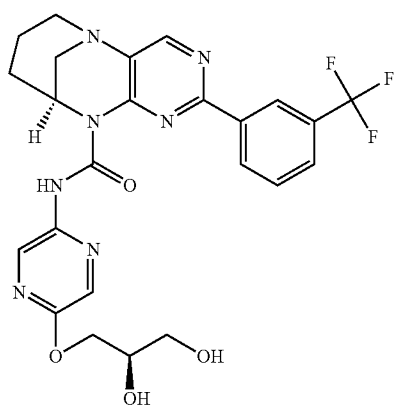
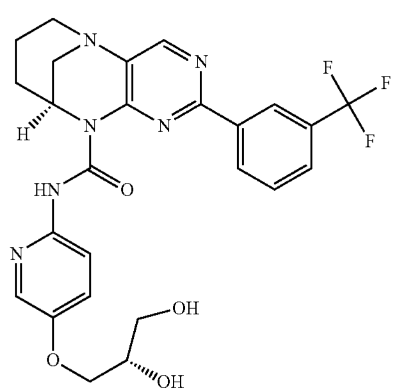
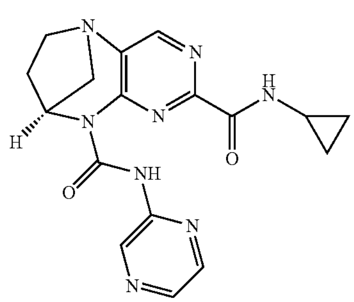
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
96		(9S)-N-{6-[(2S)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraaza-tricyclo[7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-8-carboxamide	A	A
97		(9S)-N-{5-[(2R)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-8-carboxamide	A	A
98		(9S)-N-{5-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-8-carboxamide	A	A
99		(9S)-5-N-cyclopropyl-8-N-(pyrazin-2-yl)-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2(7),3,5-triene-5,8-dicarboxamide		B

TABLE 1-continued

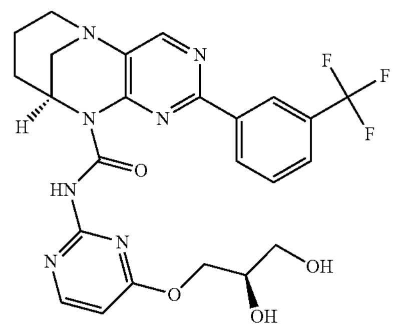
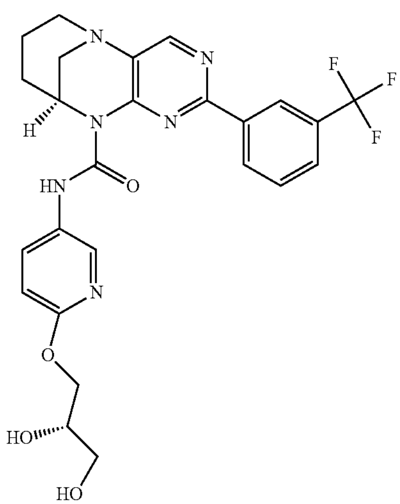
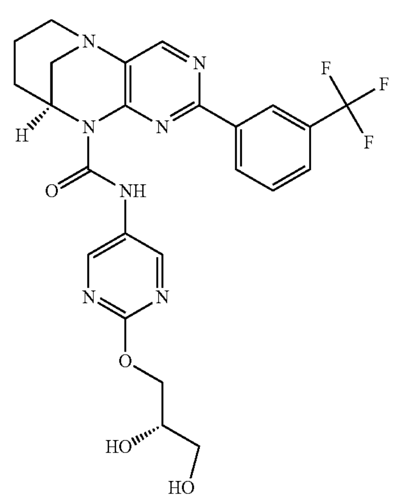
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
100		(9S)-N-{4-[(2R)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-8-carboxamide	A	A
101		(9S)-N-{6-[(2S)-2,3-dihydroxypropoxy]pyridin-3-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-8-carboxamide	A	A
102		(9S)-N-{2-[(2S)-2,3-dihydroxypropoxy]pyrimidin-5-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-8-carboxamide	A	A

TABLE 1-continued

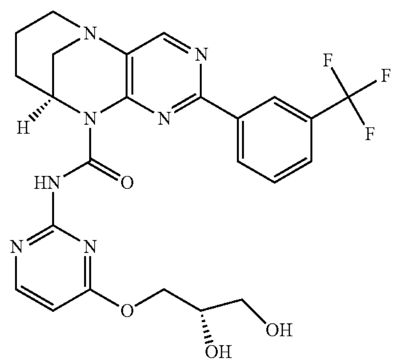
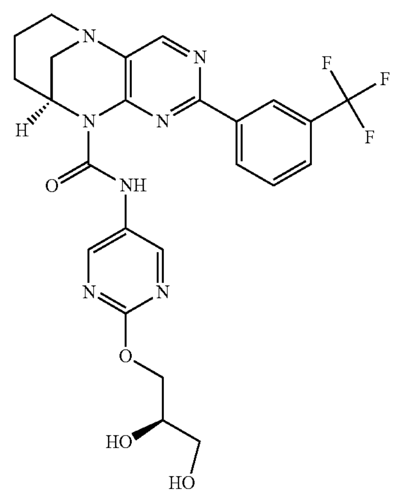
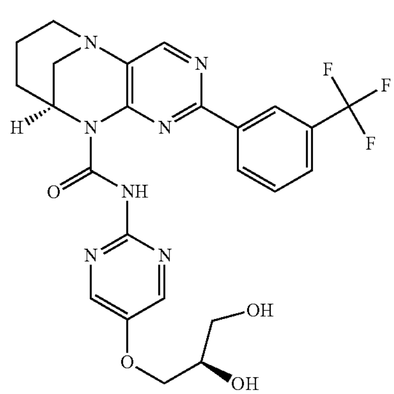
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
103		(9S)-N-{4-[(2S)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-8-carboxamide	B	A
104		(9S)-N-{2-[(2R)-2,3-dihydroxypropoxy]pyrimidin-5-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraaza-tricyclo[7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-8-carboxamide	A	A
105		(9S)-N-{5-[(2R)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-8-carboxamide	A	A

TABLE 1-continued

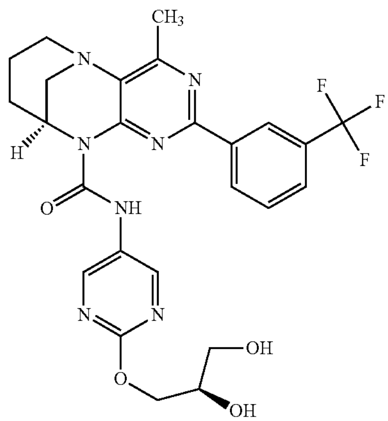
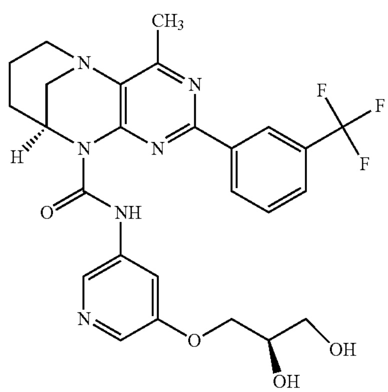
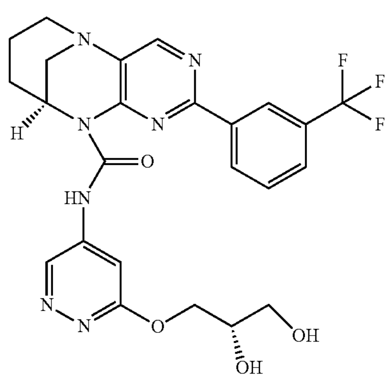
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
106		(9S)-N-{2-[(2R)-2,3-dihydroxypropoxy]pyrimidin-5-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2,4,6-triene-8-carboxamide	A	A
107		(9S)-N-{5-[(2R)-2,3-dihydroxypropoxy]pyridin-3-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-8-carboxamide	A	A
108		(9S)-N-{6-[(2S)-2,3-dihydroxypropoxy]pyridazin-4-yl}-5-[3-(trifluoromethyl) phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-8-carboxamide	A	A

TABLE 1-continued

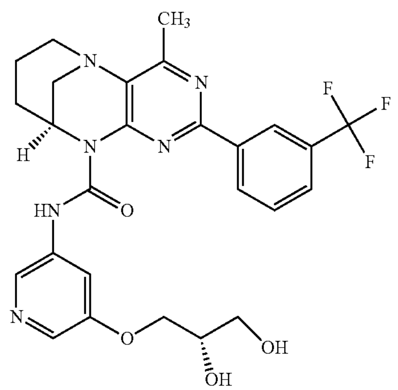
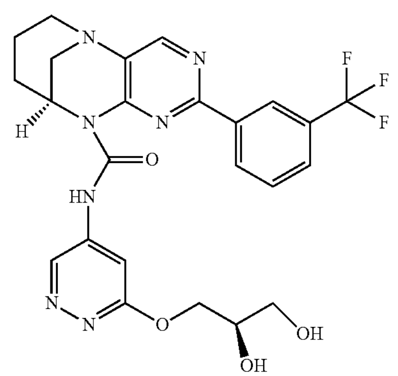
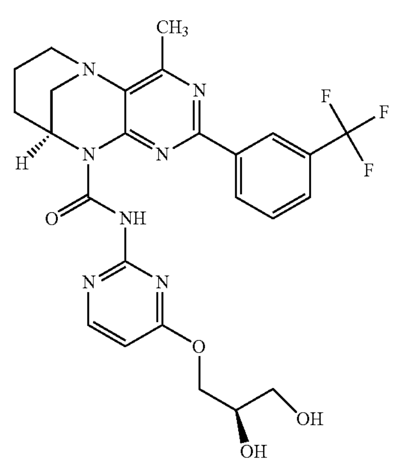
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
109		(9S)-N-{5-[(2S)-2,3-dihydroxypropoxy]pyridin-3-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-8-carboxamide	A	A
110		(9S)-N-{6-[(2R)-2,3-dihydroxypropoxy]pyridazin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-8-carboxamide	A	A
111		(9S)-N-{4-[(2R)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2,4,6-triene-8-carboxamide	A	A

TABLE 1-continued

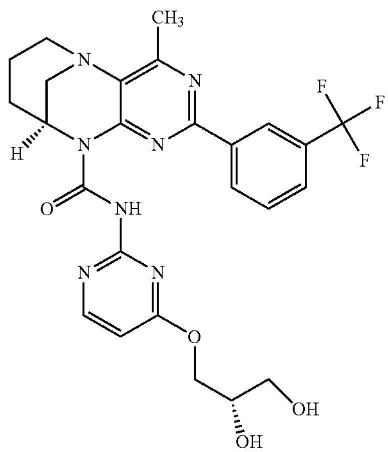
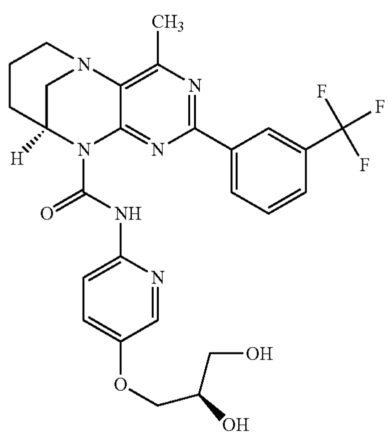
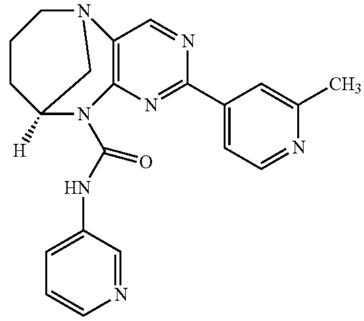
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
112		(9S)-N-{4-[(2S)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-8-carboxamide	A	A
113		(9S)-N-{5-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-8-carboxamide	A	A
114		(9S)-5-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-8-carboxamide	B	A

TABLE 1-continued

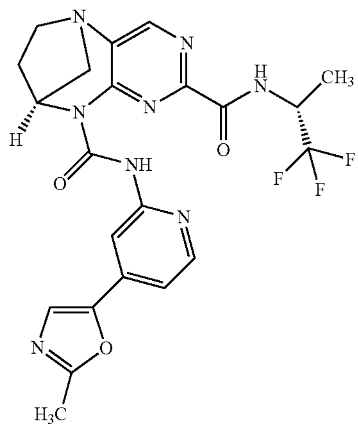
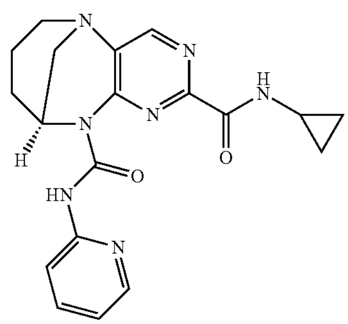
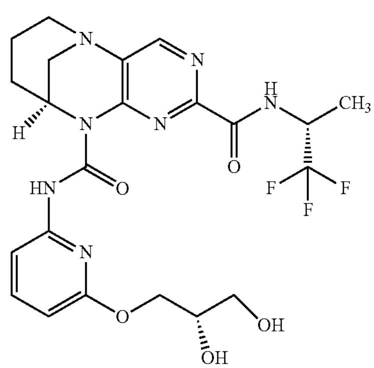
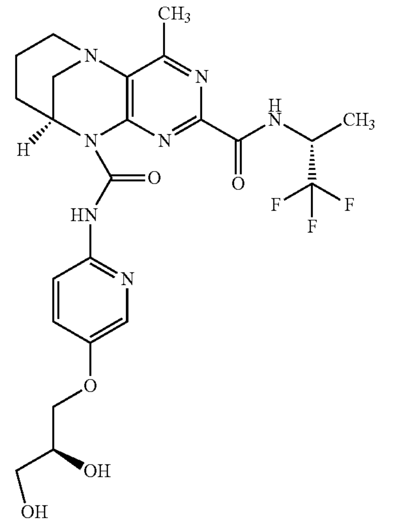
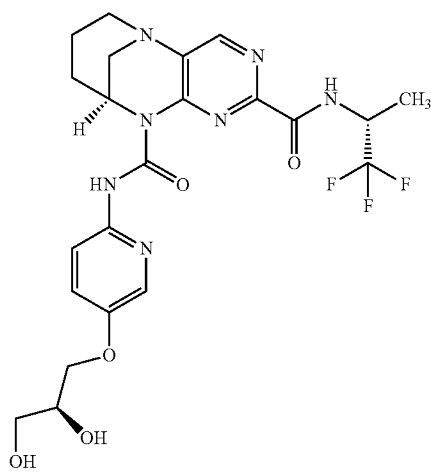
Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
115		(9S)-8-N-[4-(2-methyl-1,3-oxazol-5-yl)pyridin-2-yl]-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2},^{7}]dodeca-2,4,6-triene-5,8-dicarboxamide	B	A
116		(9S)-5-N-cyclopropyl-8-N-(pyridin-2-yl)-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-5,8-dicarboxamide	C	A
117		(9S)-8-N-{6-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-5,8-dicarboxamide	B	A

