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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 May 2016 (26.05.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/079709 A1

(51) International Patent Classification:
C07D 471/18 (2006.01) *A61P 9/00* (2006.01)
A61K 31/551 (2006.01) *A61P 25/28* (2006.01)
A61P 3/10 (2006.01)

(21) International Application Number:
PCT/IB2015/058977

(22) International Filing Date:
19 November 2015 (19.11.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/081,916 19 November 2014 (19.11.2014) US

(71) Applicant: **GLAXOSMITHKLINE INTELLECTUAL PROPERTY (NO.2) LIMITED** [GB/GB]; 980 Great West Road, Brentford Middlesex TW89GS (GB).

(72) Inventors: **ELLIS, James Lamond**; 1250 South Collegeville Road, Collegeville, Pennsylvania 19426 (US). **EVANS, Karen Anderson**; 1250 South Collegeville Road, Collegeville, Pennsylvania 19426 (US). **FOX, Ryan Michael**; 1250 South Collegeville Road, Collegeville, Pennsylvania 19426 (US). **MILLER, William Henry**; 1250 South Collegeville Road, Collegeville, Pennsylvania 19426 (US). **SEEFELD, Mark Andrew**; 1250 South Collegeville Road, Collegeville, Pennsylvania 19426 (US).

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

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

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

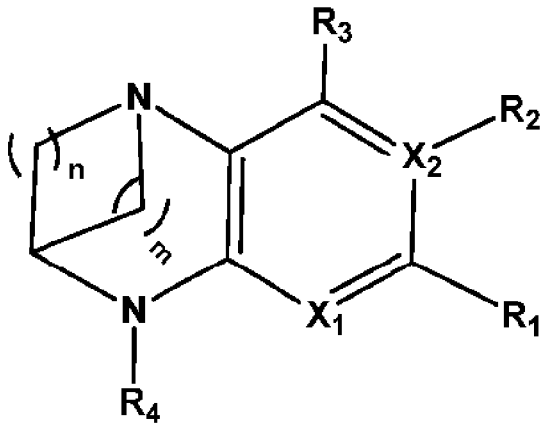
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

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

(54) Title: SUBSTITUTED BRIDGED UREA ANALOGS AS SIRTUIN MODULATORS



(I);

(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 for use 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.

WO 2016/079709 A1

SUBSTITUTED BRIDGED UREA ANALOGS AS SIRTUIN MODULATORS

FIELD OF THE INVENTION

In general, the present invention relates to substituted bridged urea analog compounds of Formulas (I) to (V), corresponding anlogs or derivatives thereof, or pharmaceutically acceptable salts thereof, corresponding pharmaceutical compositions, processes for making, methods and uses 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

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.

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).

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.

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 alsobeen 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.

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.

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).

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.

In addition to therapeutic potential, structural and biophysical studies of SIRT1 activity and activation by small molecule sirtuin modualtors 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.

The present invention is directed to overcoming these and other problems encountered in

the art.

SUMMARY OF THE INVENTION

In general, the present invention relates to substituted bridged urea analog compounds of Formulas (I) to (V), 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.

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

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

The present invention also relates to methods and uses for using Sirtuin Modulator compounds as defined herein in treating, preventing and in therapies for 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

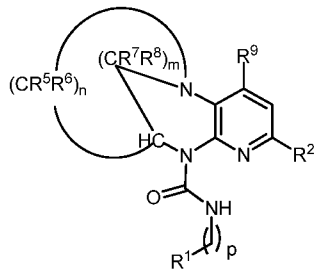
In general, the present invention relates to substituted bridged urea analog compounds of Formulas (I) to (V), corresponding anlogs or derivatives thereof, or pharmaceutically acceptable salts thereof, corresponding pharmaceutical compositions, processes for making and use of such compounds, alone or 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

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

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

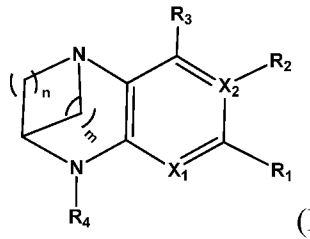


(I), or

a pharmaceutically acceptable salt thereof, corresponding pharmaceutical compositions, combinations with other therapeutic agents, methods for making and methods and 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.

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

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



(I);

where:

X_1 or X_2 independently is selected from -N or -C;

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 $-C(O)-NR_bR_c$;

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

R^4 is hydrogen or $-C(O)NR_bR_c$;

where:

when X_2 is -N, R_2 is non-existent; or

when X_2 is -C, R_2 is as defined above;

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, $-(CH_2)_xOH$, $-C\equiv N$, $-NR_dR_e$, -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, $-O-(CH_2)_xCH(OH)CH_2(OH)$, or $-C(O)OR_f$;

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, $-(CH_2)_xC_1.C_6$-cycloalkyl, heterocyclyl, -N-heterocyclyl, aryl, heteroaryl, or $-(CH_2)_x$heteroaryl, $-(CHR_g)_x$heteroaryl;

where:

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

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-$(CH_2)_xCH(OH)CH_2(OH)$, -$(CH_2)_x$-OH, or -C(O)-OH;

m is an integer from 1 to 3;

n is an integer selected from 1 to 3;

x is 0 or an integer from 1 to 6; or

a pharmaceutically salt thereof.

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 (V)**, respectively corresponding analogs (i.e., with hydrogen substitution at the R^2 position) and throughout the instant application, where it is provided that:

when n = 1, m ≠ 1; and

when n = 3, m ≠ 3.

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.

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

m is 1;

n is 2 or 3; and

R^4 is hydrogen.

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

m is 1;

n is 2 or 3; and

R^4 is –C(O)NR_bR_c, wherein each R_b and R_c is as defined above.

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

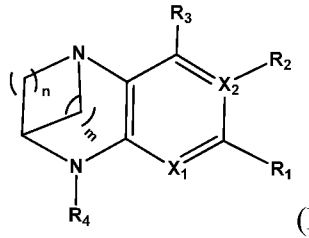
m is 1;

n is 2 or 3;

R^1 is hydrogen, halogen, -CN, carbocyclyl, heterocyclyl, -N-substituted heterocyclyl, aryl or heteroaryl; and

R4 is –C(O)NRbRc, wherein Rb and Rc is as defined above in claim 1.

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



(II);

where:

X_1 or X_2 independently is selected from -N or -C;

R^1 is hydrogen, halogen, -CN, carbocyclyl, heterocyclyl, -N-substituted heterocyclyl, aryl or heteroaryl;

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;

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

R^4 is hydrogen or –C(O)NR_bR_c;

where:

when X_2 is -N, R_2 is non-existent; or

when X_2 is -C, R_2 is as defined above;

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;

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;

where:

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

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-$(CH_2)_xCH(OH)CH_2(OH)$, -$(CH_2)_x$-OH, or -C(O)-OH;

m is an integer from 1 to 3;

n is an integer selected from 1 to 3;

x is 0 or an integer from 1 to 6; or

a pharmaceutically salt thereof.

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 (V)**, respectively corresponding analogs (i.e., with hydrogen substitution at the R^2 position) and throughout the instant application, where it is provided that:

when n = 1, m ≠ 1; and

when n = 3, m ≠ 3.

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.

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

m is 1;

n is 2 or 3; and

R^4 is hydrogen.

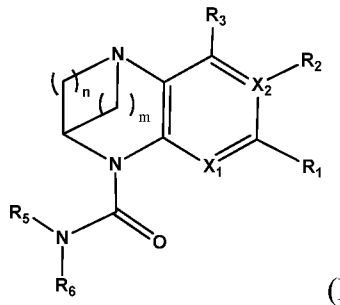
In another aspect, the present invention relates to a compound of Formula (I), where:

m is 1;

n is 2 or 3; and

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

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



(III);

where:

X_1 or X_2 independently is selected from -N or -C;

where:

when X_2 is -N, R_2 is non-existent; or

when X_2 is -C, R_2 is as defined above;

R^1 is hydrogen, halogen, -CN, carbocyclyl, heterocyclyl, -N-substituted heterocyclyl, aryl or heteroaryl;

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;

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

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, -$(CH_2)_xC_1$.C_6cycloalkyl, heterocyclyl, -N-heterocyclyl, aryl, heteroaryl, or -$(CH_2)_x$heteroaryl, -$(CHR_g)_x$heteroaryl;

wherein:

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-$(CH_2)_xCH(OH)CH_2(OH)$, or $-C(O)OR_f$;

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, -$(CH_2)_xC_1$-C_6-cycloalkyl, heterocyclyl, -N-heterocyclyl, aryl, heteroaryl, or -$(CH_2)_x$heteroaryl;

where:

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;

where:

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;

m is an integer from 1 to 3;

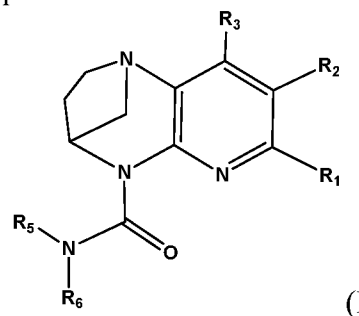
n is an integer selected from 2 to 3;

x is 0 or an integer from 1 to 6; or

a pharmaceutically salt thereof.

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

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



(IV);

where:

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;

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

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, -$(CH_2)_xC_1$.C_6cycloalkyl, heterocyclyl, -N-heterocyclyl, aryl, heteroaryl, or -$(CH_2)_x$heteroaryl, -$(CHR_g)_x$heteroaryl;

where:

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;

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, -$(CH_2)_xC_1$.C_6-cycloalkyl, heterocyclyl, -N-heterocyclyl, aryl, heteroaryl, or -$(CH_2)_x$heteroaryl;

where:

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;

where:

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;

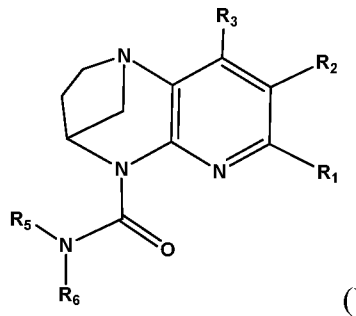
m is an integer from 1 to 3;

n is an integer selected from 2 to 3;

x is 0 or an integer from 1 to 6; or

a pharmaceutically salt thereof.

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



(V);

where:

R^1 is hydrogen, halogen, -CN, carbocyclyl, heterocyclyl, -N-substituted heterocyclyl, aryl, or heteroaryl;

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;

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

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, -$(CH_2)_xC_1$.C_6cycloalkyl, heterocyclyl, -N-heterocyclyl, aryl, heteroaryl, or -$(CH_2)_x$heteroaryl, -$(CHR_g)_x$heteroaryl;

where:

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;

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, -$(CH_2)_xC_1$.C_6-cycloalkyl, heterocyclyl, -N-heterocyclyl, aryl, heteroaryl, or -$(CH_2)_x$heteroaryl;

where:

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;

where:

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;

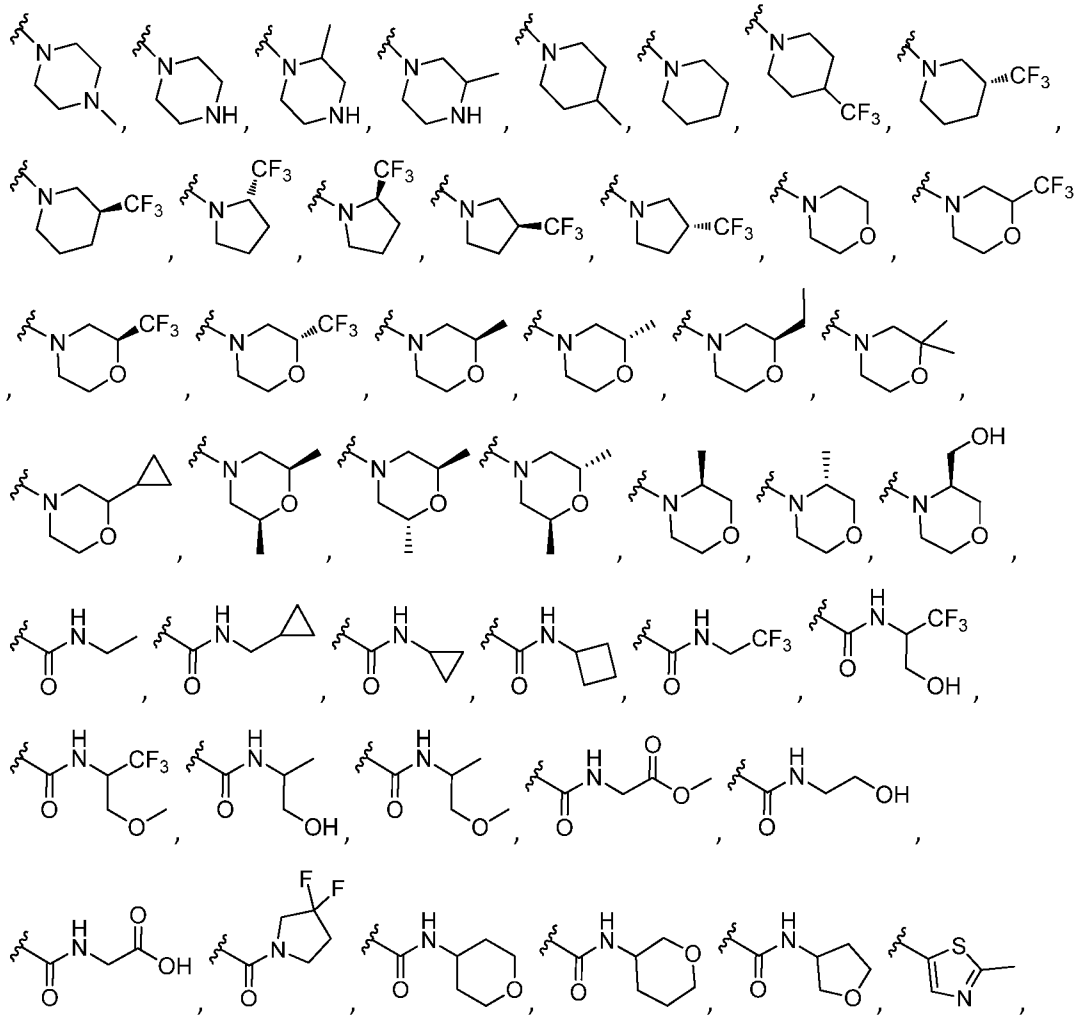
m is an integer from 1 to 3;

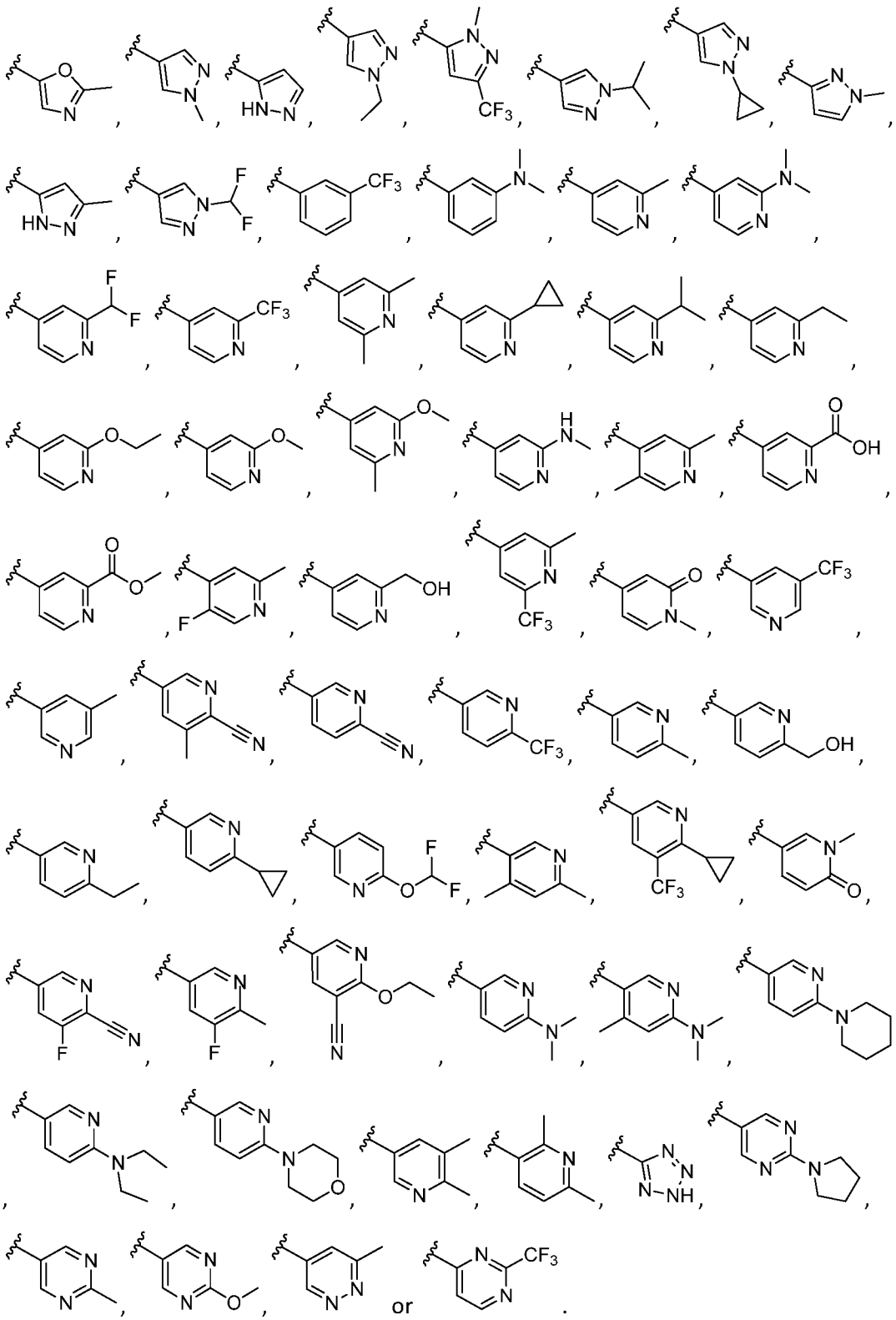
n is an integer selected from 2 to 3;

x is 0 or an integer from 1 to 6; or

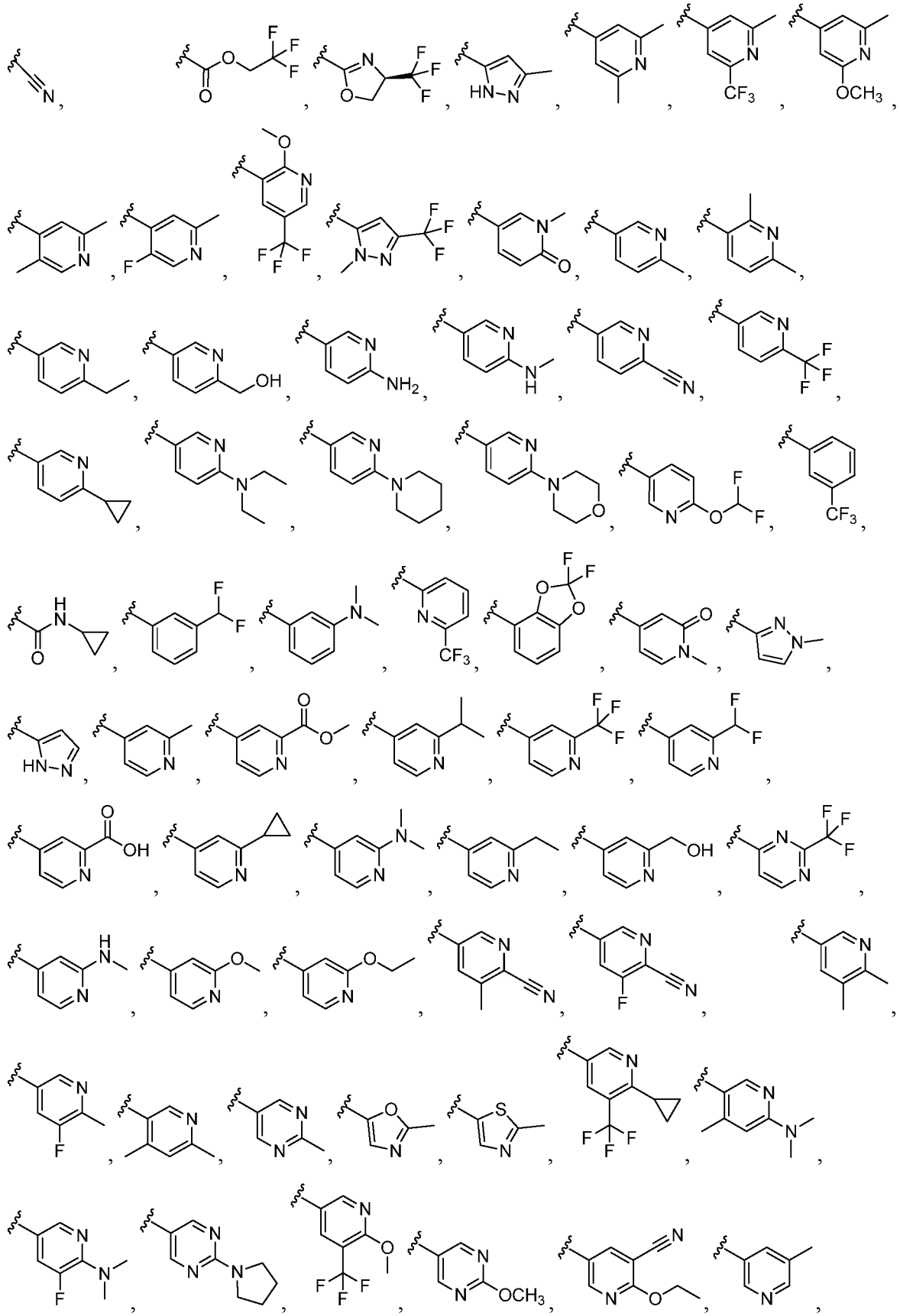
a pharmaceutically salt thereof.

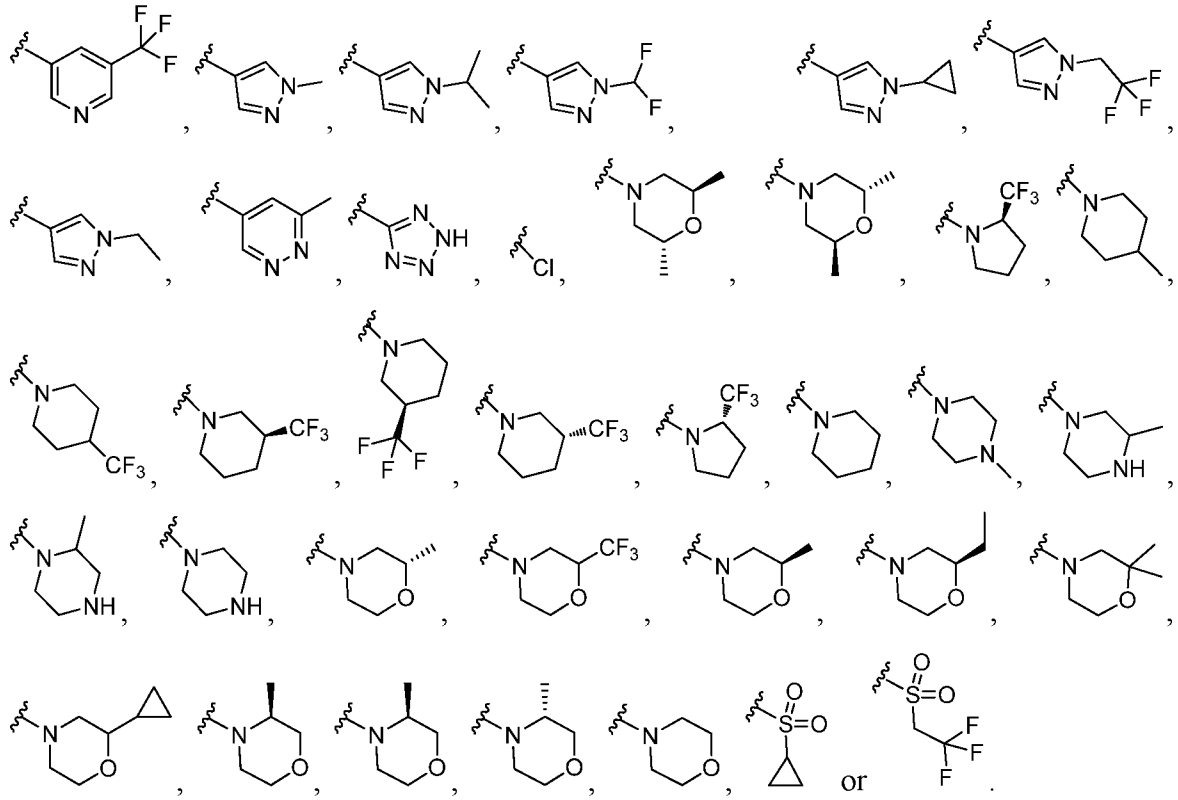
In another aspect, the present invention relates to compounds of Formulas (I) to (V), respectively, wherein R^1 is selected from:



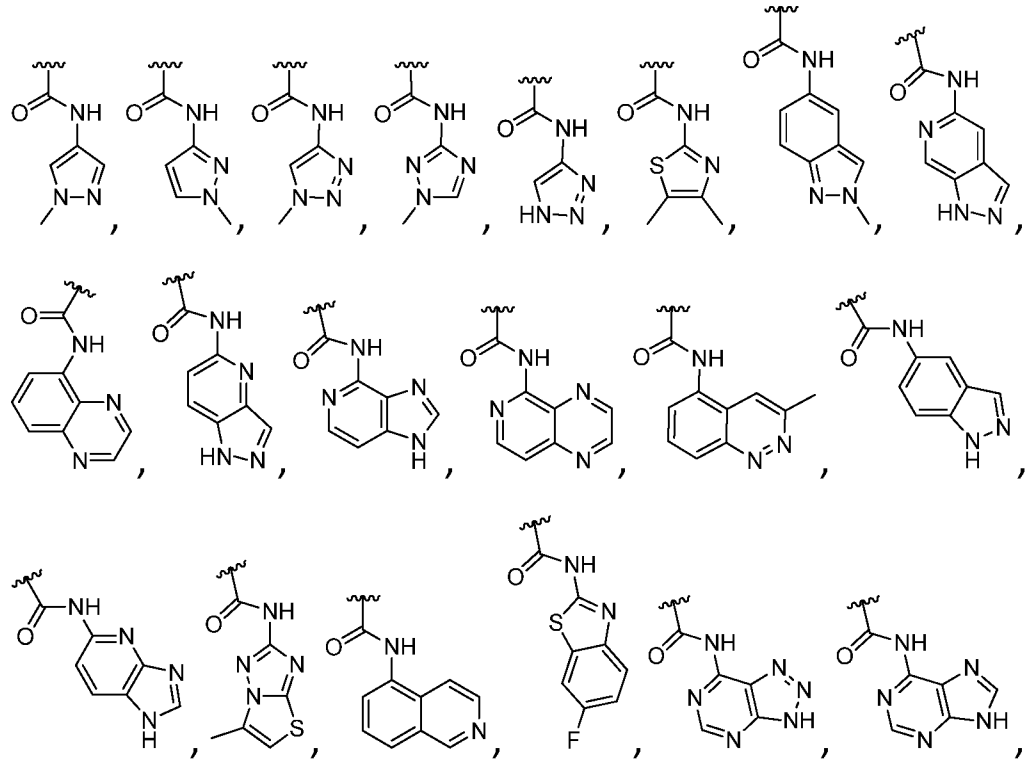


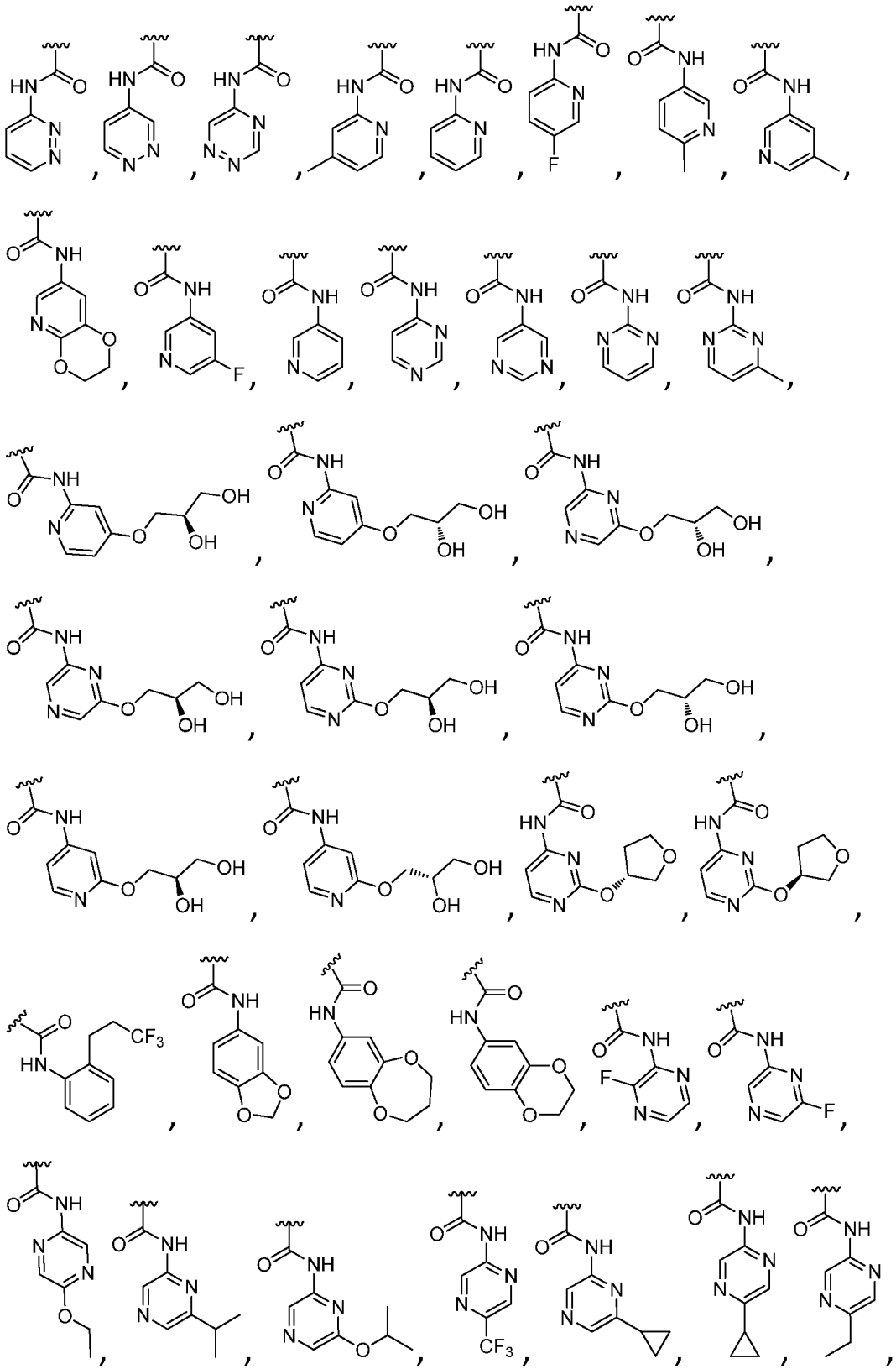
In another aspect, the present invention relates to compounds of Formulas (I) to (V), respectively, wherein R^1 is selected from:

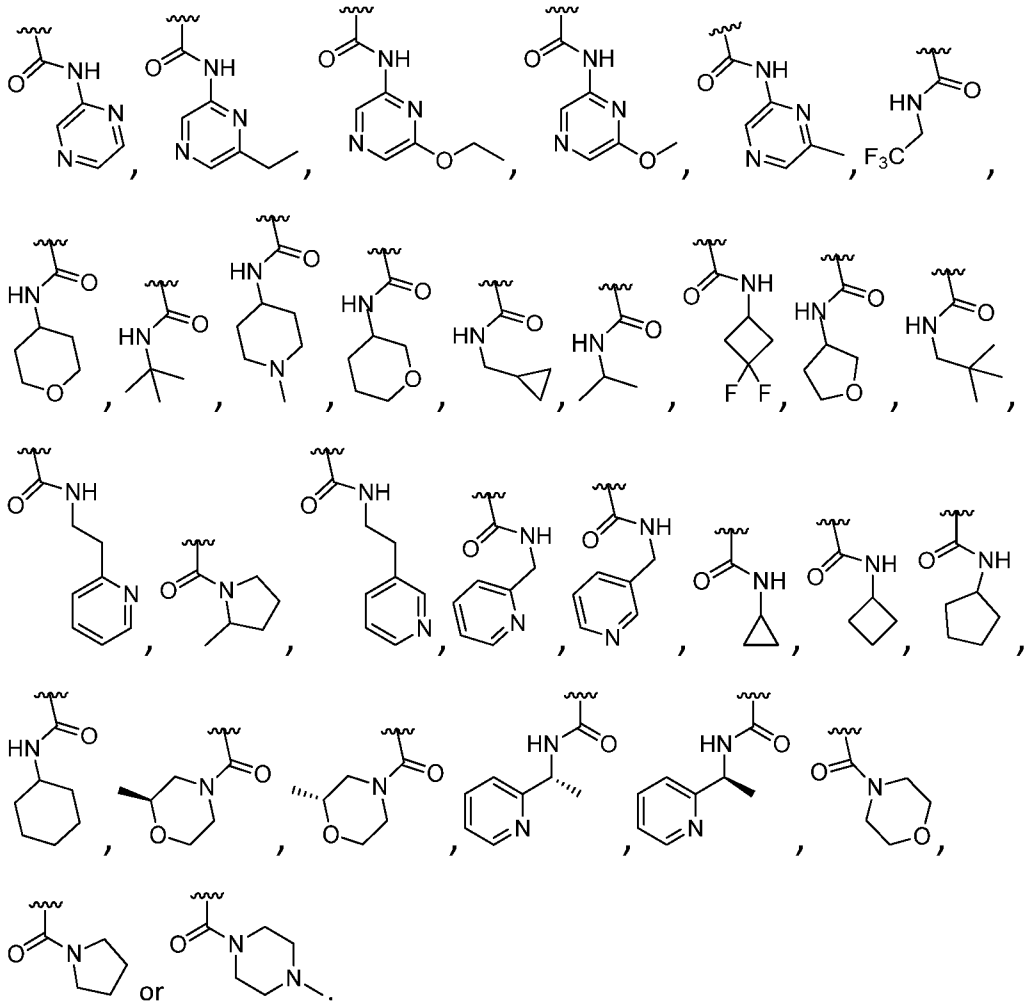




In another aspect, the present invention relates to compound(s) of Formulas (I) to (V), respectively, where R^4 is selected from:

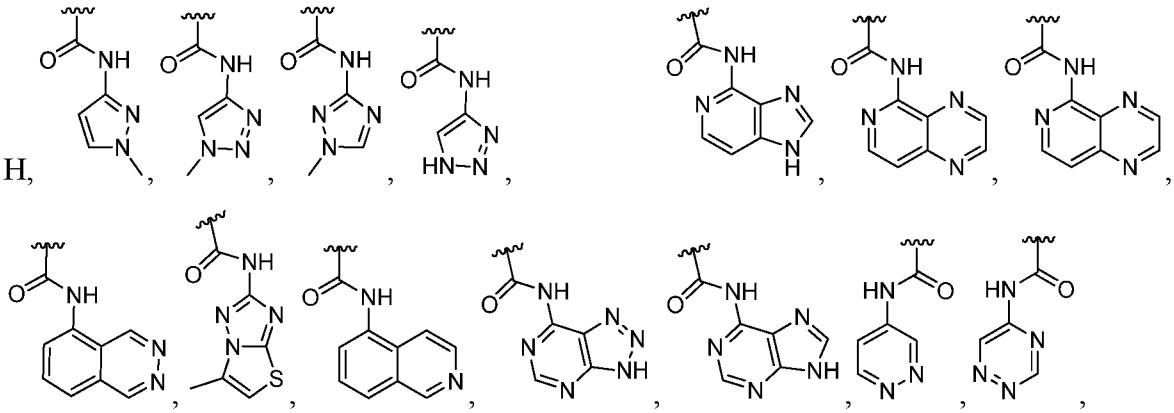


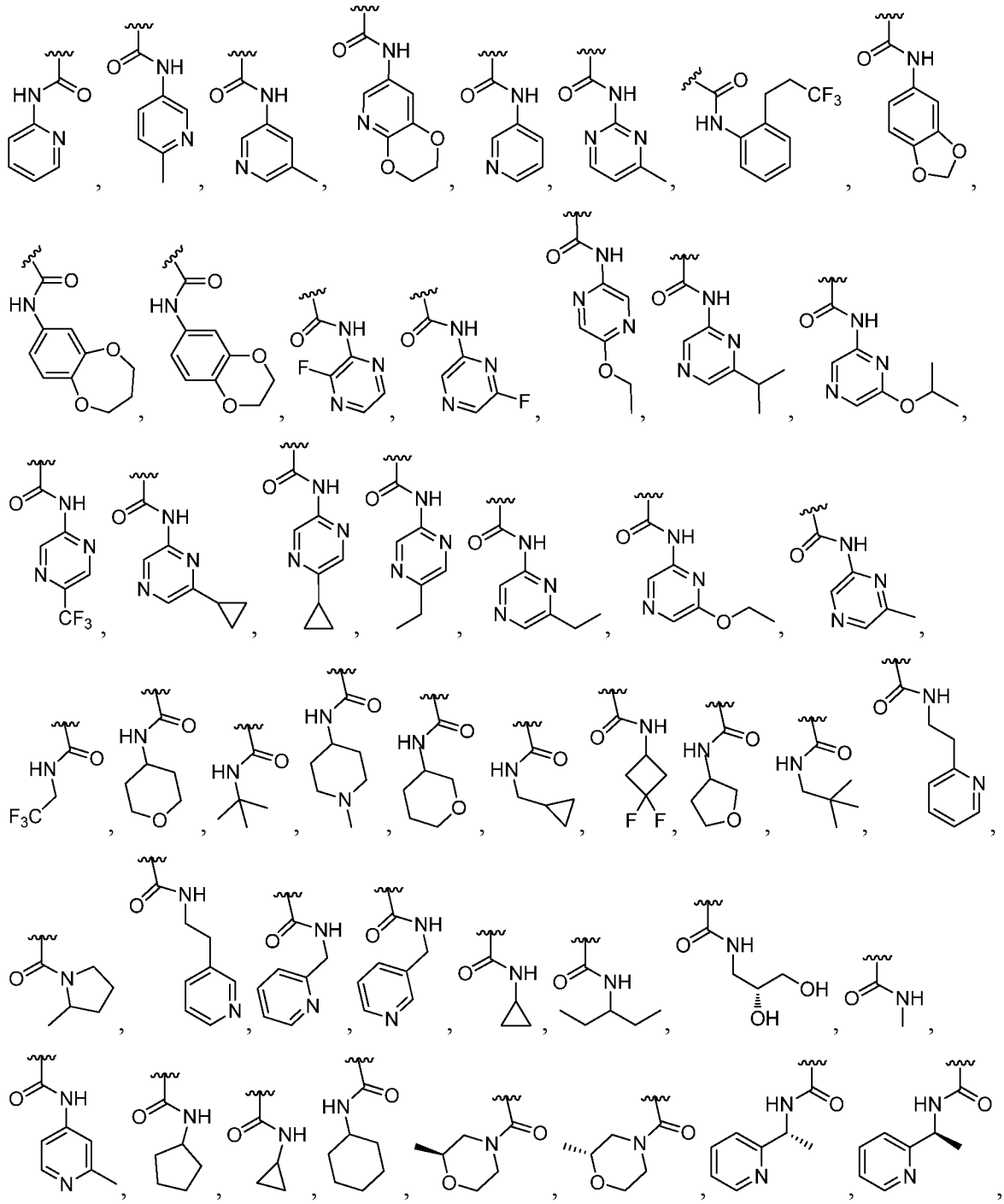


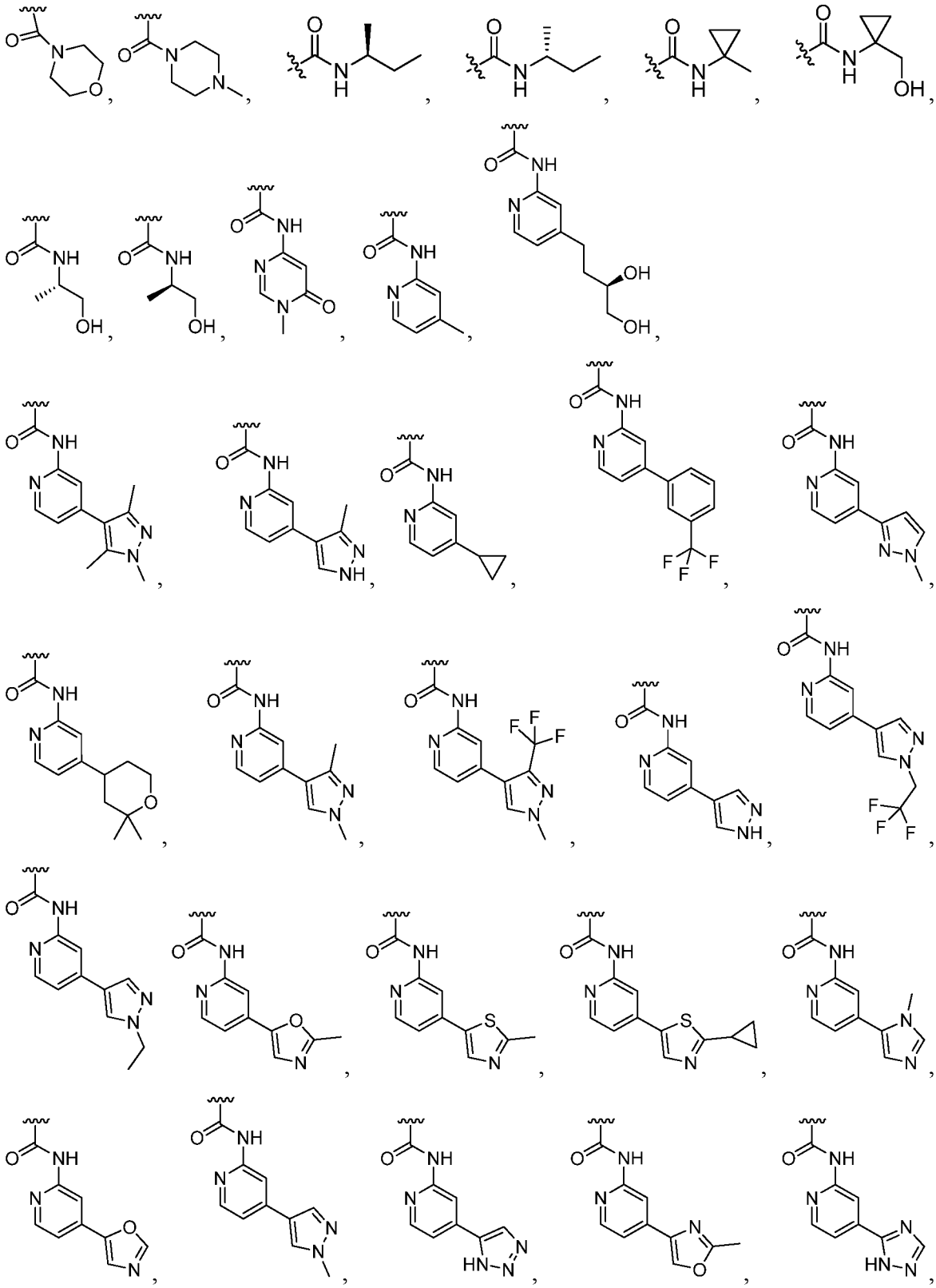


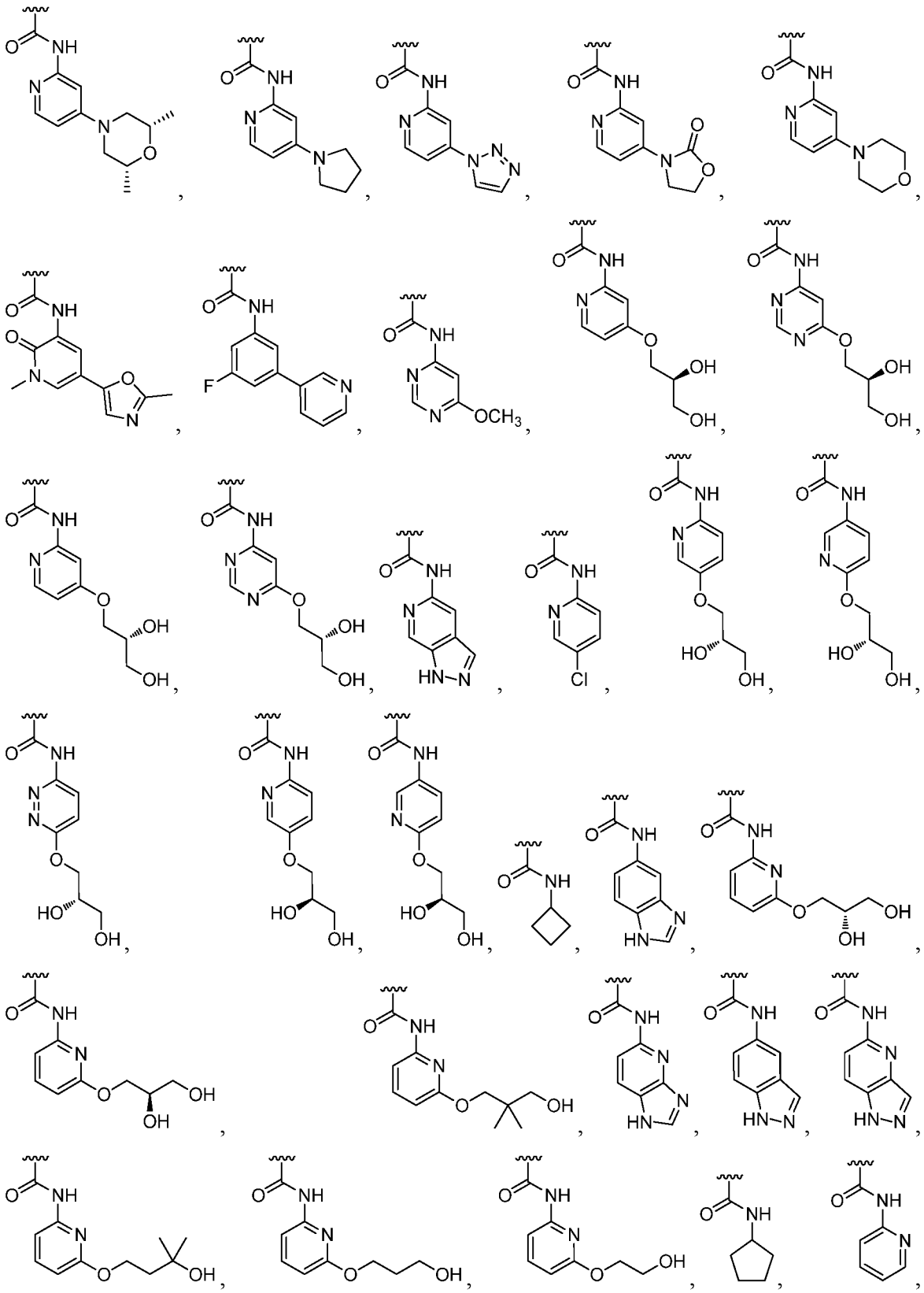
In another aspect, the present invention relates to compound(s) of Formulas (I) to (V), respectively, where R^4 is selected from:

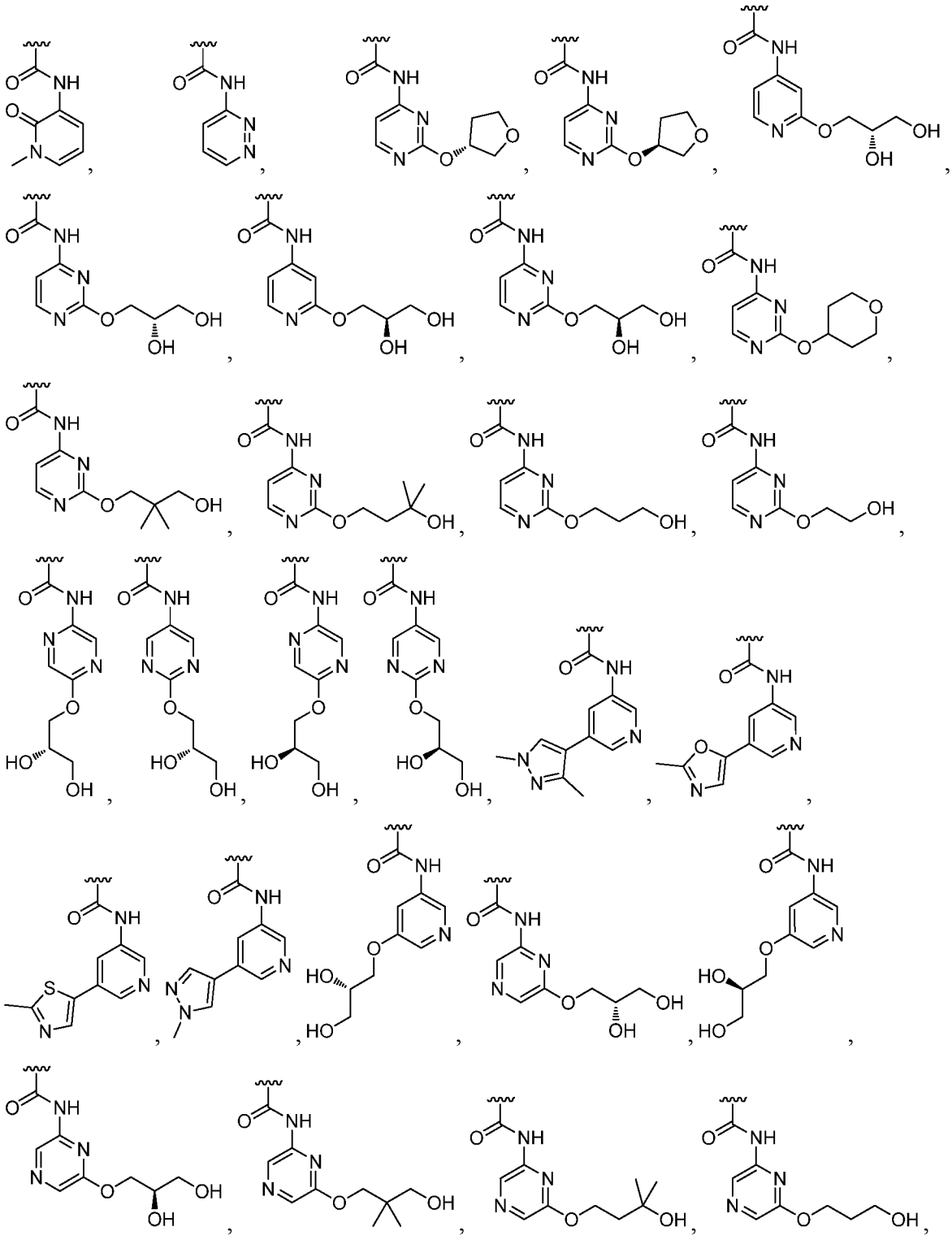
H,

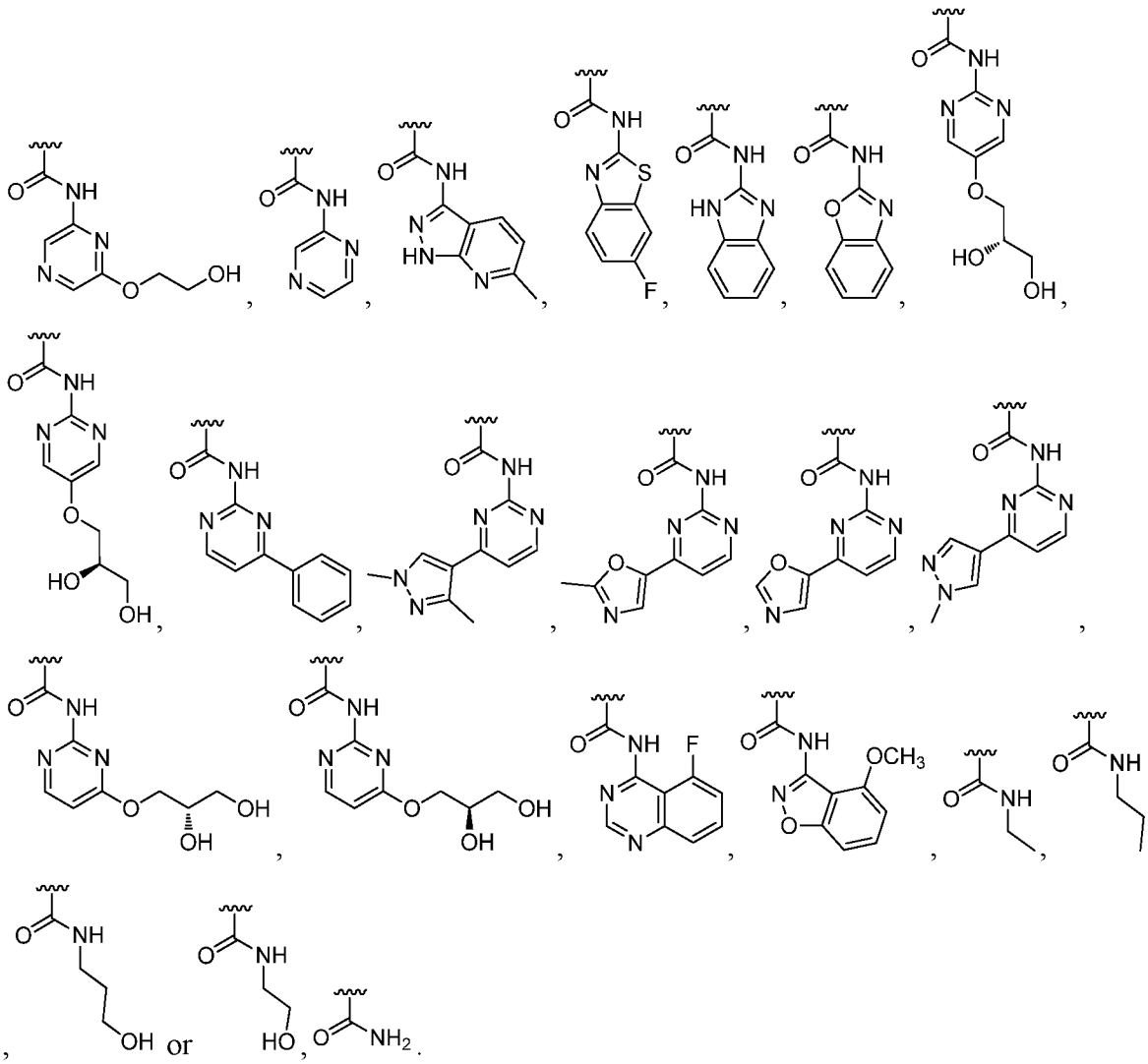










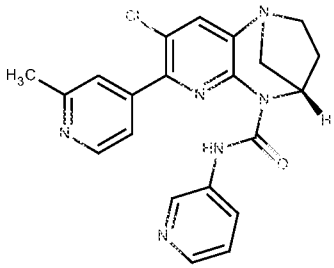
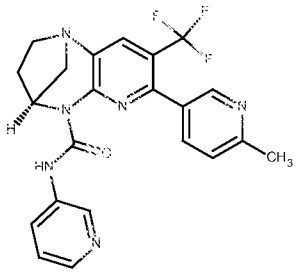
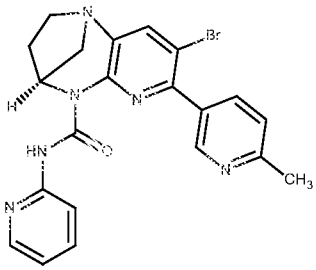
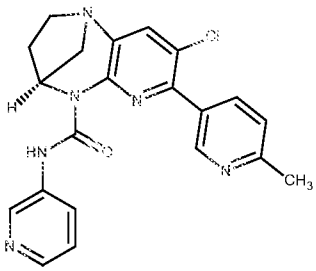


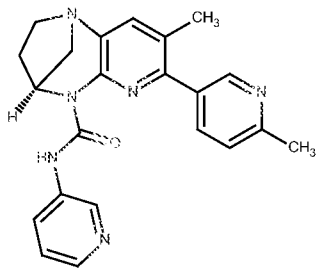
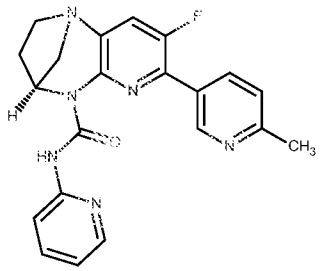
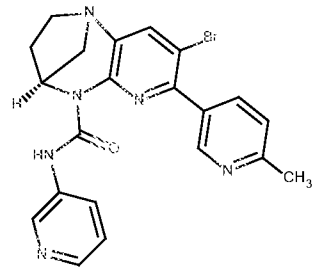
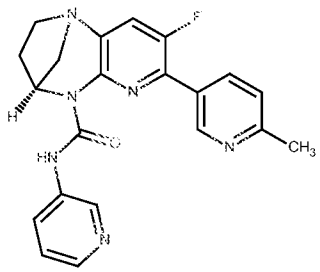
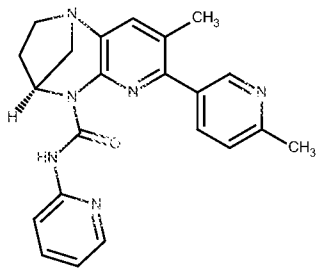
5

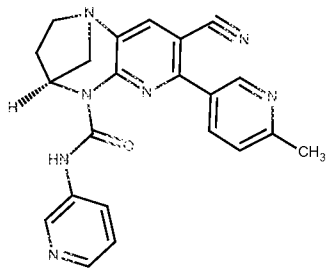
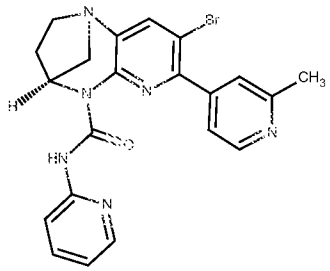
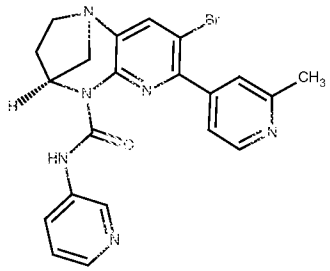
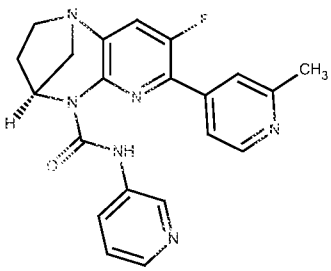
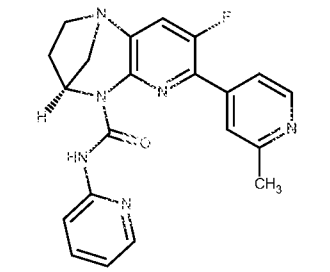
In another aspect, the present invention relates to a compound which is as defined in Table 1 of the instant specification starting at page 684:

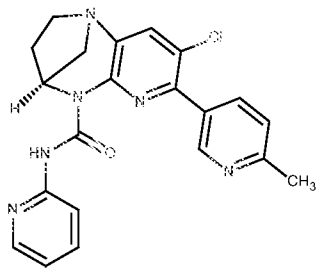
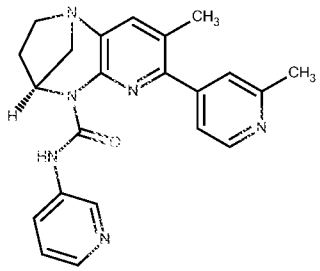
In another aspect, the present invention relates to a compound, which include, but are not limitd to compounds, as defined in the Charts set forth below set forth below:

Chart 1

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

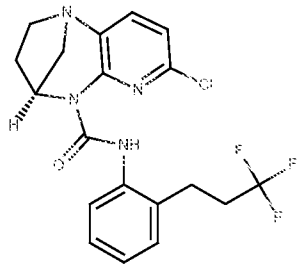
Structure	Chemical Name: Generated by ChemAxon
	(9S)-4-methyl-5-(6-methylpyridin-3-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-4-fluoro-5-(6-methylpyridin-3-yl)-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide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

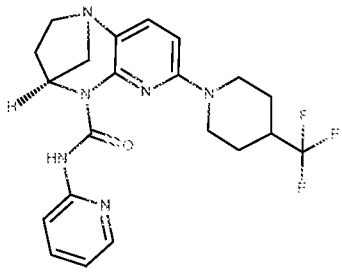
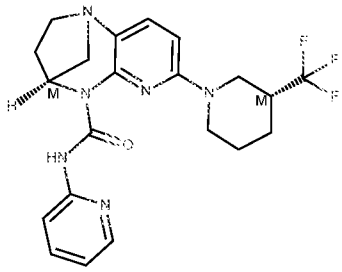
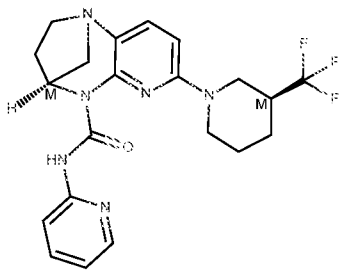
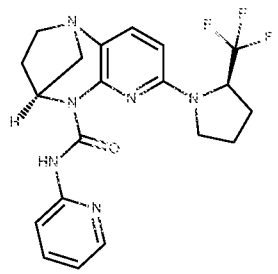
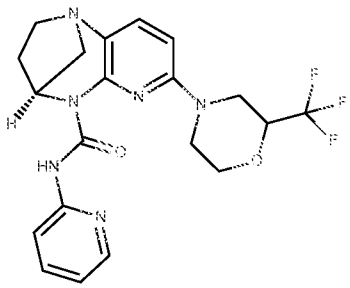
Structure	Chemical Name: Generated by ChemAxon
	(9S)-4-cyano-5-(6-methylpyridin-3-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-4-bromo-5-(2-methylpyridin-4-yl)-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-4-bromo-5-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-1,6,8-triaz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

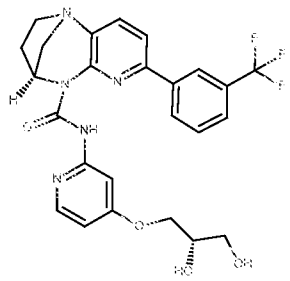
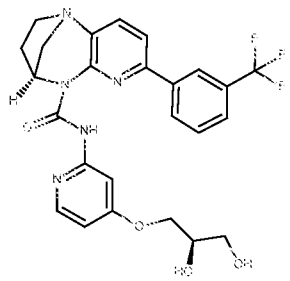
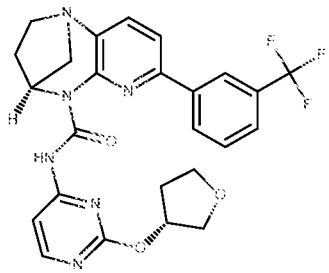
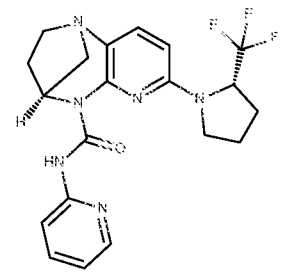
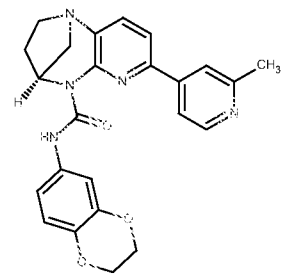
Structure	Chemical Name: Generated by ChemAxon
	(9S)-4-chloro-5-(6-methylpyridin-3-yl)-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-4-methyl-5-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

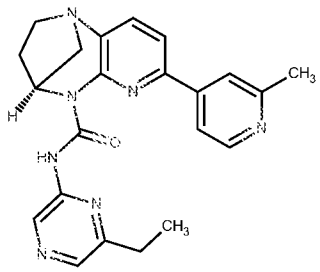
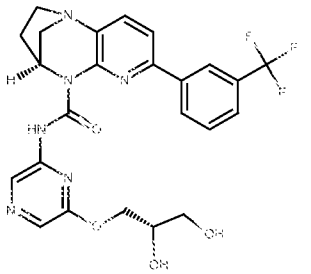
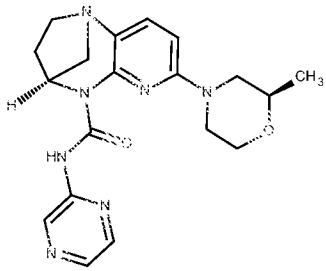
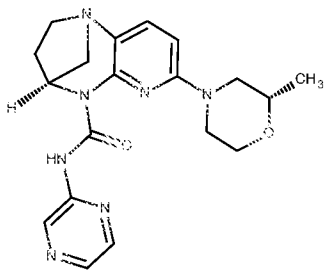
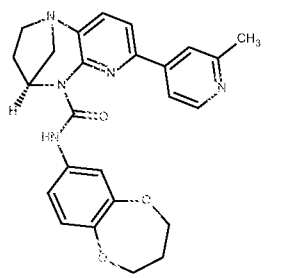
In another aspect, the present invention relates to a compound which is a corresponding analog or derivative of the present invention s (i.e., with hydrogen substitution at the R^2 position):

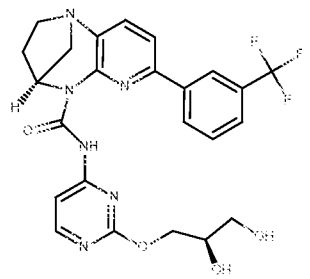
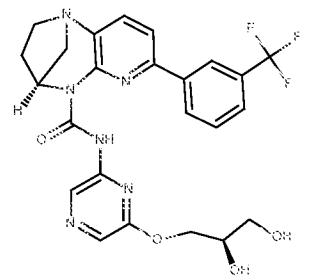
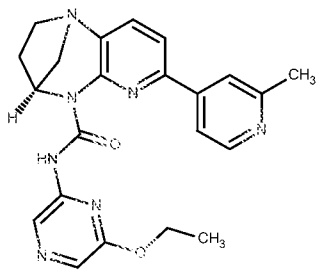
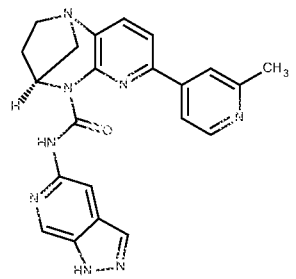
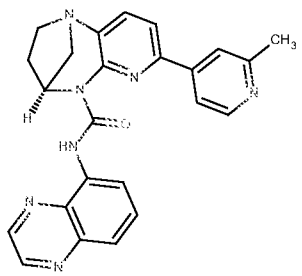
Chart 2 - No Meta Substitution Pyridine Compounds

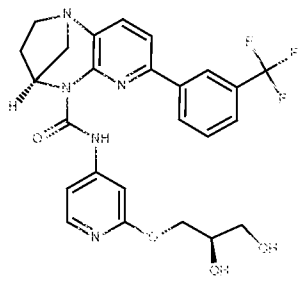
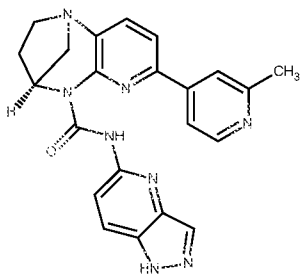
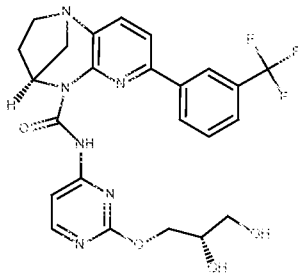
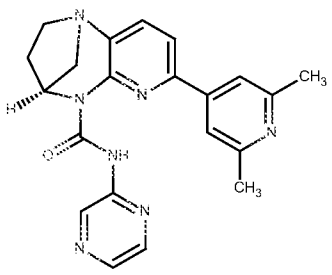
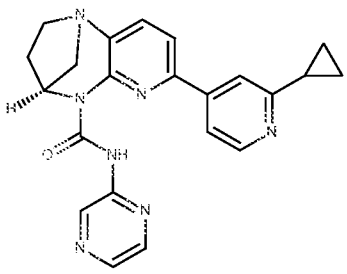
Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-chloro-N-[2-(3,3,3-trifluoropropyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

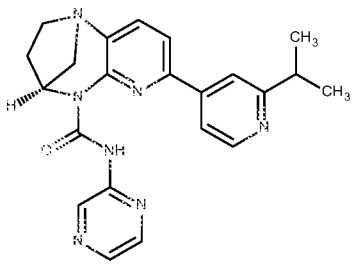
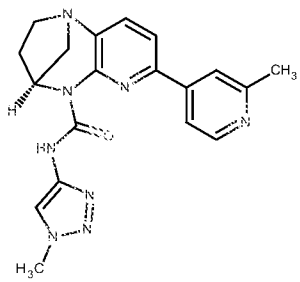
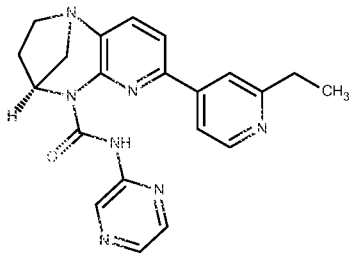
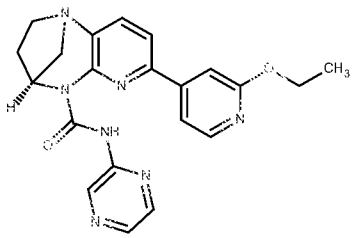
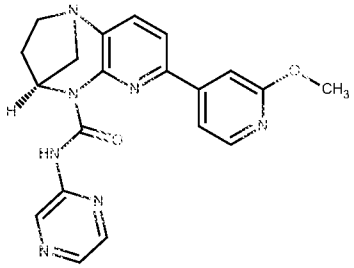
Structure	Chemical Name: Generated by ChemAxon
	(9S)-N-(pyridin-2-yl)-5-[4-(trifluoromethyl)piperidin-1-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-N-(pyridin-2-yl)-5-[(3R)-3-(trifluoromethyl)piperidin-1-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide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

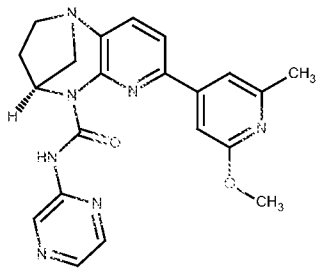
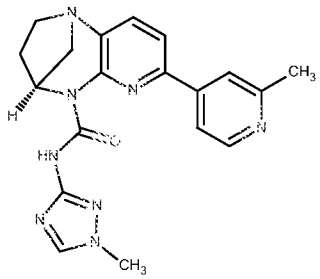
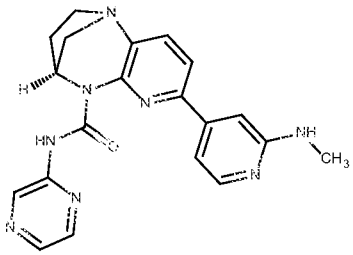
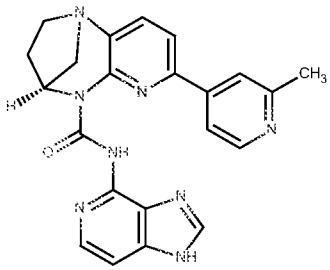
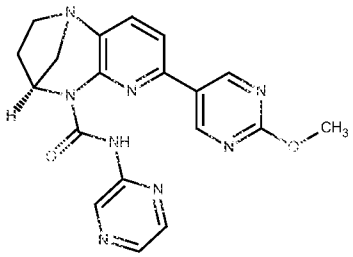
Structure	Chemical Name: Generated by ChemAxon
	(9S)-N-{4-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-{4-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-{2-[(3R)-oxolan-3-yloxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-(pyridin-2-yl)-5-[(2S)-2-(trifluoromethyl)pyrrolidin-1-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-(2,3-dihydro-1,4-benzodioxin-6-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

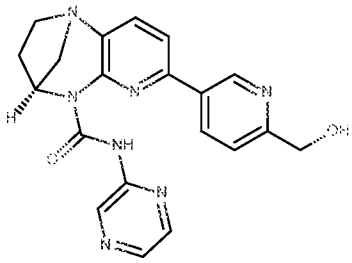
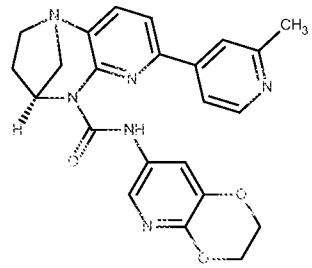
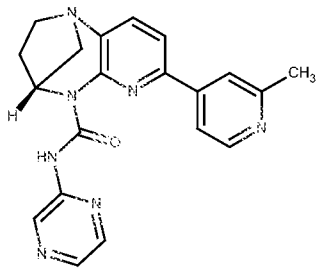
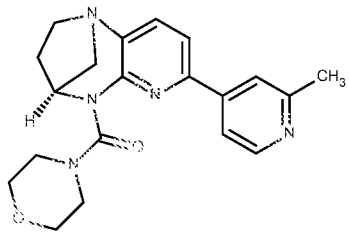
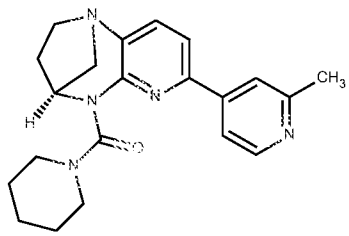
Structure	Chemical Name: Generated by ChemAxon
	(9S)-N-(6-ethylpyrazin-2-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-{6-[(2S)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-[(2R)-2-methylmorpholin-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-5-[(2S)-2-methylmorpholin-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-N-(3,4-dihydro-2H-1,5-benzodioxepin-7-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide

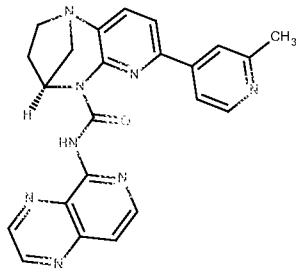
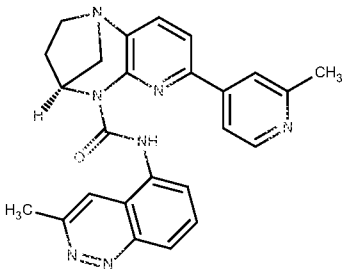
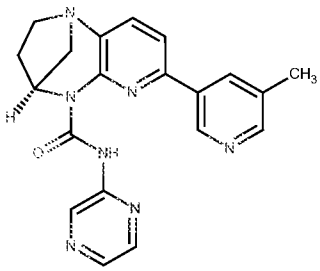
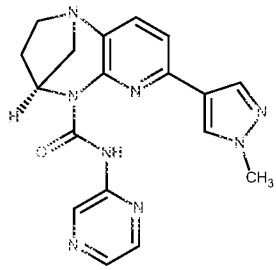
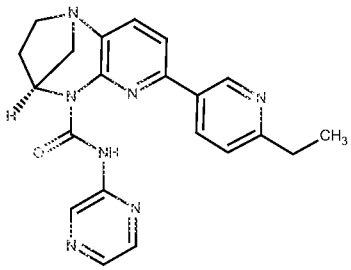
Structure	Chemical Name: Generated by ChemAxon
	(9S)-N-{2-[(2R)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-{6-[(2R)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-(6-ethoxypyrazin-2-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(2-methylpyridin-4-yl)-N-{1H-pyrazolo[3,4-c]pyridin-5-yl}-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(2-methylpyridin-4-yl)-N-(quinoxalin-5-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide

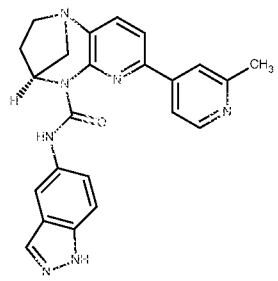
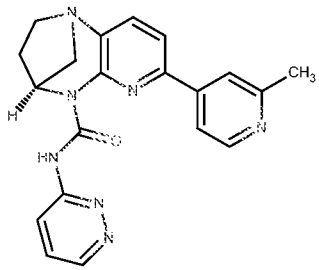
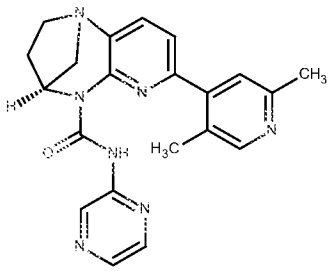
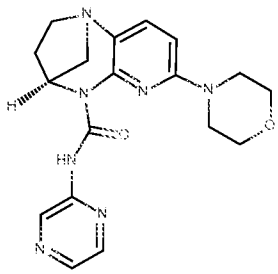
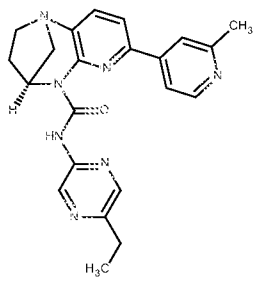
Structure	Chemical Name: Generated by ChemAxon
	(9S)-N-{2-[(2R)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(2-methylpyridin-4-yl)-N-{1H-pyrazolo[4,3-b]pyridin-5-yl}-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-{2-[(2S)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(2,6-dimethylpyridin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-5-(2-cyclopropylpyridin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide

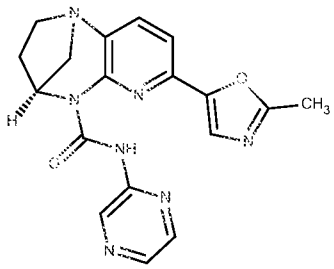
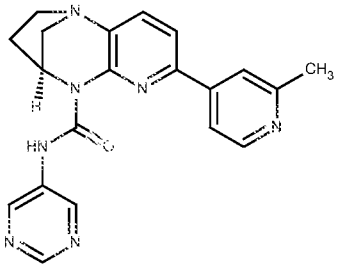
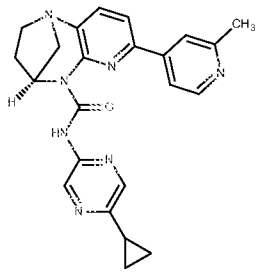
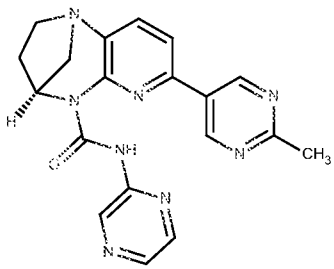
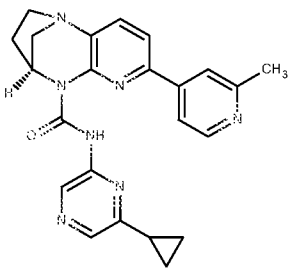
Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-[2-(propan-2-yl)pyridin-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-N-(1-methyl-1H-1,2,3-triazol-4-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(2-ethylpyridin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(2-ethoxypyridin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(2-methoxypyridin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

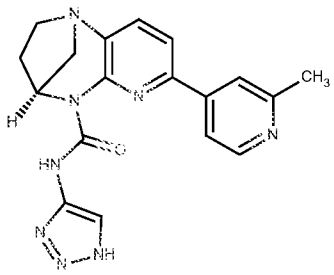
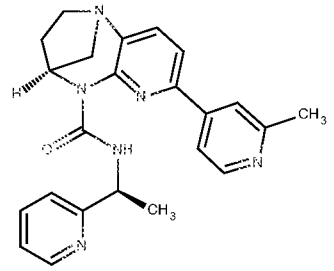
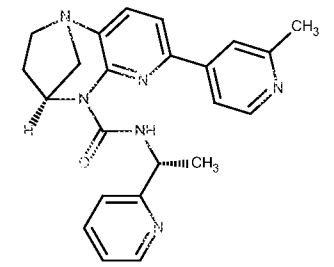
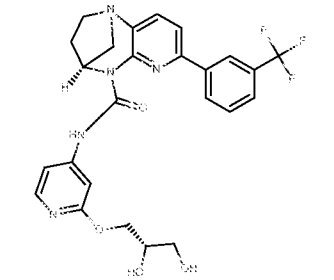
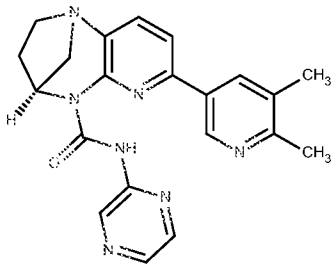
Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-(2-methoxy-6-methylpyridin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-(1-methyl-1H-1,2,4-triazol-3-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-[2-(methylamino)pyridin-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-{1H-imidazo[4,5-c]pyridin-4-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-5-(2-methoxypyrimidin-5-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

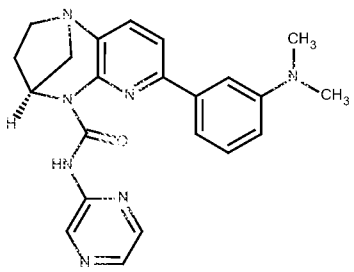
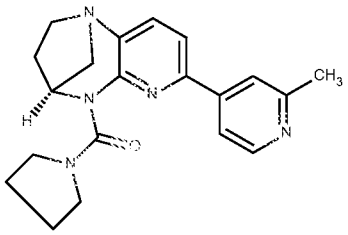
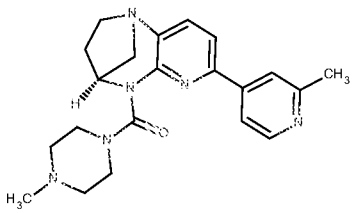
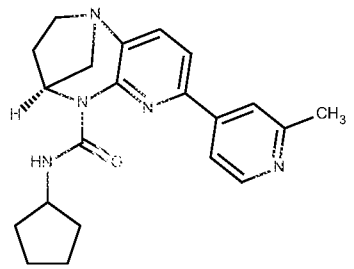
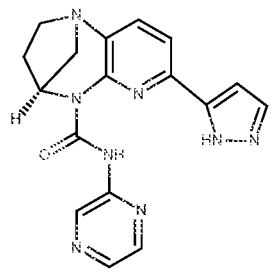
Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-[6-(hydroxymethyl)pyridin-3-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-{2H,3H-[1,4]dioxino[2,3-b]pyridin-7-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9R)-5-(2-methylpyridin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(2-methylpyridin-4-yl)-8-(morpholine-4-carbonyl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene
	(9S)-5-(2-methylpyridin-4-yl)-8-(piperidine-1-carbonyl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene

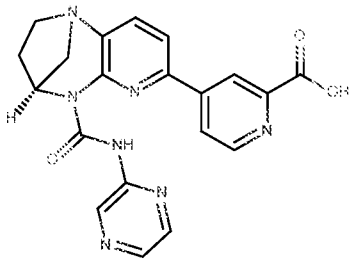
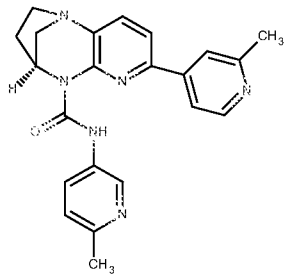
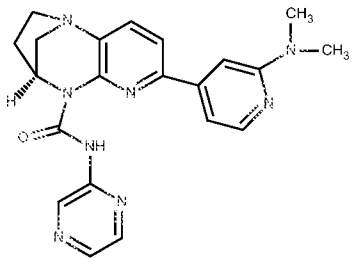
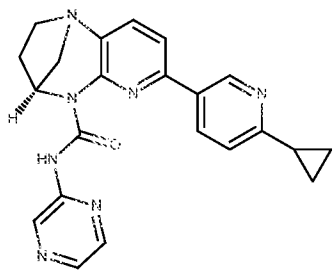
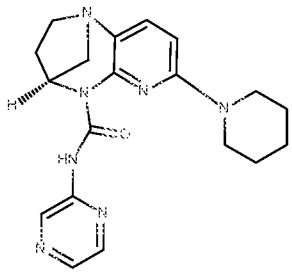
Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-(2-methylpyridin-4-yl)-N-{pyrido[3,4-b]pyrazin-5-yl}-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-N-(3-methylcinnolin-5-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(5-methylpyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(1-methyl-1H-pyrazol-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(6-ethylpyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

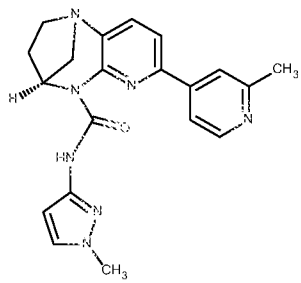
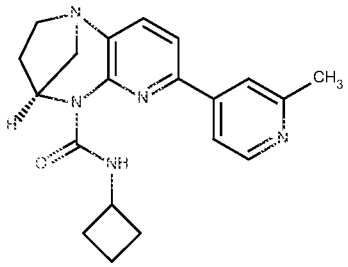
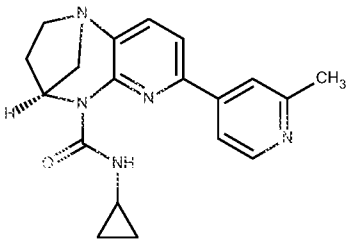
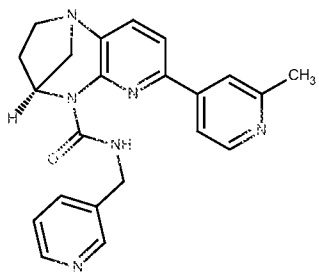
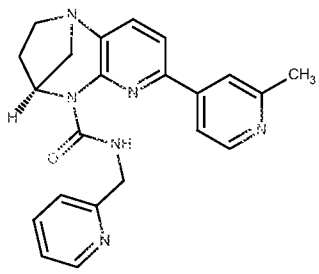
Structure	Chemical Name: Generated by ChemAxon
	(9S)-N-(1H-indazol-5-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(2-methylpyridin-4-yl)-N-(pyridazin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(2,5-dimethylpyridin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-5-(morpholin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-N-(5-ethylpyrazin-2-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

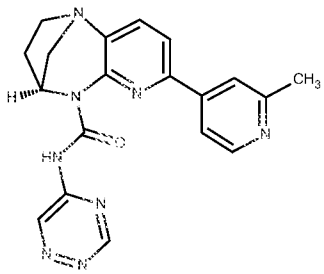
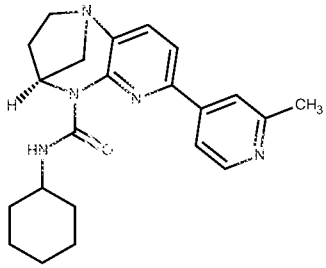
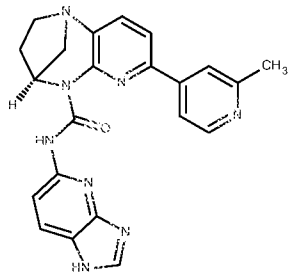
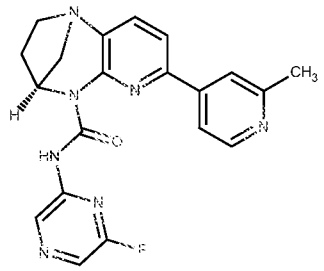
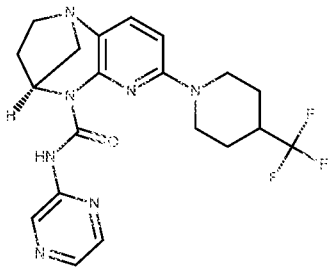
Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-(2-methyl-1,3-oxazol-5-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(2-methylpyridin-4-yl)-N-(pyrimidin-5-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-(5-cyclopropylpyrazin-2-yl)-5-(2-methylpyridin-4-yl)-1,6,8-tria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

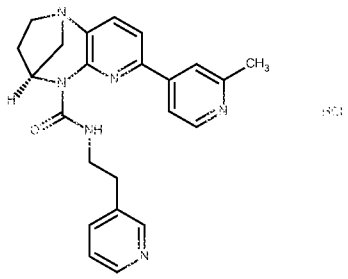
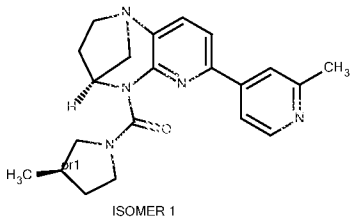
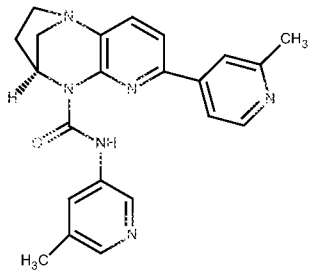
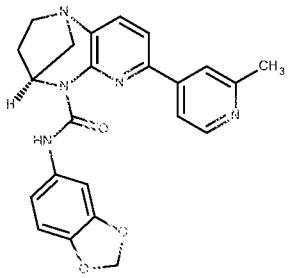
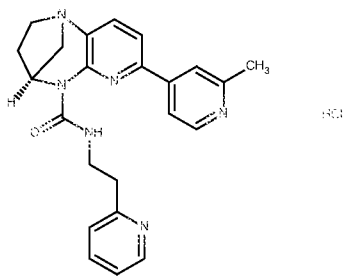
Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-(2-methylpyridin-4-yl)-N-(1H-1,2,3-triazol-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(2-methylpyridin-4-yl)-N-[(1S)-1-(pyridin-2-yl)ethyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-5-(2-methylpyridin-4-yl)-N-[(1R)-1-(pyridin-2-yl)ethyl]-1,6,8-triazatricyclo[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]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-5-(5,6-dimethylpyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

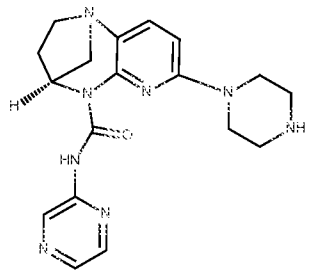
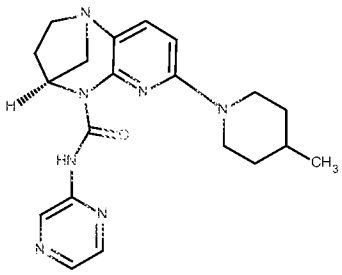
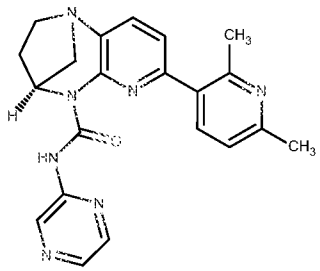
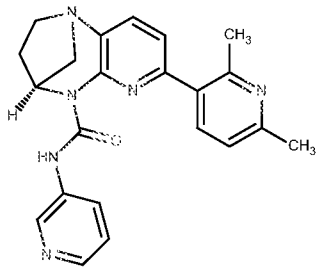
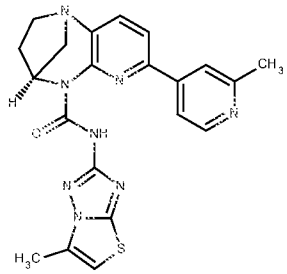
Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-[3-(dimethylamino)phenyl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(2-methylpyridin-4-yl)-8-(pyrrolidine-1-carbonyl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene
	(9S)-8-(4-methylpiperazine-1-carbonyl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene
	(9S)-N-cyclopentyl-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-N-(pyrazin-2-yl)-5-(1H-pyrazol-5-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

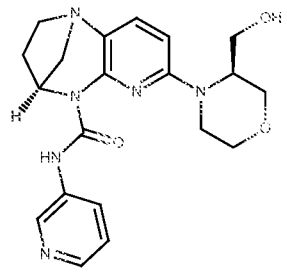
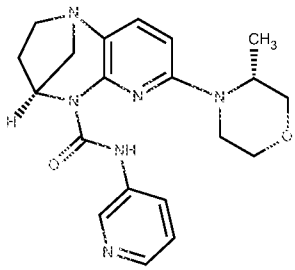
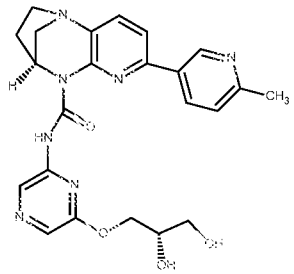
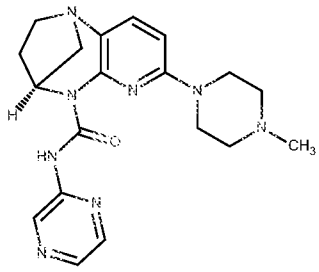
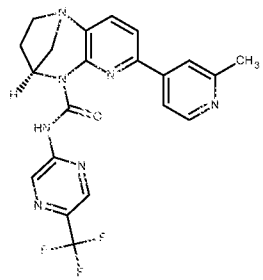
Structure	Chemical Name: Generated by ChemAxon
	4-[(9S)-8-[(pyrazin-2-yl)carbamoyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-trien-5-yl]pyridine-2-carboxylic acid
	(9S)-N-(6-methylpyridin-3-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-[2-(dimethylamino)pyridin-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(6-cyclopropylpyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(piperidin-1-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide

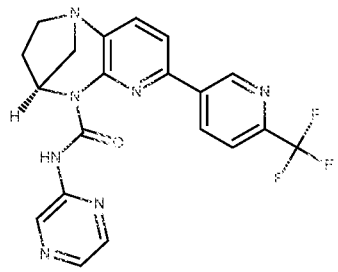
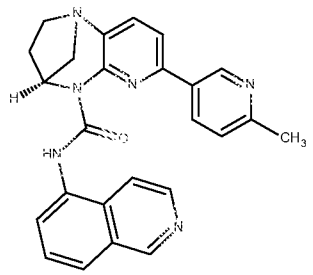
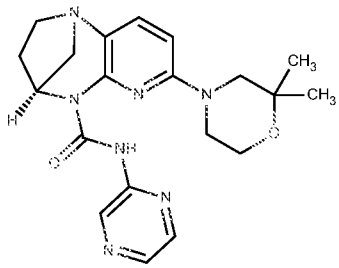
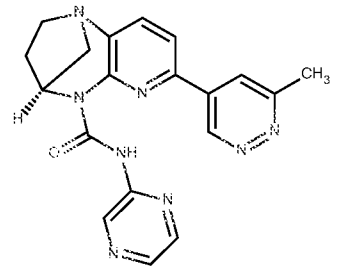
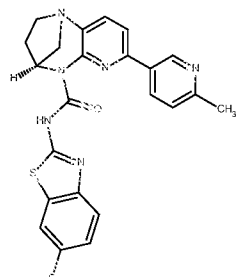
Structure	Chemical Name: Generated by ChemAxon
	(9S)-N-(1-methyl-1H-pyrazol-3-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-N-cyclobutyl-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-cyclopropyl-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.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

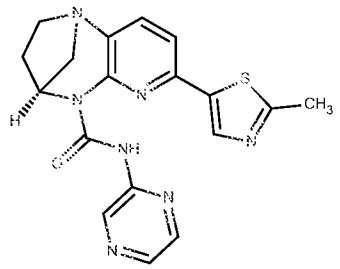
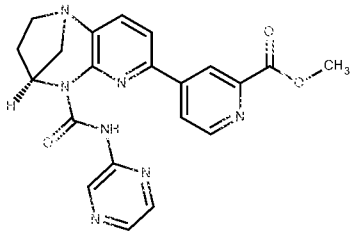
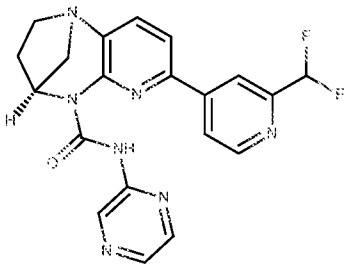
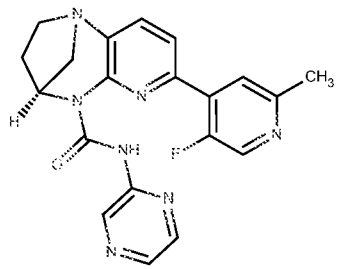
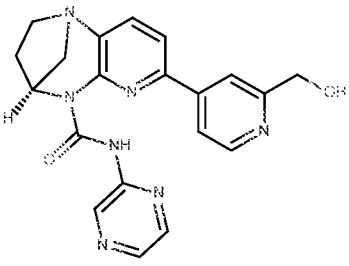
Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-(2-methylpyridin-4-yl)-N-(1,2,4-triazin-5-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-N-cyclohexyl-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-N-{1H-imidazo[4,5-b]pyridin-5-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-(6-fluoropyrazin-2-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-(pyrazin-2-yl)-5-[4-(trifluoromethyl)piperidin-1-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

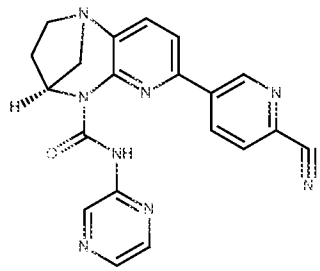
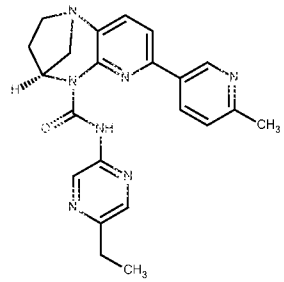
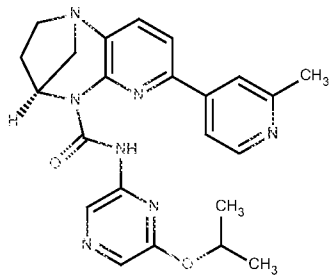
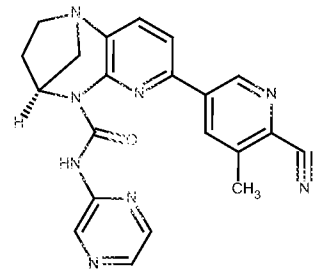
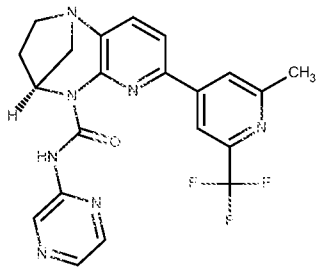
Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-(2-methylpyridin-4-yl)-N-[2-(pyridin-3-yl)ethyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide hydrochloride
 ISOMER 1	(9S)-5-(2-methylpyridin-4-yl)-8-[(3R)-3-methylpyrrolidine-1-carbonyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene
	(9S)-N-(5-methylpyridin-3-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-(2H-1,3-benzodioxol-5-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(2-methylpyridin-4-yl)-N-[2-(pyridin-2-yl)ethyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide hydrochloride

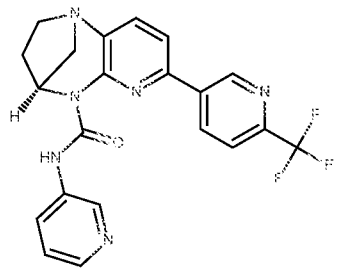
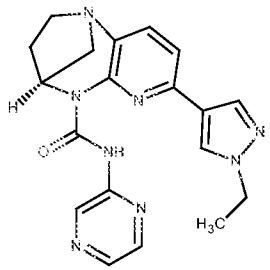
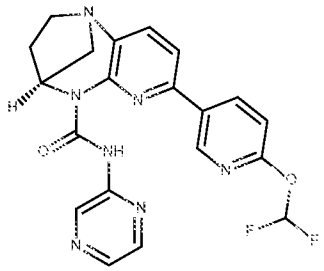
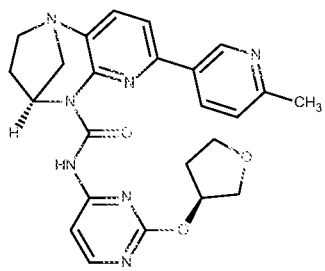
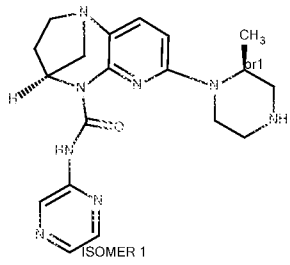
Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-(piperazin-1-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-5-(4-methylpiperidin-1-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-5-(2,6-dimethylpyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(2,6-dimethylpyridin-3-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-{6-methyl-[1,2,4]triazolo[3,2-b][1,3]thiazol-2-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

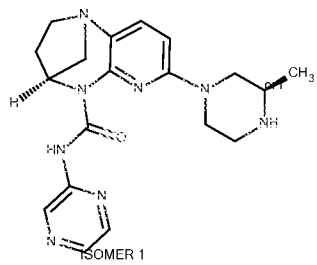
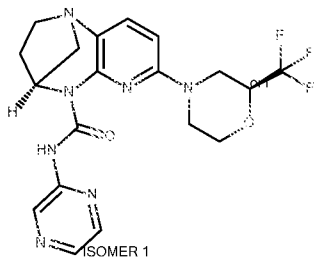
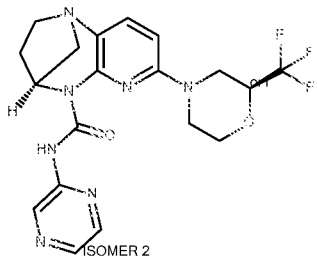
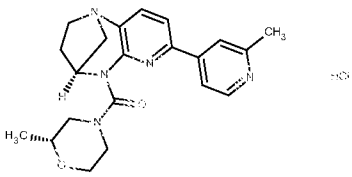
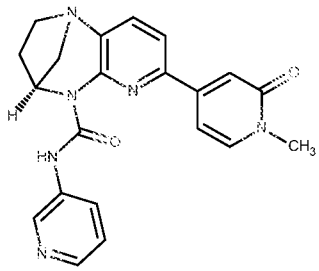
Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-[(3S)-3-(hydroxymethyl)morpholin-4-yl]-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-[(3R)-3-methylmorpholin-4-yl]-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-{6-[(2S)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-(6-methylpyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(4-methylpiperazin-1-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(2-methylpyridin-4-yl)-N-[5-(trifluoromethyl)pyrazin-2-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

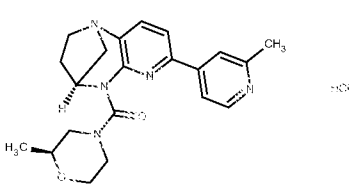
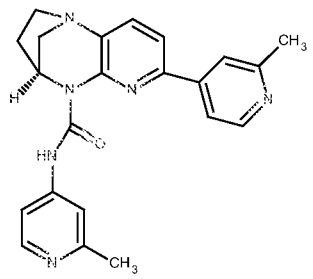
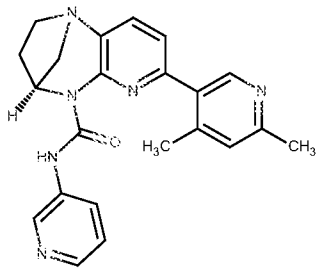
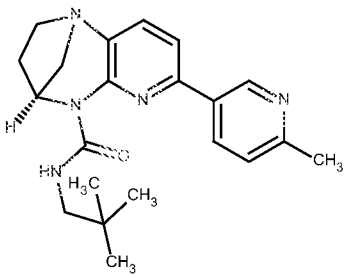
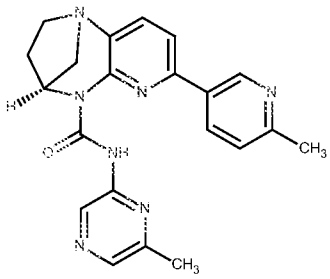
Structure	Chemical Name: Generated by ChemAxon
	(9S)-N-(pyrazin-2-yl)-5-[6-(trifluoromethyl)pyridin-3-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-(isoquinolin-5-yl)-5-(6-methylpyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-5-(2,2-dimethylmorpholin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(6-methylpyridazin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-(6-fluoro-1,3-benzothiazol-2-yl)-5-(6-methylpyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide

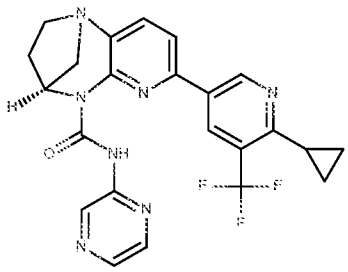
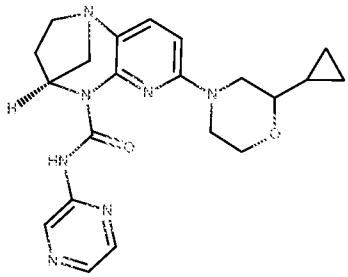
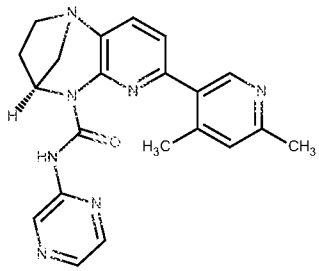
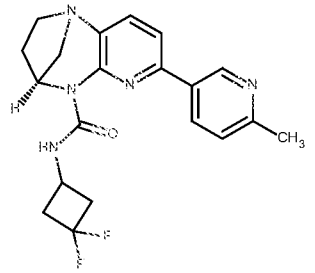
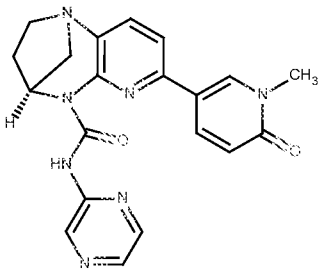
Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-(2-methyl-1,3-thiazol-5-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	methyl 4-[(9S)-8-[(pyrazin-2-yl)carbamoyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-trien-5-yl]pyridine-2-carboxylate
	(9S)-5-[2-(difluoromethyl)pyridin-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(5-fluoro-2-methylpyridin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-[2-(hydroxymethyl)pyridin-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

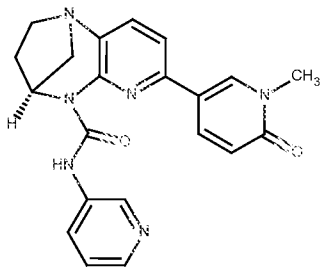
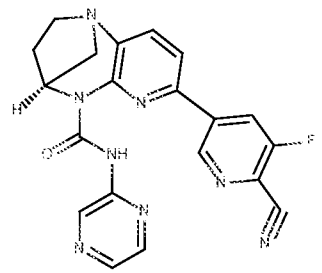
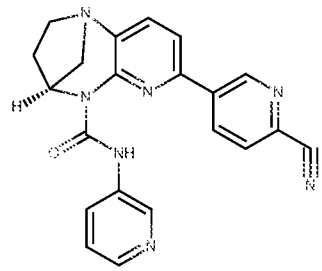
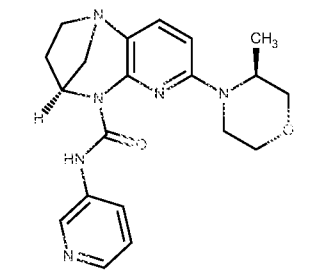
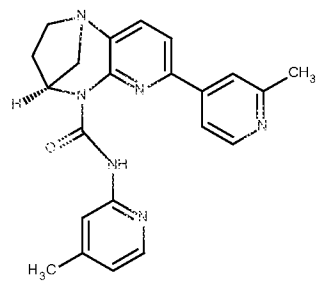
Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-(6-cyanopyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-N-(5-ethylpyrazin-2-yl)-5-(6-methylpyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-5-(2-methylpyridin-4-yl)-N-[6-(propan-2-yloxy)pyrazin-2-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(6-cyano-5-methylpyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-[2-methyl-6-(trifluoromethyl)pyridin-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

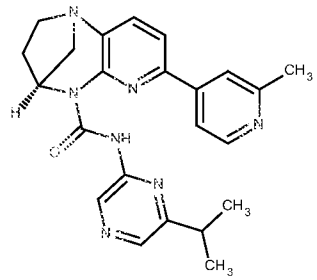
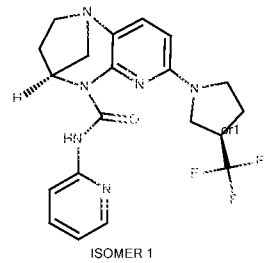
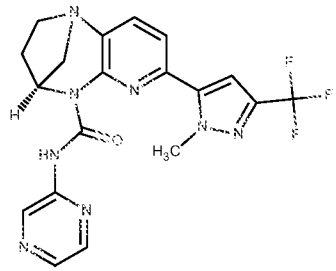
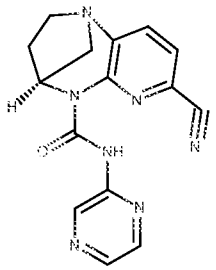
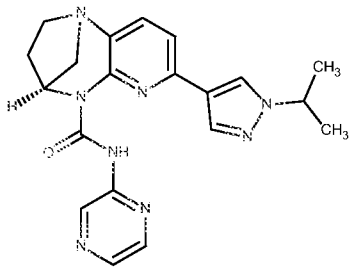
Structure	Chemical Name: Generated by ChemAxon
	(9S)-N-(pyridin-3-yl)-5-[6-(trifluoromethyl)pyridin-3-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(1-ethyl-1H-pyrazol-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-[6-(difluoromethoxy)pyridin-3-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(6-methylpyridin-3-yl)-N-{2-[(3S)-oxolan-3-yloxy]pyrimidin-4-yl}-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-5-[(2S)-2-methylpiperazin-1-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide

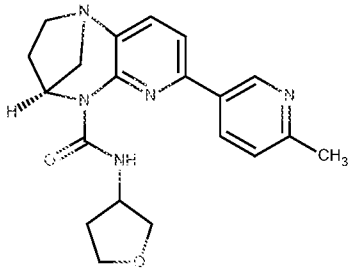
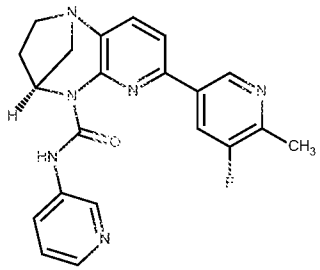
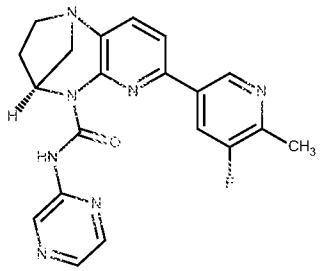
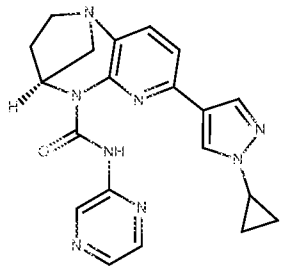
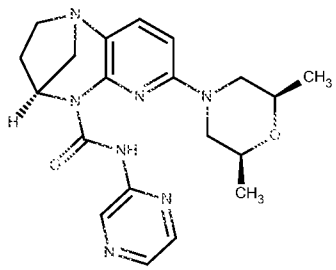
Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-[(3R)-3-methylpiperazin-1-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-N-(pyrazin-2-yl)-5-[(2S)-2-(trifluoromethyl)morpholin-4-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-(pyrazin-2-yl)-5-[(2S)-2-(trifluoromethyl)morpholin-4-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-8-[(2R)-2-methylmorpholine-4-carbonyl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene hydrochloride
	(9S)-5-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

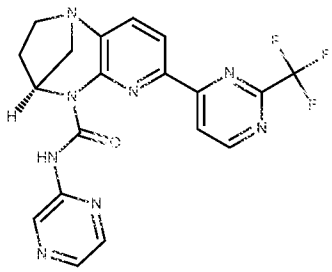
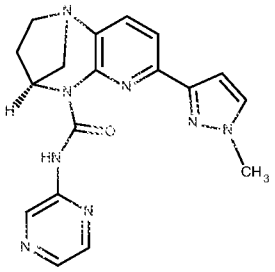
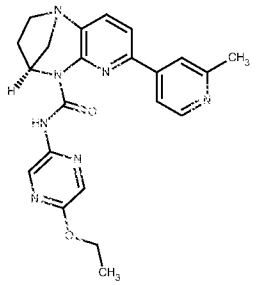
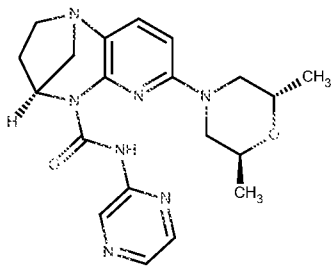
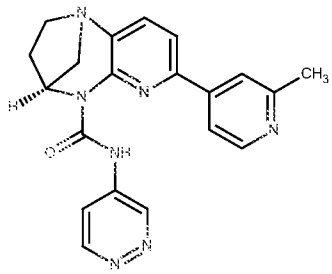
Structure	Chemical Name: Generated by ChemAxon
	(9S)-8-[(2S)-2-methylmorpholine-4-carbonyl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene hydrochloride
	(9S)-N,5-bis(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(4,6-dimethylpyridin-3-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-(2,2-dimethylpropyl)-5-(6-methylpyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-(6-methylpyrazin-2-yl)-5-(6-methylpyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide

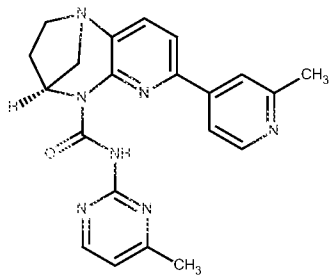
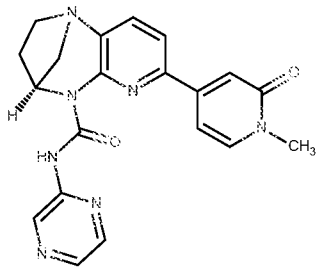
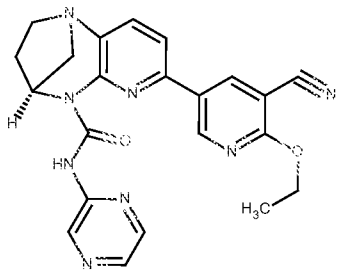
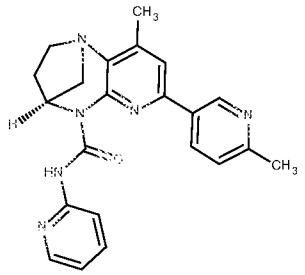
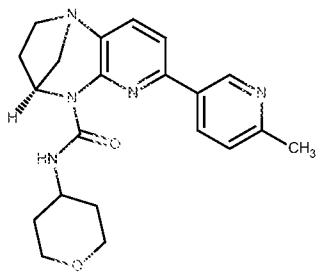
Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-[6-cyclopropyl-5-(trifluoromethyl)pyridin-3-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-5-(2-cyclopropylmorpholin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-5-(4,6-dimethylpyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-(3,3-difluorocyclobutyl)-5-(6-methylpyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

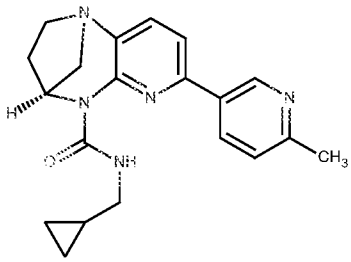
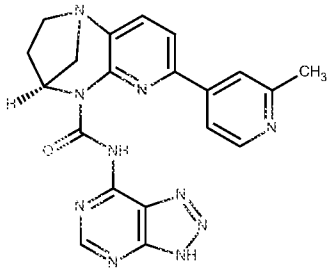
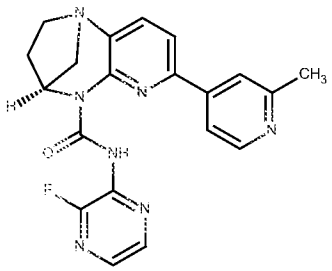
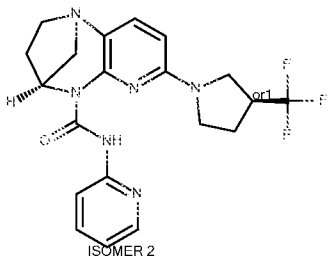
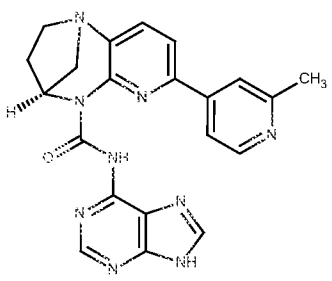
Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(6-cyano-5-fluoropyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(6-cyanopyridin-3-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-5-[(3S)-3-methylmorpholin-4-yl]-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-(4-methylpyridin-2-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide

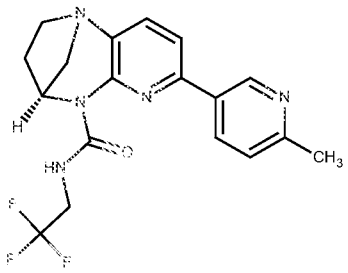
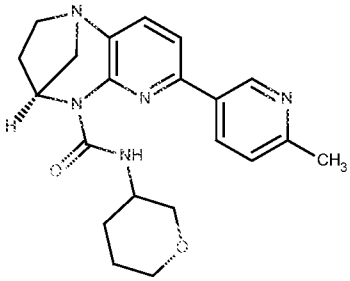
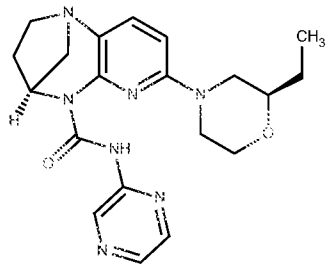
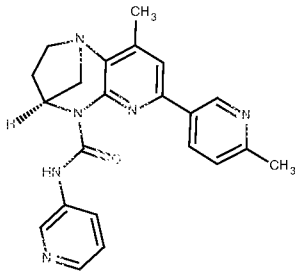
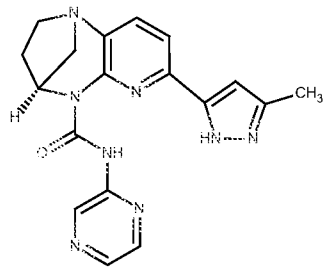
Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-(2-methylpyridin-4-yl)-N-[6-(propan-2-yl)pyrazin-2-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
 ISOMER 1	(9S)-N-(pyridin-2-yl)-5-[(3R)-3-(trifluoromethyl)pyrrolidin-1-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-5-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-cyano-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-[1-(propan-2-yl)-1H-pyrazol-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide

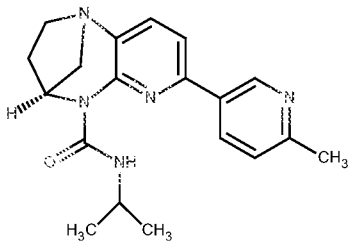
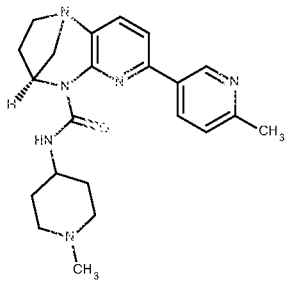
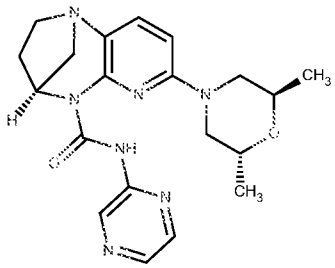
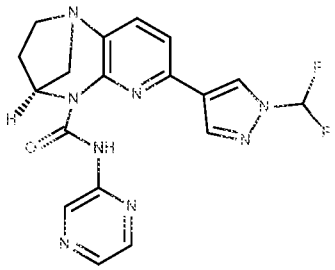
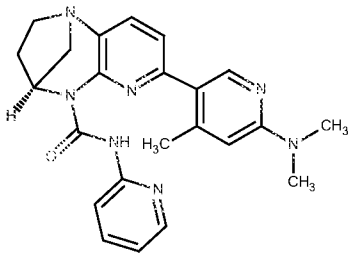
Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-(6-methylpyridin-3-yl)-N-(oxolan-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-5-(5-fluoro-6-methylpyridin-3-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(5-fluoro-6-methylpyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(1-cyclopropyl-1H-pyrazol-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

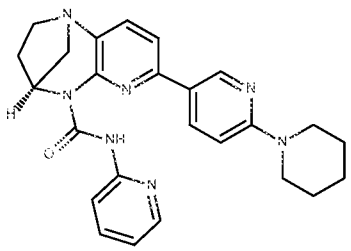
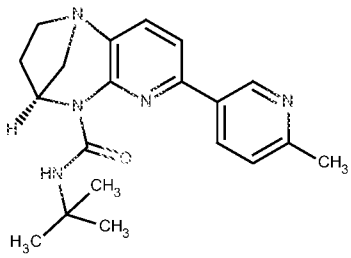
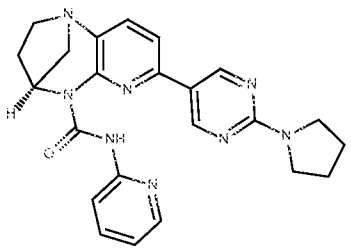
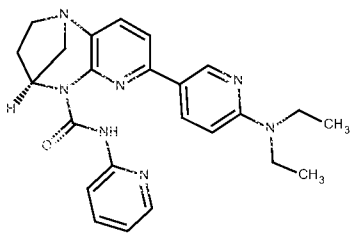
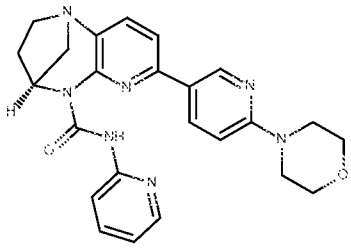
Structure	Chemical Name: Generated by ChemAxon
	(9S)-N-(pyrazin-2-yl)-5-[2-(trifluoromethyl)pyrimidin-4-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(1-methyl-1H-pyrazol-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-(5-ethoxypyrazin-2-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-[(2S,6S)-2,6-dimethylmorpholin-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(2-methylpyridin-4-yl)-N-(pyridazin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide

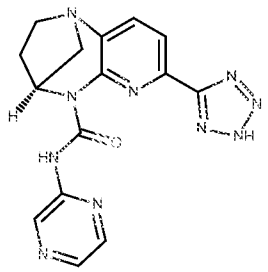
Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-(2-methylpyridin-4-yl)-N-(4-methylpyrimidin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-5-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(5-cyano-6-ethoxypyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-3-methyl-5-(6-methylpyridin-3-yl)-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-5-(6-methylpyridin-3-yl)-N-(oxan-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

Structure	Chemical Name: Generated by ChemAxon
	(9S)-N-(cyclopropylmethyl)-5-(6-methylpyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-5-(2-methylpyridin-4-yl)-N-{3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl}-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-N-(3-fluoropyrazin-2-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-N-(pyridin-2-yl)-5-[(3S)-3-(trifluoromethyl)pyrrolidin-1-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(2-methylpyridin-4-yl)-N-(9H-purin-6-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide

Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-(6-methylpyridin-3-yl)-N-(2,2,2-trifluoroethyl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-(6-methylpyridin-3-yl)-N-(oxan-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-[(2R)-2-ethylmorpholin-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[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)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-5-(3-methyl-1H-pyrazol-5-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-(6-methylpyridin-3-yl)-N-(propan-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide
	(9S)-N-(1-methylpiperidin-4-yl)-5-(6-methylpyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-[(2R,6R)-2,6-dimethylmorpholin-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-[1-(difluoromethyl)-1H-pyrazol-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-[6-(dimethylamino)-4-methylpyridin-3-yl]-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

Structure	Chemical Name: Generated by ChemAxon
	(9S)-5-[6-(piperidin-1-yl)pyridin-3-yl]-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-tert-butyl-5-(6-methylpyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-N-(pyridin-2-yl)-5-[2-(pyrrolidin-1-yl)pyrimidin-5-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-[6-(diethylamino)pyridin-3-yl]-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide
	(9S)-5-[6-(morpholin-4-yl)pyridin-3-yl]-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide

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

TERMS AND DEFINITIONS

Section 1

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.

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.

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

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.

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).

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.

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.

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

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

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

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.

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.

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.

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.

"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, C2-C6 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.

"Alkoxy" refers to an alkyl moiety attached through an oxygen bridge (i.e. a –O-C1-C6 alkyl group wherein C1-C6 is defined herein). Examples of such groups include methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy.

"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, C2-C6 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.

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 carbocyclegroups include carbocyclic aromatic groups such as phenyl, naphthyl, and anthracyl.

"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.

"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.

"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.

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

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 fromnon-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 fromnon-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.

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, C3-C6 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.

A "cycloalkenyl" group is a cyclic hydrocarbon ring containing one or more double bonds within the ring. For example, C3-C6 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.

"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.

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.

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 fromnon-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 fromnon-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.

“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.

"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.

"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.

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.

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

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.

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. 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, WI, Cat. No.489,689-2).

ISOTOPES

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.

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

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

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.

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.

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).

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-bromophenyl-sulfonic 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.

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%).

“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.

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

"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.

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.

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.

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.

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 enviornment, 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.

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."

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.

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.

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.

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.

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.

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

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.

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.

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.

"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.

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.

"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.

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}.

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

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.

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.

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.

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).

"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.

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.

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

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.

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.

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).

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).

"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 described herein.

"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.

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

"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).

"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.

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

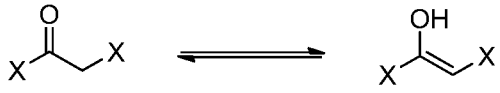
Accession No. AAH01042, NP_036371, or NP_001017524) and mouse SIRT3 (GenBank Accession No. NP_071878) proteins, and equivalents and fragments thereof. In certain embodiments, a SIRT4 protein includes human SIRT4 (GenBank Accession No. NM_012240 or NP_036372). In certain embodiments, a SIRT5 protein includes 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).

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-diemnsional 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.

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.

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:



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.

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.

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

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

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.

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

g (grams);	mg (milligrams);
kg (kilograms);	µg (micrograms);
L (liters);	mL (milliliters);
µL (microliters);	psi (pounds per square inch);
M (molar);	mM (millimolar);
µM (micromolar);	nM (nanomolar);
pM (picomolar);	nm (nanometers);
mm (millimeters);	wt (weight);
N (Normal);	CFU (colony forming units);
I. V. (intravenous);	Hz (Hertz);
MHz (megahertz);	mol (moles);
mmol (millimoles);	RT (room temperature);
min (minutes);	h (hours);
b.p. (boiling point);	TLC (thin layer chromatography);
T_r (retention time);	RP (reverse phase);
MeOH (methanol);	*i*-PrOH (isopropanol);
TEA (triethylamine);	TFA (trifluoroacetic acid);
TFAA (trifluoroacetic anhydride);	THF (tetrahydrofuran);
DMSO (dimethylsulfoxide);	EtOAc (ethyl acetate);
DME (1,2-dimethoxyethane);	DCM (dichloromethane);
DCE (dichloroethane);	DMF (*N*,*N*-dimethylformamide);
DMPU (*N*,*N*'-dimethylpropyleneurea);	CDI (1,1-carbonyldiimidazole);
IBCF (isobutyl chloroformate);	AcOH (acetic acid);
HOAt (1-hydroxy-7-azabenzotriazole);	
THP (tetrahydropyran);	NMM (N-methylmorpholine);
Pd/C (Palladium on Carbon);	MTBE (*tert*-butyl methyl ether);
HOBT (1-hydroxybenzotriazole);	mCPBA (meta-chloroperbenzoic acid;

EDC (1-[3-dimethylamino) propyl]-3-ethylcarbodiimide hydrochloride);
Boc (*tert*-butyloxycarbonyl); FMOC (9-fluorenylmethoxycarbonyl);
DCC (dicyclohexylcarbodiimide); CBZ (benzyloxycarbonyl);
Ac (acetyl); atm (atmosphere);
TMSE (2-(trimethylsilyl)ethyl); TMS (trimethylsilyl);
TIPS (triisopropylsilyl); TBS (*t*-butyldimethylsilyl);
DMAP (4-dimethylaminopyridine); BSA (bovine serum albumin)
NAD (nicotinamide adenine dinucleotide);
HPLC (high pressure liquid chromatography);
LC/MS (liquid chromatography/mass spectrometry);
BOP (bis(2-oxo-3-oxazolidinyl)phosphinic chloride);
TBAF (tetra-*n*-butylammonium fluoride);
HBTU(O-Benzotriazole-1-yl-N,N,N',N'-tetramethyluroniumhexafluoro phosphate).
HEPES (4-(2-hydroxyethyl)-1-piperazine ethane sulfonic acid);
DPPA (diphenylphosphoryl azide); LAH (Lithium aluminum hydride);
fHNO_3 (fuming HNO_3); NaOMe (sodium methoxide);
EDTA (ethylenediaminetetraacetic acid);
TMEDA (N,N,N',N'-tetramethyl-1,2-ethanediamine);
NBS (N-bromosuccinimide); DIPEA (diisopropylethylamine);
dppf (1,1'-bis(diphenylphosphino)ferrocene); and
NIS (N-iodsuccinimide).

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

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.

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.

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.

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.

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.

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.

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.

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

COMPOUND PREPARATION

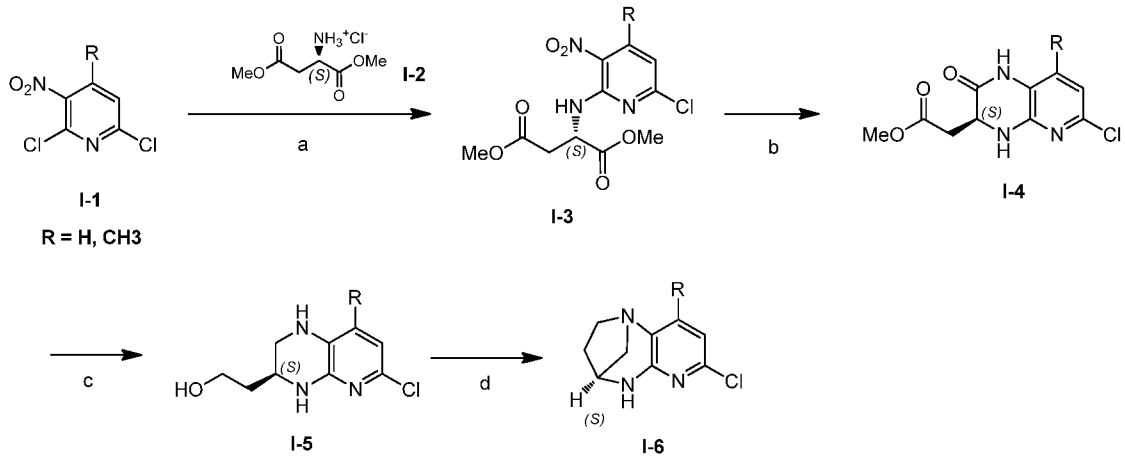
According to another embodiment, the present invention provides methods of producing the above-defined compounds. The compounds may be synthesized using conventional techniques. Advantageously, these compounds are conveniently synthesized from readily available starting materials.

Synthetic chemistry transformations and methodologies useful in synthesizing the compounds described herein are known in the art and include, for example, those described in R. Larock, *Comprehensive Organic Transformations* (1989); T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis, 2d. Ed.* (1991); L. Fieser

and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis* (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis* (1995).

General Procedures

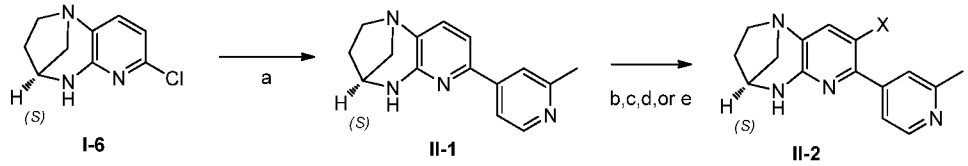
Scheme I



Reagents: (a) THF, $NaHCO_3$, 45°C; (b) Fe, i-PrOH, HOAc, 70°C; (c) $LiAlH_4$, THF, 60°C; (d) $POCl_3$.

The commercial chloropyridine (**I-1**) was reacted with a nucleophilic amine (**I-2**) in the presence of a base (to scavenge HCl) in an aprotic solvent (eg., THF, DMF, dioxane) to provide the regioselective addition product (**I-3**). The nitro functionality of species (**I-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 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 **I-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. 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**).

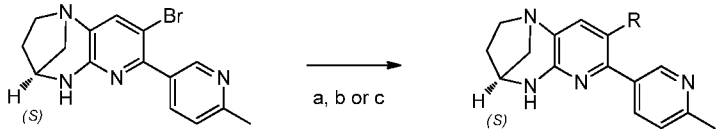
Scheme II



Reagents: (a) $Pd_2(dba)_3$, X-Phos, K_3PO_4, $ArB(OH)_2$, dioxane/H_2O; (b) NBS, $CHCl_3$, 60°C; (c) NCS, $CHCl_3$, 60°C; (d) NIS, $CHCl_3$, 60°C; (e) N-Fluoro-N'-chloromethyltriethylenediamine bis(tetrafluoroborate), triflic acid, 60°C.

The chloro functionality of compound **I-6** was coupled with a boronic acid using Suzuki coupling chemistry to give **II-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 **II-1** was reacted with an electrophilic halogenating reagent, such as NCS, NBS, NIS or N-Fluoro-N'-chloromethyltriethylenediamine bis(tetrafluoroborate) in an appropriate solvent to give the corresponding halogenated species **II-2** in a regioselective manner. Many methods exist to effect the halogenation of an aromatic ring and are well-known to those skilled in the art.

Scheme III

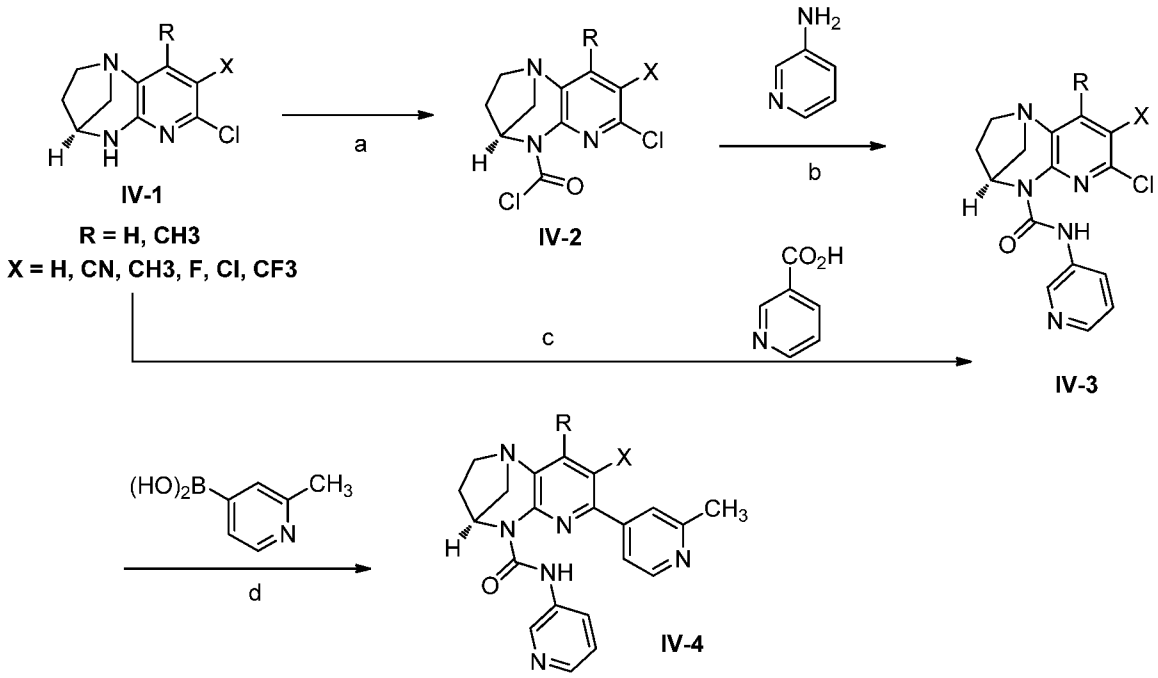


Reagents: (a) $Zn(CN)_2$, $Zn(OAc)_2$, DPPF, $Pd_2(dba)_3$, DMF, 110°C (b) CuCl, KO*t*-Bu, $CF_3Si(CH_3)_3$, 1,10-phenanthroline, DMPU, 35°C. (c) $CH_3B(OH)_2$, K_3PO_4, X-Phos, $Pd_2(dba)_3$, dioxane/H_2O, 75°C.

The halogen group of compound **III-1** can be substituted by a variety of functionality using metal mediated intermediates to give compounds **III-2**. Organometallic couplings are typically run using a palladium(0) catalyst such as $Pd(PPh_3)_4$ or other metals such as Cu or Sn, with a base, for example KO*t*-Bu or K_3PO_4, in a mixture containing polar solvents such as DMPU, dioxane, or DMF. Methods for palladium-mediated couplings are

described in standard reference volumes, such as Schlosser "Organometallics in Synthesis" (published by Wiley and sons). Many methods exist to effect the metal catalyzed substitution of a halide on an aromatic ring and are well-known to those skilled in the art.

Scheme IV

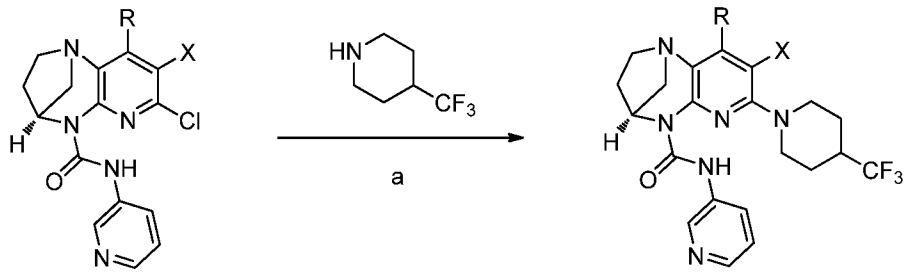


Reagents: (a) TEA, triphosgene, DCM; (b) Aniline,TEA, DCM; (c) DPPA, $ArCO_2H$, 60°C; (d) $Pd_2(dba)_3$, X-Phos, K_3PO_4, dioxane/H_2O.

Amine (**IV-1**) was reacted with an acylating reagent, such as triphosgene or carbonyl diimidazole in an aprotic solvent (DCM, $CHCl_3$, THF, etc.) to give the reactive acyl intermediate species (**IV-2**). The reactive acyl compound (**IV-2**) 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 (**IV-3**). Alternatively, an appropriate carboxylic acid can be treated with DPPA followed by an in situ addition of amines (**IV-1**) at elevated temperature to generate the urea (**IV-3**). This type of reaction involves a Curtius rearrangement (*Org. React.* **3**, 337 **1946**) and is well known to those skilled in the art. The chloro functionality of urea **IV-3** was selectively coupled with a boronic acid using Suzuki coupling chemistry to give (**IV-4**). 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). The order of this reaction sequence can be reversed such that **IV-1** is first reacted under Suzuki conditions followed by urea formation using the above mentioned conditions to yield **IV-4**.

Scheme VI



IV-3 **VI-1**

Reagents: (a) palladium acetate, K_2CO_3, dioxane/H_2O, dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine

The chloro functionality of urea **IV-3** was selectively displaced by an alkyl amine using Buchwald-Hartwig amination conditions to give (**VI-1**). Buchwald-Hartwig reactions are typically run using a palladium(0) catalyst such as $Pd(PPh_3)_4$ with an bulky Bronstead base, for example KO*t*-Bu or KHMDS, containing ethereal solvents such as DME, dioxane, or THF. Methods for palladium-mediated amine couplings are described in Hartwig, J.F. (1998), *Transition Metal Catalyzed Synthesis of Arylamines and Aryl Ethers from Aryl Halides and Triflates: Scope and Mechanism*, *Angew. Chem. Int. Ed.* **37**: 2046–2067.

Compound Characteristics and Properties

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%.

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.

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, CA; world wide web at biovision.com) and Thomas Scientific (Swedesboro, NJ; world wide web at tomassci.com).

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 IC_{50} 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.

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.

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.

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.

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

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

In certain embodiments, the invention provides methods and 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 and uses of the present invention comprise administering to a subject in need thereof a pharmaceutically effective amount of a sirtuin-modulating compound, e.g., a sirtuin-modulating compound.

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.

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.

In certain embodiments, methods and 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.

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 x SSC at 65 °C. 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.

In certain embodiments, methods and 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.

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

Aging/Stress

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 and use of the present invention comprise contacting the cell with a sirtuin-modulating compound.

The methods and 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.

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).

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.

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.

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 and 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.

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.

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.

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 and uses for decreasing the rate of senescence of a subject, e.g., after onset of senescence; methods and uses for extending the lifespan of a subject; methods and uses for treating or preventing a disease or condition relating to lifespan; methods and uses for treating or preventing a disease or condition relating to the proliferative capacity of cells; and methods and 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.

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.

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.

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

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.

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 and 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.

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.

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

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.

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.

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.

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 (ED_{50}) 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

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.

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.

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.

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.

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.

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

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.

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.

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.

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.).

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.

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.

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.

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.

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.

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.

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

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.

Accordingly, the present invention provides anticoagulation 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.

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.

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, methods and 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. 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.

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

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.

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.

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 and uses may be used for treating or preventing obesity.

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."

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.

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

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.

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

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.

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.

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.

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

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.

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.

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.

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.

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.

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.

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

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.

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.

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).

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.

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.

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.

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.

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.

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.

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.

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

In certain embodiments, the invention provides methods and uses for treating diseases or disorders that would benefit from increased mitochondrial activity. The methods and uses of the present invention 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.

In certain embodiments, methods and uses for treating diseases or disorders that would benefit from increased mitochondrial activity may comprise identifying a subject suffering from a mitochondrial dysfunction. Methods and 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.

In certain embodiments, the invention provides methods and 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.

In exemplary embodiments, the invention provides methods and 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.

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.

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).

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.

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

Muscle Performance

In other embodiments, the invention provides methods and 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 and uses involve administering an amount of a sirtuin-modulating compound that increase mitochondrial activity, increase mitochondrial biogenesis, and/or increase mitochondrial mass.

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.

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.

It is contemplated that the methods and 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.

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

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.

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.

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.

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.

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 and 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).

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.

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

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.

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.

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.

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.

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.

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.

In one aspect, the present invention relates to a method, where diseases related to aging or stress, diabetes, metabolic dysfunctions, neurodegenerative diseases,

cardiovascular disease, cance or inflammatory disease are selected from psoriasis, atopic dermatitis, acne, rosacea, inflammatory bowel disease, osteoporosis, sepsis, arthritis, COPD, systemic lupus erythematosus and ophthalmic inflammation.

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

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.

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

Yet other methods and uses contemplated herein include screening methods 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.

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.

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.

Methods and 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 1μM to about 10mM, preferably from about 10μM to 1mM, even more preferably from about 100μM to 1mM, such as about 200μM. 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 100μM, preferably from about 0.1 to 10μM, such as 1μM. 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 IN THERAPY

The present invention also relates to methods and 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.

In another aspect, the invention provides and 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 and uses comprise administering to a subject in need thereof a pharmaceutically effective amount of a sirtuin-modulating compound.

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.

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.

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 comprisesadministering 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.

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.

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.

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 .

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

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.

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.

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.

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.

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.

In another aspect, the present invention relates to a method for treating psoriasis, which comprises administering a compound of Formulas (I) to (V), 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.

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

In general, the present invention relates to substituted bridged urea analog compounds of Formulas (I) to (V), corresponding anlogs or derivatives thereof 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.

In particular, the present invention relates to novel compounds of Formulas (I) to (V), 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 (V), respectively.

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 (V), corresponding anlogs or derivatives thereof (i.e., with hydrogen substitution at the R^2 position) or a pharmaceutical acceptable salt thereof .

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

In another aspect, the present invention relates to a pharmaceutical composition comprising a compound of Formulas (I) to (V), 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.

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.).

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.

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); non-aqueous 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.

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.

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 multi-dose 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.

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.

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.

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).

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.

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.

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.

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.

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.

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

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.

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.

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.

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).

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.

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).

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.

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.

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.

Cells, e.g., treated *ex vivo* with a compound as described herein, can be administered according to methods 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.

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.

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

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.

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).

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.

The practice of the present methods 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, 2nd 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. Patent 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).

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

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.

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.

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.

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 ^{o}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

LCMS with PDA:

Waters Allaince2695-2996/Quattromicro

Agilent-1200/SQD

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

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

^{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

Acq. Method Conditions: RND-ABC-6-MIN

Column: XBridge BEH C18 (50mmx4.6mm, 2.5µm)

Mobile Phase: A: 5mM 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 Rate1.3 ml/min

MS Parameters:

Mass Range: 100-1000

Scan Time: 0.5 Sec

Inter-Scan delay: 0.1 sec

Run Time: 6.0 min

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

Column: Acquity BEH C18 (50mmx2.1mm, 1.7um)

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: 0.6mL/min

MS Parameters:

Mass Range: 100-1000

Scan Time: 0.5 Sec

Inter-Scan delay: 0.1 sec

Run Time: 4.5 min

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

Column: Acquity BEH C18 (50mmx2.1mm, 1.7um)

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: 0.6mL/min

MS Parameters:

Mass Range: 100-1000

Fragmentor: 100

Step Size: 0.1

Run Time: 4.5 min

Acq. Method Conditions: RND-ABC-6.5-MIN

Column: XBridge BEH C18 (50mmx4.6mm, 2.5µm)

Mobile Phase: A: 5mM 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 Rate1.3 ml/min

MS Parameters:

Mass Range: 100-1000

Fragmentor: 100

Step Size: 0.1

Run Time: 6.5 min

Acq. Method Conditions: RND-ABC-10-MIN

Column: XBridge BEH C18 (50mmx4.6mm, 2.5µm)

Mobile Phase: A: 5mM 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 Rate1.3 ml/min

MS Parameters:

Mass Range: 100-1000

Fragmentor: 100

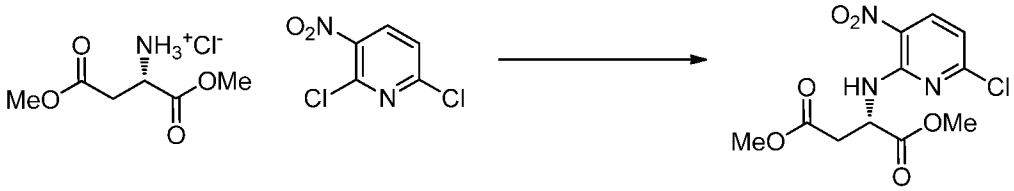
Step Size: 0.1

Run Time: 10.0 min

INTERMEDIATES

Synthesis of bicyclic pyridine cores

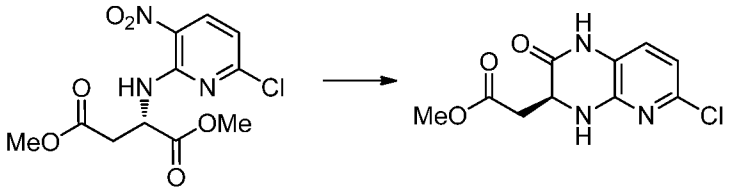
Synthesis of (S)-Dimethyl 2-((6-chloro-3-nitropyridin-2-yl)amino)succinate



To a 2 L flask equipped with a thermometer, a reflux condenser, and a mechanical stirrer was added 2,6-dichloro-3-nitropyridine (100 g, 0.52 mol), (S)-aspartic acid dimethyl ester hydrochloride (205 g, 1.04 mol), $NaHCO_3$ (174 g, 2.07 mol) and tetrahydrofuran (1 L). The reaction was stirred at 40 °C for 16 h, and was monitored for the disappearance of 2,6-dichloropyridine by HPLC. After the reaction was complete, the solids were filtered away and washed with ethyl acetate (3 x 300 mL). The combined filtrate and washings were concentrated to dryness, and the residue was taken up in 1 L of ethyl acetate. The solution was stirred with charcoal (200 g) at ambient temperature for 2 h, and the charcoal was filtered away and washed with additional ethyl acetate (3 x 200 mL). The combined filtrate and washings were concentrated in vacuo to obtain crude (S)-dimethyl 2-((6-chloro-3-nitropyridin-2-yl)amino)succinate (180 g, >100%) as a yellow oil. This was used in the next step without further purification. LRMS (*m/z*): 318.0 [M+H]+; HRMS (*m/z*): [M+H]+ calcd for $C_{11}H_{13}N_3O_6Cl$, 318.0493; found, 318.0492; ^{1}H-NMR (300 MHz, DMSO-*d*6): δ 9.00 (d, J = 7.9 Hz, 1H, -NH), 8.50 (d, J = 8.6 Hz, 1H), 6.92 (d, J = 8.6 Hz,

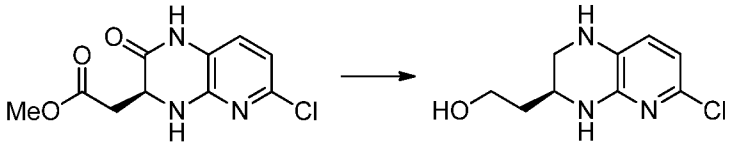
1H), 5.23 (m, J = 5.7, 7.9 Hz, 1H, -CHNH), 3.67 (s, 3H), 3.63 (s, 3H), 3.06 (m, J = 5.8 Hz, 2H, -$CHCH_2$); ^{13}C-NMR (APT) (75 MHz, DMSO-*d*6): δ 170.93 (C), 170.65 (C), 154.65 (C), 150.59 (C), 138.82 (CH), 127.28 (C), 112.81 (CH), 52.23 (CH_3), 51.74 (CH_3), 50.20 (CH), 35.31 (CH_2).

Synthesis of (S)-Methyl 2-(6-chloro-2-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-3-yl)acetate



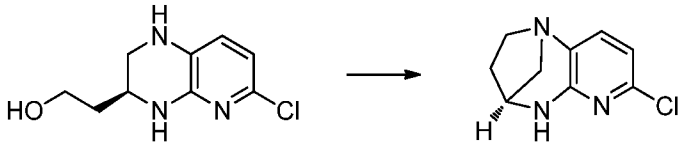
To a 5 L three necked flask equipped with a thermometer, a reflux condenser, and a mechanical stirrer was charged with crude (S)-dimethyl 2-((6-chloro-3-nitropyridin-2-yl)amino)succinate (180 g, 0.52 mol), iron powder (146 g, 2.59 mol), 2-propanol (2 L) and water (700 mL). The mixture was stirred at 40 °C, and then acetic acid (15.5 g, 0.259 mmol) was added at a rate sufficient to keep the internal temperature below 70 °C. The reaction was stirred at 70 °C for 30 min, HPLC indicated that the reaction was complete. The mixture was cooled to 40 °C, then Na_2CO_3 (165 g, 1.55 mol) was added, and the mixture was stirred for 1 h. The solids were filtered, and the solids were washed with tetrahydrofuran (3 x 500 mL). The combined filtrate and washings were concentrated in vacuo, and then the residue was stirred in ethanol (1 L) for 12 hrs. The solid was filtered and washed with cold ethanol, and dried in vacuo to obtain (S)-methyl 2-(6-chloro-2-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-3-yl)acetate as an off-white solid (91 g, 68%). LRMS (*m/z*): 256.0 [M+H]+; HRMS (*m/z*): [M+H]+ calcd for $C_{10}H_{11}N_3O_3Cl$, 256.0489; found, 256.0487; ^{1}H-NMR (300 MHz, DMSO-*d*6): δ 10.55 (br s, 1H, -NHCO), 7.35 (br s, 1H, -NHCH), 6.92 (d, J = 7.9 Hz, 1H), 6.57 (d, J = 7.8 Hz, 1H), 4.43 (m, J = 1.4, 5.1 Hz, 1H, -NHCH), 3.57 (s, 3H, -CO_2Me), 2.79 (m, J = 5.1, 16.4 Hz, 2H, -$CHCH_2$); ^{13}C-NMR (APT) (75 MHz, DMSO-*d*6): δ 170.32 (C), 164.96 (C), 146.13 (C), 140.32 (C), 122.41 (CH), 119.47 (C), 111.31 (CH), 51.81 (CH), 51.39 (CH_3), 37.01 (CH_2).

Synthesis of (S)-2-(6-Chloro-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-3-yl)ethanol



A 5 L 3-necked flask equipped with a mechanical stirrer, a reflux condenser, and a nitrogen inlet was charged with $LiAlH_4$ (60 g, 1.58 mol). The flask was cooled with an ice bath, and tetrahydrofuran (500 mL) was added. The stirred mixture was cooled to 0 °C, then a solution of (S)-methyl 2-(6-chloro-2-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-3-yl)acetate (81 g, 0.32 mol) in tetrahydrofuran (2 L) was added, while keeping the internal temperature below 5 °C. After the addition was complete, the reaction was heated at reflux for 16 h, while monitoring for the appearance of product by HPLC. The ester reduction occurred rapidly, while the lactam reduction required longer for complete reduction. The reaction was cooled to 5 °C, and then water (60 mL) was added while keeping the internal temperature below 10 °C. After addition was complete, the reaction was stirred for 15 min, then 15% (w/w) NaOH(aq) (60 mL) was added while keeping the internal temperature below 5 °C. After addition was complete, the reaction was stirred for 15 min, then water (180 mL) was added and the mixture was stirred at ambient temperature for 1 h. The solids were filtered off and washed with tetrahydrofuran (3 x 150 mL). The filtrate and washings were concentrated in vacuo, then the solid residue was dried in vacuo to obtain (S)-2-(6-chloro-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-3-yl)ethanol as a brown solid (55 g, 81%). LRMS (*m/z*): 214.1 [M+H]+; HRMS (*m/z*): [M+H]+ calcd for $C_9H_{13}N_3OCl$, 214.0747; found, 214.0743; ^{1}H-NMR (300 MHz, DMSO-*d*6): δ 6.60 (br s, 1H, -NHCH$(CH_2)_2$OH), 6.58 (d, J = 7.8 Hz, 1H), 6.32 (d, J = 7.8 Hz, 1H), 5.69 (m, 1H, -NHCH$_2$), 4.57 (t, J = 5.0 Hz, 1H, -OH), 3.56 (m, J = 5.8 Hz, 2H, -CH_2OH), 3.47 (m, 1H, -NHCH$(CH_2)_2$OH), 3.22 (m, J = 2.7, 11.1 Hz, 1H, -NHCHH'), 2.84 (m, J = 1.6, 6.7, 11.1 Hz,1H, -NHCHH'), 1.65 (m, J = 6.7 Hz, 1H, -CHH'CH_2OH), 1.54 (m, J = 6.3 Hz, 1H, -CHH'CH_2OH); ^{13}C-NMR (APT) (75 MHz, DMSO-*d*6): δ 146.75 (C), 134.44 (C), 128.20 (C), 118.97 (CH), 110.59 (CH), 57.97 (CH_2), 47.47 (CH), 43.99 (CH_2), 36.60 (CH_2).

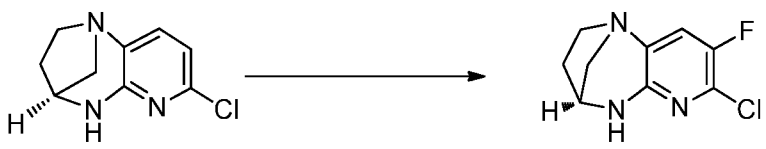
Synthesis of (4S)-7-Chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine



To a solution of (S)-2-(6-chloro-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-3-yl)ethanol (**5**; 50 g, 0.234 mol) in CH_2Cl_2 (500 mL) was added triethylamine (95 g, 0.936 mol). The mixture was stirred at ambient temperature until it was homogeneous, and then cooled to 0 °C. To the reaction mixture was added dropwise $POCl_3$ (54 g, 0.351 mol) while maintaining the temperature between 0 - 5 °C. Cooling was removed and the reaction was stirred at ambient temperature for 2 h, while monitoring for the disappearance of the starting alcohol by HPLC. After the reaction was complete, 1.2M $NaHCO_3$(aq.) (200 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were extracted with 1M HCl(aq.) (4 x 300 mL), and the combined HCl layers were adjusted to pH 8 with solid $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 (4 x 300 mL), and this set of CH_2Cl_2 layers were dried (Na_2SO_4), filtered, and treated with charcoal (50 g). The mixture was stirred at ambient temperature for 3 h, filtered, and the charcoal was washed with CH_2Cl_2 (200 mL). The combined filtrate and wash solution were concentrated to dryness, and the solid residue was dried in vacuo to obtain (4S)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine as an off-white crystalline solid (30 g, 66%). LRMS (*m/z*): 196.1 [M+H]+; HRMS (*m/z*): [M+H]+ calcd for $C_9H_{11}N_3Cl$, 196.0642; found, 196.0637; ^{1}H-NMR (300 MHz, DMSO-*d*6): δ 7.47 (br d, J = 4.5 Hz, 1H, -NH), 7.09 (d, J = 7.7 Hz, 1H), 6.39 (d, J = 7.7 Hz, 1H), 3.89 (m, J = 5.0 Hz, 1H, CHNH), 2.95-3.13 (m, 2H, -NCH_2CH_2CHNH), 2.77 (m, 2H, -NCHH'CHNH), 1.98 (m, J = 5.0 Hz, 1H, -NHCHCHH'CH_2N), 1.86 (m, J = 6.9 Hz, 1H, -NHCHCHH'CH_2N); ^{13}C-NMR (APT) (75 MHz, DMSO-*d*6): δ 153.45 (C), 144.50 (C), 134.32 (CH), 133.19 (C), 109.73 (CH), 59.88 (CH_2), 53.07 (CH_2), 50.08 (CH), 38.38 (CH_2).

<u>Synthesis of 3 substituted bicyclic pyridine core</u>

Synthesis of (4S)-7-chloro-8-fluoro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4] diazepine:

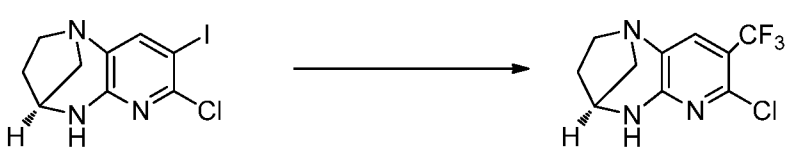


N-Fluoro-*N'*-chloromethyltriethylenediamine bis(tetrafluoroborate) (15.20 g, 42.9 mmol) was added to a solution of (4*S*)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (7 g, 35.8 mmol) in triflic acid (70 mL) at room temperature and heated to 70 °C for 36 h. Then the reaction mixture neutralized with aq. $NaHCO_3$ solution and extracted with ethyl acetate (3x500 mL). The combined organic layer was washed with water (2x500 mL) and brine (100 mL), dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to obtain the crude residue. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 1% MeOH in DCM) to afford (4*S*)-7-chloro-8-fluoro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (200 mg, 0.805 mmol, yield: 2.25 %) as an off white solid. (TLC: Eluent: 5% methanol in DCM, R_f: 0.4), LCMS (*m/z*) 214.1 $[M+H]^+$.

4*S*)-7-chloro-8-iodo-2, 3, 4, 5-tetrahydro-1, 4-methanopyrido [2, 3-*b*][1, 4]diazepine

To a stirring solution of (4*S*)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*]*[*1,4]diazepine (10g, 51.1 mmol) in chloroform (170 mL) was added NIS (14.95 g, 66.4 mmol). The reaction mixture was stirred at 70 °C for 1 h. The reaction mixture allowed to room temperature, diluted with water (50 ml) and extracted with $CHCl_3$ (2x 100 ml). The combined organic layer was washed with brine solution and dried over anhydrous Na_2SO_4, evaporated under reduced pressure to obtain the crude product. The crude product was purified by flash column chromatography (silica-gel:100-200 mesh) to afford (4*S*)-7-chloro-8-iodo-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (7.4 g, 20.53 mmol, 40.2 % yield) as a yellow solid (TLC System: Neat EtOAc, (R_f: 0.4). LCMS (*m/z*) 321.96, $[M+H]^+$.

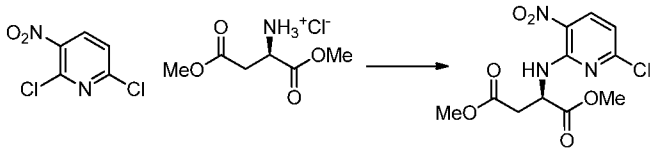
Synthesis (4*S*)-7-chloro-8-(trifluoromethyl)-2, 3, 4, 5-tetrahydro-1, 4-methanopyrido[2, 3-*b*][1, 4]diazepine



To a stirring solution of copper(I) chloride (1.355 g, 13.68 mmol), potassium tert-butoxide (1.535 g, 13.68 mmol) in DMPU (34 mL) were added trifluoromethyltrimethylsilane (1.983 mL, 13.68 mmol), 1,10-phenanthroline (2.466 g, 13.68 mmol) and (4*S*)-7-chloro-8-

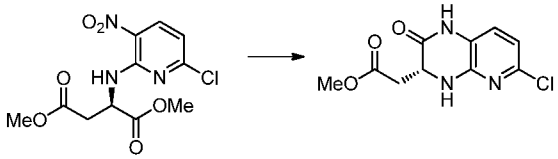
iodo-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (2.2 g, 6.84 mmol) at room temperature. The reaction mixture was stirred at RT for 24 h and poured the reaction mixture in to cold water (210 mL) and extracted with ethyl acetate (2x200 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under vacuum to obtain the crude compound. The crude product was purified by flash column chromatography (Silica-gel: 100-200 mesh, eluent: 3% CH_2Cl_2 in EtOAc) to afford (4*S*)-7-chloro-8-(trifluoromethyl)-2, 3, 4, 5-tetrahydro-1, 4-methanopyrido [2, 3-*b*][1, 4]diazepine (650 mg, 2.465 mmol, yield: 36.0 %) as an off white solid (TLC System: neat EtOAc, R_f: 0.5). LCMS (*m/z*): 264.14 $[M+H]^+$, Rt = 1.78 min.

Synthesis of (R)-dimethyl 2-((6-chloro-3-nitropyridin-2-yl)amino)succinate



To a suspension of (R)-dimethyl 2-aminosuccinate hydrochloride (25 g, 127 mmol) in Tetrahydrofuran (THF) (130 mL) was added sodium bicarbonate (21.25 g, 253 mmol) and 2,6-dichloro-3-nitropyridine (12.21 g, 63.3 mmol) under nitrogen. The reaction mixture was stirred at 40 °C for 16 hr. The reaction mixture was filtered and washed with EtOAc (3 X 25mL), the filtrate was concentrated to give the crude product which was then added to a silica gel column and was eluted with (9:1) Hex/EtOAc. Collected fractions were evaporated to obtain the desired product (16 g, 49.4 mmol, 39.0 %), LCMS (*m/z)* 318.1 $[M+H]^+$.

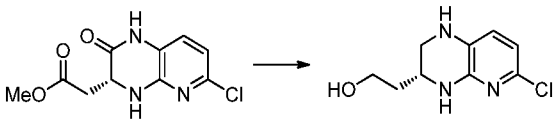
Synthesis of (R)-methyl 2-(6-chloro-2-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-3-yl)acetate



To a solution of (R)-dimethyl 2-((6-chloro-3-nitropyridin-2-yl)amino)succinate (16 g, 50.4 mmol) in isopropanol (200 mL) and Water (60 mL) was added iron (14.06 g, 252 mmol)heated to 40°C. To the above reaction mixture was added acetic acid (1.442 mL, 25.2 mmol) and heated to 70°C for 1hr. The reaction mixture was cooled to room temperature, filtered through celite and washed with EtOAc (3 X 20mL), the filtrate was concentrated and dried. The reaction crude was recrystallized from ethanol to give the

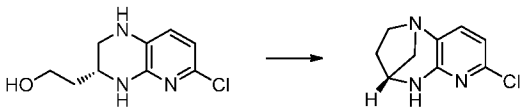
desired product (11.5 g, 43.4 mmol, 86 %), LCMS (*m/z)* 256.1 $[M+H]^+$.

Synthesis of (R)-2-(6-chloro-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-3-yl)ethanol



To a suspension of lithium aluminum hydride (8.54 g, 225 mmol) in Tetrahydrofuran (THF) (12 mL) was added a solution of (R)-methyl 2-(6-chloro-2-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-3-yl)acetate (11.5 g, 45.0 mmol) in Tetrahydrofuran (THF) (60 mL) dropwise at 0°C under Nitrogen atmosphere. The reaction mixture was heated to 70 °C for 16 hr. The reaction mixture was cooled to 0°C, quenched with water (8 mL), keeping the internal temperature below 5°C. After addition was complete, the reaction was stirred for 15 min. Next, 10mL of 15%(W/W) NaOH(aq.) was added, keeping the internal temp below 5°C, After addition was complete, the reaction was stirred for 15min.To complete the workup, 12mL of water was added then the mixture was stirred at room temperature for 1h.The solids were filtered and washed with THF(3x20mL)The filtrate and washings were concentrated in vacuo. The crude was added to a silica gel column and was eluted with (3:7) Hex/EtOAc. Collected fractions were evaporated to obtain the desired product (6 g, 27.0 mmol, 60.1 %), LCMS (*m/z*) 214.1 $[M+H]^+$.

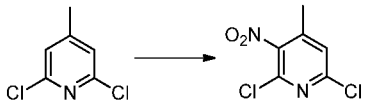
Synthesis of (4R)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine



To a solution of (R)-2-(6-chloro-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-3-yl)ethanol (7 g, 32.8 mmol) in dichloromethane (DCM) (70 mL) was added triethylamine (18.27 mL, 131 mmol) under nitrogen. The mixture was stirred at room temperature until it was homogeneous, Then it was cooled to 0°C.Next $POCl_3$ (4.58 mL, 49.1 mmol) was added dropwise maintaining the temperature 0°C to 5°C.The reaction mixture was stirred at 25 °C for 2 hr. After the reaction was completed 100mL 1.2M $NaHCO_3$(aq.) was added. The layers were separated and the aqueous layer was extracted with DCM (2x200mL).The combined organic layers were concentrated to dryness. The solid residue was dried in vacuo. The crude product 8g was added to a silica gel column and was eluted with 70%EtOAc/Pet ether. Collected fractions was evaporated to obtain the desired product (5.2 g, 26.5 mmol, 81 % yield), LCMS (*m/z)* 195.9 $[M+H]^+$.

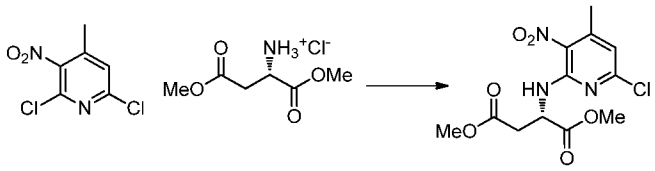
Synthesis of 4 substituted bicyclic pyridine core

Synthesis of 2,6-dichloro-4-methyl-3-nitropyridine



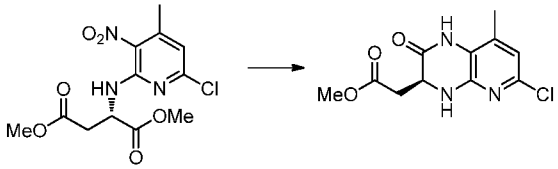
Nitric acid (1.5 mL, 33.6 mmol) was added to a solution of sulfuric acid (2.5 mL, 46.9 mmol) stirred under nitrogen at 0°C. Then 2,6-dichloro-4-methylpyridine (0.500 g, 3.09 mmol) was added at 0°C. Then the reaction mixture was stirred at 100 °C for 16 hr. The reaction was monitored by TLC. After completion, the reaction mixture was quenched with crushed ice and neutralized with NH_4OH solution and filtered the solid and dried under vacuum to give the desired product (0.300 g, 1.443 mmol, 46.8 % yield) as a pale yellow solid, LCMS (*m/z*) 206.8 $[M+H]^+$.

Synthesis of (S)-dimethyl 2-((6-chloro-4-methyl-3-nitropyridin-2-yl)amino)succinate



A suspension of 2,6-dichloro-4-methyl-3-nitropyridine (300 mg, 1.449 mmol) and sodium bicarbonate (243 mg, 2.90 mmol) in Tetrahydrofuran (THF) (20 mL)) was added (S)-dimethyl 2-aminosuccinate hydrochloride (430 mg, 2.174 mmol) at 0 °C under nitrogen. Then the reaction mixture was stirred at 65 °C for 24 hr. The reaction was monitored by TLC. The reaction mass filtered and washed with EtOAc (2 x 30 mL). The filtrate was concentrated under reduced pressure to give the crude material. The crude product was added to a neutral alumina column and was eluted with Hex/EtOAc (9:1).Collected fractions were concentrated under reduced pressure to afford the desired product (250 mg, 0.742 mmol, 51.2 % yield) as yellow gummy liquid, LCMS (*m/z*) 339.1 $(M+H)^+$.

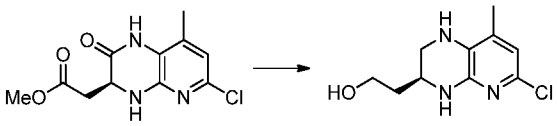
Synthesis of (S)-methyl 2-(6-chloro-8-methyl-2-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-3-yl)acetate



To a suspension of (S)-dimethyl 2-((6-chloro-4-methyl-3-nitropyridin-2-yl)amino)succinate (6.0 g, 18.09 mmol) and iron (5.05 g, 90 mmol) in isopropanol (80 mL)

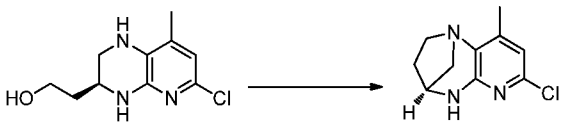
and Water (20 mL) stirred at 40 °C was added acetic acid (1.553 mL, 27.1 mmol). The reaction mixture was stirred at 80 °C for 1 hr. Reaction was monitored by TLC. The reaction mixture was cooled to room temperature, and quenched with saturated sodium bicarbonate solution and extracted with EtOAc. Organic layer washed with brine solution and dried out with sodium sulfate, filtered and evaporated to give the desired product (4.0 g, 14.32 mmol, 79 % yield), LCMS (*m/z*) 269.9 $[M+H]^+$.

Synthesis of (S)-2-(6-chloro-8-methyl-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-3-yl)ethanol



To a solution of aluminum chloride (0.173 g, 1.298 mmol), in Tetrahydrofuran (THF) (2.5 mL) stirred under nitrogen was added 2M solution of lithium aluminum hydride (2.220 mL, 4.44 mmol) in THF dropwise at a rate to control gas evolution. This gave a solution of alane (AlH3) in THF. In a separate flask, a solution of (S)-methyl 2-(6-chloro-8-methyl-2-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-3-yl)acetate (0.250 g, 0.927 mmol) in Tetrahydrofuran (THF) (5 mL) was prepared under nitrogen, to this was added the alane solution, dropwise at -78 °C over 15 minutes. When the addition was complete, the cooling bath was removed, and the reaction was allowed to warm to ambient temperature. The reaction was monitored by TLC. The reaction mixture was quenched with 10% NaOH solution at 0 °C and stirred 1 hr and extracted with EtOAc. EtOAc layer washed with water followed by brine solution and dried out with sodium sulfate, filtered and concentrated to give the desired product (150 mg, 0.407 mmol, 43.9 % yield) as a pale yellow solid, LCMS (*m/z*) 228.2 $[M+H]^+$.

Synthesis of (4S)-7-chloro-9-methyl-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine

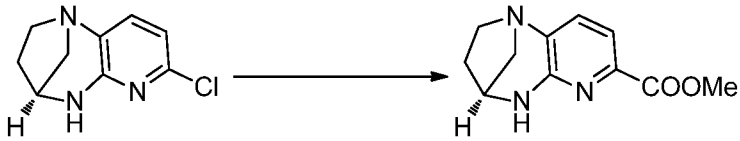


To (S)-2-(6-chloro-8-methyl-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-3-yl)ethanol (1.8 g, 7.91 mmol), was added HBr (4 mL, 35.4 mmol), the reaction mixture was stirred at 90 °C

for 18 hr. The reaction was monitored by TLC. Following completion, the reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with EtOAc. EtOAc layer washed with water followed by brine solution and dried out with sodium sulfate, filtered and concentrated to give crude product. The crude product was added to a neutral alumina and was eluted with 20% EtOAc/Hexane. Collected fractions were evaporated to afford the desired product (0.900 g, 4.27 mmol, 54.0 % yield) as a pale yellow solid, LCMS (*m/z*) 210.2 $[M+H]^+$.

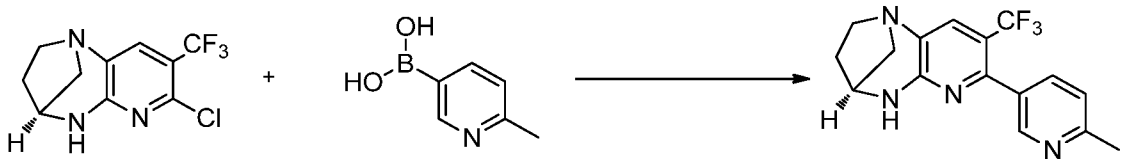
Chloride Coupling Reactions

Synthesis of (4S)-methyl 2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine-7-carboxylate



To a degassed solution of (4*S*)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (5 g, 25.55 mmol) in anhydrous MeOH (250 ml) were added TEA (17.77 mL, 127.77 mmol) and $Pd(dppf)Cl_2$ (934 mg, 1.2755 mmol) and the reaction mixture was stirred at 110 °C for 20 h under carbon monoxide atmosphere of 300 psi. The suspension was cooled to room temperature and the mixture was concentrated under reduced pressure to afford crude compound. The crude mixture was purified by flash column chromatography (100-200 silica-gel, was eluted with 2% Methanol in DCM) to afford (4*S*)-methyl-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-7-carboxylate (3 g, 13.68 mmol, 53.5 % yield) as a pale brown solid (TLC system: 5% Methanol in DCM, R_f value: 0.2), LCMS (*m/z*) 220.3 $[M+H]^+$.

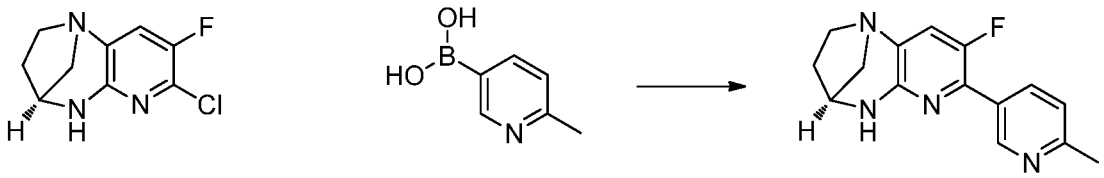
Synthesis of (4*S*)-7-(6-methylpyridin-3-yl)-8-(trifluoromethyl)-2, 3, 4, 5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine



To a degassed solution of (4*S*)-7-chloro-8-(trifluoromethyl)-2, 3, 4, 5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (350 mg, 1.328 mmol), (6-methylpyridin-3-yl)boronic acid (273 mg, 1.991 mmol) and K_3PO_4 (1096 mg, 3.98 mmol) in 1,4-dioxane (10 mL) and

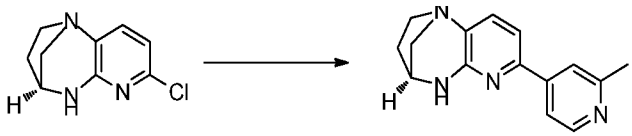
water (3 mL) were added $Pd_2(dba)_3$ (122 mg, 0.133 mmol) and x-phos (633 mg, 1.328 mmol). The reaction mixture was stirred at 100 °C for 7 h. The reaction mixture allowed to room temperature and diluted with water (70 mL), extracted with ethyl acetate (3 X 150 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product. The crude mixture was triturated with pet ether (3x25 mL) and dried under vacuum to afford (4*S*)-7-(6-methylpyridin-3-yl)-8-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (370 mg, 1.040 mmol, yield: 78 %) as an off white solid (TLC System: 5% Methanol in EtOAc, Rf: 0.3). LCMS (*m/z*) 320.90 $[M+H]^+$.

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



K_3PO_4 (397 mg, 1.872 mmol) was added to a stirred solution of (4S)-7-chloro-8-fluoro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (200 mg, 0.936 mmol) & (6-methylpyridin-3-yl)boronic acid (167 mg, 1.217 mmol) in 1,4-dioxane (10 mL) and water (1 mL) then degassed for 15 min before adding x-phos (44.6 mg, 0.094 mmol) followed by addition of $Pd_2(dba)_3$ (42.9 mg, 0.047 mmol). The reaction was heated at 90 °C for 2 h 45 min. The reaction mixture was cooled to RT, filtered through a pad of celite, washed with ethyl acetate (10 mL x2), and the solvent removed under reduced pressure. The organic compound was extracted with ethyl acetate (20 mL x2), washed with water (2 x 20 mL) and brine (20 mL). The extracts were dried over anhyd. Na_2SO_4 and the solvent removed *in* vacuo to afford crude compound. The crude compound was purified by column chromatography using 100-200 silica gel and eluting with 1% MeOH in DCM to afford (4S)-8-fluoro-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (220 mg, 0.705 mmol, 75 % yield) as an off-white solid, LCMS (*m/z*) 271.15 $[M+H]^+$.

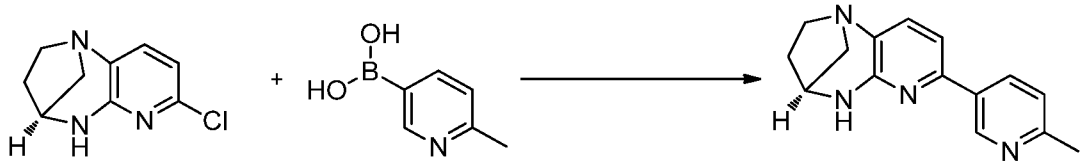
Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine



To a degassed solution of (4*S*)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (30 g, 153 mmol), (2-methylpyridin-4-yl)boronic acid (25.2 g, 184 mmol) and Potassium Phosphate Tri basic (65.1 g, 307 mmol) in 1-butanol (300 mL) and water (50.0 mL) were added tris(dibenzylideneacetone)dipalladium(0) (7.02 g, 7.67 mmol) and dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (7.31 g, 15.33 mmol). The reaction mixture was heated at 100 °C for 3h. The n-butanol solvent was evaporated under reduced pressure. The resulting residue was diluted with water (200 ml) and extracted with DCM (2x 400 ml). The combined organic layer was washed with water, brine, dried over sodium sulfate and solvent was evaporated under reduced pressure to obtain the crude product. The crude product was triturated with diethyl ether and n-pentane (1:1) for 3 times (3X250 mL) afford (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (25 g, 99.2 mmol, 62%) as an off white solid (TLC: 10% MeOH in EtOAc R_f: 0.2), LCMS (*m/z*) 252.9 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.45 (dd, *J* = 5.2, 0.8 Hz, 1H), 7.73 (dt, *J* = 1.4, 0.7 Hz, 1H), 7.67 - 7.60 (m, 1H), 7.24 - 7.16 (m, 2H), 7.10 (d, *J* = 7.7 Hz, 1H), 3.93 (td, *J* = 5.0, 2.5 Hz, 1H), 3.19 - 2.98 (m, 2H), 2.92 - 2.71 (m, 2H), 2.50 (s, 3H), 2.11 - 1.96 (m, 1H), 1.94 - 1.81 (m, 1H).

Synthesis of (4*S*)-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine .

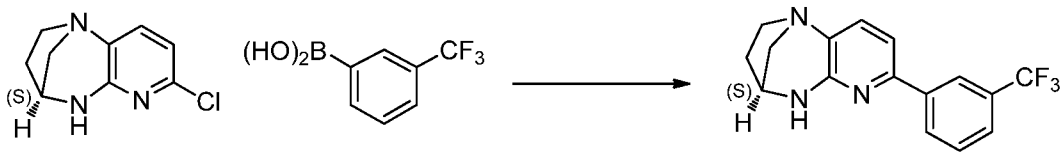


To a degassed solution of (4*S*)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (10 g, 51.1 mmol), (6-methylpyridin-3-yl)boronic acid (10.50 g, 77 mmol) and Potassium Phosphate Tri basic (21.70 g, 102 mmol) in 1,4-dioxane (100 mL) and water (20.0 mL) were added tris(dibenzylideneacetone)dipalladium(0) (4.68 g, 5.11 mmol) and x-phos (4.87 g, 10.22 mmol). The reaction mixture was heated at 100 °C for 8h. The solvent was evaporated under reduced pressure; the obtained residue was diluted

with water (200 ml) and extracted with DCM (2x 100 ml). The combined organic layer was washed with water, brine, dried over sodium sulfate and solvent was evaporated under reduced pressure to obtain the crude product. The crude product was triturated with diethyl ether and n-pentane (1:1) for 3 times (3X100 mL) to afford (4S)-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine. (11.2 g, 44.4 mmol, 65 %) as an off white solid (TLC: 10% MeOH in EtOAc R_f: 0.3). LCMS (*m/z*): 253.1 [M+H], Rt =2.86 min.

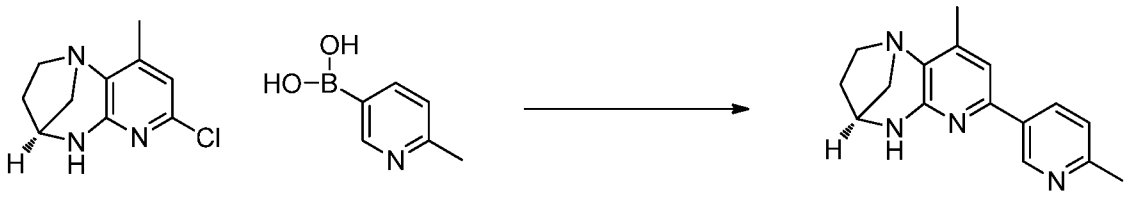
^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.97 (d, *J*=2.19 Hz, 1 H), 8.06 (dd, *J*=8.11, 2.41 Hz, 1 H), 7.28 - 7.11 (m, 1 H), 6.94 (d, *J*=7.89 Hz, 1 H), 6.74 (d, *J*=7.67 Hz, 1 H), 5.21 (s, 1 H), 4.08 – 3.98 (m, 1 H), 3.36 - 3.12 (m, 3 H), 2.99 - 2.89 (m, 1 H), 2.56 (s, 3 H), 2.17 - 2.10 (m, 2 H).

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



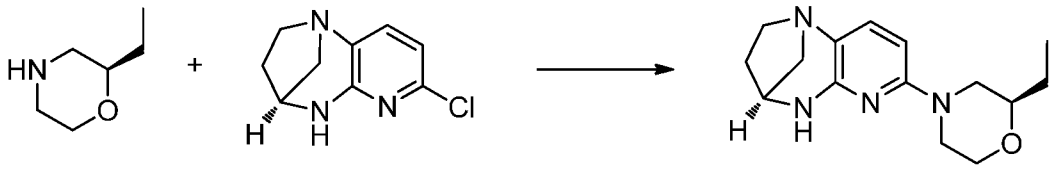
A suspension of (4S)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (20 g, 102 mmol), (3-(trifluoromethyl)phenyl)boronic acid (29.1 g, 153 mmol) and Cs_2CO_3 (100 g, 307 mmol)in 1,4-Dioxane (100 mL) and Water (10 mL) was stirred and degassed with argon at room temp for 15 mins. Next, palladium(II) acetate (0.574 g, 2.56 mmol) and 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (2.437 g, 5.11 mmol) were added to the reaction mixture. Then the reaction mixture was stirred at110 °C for 2 hr. The reaction mass was filtered through celite and concentrated. The residue was diluted with EtOAc and washed with saturated $NaHCO_3$ followed by brine solution and dried out with sodium sulfate, filtered and evaporated. The crude product was added to a silica gel column and was eluted with Hex/EtOAc (1:1). Collected fractions were evaporated to afford (4S)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (18 g, 58.3 mmol, 57.0 % yield) as white solid, LCMS (*m/z*) 306.1 $(M+H)^+$.

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



A suspension of (4S)-7-chloro-9-methyl-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (0.900 g, 4.29 mmol) , (6-methylpyridin-3-yl)boronic acid (0.882 g, 6.44 mmol) and tripotassium phosphate (2.73 g, 12.88 mmol) in 1,4-Dioxane (14.4 mL) & Water (3.6 mL) was stirred and degassed with argon at room temp for 15 mins. Then $Pd_2(dba)_3$ (0.393 g, 0.429 mmol) and X-Phos (0.409 g, 0.858 mmol) were added to the reaction mixture. The reaction mixture was stirred 16 hr at 90 °C. The reaction was monitored by TLC (50% EtOAc/Hexanes). The reaction mixture was cooled to room temp and filtered through celite and washed with EtOAc. The filtrate was concentrated and dissolved with EtOAc. The EtOAc layer was washed with water followed by brine solution and dried over sodium sulfate, filtered and concentrated to give crude(4S)-9-methyl-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (0.700g, 2.60 mmol, 60.7 % yield) as a off-white solid, LCMS (*m/z*) 267.0 $[M+H]^+$.

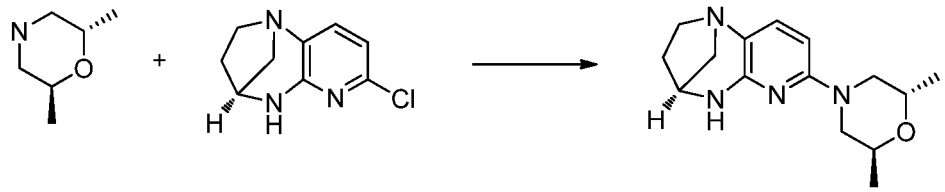
Synthesis of (2R)-2-ethyl-4-((4S)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepin-7-yl)morpholine



A suspension of (4S)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (900 mg, 4.60 mmol), (R)-2-ethylmorpholine (1060 mg, 9.20 mmol) and KOtBu (1032 mg, 9.20 mmol) in 1,2-Dimethoxyethane (DME) (20 mL) stirred under nitrogen and degassed at room temperature for 15 min, was added (1,3-Bis(2,6-di-isopropylphenyl)-4,5-dihydroimidazol-2-ylidene)chloro) (3-phenylallyl)palladium(2) (120 mg, 0.184 mmol). The reaction mixture was stirred at 90 °C for 12 hr. The reaction mass filtered through celite pad and the filtrate concentrated. Reaction mixture was diluted with water and extracted with EtOAc (2 x 20 mL). The organic layers were washed with water followed

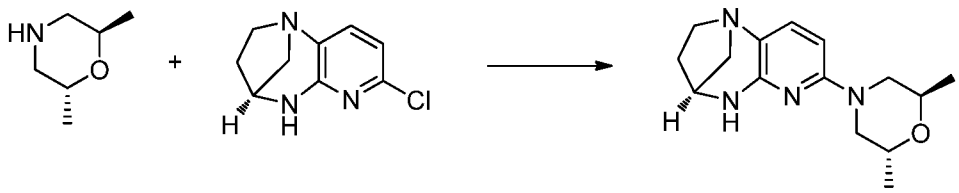
by brine solution and dried out with sodium sulfate. The organic layer was concentrated under reduced pressure. The Crude compound was purified by column chromatography (Neutral alumina) product was eluted with 20% ethyl acetate in hexane. Collected fractions evaporated under reduce pressure and dried under high vacuum to afford (2R)-2-ethyl-4-((4S)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepin-7-yl)morpholine (750 mg, 2.73 mmol, 59.4 % yield) as a Pale yellow solid, LCMS (*m/z*) 275.3 $[M+H]^+$.

Synthesis of (2S,6S)-2,6-dimethyl-4-((4S)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepin-7-yl)morpholine



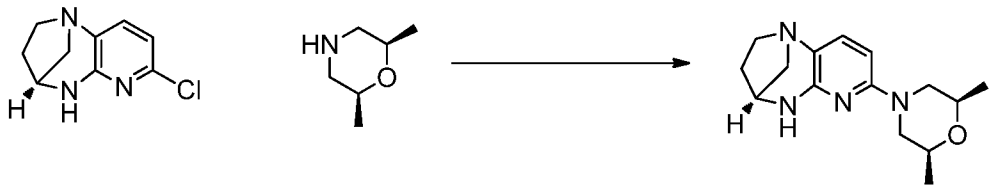
A suspension of (4S)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (0.800 g, 4.09 mmol), (2S,6S)-2,6-dimethylmorpholine (0.942 g, 8.18 mmol) and KOtBu (0.918 g, 8.18 mmol) in 1,2-Dimethoxyethane (DME) (30 mL) was stirred and degassed with argon at room temp for 15 mins. Then (1,3-Bis(2,6-di-isopropylphenyl)-4,5-dihydroimidazol-2-ylidene)chloro) (3-phenylallyl)palladium(II) (0.106 g, 0.164 mmol) added to the reaction mixture. Then the reaction mixture was stirred 16 hr at 90 °C. The reaction was monitored by TLC. After completion, the reaction mass filtered through celite and the filtrate concentrated under reduced pressure. The resulting reaction mixture was diluted with EtOAc and washed with water followed by brine solution and dried out with sodium sulfate, filtered and evaporated to get crude. The crude product was added to a neutral alumina and was eluted with (1:2) EtOAc/Hexane. Collected fractions were evaporated to afford (2S,6S)-2,6-dimethyl-4-((4S)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepin-7-yl)morpholine (0.780 g, 2.79 mmol, 68 % yield) as a off-white solid, LCMS (*m/z*) 275.3 $[M+H]^+$.

Synthesis of (2R,6R)-2,6-dimethyl-4-((4S)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepin-7-yl)morpholine



A suspension of (4S)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (0.800 g, 4.09 mmol), (2R,6R)-2,6-dimethylmorpholine (0.942 g, 8.18 mmol) and KOtBu (0.918 g, 8.18 mmol) in 1,2-Dimethoxyethane (DME) (30 mL) stirred and degassed with argon at room temperature for 15 mins. Then (1,3-Bis(2,6-di-isopropylphenyl)-4,5-dihydroimidazol-2-ylidene)chloro) (3-phenylallyl)palladium(2) (0.106 g, 0.164 mmol) added to the reaction mixture. Then the reaction mixture was stirred 16 hr at 90 °C. The reaction was monitored by TLC (TLC:100% EtOAc R_f value: 0.2). The reaction mass filtered through celite and distill out the solvent completely. Reaction mixture was diluted with EtOAc and washed with water followed by brine solution and dried out with sodium sulfate, filtered and evaporated to get crude. The crude product was added to a neutral alumina and was eluted with (1:1) EtOAc/Hexane. Collected fractions were evaporated to afford (2R,6R)-2,6-dimethyl-4-((4S)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepin-7-yl)morpholine (0.800 g, 2.75 mmol, 67.3 % yield) as an off-white solid, LCMS (*m/z*) 275.0 $[M+H]^+$.

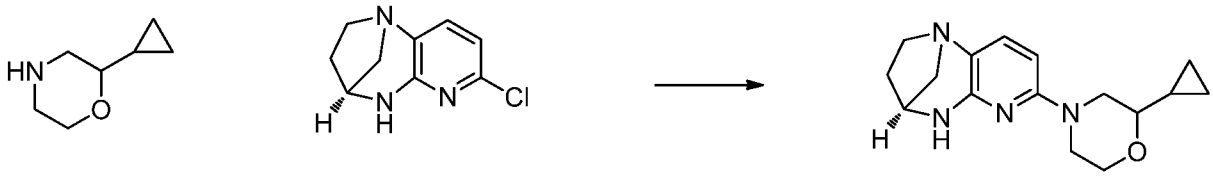
Synthesis of (2S,6R)-2,6-dimethyl-4-((4S)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepin-7-yl)morpholine



A suspension of (4S)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1.00 g, 5.11 mmol) , (2S,6R)-2,6-dimethylmorpholine (1.177 g, 10.22 mmol) and KOtBu (1.147 g, 10.22 mmol) in 1,2-Dimethoxyethane (DME) (20 mL) was stirred and degassed with argon at room temp for 15 mins. Then (1,3-Bis(2,6-di-isopropylphenyl)-4,5-dihydroimidazol-2-ylidene)chloro) (3-phenylallyl)palladium(II) (0.133 g, 0.204 mmol) was added to the reaction mixture. The reaction mixture was stirred 16 hr at 90 °C. The reaction mass was filtered through celite and the solvent evaporated. The reaction mixture

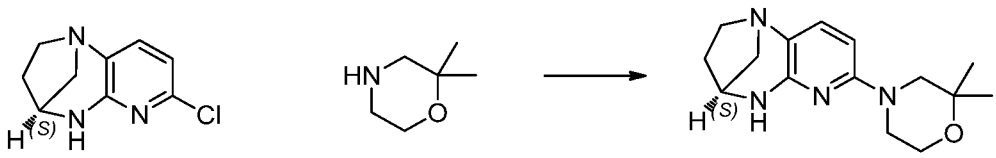
was diluted with EtOAc and washed with water followed by brine solution and dried over sodium sulfate, filtered and evaporated to give crude (2S,6R)-2,6-dimethyl-4-((4S)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepin-7-yl)morpholine (0.820 g, 2.86 mmol, 56.0 % yield). The crude product was added to neutral alumina and was eluted with 20% EtOAc/Hexane to afford (2S,6R)-2,6-dimethyl-4-((4S)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepin-7-yl)morpholine (0.820 g, 2.86 mmol, 56.0 % yield) as an off-white solid, LCMS (*m/z*) 275.2 $[M+H]^+$.

Synthesis of 2-cyclopropyl-4-((4S)-2,3,4,5-tetrahydro-1, 4-methanopyrido [2, 3-*b*] [1, 4] diazepine-7-morpholine



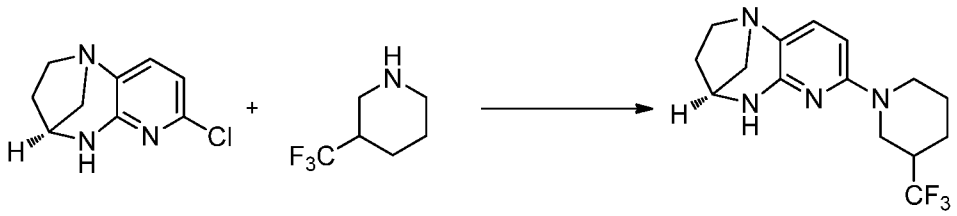
To a solution of (4S)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1 g, 5.11 mmol) in 1,2-Dimethoxyethane (DME) (15 mL) with stirring at 0°C was added 2-cyclopropylmorpholine (0.650 g, 5.11 mmol) and potassium tert-butoxide (0.574 g, 5.11 mmol). The solution was then degassed for 15 min and cinnamyl chloro[1,3-bis(diisopropylphenyl)-2-imidazolidinyliin]Pd(II) (3.32 g, 5.11 mmol) was added. The reaction was then stirred for 16 h at 90°C. The reaction mixture was quenched with 15 ml of water and extracted with 15 ml of ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to afford the crude compound. The crude product was added to a 100-200 silica gel column and was eluted with 2% DCM/MeOH 2-cyclopropyl-4-((4S)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepin-7-yl)morpholine (1 g, 3.49 mmol, 68.3 % yield) to give the product as an off white solid, LCMS (*m/z*) 287.2 $[M+H]^+$.

Synthesis of 2,2-dimethyl-4-((4S)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepin-7-yl)morpholine



A suspension of (4S)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1.0 g, 5.11 mmol), 2,2-dimethylmorpholine (1.177 g, 10.22 mmol) and KOtBu (1.147 g, 10.22 mmol) in 1,2-Dimethoxyethane (DME) (20 mL) was stirred and degassed with argon at room temp for 15 mins. Then (1,3-Bis(2,6-di-isopropylphenyl)-4,5-dihydroimidazol-2-ylidene)chloro) (3-phenylallyl)palladium(2) (0.133 g, 0.204 mmol) was added to the reaction mixture. The reaction mixture was stirred 16 hr at 90 °C. The reaction mass was filtered through celite and the solvent evaporated. The reaction mixture was diluted with EtOAc and washed with water followed by brine solution. The solution was dried over sodium sulfate, filtered and evaporated to give the crude product. The crude product was added to a neutral alumina column and was eluted with DCM to afford 2,2-dimethyl-4-((4S)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepin-7-yl)morpholine (0.800 g, 2.67 mmol, 52.3 % yield) as a white solid, LCMS (*m/z*) 275.0 $[M+H]^+$.

Synthesis of (4*S*)-7-(3-(trifluoromethyl)piperidin-1-yl)-2,3,4,5-tetrahydro-1,4-methano pyrido[2,3-*b*][1,4]diazepine

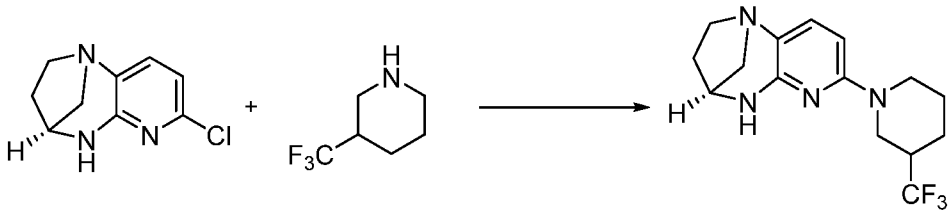


To a degassed solution of (4S)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 2.56 mmol), 3-(trifluoromethyl)piperidine (783 mg, 5.11 mmol (S-isomer with unequal enatiomeric mixture)) in 1,2-dimethoxy ethane (15 mL) were added potassium tert-butoxide (574 mg, 5.11 mmol) and Umicorecatalyst (33.2 mg, 0.051 mmol) at 30 °C. The reaction mixture was heated at 80 °C for 17 h. The reaction mixture was cooled RT and poured in cold water (70 mL), extracted with ethyl acetate (2x150 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, eluent: 1 to 3% of methanol in ethyl acetate) to afford 400mg of (4S)-7-(3-(trifluoromethyl)piperidin-1-yl)-2,3,4,5-tetrahydro-1,4-methanopy rido[2,3-b][1,4]diazepine. Chiral HPLC indicated 53:44 enantiomeric mixture, this unequal mixture of enantiomers were purified by chiral prep HPLC to obtained two separated peaks (Chiral Prep conditions: 4g-40%-100bar 10

0.5%DEA in Methanol, chiralpak, AD-H (4.6mm*250mm)) as fastest eluent peak: 210 mg **(peak-I**, 0.673 mmol, 15% yield) as a white solid (TLC: 10% MeOH in EtOAc R_f: 0.4) and slowest eluent peak: 310 mg (**peak-II**, 310 mg, 0.993 mmol, 22%) as a white solid (TLC: 10% MeOH in EtOAc, R_f: 0.4), LCMS (*m/z*) 313.2 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 6.92 (d, *J*=8.33 Hz, 1 H), 6.56 (d, *J*=4.38 Hz, 1 H), 5.83 (d, *J*=8.11 Hz, 1 H), 4.43 (d, *J*=12.28 Hz, 1 H), 3.93 (d, *J*=12.28 Hz, 1 H), 3.87 - 3.72 (m, 1 H), 3.10 – 2.83 (m, 2 H), 2.82 - 2.71 (m, 1 H), 2.70 - 2.55 (m, 3 H), 2.46 - 2.18 (m, 1 H), 2.11 – 1.86 (m, 2 H), 1.86 - 1.65 (m, 2 H), 1.55 - 1.32 (m, 2 H).

Synthesis of (4*S*)-7-(3-(trifluoromethyl)piperidin-1-yl)-2,3,4,5-tetrahydro-1,4-methano pyrido[2,3-*b*][1,4]diazepine

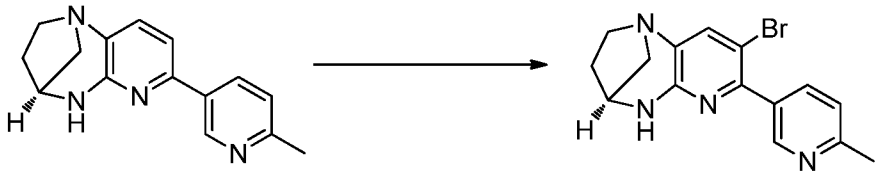


To a degassed solution of (4S)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 2.56 mmol), (R-isomer with unequal enatiomeric mixture) 3-(trifluoromethyl)piperidine (783 mg, 5.11 mmol) in 1,2-dimethoxy ethane (15 mL) were added potassium tert-butoxide (574 mg, 5.11 mmol) and Umicorecatalyst (33.2 mg, 0.051 mmol) at 30 °C. The reaction mixture was heated at 80 °C for 17 h. The reaction mixture was cooled to room temperature and poured in cold water (70 mL), extracted with ethyl acetate (2x150 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, eluent: 1 to 3% of methanol in ethyl acetate) to afford (4S)-7-(3-(trifluoromethyl)piperidin-1-yl)-2,3,4,5-tetrahydro-1,4-methanopy rido[2,3-b][1,4]diazepine. After column chromatography 500 mg of compound was isolated, Chiral HPLC indicated 36:63 enantiomeric mixture, this unequal mixture of enantiomers were purified by chiral prep HPLC to obtained two separated peaks (Chiral Prep conditions: 4g-40%-100bar 10 0.5%DEA in Methanol, chiralpak, AD-H (4.6*250) mm5u) as fastest eluent peak:140 mg (peak-I) and slowest eluent peak: 310 mg (**peak-II**, 310 mg, 0.993 mmol, 22%) as a white solid (TLC: 10% MeOH in EtOAc, R_f: 0.4), LCMS (*m/z*) 313.2$[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 6.92 (d, *J*=8.33 Hz, 1 H), 6.56 (d, *J*=4.60 Hz, 1 H), 5.83 (d, *J*=8.33 Hz, 1 H), 4.41 (dt, *J*=12.50, 1.86 Hz, 1 H), 3.93 (d, *J*=12.50 Hz, 1 H), 3.81 (td, *J*=4.88, 2.74 Hz, 1 H), 3.07 – 2.88 (m, 2 H), 2.80 - 2.55 (m, 4 H), 2.48 - 2.27 (m, 1 H), 2.01 – 1.88 (m, 2 H), 1.85 - 1.65 (m, 2 H), 1.52 - 1.38 (m, 1 H), 1.36 - 1.20 (m, 1 H).

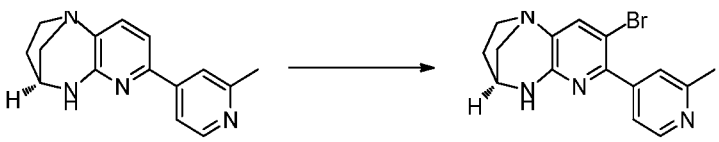
Modification of 3-Substituted pyridine bi-aryl compounds

Synthesis of (4*S*)-8-bromo-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methano pyrido[2,3-*b*][1,4]diazepine



To a solution of (4*S*)-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (1 g, 3.96 mmol) in chloroform (10 mL) stirred under nitrogen at 20°Cwas added NBS (0.776 g, 4.36 mmol). The reaction mixture was stirred at 70 °C for 2 h. The reaction mixture was allowed to room temperature and quenched with sat. $NaHCO_3$, extracted with $CHCl_3$ (2x 100 ml). The combined organic layer was washed with brine solution and dried over anhydrous Na_2SO_4, evaporated under reduced pressure to obtain the crude compound. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 3% MeOH in EtOAc) to afford (4*S*)-8-bromo-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (650 mg, 1.962 mmol, yield: 49.5 %) as a yellow solid(TLC System: 10% MeOH in EtOAc, R_f: 0.4), LCMS (*m/z*) 331.1 $[M+H]^+$.

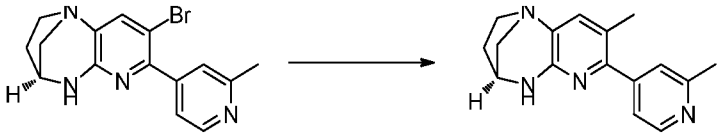
Synthesis of (4S)-8-bromo-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine



To a solution of (4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (10 g, 39.6 mmol) in Chloroform (150 mL) stirred under nitrogen at 25°C was added NBS (7.76 g, 43.6 mmol). The reaction mixture was stirred at 70 °C for 2 h. The reaction mixture allowed to room temperature and reaction was quenched with sat $NaHCO_3$ (100 ml) and extracted with $CHCl_3$ (2x 150 ml). Combined organic layer washed

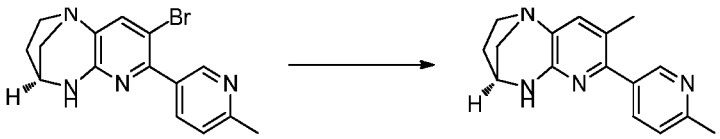
with brine solution and dried over Na_2SO_4. Then evaporated under reduced pressure gave crude compound. Crude product was purified by using flash chromatography (100-200 mesh) to obtained (4S)-8-bromo-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (4.5 g, 13.27 mmol, 33.5 % yield) as a yellow solid (TLC System: 10% MeOH/ EtOAC, R_f 0.3), LCMS (*m/z*) 330.9 $[M+H]^+$.

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



To a degassed a solution of (4S)-8-bromo-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1 g, 3.02 mmol), methylboronic acid (0.271 g, 4.53 mmol) and K_3PO_4 (2.493 g, 9.06 mmol) in 1,4-Dioxane (20 mL) and Water (5 mL), was added solid $Pd_2(dba)_3$ (0.276 g, 0.302 mmol) and X-Phos (0.288 g, 0.604 mmol). The reaction mixture was stirred at 100 °C for 15 hr. The reaction was monitored by TLC and LCMS (TLC System:- 5% methanol in ethyl acetate, R_f: 0.3,). The reaction mixture was diluted with water (150 mL) and extracted with ethyl acetate (3 x 350 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. Collected fractions: were concentrated to give (4S)-8-methyl-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (0.45 g, 1.436 mmol, 47.6 % yield), LCMS (*m/z*) 267.0 $[M+H]^+$.

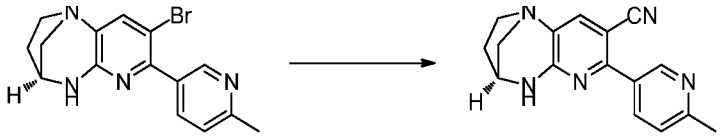
Synthesis of (4*S*)-8-methyl-7-(6-methylpyridin-3-yl)-2, 3, 4, 5-tetrahydro-1, 4-methano pyrido [2, 3-*b*][1,4]diazepine:



To a degassed solution of (4*S*)-8-bromo-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (1 g, 3.02 mmol), methylboronic acid (0.271 g, 4.53 mmol) and K_3PO_4 (2.493 g, 9.06 mmol) in 1,4-dioxane (20 mL) and water (5 mL), were added $Pd_2(dba)_3$ (0.276 g, 0.302 mmol) and x-phos (0.288 g, 0.604 mmol). The reaction mixture was stirred at 100 °C for 15 h. The reaction mixture was cooled to room

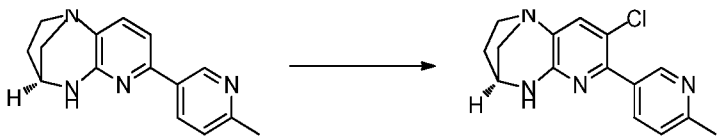
temperature, diluted with water (150 mL) and extracted with ethyl acetate (3 x 350 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude compound. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, was eluted with 3% CH_2Cl_2/EtOAc) to afford (4*S*)-8-methyl-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (550 mg, 2.044 mmol, 67.7 %) as a yellow solid (TLC System: 5% methanol in ethyl acetate, R_f: 0.3), LCMS (*m/z*). 267.3 $[M+H]^+$.

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



To a degassed solution of (4*S*)-8-bromo-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (600 mg, 1.812 mmol), $Zn(CN)_2$ (638 mg, 5.43 mmol) and added $Zn(OAc)_2$ (199 mg, 1.087 mmol) in N,N-Dimethylformamide (DMF) (12 mL) was added $Pd_2(dba)_3$ (332 mg, 0.362 mmol) and DPPF (402 mg, 0.725 mmol) at room temperature. The reaction mixture was stirred at 100 °C for 3 h and allowed to room temperature, diluted with water (30 mL), extracted with ethyl acetate (3 X 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude compound. The crude compound was purified by flash column chromatography (silica-gel: 100-200 mesh) to afford (4*S*)-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine-8-carbonitrile (350 mg, 1.262 mmol, yield: 69.7 %) as a yellow solid (TLC System: 10% MeOH in EtOAc, R_f: 0.3), LCMS (*m/z*) 278.2, $[M+H]^+$.

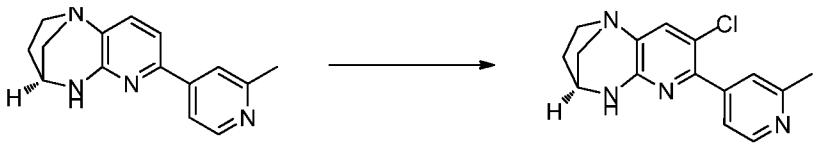
Synthesis of (4*S*)-8-chloro-7-(6-methylpyridin-3-yl)-2, 3, 4, 5-tetrahydro-1, 4-methanopyrido[2, 3-*b*][1, 4]diazepine



To a stirring solution of (4*S*)-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (1 g, 3.96 mmol) in chloroform (15 mL) was added *N*-chloro succinimide (NCS, 1.058 g, 7.93 mmol) at room temperature. The reaction mixture was stirred at 70 °C for 3 h and allowed to room temperature, diluted with water

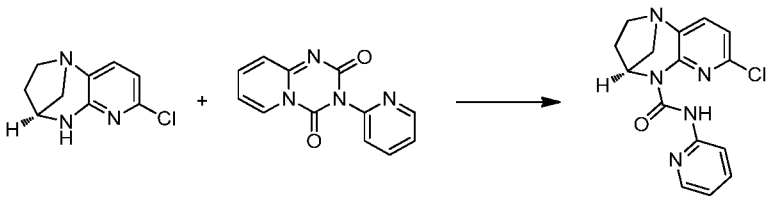
(20 ml) and extracted with CH_2Cl_2 (2x 20 ml). The combined organic layer was washed with brine and dried over sodium sulfate, evaporated under reduced pressure to obtain the crude product. The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 3% MeOH in EtOAc) to afford (4*S*)-8-chloro-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 1.032 mmol, 26.0 % yield) as an off white solid (TLC System: 10% MeOH in EtOAc, R_f 0.4), LCMS (*m/z*) 287.11 $[M+H]^+$.

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



To a stirred solution of (4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (2.5 g, 9.91 mmol) in $CHCl_3$ (25 mL), was added 1-chloropyrrolidine-2,5-dione (1.59 g, 11.9 mmol) at RT. The reaction solution was allowed to stir for 2 h at 60 C. The reaction solution was partitioned between $CHCl_3$ and H_2O. The organic layer was separated, dried over Na_2SO_4, concentrated under vacuum and applied directly to a silica gel column using EtOAc/EtOH (3:1) as eluent to give (1.5 g, 52%) as a yellow foam. LCMS (*m/z*) 287 $[M+H]^+$.

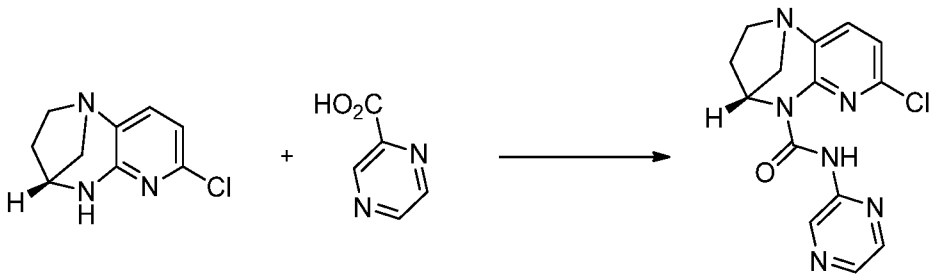
Synthesis of (4S)-7-chloro-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



To a solution of (4S)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1.2g, 6.13 mmol) in Tetrahydrofuran (THF) (50 mL) stirred under nitrogen at 0°Cwas added 3-(pyridin-2-yl)-2H-pyrido[1,2-a][1,3,5]triazine-2,4(3H)-dione (1.768 g, 7.36 mmol). The reaction mixture was stirred at 80 °C for 16 hr before being poured in to cold water (100 mL) and extracted with ethyl acetate (200 mL), The organic layer was successively washed with water (70 mL) and brine (70 mL), dried over anhydrous sodium

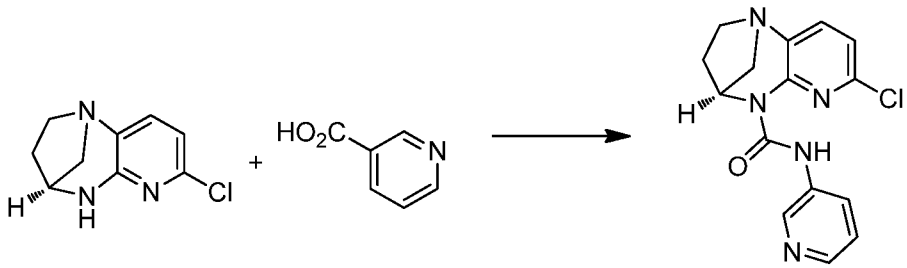
sulfate under reduced pressure. The crude residue was purified by column chromatography using (100-200 mesh) gradient mixture of 30% to 70 % as eluent. To give 1.3g (66%) of the title compound as an off white mass, LCMS (*m/z*) 316.2 $(M+H)^+$.

Synthesis of (4R)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



To a solution of pyrazine-2-carboxylic acid (800 mg, 6.45 mmol), DPPA (3548 mg, 12.89 mmol) and triethylamine (4.49 mL, 32.2 mmol) in Tetrahydrofuran (THF) (30 mL) stirred under nitrogen at 0°C was added. The reaction was stirred and warmed to RT for 2 h. Next, (4R)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1009 mg, 5.16 mmol). The reaction mixture was stirred at 90 °C for 16 hr. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (200 mL X2). 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 Hex/EtOAc. Collected fractions to give the desired product (1.4 g, 3.71 mmol, 58%), LCMS (*m/z*) 317.2 $(M+H)^+$.

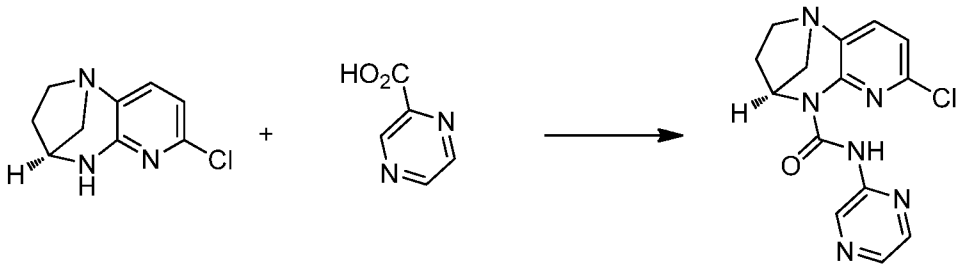
Synthesis of (4S)-7-chloro-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



DIPEA (31.9 mL, 183 mmol) followed by DPPA (15.09 g, 54.8 mmol) were added to a stirred solution of nicotinic acid (4.5 g, 36.6 mmol) in Tetrahydrofuran (THF) (60 mL) at RT and stirred for 2 h. Then (4S)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (5.01 g, 25.6 mmol) was added to the reaction mixture and stirred to 80

°C for 16 h. Reaction mixture was cooled to room temperature, diluted with water (60 mL), extracted with ethyl acetate (2X50 mL), washed with brine (50 mL). Organic layer was separated, dried over sodium sulfate, filtered and concentrated to get crude compound. Crude compound was purified by column chromatography using silica gel (100-200 mesh), 1% methanol in DCM to give the desired product (4 g, 12.03 mmol, 32.9 % yield), LCMS: (*m/z*) 316.2 $(M+H)^+$.

Synthesis of (4S)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



To a stirred solution of pyrazine-2-carboxylic acid (4.08 g, 32.9 mmol) in Tetrahydrofuran (THF) (100 ml) at 0C was added diphenyl phosphorazidate (14.19 ml, 65.8 mmol) followed by TEA (22.94 ml, 165 mmol). The solution was warmed to room temperature and stirring continued for 3h. Next, solid (4S)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (5.6 g, 28.6 mmol) was added and the mixture heated to reflux. The reaction was stirred for 2h at reflux before being cooled to RT and stirring was continued overnight. The next day, the mixture was diluted with water and extracted with EtOAc (three times). The combined EtOAc Extracts were dried over Na_2SO_4 and concentrated to give the crude product. The dark residue purified by silica gel chromatography: 330g column, 100ml/min, 0-25%EtOAc/MeOH over 30min. The fractions containing product were combined to give the desired product as yellow oil. To this oil was added Et_2O (50ml) and it was concentrated under reduced pressure. This caused the product to crystallize to a light yellow solid (6.9g, 76% yield). ^1H NMR (400 MHz, $CDCl_3$) δ=12.61 (s, 1H), 9.47 (d, *J* = 1.4 Hz, 1H), 8.68 – 7.99 (m, 2H), 7.50 (d, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 5.65 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.30 – 3.15 (m, 1H), 3.11 (dt, *J* = 12.1, 2.1 Hz, 1H), 3.00 (dd, *J* = 12.1, 3.2 Hz, 1H), 2.39 – 2.22 (m, 1H), 2.11 – 1.97 (m, 2H); LCMS (*m/z*) 316.9 $(M+H)^+$.

Synthesis of (4S)-7-chloro-8-fluoro-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

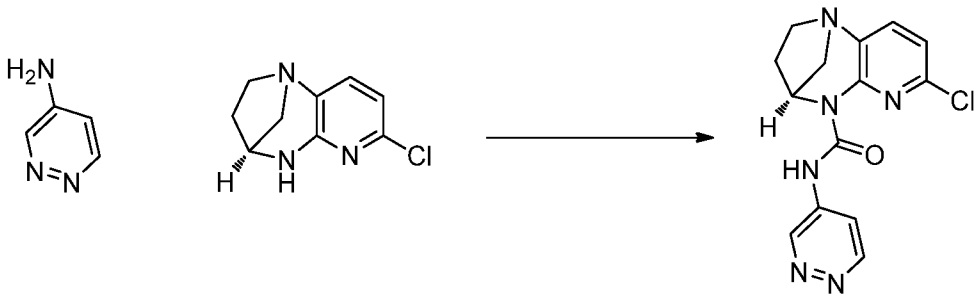
Triethylamine (1.63 mL, 11.737 mmol) followed by triphosgene (696 mg, 2.347 mmol) were added to a solution of (4*S*)-7-chloro-8-fluoro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (500 mg, 2.347 mmol) in THF (20 mL) then stirred at RT for 30 min and 3-aminopyridine (441 mg, 4.694 mmol) was added and heated to 70 °C for 16 h. Then the reaction mixture was cooled to RT and diluted with water. The reaction mixture was extracted with ethyl acetate (3x50 mL). The combined organic layer was washed with water (2x50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, solvent removed under reduced pressure to obtain the crude residue. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 90% ethyl acetate in hexane) to afford (4*S*)-7-chloro-8-fluoro-*N*-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (410 mg, 1.231 mmol, 0.805 mmol, yield: 34.6 %) as an off white solid (TLC: Eluent: neat ethyl acetate, R_f: 0.4) LCMS (*m/z*) 333.9 $(M+H)^+$.

Synthesis of (4S)-7-chloro-8-fluoro-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

Triethylamine (1.63 mL, 11.737 mmol) followed by triphosgene (696 mg, 2.347 mmol) were added to a solution of (4*S*)-7-chloro-8-fluoro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (500 mg, 2.347 mmol) in THF (20 mL) then stirred at room temperature for 30 min and 2-aminopyridine (441 mg, 4.694 mmol) was added and heated to 70 °C for 16 h. Then the reaction mixture was cooled to RT, diluted with

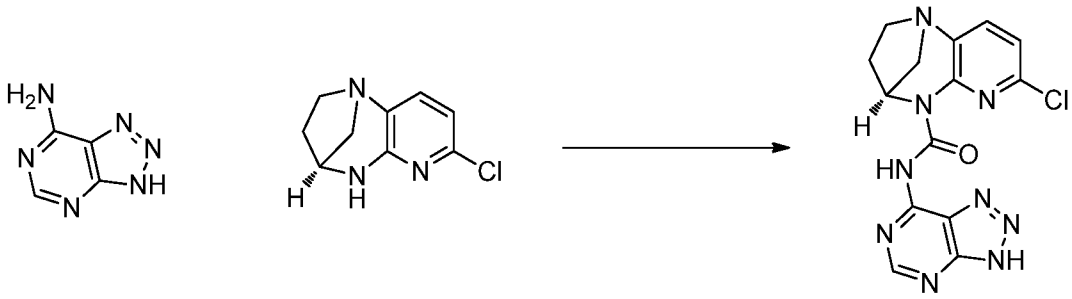
water. The aqueous layer was extracted with ethyl acetate (3x50 mL). The combined organic layer was washed with water (2x50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure to obtain the crude residue. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 90% ethyl acetate in hexane) to afford (4*S*)-7-chloro-8-fluoro-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (350 mg, 1.051 mmol, 34.18 % yield) as an off white solid (TLC: Eluent: 100% ethyl acetate, R_f: 0.4), LCMS (*m/z*) 334.1 $(M+H)^+$.

Synthesis of (4S)-7-chloro-N-(pyridazin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



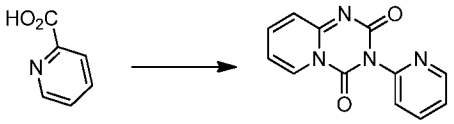
To a solution of pyridazine-4-carboxylic acid (0.5 g, 4.03 mmol) was added diphenyl phosphorazidate (1.308 mL, 6.04 mmol) and DIPEA (2.111 mL, 12.09 mmol) in THF (10 mL) which was stirred under nitrogen at 0°C. The reaction mixture was stirred at 30 °C for 2h and (4S)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (0.473 g, 2.417 mmol) was added at 30 °C. The reaction mixture was stirred at 90 °C for 6h. The THF was evaporated under reduced pressure and the residue diluted with water and extracted into DCM. The organic layer was washed with water, brine and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The crude compound was purified by trituration with diethyl ether and n-pentane(1:1) to give the product (320 mg, 0.91 mmol, 23 % yield) as an off-white solid. LCMS (*m/z*) 316.9 $[M+H]^+$.

Synthesis of (4S)-N-(3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl)-7-chloro-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



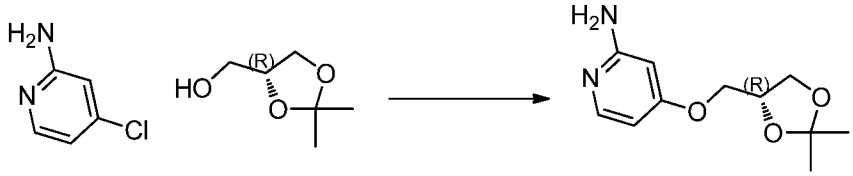
To a solution of (4S)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 2.56 mmol) in Tetrahydrofuran (THF) (10 mL) stirred under nitrogen at room temp was added triphosgene (758 mg, 2.56 mmol) and stirred for 30 min at RT, then triethylamine (0.356 mL, 2.56 mmol) and 3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-amine (417 mg, 3.07 mmol) were added. The reaction mixture was stirred at 60 °C for 16 hr. The reaction was monitored by TLC(10% Methanol in DCM). The reaction mixture was quenched with 25 ml of water and extracted with 25 ml of ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to afford the crude compound. The crude product was added to a 100-200 silica gel column and was eluted with 3% DCM/MeOH to afford pure compound (4S)-N-(3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl)-7-chloro-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (200 mg, 0.527 mmol, 20.63 % yield) as an off white solid, LCMS (*m/z*) 357.9 $[M+H]^+$.

Synthesis of 3-(pyridin-2-yl)-2H-pyrido[1,2-a][1,3,5]triazine-2,4(3H)-dione



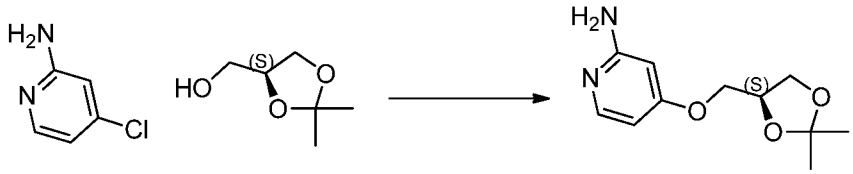
To a solution of picolinic acid (1 g, 8.12 mmol) in Toluene (25 mL) stirred under nitrogen at room temp was added diphenyl phosphorazidate (2.235 g, 8.12 mmol) and TEA (1.132 mL, 8.12 mmol) and stirred for 30 min at room temperature. After that the reaction mixture was stirred at 80 °C for 2 hr. Next, the reaction mixture was cooled to room temperature and filtered, the solid was washed with toluene to afford compound 3-(pyridin-2-yl)-2H-pyrido[1,2-a][1,3,5]triazine-2,4(3H)-dione (600 mg, 2.352 mmol, 29.0 % yield), LCMS (*m/z*) 241.2 $[M+H]^+$.

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



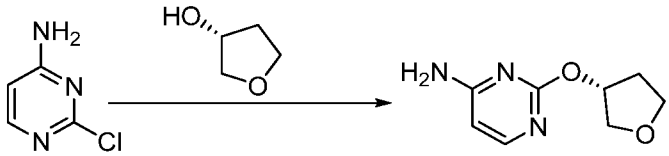
To a suspension of (R)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (3.000 g, 22.70 mmol), 4-chloropyridin-2-amine (1.459 g, 11.35 mmol) and sodium (0.522 g, 22.70 mmol) in a sealed tube. The reaction mixture was stirred at 140 °C for 16h. Next, the reaction mixture was cooled to room temperature, dissolved 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 (1.1g, 21%), LCMS (*m/z*) 225.2 $[M+H]^+$.

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



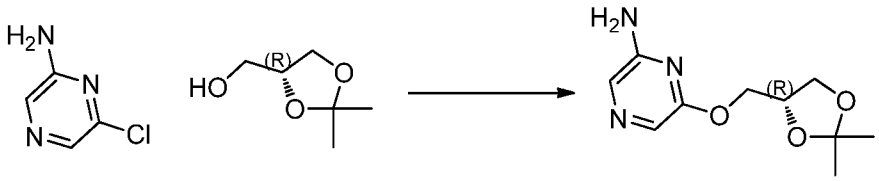
To a suspension of (S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (3.000 g, 22.70 mmol), 4-chloropyridin-2-amine (1.459 g, 11.35 mmol) and sodium (0.522 g, 22.70 mmol) in a sealed tube. The reaction mixture was stirred at 140 °C for 16h before being cooled to room temperature, dissolved in MeOH and poured 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 (1.2g, 22%), LCMS (*m/z*) 225.2 $[M+H]^+$.

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



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 (3x50 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.

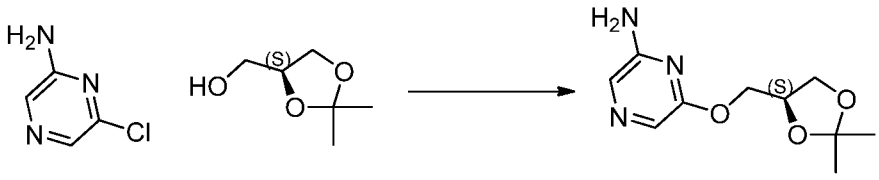
Synthesis of (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine



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 (2.8g, 11.9 mmol, 31%), LCMS (*m/z*) 225.9 $[M+H]^+$.

N31748-19

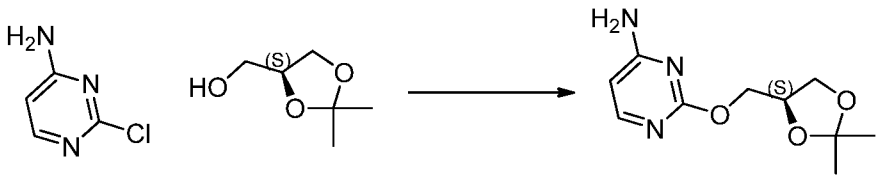
Synthesis of (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine



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

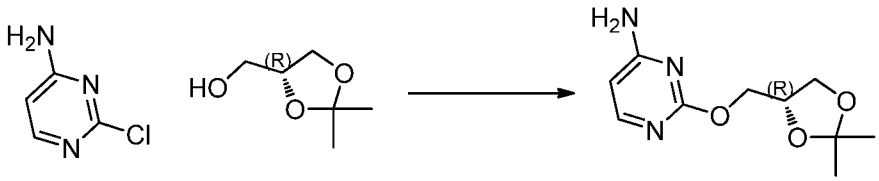
tube and heated at 130 °C for 16 hr and then the reaction mixture was quenched with methanol and ice cold water (100 mL) and extracted with ethyl acetate (5 x 50 mL). The combined organic layers were washed with water, saturated brine solution, dried over anhydrous sodium sulfate, filtered and concentrated 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



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 $[M+H]^+$.

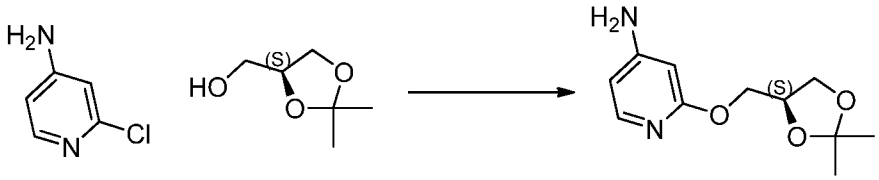
Synthesis of (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine



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 16h. The reaction mixture was poured in to water and extracted with EtOAc (3 X 100mL). 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 (2.5g, 10.42 mmol, 46%), LCMS (*m/z*) 226.2 $[M+H]^+$.

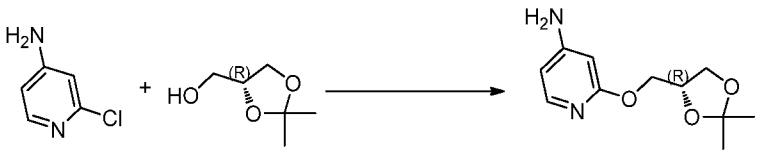
Synthesis of (S)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine



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

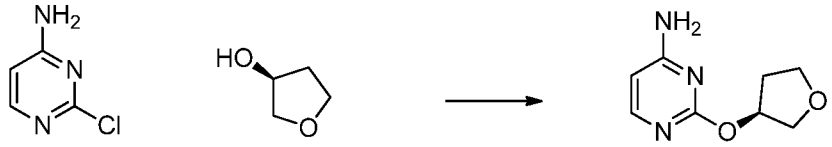
The reaction mixture was dissolved in MeOH, poured in to ice water and extracted with EtOAc (3 X 100mL). Then the combined organic layer was washed with water, brine solution, dried over sodium sulfate and evaporated to get 4.0 g of crude compound. The crude compound was purified by column chromatography 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



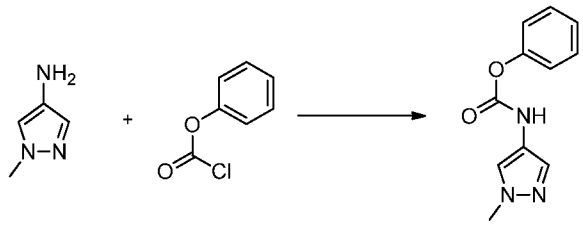
To a solution of 2-chloropyridin-4-amine (4 g, 31.1 mmol), (R)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (2.056 g, 15.56 mmol) and sodium (0.715 g, 31.1 mmol) in sealed tube at room temperature. The reaction mixture was stirred at 140 °C for 48 hr. The reaction mixture was cooled to room temp and quenched 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



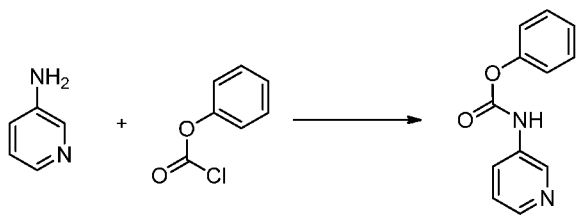
To a stirred solution of 2-chloropyrimidin-4-amine (2 g, 15.44 mmol) in Tetrahydrofuran (THF) (20 mL) was added NaH (0.741 g, 30.9 mmol) portion wise over a period of 5 min at room temperature. Then the reaction was stirred at 30 °C for about 10 min. To the above reaction added (S)-tetrahydrofuran-3-ol (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 phenyl (1-methyl-1H-pyrazol-4-yl)carbamate



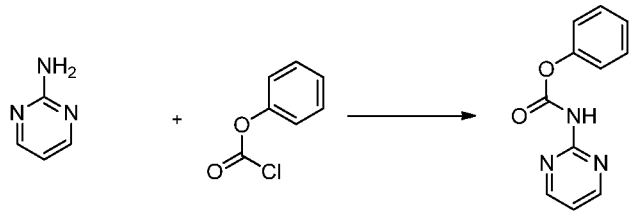
Phenyl carbonochloridate (2.90 g, 18.53 mmol) was added to a stirred solution of pyridine (3.12 mL, 38.6 mmol) in Dichloromethane (DCM) (50 mL) at 0 °C and stirred for 15min and followed by addition of 1-methyl-1H-pyrazol-4-amine (1.5g, 15.45 mmol) at same temperature. The reaction mixture was stirred at room temperature for 4h. After consumption of starting material (monitored by TLC), ice cold water was added, separated organic layer was washed with water and brine. The organic layer was filtered through sodium sulfate and concentrated to get crude compound. The crude compound was purified by column chromatography by using 60-120(silica gel) and eluted in 50% ethyl acetate in hexane to afford the desired product (1.6g, 6.41 mmol, 42 % yield) as light brown solid, LCMS (*m/z*) 218.1 $(M+H)^+$.

Synthesis of phenyl pyridin-3-ylcarbamate



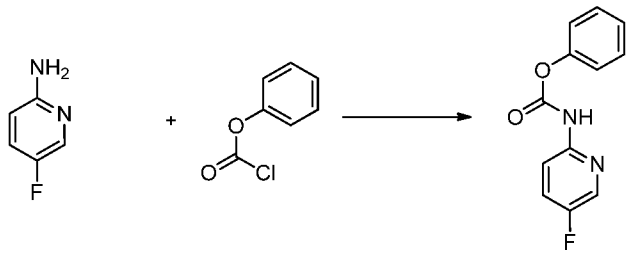
To a solution of phenyl carbonochloridate (2.163 g, 13.81 mmol), and pyridine (1.375 mL, 17.00 mmol) in Dichloromethane (DCM) (30 mL) stirred under nitrogen at room temp was added pyridin-3-amine (1.0 g, 10.63 mmol). The reaction mixture was stirred at RT for 30 min. The reaction mixture was quenched with saturated sodium bicarbonate solution. Separated organic layer and the aqueous layer extracted with DCM (50 ml). Combined DCM layer washed with water and dried out with sodium sulfate, filtered and concentrated under high vacuum to get crude product. The Crude product was added to a silica gel column and was eluted with 20% EtOAc/Hexane. Collected fractions were evaporated to afford the desired product (1.3 g, 6.01 mmol, 57%) as a white solid, LCMS (*m/z*) 215.1 $(M+H)^+$.

Synthesis of phenyl pyrimidin-2-ylcarbamate



To a solution of phenyl carbonochloridate (2.140 g, 13.67 mmol), and pyridine (1.361 mL, 16.82 mmol) in dichloromethane (DCM) (10 mL) stirred under nitrogen at room temperature was added pyrimidin-2-amine (1.0 g, 10.51 mmol). The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was quenched with saturated sodium bicarbonate solution. Separated organic layer and the aqueous layer extracted with DCM (50 ml). Combined DCM layer washed with water and dried out with sodium sulfate, filtered and concentrated under high vacuum to get crude product. This was added to a silica gel column and was eluted with 20% EtOAc/Hexane. Collected fractions were evaporated to afford the desired product (1.6 g, 6.49 mmol, 61.7 %), LCMS (*m/z*) 216.3 $(M+H)^+$.

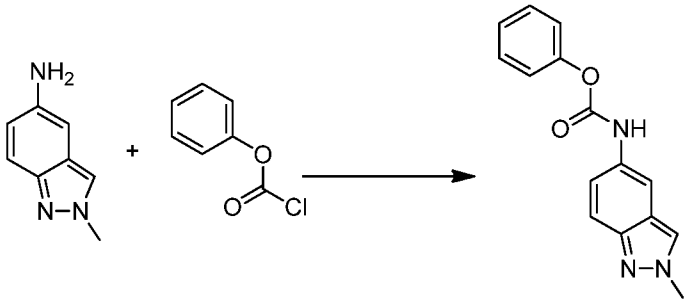
Synthesis of phenyl (5-fluoropyridin-2-yl)carbamate



To a solution of phenyl carbonochloridate (1.397 g, 8.92 mmol), and Pyridine (0.721 mL, 8.92 mmol) in dichloromethane (DCM) (40 mL) stirred under nitrogen at room temp was

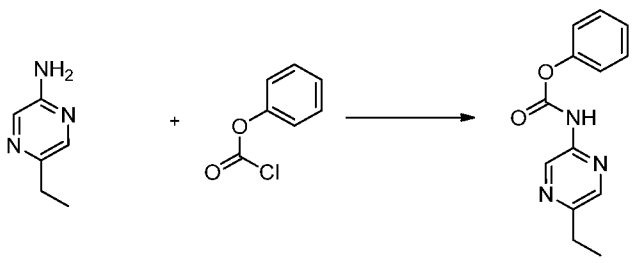
added 5-fluoropyridin-2-amine (1.0 g, 8.92 mmol). The reaction mixture was stirred at RT for 30 min. The reaction mixture was quenched with saturated sodium bicarbonate solution. Separated organic layer and the aqueous layer extracted with DCM (20 ml). Combined organic layer washed with water followed by brine solution and dried out with sodium sulfate, filtered and concentrated under vacuum to give the desired product (1.4 g, 5.94 mmol, 67%), LCMS (*m/z*) 233.2 $(M+H)^+$.

Synthesis of phenyl (2-methyl-2H-indazol-5-yl)carbamate



To a solution of phenyl carbonochloridate (1.064 g, 6.79 mmol), and pyridine (0.550 mL, 6.79 mmol) in Dichloromethane (DCM) (40 mL) stirred under nitrogen at room temp was added 2-methyl-2H-indazol-5-amine (1 g, 6.79 mmol). The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was quenched with saturated sodium bicarbonate solution. Separated organic layer, aqueous layer extracted with DCM (20 ml). Combined organic layer washed with water followed by brine solution and dried out with sodium sulfate and concentrated under vacuum to get phenyl (2-methyl-2H-indazol-5-yl)carbamate (1.3 g, 4.82 mmol, 70.9 % yield), LCMS (*m/z*) 268.1 $(M+H)^+$.

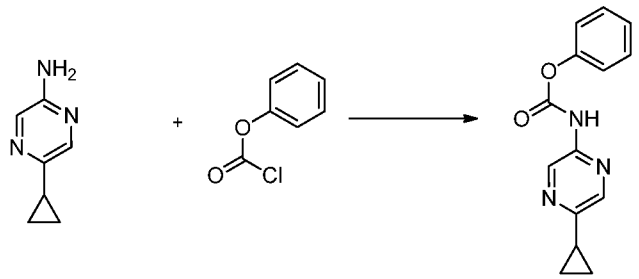
Synthesis of Phenyl (5-ethylpyrazin-2-yl)carbamate



Pyridine (1.051 mL, 12.99 mmol) was added dropwise to a stirred solution of phenyl carbonochloridate (1.324 mL, 10.56 mmol) in dichloromethane (DCM) (20 ml) at room temperature and stirred for 30 minutes. Then 5-ethylpyrazin-2-amine (1 g, 8.12 mmol) dissolved in dichloromethane (DCM) (10 ml) was added dropwise at room temperature

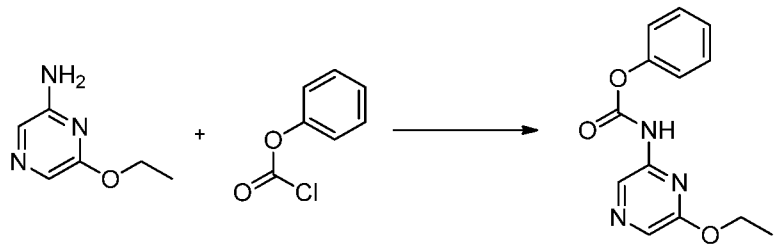
and stirred at 50 °C for 16 h. Allowed the reaction mixture to room temperature, diluted with DCM (3X50 mL), washed with water (2X30 mL) and brine (30 mL). Separated the organic layer and dried over sodium sulfate, filtered and concentrated. Residue was purified by column chromatography using silica gel (100-200 mesh) by 10% ethyl acetate in pet ether as eluent to get desired product as off white fluffy solid (1.6 g, 6.58 mmol, 81%), LCMS (*m/z*) 244.2 $(M+H)^+$.

Synthesis of Phenyl (5-cyclopropylpyrazin-2-yl)carbamate



Pyridine (0.598 mL, 7.40 mmol) was added dropwise to a stirred solution of phenyl carbonochloridate (0.928 mL, 7.40 mmol) in dichloromethane (DCM) (15 ml) at 0 °C and stirred at RT for 30 minutes. Then 5-cyclopropylpyrazin-2-amine (1 g, 7.40 mmol) dissolved in dichloromethane (DCM) (5 ml) was added dropwise at 0 °C and stirred at RT for 3 h. The reaction mixture was diluted with DCM (3X50 mL), washed with water (2X20 mL) and brine (20 mL). Separated the organic layer and dried over sodium sulfate, filtered and concentrated. Residue was purified by column chromatography using silica gel (100-200 mesh). 10% ethyl acetate in pet ether as eluent to give the desired product (1.4 g, 5.31 mmol, 72 %) as off white fluffy solid, LCMS (*m/z*) 256.2 $(M+H)^+$.

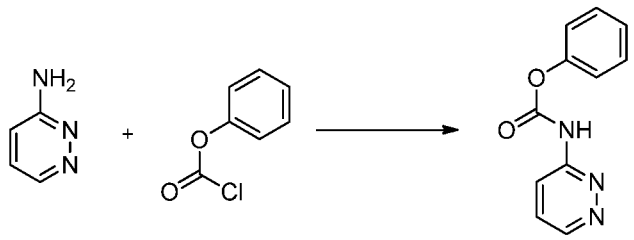
Synthesis of phenyl (6-ethoxypyrazin-2-yl)carbamate



Pyridine (0.930 mL, 11.50 mmol) was added to a solution of phenyl carbonochloridate (1.463 g, 9.34 mmol) in DCM (15 mL) at room temperature and stirred for 20 min, then 6-ethoxypyrazin-2-amine (1.0 g, 7.19 mmol) in DCM (15 mL) was added and continued for another 40 min. The reaction mixture was diluted with DCM (2X20 mL), washed with water (20 mLx2) and brine (10 mL). Organic extracts were dried over Na_2SO_4 and solvent

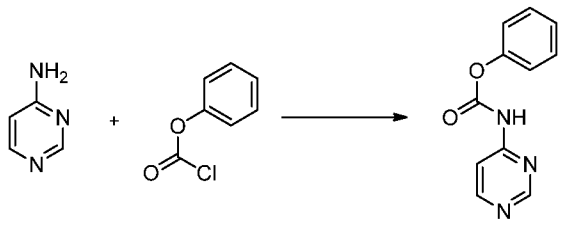
removed *in* vacuo to obtain the desired product (1.65 g, 5.22 mmol, 72.6 % yield) as a yellow solid, LCMS (*m/z*) 260.2 $(M+H)^+$.

Synthesis of phenyl pyridazin-3-ylcarbamate



To a solution of phenyl carbonochloridate (1.070 g, 6.83 mmol), pyridine (0.665 g, 8.41 mmol) in dichloromethane (10 ml) stirred under nitrogen at 25°C was added a suspension of pyridazin-3-amine (0.5 g, 5.26 mmol) in dichloromethane (5ml) during 5 min. The reaction mixture was stirred at 25 °C for 1 hr. Next, the organic phase was washed with water 3 mL, saturated brine 3 mL, dried over sodium sulfate and concentrated in vacuo to give the crude product as a white solid. The compound was washed with hexane, dried under reduced pressure, LCMS (*m/z*) 216.2 $(M+H)^+$.

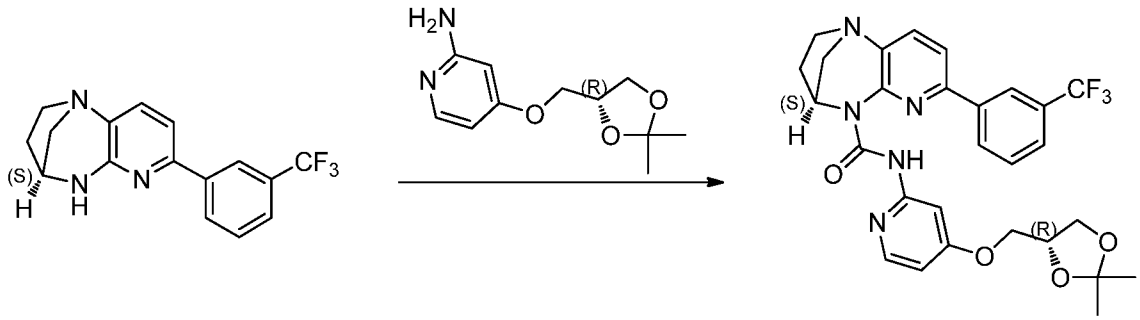
Synthesis of phenyl pyrimidin-4-ylcarbamate



To a solution of phenyl carbonochloridate (1.070 g, 6.83 mmol), pyridine (0.665 g, 8.41 mmol) in DCM (15 ml) stirred under nitrogen at 25°C was added a suspension of pyrimidin-4-amine (0.5 g, 5.26 mmol) in DCM (5 ml) dropwise during 5 min. The reaction mixture was stirred at 25 °C for 1 hr. The organic phase was washed with water 3 mL, brine 3 mL, dried over sodium sulfate and concentrated under vacuo to give the crude product as a off-white solid. The crude compound was washed with Hexane and then dried under reduced pressure to give the desired product (500 mg, 1.95 mmol, 37%), LCMS (*m/z*) 215.9 $(M+H)^+$.

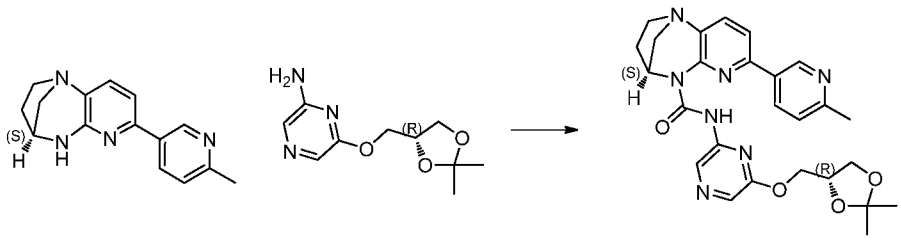
SYNTHESIS OF ADVANCED BICYCLIC INTERMEDIATES

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



To a solution of (4R)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (499.5 mg, 1.636 mmol), in Tetrahydrofuran (THF) (20 mL) stirred under nitrogen at room temp was added TEA (1.368 mL, 9.82 mmol), triphosgene (486 mg, 1.636 mmol). This was stirred at room temperature for 15 min and then a solution of (R)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (1101 mg, 4.91 mmol) in THF (5 mL) dropwise over 5 min. The reaction mixture was stirred at 65 °C for 16h before being poured in to water and extracted with EtOAc (3 X 100mL). Then the combined organic layer was washed with water, brine solution, dried over sodium sulfate and evaporated to give the crude product. The crude compound was purified by reverse phase chromatography (0.1%HCOOH&Water)/MeOH to give the desired product (450 mg, 49%), LCMS (*m/z*) 555.9 $(M+H)^+$.

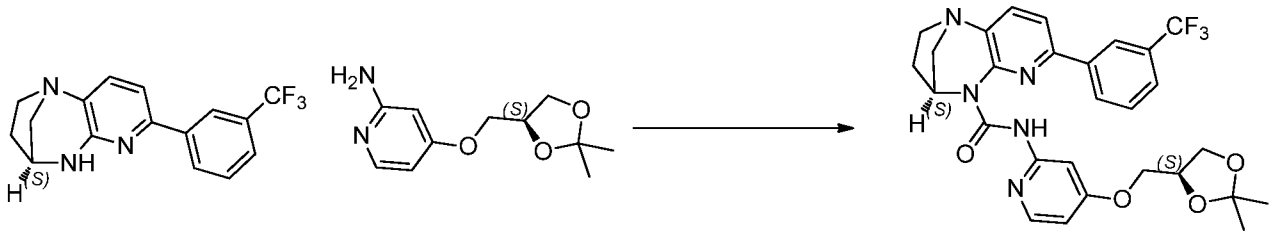
Synthesis of (4S)-N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(6-methylpyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



To a solution of (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine (803 mg, 3.57 mmol) in Tetrahydrofuran (THF) (20 mL) at 30 °C was added triphosgene (423 mg, 1.427 mmol) and stirred for 30 min at same temperature. Then added TEA (1.657

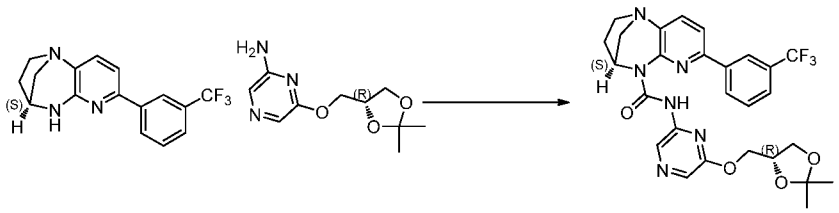
mL, 11.89 mmol) followed by (4S)-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (600 mg, 2.378 mmol) at room temperature. The reaction mixture was stirred at 65 °C for 16hr. Reaction was monitored by TLC and crude LCMS. THF evaporated under reduced pressure, residue diluted with water and extracted into DCM. Organic layer dried over Na_2SO_4, solvent evaporated under reduced pressure to afford crude product. The crude compound was purified by column chromatography using silica gel as an stationary phase (100-200 mesh) and 2-3% of MeOH/EtOAc as an eluent. Pure fractions were collected and concentrated under reduced pressure to afford pure product 0.4g as an off white solid (450 mg, 0.71 mmol, 30%), LCMS (*m/z*) 504.3 $(M+H)^+$.

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



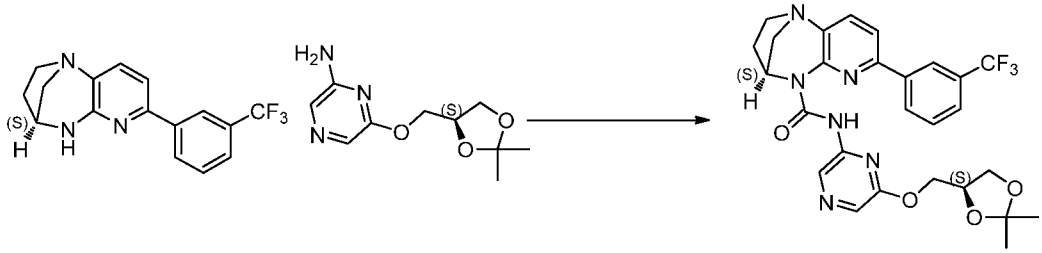
To a solution of (4R)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (545 mg, 1.785 mmol) in Tetrahydrofuran (THF) (20 mL) stirred under nitrogen at room temp was added TEA (1.493 mL, 10.71 mmol), triphosgene (530 mg, 1.785 mmol). Then the reaction mixture was stirred for 15 min before a solution of (S)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (1201 mg, 5.36 mmol) in THF (5 mL) was added dropwise over 5 min. The reaction mixture was stirred at 65 °C for 16h before being cooled to room temperature and poured in to water and extracted with EtOAc (3 X 100mL). Then the combined organic layer was washed with water, brine solution, dried over sodium sulfate and evaporated to give the crude product. This was purified by reverse phase column chromatography (0.1%HCOOH&Water)/MeOH to give the desired product (500mg, 49%), LCMS (*m/z*) 556.3 $(M+H)^+$.

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



To a stirred solution of (4*S*)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (850 mg, 2.78 mmol) in 40 mL of THF (sealed tube) was added triphosgene (324 mg, 1.093 mmol) at 25 °C and stirred for 30 min. To this reaction mixture was added (*R*)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine (938 mg, 4.16 mmol) was added and the reaction mixture was stirred at 65 °C for 16 h. The reaction mixture was allowed to cool to room temperature and the mixture was poured into cold water (70 mL) and extracted with ethyl acetate (3x50 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 (4*S*)-*N*-(6-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (900 mg, 1.618 mmol 57% yield) as a white solid (TLC: eluent: 10% MeOH in DCM, R_f=0.3), LCMS (*m/z*) 557.3 $(M+H)^+$.

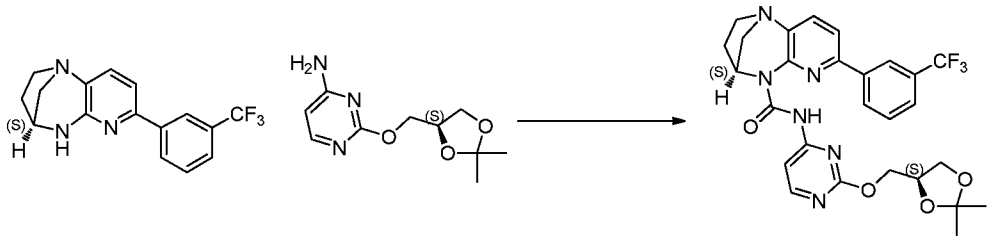
Synthesis of (4S)-N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



To a solution of (4S)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (723 mg, 2.368 mmol) in tetrahydrofuran (THF) (25 mL) and add triphosgene (351 mg, 1.184 mmol) the reaction mixture was stirred at room

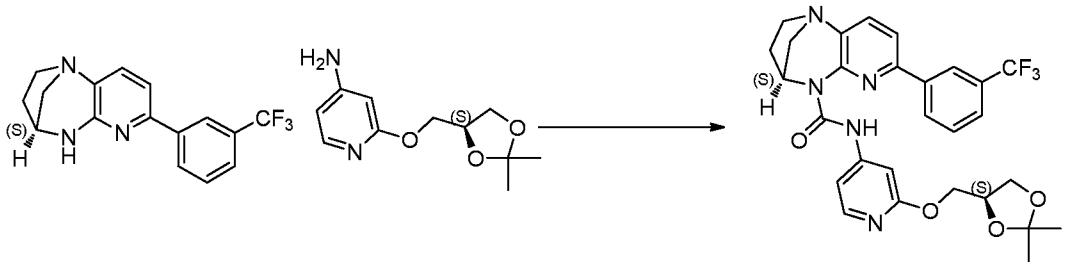
temperature for 30 min before adding TEA (1.650 mL, 11.84 mmol) and (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine (800 mg, 3.55 mmol). The reaction mixture was stirred at 65 °C for 16 hr before cooling to room temperature and poured in to water and extracted with EtOAc (3 X 100mL). Then the combined organic layer was washed with water, brine solution, dried over sodium sulfate and evaporated to give the crude compound which was purified by reverse phase column and eluted with 83% of (0.1%HCOOH&Water)/MeOH to get pure compound (300 mg, 0.534 mmol, 23%), LCMS (*m/z*) 557.4 $(M+H)^+$.

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



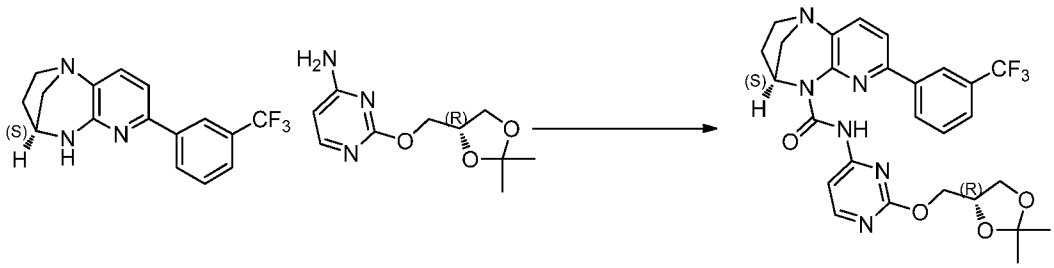
To a solution of (4S)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (600 mg, 1.965 mmol) in Tetrahydrofuran (THF) (10 mL) was added triphosgene (583 mg, 1.965 mmol), TEA (1.644 mL, 11.79 mmol) stirred at rt for 15 min and add a solution of (S)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine (1328 mg, 5.90 mmol) in THF (5 mL) over 1 min. The reaction mixture was stirred at 65 °C for 16 hr before being poured in to water and extracted with EtOAc (3 X 50mL). Then the combined organic layer was washed with water, brine solution, dried over sodium sulfate and evaporated to give 600 mg. The crude compound was purified by reverse phase column and eluted with 90% (0.1%HCOOH&Water)/MeOH to give the desired compound (450 mg, 0.76 mmol, 39%), LCMS (*m/z*) 557.2 $(M+H)^+$.

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



To a solution of (4S)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (600 mg, 1.965 mmol) in Tetrahydrofuran (THF) (10 mL) was added TEA (1.644 mL, 11.79 mmol), triphosgene (583 mg, 1.965 mmol) stirred at for 15 min and added (S)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (1322 mg, 5.90 mmol) portion wise. The reaction mixture was stirred at 65 °C for 16 hr and progress of the reaction was monitored by TLC. The reaction mixture was poured in to ice water and extracted with EtOAc (3 X 100mL). Then the combined organic layer was washed with water, brine solution, dried over sodium sulfate and evaporated to give the crude product. The crude compound was purified by reverse phase column and eluted with 93% (0.1%HCOOH&Water)/MeOH to give the desired product (450 mg, 0.807 mmol, 41.1 % yield), LCMS (*m/z*) 556.4 $(M+H)^+$.

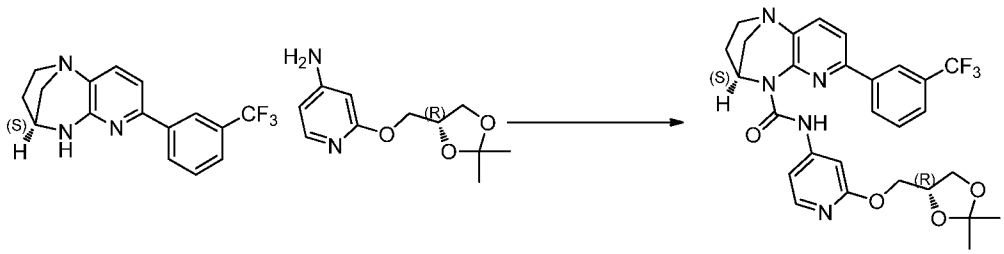
Synthesis of (4S)-N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



To a solution of (4R)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (400 mg, 1.310 mmol) in Tetrahydrofuran (THF) (10 mL) and add TEA (1.096 mL, 7.86 mmol), triphosgene (389 mg, 1.310 mmol) stirred at room temp for 15 min was added a solution of (R)-2-((2,2-dimethyl-1,3-dioxolan-4-

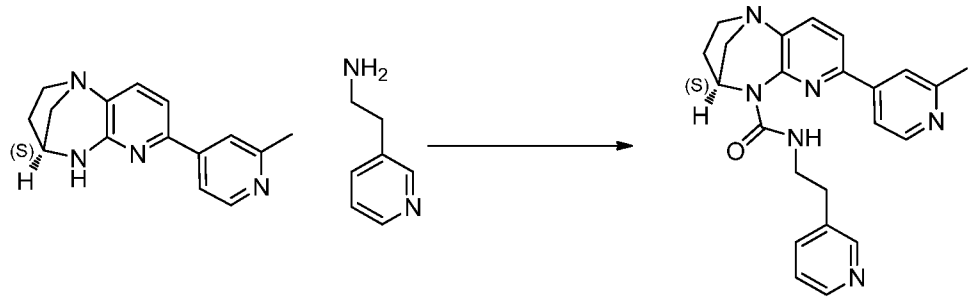
yl)methoxy)pyrimidin-4-amine (885 mg, 3.93 mmol) in THF(2.0 mL). The reaction mixture was stirred at 65 °C for 16 hr. The reaction mixture was poured in to water and extracted with EtOAc (3 X 100mL). Then the combined organic layer was washed with water, brine solution, dried over sodium sulfate and evaporated to dryness. The crude compound was purified by reverse phase column and eluted with 90% (0.1%HCOOH&Water)/MeOH to get pure compound (350 mg, 0.602 mmol, 46%), LCMS (*m/z*) 557.0 $(M+H)^+$.

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



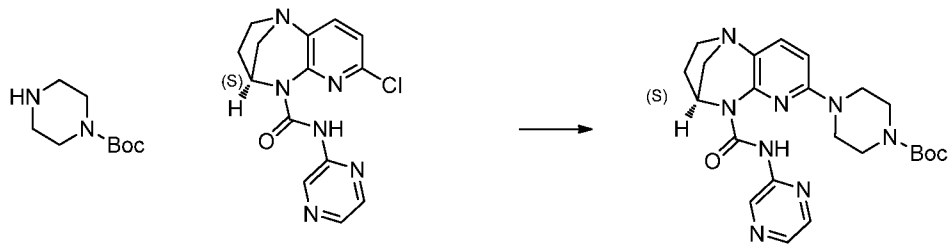
To a solution of (4S)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1 g, 3.28 mmol), in Tetrahydrofuran (THF) (15 mL) stirred under nitrogen at room temp was added a solution of TEA (2.74 mL) and triphosgene stirred under nitrogen at room temp for 30 minutes. To this (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (2.204 g, 9.83 mmol) in Tetrahydrofuran (THF) (8 mL) (2.204 g) was added. The reaction mixture was stirred at 60 °C for16 hr. The reaction mixture was concentrated and the residue was taken up in DCM (100 mL). The solution was washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The crude product was added to a silica gel column and was eluted with EtOAc/pet ether (60:20) collected fractions were evaporated to give the desired product (600 mg, 0.92 mmol, 28%) as an off white semi solid, LCMS (*m/z*) 556.3 $(M+H)^+$.

Synthesis of (4S)-7-(2-methylpyridin-4-yl)-N-(2-(pyridin-3-yl)ethyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



To a solution of (4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (400 mg, 1.585 mmol), triethylamine (1.105 mL, 7.93 mmol) and triphosgene (282 mg, 0.951 mmol) in Tetrahydrofuran (THF) (20 mL) stirred under nitrogen at room temp for 30 min was added a solution of 2-(pyridin-3-yl)ethanamine (387 mg, 3.17 mmol) in THF (5 mL) dropwise over 5 min. The reaction mixture was stirred at 65 °C for 16 hr and progress of the reaction was monitored by TLC. The reaction mixture was poured in to ice water and extracted with EtOAc (3 X 100mL). Then the combined organic layer was washed with water, brine solution, dried over sodium sulfate and evaporated to give the crude compound. The crude compound was purified by reverse phase column and eluted with 25-30% (0.1%HCOOH&Water)/MeOH give the final product (250 mg, 0.599 mmol, 37.8 % yield), LCMS (*m/z*) 401.1 $(M+H)^+$.

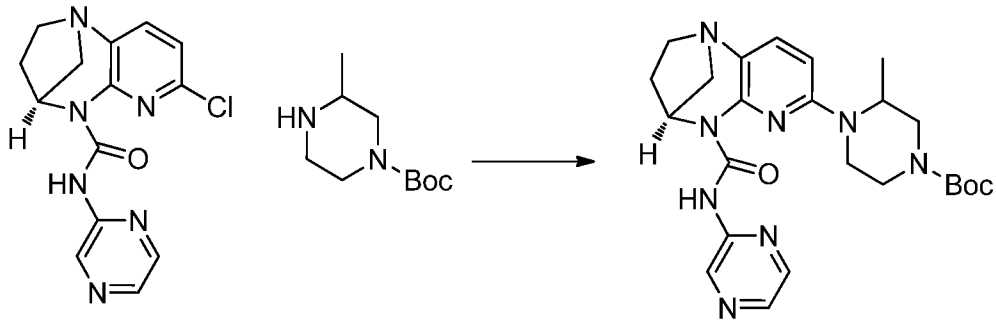
Synthesis of tert-butyl 4-((4S)-5-(pyrazin-2-ylcarbamoyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepin-7-yl)piperazine-1-carboxylate



To a degassed solution of (4S)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (600 mg, 1.894 mmol) and tert-butyl piperazine-1-carboxylate (706 mg, 3.79 mmol) in 1,4-Dioxane (10 mL) was added subsequentially at 20°C Cs_2CO_3 (1852 mg, 5.68 mmol), xphos (361 mg, 0.758 mmol) and $PdOAc_2$ (85 mg, 0.379 mmol). The reaction mixture was stirred at 100 °C for 16 hr. The reaction mixture was poured in to cold water (20 mL) and extracted with ethyl acetate (50

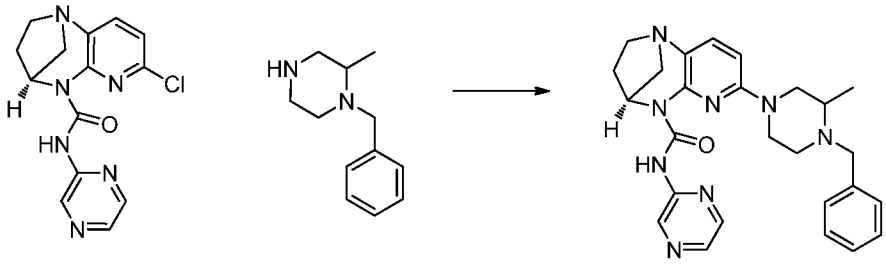
mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product. The crude product was added to a silica gel column and was eluted with 3% DCM/MeOH to give tert-butyl 4-((4S)-5-(pyrazin-2-ylcarbamoyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepin-7-yl)piperazine-1-carboxylate (359 mg, 0.616 mmol, 32.5 % yield), LCMS (*m/z*) 467.3 $(M+H)^+$.

Synthesis of tert-butyl 3-methyl-4-((4S)-5-(pyrazin-2-ylcarbamoyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepin-7-yl)piperazine-1-carboxylate



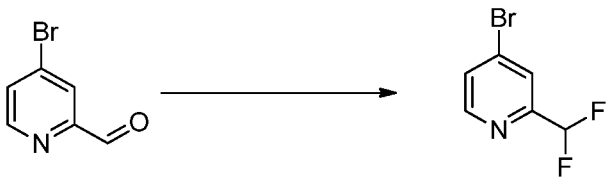
To a degassed solution of (4S)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (800 mg, 2.53 mmol), tert-butyl 3-methylpiperazine-1-carboxylate (1012 mg, 5.05 mmol) in 1,4-Dioxane (10 mL) and was added sequentially at 20°C Cs_2CO_3 (2469 mg, 7.58 mmol) and xphos (482 mg, 1.010 mmol),$PdOAc_2$ (113 mg, 0.505 mmol). The reaction mixture was stirred at 100 °C for 16 hr. The reaction was monitored by TLC. The reaction mixture was poured in to cold water (20 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to give crude. The crude product was added to a silica gel column and was eluted with 2% DCM/MeOH. Collected fractions are evaporated to give the desired product (397.5 mg, 0.670 mmol, 26.5 % yield), LCMS (*m/z*) 481.1 $(M+H)^+$.

Synthesis of (4S)-7-(4-benzyl-3-methylpiperazin-1-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



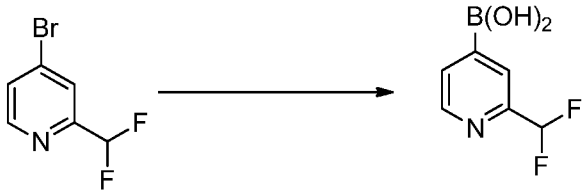
To a degassed solution of in (4S)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (500 mg, 1.579 mmol),1-benzyl-2-methylpiperazine (601 mg, 3.16 mmol) in 1,4-Dioxane (20 mL) was added sequentially at 20°C Cs_2CO_3 (1543 mg, 4.74 mmol) and cinnamyl chloro[1,3-bis(diisopropylphenyl)-2-imidazolidinyliin]Pd(II) (51.3 mg, 0.079 mmol) .The reaction mixture was stirred at 110 °C for 16 hrs. The reaction mixture was poured into cold water (50 mL) and extracted with ethyl acetate (200 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 3% DCM/MeOH to give (4S)-7-(4-benzyl-3-methylpiperazin-1-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (501.5 mg, 0.885 mmol, 56.0 % yield), LCMS (*m/z*) 471.3 $(M+H)^+$.

Synthesis of 4-bromo-2-(difluoromethyl)pyridine



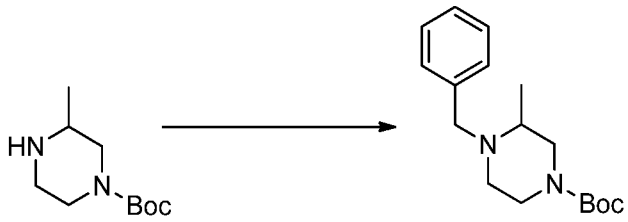
DAST (0.620 mL, 4.69 mmol) was added dropwise to a solution of 4-bromopicolinaldehyde (700 mg, 3.76 mmol) in Chloroform (21 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 12h. The reaction mixture was poured in to saturated $NaHCO_3$ solution (20 mL), and was extracted with DCM (2X 20 mL). The DCM layer was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford 4-bromo-2-(difluoromethyl)pyridine (400 mg, 1.870 mmol, 49.7 % yield) as light yellow solid, LCMS (*m/z*) 208.0 $[M+H]^+$.

Synthesis of (2-(difluoromethyl)pyridin-4-yl)boronic acid



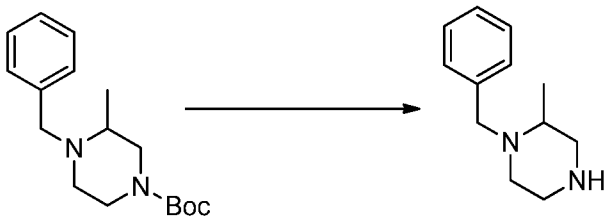
Potassium acetate (472 mg, 4.81 mmol) was added to a stirred solution of 4-bromo-2-(difluoromethyl)pyridine (400 mg, 1.923 mmol), and bis(pinacolato)diboron (610 mg, 2.404 mmol) in 1,4-Dioxane (10 mL) at 28 °C. The reaction mixture was degassed for 15 min, was added $PdCl_2(dppf)$ (4.22 mg, 5.77 µmol). The reaction mixture was further degassed for 15 min, and the reaction mixture was stirred for 48 hr at 80 °C. The reaction mixture was cooled to 28 °C, was evaporated and crude was partitioned between water (10 mL) and EtOAc (25 mL). EtOAc layer was separated and was dried over anhydrous Na_2SO_4, filtered, and filtrate was evaporated to afford (2-(difluoromethyl)pyridin-4-yl)boronic acid (330 mg, 1.107 mmol, 57.6 % yield) as brown solid, LCMS (*m/z*) 174.1 $[M+H]^+$.

Synthesis of tert-butyl 4-benzyl-3-methylpiperazine-1-carboxylate



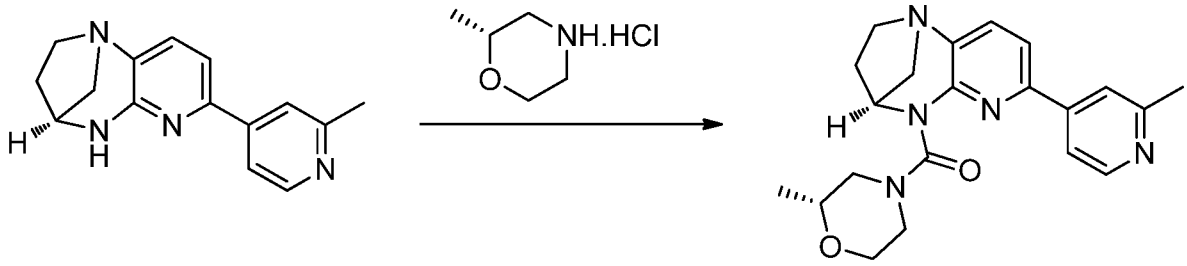
To a solution of tert-butyl 3-methylpiperazine-1-carboxylate (1 g, 4.99 mmol), in N,N-Dimethylformamide (DMF) (100 mL) was added K_2CO_3 (2.070 g, 14.98 mmol) at 0 °C. After stirring 10 min at 0 °C benzyl bromide (0.891 mL, 7.49 mmol) was added dropwise and the reaction mixture was stirred at 35 °C for 16 hr and the reaction was monitored by TLC. The reaction mixture was poured in to aq $NaHCO_3$ (50 mL) and extracted with ethyl acetate (200 mL) and washed with water and then brine. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to give crude. The crude product was added to a silica gel column and was eluted with 10%Hex/EtOAc. Collected fractions are evaporated to give tert-butyl 4-benzyl-3-methylpiperazine-1-carboxylate (1 g, 3.17 mmol, 63.4 % yield), LCMS (*m/z*) 174.1 $[M+H]^+$.

Synthesis of 1-benzyl-2-methylpiperazine



To a solution of tert-butyl 4-benzyl-3-methylpiperazine-1-carboxylate (1.4 g, 4.82 mmol) in Dichloromethane (DCM) (25 mL) was added TFA (1.857 mL, 24.10 mmol) at 0 °C and the reaction mixture was stirred at 35 °C for 3 hr. The reaction was monitored by TLC. The solvent was evaporated under reduced pressure to give the crude product. The residue was triturated with Diethyl ether (2 x 50 mL). The resulting solid was filtered and washed with Diethyl ether. This was dried under reduced pressure to give 1-benzyl-2-methylpiperazine Trifluoroacetic acid salt (800 mg, 2.63 mmol, 54.5 % yield)

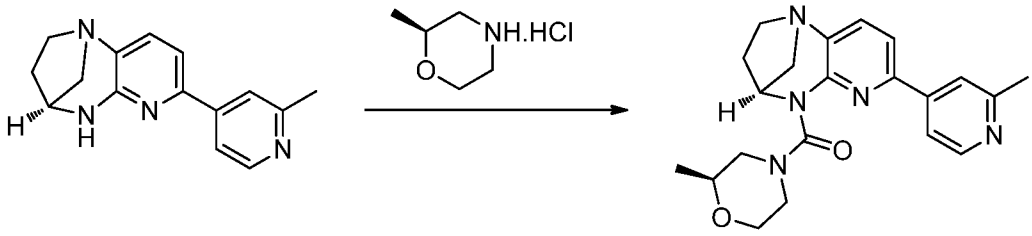
Synthesis of ((*R*)-2-methylmorpholino)(4*S*)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepin-5(2*H*)-yl)methanone:



Triphosgene (0.529 g, 1.783 mmol) was added to a stirred solution of triethylamine (1.243 mL, 8.92 mmol) and (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido [2,3-b][1,4]diazepine (0.45 g, 1.783 mmol) in tetrahydrofuran (50 mL) at room temperature and stirred for 1 h and followed by addition of (*R*)-2-methylmorpholine hydrochloride (0.368 g, 2.68 mmol) and heated to 70 °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 and brine. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to get crude compound (TLC eluent: 10% MeOH in ethyl acetate; UV active; R_f~0.4). Crude compound was purified through

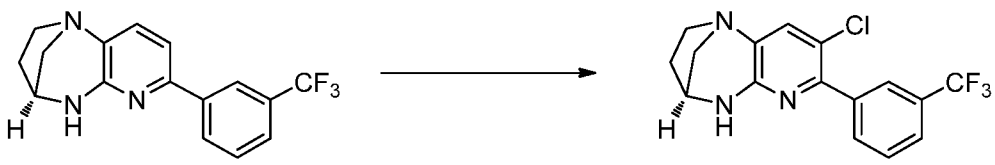
column chromatography using neutral alumina and eluted in 50% ethyl acetate in hexane to afford (*R*)-2-methylmorpholino)((4S)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepin-5(2*H*)-yl)meth-anone (0.2g, 0.514 mmol, 32.4 % yield) as gummy compound, LCMS (*m/z*) 380.3 $(M+H)^+$.

Synthesis of ((*S*)-2-methylmorpholino)((4*S*)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepin-5(2*H*)-yl)methanone



Triphosgene (0.470 g, 1.585 mmol) was added to a stirred solution of triethylamine (1.105 mL, 7.93 mmol) and (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido [2,3-b][1,4]diazepine (0.4g, 1.585 mmol) in tetrahydrofuran (50 mL) at room temperature and stirred for 1h and followed by addition of (*S*)-2-methylmorpholine hydrochloride (0.327 g, 2.378 mmol) and heated to 70 °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 and brine. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to get crude compound (TLC eluent: 10% MeOH in ethyl acetate; UV active; R_f~0.4). Crude compound was purified through column chromatography using neutral alumina and eluted in 50% ethyl acetate in hexane to afford (*S*)-2-methylmorpholino)((4S)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepin-5(2*H*)-yl)meth-anone (0.2g, 0.514 mmol, 32.4 % yield) as gummy compound, LCMS (*m/z*) 480.3 $(M+H)^+$.

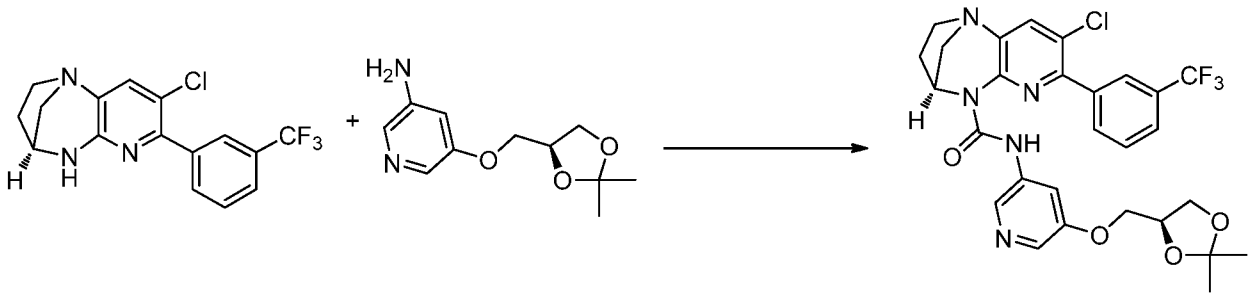
Synthesis of (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine



To a solution of (4S)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (10.0 g, 32.8 mmol) in Chloroform (50 mL) stirred

under nitrogen at 0°C was added N-chlorosuccinimide (6.56 g, 49.1 mmol) portion wise during 10 min. The reaction mixture was stirred at 50 °C for 6 hr. After completed of the reaction mixture was quenched with ice cold water (60 ml) and extracted with DCM (3x60 ml),DCM layer was separated and was washed with brine (2x30 ml), DCM layer was separated and dried over anhydrous sodium sulphate, filtered it and concentrated to get the crude. Crude was purified by flash chromatography on neutral alumina. Crude was diluted with DCM and absorbed with neutral alumina and eluted with 30% EtOAc in pet ether – 50% EtOAc in pet ether fractions were collected and concentrated to get (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (6.3 g, 18.12 mmol, 55.3 % yield) as a pale yellow solid, LCMS (*m/z*) 340.1 $[M+H]^+$.

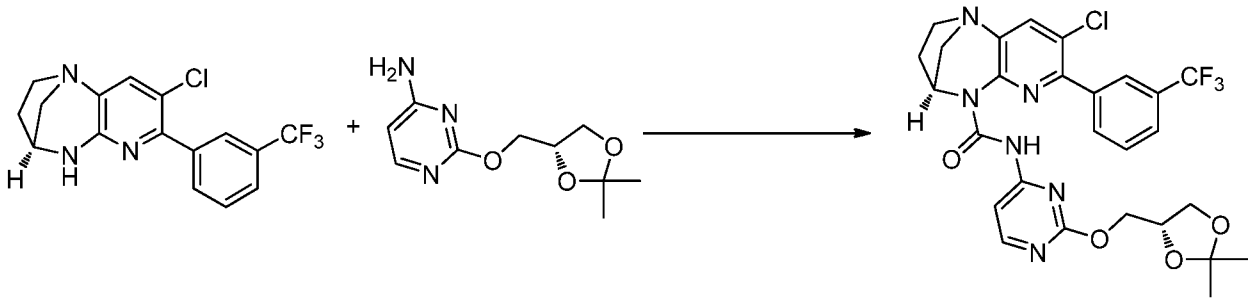
Synthesis of (4S)-8-chloro-N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



(4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.472 mmol), triethylamine (1.231 mL, 8.83 mmol) were taken in Tetrahydrofuran (THF) (50 mL) at 0 °C, the resulting yellow solution was stirred for 10 min. Then added triphosgene (437 mg, 1.472 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 (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine (330 mg, 1.472 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. Column was eluted 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 the (4S)-8-chloro-N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (210 mg, 0.331 mmol, 22.47 % yield) as an off white solid, LCMS (*m/z*): 590.15 $[M+H]^+$.

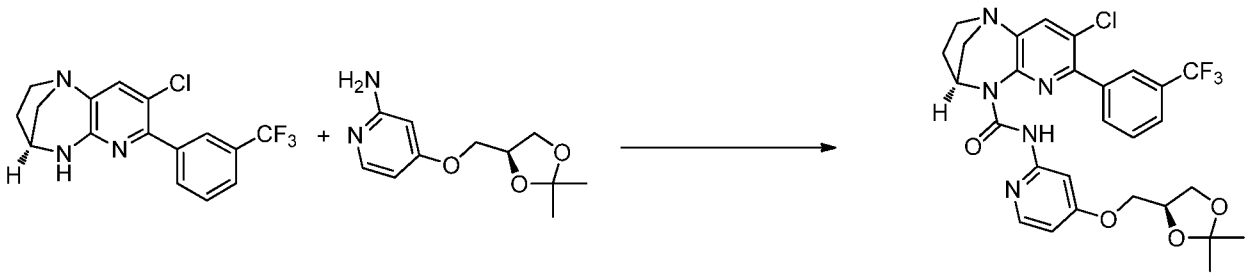
Synthesis of (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine



To a solution of (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (7 g, 20.60 mmol) in Tetrahydrofuran (THF) (120 mL) was added triethylamine (17.23 mL, 124 mmol) and triphosgene (6.11 g, 20.60 mmol). The reaction mixture was stirred at room temp for 30 min. To this reaction mixture was added (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine (11.60 g, 51.5 mmol) and stirred at 65 °C for 12 hr. The reaction mixture was cooled to room temp, solvent evaporated under reduced pressure completely and was partitioned between water (100 mL) and EtOAc (2 x 200 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 25-30% EtOAc in Hexane (gradient system) to afford the desired product (7.2 g) as a white solid. The product (6.9 g) was diluted in ethanol (100 ml) and treated with a Silicycle palladium scavenger (3.5 g) and stirred at 55 °C for 3hr. 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 (4S)-8-chloro-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-

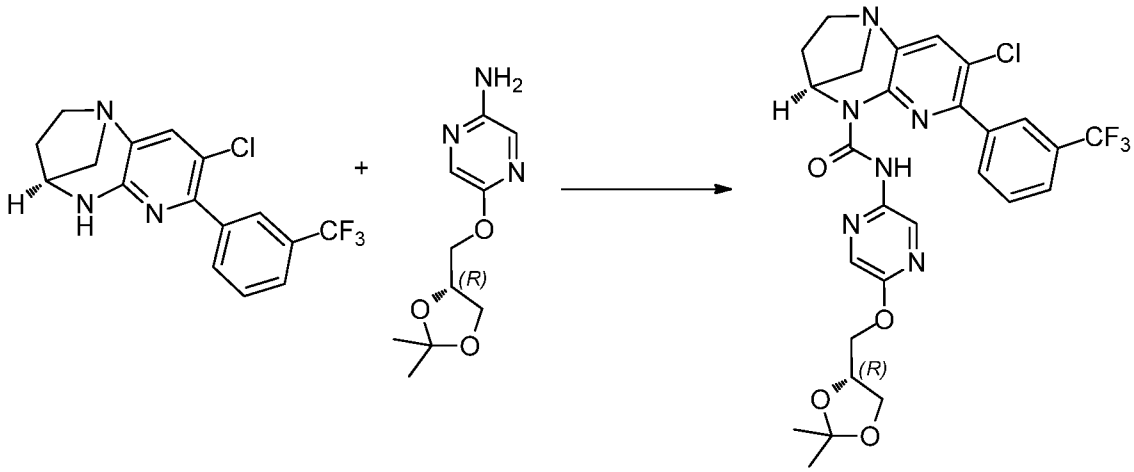
carboxamide (6.9 g, 11.65 mmol, 56.6 % yield) as a white solid. LCMS (*m/z*): 591.16 $[M+H]^+$.

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



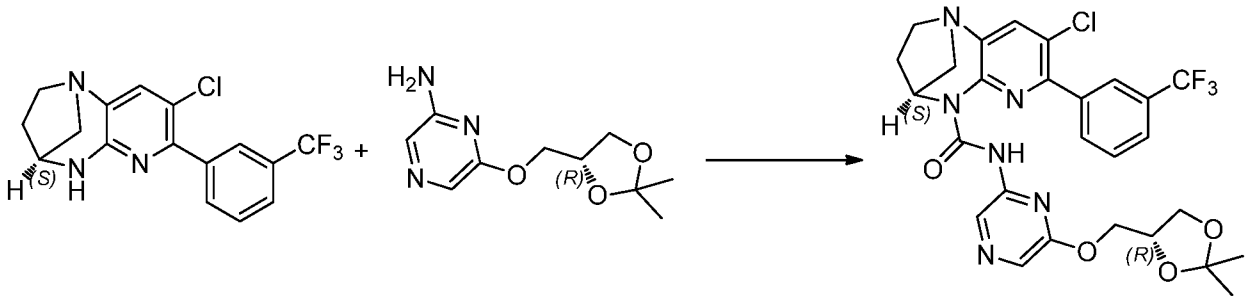
To solid (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (3.0 g, 8.83 mmol) in Tetrahydrofuran (THF) (30 mL) stirred under nitrogen at room temp was added solid triphosgene (1.572 g, 5.30 mmol) stirred under nitrogen at room temp for 30 minutes. To this DIPEA (7.71 mL, 44.2 mmol) and (S)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (2.97 g, 13.25 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 concentrated and the residue was taken up in dichloromethane (100 mL). The solution was washed with water and brine, dried over Na_2SO_4, filtered and concentrated to get crude compound. The crude product was added to a neutral alumina column and was eluted wit 50% EtOAc/Pet ether. Collected fractions and concentrated to get compound and washed with pentane to get pure compound, LCMS (*m/z*) 590.43 $[M+H]^+$.

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



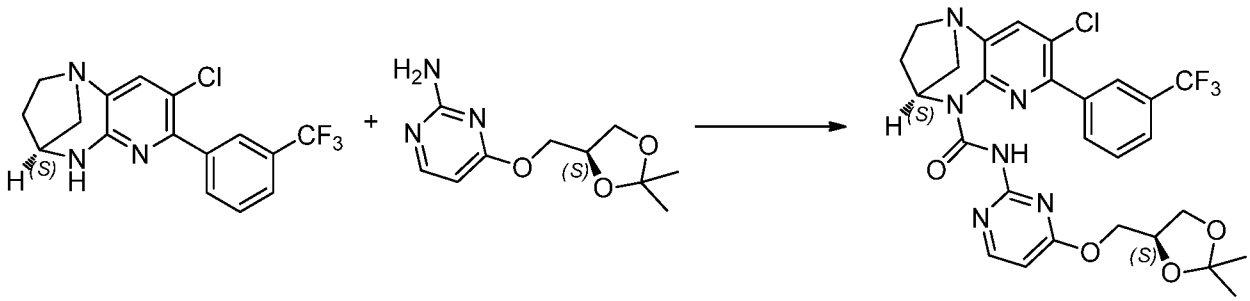
To a stirred solution of (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.472 mmol) in Tetrahydrofuran (THF) (20 mL), was added triphosgene (437 mg, 1.472 mmol) and followed by triethylamine (1.231 mL, 8.83 mmol) at room temperature. The reaction mixture was stirred for 45 min and added a solution of (*R*)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine (663 mg, 2.94 mmol) in Tetrahydrofuran (THF) (5 mL). The reaction mixture was stirred at 65 °C for 12 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 x 25 mL), combined organic layers was dried over anhydrous Na_2SO_4 filtered and concentrated to obtain desired crude product. Crude product was purified by column chromatography using 100-200 silica gel (eluent 35-50% EtOAc in pet ether) to obtain the desired pure product (4S)-8-chloro-N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (500 mg, 0.837 mmol, 56.9 % yield) as off-white solid, LCMS (*m/z*): 590.8 $[M+H]^+$.

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



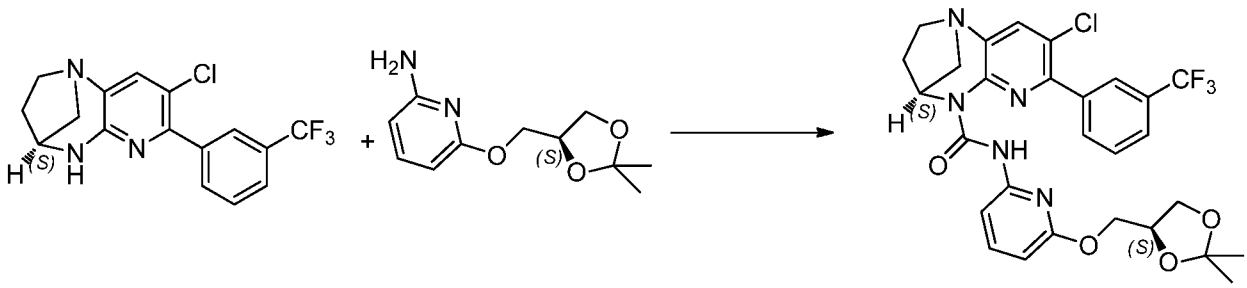
DIPEA (13.69 g, 106 mmol) followed by triphosgene (10.48 g, 35.3 mmol) were added to a solution of (4*S*)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (12.0 g, 35.3 mmol) in Tetrahydrofuran (THF) (200 mL) at 25°C, stirred for 1h and (*R*)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine (15.91 g, 70.6 mmol) was added and heated at 70 °C for 18 h. The reaction mixture was cooled to 28°C and was partitioned between water (50 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 product. The crude product was purified by combiflash column chromatography (column:C18, eluted with 90% ACN in 1% formic acid in water), further triturated with ethanol to afford (4*S*)-8-chloro-*N*-(6-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (6.0 g, 10.14 mmol, 28.7 % yield), as white solid, LCMS (*m/z*): 591.25$[M+H]^+$.

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



NaH (0.283 g, 5.89 mmol) was added to a solution of (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1.0 g, 2.94 mmol) in Tetrahydrofuran (THF) (15 mL) at RT, stirred for 1h and (S)-phenyl (4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)carbamate (2.033 g, 5.89 mmol) was added slowly and stirred at 70 °C for 18 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. The crude compound was purified by combiflash column chromatography (column: C18, eluted with 90% ACN in 1% formic acid in water), further purified by column chromatography (silica-gel: 100-200 mesh, eluted with 90% EtOAc in hexane) to afford (4S)-8-chloro-N-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (400 mg, 0.659 mmol, 22.38 % yield), as a white solid LCMS(*m/z*), 591.50 $(M+H)^+$.

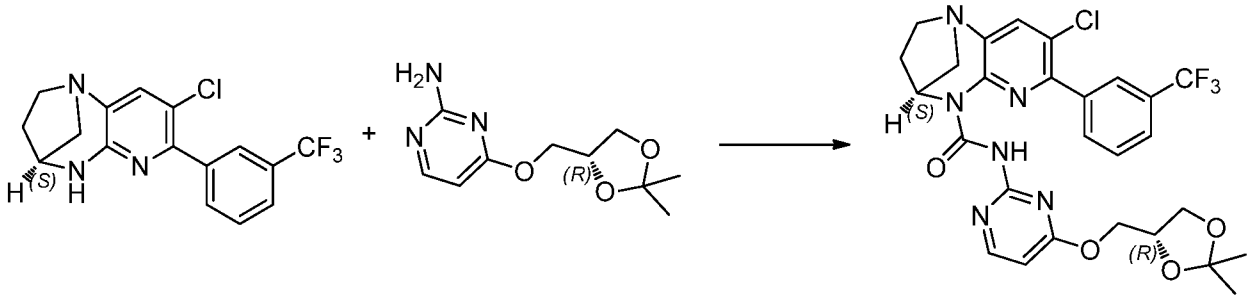
Synthesis of (4S)-8-chloro-N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



(4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (15 g, 44.2 mmol) was dissolved in Tetrahydrofuran (THF) (200 mL) stirred under nitrogen at 0°C were added triphosgene (10.48 g, 35.3 mmol), triethylamine (30.8 mL, 221 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 (14.85 g, 66.2 mmol) was added and stirred for 16 h at 80 °C. The reaction mixture allowed to room temperature and quenched with 500 ml of water and extracted with 3x800 ml of ethyl

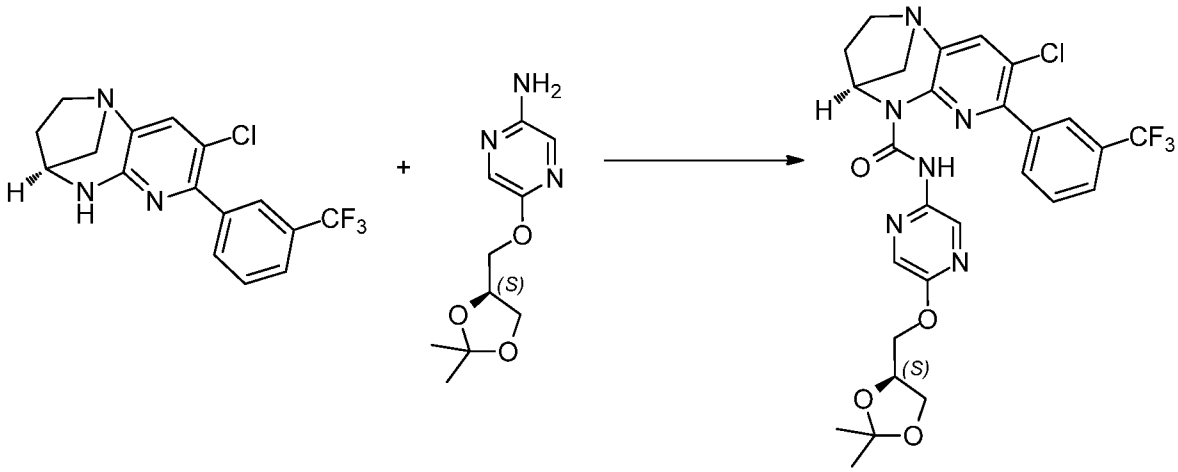
acetate. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain crude. The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh) to afford (4S)-8-chloro-N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (9.3 g, 15.66 mmol, 35.5 % yield) as an off white solid, LCMS (*m/z*): 590.16 $[M+H]^+$.

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



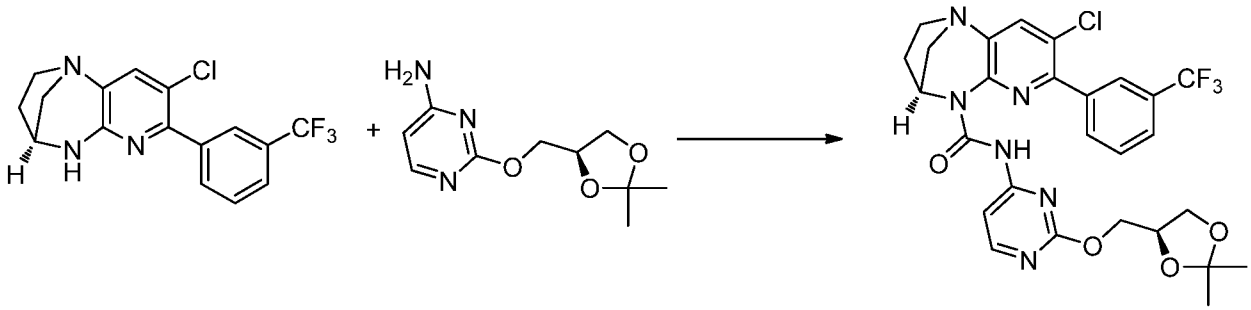
To a solution of (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.472 mmol) in THF (30 ml) and was added triphosgene (218 mg, 0.736 mmol), at 0°C and stirred to RT for 1 h. Then DIPEA (0.771 mL, 4.42 mmol) and (R)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-amine (663 mg, 2.94 mmol) was added 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 (50 mL) and extracted with ethyl acetate (2x100 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 5% methanol in DCM as eluent to afford the (4S)-8-chloro-N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (200 mg, 0.335 mmol, 22.77 % yield) as a white solid LCMS (*m/z*): 591.38 $[M+H]^+$.

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



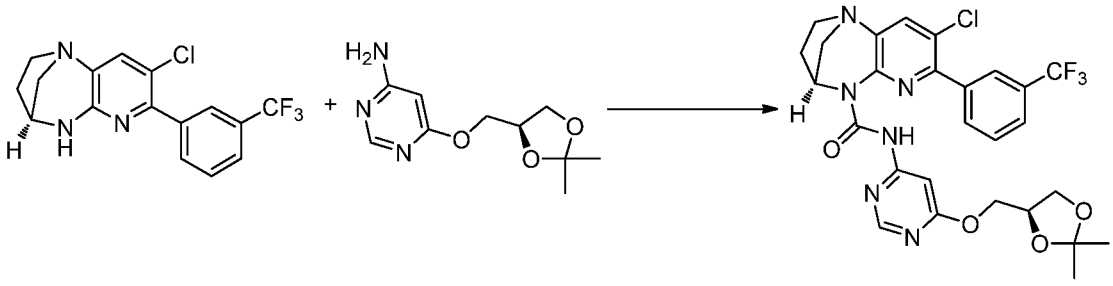
To a stirred solution of (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.472 mmol) in Tetrahydrofuran (THF) (20 mL), was added triphosgene (437 mg, 1.472 mmol) and followed by triethylamine (1.231 mL, 8.83 mmol) at RT. The reaction mixture was stirred for 45 min and added a solution of (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine (497 mg, 2.208 mmol) in Tetrahydrofuran (THF) (5 mL). The reaction mixture was stirred at 65 °C for 12 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 x 25 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to obtain desired crude product. Crude product was purified by column chromatography using 100-200 silica gel (eluent 35-50% EtOAc in pet ether) to obtain the desired pure product (4S)-8-chloro-N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (500 mg, 0.834 mmol, 56.7 % yield) as off-white solid. LCMS (*m/z*): **591.16** $[M+H]^+$.

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



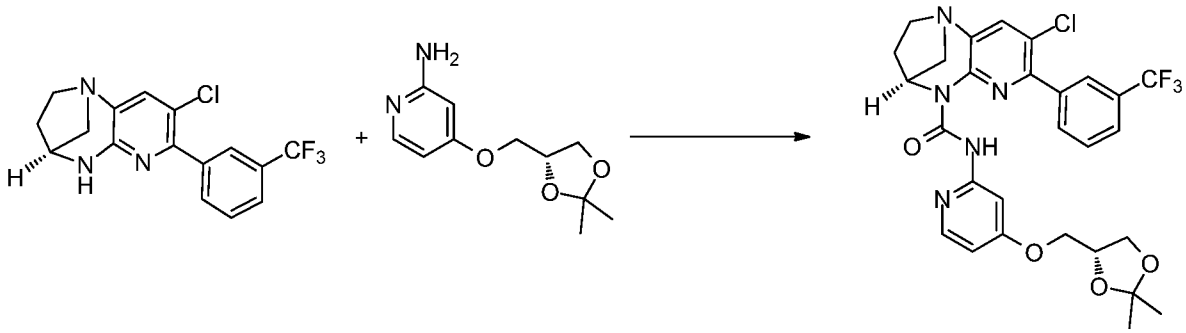
A solution of (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (30 g, 88 mmol), triphosgene (26.2 g, 88 mmol) and triethylamine (61.5 mL, 442 mmol) in Tetrahydrofuran (THF) (300 mL) was stirred under nitrogen at room temp for 15 min. To this reaction mixture (S)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine (59.7 g, 265 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 (200 mL) and extracted with EtOAc (3 X 200 mL). The combined organic layer was washed with water (200 mL), brine solution (200 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 Pet ether to afford pure (4S)-8-chloro-N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (23 g, 38.8 mmol, 44.0 % yield) as off white solid, LCMS (*m/z*): 591.4 $[M+H]^+$

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



TEA (0.821 mL, 5.89 mmol) was added to a stirred solution of (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (0.4 g, 1.177 mmol) in Tetrahydrofuran (THF) (50 mL) at room temperature and followed by addition of triphosgene (0.349 g, 1.177 mmol) at same temperature and stirred for 1h. (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine (0.796 g, 3.53 mmol) and stirred at 65 °C for 15h. 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 (4S)-8-chloro-N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (0.25g, 0.414 mmol, 35.2 % yield) as white solid, LCMS (*m/z*): 591.1 $[M+H]^+$

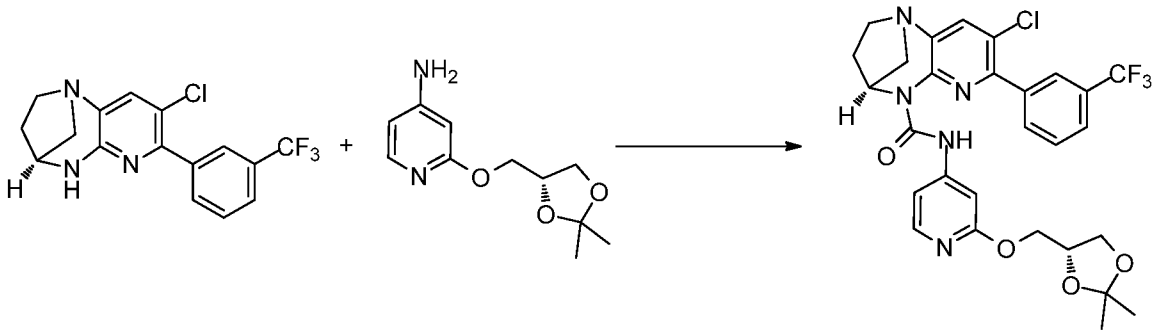
Synthesis of (4S)-8-chloro-N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



Triethylamine (24.62 mL, 177 mmol) and triphosgene (8.73 g, 29.4 mmol) was added to a stirred solution of (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (10 g, 29.4 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 (13.20 g, 58.9 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 aluminia and was eluted with 30% 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 3hr. 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 (4S)-8-chloro-N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (8.0 g, 13.52 mmol, 45.9 % yield) as a white solid, LCMS (*m/z*): 590.07 $[M+H]^+$.

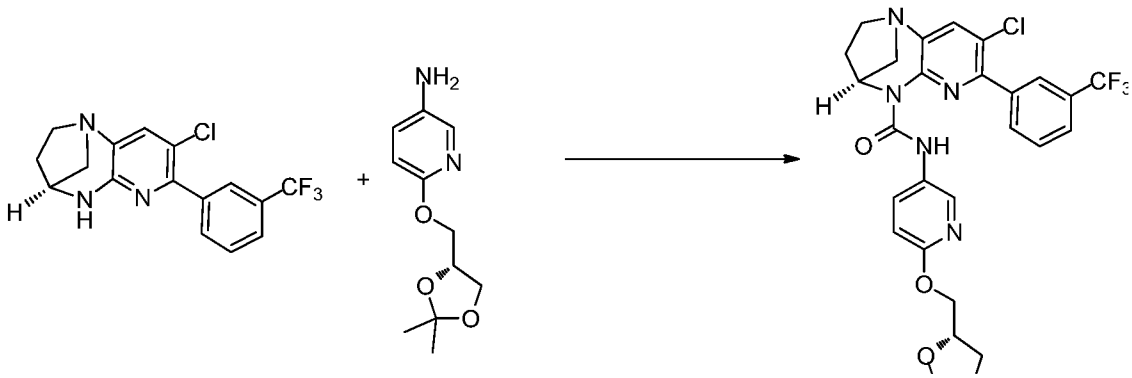
Synthesis of (4S)-8-chloro-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



To a solution of (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (25 g, 73.6 mmol), triphosgene (13.10 g, 44.2 mmol) in Tetrahydrofuran (THF) (400 mL) stirred under nitrogen at 0°C and added DIPEA (64.3 mL, 368 mmol). Then the reaction mixture was stirred at 30 °C for 30 min and added (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (18.15 g, 81 mmol) then the reaction mixture was stirred at 70 °C for 16h. The reaction was monitored by LCMS and TLC. The reaction mixture was poured in to the cold water (100 mL) and extracted with ethyl acetate (2x 300 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude compound was purified by flash chromatography (100-200 mesh, 90% Ethyl acetate in pet ether) to afford (4S)-8-chloro-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (18.5 g, 30.9 mmol,

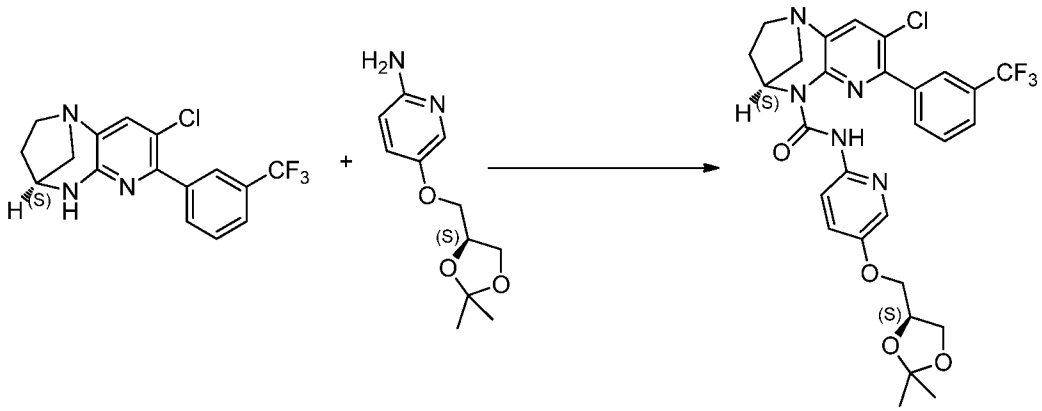
41.9 % yield) as a yellow solid. LCMS (*m/z*): 590.12 $[M+H]^+$.

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



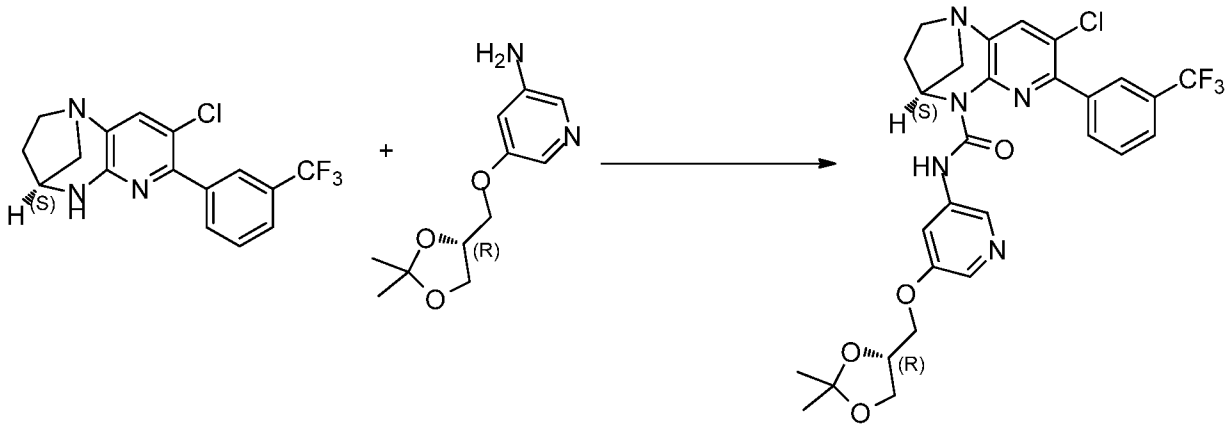
TEA (1.026 mL, 7.36 mmol) followed by triphosgene (437 mg, 1.472 mmol) were added to a solution of (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.472 mmol) in Tetrahydrofuran (THF) (20 mL) at RT and stirred for 1h and (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine (330 mg, 1.472 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 x 3). Organic layers were separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude then it was further purified by column chromatography (using 100-200 silicagel, column eluted at 50% ethyl acetate in hexane) to afford the (4S)-8-chloro-N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (350 mg, 0.593 mmol, 40.3 % yield) as an off white solid, LCMS (*m/z*): 590.16 $[M+H]^+$.

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



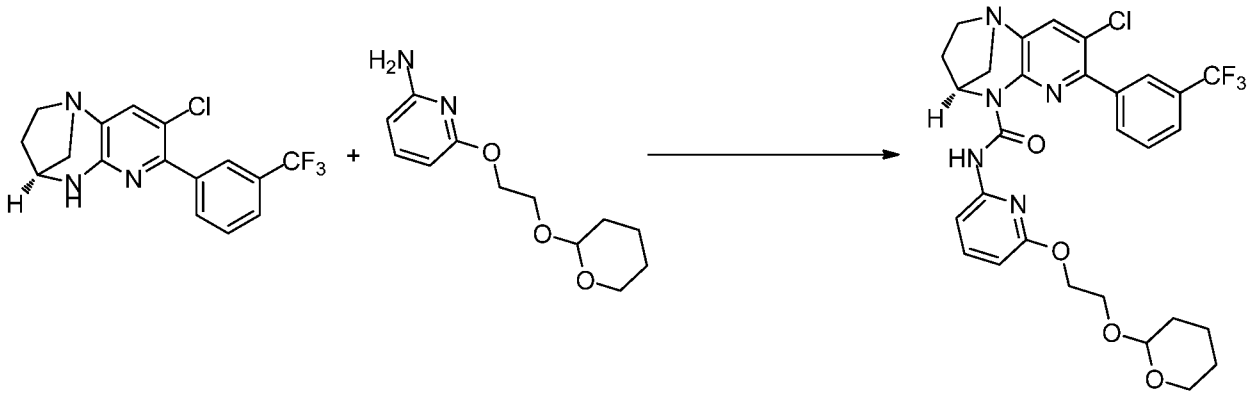
DIPEA (571 mg, 4.42 mmol) followed by triphosgene (437 mg, 1.472 mmol) were added to a solution of (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (660 mg, 2.94 mmol) in Tetrahydrofuran (THF) (20 mL) at 25 °C, stirred for 1h and (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.472 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 (TLC eluent: 100% ethyl acetate R_f 0.3; UV active). The crude compound was purified by column chromatography (C-18: eluted with 70% methanol in 1% aq formic acid) to afford (4S)-8-chloro-N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (200 mg, 0.339 mmol, 23.03 % yield), as a brownish sticky, LCMS (*m/z*) 590.43 $(M+H)^+$.

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



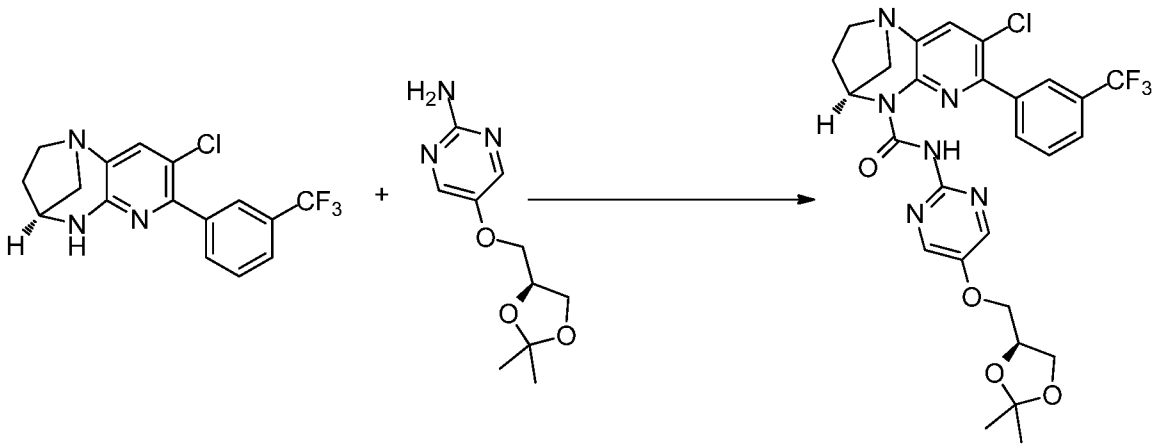
(4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (8 g, 23.55 mmol), TEA (16.41 mL, 118 mmol) were taken in Tetrahydrofuran (THF) (80 mL) at 0 °C, the resulting yellow solution was stirred for 10 min at room temperature. Then added triphosgene (6.99 g, 23.55 mmol) in one portion at 0 °C. The resulting yellow suspension was stirred for 45 min at room temperature. The THF (10 mL) solution of (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine (7.92 g, 35.3 mmol) was added to the above yellow suspension at 0 °C over a period of 2 min. The resulting yellow suspension was heated to 70 °C for 24 hr. The reaction progress was monitored by TLC 5% MeOH in DCM, TLC indicated formation of multiple spots and completion of SM after 24 h. Reaction mixture was cooled to room temperature, then diluted with water (20 mL), extracted with EtOAc (2 x 40 mL), separated the organic layer washed with brine(20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain crude yellow solid. The crude material was purified by combiflash using silica gel column (12 g, 5% MeOH in DCM). Fraction containing pure compound were combined and concentrated to afford the desired compound (4S)-8-chloro-N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (11 g, 18.53 mmol, 79 % yield) as yellow solid, LCMS (*m/z*): 590.06 $[M+H]^+$.

Synthesis of (4S)-8-chloro-N-(6-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



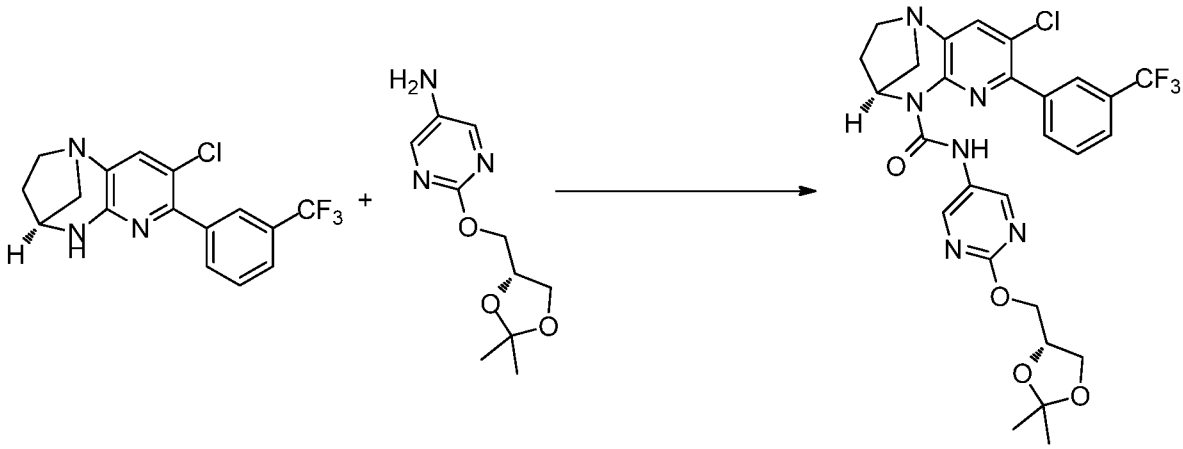
To a solution of (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (400 mg, 1.177 mmol) in Tetrahydrofuran (THF) (30 mL) was added triethylamine (0.985 mL, 7.06 mmol) and triphosgene (349 mg, 1.177 mmol) stirred under nitrogen at room temp for 30 min, to this reaction mixture was added 6-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)pyridin-2-amine (701 mg, 2.94 mmol) and stirred at 65 °C for 16 hr.TLC eluent: 70 % Ethyl acetate in Hexane R_f :0.3, UV active. The reaction mixture was cooled to room temp, solvent evaporated under reduced pressure completely and was partitioned between water (10 mL) and EtOAc (2 X 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 25-30-% EtOAc in pet ether fractions were collected and concentrated to get (4S)-8-chloro-N-(6-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (300 mg, 0.478 mmol, 40.6 % yield) as a pale yellow solid, LCMS (*m/z*): 604.14 $[M+H]^+$.

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



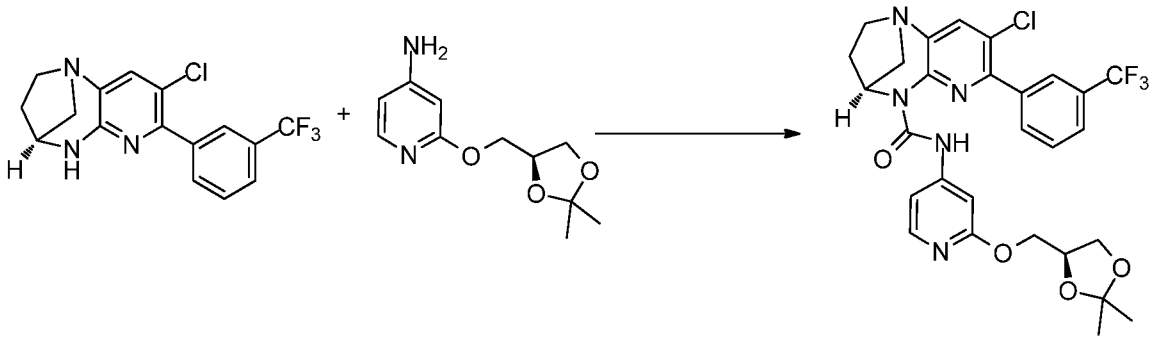
Triphosgene (437 mg, 1.472 mmol) was added to a stirred solution of (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.472 mmol), and TEA (1.231 mL, 8.83 mmol) in Tetrahydrofuran (THF) (50 mL) under nitrogen at 28°C. The reaction mixture was stirred at RT for 30 min. and was added (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-amine (663 mg, 2.94 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 (2 mL) and EtOAc (2x 25mL). 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 (4S)-8-chloro-N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (300 mg, 0.495 mmol, 33.6 % yield) as off white solid, LCMS (*m/z*): 591.19 $[M+H]^+$.

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



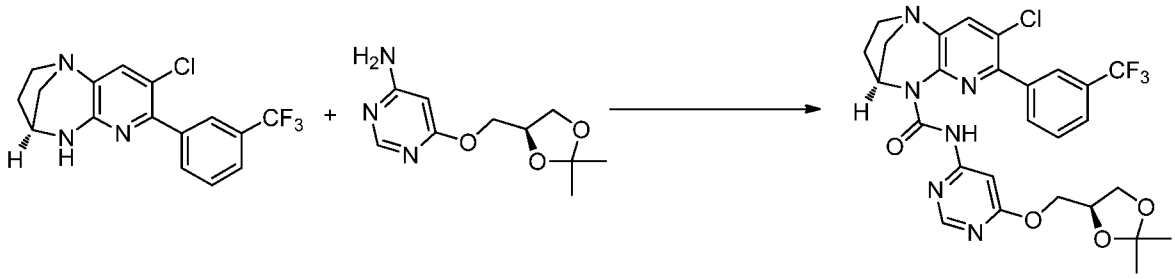
triphosgene (393 mg, 1.325 mmol) was added to a stirred solution of (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (450 mg, 1.325 mmol) and triethylamine (1.108 mL, 7.95 mmol) in triphosgene (393 mg, 1.325 mmol) at 28^{O}C. The reaction mixture was stirred for 2 h and was added (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-amine (746 mg, 3.31 mmol). The reaction mixture was stirred for 10 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 X 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 40-45% EtOAc in pet ether fractions were collected and concentrated to get (4S)-8-chloro-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (450 mg, 0.761 mmol, 57.4 % yield) as a off white solid, LCMS (*m/z*): 591.17 $[M+H]^+$.

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



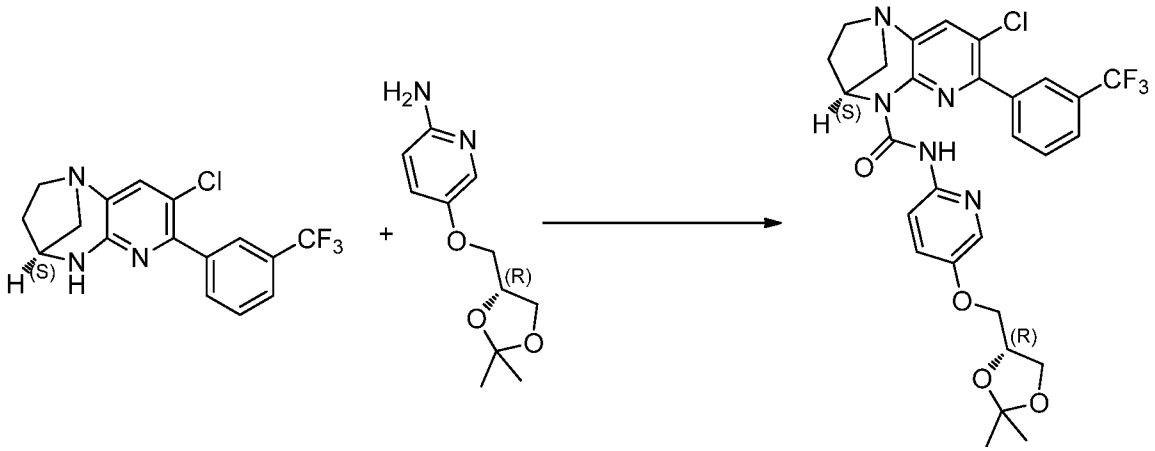
Triphosgene (21.84 g, 73.6 mmol) was added to a stirred solution of (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (25.0 g, 73.6 mmol), and TEA (51.3 mL, 368 mmol) in Tetrahydrofuran (THF) (200 mL) at 25°C. The reaction mixture was stirred for 60 min and was added (S)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (49.5 g, 221 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 (20 ml) and brine solution (20 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, eluted by 30-40% EtOAc/pet ether to get the desired compound as a solid. This was again triturated with the 30% Diethylether/pentane to get the desired compound as a off white solid. This compound was diluted in ethanol (600 ml) and treated with Silicycle palladium scavenger (12 g) and stirred at 50°C for 3hr. This 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 get the (4S)-8-chloro-N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (22.0 g, 37.1 mmol, 50.4 % yield) as a white solid, LCMS (*m/z*): 590.07 $[M+H]^+$.

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



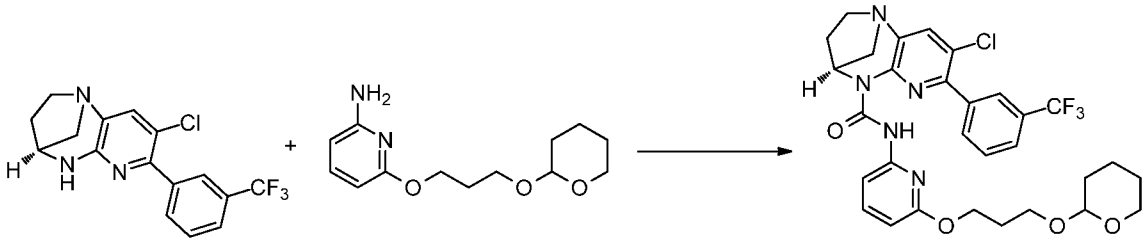
To a solution of (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (8.5 g, 25.02 mmol) in Tetrahydrofuran (THF) (250 mL) was added triphosgene (7.42 g, 25.02 mmol) followed by triethylamine (20.92 mL, 150 mmol), the resulting suspension was stirred at RT for 20 min. (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine (11.27 g, 50.0 mmol) was added to the reaction mass and the resulting suspension was heated to 70 °C for 16 hr. Reaction was monitored by TLC (it shows absence of SM and the formation of new spot at R_f: 0.6). Crude material was purified by column chromatography over silica gel (100-200 silica gel, 0-3%MeOH in DCM). Fractions containing pure compound were combined and concentrated to afford the desired compound (4S)-8-chloro-N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (8.5 g, 13.19 mmol, 52.7 % yield) an off-white solid, LCMS (*m/z*): 591.07 $(M+H)^+$.

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



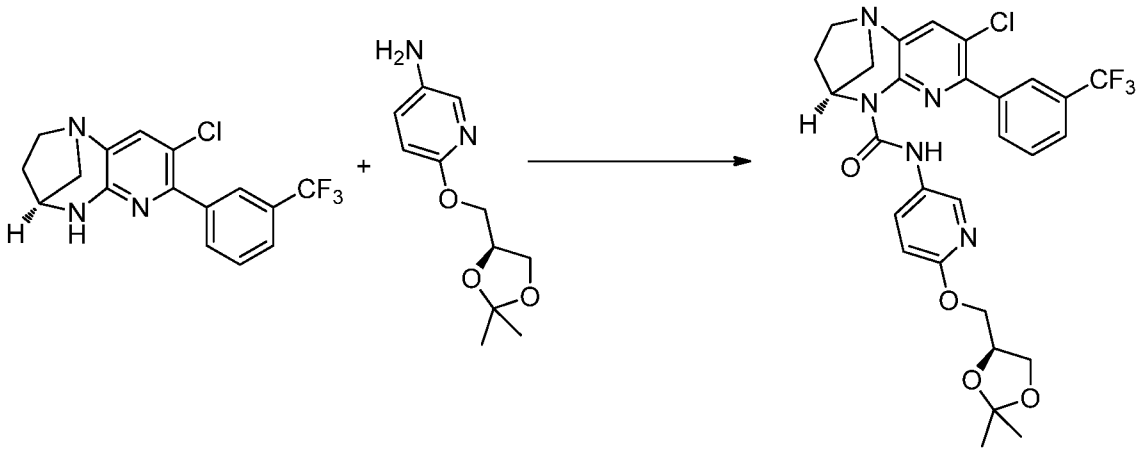
To a solution of(4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.472 mmol) in Tetrahydrofuran (THF) (15 mL) and triphosgene (262 mg, 0.883 mmol) at 0°C and stirred to RT for 30mins. Then DIPEA (1.285 mL, 7.36 mmol) and (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (578 mg, 2.58 mmol) was added sub sequentially and stirred at 75°C for 15hr 30mins. The reaction was monitored by TLC and LCMS. The reaction mixture was poured into saturated $NaHCO_3$ solution (50 mL) and extracted with ethyl acetate (2x150 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude compound. The crude was purified by column chromatography (100-200 silica gel) using gradient mixture of 80% EtOAc in Pet ether as eluent, to afford pure compound (4S)-8-chloro-N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (450 mg, 0.691 mmol, 47.0 % yield), LCMS (*m/z*): 590.37 $(M+H)^+$.

Synthesis of (4S)-8-chloro-N-(6-(3-((tetrahydro-2H-pyran-2-yl)oxy)propoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



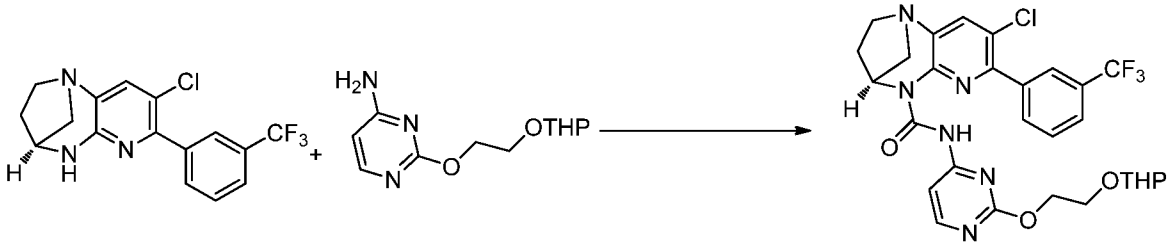
Triphosgene (437 mg, 1.472 mmol) was added to a stirred solution of (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.472 mmol) and TEA (1.231 mL, 8.83 mmol) in Tetrahydrofuran (THF) (25 mL) at room temp. The reaction mixture was stirred for 4 h and 6-(3-((tetrahydro-2H-pyran-2-yl)oxy)propoxy)pyridin-2-amine (743 mg, 2.94 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 500 mL of Ethyl acetate. Organic layer washed with water (200 mL) followed by brine solution (100 mL), 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 in the next step, LCMS (*m/z*): 618.10 $(M+H)^+$.

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



DIPEA (571 mg, 4.42 mmol) followed by triphosgene (437 mg, 1.472 mmol) were added to a solution of (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.472 mmol) in Tetrahydrofuran (THF) (20 mL) at 25 °C, stirred for 1h and (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine (660 mg, 2.94 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 (TLC eluent: 100% ethyl acetate R_f:0.3; UV active). The crude compound was purified by column chromatography (C-18: eluted with 70% methanol in 1% aq formic acid) to afford (4S)-8-chloro-N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (350 mg, 0.583 mmol, 39.6 % yield), as a brownish sticky, LCMS (*m/z*): 590.43 $(M+H)^+$.

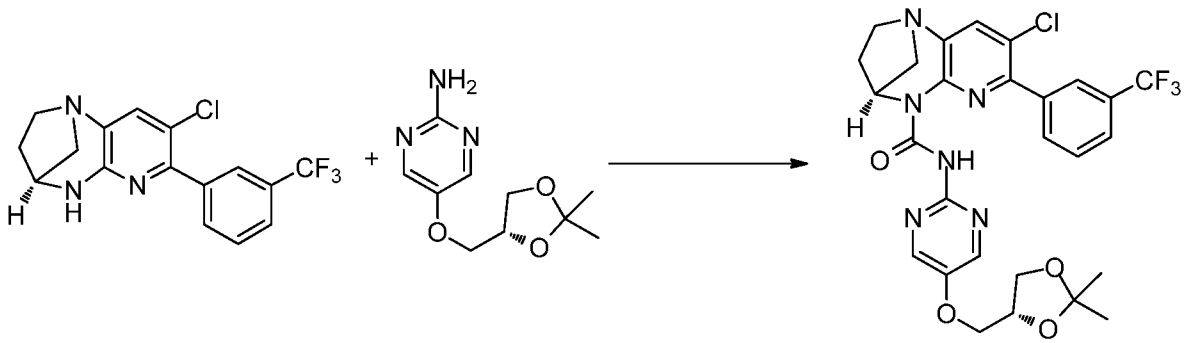
Synthesis of (4S)-8-chloro-N-(2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



TEA (0.821 mL, 5.89 mmol) followed by triphosgene (175 mg, 0.589 mmol) were added to a stirred solution of (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (400 mg, 1.177 mmol) in Tetrahydrofuran (THF) (15 mL) at RT stirred for 1h and 2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)pyrimidin-4-amine (310 mg, 1.295 mmol) was added and heated at 80 °C for 15 h. The reaction mixture was cooled to 28 °C and was partitioned between water (15 mL) and EtOAc (30 mL x 2). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude as a gum. It was purified by column chromatography (using 100-200 silica gel, column eluted at 90% ethyl acetate in hexane) to afford (4S)-8-chloro-N-(2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-

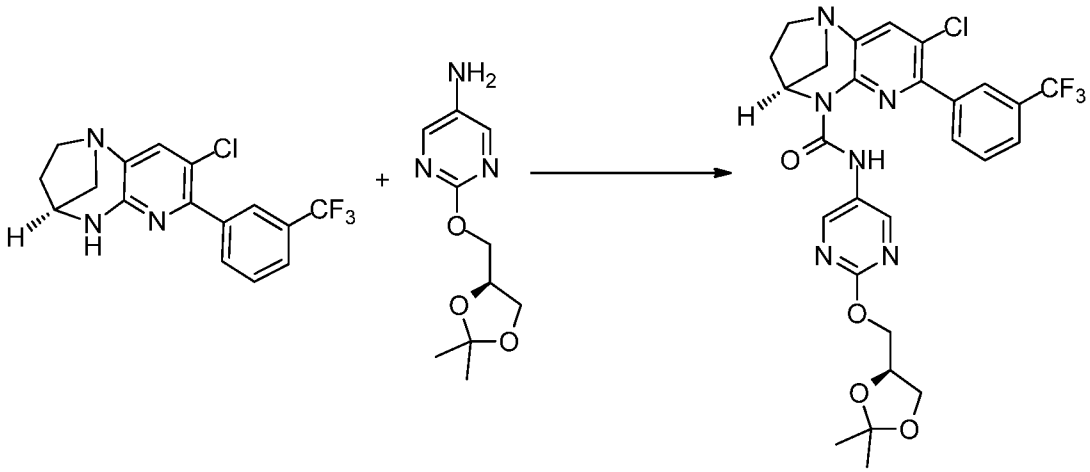
carboxamide (310 mg, 0.505 mmol, 42.9 % yield) as an off white solid, LCMS (*m/z*): 603.41 $(M+H)^+$.

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



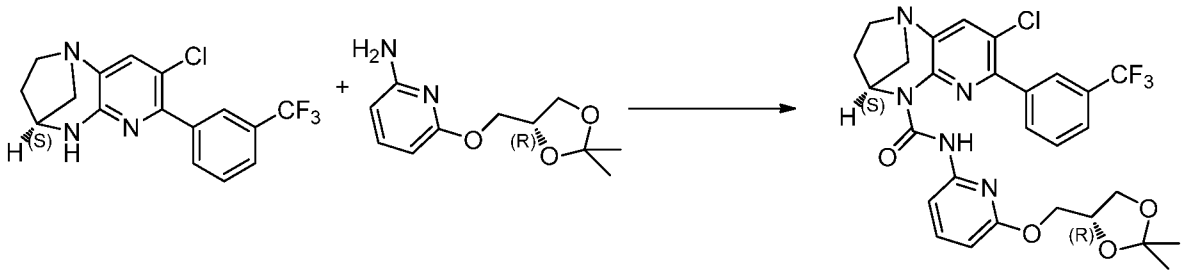
A solution of (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (400 mg, 1.177 mmol), triphosgene (349 mg, 1.177 mmol) and triethylamine (0.821 mL, 5.89 mmol) in Tetrahydrofuran (THF) (20 mL) was stirred under nitrogen at room temp for 15 min. To this reaction mixture (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-amine (796 mg, 3.53 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 X 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. TLC eluent: 100%EtOAc/Hexane, R_f:0.1, UV active. The crude compound was purified by column chromatography using Neutral Alumina and eluted with 50% EtOAc in Pet ether to afford pure (4S)-8-chloro-N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (350 mg, 0.590 mmol, 50.1 % yield) as off white solid, LCMS (*m/z*): 591.26 $[M+H]^+$.

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



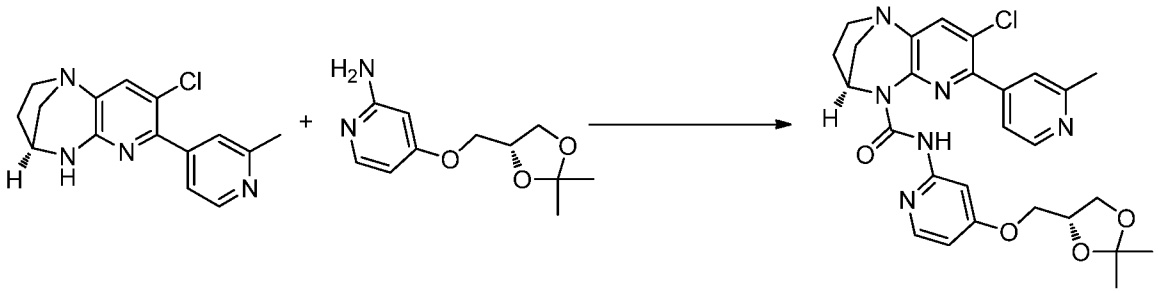
TEA (0.985 mL, 7.06 mmol) and triphosgene (349 mg, 1.177 mmol) was added to a stirred solution of (4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (400 mg, 1.177 mmol) in Tetrahydrofuran (THF) (40 mL) under nitrogen at room temp. The reaction mixture was stirred at RT for 30 min. (S)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-amine (530 mg, 2.355 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 product was purified by column chromatography using neutral alumina and was eluted with 30% EtOAc in Hexane (gradient system) to afford the desired product ((4S)-8-chloro-N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (300 mg, 0.495 mmol, 42.1 % yield) as a pale yellow solid (TLC eluent:70% EtOAc in Hexane: R_f 0.5; UV active), LCMS (*m/z*): 591.19 $[M+H]^+$.