TABLE 1-continued

Ex. Nos.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
118		(9S)-8-N-{5-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-3-methyl-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-5,8-dicarboxamide	A	A
119		(9S)-8-N-{5-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-5,8-dicarboxamide	A	A

Example 121 Full-Length SIRT1 Production

[1305] Full-length human SIRT1 (hSIRT1) proteins were expressed with a C-terminal His_6 tag and purified as described in Hubbard. et al. (2013) Science 339, 1216. Each cell paste was resuspended in buffer A (50 mM Tris-HCl pH 7.5, 250 mM NaCl, 25 mM imidazole, and 0.1 mM TCEP) with 1,000 U Benzonase nuclease (Sigma Aldrich) supplemented with complete, EDTA-free Protease Inhibitor Cocktail Tablets (Roche) on ice. Cells were disrupted by pulse sonication with 50% on and 50% off for 12 minutes total at 40 W. Insoluble debris was removed by centrifugation. Clarified supernatant was directly loaded onto a 1 mL HisTrap FF Crude column (GE Lifesciences). After washing with buffer A, SIRT1 was eluted with buffer B (50 mM Tris-HCl pH 7.5, 250 mM NaCl, 500 mM imidazole and 0.1 mM TCEP). Protein was further purified by size exclusion chromatography in buffer C (50 mM Tris-HCl pH 7.5, 300 mM NaCl, 0.1 mM TCEP) using a Hi-load Superdex 200 16/60 column (GE Lifesciences). Enzyme concentrations were determined by Bradford assay using BSA as a standard. Final protein purity was assessed by gel densitometry. Proteins were confirmed by LC/MS. All proteins were greater than 90% pure.

Example 122. SIRT1 Deacetylation Reactions

[1306] SIRT1 deacetylation reactions were performed in reaction buffer (50 mM HEPES-NaOH, pH 7.5, 150 mM NaCl, 1 mM DTT, and 1% DMSO) at 25° C. monitoring either nicotinamide production using the continuous PNC1/GDH coupled assay (Smith, B. C. et al. (2009) Anal Biochem 394, 101) or O-acetyl ADP ribose (OAcADPr) production by mass spectrometry (Hubbard. et al. (2013) Science 339, 1216). Final concentrations of the PNC1/GDH coupling system components used were 20 units/mL bovine GDH (Sigma-Aldrich), 1 uM yeast PNC1, 3.4 mM α-ketoglutarate, and 220 μM NADH or NADPH. An extinction coefficient of 6.22 $mM^{-1}cm^{-1}$ and a pathlength of 0.81 cm was used to convert the absorbance at 340 nm to product concentration for the 150 uL reactions used. Assays monitoring OAcADPr production were performed in reaction buffer with 0.05% BSA and time points were taken by quenching the deacetylation reaction with a stop solution which gave a final concentration of 1% formic acid and 5 mM nicotinamide. Quenched reactions were diluted 5-fold with 1:1 acetonitrile:methanol and spun at 5,000×g for 10 minutes to precipitate protein before being analyzed with an Agilent RapidFire 200 High-Throughput Mass Spectrometry System (Agilent, Wakefield, Mass.) coupled to an ABSciex API 4000 mass spectrometer fitted with an electrospray ionization source. The p53-based Ac-p53(W5) (Ac-RHKK^{AC}W—NH_2) and TAMRA (Ac-EE-K(biotin)-GQST-SSHSK(Ac)NleSTEG-K(5TMR)-EE-NH_2) peptides were obtained from American Century Peptide and Biopeptide, Inc, respectively.). Substrate K_M determinations were performed by varying one substrate concentration at a fixed, saturating concentration of the second substrate. SIRT1 activation and inhibition assays were run in reaction buffer with 0.05% BSA at 25° C. and analyzed using the OAcADPr assay. Enzyme and compound were pre-incubated for 20 minutes before addition of substrates. For the activation screen of full-length hSIRT1, compounds were tested in duplicate with a dose response. In order to be sensitive to K_M-modulating activators, substrate concentrations of approximately one-tenth their K_M values were used. The dose-dependence of five compounds was tested and the fold-activation data were described by Eq. 1

$$\frac{v_x}{v_{?}} = b + \frac{RV_{?} - b}{1 + \frac{EC_{50}}{[X]_{?}}} \qquad \text{(Eq. 1)}$$

? indicates text missing or illegible when filed

where v_x/v_0 is the ratio of the reaction rate in the presence (v_x) versus absence (v_0) of activator (X), RV_{max} is the relative velocity at infinite activator concentration, EC_{50} is the concentration of activator required to produce one-half RV_{max} and b is the minimum value of v_x/v_o.

Example 123

[1307] The present invention relates to Sirtuin Modulators, which are known in the scientific literature for being useful for increasing lifespan of a cell, and in treating and/or preventing a wide variety of diseases and disorders, which include, but are not limited to, for example, diseases or disorders related to aging or stress, diabetes, obesity, neurodegenerative diseases, cardiovascular disease, blood clotting disorders, inflammation, cancer, and/or flushing as well as diseases or disorders that would benefit from increased mitochondrial activity.

[1308] In addition to therapeutic potential, structural and biophysical studies of SIRT1 activity and activation by small molecule sirtuin modulators would be useful in advancing understanding of the biological function of sirtuins, mechanism of action of sirtuin activation and to aid in development of assays that identify novel sirtuin modulators.

[1309] Based on the foregoing, the following literature references, respectively, are cited to demonstrate the utility of compounds of the present invention as Sirtuin Modulators and its interconnection with various diseases as exemplified or disclosed in the following references:

[1310] 1. Marcia C. Haigis and David A. Sinclair, Mammalian Sirtuins: Biological Insights and Disease Relevance, *Annu Rev Pathol.* 2010; 5: 253-295.

[1311] Haigis and Sinclair teach:

[1312] "Aging is accompanied by a decline in the healthy function of multiple organ systems, leading to increased incidence and mortality from diseases such as type II diabetes mellitus, neurodegenerative diseases, cancer, and cardiovascular disease. Historically, researchers have focused on investigating individual pathways in isolated organs as a strategy to identify the root cause of a disease, with hopes of designing better drugs. Studies of aging in yeast led to the of a family of conserved enzymes known as the sirtuins, which affect multiple pathways that increase the life span and the overall health of organisms. Since the discovery of the first known mammalian sirtuin, SIRT1, 10 years ago, there have been major advances in our understanding of the enzymology of sirtuins, their regulation, and their ability to broadly improve mammalian physiology and health span. This review summarizes and discusses the discovery advances of the past decade and the challenges that will confront the field in the coming years (see, ABSTRACT, therein and reference)."

[1313] 2. Gizem Donmezl et. al., SIRT1 and SIRT2: emerging targets in neurodegeneration, EMBO Mol Med (2013) 5, 344-352.

[1314] Gizem Donmezl et. al., teaches:

[1315] "Sirtuins are NAD-dependent protein deacetylases known to have protective effects against age-related diseases such as cancer, diabetes, cardiovascular and neurodegenerative diseases. In mammals, there are seven sirtuins (SIRT1-7), which display diversity in subcellular localization and function. While SIRT1 has been extensively investigated due to its initial connection with lifespan extension and involvement in calorie restriction, important biological and therapeutic roles of other sirtuins have only recently been recognized. Here, we review the potential roles and effects of SIRT1 and SIRT2 in neurodegenerative diseases. We discuss different functions and targets of SIRT1 and SIRT2 in a variety of neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's Disease (HD). We also cover the role of SIRT1 in neuronal differentiation due to the possible implications in neurodegenerative conditions, and conclude with an outlook on the potential therapeutic value of SIRT1 and SIRT2 in these disorders (see, ABSTRACT, therein and reference)."

[1316] 3. Bracke et al., Targeted silencing of DEFB4 in a bioengineered skin-humanized mouse model for psoriasis: development of siRNA SECosome-based novel therapies; *Exp Dermatol.* 2014 March; 23(3): 199-201. doi: 10.1111/exd.12321.

[1317] In particular, Bracke et al. teaches

[1318] "Psoriasis is a complex inflammatory skin disease that presents a wide variety of clinical manifestations. Human 3 defensin-2 (hBD-2) is highly up-regulated in psoriatic lesions and has been defined as a biomarker for disease activity. We explored the potential benefits of targeting hBD-2 by topical application of DEFB4-siRNA-containing SECosomes in a bioengineered skin-humanized mouse model for psoriasis. A significant improvement in the psoriatic phenotype was observed by histological examination, with a normalization of the skin architecture and a reduction in the number and size of blood vessels in the dermal compartment. Treatment leads to the recovery of transglutaminase activity, filaggrin expression and stratum corneum appearance to the levels similar to those found in normal regenerated human skin. The availability of a reliable skin-humanized mouse model for psoriasis in conjunction with the use of the SECosome technology may provide a valuable preclinical tool for identifying potential therapeutic targets for this disease."

[1319] 4. Karline Guilloteau et al., Skin Inflammation Induced by the Synergistic Action of IL-17A, IL-22 Recapitulates Some Features of Psoriasis Oncostatin M, IL-la, and TNF-α, *J Immunol* 2010; 184:5263-5270.

[1320] Guilloteau et al. teaches:

[1321] "Keratinocytes play a crucial role in the regulation of skin inflammation, responding to environmental and immune cells stimuli. They produce soluble factors that can act in an autocrine or paracrine manner on immune cells or directly on aggressors. A screening of the activities of 36 cytokines on keratinocyte gene expression identified IL-17A, IL-22, oncostatin M, TNF-α, and IL-la as potent cytokines in inducing cutaneous inflammation. These five proinflammatory cytokines synergistically increased production of CXCL8 and b-defensin 2 (BD2). In addition, ex vivo studies on human skin explants demonstrated upregulation of BD2, S100A7, and CXCL8 expression in response to the same combination of cytokines. In vivo intradermal injection of these five cytokines in mouse increased CXCL1, CXCL2, CXCL3, S100A9, and BD3 expression, associated with neutrophil infiltration. We confirmed and extended this synergistic effect using quantitative real-time PCR analysis and observed increased expression of nine chemokines and 12 antimicrobial peptides. Production of CXCL, CXCL5, and CXCL8 by keratinocytes stimulated in the presence of this cytokine combination was associated with increased neutrophil chemotactic activity. Similarly, high production of BD2, BD3, and S100A7 was associated with an increased antimicrobial activity. Finally, the transcriptional profile observed in this in vitro model of inflammatory keratinocytes correlated with the one of lesional psoriatic skin. Our results demonstrate the important potentiating activities of IL-17A, IL-22, oncostatin M, TNF-α, and IL-la on keratinocytes. This is particularly interesting in the context of psoriasis where these cytokines are overexpressed and could synergize to play an important role in upregulation of chemokines and antimicrobial peptides production. The Journal of Immunology, 2010, 184: 5263-5270 (see, ABSTRACT, therein and reference)".

Example 124

Description of Assays:

PBMC Assay

[1322] Sirtuin 1 (Sirt1) is a homolog of silent information regulator 2 (Sir2) and a member of the NAD dependent class III histone deacetylase. Sirt1 deacetylates lysine residues on histones, trasncription factors and nonhistone proteins. Sirt1 has been shown to be involved in aging, cell cycle regulation, apoptosis, metabolic modulation and inflammation. The activation of Sirt1 causes deacetylation at lysine 310 of RelA/p65 subunit of nuclear factor kB (NF-kB) transcriptional factor which inhibits NF-kB transcription and downregulates levels of TNFalpha. TNFalpha is a pleitotropic cytokine that is mainly produced by macrophages and monocytes. TNFalpha is closely involved in immune defense and chronic inflammation including Psoriasis. The expression of type-1 cytokines such as TNFa was known to be increased in psoriatic skin and it plays important role in the etiology of psoriasis (Uyemura K et al, 1993, J. Invest Dermatol, 101, p701). Importantly, anti-TNF agent has been in clinical use for psoriasis. Therefore, Sirt1 activators that induce a reduction in TNFa expression in inflammatory cells should have therapeutic effect in moderate to severe psoriatic patients.