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



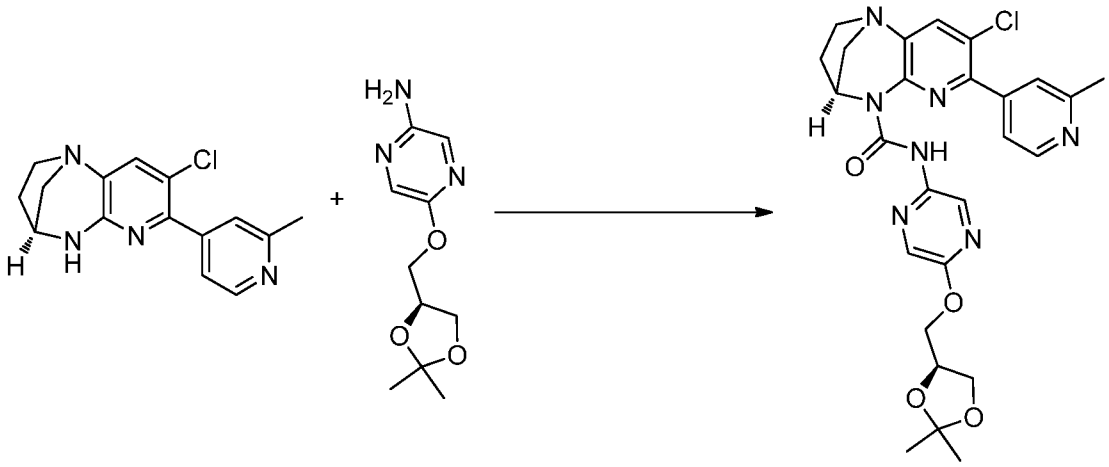
To a solution of(4S)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (10 g, 29.4 mmol) in THF (300 ml) and was added triphosgene (4.37 g, 14.72 mmol), at 0°C and stirred to RT for 1 h. Then TEA (20.51 mL, 147 mmol) and (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (13.20 g, 58.9 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 (300 mL) and extracted with ethyl acetate (1000 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 Pet ether as eluent, to afford (4S)-8-chloro-N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (8.2 g, 13.81 mmol, 46.9 % yield). Material was then purified by Pd Scavenger resin process. To a stirred solution of (4S)-8-chloro-N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide(8.2g) in Ethanol (250ml) at 50 °C was added Pd scavenger resin (4.5 g) and stirred for 5 h at 70°C. Then cooled to 40°C, the reaction mixture was filtered and concentrated under reduced pressure to afford ((4S)-8-chloro-N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide(8 g) as a white solid, LCMS (*m/z*)590.12 $[M+H]^+$.

Synthesis of (4S)-8-chloro-N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



Triethylamine (1.312 ml, 9.42 mmol) and triphosgene (466 mg, 1.569 mmol) was added to a stirred solution of (4S)-8-chloro-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (450 mg, 1.569 mmol) in Tetrahydrofuran (THF) (30 mL) under nitrogen at room temp. The reaction mixture was stirred at RT for 30 min. (R)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (704 mg, 3.14 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 give crude as brown solid. The crude was purified by column chromatography using neutral alumina and was eluted with 50% EtOAc in Hexane to afford the desired product (4S)-8-chloro-N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (450 mg, 0.383 mmol, 24.40 % yield) as pale yellow solid, LCMS (*m/z*): 536.9 $[M+H]^+$.

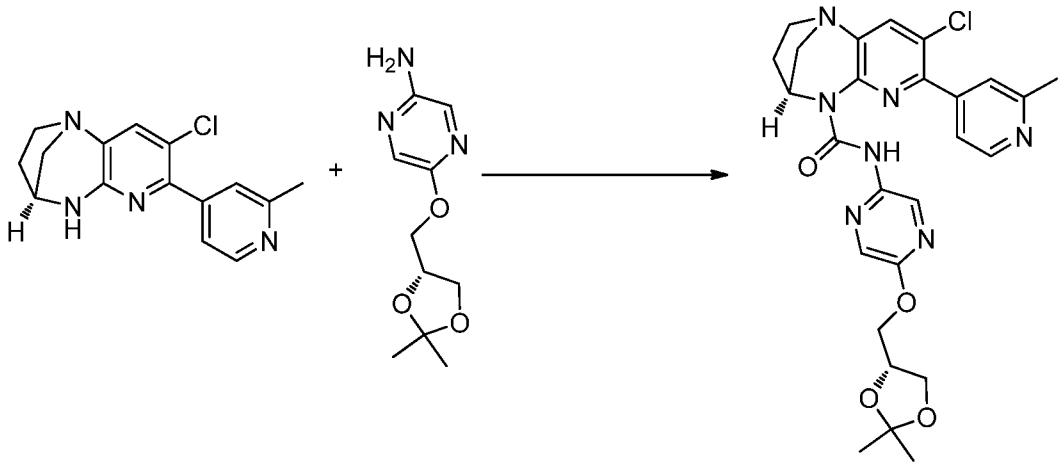
Synthesis of (4S)-8-chloro-N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



To a stirred solution of (4S)-8-chloro-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.744 mmol) in Tetrahydrofuran (THF) (10 mL), was added triphosgene (517 mg, 1.744 mmol) and followed by triethylamine (1.458 mL, 10.46 mmol) at rt. The reaction mixture was stirred for 45 min and added a solution of(S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine (785 mg, 3.49 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 (50mL) and extracted with Ethyl acetate (50mLX2). 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 (4S)-8-chloro-N-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (250 mg, 0.447 mmol, 25.6 % yield) as light yellow solid

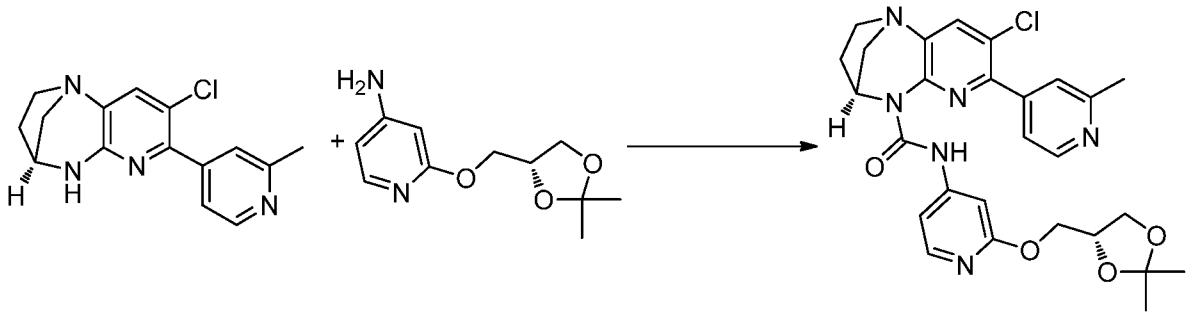
LCMS (*m/z*): 538.14 $[M+H]^+$.

Synthesis of (4S)-8-chloro-N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



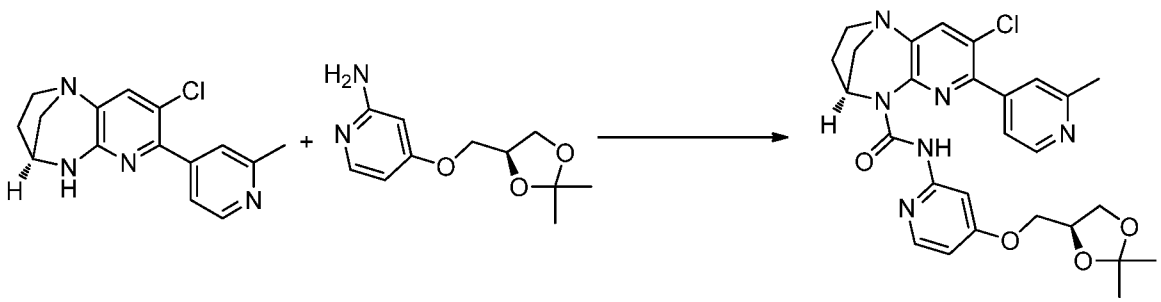
To a stirred solution of (4S)-8-chloro-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.744 mmol) in Tetrahydrofuran (THF) (5 mL) was added triphosgene (517 mg, 1.744 mmol) at RT, reaction mixture was stirred at RT for 30 min, then (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine (589 mg, 2.62 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 x 30 mL), organic layers were combined and washed with brine solution(30 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 with 40% EtOAc in Hexane to afford (4S)-8-chloro-N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (450 mg, 0.807 mmol, 46.3 % yield) as a pale yellow solid. LCMS (*m/z*): 538.47$(M+H)^+$.

Synthesis of (4S)-8-chloro-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



To a solution of (4S)-8-chloro-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (350 mg, 1.221 mmol), triphosgene (217 mg, 0.732 mmol) in Tetrahydrofuran (THF) (15 mL) stirred under nitrogen at 0°C and added triphosgene (217 mg, 0.732 mmol). Then the reaction mixture was stirred at 30 °C for 30 min and added (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (411 mg, 1.831 mmol) then the reaction mixture was stirred at 70 °C for 15h 30 min. The reaction was monitored by LCMS. The reaction mixture was poured in to the cold water (20 mL) and extracted with ethyl acetate (2x 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the crude. The crude compound was purified by flash chromatography (100-200 mesh) and obtained (4S)-8-chloro-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (450 mg, 0.778 mmol, 63.7 % yield) as a yellow solid, LCMS (*m/z*): 536.9 $[M+H]^+$.

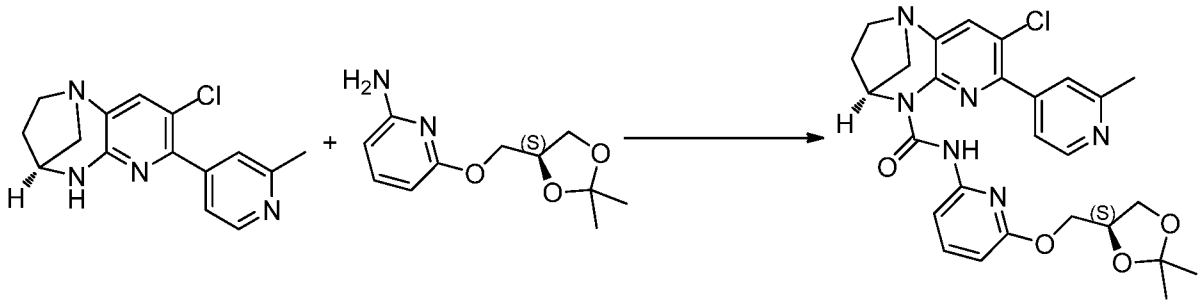
Synthesis of (4S)-8-chloro-N-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



To a solution of (4S)-8-chloro-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-

methanopyrido[2,3-b][1,4]diazepine (250 mg, 0.872 mmol),triphosgene (155 mg, 0.523 mmol)in Tetrahydrofuran (THF) (20 mL) stirred under nitrogen at 0°C and added DIPEA (0.761 mL, 4.36 mmol). Then the reaction mixture was stirred at 30 °C for 30 min and added (S)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (293 mg, 1.308 mmol), then the reaction mixture was stirred at 70 °C for 15h 30 min. The reaction was monitored by LCMS and TLC. The reaction mixture was poured in to the cold water (20 mL) and extracted with ethyl acetate (2x 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude compound was purified by flash chromatography (100-200 mesh, 90% Ethyl acetate in pet ether) to afford (4S)-8-chloro-N-(4-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (230 mg, 0.417 mmol, 47.9 % yield), LCMS (*m/z*): 537.05 $[M+H]^+$.

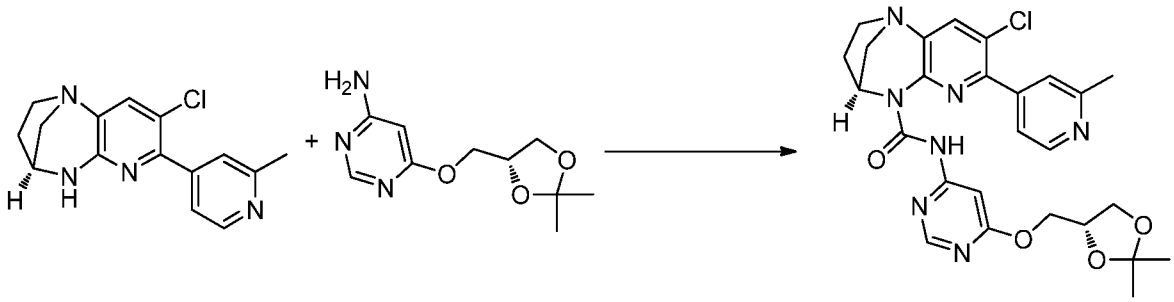
Synthesis of (4S)-8-chloro-N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



To a solution of (4S)-8-chloro-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (400 mg, 1.395 mmol) in Tetrahydrofuran (THF) (30 mL) was added triphosgene (400 mg, 1.348 mmol), the resulting solution was stirred at RT for 20 min. A solution of (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (626 mg, 2.79 mmol) in THF (10 mL) was added to the reaction mass and the resulting suspension was heated to 60 °C for 16 hr. After the completion of reaction (monitored by TLC, two spots observed at polar and non-polar), added water (20 ml) to the reaction mass and extracted with ethyl acetate (2X20 ml). Organic layer was dried over Na_2SO_4 filtered and concentrated under reduced pressure to obtain dark brown liquid.

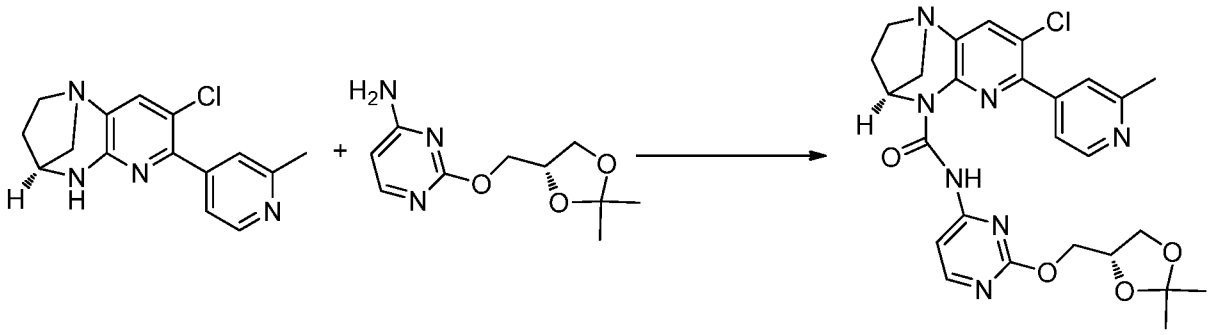
Crude material was purified by combi flash using silica gel column (12 g, 80%EtOAc in pet ether). Fractions containing pure compound were combined and concentrated to afford the desired compound(4S)-8-chloro-N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (330 mg, 0.596 mmol, 42.7 % yield) as a pale brown solid. LCMS (*m/z*): 537.2 $(M+H)^+$.

Synthesis of (4S)-8-chloro-N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



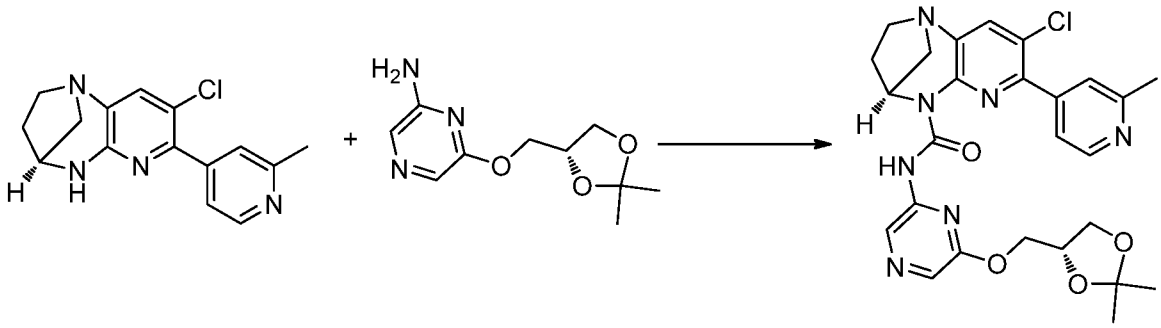
Triethylamine (1.458 mL, 10.46 mmol) and triphosgene (517 mg, 1.744 mmol) were added to a stirred solution of (4S)-8-chloro-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.744 mmol) in Tetrahydrofuran (THF) (25 mL) at RT, stirred for 30 min. (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine (589 mg, 2.62 mmol) was added to above reaction mixture, stirred at 70 °C for 16 h. Allowed the reaction mixture to room temperature, organic solvent from reaction mixture was removed by rotary evaporation, residue was partitioned between water (40 mL) and EtOAc (80 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 column chromatography using silica gel (100-200 mesh) 40 % Ethyl acetate in hexane as a eluent to afford (4S)-8-chloro-N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (225 mg, 0.383 mmol, 21.94 % yield) as a pale yellow solid. (TLC eluent: 5% MeOH in DCM R_f: 0.4; UV active). LCMS (*m/z*): 538.28 $[M+H]^+$.

Synthesis of (4S)-8-chloro-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



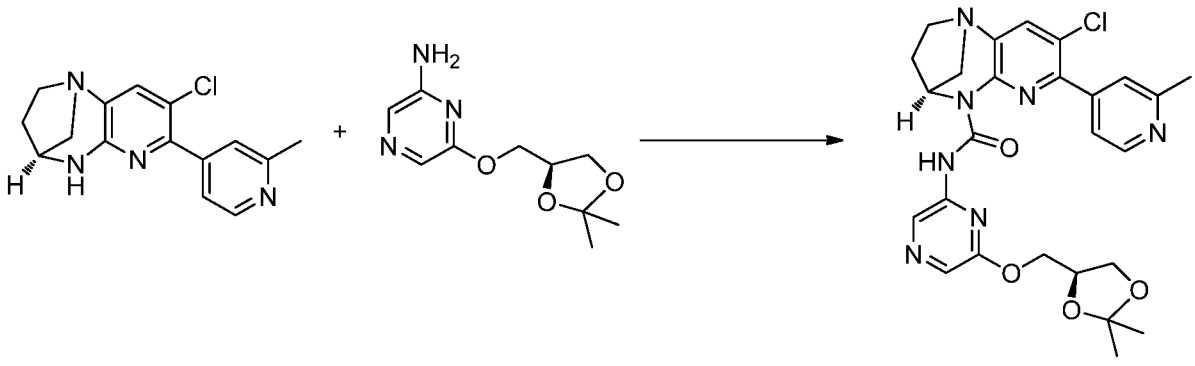
To a solution of (4S)-8-chloro-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.744 mmol) in Tetrahydrofuran (THF) (30 mL) was added triethylamine (1.458 mL, 10.46 mmol) and triphosgene (517 mg, 1.744 mmol). The reaction mixture was stirred at room temp for 30 min. To this reaction mixture was added (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine (1178 mg, 5.23 mmol) and stirred at 65 °C for .Reaction was monitored by TLC. The solvent was removed under reduced pressure, diluted with water (20 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with water (30mL), saturated brine solution (10 mL), dried over anhydrous sodium sulphate, filtered and concentrated. The crude compound was dissolved in DCM (15 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 afford pure (4S)-8-chloro-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (200 mg, 0.370 mmol, 21.23 % yield) as an off-white solid, LCMS (*m/z*): 536.25 $(M+H)^+$.

Synthesis of (4S)-8-chloro-N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



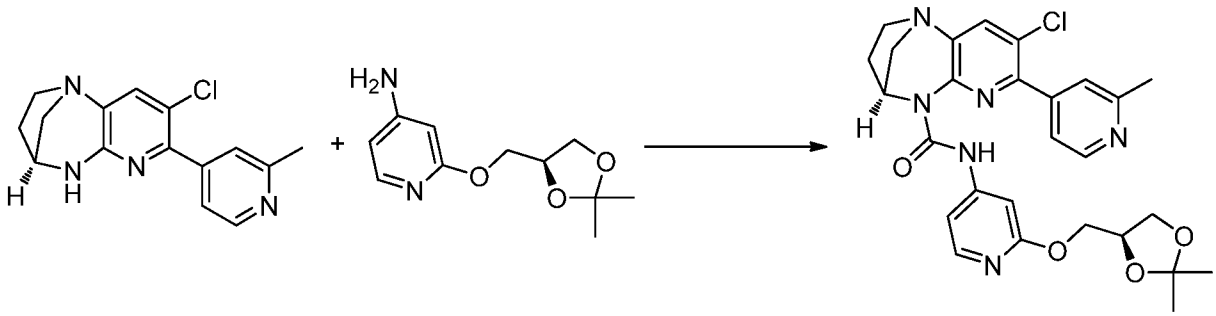
TEA (0.729 mL, 5.23 mmol) followed by triphosgene (517 mg, 1.744 mmol) were added to a solution of (4S)-8-chloro-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.744 mmol) in Tetrahydrofuran (THF) (20 mL) at 25 °C, stirred for 1h and (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine (785 mg, 3.49 mmol) was added and heated at 70 °C for 15 h. The reaction mixture was cooled to 28 °C and was partitioned between water (50 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 as gum (TLC eluent: Neat ethyl acetate R_f: 0.4; UV active). The crude product was purified by column chromatography (silica-gel: 100-200 mesh, eluted with 90% EtOAc in hexane) to afford (4S)-8-chloro-N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (250 mg, 0.428 mmol, 24.53 % yield) as an off white solid, LCMS (*m/z*): 538.35 $(M+H)^+$.

Synthesis of (4S)-8-chloro-N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



To a solution of (4S)-8-chloro-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.744 mmol) in Tetrahydrofuran (THF) (50 mL) stirred under nitrogen atmosphere at room temp was added triethylamine (1.458 mL, 10.46 mmol) and triphosgene (517 mg, 1.744 mmol). The reaction mixture was stirred at RT for 30 min and subsequently (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine (785 mg, 3.49 mmol) was added. Then 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 200 mL of Ethyl Acetate. Organic layer washed with water (100 mL) followed by brine solution (50mL) and dried out with Na_2SO_4, filtered and concentrated to get crude product. The crude product was submitted to silica gel (100-200 mesh) and was eluting by 100% Ethyl Acetate to afford a compound (4S)-8-chloro-N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (230 mg, 0.396 mmol, 22.72 % yield) as a white solid, LCMS (*m/z*): 537.9 $(M+H)^+$.

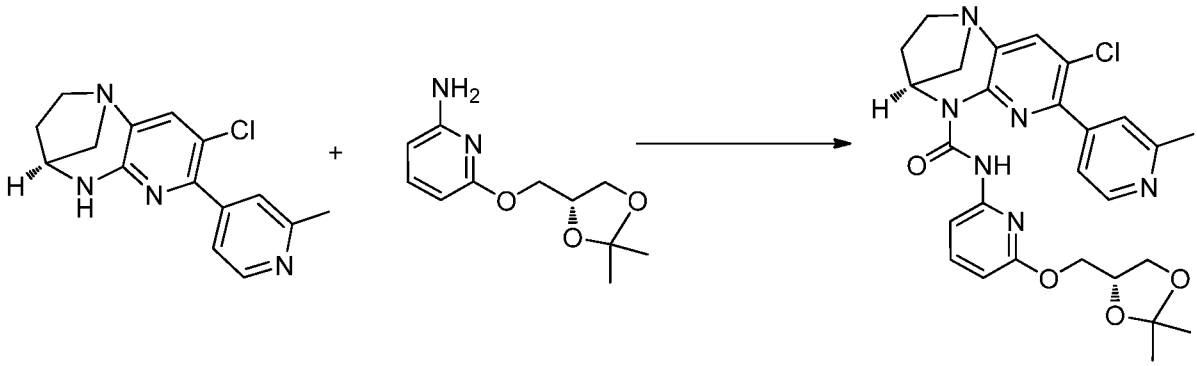
Synthesis of (4S)-8-chloro-N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



Triphosgene (414 mg, 1.395 mmol) was added to a stirred solution of (4S)-8-chloro-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (400.0 mg, 1.395 mmol), and TEA (0.972 mL, 6.97 mmol) in Tetrahydrofuran (THF) (20.0 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 (938 mg, 4.18 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 flash chromatography on neutral alumina eluted by 20-30% EtOAc/pet ether to get the (4S)-8-chloro-N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (380.0 mg, 0.677 mmol, 48.5 % yield) as a white solid, LCMS (*m/z*): 537.34 $(M+H)^+$.

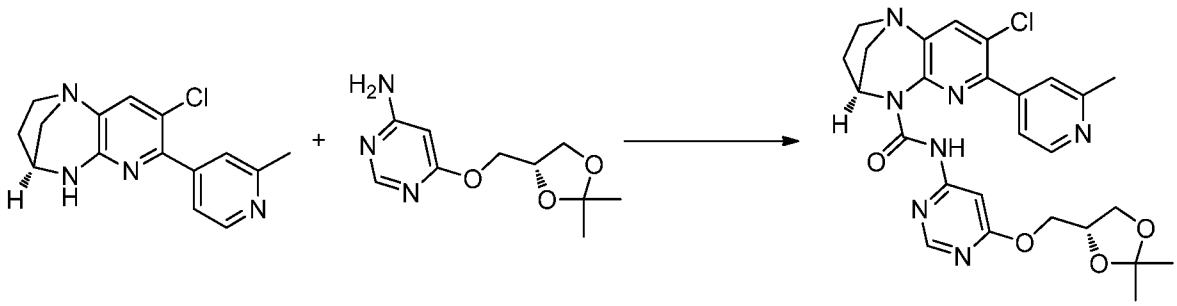
Synthesis of (4S)-8-chloro-N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



Triphosgene (414 mg, 1.395 mmol) was added to a stirred solution of (4S)-8-chloro-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (400 mg, 1.395 mmol) in Tetrahydrofuran (THF) (10 mL) at room temperature. The reaction mixture was stirred for 45 min at RT and then triethylamine (1.167 mL, 8.37 mmol) and (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (626 mg, 2.79 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 ((4S)-8-chloro-N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-

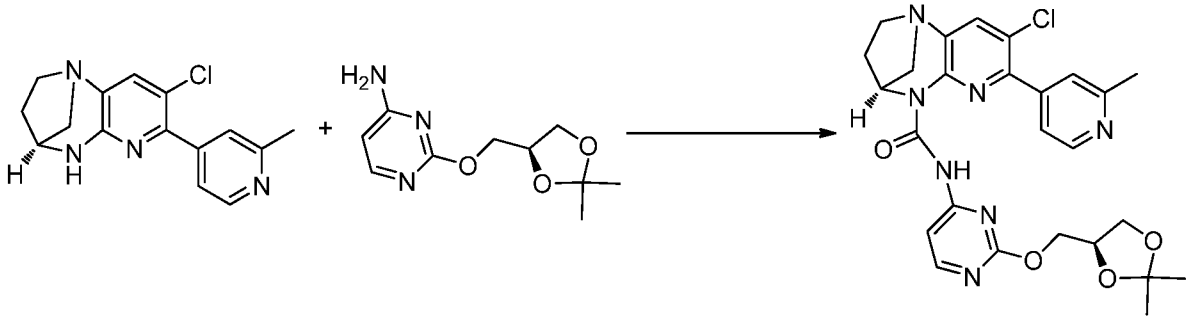
methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (300 mg, 0.531 mmol, 38.0 % yield) as a white solid, LCMS (*m/z*): 537.2 $[M+H]^+$.

Synthesis of (4S)-8-chloro-N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



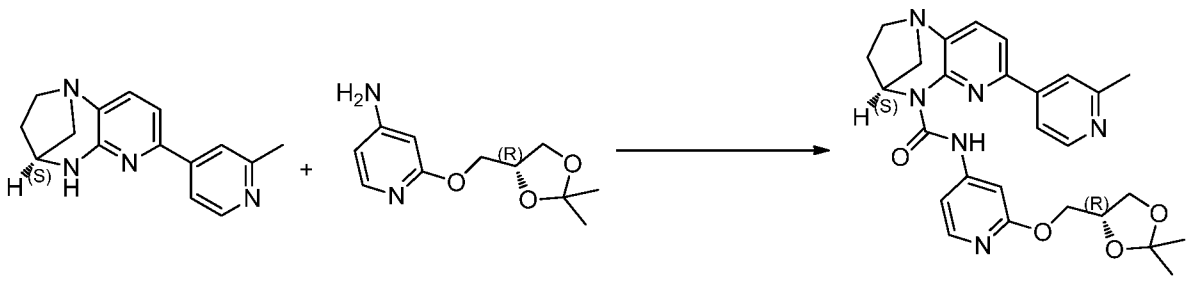
TEA (0.972 mL, 6.97 mmol) was added to a stirred solution of (4S)-8-chloro-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (0.4 g, 1.395 mmol) in Tetrahydrofuran (THF) (50 mL) at room temperature and followed by addition of triphosgene (0.414 g, 1.395 mmol) at same temperature and stirred for 1h. (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine (0.943 g, 4.18 mmol) was added and stirred at 65 °C for 15h. Cooled to room temperature and diluted with ethyl acetate (50 mL) and water (50 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. crude compound was purified through column chromatography by using neutral alumina and eluted in 50% ethyl acetate in hexane to afford (4S)-8-chloro-N-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (0.350g, 0.644 mmol, 46.2 % yield) as white solid, LCMS (*m/z*): 538.28 $[M+H]^+$.

Synthesis of (4S)-8-chloro-N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



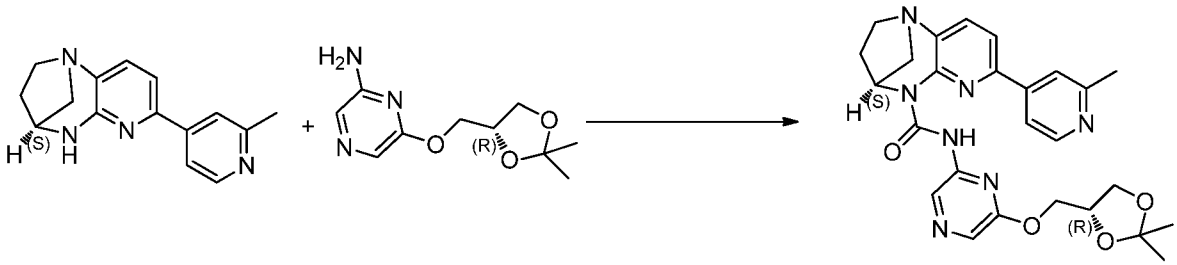
A solution of (4S)-8-chloro-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (300 mg, 1.046 mmol), triphosgene (310 mg, 1.046 mmol) and triethylamine (0.875 mL, 6.28 mmol) in Tetrahydrofuran (THF) (5 mL) was stirred under nitrogen at room temp for 15 min. To this reaction mixture (S)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine (707 mg, 3.14 mmol) was added. The reaction mixture was stirred at 70 °C for 16 hr 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 X 20 mL). Then the combined organic layer was washed with water (10 mL), brine solution (10 mL), dried over Na_2SO_4 and evaporated to get crude compound. The crude compound was purified by column chromatography using Neutral Alumina and eluted with 100% EtOAc to get (4S)-8-chloro-N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (250 mg, 0.379 mmol, 36.2 % yield), LCMS (*m/z*): 537.9 $[M+H]^+$.

Synthesis of (4S)-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



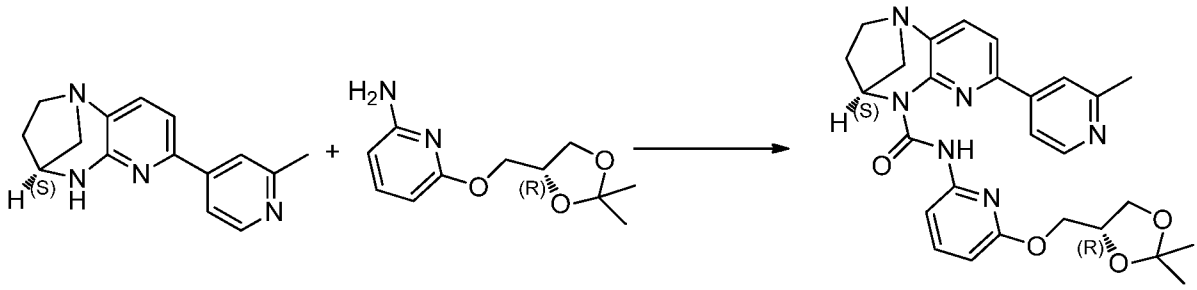
To solid (4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (400 mg, 1.585 mmol) in THF (30 mL) stirred under nitrogen at room temp was added solid triphosgene (282 mg, 0.951 mmol) stirred under nitrogen at room temp for 30 minutes. To this DIPEA (1.384 mL, 7.93 mmol) and (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (533 mg, 2.378 mmol) 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 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 was added to a neutral alumina column and was eluted wit50% EtOAc/Pet ether Collected fractions and concentrated to get some impure compound again purified with prep HPLC to get pure compound (4S)-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (150 mg, 0.298 mmol, 18.83 % yield), LCMS (*m/z*): 503.39 $[M+H]^+$.

Synthesis of (4S)-N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



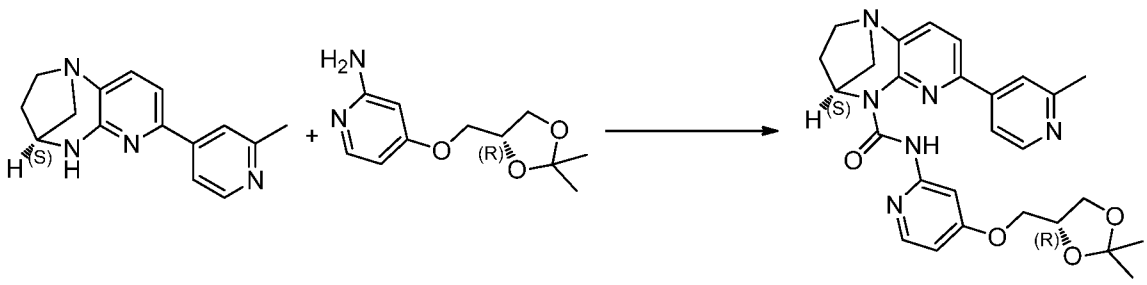
To a solution of (4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (300 mg, 1.189 mmol) in Tetrahydrofuran (THF) (5 mL) stirred under nitrogen at room temp was added triphosgene (353 mg, 1.189 mmol) and TEA (0.166 mL, 1.189 mmol) and stirred for 2 h, To this (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine (268 mg, 1.189 mmol) was added and the reaction mixture was stirred at 60 °C for 16 hr. Reaction mixture was quenched with ice water and extracted with 2x15 ml of ethyl acetate, combined organic layers were washed with 10 of water and 5 ml of brine solution, organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford crude compound, LCMS (*m/z*): 504.40 $[M+H]^+$.

Synthesis of (4S)-N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



To a solution of (4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.982 mmol) in Tetrahydrofuran (THF) (15 mL) stirred under nitrogen at room temp was added triphosgene (588 mg, 1.982 mmol) and TEA (1.657 mL, 11.89 mmol) stirred for 2 h, To this (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (889 mg, 3.96 mmol) was added and the reaction mixture was stirred at 60 °C for 16 hr. Reaction was monitored by TLC. Reaction mixture was quenched with ice water and extracted with 2x15 ml of ethyl acetate, combined organic layers were washed with 15 of water and 15 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 100-200 silica gel column and was eluted with 2%of DCM/MeOH to afford pure compound (4S)-N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (350 mg, 0.612 mmol, 30.9 % yield) as pale yellow solid, LCMS (*m/z*): 503.39$[M+H]^+$.

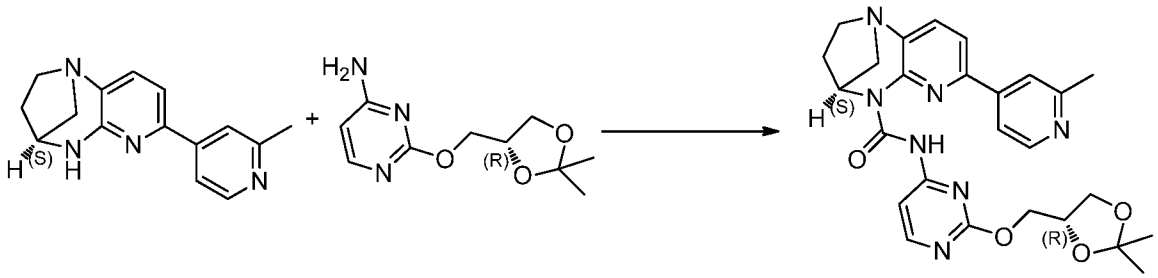
Synthesis of (4S)-N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



To a solution of (4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-

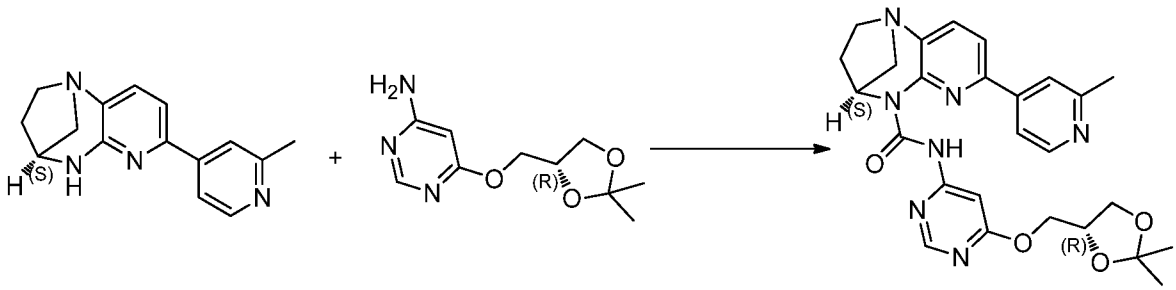
b][1,4]diazepine (300 mg, 1.189 mmol) in Tetrahydrofuran (THF) (10 mL) stirred under nitrogen at room temp was added triphosgene (353 mg, 1.189 mmol) and TEA (0.994 mL, 7.13 mmol) and stirred for 2 h, To this (R)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (533 mg, 2.378 mmol) was added and the reaction mixture was stirred at 60 °C for 16 hr. Reaction was monitored by TLC. Reaction mixture was quenched with ice water and extracted with 2x15 ml of ethyl acetate, combined organic layers were washed with 15 of water and 15 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 100-200 silica gel column and was eluted with 2% of DCM/MeOH to afford pure compound (4S)-N-(4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (200 mg, 0.277 mmol, 23.27 % yield) as pale brown solid, LCMS (*m/z*): 503.45$[M+H]^+$.

Synthesis of (4S)-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



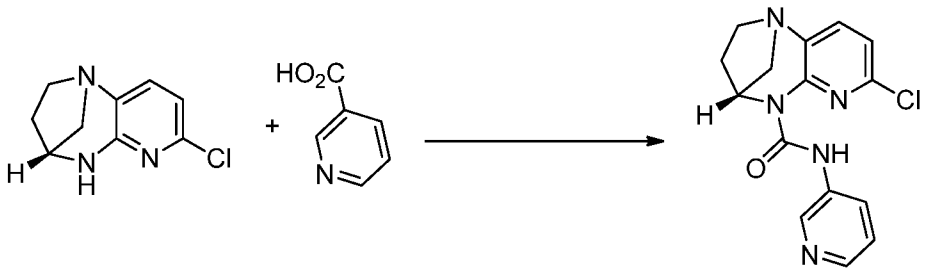
Triethylamine (1.381 mL, 9.91 mmol) followed by triphosgene (294 mg, 0.991 mmol) were added to a stirred solution of (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine (580 mg, 2.58 mmol) in Tetrahydrofuran (THF) (100 mL) at RT and stirred for 5 h. Then (4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.982 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 (50 mL), extracted with ethyl acetate (2 X 75 mL) and washed with brine (100 mL). Organic layer was separated, dried over Na_2SO_4, filtered and concentrated to get crude compound, LCMS: (*m/z*): 504.46 $[M+H]^+$.

Synthesis of (4S)-N-(6-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



Triphosgene (353 mg, 1.189 mmol) followed by triethylamine (1.657 mL, 11.89 mmol) were added to a stirred solution of (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine (893 mg, 3.96 mmol) in Tetrahydrofuran (THF) (20 mL) at RT and stirred for 1h. Then (4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.982 mmol) was added to the reaction mixture and stirred at 80 °C for 15 h. Reaction mixture was cooled to RT, diluted with water (50 mL), extracted with ethyl acetate (2X70 mL), washed with brine solution (20 mL). Organic layer was separated, dried over Na_2SO_4, filtered and concentrated to get crude compound, LCMS (*m/z*): 504.28 $[M+H]^+$.

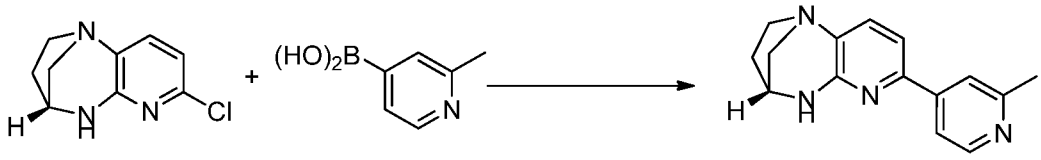
Synthesis of (4R)-7-chloro-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



To a suspension of nicotinic acid (2.8 g, 22.74 mmol) in Tetrahydrofuran (100 mL)stirred under nitrogen at 20°C was added a solution of DPPA (9.39 g, 34.1 mmol) ,DIPEA (11.92 mL, 68.2 mmol) and stirred at same temperature for another 1h, was added a solid of (4R)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (3.56 g, 18.20 mmol). The reaction mixture was stirred at 80 °C for 16 hr. The reaction was monitored by TLC and LCMS. The reaction mixture was directly evaporated under reduced pressure, diluted

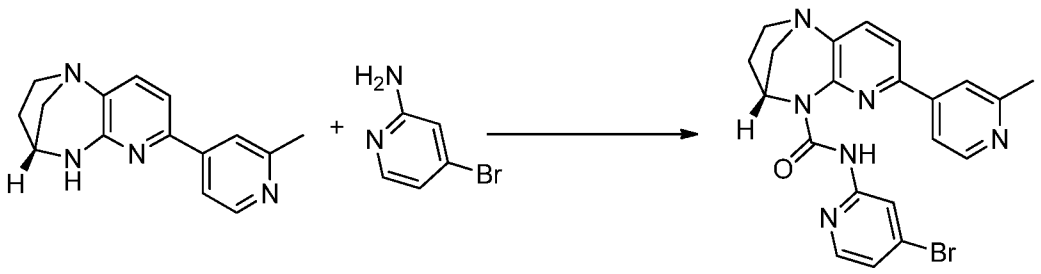
with ethyl acetate (200 ml) and successively washed with water. The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give. The crude was purified by column chromatography (100-200 silica gel) using gradient mixture of 1%Methonal in EtOAc as eluent to afford the (4R)-7-chloro-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (4 g, 12.13 mmol, 53.3 % yield) as an off white solid, LCMS (*m/z*): 316.19 $[M+H]^+$.

Synthesis of (4R)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine



To a degassed solution of (4R)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (2 g, 10.22 mmol),(2-methylpyridin-4-yl)boronic acid (2.100 g, 15.33 mmol)and K_3PO_4 (6.51 g, 30.7 mmol) in 1,4-Dioxane (40 mL);Water (10 mL) and was added x-phos (1.949 g, 4.09 mmol), $Pd_2(dba)_3$ (1.872 g, 2.044 mmol).The reaction mixture was stirred at 110 °C for 3 hr. The reaction was monitored by TLC. The reaction mixture was poured in to cold water (50 mL) and extracted with ethyl acetate (2x100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was added to a silica gel column and was eluted with 2%DCM/MeOH. Collected fractions are evaporated to afford (4R)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1.2 g, 4.71 mmol, 46.1 % yield) as an off white solid, LCMS (*m/z*): 253.0 $[M+H]^+$.

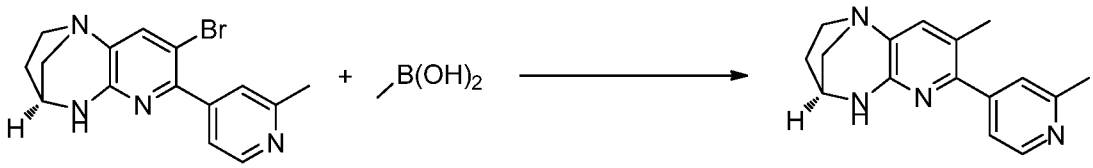
Synthesis of (4R)-N-(4-bromopyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



To solid (4R)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-

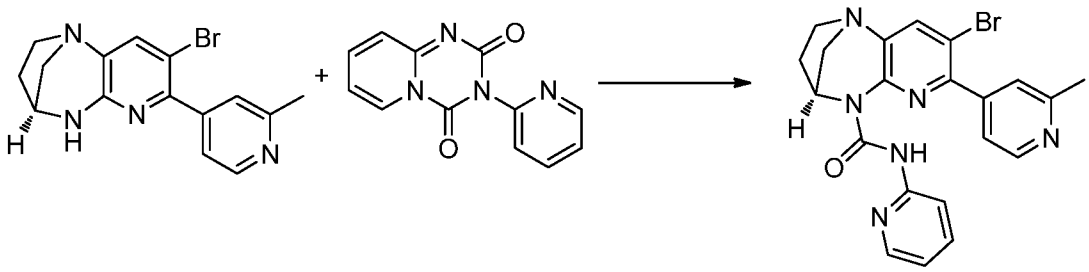
b][1,4]diazepine (1.2 g, 4.76 mmol) in Tetrahydrofuran (THF) (80 mL) stirred under nitrogen at room temp was added solid triphosgene (0.847 g, 2.85 mmol) stirred under nitrogen at room temp for 30 minutes. To this DIPEA (4.15 mL, 23.78 mmol) and 4-bromopyridin-2-amine (1.234 g, 7.13 mmol) was added. The reaction mixture was stirred at 75 °C for 16hr. Reaction was monitored by TLC and LCMS. The reaction mixture was diluted with water (60 ml) and extracted with ethyl acetate (3X100 ml). The organic layer was separated and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product. The crude was purified by flash chromatography using silica gel (100-200 mesh) by using 2.5% Methanol-DCM as an eluent to afford the pure compound (4R)-N-(4-bromopyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (1 g, 2.194 mmol, 46.1 % yield)as an pale yellow solid LCMS (*m/z*) 453.26 $[M+H]^+$.

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



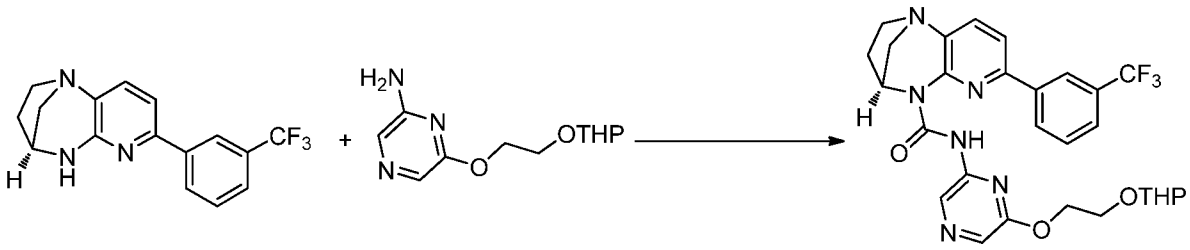
To a de gassed a solution of (4S)-8-bromo-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1 g, 3.02 mmol), methylboronic acid (0.361 g, 6.04 mmol) and K_3PO_4 (1.923 g, 9.06 mmol) in 1,4-Dioxane (20 mL) and Water (5 mL), was added solid $Pd_2(dba)_3$ (0.276 g, 0.302 mmol) and x-phos (0.288 g, 0.604 mmol). The reaction mixture was stirred at 100 °C for 15.5 hr. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 X 50 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure to gave semi pure compound. The crude product was purified by flash chromatography(100-200 mesh) and was eluted with 3% DCM/EtOAc to obtain (4S)-8-methyl-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.802 mmol, 59.7 % yield) as yellow solid, LCMS (*m/z*): 267.1 $[M+H]^+$.

Synthesis of (4S)-8-bromo-7-(2-methylpyridin-4-yl)-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



To a solution of (4S)-8-bromo-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (600 mg, 1.812 mmol) in Tetrahydrofuran (THF) (20 mL) was added NaH (65.2 mg, 2.72 mmol) stirred under nitrogen at 0°C. Then the reaction mixture was stirred at 30 °C for 1h and added 3-(pyridin-2-yl)-2H-pyrido[1,2-a][1,3,5]triazine-2,4(3H)-dione (522 mg, 2.174 mmol), then the reaction mixture was stirred at 70 °C for 15h. monitored by LCMS. The reaction mixture was poured in to the cold water (20 mL) and extracted with ethyl acetate (0 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude compound was purified by flash chromatography (100-200 mesh, 2% MeOH/DCM as eluent) to afford the desired product (4S)-8-bromo-7-(2-methylpyridin-4-yl)-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (320 mg, 0.579 mmol, 31.9 % yield) as white solid, LCMS (*m/z*): 450.8 $[M+H]^+$.

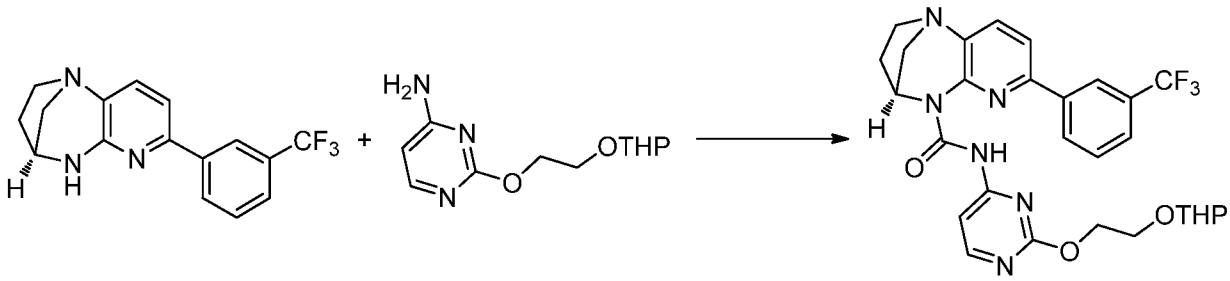
Synthesis of (4S)-N-(6-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



TEA (1.141 mL, 8.19 mmol) followed by triphosgene (486 mg, 1.638 mmol) were added to a solution of (4S)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.638 mmol) in Tetrahydrofuran (THF) (20 mL) at RT and stirred for 1h and 6-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)pyrazin-2-amine (431 mg, 1.802 mmol) was added and heated at 80 °C for 15 h. The reaction

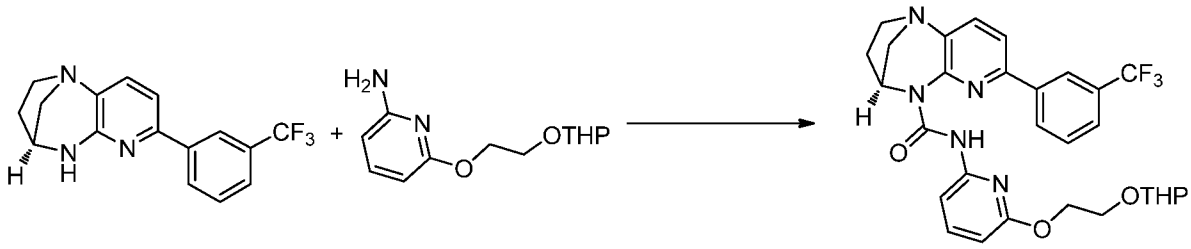
mixture was cooled to 28 °C and was partitioned between water (25 mL) and EtOAc (30 mL x 2). Organic layers were separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get (4S)-N-(6-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (310 mg, 0.498 mmol, 30.4 % yield) as an off white solid, LCMS: 571.35 $(M+H)^+$.

Synthesis of (4S)-N-(2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



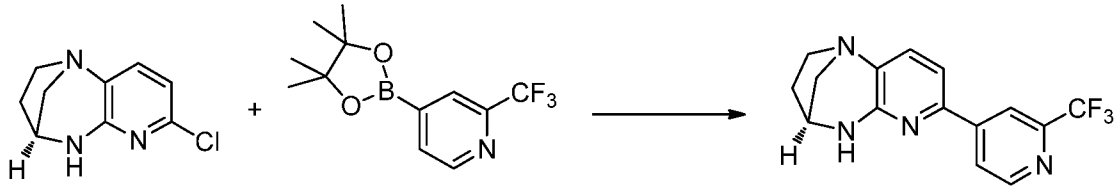
TEA (1.141 mL, 8.19 mmol) followed by triphosgene (486 mg, 1.638 mmol) were added to a solution of (4S)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.638 mmol) in Tetrahydrofuran (THF) (25 mL) at RT then stirred for 1h and 2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)pyrimidin-4-amine (431 mg, 1.802 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 (25 mLx2). Organic layers were separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get (4S)-N-(2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (300 mg, 0.510 mmol, 31.1 % yield) an off white solid, LCMS (*m/z*): 571.11 $(M+H)^+$.

Synthesis of (4S)-N-(6-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



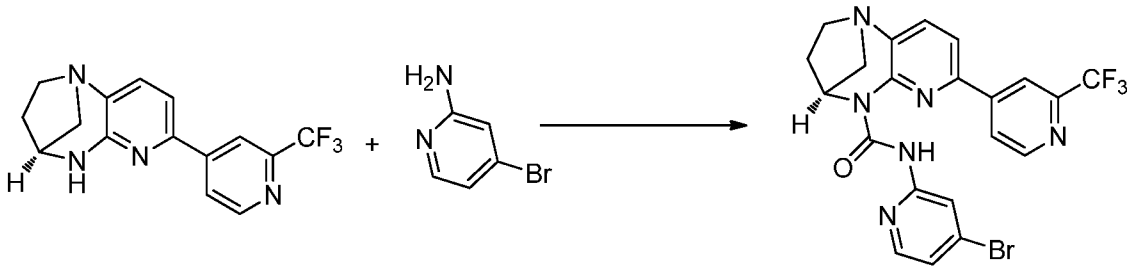
To a solution of (4S)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (350 mg, 1.146 mmol) in Tetrahydrofuran (THF) (20 mL) was added triethylamine (0.959 mL, 6.88 mmol) and triphosgene (340 mg, 1.146 mmol) stirred under nitrogen at room temp for 1 h, To this reaction mixture was added 6-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)pyridin-2-amine (820 mg, 3.44 mmol) and stirred at 65 °C for 16 h.TLC eluent: 70 % Ethyl acetate in Hexane R_f:0.3, UV active. The reaction mixture was cooled to room temp; solvent evaporated under reduced pressure completely and was partitioned between water (10 mL) and EtOAc (2 X 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 (4S)-N-(6-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (300 mg, 0.524 mmol, 45.7 % yield) as off white solid, LCMS (*m/z*): 570.2 $[M+H]^+$.

Synthesis of (4S)-7-(2-(trifluoromethyl)pyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine



4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine (9.07 g, 33.2 mmol) and K_3PO_4 (16.27 g, 77 mmol) were added to a stirred solution of (4S)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (5.0 g, 25.6 mmol) in 1,4-Dioxane (160 mL) and Water (40 mL) at RT and degassed for 30 min. Then $Pd_2(dba)_3$ (2.340 g, 2.56 mmol) and X-phos (2.437 g, 5.11 mmol) were added to the reaction mixture at RT and again degassed for 5 mins. Then the reaction mixture was stirred at 80 °C for 18hr. The reaction mixture was cooled to RT, diluted with water (100 mL), extracted with ethyl acetate (2X100 mL) and washed with brine (50 mL). Organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated (TLC eluent: 100% ethyl acetate R_f 0.2; UV active). The crude compound was purified by flash column chromatography (silica 60-120 mesh) eluted with 80% of ethyl acetate in petether to afford (4S)-7-(2-(trifluoromethyl)pyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (6.5 g, 20.88 mmol, 82 % yield) as a yellow solid, LCMS (*m/z*): 307.0 $(M+H)^+$.

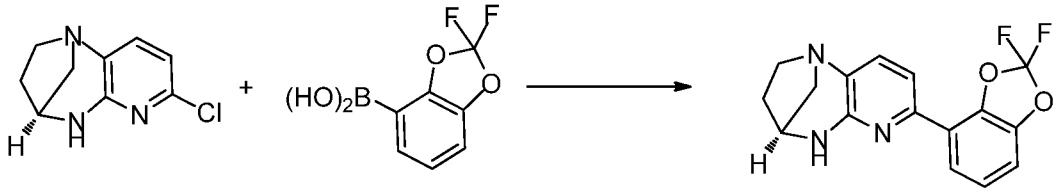
Synthesis of (4S)-N-(4-bromopyridin-2-yl)-7-(2-(trifluoromethyl)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



DIPEA (7.60 g, 58.8 mmol) followed by triphosgene (5.81 g, 19.59 mmol) were added to a solution of (4S)-7-(2-(trifluoromethyl)pyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (6.0 g, 19.59 mmol) in Tetrahydrofuran (THF) (120 mL) at 25 °C, stirred for 1h and 4-bromopyridin-2-amine (6.78 g, 39.2 mmol) was added and heated at 70 °C for 18 hr. The reaction mixture was cooled to 28 °C and was partitioned between water (100 mL) and EtOAc (100 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated (TLC eluent: 100% ethyl acetate R_f 0.3; UV active). The crude compound was purified by column chromatography (60-120 mesh) silica gel, eluted at 70% Ethyl acetate in hexane) to afford (4S)-N-(4-bromopyridin-2-yl)-7-(2-(trifluoromethyl)pyridin-4-yl)-3,4-dihydro-1,4-

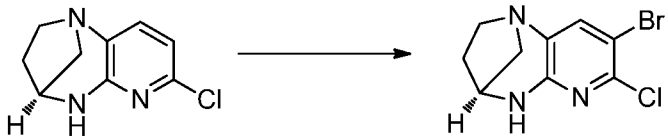
methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (4.5 g, 8.40 mmol, 42.9 % yield), as a off white solid, LCMS (m/z): 506.94 $(M+H)^+$.

Synthesis of (4S)-7-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine



A solution of (4S)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (0.6 g, 3.07 mmol) in 1,4-Dioxane (20 mL), Water (4.00 mL) was purged with nitrogen gas for 10 min, then(2,2-difluorobenzo[d][1,3]dioxol-4-yl)boronic acid (0.929 g, 4.60 mmol) and K_2CO_3 (1.272 g, 9.20 mmol) was added, again purged with nitrogen gas for 10 min then $Pd(Ph_3P)_4$ (0.106 g, 0.092 mmol) was added. The resulting reaction mixture was heated at 100 °C for 16 hr. Reaction mixture was cooled to room temperature and added water(50 mL) and stirred for 20 min. Obtained solid was filtered, washed with diethyl(10 mL) ether and n-pentane(5 mL),to get (4S)-7-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (420 mg, 1.055 mmol, 34.4 % yield) as Brown solid, LCMS (*m/z*): 318.10 $(M+H)^+$.

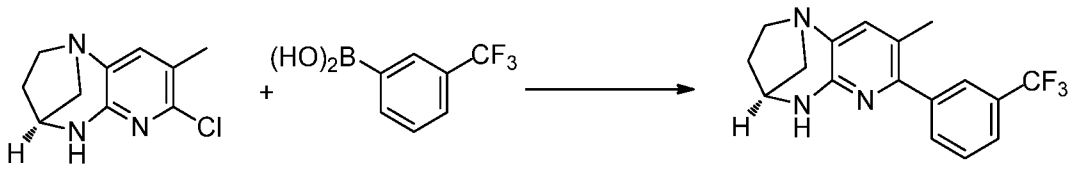
Synthesis of (4S)-8-bromo-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine



To a stirred solution of (4S)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (3 g, 15.33 mmol) in Chloroform (20 mL) was added NBS (3.00 g, 16.87 mmol) at 70 °C under Nitrogen atmosphere. The resulting reaction mixture was stirred at 70 °C for 1 hr. Progress of the reaction was monitored by TLC, TLC indicated SM was consumed and non polar spot was formed. Reaction mixture was cooled to RT and diluted with water (100 mL), extracted with DCM (2x 100 mL). Organic layers were combined and washed with water (100 mL), brine solution (50 mL), dried over anhydrous Na_2SO_4,

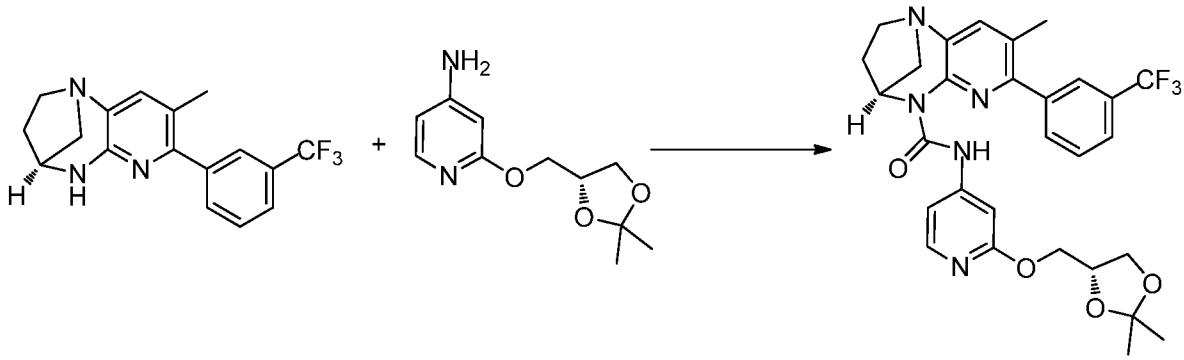
filtered and concentrated under reduced pressure to get yellow sticky compound which was washed with n-pentane and dried well to afford (4S)-8-bromo-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (2 g, 7.28 mmol, 47.5 % yield) as a yellow solid, LCMS (*m/z*): 276.05 $(M+H)^+$.

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



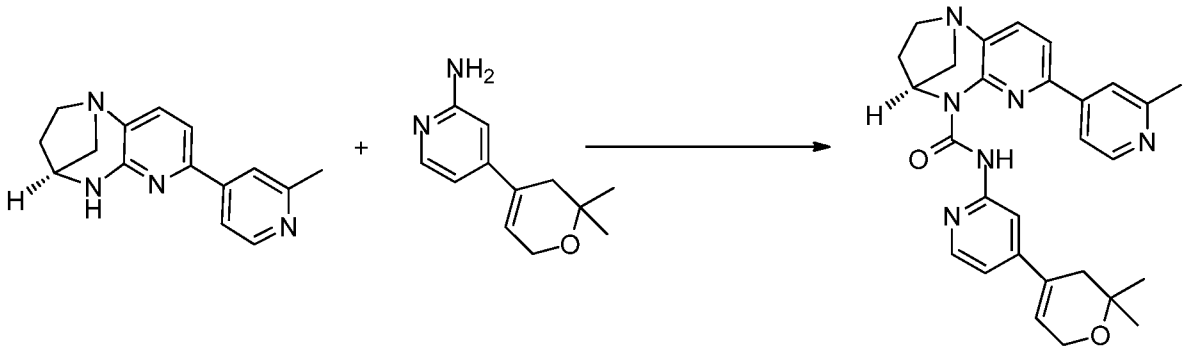
A suspension of (4S)-7-chloro-8-methyl-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (400 mg, 1.908 mmol),(3-(trifluoromethyl)phenyl)boronic acid (290 mg, 1.526 mmol) and cesium carbonate (622 mg, 1.908 mmol) in 1,4-Dioxane (10 mL) & Water (3.3 mL) stirred and degassed with argon at room temp for 15 mins, $PdCl_2(dppf)$-CH_2Cl_2 adduct (1558 mg, 1.908 mmol) was added to the reaction mixture. Then the reaction mixture was stirred 16 hr at 90 °C. The reaction mixture was cooled to room temp, and filtered through celite and washed with EtOAc (100 ml).Take filtrate and concentrated and dissolved with EtOAc (50 ml).EtOAc layer washed with water (100 ml) followed by brine solution (100 ml) and dried out with Na_2SO_4, filtered and concentrated to get crude product. Crude product was purified using silica gel (100-200 mesh) and 50% of EtOAc in Hexane as an eluent to afford(4S)-8-methyl-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.518 mmol, 80 % yield) (TLC eluent: Neat EtOAc: R_f-0.4.; UV active), LCMS (*m/z*): 320.18 $[M+H]^+$.

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



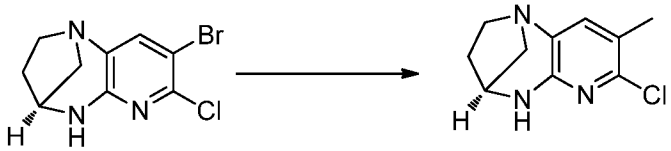
To solid (4S)-8-methyl-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.566 mmol) in Tetrahydrofuran (THF) (15 mL) was added solid triphosgene (279 mg, 0.939 mmol), DIPEA (1.641 mL, 9.39 mmol) and stirred under nitrogen at room temp for 30 minutes. To this (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (562 mg, 2.505 mmol) was added sub sequentially under sealed tube condition at 80°C for 15 h 30mins. The reaction was monitored by TLC and LCMS. The reaction mixture was diluted with water (100 ml) and extracted with ethyl acetate (2 X 100 ml). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product. The crude product was purified by column chromatography using silica gel(100-200) and was eluted with 70% EtOAc in Hexane (gradient system) to afford (4S)-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-8-methyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (400 mg, 0.689 mmol, 44.0 % yield), LCMS (*m/z*): 570.34 $[M+H]^+$.

Synthesis of (4S)-N-(4-(2,2-dimethyl-3,6-dihydro-2H-pyran-4-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



TEA (0.998 mL, 7.16 mmol) and triphosgene (354 mg, 1.194 mmol) was added to a stirred solution of (4S)-7-(m-tolyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (300 mg, 1.194 mmol) in Tetrahydrofuran (THF) (50 mL) under nitrogen at room temp. The reaction mixture was stirred at RT for 30 min, 4-(2,2-dimethyl-3,6-dihydro-2H-pyran-4-yl)pyridin-2-amine (731 mg, 3.58 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 (4S)-N-(4-(2,2-dimethyl-3,6-dihydro-2H-pyran-4-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (220 mg, 0.370 mmol, 31.0 % yield) as a brown solid, LCMS (*m/z*): 483.26 $[M+H]^+$.

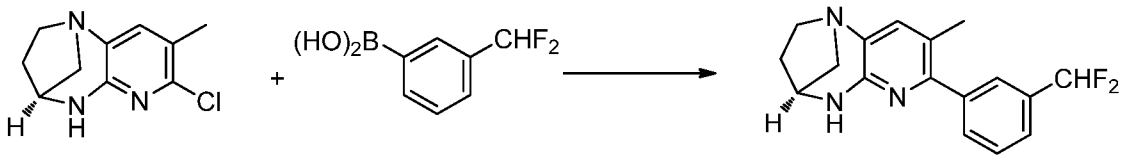
Synthesis of 7-chloro-8-methyl-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine



A suspension of 8-bromo-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1 g, 3.64 mmol), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (0.457 g, 3.64 mmol) and potassium carbonate (1.510 g, 10.93 mmol) in 1,4-Dioxane (15 mL) & Water (5 mL) stirred and degassed with argon at room temp for 15 min, $PdCl_2$(dppf)-

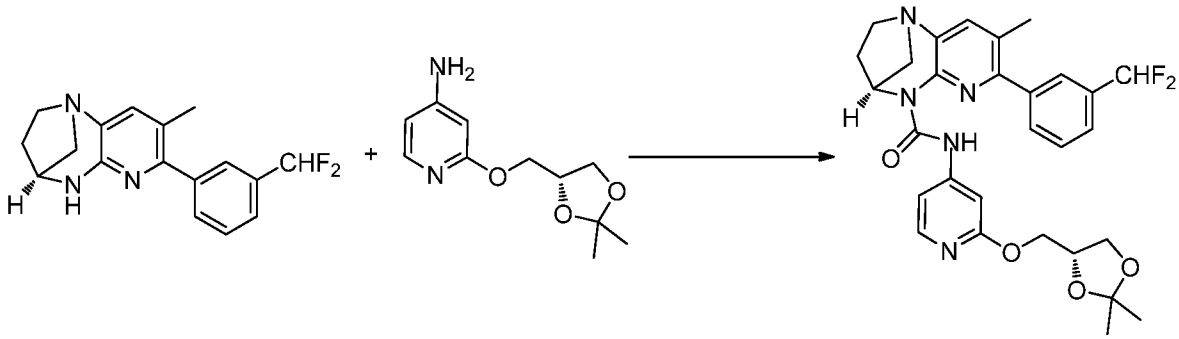
CH_2Cl_2 adduct (2.97 g, 3.64 mmol) was added to the reaction mixture. Then the reaction mixture was stirred 16 hr at 90 °C. The reaction mixture was cooled to room temp, and filtered through celite and washed with EtOAc (100 ml). Filtrate was concentrated and dissolved with EtOAc (100 ml).EtOAc layer washed with water (100 ml) followed by brine solution (50 ml) and dried out with Na_2SO_4, filtered and concentrated to get crude product. The crude product was purified by column chromatography using neutral alumina and was eluted with 40% EtOAc in Hexane (gradient system) to afford the desired product 7-chloro-8-methyl-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 2.194 mmol, 60.2 % yield) as a pale yellow solid, LCMS (*m/z*): 210.11 $[M+H]^+$.

Synthesis of (4S)-7-(3-(difluoromethyl)phenyl)-8-methyl-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine



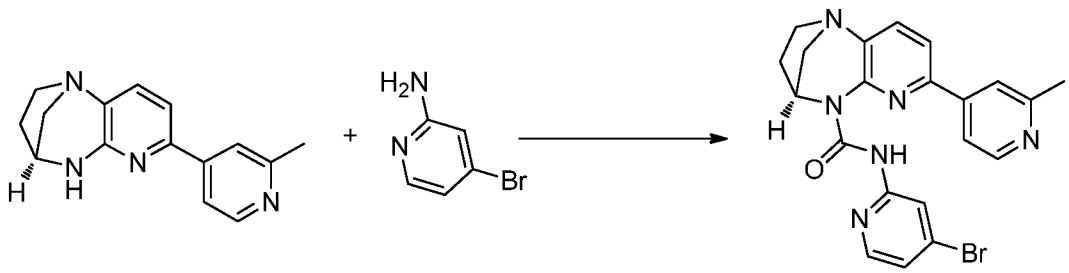
A suspension of (4S)-7-chloro-8-methyl-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (400 mg, 1.908 mmol),(3-(difluoromethyl)phenyl)boronic acid (328 mg, 1.908 mmol) and potassium carbonate (791 mg, 5.72 mmol) in 1,4-Dioxane (15 mL) & Water (4 mL) stirred and degassed with argon at room temp for 15 min, $PdCl_2(dppf)$-CH_2Cl_2 adduct (1558 mg, 1.908 mmol) was added to the reaction mixture. Then the reaction mixture was stirred 16 hr at 90 °C. The reaction mixture was cooled to room temp, and filtered through celite and washed with EtOAc (100 ml). Filtrate was concentrated and dissolved with EtOAc (50 ml).EtOAc layer washed with water (50 ml) followed by brine solution (50 ml) and dried out with Na_2SO_4, filtered and concentrated to get crude product. The crude product was purified by column chromatography using silica gel(100-200) and was eluted with 50% EtOAc in Hexane (gradient system) to afford the desired product (4S)-7-(3-(difluoromethyl)phenyl)-8-methyl-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (300 mg, 0.969 mmol, 50.8 % yield) as a pale yellow solid LCMS (*m/z*):302.11 $[M+H]^+$.

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



To solid (4S)-7-(3-(difluoromethyl)phenyl)-8-methyl-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (250 mg, 0.830 mmol) in Tetrahydrofuran (THF) (15 mL) was added solid triphosgene (148 mg, 0.498 mmol), DIPEA (0.869 mL, 4.98 mmol) and stirred under nitrogen at room temp for 30 minutes. To this (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (298 mg, 1.327 mmol) was added sub sequentially under sealed tube condition at 75°C for 15 h 30mins. The reaction was monitored by TLC and LCMS. The reaction mixture was diluted with water (10 ml) and extracted with ethyl acetate (2 X 50 ml). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product, LCMS (*m/z*): 551.91 $[M+H]^+$.

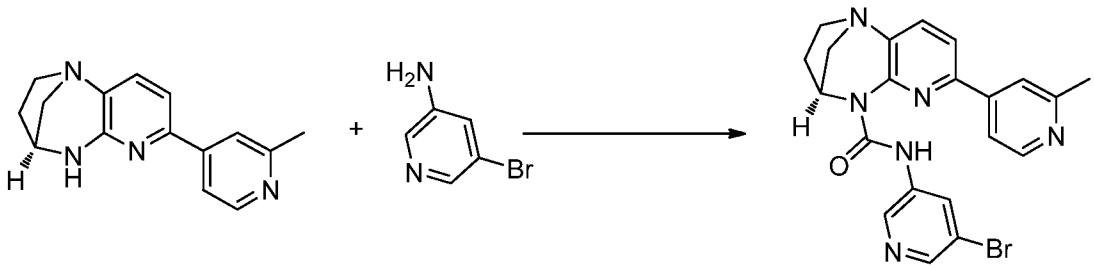
Synthesis of (4S)-N-(4-bromopyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



To solid (4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (2.5 g, 9.91 mmol) in Tetrahydrofuran (THF) (40 mL) stirred under nitrogen at room temp was added solid triphosgene (1.764 g, 5.94 mmol) stirred under nitrogen at room temp for 30 minutes. To this DIPEA (8.65 mL, 49.5 mmol) and 4-bromopyridin-2-amine (2.57 g, 14.86 mmol), was added. The reaction mixture was stirred

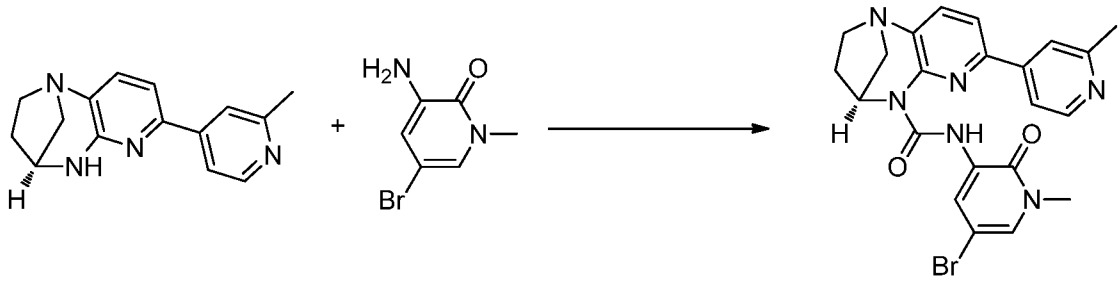
at 65 °C for16 hr. Reaction was monitored by TLC. The organic phase was added ethyl acetate and washed with water 50 mL and saturated brine 100 mL dried over Na_2SO_4 and evaporated in vacuo to give the crude products as a brown solid, The crude product was added to a neutral alumina column and was eluted with EtOAc Collected fractions to get compound was washed with diethyl ether and pentane and filtered and washed with diethyl ether to get pure compound(4S)-N-(4-bromopyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (1.72 g, 2.97 mmol, 30.0 % yield), LCMS (*m/z*): 453.20 $[M+H]^+$.

Synthesis of (4S)-N-(5-bromopyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



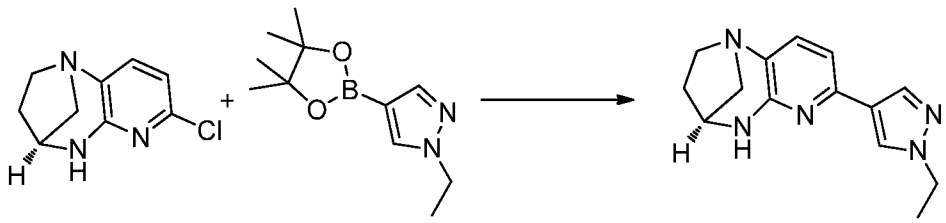
To a stirred solution of (4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (8 g, 31.7 mmol), in Tetrahydrofuran (THF) (130 mL) in Tetrahydrofuran (THF) (130 mL) and were added triphosgene (5.65 g, 19.02 mmol), DIPEA (27.7 mL, 159 mmol). Stirred under nitrogen at room temp for 30 minutes. To this and 5-bromopyridin-3-amine (8.23 g, 47.6 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 partitioned between ethyl acetate (200 mL) and water (100 mL). The organic solution was washed with water and brine, dried over Na_2SO_4, filtered and concentrated to get crude compound. The crude product was added to a neutral alumina column and was eluted wit 50% EtOAc/petether Collected fractions and concentrated to get compound and washed with pentane to get pure compound (4S)-N-(5-bromopyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (6.2 g, 12.72 mmol, 40.1 % yield) as a white solid, LCMS (*m/z*): 451.19 $[M+H]^+$.

Synthesis of (4S)-N-(5-bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



To a stirred solution of (4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1.0 g, 3.96 mmol) in Tetrahydrofuran (THF) (30 mL) was added TEA (2.76 mL, 19.82 mmol) and triphosgene (1.176 g, 3.96 mmol) under Nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 1 hr. 3-amino-5-bromo-1-methylpyridin-2(1H)-one (0.805 g, 3.96 mmol) was added to the reaction mixture and stirred at 70 °C for 16 hr. Progress of the reaction was monitored by TLC. Reaction mixture was diluted with water (50 mL), extracted with EtOAc (3X 50 mL), organic layers were combined and dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford crude compound. The crude was purified by column chromatography (100-200 mesh silica gel, eluted with 2% MeOH in DCM) to afford (4S)-N-(5-bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (800 mg, 1.338 mmol, 33.8 % yield) brown solid compound, LCMS (*m/z*): 481.22$[M+H]^+$.

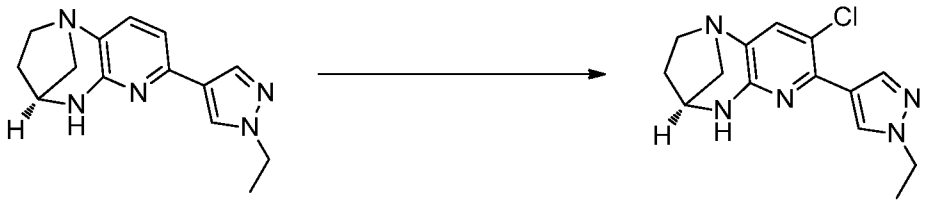
Synthesis of (4S)-7-(1-ethyl-1H-pyrazol-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine



To a solution of (4S)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (3 g, 15.33 mmol), 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (4.09 g, 18.40 mmol) in 1,4-Dioxane (40 mL),Water (10.00 mL) stirred under nitrogen at

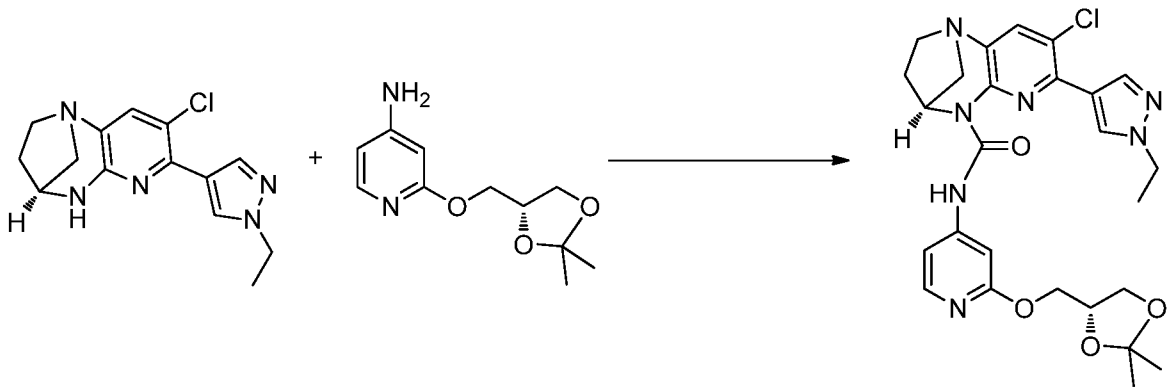
room temp was added tripotassium phosphate (9.76 g, 46.0 mmol). The reaction mass was degassed for 15 min with Nitrogen. To this added $PdCl_2(dppf)$-CH_2Cl_2 adduct (1.252 g, 1.533 mmol) at RT and degassed for another 15 min. The reaction mixture was stirred at 100 °C for 16 hr. Progress of the reaction was monitored by TLC. TLC indicated starting material was consumed to form new spot. Cooled the reaction mass to room temperature, diluted with Ethyl acetate (100mL), filtered through celite, collected the filtrate, and washed with water (100mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to get crude compound. The crude product was added to a silica gel (100-200) column and was eluted with DCM/MeOH, 5% MeOH/DCM. Concentrated the product fractions to afford (4S)-7-(1-ethyl-1H-pyrazol-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (2 g, 7.83 mmol, 51.1 % yield) as green solid, LCMS (*m/z*): 256.22 $(M+H)^+$.

Synthesis of (4S)-8-chloro-7-(1-ethyl-1H-pyrazol-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine



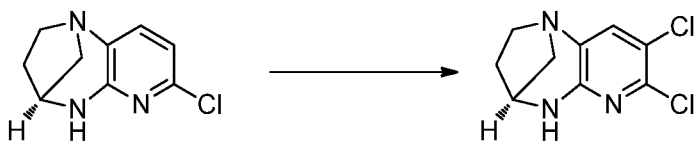
To a solution of (4S)-7-(1-ethyl-1H-pyrazol-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (2 g, 7.83 mmol), in Chloroform (20 mL) stirred under nitrogen at room temp was added NCS (1.255 g, 9.40 mmol). The reaction mixture was stirred at RT for 1 hr. Progress of the reaction was monitored by TLC. TLC indicated starting material was consumed to form new spot with 0.3 R_f. Water (50mL) added to the reaction mixture and extracted with DCM (50mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to get crude as brown sticky compound. The crude product was added to a silica gel (100-200) column and was eluted with CH_2Cl_2/MeOH, 3% Methanol in DCM product was eluted. Concentrated the product fractions to afford (4S)-8-chloro-7-(1-ethyl-1H-pyrazol-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1.2 g, 3.15 mmol, 40.2 % yield) as Light brown sticky compound, LCMS (*m/z*): 290.04 $(M+H)^+$.

Synthesis of (4S)-8-chloro-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(1-ethyl-1H-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



To a solution of (4S)-8-chloro-7-(1-ethyl-1H-pyrazol-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.726 mmol), in Tetrahydrofuran (THF) (20 mL) stirred under nitrogen at room temp as added TEA (1.203 mL, 8.63 mmol), triphosgene (512 mg, 1.726 mmol). The reaction mixture was stirred at RT for 30 min. To this added (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (387 mg, 1.726 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 6 hr. Progress of the reaction was monitored by TLC. TLC indicated starting material was consumed to form new spot with 0.4 R_f. Cooled the reaction mass to RT, diluted with water (100mL) and extracted with ethyl acetate (100mL). 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 combiflash silica gel (40 g) column and was eluted with 3%DCM/MeOH. Concentrated the pure product fractions to afford (4S)-8-chloro-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(1-ethyl-1H-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (500 mg, 0.881 mmol, 51.1 % yield)(N37522-56-A2) as Off-white solid, LCMS (*m/z*): 539.95$(M+H)^+$.

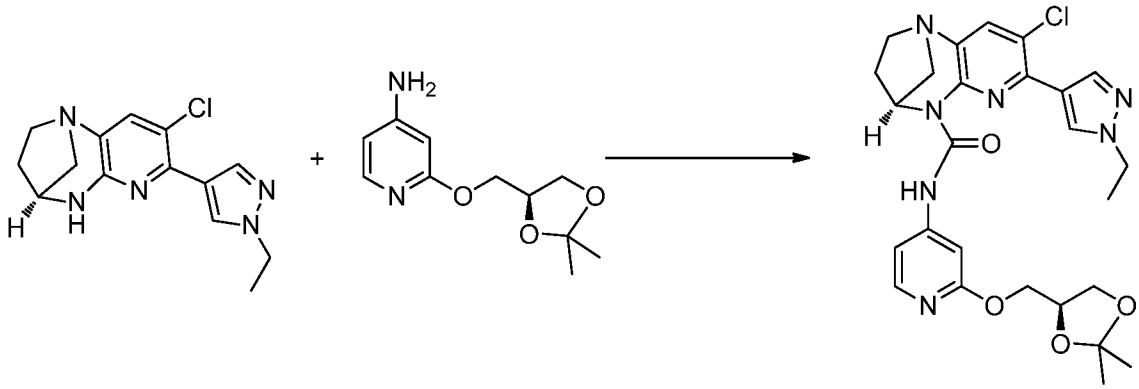
Synthesis of (4S)-7,8-dichloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine



To a stirred solution of (4S)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-

b][1,4]diazepine (5 g, 25.6 mmol) in Chloroform (50 mL) were added NCS (5.12 g, 38.3 mmol) lot wise at 0 °C and stirred for 6 hr at 26 °C. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between water (50 mL) and DCM (2X100 mL). Organic layer was separated and dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford pure (4S)-7,8-dichloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (5 g, 18.83 mmol, 73.7 % yield) as a pale yellow solid, LCMS (*m/z*): 230.02 [M+H

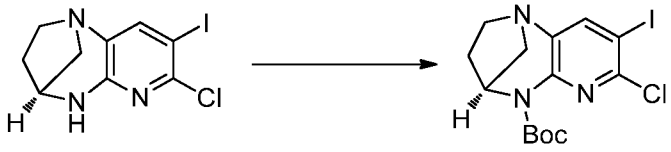
Synthesis of (4S)-8-chloro-N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(1-ethyl-1H-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



To a solution of (4S)-8-chloro-7-(1-ethyl-1H-pyrazol-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.726 mmol), in Tetrahydrofuran (THF) (30 mL) stirred under nitrogen at room temp as added TEA (1.203 mL, 8.63 mmol), triphosgene (512 mg, 1.726 mmol). The reaction mixture was stirred at RT for 30 min. To this added (S)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (387 mg, 1.726 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 6 hr. Progress of the reaction was monitored by TLC. TLC indicated starting material was consumed. Cooled the reaction to room temperature, diluted with water (50mL), extracted with Ethyl acetate (100mL). 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 combiflash silica gel (40 g) column and was eluted with DCM/MeOH. 2%Methanol in DCM product was eluted. Concentrated the product fractions to afford (4S)-8-chloro-N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(1-ethyl-1H-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (450 mg,

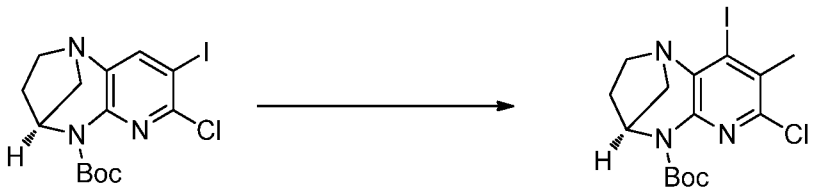
0.802 mmol, 46.5 % yield), LCMS (*m/z*): 540.30 $(M+H)^+$.

Synthesis of (4S)-tert-butyl 7-chloro-8-iodo-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxylate



To a suspension of (4S)-7-chloro-8-iodo-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (31 g, 96 mmol) in Tetrahydrofuran (THF) (300 mL), Boc_2O (33.6 mL, 145 mmol) and DMAP (14.13 g, 116 mmol) added to the reaction mixture. Then the reaction mixture was stirred 20 hr at 65°C. The reaction was monitored by TLC. The reaction mass diluted with water (100mL) and extracted with EtOAc by twice (2 X 250 mL). The combined organic layers washed with brine solution and dried out with Na_2SO_4, filtered and evaporated to get crude product. The crude product was submitted to Neutral Alumina by eluting 3%Ethyl Acetate in petether to get pure compound of (4S)-tert-butyl 7-chloro-8-iodo-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxylate (26.8 g, 51.3 mmol, 53.2 % yield), LCMS (*m/z*): 422.00 $(M+H)^+$.

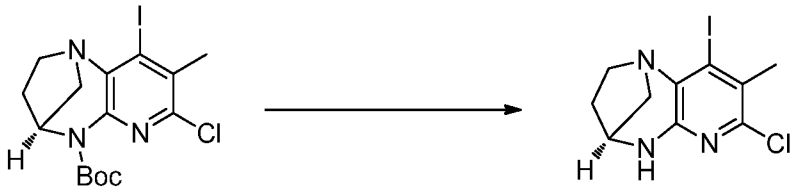
Synthesis of (4S)-tert-butyl 7-chloro-9-iodo-8-methyl-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxylate



LDA (23.72 mL, 47.4 mmol) was added to a stirred solution of (4S)-tert-butyl 7-chloro-8-iodo-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxylate (10.0 g, 23.72 mmol) in Tetrahydrofuran (THF) (100 mL) stirred under nitrogen at -78 °C. Then the reaction mixture was stirred at -78 °C for 30 minutes. Then methyl iodide (2.97 mL, 47.4 mmol) was added to reaction mixture at -78 °C. Then the reaction was warmed to room temp. Then reaction was stirred at room temp for 16 hr. Reaction was monitored by TLC. The reaction mixture was quenched with saturated NH_4Cl solution and extracted

with EtOAc. EtOAc layer washed with water followed by brine solution and dried out with Na_2SO_4, filtered and concentrated to get crude product. The crude product was added to a neutral alumina and was eluted with 1% EtOAc/Hexane. Collected fractions were evaporated to afford (4S)-tert-butyl 7-chloro-9-iodo-8-methyl-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxylate (4.0 g, 8.07 mmol, 34.0 % yield) as a off-white solid, LCMS (*m/z*): 436.04 $(M+H)^+$.

Synthesis of (4S)-7-chloro-9-iodo-8-methyl-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine



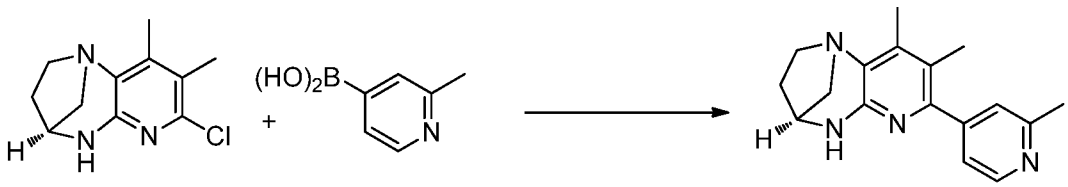
Ether in HCl was added to a stirred solution of (4S)-tert-butyl 7-chloro-9-iodo-8-methyl-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxylate (1.5 g, 3.44 mmol) under nitrogen at 0 °C. The reaction mixture was stirred at 26 °C for 6 hr. Reaction was monitored by TLC. Filter the reaction mass and take the solid and quenched with saturated $NaHCO_3$ solution (50 ml) and extracted with DCM (100 ml).DCM layer washed with water followed by brine solution and dried out with Na_2SO_4, filtered and concentrated to get crude (4S)-7-chloro-9-iodo-8-methyl-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1.0 g, 2.55 mmol, 74.2 % yield) as a white solid, LCMS (*m/z*): 336.8 $(M+H)^+$.

Synthesis of (4S)-7-chloro-8,9-dimethyl-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine

A suspension of (4S)-7-chloro-9-iodo-8-methyl-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (2.5 g, 7.45 mmol),Trimethylboroxine (2.483 mL, 7.45 mmol) and potassium carbonate (3.09 g, 22.35 mmol) in 1,4-Dioxane (50 mL) & Water (5 mL) stirred and degassed with argon at room temp for 15 mins, tetrakis(triphenylphosphine)palladium(0) (0.861 g, 0.745 mmol) was added to the reaction

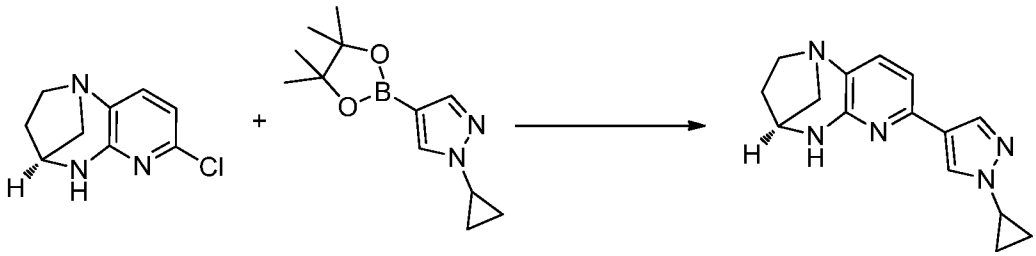
mixture. Then the reaction mixture was stirred 16 hr at 90 °C. The reaction was monitored by TLC. The reaction mixture was cooled to room temp and filtered through celite and washed with EtOAc. The Filtrate was concentrated and dissolved with EtOAc. EtOAc layer washed with water followed by brine solution and dried out with Na_2SO_4, filtered and concentrated to get crude product. The crude product was added to neutral alumina and was eluted with 10% EtOAc/Hexane. Collected fractions were evaporated to afford (4S)-7-chloro-8,9-dimethyl-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1.2 g, 5.08 mmol, 68.2 % yield) as a pale yellow solid, LCMS (*m/z*): 224.08 $(M+H)^+$.

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



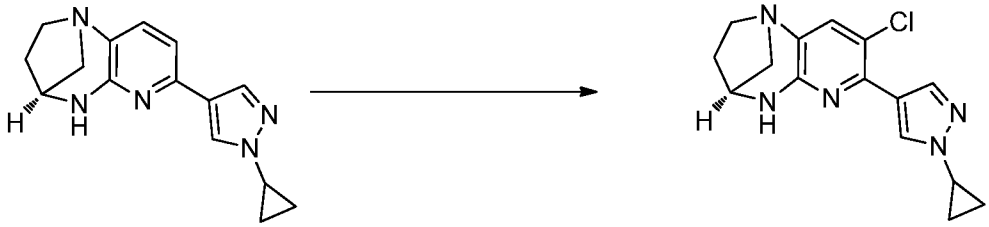
A suspension of (4S)-7-chloro-8,9-dimethyl-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1.200 g, 5.36 mmol), (2-methylpyridin-4-yl)boronic acid (0.918 g, 6.71 mmol) and tripotassium phosphate (3.42 g, 16.09 mmol) in 1,4-Dioxane (20 mL) & Water (3.0 mL) stirred and degassed with argon at room temp for 15 mins. Then $Pd_2(dba)_3$ (0.246 g, 0.268 mmol) and X-Phos (0.256 g, 0.536 mmol) added to the reaction mixture. Then the reaction mixture was stirred 16 hr at 90 °C. The reaction was monitored by TLC. The reaction mixture was cooled to room temp and filtered through celite and washed with EtOAc. Take filtrate and concentrated and dissolved with EtOAc. EtOAc layer washed with water followed by brine solution and dried out with Na_2SO_4, filtered and concentrated to get crude product. The crude product was added to a neutral alumina and was eluted with DCM. Collected fractions were evaporated to afford (4S)-8,9-dimethyl-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (0.700 g, 2.495 mmol, 46.5 % yield) as a pale yellow solid. LCMS (*m/z*): 281.30 $(M+H)^+$.

Synthesis of (4S)-7-(1-cyclopropyl-1H-pyrazol-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine



Tripotassium phosphate (6.51 g, 30.7 mmol) and 1-cyclopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.87 g, 12.27 mmol) were added to a stirred solution of (4S)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (2 g, 10.22 mmol) in mixture of 1,4-Dioxane (40 mL),Water (10.00 mL) at RT. Purged with argon for 5 min, then added $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.835 g, 1.022 mmol) stirred the reaction mixture at 110 °C for 16 h. Allowed the reaction mixture to RT, diluted with water (150 mL) extracted with Ethyl acetate (2x300 mL), washed with brine (200 mL). 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) and was eluted with 10% MeOH-DCM to afford (4S)-7-(1-cyclopropyl-1H-pyrazol-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1 g, 3.52 mmol, 34.4 % yield), LCMS (*m/z*): 268.13 $[M+H]^+$.

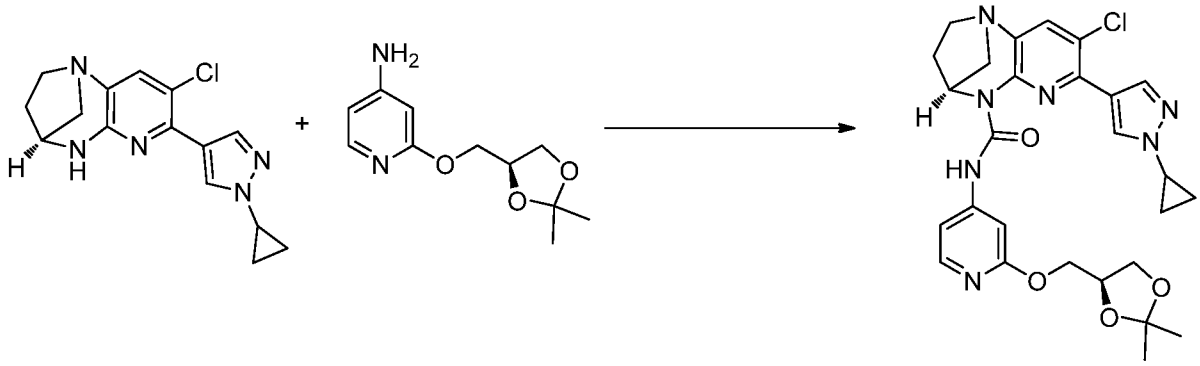
Synthesis of (4S)-8-chloro-7-(1-cyclopropyl-1H-pyrazol-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine



(4S)-7-(1-cyclopropyl-1H-pyrazol-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1 g, 3.74 mmol) was dissolved in Chloroform (100 mL) stirred under nitrogen at 0 °C were added NCS (0.500 g, 3.74 mmol). The reaction mixture was stirred for 20 min at RT. The reaction mixture allowed to room temperature and quenched with 90 ml of water and extracted with 2x150 mL of DCM. The combined organic layer was

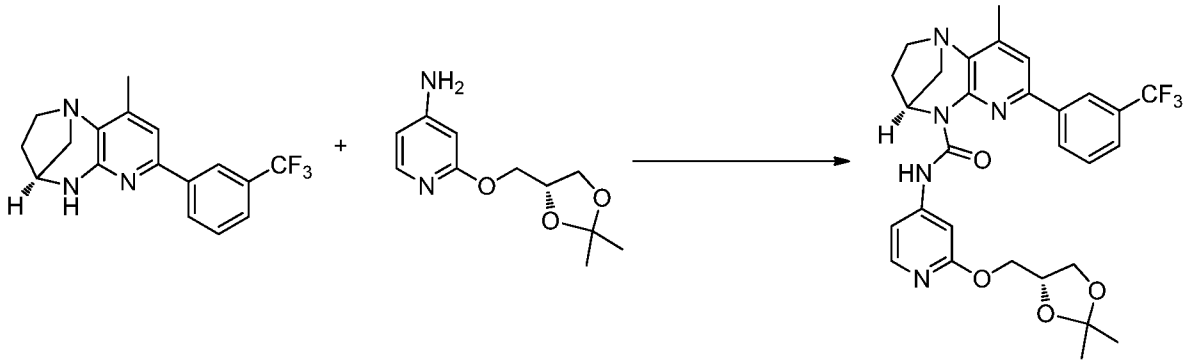
dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude material. The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh) and was eluted with 10% MeOH-DCM to afford (4S)-8-chloro-7-(1-cyclopropyl-1H-pyrazol-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (850 mg, 2.54 mmol, 67.8 % yield), LCMS (*m/z*): 302.42 $[M+H]^+$.

Synthesis of (4S)-8-chloro-7-(1-cyclopropyl-1H-pyrazol-4-yl)-N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



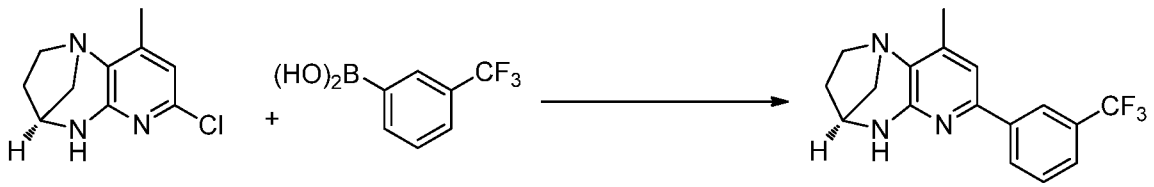
(4S)-8-chloro-7-(1-cyclopropyl-1H-pyrazol-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (400 mg, 1.325 mmol) was dissolved in Tetrahydrofuran (THF) (20 mL) stirred under nitrogen at 0 °C were added triphosgene (393 mg, 1.325 mmol),TEA (0.924 mL, 6.63 mmol). The reaction mixture was stirred for 30 min at room temperature. To this (S)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (446 mg, 1.988 mmol) was added and stirred for 16 h at 80 °C in a sealed tube. The reaction mixture allowed to room temperature and quenched with 50 ml of water and extracted with 2x150 ml of ethyl acetate. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude. The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh) and was eluted with 1% MeOH-DCM to afford (4S)-8-chloro-7-(1-cyclopropyl-1H-pyrazol-4-yl)-N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (285 mg, 0.510 mmol, 38.4 % yield) as an Off white Solid, LCMS (*m/z*): 552.50 $[M+H]^+$.

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



To a solution of(4S)-9-methyl-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (450 mg, 1.409 mmol) in THF (30 ml) and triphosgene (251 mg, 0.846 mmol) at 0°C. Then TEA (0.196 mL, 1.409 mmol) was added and stirred to RT for 1 h. and (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (474 mg, 2.114 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 (2x100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude. The crude product was added to a Neutral alumina column and was eluted with 20%Ethylacetate in Petether. Collected fractions are evaporated to afford (4S)-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-9-methyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (400 mg, 0.690 mmol, 48.9 % yield) as a white solid, LCMS (*m/z*): 569.93 $[M+H]^+$.

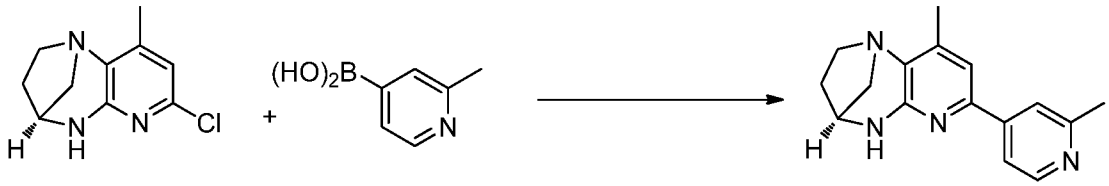
Synthesis of (4S)-9-methyl-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine



To a degassed solution of (4S)-7-chloro-9-methyl-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (600 mg, 2.86 mmol),(3-(trifluoromethyl)phenyl)boronic acid (815 mg, 4.29 mmol) and K_3PO_4 (1822 mg, 8.58

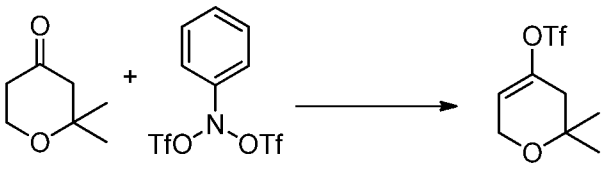
mmol) in 1,4-Dioxane (40 mL);Water (10 mL) and was added x-phos (273 mg, 0.572 mmol),$Pd_2(dba)_3$ (262 mg, 0.286 mmol). The reaction mixture was stirred at 110 °C for 3 hr. The reaction was monitored by TLC. The reaction mixture was poured in to ice (50mL) and extracted with ethyl acetate (3x100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product, that was added to a Neutral alumina column and was eluted with 40%Ethylacetate in Petether Collected fractions are evaporated to afford (4S)-9-methyl-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (600 mg, 1.691 mmol, 59.1 % yield)as an pale Yellow solid, LCMS (*m/z*): 320.13 $[M+H]^+$.

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



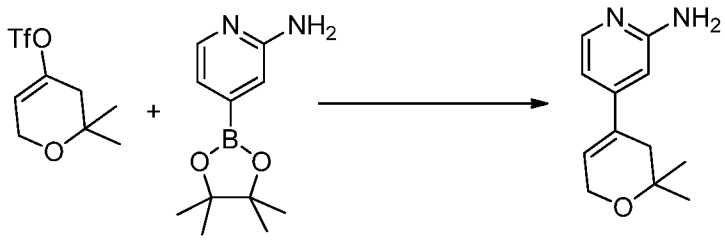
To a degassed solution of (4S)-7-chloro-9-methyl-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 2.385 mmol),(2-methylpyridin-4-yl)boronic acid (490 mg, 3.58 mmol) and K_3PO_4 (1519 mg, 7.15 mmol) in 1,4-Dioxane (40 mL);Water (10 mL) and was added x-phos (227 mg, 0.477 mmol), $Pd_2(dba)_3$ (218 mg, 0.238 mmol). The reaction mixture was stirred at 110 °C for 3 hr. The reaction was monitored by TLC. The reaction mixture was poured in to ice (50mL) and extracted with ethyl acetate (3x100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product, that was added to a Neutral alumina column and was eluted with 40%Ethylacetate in Petether Collected fractions are evaporated to afford (4S)-9-methyl-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (450 mg, 1.653 mmol, 69.3 % yield) as a pale Yellow solid LCMS (*m/z*) 267.21 $[M+H]^+$.

Synthesis of 2,2-dimethyl-3,6-dihydro-2H-pyran-4-yl trifluoromethanesulfonate



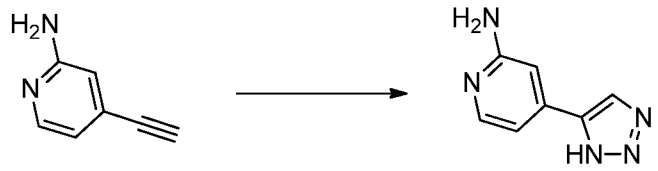
LDA (2.75 mL, 20.29 mmol) was added to a stirred solution of 2,2-dimethyldihydro-2H-pyran-4(3H)-one (2.0 g, 15.60 mmol) in Tetrahydrofuran (THF) (40 mL) at -78 °C and stirred for 20 mins. 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (3.98 mL, 18.73 mmol) was added at -78 °C and stirred at 28 °C for 19 hr. Reaction mixture was quenched with saturated sodium bicarbonate solution, diluted with water (10 mL), extracted with ether (2X30 mL), washed with brine solution (20 mL). Organic layer was separated, dried over Na_2SO_4, filtered and concentrated to get crude product. Crude product was purified by column chromatography using (100-200) silica gel column chromatography and was eluted with 15% EtOAc in Hexane (gradient system) to afford the desired product 2,2-dimethyl-3,6-dihydro-2H-pyran-4-yl trifluoromethanesulfonate (2.4 g, 5.98 mmol, 38.3 % yield) as a pale yellow liquid GCMS (*m/z*): 260 $[M+H]^+$.

Synthesis of 4-(2,2-dimethyl-3,6-dihydro-2H-pyran-4-yl)pyridin-2-amine



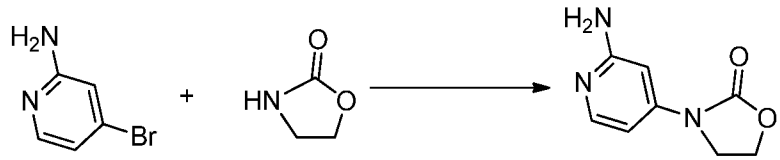
A suspension of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (1.0 g, 4.54 mmol), 2,2-dimethyl-3,6-dihydro-2H-pyran-4-yl trifluoromethanesulfonate (2.365 g, 9.09 mmol) and tripotassium phosphate (2.89 g, 13.63 mmol) in 1,4-Dioxane (30 mL) stirred and degassed with argon at room temp for 15 mins.$PdCl_2(dppf)$-CH_2Cl_2 adduct (0.186 g, 0.227 mmol) was added to the reaction mixture. Then the reaction mixture was stirred 4 hr at 90 °C. The reaction was monitored by TLC. The reaction mixture was cooled to room temp and filtered through celite and washed with EtOAc (20 ml). Take filtrate and concentrated and dissolved with EtOAc (20 ml). EtOAc layer washed with water (10 ml) followed by brine solution (10 ml) and dried out with Na_2SO_4, filtered and concentrated to get crude product. The crude product was purified by column chromatography using neutral alumina and was eluted with 100% DCM (gradient system) to afford the desired product 4-(2,2-dimethyl-3,6-dihydro-2H-pyran-4-yl)pyridin-2-amine (0.8 g, 3.79 mmol, 83 % yield) as a brown solid, LCMS (*m/z*): 205.2 $[M+H]^+$.

Synthesis of 4-(1H-1,2,3-triazol-5-yl)pyridin-2-amine



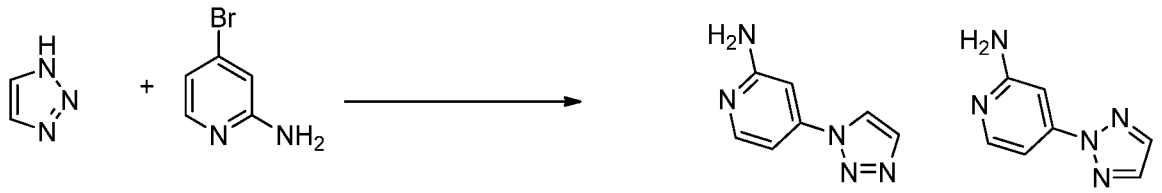
To a stirred suspension of4-ethynylpyridin-2-amine (350 mg, 2.96 mmol) in TMSN3 (0.5mL, 3.77 mmol) at 150 °C in microwave. The resulting reaction mixture was stirred for 30 min at same temperature. The progress of the reaction was monitored by TLC. Reaction mixture was filtered, solid compound was washed with DCM (2 ml) and dried to get 4-(1H-1,2,3-triazol-5-yl)pyridin-2-amine (360 mg, 1.832 mmol, 61.8 % yield) of light yellow solid, LCMS (*m/z*): 162.1 $[M+H]^+$.

Synthesis of 3-(2-aminopyridin-4-yl)oxazolidin-2-one



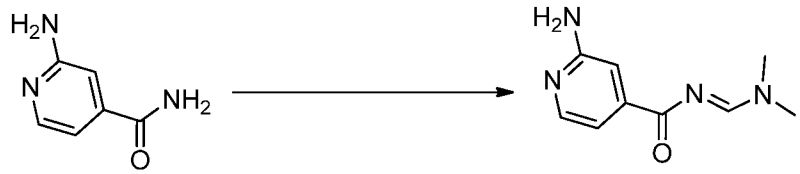
To a stirred solution of 4-bromopyridin-2-amine (1 g, 5.78 mmol) in 1,4-Dioxane (10 ml) was added oxazolidin-2-one (0.755 g, 8.67 mmol), potassium carbonate (1.598 g, 11.56 mmol) , copper(I) iodide (0.110 g, 0.578 mmol), N,N'-dimethylethylenediamine (0.102 g, 1.156 mmol) at rt. The resulting reaction mixture was stirred in microwave at 110 °C for 1 hr. The progress of the reaction was monitored by TLC. Reaction mixture solvent was evaporated, diluted with water(10mL) and stirred for 20 minutes solid was formed, filtered and dried to obtained 3-(2-aminopyridin-4-yl)oxazolidin-2-one (580 mg, 3.11 mmol, 53.8 % yield) as pale yellow solid, LCMS (*m/z*): 180.0 $[M+H]^+$.

Synthesis of 4-(1H-1,2,3-triazol-1-yl)pyridin-2-amine AND 4-(2H-1,2,3-triazol-2-yl)pyridin-2-amine



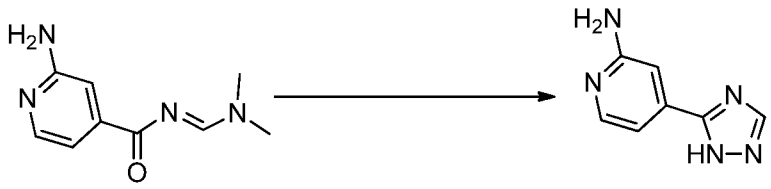
To a solution of 1H-1,2,3-triazole (0.599 g, 8.67 mmol), 4-bromopyridin-2-amine (1 g, 5.78 mmol) in 1,4-Dioxane (10 mL) was added K_2CO_3 (1.598 g, 11.56 mmol),copper(I) iodide (0.110 g, 0.578 mmol) and N,N dimethyl ethylene diamine (0.126 mL, 1.156 mmol) room temp. The reaction mixture was stirred at 110 °C for 1 hr in MW. The reaction mixture was quenched under with water (30 mL) and extracted with Ethyl acetate (2 X 50 mL) and followed by 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 purified to afford 4-(1H-1,2,3-triazol-1-yl)pyridin-2-amine (0.1g, 0.562 mmol, 9.72 % yield) as off white solid and 4-(2H-1,2,3-triazol-2-yl)pyridin-2-amine (0.3g, 1.787 mmol, 30.9 % yield) as off white solid, LCMS (*m/z*): 162.0 $[M+H]^+$.

Synthesis of (E)-2-amino-N-((dimethylamino)methylene)isonicotinamide



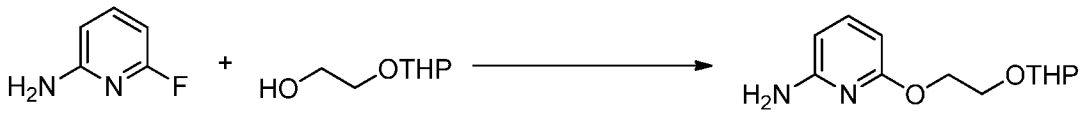
To a stirred solution of 2-aminoisonicotinamide (5 g, 36.5 mmol) in N,N-Dimethylformamide (DMF) (50 mL) was added 1,1-dimethoxy-N,N-dimethylmethanamine (9.76 mL, 72.9 mmol) at rt. The resulting reaction mixture was stirred for 4 hr at 27 °C. The progress of the reaction was monitored by TLC. Reaction mixture solvent was evaporated, diluted with EtOAc (5X20 mL) and ice cold water, separated organic layer and concentrated under vacuum to obtained of (E)-2-amino-N-((dimethylamino)methylene)isonicotinamide (4.5 g, 23.41 mmol, 64.2 % yield) as off white solid, LCMS (*m/z*): 193.01 $[M+H]^+$.

Synthesis of 4-(1H-1,2,4-triazol-5-yl)pyridin-2-amine



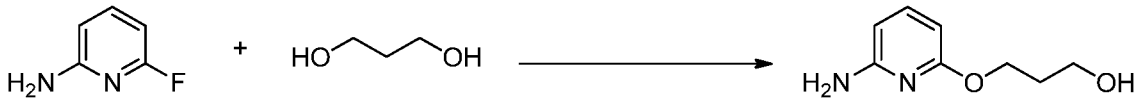
To a stirred suspension of (E)-2-amino-N-((dimethylamino)methylene)isonicotinamide (4 g, 20.81 mmol) in Ethanol (40 mL) was added hydrazine hydrate (1.042 g, 20.81 mmol) at RT. The resulting reaction mixture was stirred for 16 hr at same temperature. The progress of the reaction was monitored by TLC. Reaction mixture was filtered, solid compound was washed with EtOAc (20ml) and filtrate was dried to get 2 g (LCMS showed 40% desired)of solid compound. The compound was purified by prep HPLC to afford 4-(1H-1,2,4-triazol-5-yl)pyridin-2-amine (750 mg, 4.40 mmol, 21.13 % yield) as an brown color solid, LCMS (*m/z*): 162.0 $[M+H]^+$.

Synthesis of 6-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)pyridin-2-amine



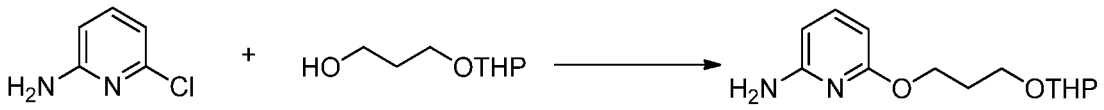
2-((tetrahydro-2H-pyran-2-yl)oxy)ethanol (1.5 g, 10.26 mmol) in N-Methyl-2-pyrrolidone (NMP) (4 mL) was added to a suspension of NaH (0.616 g, 25.7 mmol) at 0 °C and the reaction mixture was stirred for 30 min at 28 °C. 6-fluoropyridin-2-amine (1.150 g, 10.26 mmol) was added to the reaction mixture at 0°C, and the reaction mixture was stirred at 120 °C for 16 hr. The reaction mixture was quenched with cold water and extracted with dichloromethane(2 x 60 mL). The organic layer was washed with water (30 mL) and saturated brine solution(20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Crude was purified by flash chromatography on neutral alumina. Crude was diluted with DCM and absorbed with neutral alumina and eluted with 20-25-% EtOAc in pet ether fractions were collected and concentrated to get 6-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)pyridin-2-amine (700 mg, 2.66 mmol, 25.9 % yield), LCMS (*m/z*): 239.0 $[M+H]^+$.

Synthesis of 3-((6-aminopyridin-2-yl)oxy)propan-1-ol



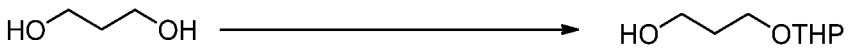
propane-1,3-diol (1.358 g, 17.84 mmol) was added to a stirred solution of NaH (1.070 g, 44.6 mmol) in N-Methyl-2-pyrrolidone (NMP) (5 mL) at 0° C and stirred for 1h and followed by addition of 6-fluoropyridin-2-amine (1.0 g, 8.92 mmol) and stirred for 2h at 80 °C. Reaction mass was cooled to room temperature, slowly added to ice cold water and diluted with ethyl acetate. The separated organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated to obtain crude compound. The crude compound was purified by using 100-200 silica gel and eluted in 100% ethyl acetate to afford 3-((6-aminopyridin-2-yl)oxy)propan-1-ol (0.4g, 1.760 mmol, 19.73 % yield) as brown viscous, LCMS (*m/z*): 169.22 $[M+H]^+$.

Synthesis of 6-(3-((tetrahydro-2H-pyran-2-yl)oxy)propoxy)pyridin-2-amine



3-((tetrahydro-2H-pyran-2-yl)oxy)propan-1-ol (4.2 g, 26.2 mmol) in 1,4-Dioxane (20 mL) was added to a solution of NaH (1.307 g, 32.7 mmol) in 1,4-Dioxane (20 mL) at 0 °C, and the reaction mixture was stirred for 30 min at 28 °C. 6-chloropyridin-2-amine (2.8g, 21.78 mmol) in 1,4-Dioxane (20 mL) was added to the reaction mixture at 0 °C, and the reaction mixture was stirred for 10 hr at 100 °C. The reaction mixture was partitioned between water (20 mL) and DCM (2 X 25 mL). DCM layer was washed with saturated $NaHCO_3$ solution, was separated and dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to crude 6-(3-((tetrahydro-2H-pyran-2-yl)oxy)propoxy)pyridin-2-amine (5.5 g, 18.12 mmol, 83 % yield) as brown oil, LCMS (*m/z*): 253.2 $[M+H]^+$.

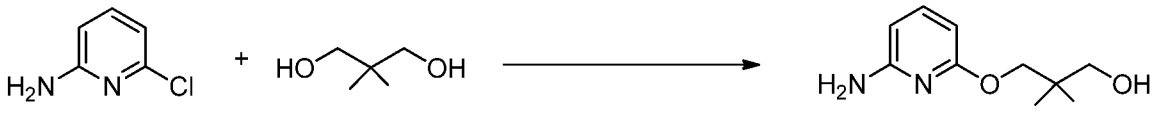
Synthesis of 3-((tetrahydro-2H-pyran-2-yl)oxy)propan-1-ol



p-toluenesulfonic acid monohydrate (0.678 g, 3.57 mmol) was added to a stirred solution of propane-1,3-diol (5.43 g, 71.3 mmol), and 3,4-dihydro-2H-pyran (3g, 35.7 mmol) in

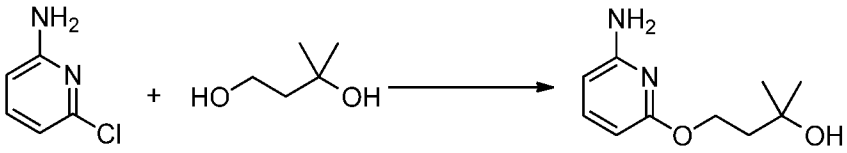
Dichloromethane (DCM) (50 mL) at 0 °C. The reaction mixture was stirred for 2h at 28 °C. The reaction mixture was partitioned between water (20 mL) and DCM (2 X 25 mL). DCM layer was washed with saturated $NaHCO_3$ solution, was separated and dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to crude 3-((tetrahydro-2H-pyran-2-yl)oxy)propan-1-ol (4.2g, 26.2 mmol, 73.5 % yield) as colorless oil.

Synthesis of 3-((6-aminopyridin-2-yl)oxy)-2,2-dimethylpropan-1-ol



2,2-dimethylpropane-1,3-diol (3.0 g, 28.8 mmol) was added to the stirred solution of NaH (2.304 g, 57.6 mmol) in N-Methyl-2-pyrrolidone (NMP) (25 mL) at 0 °C. The reaction mixture was stirred at room temperature for 30 min. 6-chloropyridin-2-amine (4.44 g, 34.6 mmol) was added to the reaction mixture at 0°C. The reaction mixture was stirred at 100 °C for 16 h and progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature quenched with ice cold water and extracted with ethyl acetate (3X30 mL). The organic layer was washed with water (30 mL) and saturated brine solution (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to get crude compound TLC eluent: 50%EtOAc/Hexane, R_f:0.3, UV active. The crude compound was purified by column chromatography using Neutral Alumina and eluted with 5% EtOAc in Petether to obtaine pure 3-((6-aminopyridin-2-yl)oxy)-2,2-dimethylpropan-1-ol (1.5 g, 6.79 mmol, 23.56 % yield) as off white solid. LCMS: (*m/z*): 197.16 $[M+H]^+$.

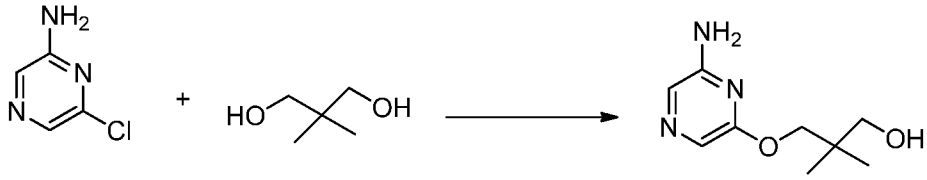
Synthesis of 4-((6-aminopyridin-2-yl)oxy)-2-methylbutan-2-ol



To a stirred suspension of NaH (1.167 g, 29.2 mmol) in N-Methyl-2-pyrrolidone (NMP) (2 mL) under nitrogen at 0°C was added a solution of 3-methylbutane-1,3-diol (3.04 g, 29.2 mmol) in N-Methyl-2-pyrrolidone (NMP) (2 mL) dropwise during 10 min at 0°C. After 10 min added a solution of 6-chloropyridin-2-amine (2.5 g, 19.45 mmol) in N-Methyl-2-

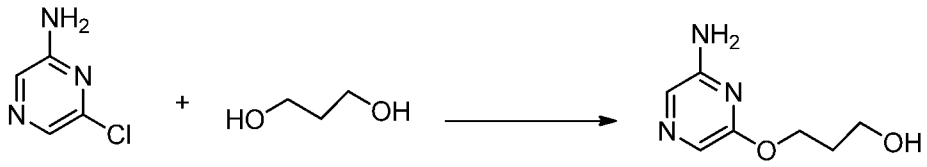
pyrrolidone (NMP) (2 mL) dropwise during 10 min at 0°C. The reaction mixture was heated at 120 °C for 16 hr. Progress of the reaction was monitored by TLC. Reaction mixture was poured into ice water and extracted with EtOAc (3X 30 ml), organic solvent was dried over Na_2SO_4 and concentrated under vacuum to get crude. The crude was purified by column chromatography by using silica gel (100-200 mesh) by eluting with 50-70% EtOAc in hexane to get 4-((6-aminopyridin-2-yl)oxy)-2-methylbutan-2-ol (1.5 g, 7.51 mmol, 38.6 % yield) as an off-white solid, LCMS (*m/z*): 197.29 $[M+H]^+$.

Synthesis of 3-((6-aminopyrazin-2-yl)oxy)-2,2-dimethylpropan-1-ol



To a stirred suspension of NaH (2.316 g, 57.9 mmol) in 1,4-Dioxane (20 mL) under nitrogen at 0°C was added a solution of 2,2-dimethylpropane-1,3-diol (4.02 g, 38.6 mmol) in 1,4-Dioxane (20 mL) dropwise during 10 min at 0°C. After 10 min added a solution of 6-chloropyrazin-2-amine (5 g, 38.6 mmol) in 1,4-Dioxane (20 mL) was added dropwise during 10 min at 0°C.The reaction mixture was heated at 120 °C for 48 hr. TLC indicates small amount starting material along with product. Reaction mixture was poured into ice cold water (60 mL), aqueous layer was extracted with EtOAc (2 x 100 mL). The organic layer was washed with brine (50 mL). 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 (0-50% EtOAc in petether) to obtain 3-((6-aminopyrazin-2-yl)oxy)-2,2-dimethylpropan-1-ol (1 g, 4.95 mmol, 12.84 % yield), LCMS (*m/z*): 198.00 $[M+H]^+$.

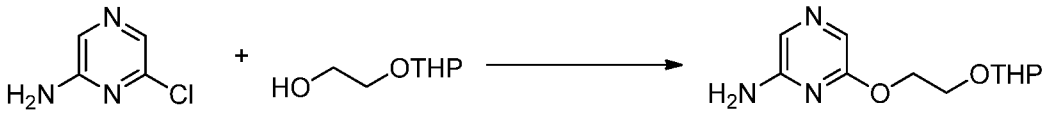
Synthesis of 3-((6-aminopyrazin-2-yl)oxy)propan-1-ol



To a suspension of NaH (1.389 g, 34.7 mmol) in NMP (2 mL) was added a solution of

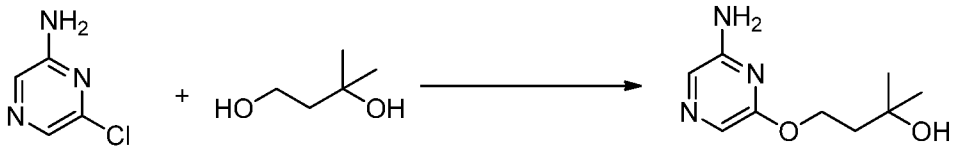
propane-1,3-diol (2.64 g, 34.7 mmol) in NMP (2 mL) under Nitrogen at 0 °C, the reaction mixture was stirred for 1h at RT. Then a solution of 6-chloropyrazin-2-amine (3 g, 23.16 mmol) in NMP (6 mL) was added drop by drop over 15 min, at 0 °C and heated at 140 °C for 16 hr. The reaction mixture was cooled to rt, quenched with water (50 mL) and extracted with EtOAc (3x150mL). The combined organics were washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated to get crude product. The crude was added to a silica gel column and was eluted with (70%) EtOAc/Pet Ether. Collected fractions were evaporated to obtain compound 3-((6-aminopyrazin-2-yl)oxy)propan-1-ol (1.5 g, 8.21 mmol, 35.5 % yield) as Off-white solid, LCMS (*m/z*): 170.09 $[M+H]^+$.

Synthesis of 6-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)pyrazin-2-amine



NaH (60%) (0.556 g, 23.16 mmol) was added to a stirred solution of 2-((tetrahydro-2H-pyran-2-yl)oxy)ethanol (3.39 g, 23.16 mmol) in 1,4-Dioxane (100 mL) at 0 °C then stirred at RT for 30 min and 6-chloropyrazin-2-amine (3 g, 23.16 mmol) was added at 0 °C then it was kept at 80 °C for 16 h. The reaction mixture was cooled to RT, and was quenched with ice cold water (50 mL) then partitioned between ice cold water (20 mLX2) and ethyl acetate (20 mL x 2). 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 60% ethyl acetate in hexane) to afford the 6-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)pyrazin-2-amine (5 g, 20.06 mmol, 87 % yield) as gum oil, LCMS (*m/z*): 240.13 $[M+H]^+$.

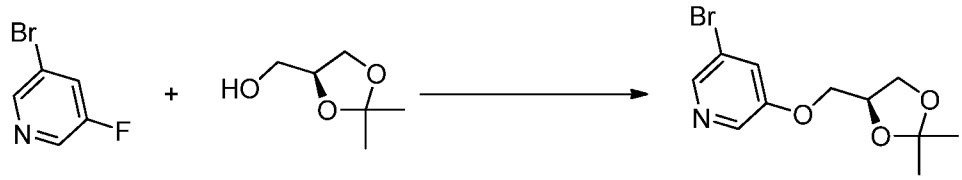
Synthesis of 4-((6-aminopyrazin-2-yl)oxy)-2-methylbutan-2-ol



To a stirred suspension of NaH (0.463 g, 11.58 mmol) in 1,4-Dioxane (5.00 mL) under nitrogen at 0°C was added a solution of 3-methylbutane-1,3-diol (1.206 g, 11.58 mmol) in

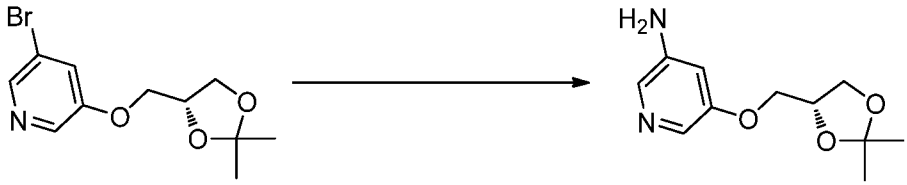
1,4-Dioxane (5.00 mL) dropwise during 10 min at 0°C. After 10 min added a solution of 6-chloropyrazin-2-amine (1.0 g, 7.72 mmol) in 1,4-Dioxane (10.00 mL) dropwise during 10 min at 0°C.The reaction mixture was stirred at 100 °C for 16 hr. Progress of the reaction was monitored by TLC. Reaction mixture was poured into ice water and extracted with EtOAc (3X 25 ml), organic solvent was dried over Na_2SO_4 and concentrated under vacuum to get crude. The crude was purified by column chromatography by using silica gel (100-200 mesh) by eluting with 50-70% EtOAc in hexane to get 4-((6-aminopyrazin-2-yl)oxy)-2-methylbutan-2-ol (1.0 g, 5.04 mmol, 65.3 % yield) as brown solid, LCMS (*m/z*): 199.08 $[M+H]^+$.

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



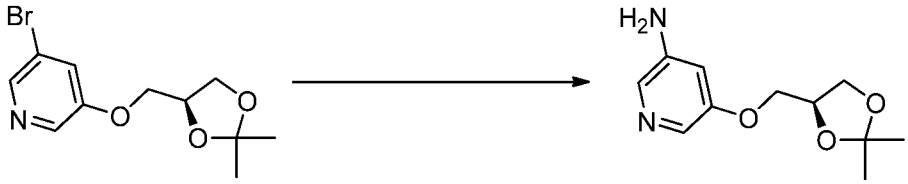
Cesium carbonate (37.0 g, 114 mmol) was taken into multi-neck RB. Then flask was cooled to 0 °C and N-Methyl-2-pyrrolidone (NMP) (100 mL) was added slowly over a period of 3 minutes. The resulting reaction mixture was stirred under nitrogen for 15 min. Then (S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (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 (2X300 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



(R)-3-bromo-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridine (50g, 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 $[M+H]^+$.

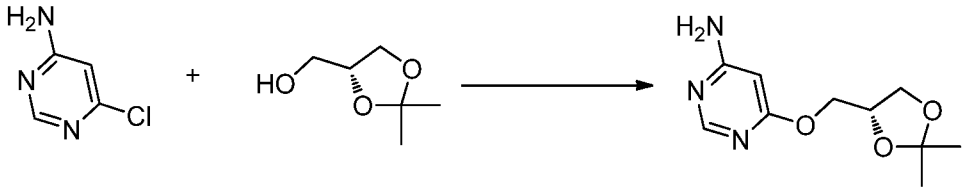
Synthesis of (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine



(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-

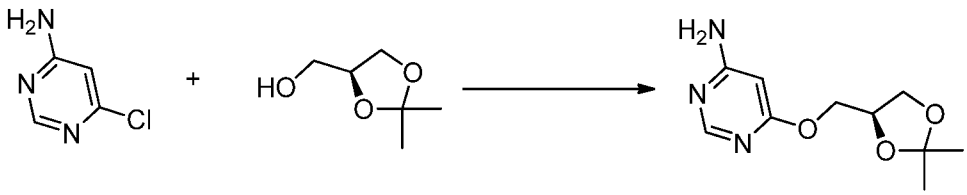
dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-amine (6 g, 25.8 mmol, 74.2 % yield) as an pale brown solid, LCMS (*m/z*): 225.10 $[M+H]^+$.

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



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 1h. 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 X 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 $(M+H)^+$.

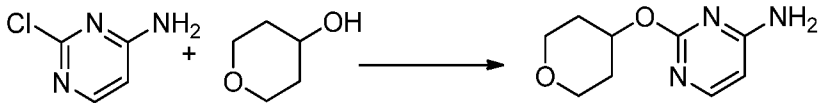
Synthesis of (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-amine



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 1h. 6-

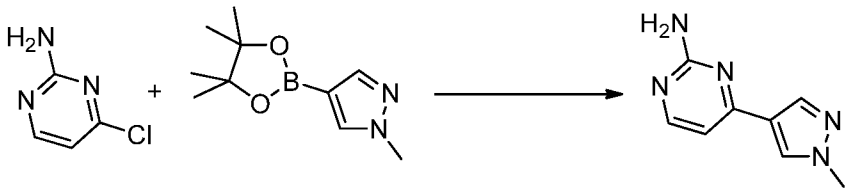
chloropyrimidin-4-amine (15.68 g, 121 mmol) was added to the reaction mass portion wise at rt and the resulting suspension was heated to 90 °C for 48 hr. After the completion of reaction (monitored by TLC, starting material completely consumed and new spot observed at polar), reaction mass was poured into ice water (200 mL) and extracted with ethyl acetate (2X400 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



To a solution of tetrahydro-2H-pyran-4-ol (25g, 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 1hr 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 (3X200 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 $[M+H]^+$.

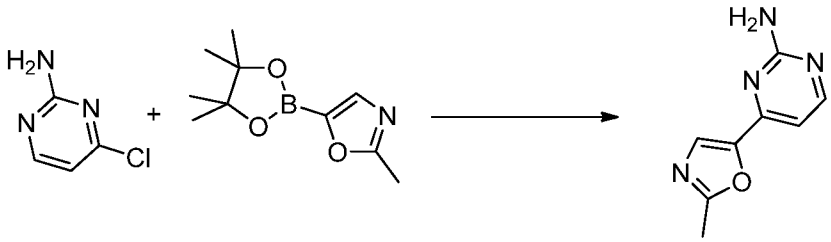
Synthesis of 4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine



To a degassed solution of 4-chloropyrimidin-2-amine (800 mg, 6.18 mmol), solid 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1927 mg, 9.26 mmol) and K_3PO_4 (3932 mg, 18.53 mmol) in 1,4-Dioxane (20 mL),Water (5.00 mL)

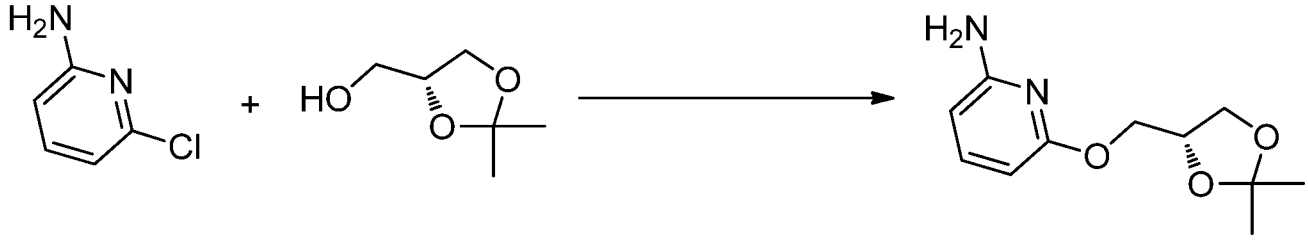
stirred under at room temp. Then added $PdCl_2(dppf)$-CH_2Cl_2 adduct (756 mg, 0.926 mmol)and degassed for 5 min. Then reaction mixture was stirred at 80 °C for 15h 30min.The reaction mixture was monitored by TLC. The reaction was cooled to RT. The organic phase was evaporated and added water 50 mL and Extracted with Ethyl acetate (3x 70 ml) and washed with saturated brine 50 mL dried over Na_2SO_4 and evaporated in vacuum to give the crude product. The crude compound was purified by flash column chromatography (Neutral alumina, eluent: 90% EtOAc in Pet ether) to afford 4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (600 mg, 3.42 mmol, 55.5 % yield) as an off white solid, LCMS (*m/z*): 176.1 $[M+H]^+$.

Synthesis of 4-(2-methyloxazol-5-yl)pyrimidin-2-amine



To a stirred solution of 4-chloropyrimidin-2-amine (1.5 g, 11.58 mmol) in 1,4-Dioxane (20 mL) and Water (5 mL) mixture, were added potassium phosphate (3.69 g, 17.37 mmol) and 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (2.421 g, 11.58 mmol) at Room temperature. The reaction mass was degassed for 15 min with nitrogen, added $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.095 g, 0.116 mmol) and the resulting reaction mass was stirred for 16 hr at 80 °C under Nitrogen, Progress of the reaction was monitored by TLC, TLC indicated formation of a polar multiple sports and SM was consumed. Reaction mass was concentrated and diluted with 50 ml of water and 60 ml of DCM, pass through Hi-flow bed, separated organic layer, extracted with DCM (2X 50 ml), combined organic layers, dried over Na_2SO_4, filtered and concentrated to get crude compound. The crude product was purified by combiflash chromatography using silica gel column (24 g, 60% EtOAc in pet ether). Column was eluted with a gradient of EtOAc in Hexane. Desired compound was eluted with 60% EtOAc in Hexane. Fractions containing pure compound were concentrated under reduced pressure to afford the 4-(2-methyloxazol-5-yl)pyrimidin-2-amine (1.2 g, 6.66 mmol, 57.5 % yield) as an off-white color solid. LCMS (*m/z*):177.11 $[M+H]^+$.

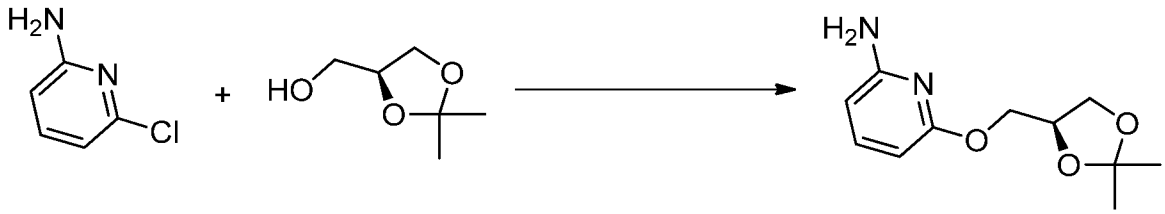
Synthesis of (R)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine



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.

Reaction mixture was poured into ice cold water (600 mL), aqueous layer was extracted with EtOAc (2 x 500 mL). The organic layer was washed with water (3 x 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.

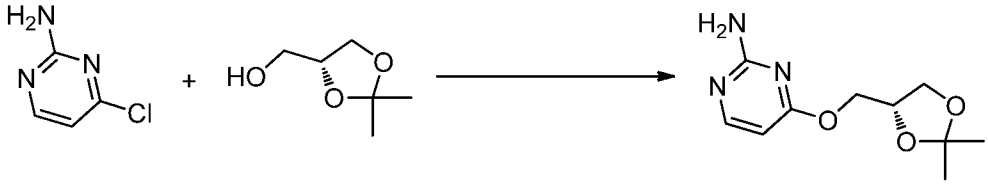
Synthesis of (S)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine



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

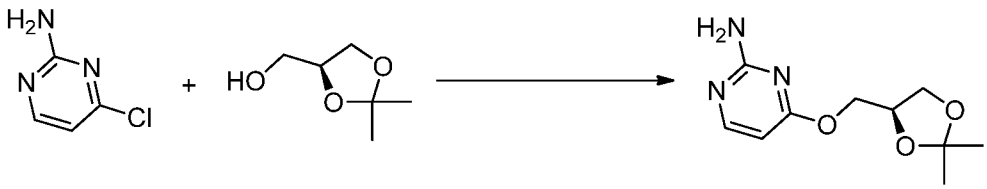
was extracted with EtOAc (3 x 1000 mL). The combined organic layer was washed with water (3 x 1000 mL) to remove excess NMP. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain crude product. Crude product was purified by column chromatography using 100-200 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. LCMS (*m/z*): 225 $[M+H]^+$.

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



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 1h. 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 X 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 $[M+H]^+$.

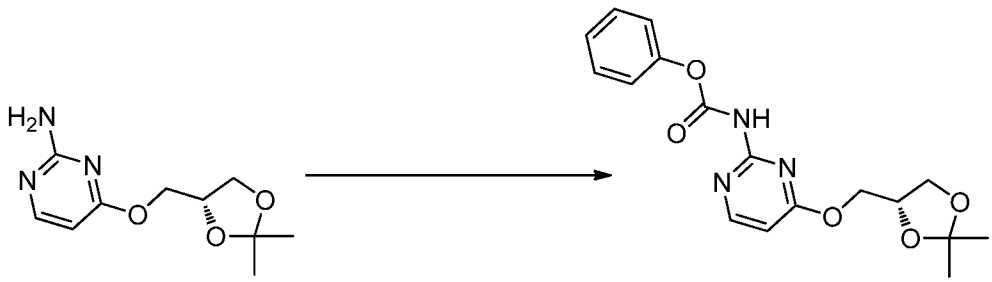
Synthesis of (S)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-amine



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 1h. 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

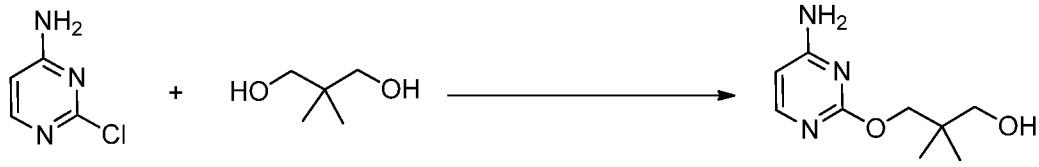


To a solution of phenyl carbonochloridate (2.71 g, 17.31 mmol) and pyridine (1.724 mL, 21.31 mmol) in Dichloromethane (DCM) (50 mL) stirred under nitrogen at room temp was added (R)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-amine (3.0 g, 13.32 mmol). The reaction mixture was stirred at 28 °C for 2 hr. The Reaction was monitored by TLC. The reaction mixture was diluted with water (75mL) extracted with DCM (2 X 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 2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)pyrimidin-4-amine

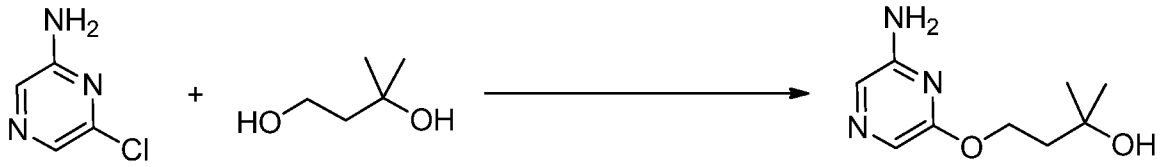
NaH (0.741 g, 30.9 mmol) was added to a stirred solution of 2-((tetrahydro-2H-pyran-2-yl)oxy)ethanol (4.51 g, 30.9 mmol) in 1,4-Dioxane (120 mL) at 0 °C then stirred at RT for 30 min and 2-chloropyrimidin-4-amine (4g, 30.9 mmol) was added at 0 °C then it was kept at 80 °C for 16 h. The reaction mixture was cooled to RT, and was quenched with ice cold water (50 mL) then partitioned between ice cold water (50 mLX2) and ethyl acetate (50 mL x 2). 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 60% ethyl acetate in hexane) to afford 2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)pyrimidin-4-amine (4 g, 16.05 mmol, 52.0 % yield) as a gum oil, LCMS (*m/z*): 239.9 $[M+H]^+$.

Synthesis of 3-((4-aminopyrimidin-2-yl)oxy)-2,2-dimethylpropan-1-ol



To a stirred suspension of NaH (2.316 g, 57.9 mmol) in Tetrahydrofuran (THF) (20 mL) under nitrogen at 0°C was added a solution of 2,2-dimethylpropane-1,3-diol (4.02 g, 38.6 mmol) in Tetrahydrofuran (THF) (20 mL) dropwise during 10 min at 0°C. After 10 min added a solution of 2-chloropyrimidin-4-amine (5 g, 38.6 mmol) in Tetrahydrofuran (THF) (20 mL) was added dropwise during 10 min at 0°C.The reaction mixture was heated at 120 °C for 16 hr. TLC indicates small amount starting material along with product. Reaction mixture was poured into ice cold water (60 mL), aqueous layer was extracted with EtOAc (2 x 100 mL). The organic layer was washed with brine (50 mL). 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 (0-50% EtOAc in petether) to get 3-((4-aminopyrimidin-2-yl)oxy)-2,2-dimethylpropan-1-ol (800 mg, 4.04 mmol, 10.47 % yield), LCMS (*m/z*): 198.09 $[M+H]^+$.

Synthesis of 4-((6-aminopyrazin-2-yl)oxy)-2-methylbutan-2-ol



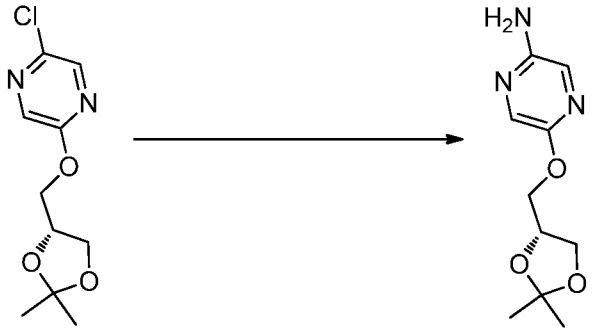
To a stirred suspension of NaH (0.463 g, 11.58 mmol) in 1,4-Dioxane (5.00 mL) under nitrogen at 0°C was added a solution of 3-methylbutane-1,3-diol (1.206 g, 11.58 mmol) in 1,4-Dioxane (5.00 mL) dropwise during 10 min at 0°C. After 10 min added a solution of 6-chloropyrazin-2-amine (1.0 g, 7.72 mmol) in 1,4-Dioxane (10.00 mL) dropwise during 10 min at 0°C.The reaction mixture was stirred at 100 °C for 16 hr. Progress of the reaction was monitored by TLC. Reaction mixture was poured into ice water and extracted with EtOAc (3X 25 ml) , organic solvent was dried over Na_2SO_4 and concentrated under vacuum to get crude. The crude was purified by column chromatography by using silica gel (100-200 mesh) by eluting with 50-70% EtOAc in hexane to get 4-((6-aminopyrazin-2-yl)oxy)-2-methylbutan-2-ol (1.0 g, 5.04 mmol, 65.3 % yield) as brown solid, LCMS (*m/z*): 199.08 $[M+H]^+$.

Synthesis of 4-((4-aminopyrimidin-2-yl)oxy)-2-methylbutan-2-ol

N35296-64

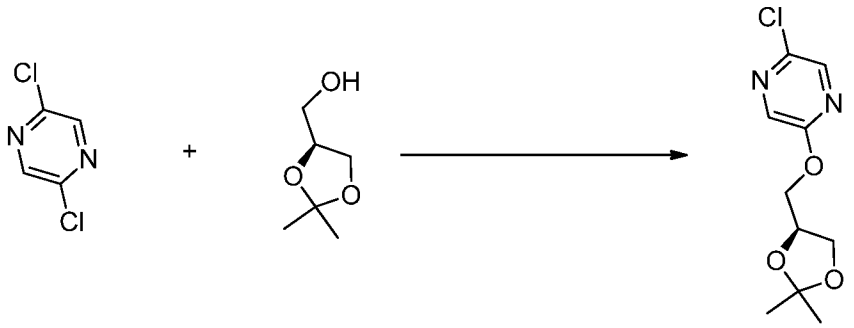
To a stirred suspension of NaH (1.698 g, 42.5 mmol) in 1,4-Dioxane (100 mL) under nitrogen at 0°C was added a solution of 3-methylbutane-1,3-diol (4.42 g, 42.5 mmol) in 1,4-Dioxane (50 mL) dropwise during 15 min at 0°C. After 10 min added 2-chloropyrimidin-4-amine (5.00 g, 38.6 mmol) portion wise during 15 min at 0°C. The reaction mixture was heated at 100 °C for 16 hr. Progress of the reaction was monitored by TLC. Reaction mixture was poured into ice water, concentrated to get sticky mass as a crude. The crude was purified by column chromatography by using silica gel (60-120 mesh) by eluting with 50-70% EtOAc in hexane to get 4-((4-aminopyrimidin-2-yl)oxy)-2-methylbutan-2-ol (6.3 g, 29.6 mmol, 77 % yield) as and off-white solid, LCMS (*m/z*): 198.30 $[M+H]^+$.

Synthesis of (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-amine N35281-46



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(3x 200mL), 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 $(M+H)^+$.

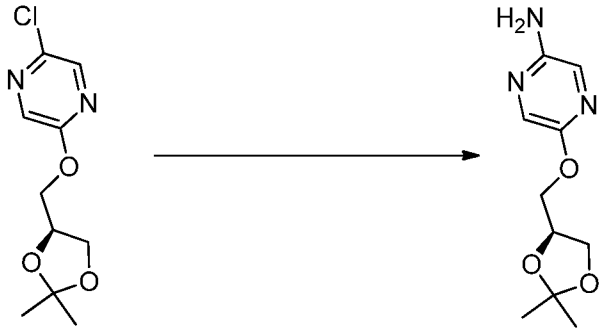
Synthesis of (S)-2-chloro-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazine



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

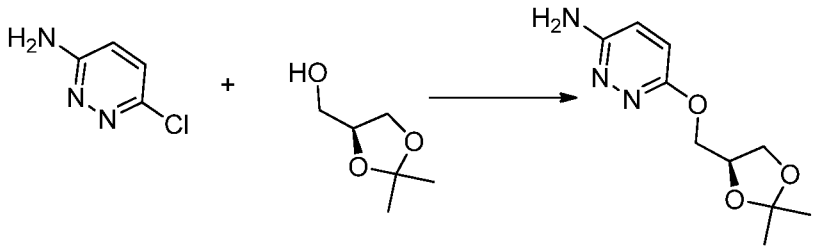
cooled to rt, added water(100mL) and extracted with Ethyl acetate(100mL). The organic layer was washed with water(100mLX2). The organic layer was dried over Na_2SO_4 and filtered and concentrated to get crude as light brown liquid. The crude product was added to a silica gel (60-120) column and was eluted 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



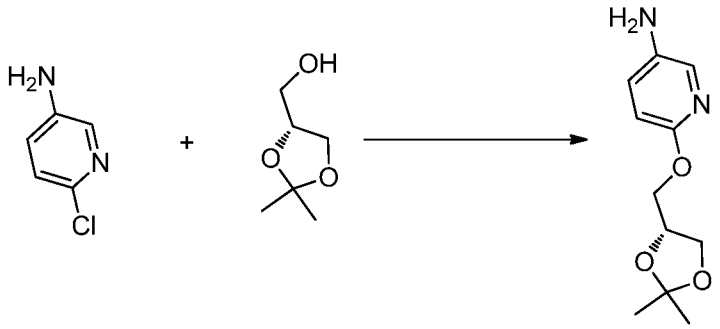
To a solution of (S)-2-chloro-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazine (10 g, 40.9 mmol), in Tetrahydrofuran (THF) (10 mL) stirred at room temp was added ammonium hydroxide (63.7 mL, 409 mmol) and copper(II) sulfate (3.26 g, 20.44 mmol) at rt. The reaction mixture was stirred in sealed tube at 130 °C for 2days. Progress of the reaction was monitored by TLC. TLC indicated starting material was consumed. Cooled the reaction mass to rt, diluted with water(100mL), Extracted with ethyl acetate (250mLX2). 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



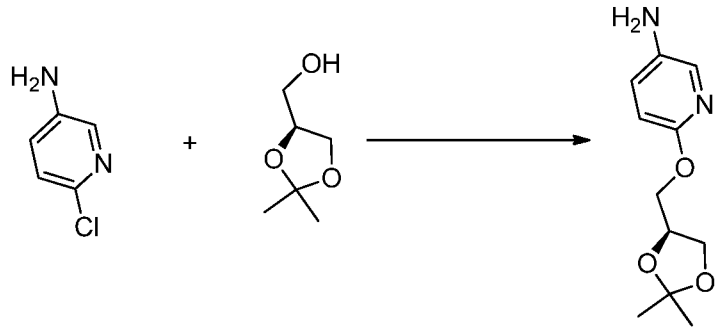
To a suspension of KOtBu (12.99 g, 116 mmol) in1,4-Dioxane (300 mL) was added dropwise a solution of (S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (4.08 g, 30.9 mmol) in 20 ml under Nitrogen at 0°C. The resulting suspension was stirred at rt for 1h.6-chloropyridazin-3-amine (5 g, 38.6 mmol) was added 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 X 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



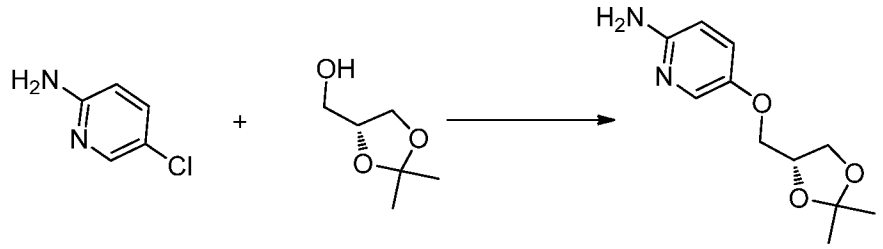
(R)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (27.8 g, 210 mmol) was added to a stirred solution of KOtBu (45.8 g, 408 mmol) in NMP (200 mL) at 0 ℃ then stirred at RT for 1 h and cooled to 0 ℃, 6-chloropyridin-3-amine (15 g, 117 mmol) was added and heated to 110 ℃ for 144 h. The reaction mixture cooled to RT and partitioned between water (500 mLX2) and EtOAc (200 mL x 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



(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 88h. The reaction mixture cooled to RT and partitioned between water (50 mLX2) and EtOAc (100 mL x 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 $(M+H)^+$.

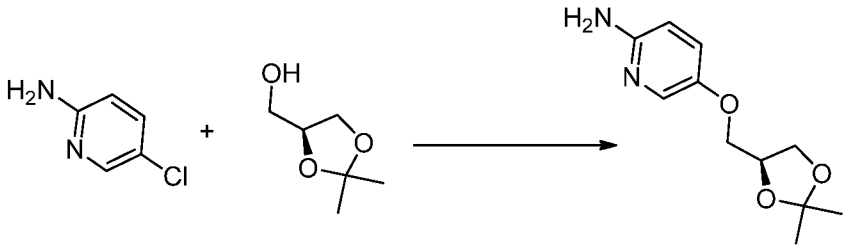
Synthesis of (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine



(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 mLX2) and EtOAc (500 mL x 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

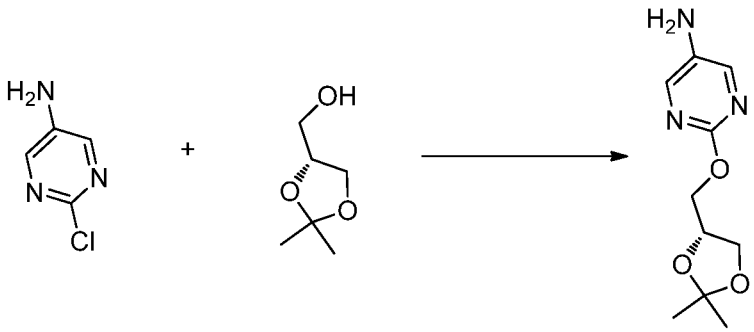
acetate in hexane) to afford the (R)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-amine (10 g, 40.1 mmol, 22.50 % yield) as a brown oil, LCMS: 225.0 (M+H).

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



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 $(M+H)^+$.

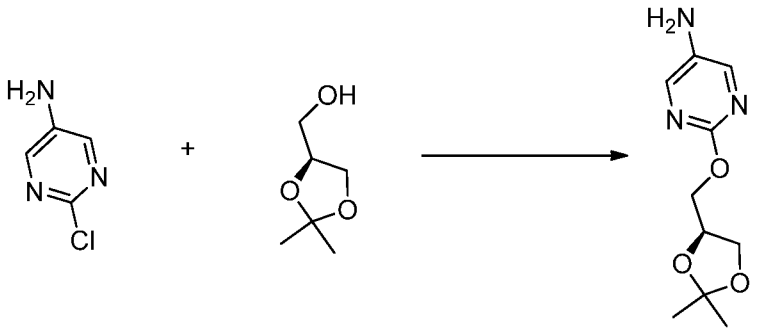
Synthesis of (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-amine



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 1h at

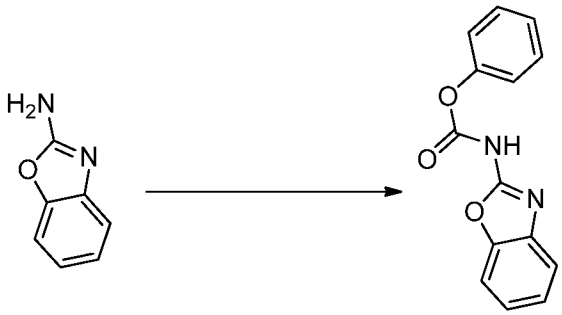
28°C. 2-chloropyrimidin-5-amine (10 g, 77 mmol) in Tetrahydrofuran (25 mL) was added and stirred for 16 hr at 70 °C. The reaction mixture was quenched with cold water (30 mL) and extracted with ethyl acetate(3 x 80 mL). The organic layer was washed with water (2 X 50 mL) and saturated brine solution (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



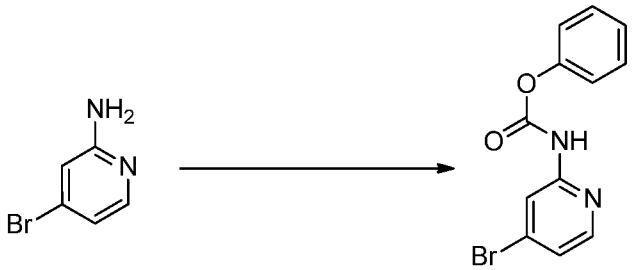
To a suspension of NaH (6.17 g, 154 mmol) in THF (100 ml) was added (S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (13.26 g, 100 mmol) in THF (50 ml) was added to the reaction mixture at 0 °C, and the reaction mixture was stirred for 1h at 25°C.to this 2-chloropyrimidin-5-amine (10 g, 77 mmol) in THF (50 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 (3x20 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 phenyl benzo[d]oxazol-2-ylcarbamate



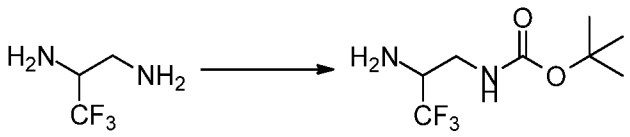
To a solution of pyridine (0.965 mL, 11.93 mmol), phenyl carbonochloridate (1.517 g, 9.69 mmol) in Dichloromethane (DCM) (15 mL) stirred under nitrogen at room temp was added benzo[d]oxazol-2-amine (1 g, 7.46 mmol). The reaction mixture was stirred at 30 °C for 3 hr. Reaction was monitored by TLC. The reaction mixture was diluted with water(20 mL), dichloromethane (2 X 50 mL) and separated the organic layer. The organic layer was washed with saturated brine solution (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude was triturated with 50%ether in hexane and submitted for analysis, LCMS (*m/z*): 255.19 $[M+H]^+$.

Synthesis of phenyl (4-bromopyridin-2-yl)carbamate



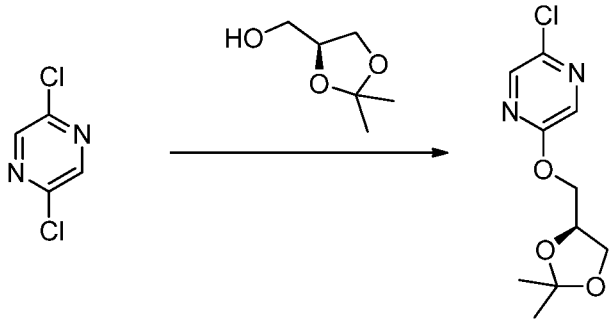
To a mixture of phenyl carbonochloridate (4.98 g, 31.8 mmol) and Py (3.04 mL, 37.6 mmol) in DCM (40 mL) was added dropwise a solution of 4-bromopyridin-2-amine (5 g, 28.9 mmol) in DCM (30 mL) at rt. The resulting solution was stirred at rt for 2 hr. After the completion of reaction (monitored by TLC, Starting material completely consumed and new spot observed at just above of SM), added sat. sodium bicarbonate solution (60 mL) to the reaction mass and the aqueous layer was extracted with DCM (2 x 70 ML). Combined organic layer was dried over Na_2SO_4 filtered and concentrated under reduced pressure to get off-white solid. Obtained solid was stirred in petether (50 mL), filtered and dried to get phenyl (4-bromopyridin-2-yl)carbamate (4 g, 6.66 mmol, 23.03 % yield) as a white solid, LCMS (*m/z*): 293.2 $(M+H)^+$.

Synthesis of tert-butyl (2-amino-3,3,3-trifluoropropyl)carbamate



To a solution of 3,3,3-trifluoropropane-1,2-diamine dihydrochloride (1 g, 4.97 mmol), DIPEA (2.61 mL, 14.92 mmol) in Dichloromethane (DCM) (60 mL) stirred under nitrogen at room temperature was added a solution of Boc_2O (0.924 mL, 3.98 mmol) in Dichloromethane (DCM) (10 mL) dropwise at room temperature. The reaction mixture was stirred at room temperature for 3 hr. Progress of the reaction was monitored by TLC. TLC indicated formation of a non-polar spot and complete consumption of SM. Reaction mixture was diluted with cold water (50 ml) and extracted with DCM (2 x 30 ml). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain tert-butyl (2-amino-3,3,3-trifluoropropyl)carbamate (800 mg, 3.51 mmol, 70.5 % yield) as colorless oil.

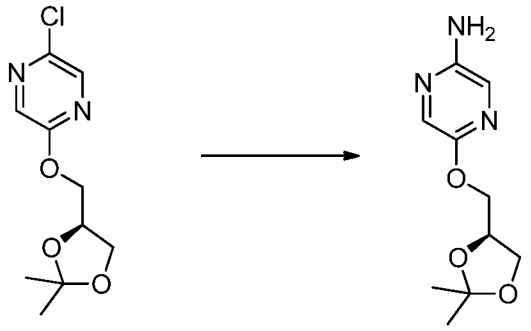
Synthesis of (*S*)-2-chloro-5-((2, 2-dimethyl-1, 3-dioxolan-4-yl) methyl) pyrazine



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 x 300 mL). The combined organic layer was washed with water (2 x 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 %

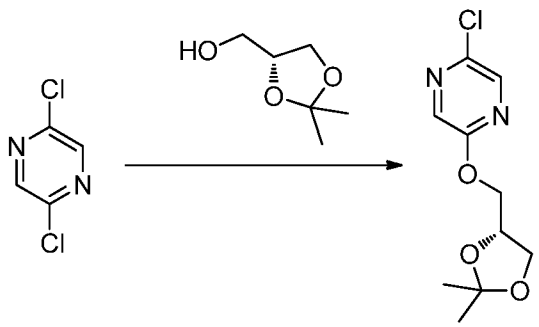
EtOAc in Hexane) to afford the desired product (*S*)-2-chloro-5-((2, 2-dimethyl-1, 3-dioxolan-4-yl) methoxy) pyrazine (200 g, 768 mmol, 76 % yield) as a yellow liquid. LCMS (*m/z*): 245.1 $[M+H]^+$.

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



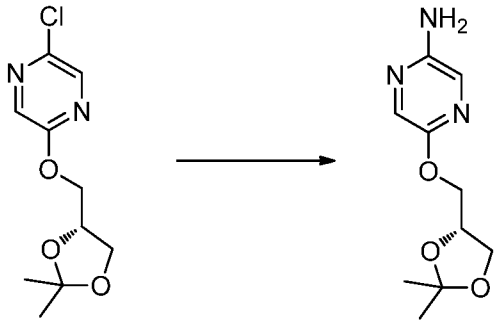
To a stirred solution of (*S*)-2-chloro-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazine (120 g, 490 mmol) in THF (30 mL) were added ammonium hydroxide (1000 mL, 6420 mmol) and copper(II) sulfate (15.66 g, 98 mmol) in a sealed tube and the resulte reaction mixture was stirred at 120 °C for 48 h (TLC System: 50% Ethyl acetate in Petether, R_f: 0.4, UV active). The reaction mixture was diluted with water (300 mL), extracted with EtOAc (3x 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. LCMS (*m/z*): 226.13 $[M+H]^+$.