[1323] A PBMC/TNFalpha cell based assay was developed to identify activators of Sirt1 that inhibit the release of TNFalpha in response to lipopolysaccharide (LPS) stimulation of peripheral blood mononuclear cells (PBMC's). Briefly, PBMC's were stimulated by LPS, leading to an increase in the production of TNFalpha secretion. TNFalpha protein level was measured by TNFalpha HTRF (homogeneous time resolved fluorescence) kit (CisBio, Inc). Cell lysis and TNFalpha detection were performed according to manufacturer's instructions. Sirt1 activators were tested in the presence of LPS to evaluate their inhibitory effect on TNFa release and IC50 were determined in a dose-response experiment.

Beta-Defensin 2 (bD2) ASSAY

[1324] Sirtuin is a family of NAD-dependent deacetylases which have broad physiological functions and have been implicated in a number of autoimmune and metabolic disorders including rheumatoid arthritis and type I diabetes. Substrates of SIRT1 are diverse and include inflammatory components with well established roles in innate and adaptive immune response such as NF □B, AP-1, FOXO, and p53.

[1325] Psoriasis is a chronic inflammatory skin disorder induced by genetic, autoimmune, and environmental factors. Lesions are characterized by hyperproliferation of keratinocytes in the epidermis and infiltration of inflammatory cells resulting in chronic erythmatous plaques covered by white scales. Previous studies have shown that SIRT1 can impede the effects of IL-22, a key cytokine in psoriasis, through direct inhibition of STAT3 acetylation (Sestito et al, 2011). In addition, both SIRT1 overexpression and resveratrol treatment (SIRT1 activation) can induce keratinocyte differentiation (Blander et al, 2009).

[1326] Beta-defensin 2 (bD2) is an antimicrobial peptide that can be secreted from the epithelia where it acts as a chemoattractant for memory T-cells, immature dendritic cells, and neutrophils. As such, bD2 is a major part of the inflammatory response in the skin. Not only is bD2 induced in lesional epidermal cells of psoriasis patients compared to normal skin, but it is also a serum biomarker for disease severity in psoriasis patients (Jansen et al, 2009; Kamsteeg et al 2009). In addition, bD2 may be genetically linked to psoriasis as a recent study uncovered a significant association between increased beta-defensin gene copy number and psoriasis risk (Hollox et al, 2008). Of note, topical delivery of bD2 siRNA resulted in recovery of normal skin architecture and protein expression in a bioengineered skin-humanized mouse model for psoriasis (Bracke et al, 2014).

[1327] An in vitro keratinocyte inflammation assay generated to mimic psoriatic inflammation was previously described (Guilloteau et al, 2010; Teng et al 2014). In these studies, a cytokine cocktail of IL-lalpha, IL-17A, IL-22, OSM, and TNFalpha (referred to as "M5") was found to synergize to produce a "psoriasiform" transcriptional profile in primary human keratinocytes in vitro. In these studies, bD2 was one of the strongest responders to the induction of keratinocyte inflammation.

[1328] Therefore, this assay was further developed in order to assess the efficacy of SIRT1 activator compounds for the topical psoriasis program. Specifically, conditions were optimized for an immortalized human keratinocyte cell line (HaCaT) treated in vitro with the M5 cytokine combination to induce psoriatic inflammation (as in reference above). In a 48 hour time frame, bD2 secretion, as measured by a bD2 ELISA assay (Alpha Diagnostics), is significantly increased compared to unstimulated keratinocytes. This bD2 induction can be suppressed with treatment of compounds known to suppress psoriatic inflammation or, importantly, with a subset of SIRT1 activators. In parallel, cytotoxicity over the length of the 48 hour assay is ascertained by a CellTiter-Glo Luminescent Cell Viability Assay (Promega) to determine whether toxicity might play a role in bD2 response.

REFERENCES

[1329] Blander G, Bhimavarapu A, Mammone T, Maes D, Elliston K, Reich C, Matsui M S, Guarente L, Loureiro J J. SIRT1 promotes differentiation of normal human keratinocytes. *J Invest Dermatol.* 2009 January; 129(1):41-9.

[1330] Bracke S, Carretero M, Guerrero-Aspizua S, Desmet E, Illera N, Navarro M, Lambert J, Del Rio M. Targeted silencing of DEFB4 in a bioengineered skin-humanized mouse model for psoriasis: development of siRNA SECosome-based novel therapies. *Exp Dermatol.* 2014 March; 23(3):199-201.

[1331] Guilloteau K, Paris I, Pedretti N, Boniface K, Juchaux F, Huguier V, Guillet G, Bernard F X, Lecron J C, Morel F. Skin Inflammation Induced by the Synergistic Action of IL-17A, IL-22, Oncostatin M, I L-lalpha, and TNFalpha Recapitulates Some Features of Psoriasis. *J Immunol.* 2010 Mar. 24.

[1332] Jansen P A, Rodijk-Olthuis D, Hollox E J, Kamsteeg M, Tjabringa G S, de Jongh G J, van Vlijmen-Willems I M, Bergboer J G, van Rossum M M, de Jong E M, den Heijer M, Evers A W, Bergers M, Armour J A, Zeeuwen P L, Schalkwijk J. Beta-defensin-2 protein is a serum biomarker for disease activity in psoriasis and reaches biologically relevant concentrations in lesional skin. *PLoS One.* 2009; 4(3):e4725.

[1333] Kamsteeg M, Jansen P A, van Vlijmen-Willems I M, van Erp P E, Rodijk-Olthuis D, van der Valk P G, Feuth T, Zeeuwen P L, Schalkwijk J. Molecular diagnostics of psoriasis, atopic dermatitis, allergic contact dermatitis and irritant contact dermatitis. *Br J Dermatol.* 2010 March; 162(3):568-78.

[1334] Sestito R, Madonna S, Scarponi C, Cianfarani F, Failla C M, Cavani A, Girolomoni G, Albanesi C. STAT3-dependent effects of IL-22 in human keratinocytes are counterregulated by sirtuin 1 through a direct inhibition of STAT3 acetylation. *FASEB J.* 2011 March; 25(3):916-27.

[1335] Teng X, Hu Z, Wei X, Wang Z, Guan T, Liu N, Liu X, Ye N, Deng G, Luo C, Huang N, Sun C, Xu M, Zhou X, Deng H, Edwards C K 3rd, Chen X, Wang X, Cui K, Wei Y, Li J. IL-37 ameliorates the inflammatory process in psoriasis by suppressing proinflammatory cytokine production. *J Immunol.* 2014 Feb. 15; 192(4): 1815-23.

Psoriasis & IL-17

[1336] Psoriasis is a chronic, relapsing, inflammatory autoimmune skin disorder with a multi-factorial pathogenesis influenced by genetic, environmental, and immunopathologic factors (Griffiths C E et al., Lancet 2007; 370: 263-71). Psoriasis is characterized by recurrent episodes of raised, well-demarcated erythematous oval plaques with adherent silvery scales. Histologically, the hallmark of psoriasis is the presence of a thickened nucleated keratinocyte layer, with exaggeration of the rete pegs, caused by hyperproliferation of keratinocytes and dermal infiltration by activated T cells, neutrophils, and dendritic cells (Schon M P N. Engl. J. Med. 352: 1899-1912).

[1337] An accumulating body of evidence suggests psoriasis as a Th17-mediated disease, driven by its signature cytokines IL-17 A, IL-17 F and IL-22. IL-22 induces proliferation of keratinocytes, whereas IL-17A stimulates keratinocytes to secrete chemokines and other proinflammatory mediators that recruit additional inflammatory cells, including neutrophils, dendritic cells, and innate lymphoid cells (Martin D A et al, J Invest Dermatol 2013; 133:17-26).

[1338] The clinical validation of the IL-17 pathway in mediating psoriasis is demonstrated by successful Ph3 studies that show significant improvement of disease using monoclonal antibody therapy targeting IL-17 (Langley et al., NEJM 2014). In addition, global transcription profiling in psoriasis lesions following IL-17 inhibition suppressed multiple inflammatory factors from keratinocytes and leukocyte subsets to similar levels as observed in non-lesional skin (Russell et al., J Immunol 2014, 192: 3828-3836). Taken together, these findings support the role of TL-17 in mediating psoriasis pathogenesis.

Method (Ex Vivo Skin Assay)

[1339] Stimulation of skin-resident immune cells in ex vivo human skin explants using a Th17 cytokine cocktail results in a dramatic upregulation of Th17 related cytokines (IL-17A, IL-17F and IL-22), which establishes this system as a human tissue-based model for psoriasis. The ability of test compounds to modulate the expression of IL-17A, IL-17 F and IL-22 was assessed using the ex vivo skin culture method post stimulation with Th17 cytokine cocktail.

[1340] Briefly, ex vivo human skin obtained from abdominoplasty surgery was processed to remove fat and the tissue was dermatomed to ~750 microns. Dermatomed skin was then cleaned in two serial rinses of 5-10 minutes each in room temperature PBS containing an antibiotic/antimycotic solution. The skin section was cut with disposable single-use biopsy punches to 10 mm diameter round sections, which were then placed in the upper chamber of a 0.4 μm PCF membrane transwell (Millicell #PIHP01250) containing 30 μl of a 64% bovine collagen solution (Organogenesis, #200-055) prepared with Cornification media. The skin samples were allowed to set on the collagen solution for 30 min at 37° C. in a humidified chamber. The skin samples on transwells were transferred to 6-well plates (1 sample per well) and the lower chamber was filled with 1 ml complete media (Cornification Media).

[1341] On the first day following abdominoplasty surgery, skin explants were cultured in Cornification media and allowed to incubate overnight at 37° C. Specifically, human skin explants (N=3 per condition) were stimulated with the Th17 cocktail (CD3, 1 μg/ml, CD28, 2 μg/ml, IL-1b, 10 ng/ml, IL-6, 5 ng/ml, TGFb, 1 ng/ml, IL-21, 10 ng/ml, anti-IL-4, 1 μg/ml and anti-INFg, 1 μg/ml). Test compound at 1,3 and 10 uM was added at the same time as Th17 cocktail. Tissue was harvested 24 hrs after Th17 activation and RNA was isolated for transcript quantification (IL-17A, IL-17F, IL-22) using qPCR.

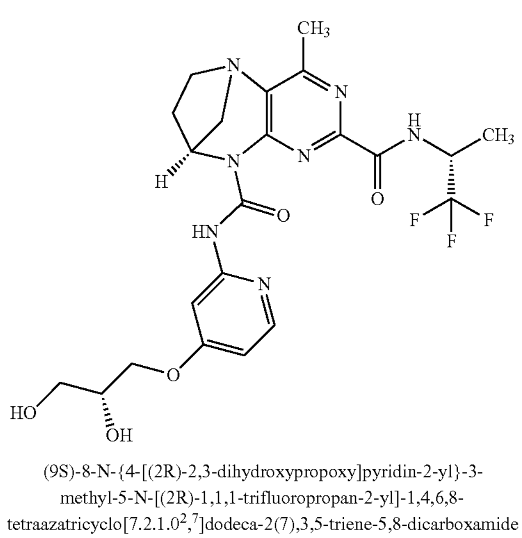
[1342] Total RNA was isolated from −40 mg of tissue using Qiagen's Mini RNA Isolation kit (Cat #74106). Briefly, tissue was minced and homogenized in the Precellys-24 machine using 300 μl of RLT buffer supplemented with 1% 2-Beta-Mercapto-Ethanol at 6300 rpm for 30 seconds for 10 cycles with a 2-minute ice break. 490 μl of water containing 10 μl Proteinase K was added to the homogenate and digested at 55° C. for 15 minutes. Digested tissue was spun down for 3 minutes at 10,000 G to pellet cell debri and the supernatant was used for RNA isolation using Qiagen's RNeasy mini columns according to manufacturer's protocol. Total RNA was quantified using Nanodrop 2000 and analyzed on Agilent bioanalyser (files attached). 1.4 μg of RNA was used as template in a 20 μl PCR volume using Invitrogen SuperScript VILO cDNA Synthesis kit (#11754-050) to create a cDNA template. Then cDNA was diluted 1:25 for the subsequent qPCR with the specific TaqMan probe for each gene to be quantified. RNA levels of gene of interest's relative expression were calculated using the Delta Delta CT formula.