Synthesis of (*R*)-2-chloro-5-((2, 2-dimethyl-1, 3-dioxolan-4-yl) methoxy)pyrazine



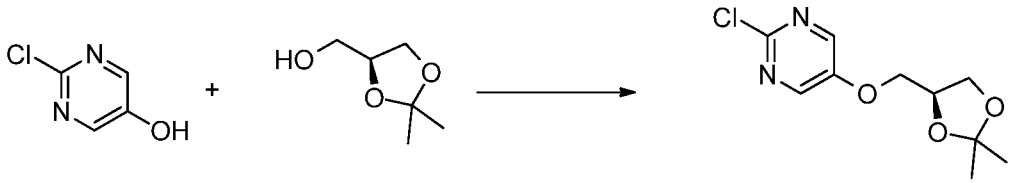
To a stirred suspension of cesium carbonate (32.8 g, 101 mmol) in DMF (100 mL) was added (*R*)-(2,2-dimethyl-1,3-dioxolan-4-yl) methanol (8.87 g, 67.1 mmol) at 0 °C and stirred at room temperature for 30 min. Then 2,5-dichloropyrazine (10 g, 67.1 mmol) was added and the resulting reaction mixture was stirred at 100 °C for 4 h. (TLC System: 20% Ethyl acetate in Hexane, R_f: 0.5, UV active). The reaction mixture was diluted with ice cold water (200 mL), extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with water (2x50 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



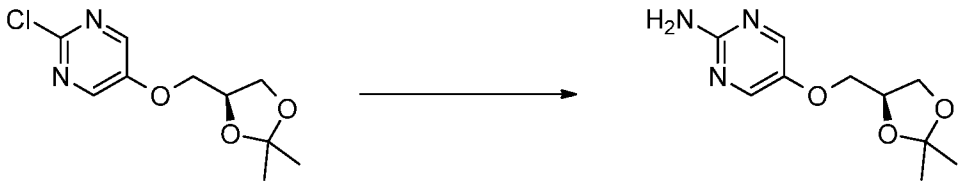
To a stirred solution of (*R*)-2-chloro-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazine (8 g, 32.7 mmol) in Tetrahydrofuran (10 mL) was added ammonium hydroxide (400 mL, 2568 mmol) and copper(II) sulfate (1.044 g, 6.54 mmol) in a sealed tube and the reaction mixture was stirred at 120 °C for 48 h. (TLC System: 50% Ethyl acetate in Hexane, R_f: 0.4, UV active). The reaction mixture was diluted with water (200 mL), extracted with EtOAc (3x 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



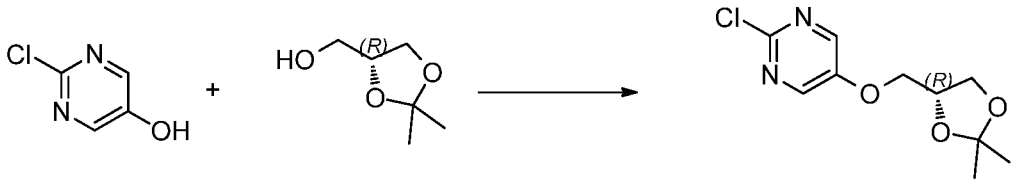
To a stirred solution of 2-chloropyrimidin-5-ol (13 g, 100 mmol) in THF (100 mL) at 0 °C was added (*S*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (13.16 g, 100 mmol), triphenylphosphine (32.7 g, 124 mmol) followed by DEAD (19.71 mL, 124 mmol) and reaction was stirred at RT for 4 h. (TLC eluting system: 30% EtOAc in pet ether; R_f-0.5; UV active). The reaction mixture was quenched with water (50 mL) and extracted into EtOAc (2x75 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 (20g, 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



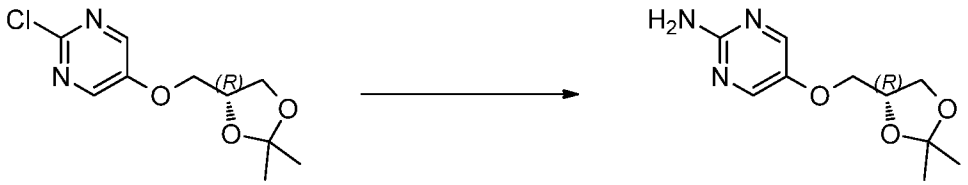
A mixture of (*S*)-2-chloro-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidine (10 g, 40.9 mmol) and aq.ammonia (66.3 ml, 1226 mmol) in a sealed tube was heated at 120 °C for 24 h. (TLC eluting system: 100% EtOAc; R_f-0.2; UV active). The reaction mixture was cooled to RT, quenched with water (50 mL) and extracted into EtOAc (2x75 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 (6.6g, 28.6 mmol, 70.0 % yield) as an off white solid. LCMS (*m/z*): 226.17; $[M+H]^+$.

Synthesis of (*R*)-2-chloro-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidine



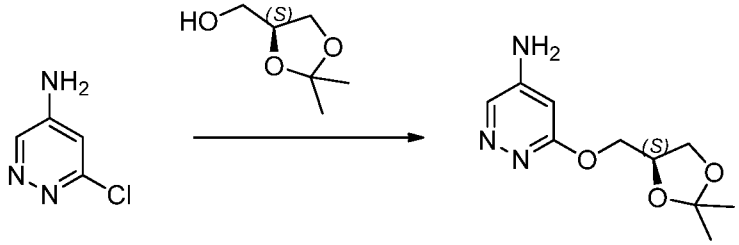
To a stirred solution of 2-chloropyrimidin-5-ol (20 g, 153 mmol) in THF (100 mL) at 0 °C was added (*R*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (24.30 g, 184 mmol), triphenylphosphine (50.2 g, 192 mmol) followed by DEAD (30.3 mL, 192 mmol) and the reaction was stirred at RT for 12 h. (TLC eluting system: 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



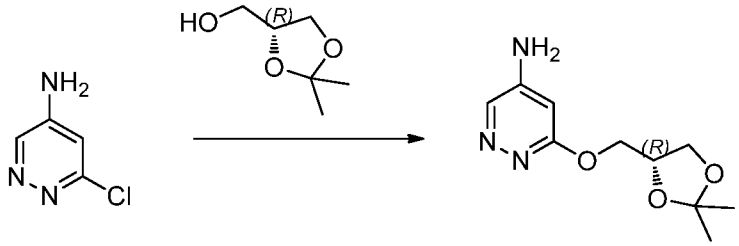
A mixture of (*R*)-2-chloro-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidine (5 g, 20.44 mmol) and aq.ammonia (50 ml, 924 mmol) in a sealed tube was heated 120 °C for 48 h. (TLC eluting system: 100% EtOAc; R_f-0.2; UV active). The reaction mixture was cooled to RT, quenched with water (50 mL) and extracted into DCM (2x75 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



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 (2x80 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 $[M+H]^+$.

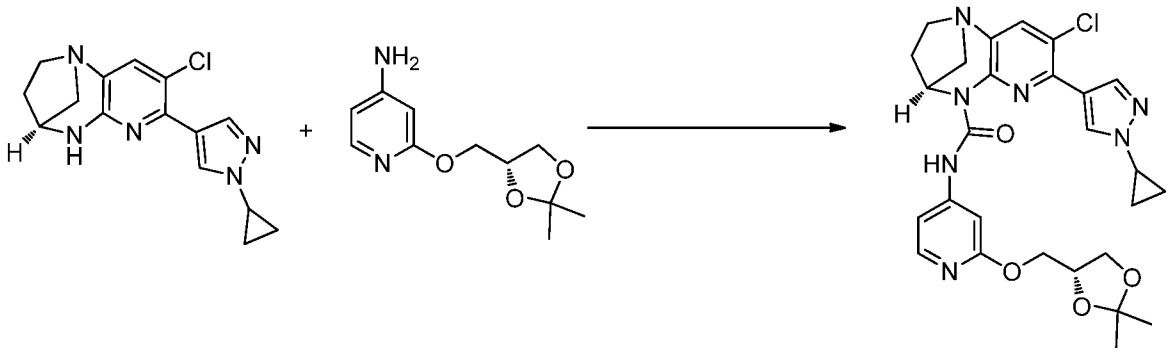
Synthesis of (*R*)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridazin-4-amine



To a stirred suspension of potassium tert-butoxide (7.80 g, 69.5 mmol) in1,4-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 (2x80 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

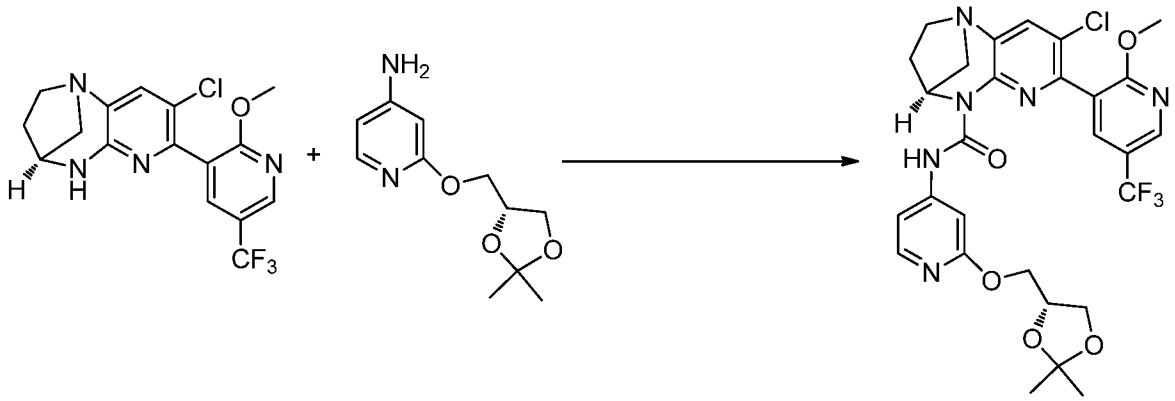
crude compound. The crude product was purified by flash column chromatography (Neutral alumina, Eluent: 65% Ethyl acetate in Pet ether) to afford the desired product (*R*)-6-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridazin-4-amine (2.2 g, 9.66 mmol, 41.7 % yield) as an off white solid. LCMS (*m/z*): 226.05 $[M+H]^+$, *Rt* = 1.00 min.

(4S)-8-chloro-7-(1-cyclopropyl-1H-pyrazol-4-yl)-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



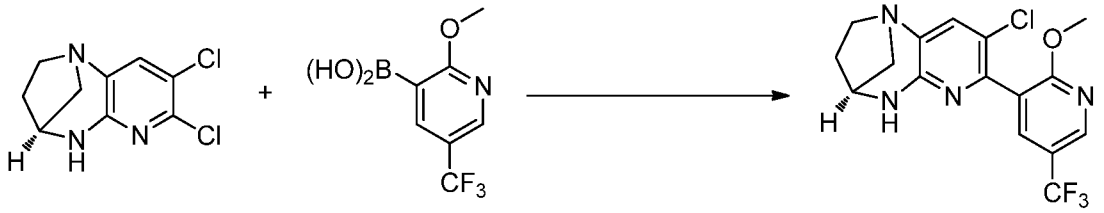
(4S)-8-chloro-7-(1-cyclopropyl-1H-pyrazol-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (400 mg, 1.325 mmol) was dissolved in Tetrahydrofuran (THF) (30 mL) stirred under nitrogen at 0 °C were added triphosgene (393 mg, 1.325 mmol), TEA (0.924 mL, 6.63 mmol). The reaction mixture was stirred for 30 min at room temperature. To this (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (297 mg, 1.325 mmol) was added and stirred for 16 h at 80 °C in a sealed tube. The reaction mixture allowed to room temperature and quenched with 50 ml of water and extracted with 2x150 ml of ethyl acetate, The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain Crude. The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh) and was eluted with 2% MeOH-DCM to afford (4S)-8-chloro-7-(1-cyclopropyl-1H-pyrazol-4-yl)-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (210 mg, 0.377 mmol, 28.4 % yield), LCMS (*m/z*): 552.10 $[M+H]^+$.

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



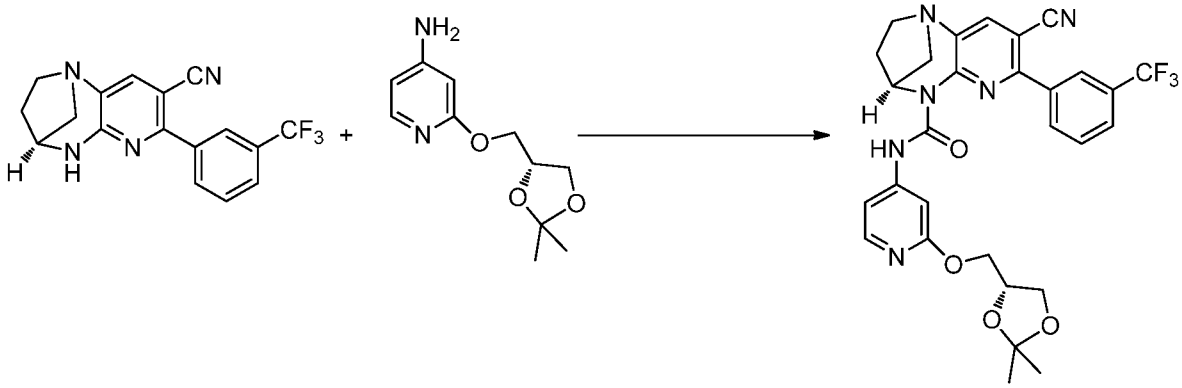
To a stirred solution of (4S)-8-chloro-7-(2-methoxy-5-(trifluoromethyl)pyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (550 mg, 1.483 mmol) in Tetrahydrofuran (THF) (50 mL) were added TEA (1.241 mL, 8.90 mmol) and triphosgene (440 mg, 1.483 mmol) at 25 °C and stirred for 1 hr then (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (665 mg, 2.97 mmol) was added and heated at 65 °C for 15 hr. The reaction mixture was cooled to room temperature, concentrated under vacuum and the residue was partitioned between water (20 mL) and DCM (2X30 mL). Organic layer was separated and dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude compound. 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 81 % 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 (4S)-8-chloro-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(2-methoxy-5-(trifluoromethyl)pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (400 mg, 0.597 mmol, 40.2 % yield) as an off-white solid, LCMS (*m/z*): 621.22 $[M+H]^+$.

(4S)-8-chloro-7-(2-methoxy-5-(trifluoromethyl)pyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine



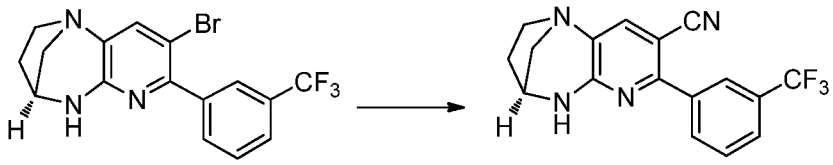
To a stirred solution of (4S)-7,8-dichloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1.0 g, 4.35 mmol), (2-methoxy-5-(trifluoromethyl)pyridin-3-yl)boronic acid (1.152 g, 5.22 mmol) and Cs_2CO_3 (4.25 g, 13.04 mmol) in 1,4-Dioxane (10 mL) & Water (1 mL) at room temp and the reaction mixture was degassed with argon at room temp for 15 mins. $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.355 g, 0.435 mmol) was added to the reaction mixture. Then the reaction mixture was stirred 110 °C for 16 hr. The reaction was monitored by TLC. The reaction mixture was cooled to room temp and filtered through celite and washed with EtOAc. Take filtrate and concentrated and dissolved with EtOAc. EtOAc layer washed with water followed by brine solution and dried out with Na_2SO_4, filtered and concentrated 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 72 % 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 (4S)-8-chloro-7-(2-methoxy-5-(trifluoromethyl)pyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (650 mg, 1.578 mmol, 36.3 % yield) as a brown color solid, LCMS (*m/z*): 371.45 $[M+H]^+$.

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



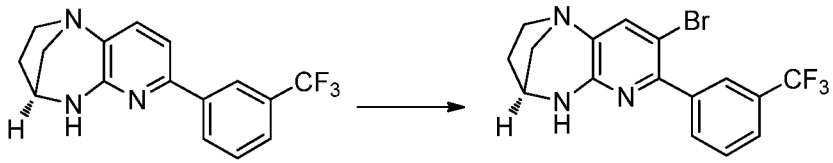
To a stirred solution of (4S)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine-8-carbonitrile (300 mg, 0.908 mmol) in Tetrahydrofuran (THF) (30 mL) were added TEA (0.760 mL, 5.45 mmol) and triphosgene (270 mg, 0.908 mmol) at 25 °C and stirred for 1 hr then (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (407 mg, 1.816 mmol) was added and heated at 65 °C for 15 hr. The reaction mixture was cooled to room temperature, concentrated under vacuum and the residue was partitioned between water (20 mL) and DCM (2X30 mL). Organic layer was separated and dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude compound. The crude product was combined with another batch of the same material and 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 84 % 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 (4S)-8-cyano-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (250 mg, 0.381 mmol, 41.9 % yield) as an off-white solid, LCMS (*m/z*): 581.23 $[M+H]^+$.

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



To a stirred solution of (4S)-8-bromo-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.301 mmol), $Zn(CN)_2$ (764 mg, 6.51 mmol) and $Zn(OAc)_2$ (287 mg, 1.562 mmol) in N,N-Dimethylformamide (DMF) (20 mL) at room temp. and the reaction mixture was degassed with argon at room temp for 15 mins.$Pd_2(dba)_3$ (238 mg, 0.260 mmol) & DPPF (289 mg, 0.521 mmol) was added to the reaction mixture. Then the reaction mixture was stirred 110 °C for 16 hr. The reaction was monitored by TLC. The reaction mixture was cooled to room temp and filtered through celite and washed with EtOAc. Take filtrate and concentrated and dissolved with EtOAc. EtOAc layer washed with water followed by brine solution and dried out with Na_2SO_4, filtered and concentrated 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 60 % 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 (4S)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine-8-carbonitrile (350 mg, 1.016 mmol, 78 % yield) as an off-white solid, LCMS (*m/z*): 331.11 $[M+H]^+$.

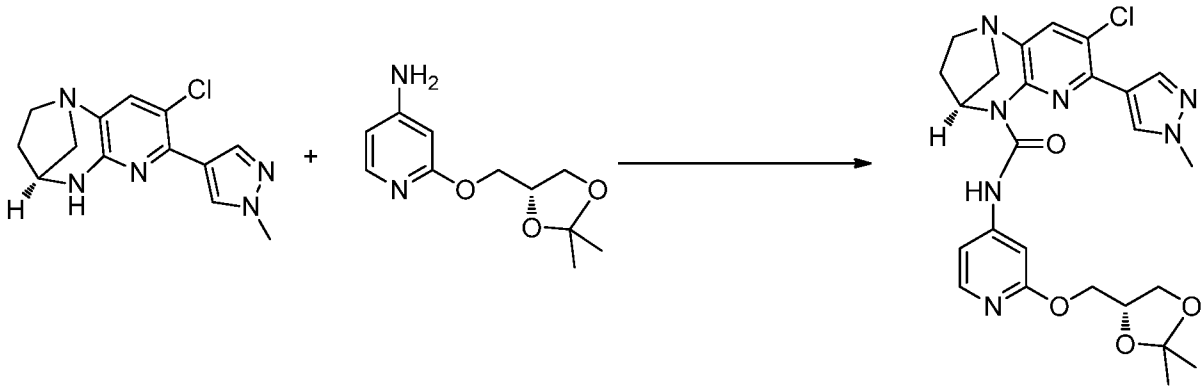
Synthesis of (4S)-8-bromo-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine



To a stirred solution of (4S)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1 g, 3.28 mmol) in Chloroform (15 mL) were added NBS (0.758 g, 4.26 mmol) lot wise at 0 °C and stirred for 5 hr at 30 °C. The reaction mixture was concentrated under vacuum and the residue was partitioned between water (20

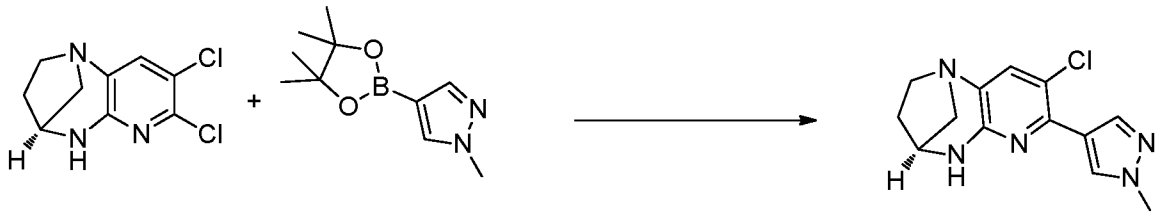
mL) and DCM (2X20 mL). Organic layer was separated and dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford pure (4S)-8-bromo-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (0.800 g, 2.025 mmol, 61.8 % yield) as an off-white solid, LCMS (*m/z*): 384.07 $[M+H]^+$.

Synthesis of (4S)-8-chloro-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



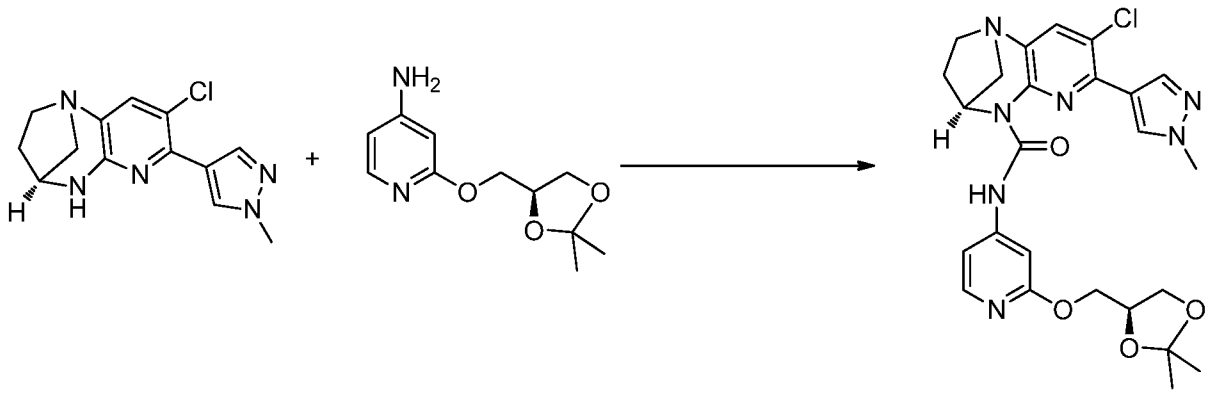
To a solution of (4S)-8-chloro-7-(1-methyl-1H-pyrazol-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (440 mg, 1.596 mmol) in Tetrahydrofuran (THF) (10 mL) at 25 °C were added TEA (1.112 mL, 7.98 mmol) followed by triphosgene (474 mg, 1.596 mmol) were added, stirred for 1h and (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (358 mg, 1.596 mmol) was added and heated at 80 °C for 15h. The reaction mixture was cooled to 28 °C and was partitioned between water (100 mL) and EtOAc (2 X 100 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 using neutral alumina and 1-2% of MeOH in DCM as an eluent to afford (4S)-8-chloro-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (330 mg, 0.593 mmol, 37.1 % yield), LCMS (*m/z*): 526.18 $[M+H]^+$.

Synthesis of (4S)-8-chloro-7-(1-methyl-1H-pyrazol-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine



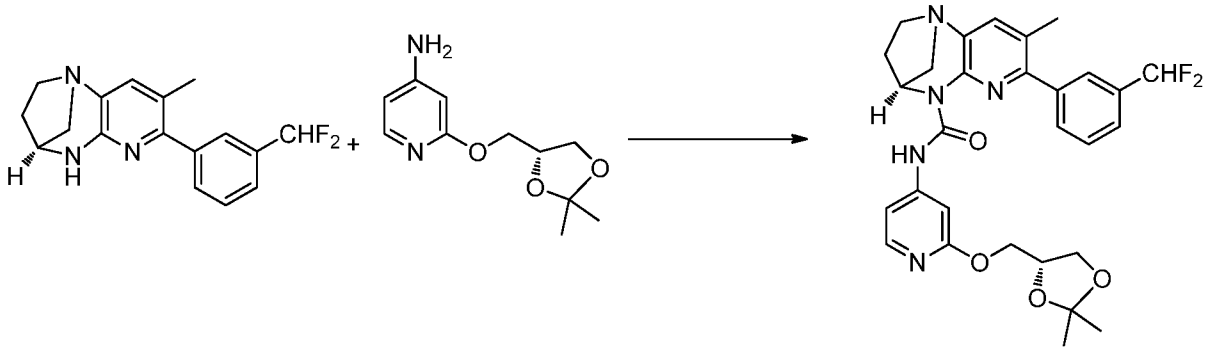
To a solution of (4S)-7,8-dichloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (4.300 g, 18.69 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (4.67 g, 22.43 mmol) in 1,4-Dioxane (100.0 mL) and Water (25.00 mL) Cs_2CO_3 (18.27 g, 56.1 mmol) was added at RT and degassed for 20 min. Then $PdCl_2(dppf)$-CH_2Cl_2 adduct (1.526 g, 1.869 mmol) was added to the reaction mixture at RT and again degassed for 10 mins. Then the reaction mixture was stirred to 110 °C for 16 h (TLC eluent: 10% MeOH/ethyl acetate R_f:0.3; UV active). Reaction mixture was cooled to RT, diluted with water (100 mL), extracted with ethyl acetate (2X 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to afford crude product. The crude product was purified by column chromatography using 100-200 mesh silica gel and 0-15% of Methanol in DCM as an eluent. Collected fractions were concentrated under reduced pressure to afford (4S)-8-chloro-7-(1-methyl-1H-pyrazol-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1.5 g, 3.41 mmol, 18.27 % yield). The purity of the product is 62.76% and it showed 34.97% of starting material. LCMS (*m/z*): 276.53 $[M+H]^+$.

Synthesis of (4S)-8-chloro-N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



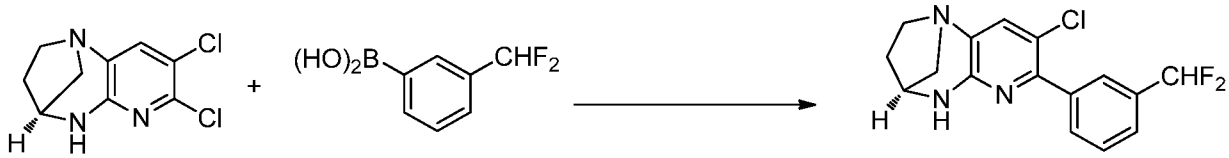
To a solution of (4S)-8-chloro-7-(1-methyl-1H-pyrazol-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (700 mg, 2.54 mmol) in Tetrahydrofuran (THF) (100 mL) at 25 °C were added TEA (1.769 mL, 12.69 mmol) followed by triphosgene (753 mg, 2.54 mmol)were added, stirred for 1h and (S)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (569 mg, 2.54 mmol) was added and heated at 80 °C for 15h. The reaction mixture was cooled to 28 °C and was partitioned between water (100 mL) and EtOAc (2 X 100 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 using 100-200 mesh silica gel and 2-6% of MeOH in DCM as an eluent to afford (4S)-8-chloro-N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (350 mg, 0.659 mmol, 26.0 % yield) as an light brown colored solid, LCMS (*m/z*): 526.29 $[M+H]^+$.

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



To solid (4S)-7-(3-(difluoromethyl)phenyl)-8-methyl-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (400 mg, 1.327 mmol) in Tetrahydrofuran (THF) (5 mL) was added solid triphosgene (236 mg, 0.796 mmol), DIPEA (1.391 mL, 7.96 mmol) and stirred under nitrogen at room temp for 30 minutes. To this (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (476 mg, 2.124 mmol) was added sub sequentially under sealed tube condition at 75°C for 15 h 30mins. The reaction was monitored by TLC and LCMS. The reaction mixture was diluted with water (50 ml) and extracted with ethyl acetate (2 X 50 ml). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product. The crude was submitted for analysis, LCMS (*m/z*): 572.16 $[M+H]^+$.

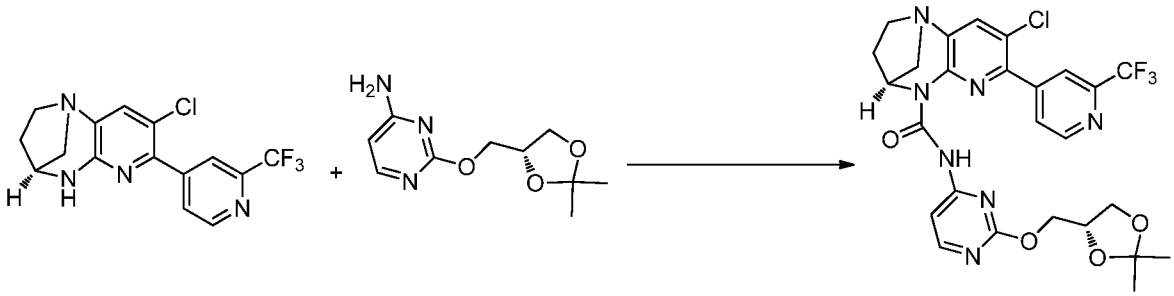
(4S)-8-chloro-7-(3-(difluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine



A suspension of (4S)-7,8-dichloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (400 mg, 1.738 mmol),(3-(difluoromethyl)phenyl)boronic acid (299 mg, 1.738 mmol) and potassium carbonate (721 mg, 5.22 mmol) in 1,4-Dioxane (10 mL) & Water (1.5 mL) stirred and degassed with argon at room temp for 15 mins, $PdCl_2$(dppf)-CH_2Cl_2 adduct (1420 mg, 1.738 mmol) was added to the reaction mixture. Then the reaction mixture was stirred 16 hr at 90 °C. The reaction mixture was cooled to room

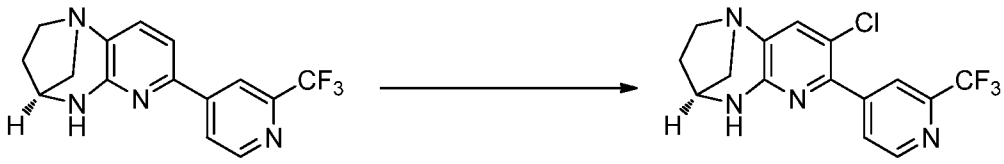
temp, and filtered through celite and washed with EtOAc (100 ml). Take filtrate and concentrated and dissolved with EtOAc (50 ml).EtOAc layer washed with water (100 ml) followed by brine solution (100 ml) and dried out with Na_2SO_4, filtered and concentrated to get crude product. The crude product was purified by column chromatography using silica gel(100-200) and was eluted with 50% EtOAc in Hexane (gradient system) to afford the desired product (4S)-8-chloro-7-(3-(difluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.554 mmol, 89 % yield) as a pale yellow solid, LCMS (*m/z*): 302.11 $[M+H]^+$.

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



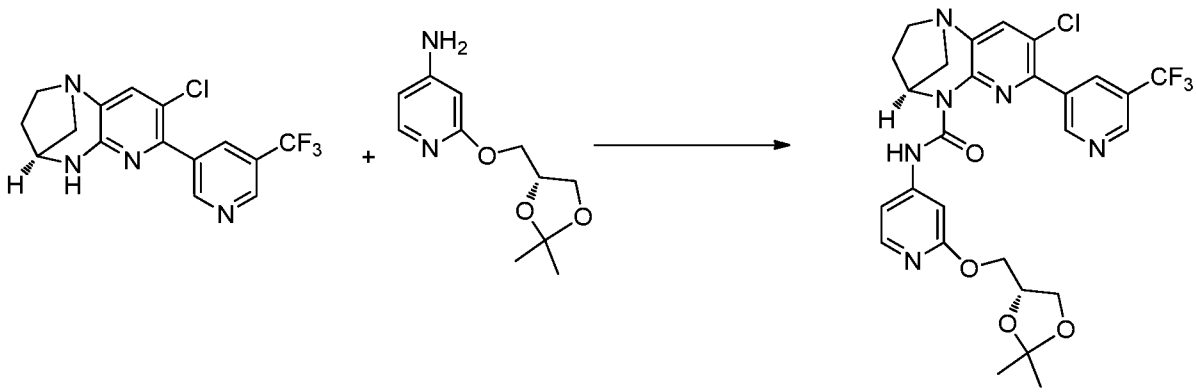
To a stirred solution of (4S)-8-chloro-7-(2-(trifluoromethyl)pyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (350 mg, 1.027 mmol) in Tetrahydrofuran (THF) (50 mL) and was added TEA (1.432 mL, 10.27 mmol) and triphosgene (610 mg, 2.054 mmol) at RT. The reaction mixture was stirred at RT for 1h. Then added (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (230 mg, 1.027 mmol) to reaction mixture. The resulting reaction mixture was stirred at 65 °C for 16 hr. The progress of the reaction was monitored by TLC, it showed the starting material was consumed. The reaction mixture was cool to RT and dilute with water(100ml) and extracted with ethyl acetate(2*60ml),the combined organic layers were washed with brine solution and dried over Na_2SO_4,filtered and evaporated under vacuum to get crude compound. The crude compound was purified by column chromatography by using Neutral alumina, eluted in (2:8)EtOAc & Hexane. The fractions were concentrated under vacuum to get (4S)-8-chloro-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(2-(trifluoromethyl)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (250 mg, 0.286 mmol, 27.8 % yield) as light yellow gummy, LCMS (*m/z*): 591.2 $(M+H)^+$.

(4S)-8-chloro-7-(2-(trifluoromethyl)pyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine



To a stirred suspension of (4S)-7-(2-(trifluoromethyl)pyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1.4 g, 4.57 mmol) in Chloroform (20 mL) stirred under nitrogen at 0°C was added NCS (0.610 g, 4.57 mmol). The reaction mixture was stirred at RT for 12h. The reaction mixture was dilute with water (100ml) and extracted with EtOAc(2*100ml),combined organics were washed with brine solution and dried over Na_2SO_4,filtered and evaporated under vacuum to get crude compound. The crude compound was purified by column chromatography by using Neutral alumina ,eluted in (1:9)EtOAc & Hexane. The fractions were evaporated under vacuum to get (4S)-8-chloro-7-(2-(trifluoromethyl)pyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (700 mg, 1.883 mmol, 41.2 % yield) as gummy compound, LCMS (*m/z*): 340.97 $(M+H)^+$.

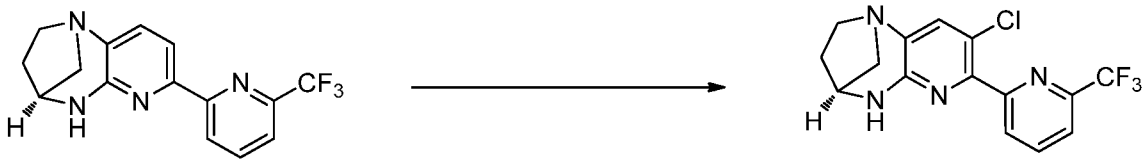
Synthesis of (4S)-8-chloro-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(5-(trifluoromethyl)pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



To a stirred solution of(4S)-8-chloro-7-(5-(trifluoromethyl)pyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (300 mg, 0.880 mmol) in THF (15 mL) was added TEA (0.736 mL, 5.28 mmol) and triphosgene (261 mg, 0.880 mmol) under nitrogen at 0 °C in a sealed tube. Stirred the reaction mixture at 25°C for 1hr. Then added (R)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-amine (395 mg, 1.761 mmol) to the reaction mass at 0° C and heated the reaction to 70°C, maintained it at 70°C for 16

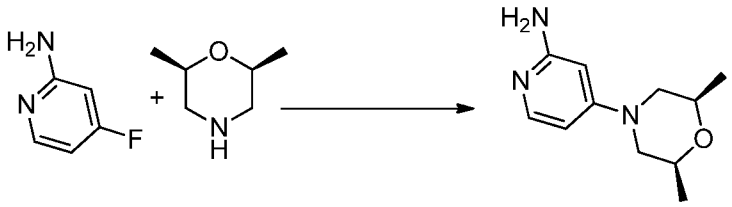
hr. Reaction mixture was cooled to room temperature, water (50 mL) was added and extracted with EtOAc(2x40mL). The combined organic layers were washed with brine solution (50mL), organic layer was dried over Na_2SO_4 and concentrated it to get crude compound. The Crude compound was purified by column chromatography (C-18: eluted with 65% ACN in 1% aq ammonium bicarbonate to afford(4S)-8-chloro-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(5-(trifluoromethyl)pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (185 mg, 0.313 mmol, 35.6 % yield) as an pale yellow solid, LCMS (*m/z*): 591.20 $[M+H]^+$.

Synthesis of (4S)-8-chloro-7-(6-(trifluoromethyl)pyridin-2-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine



To a stirred solution of (4S)-7-(6-(trifluoromethyl)pyridin-2-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (150 mg, 0.490 mmol) in Chloroform (10 mL) was added NCS (65.4 mg, 0.490 mmol)under nitrogen at 0 ºC. Reaction was allowed to RT and maintained it at 25° C for 16 hr. Reaction mixture was quenched with water (20mL) and extracted with EtOAc(2x30mL).The combined organic layers were washed with brine solution(50mL),organic layer was dried over Na_2SO_4 and concentrated it to get crude compound. The crude product was added to a silica gel (60-120) column and was eluted with 50%EtOAC-Petether. Collected fractions were concentrated to get (4S)-8-chloro-7-(6-(trifluoromethyl)pyridin-2-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (60 mg, 0.154 mmol, 31.4 % yield) as a pale yellow solid, LCMS (*m/z*): 341.15 $[M+H]^+$.

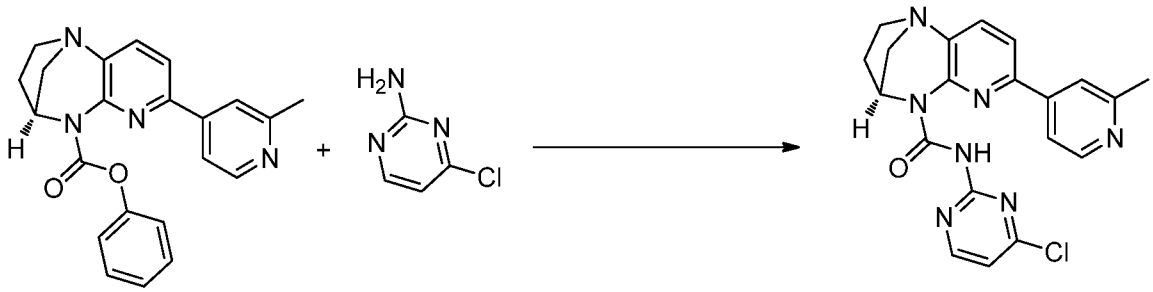
Synthesis of 4-((2S,6R)-2,6-dimethylmorpholino)pyridin-2-amine



To a suspension of 4-fluoropyridin-2-amine (2.0 g, 17.84 mmol) in (2S,6R)-2,6-dimethylmorpholine (4.11 g, 35.7 mmol) was added potassium carbonate (7.40 g, 53.5

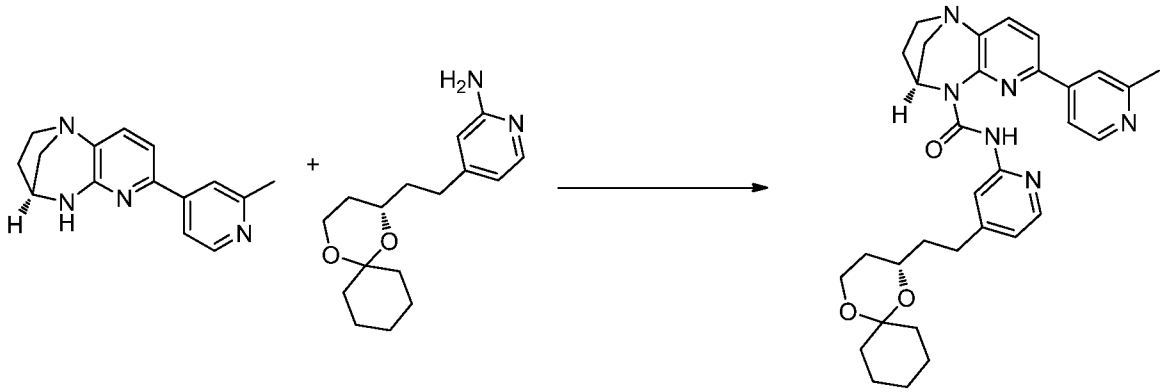
mmol), copper(I) iodide (0.340 g, 1.784 mmol) and N,N'-dimethylethylenediamine (0.315 g, 3.57 mmol) at rt. The resulting reaction mixture was stirred in microwave at 110 °C for 1 hr (TLC system: 10% MeOH in DCM, R_f-:0.1; UV active). The reaction mixture quenched in ice water(20 mL) and extracted with EtOAc(3X40 mL). The combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4, filtered and evaporated to get crude compound. The crude compound was purified by column chromatography using neutral alumina and eluted at 50% EtOAc in pet ether to afford 4-((2S,6R)-2,6-dimethylmorpholino)pyridin-2-amine (1.0 g, 4.72 mmol, 26.4 % yield) as an pale yellow solid, LCMS (*m/z*): 208.05 $[M+H]^+$.

Synthesis of (4S)-N-(4-chloropyrimidin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



To a stirred solution of 4-chloropyrimidin-2-amine (2.61 g, 20.14 mmol) in Tetrahydrofuran (THF) (60 mL) at -78 °C was added LiHMDS (67.1 mL, 67.1 mmol) and stirred for 1 hr at -78 °C, then (4S)-phenyl 7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxylate (5 g, 13.43 mmol) was added and stirred at 25 °C for 18 hr. The reaction mixture was partitioned between water (50 mL) and EtOAc (800 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude. The residue was triturated with diethyl ether (3 x 30 mL). The resulting solid was filtered to afford (4S)-N-(4-chloropyrimidin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (2.1 g, 4.86 mmol, 36.2 % yield) as pale yellow solid, LCMS (*m/z*): 408.17 $[M+H]^+$.

(4S)-N-(4-(2-((S)-1,4-dioxaspiro[4.5]decan-2-yl)ethyl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

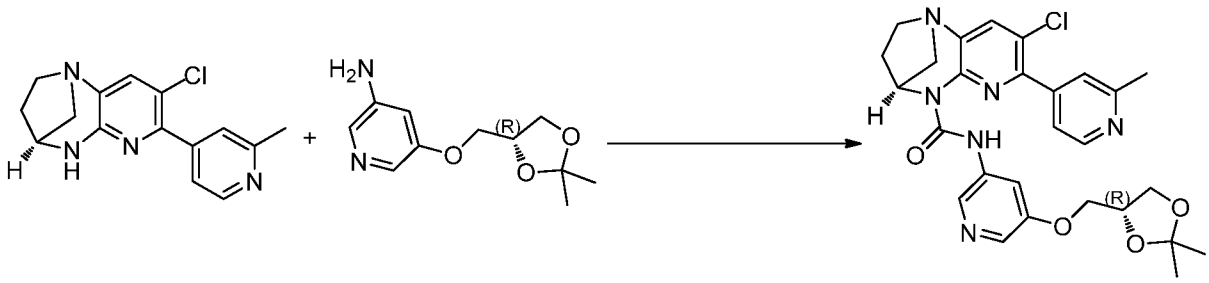


To a stirred solution of (4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (0.962 g, 3.81 mmol) in Tetrahydrofuran (THF) (40 mL) was added triphosgene (0.905 g, 3.05 mmol) and TEA (1.594 mL, 11.44 mmol) at room temperature under Nitrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 1 hr. To the reaction mixture was added a solution of (S)-4-(2-(1,4-dioxaspiro[4.5]decan-2-yl)ethyl)pyridin-2-amine (1.0 g, 3.81 mmol) in Tetrahydrofuran (THF) (20 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 (50 mL), extracted with EtOAc (3 X 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 obtained crude compound. The crude was purified by column chromatography (100-200 mesh silica gel, eluent 4% MeOH in DCM) to afford (4S)-N-(4-(2-((S)-1,4-dioxaspiro[4.5]decan-2-yl)ethyl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (800 mg, 1.219 mmol, 32.0 % yield) as a brown solid, LCMS (*m/z*): 541.27 $[M+H]^+$.

Synthesis of (1H-imidazol-1-yl)((4S)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepin-5(2H)-yl)methanone

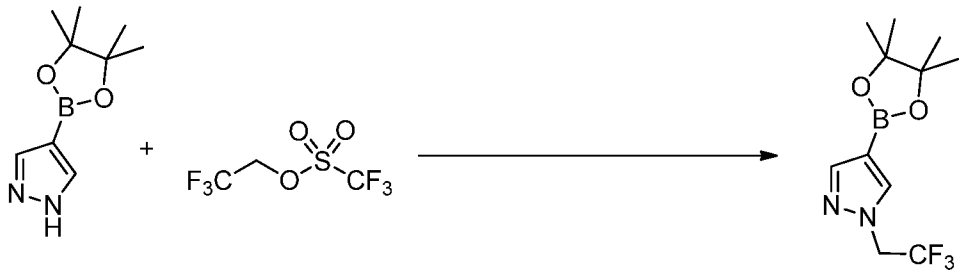
TEA (1.370 mL, 9.83 mmol) was added to a stirred solution was (4S)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1 g, 3.28 mmol) in Tetrahydrofuran (THF) (40 mL) at 28°C. The reaction mixture was stirred for1 h at 28°C. CDI (1.062 g, 6.55 mmol) was added the reaction mixture, and was stirred for 12h at 60 °C. The reaction mixture was cooled to 28 °C and was partitioned between water (20 mL) and EtOAc (2X 35 mL). EtOAc layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford crude. The crude was purified by washing with diethyl ether (2X 25 mL) to afford pure (1H-imidazol-1-yl)((4S)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepin-5(2H)-yl)methanone (850 mg, 2.097 mmol, 64.0 % yield) as Off white solid. LCMS (*m/z*): 400.30 $[M+H]^+$.

Synthesis of (4S)-8-chloro-N-(5-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



(4S)-8-chloro-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (0.5 g, 1.744 mmol), triethylamine (1.458 mL, 10.46 mmol) were taken in Tetrahydrofuran (THF) (20 mL) at 0 °C, the resulting yellow solution was stirred for 10 min. Then added triphosgene (0.517 g, 1.744 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 (0.391 g, 1.744 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 Na_2SO_4 filtered, concentrated under reduced pressure to afford brown viscous oil. The crude reaction mass was taken into next step without any purification, LCMS (*m/z*): 537.00 $[M+H]^+$.

Synthesis of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoroethyl)-1H-pyrazole

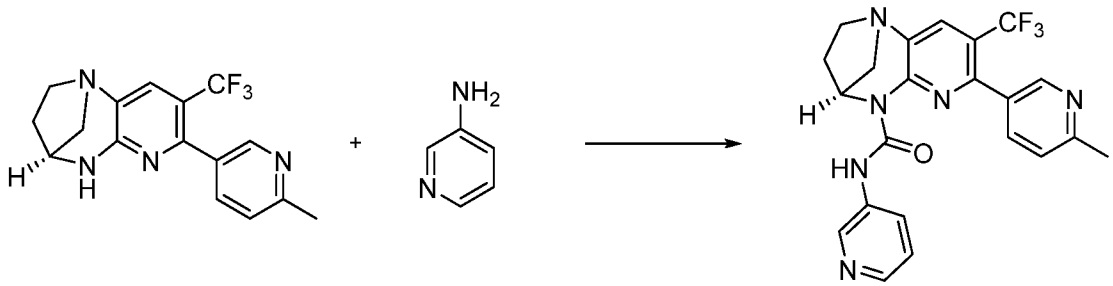


To a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (5.0 g, 25.8 mmol) in N,N-Dimethylformamide (DMF) (50 mL) and was added Cs2CO3 (16.79 g, 51.5 mmol) at RT and 2,2,2-trifluoroethyl trifluoromethanesulfonate (4.45 mL, 30.9 mmol) added drop wise at RT.The reaction mixture was stirred at 100 °C for 3 hr. The reaction mixture was diluted with water(100 mL) and extracted with EtOAc (2 X 100 mL), the combined organics were washed with cold water(3 X 100ml) and brine solution (100ml) and dried over Na_2SO_4,filtered and evaporated under vacuo to get 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoroethyl)-1H-pyrazole (1.8 g, 3.39 mmol, 13.16 % yield) as an off white gummy liquid

COMPOUND EXAMPLES

Example 1

Synthesis of (4*S*)-7-(6-methylpyridin-3-yl)-*N*-(pyridin-3-yl)-8-(trifluoromethyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



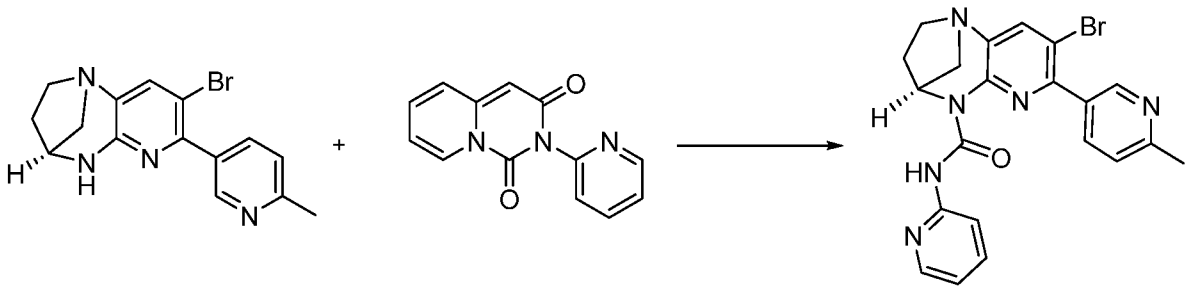
To a solution of (4*S*)-7-(6-methylpyridin-3-yl)-8-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (200 mg, 0.624 mmol), triphosgene (111 mg, 0.375 mmol) in tetrahydrofuran (10 mL) were added solid of pyridin-3-amine (88 mg, 0.937 mmol) and DIPEA (242 mg, 1.873 mmol) at 0 °C and stirred it for 30 min. The reaction mixture was heated to 75 °C for 16 h in sealed tube. Allowed to cool to room temperature and was poured in to saturated $NaHCO_3$ solution (100 mL) and extracted with ethyl acetate

(3x50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure to obtain the crude compound, which was purified by flash column chromatography to afford (4*S*)-7-(6-methylpyridin-3-yl)-*N*-(pyridin-3-yl)-8-(trifluoromethyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (127 mg, 45.3% yield) as an off white solid (TLC: eluent, 5% methanol in ethyl acetate; R_f = 0.3), LCMS (*m/z*): 441.23 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.67 (s, 1 H), 8.69 (d, *J*=2.19 Hz, 2 H), 8.37-8.16 (m, 4 H), 8.03 (ddd, *J*=8.33, 2.63, 1.53 Hz, 2 H), 7.89 (s, 2 H), 7.76 (dd, *J*=8.00, 2.30 Hz, 2 H), 7.32 (d, *J*=7.89 Hz, 2 H), 7.27-7.20 (m, 2 H), 5.70 (dd, *J*=5.81, 3.18 Hz, 2 H), 3.38-3.12 (m, 4 H), 3.11-3.02 (m, 2 H), 2.68 (s, 6 H), 2.37 (dddd, *J*=14.20, 10.03, 6.03, 4.17 Hz, 2 H), 2.24-2.01 (m, 2 H).

Example 2

Synthesis of (4*S*)-8-bromo-7-(6-methylpyridin-3-yl)-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methano pyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



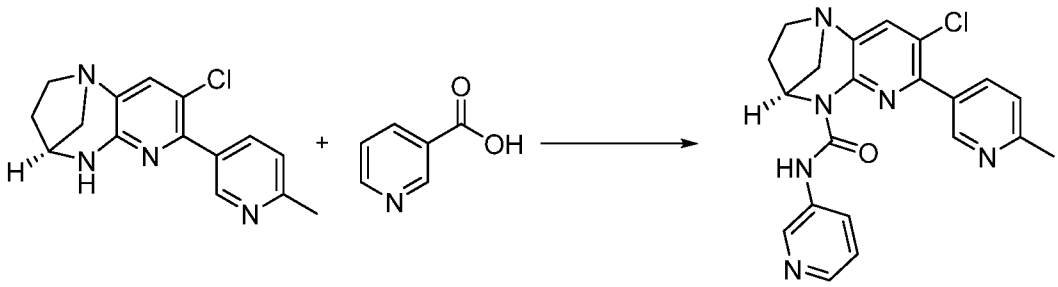
To a stirred solution of (4*S*)-8-bromo-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diaze pine (350 mg, 1.057 mmol) in THF (20 mL) was added NaH (38.0 mg, 1.585 mmol) at 0 °C. Then the reaction mixture was stirred at 30 °C for 1h and added 3-(pyridin-2-yl)-2*H*-pyrido[1,2-a][1,3,5]triazine-2,4(3*H*)-dione (305 mg, 1.268 mmol). The reaction mixture was stirred at 70 °C for 15 h. Allowed to cool to RT and the reaction mixture was poured in to the cold water (20 mL) and extracted with ethyl acetate (2X20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtained the crude compound. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 3% MeOH in EtOAc) and obtained 500 mg with 90% purity by LCMS. The semi pure compound was purified by prep HPLC (Column: XS PHENYL HEXYL(250 X4.6mm, 5µ), Mobile Phase: A: 0.01 M Ammonium Bicarbonate B: ACN, Gradient: Time/ %B: 0/10, 1/10, 10/50, 15/50, 18/98, 20/98, 20.1/10, 25/10, Column Temp: Ambient, Flow

Rate:1.0ml/min, Diluent: ACN) to afford (4*S*)-8-bromo-7-(6-methylpyridin-3-yl)-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methano pyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (275 mg, 0.61 mmol, 47% yield) as an off white solid (TLC: 10% MeOH in Ethyl acetate, R_f: 0.5), LCMS (*m/z*): 451.13 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.89 (s, 1 H), 8.88 (d, *J*=2.19 Hz, 1 H), 8.32 (d, *J*=2.41 Hz, 1 H), 8.26 (dd, *J*=4.82, 1.32 Hz, 1 H), 8.04 (d, *J*=8.20 Hz 1 H), 7.83 (s, 1 H), 7.66 (t, *J*=7.20 Hz 1 H), 7.33 (d, *J*=7.89 Hz, 1 H), 6.98 (m, 1 H), 5.67 (dd, *J*=6.03, 3.18 Hz, 1 H), 3.49 (d, *J*=5.04 Hz, 1 H), 3.37 - 3.17 (m, 2 H), 3.02 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.67 (s, 3 H), 2.34 (dddd, *J*=14.14, 10.08, 6.03, 3.95 Hz, 1 H), 2.18 - 2.01 (m, 1 H).

Example 3

Synthesis of (4*S*)-8-chloro-7-(6-methylpyridin-3-yl)-*N*-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



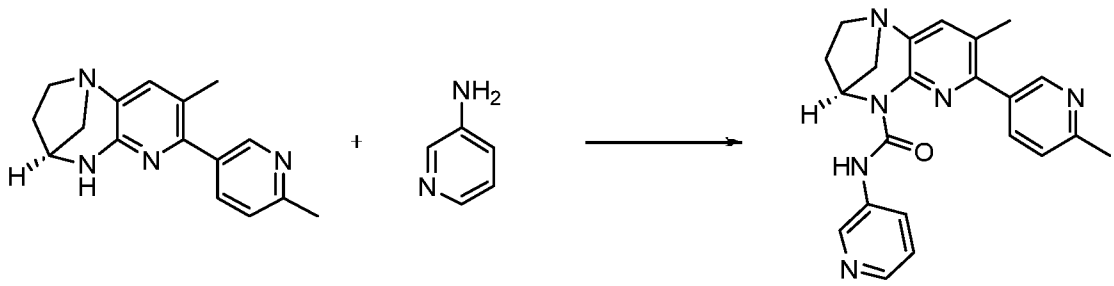
A solution of Nicotinic acid (180 mg, 1.465 mmol), DPPA (537 mg, 1.953 mmol) and triethylamine (0.680 mL, 4.88 mmol) in THF (20 mL) stirred at 30 °C for 2h and added (4*S*)-8-chloro-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (280 mg, 0.976 mmol). The reaction mixture was stirred at 70 °C for 14h. The reaction mixture was poured in to the cold water (50 mL) and extracted with ethyl acetate (2X30 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, eluent: 3% MeOH in EtOAc) to afford (4*S*)-8-chloro-7-(6-methylpyridin-3-yl)-*N*-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (90 mg, 0.22 mmol, 15% yield) as a white solid (TLC: 10% MeOH in Ethyl acetate, R_f: 0.3), LCMS (*m/z*): 407.25 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.63 (s, 1 H), 8.90 (d, *J*=1.97 Hz, 1 H), 8.36 (d, *J*=2.19 Hz, 1 H), 8.31 - 8.21 (m, 1 H), 8.21 - 8.02 (m, 1 H), 8.02 – 7.92 (m, 1 H), 7.66 (s, 1 H), 7.34 (d, *J*=8.11 Hz, 1 H), 7.27 - 7.21 (m, 1 H), 5.67 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.37 -

3.11 (m, 2 H), 3.11 – 2.92 (m, 2 H), 2.67 (s, 3 H), 2.42 - 2.22 (m, 1 H), 2.21 - 2.04 (m, 1 H).

Example 4

Synthesis of (4*S*)-7-(6-methylpyridin-3-yl)-*N*-(pyridin-3-yl)-8-(trifluoromethyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

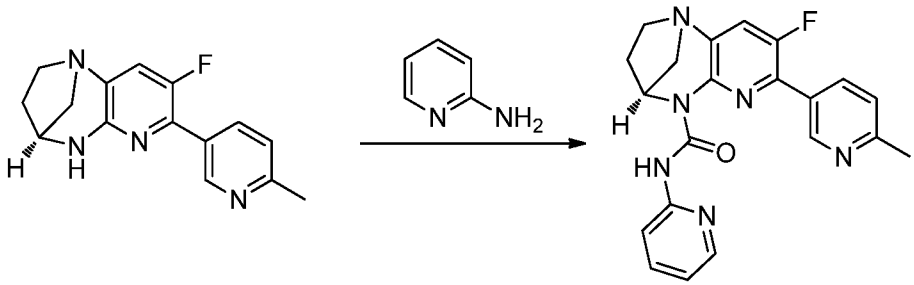


To a solution of (4*S*)-7-(6-methylpyridin-3-yl)-8-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (200 mg, 0.624 mmol) in THF (10 mL) was added triphosgene (111 mg, 0.375 mmol) at 0 °C and stirred at RT for 30 min. Then pyridin-3-amine (88 mg, 0.937 mmol) and DIPEA (242 mg, 1.873 mmol) were added. The reaction mixture was heated at 75 °C for 16 h in sealed tube. The reaction mixture was poured in to saturated $NaHCO_3$ solution (100 mL) and extracted with ethyl acetate (3X50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain semi pure compound. Which was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 3% MeOH in DCM) to afford (4*S*)-7-(6-methylpyridin-3-yl)-*N*-(pyridin-3-yl)-8-(trifluoromethyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (127 mg, 0.288 mmol, 45.3%) as an off white solid (TLC: R_f = 0.3, 5% methanol in ethyl acetate), LCMS (*m/z*): 441.23 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.67 (s, 1 H), 8.69 (d, *J*=2.19 Hz, 1 H), 8.37 - 8.16 (m, 2 H), 8.03 (ddd, *J*=8.33, 2.63, 1.53 Hz, 1 H), 7.89 (s, 1 H), 7.76 (dd, *J*=8.00, 2.30 Hz, 1 H), 7.32 (d, *J*=7.89 Hz, 1 H), 7.27 - 7.20 (m, 1 H), 5.70 (dd, *J*=5.81, 3.18 Hz, 1 H), 3.38 - 3.12 (m, 3 H), 3.02-3.11 (m, 1 H), 2.68 (s, 3 H), 2.39 (s, 3 H), 2.37 (dddd, *J*=14.20, 10.03, 6.03, 4.17 Hz, 1 H), 2.24 - 2.01 (m, 1 H).

Example 5

Synthesis of (4*S*)-8-fluoro-7-(6-methylpyridin-3-yl)-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

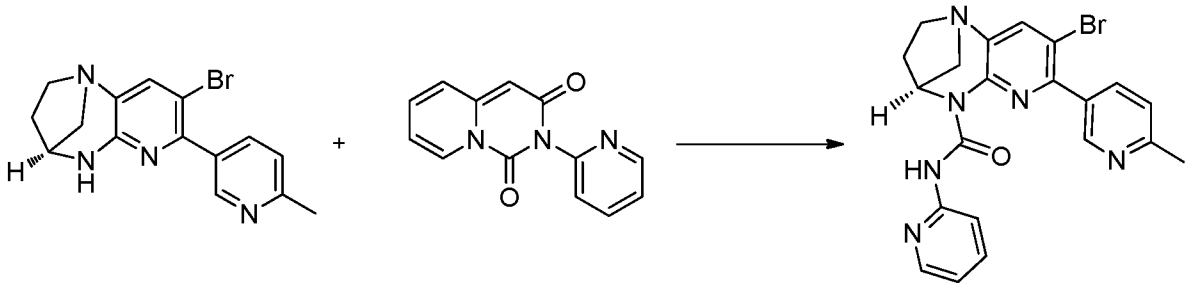


Triethylamine (0.516 mL, 3.70 mmol) followed by triphosgene (220 mg, 0.740 mmol) were added to a stirred solution of (4*S*)-8-fluoro-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (200 mg, 0.740 mmol) in Tetrahydrofuran (THF) (15 mL, in sealed tube) at RT and stirred for 30 min then pyridin-2-amine (84 mg, 0.888 mmol) was added and heated at 80 °C for 15 h. The reaction mixture was cooled to room temperature and was partitioned between water (25 mL) and EtOAc (40 mL), organic layer was separated and dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to obtain the crude compound. The crude mixture was purified by prep HPLC (Mobile Phase-A: 10mM Ammonium Bicarbonate (Aq): Mobile Phase-B: Acetonitrile. Column: YMC packed (100x25)5µ: Method -T/%B: 0.1/50,9/50,9.1/100, 12/100, 12.1/50. Flow: 20ml/min. Solubility: THF+ACN+MeOH.) to afford the (4*S*)-8-fluoro-7-(6-methylpyridin-3-yl)-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (65 mg, 0.165 mmol, 22.33 % yield) as an off white solid (TLC eluent: Neat ethyl acetate R_f: 0.5), LCMS (*m/z*): 391.23 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:13.09 (s, 1 H), 9.18 (s, 1 H), 8.47 (dd, *J*=8.4, 2.41 Hz, 1 H), 8.36-8.34 (m, 1 H), 8.14 (d, *J*=7.6 Hz, 1 H), 7.71 – 7.66 (m, 1 H) 7.42 (d, *J*=10.4 Hz, 1 H), 7.35 (d, *J*= 8 Hz, 1 H), 5.68 (dd, *J*=6.03, 3.2 Hz, 2.8 Hz, 1 H), 7.01-6.96 (m, 1 H), 3.36-3.14 (m, 3 H), 3.02-2.88 (m, 1 H), 2.66 (s, 3 H), 2.30 -2.29 (m, 1 H), 2.10 – 2.04 (m, 1 H).

Example 6

Synthesis of (4*S*)-8-bromo-7-(6-methylpyridin-3-yl)-*N*-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

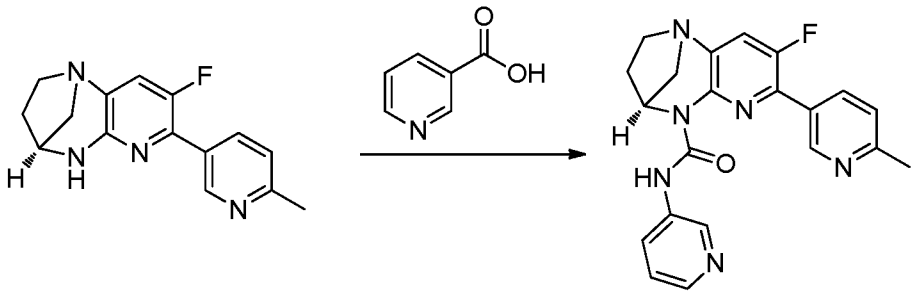


To a stirred solution of (4*S*)-8-bromo-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (250 mg, 0.755 mmol) in THF (10 mL) was added triphosgene (134 mg, 0.453 mmol) at 0 °C. Then the reaction mixture was stirred at 30 °C for 30 min and added pyridin-3-amine (142 mg, 1.510 mmol). The reaction mixture was stirred at 70 °C for 15 h. Allowed to cool to RT and the reaction mixture was poured in to the cold water (20 mL) and extracted with ethyl acetate (2X20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the crude compound. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 3% MeOH in EtOAc) to afford 500 mg with 90% purity by LCMS. The semi pure compound was purified by prep HPLC (Column: XS PHENYL HEXYL(250 X4.6mm, 5µ), Mobile Phase: A: 0.01 M Ammonium Bicarbonate B: ACN, Gradient: Time/ %B: 0/10, 1/10, 10/50, 15/50, 18/98, 20/98, 20.1/10, 25/10, Column Temp: Ambient, Flow Rate:1.0ml/min, Diluent: ACN) to obtain (4*S*)-8-bromo-7-(6-methylpyridin-3-yl)-*N*-(pyridin-3-yl)-3,4-dihydro-1,4-methano pyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide (195 mg, 0.413 mmol, 54.7 % yield) as a yellow solid (TLC: 10% MeOH in Ethyl acetate, R_f: 0.4), LCMS (*m/z*): 451.17 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.60 (s, 1 H), 8.88 (d, *J*=2.19 Hz, 1 H), 8.36 - 8.22 (m, 2 H), 8.12 - 8.02 (m, 1 H), 7.90 (dd, *J*=8.00, 2.30 Hz, 1 H), 7.83 (s, 1 H), 7.33 (d, *J*=7.89 Hz, 1 H), 7.22 (dd, *J*=8.44, 4.71 Hz, 1 H), 5.67 (dd, *J*=6.03, 3.18 Hz, 1 H), 3.39-3.09 (m, 3 H), 3.02 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.67 (s, 3 H), 2.34 (dddd, *J*=14.14, 10.08, 6.03, 3.95 Hz, 1 H), 2.18 - 2.04 (m, 1 H)

Example 7

Synthesis of (4*S*)-8-fluoro-7-(6-methylpyridin-3-yl)-*N*-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

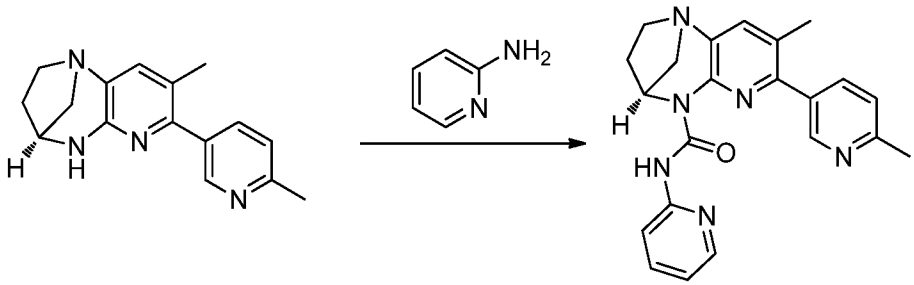


Triethylamine (0.516 mL, 3.70 mmol) followed by DPPA (407 mg, 1.480 mmol) were added to a stirred solution of nicotinic acid (109 mg, 0.888 mmol) in THF (10 mL) at RT after 2 h (4*S*)-8-fluoro-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*] [1,4] diazepine (200 mg, 0.740 mmol) was added and heated to 80 °C for 16 h. The reaction mixture was cooled to RT and was partitioned between water (25 mL) and EtOAc (30 mL), organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated under reduced pressure to obtain the crude compound. The crude mixture was purified by prep HPLC (Mobile Phase-A: 10mM Ammonium Bicarbonate (Aq): Mobile Phase-B: Acetonitrile Column: YMC packed (100x25)5µ: Method - T/%B: 0.1/40,9/40,9.1/100, 13/100, 13.1/40. Flow: 20ml/min Solubility: THF+ACN+MeOH) to afford the (4*S*)-8-fluoro-7-(6-methylpyridin-3-yl)-*N*-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (52 mg, 0.133 mmol, 17.93 % yield) as an off white solid (TLC eluent: 5% MeOH in DCM, Rf: 0.2), LCMS (*m/z*): 391.30 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$-*d*): δ ppm 12.65 (s, 1 H), 8.96 (s, 1 H), 8.48 (d, *J* = 2.4 Hz, 1 H), 8.28 (dd, *J*=4.6, 1.2 Hz, 1 H), 8.18 -8.14 (m, 1 H), 8.05-7.89 (m, 1 H), 7.44 (d, *J*=10 Hz, 1 H), 7.35 (d, *J*=8 Hz, 1 H), 7.28-7.22 (m, 1 H), 5.68 (dd, *J*= 6, 3.2 Hz, 1 H), 3.36-3.14 (m, 3H), 3.05 -3.00 (m, 1H), 2.66 (s, 3H), 2.39-2.31 (m, 1 H), 2.13-2.04 (m, 1 H).

Example 8

Synthesis of (4*S*)-8-methyl-7-(6-methylpyridin-3-yl)-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

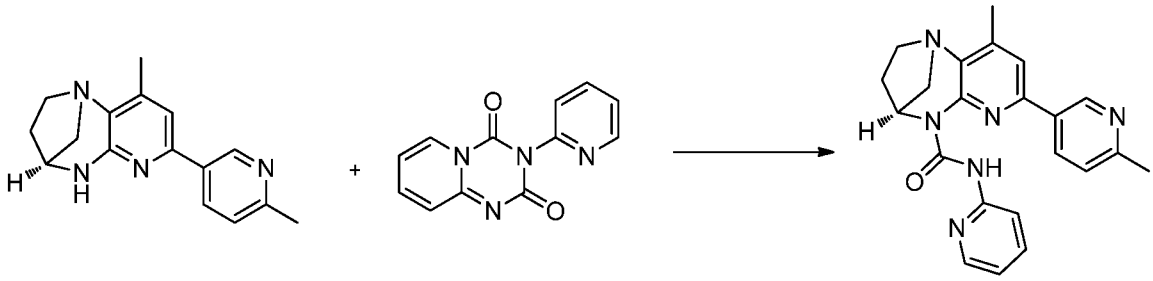


To a stirred solution of (4*S*)-8-methyl-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (200 mg, 0.751 mmol) in THF (15 ml) was added triphosgene (134 mg, 0.451 mmol) at 0 °C and stirred to RT for 1 h. Then pyridin-2-amine (106 mg, 1.126 mmol) and DIPEA (291 mg, 2.253 mmol) were added sub sequentially, heated the reaction mixture at 75°C for 16 h in sealed tube. The reaction mixture was poured in to saturated $NaHCO_3$ solution (50 mL) and extracted with ethyl acetate (3x50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude compound. The crude compound was purified by flash column chromatography (silica-gel: 100-200 mesh, using gradient mixture of 1% methanol in dichloromethane) to afford (4*S*)-8-methyl-7-(6-methylpyridin-3-yl)-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (150 mg, 0.386 mmol, 51.4 % yield) as a white solid (TLC System: R_f: 0.3, eluent: 5% Methanol in dichloromethane), LCMS (*m/z*): 387.29 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.32 (s, 1 H), 8.79 (d, *J*=2.41 Hz, 1 H), 8.27 (ddd, *J*=4.82, 1.97, 0.88 Hz, 1 H), 8.15 - 8.06 (m, 2 H), 7.64 (td, *J*=7.78, 1.97 Hz, 1 H), 7.44 (s, 1 H), 7.33 (d, *J*=8.11 Hz, 1 H), 6.94 (ddd, *J*=7.29, 4.88, 0.99 Hz, 1 H), 5.65 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.37 - 3.12 (m, 3 H), 2.99 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.65 (s, 3 H), 2.41 (s, 3 H), 2.35 - 2.25 (m, 1 H), 2.16 - 2.06 (m, 1 H).

Example 9

Synthesis of (4*S*)-9-methyl-7-(6-methylpyridin-3-yl)-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

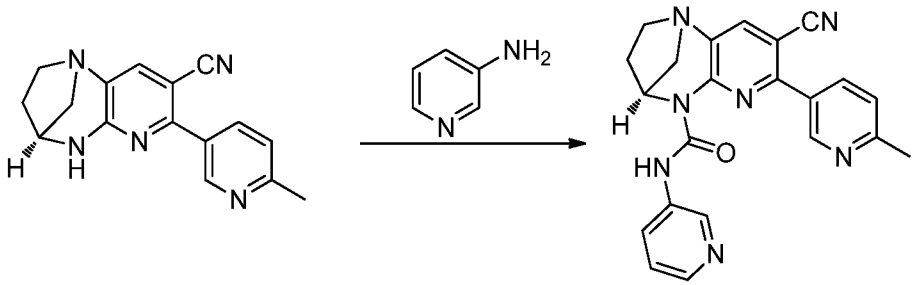


Sodium hydride (NaH) (0.270 g, 6.76 mmol) was added to a stirred solution of (4*S*)-9-methyl-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (0.300 g, 1.126 mmol) in tetrahydrofuran (30 mL) under nitrogen at room temperature. The reaction mixture was stirred for 30 minutes. 3-(Pyridin-2-yl)-2*H*-pyrido[1,2-a][1,3,5]triazine-2,4(3*H*)-dione (0.406 g, 1.690 mmol) was added at room temperature and stirred at 65 °C for 24 hours. The reaction mixture was cooled to room temperature and was partitioned between ice cold water (30 mL) and EtOAc (100 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude as brown solid (TLC eluent: 70% EtOAc in hexane: R_f-0.3; UV active). The crude residue was purified by column chromatography using neutral alumina and was eluted with 20% EtOAc in hexane to afford pure (4*S*)-9-methyl-7-(6-methylpyridin-3-yl)-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyri-do[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (75.7 mg, 0.193 mmol, 17.15 % yield) as off-white solid, LCMS (*m/z*): 387.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.59 - 14.03 (m, 1 H), 9.07 (d, *J* = 2.19 Hz, 1 H), 8.59 (dd, *J* = 8.22, 2.52 Hz, 1 H), 8.30 - 8.51 (m, 1 H), 8.18 (d, *J* = 8.55 Hz, 1 H), 7.58 - 7.83 (m, 1 H), 7.28 - 7.40 (m, 2 H), 6.91 - 7.05 (m, 1 H), 5.69 (dd, *J* = 5.92, 3.07 Hz, 1 H), 3.06 - 3.23 (m, 3 H), 2.94 - 3.05 (m, 1 H), 2.63 (s, 3 H), 2.49 (s, 3 H), 2.24 - 2.38 (m, 1 H), 1.99 - 2.12 (m, 1 H)

Example 10

Synthesis of (4*S*)-8-cyano-7-(6-methylpyridin-3-yl)-*N*-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido [2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

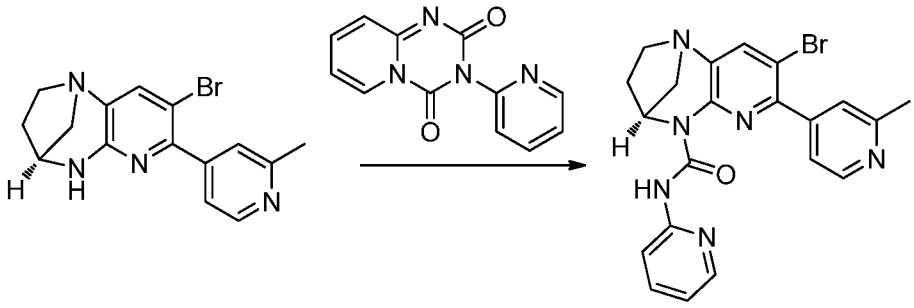


To a stirred solution of (4*S*)-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-8-carbonitrile (200 mg, 0.721 mmol) in THF (15 ml, in sealed tube) was added triphosgene (128 mg, 0.433 mmol) at 0°C and stirred to RT for 1 h. Then pyridin-3-amine (102 mg, 1.082 mmol) and DIPEA (280 mg, 2.164 mmol) was added sub sequentially and heated at 75 °C for 16 h. The reaction mixture was poured in to saturated $NaHCO_3$ solution (50 mL) and extracted with ethyl acetate (3x50 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 column chromatography (silica-gel: 100-200 mesh, using gradient mixture of 1% methanol in dichloromethane as eluent) to afford (4*S*)-8-cyano-7-(6-methylpyridin-3-yl)-*N*-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (140 mg, 0.350 mmol, 48.5 % yield) as an off white solid (TLC System: R_f: 0.3, eluent: 5% Methanol in dichloromethane), LCMS (*m/z*): 398.29 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.58 (s, 1 H), 8.98 (d, *J*=2.19 Hz, 1 H), 8.44 (d, *J*=2.41 Hz, 1 H), 8.31 (dd, *J*=4.71, 1.43 Hz, 1 H), 8.12 - 8.02 (m, 2 H), 7.84 (s, 1 H), 7.38 (d, *J*=8.11 Hz, 1 H), 7.29 - 7.24 (m, 1 H), 5.71 (dd, *J*=5.92, 2.85 Hz, 1 H), 3.33 - 3.21 (m, 2 H), 3.02 - 3.17 (m, 2 H), 2.69 (s, 3 H), 2.45 - 2.32 (m, 1 H), 2.22 - 2.08 (m, 1 H).

Example 11

Synthesis of (4*S*)-8-bromo-7-(2-methylpyridin-4-yl)-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

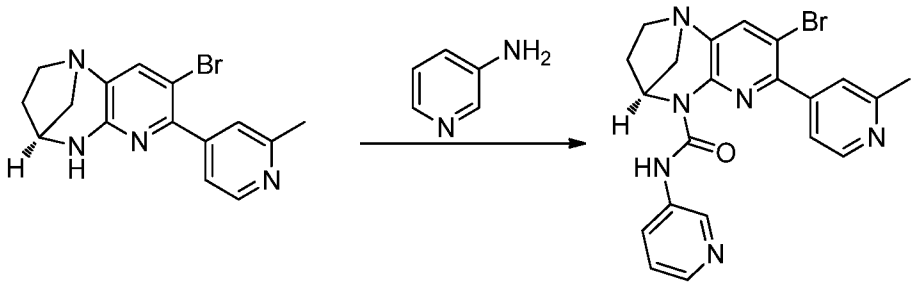


To a stirred solution of (4*S*)-8-bromo-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 0.906 mmol) in THF (20 mL) was added NaH (65.2 mg, 2.72 mmol) at 0 °C. Then the reaction mixture was stirred at 30 °C for 1h and added 3-(pyridin-2-yl)-2*H*-pyrido[1,2-*a*][1,3,5]triazine-2,4(3*H*)-dione (435 mg, 1.812 mmol), then the reaction mixture was stirred at 70 °C for 15 h. The reaction mixture was poured in to the cold water (10 mL) and extracted with ethyl acetate (2x20 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain the crude product. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 3% MeOH in EtOAc) to afford (4*S*)-8-bromo-7-(2-methylpyridin-4-yl)-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methano pyrido [2,3-*b*] [1,4]diazepine-5(2*H*)-carboxamide (290 mg, 0.639 mmol, 70.5 % yield) as an off white solid (TLC System: R_f- 0.3, eluent: 5% methanol in dichloromethane), LCMS (*m/z*): 451.24 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.85 (s, 1 H), 8.63 (d, *J*=5.26 Hz, 1 H), 8.30 - 8.25 (m, 1 H), 8.15 - 8.09 (m, 1 H), 7.82 (s, 1 H), 7.76 (s, 1 H), 7.70 - 7.63 (m, 2 H), 7.02 – 6.93 (m, 1 H), 5.66 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.38 - 3.09 (m, 3 H), 3.01 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.72 (s, 3 H), 2.34 (dddd, *J*=14.20, 10.08, 6.08, 3.84 Hz, 1 H), 2.16 - 2.02 (m, 1 H).

Example 12

Synthesis of (4*S*)-8-bromo-7-(2-methylpyridin-4-yl)-*N*-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

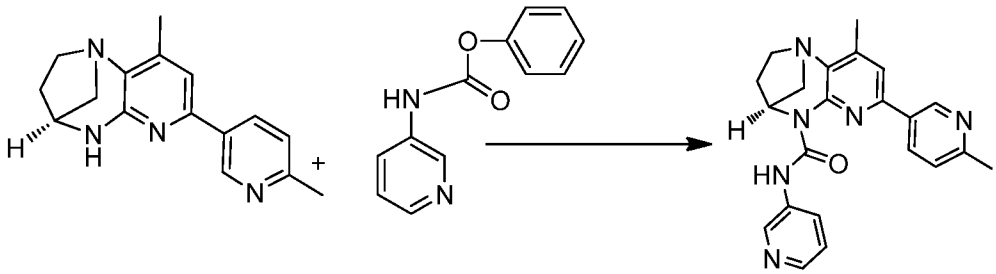


To a stirred solution of (4*S*)-8-bromo-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (250 mg, 0.755 mmol) in THF (10 mL) was added triphosgene (134 mg, 0.453 mmol) at 0 °C. Then the reaction mixture was stirred at 30 °C for 30 min and added pyridin-3-amine (142 mg, 1.510 mmol). The reaction mixture was stirred at 70 °C for 15 h. Allowed to cool to RT and the reaction mixture was poured in to the cold water (20 mL) and extracted with ethyl acetate (2X20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude compound. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 3% MeOH in EtOAc) to obtain 500 mg with 90% purity by LCMS. The semi pure compound was purified by prep HPLC (Column: XS PHENYL HEXYL(250 X4.6mm, 5µ), Mobile Phase: A: 0.01 M Ammonium Bicarbonate B: ACN, Gradient: Time/ %B: 0/10, 1/10, 10/50, 15/50, 18/98, 20/98, 20.1/10, 25/10, Column Temp: Ambient, Flow Rate:1.0ml/min, Diluent: ACN) to afford (4S)-8-bromo-7-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (175 mg, 0.387 mmol, 51.3 % yield) as an off white solid (TLC: 10% MeOH in Ethyl acetate, R_f: 0.3), LCMS (*m/z*): 451.21 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.56 (s, 1 H), 8.69 (d, *J*=5.26 Hz, 1 H), 8.43 (d, *J*=2.63 Hz, 1 H), 8.28 (dd, *J*=4.71, 1.42 Hz, 1 H), 8.02 – 7.94 (m, 1 H), 7.83 (s, 1 H), 7.49 - 7.41 (m, 2 H), 7.21 (dd, *J*=8.33, 4.82 Hz, 1 H), 5.67 (dd, *J*=5.81, 3.18 Hz, 1 H), 3.38-3.11 (m, 3 H), 3.05-2.98 (m, 1 H), 2.69 (s, 3 H), 2.35 (dddd, *J*=14.20, 10.03, 6.03, 3.95 Hz, 1 H), 2.15-2.01 (m, 1 H).

Example 13

Synthesis of (4*S*)-9-methyl-7-(6-methylpyridin-3-yl)-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

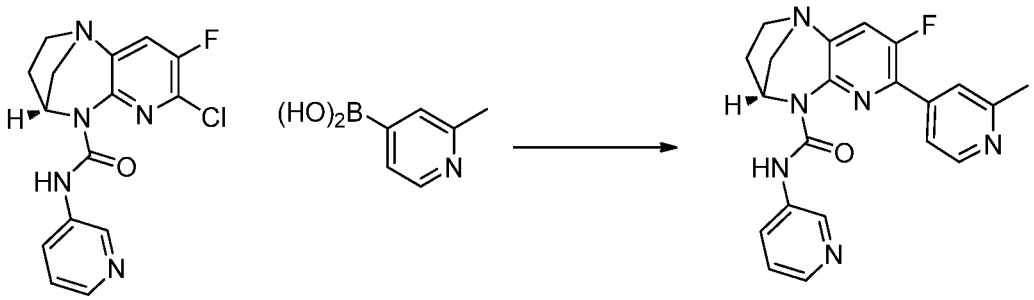


N,N-Dimethylaminopyridine (0.482 g, 3.94 mmol) was added to a stirred solution of of (4*S*)-9-methyl-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazep-ine (0.350 g, 1.314 mmol) and phenyl pyridin-3-ylcarbamate (0.845 g, 3.94 mmol) in tetrahydrofuran (20 mL) under nitrogen atmosphere at room temperature. The reaction was stirred at 65°C for 48 hours. Reaction was cooled to room temperature and the solvent was removed under reduced pressure, and was partitioned between water (20mL) and EtOAc (70 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude as brown solid (TLC eluent: 100% EtOAc: R_f-0.3; UV active). Added ethyl acetate to reaction mass and stirred for 10 minutes. Filtered the reaction mass and washed with EtOAc. Filtrate was concentrated to get brown solid (TLC eluent: 100% EtOAc: R_f-0.2; UV active). The crude was purified by column chromatography using neutral alumina and was eluted with 60% EtOAc in hexane to afford pure (4*S*)-9-methyl-7-(6-methylpyridin-3-yl)-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4] diazepine-5(2*H*)-carboxamide (0.115 g, 0.296 mmol, 22.56 % yield) as a white solid, LCMS (*m/z*) 387.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.29 (s, 1 H), 8.92 (d, *J* = 1.97 Hz, 1 H), 8.53 (d, *J* = 2.19 Hz, 1 H), 8.28 (br d, *J* = 3.51 Hz, 1 H), 8.19 (br d, *J* = 8.33 Hz, 1 H), 7.99 (dd, *J* = 8.00, 2.30 Hz, 1 H), 7.32 (d, *J* = 7.89 Hz, 1 H), 7.22 - 7.29 (m, 1 H), 7.19 (s, 1 H), 5.68 (dd, *J* = 5.92, 3.07 Hz, 1 H), 3.17 (t, *J* = 7.34 Hz, 2 H), 3.07 - 3.13 (m, 1 H), 2.97 - 3.05 (m, 1 H), 2.64 (s, 3 H), 2.50 (s, 3 H), 2.32 (td, *J* = 13.76, 6.47 Hz, 1 H), 1.99 - 2.14 (m, 1 H)

Example 14

Synthesis of (4*S*)-8-fluoro-7-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

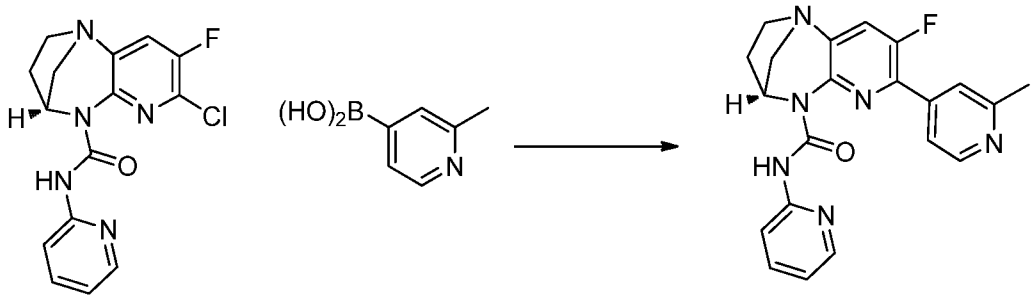


K_3PO_4 (515 mg, 2.427 mmol) was added to a solution of (4*S*)-7-chloro-8-fluoro-*N*-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (405 mg, 1.213 mmol), (2-methylpyridin-4-yl)boronic acid (216 mg, 1.578 mmol) in 1,4-dioxane (20 mL) and water (3 mL). The reaction mixture was degassed for 15 min then $Pd_2(dba)_3$ (55.6 mg, 0.061 mmol) and X-phos (57.8 mg, 0.121 mmol) were added at RT and heated the reaction mixture at 80 °C for 3 h. The reaction mixture was cooled to RT and was partitioned between water (25 mL) and EtOAc (60 mL). The separated organic layer was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude product. The crude compound was purified by (silica-gel: 100-200 mesh, eluent: 90% Ethylacetate in hexane) to afford (4*S*)-8-fluoro-7-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (195 mg, 0.487 mmol, 40.1 % yield) as an off white solid (TLC eluent: Neat ethyl acetate R_f: 0.2), LCMS (*m/z*): 391.30 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$-*d*): δ ppm 12.7 (s, 1H), 8.68 (d, *J* = 4.8 Hz, 1H), 8.58 (d, *J* = 2.4 Hz, 1H), 8.31 (dd, *J* = 1.6 Hz, 4.8 Hz, 1H), 8.11-8.07 (m, 1H), 7.60 (s, 1H), 7.55-7.53 (m, 1H), 7.45 (d, *J* = 10.4 Hz, 1H), 7.27-7.24 (m, 1H), 5.70-5.68 (m, 1H), 3.33-3.14 (m, 3H), 3.05-3.01 (m, 1H), 2.68 (s, 3H), 2.38-2.30 (m, 1H), 2.12-2.06 (m, 1H).

Example 15

Synthesis of (4*S*)-8-fluoro-7-(2-methylpyridin-4-yl)-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

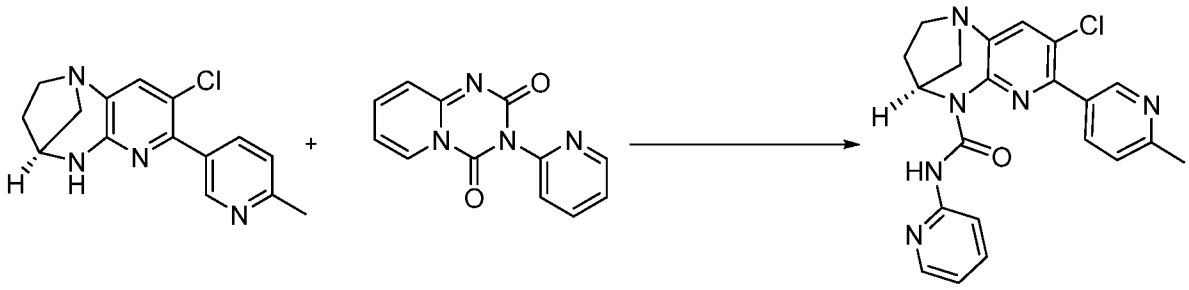


K_3PO_4 (445 mg, 2.097 mmol) was added to a stirred solution of (4*S*)-7-chloro-8-fluoro-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (350 mg, 1.049 mmol), (2-methylpyridin-4-yl)boronic acid (187 mg, 1.363 mmol) in 1,4-dioxane (10 mL) and water (2 mL). The reaction mixture was degassed for 15 min, $Pd_2(dba)_3$ (48.0 mg, 0.052 mmol) and x-phos (50.0 mg, 0.105 mmol) were added. The reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was cooled to RT and was partitioned between water (25 mL) and EtOAc (60 mL). The separated 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: 90% Ethyl acetate in hexane) to afford (4*S*)-8-fluoro-7-(2-methylpyridin-4-yl)-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (120 mg, 0.306 mmol, 29.2 % yield) as an off white solid (TLC eluent: Neat ethyl acetate R_f:.0.4), LCMS (*m/z*): 391.27 $[M+H]^+$

.^{1}H NMR (400 MHz, $CDCl_3$-*d*): δ ppm 13.05 (s, 1H), 8.63 (d, *J* = 5.6 Hz, 1H), 8.35-8.33 (m, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 8.09 (s, 1H), 7.81-7.80 (m, 1H), 7.71 - 7.67 (m, 1H), 7.43 (d, *J* = 10.4 Hz, 1H), 7.25 - 6.99 (m, 1H), 5.71-5.68 (m, 1H), 3.32-3.14 (m, 3H), 3.03-2.99 (m, 1H), 2.74 (s, 3H), 2.36 -2.32 (m, 1H), 2.09-2.05 (m,1H).

Example 16

Synthesis of (4*S*)-8-chloro-7-(6-methylpyridin-3-yl)-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

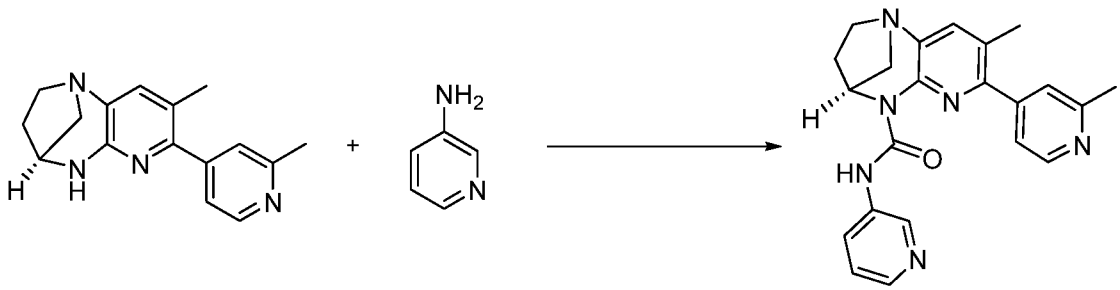


A solution of (4*S*)-8-chloro-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (350 mg, 1.221 mmol), NaH (43.9 mg, 1.831 mmol) in Tetrahydrofuran (THF) (20 mL) stirred under nitrogen at 0°C. Then the reaction mixture was stirred at 30 °C for 30 min and 3-(pyridin-2-yl)-2*H*-pyrido[1,2-a][1,3,5]triazine-2,4(3*H*)-dione (352 mg, 1.465 mmol) was added. The reaction mixture was stirred at 70 °C for 16h. The reaction mixture was poured in to the cold water (50 mL) and extracted with ethyl acetate (2x75 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum to obtain crude compound. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 3% MeOH in EtOAc) and obtained 500 mg with 90% purity by LCMS. The semi pure compound was purified by prep HPLC (Column: XS PHENYL HEXYL(250 X4.6mm, 5µ), Mobile Phase: A: 0.01 M Ammonium Bicarbonate B: ACN, Gradient: Time/ %B: 0/10, 1/10, 10/50, 15/50, 18/98, 20/98, 20.1/10, 25/10, Column Temp: Ambient, Flow Rate:1.0ml/min, Diluent: ACN) to afford (4S)-8-chloro-7-(6-methylpyridin-3-yl)-N-(pyridin-2-yl)-3,4-dihydro-1,4-methano pyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (240 mg, 0.589 mmol, 48.3 % yield) as an off white solid (TLC System; R_f- 0.3, 5% methanol in dichloromethane), LCMS (*m/z*): 407.29$[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 12.93 (s, 1 H), 9.07 (d, *J*=2.19 Hz, 1 H), 8.28 (ddd, *J*=4.82, 1.97, 0.88 Hz, 1 H), 8.21 (dd, *J*=8.11, 2.41 Hz, 1 H), 8.11 -8.06 (m, 1 H), 7.68-7.63 (m, 2 H), 7.33 (d, *J*=8.11 Hz, 1 H), 6.96 (ddd, *J*=7.29, 4.88, 0.99 Hz, 1 H), 5.66 (dd, *J*=6.03, 3.18 Hz, 1 H), 3.35 - 3.12 (m, 3 H), 3.01 (dd, *J*=12.28, 3.29 Hz, 1 H), 2.63 (s, 3 H), 2.33 (dddd, *J*=14.14, 10.03, 5.86, 3.73 Hz, 1 H), 2.09 (dt, *J*=14.20, 7.04 Hz, 1 H).

Example 17

Synthesis of (4*S*)-8-methyl-7-(2-methylpyridin-4-yl)-*N*-(pyridin-3-yl)-3,4-dihydro-1,4-methano pyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

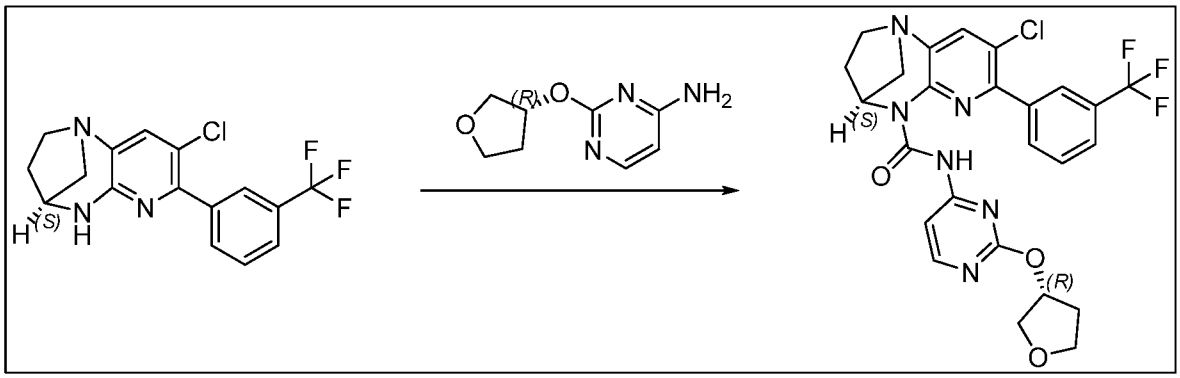


To a solution of (4S)-8-methyl-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (300 mg, 1.126 mmol), triphosgene (201 mg, 0.676 mmol), DIPEA (728 mg, 5.63 mmol) in Tetrahydrofuran (THF) (10 mL) stirred under nitrogen at 20°C for 30min, solid pyridin-3-amine (159 mg, 1.690 mmol) was added. The reaction mixture was stirred at 65 °C for 16 h. The reaction mixture was diluted with saturated $NaHCO_3$ solution and extracted with ethyl acetate (3 X 150 mL). The organic layer was dried over anhydrous Mg_2SO_4, filtered, concentrated under vacuum to obtain crude compound. The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 3% MeOH in EtOAc) and obtained (4S)-8-methyl-7-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (200 mg, 0.499 mmol, 44.3 % yield) as a off white solid. (TLC System:- R_f:- 0.5, 10% Methanol in ethyl acetate), LCMS (*m/z*): 387.31 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 13.01 (s, 1 H), 8.67 (d, *J*=5.26 Hz, 1 H), 8.45 (d, *J*=2.41 Hz, 1 H), 8.26 (dd, *J*=4.82, 1.32 Hz, 1 H), 8.09 - 7.94 (m, 1 H), 7.47 (s, 1 H), 7.34 (s, 1 H), 7.20 (dd, *J*=8.33, 4.60 Hz, 1 H), 5.66 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.35 - 3.11 (m, 3 H), 3.00 (dd, *J*=12.28, 3.29 Hz, 1 H), 2.68 (s, 3 H), 2.38 - 2.28 (m, 4 H), 2.11 - 1.98 (m, 1 H), 2.11 - 1.98 (m, 1 H).

Example 18

Synthesis of (4*S*)-8-chloro-*N*-(2-(((*R*)-tetrahydrofuran-3-yl)oxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

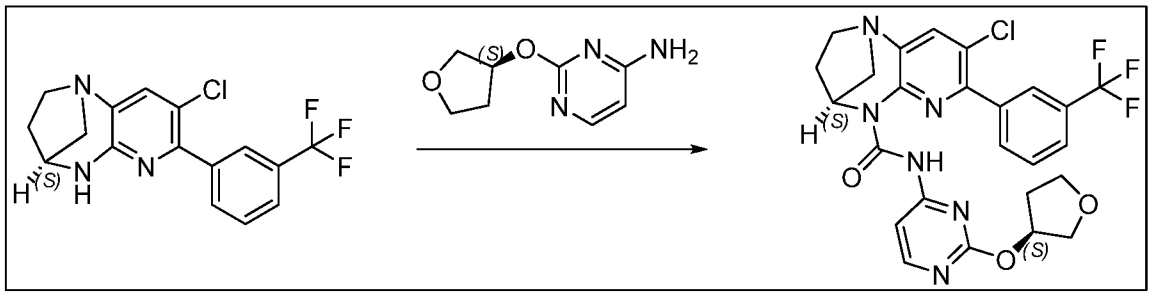


To a stirred solution of (4*S*)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300mg, 0.883 mmol) in THF (15 mL, in sealed tube) was added triphosgene (157 mg, 0.530 mmol) at RT, and stirred for 30 min, then TEA (0.738 mL, 5.30 mmol) and (*R*)-2-((tetrahydrofuran-3-yl)oxy)pyrimidin-4-amine (192 mg, 1.060 mmol) were added and stirred at 80 °C for 16 h. (TLC eluent: 10%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 (4*S*)-8-chloro-*N*-(2-(((*R*)-tetrahydrofuran-3-yl)oxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide (110 mg, 0.195 mmol, 22.12 % yield) as an off white solid. LCMS (*m/z*): 547.10 $[M+H]^+$, Rt = 2.65 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.02 (s, 1 H), 8.41 (d, *J*=5.48 Hz, 1 H), 8.08 - 7.97 (m, 2 H), 7.95 - 7.86 (m, 1 H), 7.86 - 7.73 (m, 2 H), 7.73 - 7.57 (m, 1 H), 5.46 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.92 (dd, *J*=4.38, 1.53 Hz, 1 H), 3.76 (q, *J*=7.60 Hz, 1 H), 3.69 - 3.59 (m, 1 H), 3.54 (dd, *J*=10.52, 1.75 Hz, 1 H), 3.39 (dd, *J*=10.41, 4.71 Hz, 1 H), 3.29 (s, 1 H), 3.25 - 3.07 (m, 2 H), 3.07 - 2.79 (m, 1 H), 2.41 - 2.13 (m, 1 H), 1.99 (t, *J*=6.69 Hz, 1 H), 1.91 - 1.63 (m, 2 H).

Example 19

Synthesis of (4*S*)-8-chloro-*N*-(2-(((*S*)-tetrahydrofuran-3-yl)oxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

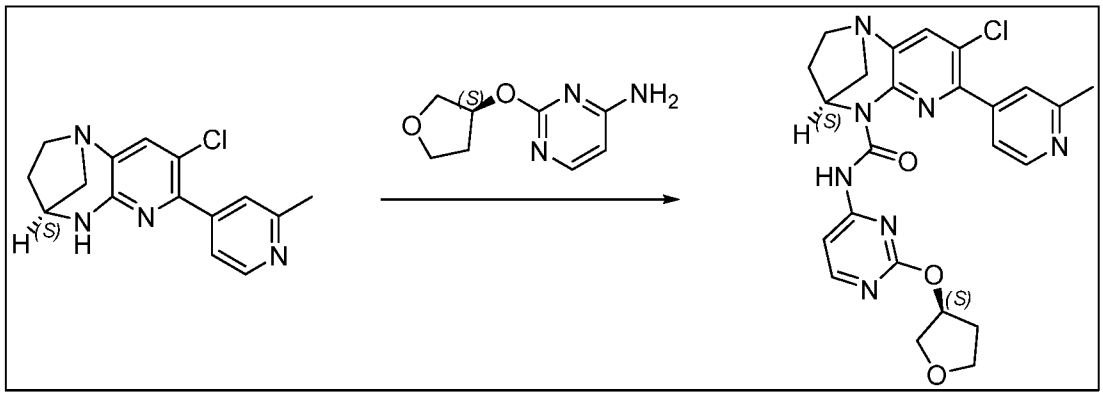


To a stirred solution of (4*S*)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (400 mg, 1.177 mmol) in THF (10 mL, in sealed tube) were added tri-phosgene (349 mg, 1.177 mmol) and TEA (0.985 mL, 7.06 mmol) at RT, and stirred for 30 min, then (*S*)-2-((tetrahydrofuran-3-yl)oxy)pyrimidin-4-amine (427 mg, 2.355 mmol) was added and heated at 80 °C for 16 h. (TLC eluent: Neat EtOAc, R_f: 0.2). The reaction mixture was cooled to room temperature; THF was distilled off and was partitioned between water (25 mL) and EtOAc (2x 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: 90% EtOAc in hexane) to afford the desired product (4*S*)-8-chloro-*N*-(2-(((*S*)-tetrahydrofuran-3-yl)oxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (150 mg, 0.272 mmol, 23.10 % yield) as an off white solid. LCMS (*m/z*): 547.07 $[M+H]^+$, Rt = 2.62 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.97 (s, 1 H), 8.34 (d, *J*=5.70 Hz, 1 H), 8.12 -7.92 (m, 2 H), 7.87 - 7.46 (m, 4 H), 5.65 (dd, *J*=5.92, 3.07 Hz, 1 H), 5.07 (ddt, *J*=6.77, 4.63, 2.19, 2.19 Hz, 1 H), 4.07 - 3.46 (m, 4 H), 3.38 - 3.09 (m, 3 H), 3.03 (dd, *J*=12.28, 3.29 Hz, 1 H), 2.36 (dddd, *J*=14.22, 10.06, 6.08, 4.06 Hz, 1 H), 2.16 - 1.97 (m, 2 H), 1.94 - 1.81(m, 1 H)

Example 20

Synthesis of (4*S*)-8-chloro-7-(2-methylpyridin-4-yl)-*N*-(2-(((*S*)-tetrahydrofuran-3-yl)oxy)pyrimidin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-car- boxamide



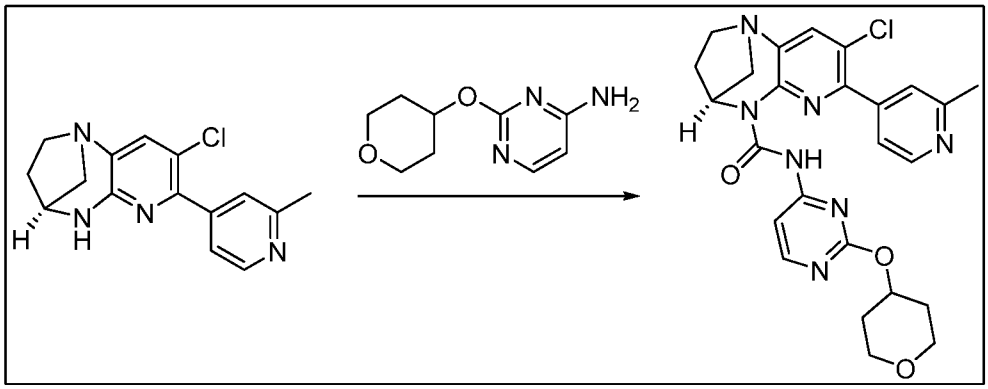
To a stirred solution of (4*S*)-8-chloro-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 1.046 mmol) in THF (15 mL, in sealed tube) were added tri-phosgene (310 mg, 1.046 mmol) and TEA (0.875 mL, 6.28 mmol) at RT, and stirred for 30 min, then (*S*)-2-((tetrahydrofuran-3-yl)oxy)pyrimidin-4-amine (379 mg, 2.092 mmol) was added and heated at 80 °C for 16 h. (TLC eluent: Neat EtOAc, R_f: 0.3). The reaction mixture was cooled to room temperature; THF was distilled off and was partitioned between water (25 mL) and EtOAc (2x 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: 90% EtOAc in hexane) to afford semi pure compound and further purified by Prep HPLC (Conditions: Column: XBridge C 18(75 X4.6mm, 3.5µ) 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:1.0ml/min: Diluent: ACN) to afford the desired product (4*S*)-8-chloro-7-(2-methylpyridin-4-yl)-*N*-(2-(((*S*)-tetrahydrofuran-3-yl)oxy)pyrimidin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (110 mg, 0.221 mmol, 21.13 % yield) as an off white solid. LCMS (*m/z*): 494.04 $[M+H]^+$, Rt = 1.67 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.93 (s, 1 H), 8.68 (d, *J*=5.26 Hz, 1 H), 8.33 (d, *J*=5.48 Hz, 1 H), 7.73 (d, *J*=5.70 Hz, 1 H), 7.68 (s, 1 H), 7.63 (s, 1 H), 7.59 (s, 1 H), 5.63 (dd, *J*=5.92, 3.07 Hz, 1 H), 5.19 (dq, *J*=5.97, 3.05 Hz, 1 H), 4.01 - 3.88 (m, 2 H), 3.85 -

3.72 (m, 2 H), 3.37 - 3.21 (m, 2 H), 3.18 - 3.11 (m, 1 H), 3.01 (dd, *J*=12.28, 3.07 Hz, 1 H), 2.73 (s, 3 H), 2.42 - 2.29 (m, 1 H), 2.11 - 2.05 (m, 3 H).

Example 21

Synthesis of (4*S*)-8-chloro-7-(2-methylpyridin-4-yl)-*N*-(2-((tetrahydro-2*H*-pyran-4-yl)oxy)pyrimidin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

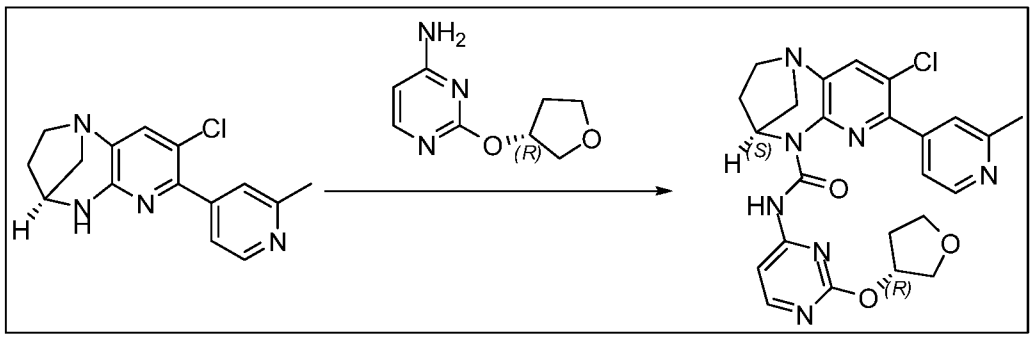


To a stirred solution of (4*S*)-8-chloro-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (300 mg, 1.046 mmol) in THF (10 mL, in sealed tube) was added triphosgene (155 mg, 0.523 mmol) at RT, and stirred for 30 min then DIPEA (0.914 mL, 5.23 mmol) and 2-((tetrahydro-2H-pyran-4-yl)oxy)pyrimidin-4-amine (408 mg, 2.092 mmol) were added and stirred at 80 °C for 16 h. (TLC System: R_f - 0.2, EtOAc). The reaction mixture was cooled to room temperature and THF was distilled off, the crude product was partitioned between water (25 mL) and EtOAc (2x 40 mL). The separated 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: 80% ethyl acetate in hexane) and obtained 57% pure material therefore it was again purified by Prep HPLC (Conditions: Column: XS PHENYL HEXYL(250 X4.6mm, 5µ),Mobile Phase: A: 0.01 M Ammonium Bicarbonate B: ACN, Gradient: Time/ %B: 0/10,1/10,10/50,15/50,18/98,20/98,20.1/10,25/10Column Temp: Ambient, Flow Rate: 0.8ml/min,Diluent: CAN) to afford the desired product (4S)-8-chloro-7-(2-methylpyridin-4-yl)-N-(2-((tetrahydro-2H-pyran-4-yl)oxy)pyrimidin-4-yl)-3,4-dihydro-1,4-methanopyrido [2,3-b][1,4]diazepine-5(2H)-carboxamide (96.6 mg, 0.183 mmol, 17.45 % yield) as a pale yellow solid. LCMS (*m/z*): 508.1 $[M+H]^+$, Rt = 1.75 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.92 (s, 1 H), 8.68 (d, *J*=5.26 Hz, 1 H), 8.35 (d, *J*=5.70 Hz, 1 H), 7.73 (d, *J*=5.48 Hz, 1 H), 7.68 (s, 1 H), 7.63 (s, 1 H), 7.59 (d, *J*=4.82 Hz, 1 H), 5.67- 5.60 (m, 1 H), 4.92 (dt, *J*=8.22, 4.22 Hz, 1 H), 4.03- 3.86 (m, 2 H), 3.56 -3.45 (m, 2 H), 3.37- 3.22 (m, 2 H), 3.19- 3.11 (m, 1 H), 3.02 (dd, *J*=12.17, 3.18 Hz, 1 H), 2.72 (s, 3 H), 2.40 -2.29 (m, 1 H), 2.07 (dt, *J*=14.52, 7.54 Hz, 1 H), 1.94 (br s, 2 H), 1.82- 1.70 (m, 2 H).

Example 22

Synthesis of (4*S*)-8-chloro-7-(2-methylpyridin-4-yl)-*N*-(2-(((R)-tetrahydrofuran-3-yl) oxy)pyrimidin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



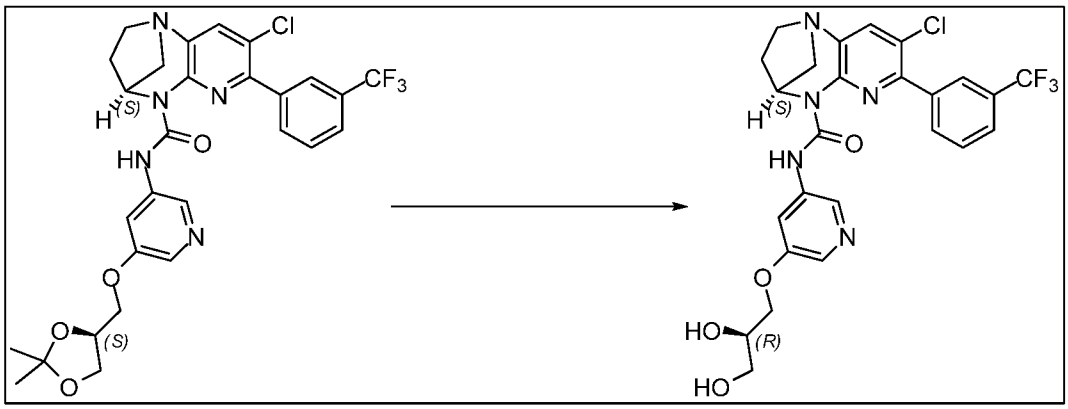
To a stirred solution of (4*S*)-8-chloro-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (200 mg, 0.697 mmol) in THF (20 mL) under nitrogen were added triethylamine (0.486 mL, 3.49 mmol) and triphosgene (103 mg, 0.349 mmol) at 0 °C and stirred for 30 min at room temperature. To this reaction mixture (*R*)-2-((tetrahydrofuran-3-yl) oxy) pyrimidin-4-amine (164 mg, 0.907 mmol) was added and stirred at 80 °C for 15 h. (TLC system: 5% Methanol in Ethyl acetae. R*f* value: 0.5.). The reaction mixture was diluted with water (10 mL) and extracted with ethylacetate (2x15 mL). The combined organic layer was washed with water (10 mL), 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 1% of MeOH in Ethyl acetate) to afford the desired product (4*S*)-8-chloro-7-(2-methylpyridin-4-yl)-*N*-(2-(((R)-tetrahydrofuran-3-yl)oxy)pyrimidin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2H)-carboxamide (120 mg, 0.237 mmol, 33.9 % yield) as a pale pink solid. LCMS (*m/z*): 494.07 $[M+H]^+$, Rt =1.69 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.98 (s, 1 H), 8.66 (d, *J*=5.04 Hz, 1 H), 8.34 (d, *J*=5.70 Hz, 1 H), 7.74 (d, *J*=5.48 Hz, 1 H), 7.68 (s, 1 H), 7.58 (s, 1 H), 7.55 - 7.52 (m, 1

H), 5.64 (dd, *J*=5.81, 3.18 Hz, 1 H), 5.17 (tt, *J*=5.26, 2.52 Hz, 1 H), 3.97 - 3.85 (m, 2 H), 3.77 - 3.65 (m, 2 H), 3.35 - 3.11 (m, 3 H), 3.03 (dd, *J*=12.28, 3.07 Hz, 1 H), 2.71 (s, 3 H), 2.42 - 2.28 (m, 1 H), 2.15 - 1.96 (m, 3 H).

Example 23

Synthesis of (4*S*)-8-chloro-*N*-(5-((*R*)-2,3-dihydroxypropoxy)pyridin-3-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

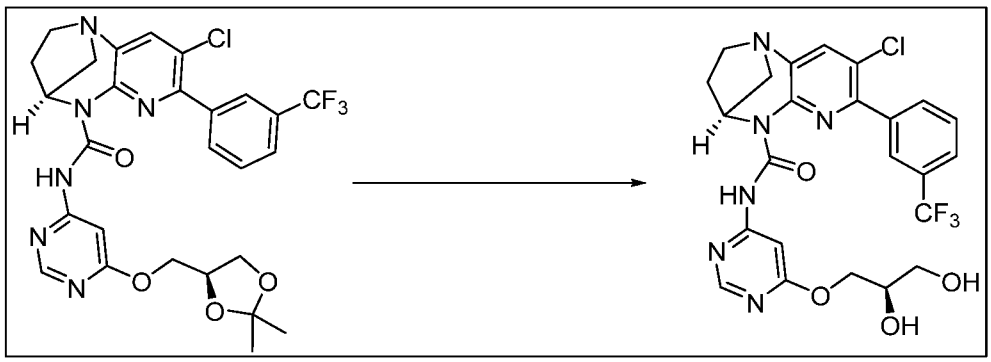


To a stirred solution of (4*S*)-8-chloro-*N*-(5-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (200 mg, 0.339 mmol) in methanol (10 mL) at 0 °C was added aq. HCl (1.0 ml, 32.9 mmol) over a period of 10 min. and stirred at 0 °C for 1 h. (TLC eluent: 10% Methanol in DCM, R_f: 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 (40 mL). Organic layer was washed with brine (20 mL), dried over sodium sulphate and filtered and concentrated under reduced pressure to afford (4*S*)-8-chloro-*N*-(5-((*R*)-2,3-dihydroxypropoxy)pyridin-3-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (120 mg, 0.217 mmol, 64.1 % yield) as an off white solid. LCMS (*m/z*): 550.09 $[M+H]^+$, Rt = 2.03 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.55 (s, 1 H), 8.02 - 8.18 (m, 2 H), 7.75 - 8.01 (m, 5 H), 7.62 (s, 1 H), 5.47 (br s, 1 H), 5.00 (br s, 2 H), 4.00 (br dd, *J*=9.21, 3.73 Hz, 1 H), 3.73 - 3.92 (m, 2 H), 3.34 - 3.60 (m, 2 H), 2.83 - 3.25 (m, 4 H), 2.12 - 2.30 (m, 1 H), 1.83 - 2.09 (m, 1 H).

Example 24

Synthesis of (4*S*)-8-chloro-N-(6-((*R*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide

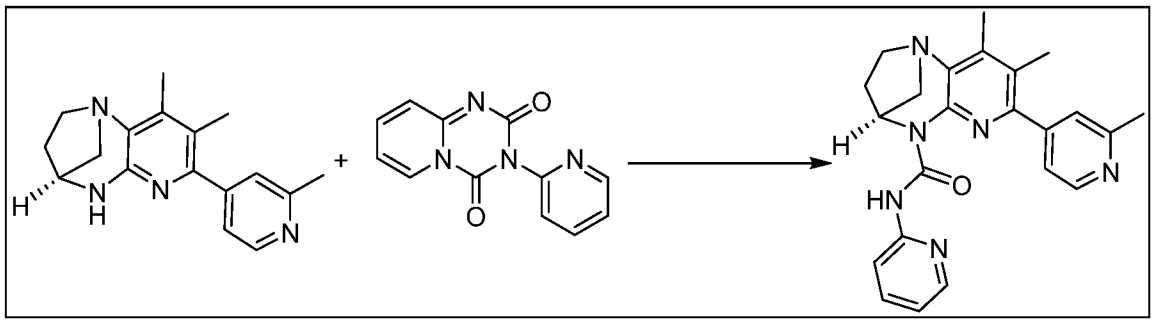


To a stirred solution of (4*S*)-8-chloro-N-(6-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl) methoxy) pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3b][1,4] diazepine-5(2H)-carboxamide (0.25g,0.423mmol) in DCM (5 mL) and methanol (10 mL) at 0 °C was added 4M HCl in dioxane (1.586 mL, 6.35 mmol) and stirred at 0°C for 4 h. (TLC eluent:10% MeOH in EtOAc: R_f-0.3; 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 (2x25 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 the desired product (4*S*)-8-chloro-N-(6-((*R*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7(3(trifluoromethyl)phenyl)-3,4-dihydro-1,4methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide as white solid. LCMS (*m/z*): 551.03 $[M+H]^+$, R_t = 2.35 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.14 (s, 1 H), 8.34 (s, 1 H), 8.16 (s, 1 H), 8.08 (br d, *J* = 7.67 Hz, 1 H), 7.77 - 7.58 (m, 3 H), 7.53 (s, 1 H), 5.63 (br s, 1 H), 4.57 - 4.36 (m, 2 H), 4.03 (br s, 1 H), 3.69 (br d, *J* = 12.93 Hz, 2 H), 3.44 (br s, 1 H), 3.30 - 3.03 (m, 3 H), 2.97 - 2.63 (m, 1 H), 2.49 (br s, 1 H), 2.35 (br dd, *J* = 9.76, 4.93 Hz, 1 H), 2.11 - 2.00 (m, 1 H).

Example 25

Synthesis of (4*S*)-8,9-dimethyl-7-(2-methylpyridin-4-yl)-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

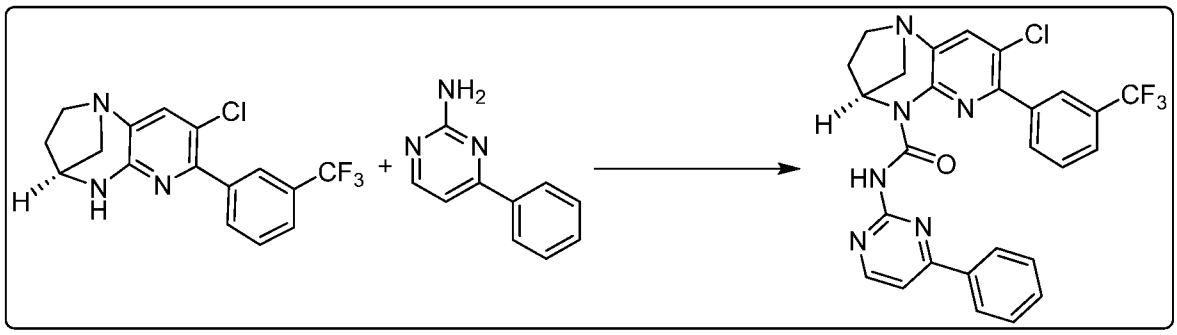


To a solution of (4*S*)-8,9-dimethyl-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (250 mg, 0.892 mmol) in THF (25 mL) under nitrogen at 0 °C was added NaH (214 mg, 5.35 mmol) and stirred at RT for 30 min. then 3-(pyridin-2-yl)-2*H*-pyrido[1,2-a][1,3,5]triazine-2,4(3*H*)-dione (321 mg, 1.338 mmol) was added and the reaction mixture was heated at 65 °C for 16 h. (TLC eluent: 70% EtOAc in Hexane: R_f-0.4; UV active). The reaction mixture was cooled to RT and partitioned between water (30 mL) and EtOAc (100 mL). Organic layer was separated, dried over anhydrous Na_2SO_4, filtered and filtrate was concentrated to give crude product. The crude was purified by column chromatography (neutral alumina, eluent: 50% ethyl acetate in hexane) to afford the desired product (4*S*)-8,9-dimethyl-7-(2-methylpyridin-4-yl)-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (0.164 g, 0.403 mmol, 45.1 % yield) as a white solid LCMS (*m/z*): 401.15 $[M+H]^+$, R_t = 1.55 min

^{1}H-NMR (400 MHz, $CDCl_3$): δppm 13.43 (s, 1 H), 8.59 (d, *J*=5.26 Hz, 1 H), 8.26 (dt, *J*=4.82, 0.99 Hz, 1 H), 8.12 (d, *J*=8.55 Hz, 1 H), 7.67 - 7.53 (m, 2 H), 7.32 (dd, *J*=5.26, 1.10 Hz, 1 H), 6.93 (ddd, *J*=7.29, 4.88, 0.99 Hz, 1 H), 5.63 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.22 - 3.05 (m, 3 H), 3.05 - 2.96 (m, 1 H), 2.70 (s, 3 H), 2.46 (s, 3 H), 2.36 - 2.24 (m, 4 H), 2.12 - 1.97 (m, 1 H)

Example 26

Synthesis of (4*S*)-8-chloro-N-(4-phenylpyrimidin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

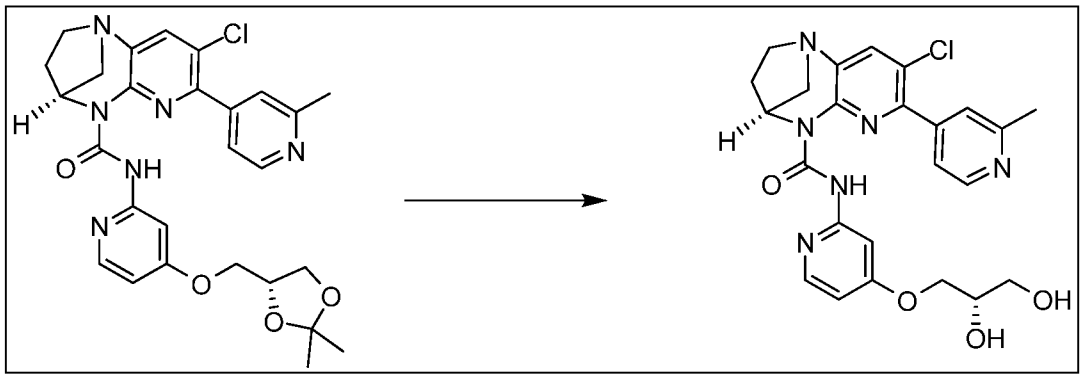


To a stirred solution of (4*S*)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (350 mg, 1.030 mmol) in THF (35 mL) under nitrogen at RT was added triethylamine (0.862 mL, 6.18 mmol), triphosgene (306 mg, 1.030 mmol) and stirred for 30 min. then 4-phenylpyrimidin-2-amine (176 mg, 1.030 mmol) was added and the reaction was heated at 65 °C for 16 h. (TLC eluent:100% EtOAc: R_f-0.2; UV active). The reaction mixture was cooled to RT, concentrated and the residue partitioned between water (30 mL) and DCM (100 mL). Organic layer was separated, dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude compound. The crude was purified by column chromatography (neutral alumina, eluent: 70% ethyl acetate in hexane) to afford (4*S*)-8-chloro-N-(4-phenylpyrimidin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (262 mg, 0.488 mmol, 47.4 % yield) as an off-white solid. LCMS (*m/z*): 537.13 $[M+H]^+$, R_t = 2.84 min

^{1}H NMR (400 MHz, $CDCl_3$): δppm 13.27 (s, 1 H), 8.65 (d, *J*=5.26 Hz, 1 H), 8.13 (s, 1 H), 8.05 (d, *J*=7.89 Hz, 1 H), 7.89 - 7.81 (m, 2 H), 7.72 (d, *J*=7.89 Hz, 1 H), 7.68 (s, 1 H), 7.58 - 7.46 (m, 2 H), 7.44 - 7.35 (m, 3 H), 5.78 (dd, *J*=5.81, 3.18 Hz, 1 H), 3.38 - 3.13 (m, 3 H), 3.03 (dd, *J*=12.17, 3.18 Hz, 1 H), 2.43 - 2.31 (m, 1 H), 2.19 - 2.07 (m, 1 H)

Example 27

Synthesis of (4*S*)-8-chloro-N-(4-((*S*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

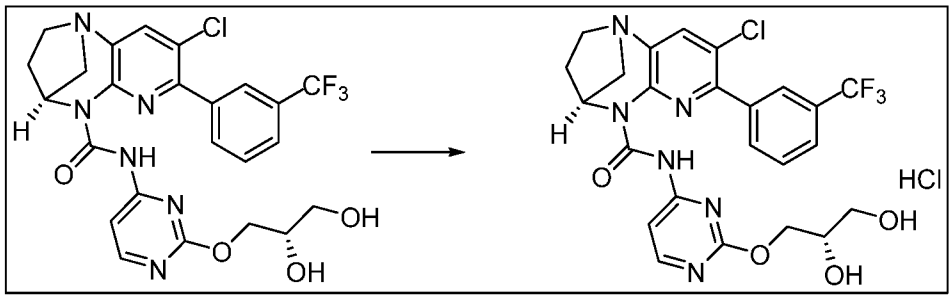


To a stirred solution of (4*S*)-8-chloro-N-(4-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (450 mg, 0.838 mmol) in methanol (10 mL) at 0 °C was added aq. HCl (0.509 mL, 16.76 mmol, 36 %) and stirred at 0 °C 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 partitioned between water (10 mL) and dichloromethane (2x20 mL). Organic layer separated dried over anhydrous sodium sulphate, filtered and filtrate was evaporated *in vacuo* to give crude compound. The crude was purified by column chromatography (neutral alumina, eluent: 5% MeOH in DCM) to afford desired product (4*S*)-8-chloro-N-(4-((*S*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (195 mg, 0.389 mmol, 46.4 % yield) as a pale yellow solid. LCMS (*m/z*): 497.10 $[M+H]^+$, R_t = 1.24 min

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.91 (s, 1 H), 8.63 (d, *J*=5.48 Hz, 1 H), 8.08 (d, *J*=5.70 Hz, 1 H), 7.80 (s, 1 H), 7.76 (d, *J*=2.19 Hz, 1 H), 7.68 (dd, *J*=5.15, 1.21 Hz, 1 H), 7.65 (s, 1 H), 6.69 - 6.46 (m, 1 H), 5.63 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.13 (s, 3 H), 3.87 - 3.81 (m, 1 H), 3.79 - 3.72 (m, 1 H), 3.36 - 3.13 (m, 3 H), 3.01 (dd, *J*=12.28, 3.29 Hz, 1 H), 2.71 (s, 4 H), 2.41 - 2.28 (m, 1 H), 2.20 - 2.03 (m, 2 H)

Example 28

Synthesis of (4*S*)-8-chloro-N-(2-((*S*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide, Hydrochloride

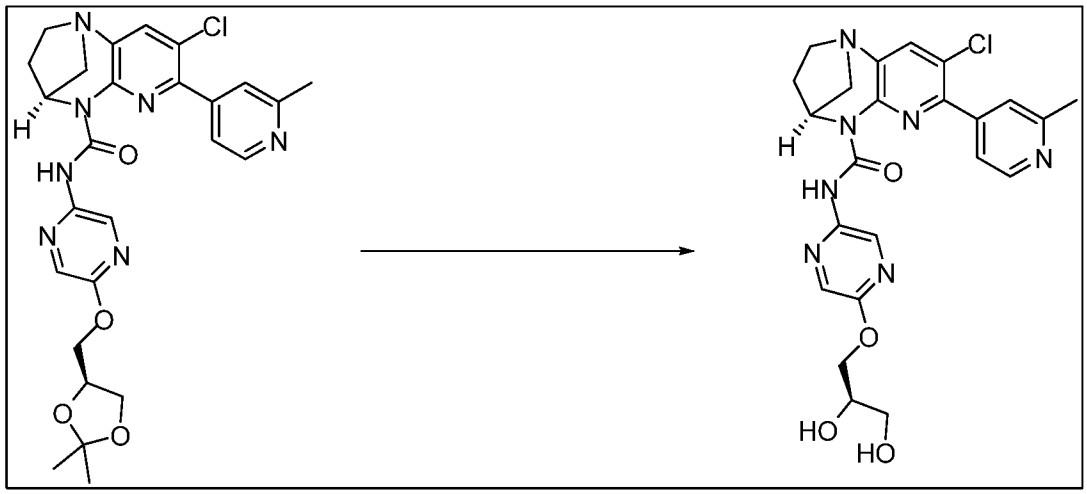


To a solution of (4*S*)-8-chloro-N-(2-((S)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (200 mg, 0.363 mmol) in methanol (5 mL) at 0 °C was added 2M HCl in diethyl ether (5 mL, 165 mmol) and stirred at RT for 2 h. . (TLC eluent: 15% MeOH in DCM: R_f=0.2.; UV active). The reaction was concentrated *in vacuo* and the residue was triturated with n-pentane (2x10 mL) to afford (4*S*)-8-chloro-N-(2-((*S*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide, Hydrochloride (160 mg, 0.270 mmol, 74.4 % yield) as an off- white solid. LCMS (*m/z*): 551.10 $[M+H]^+$, R_t = 2.17 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.95 (s, 1 H), 8.44 (d, *J*=5.70 Hz, 1 H), 8.13 - 8.08 (m, 1 H), 8.06 (s, 1 H), 7.98 (s, 1 H), 7.90 - 7.83 (m, 2 H), 7.68 (d, *J*=5.70 Hz, 1 H), 5.49 (dd, *J*=6.03, 2.96 Hz, 1 H), 3.99 - 3.85 (m, 2 H), 3.75 - 3.68 (m, 1 H), 3.43 - 3.32 (m, 3 H), 3.28 - 3.17 (m, 2 H), 3.11 (dd, *J*=11.73, 3.18 Hz, 1 H), 2.35 - 2.23 (m, 1 H), 2.04 (dt, *J*=13.98, 6.93 Hz, 1 H).

Example 29

Synthesis of (4*S*)-8-chloro-*N*-(5-((*R*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

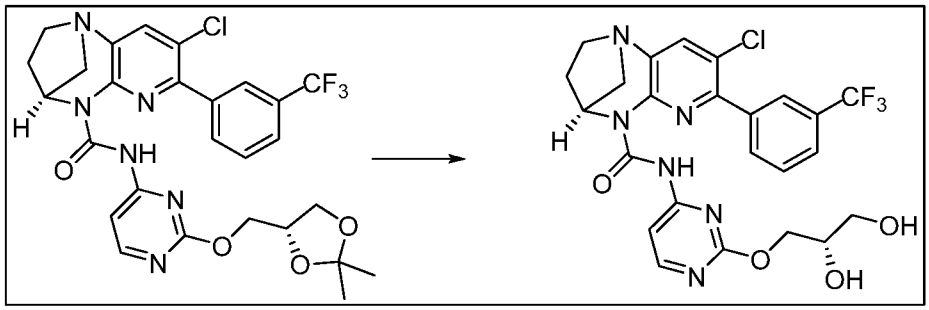


To a solution of (4*S*)-8-chloro-N-(5-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (220 mg, 0.409 mmol) in methanol (5 mL) at RT was added aq. HCl (5 mL, 10.00 mmol) and stirred for 3 h. (TLC system 5% Methanol in DCM. Rf value: 0.1). Methanol was removed under vacuum and the residue was basified with saturated $NaHCO_3$ solution at 0 °C. and the aqueous layer was extracted with DCM (2x20 mL). The organic layer was separated dried over anhydrous Na_2SO_4, filtered and concentrated to afford the crude product. The crude compound was triturated with diethylether (5 mL) to afford (4*S*)-8-chloro-N-(5-((*R*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (145 mg, 0.282 mmol, 69.0 % yield) as pale yellow solid. LCMS (m/z): 498.14 $[M+H]^+$, Rt=1.44 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.72 - 13.12 (m, 1 H), 8.92 (d, *J*=1.32 Hz, 1 H), 8.63 (d, *J*=5.26 Hz, 1 H), 7.96 (d, *J*=1.32 Hz, 1 H), 7.70 (s, 1 H), 7.66 (s, 1 H), 7.62 (dd, *J*=5.15, 1.43 Hz, 1 H), 5.66 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.37 - 4.50 (m, 2 H), 4.04 - 4.14 (m, 1 H), 3.66 - 3.83 (m, 2 H), 3.11 - 3.37 (m, 4 H), 2.98 - 3.07 (m, 1 H), 2.70 (s, 3 H), 2.29 - 2.44 (m, 2 H), 2.08 (dt, *J*=14.58, 7.40 Hz, 1 H).

Example 30

Synthesis of (4*S*)-8-chloro-N-(2-((*S*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

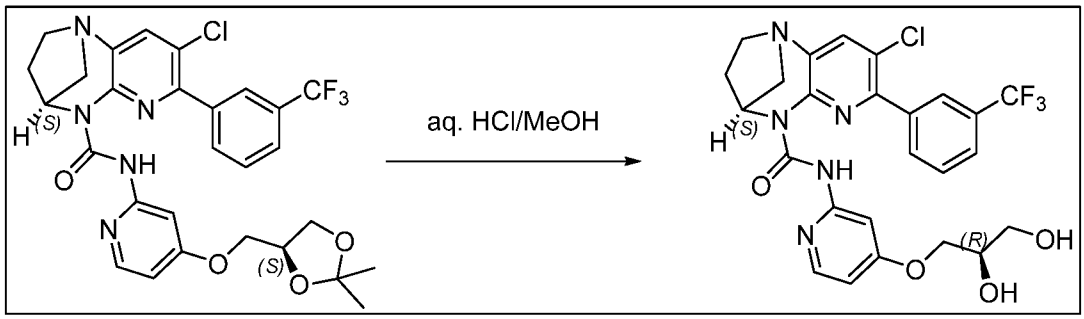


To a solution of (4*S*)-8-chloro-N-(2-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido [2,3-b][1,4]diazepine-5(2H)-carboxamide (6.5 g, 11.00 mmol) in methanol (65 mL) under nitrogen at 0 °C was added aq. HCl (15 mL, 494 mmol, 36 %) and stirred at RT for 2 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 solvent was evaporated under reduced pressure. The residue was diluted with water (30 mL) and extracted into DCM (2x100 mL). Combined organic extracts were dried over anhydrous sodium sulphate, filtered and filtrate was evaporated and crude was triturated with ether (50 mL) to afford (4*S*)-8-chloro-N-(2-((*S*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(*2H*)-carboxamide (5.2 g, 9.29 mmol, 84 % yield) as an off white solid. LCMS (*m/z*): 551.06 $[M+H]^+$, R_t = 2.14 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.05 (s, 1 H), 8.32 (d, *J*=5.70 Hz, 1 H), 8.13 - 7.92 (m, 2 H), 7.81 - 7.64 (m, 4 H), 5.64 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.21 - 4.12 (m, 2 H), 3.97 (dq, *J*=9.95, 5.09 Hz, 1 H), 3.73 - 3.57 (m, 2 H), 3.38 - 3.10 (m, 4 H), 3.02 (dd, *J*=12.28, 3.29 Hz, 1 H), 2.50 (t, *J*=6.36 Hz, 1 H), 2.35 (dddd, *J*=14.17, 10.00, 5.97, 4.06 Hz, 1 H), 2.14 - 2.00 (m, 1 H).

Example 31

Synthesis of (4*S*)-8-chloro-N-(4-((*R*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide

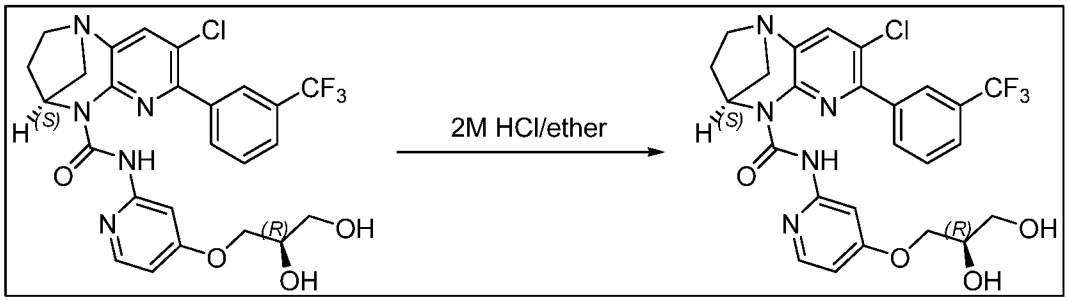


To stirred solution of (4*S*)-8-chloro-N-(4-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (3.2 g, 5.42 mmol) in Methanol (30 mL) was added hydrochloric acid (5 mL, 165 mmol) at 0 °C, 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). The solvent was evaporated and neutralized with sodium bicarbonate solution, filtered the obtained solid and washed with water and *n*-pentane (2x 20 mL) to afford the desired product (4*S*)-8-chloro-N-(4-((*R*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (1.2 g, 2.179 mmol, 40.2 % yield) as a white solid. LCMS (*m/z*): 550.09 $[M+H]^+$, Rt = 1.94 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.93 (s, 1 H), 8.20 (s, 1 H), 8.12 (d, *J*=7.67 Hz, 1 H), 8.04 (d, *J*=5.92 Hz, 1 H), 7.78 - 7.70 (m, 2 H), 7.68 - 7.59 (m, 2 H), 6.53 (dd, *J*=5.70, 2.41 Hz, 1 H), 5.63 (dd, *J*=5.81, 3.18 Hz, 1 H), 4.18 - 4.08 (m, 3 H), 3.87 - 3.68 (m, 2 H), 3.36 - 3.12 (m, 3 H), 3.01 (dd, *J*=12.28, 3.29 Hz, 1 H), 2.34 (dddd, *J*=14.11, 10.00, 6.03, 4.06 Hz, 1 H), 2.15 - 2.01 (m, 2 H), 1.58 (s, 1 H).

Example 32

Synthesis of (4*S*)-8-chloro-N-(4-((*R*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide, Hydrochloride

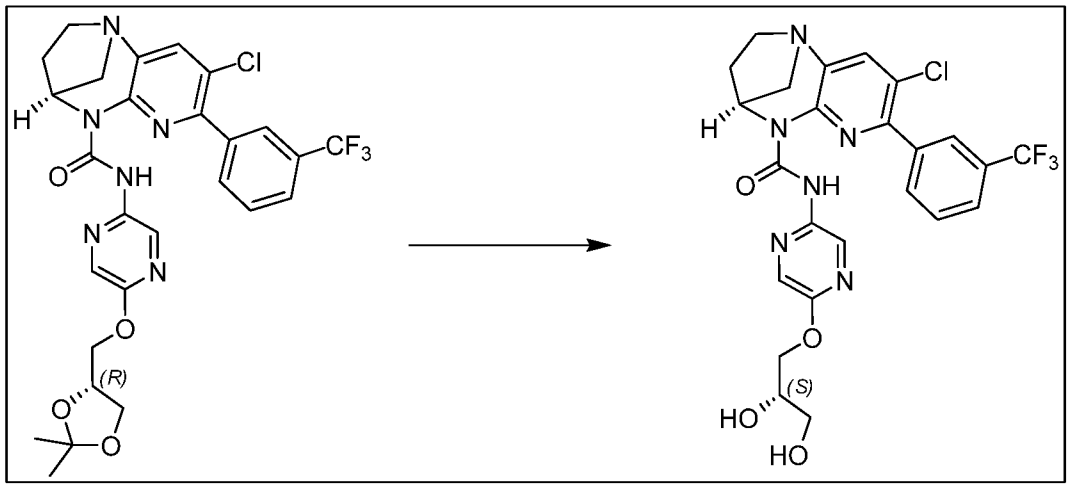


To stirred solution of (4*S*)-8-chloro-N-(4-((*R*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxa mide (100 mg, 0.182 mmol) in Methanol (10 mL) was added ether HCl (2M) (4.55 mL, 9.09 mmol) at 0 °C, over a period of 5 min. Then the reaction mixture was stirred at 30 °C for 2 h. (TLC eluent: 10% MeOH in DCM: R_f-0.5; UV active). The solvent was evaporated and washed with *n*-pentane (2 x 20 mL) to afford the desired product (4*S*)-8-chloro-N-(4-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide, Hydrochloride (65 mg, 0.110 mmol, 60.5 % yield) as an off white solid. LCMS (*m/z*): 550.09 $[M+H]^+$ R_t = 1.94 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.06 (s, 1 H), 8.22 - 8.07 (m, 4 H), 7.96 - 7.88 (m, 1 H), 7.79 - 7.85 (m, 1 H), 7.18 (s, 1 H), 6.91 (d, *J*=5.70 Hz, 1 H), 5.50 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.13 (dd, *J*=9.98, 3.84 Hz, 1 H), 3.97 (dd, *J*=9.87, 6.36 Hz, 1 H), 3.90 - 3.80 (m, 3 H), 3.53 - 3.23 (m, 6 H), 2.43 - 2.28 (m, 1 H), 2.11 (dt, *J*=13.65, 7.10 Hz, 1 H).

Example 33

Synthesis of (4*S*)-8-chloro-N-(5-((*S*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

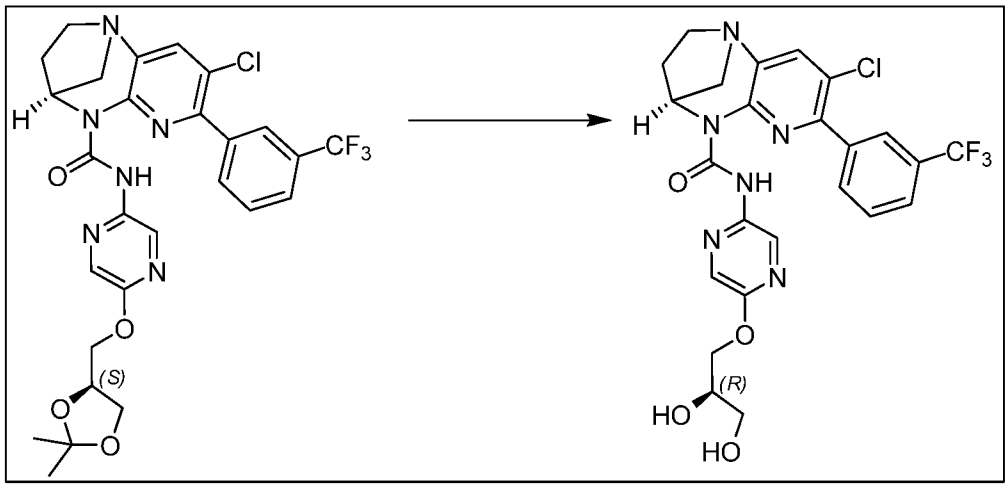


To a stirred solution of (4*S*)-8-chloro-N-(5-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (500 mg, 0.846 mmol) in methanol (10 mL) at RT was added aq. HCl (2 mL, 65.8 mmol) and stirred for 1 h. (TLC system:5% MeOH in DCM, Rf value: 0.3). Reaction mixture was concentrated to remove methanol and the reside was basified with saturated $NaHCO_3$ (10 mL) solution at 10 °C, the obtained solid was filtered, washed with water (10 mL) and dried under high vaccum to obtain desired pure product (4*S*)-8-chloro-N-(5-((*S*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (300 mg, 0.543 mmol, 64.2 % yield) as light yellow solid. LCMS (*m/z*): 551.03 $[M+H]^+$, Rt = 2.35 min

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.95 (s, 1 H), 8.89 (d, *J*=1.32 Hz, 1 H), 8.14 (s, 1 H), 8.06 (d, *J*=8.11 Hz, 1 H), 7.93 (d, *J*=1.32 Hz, 1 H), 7.57 - 7.78 (m, 3 H), 5.67 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.32 - 4.52 (m, 2 H), 4.07 (dq, *J*=9.65, 4.75 Hz, 1 H), 3.64 - 3.80 (m, 2 H), 3.11 - 3.37 (m, 4 H), 3.02 (dd, *J*=12.28, 3.29 Hz, 1 H), 2.22 - 2.47 (m, 2 H), 2.09 (dt, *J*=14.20, 7.04 Hz, 1 H)

Example 34

Synthesis of (4*S*)-8-chloro-N-(5-((*R*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

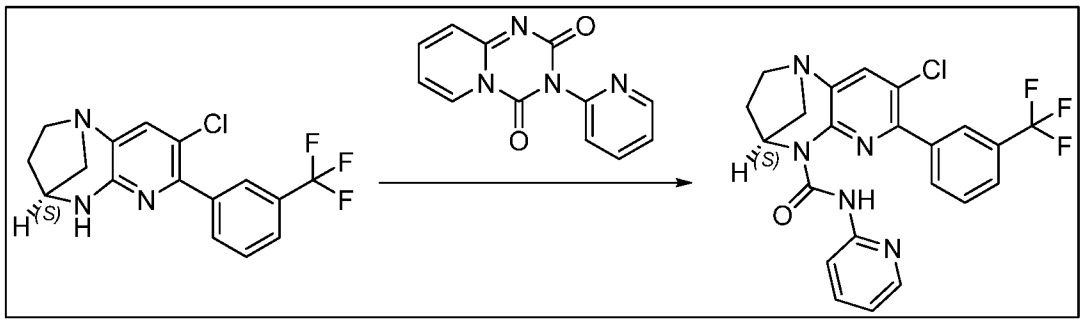


To a stirred solution of (4*S*)-8-chloro-N-(5-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (500 mg, 0.846 mmol) in methanol (10 mL) at RT was added aq. HCl (0.026 mL, 0.846 mmol) and stirred for 1 h. (TLC eluent: 5% MeOH in DCM R_f: 0.3; UV active). Reaction mixture was concentrated to remove methanol and the reside was basified with saturated $NaHCO_3$ (10 mL) solution at 10 °C, the obtained solid was filtered, washed with water (10 mL) and dried under high vaccum to obtain desired pure product (4*S*)-8-chloro-N-(5-((*R*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (350 mg, 0.631 mmol, 74.6 % yield) as light yellow solid. LCMS (*m/z*): 551.03 $[M+H]^+$; Rt = 2.45 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.95 (s, 1 H), 8.89 (d, *J*=1.32 Hz, 1 H), 8.14 (s, 1 H), 8.06 (d, *J*=7.67 Hz, 1 H), 7.93 (d, *J*=1.32 Hz, 1 H), 7.56 - 7.79 (m, 3 H), 5.67 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.34 - 4.53 (m, 2 H), 4.07 (dq, *J*=9.87, 4.97 Hz, 1 H), 3.64 - 3.82 (m, 2 H), 3.11 - 3.36 (m, 4 H), 3.02 (dd, *J*=12.28, 3.29 Hz, 1 H), 2.23 - 2.44 (m, 2 H), 1.94 - 2.20 (m, 1 H)

Example 35

Synthesis of (4*S*)-8-chloro-N-(pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

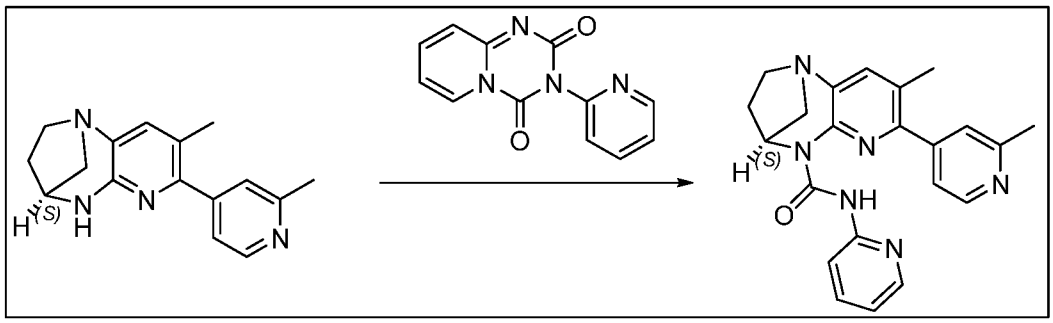


To a stirred solution of (4*S*)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 0.883 mmol) in THF (20 mL) was added NaH (31.8 mg, 1.325 mmol) at 0 °C. Then the reaction mixture was stirred at 30 °C for 30 min and added 3-(pyridin-2-yl)-2H-pyrido[1,2-*a*][1,3,5]triazine-2,4(3*H*)-dione (255 mg, 1.060 mmol). The reaction mixture was stirred at 70 °C for 15 h. (TLC: 10% MeOH in Ethylacetate, Rf: 0.8). Allowed to cool to room temperature and was diluted with cold water (20 mL), extracted with ethyl acetate (2X40 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the crude compound. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 90 % EtOAc/pet ether) and followed by prep HPLC (MP-A: 5mM Ammonium Bicarbonate (Aq) MP-B: Acetonitrile Column: symmetryc8(300x21.2)7µ Method: T/%B: ISO(20:80) Flow: 18ml/min Solubility: excess THF+ACN+MEOH) to afford the desired product (4*S*)-8-chloro-*N*-(pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (205 mg, 0.446 mmol, 50.5 % yield) as an off white solid. LCMS (*m/z*): 460.01 $[M+H]^+$, Rt: 2.83 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.91 (s, 1 H), 8.26 - 8.20 (m, 2 H), 8.16 - 8.06 (m, 2 H), 7.73 (d, *J*=7.67 Hz, 1 H), 7.68 - 7.58 (m, 3 H), 6.95 (ddd, *J*=7.29, 4.88, 0.99 Hz, 1 H), 5.68 (dd, *J*=6.03, 3.18 Hz, 1 H), 3.37 - 3.13 (m, 3 H), 3.06 - 2.94 (m, 1 H), 2.34 (dddd, *J*=14.20, 10.08, 6.08, 4.06 Hz, 1 H), 2.17- 1.98 (m, 1 H).

Example 36

Synthesis of (4*S*)-8-methyl-7-(2-methylpyridin-4-yl)-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

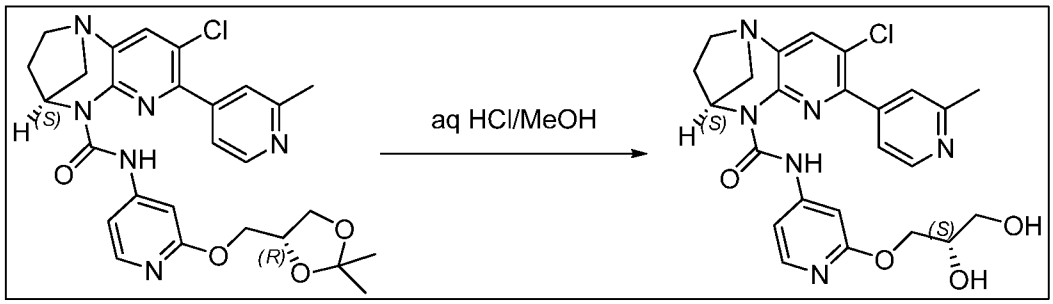


To a solution of (4*S*)-8-methyl-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 1.126 mmol) in Tetrahydrofuran (THF) (15 mL) was added NaH (54.1 mg, 2.253 mmol) at 0 °C. Then the reaction mixture was stirred at 30 °C for 1 h. under nitrogen and 3-(pyridin-2-yl)-2H-pyrido[1,2-a][1,3,5]triazine-2,4(3*H*)-dione (541 mg, 2.253 mmol) was added then the reaction mixture was stirred at 70 °C for 15 h. (TLC System;. Rf- 0.5, 5% methanol in dichloromethane).The reaction mixture was allowed to cool to room temperature and poured in to cold water (30 mL), extracted with ethyl acetate (2x50 mL). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under vacuum to obtained crude product. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 3% MeOH in EtOAc) and further purified by Prep HPLC (Conditions: MP-A: 5mM Ammonium Bicarbonate (Aq) MP-B: Acetonitrile Column: Xterra C18 (250x19) 10u Method :50:50 Flow: 18 ml/min Solubility: ACN+THF) to afford the desired product (4S)-8-methyl-7-(2-methylpyridin-4-yl)-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido [2,3-b][1,4] diazepine-5(2H)-carboxamide (132 mg, 0.339 mmol, 30.1 % yield) as an off white solid. LCMS (*m/z*): 387.0 $[M+H]^+$, Rt: 3.41 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.28 (s, 1 H), 8.61 (d, *J*=5.26 Hz, 1 H), 8.31 - 8.24 (m, 1 H), 8.13 (d, *J*=8.55 Hz, 1 H), 7.71 - 7.62 (m, 2 H), 7.45 (s, 1 H), 7.39 (dd, *J*=5.04, 1.53 Hz, 1 H), 6.95 (ddd, *J*=7.29, 4.99, 0.88 Hz, 1 H), 5.66 (dd, *J*=5.81, 3.18 Hz, 1 H), 3.34 - 3.11 (m, 3 H), 3.05 - 2.96 (m, 1 H), 2.71 (s, 3 H), 2.42 (s, 3 H), 2.36 - 2.26 (m, 1 H), 2.06 (dt, *J*=14.03, 7.02 Hz, 1 H).

Example 37

Synthesis of (4*S*)-8-chloro-N-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

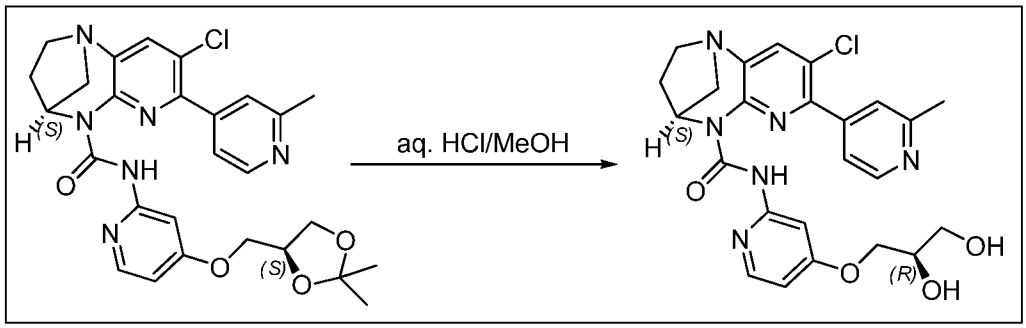


To a stirred solution of (4*S*)-8-chloro-*N*-(2-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (350 mg, 0.652 mmol) in methanol (5 mL) was added HCl (3.96 µL, 0.130 mmol) drop wise over a period of 5 min at 0 °C. Then the reaction mixture was stirred at 30 °C for 2 h. (TLC eluent: 5% MeOH in DCM: R_f-0.6) and concentrated in *vaccuo*, neutralized with Saturated $NaHCO_3$ solution and filtered the obtained solid, washed with ether (2x 20 mL) to afforded the desired product (4*S*)-8-chloro-*N*-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (180 mg, 0.361 mmol, 55.3 % yield) as an off white solid. LCMS (*m/z*): 497.10 $[M+H]^+$, Rt: 1.41 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.71 (s, 1 H), 8.66 (d, *J*=5.04 Hz, 1 H), 7.98 (d, *J*=5.70 Hz, 1 H), 7.88 (s, 1 H), 7.62 (s, 1 H), 7.58 (d, *J*=5.26 Hz, 1 H), 6.85 (d, *J*=1.53 Hz, 1 H), 6.80 - 6.76 (m, 1 H), 5.44 (dd, *J*=5.92, 2.85 Hz, 1 H), 4.85 (d, *J*=5.04 Hz, 1 H), 4.59 (t, *J*=5.70 Hz, 1 H), 4.22 (dd, *J*=10.85, 4.49 Hz, 1 H), 4.11 (dd, *J*=10.96, 6.14 Hz, 1 H), 3.76 (dq, *J*=10.61, 5.45 Hz, 1 H), 3.42 (t, *J*=5.81 Hz, 2 H), 3.23 - 3.29 (m, 1 H), 3.14 - 3.06 (m, 2 H), 3.02 - 2.94 (m, 1 H), 2.61 (s, 3 H), 2.29 - 2.19 (m, 1 H), 2.01 - 1.90 (m, 1 H).

Example 38

Synthesis of (4S)-8-chloro-N-(4-((*R*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

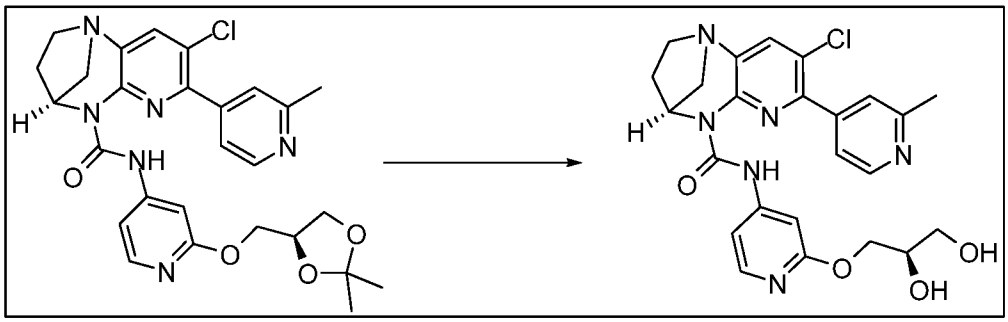


To a stirred solution of (4*S*)-8-chloro-N-(4-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (180 mg, 0.335 mmol) in methanol (8 mL) was added HCl (0.102 mL, 3.35 mmol) drop wise over a period of 5 min at 0 °C. Then the reaction mixture was stirred at 30 °C for 2 h. (TLC eluent: 5% MeOH in DCM : R_f-0.1; UV active), and evaporated the solvent. The reaction mixture was neutralized with sodium bicarbonate solution and filtered the obtained solid, washed with ether (2x 15 mL) to afford the desired product (4*S*)-8-chloro-N-(4-((*R*)-2,3-dihydroxypropoxy) pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyri do[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (88 mg, 0.174 mmol, 51.8 % yield) as a brown solid. LCMS (*m/z*): 497.1 $[M+H]^+$, Rt = 1.26 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.91 (s, 1 H), 8.62 (d, *J*=4.82 Hz, 1 H), 8.08 (d, *J*=5.48 Hz, 1 H), 7.78 (d, *J*=18.20 Hz, 2 H), 7.69 - 7.62 (m, 2 H), 6.56 (d, *J*=3.73 Hz, 1 H), 4.13 (s, 3 H), 3.89 - 3.70 (m, 2 H), 3.37 - 3.10 (m, 3 H), 3.01 (d, *J*=12.50 Hz, 1 H), 2.71 (m, 4 H), 2.65 - 2.62 (m, 1 H), 2.33 (s, 1 H), 2.21 (s, 1 H), 2.14-2.00 (m, 1 H).

Example 39

Synthesis of (4*S*)-8-chloro-N-(2-((*R*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide:

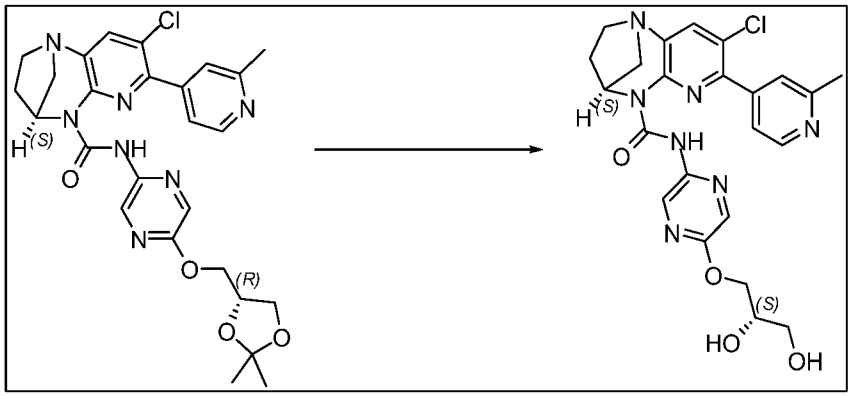


To a stirred solution of (4S)-8-chloro-N-(2-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (350.0 mg, 0.652 mmol) in Methanol (5.0 mL) was added aq HCl (0.990 mL, 32.6 mmol) at 0 °C and stirred for 5 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 (3x10 mL). Combined organic extracts were dried over anhydrous sodium sulphate, filtered and filtrate was evaporated *in vacuo* to afford the pure (4*S*)-8-chloro-N-(2-((*R*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (190.5 mg, 0.375 mmol, 57.5 % yield) as an off white solid. LCMS (*m/z*): 497.10 $[M+H]^+$, R_t =1.40 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.80 (s, 1 H), 8.70 (d, *J*=5.70 Hz, 1 H), 7.90 (d, *J*=5.92 Hz, 1 H), 7.68 (s, 1 H), 7.49 - 7.45 (m, 2 H), 6.94 (d, *J*=1.75 Hz, 1 H), 6.85 (dd, *J*=5.92, 1.75 Hz, 1 H), 5.64 (dd, *J*=6.03, 3.18 Hz, 1 H), 4.43 - 4.41 (m, 2 H), 4.29 (d, *J*=5.48 Hz, 1 H), 4.01 - 3.95 (m, 1 H), 3.72 - 3.60 (m, 2 H), 3.35 - 3.19 (m, 2 H), 3.16 - 3.10 (m, 1 H), 3.05 - 3.00 (m, 1 H), 2.92 (t, *J*=6.47 Hz, 1 H), 2.69 (s, 3 H), 2.40 - 2.30 (m, 1 H), 2.07 (dt, *J*=14.20, 7.26 Hz, 1 H).

Example 40

Synthesis of (4*S*)-8-chloro-*N*-(5-((*S*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(2-methylpyri din-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

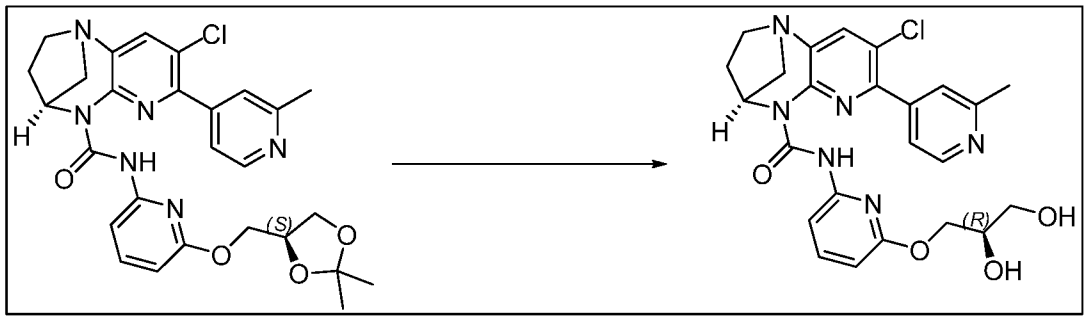


To a stirred solution of (4*S*)-8-chloro-*N*-(5-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (450 mg, 0.836 mmol) in Methanol (20 mL) was added 2.0 M HCl (5 mL, 10.00 mmol) at room temperature. The resulting reaction mixture was stirred at RT for 1 h. (TLC system: 10% MeOH in DCM, R*f*: 0.4). Reaction mixture was concentrated under reduced pressure to remove the methanol and basified with saturated sodium bicarbonate solution (20 mL), extracted with DCM (3X 30 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, the obtained semi solid was washed with Diethyl ether to obtain a solid compound, which was filtered to afford the desired product (4*S*)-8-chloro-N-(5-((*S*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (205 mg, 0.407 mmol, 48.7 % yield) as a pale yellow solid. LCMS (*m/z*): 498.14 $[M+H]^+$, R_t = 1.14 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.95 (s, 1 H) 8.92 (d, *J*=1.32 Hz, 1 H) 8.63 (d, *J*=5.26 Hz, 1 H) 7.97 (d, *J*=1.32 Hz, 1 H) 7.71 (s, 1 H) 7.67 (s, 1 H) 7.63 (d, *J*=5.04 Hz, 1 H) 5.66 (dd, *J*=5.81, 3.18 Hz, 1 H) 4.50 - 4.36 (m, 2 H) 4.09 (br s, 1 H) 3.81 - 3.66 (m, 2 H) 3.37 - 3.11 (m, 4 H) 3.06 - 2.99 (m, 1 H) 2.69 (s, 3 H) 2.46 - 2.31 (m, 2 H) 2.09 (dt, *J*=14.03, 7.02 Hz 1 H).

Example 41

Synthesis of (4*S*)-8-chloro-N-(6-((*R*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

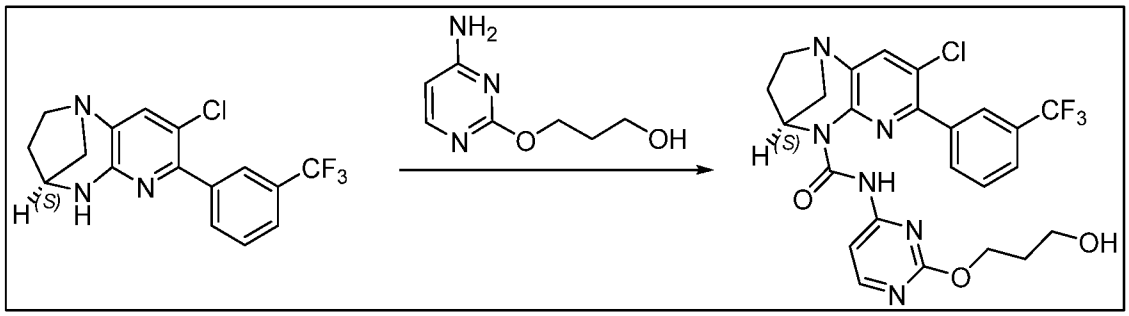


To a stirred solution of (4*S*)-8-chloro-N-(6-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide in methanol (6 mL) at 0 °C, was added aq. HCl (6 mL, 12.00 mmol, 2 M) over a period of 10 min. and the clear solution was stirred at RT for 30 min. (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 to get orange coloured precipitation. The orange solid was filtered and dried in *vacuo* to afford (4*S*)-8-chloro-N-(6-((*R*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (159 mg, 0.316 mmol, 56.6 % yield) as an orange solid. LCMS (m/z): 497.1 $[M+H]^+$, Rt = 1.54 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.44 (s, 1 H), 8.65 (d, *J*=5.04 Hz, 1 H), 7.85 (s, 1 H), 7.57 - 7.71 (m, 2 H), 7.40 - 7.57 (m, 2 H), 6.44 (dd, *J*=7.67, 1.10 Hz, 1 H), 5.48 (dd, *J*=5.81, 3.18 Hz, 1 H), 4.76 (br s, 1 H), 4.57 (br s, 1 H), 3.76 (br d, *J*=7.23 Hz, 1 H), 3.61 - 3.71 (m, 2 H), 3.32 - 3.49 (m, 2 H), 3.22 (m , 1 H), 3.04 - 3.19 (m, 2 H), 2.97 (br dd, *J*=12.06, 3.07 Hz, 1 H), 2.53 - 2.58 (m, 3 H), 2.22 (m, 1 H), 1.84 - 1.95 (m, 1 H).