EQUIVALENTS

[1343] The present invention provides among other things sirtuin-modulating compounds and methods or uses thereof. While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

1.-19. (canceled)

20. A compound or pharmaceutically acceptable salt thereof, selected from



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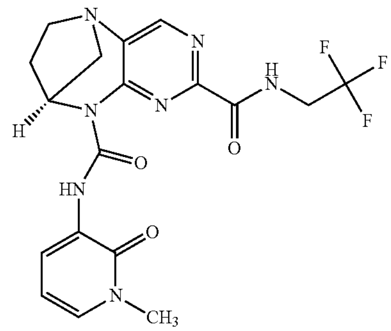

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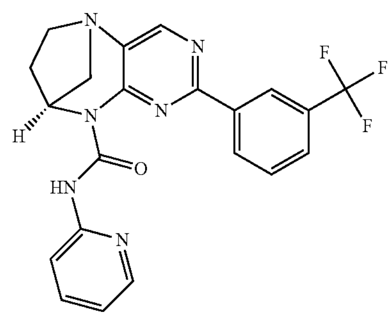

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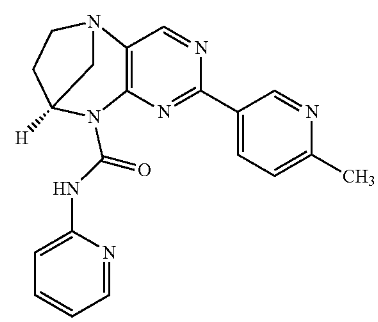

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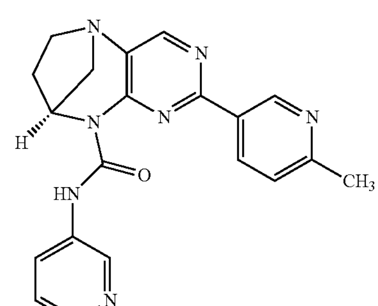

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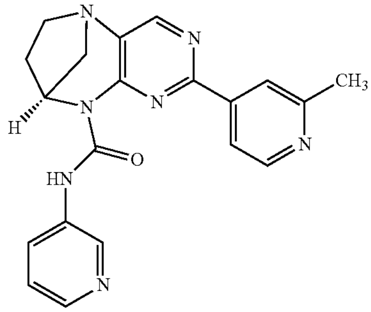

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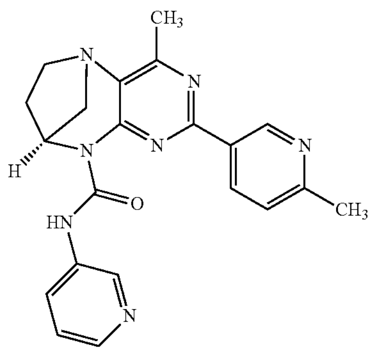

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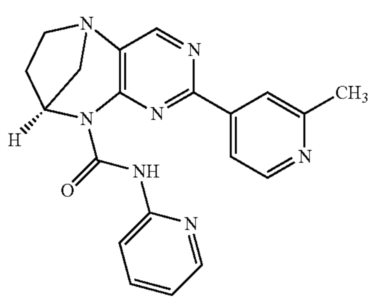

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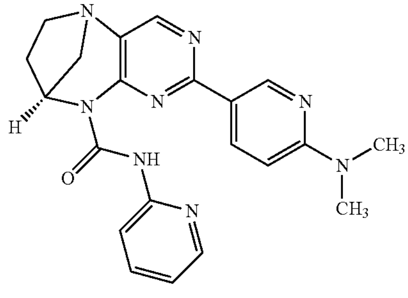

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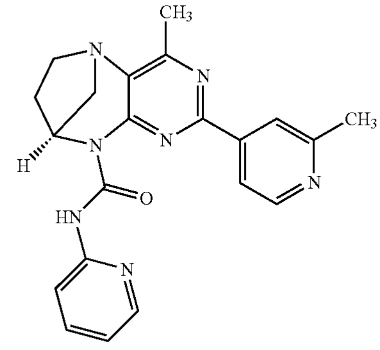

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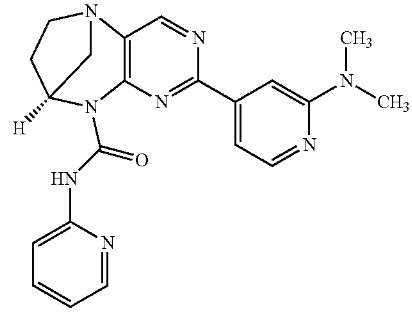

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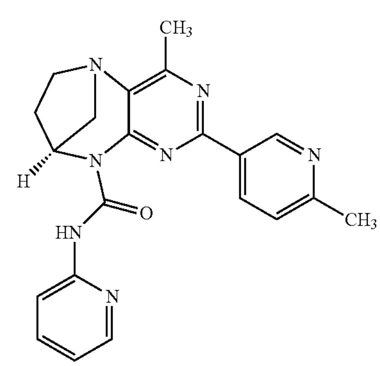

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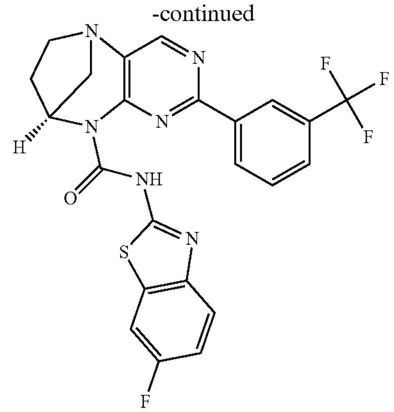

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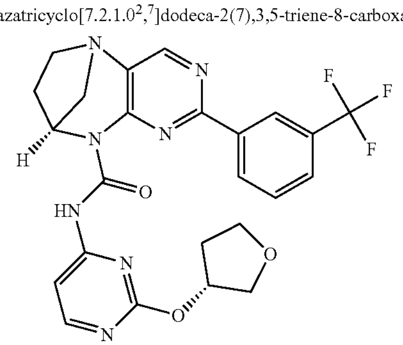

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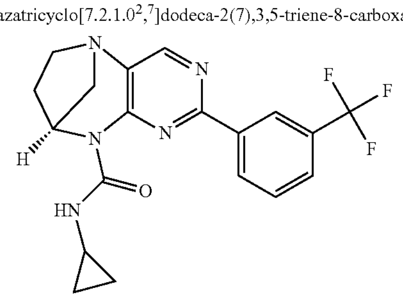

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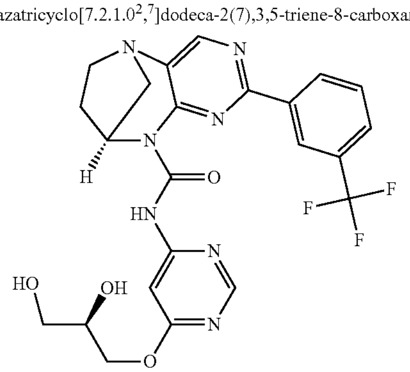

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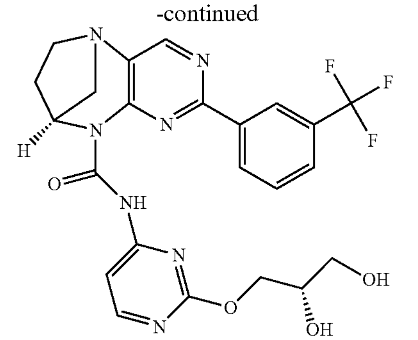

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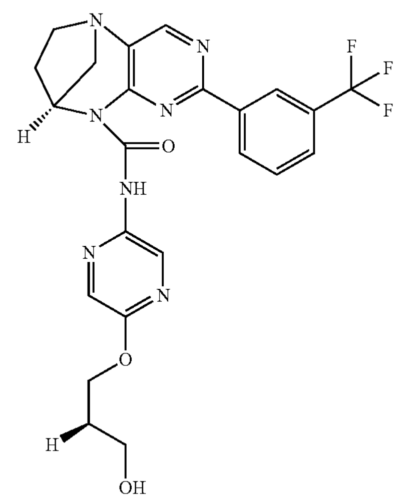

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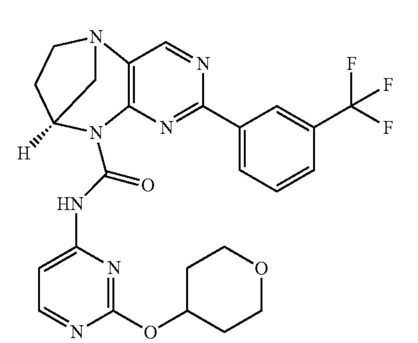

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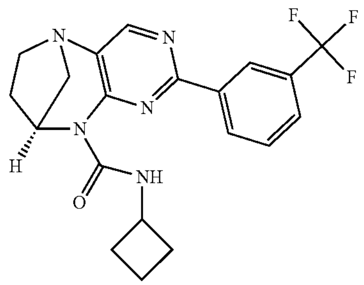

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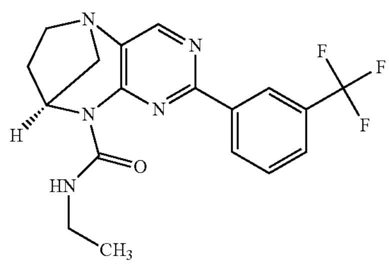

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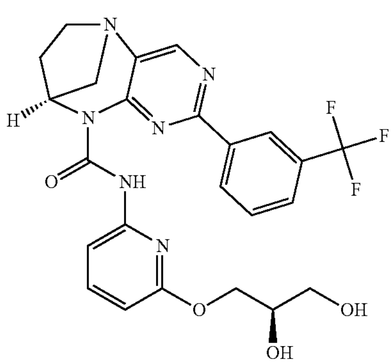

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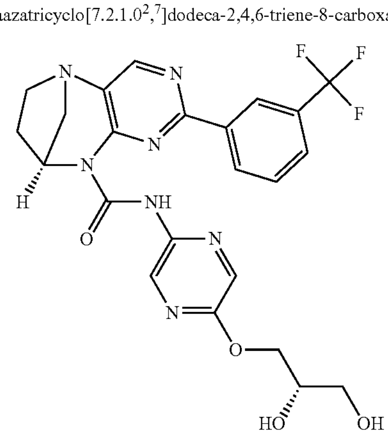

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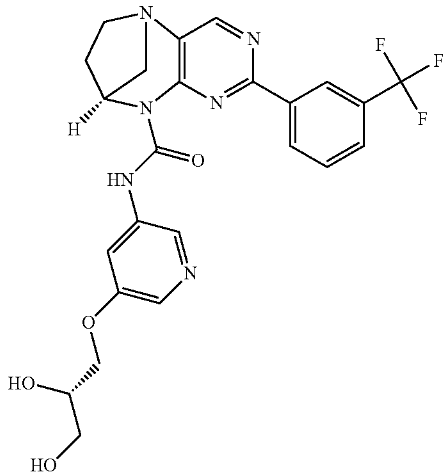

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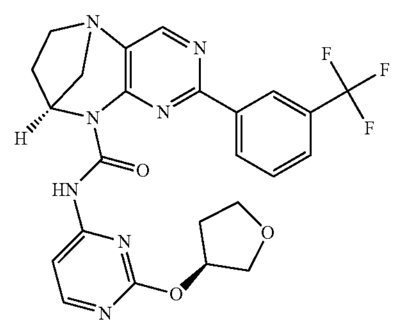

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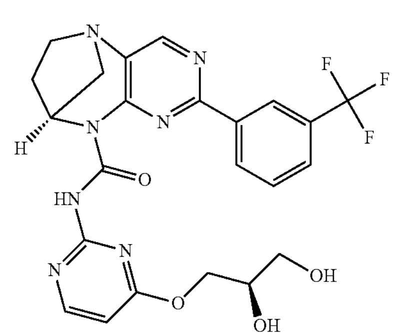

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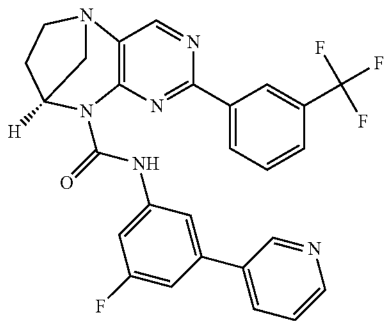

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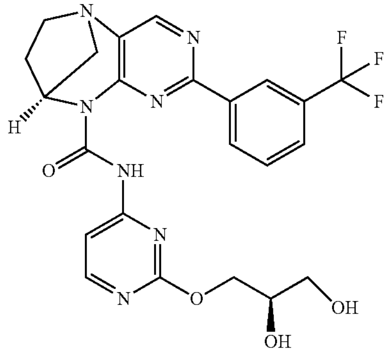

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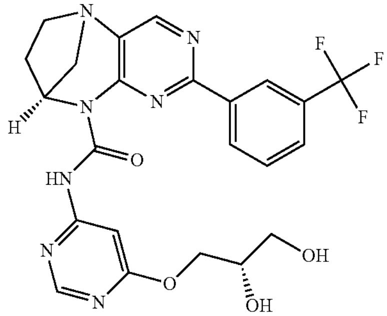
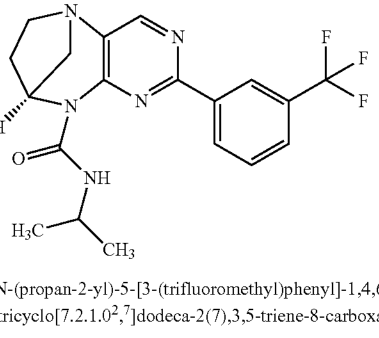


(9S)-N-{6-[(2S)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide



(9S)-N-(propan-2-yl)-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

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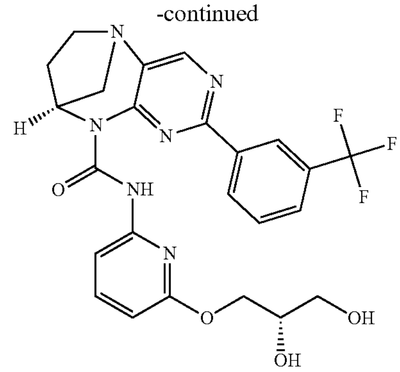
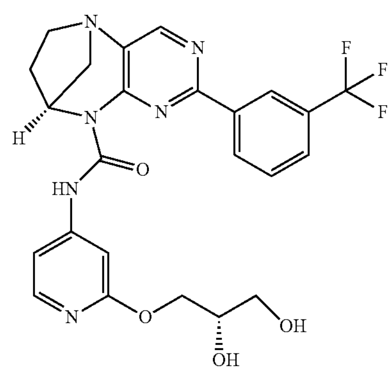
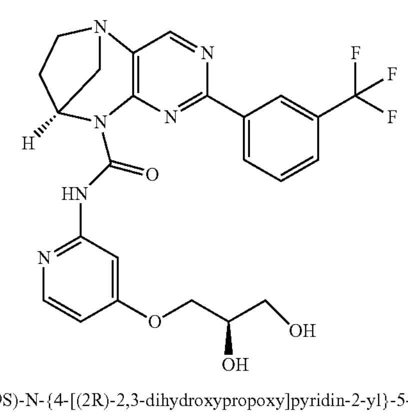


(9S)-N-{6-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide



(9S)-N-{2-[(2S)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide



(9S)-N-{4-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

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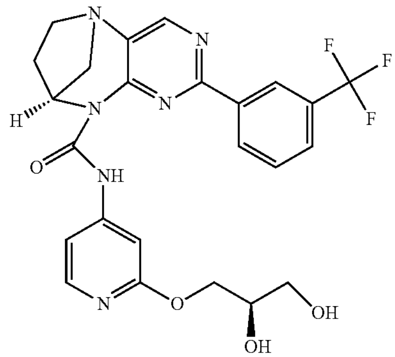
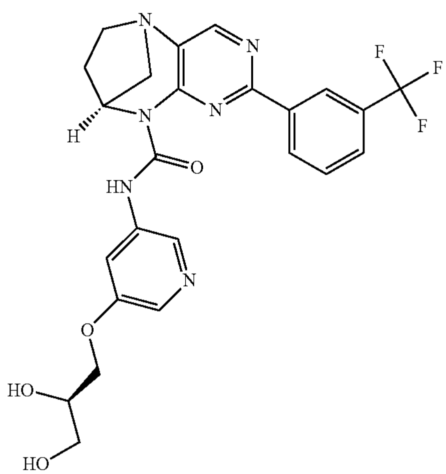
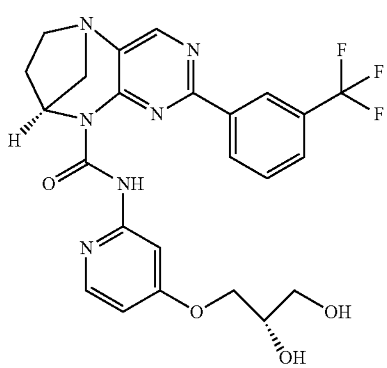


(9S)-N-{2-[(2R)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide hydrochloride



(9S)-N-{5-[(2R)-2,3-dihydroxypropoxy]pyridin-3-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide



(9S)-N-{4-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide

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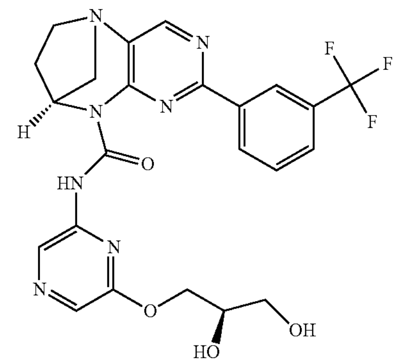

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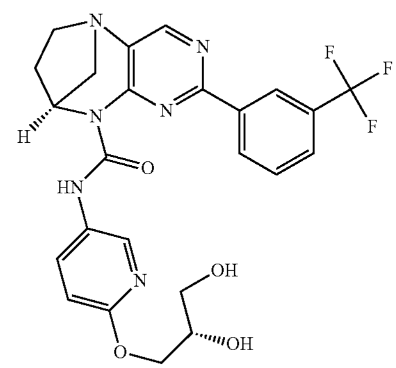

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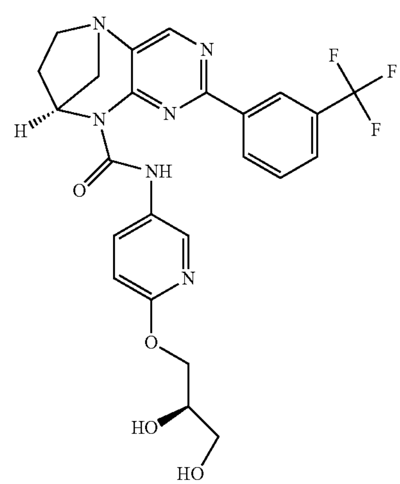

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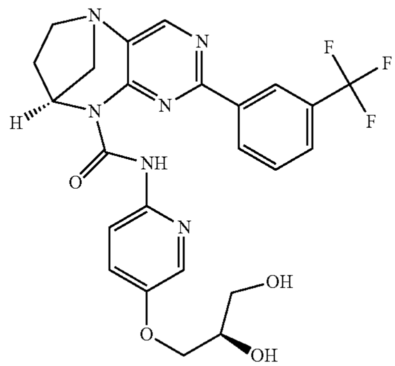
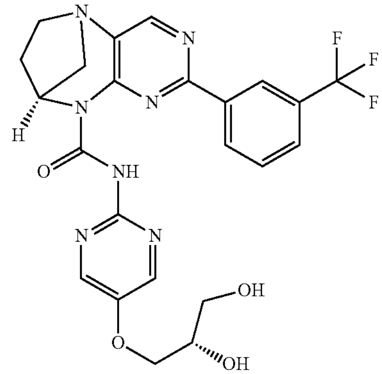
-continued



(9S)-N-{5-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide

-continued



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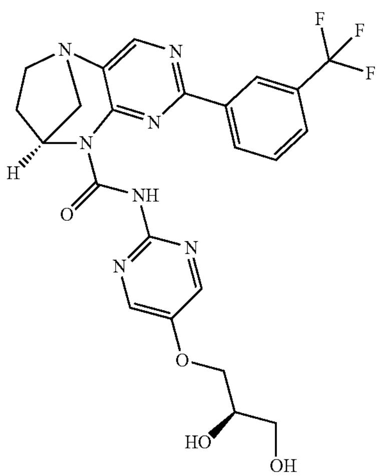

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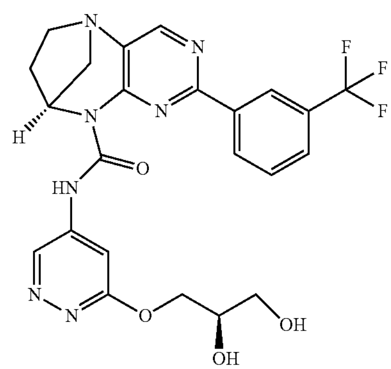
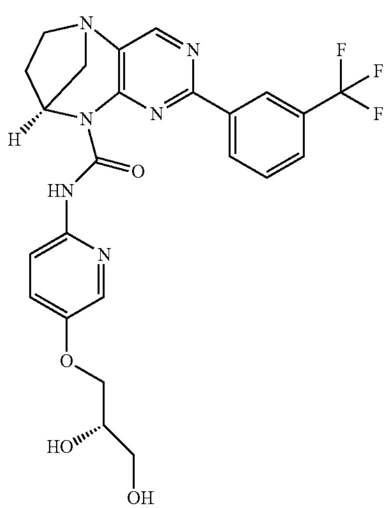


(9S)-N-{6-[(2R)-2,3-dihydroxypropoxy]pyridazin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide



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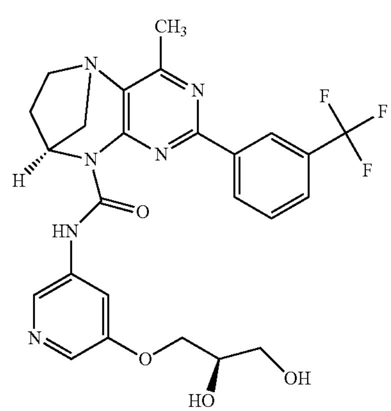

(9S)-N-{5-[(2R)-2,3-dihydroxypropoxy]pyridin-3-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

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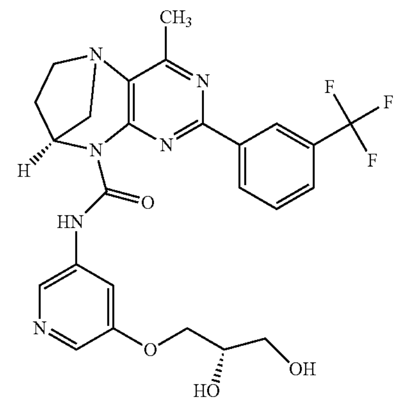
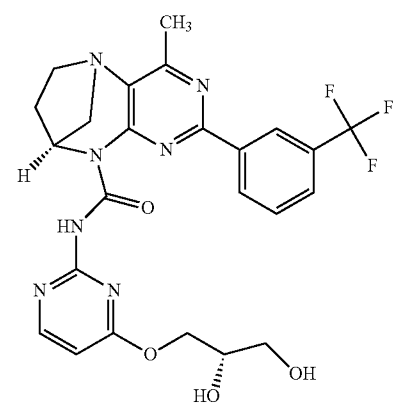
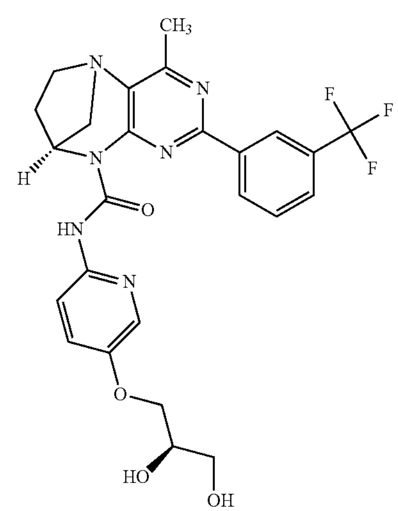


(9S)-N-{5-[(2S)-2,3-dihydroxypropoxy]pyridin-3-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

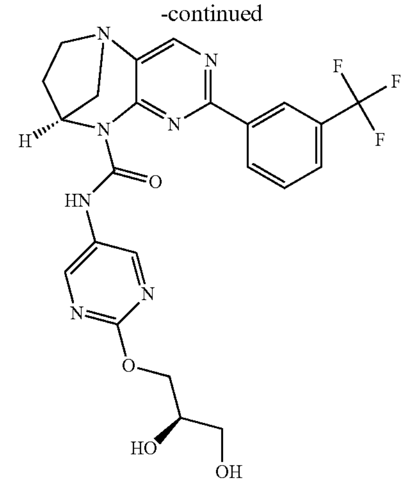


(9S)-N-{4-[(2S)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

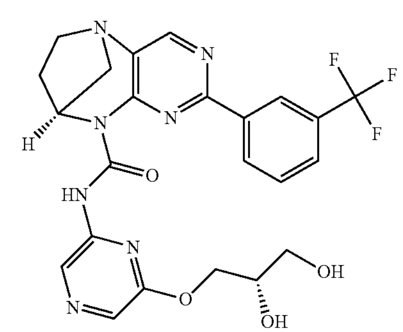


(9S)-N-{5-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

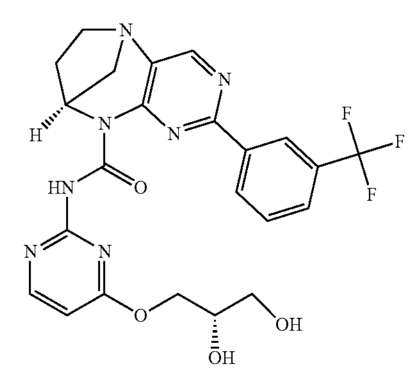
-continued



(9S)-N-{2-[(2R)-2,3-dihydroxypropoxy]pyrimidin-5-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide

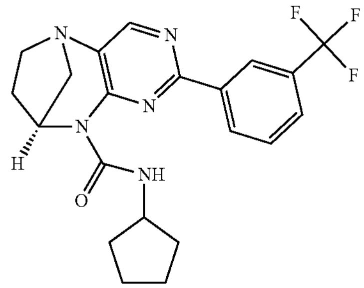


(9S)-N-{6-[(2S)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

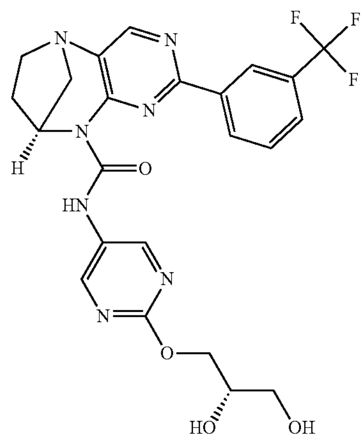


(9S)-N-{4-[(2S)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

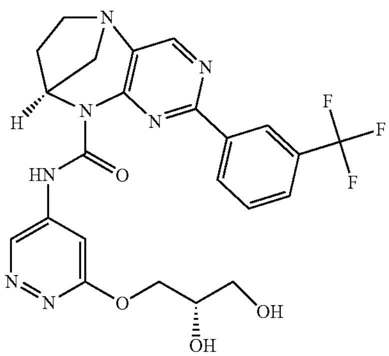
-continued



(9S)-N-cyclopentyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide



(9S)-N-{2-[(2S)-2,3-dihydroxypropoxy]pyrimidin-5-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide



(9S)-N-{6-[(2S)-2,3-dihydroxypropoxy]pyridazin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