Example 42

Synthesis of (4*S*)-8-chloro-N-(2-(3-hydroxypropoxy) pyrimidin-4-yl)-7-(3-(trifluoromet hyl) phenyl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-*b*][1,4]diazepine-5(2*H*)-carboxamide

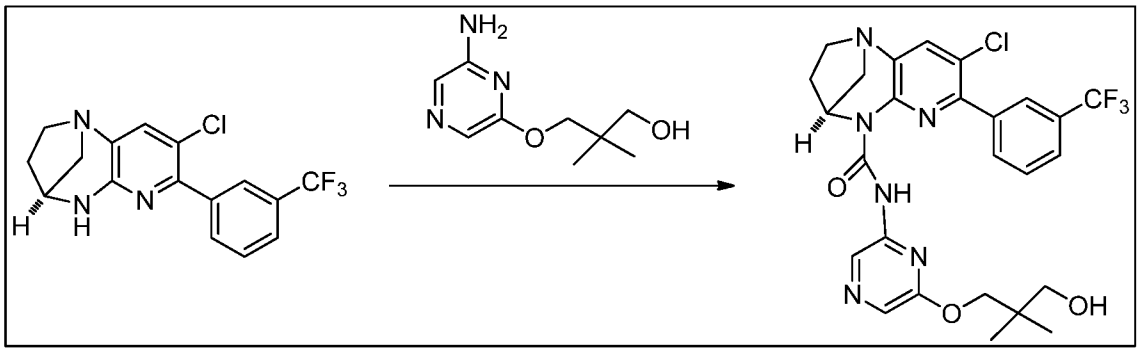


To a stirred solution of (4*S*)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 0.883 mmol) in Tetrahydrofuran (10 mL) were added triphosgene (157 mg, 0.530 mmol) and triethylamine (0.738 mL, 5.30 mmol) at room temperature and stirred for 30 min. then 3-((4-aminopyrimidin-2-yl)oxy)propan-1-ol (299 mg, 1.766 mmol) was added to the reaction mixture at 28 °C and stirred at 80 °C for 16 h. (TLC system:5% Methanol in Ethyl Acetate. R_f value: 0.4, UV). The reaction mixture was allowed to cool to room temperature and diluted with water (40 mL), extracted with ethyl acetate (2X50 mL). The combined organic layer was washed with brine solution (30 mL) and dried over anhydrous sodium sulphate, filtered and concentrated to afford the crude compound. The crude compound was purified by flash column chromatography (silica gel: 100-200 mesh, Eluent: 80% ethyl acetate in pet ether) to afford the desired product (4*S*)-8-chloro-N-(2-(3-hydroxypropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (65 mg, 0.117 mmol, 13.27% yield) as an off-white solid. LCMS (*m/z*): 535.15 $[M+H]^+$, *Rt* = 2.38 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.97 (s, 1 H), 8.40 (d, *J*=5.70 Hz, 1 H), 8.07 (d, *J*=7.89 Hz, 1 H), 8.04 (s, 1 H), 7.92 -7.86 (m, 2 H), 7.83- 7.78 (m, 1 H), 7.64 (d, *J*=5.70 Hz, 1 H), 5.46 (dd, *J*=5.70, 3.07 Hz, 1 H), 4.48 (t, *J*=5.15 Hz, 1 H), 3.97- 3.87 (m, 2 H), 3.50- 3.42 (m, 2 H), 3.25 (s, 1 H), 3.17 -3.06 (m, 2 H), 2.99 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.34- 2.19 (m, 1 H), 2.04 -1.92 (m, 1 H), 1.72 (quin, *J*=6.30 Hz, 2 H).

Example 43

Synthesis of (4*S*)-8-chloro-N-(6-(3-hydroxy-2,2-dimethylpropoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

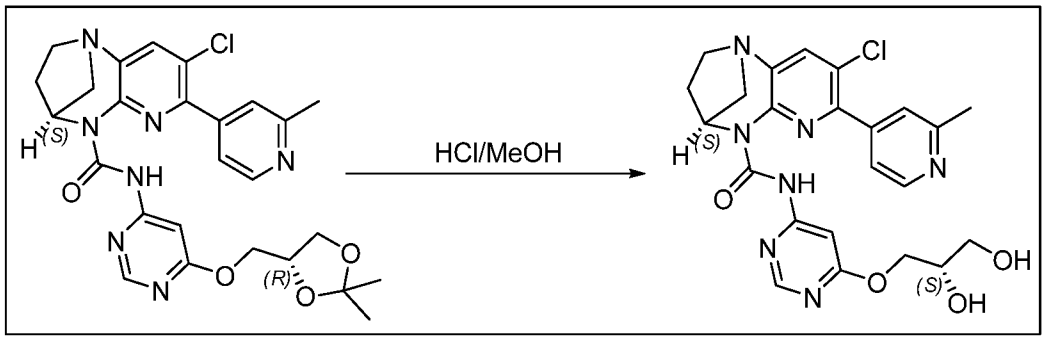


To a stirred solution of 3-((6-aminopyrazin-2-yl)oxy)-2,2-dimethylpropan-1-ol (406 mg, 2.060 mmol) in Tetrahydrofuran (15 mL) were added triphosgene (183 mg, 0.618 mmol) and triethylamine (0.862 mL, 6.18 mmol) at 10 °C and stirred for 30 min. then (4*S*)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (350 mg, 1.030 mmol) was added to the reaction mixture at 28 °C and stirred at 80 °C for 16 h. (TLC system: 5% Methanol in Ethyl Acetate. R_f value: 0.4, UV). Reaction mixture was allowed to cool to room temperature and diluted with water (40 mL), extracted with ethyl acetate (2X70 mL). The combined organic layer was washed with brine solution (30 mL) and dried over anhydrous sodium sulphate, filtered and concentrated to afford crude compound. The crude compound was purified by flash column chromatography (silica gel: 100-200 mesh, 100% ethyl acetate) to afford the desired product (4*S*)-8-chloro-N-(6-(3-hydroxy-2,2-dimethylpropoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methano pyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (146 mg, 0.256 mmol, 24.83 % yield) as an off-white solid. LCMS (*m/z*): 563.19 $[M+H]^+$, R_t=2.71 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.67 (s, 1 H), 8.88 (s, 1 H), 8.03 (s, 1 H), 7.96 (d, *J*=7.67 Hz, 1 H), 7.90 (s, 1 H), 7.75 -7.70 (m, 1 H), 7.70- 7.61 (m, 2 H), 5.70 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.74 -3.63 (m, 2 H), 3.36- 3.20 (m, 4 H), 3.11 - 3.19 (m, 2 H), 3.02 (dd, *J*=12.17, 3.18 Hz, 1 H), 2.43- 2.30 (m, 1 H), 2.09 (dt, *J*=14.31, 7.21 Hz, 1 H), 0.87 (d, *J*=1.75 Hz, 6 H).

Example 44

Synthesis of (4*S*)-8-chloro-*N*-(6-((*S*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide

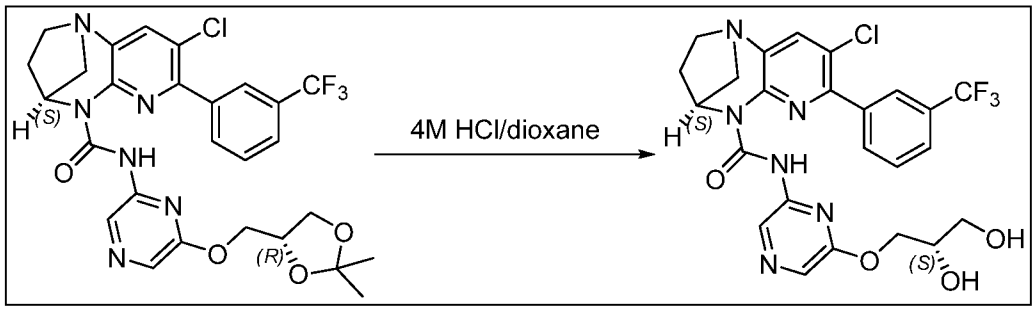


To a stirred solution of (4*S*)-8-chloro-*N*-(6-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide (185 mg, 0.344 mmol) in Methanol (5 mL) was added hydrochloric acid (0.145 mL, 1.719 mmol) at 0 °C then stirred at RT for 2 h. (TLC eluent: 10% MeOH in DCM R_f: 0.4; UV active). 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 (2x10 mL) to afford the desired product (4*S*)-8-chloro-*N*-(6-((*S*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (148 mg, 0.284 mmol, 82 % yield) as a pale brown solid. LCMS (*m/z*): 498.0 $[M+H]^+$, Rt = 1.38 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.03 (s, 1 H), 8.62 (d, *J*=5.26 Hz, 1 H), 8.47 (d, *J*=0.88 Hz, 1 H), 7.88 (s, 1 H), 7.70 (s, 1 H), 7.65 (dd, *J*=5.26, 1.32 Hz, 1 H), 7.41 (d, *J*=0.88 Hz, 1 H), 5.45 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.97 (s, 1 H), 4.67 (br s, 1 H), 4.35 (dd, *J*=10.74, 4.17 Hz, 1 H), 4.20 (dd, *J*=10.85, 6.47 Hz, 1 H), 3.82 - 3.77 (m, 1 H), 3.46 - 3.41 (m, 2 H), 3.27 - 3.23 (m, 1 H), 3.16 - 3.09 (m, 2 H), 2.98 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.61 (s, 3 H), 2.25 (td, *J*=6.85, 4.06 Hz, 1 H), 2.01-1.93 (m, 1 H).

Example 45

Synthesis of (4*S*)-8-chloro-*N*-(6-((*S*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

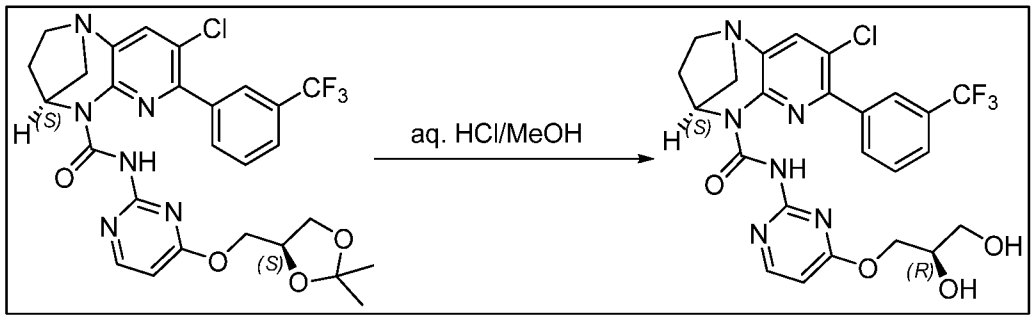


To a stirred solution of (4*S*)-8-chloro-*N*-(6-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (6.0 g, 10.15 mmol) in 1,4-Dioxane (30 mL) was added 4M HCl in dioxane (15.06 g, 50.8 mmol) at room temperature and stirred for another 4 h. (TLC system: 100% ethylacetate. Rf value: 0.2). The reaction mixture was evaporated and added saturated $NaHCO_3$ solution (50 mL), filtered the obtained solid and dried under *vaccume* to afford the desire product (4*S*)-8-chloro-*N*-(6-((*S*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido [2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (5.4 g, 9.80 mmol, 97 % yield) as a white solid. LCMS (*m/z*): 551.13 $[M+H]^+$, R_t = 2.18 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.69 (s, 1 H), 8.87 (s, 1 H), 8.05 - 7.99 (m, 2 H), 7.94 - 7.80 (m, 4 H), 5.50 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.89 (d, *J*=5.04 Hz, 1 H), 4.62 (t, *J*=5.59 Hz, 1 H), 3.83 - 3.66 (m, 3 H), 3.40 - 3.23 (m, 3 H), 3.18 - 3.07 (m, 2 H), 3.01 - 2.94 (m, 1 H), 2.30 - 2.20 (m, 1 H), 1.98 (dt, *J*=14.14, 7.18 Hz, 1 H).

Example 46

Synthesis of (4*S*)-8-chloro-N-(4-((*R*)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

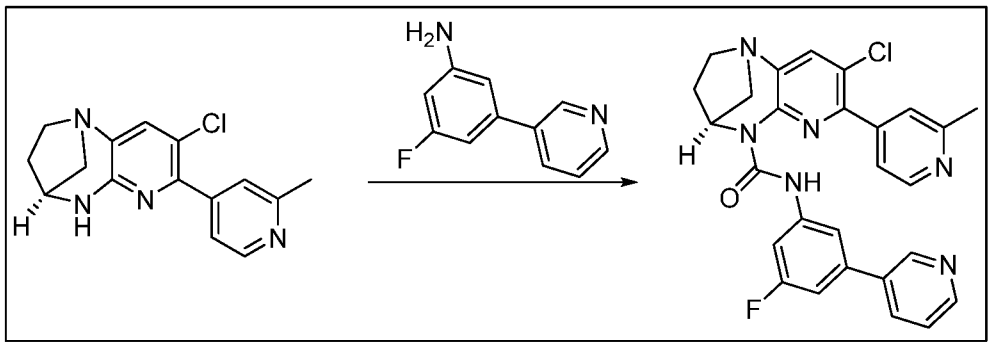


To a stirred solution of (4*S*)-8-chloro-*N*-(4-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido [2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (200 mg, 0.338 mmol) in Methanol (5 mL) was added aq HCl (0.294 mL, 3.38 mmol) at room temperature and stirred for 2 h. (TLC system: 100% ethylacetate, *R*f value: 0.3). Then the reaction mixture was quenched with saturated $NaHCO_3$ solution (10 mL) and extracted with DCM (2x30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford the desired product (4*S*)-8-chloro-*N*-(4-((*R*)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (130 mg, 0.236 mmol, 69.6 % yield) as a white solid. LCMS (*m/z*): 551.10 $[M+H]^+$, *Rt* = 1.92 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.94 (s, 1 H), 8.22 (d, *J*=5.70 Hz, 1 H), 8.11 - 8.05 (m, 2 H), 7.88 - 7.75 (m, 3 H), 6.55 (d, *J*=5.70 Hz, 1 H), 5.46 (dd, *J*=6.03, 2.96 Hz, 1 H), 4.93 (d, *J*=4.82 Hz, 1 H), 4.63 (t, *J*=5.70 Hz, 1 H), 4.23 - 4.16 (m, 1 H), 4.13 - 4.08 (m, 1 H), 3.78 - 3.71 (m, 1 H), 3.42 - 3.34 (m, 2 H), 3.28 - 3.24 (m, 1 H), 3.16 - 3.06 (m, 2 H), 2.98 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.29 - 2.19 (m, 1 H), 1.95 (dt, *J*=14.09, 7.32 Hz, 1 H).

Example 47

Synthesis of (4*S*)-8-chloro-N-(3-fluoro-5-(pyridin-3-yl)phenyl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

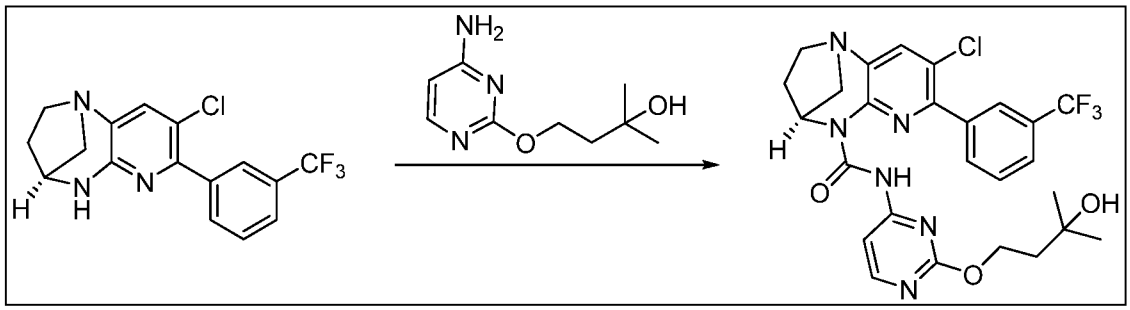


In a sealed tube, to a stirred solution of (4*S*)-8-chloro-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 1.046 mmol) in THF (15 mL) were added triphosgene (186 mg, 0.628 mmol) and triethylamine (0.875 mL, 6.28 mmol) at room temperature, and stirred for 30 min. Then, 3-fluoro-5-(pyridin-3-yl)aniline (236 mg, 1.255 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 (2x 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: 1 % methanol in ethylacetate) to afford the desired product (4*S*)-8-chloro-N-(3-fluoro-5-(pyridin-3-yl)phenyl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (150 mg, 0.295 mmol, 28.2 % yield) as a yellow solid. LCMS (*m/z*): 501.09 $[M+H]^+$, R_t = 1.89 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.80 (s, 1 H), 8.77 - 8.74 (m, 1 H), 8.68 - 8.65 (m, 1 H), 8.63 (dd, *J*=4.82, 1.75 Hz, 1 H), 7.71 - 7.66 (m, 2 H), 7.50 - 7.45 (m, 2 H), 7.40 - 7.30 (m, 3 H), 7.00 - 6.95 (m, 1 H), 5.67 (dd, *J*=5.81, 3.18 Hz, 1 H), 3.37 - 3.12 (m, 3 H), 3.06 - 3.00 (m, 1 H), 2.55 (s, 3 H), 2.40 - 2.31 (m, 1 H), 2.14 - 2.05 (m, 1 H).

Example 48

Synthesis of (4*S*)-8-chloro-N-(2-(3-hydroxy-3-methylbutoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

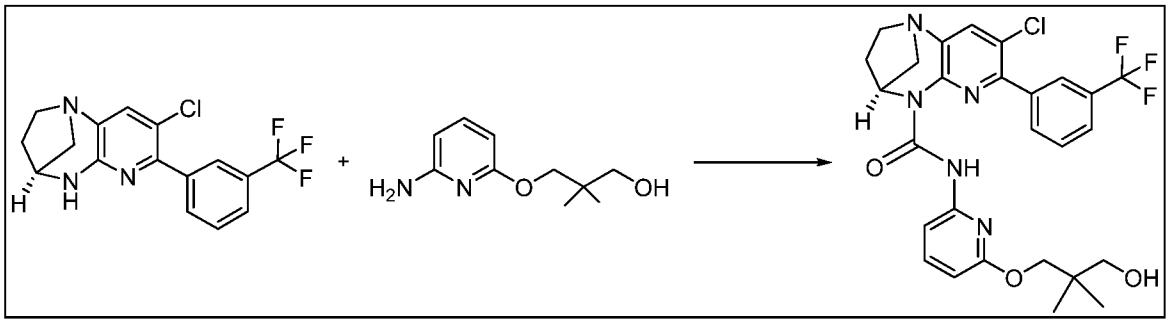


In a sealed tube, to a stirred solution of (4*S*)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 0.883 mmol) in THF (15 mL) were added triphosgene (157 mg, 0.530 mmol) and triethylamine (0.738 mL, 5.30 mmol) at room temperature and stirred for 30 min. Then, 4-((4-aminopyrimidin-2-yl)oxy)-2-methylbutan-2-ol (348 mg, 1.766 mmol) was added and stirred at 80 °C for 15 h. (TLC System: R_f- 0.4, 5% MeOH/ EtOAc). The reaction mixture was allowed to cool to room temperature and diluted with water (25 mL), extracted with EtOAc (2x 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: 1 % methanol in ethylacetate) to afford the desired product (4*S*)-8-chloro-N-(2-(3-hydroxy-3-methylbutoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (110 mg, 0.192 mmol, 21.75 % yield) as an off-white solid. LCMS (*m/z*): 563.12 $[M+H]^+$, R_t = 2.58 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.01 (s, 1 H), 8.34 (d, *J*=5.70 Hz, 1 H), 8.07 - 7.97 (m, 2 H), 7.76 - 7.63 (m, 4 H), 5.64 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.30 - 4.11 (m, 2 H), 3.43 - 3.11 (m, 3 H), 3.02 (dd, *J*=12.28, 3.29 Hz, 1 H), 2.40 - 2.28 (m, 1 H), 2.13 - 2.04 (m, 2 H), 1.88 (t, *J*=6.25 Hz, 2 H), 1.26 (s, 6 H).

Example 49

Synthesis of (4*S*)-8-chloro-N-(6-(3-hydroxy-2,2-dimethylpropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

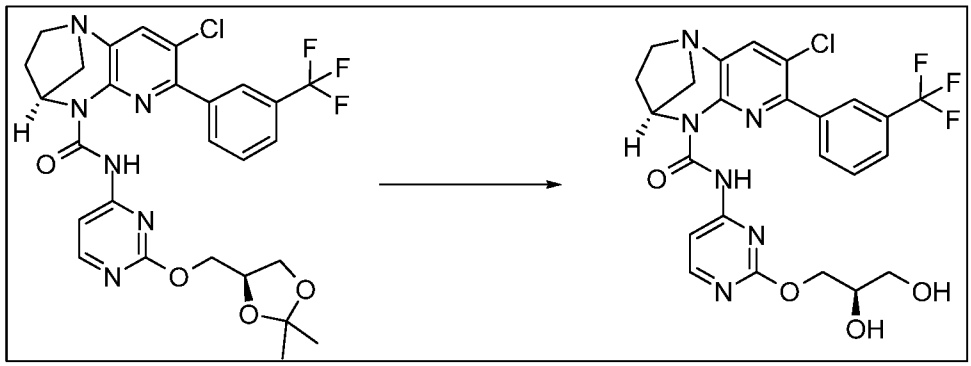


To a stirred solution of (4*S*)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (300 mg, 0.883 mmol) in THF (15 mL) under nitrogen was added triethylamine (0.738 mL, 5.30 mmol), triphosgene (262 mg, 0.883 mmol) and stirred at RT for 30 min. To this reaction mixture 3-((6-aminopyridin-2-yl)oxy)-2,2-dimethylpropan-1-ol (520 mg, 2.65 mmol) was added and heated at 70 °C for 16 h. (TLC eluent: 100%EtOAc in Hexane, R_f: 0.3, UV active). The reaction mixture was cooled to RT and water (10 mL) was added and extracted with EtOAc (3x10 mL). The combined organic extracts was dried over anhydrous sodiumsulfate, filtered and evaporated to get crude product. The crude was purified by prep HPLC (Conditions-Column: Xterra (250X21.1 mm, 10µ); Mobile Phase-A: 10 mM Ammonium Bicarbonate; Mobile phase-B: Acetionitrile; Column Temp: Ambient; Flow Rate: 18 ml/min: Diluent: THF+MEOH+ACN) to afford (4*S*)-8-chloro-N-(6-(3-hydroxy-2,2-dimethylpropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (128 mg, 0.224 mmol, 25.3 % yield). LCMS (*m/z*): 562.11 $[M+H]^+$, R_t = 2.93 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.56 (s, 1 H), 8.06 (s, 1 H), 8.01 (d, *J*=7.67 Hz, 1 H), 7.73 – 7.61 (m, 3 H), 7.57 - 7.51 (m, 2 H), 6.45 - 6.38 (m, 1 H), 5.68 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.67 (q, *J*=11.18 Hz, 2 H), 3.35 - 3.18 (m, 2 H), 3.13 (br d, *J*=7.02 Hz, 3 H), 3.00 (dd, *J*=12.28, 3.29 Hz, 1 H), 2.79 (br t, *J*=6.91 Hz, 1 H), 2.39 - 2.27 (m, 1 H), 2.14 - 2.03 (m, 1 H), 0.79 (d, *J*=5.04 Hz, 6 H)

Example 50

Synthesis of (4*S*)-8-chloro-N-(2-((*R*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide.

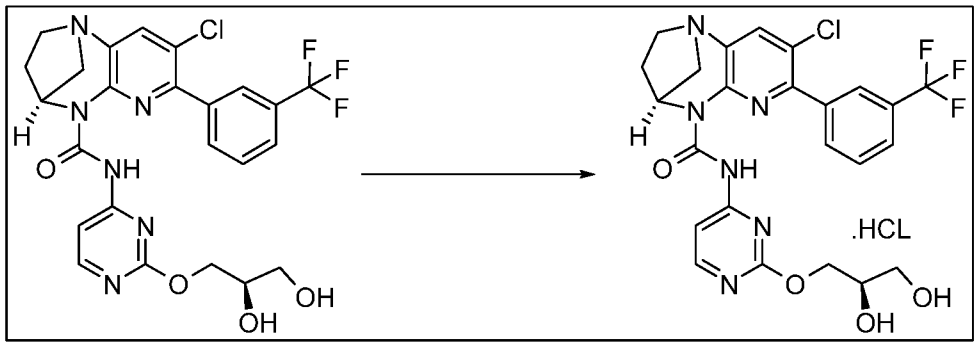


To a stirred solution of (4*S*)-8-chloro-N-(2-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (20 g, 33.8 mmol) in methanol (100 mL) under nitrogen at 0 °C was added aq. HCl (10 mL, 40.0 mmol, 36 %) and stirred at RT for 1 h. (TLC eluent: 5% Methanol in DCM, R_f: 0.3, UV active). The reaction mixture was concetrated and the residue basified with saturated $NaHCO_3$ solution (till pH-8-9) and stirred for 15 min at RT. The resultant solid was separated by filtration and taken in DMSO (20 mL) and water (600 mL) mixture and stirred at RT for 16 h. The solid was filtered, dried to afford pure (4*S*)-8-chloro-N-(2-((*R*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (15.3 g, 27.7 mmol, 82 % yield) as an off white solid. LCMS (*m/z*): 551.13 $[M+H]^+$, R_t = 2.15 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.02 (s, 1 H), 8.30 (d, *J*=5.70 Hz, 1 H), 8.06 - 7.97 (m, 2 H), 7.80 - 7.67 (m, 4 H), 5.62 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.18 - 4.04 (m, 2 H), 3.97 (dq, *J*=9.92, 5.10 Hz, 1 H), 3.77 (d, *J*=5.48 Hz, 1 H), 3.71 - 3.58 (m, 2 H), 3.37 - 3.20 (m, 2 H), 3.19 - 3.10 (m, 2 H), 3.02 (dd, *J*=12.28, 3.29 Hz, 1 H), 2.40 - 2.29 (m, 1 H), 2.14 - 2.01 (m, 1 H).

Example 51

Synthesis of (4S)-8-chloro-N-(2-((R)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide Hydrochloride

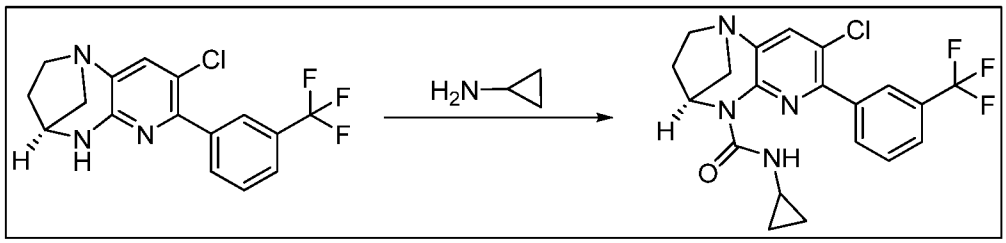


To a stirred solution of (4*S*)-8-chloro-N-(2-((*R*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (250 mg, 0.454 mmol) in diethylether (5 mL) under nitrogen at 0 °C was added 2.0 M HCl in diethylether (3 mL, 6.00 mmol) and stirred at RT for 1 h. (TLC eluent: 5% MeOH in DCM, R_f-0.3, UV active). The solvent was evaparated under reduced pressure and crude was triturated with diethylether (2x10 mL) to afford (4*S*)-8-chloro-N-(2-((*R*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide Hhydrochloride (220 mg, 0.369 mmol, 81 % yield) as a pale yellow solid. LCMS (*m/z*): 551.0 $[M+H]^+$, R_t = 3.45 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.93 (s, 1 H), 8.45 (d, *J*=5.70 Hz, 1 H), 8.15 - 7.97 (m, 3 H), 7.93 - 7.77 (m, 2 H), 7.69 (d, *J*=5.70 Hz, 1 H), 5.80 (br s, 4 H), 5.50 (br dd, *J*=5.48, 2.85 Hz, 1 H), 4.03 - 3.82 (m, 2 H), 3.77 - 3.64 (m, 1 H), 3.54 - 3.09 (m, 6 H), 2.42 - 2.28 (m, 1 H), 2.07 (dt, *J*=13.92, 7.07 Hz, 1 H).

Example 52

Synthesis of (4*S*)-8-chloro-N-cyclopropyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide.

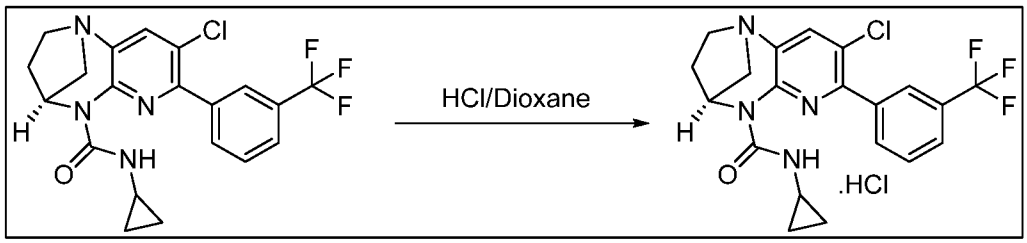


To a stirred solution of (4*S*)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (15 g, 44.2 mmol) in THF (600 mL, in sealed tube) were added triphosgene (6.55 g, 22.08 mmol) and DIPEA (38.6 mL, 221 mmol) at RT and stirred for 30 min. Then cyclopropanamine (6.30 mL, 88 mmol) was added and stirred at 80 °C for 16 h. (TLC System: R_f - 0.4, 90% EtOAc-Pet Ether). The reaction mixture was allowed to cool to room temperature and diluted it with water (500 ml), extracted with ethylacetate (3x 900 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: 80% ethyl acetate in hexane) to afford the desired product (4S)-8-chloro-N-cyclopropyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (5.1 g, 11.96 mmol, 27.1 % yield) as an off white solid. LCMS (*m/z*): 423.0 $[M+H]^+$, Rt = 2.65 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 10.05 (br s, 1 H), 7.94 -7.85 (m, 2 H), 7.71 (d, *J*=7.89 Hz, 1 H), 7.63 -7.53 (m, 2 H), 5.63 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.34 -3.13 (m, 2 H), 3.11 - 3.02 (m, 1 H), 2.97 -2.90 (m, 1 H), 2.77 (tq, *J*=7.13, 3.65 Hz, 1 H), 2.27 (dddd, *J*=14.09, 10.03, 6.14, 3.95 Hz, 1 H), 2.05 -1.96 (m, 1 H), 0.78- 0.65 (m, 2 H), 0.46 -0.35 (m, 2 H).

Example 53

Synthesis of (4*S*)-8-chloro-*N*-cyclopropyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide Hydrochloride

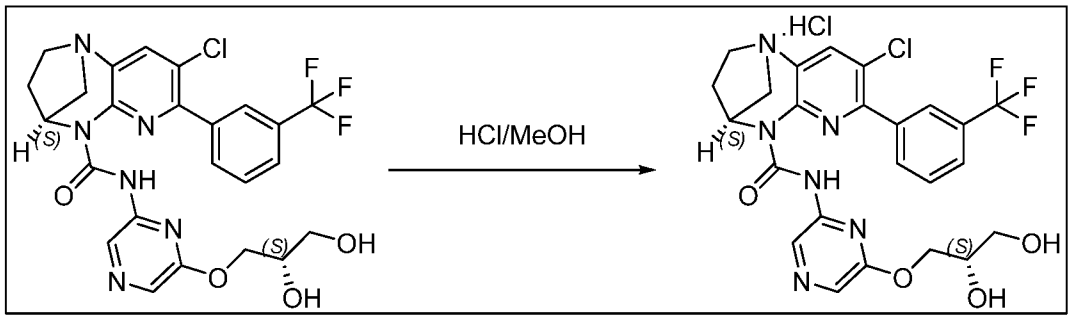


To a stirred solution of (4S)-8-chloro-N-cyclopropyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (100 mg, 0.237 mmol) in 1,4-Dioxane (3 mL) was added 4M HCl solution in 1,4 Dioxane (0.473 mL, 1.892 mmol) at 0 °C and stirred for 2 h. (TLC System: R_f - 0.1, EtOAc) at room temperature. The reaction mixture was concentrated under reduced pressure to obtain the residue and it was triturated with *n*-Pentane (3 x 10 mL). The resulting solid was filtered through a Buchner funnel, rinsed with *n*-pentane (5 mL) to afford the desired product (4S)-8-chloro-N-cyclopropyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide Hydrochloride (50 mg, 0.108 mmol, 45.7 % yield) as an off white solid. LCMS (*m/z*): 423.0 $[M+H]^+$, Rt = 2.67 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 9.65 (s, 1 H), 8.57 (s, 1 H), 7.96 -7.86 (m, 2 H), 7.79 (d, *J*=7.89 Hz, 1 H), 7.70 -7.63 (m, 1 H), 5.91 (s, 1 H), 4.03 (s, 1 H), 3.81- 3.69 (m, 2 H), 3.59 (s, 1 H), 2.82- 2.62 (m, 2 H), 2.47 (s, 1 H), 0.77 (q, *J*=6.36 Hz, 2 H), 0.49 -0.39 (m, 2 H).

Example 54

Synthesis of (4*S*)-8-chloro-*N*-(6-((*S*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(3-(trifluoro methyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxam ide Hydrochloride

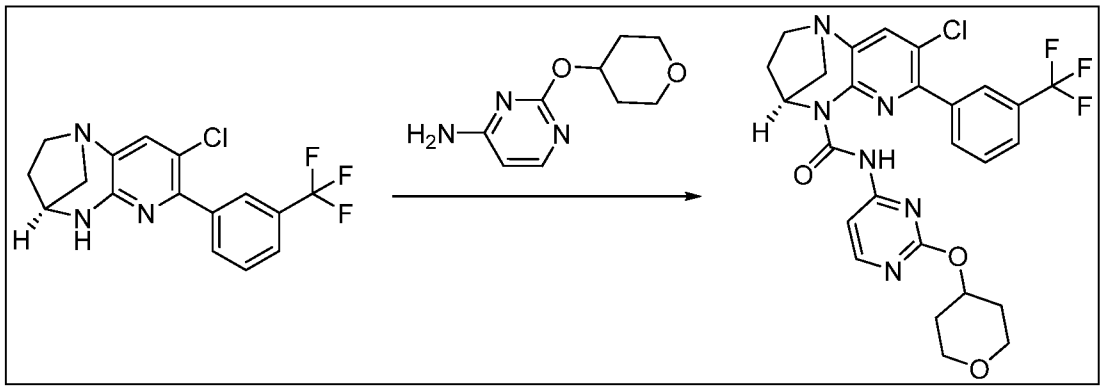


To a stirred solution of (4*S*)-8-chloro-*N*-(6-((*S*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (50 mg, 0.091 mmol) in Methanol (5 mL) was added HCl (0.028 mL, 0.908 mmol) at 0 °C and stirred at room temperature for 4 h. (TLC System: R_f - 0.1, EtOAc). The reaction mixture was concentrated under reduced pressure to obtain residue. The residue was triturated with *n*-Pentane (3 x 10 mL). The resulting solid was filtered through a Buchner funnel, rinsed with *n*-pentane (5 mL) to afford the desired product (4*S*)-8-chloro-N-(6-((*S*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide Hydrochloride (20 mg, 0.034 mmol, 37.4 % yield) as an off white solid. LCMS (*m/z*): 551.1 $[M+H]^+$, R_t = 2.19 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.62 (s, 1 H), 8.86 (s, 1 H), 8.05 - 7.99 (m, 3 H), 7.94 (s, 1 H), 7.89 - 7.84 (m, 2 H), 5.54 (dd, *J*=5.70, 2.85 Hz, 1 H), 3.82 - 3.67 (m, 5 H), 3.44 - 3.14 (m, 6 H), 2.38 - 2.28 (m, 1 H), 2.12 - 2.02 (m, 1 H).

Example 55

Synthesis of (4*S*)-8-chloro-*N*-(2-((tetrahydro-2*H*-pyran-4-yl)oxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2H)-carboxamide.



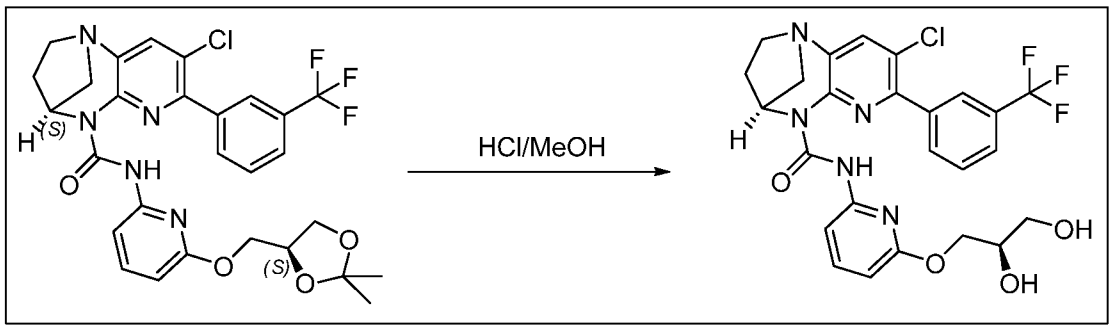
In a sealed tube, to a stirred solution of (4*S*)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (300 mg, 0.883 mmol) in THF (10 mL) was added triphosgene (131 mg, 0.442 mmol) at RT and stirred for 30 min then DIPEA (0.771 mL, 4.42 mmol) and 2-((tetrahydro-2H-pyran-4-yl)oxy)pyrimidin-4-amine (345 mg, 1.766 mmol) were added and stirred at 80 °C for 16 h. (TLC System: R_f - 0.4, 40% EtOAc-Pet Ether). The reaction mixture was allowed to room temperature and quenched with water (30 ml), extracted with ethylacetate (2x50 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: 40% ethyl acetate in hexane) and it was again purified by Prep HPLC (Conditions : Column: XBridge C 18(75 X4.6mm, 3.5µ) Mobile Phase: A: 0.01 M Ammonium Bicarbonate B: CAN Gradient: Time/ %B: 0/5,0.8/5,5/50,8/95,12/95,12.1/5,15/5 Column Temp: Ambient, Flow Rate:1.0ml/min Diluent: CAN) to afford the desired product (4*S*)-8-chloro-*N*-(2-((tetrahydro-2*H*-pyran-4-yl)oxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl) phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide (111.4 mg, 0.198 mmol, 22.46 % yield) as an off white solid. LCMS (*m/z*): 561.1 $[M+H]^+$, Rt = 2.70 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.94 (s, 1H), 8.33 (d, *J*=5.70 Hz, 1H), 8.07 (dd, *J*=2.52, 1.86 Hz, 2H), 7.79- 7.73 (m, 1H), 7.73 -7.64 (m, 3H), 5.64 (dd, *J*=5.92, 3.07 Hz, 1H), 4.87 (tt, *J*=7.56, 3.73 Hz, 1 H), 3.97- 3.85 (m, 2 H), 3.51 (ddt, *J*=11.46, 7.62, 3.51, 3.51 Hz, 2 H), 3.36- 3.10 (m, 3 H), 3.02 (dd, *J*=12.28, 3.29 Hz, 1 H), 2.35 (dddd, *J*=14.14,

10.03, 6.08, 3.95 Hz, 1 H), 2.08 (dt, *J*=14.25, 6.91 Hz, 1 H), 1.91 -1.80 (m, 2 H), 1.77-1.62 (m, 2 H).

Example 56

Synthesis of (4*S*)-8-chloro-*N*-(6-((*R*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoro methyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide.

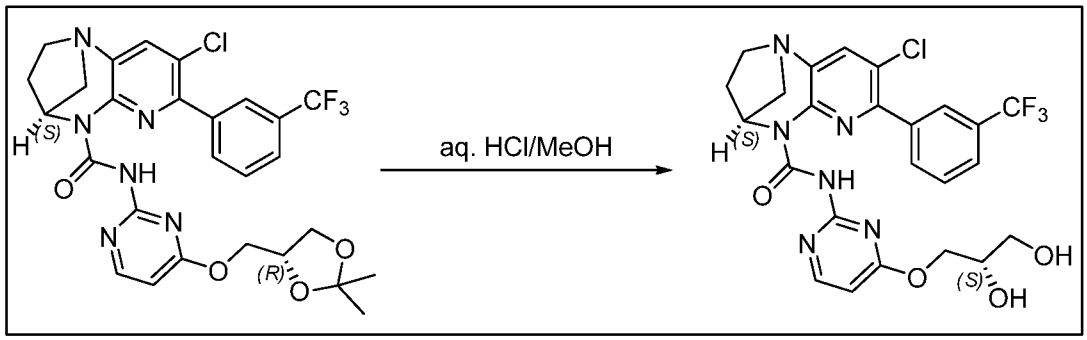


To a stirred solution of (4S)-8-chloro-*N*-(6-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (9.1 g, 15.42 mmol) in Methanol (100 mL) was added HCl (4.69 mL, 154 mmol) at 0 °C. The reaction mixture was stirred for 1 h. (TLC System: R_f - 0.4, Neat EtOAc) at room temperature and concentrated under reduced pressure to obtain residue. The residue was neutralized with saturated sodium bicarbonate solution and afforded solid product was filtered and dried to afford the desired product (4*S*)-8-chloro-N-(6-((*R*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (5.75 g, 10.39 mmol, 67.3 % yield) as an off white solid. LCMS (*m/z*): 550.16 $[M+H]^+$, Rt =4.23 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.44 (s, 1 H), 8.07 -7.99 (m, 2 H), 7.90 -7.80 (m, 3 H), 7.69 -7.57 (m, 2 H), 6.43 (dd, *J*=7.45, 1.10 Hz, 1 H), 5.49 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.76 (d, *J*=4.82 Hz, 1 H), 4.53 (t, *J*=5.59 Hz, 1 H), 3.76 -3.59 (m, 3 H), 3.37- 3.30 (m, 3 H), 3.17- 3.08 (m, 2 H), 2.98 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.33- 2.19 (m, 1 H), 2.05- 1.88 (m, 1 H).

Example 57

Synthesis of (4*S*)-8-chloro-N-(4-((*S*)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

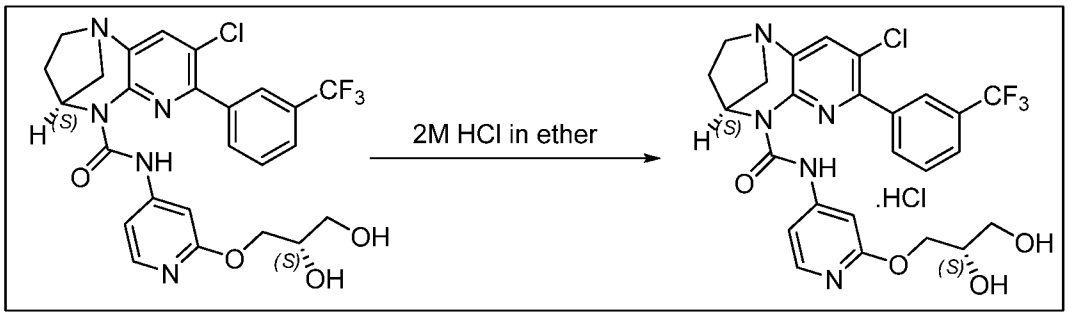


To a stirred solution of (4*S*)-8-chloro-N-(4-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (200 mg, 0.338 mmol) in Methanol (8 mL) was added hydrochloric acid (1.0 mL, 11.85 mmol) at 0 °C then stirred at room temperature 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 (2x10 mL), Diethy ether (2x10 mL) to afford the desired product (4*S*)-8-chloro-N-(4-((*S*)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (92 mg, 0.162 mmol, 47.8 % yield) as an off white solid. LCMS (*m/z*): 551.13 $[M+H]^+$, R_t = 1.94 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.40 (s, 1 H), 8.19 (d, *J*=5.70 Hz, 1 H), 8.15 (s, 1 H), 8.07 (d, *J*=7.45 Hz, 1 H), 7.74 (s, 1 H), 7.68 (s, 1 H), 7.66 - 7.59 (m, 1 H), 6.42 (d, *J*=5.70 Hz, 1 H), 5.73 (dd, *J*=5.92, 3.29 Hz, 1 H), 4.65 (dd, *J*=12.17, 5.15 Hz, 1 H), 4.48 (dd, *J*=12.06, 4.60 Hz, 1 H), 4.25 (d, *J*=6.36 Hz, 1 H), 3.97 - 3.88 (m, 1 H), 3.67 - 3.59 (m, 2 H), 3.41- 3.10 (m, 4 H), 2.99 (dd, *J*=12.39, 3.40 Hz, 1 H), 2.33 (qd, *J*=10.05, 3.62 Hz, 1 H), 2.14 - 2.00 (m, 1 H).

Example 58

Synthesis of (4*S*)-8-chloro-N-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide, Hydrochloride

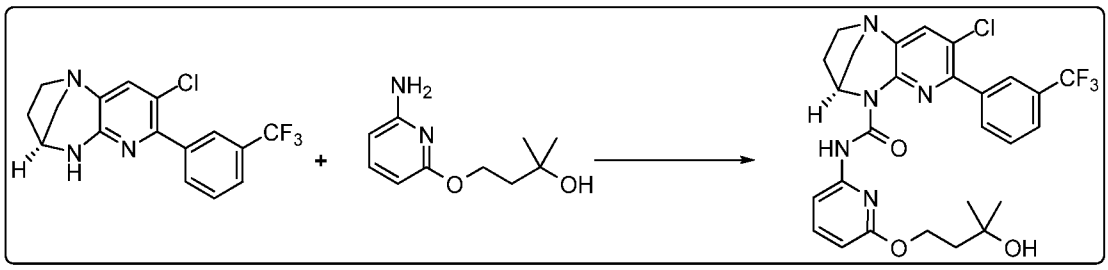


To a stirred solution of (4*S*)-8-chloro-N-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (100 mg, 0.182 mmol) in Diethyl ether (10 mL), 2M HCl in Ether (5 mL, 0.182 mmol) was added drop wise over a period of 2 min. at 0 °C. Then the reaction mixture was stirred at 30 °C for 2 h. (TLC system: 5% Methanol in dichloro methane, R_f: 0.1).and the reaction mixture was evaporated and washed with *n*-pentane (2 X 20 mL) to afford the desired product (4*S*)-8-chloro-N-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide, Hydrochloride (92 mg, 0.155 mmol, 85 % yield) as an off White solid. LCMS (*m/z*): 550.16 $[M+H]^+$, R_t = 2.20 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.76 (s, 1 H), 8.11 (d, *J*=1.32 Hz, 2 H), 7.99 - 7.92 (m, 2 H), 7.89 - 7.82 (m, 1 H), 7.09 (d, *J*=1.32 Hz, 1 H), 6.66 (dd, *J*=6.03, 1.64 Hz, 1 H), 5.46 (dd, *J*=5.59, 2.96 Hz, 1 H), 4.23 (dd, *J*=10.52, 4.38 Hz, 1 H), 4.11 (dd, *J*=10.52, 6.14 Hz, 1 H), 3.82 - 3.73 (m, 1 H), 3.43 (d, *J*=5.70 Hz, 1 H), 3.39 - 3.30 (m, 3 H), 3.25 - 3.16 (m, 2 H), 3.13 - 3.07 (m, 3 H), 2.37 - 2.25 (m, 1 H), 2.01 (dt, *J*=14.09, 7.10 Hz, 1 H).

Example 59

Synthesis of (4*S*)-8-chloro-N-(6-(3-hydroxy-3-methylbutoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide:

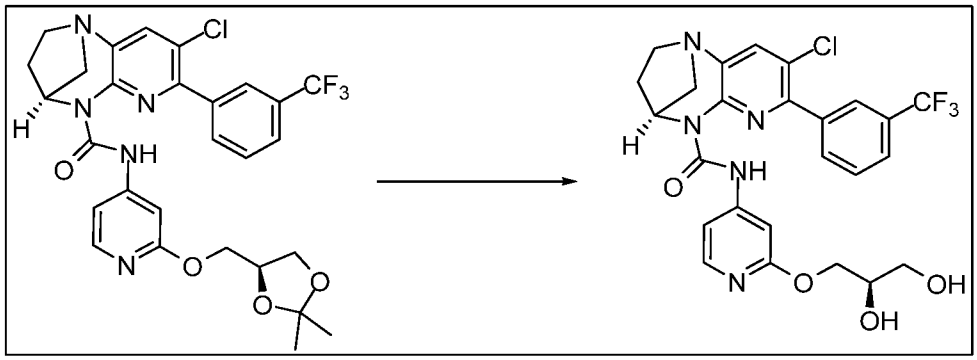


To a stirred solution of (4*S*)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.472 mmol) in THF (40 mL) at RT was added TEA (1.026 mL, 7.36 mmol), triphosgene (262 mg, 0.883 mmol) stirred for 30 min. then 4-((6-aminopyridin-2-yl)oxy)-2-methylbutan-2-ol (578 mg, 2.94 mmol) was added and reaction mixture was heated 100 °C for 16 h. (TLC eluent system: 100% EtOAc,Rf-0.5,UV active). The reaction mixture was cooled to room temperature and was partitioned between water (5 mL) and EtOAc (15 mL). Organic layer was separated, dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude. The crude compound was purified by chromatography (neutral alumina, eluent: 30% ethyl acetate in hexane) to afford (4*S*)-8-chloro-N-(6-(3-hydroxy-3-methylbutoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (590 mg, 1.049 mmol, 71.3 % yield) as white solid LCMS (*m/z*): 561.98 $[M]^+$, R_t =2.85 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.51 (s, 1 H), 8.02 (s, 1 H), 7.83 - 7.98 (m, 1 H), 7.58 - 7.76 (m, 4 H), 7.58 - 7.76 (m, 1 H), 6.36 (d, *J*=8.11 Hz, 1 H), 5.68 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.79 - 3.95 (m, 2 H), 3.11 - 3.36 (m, 3 H), 2.94 - 3.11 (m, 1 H), 2.34 (br dd, *J*=9.98, 4.06 Hz, 1 H), 2.21 - 2.29 (m, 1 H), 1.95 - 2.21 (m, 1 H), 1.72 (t, *J*=5.92 Hz, 2 H), 1.19 (s, 6 H).

Example 60

Synthesis of (4*S*)-8-chloro-N-(2-((*R*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide, Hydrochloride:

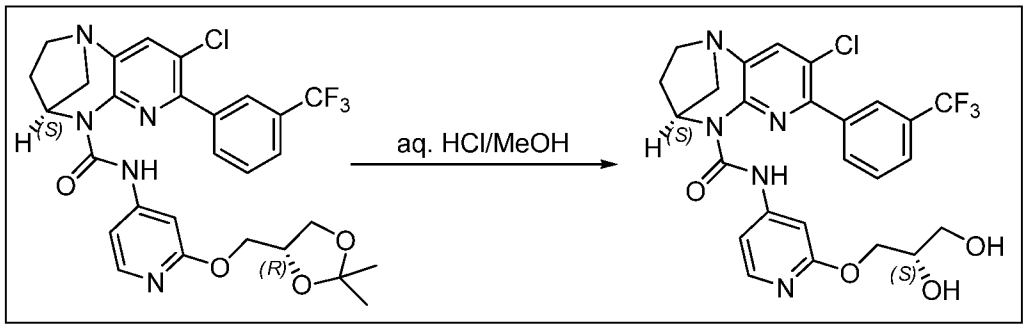


To a stirred solution of (4*S*)-8-chloro-N-(2-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (22.0 g, 37.3 mmol) in methanol (50 mL) was added aq. HCl (22 mL, 261 mmol, 36 %) at 0 °C and stirred at RT for 5 h. After completion of the reaction, the volatiles were evaporated under reduced pressure to get the crude. The crude was triturated with the ethyl acetate (2x10 mL), diethyl ether (10 mL) and solid was Lyophilised to afford pure (4*S*)-8-chloro-N-(2-((*R*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide, Hydrochloride (15.792 g, 26.9 mmol, 72.1 % yield) as an off white solid. LCMS (*m/z*): 550.16 $[M+H]^+$, R_t =2.21 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.78 (s, 1 H), 8.13- 8.03 (m, 3 H), 8.00 (d, *J*=6.14 Hz, 1 H), 7.96 - 7.92 (m, 1 H), 7.89 - 7.83 (m, 1 H), 7.13 (brS, 3 H), 6.71 (dd, *J*=6.14, 1.75 Hz, 1 H), 5.48 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.24 (dd, *J*=10.52, 4.17 Hz, 1 H), 4.12 (dd, *J*=10.52, 6.36 Hz, 1 H), 3.83 - 3.76 (m, 1 H), 3.62 - 3.51 (m, 1 H), 3.51 - 3.41 (m, 5 H), 2.49 - 2.40 (m, 1 H), 2.20 - 2.03 (m, 1 H).

Example 61

Synthesis of (4*S*)-8-chloro-N-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide

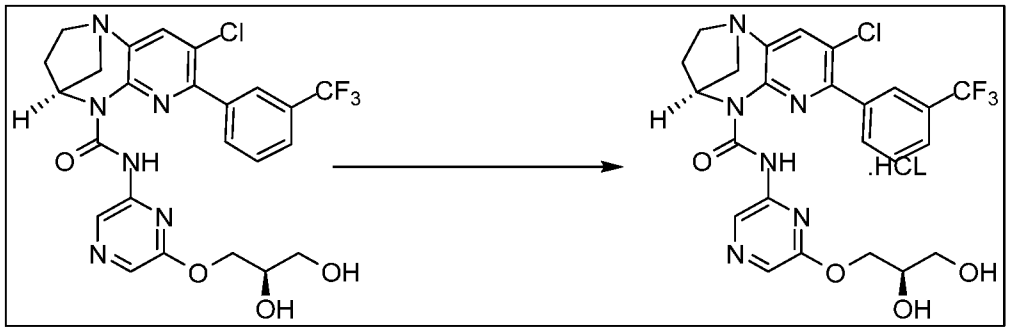


To a stirred solution of (4*S*)-8-chloro-N-(2-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (18.4 g, 31.2 mmol) in methanol (50 mL) was added HCl (9.48 mL, 312 mmol) drop wise over a period of 5 min at 0 °C. 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. The reaction mixture was neutralized with sodium bicarbonate solution and filtered the obtained solid, washed with ether (2x 50 mL) and *n*-pentane (2x 50 mL) to afford the desired product (4*S*)-8-chloro-N-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (15.6 g, 28.3 mmol, 91 % yield) as an off white solid. LCMS (*m/z*): 550.09 $[M+H]^+$, Rt: 2.22 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.77 (s, 1 H), 7.98 (s, 1 H), 7.93 (d, *J*=7.67 Hz, 1 H), 7.85 (d, *J*=5.92 Hz, 1 H), 7.80 (d, *J*=7.67 Hz, 1 H), 7.66 - 7.72 (m, 2 H), 7.03 (d, *J*=1.32 Hz, 1 H), 6.70 (dd, *J*=5.81, 1.64 Hz, 1 H), 5.65 (dd, *J*=5.48, 2.85 Hz, 1 H), 4.43 (d, *J*=4.38 Hz, 2 H), 4.28 (d, *J*=4.60 Hz, 1 H), 3.97 (d, *J*=4.38 Hz, 1 H), 3.60 - 3.70 (m, 2 H), 3.10 - 3.36 (m, 3 H), 2.99 - 3.05 (m, 1 H), 2.86 (s, 1 H), 2.29 - 2.41 (m, 1 H), 2.07 (dt, *J*=14.31, 7.43 Hz, 1 H).

Example 62

Synthesis of (4*S*)-8-chloro-N-(6-((*R*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide, Hydrochloride

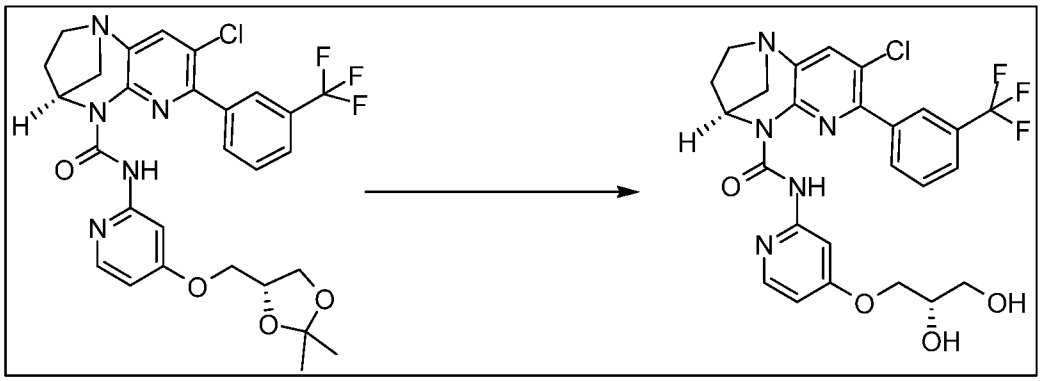


To a stirred solution of (4*S*)-8-chloro-N-(6-((*R*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (200 mg, 0.363 mmol) in diethylether (5 mL) at 0 °C was added 2M HCl in diethylether (3.63 mL, 7.26 mmol) and stirred for 4 h. (TLC eluent:100% EtOAc: R_f-0; UV active). The reaction mixture was concentrated *in vacuo* and the residue was triturated with n-pentane (2x10 mL) to afford (4*S*)-8-chloro-N-(6-((*R*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide, Hydrochloride (151 mg, 0.249 mmol, 68.7 % yield) as an off white solid. LCMS (*m/z*): 551.03 $[M+H]^+$, R_t = 2.18 min

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.63 (s, 1 H), 8.86 (s, 1 H), 8.06 - 8.02 (m, 2 H), 7.99 (s, 1 H), 7.93 (s, 1 H), 7.88 - 7.81 (m, 2 H), 5.66 - 5.30 (m, 1 H), 3.90 - 3.61 (m, 3 H), 3.48 - 3.07 (m, 6 H), 2.45 -2.23 (m, 1 H), 2.12 -1.95 (m, 1 H)

Example 63

Synthesis of (4*S*)-8-chloro-N-(4-((*S*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

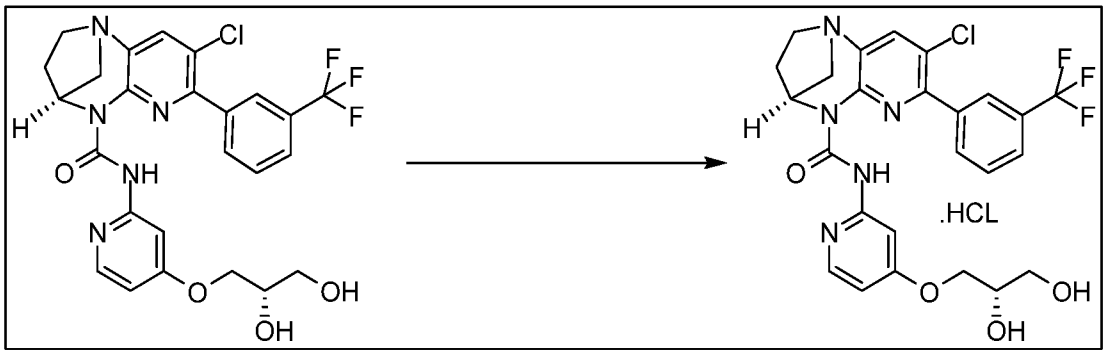


To a stirred solution of (4*S*)-8-chloro-N-(4-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (8.0 g, 13.56 mmol) in methanol (80 mL) at 0 °C was added aq. HCl (8.24 mL, 271 mmol, 36 %) and stirred at 0 °C 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 partitioned between water (40 mL) and DCM (150 mL). Organic layer was separated, dried over anhydrous sodium sulphate, filtered and filtrate was evaporated *in vacuo* and the crude was triturated with diethyl ether (50 mL) to afford (4*S*)-8-chloro-N-(4-((*S*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (5.8 g, 10.53 mmol, 78 % yield) as a white solid LCMS (*m/z*): 550.09 $[M+H]^+$, R_t = 1.96 min

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.93 (s, 1 H), 8.20 (s, 1 H), 8.12 (d, *J*=7.89 Hz, 1 H), 8.04 (d, *J*=5.70 Hz, 1 H), 7.77 - 7.71 (m, 2 H), 7.68 - 7.58 (m, 2 H), 6.53 (dd, *J*=5.81, 2.30 Hz, 1 H), 5.64 (dd, *J*=5.81, 3.18 Hz, 1 H), 4.19 - 4.08 (m, 3 H), 3.88 - 3.79 (m, 1 H), 3.79 - 3.66 (m, 1 H), 3.37 - 3.11 (m, 3 H), 3.01 (dd, *J*=12.28, 3.29 Hz, 1 H), 2.58 (d, *J*=4.17 Hz, 1 H), 2.34 (dddd, *J*=14.17, 10.00, 5.97, 4.06 Hz, 1 H), 2.15 - 1.98 (m, 2 H)

Example 64

Synthesis of (4*S*)-8-chloro-N-(4-((*S*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide, Hydrochloride

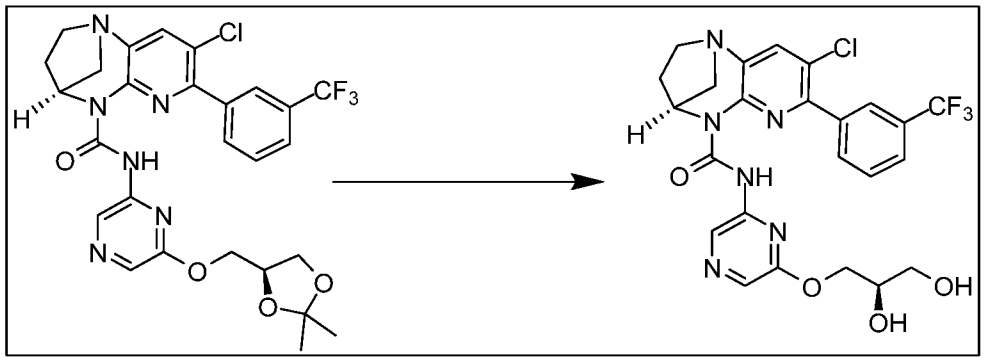


To a stirred solution of (4*S*)-8-chloro-N-(4-((*S*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (200 mg, 0.364 mmol) in diethylether (5 mL) at 0 °C was added 2M HCl in diethylether (3.64 mL, 7.27 mmol) and stirred for 4 h. (TLC eluent:100% EtOAc: R_f-0; UV active). The reaction mixture was concentrated *in vacuo* and the residue was triturated with n-pentane (2x10 mL) to afford the desired product (4*S*)-8-chloro-N-(4-((*S*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide, Hydrochloride (178 mg, 0.295 mmol, 81 % yield) as an off- white solid. LCMS (*m/z*): 550.13 $[M+H]^+$, R_t = 1.95 min

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.06 (br s, 1 H), 8.19 - 8.12 (m, 2 H), 8.08 (br d, *J*=6.14 Hz, 1 H), 8.03 (s, 1 H), 7.94 - 7.87 (m, 1 H), 7.86 - 7.77 (m, 1 H), 7.24 (br s, 1 H), 6.86 (br d, *J*=3.73 Hz, 1 H), 5.49 (br dd, *J*=5.70, 3.07 Hz, 1H), 4.11 (dd, *J*=9.98, 3.84 Hz, 1 H), 3.97 (dd, *J*=9.98, 6.25 Hz, 1 H), 3.86 - 3.78 (m, 1 H), 3.53 - 3.39 (m, 3 H), 3.33 - 3.14 (m, 3 H), 2.39 - 2.28 (m, 1 H), 2.13 - 2.00 (m, 1 H)

Example 65

Synthesis of (4*S*)-8-chloro-N-(6-((*R*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

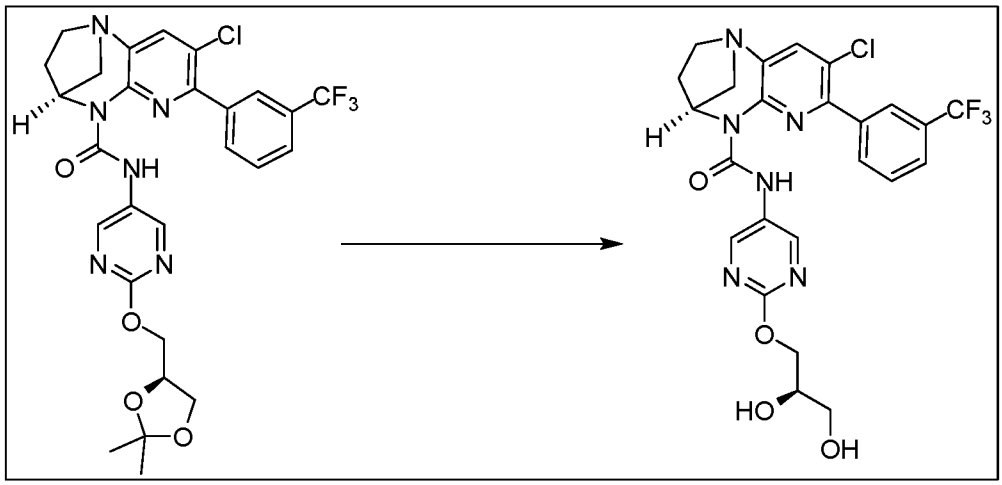


To a stirred solution of (4*S*)-8-chloro-N-(6-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (7.25 g, 12.27 mmol) in methanol (75 mL) at 0 °C was added aq. HCl (7.45 mL, 245 mmol, 36 %) 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 (50 mL) and extracted into dichloromethane (4x50 mL). Combined organic extracts were dried over anhydrous sodium sulphate, filtered and filtrate was evaporated *in vacuo* and the crude was triturated with diethylether (50 mL) to afford (4*S*)-8-chloro-N-(6-((*R*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (5.2 g, 9.38 mmol, 76 % yield) as a white solid LCMS (*m/z*): 551.10 $[M+H]^+$, R_t = 2.16 min

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.76 (s, 1 H), 8.88 (s, 1 H), 8.00 (s, 1 H), 7.95 - 7.89 (m, 2 H), 7.77 - 7.73 (m, 1 H), 7.70 - 7.65 (m, 2 H), 5.69 (dd, *J*=6.03, 3.18 Hz, 1 H), 4.04 - 3.84 (m, 3 H), 3.67 - 3.46 (m, 2 H), 3.37 - 3.21 (m, 2 H), 3.18 - 3.12 (m, 1 H), 3.03 (dd, *J*=12.28, 3.29 Hz, 1 H), 2.58 (d, *J*=4.60 Hz, 1 H), 2.36 (dddd, *J*=14.20, 10.03, 6.03, 3.95 Hz, 1 H), 2.14 - 2.03 (m, 2 H)

Example 66

Synthesis of (4*S*)-8-chloro-N-(2-((*R*)-2,3-dihydroxypropoxy)pyrimidin-5-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

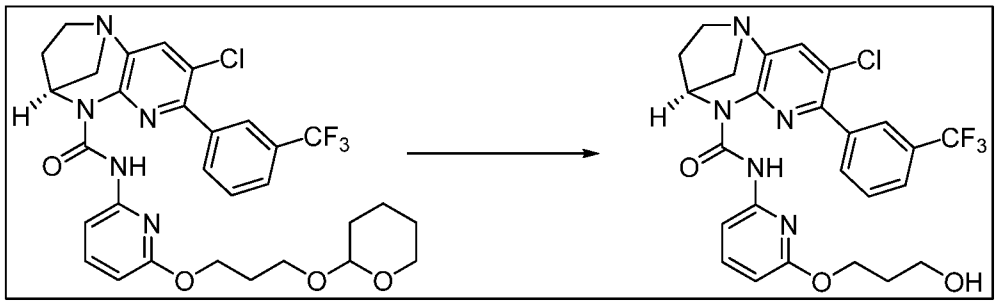


To a stirred solution of (4*S*)-8-chloro-N-(2-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (250 mg, 0.423 mmol) in methanol (5 mL) at RT was added aq. HCl (0.357 mL, 4.23 mmol, 36 %) 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 (5 mL) and extracted into dichloromethane (2x10 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) and pentane (10 mL) to afford the desired product (4*S*)-8-chloro-N-(2-((*R*)-2,3-dihydroxypropoxy)pyrimidin-5-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (157 mg, 0.278 mmol, 65.8 % yield) as an off-White solid. LCMS (*m/z*): 551.13 $[M+H]^+$, R_t = 2.15 min

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.56 (s, 1 H), 8.56 (s, 2 H), 7.98 (s, 1 H), 7.90 (d, *J*=7.67 Hz, 1 H), 7.77 (br d, *J*=7.89 Hz, 1 H), 7.70 - 7.59 (m, 2 H), 5.65 (dd, *J*=5.70, 3.07 Hz, 1 H), 4.51 - 4.38 (m, 2 H), 4.14 - 4.06 (m, 1 H), 3.81 - 3.65 (m, 2 H), 3.38 - 3.19 (m, 4 H), 3.07 - 3.00 (m, 1 H), 2.41 - 2.26 (m, 2 H), 2.09 (dt, *J*=14.31, 7.21 Hz, 1 H)

Example 67

Synthesis of (4*S*)-8-chloro-N-(6-(3-hydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

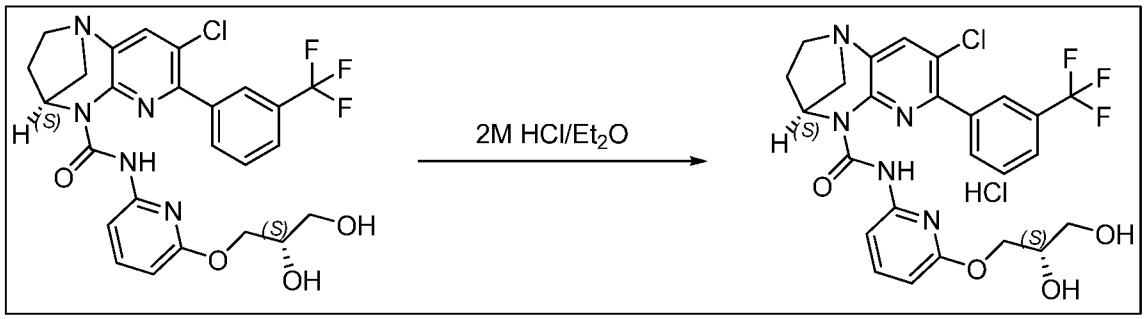


To a stirred solution of (4*S*)-8-chloro-N-(6-(3-((tetrahydro-2H-pyran-2-yl)oxy)propoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (250 mg, 0.405 mmol) in methanol (10 mL) at 0 °C was added aq. HCl (0.184 mL, 6.07 mmol) stirred 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 (5 mL). The resultant solid was filtered, triturated with pentane (15 mL) dried under reduced pressure to afford the desired product (4S)-8-chloro-N-(6-(3-hydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (61 mg, 0.113 mmol, 28.0 % yield) as an off white solid. LCMS (*m/z*): 534.14 $[M+H]^+$, Rt = 2.62 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.58 (s, 1 H), 7.89 - 8.03 (m, 2 H), 7.68 - 7.75 (m, 1 H), 7.63 - 7.67 (m, 1 H), 7.56 - 7.61 (m, 1 H), 7.50 - 7.55 (m, 1 H), 6.36 (dd, *J*=7.78, 0.77 Hz, 1 H), 5.68 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.81 - 3.94 (m, 2 H), 3.58 (q, *J*=5.70 Hz, 2 H), 3.19 - 3.36 (m, 2 H), 3.11 - 3.18 (m, 1 H), 3.01 (dd, *J*=12.28, 3.29 Hz, 1 H), 2.27 - 2.40 (m, 1 H), 2.02 - 2.17 (m, 2 H), 1.72 (quin, *J*=5.81 Hz, 2 H)

Example 68

Synthesis of (4*S*)-8-chloro-*N*-(6-((*S*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide Hydrochloride.

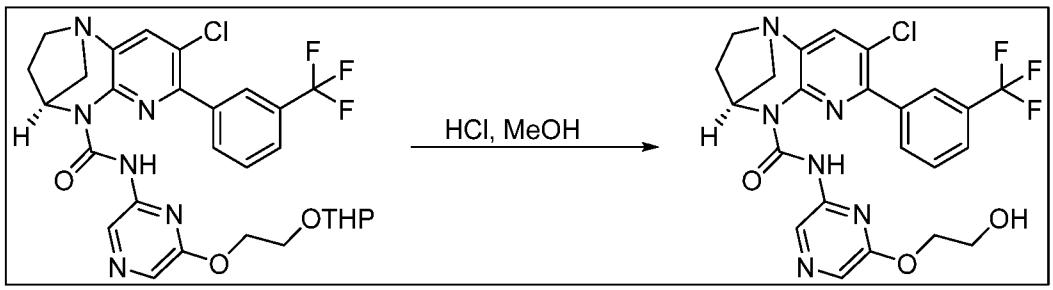


To a stirred solution of (4*S*)-8-chloro-*N*-(6-((*S*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (100 mg, 0.182 mmol) in Methanol (5 mL) was added 2M HCl in diethyl ether (8 mL, 0.182 mmol) at 0 °C and stirred at RT for 2 h. (TLC eluent: neat ethyl acetate, R_f: 0.1). Then concentrated *in vacuo* and the residue was triturated with n-pentane (10 mLx3) to afford the desired product (4*S*)-8-chloro-*N*-(6-((*S*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyr-ido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide Hydrochloride (40 mg, 0.068 mmol, 37.5 % yield) as an off white solid. LCMS (*m/z*): 550.09 $[M+H]^+$, Rt = 2.35 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.16 (s, 1 H), 8.51 (s, 1 H), 8.02 - 7.95 (m, 2 H), 7.81 (d, *J*=7.67 Hz, 1 H), 7.74 - 7.69 (m, 1 H), 7.62 - 7.56 (m, 1 H), 7.50 (d, *J*=7.67 Hz, 1 H), 6.48 (d, *J*=7.67 Hz, 1 H), 5.91 (s, 1 H), 4.02- 3.47 (m, 11 H), 2.66 (s, 1 H), 2.47 (s, 1 H).

Example 69

Synthesis of (4*S*)-8-chloro-*N*-(6-(2-hydroxyethoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

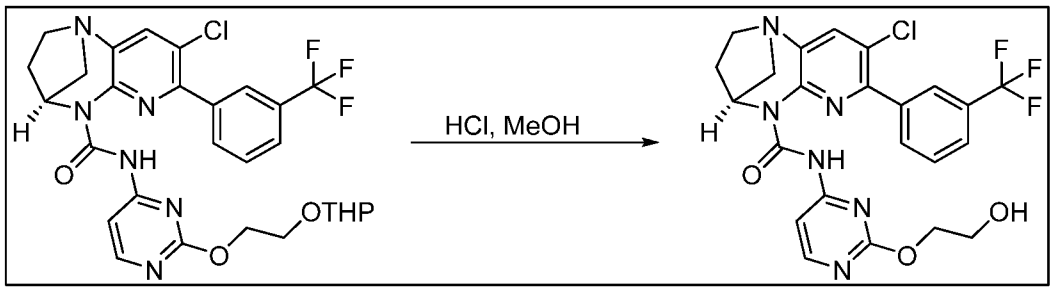


To a stirred solution of (4*S*)-8-chloro-*N*-(6-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido [2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (200 mg, 0.331 mmol) in Methanol (10 mL) was added HCl (1 mL, 32.9 mmol) at 0 °C then stirred at RT for 1 h. (TLC system: neat ethyl acetate, R_f: 0.3).The reaction mixture was concentrated *in vacuo* and the residue was neutralized with saturated $NaHCO_3$ solution and filtered the obtained solid, washed with water (20 mLx3) and n-pentane (20 mLx2) to afford the desired product (4*S*)-8-chloro-*N*-(6-(2-hydroxyethoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methano pyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (130 mg, 0.247 mmol, 74.7 % yield) as an off white solid. LCMS (*m/z*): 521.07 $[M+H]^+$, Rt = 2.39 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.75 (s, 1 H), 8.95 (s, 1 H), 7.98 (s, 1 H), 7.93 - 7.87 (m, 2 H), 7.74 - 7.70 (m, 1 H), 7.69 (s, 1 H), 7.67 - 7.61 (m, 1 H), 5.68 (dd, *J*=6.03, 2.96 Hz, 1 H), 3.88 - 3.83 (m, 2 H), 3.76 - 3.72 (m, 2 H), 3.36 - 3.21 (m, 3 H), 3.19 - 3.13 (m, 1 H), 3.04 (dd, *J*=12.28, 3.07 Hz, 1 H), 2.41 - 2.31 (m, 1 H), 2.14 - 2.04 (m, 1 H).

Example 70

Synthesis of (4*S*)-8-chloro-*N*-(2-(2-hydroxyethoxy) pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

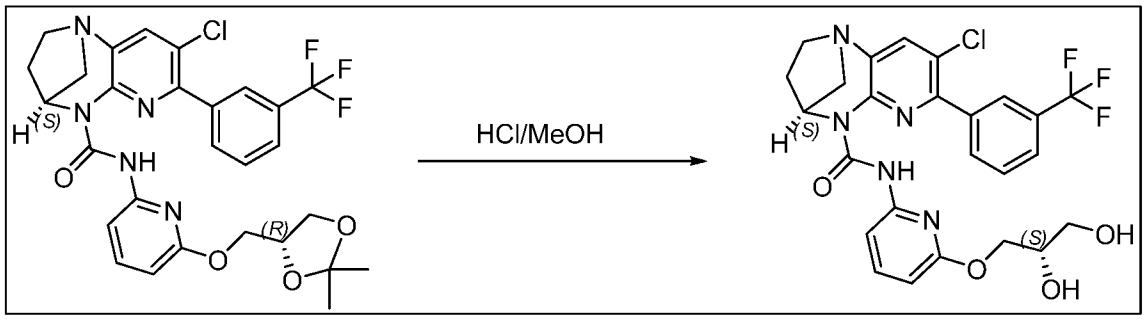


To a stirred solution of (4*S*)-8-chloro-*N*-(2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido [2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (200 mg, 0.331 mmol) in Methanol (10 mL) was added HCl (0.5 mL, 13.71 mmol) at 0 °C and stirred at RT for 1 h. (TLC eluent: neat ethyl acetate, R_f: 0.4). 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 (20 mLx3) to afford the (4*S*)-8-chloro-*N*-(2-(2-hydroxyethoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (140 mg, 0.267 mmol, 81 % yield) as an off white solid. LCMS (*m/z*): 521.04 $[M+H]^+$, Rt = 2.33 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.04 (s, 1 H), 8.34 (d, *J*=5.48 Hz, 1 H), 8.05 -7.98 (m, 2 H), 7.76 - 7.67 (m, 4 H), 5.64 (dd, *J*=6.03, 3.18 Hz, 1 H), 4.11 - 4.07 (m, 2 H), 3.84 - 3.80 (m, 2 H), 3.36 - 3.20 (m, 2 H), 3.18 - 3.13 (m, 1 H), 3.03 (dd, *J*=12.28, 3.29 Hz, 1 H), 2.50 (t, *J*=6.25 Hz, 1 H), 2.41 - 2.31 (m, 1 H), 2.13 - 2.04 (m, 1 H).

Example 71

Synthesis of (4*S*)-8-chloro-*N*-(6-((*S*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

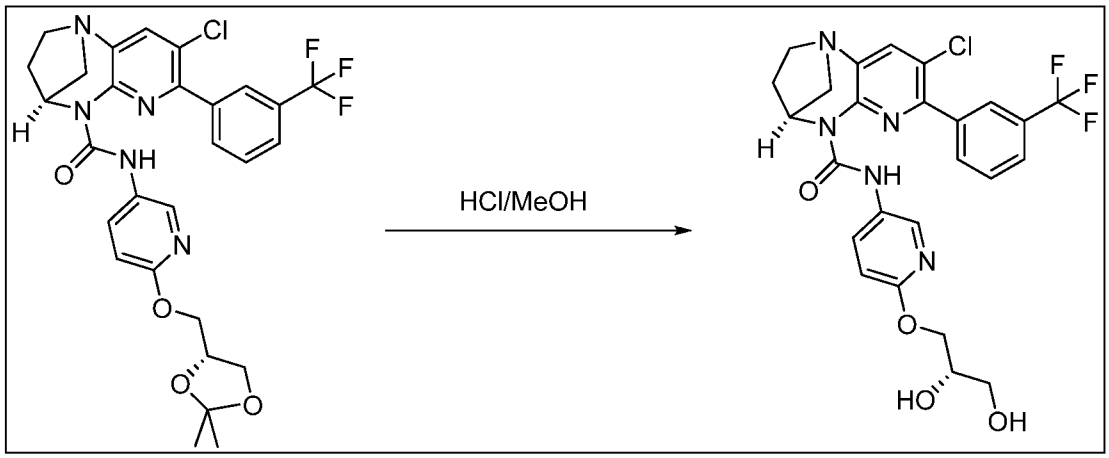


To a stirred solution of (4*S*)-8-chloro-*N*-(6-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (8 g, 13.56 mmol) in Methanol (70 mL) was added HCl (30 mL, 987 mmol) at 0 °C then stirred at RT for 2 h. (TLC system: neat ethyl acetate, R_f: 0.3). 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 mLx2) to afford the desired product (4*S*)-8-chloro-*N*-(6-((*S*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (6 g, 10.87 mmol, 80 % yield) as an off white solid. LCMS (*m/z*): 550.09 $[M+H]^+$, Rt = 2.33 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.61 (s, 1 H), 8.02 - 7.95 (m, 2 H), 7.76 - 7.72 (m, 1 H), 7.69 - 7.64 (m, 2 H), 7.58 - 7.53 (m, 1 H), 7.51 - 7.48 (m, 1 H), 6.42 (dd, *J*=7.89, 0.66 Hz, 1 H), 5.68 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.97 - 3.88 (m, 2 H), 3.75 (dq, *J*=10.14, 5.10 Hz, 1 H), 3.54 - 3.42 (m, 2 H), 3.36 - 3.19 (m, 2 H), 3.17 - 3.12 (m, 1 H), 3.01 (dd, *J*=12.17, 3.18 Hz, 1 H), 2.81 (d, *J*=5.92 Hz, 1 H), 2.38 - 2.28 (m, 2 H), 2.13 - 2.04 (m, 1 H).

Example 72

Synthesis of (4*S*)-8-chloro-*N*-(6-((*S*)-2,3-dihydroxypropoxy)pyridin-3-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

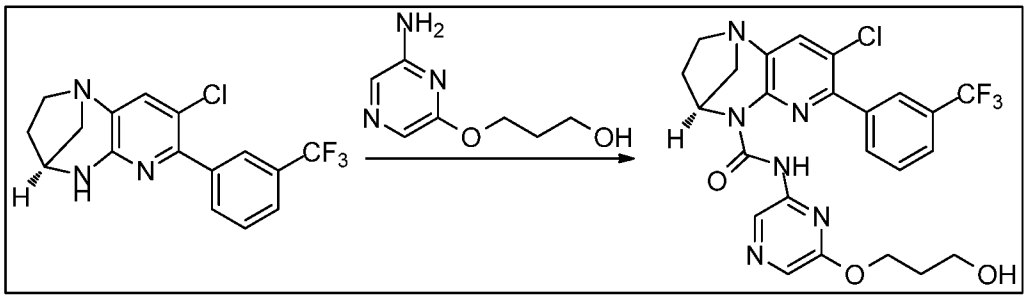


To a stirred solution of (4*S*)-8-chloro-*N*-(6-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (250 mg, 0.424 mmol) in Methanol (5 mL) and Tetrahydrofuran (5 mL) was added HCl (0.2 mL, 6.58 mmol) at 0 °C then stirred at RT for 3 h. (TLC system: neat ethyl acetate, R_f: 0.1). The reaction mixture was concentrated *in vacuo* and the residue was neutralized with saturated $NaHCO_3$ solution and extracted with ethyl acetate (30 mLx2). The combined organic layer was washed with water (15 mLx2) and brine (20 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain the crude. The crude material was triturated with n-pentane (15 mL x 3) and filtered to afford the desired product (4*S*)-8-chloro-*N*-(6-((*S*)-2,3-dihydroxypropoxy)pyridin-3-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopy rido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (175 mg, 0.318 mmol, 75 % yield) as an off white solid. LCMS (*m/z*): 550.09 $[M+H]^+$, Rt = 2.28 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.40 (s, 1 H), 8.07 (d, *J*=2.41 Hz, 1 H), 7.99 (s, 1 H), 7.93 (d, *J*=7.89 Hz, 1 H), 7.78 - 7.74 (m, 2 H), 7.68 - 7.63 (m, 2 H), 6.73 (d, *J*=8.99 Hz, 1 H), 5.66 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.42 (dd, *J*=4.60, 1.10 Hz, 2 H), 4.02 - 3.93 (m, 2 H), 3.72 - 3.61 (m, 2 H), 3.36 - 3.20 (m, 2 H), 3.16 - 3.11 (m, 1 H), 3.05 - 3.00 (m, 1 H), 2.67 (t, *J*=6.47 Hz, 1 H), 2.38 - 2.29 (m, 1 H), 2.09 (dt, *J*=14.25, 7.13 Hz, 1 H).

Example 73

Synthesis of (4*S*)-8-chloro-*N*-(6-(3-hydroxypropoxy) pyrazin-2-yl)-7-(3-(trifluoromethyl) phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

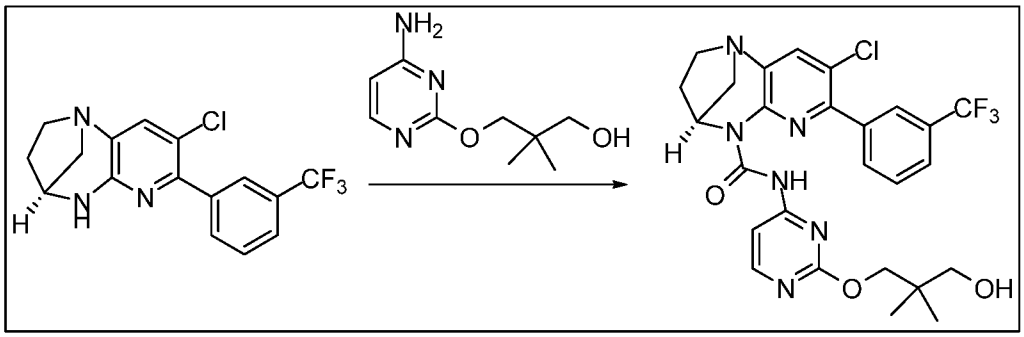


To a stirred solution of (4*S*)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 0.883 mmol) in Tetrahydrofuran (15 mL) was added triphosgene (131 mg, 0.442 mmol) under nitrogen at room temperature and stirred for 30 min. To this reaction mixture triethylamine (0.615 mL, 4.42 mmol) and 3-((6-aminopyrazin-2-yl) oxy) propan-1-ol (194 mg, 1.148 mmol) were added and stirred at 80 °C for 15 h. (TLC system: 5% Methanol in Ethyl acetae. R*f* value: 0.3). The reaction mixture was diluted with water (40 mL) and extracted with ethyl acetate (2x50 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 crude product was purified by flash column chromatography (100-200 silicagel eluted with 1% of MeOH in EtOAc) to afford the desired product (4*S*)-8-chloro-*N*-(6-(3-hydroxypropoxy) pyrazin-2-yl)-7-(3-(trifluoromethyl) phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (80 mg, 0.144 mmol, 16.33 % yield) as an off-white solid. LCMS (*m/z*): 535.08 $[M+H]^+$, Rt =2.45 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.73 (s, 1 H), 8.91 (s, 1 H), 7.99 (s, 1 H), 7.91 (d, J=7.67 Hz, 1 H), 7.87 (s, 1 H), 7.75 - 7.70 (m, 1 H), 7.68 (s, 1 H), 7.66 - 7.59 (m, 1 H), 5.69 (dd, J=5.92, 3.07 Hz, 1 H), 3.97 - 3.86 (m, 2 H), 3.67 (q, J=5.92 Hz, 2 H), 3.37 - 3.08 (m, 3 H), 3.03 (dd, J=12.17, 3.18 Hz, 1 H), 2.43 - 2.28 (m, 1 H), 2.17 - 2.00 (m, 1 H), 1.81 (q, J=5.97 Hz, 2 H), 1.67 (t, J=5.70 Hz, 1 H).

Example 74

Synthesis of (4*S*)-8-chloro-*N*-(2-(3-hydroxy-2,2-dimethylpropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

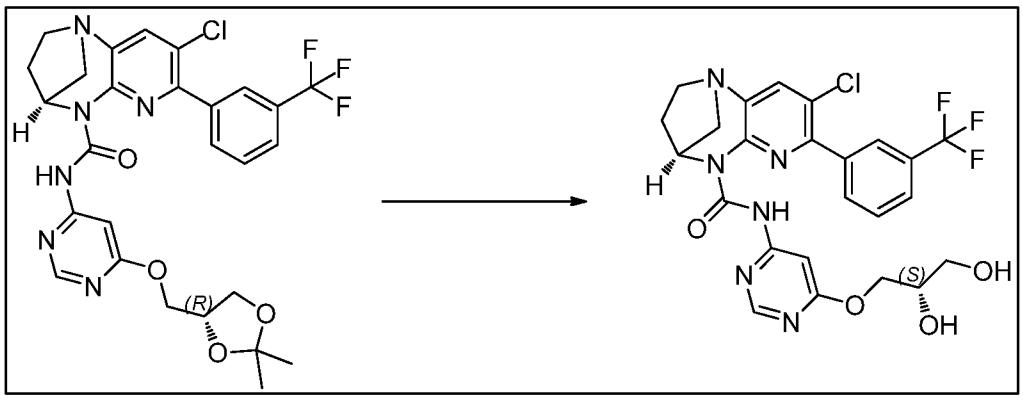


To a solution of (4*S*)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (400 mg, 1.177 mmol) in Tetrahydrofuran (20 mL) was added triphosgene (175 mg, 0.589 mmol) under nitrogen at room temperature and stirred for 30 min. To this reaction mixture triethylamine (0.821 mL, 5.89 mmol) and 3-((4-aminopyrimidin-2-yl)oxy)-2,2-dimethylpropan-1-ol (302 mg, 1.531 mmol) were added and stirred at 80 °C for 15 h. (TLC system: Ethyl acetae. R*f* value: 0.5). The reaction mixture was allowed to cool to room temperature and diluted with water (20 mL), extracted with ethyl acetate (2x50 ml). The combined organic layer was washed with brine solution (20 mL) and 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 5% of MeOH in EtOAc) to afford the desired product (4*S*)-8-chloro-*N*-(2-(3-hydroxy-2,2-dimethylpropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (120 mg, 0.211 mmol, 17.92 % yield) as an off-white solid. LCMS (*m/z*): 563.12 $[M+H]^+$, Rt =2.66 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.06 (s, 1 H), 8.32 (d, *J*=5.70 Hz, 1 H), 8.10 (s, 2 H), 7.66 - 7.79 (m, 4 H), 5.64 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.09 - 3.92 (m, 2 H), 3.36 - 3.29 (m, 3 H), 3.28 - 3.19 (m, 1 H), 3.18 - 3.12 (m, 1 H), 3.02 (dd, *J*=12.28, 3.29 Hz, 1 H), 2.94 (brs, 1 H), 2.41 - 2.30 (m, 1 H), 2.07 (dt, *J*=14.36, 7.07 Hz, 1 H), 0.97 (d, *J*=1.75 Hz, 6 H).

Example 75

Synthesis of (4*S*)-8-chloro-N-(6-((*S*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

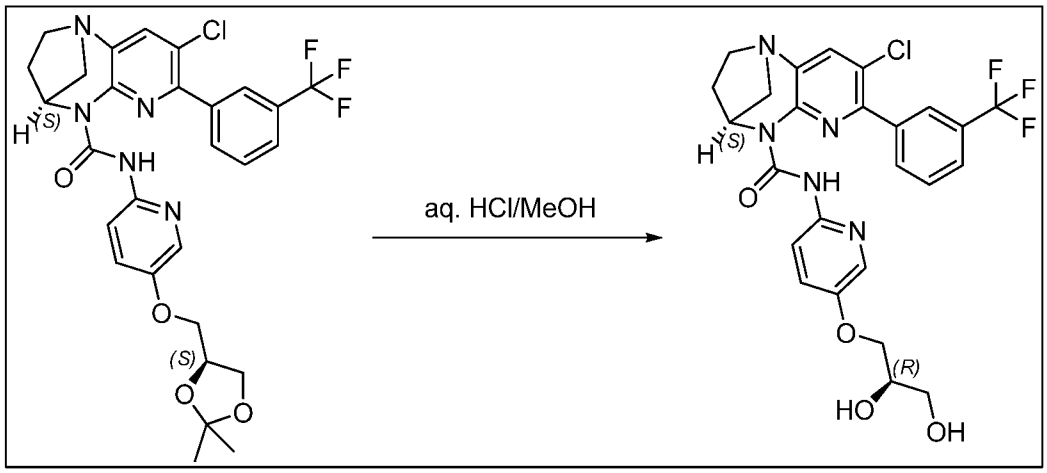


To a stirred suspension of (4*S*)-8-chloro-N-(6-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (8.5 g, 14.38 mmol) in methanol (30 mL) at 0 °C was added aqueous HCl (50 mL, 100 mmol, 2 M) and stirred at RT for 1 h. (TLC system: 10% Methanol in DCM. R_f: 0.2). The reaction mixture was basified with saturated sodium bicarbonate solution. The resultant white precipitate was filtered and dried to get crude pordut. The crude product was purified by column chromatography (Silica gel, eluted with 12% of MeOH in CH_2Cl_2) to afford (4*S*)-8-chloro-N-(6-((*S*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (5.445 g, 9.88 mmol, 68.7 % yield) as a white solid. LCMS (m/z) =551.1 $[M+H]^+$, Rt = 2.37 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.06 (s, 1 H), 8.30 (d, *J*=0.88 Hz, 1 H), 8.04 - 8.21 (m, 2 H), 7.85 - 7.94 (m, 2 H), 7.69 - 7.85 (m, 1 H), 7.39 (d, *J*=1.10 Hz, 1 H), 5.46 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.95 (d, *J*=5.26 Hz, 1 H), 4.65 (t, *J*=5.70 Hz, 1 H), 4.34 (dd, *J*=10.85, 4.06 Hz, 1 H), 4.19 (dd, *J*=10.96, 6.58 Hz, 1 H), 3.74 - 3.86 (m, 1 H), 3.35 - 3.54 (m, 2 H), 3.22 - 3.28 (m, 1 H), 2.94 - 3.22 (m, 3 H), 2.15 - 2.32 (m, 1 H), 1.88 - 2.09 (m, 1 H).

Example 76

Synthesis of (4S)-8-chloro-N-(5-((R)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide.

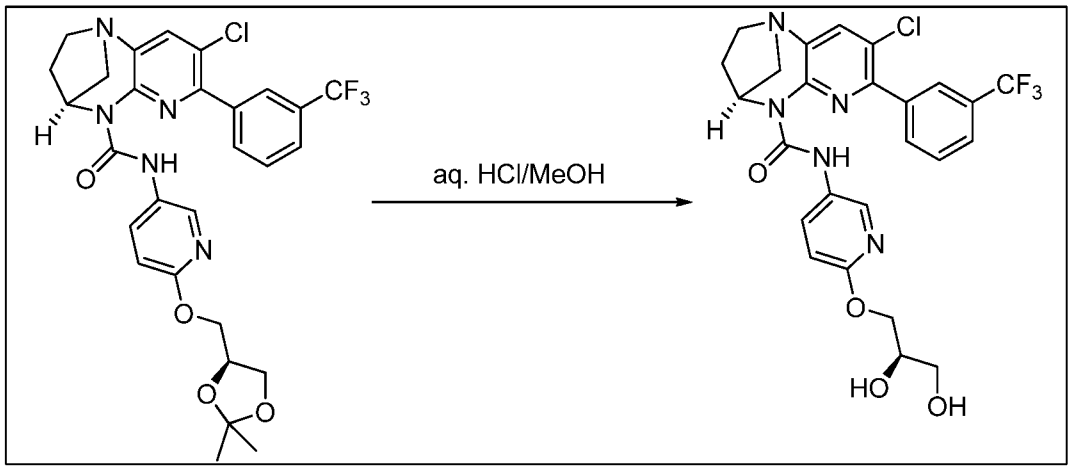


To a stirred solution of (4*S*)-8-chloro-N-(5-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide (200 mg, 0.339 mmol) in Methanol (10 mL) was added Hydrochloric acid (0.103 mL, 3.39 mmol) at 0 °C then stirred at room temperature 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 (2x10 mL) to afford the desired product (4*S*)-8-chloro-N-(5-((*R*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide (150 mg, 0.271 mmol, 80 % yield) as an off white solid. LCMS (*m/z*): 550.13 $[M+H]^+$, Rt = 2.28 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.84 (s, 1 H), 8.19 (s, 1 H), 8.10 (d, *J*=7.89 Hz, 1 H), 8.03 (d, *J*=8.99 Hz, 1 H), 7.95 (d, *J*=3.07 Hz, 1 H), 7.73 (d, *J*=7.67 Hz, 1 H), 7.67 -7.59 (m, 2 H), 7.23 (d, *J*=3.07 Hz, 1 H), 5.66 (dd, *J*=6.14, 3.07 Hz, 1 H), 4.15- 4.08 (m, 1 H), 4.08- 4.02 (m, 2 H), 3.89- 3.82 (m, 1 H), 3.79- 3.74 (m, 1 H), 3.34-3.12 (m, 3 H), 3.01 (dd, *J*=12.28, 3.29 Hz, 1 H), 2.54 (d, *J*=4.17 Hz, 1 H), 2.38-2.28 (m, 1 H), 2.15- 2.04 (m, 1 H), 1.94 (t, *J*=5.70 Hz, 1 H).

Example 77

Synthesis of (4*S*)-8-chloro-*N*-(6-((*R*)-2,3-dihydroxypropoxy)pyridin-3-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

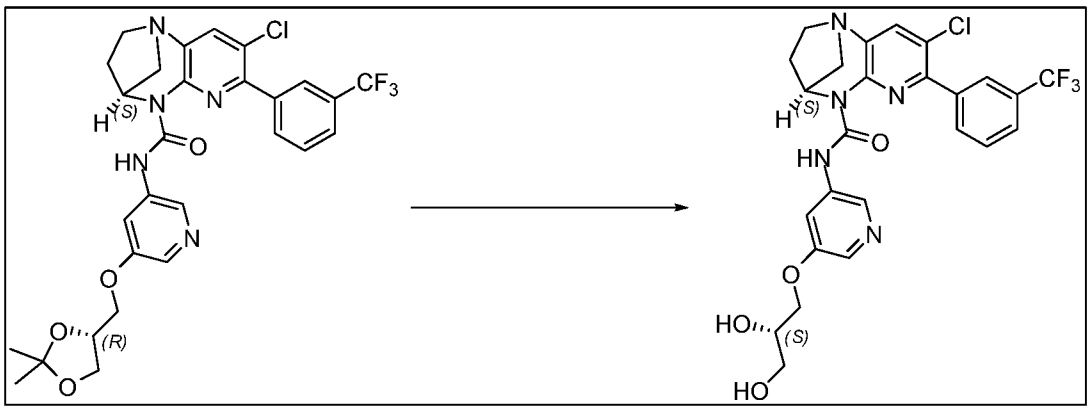


To a stirred solution of (4*S*)-8-chloro-*N*-(6-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (350 mg, 0.593 mmol) in Methanol (10 mL) was added HCl (0.180 mL, 5.93 mmol) at 0 °C and stirred at room temperature for 2 h. (TLC system: 100% ethylacetate, Rf value: 0.2). The reaction mixture was quenched with $NaHCO_3$ solution (10 mL) and extracted with DCM (2x30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to obtain the crude residue. The residue was triturated with *n*-pentane (3 x 10mL) to afford the desired product (4*S*)-8-chloro-*N*-(6-((*R*)-2,3-dihydroxypropoxy)pyridin-3-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (160 mg, 0.291 mmol, 49.0 % yield) as a white solid. LCMS (*m/z*): 550.16 $[M+H]^+$, *Rt* = 2.26 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.40 (s, 1 H), 8.07 (d, *J*=2.85 Hz, 1 H), 7.99 (s, 1 H), 7.93 (d, *J*=7.89 Hz, 1 H), 7.78 - 7.73 (m, 2 H), 7.68 - 7.62 (m, 2 H), 6.73 (d, *J*=8.77 Hz, 1 H), 5.66 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.42 (dd, *J*=4.60, 2.41 Hz, 2 H), 4.02 - 3.91 (m, 2 H), 3.72 - 3.60 (m, 2 H), 3.36 - 3.18 (m, 2 H), 3.17 - 3.11 (m, 1 H), 3.05 - 2.98 (m, 1 H), 2.68 (t, *J*=6.14 Hz, 1 H), 2.34 (dddd, *J*=14.06, 10.00, 5.97, 3.95 Hz, 1 H), 2.14 - 2.02 (m, 1 H).

Example 78

Synthesis of (4*S*)-8-chloro-*N*-(5-((*S*)-2,3-dihydroxypropoxy)pyridin-3-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide

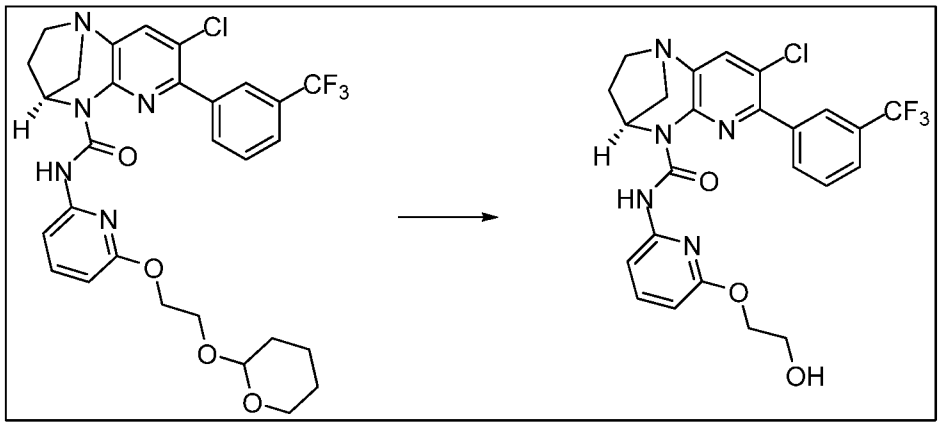


To a stirred solution of (4*S*)-8-chloro-*N*-(5-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide (9 g, 15.25 mmol) in methanol (30 mL) at 0 °C was added aq. HCl (5 mL, 165 mmol) stirred for 5 h. (TLC eluent: Mobile Phase: 10% MeOH in DCM; R_f: 0.2 ; UV active). The reaction mass was concentrated *in vaccuo* to afford brown viscous oil and dissolved of ice cold water (10 mL), neutralized with saturated bicarbonate solution and extracted with 10% MeOH in DCM (2x50 mL). The combined organic layer was washed with brine (20 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure to afford off white solid. The crude product was purified by column chromatography (silica gel eluted with 10% MeOH in CH_2Cl_2) to afford (4*S*)-8-chloro-*N*-(5-((*S*)-2,3-dihydroxypropoxy)pyridin-3-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide (6.5 g, 11.81 mmol, 77 % yield) as an off white solid. LC-MS (*m/z*): 550.13 $[M+H]^+$, Rt = 2.04 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.55 (s, 1 H), 8.07 - 8.12 (m, 2 H), 7.90 - 7.96 (m, 2 H), 7.88 (s, 1 H), 7.80 - 7.86 (m, 2 H), 7.63 (t, *J*=2.30 Hz, 1 H), 5.47 (dd, *J*=5.81, 2.96 Hz, 1 H), 4.97 (d, *J*=5.04 Hz, 1 H), 4.67 (t, *J*=5.70 Hz, 1 H), 4.00 (dd, *J*=9.43, 3.73 Hz, 1 H), 3.76 - 3.88 (m, 2 H), 3.41 - 3.48 (m, 2 H), 3.22 - 3.32 (m, 1 H), 3.10 (br d, *J*=11.84 Hz, 2 H), 2.95 - 3.03 (m, 1 H), 2.19 - 2.32 (m, 1 H), 1.91 - 2.01 (m, 1 H).

Example 79

Synthesis of (4*S*)-8-chloro-N-(6-(2-hydroxyethoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

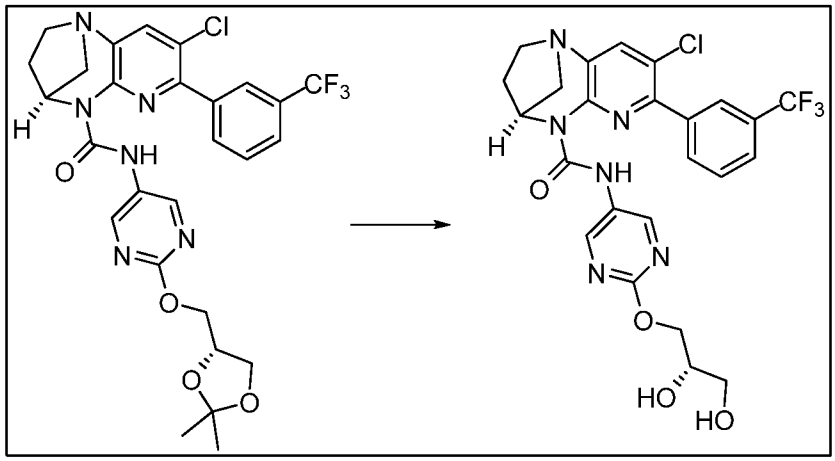


To a solution of (4*S*)-8-chloro-N-(6-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (250 mg, 0.414 mmol) in methanol (10 mL) at 0 °C was added aq. HCl (0.6 mL, 19.75 mmol, 36 %), and stirred 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) and solvent was evaporated under reduced pressure. The residue was diluted with water (10 mL) and extracted into DCM (2x20 mL). Combined organic extracts were dried over anhydrous sodium sulphate, filtered and filtrate was evaporated and the crude was triturated with 10% ethyl acetate in hexane to afford (4*S*)-8-chloro-N-(6-(2-hydroxyethoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2H)-carboxamide (62 mg, 0.117 mmol, 28.4 % yield) as an off white solid. LCMS (*m/z*): 520.17 $[M+H]^+$, R_t = 2.57 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.56 (s, 1 H), 7.99 (s, 1 H), 7.92 (d, *J*=7.45 Hz, 1 H), 7.75 - 7.69 (m, 1 H), 7.69 - 7.58 (m, 3 H), 7.57 - 7.50 (m, 1 H), 6.41 (d, *J*=7.89 Hz, 1 H), 5.68 (dd, *J*=5.81, 3.18 Hz, 1 H), 3.89 - 3.73 (m, 2 H), 3.71 - 3.58 (m, 2 H), 3.38 - 3.19 (m, 2 H), 3.18 - 3.10 (m, 1 H), 3.03 (dd, *J*=12.17, 3.18 Hz, 1 H), 2.43 - 2.24 (m, 1 H), 2.19 - 2.00 (m, 2 H).

Example 80

Synthesis of (4*S*)-8-chloro-N-(2-((*S*)-2,3-dihydroxypropoxy)pyrimidin-5-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

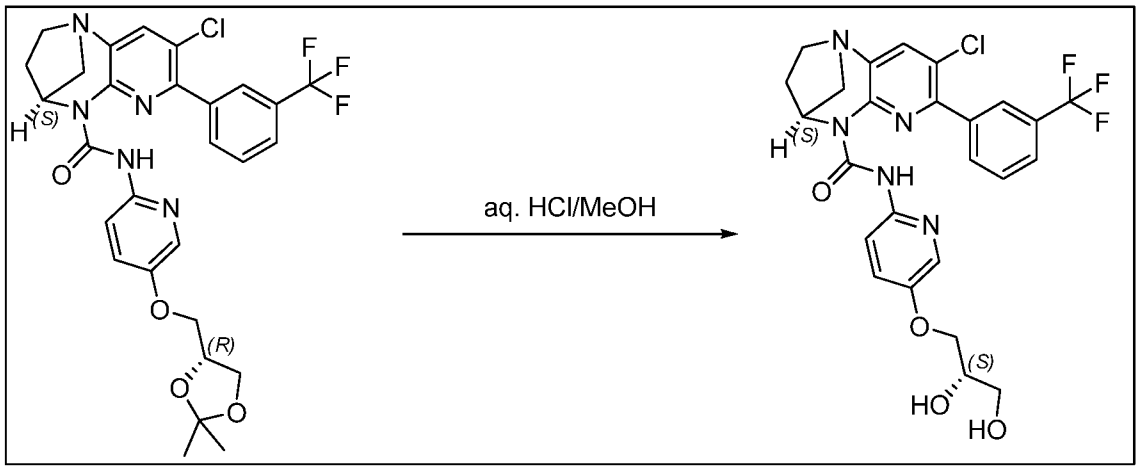


To a solution of (4*S*)-8-chloro-N-(2-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-5-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (300 mg, 0.508 mmol) in methanol (10 mL) under nitrogen at 0 °C was added aq. HCl (1.2 mL, 0.508 mmol, 36 %) and stirred for 2 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 solvent was evaporated under reduced pressure. The residue was diluted with water and stirred for 15 min. then the resultant solid was filtered through Buchner funnel, dried to afford (4*S*)-8-chloro-N-(2-((S)-2,3-dihydroxypropoxy)pyrimidin-5-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (200 mg, 0.358 mmol, 70.5 % yield) as an off white solid. LCMS (*m/z*): 551.17 $[M+H]^+$, R_t = 3.86 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.28 (s, 1 H), 8.60 - 8.46 (m, 2 H), 8.16 - 8.08 (m, 2 H), 7.95 - 7.86 (m, 2 H), 7.84 - 7.74 (m, 1 H), 5.45 (dd, *J*=5.70, 3.07 Hz, 1 H), 4.91 (d, *J*=5.26 Hz, 1 H), 4.62 (t, *J*=5.70 Hz, 1 H), 4.27 (dd, *J*=10.85, 4.28 Hz, 1 H), 4.15 (dd, *J*=10.85, 6.47 Hz, 1 H), 3.79 (dq, *J*=10.74, 5.55 Hz, 1 H), 3.43 (t, *J*=5.70 Hz, 2 H), 3.21 - 3.32 (m, 1 H), 3.18 - 3.04 (m, 2 H), 3.04 - 2.94 (m, 1 H), 2.33 - 2.20 (m, 1 H), 1.95 (dt, *J*=13.81, 7.13 Hz, 1 H).

Example 81

Synthesis of (4*S*)-8-chloro-*N*-(5-((*S*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoro methyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxam ide

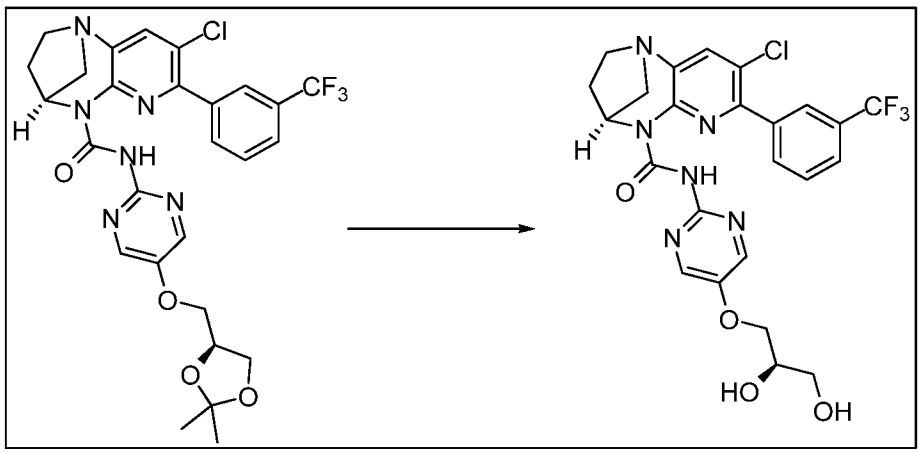


To a solution of (4*S*)-8-chloro-*N*-(5-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (400 mg, 0.678 mmol) in Methanol (15 mL) was added aq HCl (0.016 mL, 0.542 mmol) at 0 °C and stirred at RT for 1 h. (TLC system: R_f: 0.6, 10% MeOH/ DCM). The reaction mixture was evaporated and neutralized with $NaHCO_3$ solution, the obtain solid was filtered and washed with ether (2x 10 mL) to obtain semi pure compound (93% purity by LCMS). The semi pure compound was again purified by Prep HPLC ((Conditions: MP-A : 10 Mm Ammonium bi carbonate MP-B : Acetonitrile Column: Xbridge(250x19) Method - T/%B - 0/10, 1/10, 10/55 Flow : 25ml/min Solubility :ACN+MeOH+THF) to afford the desired compound (4*S*)-8-chloro-*N*-(5-((*S*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methano pyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (175 mg, 0.318 mmol, 46.9 % yield) as an off white solid. LCMS (*m/z*): 550.20 $[M+H]^+$, Rt = 2.28 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.84 (s, 1 H), 8.19 (s, 1 H), 8.10 (d, *J*=7.89 Hz, 1 H), 8.03 (d, *J*=8.99 Hz, 1 H), 7.95 (d, *J*=2.85 Hz, 1 H), 7.73 (d, *J*=7.89 Hz, 1 H), 7.65 (s, 1 H), 7.65 - 7.60 (m, 1 H), 7.25 - 7.22 (m, 1 H), 5.66 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.14 - 4.02 (m, 3 H), 3.88 - 3.82 (m, 1 H), 3.79 - 3.72 (m, 1 H), 3.36 -3.12 (m, 3 H), 3.01 (dd, *J*=12.17, 3.18 Hz, 1 H), 2.58 (s, 1 H), 2.38 - 2.28 (m, 1 H), 2.09 (dt, *J*=14.14, 6.96 Hz, 1 H), 1.98 (s, 1 H).

Example 82

Synthesis of (4*S*)-8-chloro-N-(5-((*R*)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide:

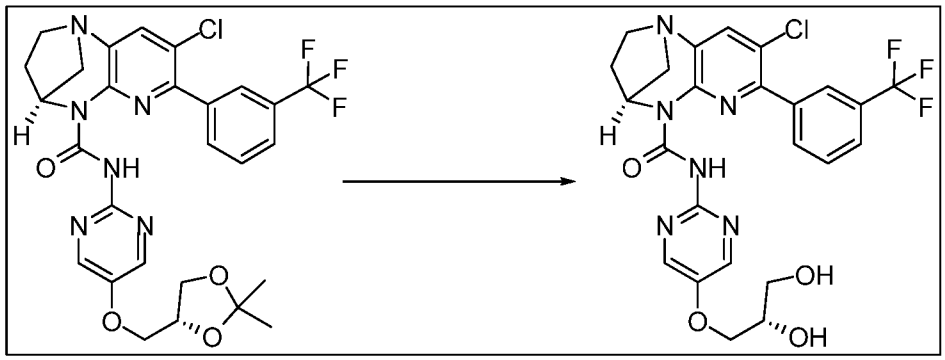


To a stirred solution of (4*S*)-8-chloro-N-(5-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (300 mg, 0.508 mmol) in methanol (15 mL) was added aq.HCl (0.015 mL, 0.508 mmol, 36 %) at 0 °C and stirred at RT for 1 h. (TLC eluent: 10%MeOH in EtOAc: R_f-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 (2x25 mL). Combined organic extracts were dried over anhydrous sodium sulphate, filtered and filtrate was evaporated under reduced pressure to afford the desired product (4*S*)-8-chloro-N-(5-((*R*)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (130 mg, 0.229 mmol, 45.1 % yield) as pale yellow solid. LCMS (*m/z*): 551.10 $[M+H]^+$, R_t =2.12 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.21 (s, 1 H), 8.29 (s, 2 H), 8.15 (s, 1 H), 7.90 - 8.11 (m, 1 H), 7.72 (br d, *J*=7.67 Hz, 1 H), 7.66 (s, 1 H), 7.57 - 7.64 (m, 1 H), 5.72 (dd, *J*=5.59, 3.18 Hz, 1 H), 4.00 - 4.22 (m, 3 H), 3.71 - 3.97 (m, 2 H), 3.08 - 3.37 (m, 3 H), 2.82 - 3.08 (m, 1 H), 2.63 (br s, 1 H), 2.26 - 2.45 (m, 1 H), 1.96 - 2.19 (m, 2 H).

Example 83

Synthesis of (4*S*)-8-chloro-N-(5-((*S*)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

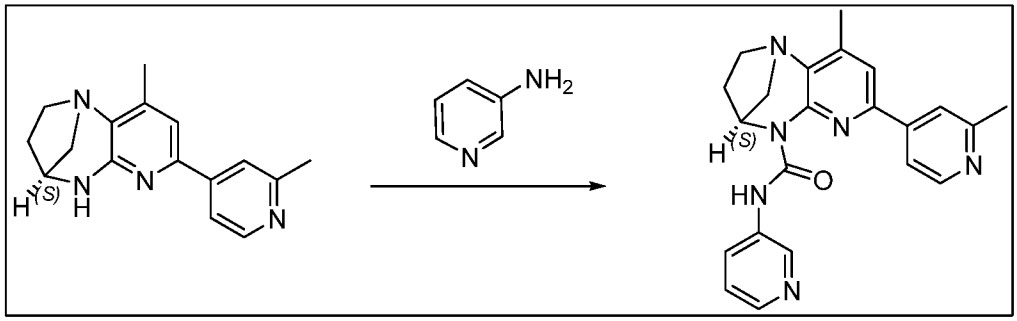


To a solution of (4*S*)-8-chloro-N-(5-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (300 mg, 0.508 mmol) in methanol (10 mL) under nitrogen at 0 °C was added aq. HCl (1 mL, 32.9 mmol, 36 %) and stirred at RT for 1 h. (TLC eluent: 5% Methanol in DCM, R_f: 0.3, UV active). To the reaction mixture was added saturated $NaHCO_3$ solution (till pH-8-9) and extracted into EtOAc (3x10 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 (2x10 mL) to afford (4*S*)-8-chloro-N-(5-((*S*)-2,3-dihydroxypropoxy)pyrimidin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (250 mg, 0.449 mmol, 88 % yield) as an off white solid. LCMS (*m/z*): 551.13 $[M+H]^+$, R_t = 2.10 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.21 (s, 1 H), 8.32 - 8.27 (m, 2 H), 8.15 (s, 1 H), 8.06 (d, *J*=7.67 Hz, 1 H), 7.72 (d, *J*=7.89 Hz, 1 H), 7.67 (s, 1 H), 7.63 - 7.56 (m, 1 H), 5.72 (dd, *J*=5.92, 3.29 Hz, 1 H), 4.16 - 4.05 (m, 3 H), 3.90 - 3.82 (m, 1 H), 3.80 - 3.73 (m, 1 H), 3.36 - 3.11 (m, 3 H), 3.01 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.68 (br s, 1 H), 2.38 - 2.27 (m, 1 H), 2.10 (dt, *J*=14.03, 7.02 Hz, 2 H).

Example 84

Synthesis of (4*S*)-9-methyl-7-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

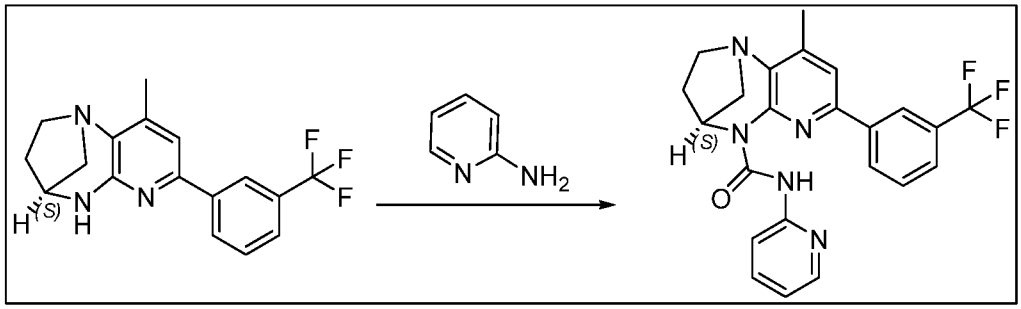


To a Stirred solution of (4*S*)-9-methyl-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (400 mg, 1.502 mmol) in Tetrahydrofuran (30 ml), were added triphosgene (267 mg, 0.901 mmol) and DIPEA (0.787 mL, 4.51 mmol) at room temperature. Then the reaction mixture was stirred for 30 min at RT. After 30 min pyridin-3-amine (212 mg, 2.253 mmol) was added and stirred at 75 °C for 16 h. (TLC system: Neat EtOAc, R*f*: 0.5). Then the reaction mixture was allowed to cool to room temperature and poured in saturated $NaHCO_3$ solution (30 mL), extracted with EtOAc (2 x 100 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 material was purified by flash column chromatography (Neutral alumina, Eluent: 50% EtoAc in Pet Ether) to afford the desired product (4*S*)-9-methyl-7-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (294 mg, 0.756 mmol, 50.3 % yield) as a white solid. LCMS (*m/z*): 387.18 $[M+H]^+$, R_t =1.27 min.

^{1}H NMR (400 MHz,$CDCl_3$): δ ppm 13.25 (s, 1 H), 8.68 - 8.61 (m, 2 H), 8.31 (dd, *J*=4.71, 1.42 Hz, 1 H), 8.19 - 8.11 (m, 1 H), 7.58 (d, *J*=0.66 Hz, 1 H), 7.49 (dd, *J*=5.26, 1.10 Hz, 1 H), 7.29 - 7.26 (m, 2 H), 5.69 (dd, *J*=6.03, 2.96 Hz, 1 H), 3.18 (t, *J*=7.45 Hz, 2 H), 3.13 - 2.99 (m, 2 H), 2.67 (s, 3 H), 2.51 (s, 3 H), 2.39 - 2.26 (m, 1 H), 2.12 - 2.00 (m, 1 H).

Example 85

Synthesis of (4*S*)-9-methyl-N-(pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

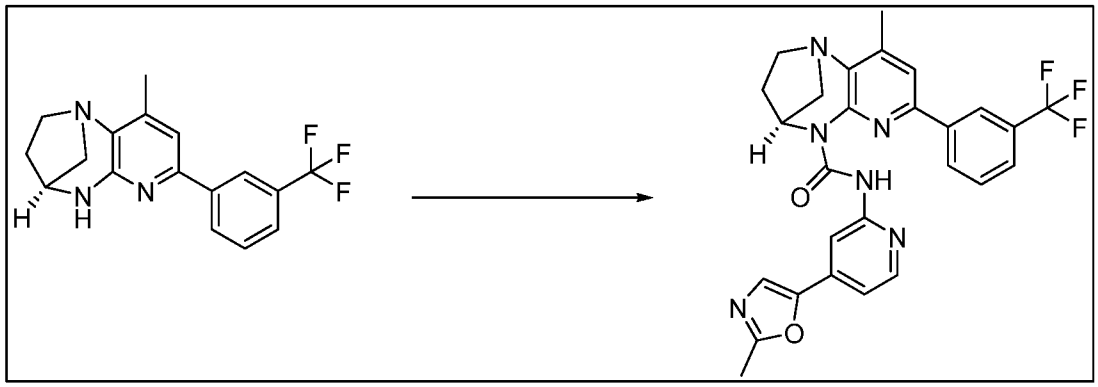


To a stirred solution of (4*S*)-9-methyl-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (250 mg, 0.783 mmol) in Tetrahydrofuran (30 ml) were added triphosgene (139 mg, 0.470 mmol) and triethyl amine (0.109 mL, 0.783 mmol) at room temperature and stirred for 30 min. After 30 min, pyridin-2-amine (111 mg, 1.174 mmol) was added and stirred at 75 °C for 16 h. (TLC system: EtOAc, R*f*: 0.6). Then the reaction mixture was allowed to cooled to room temperature and poured in saturated $NaHCO_3$ solution (30 mL), extracted with EtOAc (2 x 100 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 material was purified by flash column chromatography (Neutral alumina column, Eluent: 20% EtoAc in Pet Ether) to afford the desired product (4*S*)-9-methyl-N-(pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (70 mg, 0.158 mmol, 20.21 % yield) as a white solid. LCMS (*m/z*): 440.22 $[M+H]^+$, R_t =3.05 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.68 (br s, 1 H), 8.46 - 8.30 (m, 3 H), 8.17 (d, *J*=8.33 Hz, 1 H), 7.74 - 7.59 (m, 3 H), 7.36 - 7.24 (m, 1 H), 7.02 - 6.92 (m, 1 H), 5.71 (dd, *J*=5.59, 2.96 Hz, 1 H), 3.26 - 3.08 (m, 3 H), 3.04 - 2.95 (m, 1 H), 2.50 (s, 3 H), 2.32 (td, *J*=13.76, 5.81 Hz, 1 H), 2.17 - 2.01 (m, 1 H).

Example 86

Synthesis of (4*S*)-9-methyl-N-(4-(2-methyloxazol-5-yl)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

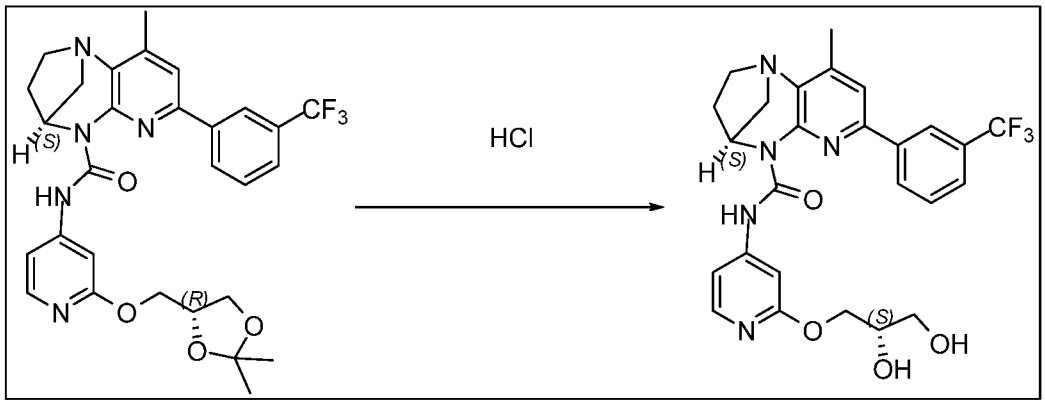


To a stirred solution of (4*S*)-9-methyl-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 0.939 mmol) in Tetrahydrofuran (30 ml) were added triphosgene (167 mg, 0.564 mmol) and DIPEA (0.820 mL, 4.70 mmol) at room temperature and stirred for 30 min. Then 4-(2-methyloxazol-5-yl)pyridin-2-amine (247 mg, 1.409 mmol) was added and stirred at 75 °C for 16 h. (TLC system: EtOAc, R*f*: 0.3). Then allowed the reaction mixture to cool to room temperature and poured in saturated $NaHCO_3$ solution (30 mL), extracted with EtOAc (2 x 100 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 material was purified by flash column chromatography (Neutral alumina column, Eluent: 40% EtoAc in Pet Ether) to afford the desired product (4*S*)-9-methyl-N-(4-(2-methyloxazol-5-yl)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide (126 mg, 0.241 mmol, 25.7 % yield) as a white solid. LCMS (*m/z*): 521.29 $[M+H]^+$; R_t = 3.13 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.81 (s, 1 H), 8.51 - 8.29 (m, 4 H), 7.72 - 7.60 (m, 2 H), 7.45 (s, 1 H), 7.32 (s, 1 H), 7.17 (dd, *J*=5.15, 1.43 Hz, 1 H), 5.72 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.23 - 3.09 (m, 3 H), 3.08 - 2.96 (m, 1 H), 2.53 (s, 3 H), 2.51 (s, 3 H), 2.34 (td, *J*=13.76, 6.47 Hz, 1 H), 2.16 - 2.02 (m, 1 H).

Example 87

Synthesis of (4*S*)-N-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-9-methyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

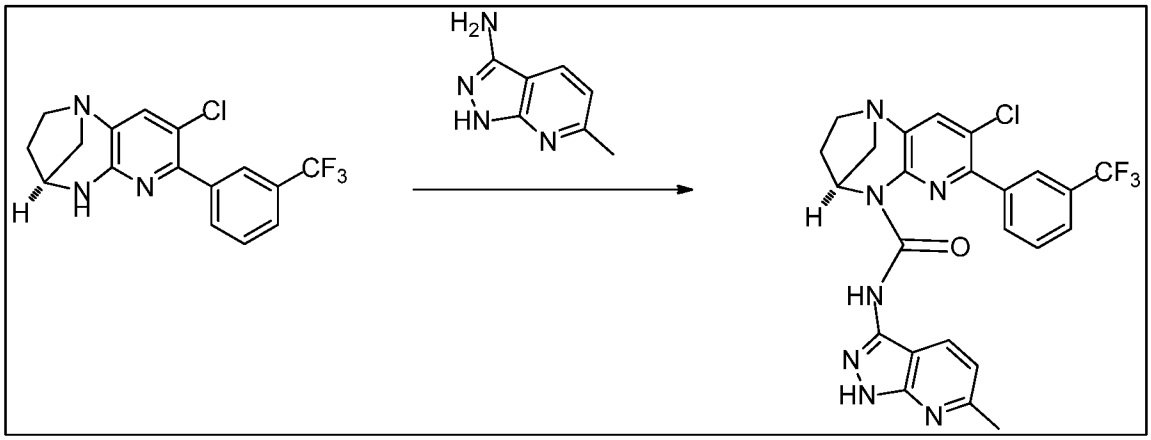


To a stirred solution of (4*S*)-N-(2-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-9-methyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diaze pine-5(2*H*)-carboxamide (400 mg, 0.702 mmol) in Methanol (30 mL) was added hydrochloric acid (2 mL, 23.70 mmol) at room temperature and stirred for 1 h. (TLC system: Neat EtOAc, R*f*: 0.3). After 1 h. the reaction mixture was concentrated under reduced pressure and quenched with saturated $NaHCO_3$ solution (30 mL), extracted with 5%MeOH in DCM (2x 50mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain semi solid, which was washed with pentane (2x 20 mL) and dried to afford the desired product (4*S*)-N-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-9-methyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (288 mg, 0.538 mmol, 77 % yield) as an off white solid. LCMS (*m/z*): 530.29 $[M+H]^+$, R_t =2.32 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.43 (s, 1 H), 8.05 (s, 1 H), 8.00 - 7.88 (m, 2 H), 7.78 - 7.62 (m, 2 H), 7.23 (s, 1 H), 7.16 (s, 1 H), 6.94 (d, *J*=4.38 Hz, 1 H), 5.67 (dd, *J*=5.26, 2.85 Hz, 1 H), 4.45 (d, *J*=4.38 Hz, 3 H), 4.03 - 3.93 (m, 1 H), 3.74 - 3.59 (m, 2 H), 3.23 - 2.99 (m, 5 H), 2.50 (s, 3 H), 2.33 (td, *J*=13.54, 6.25 Hz, 1 H), 2.13 - 1.99 (m, 1 H).

Example 88

Synthesis of (4*S*)-8-chloro-*N*-(6-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

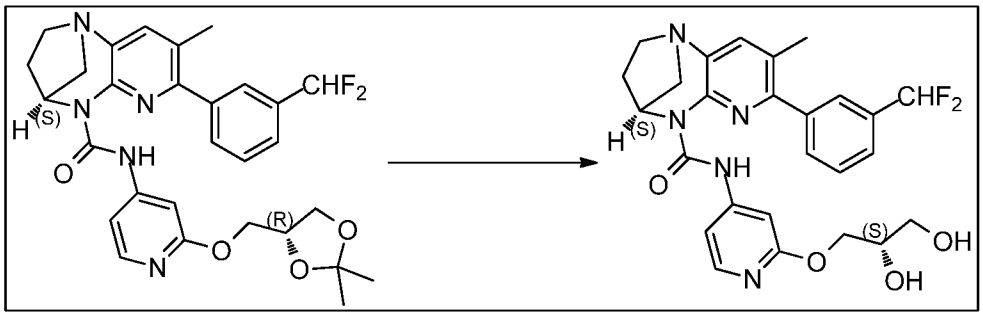


To a stirred solution of (4*S*)-8-chloro-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (600 mg, 1.766 mmol) in Tetrahydrofuran (10 mL) were added triphosgene (524 mg, 1.766 mmol) and TEA (0.738 mL, 5.30 mmol) under nitrogen atmosphere at room temperature and stirred it for 30 min. To this 6-methyl-1H-pyrazolo[3,4-b]pyridin-3-amine (523 mg, 3.53 mmol) was added sub sequentially at RT and stirred at 75 °C for 15 h. (TLC 5% MeOH\DCM R_f: 0.3; UV active). The reaction mixture was diluted with water (10 ml) and extracted with ethylacetate (2 X 20 ml). The combined organic layer was washed with saturated brine solution and dried over anhydrous sodium sulphate, concentrated under reduced pressure to give the crude compound, which was purified by coloumn chromatography (Silica gel:100-200 Mesh, Eluent: 80% EtOAc/Petether) to afford the desired product (4*S*)-8-chloro-*N*-(6-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (243 mg, 0.451 mmol, 25.5 % yield) as a white solid. LCMS (*m/z*): 514.23 $[M+H]^+$, *Rt* =2.54 min.

^{1}H NMR (400MHz, DMSO-d_6 + 1 drop TFA): δ ppm 8.54 - 8.36 (m, 1 H), 8.17 - 8.01 (m, 3 H), 7.92 (d, *J*=7.7 Hz, 1 H), 7.80 (t, *J*=7.8 Hz, 1 H), 7.18 - 7.00 (m, 1 H), 5.63 (dd, *J*=3.0, 5.6 Hz, 1 H), 3.57 - 3.38 (m, 4 H), 2.69 - 2.56 (m, 3 H), 2.49 - 2.32 (m, 1 H), 2.23 (td, *J*=7.1, 13.9 Hz, 1 H)

Example 89

Synthesis of (4*S*)-7-(3-(difluoromethyl)phenyl)-N-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-8-methyl-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide.

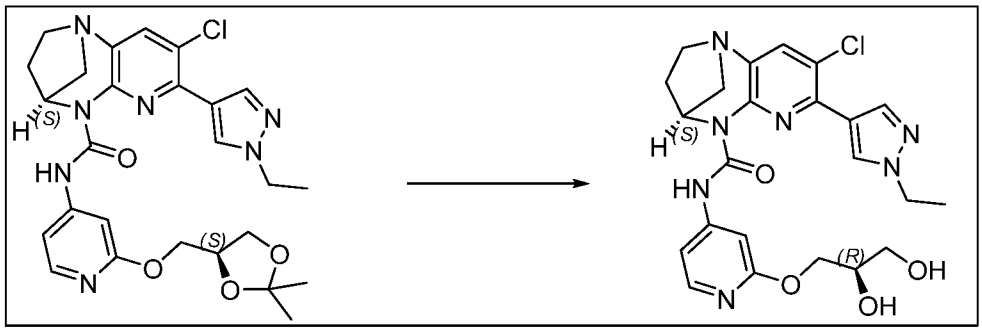


To a stirred solution of (4*S*)-7-(3-(difluoromethyl)phenyl)-N-(2-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-8-methyl-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4] diazepine-5(2*H*)-carboxamide (0.2 g, 0.363 mmol) in methanol (10 mL) was added HCl (5.51 µL, 0.181 mmol), drop wise over a period of 5 min. at 0 °C. Then the reaction mixture was stirred at 30 °C for 2 h (TLC eluent: 5% MeOH in DCM: R_f-0.3; UV active). After 2 h. the reaction mixture was concentrated *in vacuo* and the residue was neutralized with aq $NaHCO_3$ solution and obtained solid was filtered and washed with ether (2x 50 mL), *n*-pentane (2x 50 mL) to afford the desired product (4*S*)-7-(3-(difluoromethyl)phenyl)-N-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-8-methyl-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (110 mg, 0.215 mmol, 59.2 % yield) as an off white solid. LCMS (*m/z*): 512.25 $[M+H]^+$, *Rt* = 1.95 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.28 (s, 1 H), 7.88 - 7.80 (m, 3 H), 7.74 - 7.70 (m, 2 H), 7.61 (s, 1 H), 7.29 - 7.00 (m, 2 H), 6.52 (dd, *J*=5.70, 1.75 Hz, 1 H), 5.44 (dd, *J*=5.92, 3.29 Hz, 1 H), 4.85 (s, 1 H), 4.58 (s, 1 H), 4.20 (dd, *J*=10.74, 4.60 Hz, 1 H), 4.08 (dd, *J*=10.85, 6.25 Hz, 1 H), 3.76 (d, *J*=5.04 Hz, 1 H), 3.42 (s, 2 H), 3.26 - 3.17 (m, 1 H), 3.14 - 3.05 (m, 2 H), 2.94 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.31 (s, 3 H), 2.26 - 2.20 (m, 1 H), 1.95 - 1.85 (m, 1 H).

Example 90

Synthesis of (4*S*)-8-chloro-*N*-(2-((*R*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(1-ethyl-1*H*-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide.

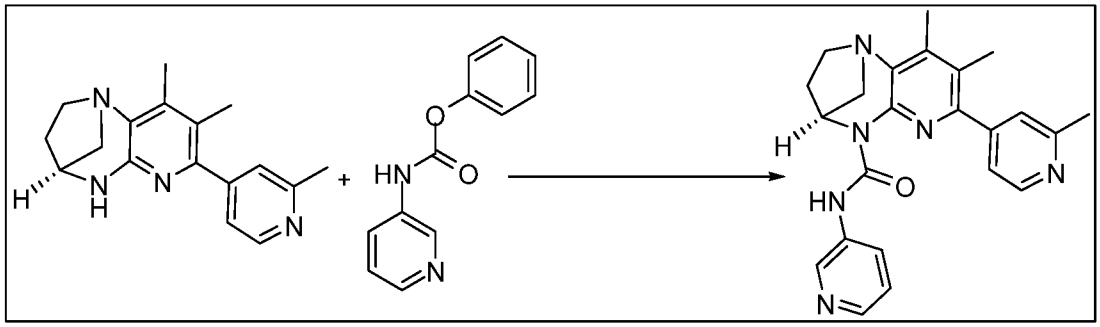


To a solution of (4*S*)-8-chloro-*N*-(2-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(1-ethyl-1*H*-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (400 mg, 0.741 mmol) in methanol (5 mL) under nitrogen at RT was added HCl (2 mL, 65.8 mmol) and stirred for 2 h. (TLC system 5% Methanol in DCM. Rf value: 0.1). The reaction mixture was concentrated and the residue at 0 °C was basified with saturated $NaHCO_3$ solution. The resultant solid was filtered and dried to get crude compound, the solid was triturated with diethylether (10 mL) to afford (4*S*)-8-chloro-*N*-(2-((*R*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(1-ethyl-1*H*-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide(230 mg, 0.458 mmol, 61.8 % yield) as an off-white solid. LCMS (*m/z*): 500.26$[M+H]^+$, *Rt* =1.75 min.

^{1}H NMR (400MHz, DMSO-d6): δ ppm 12.66 (s, 1 H), 8.43 (s, 1 H), 8.01 (t, *J*=2.7 Hz, 2 H), 7.74 (s, 1 H), 7.10 - 6.87 (m, 2 H), 5.41 (br d, *J*=3.1 Hz, 1 H), 4.86 (d, *J*=5.0 Hz, 1 H), 4.59 (br t, *J*=5.7 Hz, 1 H), 4.40 - 4.19 (m, 3 H), 4.19 - 3.96 (m, 1 H), 3.93 - 3.65 (m, 1 H), 3.43 (br t, *J*=5.7 Hz, 2 H), 3.22 (br s, 1 H), 3.16 - 3.00 (m, 2 H), 2.93 (brdd, *J*=3.1, 12.1 Hz, 1 H), 2.37 - 2.08 (m, 1 H), 1.93 (brdd, *J*=6.4, 13.8 Hz, 1 H), 1.46 (t, *J*=7.2 Hz, 3 H).

Example 91

Synthesis of (4*S*)-8,9-dimethyl-7-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

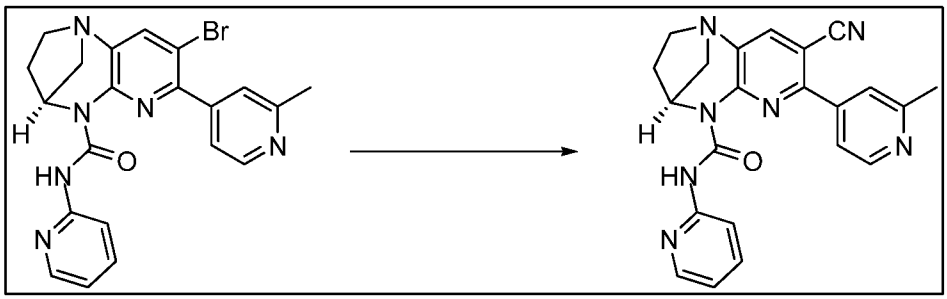


To a stirred solution of (4*S*)-8,9-dimethyl-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 1.070 mmol) in THF (30 mL) under nitrogen atmosphere at RT was added phenyl pyridin-3-ylcarbamate (688 mg, 3.21 mmol) followed by DMAP (392 mg, 3.21 mmol) and stirred at 65 °C for 16 h. (TLC eluent: 100% EtOAc: R_f-0.2; UV active). The reaction mixture was cooled to RT, concentrated and the residue 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 give crude compound. The crude product was purified by column chromatography (neutral alumina, eluent: 70% EtOAc in Hexane) to afford the desired product (4*S*)-8,9-dimethyl-7-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (238 mg, 0.590 mmol, 55.1 % yield) as a white solid. LCMS (*m/z*): 401.12 $[M+H]^+$, R_t = 1.35 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.19 (s, 1 H), 8.65 (d, *J*=5.04 Hz, 1 H), 8.42 (br s, 1 H), 8.24 (br d, *J*=4.17 Hz, 1 H), 8.03 - 7.94 (m, 1 H), 7.29 (s, 1 H), 7.23 - 7.16 (m, 2 H), 5.64 (dd, *J*=5.81, 2.96 Hz, 1 H), 3.25 - 3.14 (m, 2 H), 3.12 - 3.00 (m, 2 H), 2.67 (s, 3 H), 2.47 (s, 3 H), 2.38 - 2.28 (m, 1 H), 2.24 (s, 3 H), 2.12 – 1.99 (m, 1 H)

Example 92

Synthesis of (4*S*)-8-cyano-7-(2-methylpyridin-4-yl)-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido [2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

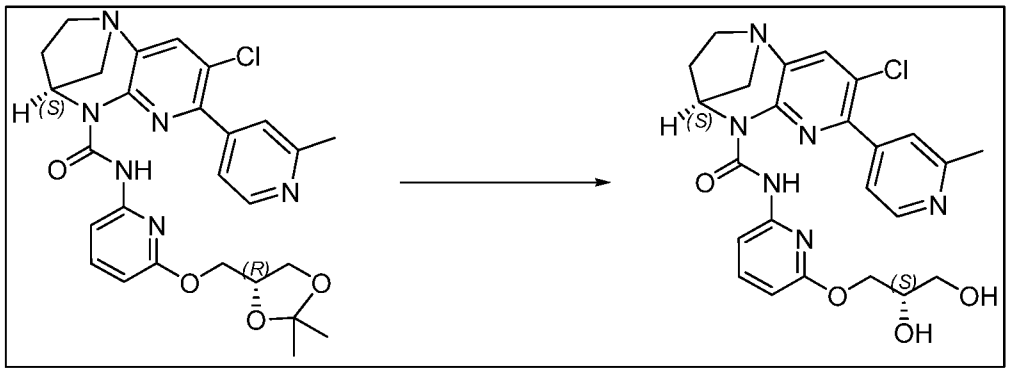


To a degassed solution of (4*S*)-8-bromo-7-(2-methylpyridin-4-yl)-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (300 mg, 0.665 mmol), $Zn(CN)_2$ (234 mg, 1.994 mmol) and added $Zn(OAc)_2$ (73.2 mg, 0.399 mmol) in N,N-Dimethylformamide (12 mL) were added solid $Pd_2(dba)_3$ (122 mg, 0.133 mmol) and DPPF (147 mg, 0.266 mmol). Then the reaction mixture was stirred at 100 °C for 15 h. (TLC System; Rf- 0.4, 5% methanol in dichloro methane). The reaction mixture was allowed to cool to room temperature and diluted with water (30 mL), extracted with ethyl acetate (3 X 50 mL). The combined organic layer was 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 (100-200 mesh) and it was further purified by Prep HPLC (Conditions: MP-A: 5mM Ammonium Bicarbonate (Aq) MP-B: Acetonitrile Column: KROMOSIL C18 (250x21.2)10µ Method: 0/50, 12/50, 12.5/100, 18/100, 18.1/50 Flow: 19ml/min Solubility: MeOH + THF + ACN) to afford the desired product (4*S*)-8-cyano-7-(2-methylpyridin-4-yl)-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (85 mg, 0.211 mmol, 31.8 % yield) as an off white solid. LCMS (*m/z*): 398.06 $[M+H]^+$, R_t = 1.97 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.92 (s, 1 H), 8.71 (d, *J*=5.26 Hz, 1 H), 8.34 - 8.29 (m, 1 H), 8.17 - 8.12 (m, 1 H), 7.96 (d, *J*=1.53 Hz, 1 H), 7.86 - 7.79 (m, 2 H), 7.74 - 7.67 (m, 1 H), 7.03 (ddd, *J*=7.29, 4.88, 0.99 Hz, 1 H), 5.71 (dd, *J*=5.81, 2.96 Hz, 1 H), 3.33 - 3.22 (m, 2 H), 3.16 - 3.02 (m, 2 H), 2.75 (s, 3 H), 2.44 - 2.31 (m, 1 H), 2.18 - 2.05 (m, 1 H).

Example 93

Synthesis of (4*S*)-8-chloro-*N*-(6-((*S*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(2-methylpyrid in-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

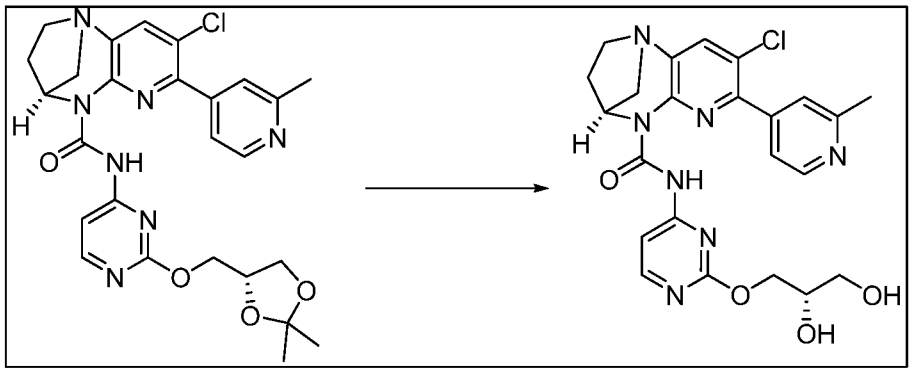


To a stirred solution of (4*S*)-8-chloro-*N*-(6-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (250 mg, 0.466 mmol) in Methanol (10 mL), was added 3M HCl (10 mL, 30.0 mmol) at RT. The resulting mixture was stirred at RT for 1 h. (TLC 5%MeOH/DCM R_f: 0.2; UV active) and the reaction mass was basified with saturated bicarbonate solution (10 mL), extracted with DCM (2X20 mL). The combined organic layer was washed with brine solution (10 mL) and dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get a brown solid and it was triturated with pentane (10 mL) and dried in vacuo to afford the desired product (4*S*)-8-chloro-*N*-(6-((*S*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (115 mg, 0.220 mmol, 47.3 % yield) as a pale yellow solid. LCMS (*m/z*): 497.1 $[M+H]^+$, *Rt* =1.54 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.44 (s, 1 H), 8.65 (d, *J*=5.04 Hz, 1 H), 7.85 (s, 1 H), 7.69 - 7.57 (m, 2 H), 7.54 - 7.45 (m, 2 H), 6.44 (dd, *J*=7.67, 0.88 Hz, 1 H), 5.48 (dd, *J*=5.70, 2.85 Hz, 1 H), 4.74 (d, *J*=4.60 Hz, 1 H), 4.67 - 4.44 (m, 1 H), 3.81 - 3.58 (m, 3 H), 3.46 - 3.38 (m, 2 H), 3.32 - 3.25 (m, 1 H), 3.19 - 3.03 (m, 2 H), 3.04 – 2.83 (m, 1 H), 2.49 (s, 3 H), 2.36- 2.05 (m, 1 H), 1.95 (dt, *J*=13.76, 7.04 Hz, 1 H).

Example 94

Synthesis of (4*S*)-8-chloro-N-(2-((*S*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide:

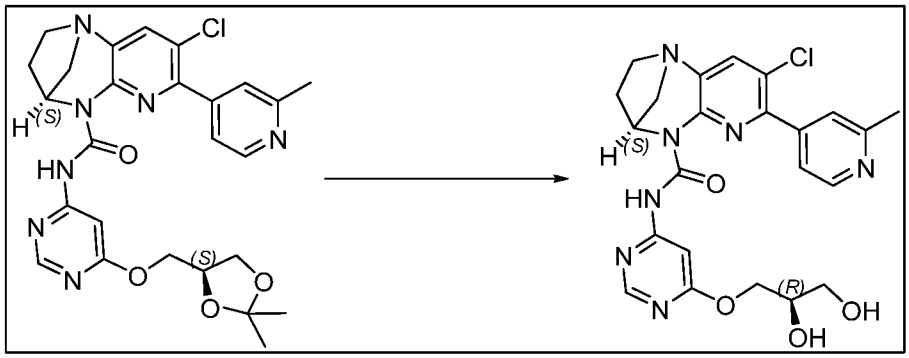


To a stirred solution of (4*S*)-8-chloro-N-(2-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (150 mg, 0.279 mmol) in methanol (5 mL) at 0 °C was added aq.HCl (0.5 mL, 16.46 mmol) and stirred at RT for 1 h. (TLC eluent: 10% MeOH in DCM, R_f= 0.3; UV active). The reaction mixture concentrated under reduced pressure, and the residue was basified with saturated sodium bicarbonate solution (till pH-8-9) and the aqueous layer was extracted with DCM (2 x 40 mL). Combined organic layer was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude product. The crude compound was triturated with ether (2 x15 mL) to afford (4*S*)-8-chloro-N-(2-((*S*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (125 mg, 0.241 mmol, 87 % yield) as an off-white solid. LCMS (*m/z*): 498.10 $[M+H]^+$, *Rt* = 1.43 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.01 (s, 1 H), 8.68 (d, *J*=5.04 Hz, 1 H), 8.34 (d, *J*=5.70 Hz, 1 H), 7.74 (d, *J*=5.48 Hz, 1 H), 7.69 (s, 1 H), 7.57 (s, 1 H), 7.52 (br d, *J*=5.26 Hz, 1 H), 5.63 (br dd, *J*=5.59, 2.74 Hz, 1 H), 3.93 - 4.09 (m, 3 H), 3.54 - 3.75 (m, 4 H), 3.19 - 3.37 (m, 2 H), 3.10 - 3.18 (m, 1 H), 2.99 - 3.08 (m, 1 H), 2.69 (s, 3 H), 2.28 - 2.43 (m, 1 H), 2.07 (dt, *J*=14.41, 7.15 Hz, 1 H).

Example 95

Synthesis of (4*S*)-8-chloro-N-(6-((*R*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

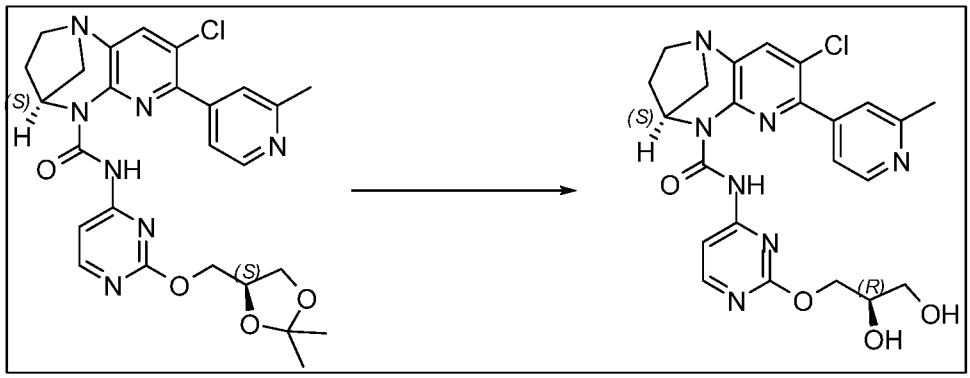


To a stirred solution of (4*S*)-8-chloro-N-(6-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (0.12g, 0.223 mmol) in DCM (5 mL) and methanol (5 mL) at 0 °C was added HCl (0.558 mL, 2.230 mmol, 4M in dioxane) and stirred for 4 h. (TLC eluent:10% MeOH in EtOAc: R_f-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 (2x25 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude product. Crude compound was purified by column chromatography (using neutral alumina and eluted 50% ethylacetate in hexane) to afford (4*S*)-8-chloro-N-(6-((*R*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (0.09 g, 0.174 mmol, 78 % yield) as an off-white solid. LCMS (*m/z*): 498.07 $[M+H]^+$, R_t = 1.40 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.02 (s, 1 H), 8.62 (d, *J* = 5.26 Hz, 1 H), 8.46 (s, 1 H), 7.88 (s, 1 H), 7.61 - 7.73 (m, 2 H), 7.41 (s, 1 H), 5.45 (br d, *J* = 2.63 Hz, 1 H), 4.74 - 5.14 (m, 2 H), 4.35 (br dd, *J* = 10.85, 4.06 Hz, 1 H), 4.21 (br dd, *J* = 10.74, 6.36 Hz, 1 H), 3.76 - 3.86 (m, 1 H), 3.43 (br d, *J* = 5.04 Hz, 2 H), 3.19 - 3.26 (m, 1 H), 3.06 - 3.15 (m, 2 H), 2.97 (br dd, *J* = 12.06, 2.85 Hz, 1 H), 2.61 (s, 3 H), 2.20 - 2.28 (m, 1 H), 1.91 - 2.05 (m, 1 H).

Example 96

Synthesis of (4*S*)-8-chloro-N-(2-((*R*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

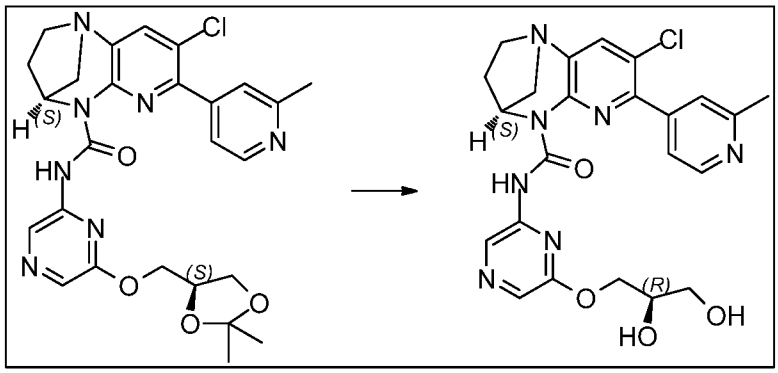


To a stirred solution of (4*S*)-8-chloro-*N*-(2-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (250 mg, 0.465 mmol) in Methanol (10 mL) under nitrogen atmosphere was added aq HCl (1.0 ml, 4.00 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 1 h. (TLC eluent: 5% Methanol in DCM, R_f: 0.3, UV active). The solvent was evaporated under reduced pressure, diluted with water, basified with saturated $NaHCO_3$ solution (till pH:8-9) and extracted with dichloromethane (3 X 10 mL). The combined organic layer was washed with brine solution (10 mL), dried over anhydrous Na_2SO_4, filtered and evaporated to obtain crude compound. The crude material was triturated with diethylether (10 mL) to afford the desired product (4*S*)-8-chloro-N-(2-((*R*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (125 mg, 0.247 mmol, 53.3 % yield) as an off white solid. LCMS (*m/z*): 498.07 $[M+H]^+$, R_t = 1.44 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.02 (s, 1 H), 8.68 (d, *J*=5.04 Hz, 1 H), 8.34 (d, *J*=5.70 Hz, 1 H), 7.75 (d, *J*=5.70 Hz, 1 H), 7.69 (s, 1 H), 7.56 (s, 1 H), 7.51 (d, *J*=4.17 Hz, 1 H), 5.63 (dd, *J*=5.81, 3.18 Hz, 1 H), 4.07 – 3.97 (m, 3 H), 3.70 (d, *J*=4.60 Hz, 2 H), 3.60 - 3.10 (m, 5 H), 3.08 – 2.99 (m, 1 H), 2.68 (s, 3 H), 2.41 - 2.29 (m, 1 H), 2.07 (m, 1 H).

Example 97

Synthesis of (4S)-8-chloro-N-(6-((*R*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2H)-carboxamide

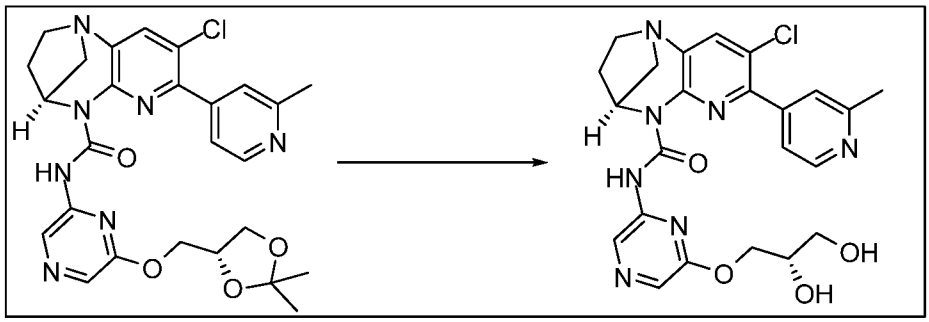


To a stirred solution of (4*S*)-8-chloro-N-(6-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxami de (180 mg, 0.335 mmol) in Methanol (10 mL) was added aq HCl (0.2 mL, 6.58 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 2 h. (TLC eluent: 5% MeOH/DCM; Rf value: 0.3; UV active). The reaction mixture was concentrated *in vacuo* and the obtained residue was neutralized with saturated $NaHCO_3$ solution (20 mL) at 0 °C and extracted with DCM (2 X 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to obtain crude compound. This compound was purified by *n*-pentane (30 mL) to afford the desired product (4*S*)-8-chloro-N-(6-((*R*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2H)-carboxamide (116 mg, 0.228 mmol, 68.3 % yield) as an off white solid. LCMS (*m/z*): 498.07 $[M+H]^+$, *Rt* =1.44 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.70 (s, 1 H), 9.00 (s, 1 H), 8.65 (d, *J*=5.26 Hz, 1 H), 7.93 (s, 1 H), 7.68 (s, 1 H), 7.59 - 7.53 (m, 1 H), 7.49 - 7.42 (m, 1 H), 5.67 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.01 - 3.91 (m, 1 H), 3.80 - 3.50 (m, 4 H), 3.39 - 3.20 (m, 2 H), 3.20 - 3.09 (m, 1 H), 3.09 - 2.99 (m, 1 H), 2.71 - 2.58 (m, 3 H), 2.47 - 2.26 (m, 1 H), 2.08 (dt, *J*=14.09, 7.10 Hz, 1 H).

Example 98

Synthesis of (4*S*)-8-chloro-N-(6-((*S*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

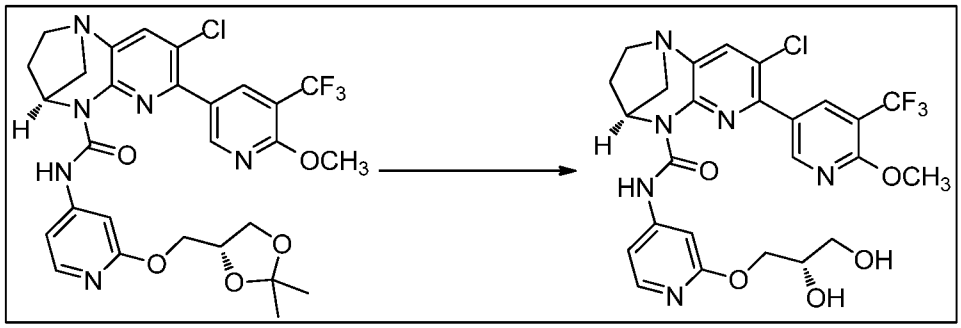


To a stirred solution of (4*S*)-8-chloro-N-(6-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (200 mg, 0.372 mmol) in 1,4-Dioxane (5.0 mL) was added 4M HCl in dioxane (0.929 mL, 3.72 mmol) at RT and was stirred for 4 h at the same temperature (TLC:Eluent: Neat ethylacetate, R_f: 0.3). 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:60% ethyl acetate in hexane) to afford the desired product (4*S*)-8-chloro-N-(6-((*S*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido [2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (120 mg, 0.240 mmol, 64.7 % yield) as a white solid. LCMS (*m/z*): 498.07 $[M+H]^+$, *Rt* = 1.44 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.70 (s, 1 H), 8.86 (s, 1 H), 8.65 (d, *J*=5.04 Hz, 1 H), 7.94 (s, 1 H), 7.89 (s, 1 H), 7.55 (s, 1 H), 7.49 (s, 1 H), 5.49 (dd, *J*=5.70, 2.85 Hz, 1 H), 4.88 (d, *J*=5.04 Hz, 1 H), 4.65 (t, *J*=5.70 Hz, 1 H), 3.88 - 3.77 (m, 2 H), 3.75 - 3.67 (m, 1 H), 3.39 (t, *J*=5.81 Hz, 2 H), 3.32 - 3.30 (m, 1 H), 3.16 - 3.09 (m, 2 H), 2.99 (dd, *J*=11.95, 3.18 Hz, 1 H), 2.55 (s, 3 H), 2.30 - 2.20 (m, 1 H), 2.04- 1.81 (m, 1 H).

Example 99

Synthesis of (4*S*)-8-chloro-N-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

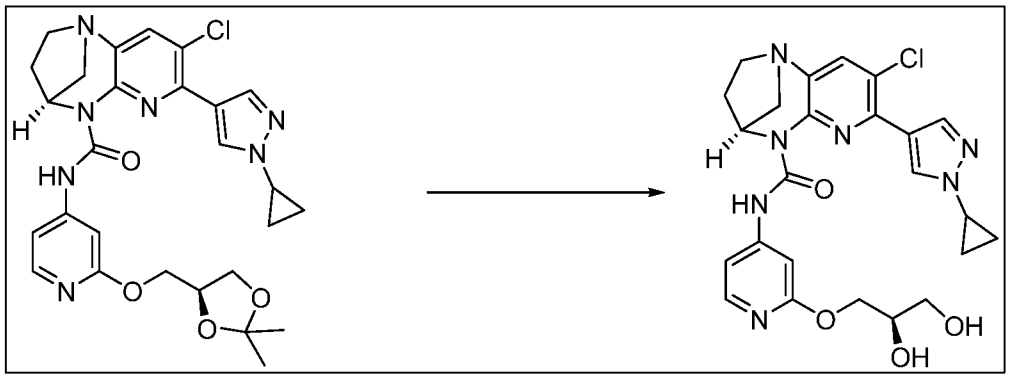


To a stirred solution of (4*S*)-8-chloro-N-(2-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (330 mg, 0.531 mmol) in methanol (5 mL) at 0 °C was added aq. HCl (0.448 mL, 5.31 mmol) and stirred 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 (2x10 mL). Combined organic extracts were dried over anhydrous sodium sulphate, filtered and filtrate was evaporated *in vacuo* to afford the desired product (4*S*)-8-chloro-N-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(6-methoxy-5-(trifluoromethyl)pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (264 mg, 0.453 mmol, 85 % yield) as an off-white solid. LCMS (*m/z*): 581.19 $[M+H]^+$, R_t = 2.24 min

^{1}H NMR (400MHz, $CDCl_3$): δ ppm 12.85 - 12.54 (m, 1 H), 8.77 (d, *J*=2.2 Hz, 1 H), 8.24 (d, *J*=2.0 Hz, 1 H), 7.90 (d, *J*=5.9 Hz, 1 H), 7.68 (s, 1 H), 7.02 (d, *J*=1.5 Hz, 1 H), 6.78 (dd, *J*=1.9, 5.8 Hz, 1 H), 5.65 (dd, *J*=3.1, 5.9 Hz, 1 H), 4.48 - 4.40 (m, 2 H), 4.24 (br s, 1 H), 4.16 (s, 3 H), 3.98 (br t, *J*=4.5 Hz, 1 H), 3.71 - 3.57 (m, 2 H), 3.35 - 3.18 (m, 2 H), 3.16 - 3.08 (m, 1 H), 3.06 - 2.95 (m, 1 H), 2.85 (br t, *J*=6.4 Hz, 1 H), 2.44 - 2.25 (m, 1 H), 2.07 (td, *J*=7.1, 14.3 Hz, 1 H).

Example 100

Synthesis of (4*S*)-8-chloro-7-(1-cyclopropyl-1*H*-pyrazol-4-yl)-*N*-(2-((*R*)-2,3-dihydroxypropoxy)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

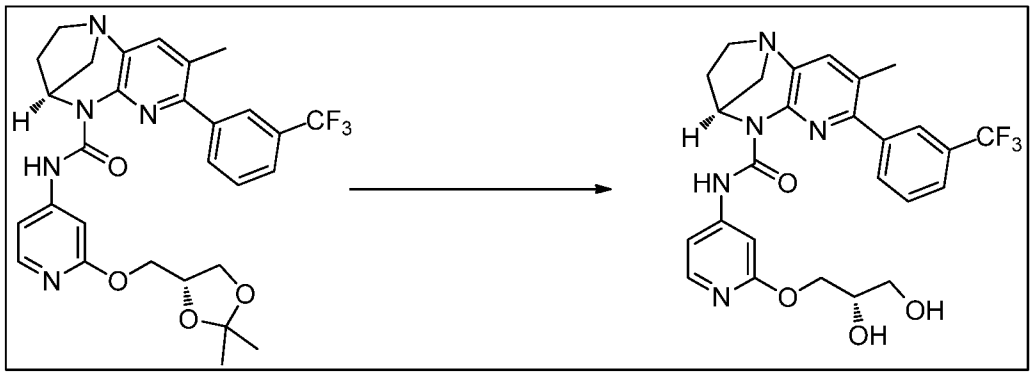


To a stirred solution of (4*S*)-8-chloro-7-(1-cyclopropyl-1*H*-pyrazol-4-yl)-*N*-(2-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (250 mg, 0.453 mmol) in methanol (5 mL) at 0 °C was added HCl (0.069 mL, 2.264 mmol) and stirred at RT for 1 h. (TLC System: Rf- 0.1, EtOAc). The reaction mixture was concentrated and the residue was neutralized with saturated sodiumbicarbonate solution. The resultant solid was filtered and dried to obtain (4*S*)-8-chloro-7-(1-cyclopropyl-1*H*-pyrazol-4-yl)-N-(2-((*R*)-2,3-dihydroxypropoxy)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (175 mg, 0.337 mmol, 74.4 % yield) as an off white solid. LCMS (*m/z*): 512.18 $[M+H]^+$. *Rt* =1.79 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.80 (s, 1 H), 8.10 (s, 1 H), 8.02 (s, 1 H), 7.97 (s, 1 H), 7.59 (s, 1 H), 7.13- 7.01 (m, 2 H), 5.62 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.52- 4.40 (m, 2 H), 4.33 (d, *J*=5.70 Hz, 1 H), 4.00 (dq, *J*=9.98, 5.01 Hz, 1 H), 3.75- 3.61 (m, 3 H), 3.35-3.07 (m, 3 H), 3.02 -2.88 (m, 2 H), 2.38- 2.23 (m, 1 H), 2.14- 1.94 (m, 1 H), 1.28 -1.19 (m, 2 H), 1.14 -1.03 (m, 2 H)

Example 101

Synthesis of (4*S*)-N-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-8-methyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

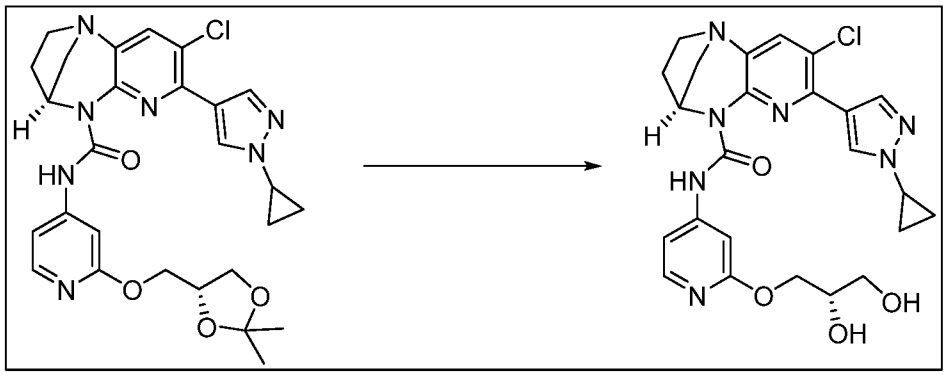


To a stirred solution of (4*S*)-N-(2-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-8-methyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diaze pine-5(2*H*)-carboxamide (300 mg, 0.527 mmol) in methanol (10 mL) at 0 °C was added HCl (8.00 µL, 0.263 mmol) drop wise over a period of 5 min. Then the reaction mixture was stirred at 30 °C for 1 h. (TLC eluent: 5% MeOH in DCM: R_f-0.3; UV active) and evaporated the solvent. The reaction mixture was neutralized with sodium bicarbonate solution and filtered the obtain solid, washed with diethyl ether (2x 50 ml), *n*-pentane (2x 50 ml) to afford pure product (4S)-N-(2-((S)-2,3-dihydroxypropoxy)pyridin-4-yl)-8-methyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (210 mg, 0.380 mmol, 72.1 % yield) as an off white solid. LCMS (*m/z*): 530.29 $[M+H]^+$, *Rt* = 2.04 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.05 (dt, *J*=14.09, 7.10 Hz, 1 H), 2.37 -2.30 (m, 4 H), 2.96 - 2.93 (m, 1 H), 3.00 (dd, *J*=12.28, 3.29 Hz, 1 H), 3.34 -3.13 (m, 3 H), 3.67 -3.60 (m, 2 H), 4.00 -3.92 (m, 1 H), 4.38 (s, 1 H), 4.42 (d, *J*=4.60 Hz, 2 H), 5.63 (dd, *J*=5.92, 3.07 Hz, 1 H), 6.68 (dd, *J*=5.81, 1.86 Hz, 1 H), 7.03 (d, *J*=1.53 Hz, 1 H), 7.49 (s, 1 H), 7.69-7.64 (m, 1 H), 7.79 -7.71 (m, 2 H), 7.85 -7.81 (m, 2 H), 13.22 (s, 1 H).