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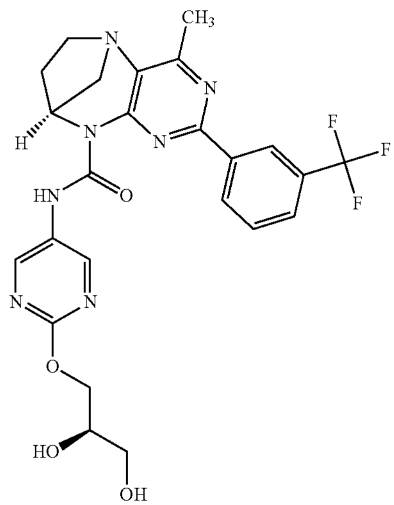
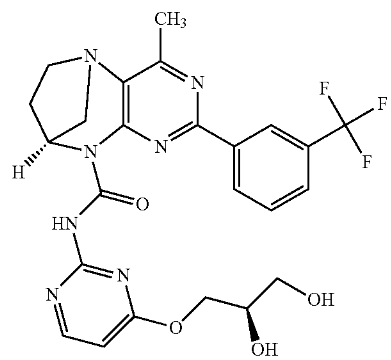
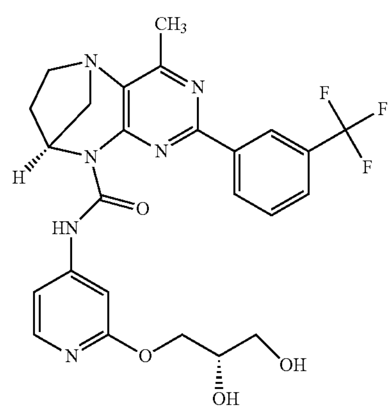


(9S)-N-{2-[(2R)-2,3-dihydroxypropoxy]pyrimidin-5-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide



(9S)-N-{4-[(2R)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide



(9S)-N-{2-[(2S)-2,3-dihydroxypropoxy]pyridin-4-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

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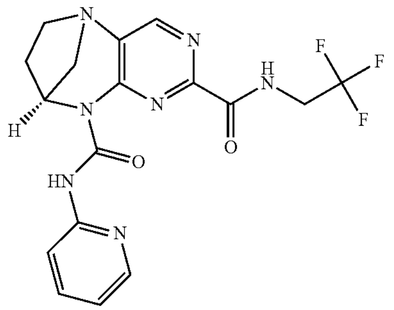
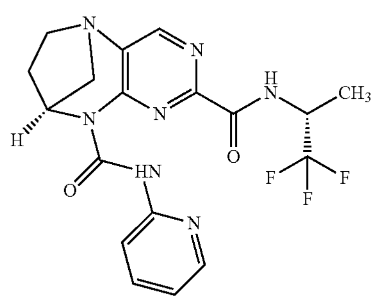
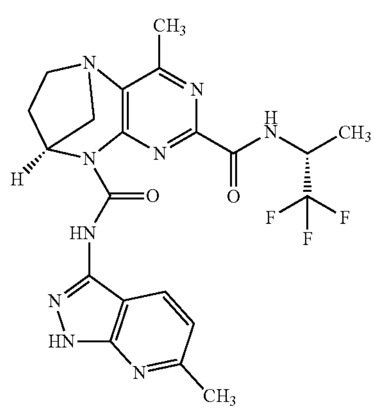


(9S)-8-N-(pyridin-2-yl)-5-N-(2,2,2-trifluoroethyl)-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-5,8-dicarboxamide



(9S)-8-N-(pyridin-2-yl)-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-5,8-dicarboxamide



(9S)-3-methyl-8-N-{6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl}-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-5,8-dicarboxamide

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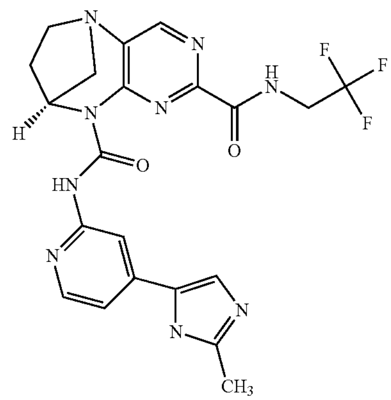
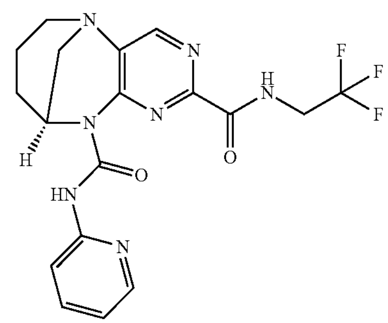
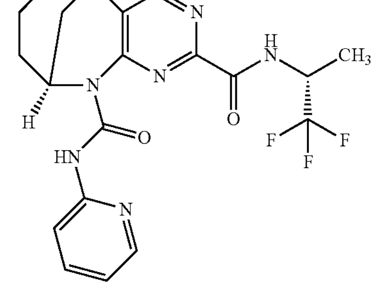


(9S)-8-N-[4-(2-methyl-1,3-oxazol-5-yl)pyridin-2-yl]-5-N-(2,2,2-trifluoroethyl)-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-5,8-dicarboxamide



(9S)-8-N-(pyridin-2-yl)-5-N-(2,2,2-trifluoroethyl)-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]dodeca-2(7),3,5-triene-5,8-dicarboxamide



(9S)-8-N-(pyridin-2-yl)-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]dodeca-2(7),3,5-triene-5,8-dicarboxamide

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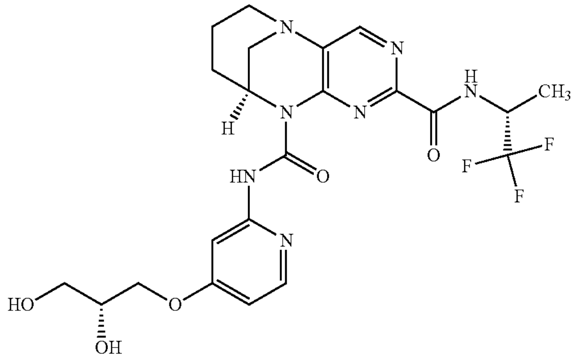
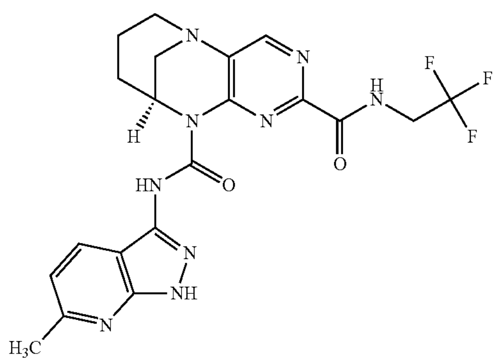
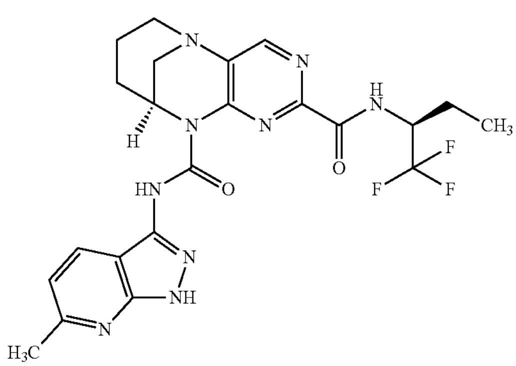


(9S)-8-N-{4-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]dodeca-2(7),3,5-triene-5,8-dicarboxamide



(9S)-8-N-{6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl}-5-N-(2,2,2-trifluoroethyl)-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-5,8-dicarboxamide



ISOMER 1

(9S)-8-N-{6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl}-5-N-[(2S)-1,1,1-trifluoro-3-hydroxypropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-5,8-dicarboxamide

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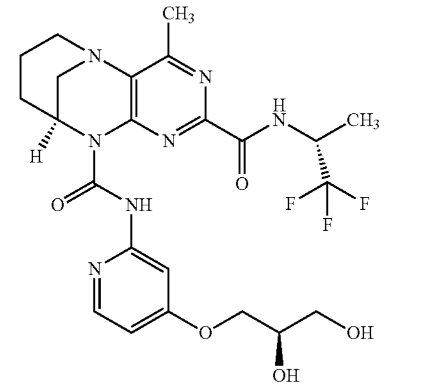
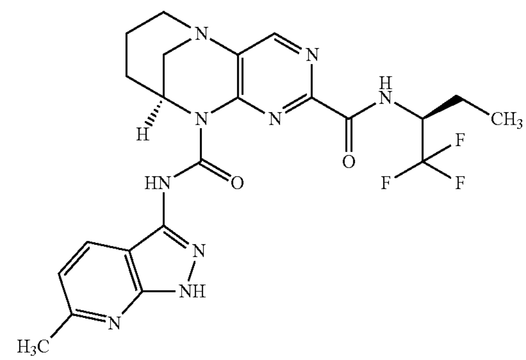
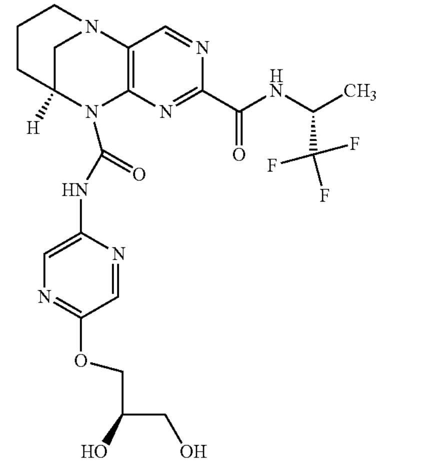


(9S)-8-N-{4-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-3-methyl-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-5,8-dicarboxamide



ISOMER 2

(9S)-8-N-{6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl}-5-N-[(2S)-1,1,1-trifluoro-3-hydroxypropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-5,8-dicarboxamide



(9S)-8-N-{5-[(2R)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-5,8-dicarboxamide

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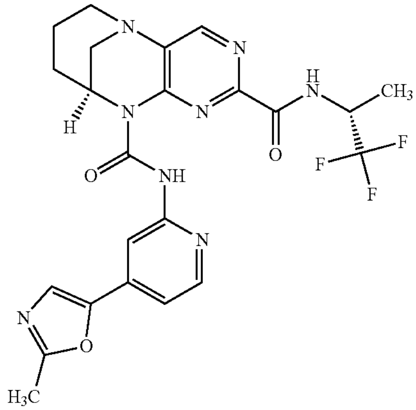
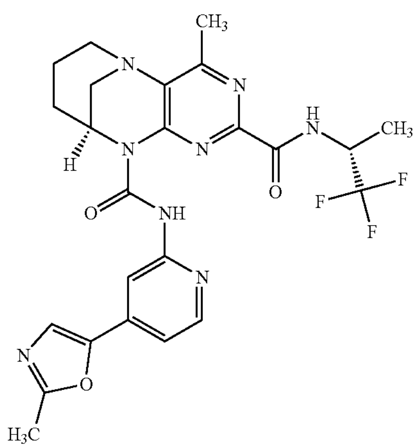


(9S)-8-N-[4-(2-methyl-1,3-oxazol-5-yl)pyridin-2-yl]-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-5,8-dicarboxamide



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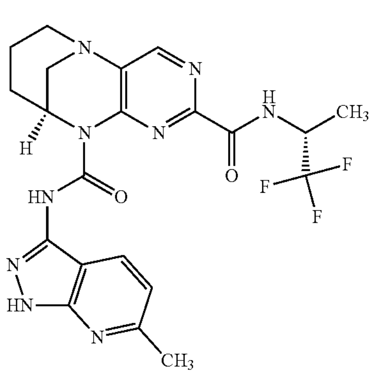

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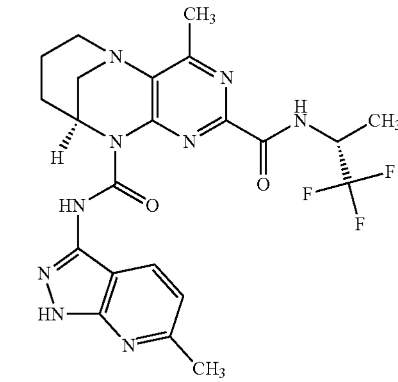

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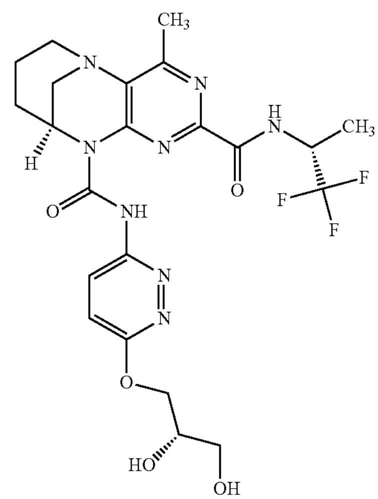

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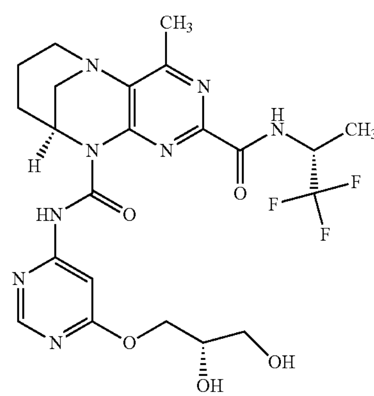

(9S)-8-N-{6-[(2S)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-5,8-dicarboxamide

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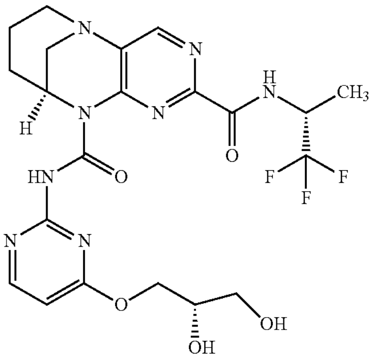
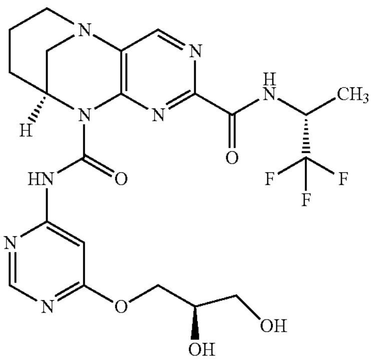