Example 102

Synthesis of (4*S*)-8-chloro-7-(1-cyclopropyl-1*H*-pyrazol-4-yl)-*N*-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

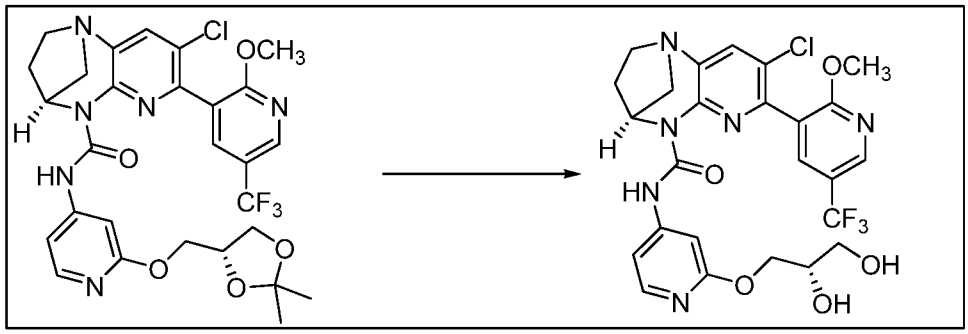


To a stirred solution of (4*S*)-8-chloro-7-(1-cyclopropyl-1*H*-pyrazol-4-yl)-*N*-(2-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide (200 mg, 0.362 mmol) in methanol (10 mL) at 0 °C was added HCl (0.055 mL, 1.812 mmol) and stirred at RT for 1 h. (TLC System: Rf- 0.1, EtOAc). The reaction mixture was concentrated under reduced pressure and the residue was neutralized with saturated sodiumbicarbonate solution. The resultant solid was filtered and dried to afford (4*S*)-8-chloro-7-(1-cyclopropyl-1*H*-pyrazol-4-yl)-*N*-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (160 mg, 0.309 mmol, 85 % yield) as an off white solid. LCMS (*m/z*): 512.00 $[M+H]^+$. *Rt* =3.15 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.81 (s, 1 H), 8.10 (s, 1 H), 8.02 (s, 1 H) 7.98 (d, *J*=5.70 Hz, 1 H), 7.59 (s, 1 H), 7.15- 6.99 (m, 2 H), 5.62 (dd, *J*=5.92, 3.07 Hz (1 H), 4.53 - 4.38 (m, 2 H), 4.01 (quin, *J*=4.82 Hz, 1 H), 3.75- 3.64 (m, 3 H), 3.36 -3.08 (m, 3 H), 2.98 (dd, *J*=12.17, 3.18 Hz, 1 H), 2.32 (qd, *J*=9.68, 4.93 Hz, 1 H), 2.04 (dt, *J*=14.25, 7.34 Hz, 1 H), 1.29- 1.17 (m, 2 H), 1.14 -1.04 (m, 2 H)

Example 103

Synthesis of (4*S*)-8-chloro-N-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(2-methoxy-5-(trifluoromethyl)pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

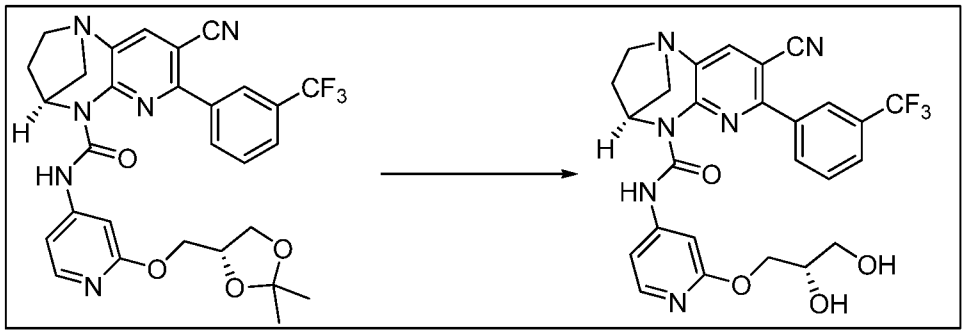


To a stirred solution of (4*S*)-8-chloro-N-(2-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(2-methoxy-5-(trifluoromethyl)pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (350 mg, 0.564 mmol) in methanol (5 mL) at 0 °C was added aq HCl (0.476 mL, 5.64 mmol) and 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 (10 mL) and extracted into dichloromethane (2x20 mL). Combined organic extracts were dried over anhydrous sodiumsulphate, filtered and filtrate was evaporated *in vacuo* to afford the crude product. The crude compound was triturated with diethylether (5 mL) to afford the desired product (4*S*)-8-chloro-N-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(2-methoxy-5-(trifluoromethyl)pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (262 mg, 0.448 mmol, 80 % yield) as a white solid. LCMS (*m/z*): 581.23$[M+H]^+$, R_t = 2.17 min

^{1}H NMR (400 MHz, $CdCl_3$): δ ppm 12.86 - 12.53 (m, 1 H), 8.63 (d, *J*=1.32 Hz, 1 H), 7.96 (d, *J*=2.19 Hz, 1 H), 7.86 (d, *J*=5.92 Hz, 1 H), 7.66 (s, 1 H), 7.00 - 6.97 (m, 1 H), 6.62 (dd, *J*=5.81, 1.86 Hz, 1 H), 5.63 (dd, *J*=5.81, 3.18 Hz, 1 H), 4.43 (d, *J*=5.04 Hz, 2 H), 4.27 - 4.19 (m, 1 H), 4.03 (s, 3 H), 3.97 (br s, 1 H), 3.72 - 3.58 (m, 2 H), 3.37 - 3.18 (m, 2 H), 3.17 - 3.08 (m, 1 H), 3.02 (dd, *J*=12.28, 3.07 Hz, 1 H), 2.82 (br t, *J*=6.47 Hz, 1 H), 2.40 - 2.26 (m, 1 H), 2.08 (dt, *J*=14.36, 7.29 Hz, 1 H).

Example 104

Synthesis of (4*S*)-8-cyano-N-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

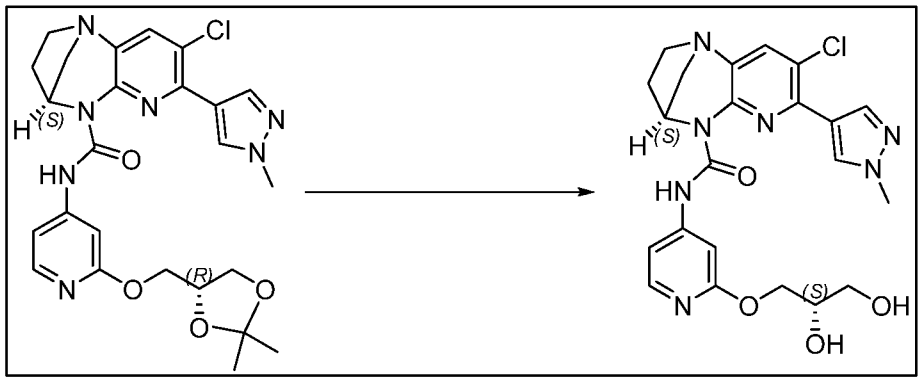


To a stirred solution of (4*S*)-8-cyano-N-(2-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (220 mg, 0.379 mmol) in methanol (5 mL) at 0 °C was added aq HCl (0.320 mL, 3.79 mmol) and stirred 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 (5 mL) and extracted into dichloromethane (2x10 mL). Combined organic extracts were dried over anhydrous sodiumsulphate, filtered and filtrate was evaporated *in vacuo* to afford the crude product. The crude product was triturated with diethylether (5 mL) to afford the desired product (4*S*)-8-cyano-N-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (201 mg, 0.366 mmol, 96% yield) as a white solid. LCMS (*m/z*): 541.20 $[M+H]^+$, R_t = 2.00 min

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.81 - 12.55 (m, 1 H), 8.17 - 8.01 (m, 2 H), 7.97 - 7.82 (m, 3 H), 7.81 - 7.71 (m, 1 H), 7.06 (d, *J*=1.75 Hz, 1 H), 6.76 (dd, *J*=5.81, 1.86 Hz, 1 H), 5.69 (dd, *J*=5.81, 2.74 Hz, 1 H), 4.44 (d, *J*=5.04 Hz, 2 H), 4.29 - 4.07 (m, 1 H), 4.02 - 3.91 (m, 1 H), 3.65 (br s, 2 H), 3.38 - 3.21 (m, 2 H), 3.18 - 3.01 (m, 2 H), 2.80 (br s, 1 H), 2.44 - 2.33 (m, 1 H), 2.12 (dt, *J*=14.52, 7.54 Hz, 1 H).

Example 105

Synthesis of (4*S*)-8-chloro-*N*-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(1-methyl-1*H*-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

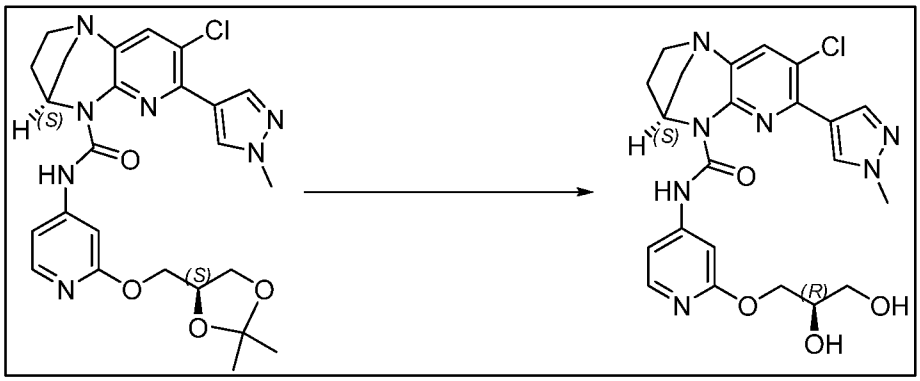


To a stirred solution of (4*S*)-8-chloro-*N*-(2-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(1-methyl-1*H*-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (280 mg, 0.532 mmol) in methanol (20 mL) at 0 °C was added HCl (2.0 ml, 65.8 mmol) and stirred at RT for 1 h. (TLC system: 10% MeOH in DCM. R*f*value: 0.2). The reaction mixture was concentrated under reduced pressure and the residue was neutralized with 10% aq.$NaHCO_3$ solution (30 mL). The precipitated solid was filtered, dried under reduced pressure to obtain crude compound. The product was triturated with pentane and diethylether (1:1) to afford (4*S*)-8-chloro-N-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (150 mg, 0.304 mmol, 57.1 % yield) as an off white solid. LCMS (*m/z*): 486.15 $[M+H]^+$, *Rt* =1.62 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.85 - 12.83 (m, 1 H), 8.06 - 7.96 (m, 3 H), 7.59 (s, 1 H), 7.14 - 6.97 (m, 2 H), 5.63 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.49 - 4.42 (m, 2 H), 4.03 (s, 4 H), 3.72 - 3.64 (m, 2 H), 3.32 - 3.07 (m, 3 H), 3.02 - 2.88 (m, 1 H), 2.35 - 2.27 (m, 1 H), 2.04 (dt, *J*=14.14, 7.18 Hz, 1 H).

Example 106

Synthesis of (4*S*)-8-chloro-*N*-(2-((*R*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(1-methyl-1*H*-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

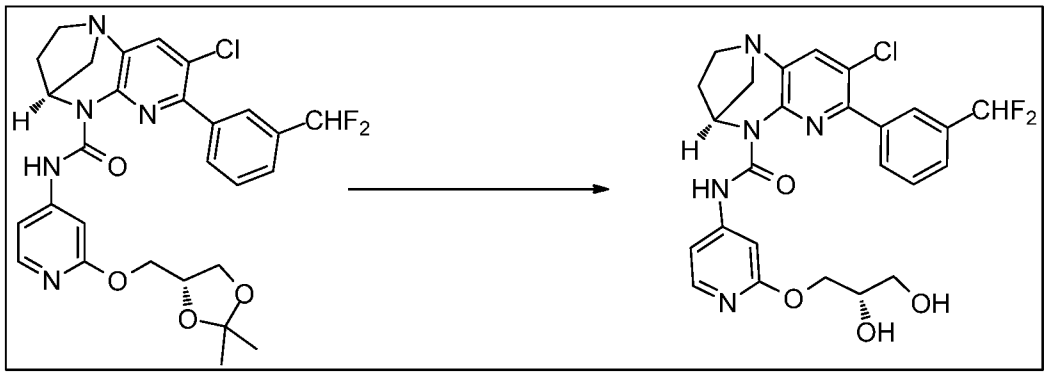


To a solution of (4*S*)-8-chloro-*N*-(2-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(1-methyl-1*H*-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)carboxamide (290 mg, 0.551 mmol) in methanol (10 mL) at 0 °C was added HCl (2.0 ml, 65.8 mmol) and stirred at RT for 1 h. The reaction mixture was evaporated under reduced pressure to remove the methanol solvent and neutralized with 10% $NaHCO_3$ solution (20 mL). The resultant solid was filtered and washed thoroughly with water (3x20 mL), dried under vacuum to afford (4*S*)-8-chloro-*N*-(2-((*R*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(1-methyl-1*H*-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)carboxamide (160 mg, 0.327 mmol, 59.3 % yield) as an off white solid. LCMS (*m/z*): 486.19 $[M+H]^+$, *Rt* =1.63 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.82 (s, 1 H), 8.07 - 7.92 (m, 3 H), 7.59 (s, 1 H), 7.11 - 7.04 (m, 2 H), 5.62 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.49 - 4.40 (m, 2 H), 4.36 (br d, *J*=4.17 Hz, 1 H), 4.03 - 3.96 (m, 4 H), 3.70 - 3.64 (m, 2 H), 3.35 - 3.17 (m, 2 H), 3.14 - 3.09 (m, 1 H), 3.04 - 2.95 (m, 2 H), 2.42 - 2.29 (m, 1 H), 2.04 (dt, *J*=14.20, 7.04 Hz, 1 H).

Example 107

Synthesis of (4*S*)-8-chloro-7-(3-(difluoromethyl)phenyl)-N-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

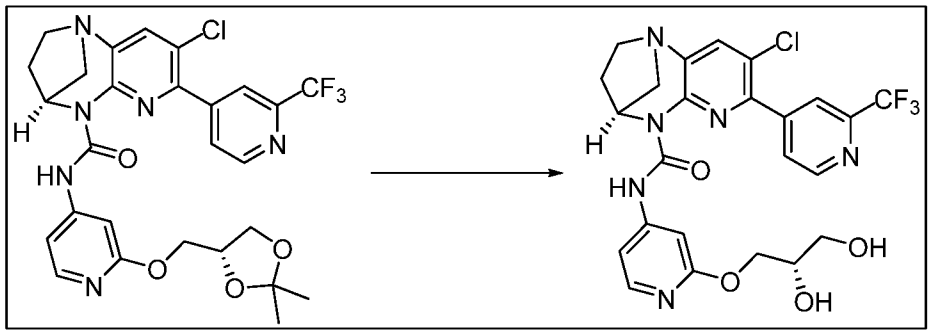


To a stirred solution of (4*S*)-8-chloro-7-(3-(difluoromethyl)phenyl)-N-(2-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepi ne-5(2*H*)-carboxamide (300 mg, 0.524 mmol) in methanol (10 mL) at 0 °C was added HCl (7.97 µL, 0.262 mmol) drop wise over a period of 5 min. Then the reaction mixture was stirred at 30 °C for 1 h. (TLC eluent: 5% MeOH in DCM: R_f-0.3; UV active).and evaporated the solvent. The reaction mixture was neutralized with sodium bicarbonate solution (10 mL) and filtered the obtain solid, washed with diethyl ether (2x 50 ml) and *n*-pentane (2x 50 ml) to afford pure product (4*S*)-8-chloro-7-(3-(difluoromethyl)phenyl)-N-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (100 mg, 0.188 mmol, 35.8 % yield) as an off white solid. LCMS (*m/z*): 532.37 $[M+H]^+$, *Rt* = 2.06 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.86 (s, 1 H), 7.86 (d, *J*=5.48 Hz, 3 H), 7.73 - 7.57 (m, 3 H), 7.01 (s, 1 H), 6.91 -6.58 (m, 2 H), 5.65 (d, *J*=2.85 Hz, 1 H), 4.43 (d, *J*=4.60 Hz, 2 H), 4.29 (d, *J*=5.04 Hz, 1 H), 3.97 (d, *J*=4.82 Hz, 1 H), 3.73 -3.53 (m, 2 H), 3.37 -3.18 (m, 2 H), 3.17 -3.10 (m, 1 H), 3.02 (dd, *J*=12.39, 2.96 Hz, 1 H), 2.89 (t, *J*=6.36 Hz, 1 H), 2.35 (td, *J*=9.32, 4.17 Hz, 1 H), 2.07 (dt, *J*=14.20, 7.26 Hz, 1 H).

Example 108

Synthesis of (4*S*)-8-chloro-N-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(2-(trifluoromethyl)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide:

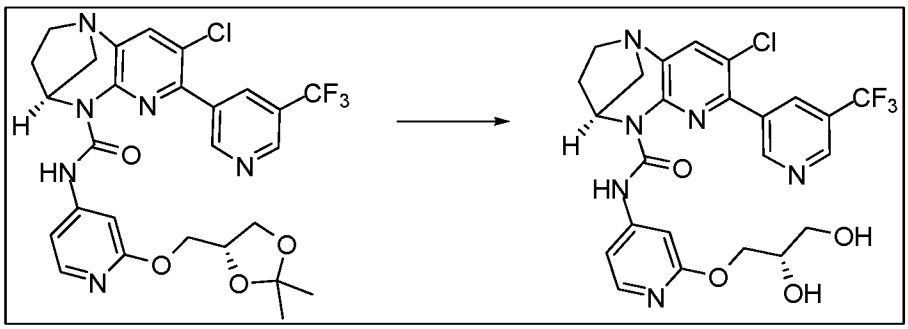


To a stirred solution of (4*S*)-8-chloro-N-(2-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(2-(trifluoromethyl)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (250 mg, 0.423 mmol) in methanol (10 mL) at 0 °C, was added aq. HCl (2 mL, 24.00 mmol) and stirred at RT for 1 h. (TLC eluent: 5% MeOH in DCM R*f*-0.2; UV active). The reaction mixture was concentrated under reduced pressure and the residue was neutralized with saturated $NaHCO_3$ solution (20 mL) then extracted with 10% MeOH in DCM (2 x 50 mL). Combined organic layer was dried over anhydrous sodiumsulphate, filtered and filtrate was evaporated to get crude compound. The crude was purified by chromatography (GRACE using C-18 reserval column, Mobile phase A: 0.1% Formic Acid in water; B: acetonitrile, eluent 55-59% B in A). Combined product fractions were concentrated, basified with saturated $NaHCO_3$ solution. The precipitated solid was filtered and dried to afford (4*S*)-8-chloro-N-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(2-(trifluoromethyl)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (186 mg, 0.337 mmol, 80 % yield). LCMS (*m/z*): 551.17 $[M+H]^+$. *Rt* =1.98 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.34 (s, 1 H), 9.00 (d, *J*=5.04 Hz, 1 H), 8.27 - 8.31 (m, 1 H), 8.14 (d, *J*=4.82 Hz, 1 H), 7.94 (s, 1 H), 7.90 (d, *J*=5.70 Hz, 1 H), 7.00 (d, *J*=1.75 Hz, 1 H), 6.58 (dd, *J*=5.81, 1.86 Hz, 1 H), 5.45 (dd, *J*=5.92, 2.85 Hz, 1 H), 4.85 (br s, 1 H), 4.58 (br d, *J*=1.10 Hz, 1 H), 4.21 (dd, *J*=10.74, 4.60 Hz, 1 H), 4.10 (dd, *J*=10.85, 6.25 Hz, 1 H), 3.73 - 3.79 (m, 1 H), 3.42 (br d, *J*=5.26 Hz, 2 H), 3.23 - 3.28 (m, 3 H), 3.06 - 3.17 (m, 1 H), 2.22 - 2.34 (m, 1 H), 1.90 - 2.00 (m, 1 H).

Example 109

Synthesis of (4*S*)-8-chloro-*N*-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(5-(trifluoromethyl)pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide:

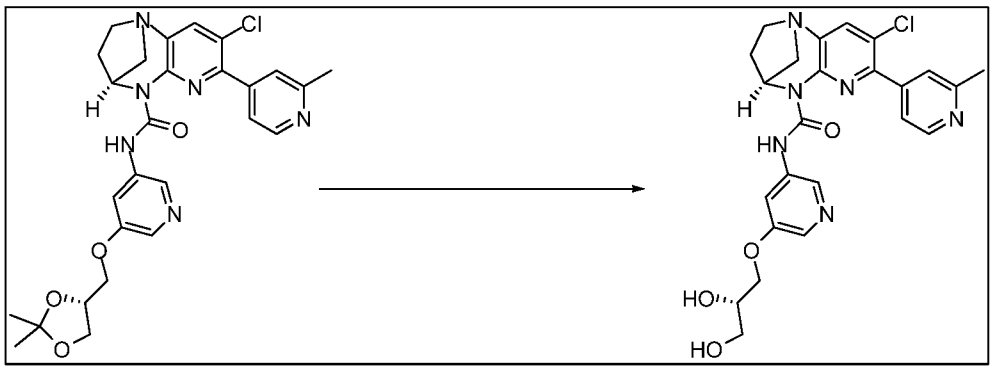


To a stirred solution of (4*S*)-8-chloro-*N*-(2-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(5-(trifluoromethyl)pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (180 mg, 0.305 mmol) in methanol (10 mL) at 0 °C was added HCl (3ml, 99 mmol) and stirred at RT for 2 h. (TLC system: 10%MeOH in DCM in , Rf value: 0.25). The reaction mixture was basified with saturated $NaHCO_3$ solution (upt pH 8-9) and extracted with ethylacetate (3x30 mL). Combined organic layer was dried over sodiumsulphate, concentrated and purified by coloumn chromatography (GRACE instrument, C-18 Reversal dolumn, eluted with 27% acetonitrile in 1% Formic acid) to afford (4*S*)-8-chloro-*N*-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(5-(trifluoromethyl)pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (105 mg, 0.190 mmol, 62.5 % yield) as an off white solid. LCMS (*m/z*): 551.17 $[M+H]^+$. *Rt* =1.93 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.37 (s, 1 H), 9.29 (d, *J*=1.97 Hz, 1 H), 9.16 (d, *J*=1.32 Hz, 1 H), 8.63 (s, 1 H), 7.94 (s, 1 H), 7.88 (d, *J*=5.70 Hz, 1 H), 7.00 (d, *J*=1.75 Hz, 1 H), 6.56 (dd, *J*=5.81, 1.86 Hz, 1 H), 5.45 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.84 (d, *J*=5.04 Hz, 1 H), 4.57 (t, *J*=5.70 Hz, 1 H), 4.21 (dd, *J*=10.74, 4.60 Hz, 1 H), 4.09 (dd, *J*=10.85, 6.25 Hz, 1 H), 3.76 (dq, *J*=10.80, 5.54 Hz, 1 H), 3.37 - 3.46 (m, 2 H), 3.22 - 3.33 (m, 1 H), 3.05 - 3.19 (m, 2 H), 2.96 - 3.04 (m, 1 H), 2.17 - 2.36 (m, 1 H), 1.85 - 2.00 (m, 1 H)

Example 110

Synthesis of (4*S*)-8-chloro-*N*-(5-((*S*)-2,3-dihydroxypropoxy)pyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

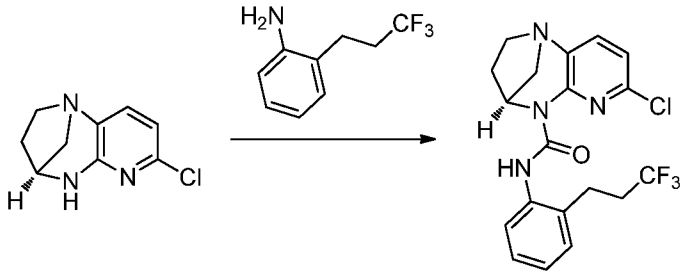


To a solution of (4*S*)-8-chloro-*N*-(5-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (0.4 g, 0.745 mmol) in methanol (6 mL) at 0 °C was added HCl (5 mL, 165 mmol) over a period of 10 min. and stirred at RT for 5 h. (TLC eluent: 10% MeOH in DCM, Rfvalue: 0.2; UV active). Reaction mixture was concentrated and the residue was taken in water (30 mL) and neutralized with saturated bicarbonate solution and the aqueous layer extracted with 10% MeOH in DCM (3x30 mL). Combined organic layer was washed with brine (20 mL), dried over anhydrous sodiumsulphate, filtered and concentrated under reduced pressure to get the crude compound. The crude was combined with previous batches and total 430 mg was purified by using combiflash chromatography (Silicagel, eluted with 10% MeOH in DCM) to afford (4*S*)-8-chloro-*N*-(5-((*S*)-2,3-dihydroxypropoxy)pyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido-[2,3-*b*][1,4]-diazepine-5(2*H*)-carboxamide (140 mg, 0.272 mmol, 36.5 % yield) as an yellow solid. LCMS (*m/z*): 497.35 $[M+H]^+$, *Rt* =1.32 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.60 (s, 1 H), 8.65 (d, *J*=5.04 Hz, 1 H), 7.97 (d, *J*=2.63 Hz, 1 H), 7.93 (d, *J*=2.19 Hz, 1 H), 7.88 (s, 1 H), 7.67 - 7.61 (m, 2 H), 7.58 (dd, *J*=5.15, 1.21 Hz, 1 H), 5.46 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.97 (d, *J*=5.04 Hz, 1 H), 4.68 (t, *J*=5.59 Hz, 1 H), 4.02 (dd, *J*=9.65, 3.73 Hz, 1 H), 3.91 - 3.85 (m, 1 H), 3.83 - 3.75 (m, 1 H), 3.45 (t, *J*=5.70 Hz, 2 H), 3.32 - 3.27 (m, 1 H), 3.16 - 3.06 (m, 2 H), 3.02 - 2.96 (m, 1 H), 2.58 (s, 3 H), 2.31 - 2.19 (m, 1 H), 2.01 - 1.91 (m, 1 H)

Example 111

Synthesis of (4*S*)-7-chloro-*N*-(2-(3,3,3-trifluoropropyl)phenyl)-3,4-dihydro-1,4-methano pyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide

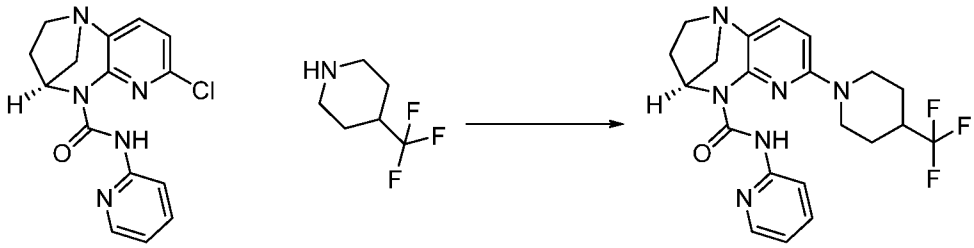


(4*S*)-7-chloro-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (250 mg, 1.278 mmol) was dissolved in tetrahydrofuran (THF) (10 mL) stirred under nitrogen at room temperature were added triphosgene (190 mg, 0.639 mmol), TEA (0.534 mL, 3.83 mmol) sequentially. The reaction mixture was stirred for 30 min at room temperature. To this 2-(3, 3,3-trifluoropropyl) aniline (483 mg, 2.56 mmol) was added and stirred for 16 h at 80 °C in a sealed tube. The reaction mixture allowed to room temperature and quenched with15 ml of water and extracted with 2x25 ml of ethyl acetate, organic layer was dried over sodium sulfate and concentrated under reduced pressure to obtain crude compound. The crude product was purified by column chromatography (silica-gel: 100-200 mesh) to afford (4*S*)-7-chloro-*N*-(2-(3,3,3-trifluoropropyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (240 mg, 0.563 mmol, 44.1 % yield) as a white solid, (R_f value: 0.35, 10% Methanol in DCM), LCMS (*m/z*): 411.16 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 11.49 (s, 1 H), 7.79 (dd, *J*=8.00, 0.99 Hz, 1 H), 7.61 (d, *J*=8.11 Hz, 1 H), 7.35 - 7.31 (m, 1 H), 7.24 - 7.29 (m, 1 H), 7.17 - 7.09 (m, 2 H), 5.44 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.21 – 2.90 (m, 6 H), 2.66 - 2.53 (m, 2 H), 2.20 (dddd, *J*=13.67, 9.95, 6.08, 3.62 Hz, 1 H), 1.91 (dt, *J*=13.70, 6.96 Hz, 1 H).

Example 112

Synthesis of (4*S*)-*N*-(pyridin-2-yl)-7-(4-(trifluoromethyl) piperidin-1-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

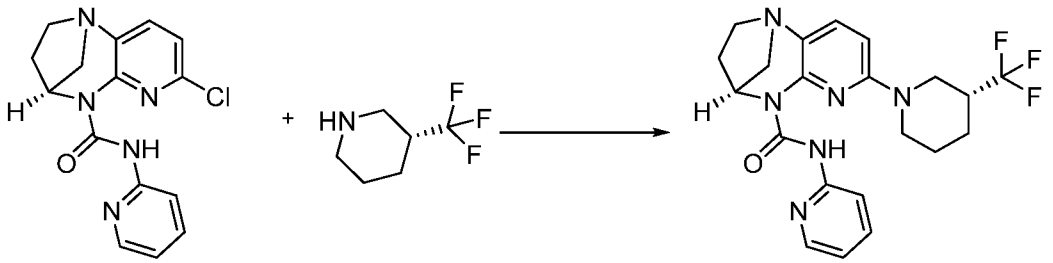


To a de-gassed solution of ((4*S*)-7-chloro-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (700 mg, 2.217 mmol), 4-(trifluoromethyl)piperidine (679 mg, 4.43 mmol) in 1,4-dioxane (20 mL) were added dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (423 mg, 0.887 mmol), potassium carbonate (919 mg, 6.65 mmol) and palladium(II) acetate (100 mg, 0.443 mmol) at 25°C. The reaction mixture was stirred at 90 °C for 16 h in sealed tube. Allowed to cool to room temperature and the mixture was poured in to cold water (70 mL) and extracted with ethyl acetate (3x50 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 (4*S*)-*N*-(pyridin-2-yl)-7-(4-(trifluoromethyl) piperidin-1-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (320 mg, 32% yield) as a white solid (TLC: eluent; ethyl acetate, R_f = 0.4), LCMS (*m/z*): 433.22 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.15 (s, 1 H), 8.34-8.18 (m, 1 H), 8.09 (dt, *J*=8.39, 0.96 Hz, 1 H), 7.77 (ddd, *J*=8.55, 7.13, 1.86 Hz, 1 H), 7.36 (d, *J*=8.77 Hz, 1 H) 7.04 (ddd, *J*=7.29, 4.88, 0.99 Hz, 1 H) 6.51 (d, *J*=8.55 Hz, 1 H) 5.43 (dd, *J*=5.92, 3.07 Hz, 1 H) 4.39 (d, *J*=12.93 Hz, 2 H), 3.17-3.04 (m, 1 H), 3.02-2.76 (m, 5 H), 2.72-2.52 (m, 1 H), 2.25-2.04 (m, 1 H), 1.96-1.76 (m, 3 H), 1.57-1.39 (m, 2 H).

Example 113

Synthesis of (4*S*)-*N*-(pyridin-2-yl)-7-((*R*)-3-(trifluoromethyl) piperidin-1-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

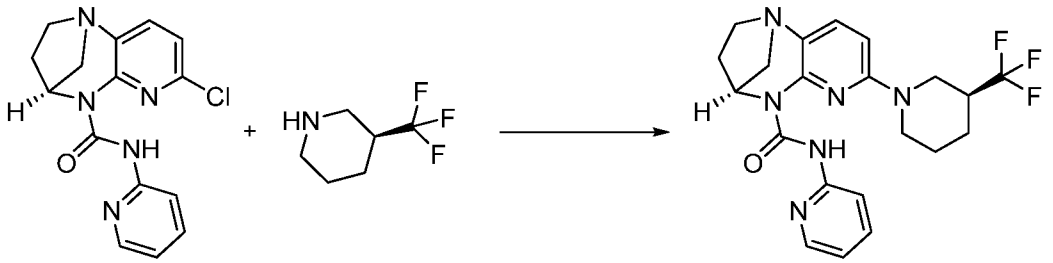


To a de-gassed solution of (4S)-7-chloro-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (750 mg, 2.375 mmol) and (70:30-R/S)-3-(trifluoromethyl)piperidine (728 mg, 4.75 mmol) in 1,4-dioxane (20 mL) were added potassium carbonate (985 mg, 7.13 mmol) and palladium(II) acetate (107 mg, 0.475 mmol) at RT. The reaction mixture was stirred at 90 °C for 16 h in sealed tube. The reaction was allowed to cool down to room temperature and poured into cold water (70 mL) and extracted with ethyl acetate (3x50 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, eluted with 1% to 2% methanol in dichloromethane) to afford (70:30, R:S) diastereometic mixture of (4S)-N-(pyridin-2-yl)-7-((R/S)-3-(trifluoromethyl) piperidin-1-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (310 mg, yield 29.6%) as an off white solid (TLC: eluent, 100% ethyl acetate, R_f: 0.4), LCMS (*m/z*): 433.2 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.10-12.94 (m, 1 H), 8.22 (d, *J*=5.15 Hz, 1 H), 8.15-7.98 (m, 1 H), 7.76 (t, *J*=7.48 Hz, 1 H), 7.45-7.28 (m, 1 H), 7.04 (ddd, *J*=7.34, 4.93, 0.88 Hz, 1 H), 6.54 (d, *J*=8.55 Hz, 1 H), 5.48-5.32 (m, 1 H), 4.35-4.12 (m, 2 H), -3.12-2.89 (m, 5 H), 2.88-2.78 (m, 1 H), 2.61-2.52 (m, 1 H), 2.25-2.04 (m, 1 H), 2.04-1.92 (m, 1 H), 1.90-1.74 (m, 2 H), 1.71-1.46 (m, 2 H).

Example 114

Synthesis of (4*S*)-*N*-(pyridin-2-yl)-7-((*S*)-3-(trifluoromethyl) piperidin-1-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide:

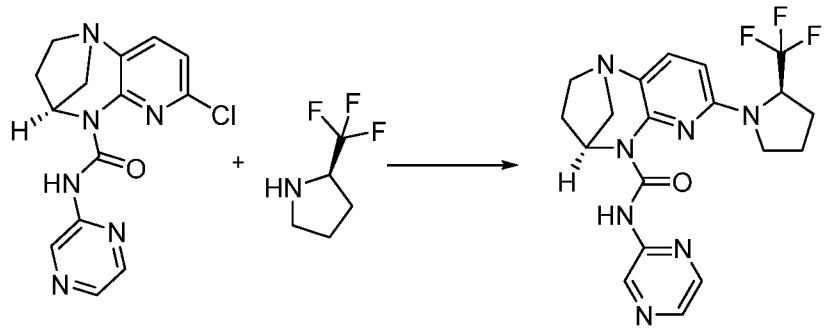


To a de-gassed solution of (4S)-7-chloro-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (550 mg, 1.742 mmol) (33:66-R/S)-3-(trifluoromethyl) piperidine (534 mg, 3.48 mmol) in 1,4-dioxane (20 mL) were added potassium carbonate (722 mg, 5.23 mmol), dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (332 mg, 0.697 mmol) and palladium(II) acetate (78 mg, 0.348 mmol) at RT. The reaction mixture was stirred at 90 °C for 16 h in sealed tube. The reaction was cooled to room temperature and poured into cold water (70 mL). The crude product was extracted with ethyl acetate (3x50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, 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 (33:67, S:R) diastereometic mixture of (4S)-N-(pyridin-2-yl)-7-((S/R)-3-(trifluoromethyl) piperidin-1-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (250 mg, 33.2% yield) as a white solid (TLC: eluent, 100% ethyl acetate, R_f 0.4), LCMS (*m/z*): 433.2 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.06-12.99 (m, 1 H), 8.22 (d, *J*=5.01 Hz, 1 H), 8.07 (dt, *J*=8.33, 0.88 Hz, 1 H), 7.76 (ddd, *J*=8.55, 7.13, 1.86 Hz, 1 H), 7.47-7.29 (m, 1 H), 7.04 (ddd, *J*=7.29, 4.88, 0.99 Hz, 1 H), 6.54 (d, *J*=8.55 Hz, 1 H), 5.51-5.36 (m, 1 H), 4.37-4.15 (m, 2 H), 3.12-2.80 (m, 6 H), 2.60-2.52 (m, 1 H), 2.25-2.04 (m, 1 H), 2.04-1.93 (m, 1 H), 1.90-1.74 (m, 2 H), 1.72-1.48 (m, 2 H).

Example 115

Synthesis of (4*S*)-N-(pyridin-2-yl)-7-((*R*)-2-(trifluoromethyl)pyrrolidin-1-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

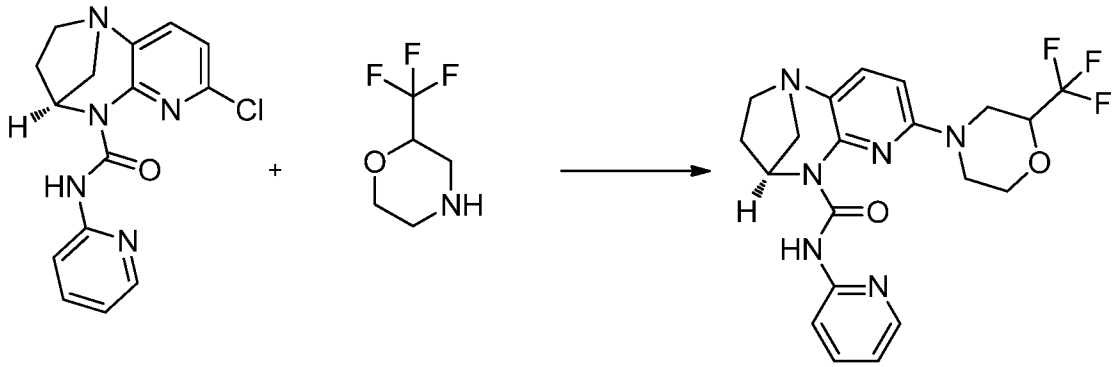


To a de-gassed solution of (4*S*)-7-chloro-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (700 mg, 2.217 mmol), (*R*)-2-(trifluoromethyl)pyrrolidine (617 mg, 4.43 mmol) in 1,4-dioxane (20 mL) were added dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (423 mg, 0.887 mmol), potassium carbonate (919 mg, 6.65 mmol) and palladium(II) acetate (100 mg, 0.443 mmol) at RT. The reaction mixture was heated at 90 °C for 16 h in sealed tube. The reaction mixture was poured in to cold water (70 mL) and extracted with ethyl acetate (3x50 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain crude compound. The crude mixture was purified by flash column chromatography (silica gel: 100-200 mesh, eluted with 1 to 2% methanol in dichloromethane) to afford (4*S*)-N-(pyridin-2-yl)-7-((*R*)-2-(trifluoromethyl)pyrrolidin-1-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (220 mg, 0.52 mmol, 32% yield) as an off white solid (TLC: 100% ethyl acetate, R_f = 0.4), LCMS (*m/z*): 419.21 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.16 (s, 1 H), 8.20 (d, *J*=6.33, 1 H), 8.06 (d, *J*=8.33 Hz, 1 H), 7.77 (td, *J*=7.84, 1.86 Hz, 1 H), 7.40 (d, *J*=8.55 Hz, 1 H), 7.05 (ddd, *J*=7.29, 4.88, 0.99 Hz, 1 H), 6.36 (d, *J*=8.77 Hz, 1 H), 5.40 (dd, *J*=5.92, 3.07 Hz, 1 H), 5.28-5.06 (m, 1 H), 3.84 (dt, *J*=10.14, 5.12 Hz, 1 H), 3.65-3.36 (m, 1 H), 3.17-2.91 (m, 2 H), 2.90-2.80 (m, 2 H), 2.25-2.04 (m, 5 H), 1.84 (dt, *J*=13.65, 7.10 Hz, 1 H).

Example 116

Synthesis of (4*S*)-N-(pyridin-2-yl)-7-(2-(trifluoromethyl)morpholino)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

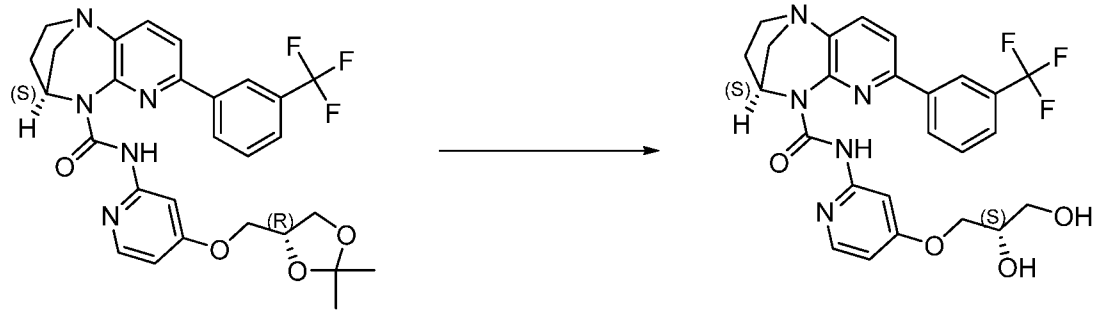


To a de-gassed solution of (4*S*)-7-chloro-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (700 mg, 2.217 mmol), 2-(trifluoromethyl)morpholine (688 mg, 4.43 mmol) in 1,4-dioxane (20 mL) were added dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (423 mg, 0.887 mmol), potassium carbonate (919 mg, 6.65 mmol) and palladium(II) acetate (100 mg, 0.443 mmol) at RT. The reaction mixture was heated at 90 °C for 16 h in sealed tube and cooled to RT then poured in to cold water (70 mL) and extracted with ethyl acetate (3x50 mL). The combined organic layer was dried over anhydrous sodium sulfate 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% of methanol in dichloromethane) to afford (4*S*)-N-(pyridin-2-yl)-7-(2-(trifluoromethyl)morpholino)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (300 mg, 0.69 mmol, 46% yield) as an off white solid (TLC: 100% ethyl acetate, R_f = 0.4), LCMS (*m/z*): 435.20 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.99 (d, *J*=4.82 Hz, 1 H), 8.20 (dt, *J*=4.82, 0.88 Hz, 1 H), 8.07 (dd, *J*=8.44, 0.77 Hz, 1 H), 7.77 (td, *J*=7.84, 1.86 Hz, 1 H), 7.43 (d, *J*=8.55 Hz, 1 H), 7.05 (ddd, *J*=7.29, 4.88, 0.77 Hz, 1 H), 6.62 (d, *J*=8.55 Hz, 1 H), 5.44 (ddd, *J*=9.98, 6.25, 3.29 Hz, 1 H), 4.34 (dd, *J*=7.13, 3.40 Hz, 1 H), 4.25 (d, *J*=12.28 Hz, 1 H), 4.14 (dd, *J*=11.62, 1.75 Hz, 1 H), 4.10-3.94 (m, 1 H), 3.87-3.67 (m, 1 H), 3.15-2.91(m, 6 H), 2.30-2.14 (m, 1 H), 1.72-1.65 (m, 1 H).

Example 117

Synthesis of (4*S*)-N-(4-((S)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluorome - thyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

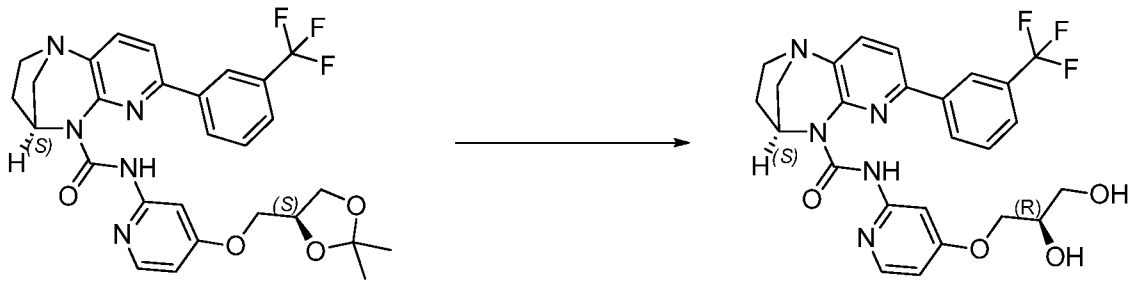


To a stirred solution of (4*S*)-N-(4-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (450 mg, 0.810 mmol) in dichloromethane (12 mL) and water (1.12 mL) at 0° C was added 4.0 M hydrochloric acid in dioxane (1.68 mL, 0.810 mmol) dropwise over a period of 5 min. Then the reaction mixture was stirred at 30° C for 3h and evaporated the solvent. The reaction mixture was neutralization with sodium bicarbonate solution and extracted with ethyl acetate (3 X 50mL) then the combined organic layers was washed with water, brine solution & dried over sodium sulfate and evaporated to give crude as brown solid (TLC eluent: 5% MeOH in DCM: R_f = 0.2; UV active). The crude compound was washed with n-pentane to afford pure (4*S*)-N-(4-((*S*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoro methyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (340mg, 0.635 mmol, 78.0 % yield) as white solid, LCMS (*m/z*): 516.3 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.42 (s, 1 H) 8.54 - 8.44 (m, 2 H) 8.10 (d, *J*=5.92 Hz, 1 H) 7.85 - 7.81 (m, 1 H) 7.80 - 7.68 (m, 4 H) 6.71 (dd, *J*=5.70, 2.41 Hz, 1 H) 5.51 (dd, *J*=5.92, 3.07 Hz, 1 H) 5.01 (d, *J*=5.26 Hz, 1 H) 4.70 (t, *J*=5.70 Hz, 1 H) 4.11 (dd, *J*=9.76, 3.84 Hz, 1 H) 3.96 (dd, *J*=9.87, 6.36 Hz, 1 H) 3.87 - 3.79 (m, 1 H) 3.51 - 3.42 (m, 2 H) 3.26 - 3.17 (m, 1 H) 3.15 - 3.06 (m, 2 H) 2.96 (dd, *J*=12.06, 3.29 Hz, 1 H) 2.25 (dddd, *J*=13.65, 9.92, 6.14, 3.62 Hz, 1 H) 1.95 (dt, *J*=13.81, 6.91 Hz, 1 H).

Example 118

Synthesis of (4*S*)-N-(4-((*R*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

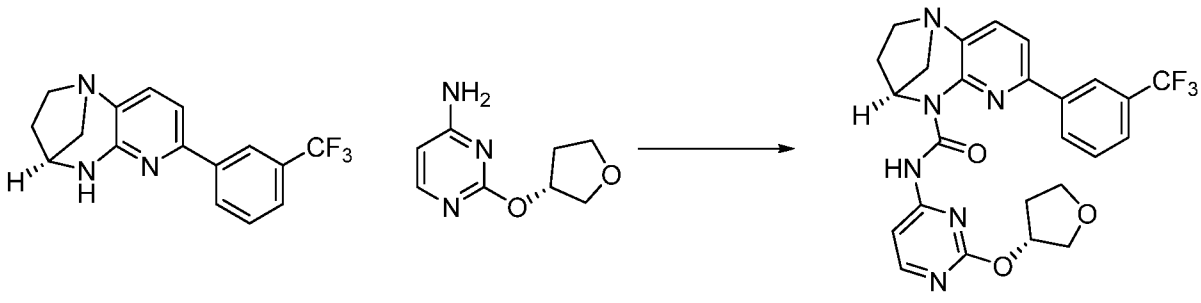


To a solution of (4*S*)-N-(4-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (500 mg, 0.900 mmol), in dichloromethane (12.5 mL) and water (1.25ml) stirred under nitrogen at 0°C was added 4.0 M hydrochloric acid in dioxane (2 mL, 0.900 mmol) in one charge over 1 min. The reaction mixture was stirred at 30 °C for 3 h and evaporated the solvent. The reaction mixture was neutralized with sodium bi carbonate solution and extracted with ethyl acetate (3 X 50 mL). The combined organic layer was washed with water, brine solution & dried over anhydrous sodium sulfate and evaporated to give crude as brown solid (TLC eluent: 5% MeOH in DCM: R_f = 0.2; UV active). The crude compound was washed with *n*-pentane to afford pure (4*S*)-N-(4-((*R*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (340mg, 0.612 mmol 68.0 % yield) as a white color solid, LCMS (*m/z*): 516.2 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.42 (s, 1 H) 8.58 - 8.44 (m, 2 H) 8.10 (d, *J*=5.70 Hz, 1 H) 7.85 – 7-68 (m, 5 H) 6.71 (dd, *J*=5.81, 2.30 Hz, 1 H) 5.52 (dd, *J*=5.70, 3.07 Hz, 1 H) 5.01 (d, *J*=5.26 Hz, 1 H) 4.70 (t, *J*=5.59 Hz, 1 H) 4.11 (dd, *J*=9.76, 3.84 Hz, 1 H) 3.96 (dd, *J*=9.76, 6.25 Hz, 1 H) 3.87 - 3.79 (m, 1 H) 3.50 - 3.43 (m, 2 H) 3.27 - 3.17 (m, 1 H) 3.16 - 3.05 (m, 2 H) 2.96 (dd, *J*=12.06, 3.07 Hz, 1 H) 2.30 - 2.20 (m, 1 H) 1.95 (dt, *J*=13.92, 7.07 Hz, 1 H).

Example 119

Synthesis of (4*S*)-*N*-(2-(((*R*)-tetrahydrofuran-3-yl)oxy)pyrimidin-4-yl)-7-(3-(trifluoromeththyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

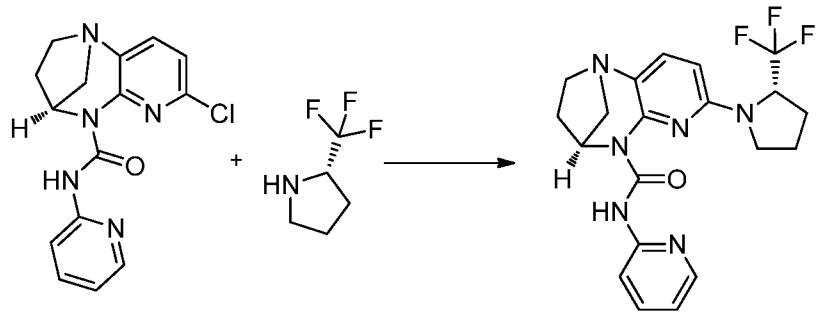


To a stirred solution of (4*S*)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (600 mg, 1.965 mmol) in THF (20 mL) were added triethylamine (0.822 mL, 5.90 mmol) and triphosgene (292 mg, 0.983 mmol) at 30°C and stirred at same temperature for 1 h. Then (*R*)-2-((tetrahydrofuran-3-yl)oxy)pyrimidin-4-amine (1068 mg, 5.90 mmol) was added at 30 °C and reaction was heated at 70 °C for 16 h. The reaction allowed to RT and solvent was evaporated under reduced pressure, the obtained residue was diluted with water (15 ml) and extracted with DCM (2x 20 ml). The combined organic layer was washed with water, brine and dried over anhydrous sodium sulfate. The organic solvent was evaporated under reduced pressure to give crude product. The crude mixture was purified by prep HPLC (Formic acid in water and acetonitrile 30%) to afford (4*S*)-*N*-(2-(((*R*)-tetrahydrofuran-3-yl)oxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)pheny l)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (310 mg, 0.605 mmol, 30.6% yield) as an off white solid. (TLC: R_f = 0.25, 10% MeOH in EtOAc), LCMS (*m/z*): 513.26 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.61 (s, 1 H), 8.50 (d, *J*=7.49 Hz, 1 H), 8.45 (d, *J*=5.62 Hz, 1 H), 8.25 (s, 1 H), 7.87 (d, *J*=7.67 Hz, 1 H), 7.81 - 7.68 (m, 4 H), 5.47 (dd, *J*=5.92, 3.07 Hz, 1 H), 5.32 (ddt, *J*=6.49, 4.36, 2.14, 2.14 Hz, 1 H), 3.91 - 3.76 (m, 1 H), 3.76 - 3.59 (m, 3 H), 3.28 - 3.05 (m, 3 H), 2.96 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.38 - 2.15 (m, 1 H), 2.14 – 1.88 (m, 3 H).

Example 120

Synthesis of (4*S*)-N-(pyridin-2-yl)-7-((*S*)-2-(trifluoromethyl)pyrrolidin-1-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

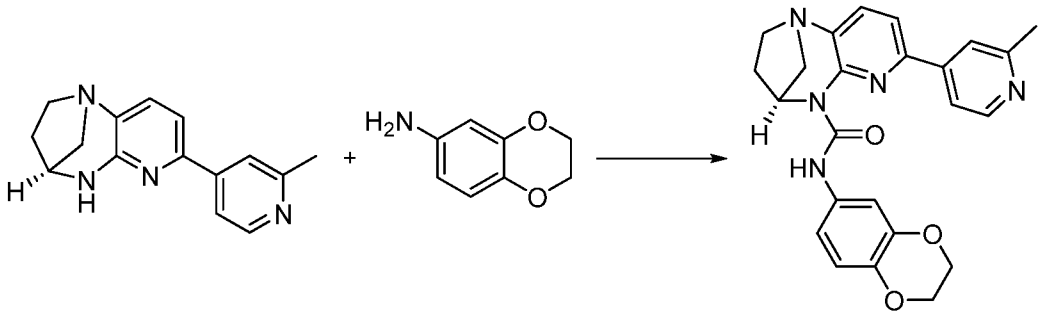


To a de-gassed solution of (4*S*)-7-chloro-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (700 mg, 2.217 mmol), (*S*)-2-(trifluoromethyl)pyrrolidine (617 mg, 4.43 mmol) in 1,4-dioxane (20 mL) were added dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (423mg,0.887mmol) and palladium(II) acetate (100 mg, 0.443 mmol) at 25 °C. The reaction mixture was heated at 90 °C for 16 h in sealed tube. The reaction mixture was poured in to cold water (70 mL) and extracted with ethyl acetate (3x50 mL). The combined organic layer was dried over anhydrous sodium sulfate 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% of MeOH in DCM) to afford (4*S*)-N-(pyridin-2-yl)-7-((*S*)-2-(trifluoromethyl)pyrrolidin-1-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (250 mg, 0.598 mmol, 35% yield) as a white solid (TLC: 100% ethyl acetate, R_f = 0.4), LCMS (*m/z*): 419.18 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.13 (s, 1 H), 8.30-8.18 (d, *J*=7.2, 1 H), 8.18-7.96 (d, *J*=8.40, 1 H), 7.77 (ddd, *J*=8.55, 7.13, 1.86 Hz, 1 H), 7.41 (d, *J*=8.55 Hz, 1 H), 7.04 (ddd, *J*=7.23, 4.82, 1.10 Hz, 1 H), 6.38 (d, *J*=8.55 Hz, 1 H), 5.48 (dd, *J*=6.03, 3.18 Hz, 1 H), 5.12-5.01 (m, 1 H), 3.84 (m, 1 H), 3.49 (q, *J*=9.65, *J*=5.70 Hz, 1 H), 3.04-2.90 (m, 4 H), 2.33-2.12 (m, 5 H), 1.72-1.80 (m, 1 H).

Example 121

Synthesis of (4*S*)-N-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

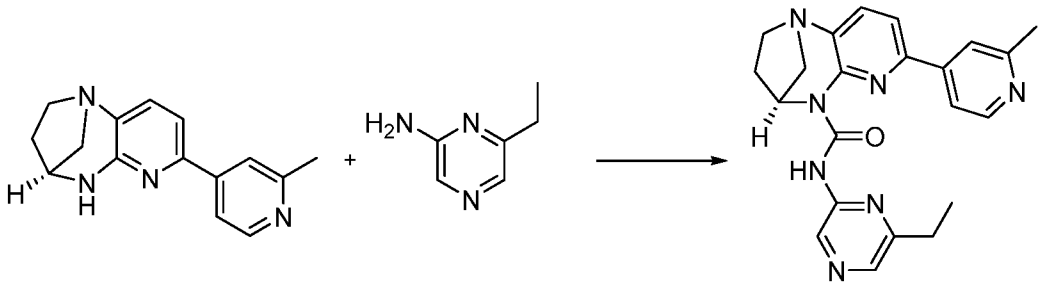


To a solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (500 mg, 1.982 mmol) in THF (30 ml) was added triphosgene (294 mg, 0.991 mmol) at 0 °C and stirred at RT for 1 h. Then 2,3-dihydrobenzo[*b*][1,4]dioxin-6-amine (899 mg, 5.94 mmol) and triethylamine (1.381 mL, 9.91 mmol) were added sequentially. The reaction mixture was heated at 70 °C for 16 h in sealed tube. The reaction mixture was poured in saturated $NaHCO_3$ solution (150 mL) and extracted with ethyl acetate (3x50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude compound. The crude mixture was purified by flash column chromatography (silica-gel:100-200 mesh, using gradient mixture of 1% methanol in dichloromethane as eluent) to afford (4*S*)-N-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (315 mg, 0.734 mmol, 51% yield) as a brown solid (TLC: 5% Methanol in dichloromethane, R_f =0.3), LCMS (*m/z*): 430.0 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.69 (s, 1 H), 8.59 (d, *J*=5.26 Hz, 1 H), 7.75-7.59 (m, 4 H), 7.16 (s, 1 H), 6.96-6.75 (dd, *J*=5.81, 2.41, 2 H), 5.46 (dd, *J*=5.81, 3.18 Hz, 1 H), 4.27-4.10 (m, 4 H), 3.24-3.02 (m, 2 H), 3.00-2.76 (m, 2 H), 2.50 (s, 3 H), 2.25-2.09 (m, 1 H), 1.91-1.71 (m, 1 H).

Example 122

Synthesis of (4*S*)-N-(6-ethylpyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

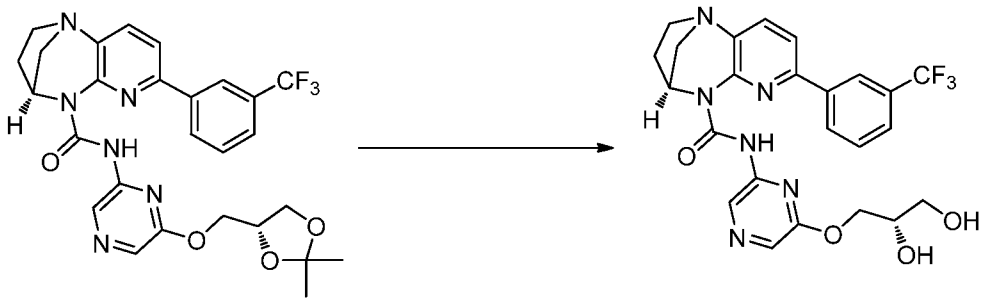


To a solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (500 mg, 1.982 mmol) in THF (25 ml) was added tri-phosgene (294 mg, 0.991 mmol) at 0 °C and stirred to RT for 1 h. Then 6-ethylpyrazin-2-amine (317 mg, 2.58 mmol), triethylamine (1.381 mL, 9.91 mmol) were added sequentially and heated the reaction mixture at 70 °C for 16 h in sealed tube. The reaction mixture was poured in saturated $NaHCO_3$ solution (150 mL) and extracted with ethyl acetate (3x50 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 column chromatography (silica-gel: 100-200 mesh, eluent: 1% methanol in dichloromethane) to afford (4*S*)-N-(6-ethylpyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (260 mg, 0.640 mmol, 32.3 % yield) as a pale yellow solid (TLC: 5% MeOH in DCM, R_f = 0.3), LCMS (*m/z*): 402.23 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.47 (s, 1 H), 9.23 (s, 1 H), 8.59 (d, *J*=5.26 Hz, 1 H), 8.29 (s, 1 H), 8.02 (d, *J*=4.82 Hz, 2 H), 7.88 (s, 1 H), 7.64 - 7.84 (d, J=7.68 Hz ,1 H), 5.52 (dd, *J*=6.03, 2.96 Hz, 1 H), 3.08 - 3.33 (m, 2 H), 2.89 - 3.08 (m, 2 H), 2.78 (q, *J*=7.60 Hz, 2 H), 2.57 (s, 3 H), 2.39 - 2.13 (m, 1 H), 2.12 – 1.88 (m, 1 H) 1.21-1.30 (m, 3H).

Example 123

Synthesis of (4*S*)-*N*-(6-((*S*)-2,3-dihydroxypropoxy) pyrazin-2-yl)-7-(3-(trifluoromethyl) phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

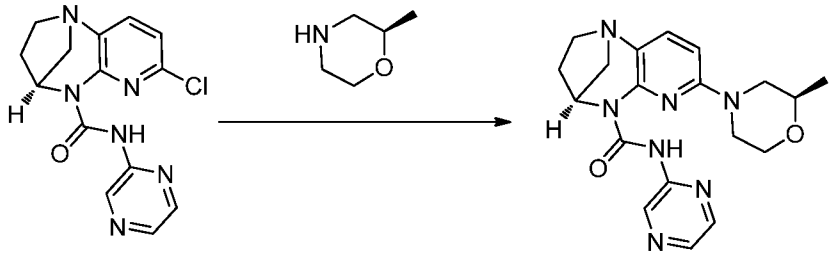


To a solution of (4*S*)-*N*-(6-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl) phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (600 mg, 1.078 mmol) in CH_2Cl_2 (16 mL) and water (1.6mL) was added 4N HCl in dioxane (2.24 mL, 8.96 mmol)at 0 °C as dropwise over a period of 5 min. Then the reaction was stirred at RT for 3 h. The reaction mixture was concentrated under reduced pressure to obtain crude product. The crude product was diluted with water and neutralized with sodium bicarbonate (15 ml) and the aqueous layer was extracted with EtOAc (2x 15 ml). The combined organic layer was washed with water, brine and dried over anhydrous Na_2SO_4, the organic solvent was evaporated under reduced pressure to afford the crude product. The crude product was triturated with di ethyl ether to afford (4*S*)-*N*-(6-((*S*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido [2,3-*b*] [1,4]diazepine-5(2*H*)-carboxamide (346 mg, 64% yield, 0.67 mmol) as an off white solid (TLC: 5% MeOH in CH_2Cl_2, R_f =0.3), LCMS (*m/z*): 517.18 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO- *d6*): δ 13.14 (s, 1H), 8.95 (s, 1H), 8.36 (d, *J* = 7.7 Hz, 1H), 8.22 (s, 1H), 7.99 (s, 1H), 7.89 - 7.79 (m, 2H), 7.74 (q, *J* = 8.0 Hz, 2H), 5.54 (s, 1H), 4.95 (d, *J* = 5.1 Hz, 1H), 4.64 (t, *J* = 5.5 Hz, 1H), 4.09 (qd, *J* = 10.7, 5.1 Hz, 2H), 3.77 (d, *J* = 5.2 Hz, 1H), 3.45 - 3.33 (m, 2H), 3.23 - 3.06 (m, 3H), 2.97 (dd, *J* = 12.0, 3.3 Hz, 1H), 2.25 (ddt, *J* = 14.0, 9.8, 4.8 Hz, 1H), 1.97 (dt, *J* = 14.1, 7.3 Hz, 1H).

Example 124

(4*S*)-7-((*R*)-2-methylmorpholino)-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

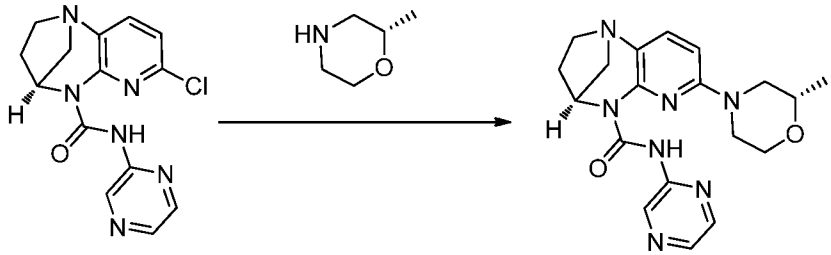


To a degassed solution of (4*S*)-7-chloro-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (700 mg, 2.210 mmol), (*R*)-2-methylmorpholine Hydrochloride (335 mg, 2.431 mmol), Cs_2CO_3 (1440 mg, 4.42 mmol) and 2-dicyclohexylphosphino-2', 4', 6'-triisopropylbiphenyl (421 mg, 0.884 mmol) in 1,4-dioxane (10 mL) was added $Pd(OAc)_2$ (99 mg, 0.442 mmol) at RT. Then the reaction mixture was heated at 100 °C for 16 h. The reaction mixture was allowed to room temperature, quenched with 2x15 ml of water and extracted with 2x50 ml of ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain crude compound. The crude product was purified by column chromatography to afford (4*S*)-7-((*R*)-2-methylmorpholino)-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide(275 mg, 0.696 mmol, 31.5 % yield) as off white solid (TLC: R_f value: 0.3, 5% Methanol in DCM), LCMS (*m/z*): 383.28 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 13.40 (s, 1H), 9.38 (d, *J* = 1.3 Hz, 1H), 8.46 - 8.17 (m, 2H), 7.40 (d, *J* = 8.6 Hz, 1H), 6.53 (d, *J* = 8.6 Hz, 1H), 5.44 (dd, *J* = 6.1, 3.1 Hz, 1H), 4.20 - 4.04 (m, 1H), 4.00 - 3.93 (m, 1H), 3.91 - 3.80 (m, 1H), 3.70 - 3.53 (m, 2H), 3.17 - 3.05 (m, 1H), 3.03 - 2.92 (m, 2H), 2.87 (ddd, *J* = 19.7, 11.9, 3.4 Hz, 2H), 2.58 (dd, *J* = 12.6, 10.4 Hz, 1H), 2.21-2.12 (m, 1H), 1.86 (dd, *J* = 14.3, 7.2 Hz, 1H), 1.22 (d, *J* = 6.2 Hz, 3H).

Example 125

Synthesis of (4*S*)-7-((*S*)-2-methylmorpholino)-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methano pyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

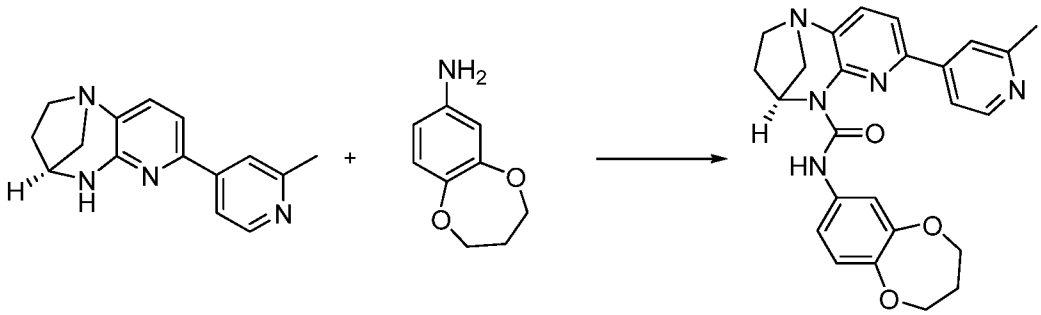


To a degassed solution of (4*S*)-7-chloro-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (700 mg, 2.210 mmol), (*S*)-2-methylmorpholine Hydrochloride (335 mg, 2.431 mmol), Cs_2CO_3 (1440 mg, 4.42 mmol) and 2-dicyclohexylphosphino-2', 4', 6'-triisopropylbiphenyl (421 mg, 0.884 mmol) in 1,4-dioxane (10 mL) was added $Pd(OAc)_2$ (99 mg, 0.442 mmol) at RT. Then the reaction mixture was heated at 100 °C for 16 h. The reaction mixture was allowed to room temperature, quenched with 2x15 ml of water and extracted with 2x50 ml of ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain crude compound. The crude product was purified by column chromatography to afford (4*S*)-7-((*S*)-2-methylmorpholino)-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide(285 mg, 0.725 mmol, 32.8 % yield) as off white solid (TLC: R_f value: 0.3, 5% Methanol in DCM), LCMS (*m/z*): 383.28 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 13.40 (s, 1H), 9.38 (d, *J* = 1.4 Hz, 1H), 8.40 - 8.14 (m, 2H), 7.40 (d, *J* = 8.6 Hz, 1H), 6.53 (d, *J* = 8.6 Hz, 1H), 5.44 (dd, *J* = 6.0, 3.1 Hz, 1H), 4.12 (s, 1H), 3.96 (ddd, *J* = 11.5, 3.6, 1.4 Hz, 1H), 3.86 (d, *J* = 12.8 Hz, 1H), 3.62 (dd, *J* = 11.8, 2.8 Hz, 2H), 3.09 (dd, *J* = 11.4, 8.4 Hz, 1H), 2.96 (s, 2H), 2.93 - 2.78 (m, 2H), 2.58 (dd, *J* = 12.6, 10.4 Hz, 1H), 2.17 (s, 1H), 1.85 (dt, *J* = 14.3, 7.3 Hz, 1H), 1.23 (d, *J* = 6.2 Hz, 3H).

Example 126

Synthesis of (4*S*)-N-(3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

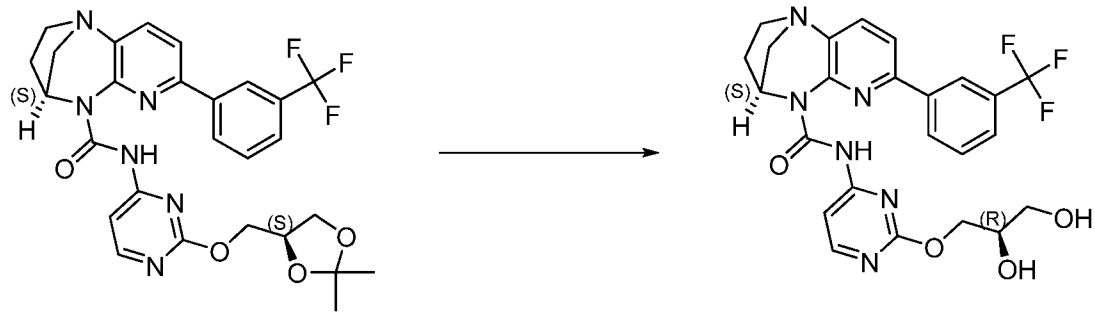


To a solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (500 mg, 1.982 mmol) in THF (30 ml) was added tri-phosgene (294 mg, 0.991 mmol) at 0 °C and stirred to RT for 1 h. Then 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-amine (426 mg, 2.58 mmol) and triethylamine (1.381 mL, 9.91 mmol) were added sequentially and heated the reaction mixture at 70 °C for 16 h in sealed tube. The reaction mixture was poured in saturated $NaHCO_3$ solution (150 mL) and extracted with ethyl acetate (3x50 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 DCM as eluent) to afford (4*S*)-N-(3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (394 mg, 0.889 mmol, 68% yield) as pale yellow solid (TLC: 5% MeOH in DCM, R_f = 0.3), LCMS (*m/z*): 444.28 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.76 (s, 1 H), 8.59 (d, *J*=5.04 Hz, 1 H), 7.79-7.58 (m, 3 H), 7.24-7.06 (m, 2 H), 6.96 (d, *J*=8.77 Hz, 1 H), 5.46 (dd, *J*=5.70, 3.07 Hz, 1 H), 4.10 (dt, *J*=19.51, 5.37 Hz, 4 H), 3.15-3.02 (m, 1 H), 3.02-2.77 (m, 3 H), 2.50 (s, 3 H), 2.46-2.18 (m, 1 H), 2.17-2.01 (m, 2 H), 2.01-1.83 - (m, 2 H).

Example 127

Synthesis of (4*S*)-N-(2-((*R*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

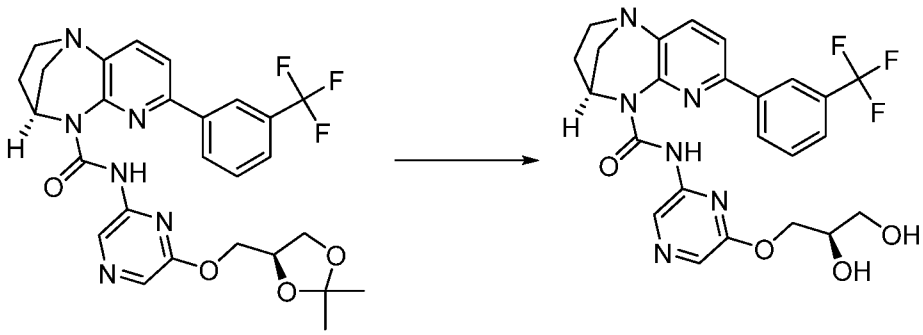


To a solution of (4*S*)-N-(2-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-car -boxamide (450 mg, 0.809 mmol) in dichloromethane (12 mL), water (1.2 mL) was added 4.0 M hydrochloric acid in 1,4-dioxane (1.68 mL, 0.809 mmol) at 0°C. The reaction mixture was stirred at 30 ° C for 3 h and concentrated the solvent. The reaction mixture was partitioned between water (10 mL) and EtOAc (25 mL). Organic layers were washed with water, brine solution, dried over anhydrous Na_2SO_4 & filtered and filtrate was evaporated to give crude (TLC eluent: 5% MeOH in DCM: R_f-0.2; UV active). The crude was purified washed with *n*-pentane and suspended in water (5 mL), stirred for 15 min and filtered to afford pure (4*S*)-N-(2-((*R*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl) phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (260 mg, 0.480 mmol, 59.4 % yield) as off white solid, LCMS (*m/z*): 517.2 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 13.58 (s, 1H), 8.60 (d, *J* = 7.5 Hz, 1H), 8.46 (d, *J* = 5.6 Hz, 1H), 8.27 (s, 1H), 7.91 - 7.78 (m, 3H), 7.75 - 7.60 (m, 2H), 5.48 (dd, *J* = 5.9, 3.0 Hz, 1H), 4.91 (d, *J* = 4.8 Hz, 1H), 4.62 (t, *J* = 5.5 Hz, 1H), 4.22 (dd, *J* = 10.8, 4.4 Hz, 1H), 4.13 (dd, *J* = 10.7, 5.9 Hz, 1H), 3.80 (q, *J* = 5.4 Hz, 1H), 3.43 (t, *J* = 5.7 Hz, 2H), 3.21 (s, 1H), 3.16 - 3.05 (m, 2H), 2.96 (dd, *J* = 12.0, 3.3 Hz, 1H), 2.29 - 2.10 (m, 1H), 2.04 - 1.84 (m, 1H).

Example 128

Synthesis of (4*S*)-N-(6-((*R*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl) phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

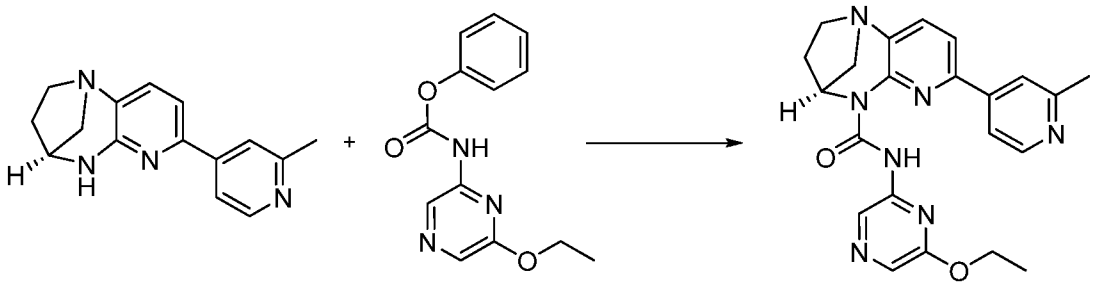


To a solution of (4*S*)-N-(6-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (300 mg, 0.539 mmol) in dichloromethane (8.0 mL), water (0.8 mL) was added 4.0 M hydrochloric acid in 1,4-dioxane (1.12 mL, 0.539 mmol) at 0 °C over 1 min (dropwise addition). The reaction mixture was stirred at 30 °C for 3 h and concentrated the solvent. The reaction mixture was partitioned between water (10 mL) and ethyl acetate (25 mL). Organic layers were washed with water, brine solution, dried over anhydrous Na_2SO_4 and evaporated to give crude compound (TLC eluent: 5% MeOH in DCM: R_f = 0.2; UV active). The crude compound was washed with *n*-pentane and suspended in water (5 mL), stirred for 15 min and filtered to afford pure (4*S*)-N-(6-((*R*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (280 mg, 0.533 mmol, 99 % yield) as off white solid, LCMS (*m/z*): 517.3 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 13.15 (s, 1H), 8.95 (s, 1H), 8.36 (d, *J* = 7.7 Hz, 1H), 8.22 (s, 1H), 7.99 (s, 1H), 7.86 (t, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.74 (q, *J* = 8.0 Hz, 2H), 5.52 (dd, *J* = 5.8, 3.0 Hz, 1H), 4.95 (d, *J* = 5.1 Hz, 1H), 4.64 (t, *J* = 5.5 Hz, 1H), 4.14 (dd, *J* = 10.7, 4.0 Hz, 1H), 4.03 (dd, *J* = 10.7, 6.1 Hz, 1H), 3.77 (q, *J* = 5.2 Hz, 1H), 3.36 (hept, *J* = 5.8 Hz, 2H), 3.22 (s, 1H), 3.12 (d, *J* = 11.3 Hz, 2H), 2.97 (dd, *J* = 11.9, 3.3 Hz, 1H), 2.26 (t, *J* = 7.0 Hz, 1H), 2.03 - 1.90 (m, 1H).

Example 129

Synthesis of (4*S*)-*N*-(6-ethoxypyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

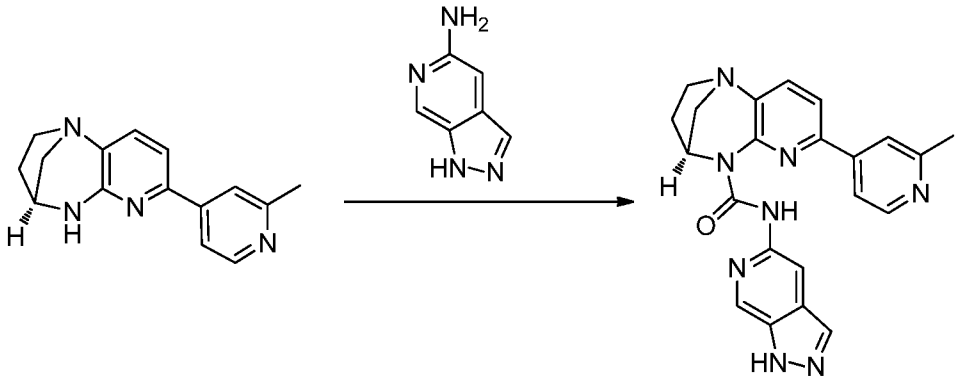


DMAP (726 mg, 5.94 mmol) and phenyl (6-ethoxypyrazin-2-yl)carbamate (1541 mg, 5.94 mmol) were added to a stirred solution of (4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.982 mmol) in THF at room temperature. The mixture was heated to 80 °C for 20 h in a sealed tube. After cooling to room temperature, the solvent was evaporated and crude product was purified by flash column chromatography (silica-gel: 100-200 mesh, 5% MeOH in DCM as an eluent). The recovered material was taken up in ethanol and the solid that separated was isolated by filtration to afford (4S)-N-(6-ethoxypyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (416 mg, 0.978 mmol, 49.3 % yield) as an off white solid(TLC eluent: 10% MeOH in DCM, R_f: 0.4), LCMS (*m/z*): 418.28 $[M+H]^+$.

^{1}H NMR (DMSO-d6, 400MHz): δ 13.18 (s, 1H), 8.95 (s, 1H), 8.53 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.98 (d, *J* = 0.5 Hz, 1H), 7.86 - 7.79 (m, 2H), 7.73 (s, 2H), 5.51 (dd, *J* = 5.9, 3.1 Hz, 1H), 4.22 (qd, *J* = 7.1, 2.3 Hz, 2H), 3.25 - 3.17 (m, 1H), 3.11 (dt, *J* = 11.7, 2.4 Hz, 2H), 2.97 (dd, *J* = 12.0, 3.3 Hz, 1H), 2.58 (s, 3H), 2.25 (dddd, *J* = 13.7, 9.9, 6.2, 3.8 Hz, 1H), 2.04 - 1.90 (m, 1H), 1.27 (t, *J* = 7.0 Hz, 3H).

Example 130

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-*N*-(1*H*-pyrazolo[3,4-*c*]pyridin-5-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

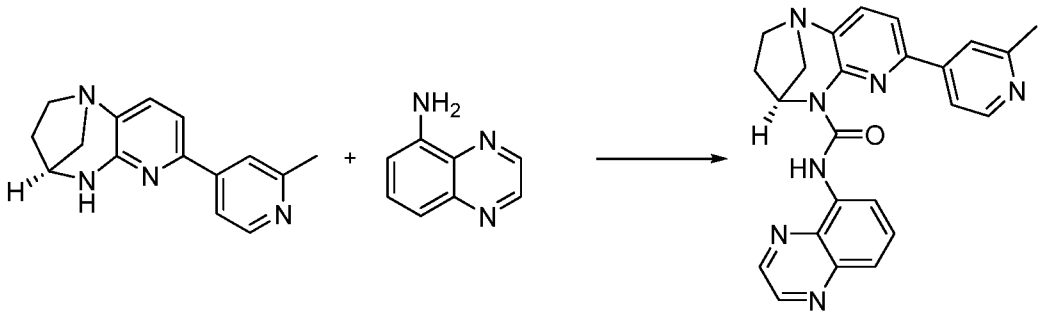


To a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 1.189 mmol) in THF (10 mL) was added triphosgene (176 mg, 0.594 mmol) at RT and stirred for 30 min. After 30 minutes triethylamine (0.829 mL, 5.94 mmol) and 1*H*-pyrazolo [3,4-*c*]pyridin-5-amine (191 mg, 1.427 mmol) were added. The reaction mixture was stirred at 65-70 °C for 16 h in sealed tube. Reaction mixture was quenched with 2x15 ml of water and extracted with 2x15 ml of ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain crude compound. The crude mixture was purified by column chromatography to afford (4*S*)-7-(2-methylpyridin-4-yl)-*N*-(1*H*-pyrazolo[3,4-*c*]pyridin-5-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (330 mg, 0.764 mmol, 64.3 % yield) as a pale yellow solid (R_f value: 0.25, Neat Ethyl acetate), LCMS (*m/z*): 413.24$[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 13.47 (s, 2H), 8.89 (t, *J* = 1.1 Hz, 1H), 8.71 - 8.57 (m, 1H), 8.44 (t, *J* = 1.0 Hz, 1H), 8.28 - 8.10 (m, 2H), 8.05 - 7.93 (m, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 5.56 (dd, *J* = 5.9, 3.1 Hz, 1H), 3.22 (tt, *J* = 8.1, 3.0 Hz, 1H), 3.15 - 3.04 (m, 2H), 2.97 (dd, *J* = 12.0, 3.3 Hz, 1H), 2.67 (s, 3H), 2.36 - 2.16 (m, 1H), 1.96 (dd, *J* = 14.0, 7.1 Hz, 1H).

Example 131

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-N-(quinoxalin-5-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

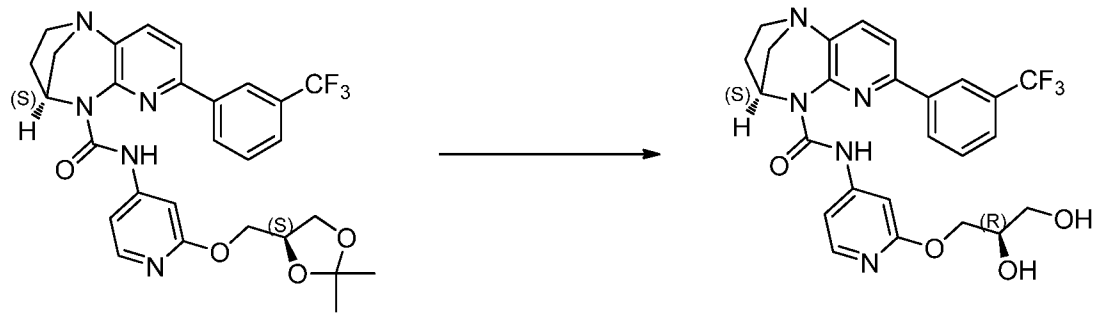


To a solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (500 mg, 1.982 mmol) in THF (30 ml) was added tri-phosgene (294 mg, 0.991 mmol) at 0 °C and stirred at RT for 1 h. Then quinoxalin-5-amine (374 mg, 2.58 mmol) and triethylamine (1.381 mL, 9.91 mmol) were added sequentially at RT and heated the reaction mixture at 70 °C for 16 h. The reaction mixture was poured in saturated $NaHCO_3$ solution (150 mL) and extracted with ethyl acetate (3x50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product. The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh, using gradient mixture of 1% MeOH in DCM as eluent) to afford (4*S*)-7-(2-methylpyridin-4-yl)-N-(quinoxalin-5-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (300 mg, 0.709 mmol, 55% yield) as pale yellow solid (TLC: 5% MeOH in DCM, R_f = 0.3), LCMS (*m*/z): 424.26 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.50 (s, 1 H), 8.91 (s, 1 H), 8.68 (dd, *J*=7.89, 1.10 Hz, 1 H), 8.48 (d, *J*=5.26 Hz, 1 H), 7.92-7.80 (m, 2 H), 7.80-7.62 (m, 4 H), 5.58 (dd, *J*=5.81, 2.96 Hz, 1 H), 3.20-3.08 (m, 4 H), 3.08-2.86 (m, 1 H), 2.26 (s, 4 H), 2.00-1.95 (m, 1 H).

Example 132

Synthesis of (4S)-N-(2-((R)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

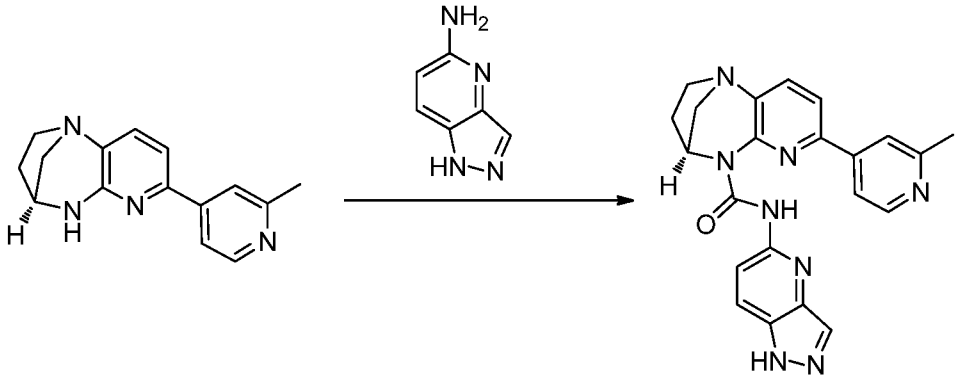


To a solution of (4*S*)-N-(2-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (450 mg, 0.810 mmol) in dichloromethane (12 mL),water (1.2 mL) was added 4.0 M hydrochloric acid in 1,4-dioxane (1.68 mL, 0.810 mmol) dropwise during 1 min at 0 °C. The reaction mixture was stirred at 30 °C for 3 h and concentrated the solvent. The reaction mixture was partitioned between water (10 mL) and EtOAc (25 mL). Organic layers were washed with water, brine solution, dried over anhydrous Na_2SO_4 and evaporated to give crude compound (TLC eluent: 5% MeOH in DCM: R_f-0.2; UV active). The crude compound was washed with *n*-pentane and the compound was suspended in water (5 mL), stirred for 15 min and filtered to afford pure (4*S*)-N-(2-((*R*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide (310 mg, 0.600 mmol, 74.0 % yield) as white solid, LCMS (*m/z*): 516.3 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 13.02 (s, 1H), 8.27 - 8.15 (m, 2H), 7.94 (d, *J* = 5.7 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.82 (t, *J* = 7.7 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 1.8 Hz, 1H), 6.80 (dd, *J* = 5.8, 1.9 Hz, 1H), 5.47 (dd, *J* = 5.9, 3.0 Hz, 1H), 4.85 (d, *J* = 5.1 Hz, 1H), 4.59 (t, *J* = 5.7 Hz, 1H), 4.23 (dd, *J* = 10.9, 4.6 Hz, 1H), 4.13 (dd, *J* = 10.9, 6.2 Hz, 1H), 3.81 - 3.65 (m, 1H), 3.43 (t, *J* = 5.6, 1.3 Hz, 2H), 3.25 - 3.03 (m, 3H), 2.97 (dd, *J* = 12.0, 3.3 Hz, 1H), 2.25 (m, *J* = 13.8, 9.7, 4.7 Hz, 1H), 1.95 (m, *J* = 14.3, 7.6 Hz, 1H).

Example 133

(4*S*)-7-(2-methylpyridin-4-yl)-*N*-(1*H*-pyrazolo[4,3-*b*]pyridin-5-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

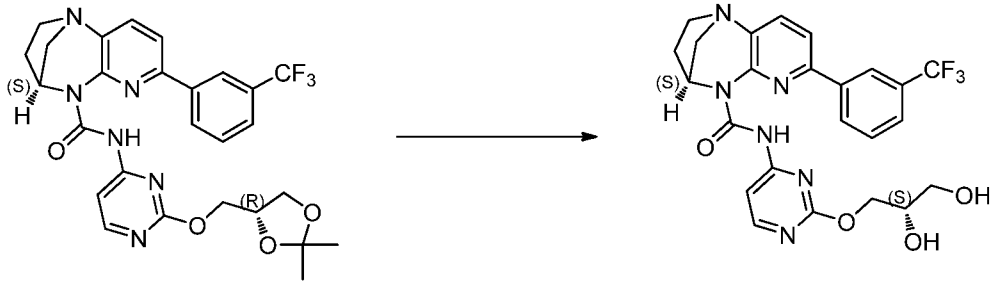


To a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (600 mg, 2.378 mmol) in THF (10 mL) was added triphosgene (353 mg, 1.189 mmol) at RT and stirred for 30 min, to this triethylamine (1.657 mL, 11.89 mmol) and 1*H*-pyrazolo [4,3-*b*] pyridin-5-amine (319 mg, 2.378 mmol) were added. The reaction mixture was stirred at 60 °C for 16 h. Reaction mixture was quenched with 2x15 ml of water and extracted with 2x15 ml of ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain crude compound. The crude product was purified by column chromatography (100-200 mesh) to afford (4*S*)-7-(2-methylpyridin-4-yl)-*N*-(1*H*-pyrazolo[4,3-*b*]pyridin-5-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (265 mg, 0.622 mmol, 26.2 % yield) as a pale yellow solid (TLC: R_f value: 0.25, Neat ethyl acetate), LCMS (*m/z*): 413.28 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-*d6*): δ 13.55 (s, 1H), 13.27 (s, 1H), 8.66 (dd, *J* = 5.4, 0.8 Hz, 1H), 8.32 (d, *J* = 9.2 Hz, 1H), 8.16 - 7.94 (m, 4H), 7.94 - 7.51 (m, 2H), 5.55 (dd, *J* = 6.0, 3.1 Hz, 1H), 3.21 (d, *J* = 8.7 Hz, 1H), 3.18 - 3.05 (m, 2H), 2.97 (dd, *J* = 12.0, 3.3 Hz, 1H), 2.69 (s, 3H), 2.35 - 2.17 (m, 1H), 1.96 (dt, *J* = 14.2, 7.6 Hz, 1H).

Example 134

Synthesis of (4S)-N-(2-((S)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(3-(trifluorometh -yl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

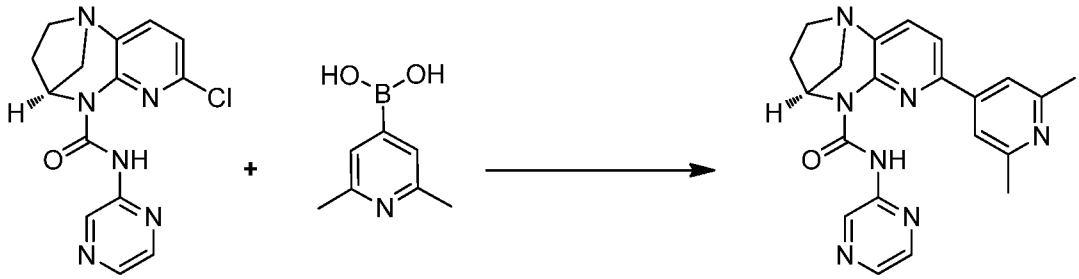


To a solution of (4*S*)-N-(2-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-car boxamide (350 mg, 0.629 mmol) in dichloromethane (8 mL),water (0.8 mL) was added 4.0 M hydrochloric acid in 1,4-dioxane (1.12 mL, 0.629 mmol) dropwise over 1 min at 0 °C. The reaction mixture was stirred at 30 °C for 3 h and concentrated the solvent. The reaction mixture was partitioned between water (10 mL) and EtOAc (25 mL). Organic layers were washed with water, brine solution, dried over anhydrous Na_2SO_4 and evaporated to give crude compound (TLC eluent: 5% MeOH in DCM: R_f = 0.2; UV active). The crude was purified by chiral separation to get (4*S*)-N-(2-((*S*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-car-boxamide (210 mg, 0.405 mmol, 64.3 % yield) as off white solid, LCMS (*m/z*): 517.3 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 13.59 (s, 1H), 8.60 (d, *J* = 7.5 Hz, 1H), 8.46 (d, *J* = 5.7 Hz, 1H), 8.27 (s, 1H), 7.90 - 7.78 (m, 3H), 7.76 - 7.69 (m, 2H), 5.48 (dd, *J* = 5.8, 3.0 Hz, 1H), 4.91 (d, *J* = 5.0 Hz, 1H), 4.63 (t, *J* = 5.5 Hz, 1H), 4.46 - 4.01 (m, 2H), 3.80 (h, *J* = 5.5 Hz, 1H), 3.44 (t, *J* = 5.5 Hz, 2H), 3.21 (s, 1H), 3.12 (dd, *J* = 10.1, 5.5 Hz, 2H), 2.96 (dd, *J* = 12.0, 3.3 Hz, 1H), 2.24 (d, *J* = 8.7 Hz, 1H), 2.03 - 1.90 (m, 1H).

Example 135

Synthesis of (4*S*)-7-(2,6-dimethylpyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

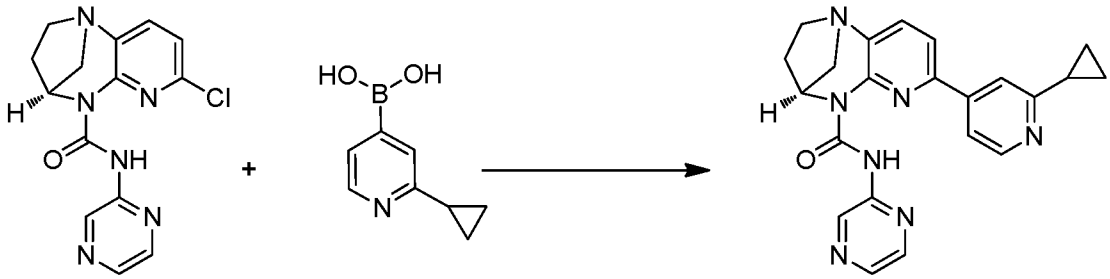


Tripotassium phosphate (804 mg, 3.79 mmol) was added to a stirred solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (600 mg, 1.894 mmol), (2,6-dimethylpyridin-4-yl)boronic acid (343 mg, 2.273 mmol) in 1-butanol (10 mL), and water (1.667 mL) at 28 °C. The reaction mixture was degassed for 15 min, was added $Pd_2(dba)_3$ (87 mg, 0.095 mmol), and X-phos (90 mg, 0.189 mmol). The reaction mixture was further degassed for 15 min, and the reaction mixture was stirred for 3 hr at 100 °C. The reaction mixture was cooled to 28 °C and was partitioned between water (10 mL) and EtOAc (25 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude as brown solid (TLC eluent: 10% MeOH in EtOAc; R_f = 0.3; UV active). The crude was purified by column chromatography using (100-200 mesh) silica gel and was eluted with 5-10% MeOH in EtOAc to afford pure (4*S*)-7-(2,6-dimethylpyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (355 mg, 0.916 mmol, 48.3 % yield) as pale yellow solid, LCMS (*m/z*): 387.44 $[M+H]^+$.

^{1}H NMR (DMSO-d_6, 400 MHz,): δ 13.77 (s, 1H), 9.43 (d, *J* = 1.5 Hz, 1H), 8.53 - 8.28 (m, 2H), 7.91 - 7.59 (m, 4H), 5.51 (dd, *J* = 6.0, 3.1 Hz, 1H), 3.25 - 2.81 (m, 4H), 2.56 - 2.46 (m, 6H), 2.26 (dddd, *J* = 13.7, 9.9, 6.1, 3.7 Hz, 1H), 1.97 (dq, *J* = 14.4, 7.5, 6.8 Hz, 1H).

Example 136

Synthesis of (4*S*)-7-(2-cyclopropylpyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

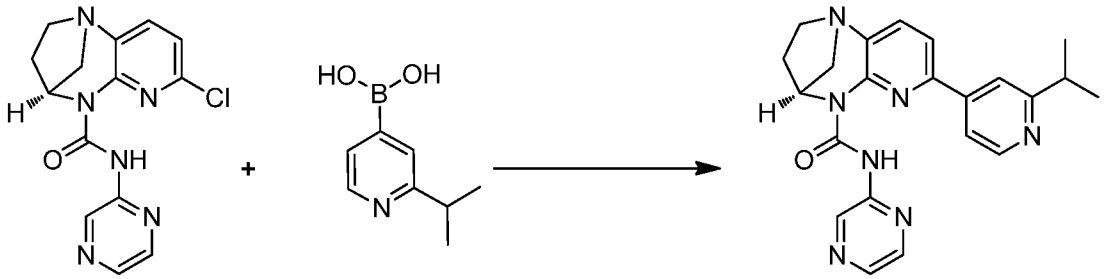


Tripotassium phosphate (670 mg, 3.16 mmol) was added to a stirred solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (500 mg, 1.579 mmol), (2-cyclopropylpyridin-4-yl)boronic acid (309 mg, 1.894 mmol) in 1,4-dioxane (10 mL), and water (1.667 mL) at 28 °C. The reaction mixture was degassed for 15 min, was added $Pd_2(dba)_3$ (72.3 mg, 0.079 mmol), and X-phos (75 mg, 0.158 mmol). The reaction mixture was further degassed for 15 min, and the reaction mixture was stirred for 3 hr at 100 °C. The reaction mixture was cooled to 28 °C and was partitioned between water (10 mL) and EtOAc (25 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude as brown solid (TLC eluent: 10% MeOH in EtOAc; R_f-0.3; UV active). The crude was purified by column chromatography using (100-200 mesh) silica gel and was eluted with 5-10% MeOH in EtOAc to afford pure (4*S*)-7-(2-cyclopropylpyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (260 mg, 0.645 mmol, 40.8 % yield) as off white solid, LCMS (*m/z*): 400.28 $[M+H]^+$.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.75 (s, 1H), 9.43 (d, *J* = 1.5 Hz, 1H), 8.54 (d, *J* = 5.4 Hz, 1H), 8.46 - 8.28 (m, 2H), 8.19 - 8.01 (m, 1H), 7.89 - 7.62 (m, 3H), 5.52 (dd, *J* = 6.0, 3.1 Hz, 1H), 3.30 - 2.86 (m, 4H), 2.27 (ddd, *J* = 13.2, 6.4, 4.1 Hz, 2H), 1.98 (dt, *J* = 14.5, 7.6 Hz, 1H), 1.17 - 0.88 (m, 4H).

Example 137

Synthesis of (4*S*)-7-(2-isopropylpyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

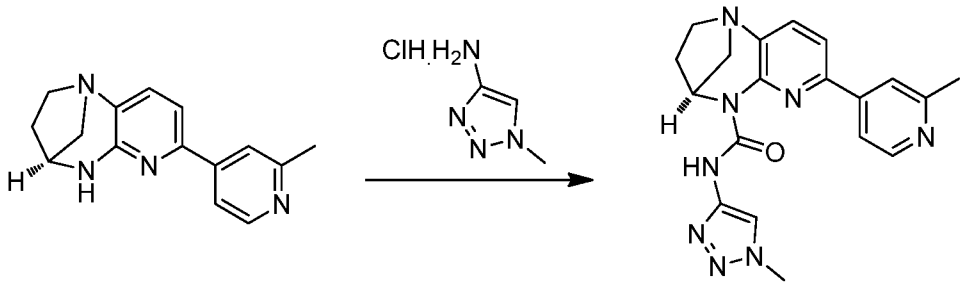


Tripotassium phosphate (670 mg, 3.16 mmol) was added to a stirred solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2H)-carboxa-mide (500 mg, 1.579 mmol), (2-isopropylpyridin-4-yl)boronic acid (313 mg, 1.894 mmol) in 1,4-dioxane (10 mL), and water (1.667 mL) at 28 °C. The reaction mixture was degassed for 15 min, was added $Pd_2(dba)_3$ (72.3 mg, 0.079 mmol), and X-phos (75 mg, 0.158 mmol). The reaction mixture was further degassed for 15 min, and the reaction mixture was stirred for 3 hr at 100 °C. The reaction mixture was cooled to 28 °C and was partitioned between water (10 mL) and EtOAc (25 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude as brown solid (TLC eluent: 10% MeOH in EtOAc: R_f = 0.3; UV active). The crude was purified by column chromatography using (100-200 mesh) silica gel and was eluted with 5-10% MeOH in EtOAc to afford pure (4*S*)-7-(2-isopropylpyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (320 mg, 0.793 mmol, 50.2 % yield) as Off white solid. LCMS (*m/z*): 402.33 $[M+H]^+$.

^{1}H NMR ($CDCl_3$,400 MHz): δ 13.65 (s, 1H), 9.57 (d, *J* = 1.5 Hz, 1H), 8.68 (d, *J* = 5.2 Hz, 1H), 8.44 - 8.07 (m, 2H), 8.02 - 7.87 (m, 1H), 7.75 - 7.58 (m, 2H), 7.48 (d, *J* = 8.0 Hz, 1H), 5.73 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.43 - 3.14 (m, 4H), 3.04 (dd, *J* = 12.1, 3.3 Hz, 1H), 2.35 (dt, *J* = 11.7, 5.0 Hz, 1H), 2.22 - 2.00 (m, 1H), 1.41 (dd, *J* = 6.9, 0.9 Hz, 6H).

Example 138

Synthesis of (4*S*)-N-(1-methyl-1*H*-1,2,3-triazol-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide

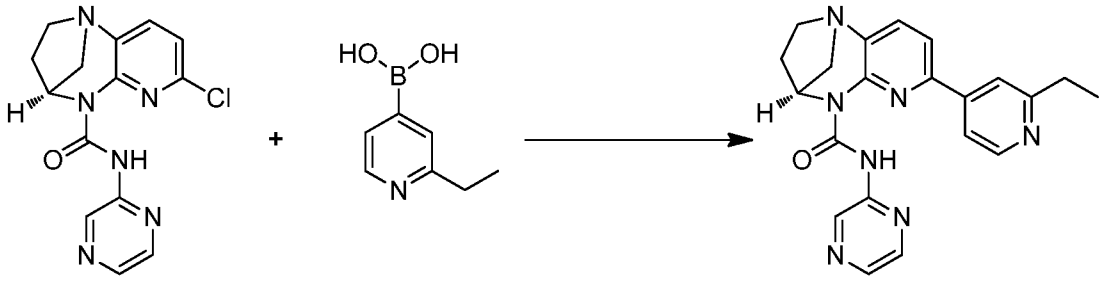


Triphosgene (0.588 g, 1.982 mmol) was added to a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (0.5g, 1.982 mmol) in tetrahydrofuran (20 mL) at 0 °C, followed by addition of triethylamine (0.829 mL, 5.94 mmol) and stirred for 30 min at 0 °C. 1-Methyl-1*H*-1, 2,3-triazol-4-amine hydro-chloride (0.4 g, 2.97 mmol) was added and heated at 70 °C for 48h. The reaction mixture was cooled to 28 °C and was partitioned between water (10 mL) and ethyl acetate (50 mL). The organic layer was separated and washed with water and brine. The Organic layer was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford crude yellow solid (TLC eluent: 10% MeOH in EtOAc: R_f = 0.2; UV active). The crude compound was purified by 100-200 silica gel by eluting with 5% MeOH in ethyl acetate to afford (4*S*)-N-(1-methyl-1*H*-1,2,3-triazol-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (0.260g, 0.686 mmol, 34.6 % yield) as an off white solid, LCMS (*m/z*): 377.28 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-*d6*): δ 13.52 (s, 1H), 8.58 (dd, *J* = 5.3, 0.8 Hz, 1H), 8.07 (s, 1H), 8.00 (d, *J* = 1.7 Hz, 1H), 7.85 - 7.75 (m, 2H), 7.71 (d, *J* = 8.0 Hz, 1H), 5.46 (dd, *J* = 5.9, 3.0 Hz, 1H), 4.06 (s, 3H), 3.30 (s, 1H), 3.24 - 3.05 (m, 2H), 2.96 (dd, *J* = 12.0, 3.2 Hz, 1H), 2.63 (s, 3H), 2.23 (dd, *J* = 13.7, 9.8, 6.1, 3.7 Hz, 1H), 2.00 - 1.86 (m, 1H).

Example 139

Synthesis of (4*S*)-7-(2-ethylpyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

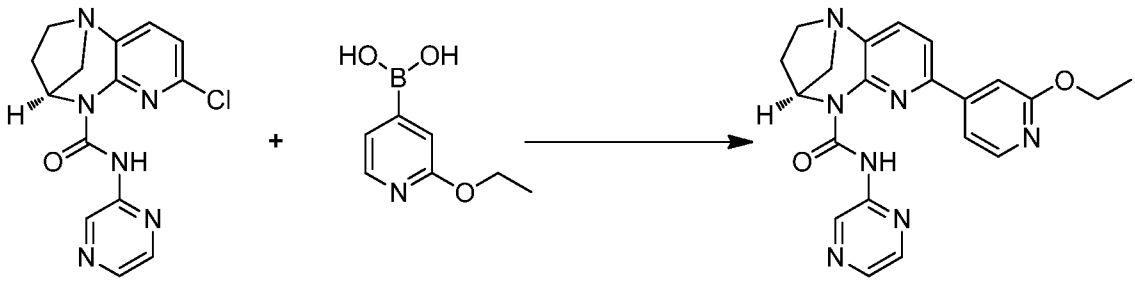


Tripotassium phosphate (804 mg, 3.79 mmol) was added to a stirred solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxa-mide (600 mg, 1.894 mmol), (2-ethylpyridin-4-yl)boronic acid (343 mg, 2.273 mmol) in *n*-butanol (10 mL) and water (1.667 mL). The reaction mixture was degassed for 15 min $Pd_2(dba)_3$ (87 mg, 0.095 mmol), and X-phos (90 mg, 0.189 mmol) were added. The reaction mixture was further degassed for 15 min, and was stirred at 100 °C for 5 hr. The reaction mixture was cooled to 28 °C and was partitioned between water (10 mL) and EtOAc (25 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered. The filtrate was evaporated to get crude (TLC eluent: 10% MeOH in EtOAc: R_f: 0.2; UV active). The crude compound was purified by (100-200 mesh) silica gel eluting with 20% MeOH in EtOAc to afford (4*S*)-7-(2-ethylpyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (418 mg, 1.074 mmol, 56.7 % yield) as an off white solid, LCMS (*m/z*): 388.26 $[M+H]^+$.

^{1}H NMR (DMSO-d_6,400 MHz): δ 13.72 (s, 1H), 9.43 (d, *J* = 1.5 Hz, 1H), 8.62 (dd, *J* = 5.3, 0.8 Hz, 1H), 8.53 - 8.21 (m, 2H), 8.08 (d, *J* = 1.7 Hz, 1H), 7.97 - 7.64 (m, 3H), 5.52 (dd, *J* = 6.0, 3.1 Hz, 1H), 3.30 (s, 1H), 3.23 - 3.08 (m, 3H), 3.03 - 2.81 (m, 2H), 2.34 - 2.16 (m, 1H), 1.99 (d, *J* = 6.8 Hz, 1H), 1.31 (t, *J* = 7.6 Hz, 3H).

Example 140

Synthesis of (4*S*)-7-(2-ethoxypyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

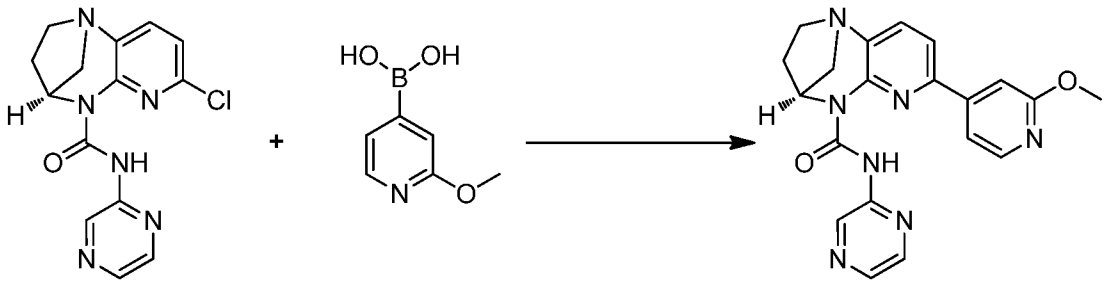


Tripotassium phosphate (804 mg, 3.79 mmol) was added to a stirred solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carbox-amide (600 mg, 1.894 mmol), (2-ethoxypyridin-4-yl)boronic acid (380 mg, 2.273 mmol) in 1-butanol (10 mL), and water (1.667 mL). The reaction mixture was degassed for 15 min $Pd_2(dba)_3$ (87 mg, 0.095 mmol), and X-phos (90 mg, 0.189 mmol) were added. The reaction mixture further degassed for 15 min, and was stirred at 100 °C for 4 hr. The reaction mixture was cooled to 28 °C and was partitioned between water (100 mL) and EtOAc (120 mL). EtOAc layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude (TLC eluent: 10% MeOH in EtOAc: R_f = 0.4; UV active). The crude compound was purified by (100-200 mesh) silica gel, eluting with 10% MeOH in ethyl acetate to afford (4*S*)-7-(2-ethoxypyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (435 mg, 1.063 mmol, 56.1 % yield) as an off white solid, LCMS (*m/z*): 404.28 $[M+H]^+$.

^{1}H NMR (DMSO-d_6,400 MHz): δ 13.73 (s, 1H), 9.39 (d, *J* = 1.5 Hz, 1H), 8.50 - 8.33 (m, 1H), 8.31 - 8.21 (m, 2H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.77 - 7.62 (m, 2H), 7.60 (d, *J* = 2.2 Hz, 1H), 5.50 (dd, *J* = 5.9, 3.0 Hz, 1H), 4.37 (q, *J* = 7.0 Hz, 2H), 3.30 (s, 1H), 3.25 - 3.03 (m, 2H), 2.97 (dd, *J* = 12.1, 3.3 Hz, 1H), 2.36 - 2.12 (m, 1H), 2.07 - 1.87 (m, 1H), 1.38 (t, *J* = 7.0 Hz, 3H).

Example 141

Synthesis of (4*S*)-7-(2-methoxypyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

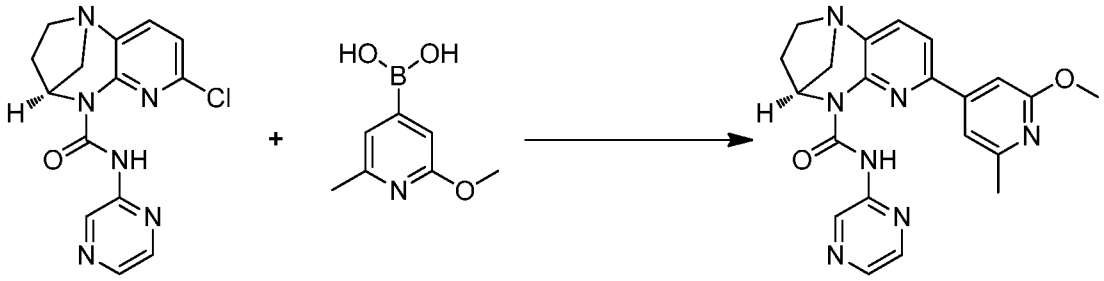


Tripotassium phosphate (804 mg, 3.79 mmol) was added to a stirred solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (600 mg, 1.894 mmol), (2-methoxypyridin-4-yl) boronic acid (348 mg, 2.273 mmol) in 1,4-dioxane (12 mL), and water (2.000 mL). The reaction mixture was degassed for 15 min, $Pd_2(dba)_3$ (87 mg, 0.095 mmol), and X-phos (90 mg, 0.189 mmol) were added. The reaction mixture further degassed for 15 min, and was stirred at 100 °C for 5 hr. The reaction mixture was cooled to 28 °C and was partitioned between water (25 mL) and EtOAc (60 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude (TLC eluent: 10% MeOH in EtOAc; R_f = 0.2; UV active). The crude compound was purified by (100-200 mesh) silica gel eluting with 20% MeOH in ethyl acetate to afford (4*S*)-7-(2-methoxypyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (310 mg, 0.793 mmol, 41.8 % yield) as pale yellow solid, LCMS (*m/z*): 390.20 $[M+H]^+$.

^{1}H NMR (DMSO-d_6 ,400 MHz): δ 13.71 (s, 1H), 9.38 (d, *J* = 1.5 Hz, 1H), 8.43 (dd, *J* = 2.5, 1.5 Hz, 1H), 8.38 (s, 1H), 8.37 (d, *J* = 2.5 Hz, 1H), 7.75 (d, *J* = 22.0 Hz, 1H), 7.77 - 7.62 (m, 2H),7.60 (s, 1H), 5.50 (dd, *J* = 5.9, 3.0 Hz, 1H), 3.94 (s, 3H), 3.30 (s, 1H), 3.25 - 3.03 (m, 2H), 3.03 - 2.88 (m, 1H), 2.25 (dd, *J* = 9.9, 3.9 Hz, 1H), 1.98 (dd, *J* = 14.2, 7.2 Hz, 1H).

Example 142

Synthesis of (4*S*)-7-(2-methoxy-6-methylpyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

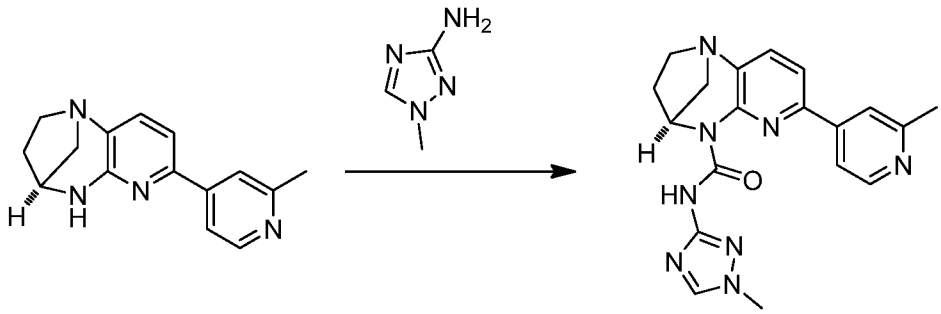


Tripotassium phosphate (804 mg, 3.79 mmol) was added to a stirred solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (600 mg, 1.894 mmol), (2-methoxy-6-methylpyridin-4-yl)boronic acid (380 mg, 2.273 mmol) in 1,4-dioxane (12 mL), and water (2.000 mL). The reaction mixture was degassed for 15 min, $Pd_2(dba)_3$ (87 mg, 0.095 mmol), and X-phos (90 mg, 0.189 mmol) were added. The reaction mixture further degassed for 15 min, and was stirred at 100 °C for 5 hr. The reaction mixture was cooled to 28 °C and was partitioned between water (25 mL) and EtOAc (60 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered. The filtrate was evaporated to get crude (TLC eluent: 10% MeOH in EtOAc; R_f = 0.3; UV active). The crude compound was purified by (100-200 mesh) silica gel eluting with 20% MeOH in ethyl acetate to afford (4*S*)-7-(2-methoxy-6-methylpyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (225 mg, 0.547 mmol, 28.9 % yield) as an off white solid, LCMS (*m/z*): 404.24 $[M+H]^+$.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.72 (s, 1H), 9.41 (d, *J* = 1.5 Hz, 1H), 8.55 - 8.26 (m, 2H), 7.86 - 7.64 (m, 3H), 7.31 (dd, *J* = 1.4, 0.7 Hz, 1H), 5.51 (dd, *J* = 6.0, 3.1 Hz, 1H), 3.91 (s, 3H), 3.22 - 3.00 (m, 3H), 2.97 (dd, *J* = 12.1, 3.3 Hz, 1H), 2.63 - 2.41 (m, 3H), 2.25 (dddd, *J* = 13.8, 9.8, 6.1, 3.6 Hz, 1H), 1.97 (dt, *J* = 14.3, 7.6 Hz, 1H).

Example 143

Synthesis of (4*S*)-N-(1-methyl-1*H*-1,2,4-triazol-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

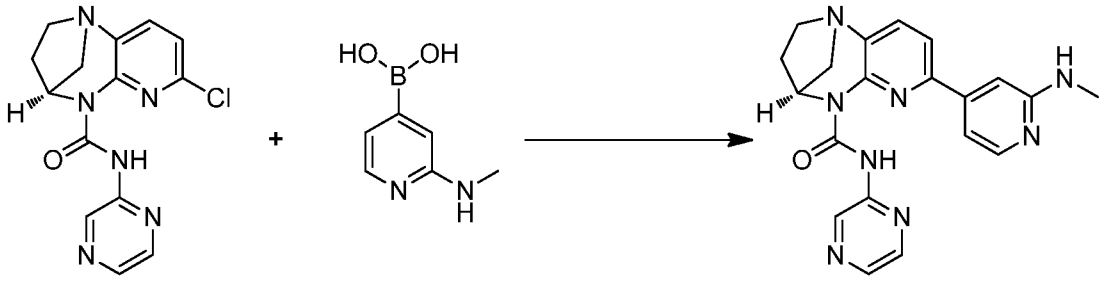


Triphosgene (0.588 g, 1.982 mmol) was added to a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (0.5g, 1.982 mmol) in tetrahydrofuran (20 mL) at 0 °C and stirred for 30min. Triethylamine (0.829 mL, 5.94 mmol) and 1-methyl-1*H*-1,2,4-triazol-3-amine (0.486 g, 4.95 mmol) was added at 0 °C. The reaction mixture was stirred for 48h at 70 °C. The reaction mixture was cooled to 28 °C, and was partitioned between water (50 mL) and DCM (50 mL). The separated organic layer was washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford crude yellow solid (TLC eluent: 10% MeOH in EtOAc: R_f-0.3; UV active). The crude compound was purified by (100-200 mesh) silica gel and was eluting with 5% MeOH in ethyl acetate to afford (4*S*)-N-(1-methyl-1*H*-1,2,4-triazol-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-car-boxamide (0.215g, 0.563 mmol, 28.4 % yield) as light yellow solid, LCMS (*m/z*): 377.28 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-*d6*): δ 13.44 (s, 1H), 8.55 (d, *J* = 5.2 Hz, 1H), 8.36 (s, 1H), 7.96 (s, 1H), 7.86 - 7.61 (m, 3H), 5.44 (dd, *J* = 5.8, 3.0 Hz, 1H), 3.83 (s, 3H), 3.27 (d, *J* = 30.5 Hz, 3H), 2.95 (dd, *J* = 12.0, 3.2 Hz, 1H), 2.59 (s, 3H), 2.23 (ddt, *J* = 16.9, 9.7, 4.4 Hz, 1H), 1.91 (dt, *J* = 14.7, 7.4 Hz, 1H).

Example 144

Synthesis of (4*S*)-7-(2-(methylamino)pyridin-4-yl)-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-meth anopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

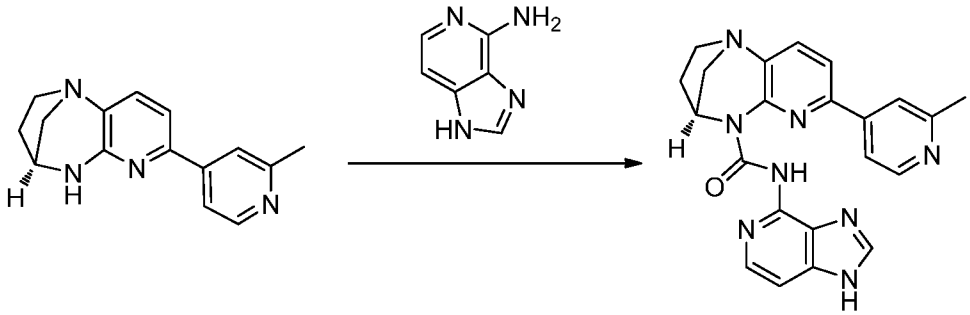


To a degassed solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (500 mg, 1.579 mmol), N-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (443 mg, 1.894 mmol) and Potassium Phosphate tri basic (670 mg, 3.16 mmol) in1,4-dioxane (15 mL) and water (2 mL) were added $Pd(OAc)_2$ (17.72 mg, 0.079 mmol) and dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (75 mg, 0.158 mmol) at RT and the reaction mixture was heated at 120 °C for 4h. The n-butanol solvent was evaporated under reduced pressure and the obtained residue diluted with water and extracted with DCM (2x50 mL). The combined organic layer was washed with water, brine, dried over anhydrous sodium sulfate and solvent evaporated under reduced pressure to obtain crude product. The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 3% MeOH in DCM) to afford (4*S*)-7-(2-(methylamino)pyridin-4-yl)-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (325 mg, 0.820 mmol, 51.9% yield) as a white solid (TLC: 10% MeOH in EtOAc, R_f: 0.2), LCMS (*m/z*): 389.2 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.64 (s, 1 H), 9.40 (d, *J*=1.53 Hz, 1 H), 8.46 - 8.31 (m, 2 H), 8.14 (d, *J*=5.48 Hz, 1 H), 7.71 (m, *J*=8.11 Hz, 1 H), 7.61 (d, *J*=8.11 Hz, 1 H), 7.22 (dd, *J*=5.37, 1.64 Hz, 1 H), 7.03 (d, *J*=0.88 Hz, 1 H), 6.40 (q, *J*=4.75 Hz, 1 H), 5.51 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.35 - 3.04 (m, 3 H), 2.96 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.85 (d, *J*=5.04 Hz, 3 H), 2.25 (dddd, *J*=13.59, 9.87, 6.03, 3.62 Hz, 1 H), 1.97 (dt, *J*=13.87, 6.99 Hz, 1 H).

Example 145

(4S)-N-(1H-imidazo[4,5-c]pyridin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

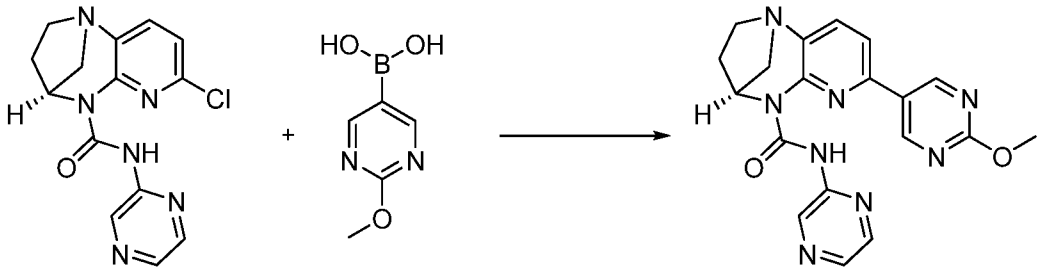


(4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (700 mg, 2.77 mmol) was dissolved in Tetrahydrofuran (THF) (10 mL) stirred under nitrogen at room temp was added triphosgene (412 mg, 1.387 mmol) and stirred for 30 min at RT, to this was added triethylamine (1.933 mL, 13.87 mmol) and 1H-imidazo[4,5-c]pyridin-4-amine (372 mg, 2.77 mmol) were added, then the reaction mixture was stirred at 60 °C for 16 hr. Reaction mixture was quenched with 2x15 ml of water and extracted with 2x15 ml of ethyl acetate, organic layer was dried over sodium sulfate and concentrated under reduced pressure to afford crude compound. The crude product was purified by column chromatography (100-200 mesh) to afford pure compound(4S)-N-(1H-imidazo[4,5-c]pyridin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (225 mg, 0.531 mmol, 19.14 % yield) as pale yellow solid. (R_f value: 0.4, 10% Methanol in DCM), LCMS (*m/z*): 413.1 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 14.03 (s, 1H), 11.93 (s, 1H), 8.65 (d, *J* = 5.3 Hz, 1H), 8.35 - 7.86 (m, 3H), 7.86 - 7.37 (m, 4H), 5.72 (dd, *J* = 5.9, 3.2 Hz, 1H), 3.21 (m, 3H), 3.06 (dd, *J* = 12.2, 3.3 Hz, 1H), 2.78 (s, 3H), 2.38 (dddd, *J* = 14.0, 9.9, 6.2, 4.2 Hz, 1H), 2.13 (dt, *J* = 14.3, 7.2 Hz, 1H).

Example 146

Synthesis of (4S)-7-(2-methoxypyrimidin-5-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

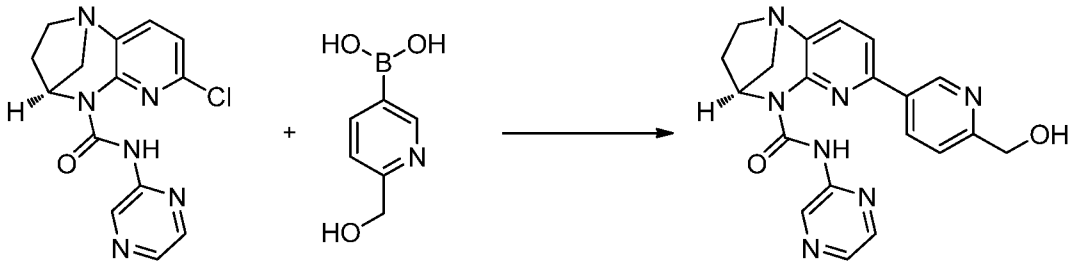


Potassium phosphate (402 mg, 1.894 mmol) and (2-methoxypyrimidin-5-yl)boronic acid (175 mg, 1.137 mmol) were added to a stirred solution of (4S)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (300 mg, 0.947 mmol) in mixture of 1-Butanol (6 mL) and water (2.0 mL) at room temperature and de-gassed the mixture with Argon for 25 min, then added $Pd_2(dba)_3$ (43.4 mg, 0.047 mmol) and X-phos (45.2 mg, 0.095 mmol), heated at 120 C for 2h. Allowed the reaction mixture to room temperature, diluted with water (40 mL) and extracted with Ethyl acetate (3x30 mL), washed with brine (30 mL). The separated organic layer was concentrated and purified by flash column chromatography (silica-gel: 100-200 mesh, 80% Ethyl acetate in petroleum ether as an eluent). The recovered material was re-crystallized by using Ethanol and pentane to afford (4S)-7-(2-methoxypyrimidin-5-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (190 mg, 0.481 mmol, 50.8 % yield) as an off white solid. (Mobile phase: 100% Ethyl acetate, R_f: 0.1), LCMS (*m/z*): 391.2 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.64 (s, 1H), 9.52 (d, *J* = 1.5 Hz, 1H), 9.24 (s, 2H), 8.40 - 8.25 (m, 2H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 5.70 (dd, *J* = 6.0, 3.1 Hz, 1H), 4.12 (s, 3H), 3.33 - 3.13 (m, 3H), 3.02 (d, *J* = 3.3 Hz, 1H), 2.36 (dddd, *J* = 13.9, 9.9, 5.9, 4.0 Hz, 1H), 2.17 - 2.04 (m, 1H).

Example 147

Synthesis of (4S)-7-(6-(hydroxymethyl)440yridine-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

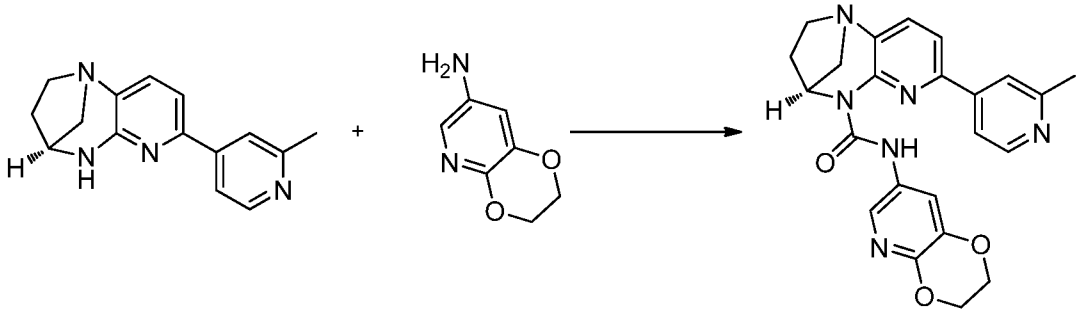


Potassium phosphate (535 mg, 2.53 mmol) and (6-(hydroxymethyl)pyridin-3-yl)boronic acid (232 mg, 1.515 mmol) were added to a stirred solution of (4S)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (400 mg, 1.263 mmol) in mixture of 1-Butanol (6 mL) and water (2.0 mL) at room temperature. De-gassed the mixture with Argon for 10 min then added $Pd_2(dba)_3$ (57.8 mg, 0.063 mmol) and X-phos (60.2 mg, 0.126 mmol). The mixture was heated at 120 C for 20h. Allowed to cool the reaction mixture to room temperature and filtered through a pad of celite, washed with ethyl acetate (10 mLx2), filtrate solvent was removed under reduced pressure to afford crude compound. Above crude was purified by flash column chromatography (silica-gel:100-200 mesh, eluted with 80% ethyl acetate in n-hexane) to afford (4S)-7-(6-(hydroxymethyl)pyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (225 mg, 0.558 mmol, 44.2 % yield) as an off white solid. (TLC: Eluent: 100% ethyl acetate R_f: 0.1), LCMS (*m/z*): 390.35 $(M+H)^+$.

^{1}HNMR(400 MHz, $CDCl_3$): δ 13.73 (s, 1H), 9.54 (d, *J* = 1.3 Hz, 1H), 9.19 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.51 (dd, *J* = 8.2, 2.3 Hz, 1H), 8.44 - 8.20 (m, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.50 - 7.39 (m, 2H), 5.71 (dd, *J* = 6.0, 3.2 Hz, 1H), 4.86 (d, *J* = 2.4 Hz, 2H), 3.67 (s, 1H), 3.46 - 3.13 (m, 3H), 3.03 (dd, *J* = 12.1, 3.3 Hz, 1H), 2.43 - 2.26 (m, 1H), 2.19 - 1.98 (m, 1H).

Example 148

Synthesis of (4S)-N-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-7-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

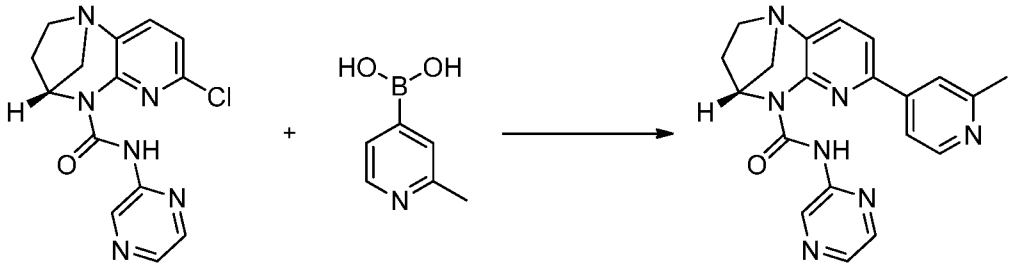


(4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (700 mg, 2.77 mmol) was dissolved in Tetrahydrofuran (THF) (10 mL) stirred under nitrogen at room temp was added triphosgene (412 mg, 1.387 mmol) and stirred for 30 min at RT, to this triethylamine (1.933 mL, 13.87 mmol) and 2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-7-amine (422 mg, 2.77 mmol) were added. The reaction mixture was stirred at 60 °C for 16 hr. Reaction mixture was quenched with 2x15 ml of water and extracted with 2x20 ml of ethyl acetate, organic layer was dried over sodium sulfate and concentrated under reduced pressure to afford crude compound (800 mg).The crude product was purified by column chromatography to afford pure compound (4S)-N-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-7-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (325 mg, 0.732 mmol, 26.4 % yield) as pale yellow solid. R_f value: 0.4,10% Methanol in DCM, LCMS (*m/z*): 413.28 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.81 (s, 1H), 8.58 (d, *J* = 5.2 Hz, 1H), 7.82 (d, *J* = 2.4 Hz, 1H), 7.78 - 7.40 (m, 5H), 5.45 (dd, *J* = 5.9, 3.0 Hz, 1H), 4.46 - 4.31 (m, 2H), 4.29 - 4.16 (m, 2H), 3.19 (d, *J* = 8.8 Hz, 1H), 3.14 - 3.03 (m, 2H), 2.96 (dd, *J* = 12.0, 3.3 Hz, 1H), 2.55 (s, 3H), 2.23 (d, *J* = 7.0 Hz, 1H), 1.93 (dd, *J* = 14.1, 7.1 Hz, 1H).

Example 149

Synthesis of (4*R*)-7-(2-methylpyridin-4-yl)-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopy- rido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

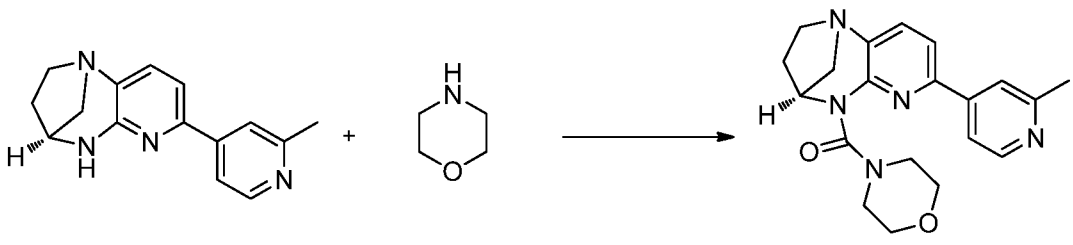


To a de-gassed solution of (4*R*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (700 mg, 2.210 mmol), (2-methylpyridin-4-yl)boronic acid (454 mg, 3.31 mmol) and K_3PO_4 (1825 mg, 6.63 mmol) in 1,4-dioxane (20 mL) and water (5.00 mL) were added X-Phos (211 mg, 0.442 mmol) and $Pd_2(dba)_3$ (202 mg, 0.221 mmol). The reaction mixture was heated at 110 °C for 2 h and allowed to cool to room temperature. Diluted with water (100 mL) and extracted with ethyl acetate (3x100 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product. The crude product was purified by flash column chromatography to afford (4*R*)-7-(2-methylpyridin-4-yl)-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (392 mg, 49.2% yield) as an off-white solid (TLC: eluent; 10 % methanol in dichloromethane, R_f= 0.3), LCMS (*m/z*): 374.18 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.76 (s, 1H), 9.43 (d, *J*=1.53 Hz, 1 H), 8.59 (d, *J*=5.26 Hz, 1 H), 8.46 (dd, *J*=2.63, 1.53 Hz, 1 H), 8.39 (d, *J*=2.41 Hz, 1 H), 8.31 (s, 1 H), 8.16-8.06 (m, 1 H), 7.92-7.78 (m, 1H), 7.78-7.69 (m, 1 H), 5.52 (dd, *J*=5.81, 3.18 Hz, 1 H), 3.37 (m, 1 H), 3.28-3.06 (m, 2H), 2.98 (dd, *J*=11.95, 3.18 Hz, 1 H), 2.61 (s, 3 H), 2.41-2.15 (m, 1 H), 2.05-1.84 (m, 1 H).

Example 150

((4S)-7-(2-methylpyridin-4-yl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-b] [1, 4] diazepine-5(2H)-yl)(Morpholino) methanone

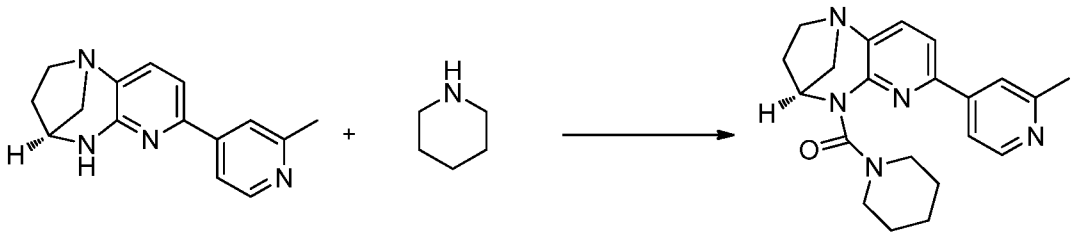


(4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (700 mg, 2.77 mmol) in Tetrahydrofuran (THF) (10 mL) stirred under nitrogen at room temp was added triphosgene (412 mg, 1.387 mmol) and stirred for 30 min at RT, To this triethylamine (1.933 mL, 13.87 mmol) and morpholine (314 mg, 3.61 mmol) were added. The reaction mixture was stirred at 60 °C for 16 hr. Reaction mixture was quenched with 2x15 ml of water and extracted with 2x20 ml of ethyl acetate, organic layer was dried over sodium sulfate and concentrated under reduced pressure to afford crude compound. The crude product was added to a 100-200 silica gel column and was eluted with 4% Methanol in DCM to afford pure compound ((4S)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepin-5(2H)-yl)(morpholino)methanone (270 mg, 0.735 mmol, 26.5 % yield) as pale brown solid (R_f value: 0.4, 10% Methanol in DCM), LCMS (*m/z*): 366.19 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d6) δ 8.52 (d, *J* = 5.2 Hz, 1H), 7.85 - 7.75 (m, 1H), 7.70 (dd, *J* = 5.2, 1.7 Hz, 1H), 7.57 - 7.30 (m, 1H), 4.38 (s, 1H), 3.50 (d, *J* = 72.2 Hz, 8H), 3.23 - 2.95 (m, 1H), 2.89 (dd, *J* = 11.6, 3.2 Hz, 1H), 2.58 - 2.32 (m, 6H), 2.33 - 1.92 (m, 2H).

Example 151

((4S)-7-(2-methylpyridin-4-yl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-b] [1, 4] diazepin-5(2H)-yl)(piperidin-1-yl) methanone



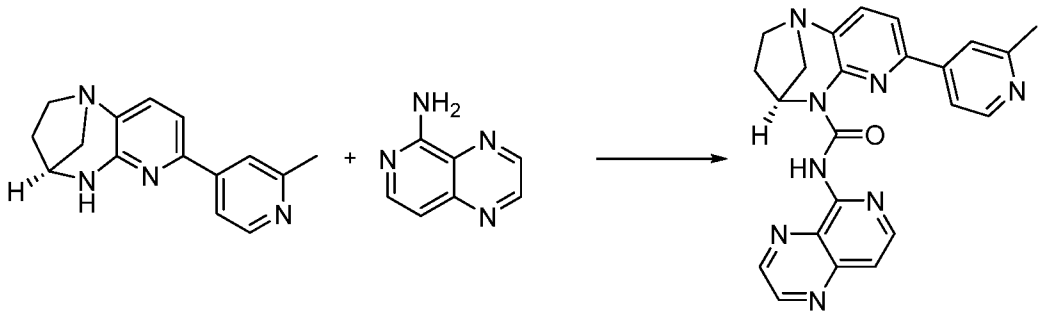
(4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (700 mg, 2.77 mmol) in Tetrahydrofuran (THF) (10 mL) stirred under nitrogen at room temp was added triphosgene (412 mg, 1.387 mmol) and stirred for 30 min at RT. To this triethylamine (1.933 mL, 13.87 mmol) and piperidine (236 mg, 2.77 mmol) were added. The reaction mixture was stirred at 60 °C for 16 hr. Reaction mixture was quenched with 2x15 ml of water and extracted with 2x20 ml of ethyl acetate, organic layer was dried over sodium sulfate and concentrated under reduced pressure to afford crude compound. The crude product was purified by column chromatography to afford pure compound ((4S)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepin-5(2H)-yl)(piperidin-1-yl)methanone (220 mg, 0.583 mmol, 21.03 % yield) as brown solid.(R_f

value: 0.4, 10% Methanol in DCM), LCMS (*m/z*): 364.21 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d6) δ 8.50 (d, *J* = 5.2 Hz, 1H), 7.79 (d, *J* = 1.8 Hz, 1H), 7.74 - 7.62 (m, 1H), 7.51 - 7.30 (m, 2H), 4.33 (t, *J* = 4.2 Hz, 1H), 3.49 (d, *J* = 71.1 Hz, 4H), 3.22 - 2.95 (m, 2H), 2.88 (dd, *J* = 11.6, 3.2 Hz, 1H), 2.61 - 2.35 (m, 6H), 2.24 - 1.94 (m, 1H), 1.55 (s, 5H).

Example 152

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-N-(pyrido[3,4-*b*]pyrazin-5-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

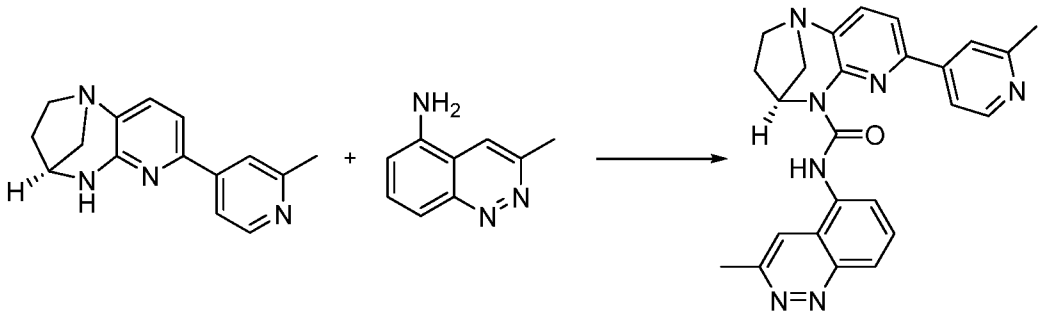


To a solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (600 mg, 2.378 mmol) in THF (30 ml) was added triphosgene (353 mg, 1.189 mmol) at 0 °C and stirred to RT for 1 h. Then pyrido[3,4-*b*]pyrazin-5-amine (452 mg, 3.09 mmol) and triethylamine (1.657 mL, 11.89 mmol) were added sequentially at RT and heated the reaction mixture at 70 °C for 16 h in sealed tube. The reaction mixture was poured in saturated $NaHCO_3$ solution (150 mL) and extracted with ethyl acetate (250 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 DCM as eluent) to afford (4*S*)-7-(2-methylpyridin-4-yl)-N-(pyrido[3,4-*b*]pyrazin-5-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (260 mg, 0.613 mmol, 38% yield) as brown solid (TLC: 5% MeOH in DCM, R_f = 0.3), LCMS (*m/z*): 425.27 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.84 (s, 1 H), 9.11 (d, *J*=1.97 Hz, 1 H), 8.58 (d, *J*=5.70 Hz, 1 H), 8.37 - 8.51 (m, 1 H), 8.19 (d, *J*=1.97 Hz, 1 H), 7.59 - 7.78 (m, 5 H), 5.54-5.50 (m, 1H), 3.22 - 3.33 (m, 1 H), 3.07 - 3.19 (m, 1 H), 3.00 (dd, *J*=11.95, 3.18 Hz, 1 H), 2.50 (dt, *J*=3.67, 1.78 Hz, 1 H), 2.21 - 2.33 (m, 4 H), 1.98 (dt, *J*=13.92, 7.07 Hz, 1 H).

Example 153

Synthesis of (4*S*)-N-(3-methylcinnolin-5-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

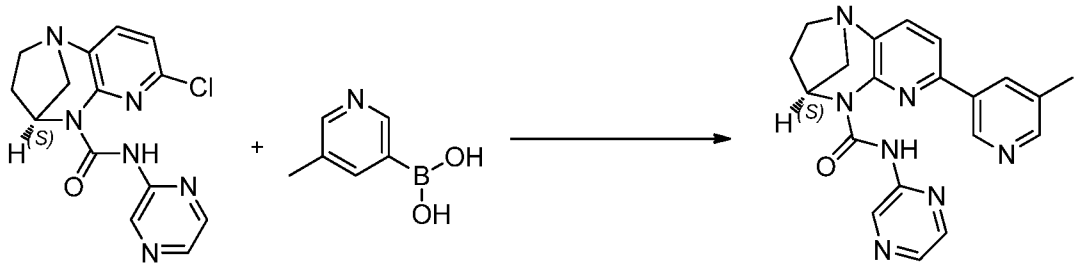


To a solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (600 mg, 2.378 mmol) in THF (30 ml) was added triphosgene (353 mg, 1.189 mmol) at 0 °C and stirred to RT for 1 h. Then 3-methylcinnolin-5-amine (492 mg, 3.09 mmol) and triethylamine (1.657 mL, 11.89 mmol) were added sequentially at RT and heated the reaction mixture at 70 °C for 16 h. The reaction mixture was poured in saturated $NaHCO_3$ solution (150 mL) and extracted with ethyl acetate (2x50 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 DCM as eluent) to afford (4*S*)-N-(3-methylcinnolin-5-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (280 mg, 0.647 mmol, 42% yield) as pale yellow solid (TLC: 5% MeOH in DCM, R_f = 0.25), LCMS (*m/z*): 438.26 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.43 (s, 1 H), 9.11 (s, 1H), 8.49 (d, *J*=5.92 Hz, 1 H), 8.39 (d, *J*=7.45 Hz, 1 H), 8.19 (s, 1H), 7.81 (t, *J*=8.11 Hz, 1 H), 7.65 (d, *J*=7.5 Hz 1 H), 7.35-7.31 (m, 3 H), 5.77 (dd, *J*=5.81, 3.18 Hz, 1 H), 3.41-3.15 (m, 3 H), 2.91 (m, 1 H), 2.30-2.25 (m, 3 H), 2.24 (s, 3 H), 2.10-1.92 (m, 1 H).

Example 154

Synthesis of (4*S*)-7-(5-methylpyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

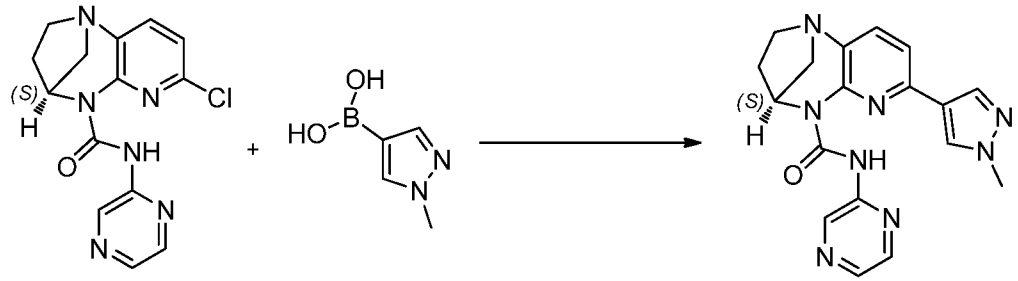


To a solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (600 mg, 1.894 mmol), (5-methylpyridin-3-yl)boronic acid (311 mg, 2.273 mmol) and K_3PO_4 (804 mg, 3.79 mmol) in 1,4-dioxane (12.00 mL), water (4.00 mL) and degassed with argon for 20 min was added X-Phos (90 mg, 0.189 mmol), tris(dibenzylideneacetone)dipalladium(0) (87 mg, 0.095 mmol) again degassed with argon for 10 min. The reaction mixture was stirred at 100 °C for 4 h and cooled to room temperature. The reaction mixture was filtered through celite then the filtrate was diluted with water and extracted with EtOAc (3 X 10mL). The combined organic layers were washed with water, brine solution & dried over sodium sulfate and evaporated to give crude compound (TLC eluent: 5% MeOH in DCM: R_f-0.3; UV active). The crude compound was purified by column chromatography using 100-200 silica gel mesh and eluted with 1 to 3% MeOH/DCM to afford pure (4*S*)-7-(5-methylpyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (356 mg, 0.938 mmol, 49.5 % yield) as off white solid, LCMS (*m/z*): 374.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.81 (s, 1H), 9.57 (d, *J* = 1.4 Hz, 1H), 8.99 (dd, *J* = 2.1, 0.8 Hz, 1H), 8.52 (dd, *J* = 2.0, 0.9 Hz, 1H), 8.47 (m, *J* = 2.2, 1.1 Hz, 1H), 8.32 - 8.28 (m, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 5.71 (dd, *J* = 6.1, 3.2 Hz, 1H), 3.35 - 3.16 (m, 3H), 3.03 (dd, *J* = 12.1, 3.3 Hz, 1H), 2.51 (s, 3H), 2.35 (dddd, *J* = 14.0, 9.9, 6.1, 4.0 Hz, 1H), 2.15 - 2.03 (m, 1H).

Example 155

Synthesis of (4*S*)-7-(1-methyl-1*H*-pyrazol-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-metha nopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

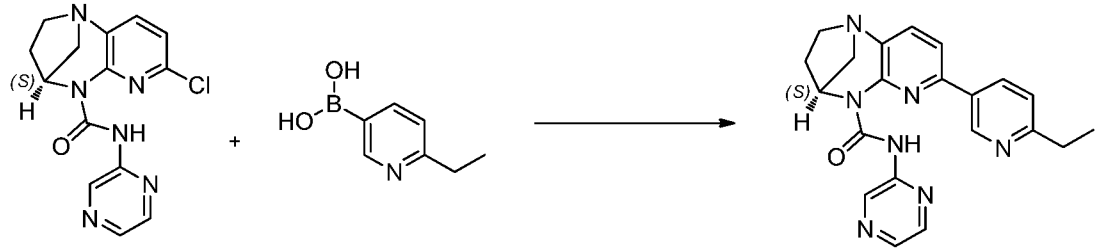


To a solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (600 mg, 1.894 mmol), (1-methyl-1H-pyrazol-4-yl)boronic acid (286 mg, 2.273 mmol) and K_3PO_4 (804 mg, 3.79 mmol) in 1,4-dioxane (12.00 mL), water (4.00 mL) and degassed with Argon for 20 min was added X-Phos (90 mg, 0.189 mmol), tris(dibenzylideneacetone)dipalladium(0) (87 mg, 0.095 mmol) again degassed with argon for 10 min. The reaction mixture was stirred at 100 °C for 4 h and cooled to room temperature. The reaction mixture was filtered through celite then the filtrate was diluted with water and extracted with EtOAc (3 X 10mL). The combined organic layers were washed with water, brine solution, dried over sodium sulfate and evaporated to give crude compound (TLC eluent: 5% MeOH in DCM: R_f-0.3; UV active). The crude compound was purified by column chromatography using 100-200 silica gel mesh and eluted with 1.5-3% MeOH/DCM to afford pure (4*S*)-7-(1-methyl-1H-pyrazol-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (354 mg, 0.963 mmol, 50.9 % yield) as pale yellow solid, LCMS (*m/z*): 363.1 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 14.09 (s, 1H), 9.39 (d, *J* = 1.5 Hz, 1H), 8.51 (d, *J* = 0.8 Hz, 1H), 8.47 (dd, *J* = 2.6, 1.6 Hz, 1H), 8.37 - 8.36 (m, 1H), 8.26 (d, *J* = 0.8 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 5.46 (dd, *J* = 6.0, 3.1 Hz, 1H), 3.92 (s, 3H), 3.22 - 3.13 (m, 1H), 3.12 - 3.02 (m, 2H), 2.94 (dd, *J* = 12.0, 3.3 Hz, 1H), 2.24 (dddd, *J* = 13.6, 9.8, 6.1, 3.8 Hz, 1H), 1.92 (m, *J* = 14.4, 7.4 Hz, 1H).

Example 156

Synthesis of (4*S*)-7-(6-ethylpyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

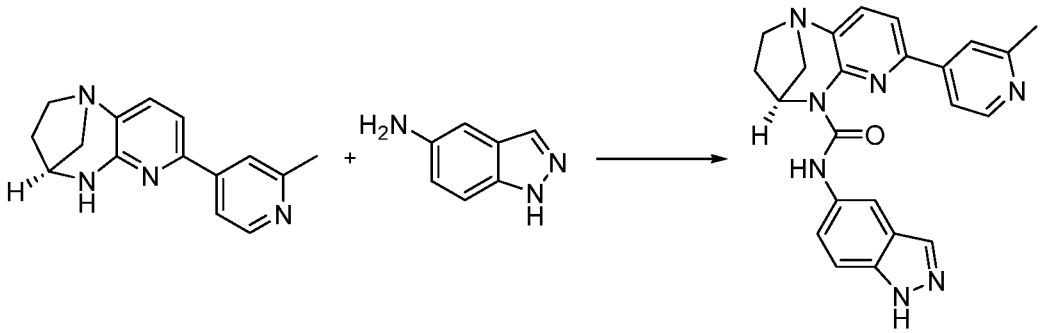


To a solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (600 mg, 1.894 mmol), (6-ethylpyridin-3-yl)boronic acid (343 mg, 2.273 mmol) and K_3PO_4 (804 mg, 3.79 mmol) in 1,4-dioxane (12.00 mL), water (3.00 mL) degassed with argon for 20 min was added X-Phos (90 mg, 0.189 mmol), tris(dibenzylideneacetone)dipalladium(0) (87 mg, 0.095 mmol) and again degassed with argon for 10 min. The reaction mixture was stirred at 100 °C for 4 h and cooled to room temperature. The reaction mixture was filtered through celite then the filtrate was diluted with water and extracted with EtOAc (3 X 10mL). The combined organic layers were washed with water, brine solution, dried over sodium sulfate and evaporated to give crude compound (TLC eluent: 5% MeOH in DCM: R_f-0.3; UV active). The crude compound was purified by column chromatography using 100-200 silica gel mesh and eluted with 1.5-3% MeOH/DCM to afford pure (4*S*)-7-(6-ethylpyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido [2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (354 mg, 0.883 mmol, 46.6 % yield) as off white solid, LCMS (*m/z*): 388.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.77 (s, 1H), 9.54 (d, *J* = 1.5 Hz, 1H), 9.22 - 9.01 (d, 1H), 8.47 (dd, *J* = 2.5 Hz, 1H), 8.35 (d, *J* = 2.4 Hz, 1H), 8.29 (d, *J* = 2.6 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.35 - 7.32 (d, 1H), 5.70 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.39 - 3.13 (m, 3H), 3.02 (dd, *J* = 12.1, 3.3 Hz, 1H), 2.92 (q, *J* = 7.6 Hz, 2H), 2.35 (dddd, *J* = 13.9, 9.9, 6.1, 4.0 Hz, 1H), 2.21 - 1.98 (m, 1H), 1.38 (t, *J* = 7.6 Hz, 3H).

Example 157

Synthesis of (4*S*)-N-(1H-indazol-5-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methano pyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

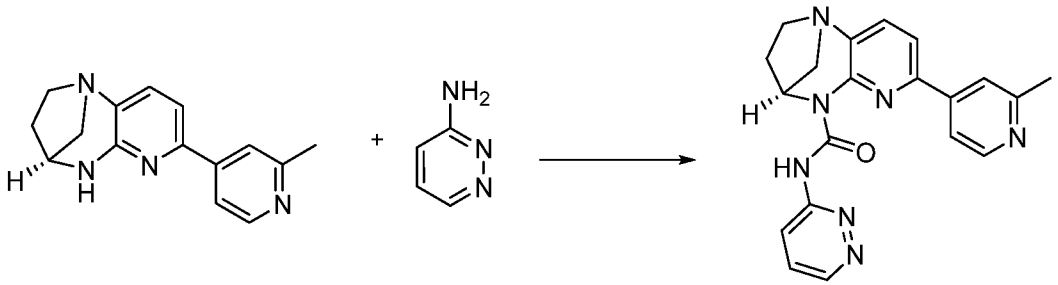


To a solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (600 mg, 2.378 mmol) in THF (30 ml) was added tri-phosgene (353 mg, 1.189 mmol) at 0 °C and stirred to RT for 1 h. Then 1*H*-indazol-5-amine (412 mg, 3.09 mmol) and triethylamine (1.657 mL, 11.89 mmol) were added sequentially at RT. The reaction mixture was heated at 70 °C for 16 h in sealed tube and was poured in saturated $NaHCO_3$ solution (180 mL), extracted with ethyl acetate (3x50 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 prep HPLC (ammonium bicarbonate and Acetonitrile) to afford (4*S*)-N-(1*H*-indazol-5-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido [2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (210 mg, 0.489 mmol, 20.54% yield) as a pale brown solid (TLC: 5% MeOH in DCM, R_f = 0.3), LCMS (*m/z*): 412.27 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.98 (s, 1 H), 12.92 (s, 1 H), 8.65 (d, *J*=5.04 Hz, 1 H), 8.09-7.94 (d, *J*=4.5 Hz, 1 H), 7.58-7.47 (m, 2 H), 7.47-7.41 (m, 2 H), 7.41-7.32 (d, *J*=8.4 Hz , 1 H), 7.32-7.17 (d, *J*=8.3 Hz, 1 H), 5.74 (dd, *J*=5.70, 3.07 Hz, 1 H), 3.37-3.11 (m, 3 H), 3.11-2.86 (m, 1 H), 2.60 (s, 3 H), 2.22 (dt, *J*=14.03, 7.02 Hz, 2 H), 1.99-1.81 (m, 1H).

Example 158

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-*N*-(pyridazin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

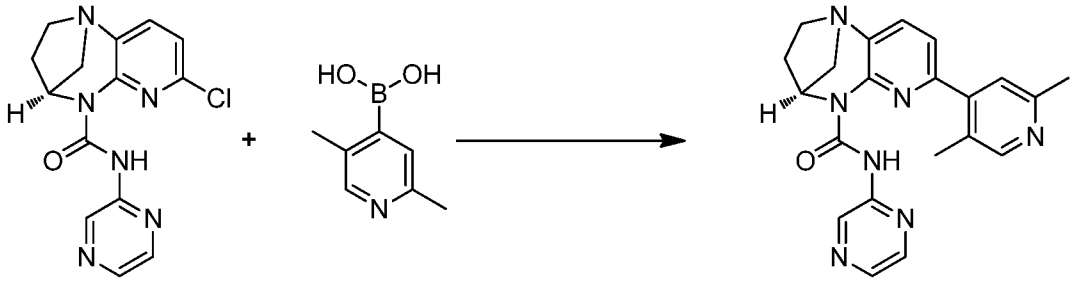


To a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (700 mg, 2.77 mmol) in THF (15 mL) was added triphosgene (412 mg, 1.387 mmol) at 30 °C and stirred for 1h. Then pyridazin-3-amine (792 mg, 8.32 mmol) and triethylamine (1.160 mL, 8.32 mmol) were added at 30 °C and heated the reaction mixture at 75 °C for 16 h. The reaction was allowed to 30 °C and poured in to cold water (30 mL), extracted with DCM (2x35 ml). The combined organic layer was washed with brine, dried over sodium sulfate and solvent was evaporated under reduced pressure to obtain crude product. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, solvent system) and prep HPLC ((10mM Ammonium Bicarbonate (Aq) MP-B: Acetonitrile Column: xbridge C18 (150x30) mm 5µ Method –t%b 0/60,13.5/60,14/100,17/100,17.1/60 Flow: 30 ml/min, Solubility: THF+ACN.+WATER) to afford (4*S*)-7-(2-methylpyridin-4-yl)-*N*-(pyridazin-3-yl)-3,4-dihydro-1,4-methanopyr ido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (270mg, 0.723 mmol, 25.7%) as a pale yellow solid (TLC: R_f: 0.4, 10% MeOH in EtOAc), LCMS (*m/z*): 374.26 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 14.16 (s, 1H), 8.94 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.66 (d, *J* = 5.3 Hz, 1H), 8.48 (dd, *J* = 9.1, 1.5 Hz, 1H), 8.38 - 830 (m, 1H), 8.22 (s, 1H), 7.83 - 7.50 (m, 3H), 5.69 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.41 - 3.16 (m, 3H), 3.03 (dd, *J* = 12.1, 3.3 Hz, 1H), 2.81 (s, 3H), 2.35 (dddd, *J* = 13.9, 10.0, 6.1, 4.0 Hz, 1H), 2.22 - 2.00 (m, 1H).

Example 159

Synthesis of (4*S*)-7-(2,5-dimethylpyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

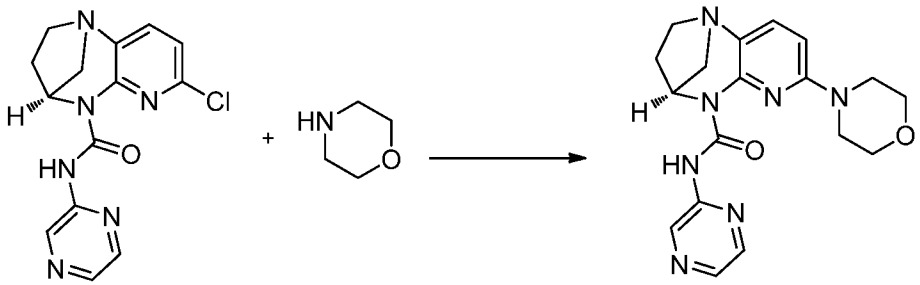


Tripotassium phosphate (804 mg, 3.79 mmol) was added to a stirred solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carbo-xamide (600 mg, 1.894 mmol), 2,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (662 mg, 2.84 mmol) in 1,4-dioxane (10 mL), and water (1.667 mL) at 28 °C. The reaction mixture was degassed for 15 min, was added $Pd_2(dba)_3$ (87 mg, 0.095 mmol), and X-phos (90 mg, 0.189 mmol). The reaction mixture was further degassed for 15 min, and the reaction mixture was stirred for 3 hr at 100 °C. The reaction mixture was cooled to 28 °C and was partitioned between water (10 mL) and EtOAc (25 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude as pink solid (TLC eluting system: 10% Methanol in EtOAc; R_f = 0.3). The crude was purified by column chromatography using (100-200 mesh) silica gel and was eluted with 5-8% methanol in EtOAc to afford pure (4*S*)-7-(2,5-dimethylpyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (337 mg, 0.860 mmol, 45.4 % yield) as off white solid, LCMS (*m/z*): 388.19 $[M+H]^+$.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 13.48 (s, 1H), 9.49 (d, *J* = 1.6 Hz, 1H), 8.46 (s, 1H), 8.34 - 8.10 (m, 2H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.45 (s, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 5.71 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.51 - 3.09 (m, 3H), 3.04 (dd, *J* = 12.1, 3.3 Hz, 1H), 2.63 (s, 3H), 2.43 (s, 3H), 2.40 - 2.27 (m, 1H), 2.20 - 1.96 (m, 1H).

Example 160

Synthesis of (4*S*)-7-morpholino-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

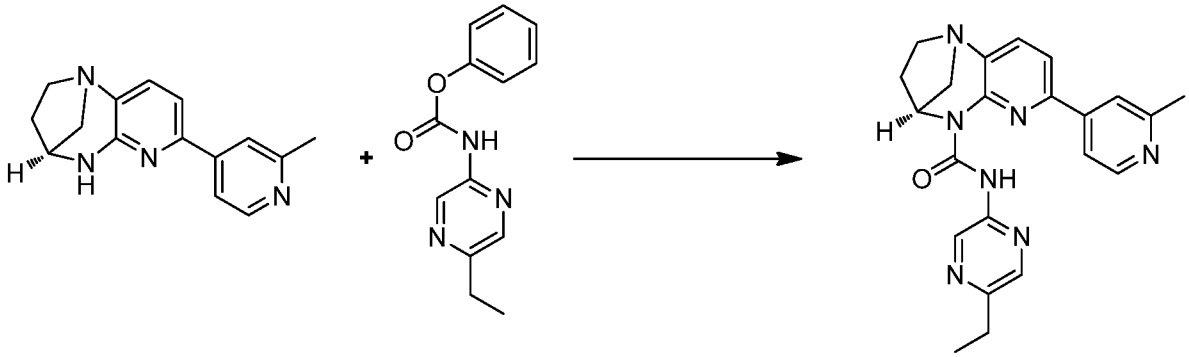


To a degassed solution of (4*S*)-7-chloro-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (600 mg, 1.894 mmol) and morpholine (0.330 mL, 3.79 mmol) in 1,4-dioxane (6 mL) were added Cs_2CO_3 (1234 mg, 3.79 mmol), x-phos (361 mg, 0.758 mmol) and $Pd(OAc)_2$ (85 mg, 0.379 mmol). The reaction mixture was stirred at 110 °C for 16 h. The reaction mixture was poured in to cold water (50 mL) and extracted with ethyl acetate (2x50 mL). The combined organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to obtain the crude product. The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 2% MeOH/DCM) to afford (4*S*)-7-morpholino-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (268 mg, 0.707 mmol, 37.3 % yield) as a pale yellow solid (TLC: R_f: 0.2, neat EtOAc), LCMS (*m/z*): 368 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.41 (s, 1H), 9.53 (d, *J* = 1.5 Hz, 1H), 8.37 - 7.90 (m, 2H), 7.39 (d, *J* = 8.6 Hz, 1H), 6.29 (d, *J* = 8.6 Hz, 1H), 5.62 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.98 - 3.72 (m, 4H), 3.62 - 3.46 (m, 4H), 3.22 (dddd, *J* = 12.2, 8.5, 3.7, 2.2 Hz, 1H), 3.18 - 3.05 (m, 2H), 2.93 (dd, *J* = 11.8, 3.3 Hz, 1H), 2.27 (dd, *J* = 10.1, 4.0 Hz, 1H), 2.01 (d, *J* = 6.9 Hz, 1H).

Example 161

Synthesis of (4*S*)-*N*-(5-ethylpyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

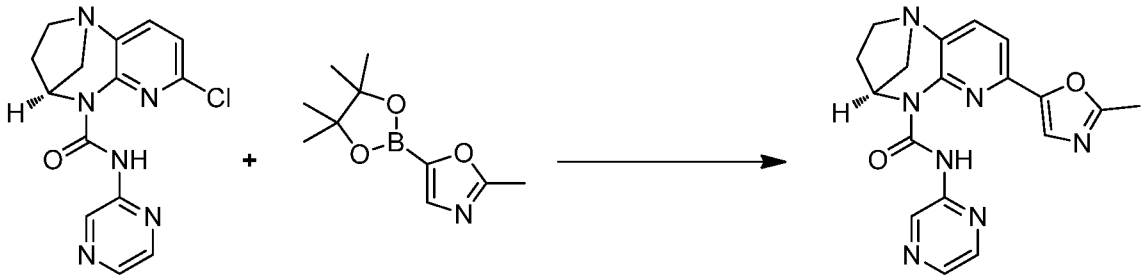


phenyl (5-ethylpyrazin-2-yl)carbamate (1446 mg, 5.94 mmol) and DMAP (726 mg, 5.94 mmol) were added to a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (500 mg, 1.982 mmol) in Tetrahydrofuran (THF) (15 mL) at RT and stirred the reaction mixture at 80 °C for 16 h. Allowed the reaction mixture to RT, diluted with ethyl acetate (2X 30 mL) washed with water (40 mL) and brine (20 mL). The organic layer was separated and dried over sodium sulfate, filtered and concentrated. Residue was purified by column chromatography using silica gel (100-200 mesh) 1% Methanol in DCM as a eluent to get the desired product. Compound was re-crystallized by using ethanol and pentane (4*S*)-N-(5-ethylpyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2H)-carboxamide (245 mg, 0.602 mmol, 30.4 % yield) as a off white Solid.(TLC : 5% Methanol in DCM. R_f: 0.4 UV), LCMS (*m/z*): 402.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.46 (s, 1H), 9.37 (s, 1H), 8.67 (dd, *J* = 5.3, 0.8 Hz, 1H), 8.20 (d, *J* = 0.6 Hz, 1H), 7.98 (ddd, *J* = 5.4, 1.8, 0.7 Hz, 1H), 7.74 - 7.54 (m, 2H), 7.48 (d, *J* = 7.9 Hz, 1H), 5.72 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.37 - 3.17 (m, 1H), 3.03 (dd, *J* = 12.1, 3.3 Hz, 1H), 2.80 (q, *J* = 7.6 Hz, 2H), 2.62 (s, 3H), 2.35 (dddd, *J* = 14.0, 9.9, 6.1, 4.1 Hz, 1H), 2.22 - 1.92 (m, 3H), 1.32 (t, *J* = 7.6 Hz, 3H).

Example 162

Synthesis of (4*S*)-7-(2-methyloxazol-5-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide:

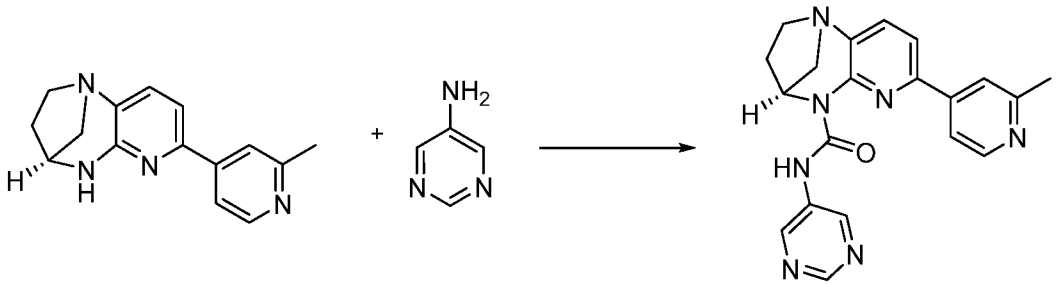


Tripotassium phosphate (804 mg, 3.79 mmol) was added to a stirred solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (600 mg, 1.894 mmol), 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (475 mg, 2.273 mmol) in 1,4-dioxane (10 mL) , and water (1.667 mL) at 28 °C. The reaction mixture was degassed for 15 min, was added $Pd_2(dba)_3$ (87 mg, 0.095 mmol), and X-phos (90 mg, 0.189 mmol). The reaction mixture was further degassed for 15 min, and the reaction mixture was stirred for 3 hr at 100 °C. The reaction mixture was cooled to 28 °C and was partitioned between water (10 mL) and EtOAc (25 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude as brown solid (TLC eluent: 10% MeOH in EtOAc; R_f = 0.2; UV active). The crude was purified by prep HPLC to give the desired product (4*S*)-7-(2-methyloxazol-5-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (153 mg, 0.418 mmol, 22.04 % yield) as white solid, LCMS (*m/z*): 364.32 $[M+H]^+$.

^{1}H NMR ($CDCl_3$,400 MHz): δ 13.72 (s, 1H), 9.54 (d, *J* = 1.5 Hz, 1H), 8.44 - 8.17 (m, 2H), 8.07 (s, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.30 - 7.13 (m, 1H), 5.67 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.45 - 3.08 (m, 3H), 3.01 (dd, *J* = 12.1, 3.3 Hz, 1H), 2.58 (s, 3H), 2.34 (dddd, *J* = 14.1, 9.9, 6.1, 4.2 Hz, 1H), 2.22 - 1.95 (m, 1H).

Example 163

Synthesis of (4S)-7-(2-methylpyridin-4-yl)-N-(pyrimidin-5-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

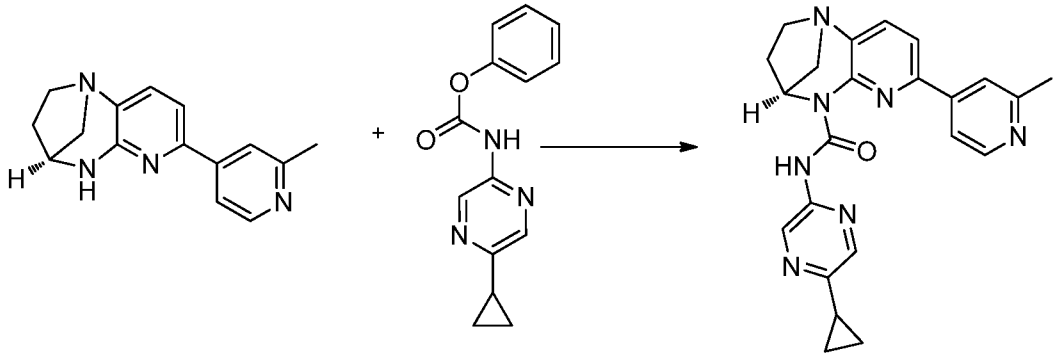


To a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (700 mg, 2.77 mmol) in THF (15 mL) was added triphosgene (823 mg, 2.77 mmol) at 30 °C and stirred for 1h. Then pyrimidin-5-amine (317 mg, 3.33 mmol) and TEA (0.387 mL, 2.77 mmol) were added at 30 °C and heated the reaction mixture at 75 °C for 16 h. The reaction was allowed to 30 °C and poured in to cold water (30 mL), extracted with DCM (2x50 ml). The combined organic layer was washed with brine, dried over sodium sulfate and solvent was evaporated under reduced pressure to obtain crude product. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, 3% MeOH in Ethyl acetate) to afford (4*S*)-7-(2-methylpyridin-4-yl)-*N*-(pyrimidin-5-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4] diazepine-5(2*H*)-carboxamide (275 mg, 0.737 mmol, 32%) as a pale yellow solid (TLC: R_f: 0.4, 10% MeOH in EtOAc), LCMS (*m/z*): 374.22 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.25 (s, 1H), 9.01 (s, 2H), 8.94 (s, 1H), 8.68 (d, *J* = 0.8 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.55 (dt, *J* = 1.6, 0.8 Hz, 1H), 7.47 (ddd, *J* = 5.2, 1.7, 0.7 Hz, 1H), 7.39 (s, 1H), 5.69 (dd, *J* = 5.9, 3.2 Hz, 1H), 3.33 - 3.13 (m, 3H), 3.04 (dd, *J* = 12.2, 3.2 Hz, 1H), 2.69 (s, 3H), 2.36 (dd, *J* = 10.1, 4.1 Hz, 1H), 2.15 - 2.04 (m, 1H).

Example 164

Synthesis of (4*S*)-*N*-(5-cyclopropylpyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

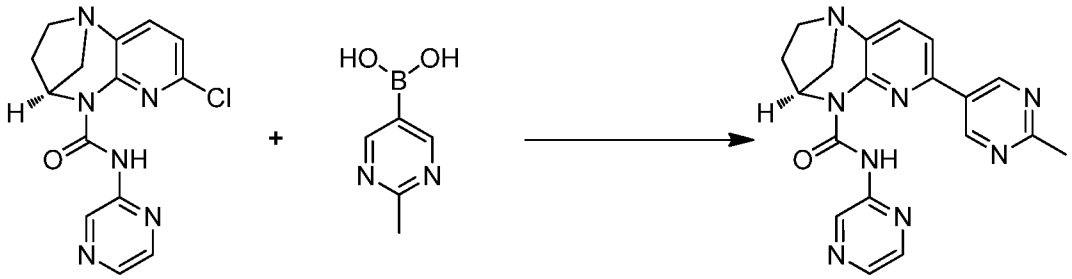


Phenyl (5-cyclopropylpyrazin-2-yl)carbamate (1214 mg, 4.76 mmol) and DMAP (581 mg, 4.76 mmol) were added to a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (400 mg, 1.585 mmol) in THF (15 mL) at RT and stirred the reaction mixture at 80 °C for 16 h. Allowed the reaction mixture to RT, diluted with Ethyl acetate (2X30 mL) washed with water (20 mL) and brine (20 mL). The organic layer was separated and dried over sodium sulfate, filtered and concentrated. Residue was purified by column chromatography using silica gel (100-200 mesh), 2% methanol in DCM as the eluent to give the desired product. Compound was re-crystallized by ethanol and pentane to afforded (4*S*)-*N*-(5-cyclopropylpyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (260 mg, 0.623 mmol, 45.2%) as an off white solid, (R_f: 0.4, TLC: 5% methanol in DCM), LCMS (*m/z*): 414.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.59 (s, 1H), 9.35 (d, *J* = 1.5 Hz, 1H), 8.62 (dd, *J* = 5.3, 0.8 Hz, 1H), 8.20 (d, *J* = 1.5 Hz, 1H), 8.07 (q, *J* = 0.9 Hz, 1H), 7.71 - 7.59 (m, 2H), 7.48 (d, *J* = 8.0 Hz, 1H), 5.71 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.37 - 3.10 (m, 3H), 3.02 (dd, *J* = 12.1, 3.3 Hz, 1H), 2.74 (s, 3H), 2.34 (dd, *J* = 10.1, 4.1 Hz, 1H), 2.07 (d, *J* = 8.0 Hz, 1H), 1.21 - 0.66 (m, 5H).

Example 165

Synthesis of (4*S*)-7-(2-methylpyrimidin-5-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

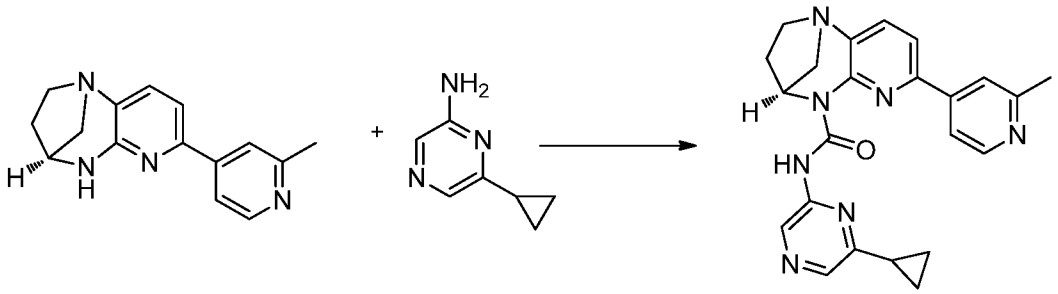


Tripotassium phosphate (804 mg, 3.79 mmol) was added to a stirred solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (600 mg, 1.894 mmol), (2-methylpyrimidin-5-yl)boronic acid (314 mg, 2.273 mmol) in 1,4-dioxane (12 mL) and water (2.000 mL). The reaction mixture was degassed for 15 min X-phos (90 mg, 0.189 mmol), and $Pd_2(dba)_3$ (87 mg, 0.095 mmol) were added. The reaction mixture was further degassed for 15 min, and was stirred at 100 °C for 6 hr. The reaction mixture was cooled to 28 °C and was partitioned between water (30 mL) and EtOAc (70 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered. The filtrate was evaporated to get crude (TLC eluent: 5% MeOH in $CHCl_3$: R_f = 0.2; UV active). The crude compound was purified by 100-200 silica gel by eluting 20% MeOH in ethyl acetate to afford (4*S*)-7-(2-methylpyrimidin-5-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (353 mg, 0.938 mmol, 49.5 % yield) as pale yellow solid, LCMS (*m/z*): 375.19 $[M+H]^+$.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 13.57 (s, 1H), 9.53 (d, *J* = 1.5 Hz, 1H), 9.33 (s, 2H), 8.38 (d, *J* = 1.6 Hz, 1H), 8.30 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 5.71 (dd, *J* = 5.9, 3.2 Hz, 1H), 3.41 - 3.11 (m, 3H), 3.04 (dd, *J* = 12.1, 3.3 Hz, 1H), 2.84 (s, 3H), 2.36 (dddd, *J* = 14.0, 9.9, 6.1, 4.1 Hz, 1H), 2.11 (d, *J* = 7.1 Hz, 1H).

Example 166

Synthesis of (4*S*)-*N*-(6-cyclopropylpyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

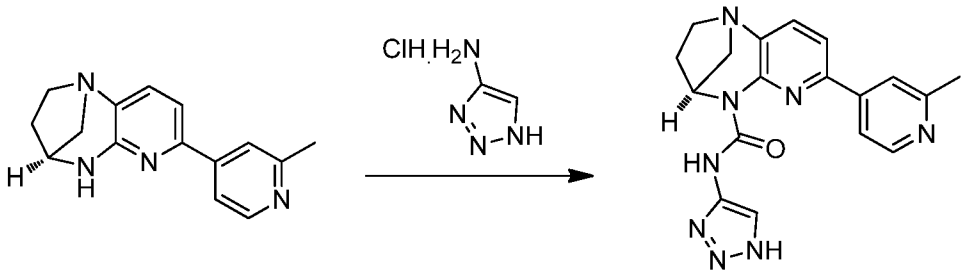


To a stirred solution of 7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (600 mg, 0.198 mmol) in THF (30 mL) was added triphosgene (353mg, 0.099 mmol) at RT and stirred for 30 min. Then 6-cyclopropylpyrazin-2-amine (321 mg, 2.378 mmol) and Et_3N (1.657mL, 0.991 mmol) were added at RT. The reaction mixture was stirred at 65 °C for 16 h. The Reaction mixture was poured in $NaHCO_3$ solution and extracted with CH_2Cl_2 (3x50 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 2% MeOH in CH_2Cl_2) to afford (4*S*)-*N*-(6-cyclopropylpyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (208 mg, 0.479 mmol, 30.2% yield) as a white solid (TLC: 10% MeOH in CH_2Cl_2, R_f: 0.5), LCMS (*m/z*): 414.29 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.11 (s, 1 H), 9.29 (s, 1 H), 8.80 (d, *J*=5.26 Hz, 1 H), 8.57 (d, *J*=4.60 Hz, 1 H), 8.15 (s, 1 H), 7.97 - 7.67 (m, 1 H), 7.64 (d, *J*=7.89 Hz, 1 H), 7.59 - 7.42 (m, 1 H), 5.72 (dd, *J*=5.92, 3.29 Hz, 1 H), 3.34 - 3.10 (m, 3 H), 3.39 - 3.09 (m, 1 H), 2.62 (s, 3 H), 2.44 - 2.18 (m, 1 H), 2.17 – 1.97 (m, 1 H), 1.13 – 0.93 (m, 4 H).

Example 167

(4*S*)-7-(2-methylpyridin-4-yl)-N-(1*H*-1,2,3-triazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

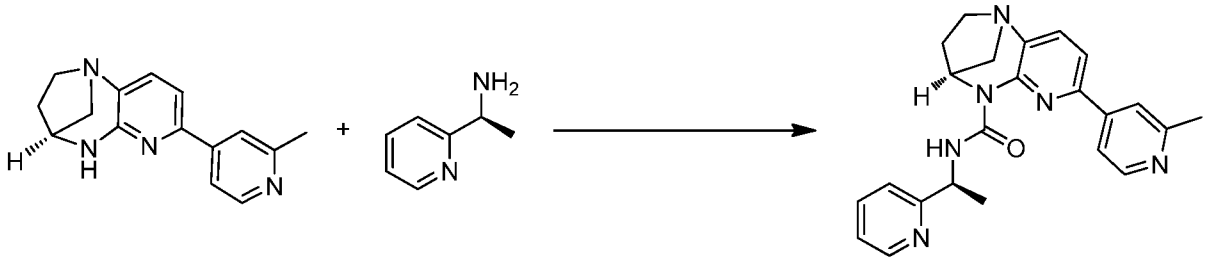


Triphosgene (0.588 g, 1.982 mmol) was added to a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine(0.5g, 1.982 mmol) in tetrahydrofuran (50 mL) at 0 °C, followed by addition of triethylamine (0.829 mL, 5.94 mmol) and 1*H*-1,2,3-triazol-4-amine hydrochloride (0.597 g, 4.95 mmol) at 0 °C. The reaction mixture was stirred for 48h at 70 °C. The reaction mixture was cooled to 28 °C and was partitioned between water (50 mL) and EtOAc (50 mL). The organic layer was separated and was washed with water and brine. The Organic layer was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford crude yellow solid (TLC eluent: 10% MeOH in EtOAc: R_f = 0.35; UV active). The crude compound was purified by 100-200 silica gel by eluting with 5% MeOH in ethyl acetate to afford (4*S*)-7-(2-methylpyridin-4-yl)-N-(1*H*-1,2,3-triazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]dia-zepine-5(2*H*)-carbo-xamide (0.21g, 0.558 mmol, 28.2 % yield) as light yellow solid, LCMS (*m/z*): 363.24 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-*d6*): δ 14.58 (s, 1H), 13.55 (s, 1H), 8.58 (d, *J* = 5.2 Hz, 1H), 7.94 (s, 2H), 7.84 - 7.75 (m, 2H), 7.71 (d, *J* = 8.0 Hz, 1H), 5.47 (dd, *J* = 5.8, 3.0 Hz, 1H), 3.27 - 3.16 (m, 1H), 3.16 - 3.01 (m, 2H), 2.97 (dd, *J* = 12.0, 3.2 Hz, 1H), 2.64 (s, 3H), 2.24 (dddd, *J* = 13.7, 9.8, 5.9, 3.7 Hz, 1H), 1.94 (dddd, *J* = 14.5, 8.7, 4.5 Hz, 1H).

Example 168

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-N-((*S*)-1-(pyridin-2-yl)ethyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

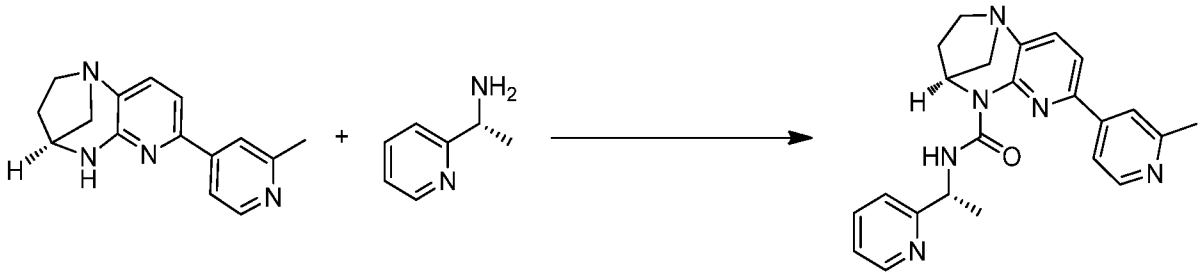


To a solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (500 mg, 1.982 mmol) in tetrahydrofuran (10 mL) was added triphosgene (588 mg, 1.982 mmol) and triethylamine (1.657 mL, 11.89 mmol). The reaction mixture was stirred at room temp for 30 min, was added (*S*)-1-(pyridin-2-yl)ethanamine and stirred at 70 °C for 16 h. The solvent was removed under reduced pressure and diluted with water and extracted with ethyl acetate (2 x 50 mL). The combined organic layer was washed with water (30mL), saturated brine solution. Organic layer was dried over anhydrous sodium sulfate, filtered and filtrate was evaporated to give the crude product as a brown solid**.** (TLC eluent: 10 % Methanol in dichloromethane, R_f = 0.3; UV active). The crude compound was purified by column chromatography (neutral alumina) product was eluted with 55-60% ethyl acetate in hexane. Collected fractions evaporated under reduce pressure to afford pure (4*S*)-7-(2-methylpyridin-4-yl)-*N*-((*S*)-1-(pyridin-2-yl)ethyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (277 mg, 0.684 mmol, 34.5 % yield) as Off-White solid, LCMS (*m/z*): 401.2 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.09 (d, *J* = 7.6 Hz, 1H), 8.56 (dd, *J* = 5.3, 0.8 Hz, 1H), 8.36 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.78 (dt, *J* = 1.4, 0.7 Hz, 1H), 7.63 - 7.60 (m, 2H), 7.59 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.31 - 7.29 (m, 2H), 7.11 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 5.64 (dd, *J* = 6.0, 3.2 Hz, 1H), 5.32 - 5.23 (m, 1H), 3.27 - 3.06 (m, 3H), 2.95 (dd, *J* = 12.0, 3.3 Hz, 1H), 2.60 (s, 3H), 2.22 (dd, *J* = 10.0, 4.0 Hz, 1H), 2.03 - 1.89 (m, 1H), 1.62 (d, *J* = 6.9 Hz, 3H).

Example 169

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-N-((*R*)-1-(pyridin-2-yl)ethyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

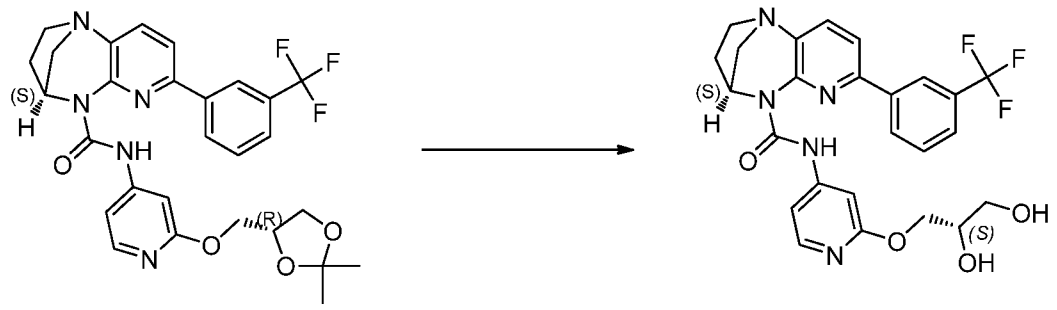


To a solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (500 mg, 1.982 mmol) in tetrahydrofuran (10 mL) was added triphosgene (588 mg, 1.982 mmol) and triethylamine (1.657 mL, 11.89 mmol) at room temperature. The reaction mixture was stirred at room temp for 30 min, was added (*R*)-1-(pyridin-2-yl) ethanamine (726 mg, 5.94 mmol) and stirred at 70 °C for 16 h. The solvent was removed under reduced pressure, diluted with water (15 mL), and was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with water (30mL), saturated brine solution then dried over anhydrous sodium sulfate. The solution was filtered and concentrated to give the crude product as a brown solid**.** (TLC eluent: 10 % methanol in dichloromethane, R_f = 0.3; UV active). The crude compound was purified by column chromatography (neutral alumina) product was eluted with 55-60% ethyl acetate in hexane to afford (4*S*)-7-(2-methylpyridin-4-yl)-*N*-((*R*)-1-(pyridin-2-yl)ethyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (240 mg, 0.595 mmol, 30.0 % yield) as yellow gum, LCMS (*m/z*): 401.2 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.06 (d, *J* = 7.5 Hz, 1H), 8.57 (dd, *J* = 5.2, 0.8 Hz, 1H), 8.43 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.78 (q, *J* = 0.9 Hz, 1H), 7.63 (ddd, *J* = 5.1, 1.9, 0.7 Hz, 1H), 7.61 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.36 - 7.30 (m, 2H), 7.13 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 5.62 (dd, *J* = 5.9, 3.2 Hz, 1H), 5.27 (p, *J* = 7.0 Hz, 1H), 3.30 - 3.21 (m, 1H), 3.18 (ddd, *J* = 12.2, 9.9, 6.9 Hz, 1H), 3.06 (dt, *J* = 12.0, 2.1 Hz, 1H), 2.92 (dd, *J* = 11.9, 3.3 Hz, 1H), 2.60 (s, 3H), 2.27 (dddd, *J* = 13.9, 9.9, 6.1, 3.9 Hz, 1H), 2.07 (dt, *J* = 14.0, 7.5 Hz, 1H), 1.62 (d, *J* = 6.9 Hz, 3H).

Example 170

Synthesis of (4*S*)-*N*-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

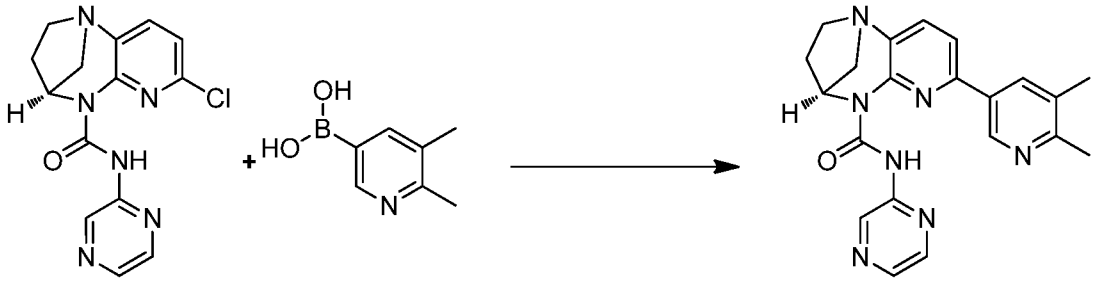


To a solution of (4*S*)-N-(2-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (600 mg, 1.080 mmol), was added a solution of 4.0 M Hydrochloric acid in Dioxane (10 mL, 1.080 mmol) at 0°C. The reaction mixture was stirred at room-temp for 3 h. The reaction mixture was evaporated the solvent and neutralized with sodium bicarbonate and extracted with EtOAc (3 X 50mL), the combined organic layer was washed with brine solution and dried over sodium sulfate and evaporated to give 350 mg of crude compound. The crude product was added to a silica gel column and was eluted with 2% MeOH/DCM Collected fractions were evaporated to give (4S)-N-(2-((S)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methano pyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (253mg, 0.487 mmol, 45.1% yield) as an off white solid. (TLC: R_f: 0.2, 5% MeOH/DCM), LCMS (*m/z*): 516.3 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.02 (s, 1 H), 8.08 - 8.33 (m, 2 H), 7.77 - 8.00 (m, 3 H), 7.76 - 7.59 (m, 2 H), 7.11 (d, *J*=1.53 Hz, 1 H), 6.80 (dd, *J*=5.70, 1.75 Hz, 1 H), 5.47 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.85 (d, *J*=5.26 Hz, 1 H), 4.58 (t, *J*=5.70 Hz, 2 H), 4.23 (dd, *J*=10.85, 4.49 Hz, 1 H), 4.12 (dd, *J*=10.74, 6.14 Hz, 1H), 3.78 (dq, *J*=10.69, 5.43 Hz, 1 H), 3.53 - 3.32 (m, 1 H), 3.25 - 3.05 (m, 3 H), 2.97 (dd, *J*=11.95, 3.18 Hz, 2 H), 2.37 - 2.18 (m, 1 H), 2.03 – 1.86 (m, 1 H).

Example 171

Synthesis of (4*S*)-7-(5,6-dimethylpyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

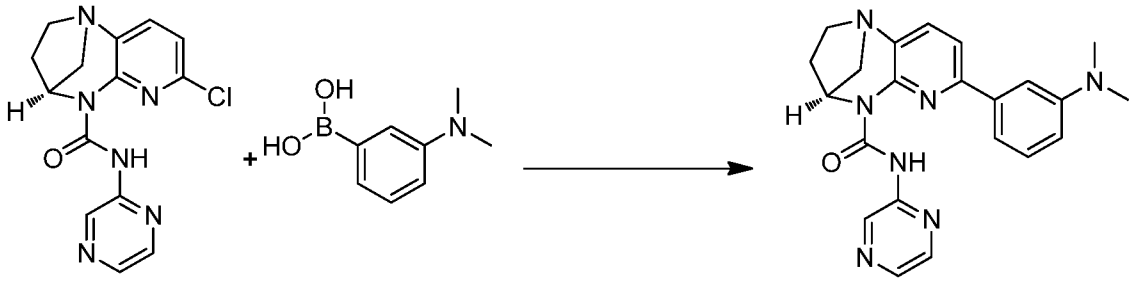


Tripotassium phosphate (804 mg, 3.79 mmol) was added to a stirred solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carbox-amide (600 mg, 1.894 mmol), (5,6-dimethylpyridin-3-yl)boronic acid (343 mg, 2.273 mmol) in 1,4-dioxane (10 mL), and water (1.667 mL) at 28 °C. The reaction mixture was degassed for 15 min, was added $Pd_2(dba)_3$ (87 mg, 0.095 mmol), and X-phos (90 mg, 0.189 mmol). The reaction mixture was further degassed for 15 min, and the reaction mixture was stirred for 3 hr at 100 °C. The reaction mixture was cooled to 28 °C and was partitioned between water (10 mL) and EtOAc (25 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude as brown solid (TLC eluent: 10% MeOH in EtOAc; R_f= 0.3; UV active). The crude was purified by column chromatography using (100-200 mesh) silica gel and was eluted with 5-10% MeOH in EtOAc to afford pure (4*S*)-7-(5,6-dimethylpyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (420 mg, 1.078 mmol, 56.9 % yield) as off white solid, LCMS (*m/z*): 388.19 $[M+H]^+$.

^{1}H NMR ($CDCl_3$,400 MHz): δ 13.85 (s, 1H), 9.57 (d, *J* = 1.4 Hz, 1H), 8.86 (d, *J* = 2.3 Hz, 1H), 8.54 - 8.34 (m, 1H), 8.34 - 8.19 (m, 2H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 5.71 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.45 - 3.08 (m, 3H), 3.02 (dd, *J* = 12.1, 3.3 Hz, 1H), 2.59 (s, 3H), 2.47 (d, *J* = 0.8 Hz, 3H), 2.35 (dddd, *J* = 14.0, 10.0, 6.1, 4.0 Hz, 1H), 2.22 - 2.00 (m, 1H).

Example 172

Synthesis of (4*S*)-7-(3-(dimethylamino)phenyl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide:



Tripotassium phosphate (804 mg, 3.79 mmol) was added to a stirred solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carbox amide (600 mg, 1.894 mmol), (3-(dimethyl amino)phenyl)boronic acid (469 mg, 2.84 mmol) in 1,4-dioxane (10 mL), and water (1.667 mL) at 28 °C. The reaction mixture was degassed for 15 min, was added $Pd_2(dba)_3$ (87 mg, 0.095 mmol), and X-phos (90 mg, 0.189 mmol). The reaction mixture was further degassed for 15 min, and the reaction mixture was stirred for 3 hr at 100 °C. The reaction mixture was cooled to 28 °C and was partitioned between water (10 mL) and EtOAc (25 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and the filtrate was evaporated to give crude as brown solid (TLC eluent: 10% MeOH in EtOAc; R_f = 0.5; UV active). The crude was purified by using column chromatography using (100-200 mesh) silica gel and was eluted with 0-5% MeOH in EtOAc to afford pure (4*S*)-7-(3-(dimethylamino)phenyl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (273 mg, 0.660 mmol, 34.8 % yield) as off white solid, LCMS (*m/z*): 402.26 $[M+H]^+$.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.66 (s, 1H), 9.39 (s, 1H), 8.35 (q, *J* = 2.7 Hz, 2H), 7.81 - 7.42 (m, 1H), 7.44 - 7.19 (m, 4H), 6.92 - 6.77 (m, 1H), 5.53 (dd, *J* = 5.9, 3.1 Hz, 1H), 3.29 - 3.00 (m, 3H), 2.98 (s, 7H), 2.25 (ddd, *J* = 13.8, 10.3, 5.4 Hz, 1H), 1.96 (dt, *J* = 14.9, 7.8 Hz, 1H).

Example 173

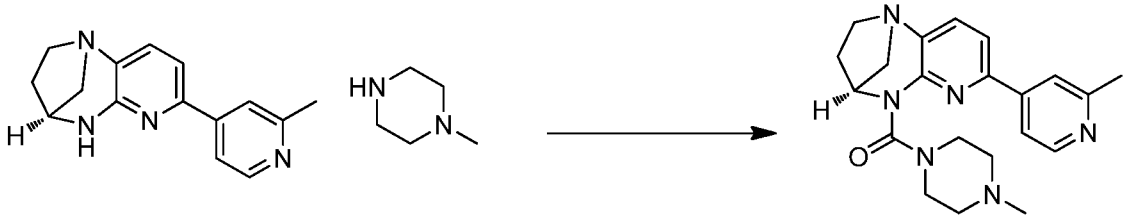
Synthesis of ((4S)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepin-5(2H)-yl)(pyrrolidin-1-yl)methanone

(4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.982 mmol) in Tetrahydrofuran (THF) (10 mL) stirred under nitrogen at room temperature was added triphosgene (294 mg, 0.991 mmol) and stirred for 30 min at RT. After 30 minutes triethylamine (1.381 mL, 9.91 mmol) and pyrrolidine (183 mg, 2.58 mmol) were added. The reaction mixture was stirred at 60 °C for 16 hr. Reaction mixture was quenched with 2x15 ml of water and extracted with 2x20 ml of ethyl acetate, organic layer was washed with water and dried over sodium sulfate and concentrated under reduced pressure to afford crude compound. The crude product was purified by 100-200 silica gel column and was eluted with 4% Methanol in DCM to afford pure compound ((4S)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepin-5(2H)-yl)(pyrrolidin-1-yl)methanone (350 mg, 0.993 mmol, 50.1 % yield) as yellow solid (R_f value: 0.4, 10% Methanol in DCM), LCMS (*m/z*): 350.25 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d6) δ 8.49 (dd, *J* = 5.2, 0.8 Hz, 1H), 7.75 (dt, *J* = 1.4, 0.7 Hz, 1H), 7.67 (ddd, *J* = 5.4, 1.7, 0.7 Hz, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 4.42 (d, *J* = 3.8 Hz, 1H), 3.44-3.24 (m, 4H), 3.14 (ddt, *J* = 12.0, 6.1, 3.3 Hz, 1H), 3.03 (dd, *J* = 13.8, 5.2 Hz, 2H), 2.89 (dd, *J* = 11.6, 3.3 Hz, 1H), 2.55 (s, 3H), 2.23 - 2.01 (m, 2H), 1.99- 1.86 (m, 4H).

Example 174

Synthesis of (4-methylpiperazin-1-yl)((4S)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepin-5(2H)-yl)methanone



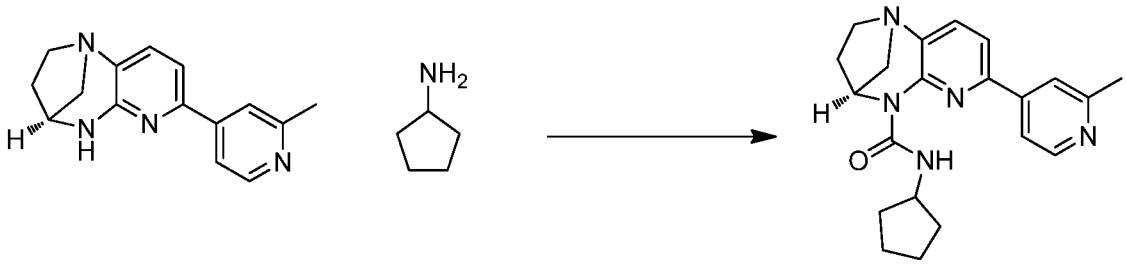
(4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine

(500 mg, 1.982 mmol) in Tetrahydrofuran (THF) (10 mL) stirred under nitrogen at room temp was added triphosgene (294 mg, 0.991 mmol) and stirred for 30 min at room temperature. After 30 minutes triethylamine (1.381 mL, 9.91 mmol) and 1-methylpiperazine (258 mg, 2.58 mmol) were added. The reaction mixture was stirred at 60 °C for 16 hr. The reaction mixture was allowed to room temperature and quenched with 2x15 ml of water and extracted with 2x20 ml of ethyl acetate, organic layer was washed with water and dried over sodium sulfate and concentrated under reduced pressure to afford crude compound 500 mg. The crude product was purified by column chromatography to afford pure compound (4-methylpiperazin-1-yl)((4S)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepin-5(2H)-yl)methanone (280 mg, 0.725 mmol, 36.6 % yield) as yellow solid, (R_f value: 0.25,10% Methanol in DCM), LCMS (*m/z*): 379.1 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d6) δ 8.51 (dd, *J* = 5.3, 0.8 Hz, 1H), 7.83 - 7.72 (m, 1H), 7.70 (ddd, *J* = 5.2, 1.7, 0.7 Hz, 1H), 7.53 - 7.36 (m, 2H), 4.36 (d, *J* = 3.9 Hz, 1H), 3.60 (s, 1H), 3.42 (s, 2H), 3.22 - 2.90 (m, 3H), 2.61 - 2.44 (m, 9H), 2.15 (d, *J* = 10.0 Hz, 5H).

Example 175

Synthesis of (4S)-N-cyclopentyl-7-(2-methylpyridin-4-yl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-b] [1, 4] diazepine-5(2H)-carboxamide



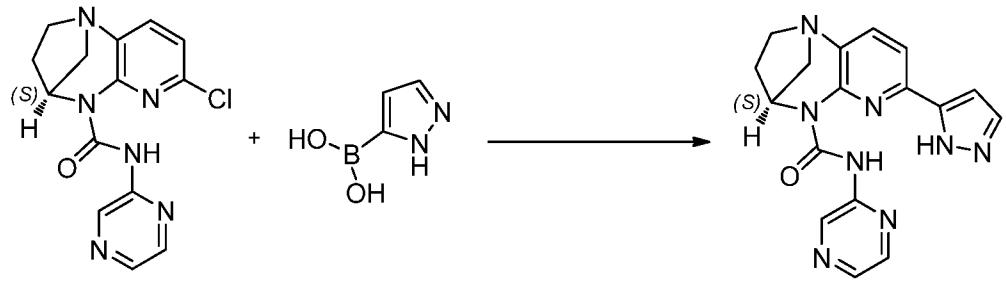
(4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.982 mmol) in Tetrahydrofuran (THF) (10 mL) stirred under nitrogen at room temp was added triphosgene (294 mg, 0.991 mmol) and stirred for 30 min at RT. To this triethylamine (1.381 mL, 9.91 mmol) and cyclopentanamine (219 mg, 2.58 mmol) were added. The reaction mixture was stirred at 60 °C for 16 hr. Reaction mixture was quenched with 2x15 ml of water and extracted with 2x20 ml of ethyl acetate, organic layer was washed with water and dried over sodium sulfate and concentrated under reduced pressure to afford crude compound 500 mg. The crude product was purified by column chromatography to afford pure compound (4S)-N-cyclopentyl-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (275 mg, 0.727

mmol, 36.7 % yield) as yellow solid, (R_f value: 0.4,10% Methanol in DCM), LCMS (*m/z*): 364.29$(M+H)^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.30 (d, *J*=6.58 Hz, 1 H), 8.56 (d, *J*=5.04 Hz, 1 H), 7.67 - 7.52 (m, 4 H), 5.41 (dd, *J*=5.81, 2.96 Hz, 1 H), 4.14 - 4.06 (m, 1 H), 3.21 - 3.02 (m, 2 H), 2.99 - 2.85 (m, 2 H), 2.54 (s, 3 H), 2.17 (dd, *J*=9.76, 3.84 Hz, 1 H), 2.03 – 1.79 (m, 3 H), 1.64 - 1.43 (m, 6 H).

Example 176

Synthesis of (4*S*)-N-(pyrazin-2-yl)-7-(1H-pyrazol-5-yl)-3,4-dihydro-1,4-methanopy - rido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



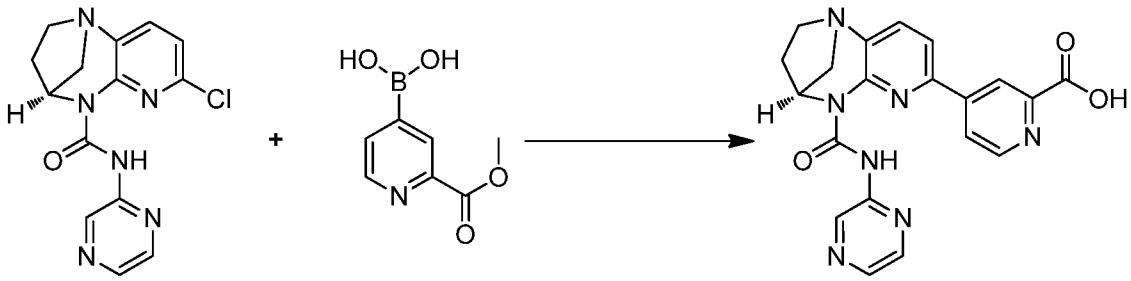
To a solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (300 mg, 0.947 mmol), (1*H*-pyrazol-5-yl)boronic acid (127 mg, 1.137 mmol) and K_3PO_4 (402 mg, 1.894 mmol) in 1,4-dioxane (9 mL), water (3 mL) degassed with argon for 20 min was added X-phos (45.2 mg, 0.095 mmol), tris(dibenzylideneacetone)dipalladium(0) (43.4 mg, 0.047 mmol) again degassed with argon for 10 min. The reaction mixture was stirred at 100 °C for 4 h and cooled to room temperature. The reaction mixture was filtered through celite then the filtrate was diluted with water and extracted with EtOAc (3 X 10 mL). The combined organic layers were washed with water, brine solution, dried over sodium sulfate and evaporated to give crude compound (TLC eluent: 5% MeOH in DCM: R_f-0.3; UV active). The crude compound was purified by column chromatography using 100-200 silica gel mesh and eluted with 2-3% MeOH/DCM to afford pure (4*S*)-N-(pyrazin-2-yl)-7-(1*H*-pyrazol-5-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (100 mg, 0.280 mmol, 29.5 % yield) as pale yellow solid, LCMS (*m/z*): 349.2 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 14.58 (s, 1H), 12.8 - 11.0 (br, 1H), 9.50 (d, J = 1.5 Hz, 1H), 8.41 (dd, J = 2.6, 1.5 Hz, 1H), 8.34 (d, J = 2.6 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.41 (d, J = 7.6 Hz, 1H), 6.97 (d, J = 17.7 Hz, 1H), 5.63 (dd, J = 6.0, 3.2 Hz, 1H), 3.33 - 3.14 (m, 3H), 3.03 (dd, J = 12.1, 3.3 Hz, 1H), 2.35 (dddd, J = 14.0, 9.9,

6.1, 4.1 Hz, 1H), 2.17 - 2.02 (m, 1H).

Example 177

Synthesis of 4-((4*S*)-5-(pyrazin-2-ylcarbamoyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepin-7-yl)picolinic acid

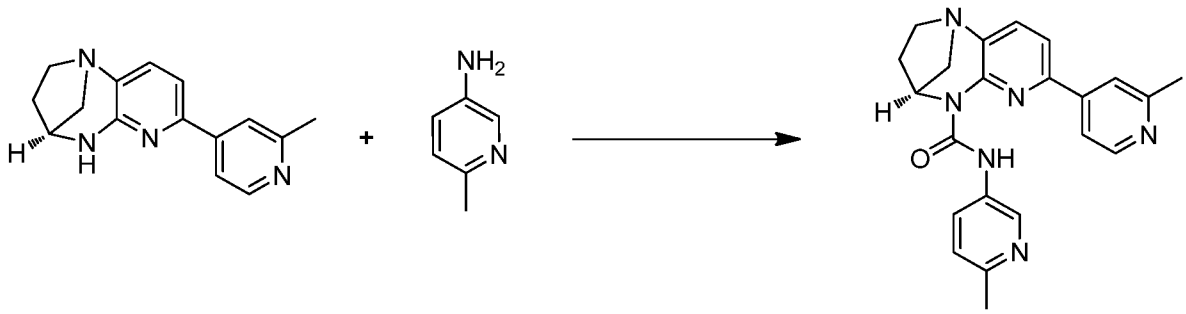


Tripotassium phosphate (6.03 g, 28.4 mmol) was added to a stirred solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (3 g, 9.47 mmol), methyl 4-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)picolinate (3.02 g, 11.37 mmol) in 1,4-dioxane (25 mL), and water (4.17 mL). The reaction mixture was degassed for 15 min, $Pd_2(dba)_3$ (0.434 g, 0.474 mmol) and X-phos (0.452 g, 0.947 mmol) were added. The reaction mixture was further degassed for 15 min, and was stirred at 100 °C for 24 hr. The reaction mixture was cooled to 28 °C and was partitioned between water (50 mL) and EtOAc (200 mL). Aqueous layer neutralized with saturated citric acid solution, precipitated solid was filtered and dried. The crude solid was triturated with methanol and water to afford 4-((4*S*)-5-(pyrazin-2-ylcarbamoyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepin-7-yl)picolinic acid (272 mg, 0.667 mmol, 7.04 % yield) as an off white solid.(TLC eluent: 20% MeOH in DCM : R_f : 0.1 ; UV active), LCMS (*m/z*): 404.1 $[M+H]^+$.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.66 (s, 1H), 9.37 (d, *J* = 0.8 Hz, 1H), 8.87 (d, *J* = 4.8 Hz, 1H), 8.62 (s, 1H), 8.42 (s, 1H), 8.38-8.34 (dd, *J* = 8.4, 2.4 Hz, 2H), 7.887 (d, *J* = 8 Hz, 1H), 7.762 (d, *J* = 8.4 Hz, 1H) 5.53-5.51 (dd, *J* = 5.6, 2.8 Hz, 1H), 3.31 - 3.23 (m, 1H), 3.15-3.09 (m, 2H), 3.08-2.97 (dd, *J* = 12, 2.8 Hz, 1H), 2.28-2.24 (m, 1H), 2.02-1.97 (m, 1H).

Example 178

Synthesis of (4*S*)-*N*-(6-methylpyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-meth anopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

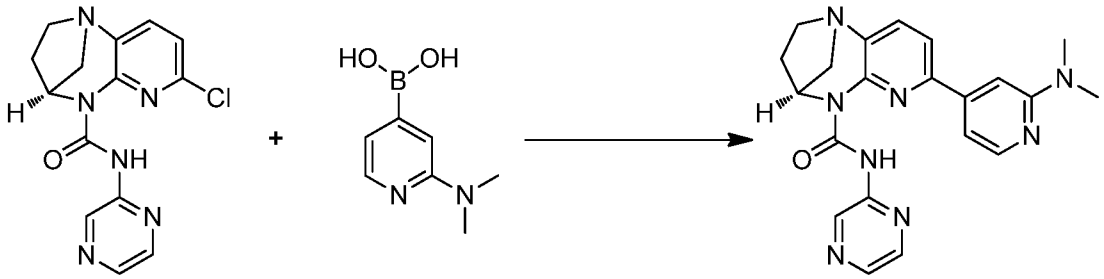


To a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (400 mg, 1.585 mmol) in THF (15 mL) was added triphosgene (282 mg, 0.951 mmol) at 30 °C and stirred for 1 h. Then Et_3N (1.105 mL, 7.93 mmol) and 6-methylpyridin-3-amine (257 mg, 2.378 mmol) were added at 30 °C and heated the reaction mixture at 65 °C for 16h. The reaction mixture was poured in to cold water (50 ml) and extracted with DCM (2x 50 ml). The combined organic layer was washed with water, brine, dried over sodium sulfate and solvent evaporated under reduced pressure to obtain crude product. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 0-15% MeOH in DCM) to afford (4S)-N-(6-methylpyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-meth anopyrid o[2,3-b][1,4]diazepine-5(2H)-carboxamide (320 mg, 0.829 mmol, 52% yield) as an off-white solid (TLC: 4% MeOH in DCM, R_f: 0.35), LCMS (*m/z*): 387.25 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.94 (s, 1 H), 8.66 (d, *J*=5.26 Hz, 1 H), 8.56 (d, *J*=2.63 Hz, 1 H), 8.00 (dd, *J*=8.44, 2.74 Hz, 1 H), 7.63 (d, *J*=8.14 Hz, 1 H), 7.57 (s, 1 H), 7.50 (d, *J*=5.35 Hz, 1 H), 7.25 - 7.38 (m, 1 H), 7.13 (d, *J*=8.55 Hz, 1 H), 5.70 (dd, *J*=5.92, 3.29 Hz, 1 H), 3.10 - 3.35 (m, 3 H), 3.02 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.58 (s, 3 H), 2.48 (s, 3 H) 2.03 - 2.22 (m, 1 H) 2.34 (dddd, *J*=14.03, 9.87, 5.92, 4.17 Hz, 1 H).

Example 179

Synthesis of (4*S*)-7-(2-(dimethylamino)pyridin-4-yl)-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-meth anopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

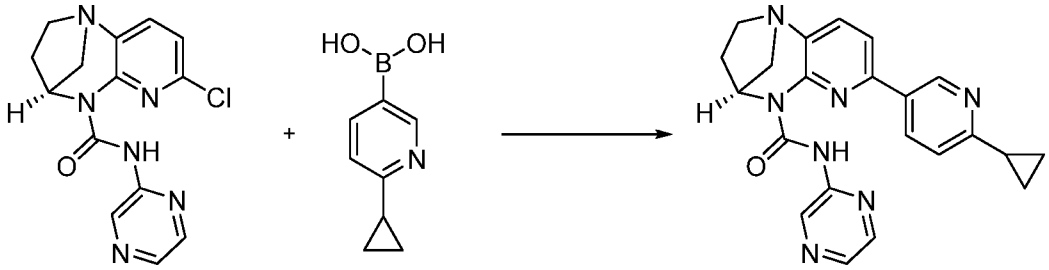


To a degassed solution of (4*S*)-7-chloro-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (300 mg, 0.947 mmol) K_3PO_4 (603 mg, 2.84 mmol) in1,4-dioxane (30 mL) and water (0.3 mL) were added x-phos (45.2 mg, 0.095 mmol) and palladium(II) acetate (10.63 mg, 0.047 mmol). Then the reaction mixture was heated at 120 °C for 12h. The solvent was evaporated under reduced pressure and extracted with DCM (2x 40 ml). The combined organic layer was washed with water, brine, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to obtain crude product. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 3% MeOH in DCM) to afford (4*S*)-7-(2-(dimethylamino)pyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido [2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (210 mg, 0.496 mmol, 52.3 % yield) as an off white solid (TLC: 10% MeOH in EtOAc, R_f: 0.2), LCMS (*m/z*): 403.31 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.56 (s, 1 H), 9.54 (s, 1 H), 8.25 - 8.11 (m, 3 H), 7.62 (m, *J*=7.89 Hz, 1 H), 7.41 (d, *J*=7.89 Hz, 1 H), 7.19 - 7.01 (m, 2 H), 5.72 (dd, *J*=5.81, 3.18 Hz, 1 H), 3.31 - 3.14 (m, 9 H), 3.02 (dd, *J*=12.17, 3.18 Hz, 1 H), 2.50 - 2.23 (m, 1 H), 2.10 (d, *J*=7.02 Hz, 1 H).

Example 180

Synthesis of (4S)-7-(6-cyclopropylpyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

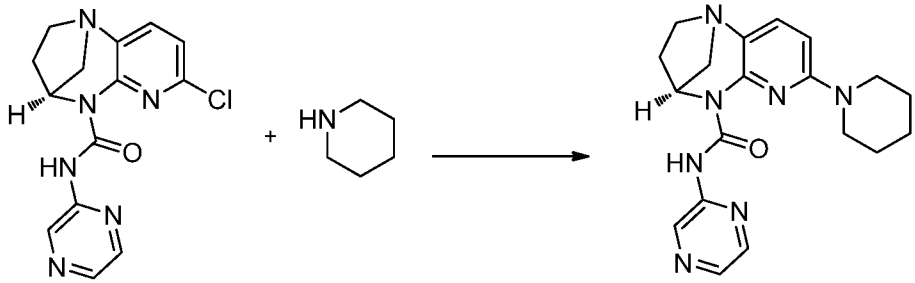


Potassium phosphate (402 mg, 1.894 mmol) and (6-cyclopropylpyridin-3-yl)boronic acid (185 mg, 1.137 mmol) were added to a stirred solution of (4S)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (300 mg, 0.947 mmol) in a mixture of 1-Butanol (6 mL) and Water (2.0 mL) at RT. Purged with Argon for 30 min, then added $Pd_2(dba)_3$ (43.4 mg, 0.047 mmol) and x-phos (45.2 mg, 0.095 mmol)) stirred the reaction mixture at 120 C for 3h. Allowed the reaction mixture to RT, diluted with ethyl acetate (100 mL) washed with water (30 mL) and brine (40 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (silica-gel: 100-200 mesh, 80% Ethyl acetate in petroleum ether as an eluent). The recovered material was re-crystallized by using Ethanol and pentane to afford (4S)-7-(6-cyclopropylpyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (130 mg, 0.322 mmol, 34.0 % yield) as an off white solid (TLC Eluent: 100% Ethyl acetate, R_f: 0.2), LCMS (*m/z*): 400.25 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.79 (s, 1H), 9.53 (d, *J* = 1.5 Hz, 1H), 9.01 (dd, *J* = 2.4, 0.8 Hz, 1H), 8.42 - 8.22 (m, 3H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.45 - 7.19 (m, 2H), 5.70 (dd, *J* = 5.9, 3.2 Hz, 1H), 3.34 - 3.16 (m, 3H), 3.02 (dd, *J* = 12.1, 3.3 Hz, 1H), 2.34 (dd, *J* = 10.1, 4.1 Hz, 1H), 2.19 - 2.02 (m, 2H), 1.20 - 0.96 (m, 4H).

Example 181

Synthesis of (4*S*)-7-(piperidin-1-yl)-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide .



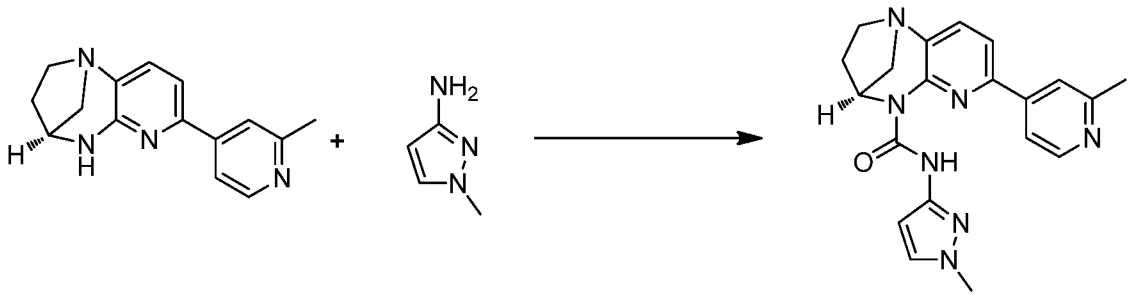
To a degassed solution of (4*S*)-7-chloro-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (600 mg, 1.894 mmol) and piperidine (0.375 mL, 3.79 mmol) in 1,4-dioxane (10 mL) were added Cs_2CO_3 (1852 mg, 5.68 mmol), x-phos (361 mg, 0.758 mmol) and $Pd(OAc)_2$ (85 mg, 0.379 mmol). The reaction mixture was stirred at 100 °C for 16 h and poured it in to cold water (20 mL), extracted with ethyl acetate (2x50 mL). The combined organic layer was dried over

anhydrous sodium sulfate and concentrated under reduced pressure to obtain the crude product. The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 5% methanol in DCM) to obtain (4*S*)-7-(piperidin-1-yl)-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (284 mg, 0.762 mmol, 40.2 % yield) as a pale yellow solid (TLC: R_f: 0.2, neat EtOAc), LCMS (*m/z*): 366.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.51 (s, 1H), 9.52 (d, *J* = 1.5 Hz, 1H), 8.29 - 8.19 (m, 1H), 8.18 (s, 1H), 7.33 (d, *J* = 8.6 Hz, 1H), 6.29 (d, *J* = 8.6 Hz, 1H), 5.61 (dd, *J* = 6.1, 3.3 Hz, 1H), 3.55 (t, *J* = 4.9 Hz, 4H), 3.22 (dddd, *J* = 12.2, 8.6, 3.7, 2.3 Hz, 1H), 3.16 - 3.07 (m, 2H), 2.90 (dd, *J* = 11.8, 3.3 Hz, 1H), 2.34 - 2.22 (m, 1H), 2.00 (dddd, *J* = 14.1, 8.7, 6.8, 2.0 Hz, 1H), 1.78 - 1.64 (m, 6H).

Example 182

Synthesis of (4*S*)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

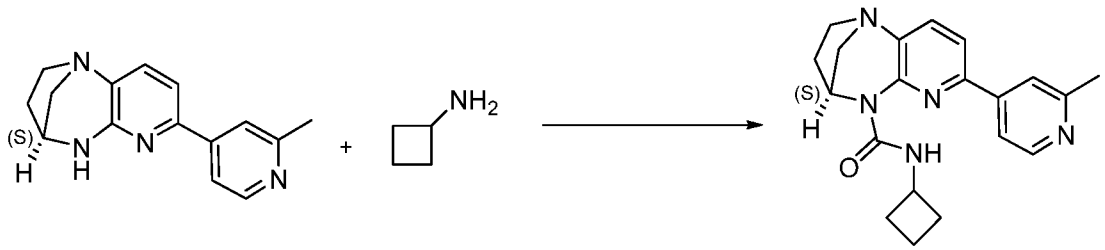


To a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (200 mg, 0.793 mmol), Et_3N (0.331 mL, 2.378 mmol) in THF (10 mL) was added triphosgene (118 mg, 0.396 mmol) at 25 °C and stirred the reaction mixture for 30 minutes at RT. Then 1-methyl-1*H*-pyrazol-3-amine (231 mg, 2.378 mmol) in THF (2ml) was added dropwise. The reaction mixture was stirred at 65 °C for 16 h. The organic solvent was evaporated in vacuo and the crude was diluted with DCM (20ml). The organic layer was washed with water (5 mL), saturated brine (5 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo to obtain the crude product. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 2% MeOH in DCM) to afford (4*S*)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (185 mg, 0.490 mmol, 61.8% yield) as a white solid (TLC: 5% MeOH in DCM, R_f: 0.5), LCMS (*m/z*): 376.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.37 (s, 1 H), 8.61 (d, *J*=5.26 Hz, 1 H), 8.05-7.83 (m, 1 H), 7.68-7.55 (m, 2 H), 7.43 (d, *J*=7.89 Hz, 1 H), 7.35-7.17 (m, 1 H), 6.63 (d, *J*=2.19 Hz, 1 H), 5.69 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.84 (s, 3 H), 3.34-3.10 (m, 3 H), 3.00 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.75 (s, 3 H), 2.32 (dddd, *J*=14.03, 9.92, 5.97, 4.06 Hz, 1 H) 2.21 – 1.99 (m, 1 H).

Example 183

Synthesis of (4*S*)-N-cyclobutyl-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methano-pyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

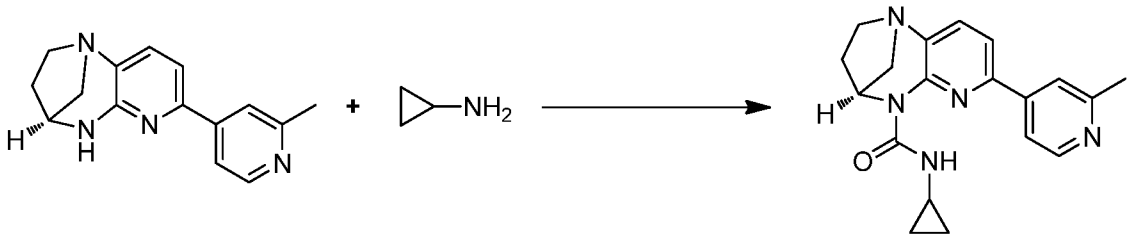


To a solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (400 mg, 1.585 mmol), triethylamine (1.105 mL, 7.93 mmol) and triphosgene (282 mg, 0.951 mmol) in tetrahydrofuran (20 mL) stirred under nitrogen at room temp for 30 min was added a solution of cyclobutanamine (225 mg, 3.17 mmol) in THF (5mL). The reaction mixture was stirred at 65 °C for 16 h and cooled to room temperature. The reaction mixture was poured in to ice water and extracted with EtOAc (3 X 15mL). The combined organic layers were washed with water, brine solution, dried over sodium sulfate and evaporated to give crude compound (TLC eluent: 5% MeOH in DCM: R_f-0.3; UV active). The crude compound was purified by Grace reverse phase column and eluted with 30% (0.1% HCOOH in Water)/MeOH to get (4*S*)-N-cyclobutyl-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (369 mg, 1.053 mmol, 66.4 % yield) as pale yellow solid, LCMS (*m/z*): 350.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.76 - 10.60 (m, 1H), 8.61 (dd, J = 5.3, 0.8 Hz, 1H), 7.60 (dt, J = 1.6, 0.7 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.49 (ddd, J = 5.3, 1.7, 0.7 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 5.62 (dd, J = 6.0, 3.2 Hz, 1H), 4.52 - 4.36 (m, 1H), 3.28 - 3.13 (m, 2H), 3.07 (dt, J = 11.9, 2.1 Hz, 1H), 2.94 (dd, J = 12.0, 3.3 Hz, 1H), 2.65 (s, 3H), 2.51 - 2.39 (m, 2H), 2.26 (dddd, J = 13.9, 10.0, 6.1, 4.1 Hz, 1H), 2.08 - 1.90 (m, 3H), 1.84 - 1.72 (m, 2H).

Example 184

Synthesis of (4*S*)-N-cyclopropyl-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

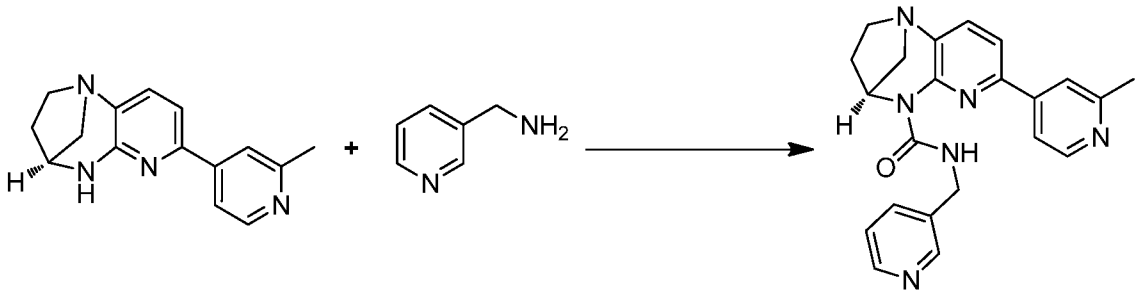


Triphosgene (706 mg, 2.378 mmol) was added to a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (600 mg, 2.378 mmol), and TEA (1.657 mL, 11.89 mmol) in tetrahydrofuran (25 mL) at 0 °C. The reaction mixture was stirred for 1hr and was added cyclopropanamine (272 mg, 4.76 mmol), and was stirred for 16 hr at 60 °C. The reaction mixture was cooled to 28 °C and was partitioned between water (10 mL) and EtOAc (25 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford crude yellow solid (TLC eluent: 10% MeOH in EtOAc: R_f-0.2; UV active). The crude was purified by column chromatography using (100-200 mesh) silica gel and was eluted with 10% MeOH in EtOAc to afford pure (4*S*)-N-cyclopropyl-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (218 mg, 0.638 mmol, 26.8 % yield) as yellow solid, LCMS (*m/z*): 336.24 $[M+H]^+$.

^{1}H NMR ($CDCl_3$,400 MHz): δ 10.59 (s, 1H), 8.60 (d, *J* = 5.4 Hz, 1H), 7.68 - 7.50 (m, 2H), 7.42 (dd, *J* = 5.2, 1.7 Hz, 1H), 7.38 - 7.21 (m, 1H), 5.66 (dd, *J* = 5.9, 3.2 Hz, 1H), 3.36 - 3.12 (m, 2H), 3.07 (dt, *J* = 12.0, 2.1 Hz, 1H), 3.01 - 2.82 (m, 2H), 2.66 (s, 3H), 2.27 (dddd, *J* = 13.8, 9.9, 6.0, 4.0 Hz, 1H), 2.02 (dt, *J* = 14.6, 7.3 Hz, 1H), 0.91 - 0.79 (m, 2H), 0.69 - 0.51 (m, 2H).

Example 185

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-N-(pyridin-3-ylmethyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

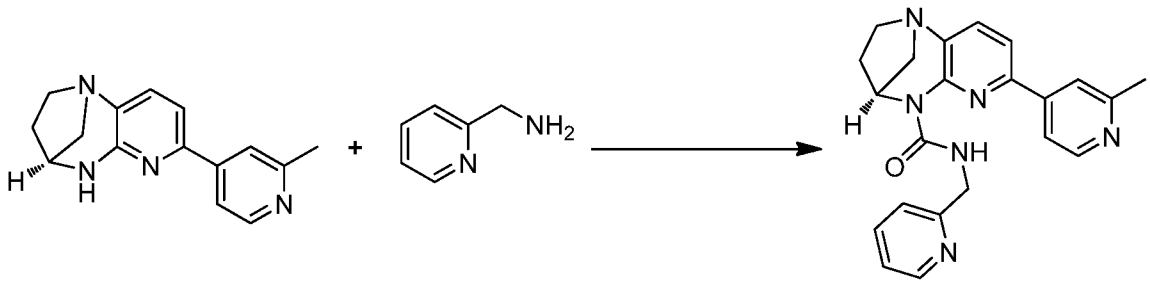


Triphosgene (706 mg, 2.378 mmol) was added to a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (600 mg, 2.378 mmol), and TEA (1.657 mL, 11.89 mmol) in tetrahydrofuran (30 mL) at 0 °C. The reaction mixture was stirred for 1hr and was added pyridin-3-ylmethanamine (514 mg, 4.76 mmol), and was stirred for 16 hr at 60 °C. The reaction mixture was cooled to 28 °C and was partitioned between water (10 mL) and EtOAc (25 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford crude yellow solid (TLC eluent: 10% MeOH in EtOAc: R_f = 0.2; UV active). The crude compound was purified by reverse phase column (Column: C18, 40µm) and eluted with 20% (0.1%HCOOH&Water)/MeOH to afford pure (4*S*)-7-(2-methylpyridin-4-yl)-N-(pyridin-3-ylmethyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (193 mg, 0.498 mmol, 20.93 % yield) as yellow solid, LCMS (*m/z*): 387.32 $[M+H]^+$.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.89 (t, *J* = 5.7 Hz, 1H), 8.75 - 8.60 (m, 1H), 8.56 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.40 (d, *J* = 5.3 Hz, 1H), 7.72 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.44 - 7.21 (m, 3H), 7.15 (dd, *J* = 5.3, 1.8 Hz, 1H), 5.66 (dd, *J* = 5.9, 3.2 Hz, 1H), 4.63 (d, *J* = 5.4 Hz, 2H), 3.37 - 3.15 (m, 2H), 3.11 (dt, *J* = 12.2, 2.1 Hz, 1H), 2.98 (dd, *J* = 12.0, 3.3 Hz, 1H), 2.49 (s, 3H), 2.39 - 2.23 (m, 1H), 2.05 (dt, *J* = 14.6, 7.8 Hz, 1H).

Example 186

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-N-(pyridin-3-ylmethyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

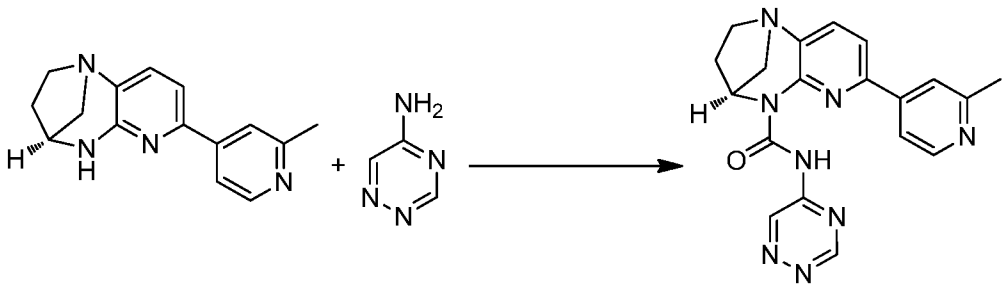


Triphosgene (706 mg, 2.378 mmol) was added to a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (600 mg, 2.378 mmol), and TEA (1.657 mL, 11.89 mmol) in tetrahydrofuran (25 mL) at 0 °C. The reaction mixture was stirred for 1hr and was added pyridin-2-ylmethanamine (514 mg, 4.76 mmol), and was stirred for 16 hr at 60 °C. The reaction mixture was cooled to 28 °C and was partitioned between water (10 mL) and EtOAc (25 mL). EtOAc layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford crude as yellow solid (TLC eluent: 10% MeOH in EtOAc: R_f = 0.2; UV active). The crude compound was purified by reverse phase column (Column: C18, 40µm) and eluted with 20% (0.1%HCOOH&water)/MeOH to afford pure (4*S*)-7-(2-methylpyridin-4-yl)-N-(pyridin-2-ylmethyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (190 mg, 0.492 mmol, 20.67 % yield) as off-white solid, LCMS (*m/z*): 387.22 $[M+H]^+$.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.04 (t, *J* = 5.4 Hz, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 8.40 (dt, *J* = 4.7, 1.5 Hz, 1H), 7.64 (td, *J* = 7.7, 1.9 Hz, 1H), 7.60 - 7.49 (m, 2H), 7.44 (dd, *J* = 5.3, 1.7 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.33 - 7.22 (m, 1H), 7.22 - 7.10 (m, 1H), 5.68 (dd, *J* = 6.0, 3.2 Hz, 1H), 4.78 (d, *J* = 5.0 Hz, 2H), 3.34 - 3.04 (m, 3H), 2.97 (dd, *J* = 12.0, 3.3 Hz, 1H), 2.49 (s, 3H), 2.28 (dddd, *J* = 13.8, 10.0, 5.9, 4.0 Hz, 1H), 2.06 (dt, *J* = 14.5, 7.3 Hz, 1H).

Example 187

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-N-(1,2,4-triazin-5-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

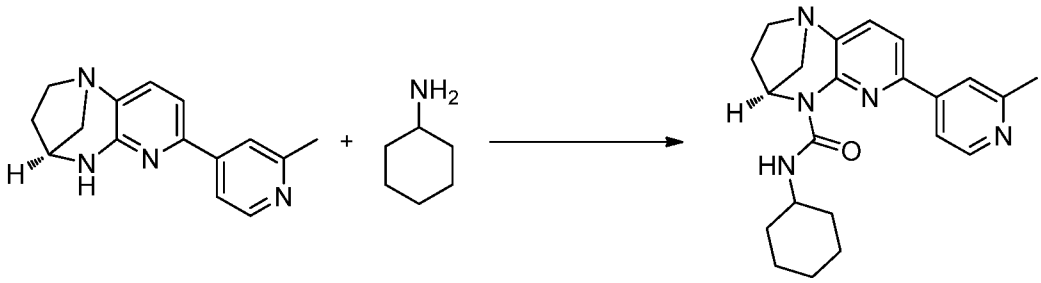


To a solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (0.250 g, 0.991 mmol) in tetrahydrofuran (30 mL) stirred under nitrogen at room temperature was added triethylamine (2.486 mL, 17.83 mmol) and triphosgene (0.294 g, 0.991 mmol). Then reaction mixture was stirred at room temperature for 30 minutes. 1,2,4-triazin-5-amine (0.286 g, 2.97 mmol) was added at rt. Then the reaction mixture was stirred at 65 °C for 16 hr. The reaction mixture was cooled to room temperature and distilled out the solvent completely 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 give crude as brown solid (TLC eluent: 100% EtOAc: R_f-0.4; UV active). The crude was purified by column chromatography using (100-200 mesh) silica gel and was eluted with 100% EtOAc to afford pure get (4*S*)-7-(2-methylpyridin-4-yl)-N-(1,2,4-triazin-5-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (0.044 g, 0.117 mmol, 11.76 % yield) as off-white solid, LCMS (*m/z*): 375.2 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 14.23 (s, 1H), 10.27 (d, *J* = 2.0 Hz, 1H), 9.27 (d, *J* = 2.1 Hz, 1H), 8.65 (dd, *J* = 5.3, 0.8 Hz, 1H), 7.96 (dt, *J* = 1.9, 0.7 Hz, 1H), 7.73 - 7.61 (m, 2H), 7.54 (d, *J* = 8.0 Hz, 1H), 5.69 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.31 - 3.14 (m, 3H), 3.05 (dd, *J* = 12.2, 3.3 Hz, 1H), 2.73 (s, 3H), 2.38 (dddd, *J* = 13.9, 9.9, 6.1, 4.2 Hz, 1H), 2.15 - 2.02 (m, 1H).

Example 188

(4S)-N-cyclohexyl-7-(2-methylpyridin-4-yl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-b] [1, 4] diazepine-5(2H)-carboxamide

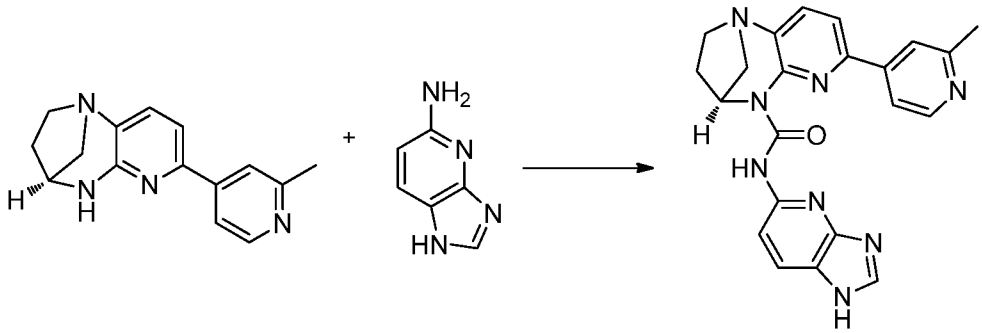


(4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.982 mmol) in Tetrahydrofuran (THF) (10 mL) stirred under nitrogen at room temp was added triphosgene (294 mg, 0.991 mmol) and stirred for 30 min at RT. To this triethylamine (1.381 mL, 9.91 mmol) and cyclohexanamine (255 mg, 2.58 mmol) were added and the reaction mixture was stirred at 60 °C for 16 hr. Reaction mixture was quenched with 2x15 ml of water and extracted with 2x20 ml of ethyl acetate, organic layer was dried over sodium sulfate and concentrated under reduced pressure to afford crude compound. The crude product was purified by column chromatography to afford pure compound (4S)-N-cyclohexyl-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (265 mg, 0.701 mmol, 35.4 % yield) as off white solid, (R_f value: 0.4, 10% Methanol in DCM), LCMS (*m/z*): 378.36 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.36 (d, *J*=7.02 Hz, 1 H), 8.59 (d, *J*=5.26 Hz, 1 H), 7.56 (d, *J*=5.26 Hz, 1 H), 7.54 - 7.52 (m, 1 H), 7.45 (dd, *J*=5.15, 1.21 Hz, 1 H), 7.29 (d, *J*=7.89 Hz, 1 H), 5.64 (dd, *J*=5.92, 3.29 Hz, 1 H), 3.87 - 3.74 (m, 1 H), 3.06 - 3.30 (m, 3 H), 2.95 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.65 (s, 3 H), 2.26 (dddd, *J*=14.00, 9.89, 5.92, 4.17 Hz, 1 H), 2.14 – 1.98 (m, 3 H), 1.81 - 1.61 (m, 3 H), 1.45 - 1.14 (m, 5 H)

Example 189

Synthesis of (4S)-N-(1H-imidazo[4, 5-b]pyridin-5-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2, 3-b][1, 4]diazepine-5(2H)-carboxamide

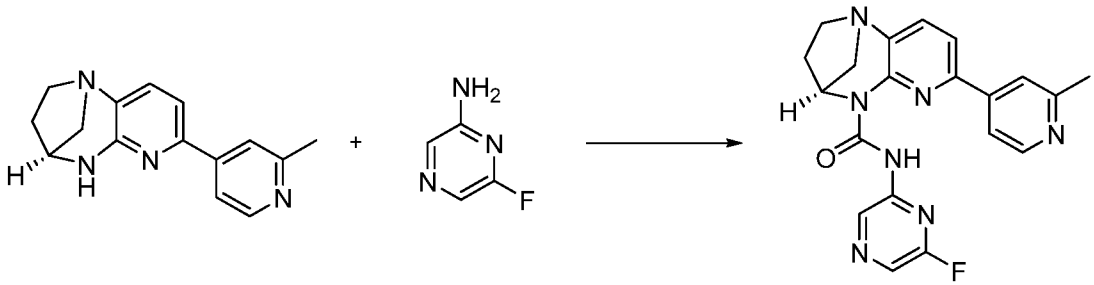


To a solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (600 mg, 2.378 mmol) in THF (30 ml) was added triphosgene (353 mg, 1.189 mmol) at 0 °C and stirred at room temperature for 1 h. Then 1*H*-imidazo[4,5-*b*]pyridin-5-amine (415 mg, 3.09 mmol) and triethylamine (1.657 mL, 11.89 mmol) were added sequentially and the reaction was heated at 70 °C for 16 h in sealed tube. The reaction mixture was allowed to cool to room temperature, poured in saturated $NaHCO_3$ solution (150 mL) and extracted with ethyl acetate (3x50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude product. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, using gradient mixture of 1% methanol in dichloromethane as eluent) to afford (4*S*)-N-(1*H*-imidazo[4, 5-*b*]pyridin-5-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2, 3-*b*][1, 4]diazepine-5(2*H*)-carboxamide (160 mg, 0.388 mmol, 25%) as pale yellow solid (TLC: 5% methanol in DCM, R_f = 0.3), LCMS (*m/z*): 413.28 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d6): δ 13.43 (s, 1H), 12.30-11.54(m, 1H), 8.72 (d, *J* = 5.4 Hz, 1H), 8.34 (s, 1H), 8.19 - 8.10 (m, 3H), 8.04 (d, *J* = 8.7 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 5.55 (dd, *J* = 6.0, 3.1 Hz, 1H), 3.12 (d, *J* = 11.5 Hz, 2H), 2.98 (d, *J* = 3.3 Hz, 1H), 2.95 (d, *J* = 3.3 Hz, 1H), 2.70 (s, 3H), 2.25 (m, *J* = 13.9, 4.7 Hz, 1H), 1.96 (dt, *J* = 14.3, 7.4 Hz, 1H).

Example 190

Synthesis of (4S)-N-(6-fluoropyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

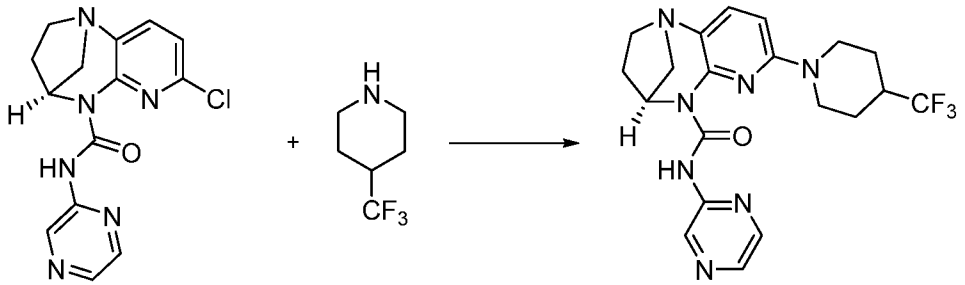


Triethylamine (1.105 mL, 7.93 mmol) and triphosgene (235 mg, 0.793 mmol) were added to a stirred solution of (4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (400 mg, 1.585 mmol) in Tetrahydrofuran (THF) (20 mL) at 25 °C, after 30 min, 6-fluoropyrazin-2-amine (359 mg, 3.17 mmol) was added and heated to 70 °C for 16 h. Allowed the reaction mixture to room temperature, organic solvent was removed by rotary evaporation. Residue was diluted with water (50 mL) and extracted with ethyl acetate (3x60 mL). The combined organic layers washed with brine (60 mL) and dried over Na_2SO_4, filtered and concentrated to get crude compound. Crude compound was purified by flash column chromatography (silica gel: 100-200 mesh, 2% MeOH in DCM as an eluent) to get (4S)-N-(6-fluoropyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (210 mg, 0.522 mmol, 32.9 % yield) as a pale yellow solid (TLC Eluent:10% MeOH in DCM, R_f: 0.4), LCMS (*m/z*): 392.26 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.82 (s, 1H), 9.48 (d, *J* = 4.6 Hz, 1H), 8.66 (d, *J* = 5.3 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 2.2 Hz, 1H), 7.71 - 7.40 (m, 2H), 7.26 (s, 1H), 5.75 - 5.63 (m, 1H), 3.26 (dd, *J* = 9.7, 6.9 Hz, 3H), 3.05 (d, *J* = 3.3 Hz, 1H), 2.75 (s, 3H), 2.36 (dddd, *J* = 13.9, 9.9, 5.9, 3.9 Hz, 1H), 2.16 - 1.93 (m, 1H).

Example 191

Synthesis of (4*S*)-N-(pyrazin-2-yl)-7-(4-(trifluoromethyl)piperidin-1-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

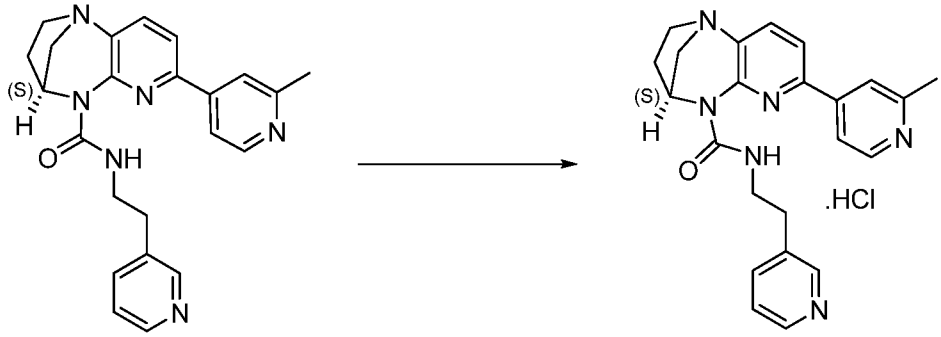


To a de-gassed solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (800 mg, 2.53 mmol) and 4-(trifluoromethyl)piperidine (580 mg, 3.79 mmol) in 1,4-dioxane (15 mL) was added Cs_2CO_3 (2469 mg, 7.58 mmol) and purged with argon gas for 15 min and followed by x-phos (241 mg, 0.505 mmol), palladium(II) acetate (56.7 mg, 0.253 mmol) were added. The reaction mixture was stirred at 100 °C for 16 h in sealed tube. The reaction mixture was allowed to cool to room temperature, poured in to cold water (30 mL) and extracted with ethyl acetate (2x50 mL). The combined organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to obtain crude product. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, using gradient mixture of 2% MeOH in DCM as eluent) to afford (4*S*)-N-(pyrazin-2-yl)-7-(4-(trifluoromethyl)piperidin-1-yl)-3,4-dihydro-1,4-methanopyrido [2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (255 mg, 0.559 mmol, 22.13 % yield) as an off white solid (TLC: 100% ethyl acetate, R_f = 0.3), LCMS (*m/z*): 434.1 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.39 (s, 1H), 9.54 (d, *J* = 1.5 Hz, 1H), 8.25 (d, *J* = 2.5 Hz, 1H), 8.19 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 1H), 6.32 (d, *J* = 8.6 Hz, 1H), 5.62 (dd, *J* = 6.0, 3.2 Hz, 1H), 4.41 – 4.30 (m, 2H), 3.30 – 3.18 (m, 1H), 3.16 – 3.08 (m, 2H), 3.00 – 2.88 (m, 3H), 2.37 – 2.19 (m, 2H), 2.09 – 1.97 (m, 3H), 1.75 – 1.61 (m, 2H).

Example 192

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-N-(2-(pyridin-3-yl)ethyl)-3,4-dihydro-1,4-me-thanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide hydrochloride

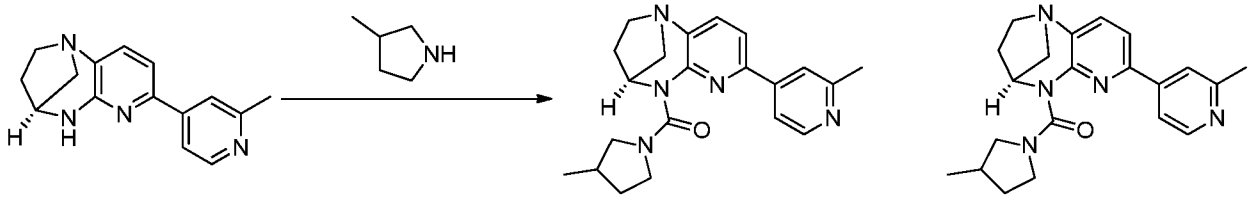


2.0 M Hydrochloric acid in diethyl ether (2 mL, 4.00 mmol) was added to (4*S*)-7-(2-methylpyridin-4-yl)-N-(2-(pyridin-3-yl)ethyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4] diazepine-5(2*H*)-carboxamide (250 mg, 0.624 mmol) at 0°C. The reaction mixture was stirred at 28 °C for 4 h and concentrated to give crude compound (TLC eluent: 5% MeOH in DCM: R_f-0.1; UV active). The crude compound was washed with diethyl ether (2x5 mL) to afford pure (4S)-7-(2-methylpyridin-4-yl)-N-(2-(pyridin-3-yl)ethyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide hydrochloride (274 mg, 0.606 mmol, 97 % yield) as yellow solid, LCMS (*m/z*): 401.1 $[M+H]^+$.

^{1}H NMR (400 MHz, CD_3OD): δ 8.89 (s, 2H), 8.72 (d, *J* = 4.7 Hz, 1H), 8.65 (d, *J* = 6.7 Hz, 1H), 8.44 (s, 1H), 8.32 (s, 1H), 8.17 (d, *J* = 7.1 Hz, 1H), 8.06 - 7.92 (m, 2H), 5.67 (d, *J* = 5.2 Hz, 1H), 3.99-3.75 (m, 6H), 3.32-3.20 (m, 2H), 2.93 (s, 3H), 2.72-2.53 (m, 1H), 2.42-2.37 (s, 1H).

Example 193

Synthesis of ((4S)-7-(2-methylpyridin-4-yl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-b] [1, 4] diazepin-5(2H)-yl) (3-methylpyrrolidin-1-yl) methanone



(4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1.5 g, 5.94 mmol) in Tetrahydrofuran (THF) (20 mL) stirred under nitrogen at room temp was added triphosgene (0.882 g, 2.97mmol) and stirred for 30 min at room temperature. After 30 minutes triethylamine (4.14 mL, 29.7 mmol) and 3-methylpyrrolidine (0.658 g,

7.73 mmol) were added, then the reaction mixture was stirred at 60 °C for 16 hr. Reaction mixture was quenched with 2x25 ml of water and extracted with 2x50 ml of ethyl acetate, organic layer was dried over sodium sulfate and concentrated under reduced pressure to afford crude compound. The crude product was purified by column chromatography and was submitted for SFC, separated peaks as peak-I isolated yield ((4S)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepin-5(2H)-yl)(3-methylpyrrolidin-1-yl)methanone (210 mg, 0.574 mmol, 9.65 % yield) as pale brown solid and peak-II isolated yield ((4S)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepin-5(2H)-yl)(3-methylpyrrolidin-1-yl)methanone (180 mg, 0.494 mmol, 6.79 % yield) as pale brown solid, (R_f value: 0.4, 10% Methanol in DCM), LCMS (*m/z*): 364.32 $[M+H]^+$.

Peak-1

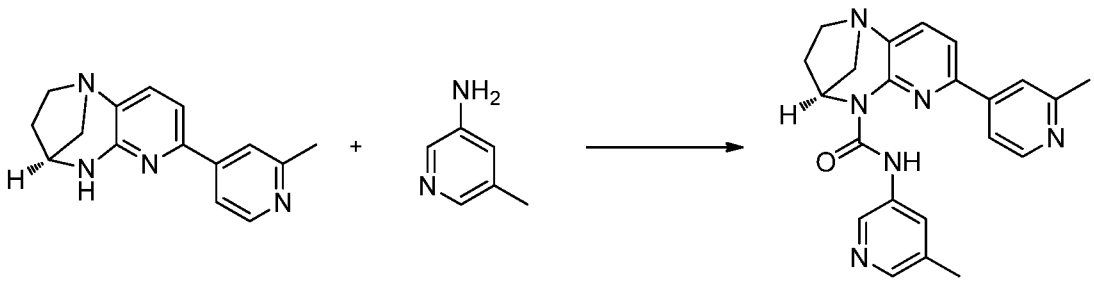
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.50 (d, *J*=5.04 Hz, 1 H), 7.76 (d, *J*=0.66 Hz, 1 H), 7.68 (dd, *J*=5.26, 1.10 Hz, 1 H), 7.52 - 7.48 (m, 1 H), 7.47 - 7.38 (m, 1 H), 4.40 (br d, *J*=2.85 Hz, 1 H), 3.48 (br s, 3 H), 3.16 – 2.98 (m, 4 H), 2.89 (dd, *J*=11.62, 3.29 Hz, 1 H),2.53 - 2.46 (m, 3 H), 2.32 - 2.20 (m, 3 H), 2.14 (br d, *J*=4.60 Hz, 2 H), 1.48 (dt, *J*=19.51, 9.76 Hz, 1 H), 1.12 – 0.98 (m, 2 H).

Peak-II

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.48 (d, *J*=5.26 Hz, 1 H), 7.76 (s, 1 H), 7.68 (dd, *J*=5.26, 1.32 Hz, 1 H), 7.40 - 7.54 (m, 2 H), 4.44 (br s, 1 H), 3.36 - 3.69 (m, 3 H), 2.99 - 3.18 (m, 4 H), 2.89 (dd, *J*=11.62, 3.29 Hz, 1 H), 2.03 - 2.33 (m, 4 H), 1.81-1.52 (m, 2 H), 1.01 (br s, 2 H).

Example 194

Synthesis of (4*S*)-*N*-(5-methylpyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-meth anopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



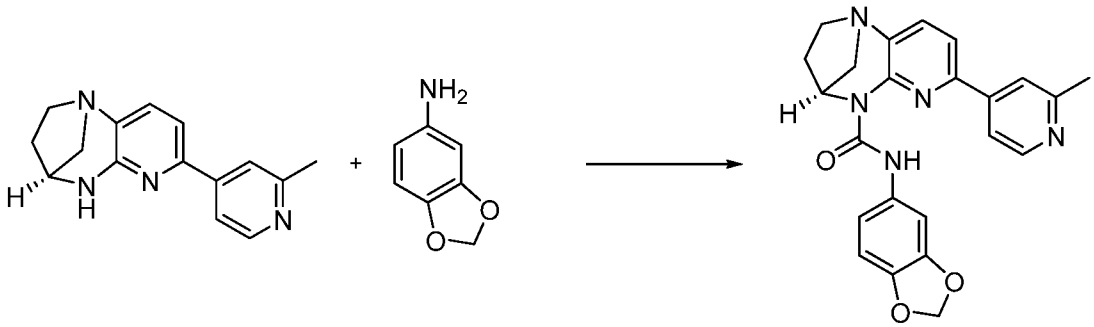
To a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (600 mg, 2.378 mmol) in THF (15 mL) was added

triphosgene (423 mg, 1.427 mmol) at 30 °C and stirred for 1 h. Then Et_3N (1.657 mL, 11.89 mmol) and 5-methylpyridin-3-amine (771 mg, 7.13 mmol) were added at 30 °C and heated the reaction mixture at 65 °C for 16h. The reaction mixture was poured in to cold water (50 ml) and extracted with DCM (2x 50 ml). The combined organic layer was washed with water, brine, dried over sodium sulfate and solvent evaporated under reduced pressure to obtain crude product. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 0-15% MeOH in DCM) to afford (4*S*)-*N*-(5-methylpyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (300 mg, 0.777 mmol, 45% yield) as a yellow solid (TLC: 10% MeOH in EtOAc, R_f: 0.4), LCMS (*m/z*): 387.36 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.00 (s, 1 H), 8.66 (d, *J*=5.04 Hz, 1 H), 8.47 (s, 1 H), 8.16 (s, 1 H), 7.99 (s, 1 H), 7.71 - 7.57 (m, 2 H), 7.50 (d, *J*=5.26 Hz, 1 H), 7.38 (d, *J*=7.89 Hz, 1 H), 5.70 (dd, *J*=5.81, 3.18 Hz, 1 H), 3.37 - 3.10 (m, 3 H), 3.03 (dd, *J*=12.06, 3.07 Hz, 1 H), 2.68 (s, 3 H), 2.45 - 2.25 (m, 4 H), 2.22 – 1.98 (m, 1 H).

Example 195

Synthesis of (4*S*)-*N*-(benzo[d][1,3]dioxol-5-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



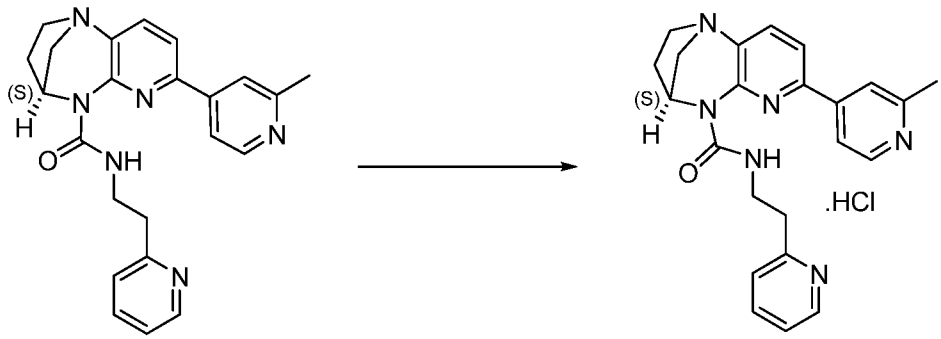
To a solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (600 mg, 2.378 mmol) in THF (15 mL), was added triphosgene (353 mg, 1.189 mmol) at 0 °C and stirred at 27 °C for 2 h, then benzo[*d*][1,3]dioxol-5-amine (391 mg, 2.85 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (307 mg, 2.378 mmol) were added at 27 °C, heated to 50 °C for 16 h. The reaction was allowed to room temperature and the reaction mixture was poured in to saturated $NaHCO_3$ solution and extracted with ethyl acetate (3x50 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 2%

methanol in dichloromethane) to afford (4*S*)-*N*-(benzo[*d*][1,3]dioxol-5-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (270 mg, 26.2% yield) (TLC: eluent, 5% Methanol in DCM; R_f= 0.4), LCMS (*m/z*): 416.30 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.81 (s, 1 H), 8.63 (d, *J*=5.26 Hz, 1 H), 7.64-7.59 (m, 2 H), 7.49 (dd, *J*=5.15, 1.43 Hz, 1 H), 7.37-7.31(m, 2 H), 6.85 (dd, *J*=8.33, 2.19 Hz, 1 H), 6.75 (d, *J*=8.33 Hz, 1 H), 5.97-5.92 (m, 2 H), 5.73-5.66 (m, 1 H), 3.33-3.10 (m, 3 H), 3.01 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.65 (s, 3 H), 2.32 (dddd, *J*=14.11, 9.84, 5.86, 4.17 Hz, 1 H), 2.09 (dt, *J*=14.03, 6.80 Hz, 1 H).

Example 196

Synthesis of (4S)-7-(2-methylpyridin-4-yl)-N-(2-(pyridin-2-yl)ethyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide hydrochloride.

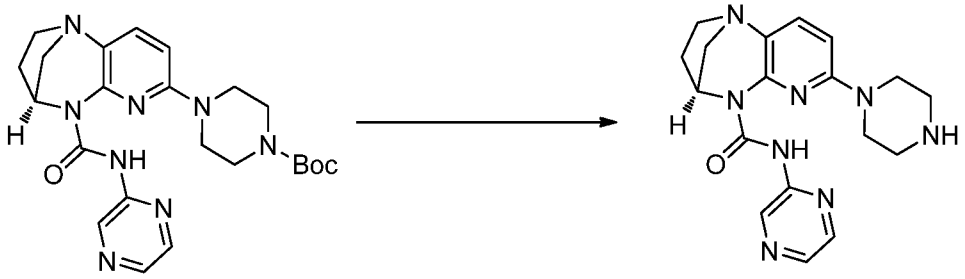


2.0 M Hydrochloric acid in diethyl ether (2 mL, 4.00 mmol) was added to (4S)-7-(2-methylpyridin-4-yl)-N-(2-(pyridin-2-yl)ethyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4] diazepine-5(2*H*)-carboxamide (300 mg, 0.749 mmol) at 0°C. The reaction mixture was stirred at 28 °C for 4 h and concentrated to give crude compound (TLC eluent: 5% MeOH in DCM: R_f-0.1; UV active). The crude compound was washed with diethyl ether (3x5 mL) to afford pure (4*S*)-7-(2-methylpyridin-4-yl)-N-(2-(pyridin-2-yl)ethyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide hydrochloride (296 mg, 0.675 mmol, 90 % yield) as yellow solid, LCMS (*m/z*) 401.2 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.88 (t, *J* = 5.9 Hz, 1H), 8.89 (d, *J* = 6.1 Hz, 1H), 8.66 (dd, *J* = 5.6, 1.7 Hz, 1H), 8.40 - 8.35 (m, 1H), 8.31 - 8.29 (m, 1H), 8.14 (dd, *J* = 6.2, 1.9 Hz, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.95 (dd, *J* = 7.9, 4.9 Hz, 2H), 7.74 (t, *J* = 6.7 Hz, 1H), 5.40 (dd, *J* = 5.6, 2.9 Hz, 1H), 3.97-3.78 (m, 2H), 3.58 - 3.26 (m, 6H), 2.84 (s, 3H), 2.32-2.25 (m, 1H), 2.19-2.03 (m, 1H).

Example 197

Synthesis of (4*S*)-7-(piperazin-1-yl)-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

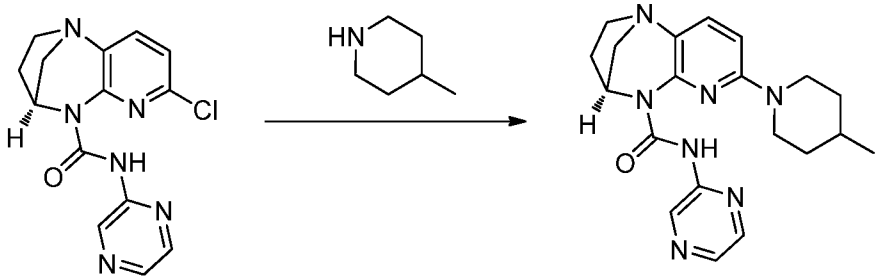


To a solution of tert-butyl 4-((4*S*)-5-(pyrazin-2-ylcarbamoyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepin-7-yl)piperazine-1-carboxylate (359 mg, 0.770 mmol) in THF (5 mL) was added a 2M solution of HCl in diethyl ether (1.924 mL, 3.85 mmol) at 0 °C and the reaction mixture was stirred at 35 °C for 4 h and the reaction mixture was cooled to 0 °C, neutralized with aq $NaHCO_3$ solution and extracted with CH_2Cl_2 (2x50 mL). The combined organic layer was washed with water, brine, 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, eluent: 3% MeOH in DCM) to afford (4*S*)-7-(piperazin-1-yl)-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (277 mg, 0.741 mmol, 96 % yield) as an off white solid (TLC: Rf: 0.3; 5% MeOH in DCM), LCMS (*m/z*): 367.2 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.41 (s, 1H), 9.53 (d, *J* = 1.5 Hz, 1H), 8.24 (d, *J* = 2.5 Hz, 1H), 8.17 (dd, *J* = 2.5, 1.5Hz,1H), 7.38 (d, *J* = 8.6 Hz, 1H), 6.30 (d, *J* = 8.6 Hz, 1H), 5.62 - 5.55 (m, 1H), 3.63 (t, *J* = 5.2 Hz, 4H), 3.26 - 3.17 (m, 1H), 3.17 - 3.06 (m, 6H), 2.92 (dd, *J* = 11.9, 3.3 Hz, 1H), 2.27 (dddd, *J* = 13.7, 9.9, 6.2, 3.8 Hz, 1H), 2.07 - 1.96 (m, 2H).

Example 198

Synthesis of (4*S*)-7-(4-methylpiperidin-1-yl)-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

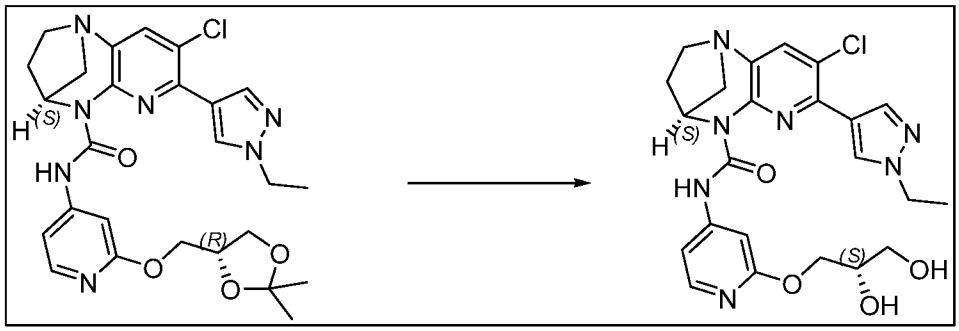


To a degassed solution of (4*S*)-7-chloro-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (600 mg, 1.894 mmol), 4-methylpiperidine (376 mg, 3.79 mmol) in 1,4-dioxane (10 mL) were added Cs_2CO_3 (1852 mg, 5.68 mmol), x-phos (361 mg, 0.758 mmol) and $Pd(OAc)_2$ (106 mg, 0.474 mmol) at RT. The reaction mixture was stirred at 110 °C for 16 h and was poured in to cold water (20 mL), extracted with ethyl acetate (2x50 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain the crude product. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 4% MeOH in DCM) to afford (4*S*)-7-(4-methylpiperidin-1-yl)-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (300 mg, 0.775 mmol, 40.9 % yield) as an off white solid (TLC: R_f: 0.4; neat EtOAc), LCMS (*m/z*): 380.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.51 (s, 1H), 9.52 (d, *J* = 1.5 Hz, 1H), 8.23 (dd, *J* = 2.5, 0.4 Hz, 1H), 8.20 (dd, *J* = 2.5, 1.5 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 1H), 6.30 (d, *J* = 8.7 Hz, 1H), 5.61 (dd, *J* = 6.1, 3.2 Hz, 1H), 4.20 (ddd, *J* = 11.4, 3.6, 2.1 Hz, 2H), 3.22 (dddd, *J* = 12.3, 8.6, 3.7, 2.2 Hz, 1H), 3.15 - 3.05 (m, 2H), 3.00 - 2.86 (m, 3H), 2.26 (dddd, *J* = 13.8, 9.9, 6.2, 3.8 Hz, 1H), 2.04 - 1.94 (m, 1H), 1.84 - 1.72 (m, 2H), 1.68 - 1.60 (m, 1H), 1.33 - 1.18 (m, 2H), 0.99 (d, *J* = 6.5 Hz, 3H).

Example 199

Synthesis of (4*S*)-8-chloro-*N*-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(1-ethyl-1*H*-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



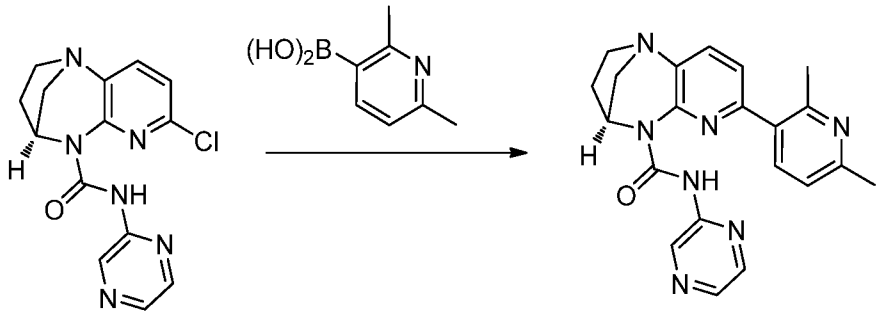
To a solution of (4*S*)-8-chloro-*N*-(2-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(1-ethyl-1*H*-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (450 mg, 0.833 mmol), in methanol (5 mL) under nitrogen at RT was added HCl (3 mL, 99 mmol) and stirred for 2 h. (TLC system 5%

Methanol in DCM. Rf value:0.1), The reaction mixture was concentrated and the residue at 0 °C was basified with saturated $NaHCO_3$ solution. The resultant solid was filtered, dried to get crude compound, this was triturated with diethylether (10 mL) to afford (4*S*)-8-chloro-*N*-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(1-ethyl-1*H*-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (280 mg, 0.556 mmol, 66.7 % yield) as an off-white solid. LCMS (*m/z*): 500.26$[M+H]^+$, *Rt*=1.74 min.

^{1}H NMR (400MHz, DMSO-d6): δ ppm 12.66 (s, 1 H), 8.43 (s, 1 H), 8.10 - 7.92 (m, 2 H), 7.73 (s, 1 H), 7.11 - 6.84 (m, 2 H), 5.52 - 5.33 (m, 1 H), 4.87 (br s, 1 H), 4.74 - 4.46 (m,1 H), 4.34 - 4.19 (m, 3 H), 4.19 - 3.96 (m, 1 H), 3.86 - 3.68 (m, 1 H), 3.43 (br d, *J*=5.5 Hz, 2 H), 3.27 - 3.15 (m,1 H), 3.14 - 2.99 (m, 2 H), 2.99 - 2.72 (m, 1 H), 2.36 - 2.08 (m,1 H), 1.93 (br dd, *J*=6.4, 13.8 Hz, 1 H), 1.46 (t, *J*=7.2 Hz, 3 H).

Example 200

Synthesis of (4S)-7-(2,6-dimethylpyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



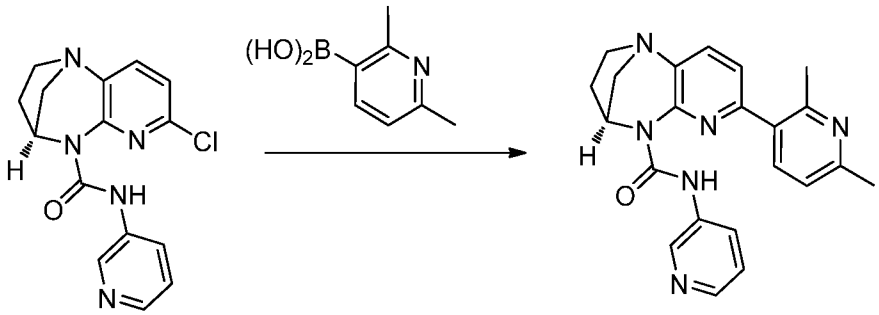
K_3PO_4 (535 mg, 2.53 mmol) was added to a stirred solution of (4S)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (400 mg, 1.263 mmol) & (2,6-dimethylpyridin-3-yl)boronic acid (248 mg, 1.642 mmol) in 1,4-Dioxane (20 mL) and Water (1 mL) then de-gassed for 15 min and x-phos (60.2 mg, 0.126 mmol) followed by $Pd_2(dba)_3$ (57.8 mg, 0.063 mmol) were added and then the reaction was heated at 90 °C for 2 h 45 min before being allowed to cool to room temperature, filtered through a pad of celite, washed with ethyl acetate (10 mLx2), from filtrate organic solvent was removed under reduced pressure. The aqueous layer was extracted with ethyl acetate (20 mLx2), washed with water (20 mLx2), brine (20 mL) and dried over Na_2SO_4. Organic solvent was removed *in* vacuum to afford crude compound. Above compound was purified by flash column chromatography (silica-gel: 100-200 mesh, eluted with 80% ethyl acetate in hexane) to afford the (4S)-7-(2,6-dimethylpyridin-3-yl)-N-(pyrazin-2-yl)-

3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (330 mg, 0.848 mmol, 67.2 % yield) as an off white solid (TLC: Eluent:100% ethyl acetate R_f : 0.3, UV active), LCMS (*m/z*): 388.28 $[M+H]^+$.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 13.5 (s, 1H), 9.45 (s, 1H), 8.22-8.25 (m, 1H), 8.18-8.20 (m, 1H), 7.77 (d, 1H, J = 7.6 Hz),7.6 (d, 1H,J = 8 Hz), 7.08 – 7.14 (m, 2H), 5.68 – 5.72 (m, 1H), 3.18 - 3.34 (m, 3H), 3.01 – 3.06 (m, 1H), 2.65 (s, 3H), 2.5 (s, 3H), 2.31 - 2.39 (m, 1H), 2.08 - 2.15 (m, 1H).

Example 201

Synthesis of (4S)-7-(2,6-dimethylpyridin-3-yl)-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

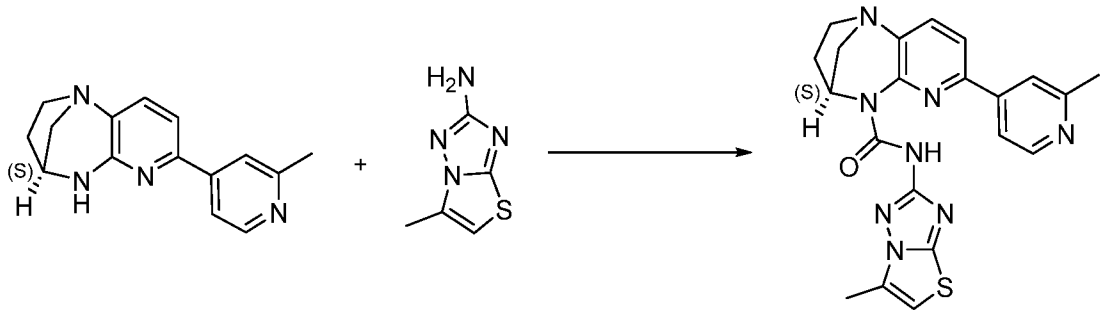


K_3PO_4 (537 mg, 2.53 mmol) was added to a stirred solution of (4S)-7-chloro-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (400 mg, 1.267 mmol) &(2,6-dimethylpyridin-3-yl)boronic acid (249 mg, 1.647 mmol) in 1,4-Dioxane (15 mL) and water (1 mL) then de-gassed for 15 min and dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (60.4 mg, 0.127 mmol), followed by $Pd_2(dba)_3$ (58.0 mg, 0.063 mmol) were added and heated at 100 °C for 2 h 45 min. Allowed the reaction mixture to RT, filtered through a pad of celite, washed with ethyl acetate (10 mLx2), filtrate solvent removed under reduced pressure. Organic compound was extracted with ethyl acetate (20 mLx2). The combined organic layers were washed with water (20 mLx2), brine (20 mL) and dried over Na_2SO_4. Organic solvent was removed under vacuum to afford crude compound. Above crude compound was purified by flash column chromatography (silica-gel: 100-200 mesh, Compound eluted with 90% ethyl acetate in hexane) to afford the (4S)-7-(2,6-dimethylpyridin-3-yl)-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (304 mg, 0.777 mmol, 61.3 % yield) as an off white solid (TLC: Eluent:100% ethyl acetate R_f : 0.4, UV active), LCMS (*m/z*): 387.31 $[M+H]^+$.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 13.13 (s, 1H), 8.33 – 8.35 (m, 1H), 8.24 – 8.26 (m, 1H), 8.10 – 8.14 (m, 1H), 7.6 (d, 1H, J = 7.6 Hz), 7.59 (d, 1H, J = 8 Hz), 7.19 -7.24 (m, 1H), 7.15 (d, 1H, J = 8 Hz H), 7.05 (d, 1H, J = 7.6 Hz), 5.67 – 5.71 (m, 1H), 3.35 - 3.4 (m, 1H), 3.19 - 3.25 (m, 2H), 3.1 – 3.36 (m, 1H), 2.6 (s, 6H), 2.29 -2.38 (m,1H), 2.17 – 2.26 (m, 1H).

Example 202

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-N-(6-methylthiazolo[3,2-*b*][1,2,4]triazol-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

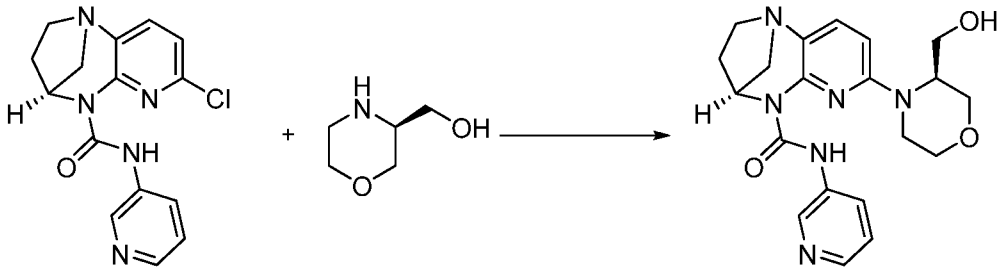


To a solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 1.189 mmol), triethylamine (0.829 mL, 5.94 mmol) and triphosgene (212 mg, 0.713 mmol) in tetrahydrofuran (10 mL) stirred under nitrogen at room temp for 30 min was added a solution of 6-methylthiazolo[3,2-*b*][1,2,4]triazol-2-amine (367 mg, 2.378 mmol) in THF (2mL) dropwise during 1 min. The reaction mixture was stirred at 65 °C for 16 h and cooled to room temperature. The reaction mixture was poured in to water and extracted with EtOAc (3 X 10mL). Then the combined organic layers were washed with water, brine solution, dried over sodium sulfate and evaporated to give crude compound (TLC eluent: 10% MeOH in DCM: R_f-0.1; UV active). The crude compound was purified by reverse phase column and eluted with 90% (0.1%HCOOH in Water)/MeOH to afford pure (4*S*)-7-(2-methylpyridin-4-yl)-N-(6-methylthiazolo[3,2-b][1,2,4]triazol-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (390 mg, 0.892 mmol, 75 % yield) as pale yellow solid, LCMS (*m/z*): 433.2 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.88 (s, 1H), 8.63 (d, *J* = 5.2 Hz, 1H), 7.91 (d, *J* = 1.9 Hz, 1H), 7.69 - 7.52 (m, 2H), 7.46 (d, *J* = 8.0 Hz, 1H), 6.48 (d, *J* = 1.6 Hz, 1H), 5.75 (dd, *J* = 5.9, 3.1 Hz, 1H), 3.35 - 3.10 (m, 3H), 3.02 (dd, *J* = 12.1, 3.3 Hz, 1H), 2.72 (s, 3H), 2.57 (d, *J* = 1.4 Hz, 3H), 2.40 - 2.25 (m, 1H), 2.19-2.05 (m, 1H).

Example 203

Synthesis of (4S)-7-((S)-3-(hydroxymethyl)morpholino)-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

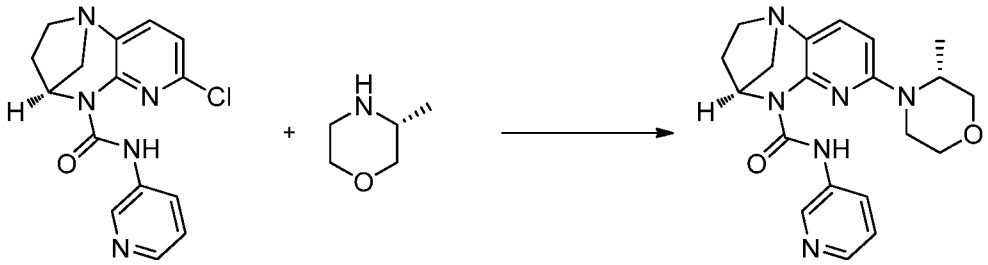


Cs_2CO_3 (5778 mg, 17.74 mmol) and (S)-morpholin-3-ylmethanol (390 mg, 3.33 mmol) were added to a stirred solution of(4S)-7-chloro-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (700 mg, 2.217 mmol) in 1,4-Dioxane (10 mL) at room temperature and purged with argon for 25 min then palladium(II) acetate (49.8 mg, 0.222 mmol) and X-phos (211 mg, 0.443 mmol) were added. The reaction was stirred at 100 °C for 8h before allowing reaction mixture to warm to room temperature. Organic solvent was removed by rotary evaporation, diluted with water (60mL) and extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with brine (50mL), dried over Na_2SO_4, filtered and concentrated to get the crude residue. The crude residue was purified by column chromatography (Silica-gel: 100-200 mesh, 2% methanol in dichloromethane as an eluent) to afford (4S)-7-((S)-3-(hydroxymethyl)morpholino)-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (275 mg, 0.691 mmol, 31.2 % yield) as an off white solid(TLC eluent:10% MeOH in DCM R_f: 0.4), LCMS (*m/z*): 397.28 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 12.38 (s, 1H), 8.51 (d, *J* = 2.6 Hz, 1H), 8.36 - 8.24 (m, 1H), 8.16 (ddd, *J* = 8.4, 2.7, 1.5 Hz, 1H), 7.44 - 7.16 (m, 2H), 6.25 (d, *J* = 8.6 Hz, 1H), 5.63 (dd, *J* = 6.2, 3.2 Hz, 1H), 4.06 (d, *J* = 7.4 Hz, 2H), 3.81 (t, *J* = 2.7 Hz, 2H), 3.69 - 3.48 (m, 2H), 3.38 - 3.03 (m, 4H), 2.90 (dd, *J* = 11.8, 3.3 Hz, 1H), 2.26 (dd, *J* = 10.1, 3.9 Hz, 1H), 2.11 - 1.87 (m, 1H), 1.26 (d, *J* = 6.6 Hz, 3H).

Example 204

Synthesis of (4*S*)-7-((*R*)-3-methylmorpholino)-*N*-(pyridin-3-yl)-3,4-dihydro-1,4-methano-pyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

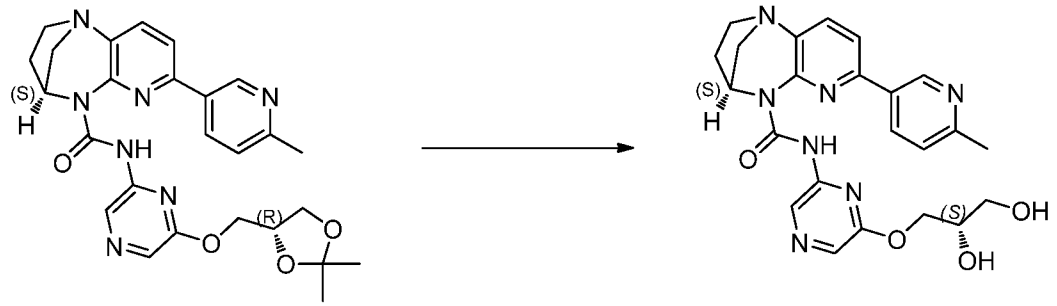


(*R*)-3-methylmorpholine (320 mg, 3.17 mmol) followed by cesium carbonate (516 mg, 1.583 mmol) were added to a stirred solution of (4*S*)-7-chloro-*N*-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (500 mg, 1.583 mmol) in 1,4-dioxane (8 mL) at RT and degassed for 30 min. Then $Pd(OAc)_2$ (71.1 mg, 0.317 mmol) and X-phos (755 mg, 1.583 mmol) were added to the reaction mixture at RT and again degassed for 15 min. The reaction mixture was stirred at 110 °C for 6 h and was then cooled to RT, diluted with water (30 mL), extracted with ethyl acetate (2X50 mL). The combined organic layer was washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated to obtain the crude product. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 2% MeOH in DCM) to afford (4*S*)-7-((*R*)-3-methylmorpholino)-*N*-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (100 mg, 0.258 mmol, 16.27 % yield) as an off white solid (TLC: R_f 0.4, 10% MeOH in DCM), LCMS (*m/z*): 381.26 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 12.38 (s, 1H), 8.51 (d, *J* = 2.6 Hz, 1H), 8.36 - 8.24 (m, 1H), 8.16 (ddd, *J* = 8.4, 2.7, 1.5 Hz, 1H), 7.44 - 7.16 (m, 2H), 6.25 (d, *J* = 8.6 Hz, 1H), 5.63 (dd, *J* = 6.2, 3.2 Hz, 1H), 4.06 (d, *J* = 7.4 Hz, 2H), 3.81 (t, *J* = 2.7 Hz, 2H), 3.69 - 3.48 (m, 2H), 3.38 - 3.03 (m, 4H), 2.90 (dd, *J* = 11.8, 3.3 Hz, 1H), 2.26 (dd, *J* = 10.1, 3.9 Hz, 1H), 2.11 - 1.87 (m, 1H), 1.26 (d, *J* = 6.6 Hz, 3H).

Example 205

Synthesis of (4*S*)-*N*-(6-((*S*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(6-methylpyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

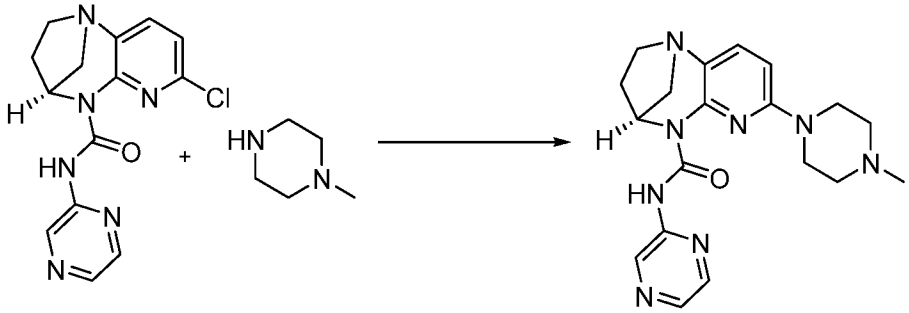


To a solution of (4*S*)-*N*-(6-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(6-methylpyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (0.4 g, 0.794 mmol) in dichloromethane (10 mL) was added 4M HCl in dioxane (0.198 g, 1.589 mmol) at 0 °C. Then the reaction mixture was stirred at 35 °C for 6h. Reaction mixture was neutralized with $NaHCO_3$ solution and extracted with DCM (2x 30 ml). The combined organic layer was washed with water (20 ml), brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to obtain crude product. The crude compound was triturated with diethylether (40 ml) and pentane (20 ml) to afford pure product (4*S*)-*N*-(6-((S)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(6-methylpyridin-3-yl)-3,4-dihydro-1,4-metha nopyrido[2,3-*b*][1,4]diazepine-5(2H)-carboxamide (0.21 g, 0.453 mmol, 65% yield) as a white solid (TLC: 10% MeOH in Ethyl acetate, R_f:0.2), LCMS (*m/z*): 464.27 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.99 (s, 1 H), 9.33 (d, *J*=2.19 Hz, 1 H), 9.13 (s, 1 H), 8.00 (d, *J*=7.78 Hz, 2 H), 7.97 (s, 1 H), 7.64 (d, *J*=8.11 Hz, 1 H), 7.19 - 7.37 (m, 2 H), 5.87 (br s, 1 H), 5.73 (dd, *J*=5.92, 3.29 Hz, 1 H), 4.74 (dd, *J*=10.96, 5.70 Hz, 1 H), 4.40 (dd, *J*=10.96, 7.45 Hz, 1 H), 4.08 - 4.30 (m, 1 H), 3.65 - 3.90 (m, 2 H), 3.10 - 3.34 (m, 4 H), 3.02 (dd, *J*=12.28, 3.29 Hz, 1 H), 2.62 (s, 3 H), 2.36 (dddd, *J*=14.14, 9.87, 5.81, 4.17 Hz, 1 H), 2.00 - 2.22 (m, 1 H).

Example 206

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-N-(pyrido[3,4-*b*]pyrazin-5-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

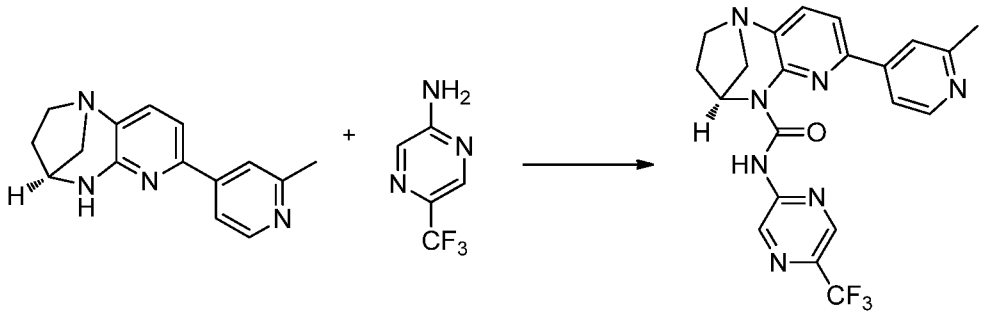


To a de-gassed solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (800 mg, 2.53 mmol) and 1-methylpiperazine (379 mg, 3.79 mmol) in 1,4-dioxane (15 mL) were added cesium carbonate (2469 mg, 7.58 mmol), x-phos (241 mg, 0.505 mmol) and palladium(II) acetate (56.7 mg, 0.253 mmol). The reaction mixture was heated at 100 °C for 16 h and poured in to cold water (45 mL), extracted with ethyl acetate (2x100 mL). The combined organic layer was dried over anhydrous sodium sulfate 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 2% MeOH in DCM) to afford (4*S*)-7-(4-methylpiperazin-1-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (268 mg, 0.693 mmol, 27.5 % yield) as a yellow solid (TLC: 100% ethyl acetate, R_f = 0.23), LCMS (*m/z*): 381.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.46 (s, 2 H), 9.53 (s, 1 H), 8.29-8.12 (m, 2 H), 7.36 (d, *J*=8.55 Hz, 1 H), 6.30 (d, *J*=8.55 Hz, 2 H), 5.61 (dd, *J*=5.92, 3.29 Hz, 2 H), 3.65-3.63 (m, 4H), 3.27-3.03 (m, 3 H), 2.91 (dd, *J*=11.73, 3.40 Hz, 1 H), 2.42-2.39 (m, 1 H), 2.39 (s, 3 H), 2.33-2.14 - (m, 1 H), 2.13-1.93 (m, 1 H).

Example 207

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-*N*-(5-(trifluoromethyl)pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

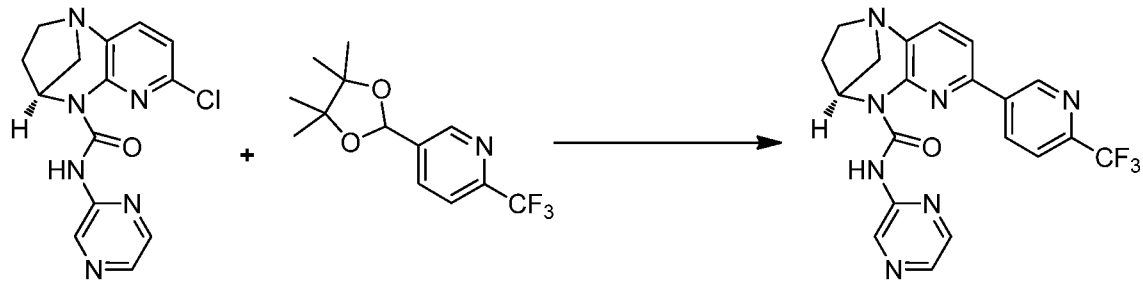


To a stirred solution of 5-(trifluoromethyl)pyrazin-2-amine (1164 mg, 7.13 mmol) in THF (10 mL) were added triethylamine (1.989 mL, 14.27 mmol) and triphosgene (706 mg, 2.378 mmol) at 25 °C and stirred for 1h. Then (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (600 mg, 2.378 mmol) was added and heated at 100 °C for 15 h in sealed tube. The reaction mixture was cooled to room temperature and extracted with ethyl acetate (2x50 mL). The combined organic layer was washed with water (20 mLx2), brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under pressure to obtain the crude product. The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 2% MeOH in DCM) to afford (4*S*)-7-(2-methylpyridin-4-yl)-*N*-(5-(trifluoromethyl)pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (125 mg, 0.283 mmol, 32% yield) as an off white solid (TLC: Eluent: 5% methanol in DCM, R_f: 0.3), LCMS (*m/z*): 442.24 $[M+H]^+$.

^{1}H-NMR ($CDCl_3$, 400 MHz): 14.1 (s, 1H), 9.7 (s, 1H), 8.66-8.62 (m, 2H), 8.0 (s, 1H), 7.69-7.64 (m, 2H), 7.5 (d, *J*= 8 Hz, 1H), 5.74-5.69 (m, 1H), 3.34-3.16 (m, 3H), 3.08-3.02 (m, 1H), 2.75 (s, 3H), 2.32-2.42 (m, 1H), 2.14-2.06 (m, 1H).

Example 208

Synthesis of (4*S*)-N-(pyrazin-2-yl)-7-(6-(trifluoromethyl)pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

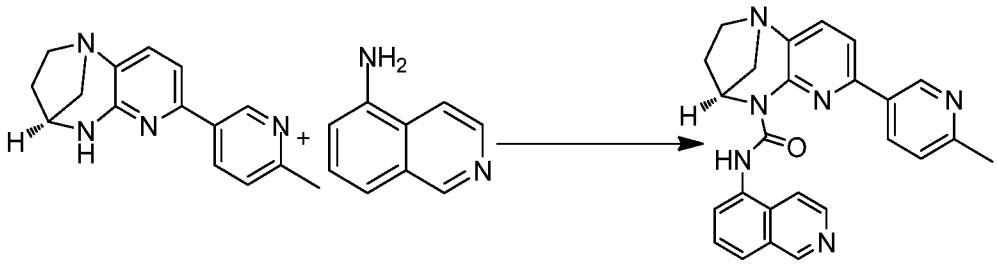


A solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (600 mg, 1.894 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine (776 mg, 2.84 mmol) and K_3PO_4 (804 mg, 3.79 mmol) in 1,4-dioxane (20 mL) and water (3 mL) was degassed with argon at room temp for 15 mins. X-phos (90 mg, 0.189 mmol), and $Pd_2(dba)_3$ (87 mg, 0.095 mmol) was added to reaction mixture. The reaction mixture was further degassed for 15 min and was stirred for 16 h at 90 °C. The reaction mixture was cooled to 28 °C and was filtered through a pad of celite and the filtrate was evaporated to give crude residue. The crude residue was diluted with water (20 mL) and extracted with ethyl acetate (2 x 80 mL). The combined organic layers were washed with water (20 mL) followed by brine solution (10 mL). The organic layer was dried over sodium sulfate, filtered and filtrate was evaporated to give as a brown solid. (TLC eluent: 100 % ethyl acetate, R_f-0.3; UV active). The Crude compound was purified by column chromatography (neutral alumina), product was eluted with 45-50% ethyl acetate in hexane to afford (4*S*)-N-(pyrazin-2-yl)-7-(6-(trifluoromethyl)pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (360 mg, 0.824 mmol, 43.5 % yield) as a off white solid, LCMS (*m/z*): 428.17 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.60 (s, 1 H), 9.52 (d, *J*=1.1 Hz, 1 H), 9.28 (d, *J*=2.2 Hz, 1 H), 8.71 (dd, *J*=8.1, 1.97 Hz, 1 H), 8.25 - 8.33 (m, 2 H), 7.84 (d, *J*=8.3 Hz, 1 H), 7.67 (d, *J*=7.9 Hz, 1 H), 7.5 (d, *J*=8 Hz, 1 H), 5.70 (dd, *J*=6.03, 3.18 Hz, 1 H), 3.11 - 3.36 (m, 3 H), 2.96 - 3.11 (m, 1 H), 2.22 - 2.43 (m, 1 H), 1.97 - 2.21 (m, 1 H).

Example 209

Synthesis of (4S)-N-(isoquinolin-5-yl)-7-(6-methylpyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

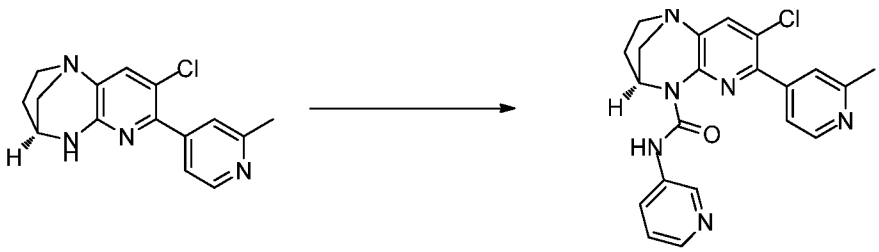


To a solution of (4S)-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (0.750 g, 2.97 mmol) in Tetrahydrofuran (THF) (40 mL) stirred under nitrogen at room temperature was added triethylamine (2.486 mL, 17.83 mmol) and triphosgene (0.882 g, 2.97 mmol). The reaction mixture was stirred at room temperature for 30 minutes before isoquinolin-5-amine (1.286 g, 8.92 mmol) was added. The reaction mixture was stirred at 65 °C for 16 hr and then the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was partitioned between water (30 mL) and Dichloromethane (100 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude as brown solid (TLC eluent: 100% EtOAc: R_f-0.2; UV active). The crude was purified by column chromatography using neutral alumina and was eluted with 100% Dichloromethane to afford pure (4S)-N-(isoquinolin-5-yl)-7-(6-methylpyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (0.315 g, 0.743 mmol, 25.00 % yield) as a off- white solid, LCMS (*m/z*): 423.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.21 (s, 1 H), 9.20 (s, 1 H), 8.88 (d, *J*=2.19 Hz, 1 H), 8.37 (d, *J*=7.23 Hz, 1 H), 7.94 (d, *J*=6.14 Hz, 1 H), 7.88 (dd, *J*=8.11, 2.41 Hz, 1 H), 7.75 (d, *J*=8.11 Hz, 1 H), 7.61 - 7.69 (m, 2 H), 7.47 (d, *J*=5.92 Hz, 1 H), 7.31 (d, *J*=7.89 Hz, 1 H), 7.08 (d, *J*=7.89 Hz, 1 H), 5.77 (dd, *J*=5.92, 3.29 Hz, 1 H), 3.21 - 3.36 (m, 3 H), 3.06 (dd, *J*=12.06, 3.07 Hz, 1 H), 2.59 (s, 3 H), 2.32 - 2.43 (m, 1 H), 2.17 (dt, *J*=14.03, 7.02 Hz, 1 H

Example 210

(9S)-4-chloro-5-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0{2,7}]dodeca-2,4,6-triene-8-carboxamide

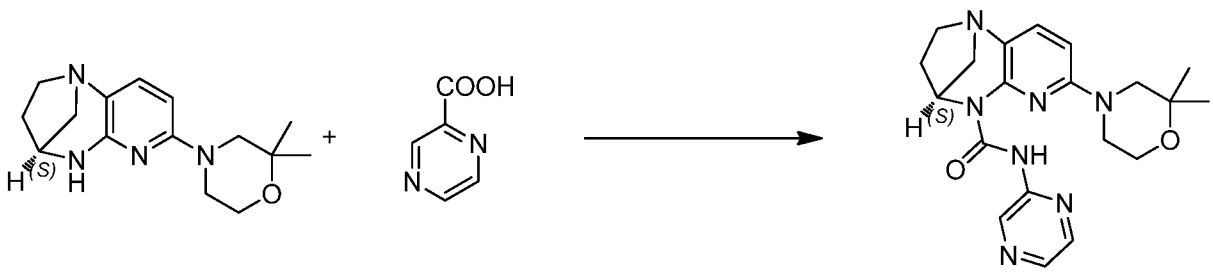


To a stirred solution of nicotinic acid (0.644 g, 5.23 mmol in THF (50 mL), was added sequentially triethylamine (3.6 mL, 26.2 mmol), and diphenyl phosphorazidate (2.26 mL, 10.46 mmol) at 0 C. The reaction solution was allowed to stir at RT for 2h. Solid (4S)-8-chloro-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (1.25 g, 4.36 mmol) was added and the reaction solution was heated to 70 C for 36 hours. The reaction solution was partitioned between EtOAc and H_2O. The organic layer was separated, dried over Na_2SO_4, concentrated under vacuum and applied directly to a silica gel column using EtOAc/EtOH (3:1) as eluent to give (1 g, 56%) as a white solid. The resulting solid was triturated with Et_2O and then dried under vacuum, LCMS (*m/z*): 407.4 $[M+H]^+$.

^{1}H-NMR (400 MHz, $CHCl_3$-*d*) δ ppm: d ppm 2.05 - 2.21 (m, 1H) 2.28 - 2.50 (m, 1H) 2.71 (s, 3H) 2.97 - 3.46 (m, 4H) 5.69 (dd, *J*=5.81, 3.03 Hz, 1H) 7.14 - 7.32 (m, 1H) 7.43 - 7.58 (m, 1H) 7.69 (s, 1H) 7.94 - 8.09 (m, 1H) 8.31 (dd, *J*=4.67, 1.39 Hz, 1H) 8.48 (d, *J*=2.27 Hz, 1H) 8.71 (d, *J*=5.05 Hz, 1H) 12.64 (s, 1H).

Example 211

Synthesis of (4*S*)-7-(2,2-dimethylmorpholino)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



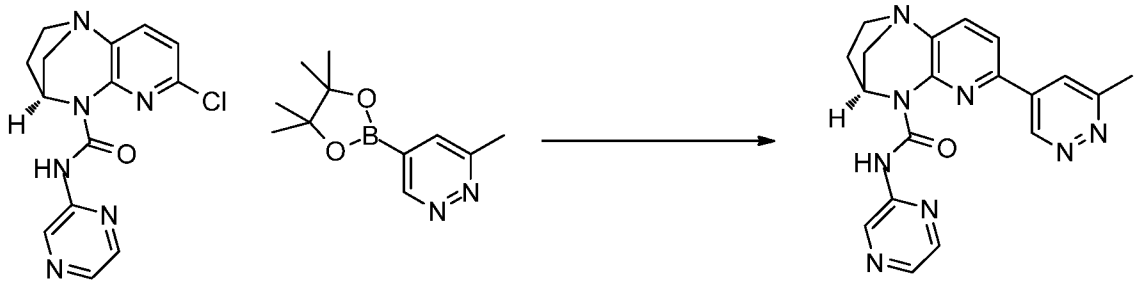
To a solution of pyrazine-2-carboxylic acid (350 mg, 2.82 mmol) in THF (15 mL) was added diphenyl phosphorazidate (1164 mg, 4.23 mmol) and DIPEA (2.463 mL, 14.10

mmol) at at 0°C. The reaction mixture was stirred under nitrogen for 2 h at 30 °C. 2,2-dimethyl-4-((4S)-2, 3, 4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepin-7-yl)morpholine (542 mg, 1.974 mmol) was added and reaction mixture was stirred at 65 °C for 16 h. The solvent was removed under reduced pressure. The crude was diluted with water (20 mL) and extracted with ethyl acetate (2 x 30 mL). T he combined organic layers were washed with water (10 mL), saturated brine solution. The organic layer was dried over anhydrous sodium sulfate, filtered and filtrate was evaporated to give crude. The crude compound was purified by column chromatography (neutral alumina) product was eluted with 10% ethyl acetate in hexane. Collected fractions were concentrated under reduced pressure to afford (4*S*)-7-(2,2-dimethylmorpholino)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (120 mg, 0.303 mmol, 10.74 % yield) as off-white solid, LCMS (*m/z*): 396.3 $[M+H]^+$.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 13.40 (s, 1 H), 9.56 (d, *J*=1.2 Hz, 1 H), 8.26 (d, *J*=2.41 Hz, 1 H), 8.06 - 8.22 (m, 1 H), 7.38 (d, *J*=8.8 Hz, 1 H), 6.28 (d, *J*=8.5 Hz, 1 H), 5.63 (dd, *J*=5.7, 3.3 Hz, 1 H), 3.90 (t, *J*=5 Hz, 2 H), 3.47 (s, 2 H), 3.41 (t, *J*=5 Hz, 2 H), 3.04 - 3.31 (m, 3 H), 2.92 (dd, *J*=11.9, 3.18 Hz, 1 H), 2.14 - 2.35 (m, 1 H), 1.89 - 2.12 (m, 1 H), 1.36 (s, 6 H).

Example 212

Synthesis of (4*S*)-7-(6-methylpyridazin-4-yl)-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



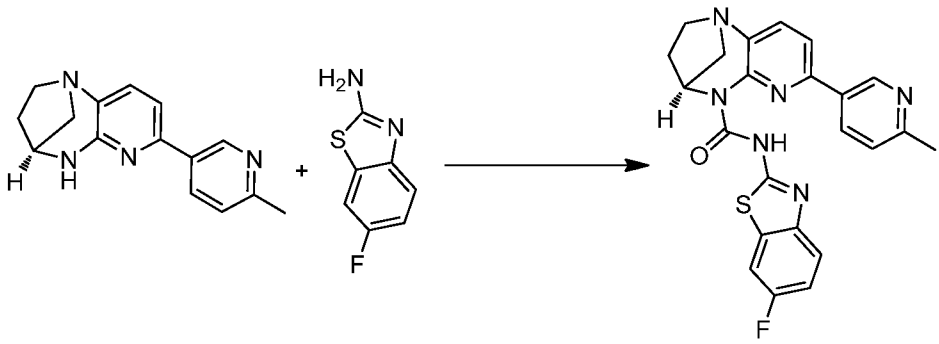
To a de-gassed solution of (4*S*)-7-chloro-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (400 mg, 1.263 mmol), 3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridazine (306 mg, 1.389 mmol) and K_3PO_4 (536 mg, 2.53 mmol) in 1,4-dioxane (15 mL) and water (2 mL) were added $Pd(OAc)_2$ (14.18 mg, 0.063 mmol) and x-phos (60.2 mg, 0.126 mmol) at 25 °C. Then the reaction mixture was stirred at 100 °C for 8 hr and then allowed the reaction mixture to cool to RT and evaporated the dioxane under vacuo. Then it was diluted with water and

extracted with DCM (3x50 mL). The combined organic layer was dried over hydrous Na_2SO_4 and the solvent was removed under reduced pressure to obtain crude product. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 2-3% of MeOH in EtOAc) to afford (4*S*)-7-(6-methylpyridazin-4-yl)-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (260 mg, 0.689 mmol, 54.6 % yield) as an off white solid (TLC: 10% MeOH in EtOAc, R_f: 0.4), LCMS (*m/z*): 375.25 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.69 (s, 1H), 9.62 - 9.53 (s, 2 H), 8.38 - 8.29 (m, 3 H), 7.71 (d, *J*=8.11 Hz, 1 H), 7.59 (d, *J*=8.11 Hz, 1 H), 5.72 (dd, *J*=5.92, 3.29 Hz, 1 H), 3.35 - 3.15 (m, 2 H), 3.12 - 3.00 (m, 2 H), 2.90 (s, 3 H), 2.48 - 2.25 (m, 1 H), 2.11 (dt, *J*=14.03, 6.80 Hz, 1 H).

Example 213

Synthesis of (4S)-N-(6-fluorobenzo[d]thiazol-2-yl)-7-(6-methylpyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



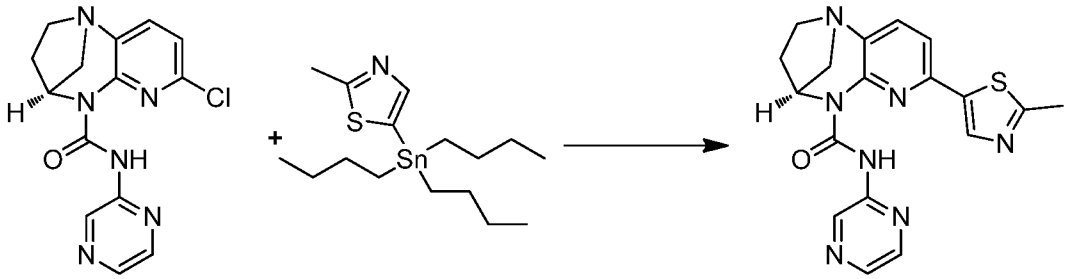
To a solution of (4S)-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (0.750 g, 2.97 mmol) in Tetrahydrofuran (THF) (40 mL) stirred under nitrogen at room temperature was added triethylamine (2.486 mL, 17.83 mmol) and triphosgene (0.882 g, 2.97 mmol). The reaction mixture was stirred at room temperature for 30 minutes before 6- fluorobenzo[d]thiazol-2-amine (1.500 g, 8.92 mmol) was added at room temperature and the reaction mixture was stirred at 65 °C for 16 hr and then cooled to room temperature and the solvent removed under reduced pressure. The resulting residue was partitioned between water (30 mL) and EtOAc (100 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude as brown solid (TLC eluent: 100% EtOAc: R_f-0.2; UV active). The crude was purified by column chromatography using neutral alumina and was eluted with 100% Dichloromethane to afford pure (4S)-N-(6-fluorobenzo[d]thiazol-2-yl)-7-(6-

methylpyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (0.313 g, 0.700 mmol, 23.53 % yield) as a pale yellow solid, LCMS (*m/z*): 447.2 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 14.74 (s, 1 H), 9.06 (d, *J*=2.19 Hz, 1 H), 8.43 (dd, *J*=8.11, 2.41 Hz, 1 H), 7.75 (dd, *J*=8.88, 4.71 Hz, 1 H), 7.66 (d, *J*=8.11 Hz, 1 H), 7.41 - 7.52 (m, 3 H), 7.14 (td, *J*=8.99, 2.63 Hz, 1 H), 5.68 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.17 - 3.33 (m, 3 H), 3.04 (dd, *J*=12.17, 3.18 Hz, 1 H), 2.68 (s, 3 H), 2.32 - 2.43 (m, 1 H), 2.12 (dt, *J*=14.20, 7.04 Hz, 1 H)

Example 214

Synthesis of (4*S*)-7-(2-methylthiazol-5-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



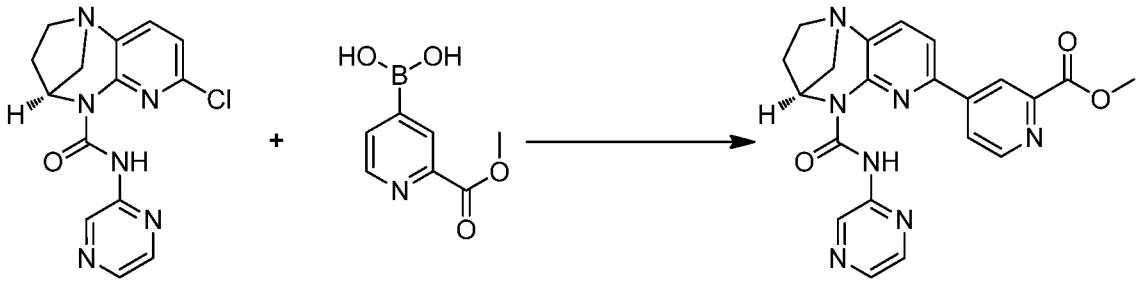
Cesium fluoride (767 mg, 5.05 mmol) was added to a stirred solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (800 mg, 2.53 mmol), 2-methyl-5-(tributylstannyl)thiazole (1177 mg, 3.03 mmol) and tri-t-butyl phosphine (511 mg, 2.53 mmol) in 1,4-Dioxane (40 mL) was degassed for 15 min, palladium (II) acetate (11.34 mg, 0.051 mmol), and copper (I) iodide (19.24 mg, 0.101 mmol) were added. The reaction mixture was further degassed for 10 min, and was stirred at 100 °C for 15 hr. The reaction mixture was cooled to 28 °C and was partitioned between water (50 mL) and EtOAc (125 mL). Organic 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 eluting with 5% MeOH in EtOAc to afford (4*S*)-7-(2-methylthiazol-5-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (230 mg, 0.600 mmol, 23.77 % yield) as off-white solid, LCMS (*m/z*): 380.18 $[M+H]^+$.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 13.30 (s, 1H), 9.53 (d, *J* = 1.6 Hz, 1H), 8.43 (s, 1H), 8.36-8.35 (dd, *J* =2.4, 1.6 Hz, 1H), 8.30 (d, *J* = 2.8 Hz 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 5.68 (dd, *J* = 6, 3.2 Hz, 1H), 3.28-3.22 (m, 2H), 3.20-3.13 (m, 1H), 3.02-2.98

(dd, *J* = 12.4, 3.6 Hz, 1H), 2.78 (s, 3H), 2.35-2.32 (m, 1H), 2.10-2.04 (m,1H).

Example 215

Synthesis of methyl 4-((4*S*)-5-(pyrazin-2-ylcarbamoyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepin-7-yl)picolinate

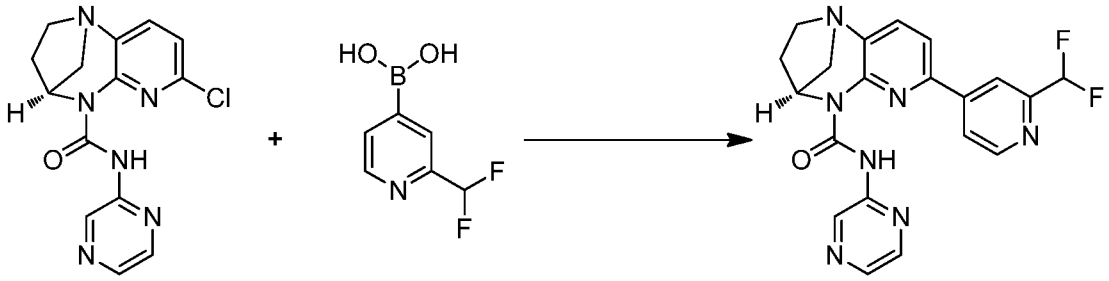


Tripotassium phosphate (2.68 g, 12.63 mmol) was added to a stirred solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (2 g, 6.31 mmol), methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinate (1.994 g, 7.58 mmol) in 1,4-dioxane (60 mL). The reaction mixture was degassed for 15 min. $Pd_2(dba)_3$ (0.289 g, 0.316 mmol) and X-phos (0.301 g, 0.631 mmol) were added. The reaction mixture was further degassed for 15 min, and was stirred at 100 °C for 18 hr. The reaction mixture was cooled to 28 °C and was partitioned between water (50 mL) and EtOAc (200 mL). Organic layer was separated and concentrated in vacuo to get crude (TLC eluent: 5% MeOH in DCM: R_f = 0.3; UV active). The crude was purified by column chromatography using (100-200 mesh) silica gel eluting with 10% MeOH in EtOAc to afford methyl 4-((4*S*)-5-(pyrazin-2-ylcarbamoyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepin-7-yl)picolinate (780 mg, 1.806 mmol, 28.6 % yield) as off white solid, LCMS (*m/z*): 418.23 $[M+H]^+$.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 13.63 (s, 1H), 9.54 (d, *J* = 1.2 Hz, 1H), 8.91-8.89 (dd, *J* = 5.2, 0.8 Hz, 1H), 8.68-8.68 (dd, *J* = 2, 0.4 Hz, 1H), 8.34-8.29 (m, 3H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 4.05 (s, 3H), 3.34-3.16 (m, 3H), 3.07-3.03 (dd, *J* = 12.4, 3.2 Hz, 1H), 2.41-2.33 (m, 1H), 2.15-2.07 (m, 1H).

Example 216

Synthesis of (4*S*)-7-(2-(difluoromethyl)pyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

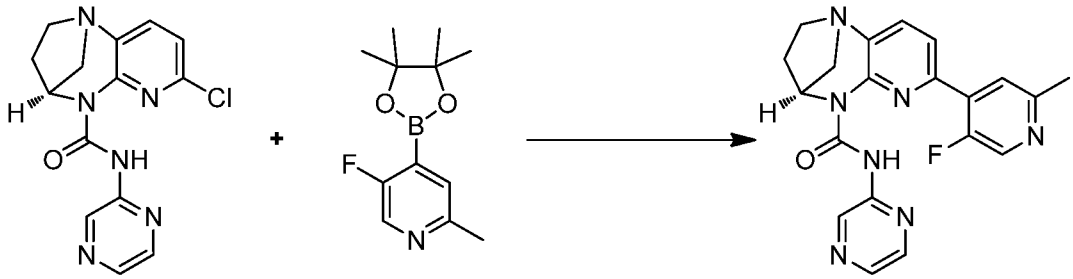


Tripotassium phosphate (670 mg, 3.16 mmol) was added to a stirred solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxa-mide (500 mg, 1.579 mmol), (2-(difluoromethyl)pyridin-4-yl)boronic acid (328 mg, 1.894 mmol) in 1,4-dioxane (10 mL), and water (1.667 mL) at 28 °C. The reaction mixture was degassed for 15 min, was added $Pd_2(dba)_3$ (145 mg, 0.158 mmol), and X-phos (75 mg, 0.158 mmol). The reaction mixture was further degassed for 15 min and the reaction mixture was stirred for 1 hr under microwave at 100 °C. The reaction mixture was cooled to 28 °C and was partitioned between water (10 mL) and EtOAc (25 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude as brown solid (TLC eluent: 10% MeOH in EtOAc: R_f= 0.3; UV active). The crude was purified by column chromatography using (100-200 mesh) silica gel and was eluted with 5-10% MeOH in EtOAc to afford pure (4*S*)-7-(2-(difluoromethyl)pyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (112 mg, 0.273 mmol, 17.27 % yield) as off white solid, LCMS (*m/z*): 410.17 $[M+H]^+$.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 13.63 (s, 1H), 9.54 (s, 1H), 8.79 (d, *J* = 5.2 Hz, 1H), 8.40 (s, 1H), 8.32 (d, *J* = 3.2 Hz, 2H), 8.06 (dd, *J* = 5.2, 0.8 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 8 Hz, 1H), 6.90-6.62 (t, *J* = 55.2 Hz, 1H), 5.73-5.71 (dd, *J* = 5.6,2.8 Hz, 1H), 3.33 - 3.16 (m, 3H), 3.06-3.03 (dd, *J* = 12.0, 3.2 Hz, 1H), 2.41-2.33 (m, 1H), 2.14-2.07 (m, 1H).

Example 217

Synthesis of (4*S*)-7-(5-fluoro-2-methylpyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

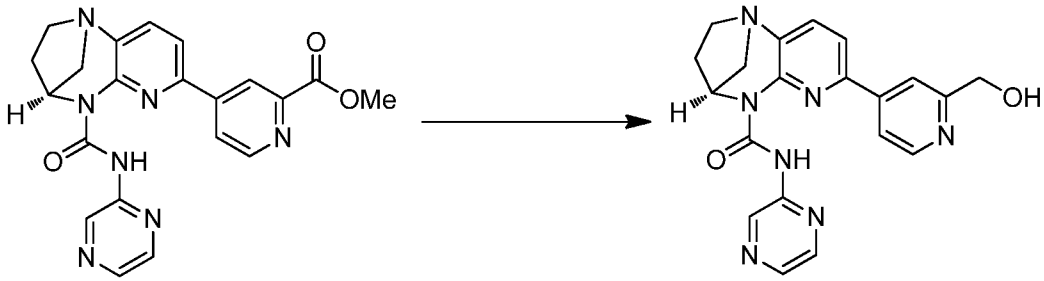


Tripotassium phosphate (804 mg, 3.79 mmol) was added to a stirred solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxa amide (600 mg, 1.894 mmol), 5-fluoro-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyridine (674 mg, 2.84 mmol) in 1,4-dioxane (20 mL), and water (3.33 mL) at 28 °C. The reaction mixture was degassed for 15 min, was added $Pd_2(dba)_3$ (173 mg, 0.189 mmol), and X-phos (90 mg, 0.189 mmol). The reaction mixture was further degassed for 15 min, and the reaction mixture was stirred for 1 hr in microwave at 100 °C. The reaction mixture was cooled to 28 °C and was partitioned between water (10 mL) and EtOAc (25 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude as brown solid (TLC eluent: 10% MeOH in EtOAc; R_f= 0.3; UV active). The crude product was washed with methanol and ether to afford (4*S*)-7-(5-fluoro-2-methylpyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (317 mg, 0.788 mmol, 41.6 % yield) as off white solid, LCMS (*m/z*): 392.20 $[M+H]^+$.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 13.54 (s, 1H), 9.57 (d, *J* = 1.6 Hz, 1H), 8.45 (d, *J* = 3.2 Hz, 1H), 8.31 (d, *J* = 2.8 Hz, 1H), 8.27-8.26 (t, *J* = 1.6 Hz, 1H), 8.09 (d, *J* = 6.8 Hz, 1H), 7.66-7.62 (t, *J* = 8 Hz, 2H), 5.73-5.71 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.34 - 3.17 (m, 3H), 3.06-3.02 (dd, *J* = 12.0, 3.2 Hz, 1H), 2.71 (s, 3H), 2.40-2.33 (m,1H), 2.13-2.06 (m, 1H).

Example 218

Synthesis of methyl 4-((4*S*)-5-(pyrazin-2-ylcarbamoyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepin-7-yl)picolinate:

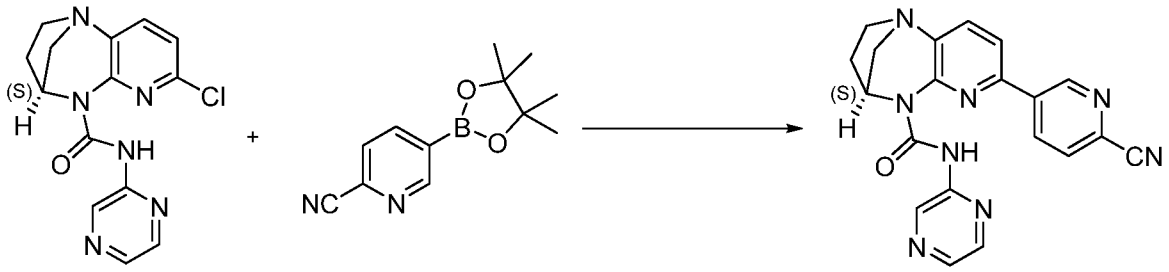


$NaBH_4$ (136 mg, 3.59 mmol) was added to a solution of methyl 4-((4*S*)-5-(pyrazin-2-ylcarbamoyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepin-7-yl)picolinate (600 mg, 1.437 mmol) in THF (100 mL) at 0°C. The reaction mixture was stirred at 28 °C for 8 h. The solvent was removed by rotary evaporation, and the residue was partitioned between ethyl acetate (40 mL) and water (20 mL). Organic layer was separated, dried over anhydrous Na_2SO_4 and filtered; filtrate was evaporated in vacuo to give crude. The crude was purified by prep HPLC to afford (4*S*)-7-(2-(Hydroxymethyl)pyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4 methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (135 mg, 0.345 mmol, 24.00 %) as off-white solid, LCMS (*m/z*): 390.22 $[M+H]^+$.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 13.66 (s, 1H), 9.60 (s, 1H), 8.68 (d, *J* = 5.2 Hz, 1H), 8.33 (s, 2H), 8.19 (s, 1H) 7.74-7.72 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 5.73-5.70 (dd, *J* = 6.0, 3.6 Hz, 1H), 4.93 (s, 2H), 3.31-3.16 (m, 3H), 3.06-3.02 (dd, *J* = 12.4, 3.2 Hz, 1H), 2.38-2.35 (m, 1H), 2.12-2.08 (t, *J* = 7.6 Hz, 1H).

Example 219

Synthesis of (4S)-7-(6-cyanopyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



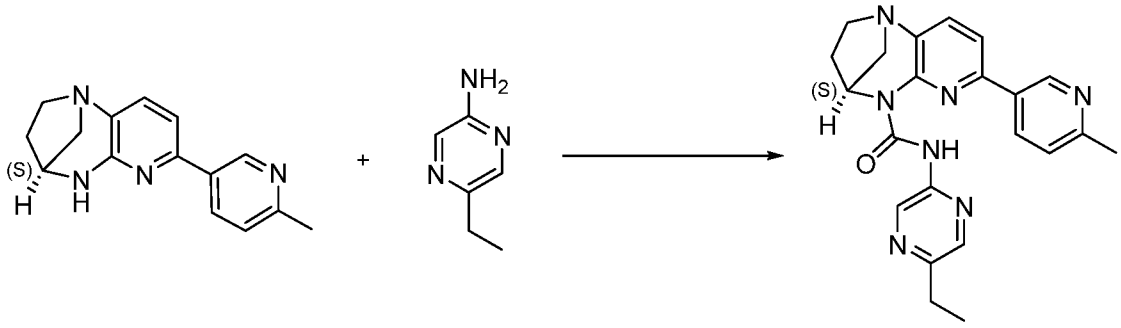
To a solution of (4S)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (600 mg, 1.894 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinonitrile (523 mg, 2.273 mmol) and K_3PO_4 (804 mg, 3.79 mmol)

in 1,4-Dioxane (20 mL), Water (3 mL) was degassed with Argon for 20 min was added X-Phos (90 mg, 0.189 mmol), Tris(dibenzylideneacetone)dipalladium(0) (87 mg, 0.095 mmol) and again degassed with Argon for 10 min. The reaction mixture was stirred at 100 °C for 16 h and cooled to room temperature. The reaction mixture was filtered through celite then the filtrate was diluted with water and extracted with EtOAc (3 X 15 mL). The combined organic layers were washed with water, brine solution, dried over sodium sulfate and evaporated to give crude compound (TLC eluent: 5% MeOH in DCM: R_f-0.1; UV active). The crude compound was purified by column chromatography using Neutral Alumina and eluted with 30%EtOAc/Pet ether to afford pure (4S)-7-(6-cyanopyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (220 mg, 0.568 mmol, 30.0 % yield) as off white solid, LCMS (*m/z*): 385.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.54 (s, 1 H) 9.54 (d, *J*=1.32 Hz, 1 H) 9.34 (dd, *J*=2.30, 0.77 Hz, 1 H) 8.66 (dd, *J*=8.11, 2.41 Hz, 1 H) 8.35 - 8.30 (m, 2 H) 7.86 (dd, *J*=8.11, 0.88 Hz, 1 H) 7.70 (d, *J*=7.89 Hz, 1 H) 7.50 (d, *J*=8.11 Hz, 1 H) 5.71 (dd, *J*=5.92, 3.29 Hz, 1 H) 3.35 - 3.14 (m, 3 H) 3.09 - 3.02 (m, 1 H) 2.43 - 2.32 (m, 1 H) 2.16 - 2.05 (m, 1 H).

Example 220

Synthesis of (4*S*)-N-(5-ethylpyrazin-2-yl)-7-(6-methylpyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



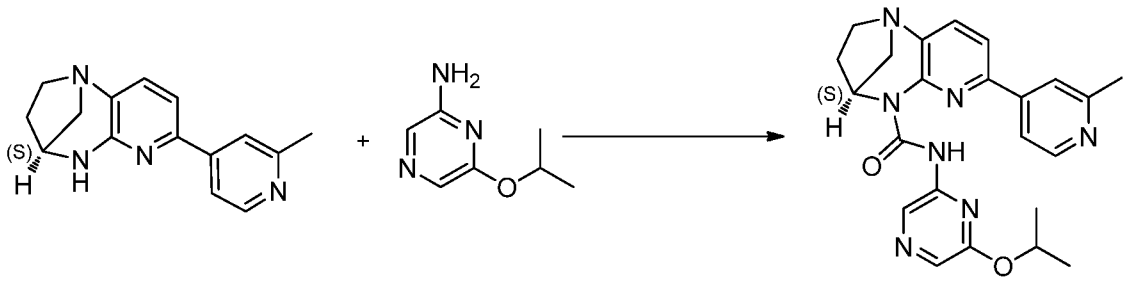
To a solution of (4S)-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (600 mg, 2.378 mmol), triphosgene (706 mg, 2.378 mmol) and triethylamine (1.989 mL, 14.27 mmol) in tetrahydrofuran (THF) (15 mL) stirred under nitrogen at room temperature for 30 min was added 5-ethylpyrazin-2-amine (879 mg, 7.13 mmol). The reaction mixture was stirred at 70 °C for 16 h and cooled to room temperature and then the reaction mixture was poured in to water and extracted with EtOAc (3 X 15 mL). The combined organic layers were washed with water, brine solution, dried over

sodium sulfate and evaporated to give crude compound (TLC eluent: 5% MeOH in DCM: R_f-0.1; UV active). The crude compound was purified by column chromatography using Neutral Alumina and eluted with 30%EtOAc/Pet ether to afford pure (4S)-N-(5-ethylpyrazin-2-yl)-7-(6-methylpyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (383 mg, 0.953 mmol, 40.1 % yield), LCMS (*m/z*): 402.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.65 (s, 1 H) 9.41 (d, *J*=1.53 Hz, 1 H) 9.11 (d, *J*=2.19 Hz, 1 H) 8.41 (dd, *J*=8.22, 2.52 Hz, 1 H) 8.22 (d, *J*=1.32 Hz, 1 H) 7.61 (d, *J*=7.89 Hz, 1 H) 7.40 (d, *J*=8.11 Hz, 1 H) 7.32 (d, *J*=8.11 Hz, 1 H) 5.70 (dd, *J*=6.03, 3.18 Hz, 1 H) 3.34 - 3.13 (m, 3 H) 3.02 (dd, *J*=12.06, 3.29 Hz, 1 H) 2.83 (q, *J*=7.53 Hz, 2 H) 2.64 (s, 3H) 2.40-2.34 (m, 1 H) 2.15 - 2.03 (m, 1 H) 1.33 (t, *J*=7.56 Hz, 3 H).