(9S)-8-N-{4-[(2S)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5,8-dicarboxamide



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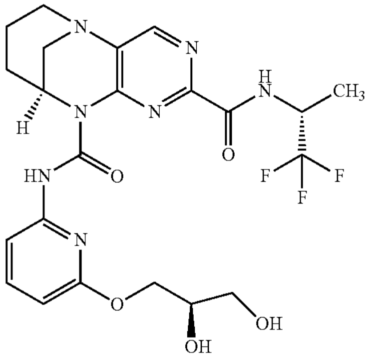

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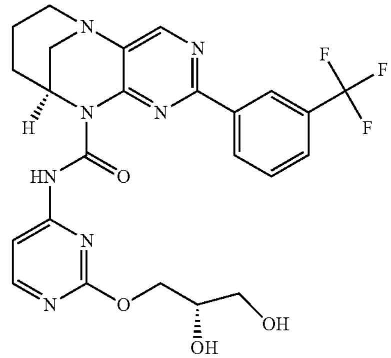

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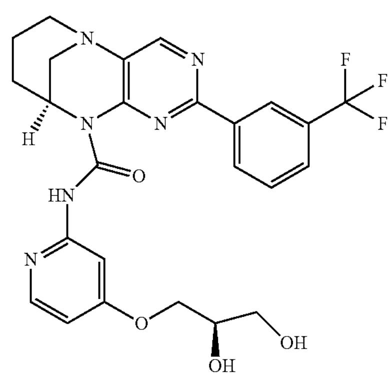

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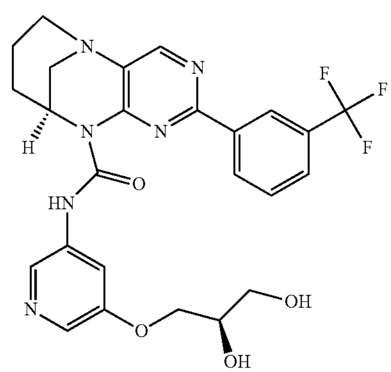

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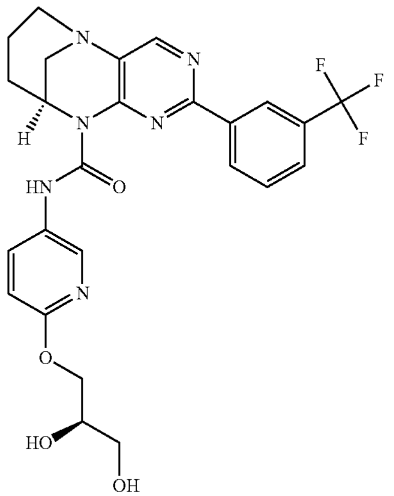
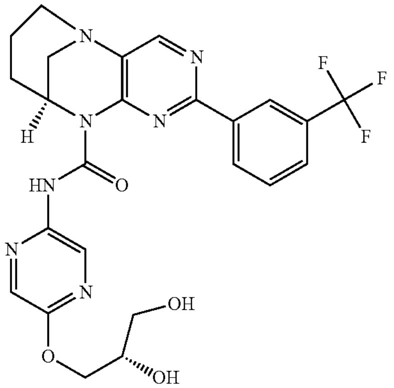


(9S)-N-{6-[(2R)-2,3-dihydroxypropoxy]pyridin-3-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-8-carboxamide



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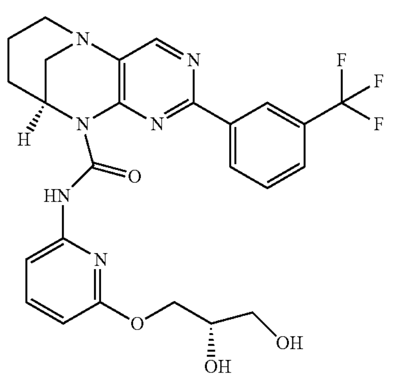

(9S)-N-{6-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-8-carboxamide

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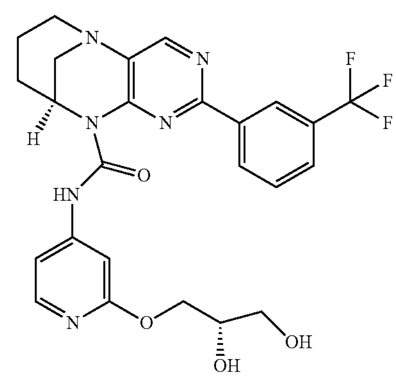

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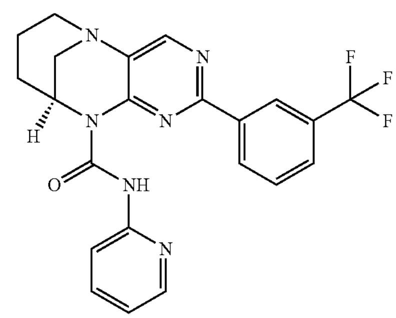
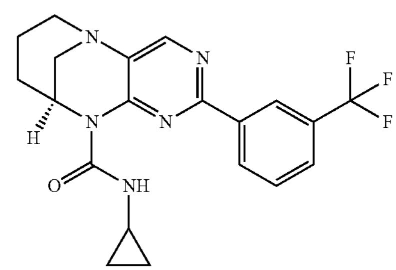
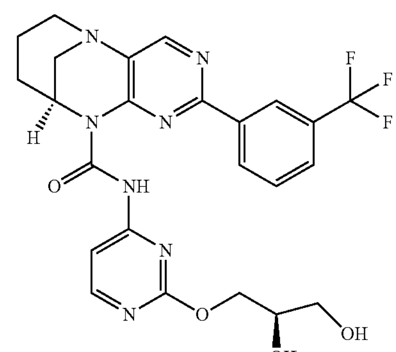


(9S)-N-(pyridin-2-yl)-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2(7),3,5-triene-8-carboxamide



(9S)-N-cyclopropyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2},^{7}]trideca-2,4,6-triene-8-carboxamide



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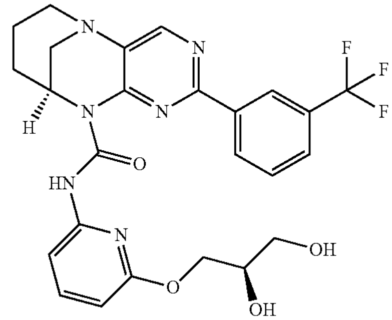

(9S)-N-{6-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-8-carboxamide

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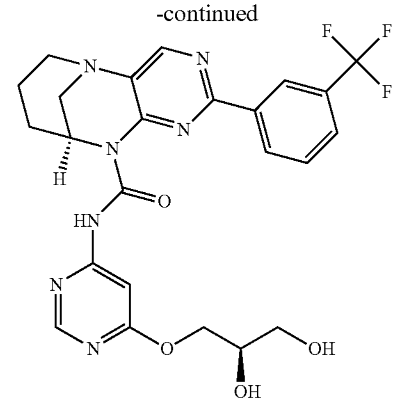
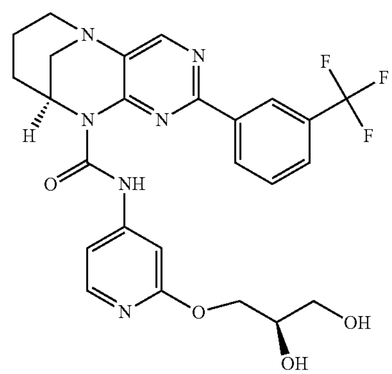
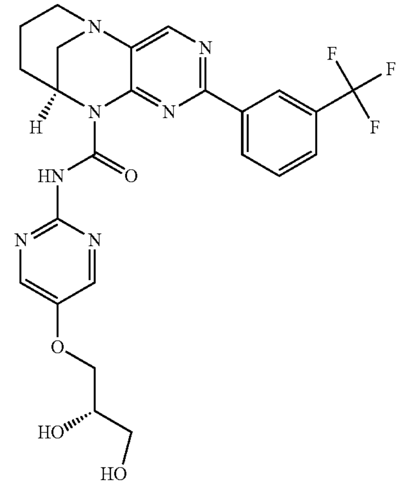


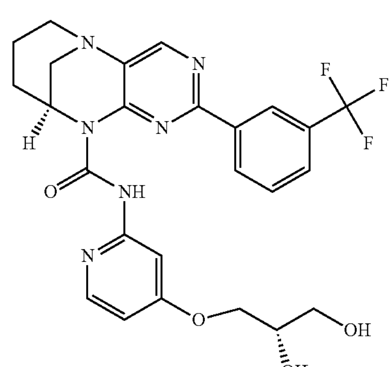
(9S)-N-{6-[(2R)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-8-carboxamide



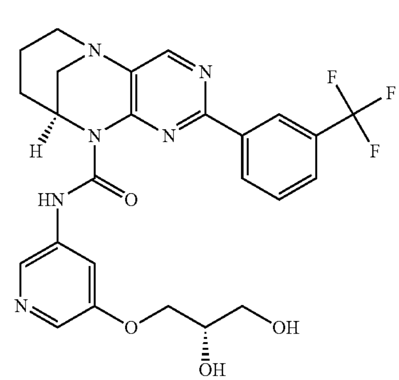
(9S)-N-{2-[(2R)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-8-carboxamide



(9S)-N-{5-[(2S)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-8-carboxamide



(9S)-N-{4-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-8-carboxamide



(9S)-N-{5-[(2S)-2,3-dihydroxypropoxy]pyridin-3-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-8-carboxamide

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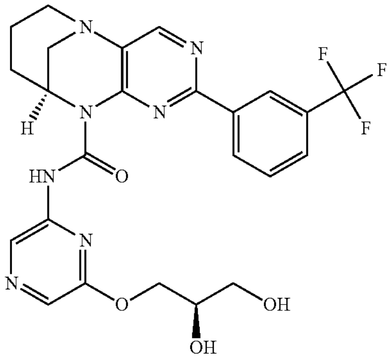
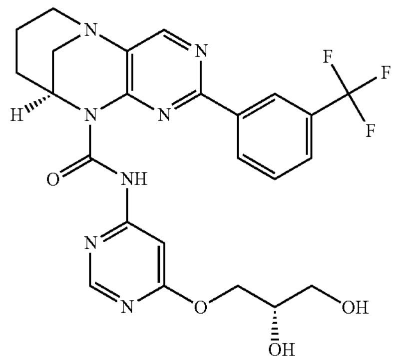


(9S)-N-{6-[(2R)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-8-carboxamide



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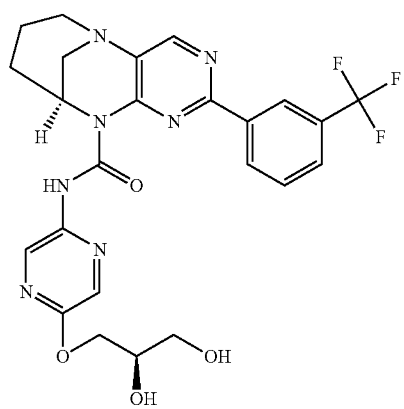

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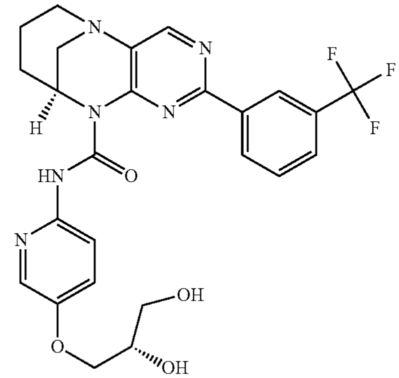

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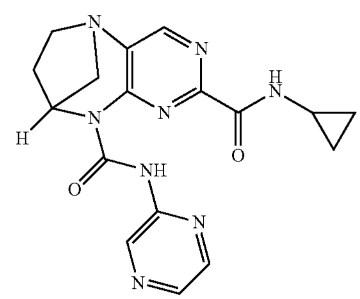

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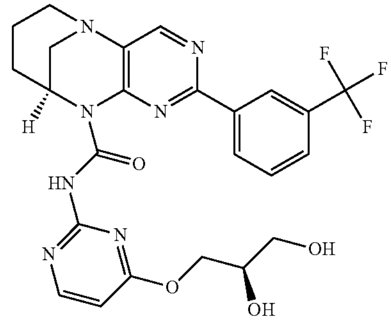

(9S)-N-{4-[(2R)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-8-carboxamide

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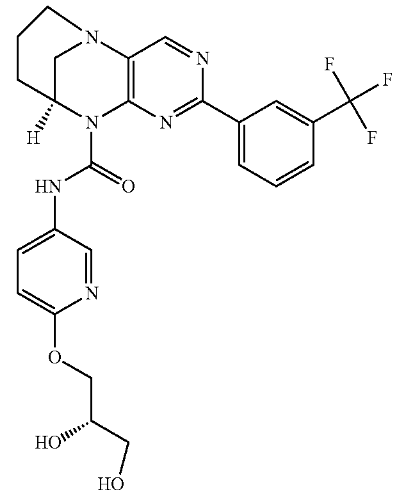

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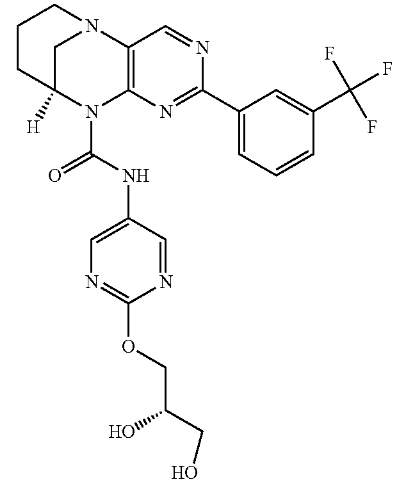

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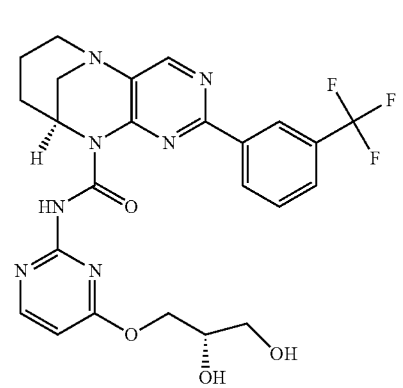

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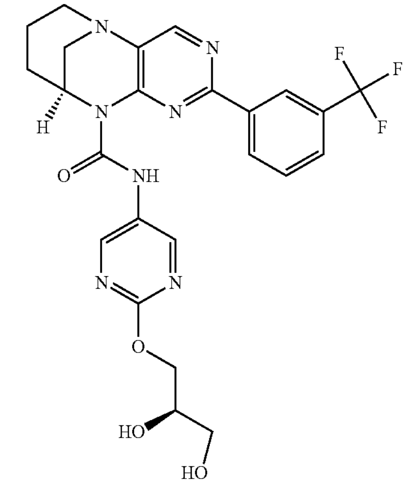
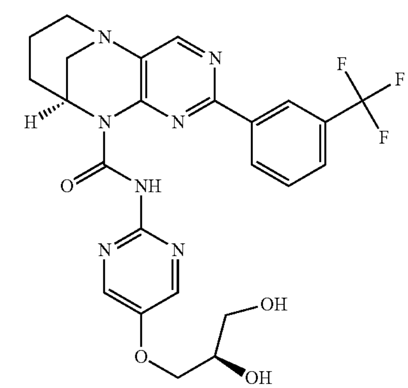
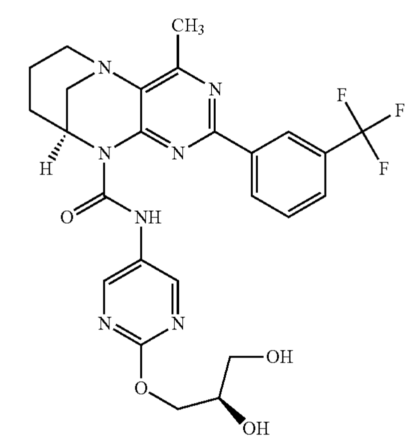


(9S)-N-{2-[(2R)-2,3-dihydroxypropoxy]pyrimidin-5-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-8-carboxamide



(9S)-N-{5-[(2R)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-8-carboxamide



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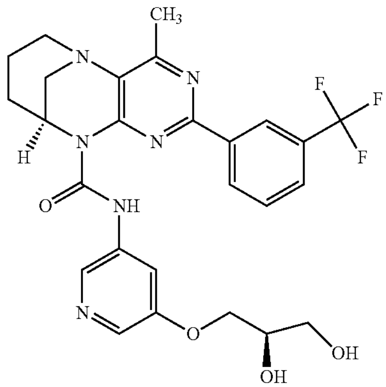
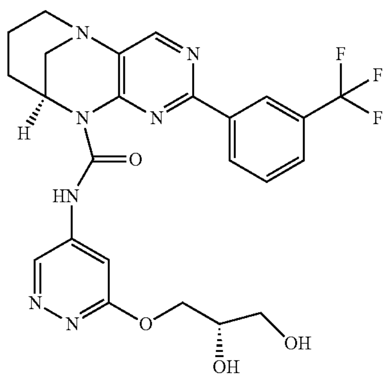
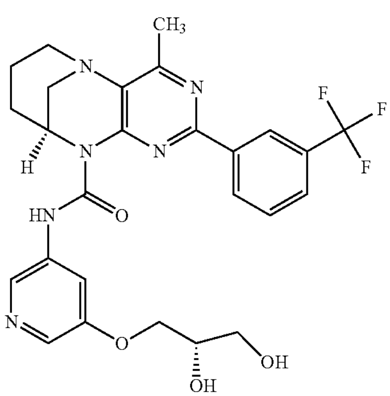


(9S)-N-{5-[(2R)-2,3-dihydroxypropoxy]pyridin-3-yl}-3-methyl-5-[3-[(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-8-carboxamide



(9S)-N-{6-[(2S)-2,3-dihydroxypropoxy]pyridazin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-8-carboxamide



(9S)-N-{5-[(2S)-2,3-dihydroxypropoxy]pyridin-3-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-8-carboxamide

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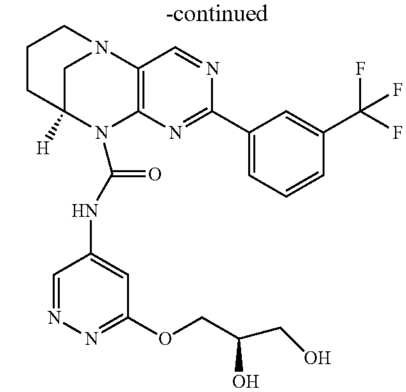

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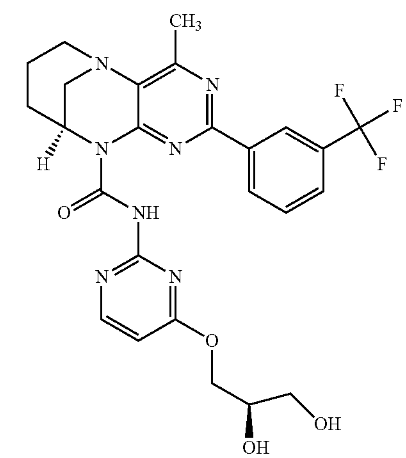
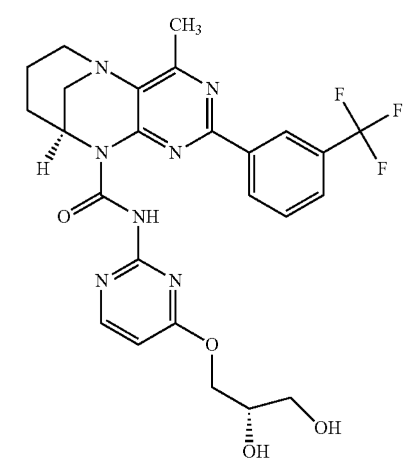


(9S)-N-{4-[(2R)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene-8-carboxamide



(9S)-N-{4-[(2S)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene-8-carboxamide

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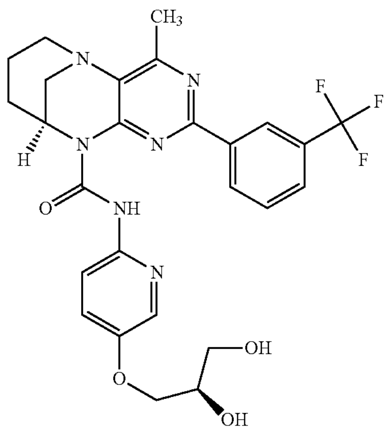
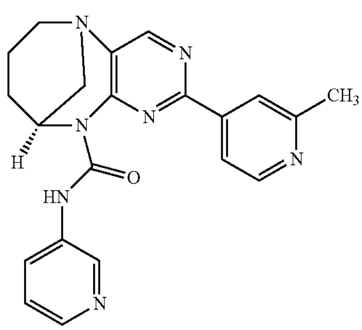
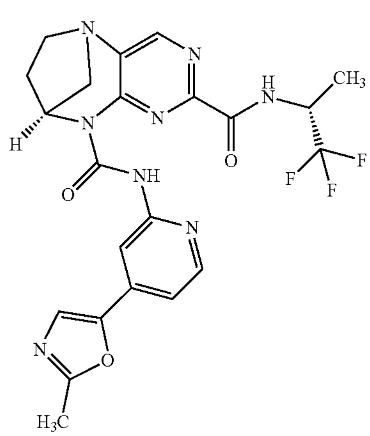


(9S)-N-{5-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-8-carboxamide



(9S)-5-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-8-carboxamide



(9S)-8-N-[4-(2-methyl-1,3-oxazol-5-yl)pyridin-2-yl]-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-5,8-dicarboxamide

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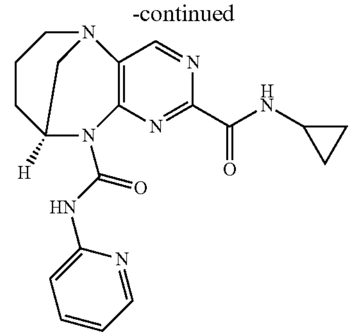
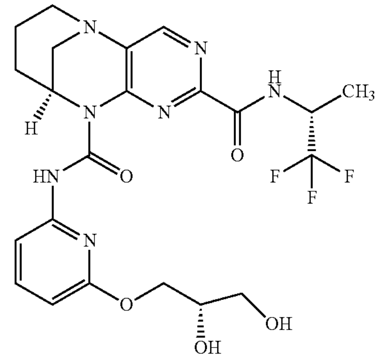
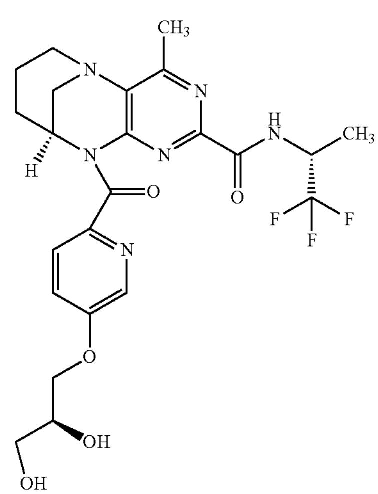


(9S)-5-N-cyclopropyl-8-N-(pyridin-2-yl)-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-5,8-dicarboxamide

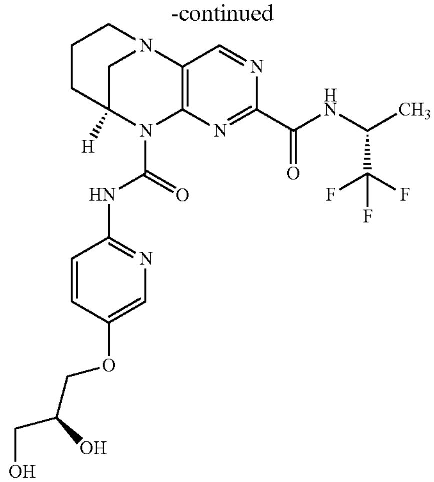


(9S)-8-N-{6-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-5,8-dicarboxamide



(9S)-8-N-{5-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-3-methyl-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-5,8-dicarboxamide

-continued



(9S)-8-N-{5-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-N-[(2R)-1,1,1-trifluoropropan-2-yl]-1,4,6,8-tetraazatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5,8-dicarboxamide

21. A pharmaceutical composition comprising a compound of claim **20** and a pharmaceutically acceptable carrier.

22. The pharmaceutical composition of claim **21** further comprising an additional active agent.

23. A method for treating insulin resistance, a metabolic syndrome, metabolic dysfunctions, diabetes, or complications thereof, or for increasing insulin sensitivity, comprising administering a compound or pharmaceutically acceptable salt according to claim **20** to a subject in need thereof.

24. A method for treating diseases or disorders resulting from diminished SIRT1 expression or activity, which comprises administering a compound or a pharmaceutically acceptable salt thereof according to claim **20** to a subject in need thereof.

25. The method according to claim **24** wherein the diseases or disorders resulting from diminished SIRT1 expression or activity are selected from aging or stress, diabetes, metabolic dysfunctions, neurodegenerative diseases, cardiovascular disease, cancer or inflammatory disease.

26. The method according to claim **24**, wherein diseases or disorders are selected from psoriasis, atopic dermatitis, acne, rosacea, warts, inflammatory bowel disease, Crohn's Disease, ulcerative colitis, osteoporosis, sepis, arthritis, COPD, systemic lupus erythematosus, phthalmic inflammation, alopetia, treatment of wounds, ocular disorders, dry eye, keratitis and uveitis.

27. A method for treating insulin resistance, a metabolic syndrome, metabolic dysfunctions, diabetes, or complications thereof, or for increasing insulin sensitivity, comprising administering a pharmaceutical composition according to claim **21** to a subject in need thereof.

28. A method for treating diseases or disorders resulting from diminished SIRT1 expression or activity, which comprises administering a pharmaceutical composition according to claim **21** to a subject in need thereof.

29. The method according to claim **28** wherein the diseases or disorders resulting from diminished SIRT1 expression or activity are selected from aging or stress, diabetes, metabolic dysfunctions, neurodegenerative diseases, cardiovascular disease, cancer or inflammatory disease.

30. The method according to claim **28**, wherein diseases or disorders are selected from psoriasis, atopic dermatitis, acne, rosacea, warts, inflammatory bowel disease, Crohn's Disease, ulcerative colitis, osteoporosis, sepis, arthritis, COPD, systemic lupus erythematosus, phthalmic inflammation, alopetia, treatment of wounds, ocular disorders, dry eye, keratitis and uveitis.

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