Example 221

Synthesis of (4*S*)-*N*-(6-isopropoxypyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

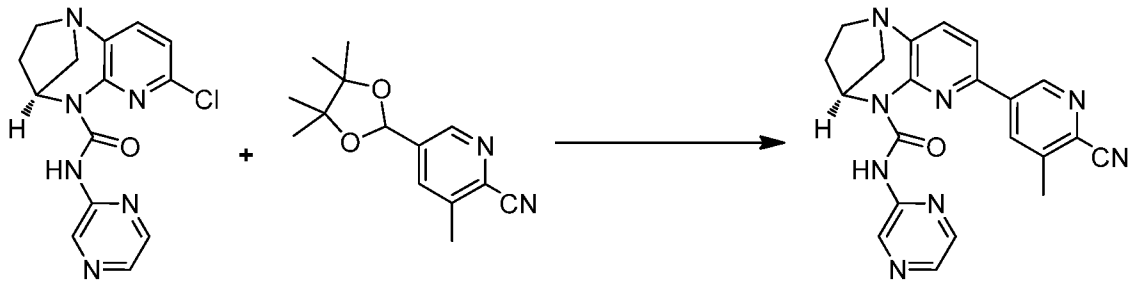


Triethylamine (1.326 mL, 9.51 mmol) followed by triphosgene (470 mg, 1.585 mmol) were added to a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (400 mg, 1.585 mmol) in tetrahydrofuran (THF) (8 mL) at RT and stirred for 30 min before 6-isopropoxypyrazin-2-amine (486 mg, 3.17 mmol) was added to the reaction mixture and stirred to 80 °C for 16 h. Reaction mixture was cooled to RT, diluted with water (50 mL), extracted with Ethyl acetate (2x40 mL), washed with brine (30 mL). Organic layer was separated, dried over sodium sulfate, filtered and concentrated. Residue was purified by flash chromatography using silica gel (100-200 mesh), 2% methanol in DCM to get (4*S*)-*N*-(6-isopropoxypyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (60 mg, 0.132 mmol, 8.33 % yield) as off-white solid (TLC: R_f: 0.4, 5% methanol in DCM), LCMS (*m/z*): 432.27 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.24 (dd, *J*=13.15, 6.14 Hz, 6 H) 2.09 (dt, *J*=14.14, 6.96 Hz, 1 H) 2.22 - 2.45 (m, 1 H) 2.65 (s, 3 H) 3.03 (dd, *J*=12.06, 3.29 Hz, 1 H) 3.13 - 3.38 (m, 3 H) 5.10 (dt, *J*=12.44, 6.17 Hz, 1 H) 5.71 (dd, *J*=6.03, 3.18 Hz, 1 H) 7.27 - 7.46 (m, 1 H) 7.51 - 7.68 (m, 2 H) 7.73 (dd, *J*=5.15, 1.43 Hz, 1 H) 7.88 (s, 1 H) 8.58 (d, *J*=5.26 Hz, 1 H) 9.03 (s, 1 H) 13.04 (s, 1 H).

Example 222

Synthesis of (4*S*)-7-(6-cyano-5-methylpyridin-3-yl)-N-(pyrazin-2-yl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-*b*] [1,4]diazepine-5(2*H*)-carboxamide



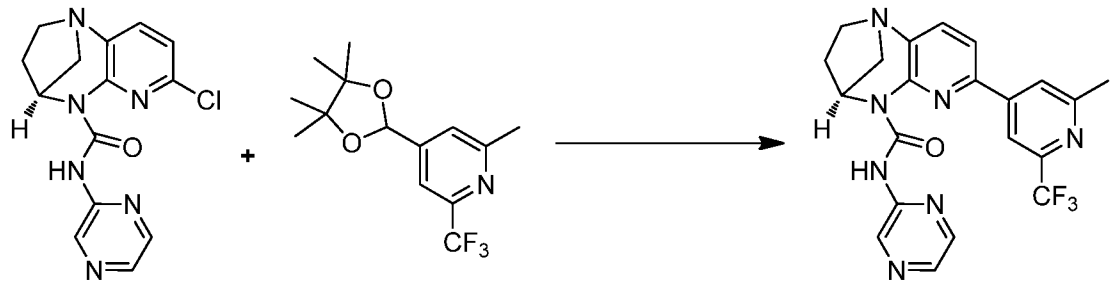
To a degassed solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (500 mg,1.579 mmol), 3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinonitrile (501 mg, 2.052 mmol) and K_3PO_4 (1.005 g, 4.74 mmol) in 1,4-dioxane (20 mL) and water (3 mL), was added X-phos (75 mg, 0.158 mmol) and $Pd(OAc)_2$ (17.72 mg, 0.079 mmol). The reaction mixture was further degassed for 15 min and the reaction mixture was stirred for 16 h at 90 °C. The reaction mixture was cooled to 28 °C and filtered through a pad of celite and filtrate was evaporated to give residue. The residue was diluted with water (20 mL) and extracted with ethyl acetate (2 x 70 mL). The combined organic layer was washed with water (10 mL) followed by brine solution (10 mL). Organic layer was dried over anhydrous sodium sulfate, filtered and filtrate was evaporated to give crude. (TLC eluent: 100 % Ethyl acetate, R_f-0.3; UV active). The crude compound was purified by column chromatography using neutral alumina, and the product was eluted with 55-60% ethyl acetate in hexane to afford pure (4*S*)-7-(6-cyano-5-methylpyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (350 mg, 0.835 mmol, 52.9 % yield) as pale yellow solid, LCMS (*m/z*): 399.22 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.61 (s, 1 H), 9.58 (d, *J*=1.5 Hz, 1 H), 9.07 (d, *J*=2.2 Hz, 1 H), 8.63 - 8.69 (m, 1 H), 8.33 (d, *J*=2.8 Hz, 1 H), 8.28 (dd, *J*=1.4, 2.6 Hz, 1 H), 7.69 (d, *J*=8.1 Hz, 1 H), 7.52 (m, *J*=8.1 Hz, 1 H), 5.72 (dd, *J*=5.9, 3.07 Hz, 1 H), 3.13 - 3.36 (m, 3

H), 3.05 (dd, *J*=12.28, 3.3 Hz, 1 H), 2.73 (S, 3 H), 2.25 - 2.44 (m, 1 H), 2.04 - 2.24 (m, 1 H).

Example 223

Synthesis of (4S)-7-(2-methyl-6-(trifluoromethyl)pyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

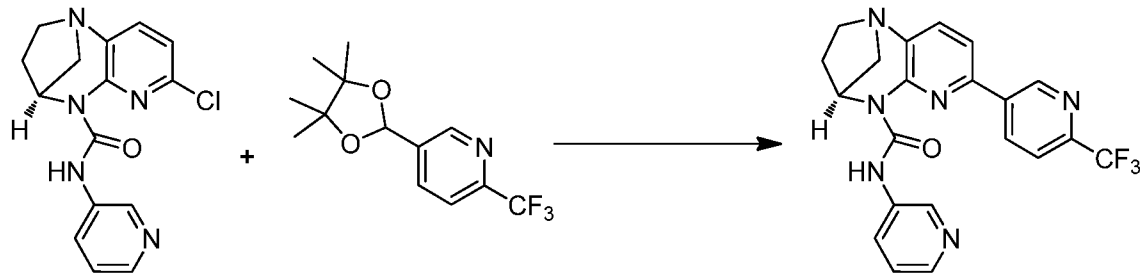


To a degassed solution of (4*S*)-7-chloro-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (400 mg, 1.263 mmol), 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)pyridine (471 mg, 1.642 mmol) and K_3PO_4 (804 mg, 3.79 mmol) in 1,4-dioxane (20 mL) and water (3 mL) was added X-phos (60.2 mg, 0.126 mmol) and $Pd_2(dba)_3$ (57.8 mg, 0.063 mmol). The reaction mixture was further degassed for 15 min and the reaction mixture was stirred for 16 h at 90 °C. The reaction mixture was cooled to 28 °C and filtered through a pad of celite and the filtrate was evaporated to give residue. The residue was diluted with water (20 mL) and extracted with ethyl acetate (2 x 70 mL). The combined organic layer was washed with water (10 mL) followed by brine solution (10 mL). The organic layer was dried over sodium sulfate, filtered and filtrate was evaporated to give crude (TLC eluent: 100 % Ethyl acetate, R_f = 0.4; UV active). The Crude compound was purified by column chromatography (neutral alumina), and the product was eluted with 45-50% ethyl acetate in hexane to afford (4*S*)-7-(2-methyl-6-(trifluoromethyl)pyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (318 mg, 0.719 mmol, 56.9 % yield) as off-white solid, LCMS (*m/z*): 442.24 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.63 (s, 1 H), 9.57 (d, *J*=1.3 Hz, 1 H), 8.22 - 8.40 (m, 2 H), 8.14 (s, 1 H), 8.11 (s, 1 H), 7.69 (d, *J*=8.1 Hz, 1 H), 7.53 (d, *J*=7.9 Hz, 1 H), 5.73 (dd, *J*=5.9, 3.0 Hz, 1 H), 3.12 - 3.37 (m, 3 H), 2.95 - 3.12 (m, 1 H), 2.79 (S, 3 H), 2.25 - 2.46 (m, 1 H), 2.00 - 2.21 (m, 1 H).

Example 224

Synthesis of (4*S*)-N-(pyridin-3-yl)-7-(6-(trifluoromethyl)pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

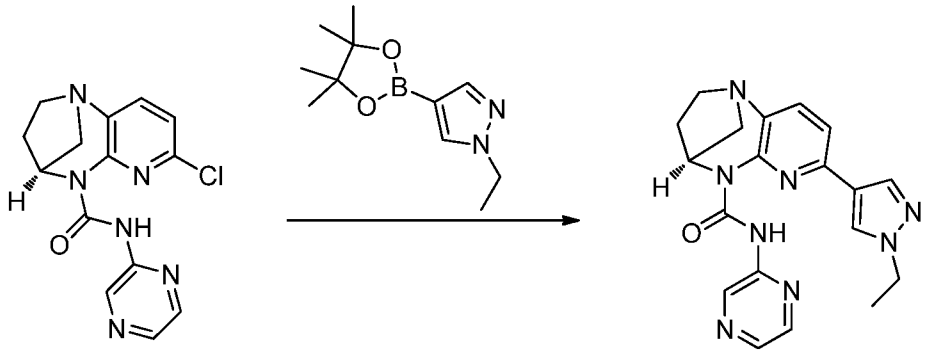


To a degassed solution of (4*S*)-7-chloro-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (500 mg, 1.583 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine (562 mg, 2.059 mmol) and K_3PO_4 (1008 mg, 4.75 mmol) in 1,4-dioxane (20 mL), and water (3 mL), was added X-phos (75 mg, 0.158 mmol) and $Pd_2(dba)_3$ (72.5 mg, 0.079 mmol). The reaction mixture was further degassed for 15 min and the reaction mixture was stirred for 16 h at 90 °C. The reaction mixture was cooled to 28 °C and filtered through a pad of celite and the filtrate was evaporated to give crude residue. The crude residue was diluted with water (20 mL) and extracted with ethyl acetate (2 x 70 mL). The combined organic layer was washed with water (10 mL) followed by brine solution (10 mL). Organic layer was dried over sodium sulfate, filtered and filtrate was evaporated to give as a brown solid (TLC eluent: 100 % ethyl acetate, R_f-0.4; UV active). The crude compound was purified by column chromatography using neutral alumina, and the product was eluted with 35-40% ethyl acetate in hexane to afford (4*S*)-N-(pyridin-3-yl)-7-(6-(trifluoromethyl)pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (400 mg, 0.924 mmol, 58.3 % yield) as off white solid, LCMS (*m/z*): 427.20 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 12.79 (s, 1 H), 9.16 (d, *J*=1.9 Hz, 1 H), 8.54 (d, *J*=2.4 Hz, 1 H), 8.32 (dd, *J*=1.2, 4.8 Hz, 1 H), 8.29 (dd, *J*=2, 8.4 Hz, 1 H), 7.99 - 8.19 (m, 1 H), 7.87 (d, *J*=8.3 Hz, 1 H), 7.69 (d, *J*=7.6 Hz, 1 H), 7.38 (d, *J*=7.9 Hz, 1 H), 7.28-7.30 (m, 1H), 5.71 (dd, *J*=5.8, 3.2 Hz, 1 H), 3.12 - 3.36 (m, 3 H), 2.94 - 3.12 (m, 1 H), 2.25 - 2.43 (m, 1 H), 2.00 - 2.23 (m, 1 H).

Example 225

Synthesis of (4*S*)-7-(2,5-dimethylpyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide:

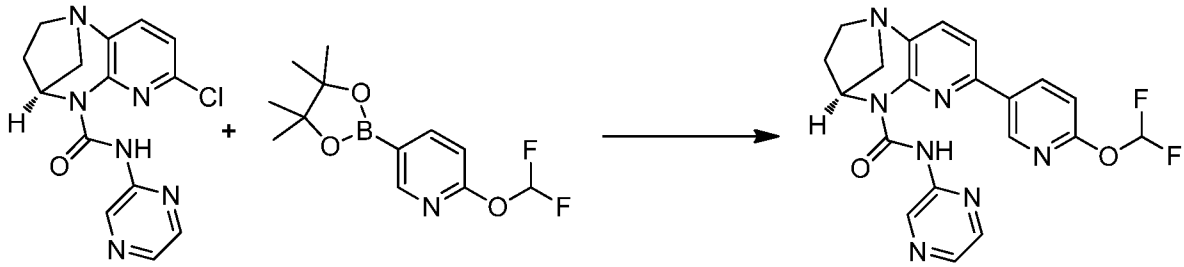


$Pd_2(dba)_3$ (0.087 g, 0.095 mmol) and X-phos (0.018 g, 0.047 mmol) was added to degassed (argon) solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (0.3 g, 0.947 mmol), 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.316 g, 1.421 mmol) and potassium dihydrogen phosphate (0.258 g, 1.894 mmol) in 1,4-dioxane (5 mL):water (1 mL). The reaction mixture was further degassed for 10 min and was stirred for 15h at 90 °C. The reaction mixture was cooled to 28 °C and was filtered through a pad of celite. The filtrate was diluted with water (50 mL) and ethyl acetate (50 mL). The organic layer was separated and was washed with water and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and filtrate was evaporated to get crude compound (TLC eluent: 10% MeOH in EtOAc; R_f-0.35 UV active). The crude compound was purified by column chromatography using neutral alumina and was eluted with 75% ethyl acetate in hexane to afford (4*S*)-7-(1-ethyl-1*H*-pyrazol-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (0.26g, 0.688 mmol, 72.6 % yield) as off-white solid, LCMS (*m/z*): 377.30 $[M+H]^+$.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 14.15 (s, 1 H), 9.60 (d, *J*=1.53 Hz, 1 H), 8.56 (s, 1 H), 8.22 - 8.30 (m, 2 H), 8.07 (s, 1 H), 7.50 (d, *J*=7.89 Hz, 1 H), 7.14 (d, *J*=7.89 Hz, 1 H), 5.66 (dd, *J*=6.03, 3.18 Hz, 1 H), 4.28 (q, *J*=7.38 Hz, 2 H), 3.11 - 3.38 (m, 3 H), 2.97 - 3.07 (m, 1 H), 2.32 (dddd, *J*=14.03, 9.98, 6.03, 3.95 Hz, 1 H), 1.97 - 2.13 (m, 1 H),1.60(d, *J*=7.20 Hz, 3 H).

Example 226

Synthesis of (4*S*)-7-(6-(difluoromethoxy)pyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

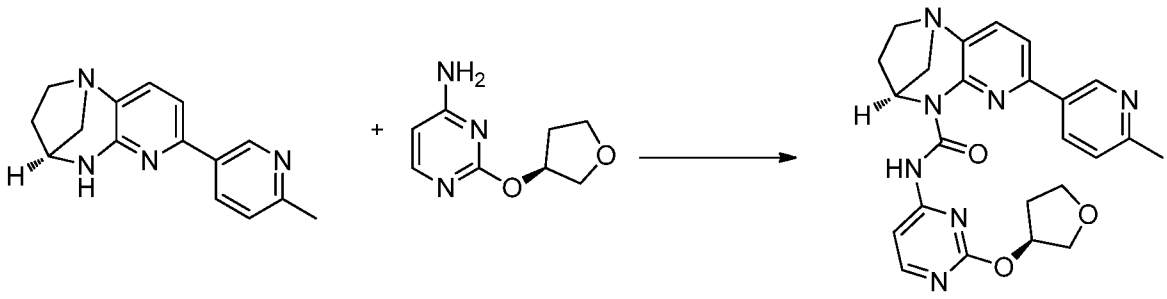


$Pd_2(dba)_3$ (0.087 g, 0.095 mmol) and X-phos (0.018 g, 0.047 mmol) was added to degassed solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)3,4dihydro1,4methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (0.3 g, 0.947 mmol), 2-(difluoromethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.385 g, 1.421 mmol) and potassium dihydrogen phosphate (0.258 g, 1.894 mmol) in 1,4-dioxane (5 mL):water (1 mL). The reaction mixture was further degassed for 10 min and was stirred for 15h at 90 °C. The reaction mixture was cooled to 28 °C and was filtered through a pad of celite. The filtrate was diluted with water (50 mL) and ethyl acetate (50 mL). The organic layer was separated and was washed with water and brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and filtrate was evaporated get crude compound (TLC eluent: 10% MeOH in EtOAc: R_f-0.4 UV active). The crude compound was purified by column chromatography using neutral alumina and was eluted with 75% ethyl acetate in hexane to afford (4*S*)-7-(6-(difluoromethoxy)pyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (0.210g, 0.493 mmol, 52.1 % yield) as Off-white solid, LCMS (*m/z*): 426.22 $[M+H]^+$.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 13.70 (s, 1 H), 9.54 (d, *J*=1.53 Hz, 1 H), 8.81 (dd, *J*=2.63, 0.66 Hz, 1 H), 8.57 (dd, *J*=8.55, 2.63 Hz, 1 H), 8.27 - 8.32 (m, 2 H), 7.74 (s, 1 H), 7.63 (d, *J*=8.11 Hz, 1 H), 7.37-7.75 (m, 1 H), 7.06 (dd, *J*=8.55, 0.66 Hz, 1 H), 5.70 (dd, *J*=5.92, 3.29 Hz, 1 H), 3.13 - 3.33 (m, 3 H), 3.03 (dd, *J*=12.17, 3.18 Hz, 1 H), 2.29 - 2.41 (m, 1 H), 2.07-2.13 (m, 1 H).

Example 227

Synthesis of (4*S*)-7-(6-methylpyridin-3-yl)-*N*-(2-(((*S*)-tetrahydrofuran-3-yl)oxy) pyrimidin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

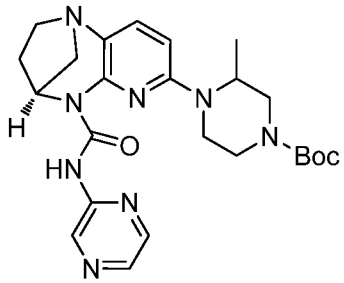


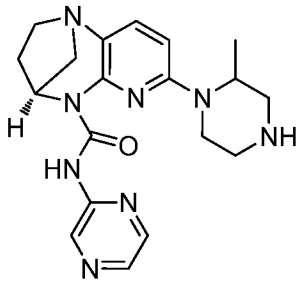
To a solution of (*S*)-2-((tetrahydrofuran-3-yl)oxy)pyrimidin-4-amine (862 mg, 4.76 mmol), triphosgene (423 mg, 1.427 mmol) in THF (15 mL) were added DIPEA (2.077 mL, 11.89 mmol) and (4*S*)-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (600 mg, 2.378 mmol) at RT. The reaction mixture was stirred at 80 °C for 16h before the THF was evaporated under reduced pressure and the residue diluted with water and extracted with DCM (2x25 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford the crude compound. The crude compound was purified by using Prep HPLC to afford (4*S*)-7-(6-methylpyridin-3-yl)-*N*-(2-(((*S*)-tetrahydrofuran-3-yl)oxy)pyrimidin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazep ine-5(2*H*)-carboxamide (195 mg, 0.421 mmol, 17.72 % yield) as a white solid (TLC: 10% MeOH in EtOAc, R_f: 0.4), LCMS (*m/z*): 460.28 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.67 (s, 1 H), 9.16 (d, *J*=2.19 Hz, 1 H), 8.38 (d, *J*=5.70 Hz, 1 H), 8.34 - 8.07 (m, 1 H), 7.80 (d, *J*=5.70 Hz, 1 H), 7.63 (d, *J*=7.89 Hz, 1 H), 7.39 (d, *J*=8.11 Hz, 1 H), 7.33 - 7.23 (m, 1 H), 5.76 - 5.58 (m, 1 H), 4.03 – 3.83 (m, 4 H), 3.35 - 3.10 (m, 3 H), 2.49 - 2.24 (m, 1 H), 2.23 - 2.00 (m, 3 H).

Example 228

Synthesis of (4*S*)-7-(2-methylpiperazin-1-yl)-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyri do[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



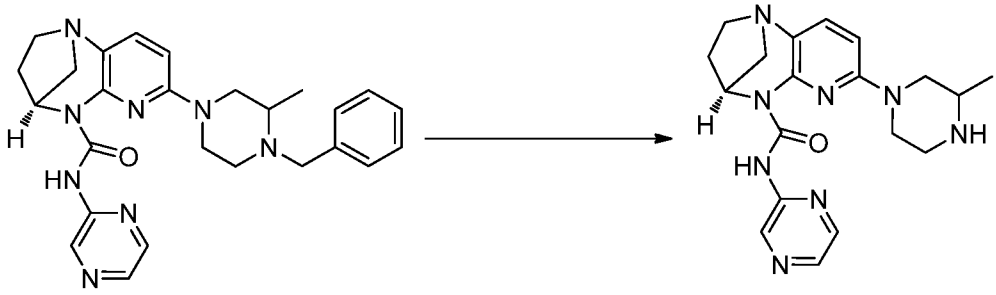


To a stirred solution of Tert-butyl3-methyl-4-((4*S*)-5-(pyrazin-2-ylcarbamoyl)-2,3,4,5-tetrahydro-1,4-methanopyrido [2,3-*b*][1,4]diazepin-7-yl)piperazine-1-carboxylate (397mg, 0.826 mmol) in THF (5 mL) was added 2M HCl solution in diethyl ether (2.065 mL, 4.13 mmol) at 0 °C and the reaction mixture was stirred at 35 °C for 4 h. The reaction mixture was neutralized with aq $NaHCO_3$ solution and extracted with CH_2Cl_2 (3x50 mL). The combined organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude product. The crude mixture was purified by Prep HPLC to afford (4*S*)-7-(2-methylpiperazin-1-yl)-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyri do[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (270 mg, 0.710 mmol, 85% yield) as an off white solid (TLC: 5% MeOH in DCM, Rf: 0.3), LCMS (*m/z*): 381 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.36 - 13.49 (m, 1 H), 9.39 (m, 1 H), 8.41 - 8.22 (m, 2 H), 7.44 - 7.29 (m, 1 H), 6.41 (dd, *J*=8.77, 2.63 Hz, 1 H), 5.44 (dd, *J*=5.26, 2.63 Hz, 1 H), 4.42 - 4.25 (m, 1 H), 3.93 - 3.68 (m, 1 H), 3.16 – 2.98 (m, 4 H), 2.90 - 2.73 (m, 3 H), 2.69 - 2.53 (m, 1 H), 2.37 - 2.27 (m, 2 H), 2.26 - 2.10 (m, 1 H), 1.99 - 1.79 (m, 1 H), 1.12 (dd, *J*=6.58, 3.95 Hz, 3 H).

Example 229

Synthesis of (4*S*)-7-(3-methylpiperazin-1-yl)-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido [2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

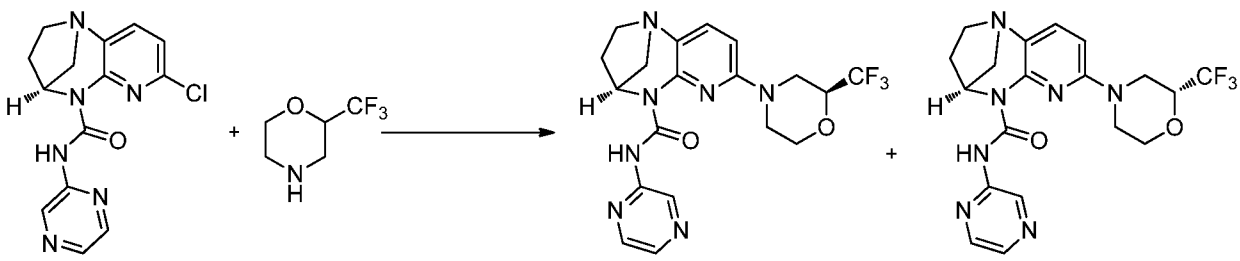


To a stirred solution of (4*S*)-7-(4-benzyl-3-methylpiperazin-1-yl)-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (450 mg, 0.956 mmol) in Methanol (10 mL) were added acetic acid (0.027 mL, 0.478 mmol) and 10% palladium hydroxide on carbon (67.1 mg, 0.096 mmol) at RT under hydrogen atmosphere (balloon pressure) and the reaction mixture was stirred at 35 °C for 4 h. After completion of reaction the reaction mixture was filtered through celite pad, the filtrate was evaporated in vacuo to give the crude product. The crude mixture was purified by Prep HPLC to afford (4*S*)-7-(3-methylpiperazin-1-yl)-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido [2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (280 mg, 0.736 mmol, 76% yield) as pale brown solid (TLC: Rf: 20% MeOH in DCM, 0.4), LCMS (*m/z*): 381.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.43 (s, 1 H), 9.55 (d, *J*=1.53 Hz, 1 H), 8.24 (d, *J*=2.63 Hz, 1 H), 8.09 - 8.20 (m, 2 H), 7.36 (d, *J*=8.55 Hz, 1 H), 6.30 (d, *J*=8.55 Hz, 1 H), 5.62 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.20 (d, *J*=12.06 Hz, 1 H), 3.95 (d, *J*=11.84 Hz, 1 H), 3.08 – 2.87 (m, 4 H) 3.25 - 3.08 (m, 4 H), 2.57 (ddd, *J*=12.33, 10.25, 2.19 Hz, 1 H), 2.27 (dddd, *J*=13.92, 9.98, 6.14, 3.73 Hz, 1 H), 2.00 (dt, *J*=14.41, 7.37 Hz, 1 H), 1.21 (d, *J*=6.14 Hz, 3 H).

Example 230, and Example 231

(4*S*)-*N*-(pyrazin-2-yl)-7-((±)-2-(trifluoromethyl)morpholino)-3,4-dihydro-1,4-methanopyrido[2,3-*b*] [1,4] diazepine-5 (2*H*)-carboxamide



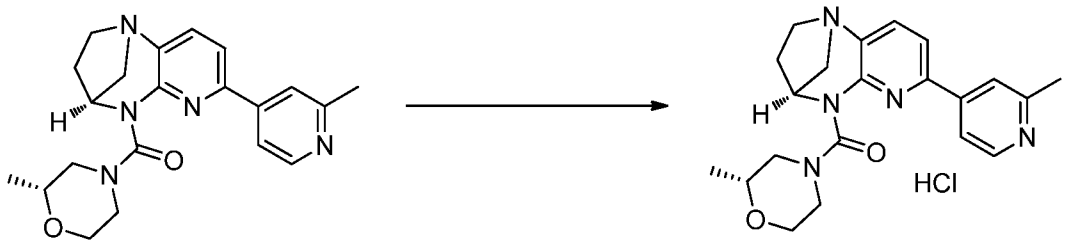
To a degassed solution of (4*S*)-7-chloro-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (2 g, 6.31 mmol) and 2-(trifluoromethyl)morpholine (1.469 g, 9.47 mmol) in 1,4-dioxane (30 mL) were added cesium carbonate (6.17 g, 18.94 mmol), x-phos (1.204 g, 2.53 mmol) and palladium(II) acetate (0.284 g, 1.263 mmol). The reaction mixture was stirred at 100 °C for 16 h in sealed tube. The reaction mixture was poured in to cold water (80 mL) and extracted with ethyl acetate (3x100 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain the crude product. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 2% MeOH in CH_2Cl_2) to afford enantiomeric mixture of (4S)-N-(pyrazin-2-yl)-7-(($\pm$)-2-(trifluoromethyl)morpholino)-3,4-dihydro-1,4-methanopyrido[2,3-b] [1,4] diazepine-5 (2H)-carboxamide. The mixture was separated by chiral prep-SFC (conditions: (Cellulose-2 (250 X 30) mm, 55.0% (100% MeOH) , 90.0g/min, 100.0bar, 42nm, 8.5min)) as peak-I (fastest eluent: 320 mg, 0.736 mmol, 42% yield) and peak-II (slowest eluent: 305 mg, 0.701 mmol, 40.5% yield) as an off white solids (TLC: neat EtOAc, R_f:-0.21), LCMS (*m/z*): 436.25 $[M+H]^+$.

Fastest eluent peak: **^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm 13.19 (s, 1 H), 9.52 (s, 1 H), 8.25 (d, *J*=2.41 Hz, 1 H), 8.21 - 8.09 (m, 1 H), 7.43 (d, *J*=8.33 Hz, 1 H), 6.35 (d, *J*=8.55 Hz, 1 H), 5.64 (dd, *J*=6.03, 3.18 Hz, 1 H), 4.21 (dd, *J*=11.84, 1.97 Hz, 1 H), 4.15 - 4.00 (m, 1 H), 4.00-3.77 (m, 3 H), 3.26 - 3.04 (m, 5 H), 3.04 – 2.82 (m, 1 H), 2.28 (dddd, *J*=13.95, 10.00, 6.19, 3.84 Hz, 1 H), 2.07 – 1.92 (m, 1 H).

Slowest eluent peak: **^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm 13.20 (s, 1 H), 9.52 (d, *J*=1.53 Hz, 1 H), 8.26 (d, *J*=2.41 Hz, 1 H), 8.16 (dd, *J*=2.41, 1.53 Hz, 1 H), 7.43 (d, *J*=8.55 Hz, 1 H), 6.35 (d, *J*=8.55 Hz, 1 H), 5.63 (dd, *J*=6.03, 3.18 Hz, 1 H), 4.21 (d, *J*=12.06 Hz, 1 H), 4.08 (ddd, *J*=10.69, 6.19, 2.85 Hz, 1 H), 4.00 – 3.92 (m, 2 H), 3.84 (td, *J*=11.56, 2.96 Hz, 1 H), 3.26 - 3.07 (m, 5 H), 3.07 – 2.82 (m, 1 H), 2.43 - 2.24 (m, 1 H), 2.21 – 1.95 (m, 1 H).

Example 232

Synthesis of ((*R*)-2-methylmorpholino)((4*S*)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepin-5(2*H*)-yl)methanone hydrochloride

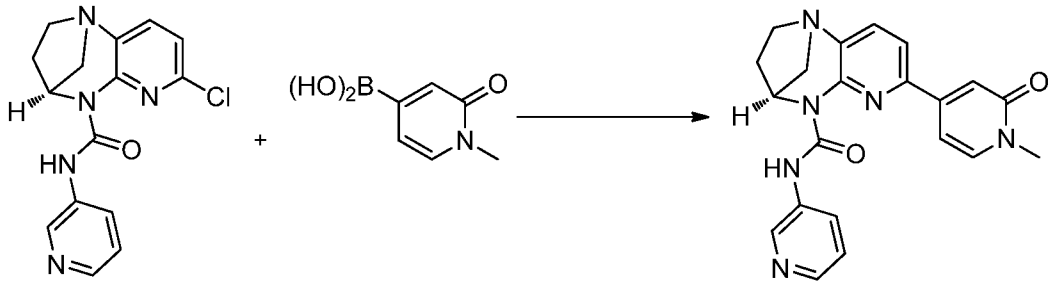


1.0 M Hydrochloric acid in dioxane (1.6 mL) was added to a stirred solution of (*R*)-2-methylmorpholino)((4*S*)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1, 4]diazepin-5(2*H*)-yl)methanone (0.21 g, 0.544 mmol) in methanol (5 mL) at 0°C. The reaction mixture was evaporated to give crude compound. The crude compound was triturated with diethyl ether (3x5 mL) to afford pure ((*R*)-2-methylmorpholino)((4*S*)-7-(2-methylpyridin-4-yl)-3,4dihydro1,4methanopyrido[2,3-b][1,4]diazepin-5(2*H*)-yl)methanone hydrochloride (105 mg, 0.253 mmol, 45 % yield) as yellow solid, LCMS (*m/z*): 380.25 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.86 (br d, *J* =5.92 Hz, 1 H), 8.41 (br s, 1 H), 8.28 (br s, 1 H), 7.82 - 8.07 (m, 2 H), 4.64 (br s, 1 H), 3.23 - 4.11 (m, 9 H), 2.99 - 3.14 (m, 1 H), 2.53 - 2.87 (m, 4 H), 2.19 - 2.43 (m, 2 H), 0.89 - 1.15 (m, 3 H)

Example 233

Synthesis of (4*S*)-7-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-*N*-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



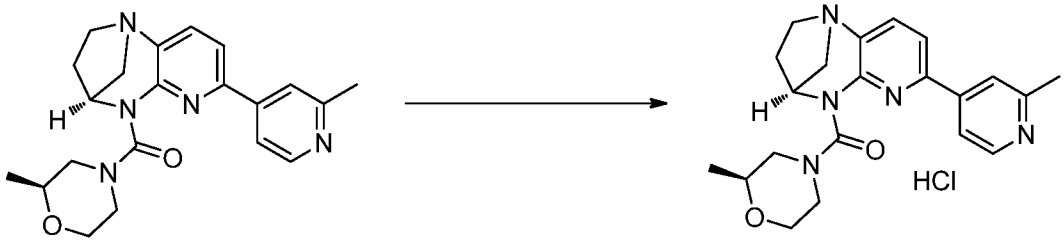
To a degassed solution of (4*S*)-7-chloro-*N*-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (400 mg, 1.267 mmol), potassium phosphate (537 mg, 2.53 mmol) and (1-methyl-2-oxo-1,2-dihydropyridin-4-yl)boronic acid (291 mg, 1.900 mmol) in mixture of 1,4-dioxane (9 mL) and water (1 mL) were added X-Phos (60.4 mg, 0.127 mmol) and $Pd(OAc)_2$ (14.22 mg, 0.063 mmol) at RT

and heated at 100 °C for 16h. Allowed the reaction mixture to RT, organic solvent was removed by rotary evaporation and diluted with water (50 mL), extracted with ethyl acetate (3x50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated to obtain the crude product. The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 03% MeOH in DCM) to afford (4*S*)-7-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-*N*-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (150 mg, 0.383 mmol, 30.2 % yield) as an off white solid (TLC: R_f 0.4, 10% MeOH/DCM), LCMS (*m/z*): 389.22 $[M+H]^+$.

^{1}H NMR (400 MHz,$CDCl_3$): δ ppm12.92 (s, 1 H), 8.57 (d, *J*=2.63 Hz, 1 H), , 8.06 - 8.32 (m, 2 H), 7.62 (d, *J*=7.89 Hz, 1 H), 7.48 (d, *J*=7.02 Hz, 1 H), 7.25 - 7.32 (m, 2 H), 6.95 (d, *J*=1.75 Hz, 1 H), 6.63 (dd, *J*=7.02, 1.97 Hz, 1 H), 5.68 (dd, *J*=5.92, 3.29 Hz, 1 H), 3.62 (s, 3H), 3.19-3.39 (m, 2 H), 3.15 (d, *J*=12.06 Hz, 1 H), 2.84 - 3.09 (m, 1 H), 2.19-2.39 (m, 1 H), 2.05-2.19 (m, 1 H).

Example 234

Synthesis of ((S)-2-methylmorpholino)((4S)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepin-5(2H)-yl)methanone hydrochloride



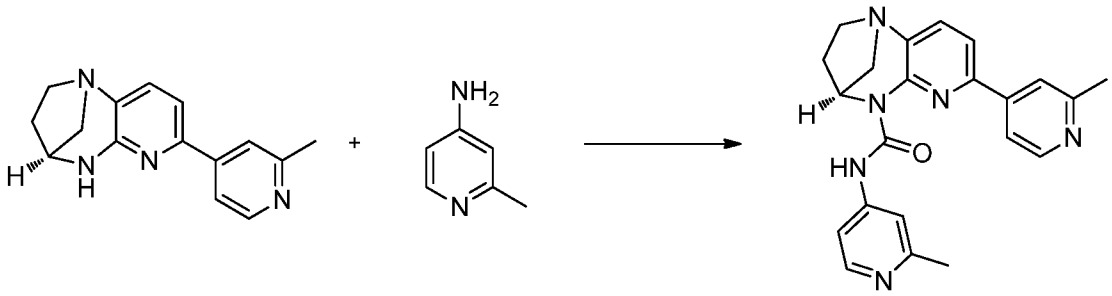
1.0 M Hydrochloric acid in dioxane (1.74 mL) was added to a stirred solution of(*S*)-2-methylmorpholino)(4*S*)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepin-5(2*H*)-yl)methanone (0.22 g, 0.580 mmol) in methanol(5 mL) at 0°C. The reaction mixture was stirred at 28 °C for 4 h. The reaction mixture was evaporated to give crude compound. The crude compound was triturated with diethyl ether (3x5 mL) to afford pure((S)-2-methylmorpholino)((4S)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4methanopyrido [2,3-b][1,4]diazepin-5(2H)-yl)methanone hydrochloride (110 mg, 0.265 mmol, 45 % yield) as yellow solid, LCMS (*m/z*): 380.25 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.86 (d, *J* = 6.36 Hz, 1 H), 8.38 - 8.45 (m, 1 H), 8.24 - 8.34 (m, 1 H), 7.86 - 7.99 (m, 2 H), 4.57 - 4.64 (m, 1 H), 4.07 (br d, *J*=10.30 Hz, 1 H),

3.35 - 3.85 (m, 10 H), 3.07 (br t, *J*=12.06 Hz, 1 H), 2.81 (s, 4 H), 2.39 (s, 2H), 0.96 - 1.17 (m,3 H).

Example 235

Synthesis of (4*S*)-*N*-7-bis(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4] diazepine-5(2*H*)-carboxamide

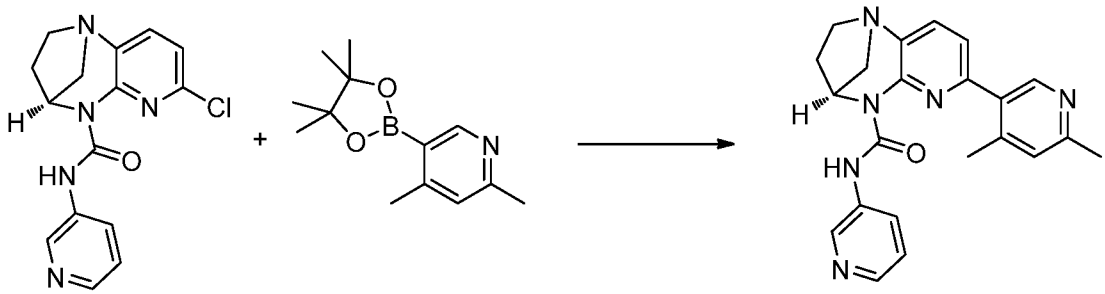


To a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (0.8 g, 3.17 mmol) in THF (15 mL) was added triphosgene (0.565 g, 1.902 mmol) at room temp and stirred for 30 min. Then 2-methylpyridin-4-amine (0.686 g, 6.34 mmol) and DIPEA (1.661 mL, 9.51 mmol) were added at room temperature. The reaction mixture was heated at 80 °C for 15 h. THF evaporated under reduced pressure and diluted with water (15 ml) and extracted with DCM (2x 20 ml). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to obtain crude compound. The crude compound was purified by flash column chromatography to afford (4*S*)-*N*-7-bis(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4] diazepine-5(2*H*)-carboxamide (120 mg, 0.31 mmol, 22%) as a white solid (TLC: 10% MeOH in EtoAc, R_f: 0.4), LCMS (*m/z*): 387.28 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.15 (s, 1 H), 8.68 (d, *J*=5.26 Hz, 1 H), 8.36 (d, *J*=5.48 Hz, 1 H), 7.70 - 7.56 (m, 1 H), 7.56 - 7.47 (m, 1 H), 7.34 - 7.42 (m, 2 H), 7.31 - 7.25 (m, 2 H), 5.68 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.20 - 3.11 (m, 3 H), 3.03 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.63 (s, 3 H), 2.52 (s, 3 H), 2.43-2.25(m, 1 H), 2.15-2.03(m, 1 H).

Example 236

Synthesis of (4*S*)-7-(4,6-dimethylpyridin-3-yl)-*N*-(pyridin-3-yl)-3,4-dihydro-1,4-methano pyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

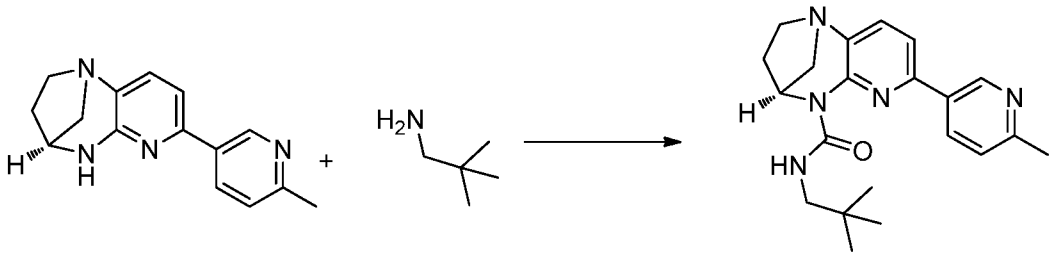


To a degassed solution of (4*S*)-7-chloro-*N*-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (400 mg, 1.267 mmol), 2,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (591 mg, 2.53 mmol) and Cs_2CO_3 (1238 mg, 3.80 mmol) in mixture of 1,4-dioxane (9 mL) and water (1 mL) were added $Pd(OAc)_2$ (14.22 mg, 0.063 mmol) and X-Phos (60.4 mg, 0.127 mmol) at RT and heated at 100 °C for 16h. Allowed the reaction mixture to RT, organic solvent was removed by rotary evaporation and diluted with water (50 mL), extracted with ethyl acetate (3x50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to obtain crude product. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 3% MeOH in DCM) to afford (4*S*)-7-(4,6-dimethylpyridin-3-yl)-*N*-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (115 mg, 0.295 mmol, 23.30 % yield) as an off white solid (TLC: R_f: 0.4, 10% MeOH in DCM), LCMS (*m/z*): 387.25 $[M+H]^+$.

^{1}H NMR (400 MHz,$CDCl_3$): δ ppm 13.07 (br s, 1 H), 8.51 (s, 1 H), 8.24 (br d, *J*=4.17 Hz, 1 H), 8.18-7.97 (m, 1 H), 7.61 (br d, *J*=7.67 Hz, 1 H), 7.34-7.16 (m, 2 H), 7.13 (m, 1 H), 5.68 (br d, *J*=2.19 Hz, 1 H), 3.38-3.11 (m, 3 H), 3.11-2.89 (m, 1 H), 2.60 (s, 3 H), 2.36 (s, 4 H) 2.30-2.03 (m, 1 H), 1.36-1.12 - (m, 1 H).

Example 237

Synthesis of (4*S*)-7-(6-methylpyridin-3-yl)-*N*-neopentyl-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

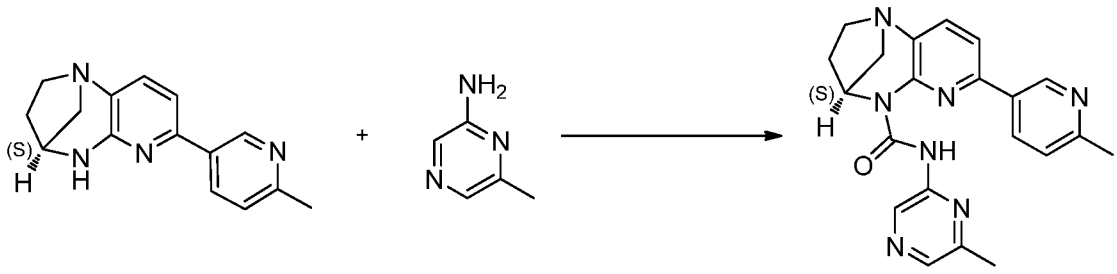


To a stirred solution of (4*S*)-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methano benzo[*b*][1,4]diazepine (250 mg, 0.991 mmol) in THF (10 mL) was added triphosgene (176 mg, 0.594 mmol) at RT and stirred for 30 min. Then DIPEA (0.519 mL, 2.97 mmol) and 2,2-dimethylpropan-1-amine (130 mg, 1.486 mmol) were added to above reaction mixture and stirred at 80 °C for 16 h. Allowed the reaction mixture to warm to RT, diluted with water (60 mL) and extracted with ethyl acetate (3x50 mL). The combined organic layer was washed with brine (60 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to obtain the crude product. The crude was purified by flash column chromatography (silica-gel 100-200 mesh, eluent: 2% MeOH in DCM) to afford (4*S*)-7-(6-methylpyridin-3-yl)-*N*-neopentyl-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (163 mg, 0.441 mmol, 44.5 % yield) as a pale yellow solid (TLC: R_f: 0.4, 10% MeOH in DCM), LCMS (*m/z*): 366.29 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 10.45 (br s, 1 H), 8.88 (s, 1 H), 7.93 (br d, *J*=7.89 Hz, 1 H), 7.54 (d, *J*=7.89 Hz, 1 H), 7.34-7.11 (m, 2 H), 5.77-5.51 (m, 1 H), 3.33-3.14 (m, 5 H), 2.95 (brdd, *J*=11.84, 3.07 Hz, 1 H), 2.61 (s, 3 H), 2.35-2.18 (m, 1 H), 2.18-1.89 (m, 1 H), 0.90 (s, 9 H).

Example 238

Synthesis of (4S)-N-(6-methylpyrazin-2-yl)-7-(6-methylpyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

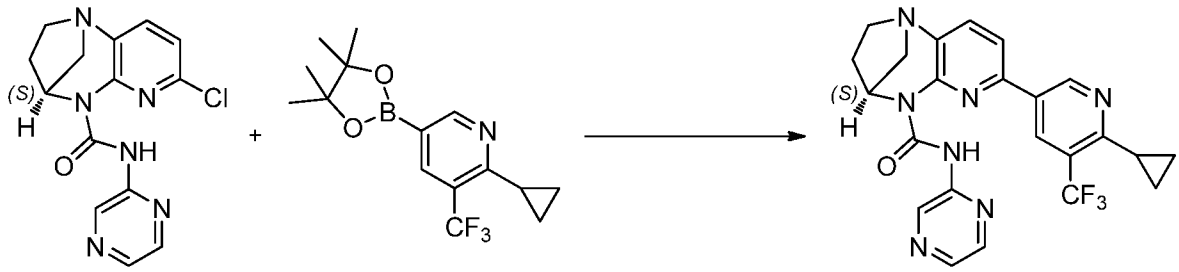


To a solution of (4S)-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (600 mg, 2.378 mmol), triphosgene (706 mg, 2.378 mmol) and triethylamine (1.989 mL, 14.27 mmol) in tetrahydrofuran (15 mL) stirred under nitrogen at room temp for 30 min was added 6-methylpyrazin-2-amine (778 mg, 7.13 mmol). The reaction mixture was stirred at 70 °C for 16 h and cooled to room temperature. The reaction mixture was poured in to water and extracted with EtOAc (3 X 15 mL). The combined organic layers were washed with water, brine solution, dried over sodium sulfate and evaporated to give crude compound (TLC eluent: 5% MeOH in DCM: R_f-0.1; UV active). The crude compound was purified by column chromatography using neutral alumina and eluted with 30% EtOAc / pet ether to afford pure (4*S*)-N-(6-methylpyrazin-2-yl)-7-(6-methylpyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (151 mg, 0.389 mmol, 16.38 % yield) as off white solid. LCMS (*m/z*): 388.2 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.79 (s, 1 H) 9.33 (s, 1 H) 9.10 (d, *J*=2.41 Hz, 1 H) 8.55 (dd, *J*=8.11, 2.41 Hz, 1 H) 8.19 (s, 1 H) 7.62 (d, *J*=7.89 Hz, 1 H) 7.43 (d, *J*=7.89 Hz, 1 H) 7.31 (d, *J*=8.11 Hz, 1 H) 5.70 (dd, *J*=5.92, 3.07 Hz, 1 H) 3.36 - 3.14 (m, 3 H) 3.02 (dd, *J*=11.95, 3.40 Hz, 1 H) 2.65 (s, 3 H) 2.56 (s, 3 H) 2.42-2.32 (m, 1 H) 2.18-2.01 (m, 1 H).

Example 239

Synthesis of (4*S*)-7-(6-cyclopropyl-5-(trifluoromethyl)pyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



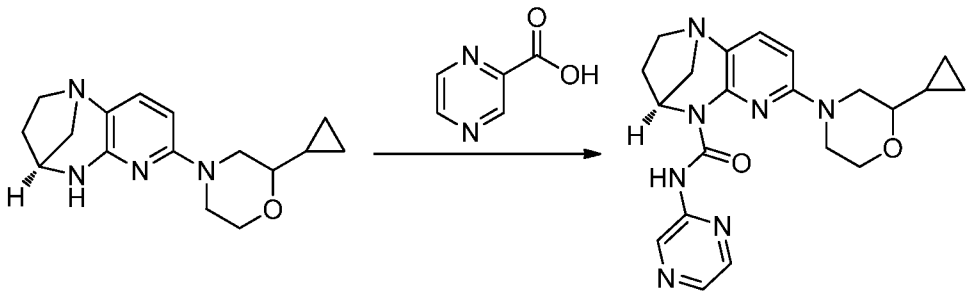
To a solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (600 mg, 1.894 mmol), 2-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridine (mg, mmol) and K_3PO_4 (804 mg, 3.79 mmol) in 1,4-dioxane (20 mL), water (3 mL) degassed with argon for 20 min was added X-Phos (90 mg, 0.189 mmol), tris(dibenzylideneacetone)dipalladium(0) (87 mg, 0.095 mmol) and again degassed with argon for 10 min. The reaction mixture was

stirred at 100 °C for 16 h and cooled to room temperature. The reaction mixture was filtered through celite then the filtrate was diluted with water and extracted with EtOAc (3 X 15 mL). The combined organic layers was washed with water, brine solution, dried over sodium sulfate and evaporated to give crude compound (TLC eluent: 5% MeOH in DCM: R_f-0.2; UV active). The crude compound was purified by column chromatography using neutral alumina and eluted with 30% EtOAc/pet ether to afford pure (4*S*)-7-(6-cyclopropyl-5-(trifluoromethyl)pyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4] diazepine-5(2*H*)-carboxamide (380 mg, 0.813 mmol, 42.85 % yield) as off white solid, LCMS (*m/z*): 468.2 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.66 (s, 1 H) 9.51 (d, *J*=1.53 Hz, 1 H) 9.08 (d, *J*=1.97 Hz, 1 H) 8.58 (d, *J*=2.19 Hz, 1 H) 8.31 - 8.24 (m, 2 H) 7.64 (d, *J*=7.89 Hz, 1 H) 7.38 (d, *J*=7.89 Hz, 1 H) 5.71 (dd, *J*=5.92, 3.07 Hz, 1 H) 3.34 - 3.14 (m, 3 H) 3.03 (dd, *J*=12.06, 3.29 Hz, 1 H) 2.47 - 2.30 (m, 2 H) 2.15 - 2.04 (m, 1 H) 1.33 - 1.28 (m, 2 H) 1.16 - 1.10 (m, 2 H).

Example 240

Synthesis of (4*S*)-7-(2-cyclopropylmorpholino)-N-(pyrazin-2-yl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-*b*] [1, 4] diazepine-5(2*H*)-carboxamide



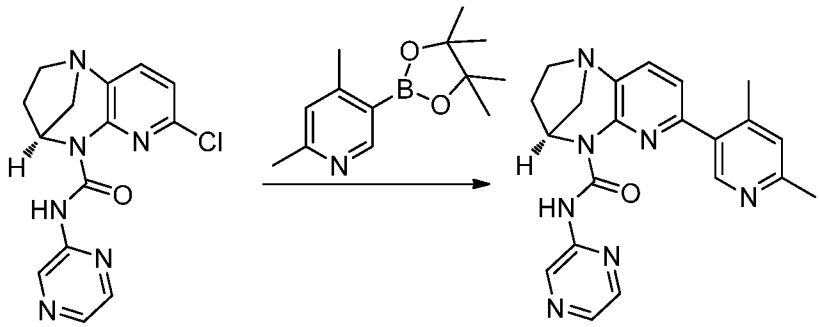
To a solution of Pyrazine-2-carboxylic acid (550 mg, 4.43 mmol) in THF (10 mL) under nitrogen at 0 °C diphenyl phosphorazidate (2439 mg, 8.86 mmol) and TEA were added (3.09 mL, 22.16 mmol) and stirred for 2 h at RT. To this reaction mixture 2-cyclopropyl-4-((4*S*)-2, 3, 4,5-tetrahydro-1,4-methanopyrido [2,3-*b*][1,4]diazepin-7-yl)morpholine (888 mg, 3.10 mmol) was added and stirred at 100 °C for 16 h. The reaction mixture was diluted with water and extracted with ethyl acetate (2x25 ml). The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude compound. The crude product was purified by flash column chromatography (100-200 silica gel eluted with 2% of MeOH in CH_2Cl_2) to afford compound (4*S*)-7-(2-cyclopropylmorpholino)-*N*-(pyrazin-2-yl)-3, 4-dihydro-1, 4-

methanopyrido [2, 3-*b*] [1, 4] diazepine-5(2*H*)-carboxamide (90 mg, 0.219 mmol, 4.95 % yield) as a pale brown solid. (TLC system:5% Methanol in DCM. R_f value: 0.3), LCMS (*m/z*): 408.33 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.32 (s, 1 H), 9.37 (d, *J*=1.32 Hz, 1 H), 8.43 - 8.13 (m, 2 H), 7.41 (d, *J*=8.55 Hz, 1 H), 6.56 (d, *J*=8.77 Hz, 1 H), 5.56 - 5.28 (m, 1 H), 4.13- 3.73 (m, 3 H), 3.55 (td, *J*=11.56, 2.52 Hz, 1 H), 3.16 - 2.63 (m, 7 H), 2.31 - 1.99 (m, 1 H), 1.85 (dt, *J*=13.92, 6.85 Hz, 1 H), 1.08- 0.76 (m, 1 H), 0.59 - 0.12 (m, 4 H)

Example 241

Synthesis of (4*S*)-7-(4,6-dimethylpyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

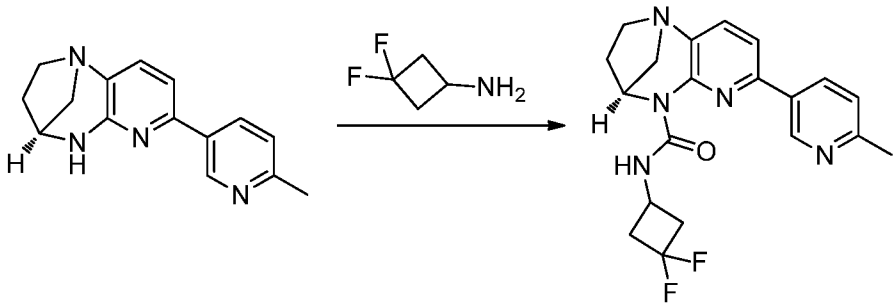


Cs_2CO_3 (1237 mg, 3.797mmol) and 2,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (590 mg, 2.531mmol) were added to a solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (400 mg, 1.265mmol) in mixture of 1,4-Dioxane (9 mL) and water (1 mL). The reaction mixture was purged with argon for 30 min. $PdOAc_2$ (28.3 mg, 0.126 mmol) and X-Phos (120.6 mg, 0.253 mmol) were added to above reaction mixture, stirred at 100 °C for 16h. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the residue was partitioned between water (40 mL) and EtOAc (80 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 column chromatography using silica gel (100-200 mesh) 2% methanol in dichloromethane as a eluent to afford (4*S*)-7-(4,6-dimethylpyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (135 mg, 0.332 mmol, 52.5 % yield) as an off white solid.(TLC eluent: 10% MeOH in DCM Rf: 0.4; UV active), LCMS (*m/z*): 388.28 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.37 (s, 1 H), 9.45 (d, *J*=1.32 Hz, 1 H), 8.54 (s, 1 H), 8.22 (d, *J*=2.63 Hz, 1 H), 8.16 - 8.20 (m, 1 H), 7.62 (d, *J*=7.67 Hz, 1 H), 7.12 (s, 1 H), 7.07 (d, *J*=7.89 Hz, 1 H), 5.71 (dd, *J*=5.81, 2.96 Hz, 1 H), 3.15 - 3.36 (m, 3 H), 3.03 (dd, *J*=12.17, 3.40 Hz, 1 H), 2.59 (s, 3 H), 2.46 (s, 3 H), 2.28 - 2.38 (m, 1 H), 2.04 - 2.17 (m, 1 H).

Example 242

Synthesis of (4*S*)-N-(3,3-difluorocyclobutyl)-7-(6-methylpyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

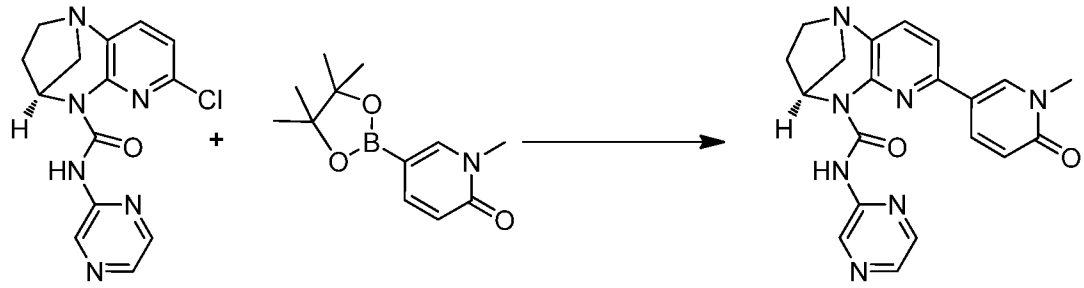


Triphosgene (212 mg, 0.714 mmol) was added slowly in portions to a stirred solution of (4*S*)-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 1.190mmol) in Tetrahydrofuran (THF) (15 mL) at RT. This reaction mixture was stirred for 30 min. DIPEA (0.623 mL, 3.57 mmol) and 3,3-difluorocyclobutanamine (191 mg, 1.785mmol) were added to above reaction mixture, stirred at 80 °C for 16 h. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the residue was partitioned between water (40 mL) and EtOAc (80 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 column chromatography using silica gel (100-200 mesh) 2% methanol in dichloromethane as a eluent to afford (4*S*)-N-(3,3-difluorocyclobutyl)-7-(6-methylpyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (113 mg, 0.283 mmol, 28.5 % yield) as an off white solid.(TLC eluent: 10% MeOH in DCM R_f: 0.4; UV active), LCMS (*m/z*): 386.27 $[M+H]^+$.

^{1}H NMR (400 MHz,$CDCl_3$): δ ppm 10.93 (br d, *J*=5.92 Hz, 1 H), 8.88 (d, *J*=2.19 Hz, 1 H), 7.94 (dd, *J*=8.11, 2.41 Hz, 1 H), 7.56 (d, *J*=7.67 Hz, 1 H), 7.31-7.22 (m, 2 H), 5.59 (dd, *J*=5.92, 3.29 Hz, 1 H), 4.29 (br s, 1 H), 3.00 - 3.29 (m, 5 H), 2.95 (dd, *J*=11.95, 3.40 Hz, 1 H), 2.66-2.50 (m, 5 H), 2.31-2.21 (m, 1 H), 2.06 -1.98(m, 1 H)

Example 243

Synthesis of (4*S*)-7-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

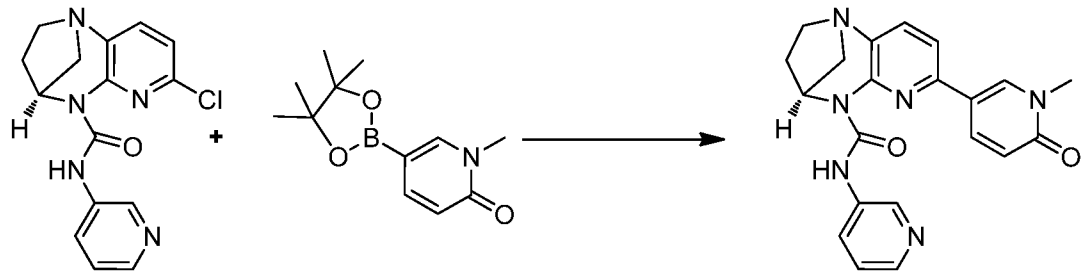


Tripotassium phosphate (804 mg, 3.79 mmol) was added to a stirred solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxa -mide (500mg, 1.579 mmol), and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one (445 mg, 1.894 mmol) in 1,4-dioxane (10 mL), and water (2.000 mL) at 28 °C. The reaction mixture was degassed for 10 min then was added $Pd_2(dba)_3$ (72.3 mg, 0.079 mmol), and X-phos (75 mg, 0.158 mmol). The reaction mixture was further degassed for 15 min. The reaction mixture was stirred for 1 hour in microwave at 100 °C. The reaction mixture was cooled to 28 °C and was partitioned between water (10 mL) and ethyl acetate (2 x 15 mL). Ethyl acetate layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford crude brown solid (TLC eluent: 10% MeOH in EtOAc: R_f-0.2; UV active). The crude was purified by column chromatography using (100-200 mesh) silica gel and was eluted with 2% MeOH in EtOAc to afford (4*S*)-7-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopy-rido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (330 mg, 0.840 mmol, 53.2 % yield) as off-white solid, LCMS (*m/z*): 390.26 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.78 (s, 1 H), 9.61 (d, *J*=1.53 Hz, 1 H), 8.57 (d, *J*=2.63 Hz, 1 H), 8.33 (d, *J*=2.63 Hz, 1 H), 8.22 (dd, *J*=2.52, 1.64 Hz, 1 H), 7.88 (dd, *J*=9.54, 2.74 Hz, 1 H), 7.57 (d, *J*=7.89 Hz, 1 H), 7.18 (d, *J*=8.11 Hz, 1 H), 6.69 (d, *J*=9.43 Hz, 1 H), 5.69 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.78 (s, 3 H), 3.12 - 3.30 (m, 3 H), 3.01 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.28 - 2.41 (m, 1 H), 2.00 - 2.13 (m, 1 H)

Example 244

Synthesis of (4*S*)-7-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

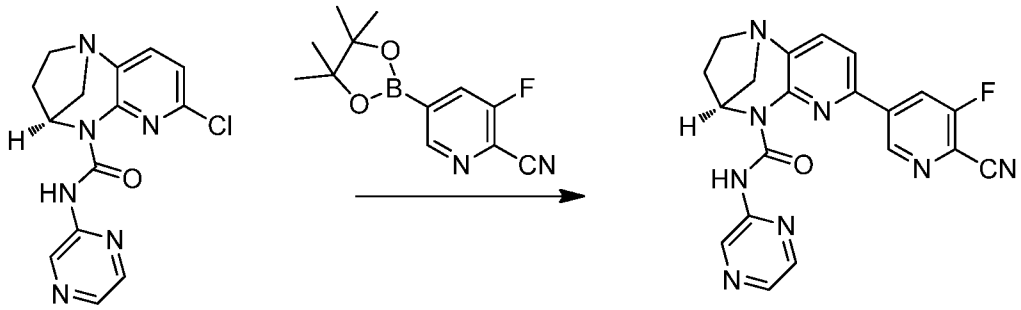


Tripotassium phosphate (672 mg, 3.17 mmol) was added to a stirred solution of (4*S*)-7-chloro-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxa-mide (500 mg, 1.583 mmol), and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one (447 mg, 1.900 mmol) in 1,4-dioxane (10 mL), and water (2.000 mL) at 28 °C. The reaction mixture was degassed for 10 min then was added $Pd_2(dba)_3$ (72.5 mg, 0.079 mmol), and X-phos (75 mg, 0.158 mmol). The reaction mixture was further degassed for 15 min. The reaction mixture was stirred for 1 hr in Microwave at 100 °C. The reaction mixture was cooled to 28 °C and was partitioned between water (10 mL) and EtOAc (25 mL). EtOAc layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford crude as brown solid (TLC eluent: 10% MeOH in EtOAc: R_f-0.2; UV active). The crude was purified by column chromatography using silica gel (100-200 mesh), and the product was eluting with 2% MeOH in Ethyl acetate to afford (4*S*)-7-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (272 mg, 0.679 mmol, 42.9 % yield) as off white solid, LCMS (*m/z*): 389.27 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.93 (s, 1 H), 8.61 (d, *J*=2.41 Hz, 1 H), 8.33 (dd, *J* = 4.71, 1.43 Hz, 1 H), 8.05 - 8.20 (m, 1 H), 7.74 - 7.87 (m, 2 H), 7.57 (d, *J* = 7.89 Hz, 1 H), 7.22 - 7.33 (m, 1 H), 7.09 (d, *J* = 7.89 Hz, 1 H), 6.65 - 6.82 (m, 1 H), 5.67 (dd, *J* = 5.81, 3.18 Hz, 1H), 3.64 (s, 3 H), 3.08 - 3.28 (m, 3 H), 3.00 (dd, *J* = 12.06, 3.29 Hz, 1 H), 2.33 (qd, *J* = 9.98, 4.49 Hz, 1 H), 2.00 - 2.12 (m, 1 H).

Example 245

Synthesis of (4*S*)-N-(1-methyl-1H-1,2,3-triazol-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

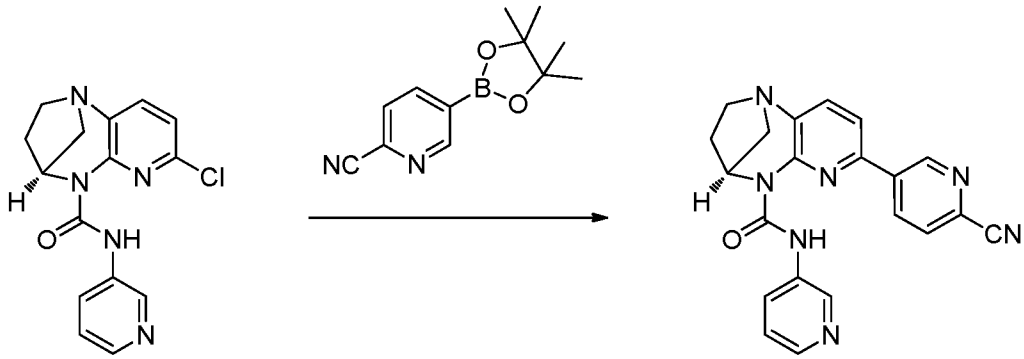


$Pd_2(dba)_3$ (0.043 g, 0.047 mmol) and X-phos (0.036 g, 0.095 mmol) was added to degassed solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b] [1,4]dia zepine-5(2H)-carboxamide (0.3g, 0.947 mmol),3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinonitrile (0.352 g, 1.421 mmol) and potassium dihydrogen phosphate (0.258 g, 1.894 mmol) in 1,4-dioxane (5 mL): water (1 mL) and heated to 90 °C for 15 hours. Cooled to room temperature and filtered through pad of celite. The filtrate was diluted with water (25 mL) and ethyl acetate (50 mL). The separated organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to get crude (TLC eluent:10% MeOH in ethyl acetate; UV active; R_f: 0.25). Crude compound was purified by column chromatography using neutral alumina and eluted in 75% ethyl acetate in hexane to afford (4*S*)-7-(6-cyano-5-fluoropyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,-4]diazepine-5(2H)-carboxamide (0.105g, 0.251 mmol, 26.5 % yield) as off-white solid, LCMS (*m/z*): 403.18 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.57 (s, 1H), 9.53 (d, *J* = 1.53 Hz, 1H), 9.11 (t, *J* =1.43 Hz, 1H), 8.69 (dd, *J* = 9.87, 1.75 Hz, 1H), 8.27 - 8.40 (m, 2H), 7.71(d, *J* = 8.11 Hz, 1H), 7.54 (d, *J* = 8.11 Hz, 1H), 5.71 (dd, *J* = 5.81, 3.18 Hz, 1H), 3.01 - 3.37 (m, 4H), 2.32 - 2.45 (m, 1H), 2.01 - 2.21 (m, 1H).

Example 246

Synthesis of (4*S*)-7-(6-cyanopyridin-3-yl)-N-(pyridin-3-yl)-3,4-dihydro-1,4-methano-pyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

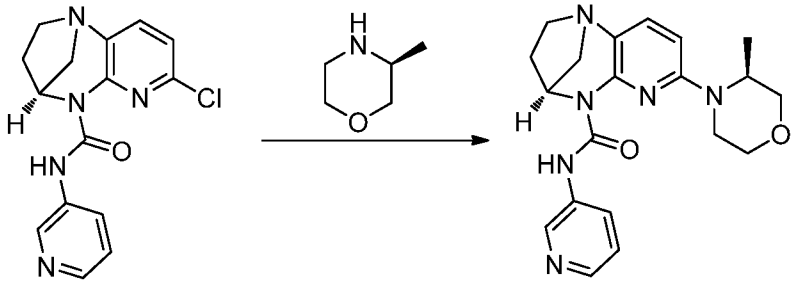


To a solution of (4*S*)-7-chloro-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (600 mg, 1.900 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinonitrile (525 mg, 2.280 mmol) and K_3PO_4 (807 mg, 3.80 mmol) in 1,4-dioxane (20 mL), water (3 mL) degassed with argon for 20 min was added X-phos (91 mg, 0.190 mmol), tris(dibenzylideneacetone)dipalladium(0) (87 mg, 0.095 mmol) again degassed with argon for 10 min. The reaction mixture was stirred at 100 °C for 16 hours and cooled to room temperature. The reaction mixture was filtered through celite then the filtrate was diluted with water and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water, brine solution, dried over sodium sulfate and evaporated to give crude compound (TLC eluent: 5% MeOH in DCM: R_f-0.3; UV active). The crude compound was purified by column chromatography using neutral alumina and eluted with 30-40% EtOAc/hexane to afford pure (4*S*)-7-(6-cyanopyridin-3-yl)-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (399 mg, 1.033 mmol, 54.4 % yield) as off white solid, LCMS (*m/z*): 384.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 12.71 (s, 1 H), 9.17 (dd, *J* = 2.2, 0.7 Hz, 1 H), 8.54 (d, *J* = 2.4 Hz, 1 H), 8.33 (dd, *J* = 4.7, 1.4 Hz, 1 H), 8.23 (dd, *J* = 8.0, 2.3 Hz, 1 H), 8.07 - 8.12 (m, 1 H), 7.87 (d, *J* = 8.1 Hz, 1 H), 7.69 (d, *J* = 8.1 Hz, 1 H), 7.38 (d, *J* = 7. 9 Hz, 1 H), 7.26 - 7.31 (m, 1 H), 5.71 (dd, *J* = 5.9, 2.8 Hz, 1 H), 3.12 - 3.34 (m, 3 H), 3.01 - 3.09 (m, 1 H), 2.36 (m, 1 H), 2.1 (m, 1 H).

Example 247

Synthesis of (4*S*)-7-((*S*)-3-methylmorpholino)-*N*-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

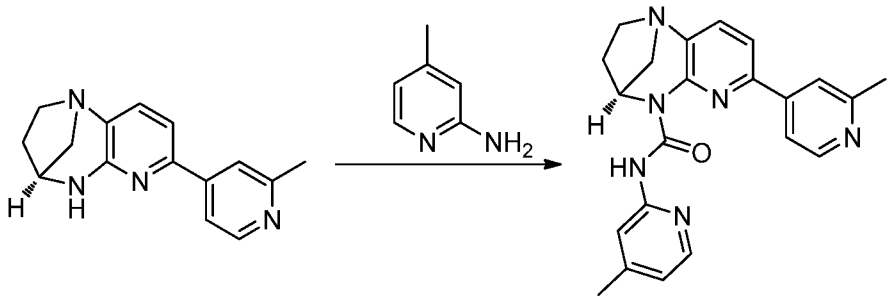


Cs_2CO_3 (3.10 g, 9.50 mmol), (*S*)-3-methylmorpholine (0.641 g, 6.33 mmol) were added to a solution of (4*S*)-7-chloro-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (1.0 g, 3.17 mmol) in 1,4-Dioxane (10 mL) in a sealed tube while purging with argon for 25 min. Subsequently $PdOAc_2$ (0.142 g, 0.633 mmol) and X-phos (0.604 g, 1.267 mmol) were added to the reaction mixture and stirred at 100 °C for 4h. The reaction was cooled to RT, solvent removed under reduced pressure, residue was partitioned between water (40 mL) and EtOAc (80 mL). Organic layer was separated and dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to yield crude compound. It was purified by column chromatography using silica gel (100-200 mesh) 2% methanol in dichloromethane as an eluent to afford (4*S*)-7-((*S*)-3-methylmorpholino)-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide (140 mg, 0.366 mmol, 11.56 % yield) as an off white solid.(TLC eluent: 10% MeOH in DCM, R_f: 0.4; UV active), LCMS (*m/z*): 381.30 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.42 (s, 1 H), 8.50 (d, *J*=2.41 Hz, 1 H), 8.31 (d, *J*=4.60 Hz, 1 H), 8.16 (br d, *J*=8.55 Hz, 1 H), 7.39 (d, *J*=8.55 Hz, 1 H), 7.31-7.26 (m, 1 H), 6.24 (d, *J*=8.55 Hz, 1 H), 5.60 (dd, *J*=5.92, 3.29 Hz, 1 H), 4.06 (brdd, *J*=11.18, 3.51 Hz, 2 H), 3.85-3.79 (m, 2 H), 3.69-3.51 (m, 2 H), 3.37-3.04 (m, 4 H), 2.91 (dd, *J*=11.84, 3.29 Hz, 1 H), 2.31-2.18 (m, 1 H), 2.07-1.97 (m, 1 H), 1.27 (d, *J*=6.80 Hz, 3 H)

Example 248

Synthesis of (4*S*)-*N*-(4-methylpyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

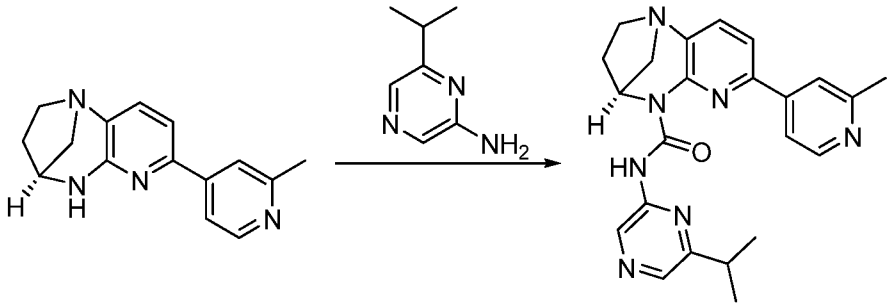


To a stirred solution of (4S)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (400 mg, 1.585 mmol) in THF (15 mL, in sealed tube) was added triphosgene (282 mg, 0.951 mmol) at RT, and stirred for 30 min, then triethylamine (1.105 mL, 7.93 mmol) and 4-methylpyridin-2-amine (257 mg, 2.378 mmol) were added and heated at 65 °C for 15 h. 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: 2% methanol in DCM) to obtain 600 mg with 60% LCMS purity. The crude compound was purified by Prep HPLC (Conditions: MP-A:10mM Ammonium Bicarbonate (Aq) MP-B: Acetonitrile Column: X-Bridge (250x30)mm 10µMethod :0/30,10/50,10.1/30,15/30 Flow: 30 ml/min Solubility: THF+ACN+MeOH) to afford (4*S*)-*N*-(4-methylpyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methano pyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (210 mg, 0.541 mmol, 34.1 % yield) as an off-white solid (TLC eluent: 10%MeOH in EtOAc, R_f: 0.4), LCMS (*m/z*): 387.27 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm: 13.48 (s, 1 H), 8.61 (d, *J*=5.26 Hz, 1 H), 8.25-8.17 (m, 2 H), 8.07 (s, 1 H), 7.71 (d, *J*=3.95 Hz, 1 H), 7.61 (d, *J*=7.89 Hz, 1 H), 7.48 (d, *J*=8.11 Hz, 1 H), 6.85 (d, *J*=4.82 Hz, 1 H), 5.70 (dd, *J*=5.70, 3.51 Hz, 1 H), 3.33-3.14 (m, 3 H), 3.14-2.89 (m, 1 H), 2.74 (s, 3 H), 2.41-2.32 (m, 4 H), 2.13-2.00 (m, 1 H).

Example 249

Synthesis of (4*S*)-*N*-(6-isopropylpyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

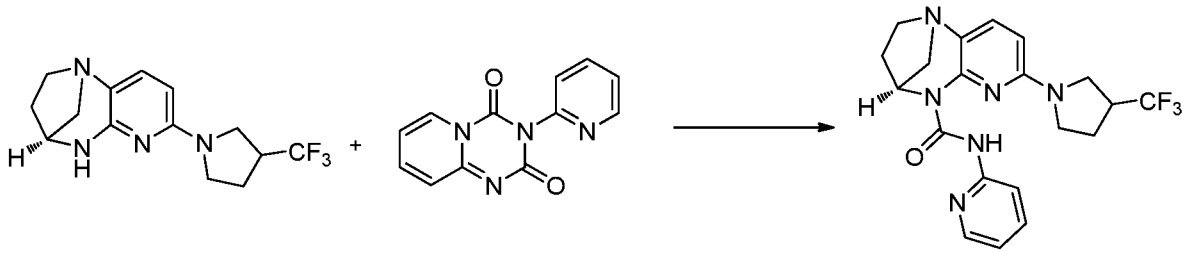


To a stirred solution of 6-isopropylpyrazin-2-amine (141 mg, 1.030 mmol) in THF (5 mL) triethylamine (0.663 mL, 4.76 mmol) and triphosgene (235 mg, 0.793 mmol) were added at RT and stirred for 30 min. Then (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (200 mg, 0.793 mmol) was added and heated at 80 °C for 16 h. The reaction mixture was cooled to room temperature 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 crude compound. The crude mixture was purified by flash column chromatography (silica gel: 100-200 mesh, eluent: 2% methanol in DCM) to obtain the (4*S*)-*N*-(6-isopropylpyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (60 mg, 0.144 mmol, 18.15% yield) as an off white solid (TLC: Eluent: 5% methanol in DCM, R_f: 0.4), LCMS (*m/z*): 416.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.34 (s, 1 H), 9.37 (s, 1 H), 8.70 (d, *J*=5.26 Hz, 1 H), 8.21 (s, 1 H), 8.00 (br d, *J*=3.73 Hz, 1 H), 7.60 - 7.69 (m, 2 H), 7.47 (d, *J*=8.11 Hz, 1 H), 5.73 (dd, *J*=5.81, 3.18 Hz, 1 H), 3.14 - 3.37 (m, 3 H), 2.98 - 3.09 (m, 2 H), 2.66 (s, 3 H), 2.27 - 2.46 (m, 1 H), 2.09 (dt, *J*=14.03, 7.23 Hz, 1 H), 1.33 (dd, *J*=7.02, 1.10 Hz, 6 H).

Example 250

Synthesis of (4*S*)-*N*-(pyridin-2-yl)-7-(3-(trifluoromethyl)pyrrolidin-1-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

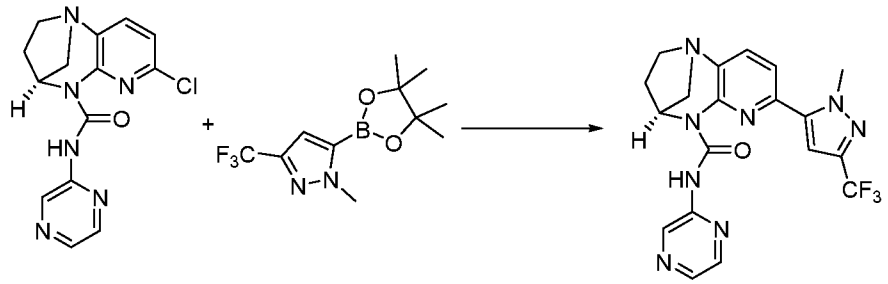


To a solution of (4*S*)-7-(3-(trifluoromethyl)pyrrolidin-1-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (Peak 1 from intermediate SFC separation) (440 mg, 1.475 mmol) in tetrahydrofuran (THF) (10 mL) was added NaH (295 mg, 7.37 mmol) at 0 °C. After 30 min 3-(pyridin-2-yl)-2*H*-pyrido[1,2-a][1,3,5]triazine-2,4(3*H*)-dione (531 mg, 2.212 mmol) was added and the reaction mixture was stirred at 70 °C for 16 h. The reaction mixture was poured on cold water (50 mL) and extracted with ethyl acetate (2x30 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield crude product. The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 90%Hex/EtOAc) to obtained (4S)-N-(pyridin-2-yl)-7-(3-(trifluoromethyl)pyrrolidin-1-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (266.8 mg, 0.631 mmol, 42.8 % yield) as an off white solid. (TLC system: R_f :04, :EtOAc), LCMS (*m/z*): 419.2 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.33 (s, 1 H), 8.19 (d, *J*=3.73 Hz, 1 H), 8.15 (d, *J*=8.33 Hz, 1 H), 7.66 - 7.60 (m, 1 H), 7.32 (d, *J*=8.55 Hz, 1 H), 6.91 (dd, *J*=6.58, 5.04 Hz, 1 H), 5.96 (d, *J*=8.33 Hz, 1 H), 5.58 (dd, *J*=6.03, 3.18 Hz, 1 H), 4.01 - 3.95 (m, 1 H), 3.86 (dd, *J*=11.29, 7.34 Hz, 1 H), 3.66 (td, *J*=8.99, 4.60 Hz, 1 H), 3.60 - 3.53 (m, 1 H), 3.23 - 3.05 (m, 4 H), 2.89 (dd, *J*=11.84, 3.51 Hz, 1 H), 2.37 - 2.18 (m, 3 H), 1.98 (dt, *J*=13.81, 6.91 Hz, 1 H).

Example 251

Synthesis of (4*S*)-7-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

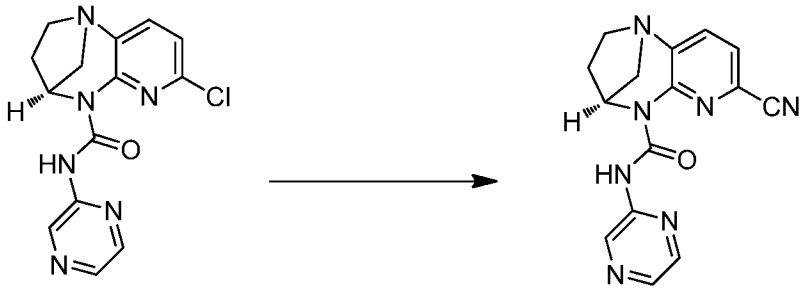


A suspension of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (0.400 g, 1.263 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)-1*H*-pyrazole (0.697 g, 2.53 mmol) and potassium phosphate tribasic (0.803 g, 3.79 mmol) in 1,4-dioxane (25 mL) and water (4 mL) was degassed with argon at room temp for 15 mins, then added X-phos (0.0601 g,0.126 mmol) and $Pd(dba)_2$ (0.046 g, 0.051 mmol). The reaction mixture was further degassed for 15 min and was stirred 16 hours at 100 °C. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to 28 °C and was diluted with water (15 mL) and extracted with EtOAc (2X 25 mL). The organic layer was washed with water followed by brine solution and dried over anhydrous sodium sulfate, filtered and filtrate was evaporated to get the crude (TLC eluent: 100% Ethyl Acetate in Hexane, R_f value: 0.3, UV active). The crude was purified by column chromatography using neutral alumina, and the product was eluted 40% ethyl acetate in pet ether to afford (4*S*)-7-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (0.208 g, 0.482 mmol, 38.2 % yield) as a white solid, LCMS (*m/z*): 431.23 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.08 (s, 1 H), 9.51 (d, *J* = 1.5 Hz, 1 H), 8.29 (d, *J* = 2.6 Hz, 1 H), 8.25 - 8.22 (m, 1 H), 7.65 (d, *J* = 7.9 Hz, 1 H), 7.21 (d, *J* = 7.9 Hz, 1 H), 7.05 (s, 1 H), 5.71 (dd, *J* = 5.8, 3.2 Hz, 1 H), 4.24 (s, 3 H), 3.33 - 3.15 (m, 3 H), 3.04 (dd, *J* = 12.2, 3.2 Hz, 1 H), 2.42 - 2.30 (m, 1 H), 2.10 (dt, *J* = 14.1, 6.9 Hz, 1 H).

Example 252

Synthesis of (4*S*)-7-cyano-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

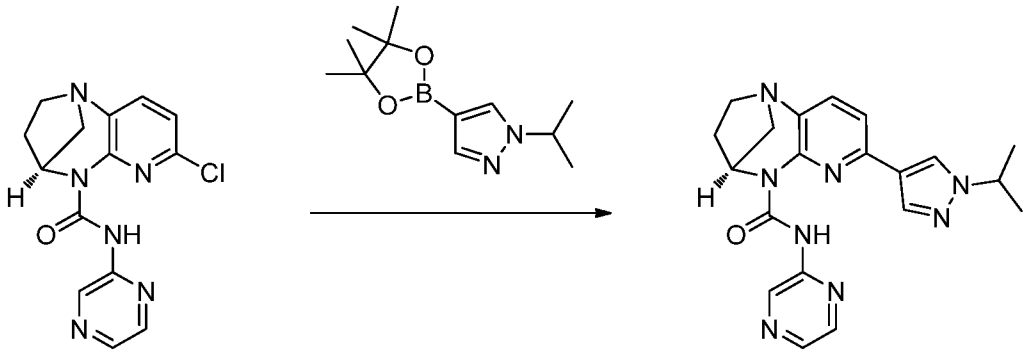


X-phos (0.018 g, 0.047 mmol) and (1,3-Bis(2,6-di-isopropylphenyl)-4,5-dihydroimidazol-2-ylidene)chloro) (3-phenylallyl)palladium(2) (0.031 g, 0.047 mmol) were added to a degassed solution of (4*S*)-7-chloro-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3 *b*][1,4]diazepine-5(2*H*)-carboxamide (0.3 g, 0.947 mmol) and potassium ferro cyanide (0.174 g, 0.474 mmol) in 1,4-dioxane (5 mL): water (1 mL) and heated to 100 °C for 15h. Cooled to room temperature and filtered through celite bed. The filtrate was diluted with water (25 mL) and ethyl acetate (100 mL). The separated organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to obtain crude compound (TLC eluent: 100% ethyl acetate; UV active; R_f~0.3). The crude mixture was purified by column chromatography using neutral alumina and eluted in 50% ethyl acetate in hexane to afford (4*S*)-7-cyano-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (0.13 g, 0.415 mmol, 43.8 % yield) as white solid, LCMS (*m/z*): 308.19 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.48 (br s, 1H), 9.45 (s, 1H), 8.32 (s, 2H), 7.62 (d, *J* = 7.89 Hz, 1H), 7.37 (d, *J* = 7.89 Hz, 1H), 5.68 (dd, *J* = 5.81, 3.18 Hz, 1H), 3.24 (t, *J* = 7.56 Hz, 2H), 2.99 - 3.14 (m, 2H), 2.36 (td, *J* = 14.09, 6.03 Hz, 1 H), 2.01 - 2.16 (m, 1H).

Example 253

Synthesis of (4*S*)-7-(1-isopropyl-1H-pyrazol-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

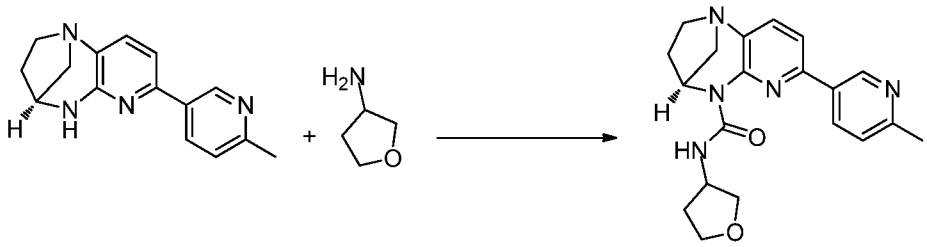


To a solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (500 mg, 1.579 mmol), 1-isopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (447 mg, 1.894 mmol) and K_3PO_4 (670 mg, 3.16 mmol) in 1,4-dioxane (15 mL), water (3 mL) degassed with argon for 20 min was added X-phos (75 mg, 0.158 mmol), tris(dibenzylideneacetone)dipalladium(0) (72.3 mg, 0.079 mmol) and again degassed with argon for 5 min. The reaction mixture was stirred at 100 °C for 16 hours and cooled to room temperature. The reaction mixture was filtered through celite then the filtrate was diluted with water and extracted with EtOAc (3 X 20 mL). The combined organic layers was washed with water, brine solution, dried over sodium sulfate and evaporated to give crude compound (TLC eluent: 5% MeOH in DCM: R_f-0.2; UV active). The crude compound was purified by column chromatography using neutral alumina and eluted with 30-40% EtOAc/hexane to afford pure (4*S*)-7-(1-isopropyl-1*H*-pyrazol-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (418 mg, 1.070 mmol, 67.8 % yield) as off white solid, LCMS (*m/z*): 391.2 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 14.14 (s, 1 H), 9.62 (d, *J* = 1.5 Hz, 1 H), 8.64 (s, 1 H), 8.26 - 8.32 (m, 2 H), 8.02 (s, 1 H), 7.50 (d, *J* = 7.9 Hz, 1 H), 7.16 (d, *J* = 8.1 Hz, 1 H), 5.67 (dd, *J* = 5.8, 3.2 Hz, 1 H), 4.61 (m, 1 H), 3.12 - 3.31 (m, 3 H), 2.99 (dd, *J* = 11.9, 3.2 Hz, 1 H), 2.32 (m, 1 H), 2.06 (m, 1 H), 1.63 (d, *J* = 6.8 Hz, 6 H).

Example 254

Synthesis of (4*S*)-7-(6-methylpyridin-3-yl)-N-(tetrahydrofuran-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2H)-carboxamide

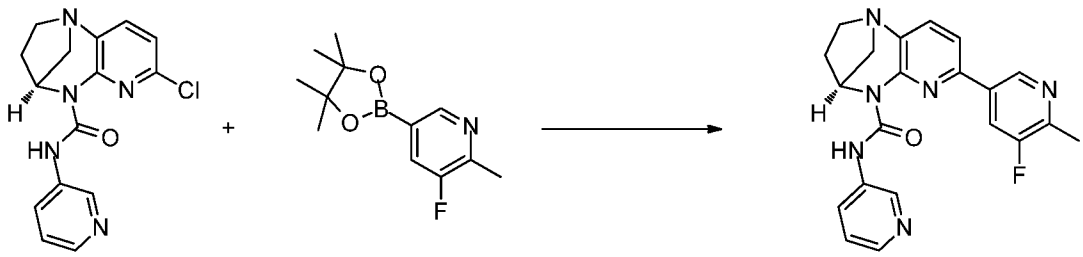


To a solution of (4S)-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (300 mg, 1.189 mmol) in tetrahydrofuran (THF) (10 mL) triphosgene (176 mg, 0.594 mmol) was added at 0 °C. After 30 min DIPEA (1.038 mL, 5.94 mmol), tetrahydrofuran-3-amine (155 mg, 1.783 mmol) was added and the reaction mixture was stirred at 70 °C for 16 h. The reaction was allowed to reach RT and then poured on cold water (50 mL) and extracted with ethyl acetate (2x 30 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to yield the crude product. The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 3% MeOH in DCM) to obtained (4*S*)-7-(6-methylpyridin-3-yl)-*N*-(tetrahydrofuran-3-yl)-3,4-dihydro-1,4-methano pyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (137.1 mg, 0.371 mmol, 31.2 % yield) as an off white solid. (TLC system: R_f: 0.2, 5%MeOH-DCM), LCMS (*m/z*): 366.2 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 10.76 (br t, *J*=6.80 Hz, 1 H), 8.89 (s, 1 H), 7.99 (dd, *J*=8.22, 2.08 Hz, 1 H), 7.54 (d, *J*=7.89 Hz, 1 H), 7.30 - 7.21 (m, 2 H), 5.62 (dd, *J*=5.81, 2.96 Hz, 1 H), 4.56 (br dd, *J*=4.82, 1.97 Hz, 1 H), 4.01 - 3.75 (m, 4 H), 3.30 - 3.06 (m, 3 H), 2.99 - 2.91 (m, 1 H), 2.62 (s, 3 H), 2.39 - 2.21 (m, 2 H), 2.07 - 1.85 (m, 2 H).

Example 255

Synthesis of (4*S*)-7-(5-fluoro-6-methylpyridin-3-yl)-N-(pyridin-3-yl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-*b*] [1, 4] diazepine-5(2*H*)-carboxamide

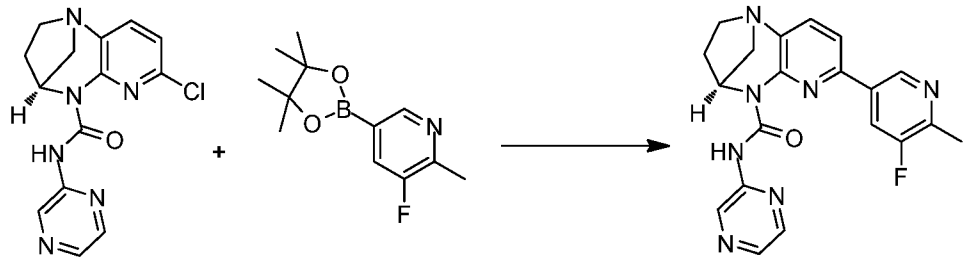


Tripotasium phosphate (323 mg, 1.520 mmol) was added to a solution of (4*S*)-7-chloro-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (240.0 mg, 0.760 mmol) and 3-fluoro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (234 mg, 0.988 mmol) in 1,4-dioxane (5.0 mL) and water (1.0 mL) at 25°C. The reaction mixture was degassed for 10 min. X-Phos (36.2 mg, 0.076 mmol) and $Pd_2(dba)_3$ (34.8 mg, 0.038 mmol) were added to reaction mixture and was further degassed for 10 min. The reaction was stirred for 1 hour at 100 °C in microwave. The reaction mixture was filtered through a pad of celite and was washed with the ethyl acetate. The filtrate was washed with the water and brine solution. The separated organic phase was dried over anhydrous sodium sulfate, filtered and evaporated to get crude (TLC eluent: 5% MeOH in DCM; UV active; R_f~0.3). The crude product was purified on grace column eluted with the 3-5% MeOH in DCM to afford pure (4*S*)-7-(5-fluoro-6-methylpyridin-3-yl)-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4] diaze-pine-5(2*H*)-carboxamide (122.0 mg, 0.312 mmol, 41.0 % yield) as off white solid, LCMS (*m/z*): 391.30 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 12.91 (s, 1 H), 8.77 (t, *J*=1.42 Hz, 1 H), 8.62 (d, *J*=2.41 Hz, 1 H), 8.32 (dd, *J*=4.71, 1.43 Hz, 1 H), 8.12 (ddd, *J*=8.33, 2.63, 1.53 Hz, 1 H), 7.73 (dd, *J*=9.87, 1.75 Hz, 1 H), 7.64 (d, *J*=7.89 Hz, 1 H), 7.27 - 7.32 (m, 2 H), 5.70 (dd, *J*=5.92, 3.29 Hz, 1 H), 3.14 - 3.34 (m, 3 H), 3.03 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.62 (d, *J*=3.07 Hz, 3 H), 2.28 - 2.38 (m, 1 H), 2.05 - 2.14 (m, 1 H)

Example 256

Synthesis of (4*S*)-7-(5-fluoro-6-methylpyridin-3-yl)-N-(pyrazin-2-yl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-*b*] [1, 4] diazepine-5(2*H*)-carboxamide:



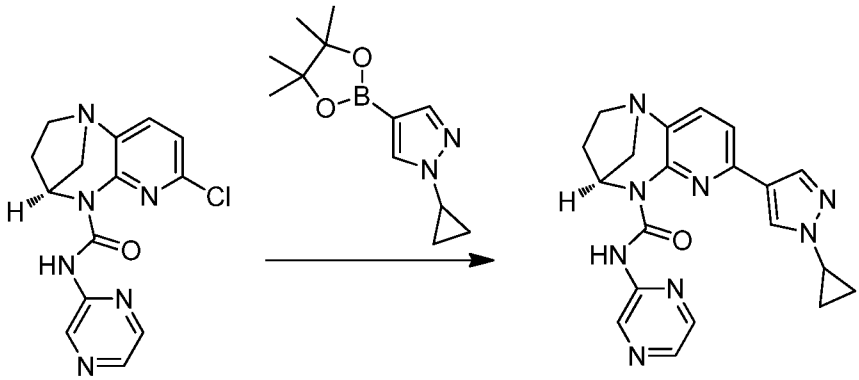
Tripotasium phosphate (402 mg, 1.894 mmol) was added to a solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (300.0 mg, 0.947 mmol), 3-fluoro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (292 mg, 1.231 mmol) in 1,4-dioxane (5.0 mL) and water (1.0 mL) at 25°C.

The reaction mixture was degassed for 10 min. X-Phos (45.2 mg, 0.095 mmol) and $Pd_2(dba)_3$ (43.4 mg, 0.047 mmol) were added to reaction mixture and was further degassed for 10 min. The reaction was stirred for 1hour at 100 °C in microwave. The reaction mixture was filtered through a pad of celite and was washed with the ethyl acetate. The filtrate was washed with the water and brine solution. The separated organic phase was dried over anhydrous sodium sulfate, filtered and evaporated to get crude (TLC eluent: 5% MeOH in DCM; UV active; R_f~0.3). The crude product was purified on grace column eluted with the 3-5% MeOH in dichloromethane to afford pure (4*S*)-7-(5-fluoro-6-methylpyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido [2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (150.0 mg, 0.365 mmol, 38.5 % yield) as off white solid, LCMS (*m/z*): 392.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.79 (s, 1 H), 9.53 (d, *J* = 1.5 Hz, 1 H), 8.88 (t, *J* = 1.5 Hz, 1 H), 8.38 (dd, *J* = 10.7, 1.97 Hz, 1 H), 8.30 - 8.34 (m, 2 H), 7.64 (d, *J* = 7.9 Hz, 1 H), 7.44 (d, *J* = 8.1Hz, 1 H), 5.70 (dd, *J* = 6.03, 3.2 Hz, 1 H), 3.1 - 3.3 (m, 3 H), 3.03 (dd, *J* = 12.1, 3.3 Hz, 1 H), 2.62 (s, 3H), 2.36 (dddd, *J* = 14.1, 9. 9, 5.9, 4.1 Hz, 1 H), 2.04 - 2.15 (m, 1 H)

Example 257

Synthesis of (4*S*)-7-(1-cyclopropyl-1H-pyrazol-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



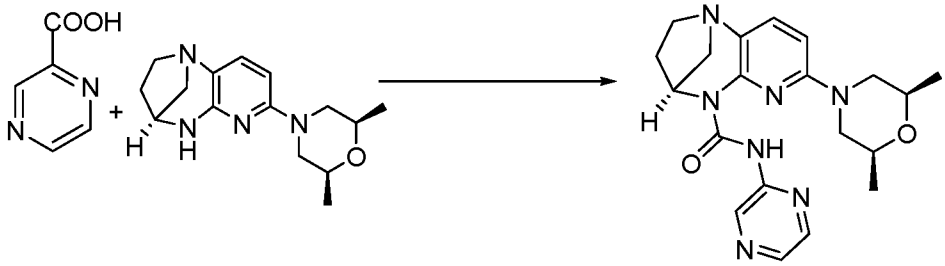
$Pd_2(dba)_3$ (0.087 g, 0.095 mmol) and X-phos (0.018 g, 0.047 mmol) was added to degassed solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4] diazepine-5(2*H*)-carboxamide (0.3 g, 0.947 mmol),1-cyclopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.333 g, 1.421 mmol) and potassium dihydrogen phosphate (0.258 g, 1.894 mmol) in 1,4-dioxane (5 mL):water (1 mL) and

heated to 90 °C for 15 hours. Cooled to room temperature and filtered through pad of celite. The filtrate was diluted with water (25 mL) and ethyl acetate (50 mL). The separated organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to get crude (TLC eluent: 10% MeOH in ethyl acetate; UV active; R_f~0.30). The crude compound was purified by column chromatography using neutral alumina and eluted in 75% ethyl acetate in hexane to afford (4*S*)-7-(1-cyclopropyl-1H-pyrazol-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido [2,3b][1,4]diazepine-5(2H)-carboxamide (0.13 g, 0.332 mmol, 35.0 % yield) off-white solid, LCMS (*m/z*): 389.32 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 14.14 (s, 1H), 9.60 (d, *J* = 1.10 Hz, 1H), 8.61 (s, 1H), 8.29 - 8.33 (m, 2H), 8.03 (s, 1H), 7.47 - 7.58 (m, 1H), 7.13 (d, *J* = 8.11 Hz, 1H), 5.66 (dd, *J* = 6.03, 3.18 Hz, 1H), 3.73 (tt, *J* = 7.43, 3.75 Hz, 1H), 3.08 - 3.34 (m, 3H), 2.99 (dd, *J* = 11.95, 3.18 Hz, 1H), 2.32 (dddd, *J* =14.11, 10.00, 6.03, 4.06 Hz, 1H), 2.02 - 2.11 (m, 1H), 1.22 - 1.32 (m, 2H), 1.07 - 1.18 (m, 2H).

Example 258

Synthesis of (4*S*)-7-((2*S*,6*R*)-2,6-dimethylmorpholino)-*N*-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



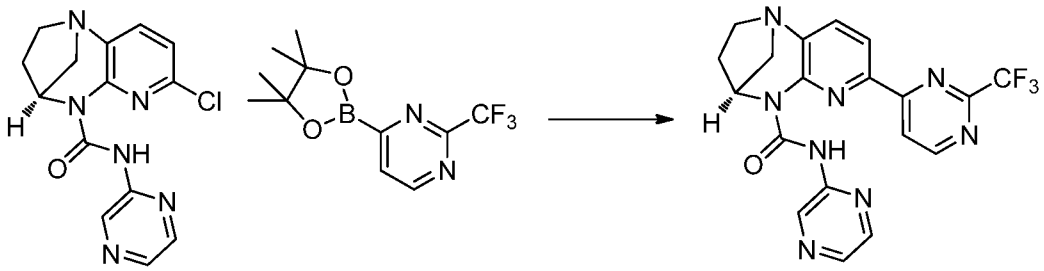
Diisopropylethylamine (3.34 mL, 19.14 mmol) was added to a stirred solution of pyrazine-2-carboxylic acid (0.475g, 3.83 mmol) in tetrahydrofuran (30 mL) stirred under argon at room temperature. Diphenyl phosphorazidate (1.053 g, 3.83 mmol) was added to the reaction mixture. The reaction mixture was stirred 2 hr at room temperature then, (2*S*,6*R*)-2,6-dimethyl-4-((4*S*)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepin-7-yl)morpho line (0.735 g, 2.68 mmol) was added to the reaction mixture and stirred 16 hours at 65 °C. The reaction mixture was cooled to room temp, and was partitioned between water (20 mL) and EtOAc (70 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude as brown solid (TLC eluent: 100% EtOAc: R_f-0.3; UV active). The crude residue was purified by column

chromatography using neutral alumina and was eluted with 15% EtOAc in hexane to afford pure (4*S*)-7-((2*S*,6*R*)-2,6-dimethylmorpholino)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide (0.132 g, 0.329 mmol, 8.58 % yield) as a off-white solid, LCMS (*m/z*): 396.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.39 (s, 1 H), 9.56 (d, *J* = 1.10 Hz, 1 H), 8.26 (s, 1 H), 8.25 (s, 1 H), 7.39 (s, 1 H), 6.30 (s, 1 H), 5.63 (dd, *J* = 5.92, 3.29 Hz, 1 H), 4.01 (br d, *J* = 12.50 Hz, 2H), 3.68 - 3.89 (m, 2H), 3.16 - 3.28 (m, 1H), 3.05 - 3.15 (m, 2 H), 2.92 (dd, *J* = 11.84, 3.29 Hz, 1 H), 2.61 (t, *J* =11.62 Hz, 2 H), 2.27 (dddd, *J* = 13.89, 9.95, 6.08, 3.62 Hz, 1 H), 1.93 - 2.06 (m, 1 H), 1.33 (d, *J* = 6.14 Hz, 6 H)

Example 259

Synthesis of (4*S*)-N-(pyrazin-2-yl)-7-(2-(trifluoromethyl)pyrimidin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



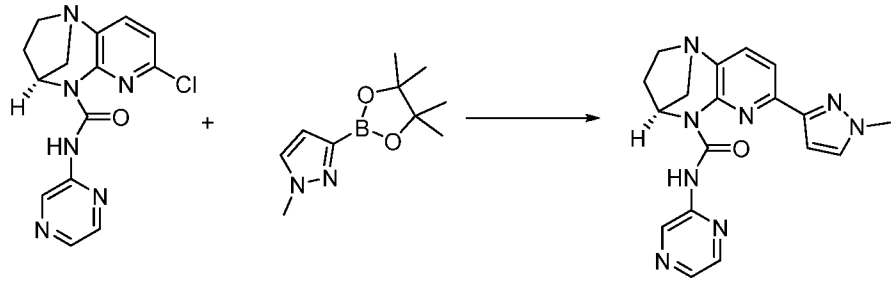
To a solution of (4S)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (300 mg, 0.947 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyrimidine (260 mg, 0.947 mmol) and K_3PO_4 (603 mg, 2.84 mmol) in 1,4-Dioxane (20 mL) was added Water (3 mL). The reaction mixture was degassed with argon at room temp for 15 min. Then to this X-Phos (45.2 mg, 0.095 mmol) and $Pd_2(dba)_3$ (43.4 mg, 0.047 mmol) was added. The reaction mixture was stirred at 90 °C for 16 hr. Reaction progress was monitored by TLC. The reaction mass filtered through celite and concentrated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with water followed by brine solution and dried out with sodium sulfate, filtered and concentrated. The Crude compound was purified by column chromatography (Neutral alumina) product was eluted with 30% ethyl acetate in Hexane. Collected fractions evaporated under reduced pressure and dried under high vacuum to afford (4S)-N-(pyrazin-2-yl)-7-(2-(trifluoromethyl)pyrimidin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-

b][1,4]diazepine-5(2H)-carboxamide (230 mg, 0.534 mmol, 56.4 % yield) as a Off-White solid, LCMS (*m/z*): 429.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.60 (s, 1 H), 9.59 (d, *J*=1.32 Hz, 1 H), 9.08 (d, *J*=5.26 Hz, 1 H), 8.83 (d, *J*=5.26 Hz, 1 H), 8.22 - 8.47 (m, 3 H), 7.75 (d, *J*=7.89 Hz, 1 H), 5.72 (dd, *J*=5.92, 3.29 Hz, 1 H), 3.15 - 3.37 (m, 3 H), 3.00 - 3.10 (m, 1 H), 2.28 - 2.46 (m, 1 H), 2.03 - 2.18 (m, 1 H)

Example 260

Synthesis of (4*S*)-7-(1-methyl-1*H*-pyrazol-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

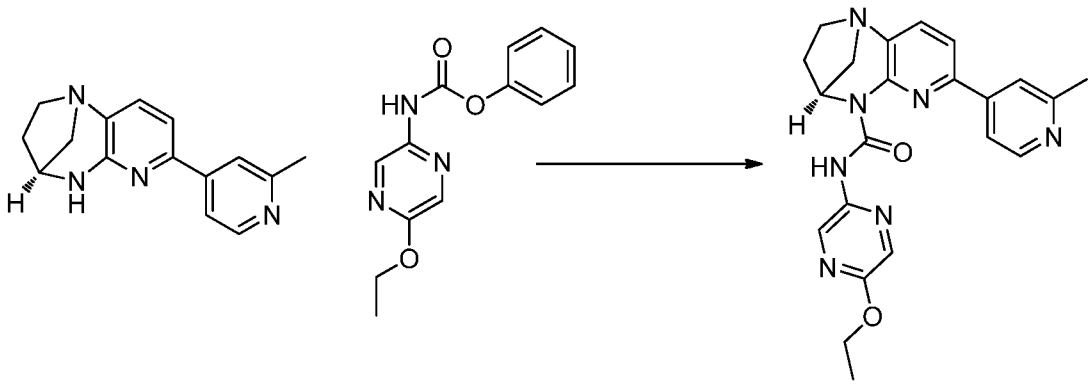


A suspension of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (0.350 g, 1.105 mmol), 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.690 g, 3.31 mmol) and potassium phosphate tribasic (0.703 g, 3.31 mmol) in 1,4-dioxane (25 mL) and water (4 mL) degassed with argon at room temp for 15 minutes. Then, to above mixture was added X-phos (53mg, 0.110 mmol) and $Pd(dba)_2$ (0.032 g, 0.055 mmol) and was further degassed for 15 minutes. The reaction mixture was stirred 16 hours at 100 °C. After completion of the reaction as indicated by TLC, cooled to 28 °C and was diluted with water (15 mL) and extracted with EtOAc (2x 25 mL). The organic layer was washed with water followed by brine solution and dried over anhydrous sodium sulfate, filtered and filtrate was evaporated to get the crude residue (TLC eluent: 5%MeOH in DCM, R_f value: 0.3, UV active). The crude residue was purified by column chromatography using neutral alumina, and the product was eluted 50% ethyl acetate in pet ether to afford (4*S*)-7-(1-methyl-1H-pyrazol-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (0.192 g, 0.527 mmol, 47.7 % yield) as off white solid, LCMS (*m/z*): 363.30 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.98 (s, 1 H), 9.56 (d, *J* = 1.32 Hz, 1 H), 8.33 - 8.27 (m, 2 H), 7.66 (d, *J* = 8.11 Hz, 1 H), 7.56 - 7.52 (m, 1 H), 7.46 (d, *J* = 2.19 Hz, 1 H), 7.42 (d, *J* = 2.41 Hz, 1 H), 5.68 (dd, *J* = 5.92, 3.29 Hz, 1 H), 3.99 (s, 3 H),3.33 - 3.12 (m, 3 H), 2.99 (dd, *J* = 12.06, 3.29 Hz, 1 H),2.36 - 2.26 (m, 1 H),2.11 - 1.98 (m, 1 H)

Example 261

Synthesis of (4*S*)-*N*-(5-ethoxypyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

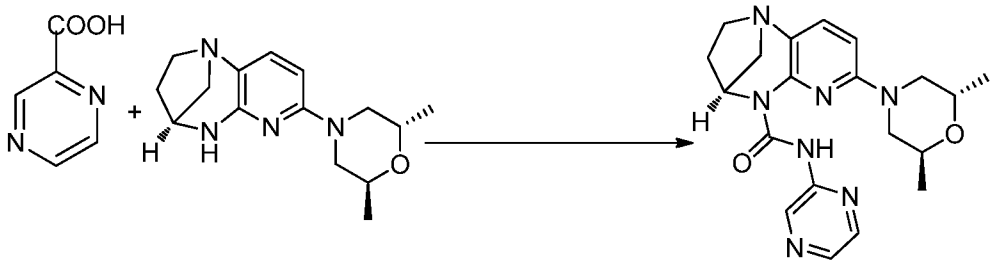


To a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (100 mg, 0.396 mmol) in THF (10 mL, in sealed tube) were added DMAP (145 mg, 1.189 mmol) and phenyl (5-ethoxypyrazin-2-yl)carbamate (308 mg, 1.189 mmol) at RT and heated at 90 °C for 16 h. The reaction mixture was cooled to room temperature 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 residue was purified by flash column chromatography (silica gel: 100-200 mesh, eluent: 2% methanol in DCM) to afford (4*S*)-*N*-(5-ethoxypyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b] [1,4]diazepine-5(2*H*)-carboxamide (38 mg, 0.090 mmol, 22.79 % yield) as an off white solid (TLC eluent: 5% methanol in DCM R_f: 0.4), LCMS (*m/z*): 418.36 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.50 (s, 1 H), 9.01 (d, *J*=1.32 Hz, 1 H), 8.61 (d, *J*=5.26 Hz, 1 H), 8.06 (s, 1 H), 7.98 (m, 1 H), 7.63 (m, 2 H), 7.47 (d, *J*=7.89 Hz, 1 H), 5.71 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.40 (q, *J*=7.02 Hz, 2 H), 3.34-3.10 (m, 3 H), 3.01 (dd, *J*= 5.94, 2.96 Hz, 1H), 2.67 (s, 3H), 2.36-2.10 (m, 2 H), 1.42 (t, *J*=7.13 Hz, 3 H).

Example 262

Synthesis of (4*S*)-7-((2*S*,6*S*)-2,6-dimethylmorpholino)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

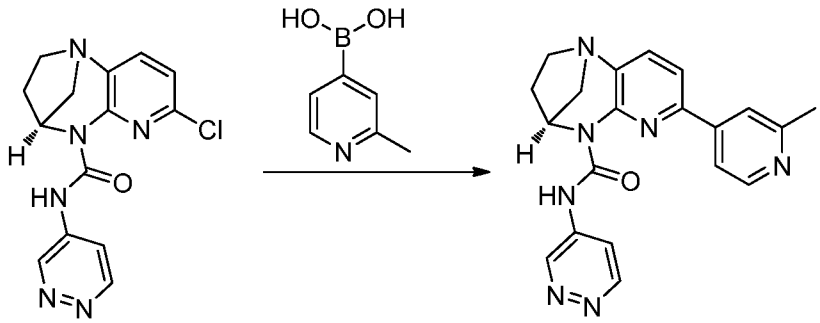


Diisopropylethylamine (3.52 mL, 20.15 mmol) was added to a stirred solution of pyrazine-2-carboxylic acid (0.500g, 4.03 mmol) in tetrahydrofuran (30 mL) and stirred under argon at room temperature. Diphenyl phosphorazidate (1.109 g, 4.03 mmol) was added to the reaction mixture and was stirred 2 hour at room temperature. Next, (2*S*, 6*S*)-2,6-Dimethyl-4-((4*S*)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepin-7-yl) morpholine (0.774g, 2.82 mmol) was added to the reaction and was stirred 16 hour at 65 °C. The reaction mixture was cooled to room temperature, and was partitioned between water (20 mL) and EtOAc (70 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude residue as brown solid (TLC eluent: 100% EtOAc: R_f-0.3; UV active). The crude was purified by column chromatography using neutral alumina and was eluted with 20% EtOAc in hexane to afford pure (4*S*)-7-((2*S*,6*S*)-2,6-dimethylmorpholino)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (0.321 g, 0.799 mmol, 19.82 % yield) as a white solid, LCMS (*m/z*): 396.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.41 (s, 1 H), 9.56 (d, *J* = 1.53 Hz, 1 H), 8.25 (d, *J* = 2.41 Hz, 1 H), 8.16 (dd, *J* = 2.41, 1.53 Hz, 1 H), 7.37 (d, *J* = 8.55 Hz, 1 H), 6.25 (d, *J* = 8.55 Hz, 1 H), 5.63 (dd, *J* = 6.03, 3.18 Hz, 1 H), 4.11 - 4.31 (m, 2 H), 3.67 (dd, *J* = 12.50, 3.29 Hz, 2 H), 3.19 - 3.34 (m, 3 H), 3.06 - 3.18 (m, 2 H), 2.92 (dd, *J* = 11.84, 3.29 Hz, 1 H), 2.27 (dddd, *J* = 13.95, 9.95, 6.03, 3.84 Hz, 1 H), 1.92 - 2.07 (m, 1 H), 1.34 (d, *J* = 6.36 Hz, 6 H)

Example 263

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-*N*-(pyridazin-4-yl)-3,4-dihydro-1,4-methano pyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

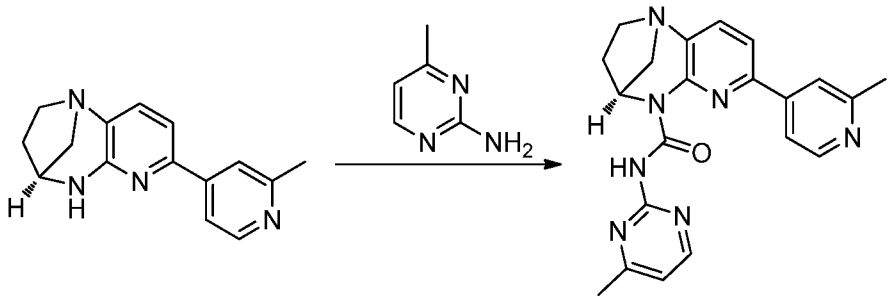


To a degassed solution of (4*S*)-7-chloro-*N*-(pyridazin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (0.3 g, 0.947 mmol) in 1,4-dioxane (10 ml)/ water (2 ml), (2-methylpyridin-4-yl)boronic acid (0.195 g, 1.421 mmol) and K_3PO_4 (0.402 g, 1.894 mmol) were added tris(dibenzylideneacetone)dipalladium(0) (0.087 g, 0.095 mmol) and x-phos (0.090 g, 0.189 mmol) at RT and heated at 100 °C for 16 h. The reaction mixture was cooled to room temperature and extracted with ethyl acetate (2x50 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: 3% methanol in EtOAc) to afford (4*S*)-7-(2-methylpyridin-4-yl)-*N*-(pyridazin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*] [1,4] diazepine-5(2*H*)-carboxamide (125 mg, 0.333 mmol, 35.1% yield) as an off white solid (TLC eluent: 10% methanol in EtOAc, R_f: 0.4), LCMS (*m/z*): 374.21 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm: 13.50 (s, 1 H), 9.10 (d, *J*=1.97 Hz, 1 H), 8.93 - 9.05 (m, 1 H), 8.72 (d, *J*=5.04 Hz, 1 H), 8.00 (dd, *J*=5.92, 2.85 Hz, 1 H), 7.69 (d, *J*=8.11 Hz, 1 H), 7.61-7.53 (m, 1 H), 7.48 (dd, *J*=5.26, 1.32 Hz, 1 H), 7.41 (d, *J*=7.58 Hz, 1 H), 5.67 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.35-3.13 (m, 3 H), 3.05 (dd, *J*=12.17, 3.18 Hz, 1 H), 2.37 (dddd, *J*=14.17, 9.84, 5.81, 4.17 Hz, 3 H), 2.39 (m, 1 H), 2.15 (m, 1 H).

Example 264

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-*N*-(4-methylpyrimidin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

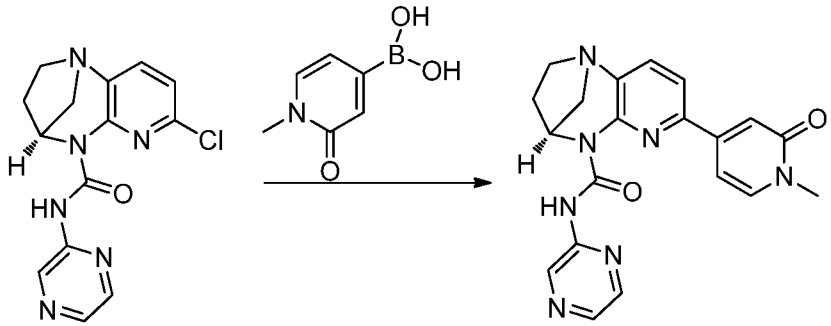


To a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (400 mg, 1.585 mmol) in THF (15 mL, sealed tube) was added triphosgene (282 mg, 0.951 mmol) at RT and stirred for 30 min. Then TEA (1.105 mL, 7.93 mmol) and 4-methylpyrimidin-2-amine (260 mg, 2.378 mmol) were added and heated at 65 °C for 15 h. The reaction mixture was cooled to room temperature; THF was distilled off and was partitioned between water (25 mL) and DCM (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: 2% methanol in DCM) to obtain 500 mg with 60% LCMS purity, which was purified by prep HPLC (MP-A: 10mM Ammonium Acetate (Aq) MP-B : Acetonitrile Column: x bridge C18 (100x19)mm 5µ Method - T/%B : 0/25/30,10/55 ,Flow: 19ml/min Solubility : THF+ACN) to afford (4*S*)-7-(2-methylpyridin-4-yl)-*N*-(4-methylpyrimidin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (226 mg, 0.582 mmol, 36.7 % yield) as an off-white solid (TLC eluent: 10%MeOH in EtOAc, R_f: 0.4), LCMS (*m/z*): 388.2 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm: 13.74 (s, 1 H), 8.63 (d, *J*=5.26 Hz, 1 H), 8.52 (d, *J*=5.04 Hz, 1 H), 7.90-7.83 (m, 2 H), 7.63 (m, *J*=8.11 Hz, 1 H), 7.47 (d, *J*=8.11 Hz, 1 H), 6.87 (d, *J*=5.04 Hz, 1 H), 5.78 (dd, *J*=5.92, 3.29 Hz, 1 H), 3.32-3.10 (m, 3 H), 3.10-2.88 (m, 1 H), 2.68 (s, 3 H), 2.54 (s, 3 H), 2.51-2.23 (m, 1 H), 2.23-1.99 (m, 1 H).

Example 265

Synthesis of (4*S*)-7-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

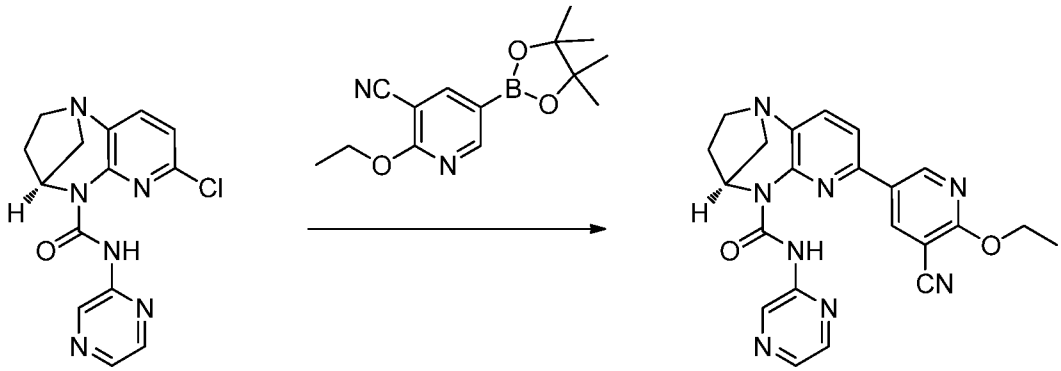


Potassium phosphate (939 mg, 4.43 mmol) and (1-methyl-2-oxo-1,2-dihydropyridin-4-yl)boronic acid (462 mg, 3.322 mmol) were added to a solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (700 mg, 2.215mmol) in mixture of 1,4-dioxane:water(10 mL, 8:2) at RT. This mixture was purged with argon for 30 min. $PdOAc_2$ (49.62 mg, 0.221 mmol) and X-Phos (211.2 mg, 0.443mmol) were added to the reaction mixture and then stirred at 100 °C for 16h. The reaction mixture was cooled to room temperature, concentrated *in vacuo*, residue was partitioned between water (40 mL) and EtOAc (80 mL). 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 column chromatography using silica gel (100-200 mesh) 3% methanol in dichloromethane as a eluent to afford(4*S*)-7-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (110 mg, 0.270 mmol, 28.5 % yield) as a pale yellow solid.(TLC eluent: 10% MeOH in DCM R_f: 0.4; UV active), LCMS (*m/z*): 390.30 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.53 (s, 1 H), 9.53 (s, 1 H), 8.34-8.28 (m, 2 H), 7.63 (d, *J*=8.11 Hz, 1 H), 7.43 (t, *J*=7.78 Hz, 2 H), 7.20 (d, *J*=1.75 Hz, 1 H), 7.04 (dd, *J*=7.23, 1.97 Hz, 1 H), 5.70 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.62 (s, 3 H),3.33-3.14 (m, 3 H), 3.03 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.40-2.30 (m, 1 H), 2.09 (dt, *J*=13.92, 6.85 Hz, 1 H)

Example 266

Synthesis of (4*S*)-7-(5-cyano-6-ethoxypyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

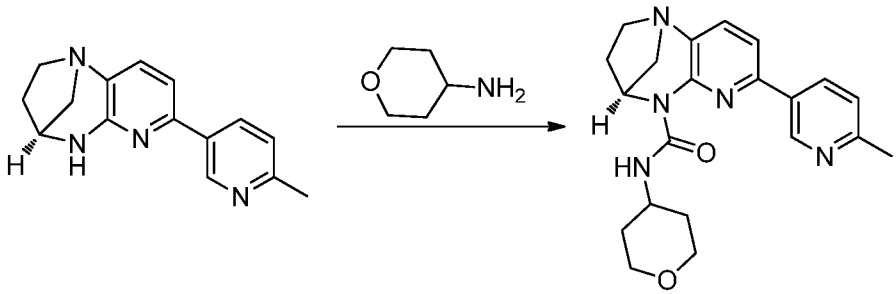


To a solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (400 mg, 1.263 mmol), 2-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinonitrile (519 mg, 1.894 mmol) and K_3PO_4 (536 mg, 2.53 mmol) in 1,4-dioxane (15 mL), water (3 mL) degassed with argon for 20 min was added x-phos (60.2 mg, 0.126 mmol), tris(dibenzylideneacetone)dipalladium(0) (57.8 mg, 0.063 mmol) and again degassed with argon for 5 min. The reaction mixture was stirred at 100 °C for 16 hours and cooled to room temperature. The reaction mixture was filtered through celite then the filtrate was diluted with water and extracted with EtOAc (3x20 mL). The combined organic layers were washed with water, brine solution, dried over sodium sulfate and evaporated to give crude compound (TLC eluent: 5% MeOH in DCM: R_f-0.3; UV active). The crude compound was purified by column chromatography using neutral alumina and eluted with 30-40% EtOAc/hexane to afford pure (4*S*)-7-(5-cyano-6-ethoxypyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5 (2*H*)-carboxamide (173 mg, 0.398 mmol, 31.5 % yield) as off white solid, LCMS (*m/z*): 429.2 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.83 (s, 1 H), 9.51 (d, *J* = 1.5 Hz, 1 H), 9.16 (d, *J* = 2.4 Hz, 1 H), 8.82 (d, *J* = 2.6 Hz, 1 H), 8.55 (dd, *J* = 2.6, 1.5 Hz, 1 H), 8.31 (d, *J* = 2.4 Hz, 1 H), 7.62 (d, *J* = 7. 9 Hz, 1 H), 7.38 (d, *J* = 7. 9 Hz, 1 H), 5.67 (dd, *J* = 6.0, 3.2 Hz, 1 H), 4.57 (q, *J* = 7.1 Hz, 2 H), 3.12 - 3.32 (m, 3 H), 3.01 (dd, *J* = 12.0, 3.3 Hz, 1 H), 2.34 (m, 1 H), 2.07 (m, 1 H), 1.48 (t, *J* = 7.1 Hz, 3 H).

Example 267

Synthesis of (4*S*)-7-(6-methylpyridin-3-yl)-N-(tetrahydro-2H-pyran-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

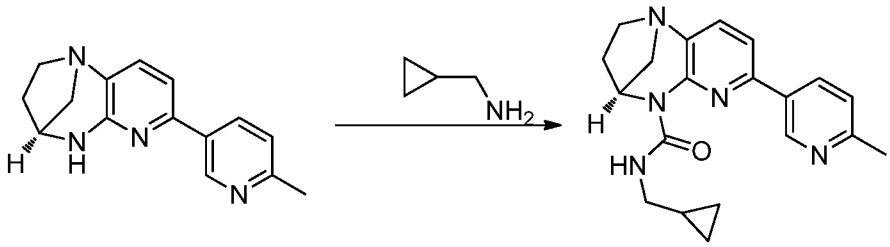


Triphosgene (212 mg, 0.714 mmol) was added slowly in portions to a stirred solution of (4*S*)-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 1.190mmol) in Tetrahydrofuran (THF) (15 mL) at RT and stirred for 30 min. DIPEA (0.622 mL, 3.57 mmol) and tetrahydro-2H-pyran-4-amine (180 mg, 1.785mmol) were added to above reaction mixture, stirred at 70 °C for 16 h. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the residue was partitioned between water (40 mL) and EtOAc (80 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 column chromatography using silica gel (100-200 mesh) 2% methanol in dichloromethane as a eluent to afford (4S)-7-(6-methylpyridin-3-yl)-N-(tetrahydro-2H-pyran-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (110 mg, 0.290 mmol, 29.2 % yield) as a Pale yellow solid. (TLC eluent: 10% MeOH in DCM R_f: 0.4; UV active), LCMS (*m/z*): 380.36 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 10.52 (br d, *J*=7.23 Hz, 1 H), 8.88 (d, *J*=1.97 Hz, 1 H), 7.92 (dd, *J*=8.11, 2.41 Hz, 1 H), 7.54 (d, *J*=7.89 Hz, 1 H), 7.28 (s, 1 H), 7.22 (d, *J*=7.89 Hz, 1 H), 5.62 (dd, *J*=5.92, 3.29 Hz, 1 H), 4.04-3.94 (m, 3 H), 3.51 (tt, *J*=11.59, 2.33 Hz, 2 H), 3.27-3.15 (m, 2 H), 3.13-3.06 (m, 1 H), 2.95 (dd, *J*=11.84, 3.29 Hz, 1 H) 2.63 (s, 3 H), 2.26 (dddd, *J*=14.00, 9.95, 5.97, 4.06 Hz, 1 H), 2.08-1.98 (m, 3 H),1.62-1.55 (m, 2 H)

Example 268

Synthesis of (4*S*)-*N*-(cyclopropylmethyl)-7-(6-methylpyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

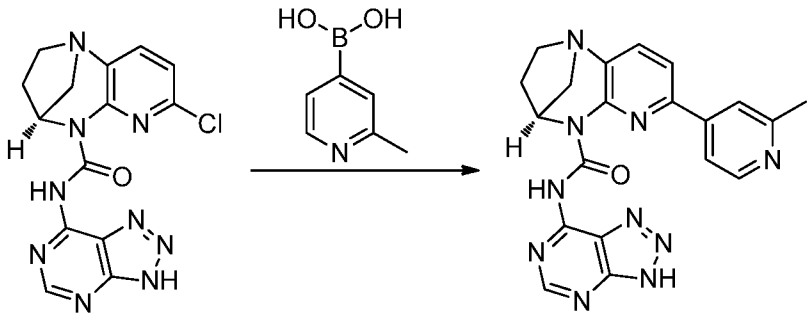


To a solution of (4*S*)-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (200 mg, 0.793 mmol) in Tetrahydrofuran (THF) (10 mL) were added TEA (0.331 mL, 2.378 mmol) and tri phosgène (141 mg, 0.476 mmol) at 0 °C and stirred to room temperature for 30 minutes. Then cyclopropylmethanamine (85 mg, 1.189 mmol) was added. The reaction mixture was stirred at 60 °C for16 h. The reaction mixture allowed to RT and solvent was evaporated and diluted with CH_2Cl_2 (25 mL). The solution was washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh, eluted with 5% MeOH/CH_2Cl_2) to obtained (4*S*)-*N*-(cyclopropylmethyl)-7-(6-methylpyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (140 mg, 0.381 mmol, 48.0 % yield) as a pale yellow solid (TLC: R_f = 0.3, Neat EtOAc), LCMS (*m/z*): 350.30 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 10.52 (br s, 1 H), 8.96 (d, *J*=1.97 Hz, 1 H), 8.02 (dd, *J*=8.00, 2.30 Hz, 1 H), 7.53 (d, *J*=7.89 Hz, 1 H), 7.26 - 7.20 (m, 2 H), 5.64 (dd, *J*=5.81, 3.18 Hz, 1 H), 3.32 - 3.05 (m, 5 H), 2.95 (dd, *J*=11.84, 3.29 Hz, 1 H), 2.62 (s, 3 H), 2.26 (dddd, *J*=14.00, 9.95, 5.97, 4.06 Hz, 1H), 2.10 – 1.98 (m, 1H), 1.08 (dddt, *J*=12.78, 7.66, 5.04, 2.38, 2.38 Hz, 1H), 0.65 - 0.52 (m, 2 H), 0.26 (q, *J*=4.97 Hz, 2 H).

Example 269

Synthesis of (4*S*)-*N*-(3*H*-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

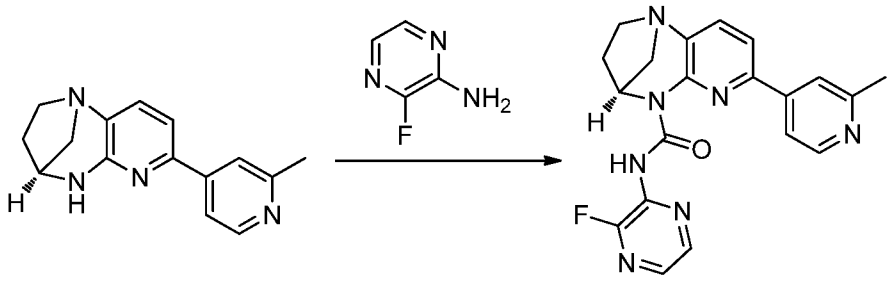


A solution of (4*S*)-N-(3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)-7-chloro-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (250 mg, 0.699 mmol) and (2-methylpyridin-4-yl) boronic acid (124 mg, 0.908 mmol) in 1,4-Dioxane (9 mL) and water (1 mL) at 25 °C was degassed for 15 min. To this reaction mixture Cs_2CO_3 (455 mg, 1.398 mmol) was added and degassed again for 15 min. Finally $PdCl_2$(dppf) (51.1 mg, 0.070 mmol) was added and the reaction mixture was stirred for 2 h at 100°C. The reaction mixture was diluted with water (10 ml) and extracted with ethyl acetate (2X10 ml). The combined organic layer was washed with water (10 ml), brine (10 ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude compound. The crude product was purified by flash column chromatography (2 times) ((100-200 silica gel eluted with 3% of CH_2Cl_2/MeOH) to afford compound. This was re-purified by prep HPLC eluting with 3% methanol in dichloromethane to afford pure (4*S*)-N-(3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (15 mg, 0.036 mmol, 5.15 % yield) as off white solid. (TLC system:5% Methanol in DCM. R_f value: 0.3), LCMS (*m/z*): 414.9 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.23 (br s, 1 H), 8.47 (br d, *J*=19.95 Hz, 2 H), 8.08 (br s, 1 H), 7.92 - 8.04 (m, 1 H), 7.67 - 7.81 (m, 2 H), 5.48 - 5.64 (m, 1 H), 3.20 - 3.26 (m, 1 H), 3.15 (br d, *J*=11.40 Hz, 2 H), 2.90 - 3.05 (m, 1 H), 2.46 (br s, 3 H), 2.20 - 2.38 (m, 1 H), 1.92 - 2.09 (m, 1 H).

Example 270

Synthesis of (4*S*)-*N*-(3-fluoropyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

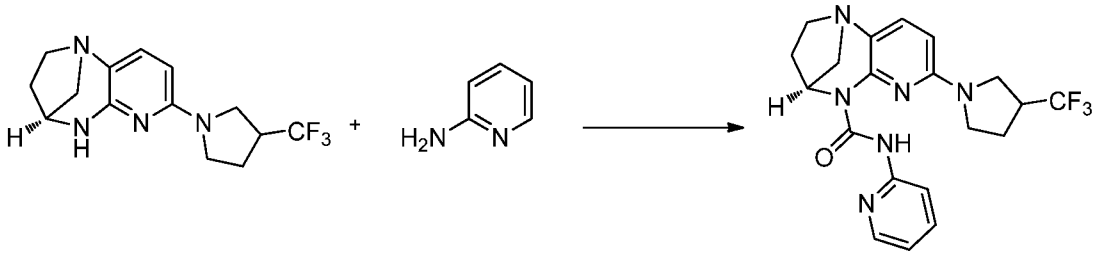


To a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (500 mg, 1.982 mmol) in THF (10 mL, sealed tube) triethylamine (1.657 mL, 11.89 mmol) and triphosgene (588 mg, 1.982 mmol) were added at RT and stirred for 30 min then 3-fluoropyrazin-2-amine (336 mg, 2.97 mmol) was added and heated at 80 °C for 15 h. The reaction mixture was cooled to room temperature 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: 2% methanol in DCM) to obtain the (4*S*)-*N*-(3-fluoropyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (27 mg, 0.068 mmol, 3.44 % yield) as an off white solid (TLC eluent: 5% methanol in DCM, R_f: 0.4), LCMS (*m/z*): 392.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.43 (s, 1 H), 8.59 (d, *J*=5.26 Hz, 1 H), 8.32 (d, *J*=2.63 Hz, 1 H), 7.90 (d, *J*=2.41 Hz, 1 H), 7.72-7.55 (m, 3 H), 7.37 (br d, *J*=4.38 Hz, 1 H), 5.73 (br dd, *J*=5.70, 3.07 Hz, 1 H), 3.36-3.02 (m, 4 H), 2.61 (m, 3 H), 2.33 (br dd, *J*=9.87, 4.17 Hz, 1 H), 2.12 (br dd, *J*=9.72 , 3.86 Hz, 1H).

Example 271

Synthesis of (4*S*)-*N*-(pyridin-2-yl)-7-(3-(trifluoromethyl)pyrrolidin-1-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide)

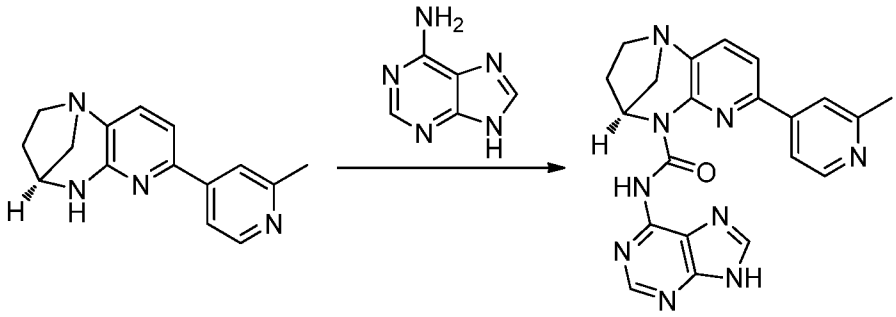


To a solution of (4S)-7-(3-(trifluoromethyl)pyrrolidin-1-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (Peak 2 from intermediate SFC separation) (350 mg, 1.173 mmol) in tetrahydrofuran (THF) (10 mL) was added triphosgene (209 mg, 0.704 mmol)at 0 °C. After 30 min DIPEA (1.025 mL, 5.87 mmol) and pyridin-2-amine (221 mg, 2.347 mmol) were added and the reaction mixture was stirred at 70 °C for 16 h. The reaction mixture was poured onto cold water (50 mL) and extracted with ethyl acetate (2x50 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to give crude compound. The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 2% MeOH in DCM) to obtain (4*S*)-*N*-(pyridin-2-yl)-7-(3-(trifluoromethyl)pyrrolidin-1-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (50.8 mg, 0.115 mmol, 9.83 % yield) as a pale yellow solid. (TLC system: R_f:02, :EtOAc), LCMS (*m/z*): 419.2 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.34 (s, 1 H), 8.25 - 8.11 (m, 2 H), 7.69 - 7.61 (m, 1 H), 7.34 (d, *J*=8.33 Hz, 1 H), 6.98 - 6.90 (m, 1 H), 5.98 (d, *J*=8.55 Hz, 1 H), 5.61 (dd, *J*=6.14, 3.29 Hz, 1 H), 4.02 (dd, *J*=11.18, 8.55 Hz, 1 H), 3.82 (dd, *J*=11.29, 7.34 Hz, 1 H), 3.70 (td, *J*=8.93, 4.28 Hz, 1 H), 3.63 - 3.51 (m, 1 H), 3.29 - 3.06 (m, 4 H), 2.90 (dd, *J*=11.84, 3.29 Hz, 1 H), 2.39 - 2.19 (m, 3 H), 2.05 - 1.91 (m, 1 H).

Example 272

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-*N*-(9*H*-purin-6-yl)-3, 4-dihydro-1, 4-methano pyrido [2, 3-*b*] [1, 4] diazepine-5(2*H*)-carboxamide

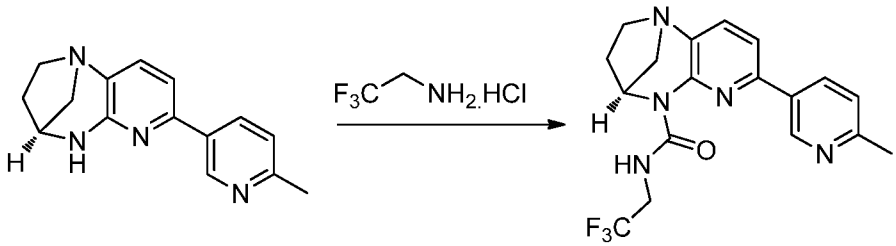


To a solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (1 g, 3.96 mmol) in Tetrahydrofuran (THF) (20 mL) triphosgene (0.588 g, 1.982 mmol) was added and stirred for 1 h. Triethylamine (2.76 mL, 19.82 mmol) was added followed by the addition of 9*H*-purin-6-amine (0.696 g, 5.15 mmol). The reaction mixture was stirred at 70°C for 16 h. The reaction mixture was diluted with water and extracted with 2x25 ml of ethyl acetate. The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude compound. The crude product was purified by flash column chromatography (100-200 silica gel eluted with 3% of CH_2Cl_2/MeOH) to afford the desired compound which was purified by prep HPLC to give (4*S*)-7-(2-methylpyridin-4-yl)-N-(9*H*-purin-6-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (25 mg, 0.057 mmol, 1.449 % yield) as a white solid. (TLC system: 5% Methanol in DCM. R_f value: 0.3), LCMS (*m/z*): 411.9 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 14.08 (br s, 1 H), 12.32 (br s, 1 H), 8.72 (s, 1 H), 8.63 (d, *J*=5.04 Hz, 1 H), 8.45 (s, 1 H), 8.20 (br s, 1 H), 7.99 (dd, *J*=5.48, 1.53 Hz, 1 H), 7.90 - 7.81 (m, 1 H), 7.81 - 7.74 (m, 1 H), 5.57 (dd, *J*=5.70, 3.07 Hz, 1 H), 3.27 - 3.07 (m, 3 H), 3.02 (br dd, *J*=11.95, 3.18 Hz, 1 H), 2.65 (s, 3 H), 2.37 - 2.18 (m,1H), 2.08 (br d, *J*=6.58 Hz, 1 H).

Example 273

Synthesis of (4*S*)-7-(6-methylpyridin-3-yl)-N-(2,2,2-trifluoroethyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

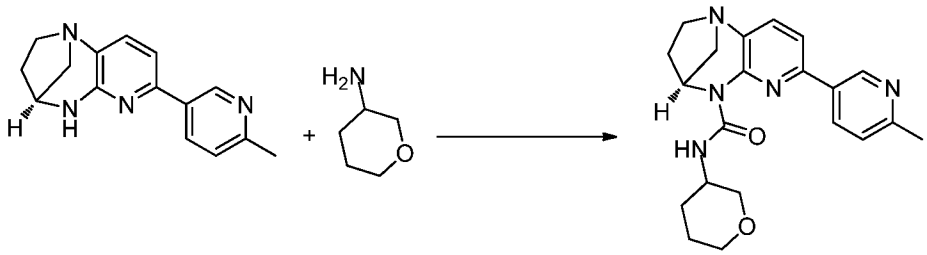


Triphosgene (212 mg, 0.74mmol) was added slowly in portions to a stirred solution of (4*S*)-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 1.190mmol) in Tetrahydrofuran (THF) (15 mL) at RT and stirred for 30 min. DIPEA (0.622 mL, 3.571mmol) and 2,2,2-trifluoroethanamine hydrochloride (242 mg, 1.785mmol) were added to above reaction mixture, stirred at 70 °C for 16 h. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and residue was partitioned between water (40 mL) and EtOAc (80 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 column chromatography using silica gel (100-200 mesh) 2% methanol in dichloromethane as a eluent to afford (4*S*)-7-(6-methylpyridin-3-yl)-N-(2,2,2-trifluoroethyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (235 mg, 0.615 mmol, 103 % yield) as a pale yellow solid.(TLC eluent: 10% MeOH in DCM R_f: 0.5; UV active), LCMS (*m/z*) 378.31 $[M+H]^+$.

^{1}H NMR (400 MHz,$CDCl_3$): δ ppm 11.12 (br t, *J*=6.03 Hz, 1 H), 8.88 (d, *J*=1.97 Hz, 1 H), 7.94 (dd, *J*=8.11, 2.41 Hz, 1 H), 7.57 (d, *J*=7.89 Hz, 1 H),7.31-7.22 (m, 2 H), 5.62 (dd, *J*=6.03, 3.18 Hz, 1 H), 4.16-4.02 (m, 2 H), 3.32-3.08 (m, 3 H), 2.96 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.62 (s, 3 H), 2.28 (dddd, *J*=14.06, 10.00, 6.08, 4.06 Hz, 1 H), 2.09-1.97 (m, 1 H)

Example 274

Synthesis of (4*S*)-7-(6-methylpyridin-3-yl)-*N*-(tetrahydro-2*H*-pyran-3-yl)-3,4-dihydro1,4-methano pyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide

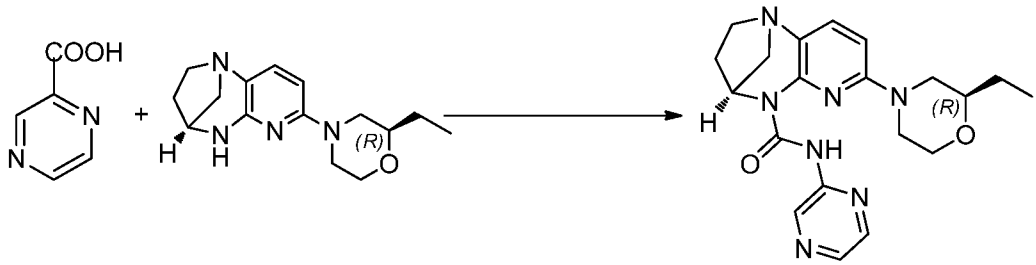


To a solution of (4S)-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (300 mg, 1.189 mmol) in Tetrahydrofuran (THF) (10 mL) was added triphosgene (176 mg, 0.594 mmol) at 0 °C. After 30 min DIPEA (1.038 mL, 5.94 mmol), tetrahydro-2H-pyran-3-amine (180 mg, 1.783 mmol) was added and the reaction mixture was stirred at 70 °C for 16 h. The reaction mixture was poured onto cold water (50 mL) and extracted with ethyl acetate (150 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to yield crude compound. The crude product was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 3% MeOH in DCM) to obtained (4*S*)-7-(6-methylpyridin-3-yl)-N-(tetrahydro-2*H*-pyran-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (114.5 mg, 0.299 mmol, 25.1 % yield) as an off white solid. (TLC system: R_f:0.2, 5% MeOH-DCM), LCMS (*m/z*): 380.0 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 10.59 (t, *J*=7.78 Hz, 1 H), 8.92 (s, 1 H), 8.07 (dt, *J*=8.11, 2.96 Hz, 1 H), 7.52 (d, *J*=7.89 Hz, 1 H), 7.27 - 7.17 (m, 2 H), 5.66 - 5.59 (m, 1 H), 4.10 - 4.00 (m, 1 H), 3.86 (dt, *J*=11.24, 3.70 Hz, 1 H), 3.71 - 3.62 (m, 2 H), 3.53 (dd, *J*=11.18, 5.70 Hz, 1 H), 3.28 - 3.06 (m, 3 H), 2.97 - 2.89 (m, 1 H), 2.60 (s, 3 H), 2.24 (dddd, *J*=16.66, 9.98, 6.25, 3.51 Hz, 1 H), 2.07 - 1.91 (m, 2 H), 1.74 - 1.66 (m, 2 H), 1.56 - 1.50 (m, 1 H).

Example 275

Synthesis of (4*S*)-7-((*R*)-2-ethylmorpholino)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

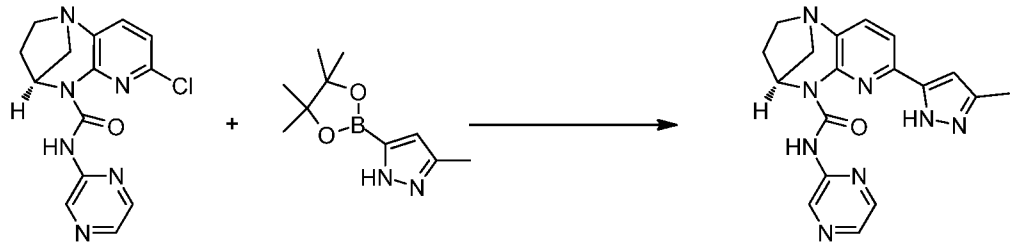


Diisopropylethylamine (2.81 mL, 16.12 mmol) was added to a stirred solution of pyrazine-2-carboxylic acid (400 mg, 3.22 mmol) in tetrahydrofuran (15 mL) stirred under argon at 30 °C. Diphenylphosphorazidate (887 mg, 3.22 mmol) was added to the reaction mixture and was stirred for 2 h at 30 °C. Then (2*R*)-2-ethyl-4-((4*S*)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepin-7-yl)morpholine (619 mg, 2.256 mmol) was added to the reaction mixture and stirred for 16 h at 65 °C. The reaction mixture was cooled to room temp and was partitioned between water (20 mL) and ethyl acetate (2 x 30 mL). The organic layer was separated and was dried over anhydrous sodium sulfate, filtered and filtrate was evaporated to give crude. (TLC eluent: 90 % Ethyl acetate in hexane, R_f = 0.3; UV active). The crude was purified by column chromatography using neutral alumina and product was eluted with 10-15% ethyl acetate in hexane to afford pure (4*S*)-7-((*R*)-2-ethylmorpholino)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (35 mg, 0.088 mmol, 2.75 % yield) as an off-white solid, LCMS (*m/z*): 396.31 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.37 (s, 1 H), 9.55 (d, *J*=1.53 Hz, 1 H), 8.25 (d, *J*=2.63 Hz, 1 H), 8.09 - 8.18 (m, 1 H), 7.38 (d, *J*=8.55 Hz, 1 H), 6.30 (d, *J*=8.55 Hz, 1 H), 5.63 (dd, *J*=6.03, 3.18 Hz, 1 H), 4.00 - 4.13 (m, 2 H), 3.86 (br d, *J*=12.93 Hz, 1 H), 3.75 (td, *J*=11.62, 2.85 Hz, 1 H), 3.45 - 3.56 (m, 1 H), 3.13 - 3.30 (m, 1 H), 3.00 - 3.17 (m, 3 H), 2.92 (dd, *J*=11.84, 3.29 Hz, 1 H), 2.69 - 2.81 (m, 1 H), 2.27 (dddd, *J*=13.89, 9.95, 6.08, 3.62 Hz, 1 H), 2.00 (dt, *J*=14.09, 6.88 Hz, 1 H), 1.59 - 1.78 (m, 2 H), 1.05 (t, *J*=7.45 Hz, 3 H).

Example 276

Synthesis of (4*S*)-7-(3-methyl-1H-pyrazol-5-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

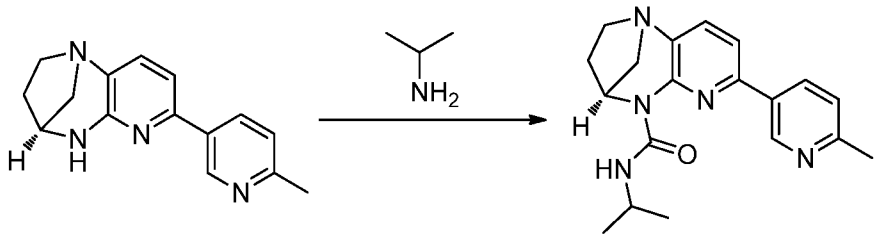


Tripotassium phosphate (469 mg, 2.210 mmol) was added to a stirred solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (350.0 mg, 1.105 mmol), 3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (276 mg, 1.326 mmol) in 1,4-dioxane (10.0 ml) and water (2.0 ml) at 28 °C. The reaction mixture was degassed for 15 min, to this was added X-phos (52.7 mg, 0.110 mmol) and $Pd_2(dba)_3$ (50.6 mg, 0.055 mmol). The reaction mixture was further degassed for 15 min and the was stirred for 16 hours at 100 °C. Then the mixture was cooled to 28 °C and was filtered through a pad of celite and was washed with ethyl acetate (40 ml). The filtrate was washed with the water (10 ml). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude as brown solid (TLC eluent: 10% MeOH in DCM; R_f-0.3; UV active). This crude was purified by grace column and was eluted with 2-5 % MeOH in dichloromethane to afford pure (4*S*)-7-(3-methyl-1H-pyrazol-5-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (181.5 mg, 0.492 mmol, 44.5 % yield) as white solid, LCMS (*m/z*): 363.27 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.80 (s, 1 H), 9.55 (d, *J*=1.10 Hz, 1 H), 8.52 (s, 1 H), 8.20 - 8.35 (m, 2 H), 7.55 (d, *J*=8.11 Hz, 1 H), 7.12 (d, *J*=7.89 Hz, 1 H), 5.68 (dd, *J*=5.92, 3.29 Hz, 1 H), 3.11 - 3.34 (m, 3 H), 2.89 - 3.11 (m, 1 H), 2.60 (s, 3 H), 2.33 (dddd, *J*=14.06, 9.95, 5.92, 4.06 Hz, 1 H), 1.97 - 2.17 (m, 1 H)

Example 277

Synthesis of (4*S*)-*N*-isopropyl-7-(6-methylpyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

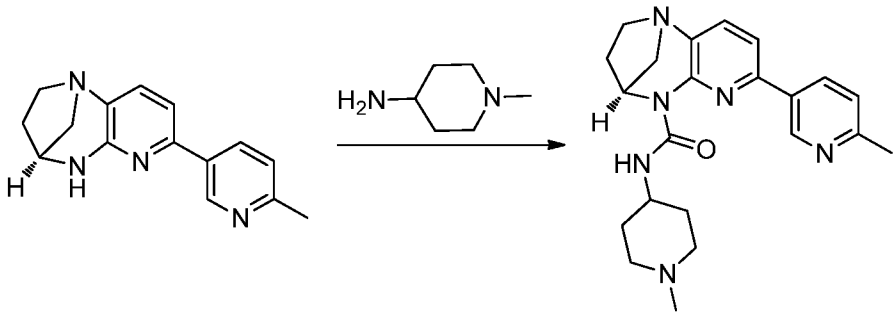


DIPEA (1.038 mL, 5.94 mmol) and followed by triphosgene (353 mg, 1.189 mmol) were added to a stirred solution of (4*S*)-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (500 mg, 1.982 mmol) in THF (15 mL, in sealed tube) at 0 °C and then stirred at RT for 30 min. Then propan-2-amine (176 mg, 2.97 mmol) was added and heated to 75 °C for 16 h. The reaction mixture was cooled to RT and was partitioned between water (25 mL) and EtOAc (60 mL). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to obtain the crude compound. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 2% MeOH in DCM) to afford the (4*S*)-*N*-isopropyl-7-(6-methylpyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (130 mg, 0.384 mmol, 19.39 % yield) as an off white solid (TLC eluent: 5% MeOH in DCM, R_f: 0.3), LCMS (*m/z*): 338.32 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 10.38 (d, *J* = 6.4 Hz, 1H), 8.91 (d, *J* = 2 Hz, 1H), 7.94 (dd, *J* = 2.4, 8 Hz, 1H), 7.52 (d, *J* = 5.6 Hz, 1H), 7.25-7.20 (m, 2H), 5.66-5.62 (m, 1H), 4.14-4.06 (m, 1H), 3.26-3.06 (m, 3H), 2.97-2.92 (m, 1H), 2.62 (s, 3H), 2.30 -2.21(m, 1H), 2.26-1.98 (m, 1H), 1.27 (d, *J* = 6.8Hz, 6 H)

Example 278

Synthesis of (4*S*)-N-(1-methylpiperidin-4-yl)-7-(6-methylpyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

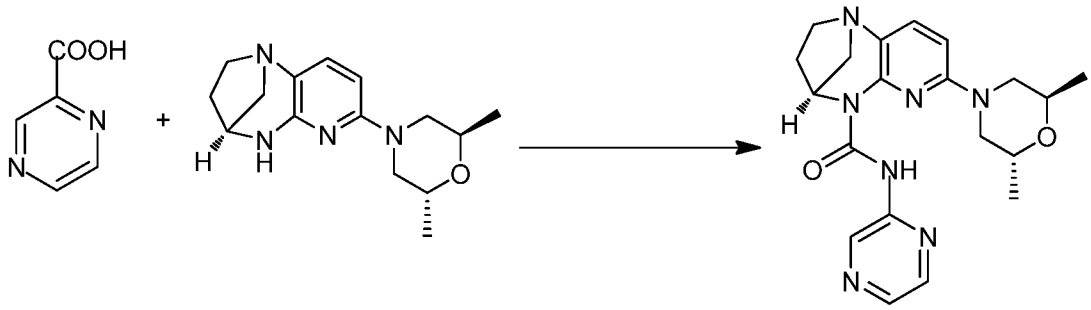


Triphosgene (423.8 mg, 1.428mmol) was added slowly in portions to a stirred solution of (4S)-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (600 mg, 2.380mmol) in Tetrahydrofuran (THF) (25 mL) at RT and stirred for 30 min. DIPEA (1.24 mL, 7.14mmol) and 1-methylpiperidin-4-amine (408 mg, 3.571mmol) were added to the reaction mixture, stirred at 70 °C for 16 h. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and residue was partitioned between water (40 mL) and EtOAc (80 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 column chromatography using silica gel (100-200 mesh) 2% methanol in dichloromethane as a eluent to afford (4*S*)-N-(1-methylpiperidin-4-yl)-7-(6-methylpyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (100 mg, 0.252 mmol, 21.21 % yield) as a off white solid as a pale yellow solid. (TLC eluent: 10% MeOH in DCM R_f: 0.4; UV active), LCMS (*m/z*): 393.33 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 10.46 (br d, *J*=7.45 Hz, 1 H), 8.88 (d, *J*=2.19 Hz, 1 H), 7.92 (dd, *J*=8.11, 2.41 Hz, 1 H), 7.53 (d, *J*=7.89 Hz, 1 H), 7.29-7.24 (m, 1 H), 7.20 (d, *J*=7.89 Hz, 1 H), 5.62 (dd, *J*=5.92, 3.29 Hz, 1 H), 3.82-3.73 (m, 1 H), 3.12 - 3.26 (m, 2 H), 3.12-3.06 (m, 1 H), 2.94 (dd, *J*=11.84, 3.29 Hz, 1 H), 2.85-2.78 (m, 1 H), 2.86-2.77 (m, 1 H), 2.62 (s, 3 H), 2.30-2.22 (m, 4 H), 2.15-1.98 (m, 5 H),1.65-1.53 (m, 2 H)

Example 279

Synthesis of (4*S*)-7-((2*R*,6*R*)-2,6-dimethylmorpholino)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

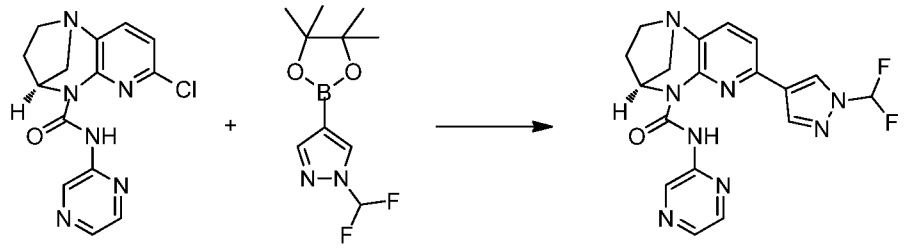


Diphenyl phosphorazidate (0.432 g, 1.571 mmol) was added to a stirred solution of pyrazine-2-carboxylic acid (0.195 g, 1.571 mmol) and DIPEA (1.372 mL, 7.86 mmol) in tetrahydrofuran (30 mL) under argon atmosphere at room temp. The reaction mixture was stirred for 2 h at room temp and subsequently (2R,6R)-2,6-dimethyl-4-((4S)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepin-7-yl)morpholine (0.302 g, 1.100 mmol) was added and the reaction mixture was stirred 16 h at 65 °C. The reaction mixture was cooled to room temp and the solvent was evaporated under reduced pressure completely, and was partitioned between water (20 mL) and EtOAc (60 mL). Organic layer was separated, dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude as brown solid (TLC eluent: 100% EtOAc: R_f-0.3; UV active). The crude was purified by column chromatography using neutral aluminia and was eluted with 20% EtOAc in Hexane to afford pure afford (4S)-7-((2R,6R)-2,6-dimethylmorpholino)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (0.081 g, 0.203 mmol, 12.93 % yield) as a white solid, LCMS (*m/z*): 396.38 $[M+H]^+$.

^{1}H NMR (400 MHz, cdcl3-*d*) δ ppm 13.42 (s, 1 H), 9.56 (d, *J*=1.32 Hz, 1 H), 8.25 (d, *J*=2.63 Hz, 1 H), 8.09 - 8.19 (m, 1 H), 7.37 (d, *J*=8.55 Hz, 1 H), 6.24 (d, *J*=8.55 Hz, 1 H), 5.63 (dd, *J*=6.03, 3.18 Hz, 1 H), 4.28 - 4.15 (m, 2 H), 3.67 (dd, *J*=12.39, 3.40 Hz, 2 H), 3.32 - 3.19 (m, 3 H), 3.17 - 3.06 (m, 2 H), 2.92 (dd, *J*=11.84, 3.29 Hz, 1 H), 2.27 (dddd, *J*=13.95, 10.00, 6.19, 3.84 Hz, 1 H), 2.00 (dt, *J*=14.09, 7.10 Hz, 1 H), 1.34 (d, *J*=6.36 Hz, 6 H)

Example 280

Synthesis of (4*S*)-7-(1-(difluoromethyl)-1H-pyrazol-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

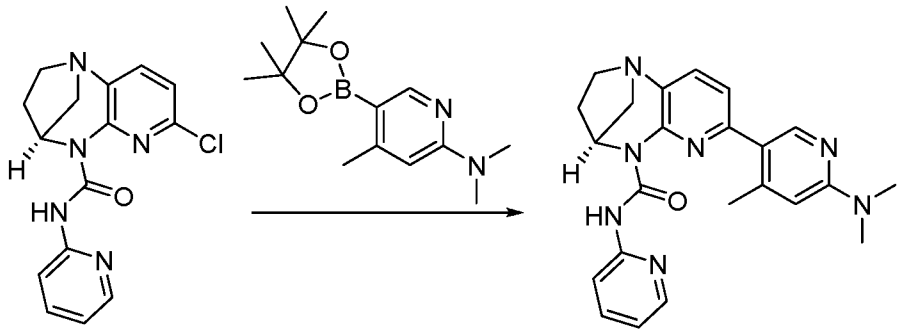


Tripotassium phosphate (469 mg, 2.210 mmol) was added to a stirred solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (350 mg, 1.105 mmol), 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (324 mg, 1.326 mmol) in 1,4-dioxane (10.0 ml) and water (2.0 ml). The reaction mixture was degassed for 10 min. $Pd_2(dba)_3$ (50.6 mg, 0.055 mmol) and X-phos (52.7 mg, 0.110 mmol) were added to the reaction mixture and was further degassed for 15 min. The reaction mixture was stirred for 16 hours at 100 °C. The reaction mixture was cooled to 28 °C and was filtered through a pad of celite and was washed with ethyl acetate (40 ml). The filtrate was washed with the water (10 ml). Organic layer was separated and was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude as brown solid (TLC eluent: 10% MeOH in DCM: R_f-0.4; UV active). The crude was purified by grace column and was eluted with 1-2% MeOH in dichloromethane to afford pure (4*S*)-7-(1-(difluoromethyl)-1H-pyrazol-4-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (280.0 mg, 0.702 mmol, 63.6 % yield) as white solid, LCMS (*m/z*): 399.30 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 14.18 (s, 1 H), 9.55 (d, *J* = 1.3 Hz, 1 H), 9.17 (s, 1 H), 8.36 - 8.27 (m, 2 H), 8.22 (s, 1 H), 7.56 (d, *J* = 7.9 Hz, 1 H), 7.26 - 7.06 (m, 2 H), 5.66 (dd, *J* = 5.9, 3.3 Hz, 1 H), 3.35 - 3.11 (m, 3 H), 3.01 (dd, *J* = 12.3, 3.3 Hz, 1 H), 2.34 (dddd, *J*=14.1, 9.8, 6.0, 4.06 Hz, 1 H), 1.93 - 2.17 (m, 1 H).

Example 281

Synthesis of (4*S*)-7-(6-(dimethylamino)-4-methylpyridin-3-yl)-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

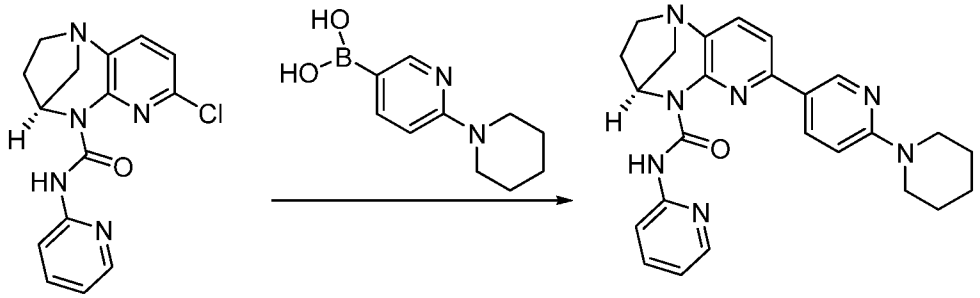


N,*N*,4-trimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (274 mg, 1.045 mmol) followed by K_3PO_4 (605 mg, 2.85 mmol) were added to a stirred solution of (4*S*)-7-chloro-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (300 mg, 0.950 mmol) in 1-Butanol (10 mL) at RT and degassed for 20 min. Then $Pd_2(dba)_3$ (43.5 mg, 0.048 mmol) and X-phos (45.3 mg, 0.095 mmol) were added to the reaction mixture and the reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was cooled to room temperature and was partitioned between water (25 mL) and EtOAc (40 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 column chromatography (silica gel: 100-200 mesh), compound was collected at 70 % EtOAc in pet ether to obtained (4*S*)-7-(6-(dimethylamino)-4-methylpyridin-3-yl)-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide(100 mg, 0.236 mmol, 24.80 % yield) as an off-white solid. (TLC eluent: 100% EtOAc in pet ether R_f: 0.4, UV active), LCMS (*m/z*): 416.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 13.31 (s, 1 H), 8.36 - 8.17 (m, 3 H), 8.17 - 7.96 (m, 1 H), 7.86 - 7.57 (m, 1 H), 6.99 (d, *J*=7.89 Hz, 1 H), 6.95 - 6.68 (m, 1 H), 6.43 (s, 1 H), 5.69 (brdd, *J*=5.59, 3.18 Hz, 1 H), 3.31 (br d, *J*=8.77 Hz, 1 H), 3.24 - 3.10 (m, 8 H), 3.10 - 2.87 (m, 1 H), 2.47 (s, 3 H), 2.40 - 2.20 (m, 1 H), 2.19 - 1.92 (m, 1 H)

Example 282

Synthesis of (4*S*)-7-(6-(piperidin-1-yl)pyridin-3-yl)-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

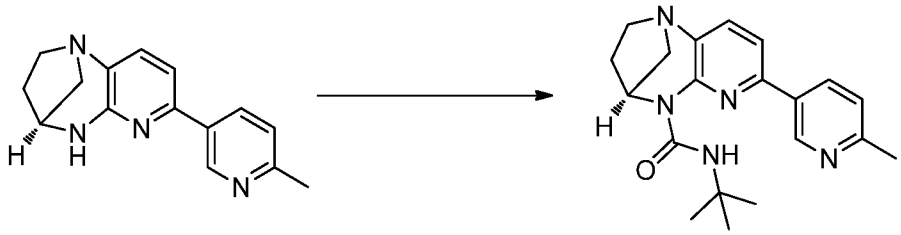


(6-(piperidin-1-yl)pyridin-3-yl)boronic acid (215 mg, 1.045 mmol) followed by K_3PO_4 (605 mg, 2.85 mmol) were added to a stirred solution of (4*S*)-7-chloro-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (300 mg, 0.950 mmol) in 1-Butanol (10 mL) at RT and degassed for 20 min. Then $Pd_2(dba)_3$ (43.5 mg, 0.048 mmol) and X-phos (45.3 mg, 0.095 mmol) were added to the reaction mixture and the reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was cooled to room temperature and was partitioned between water (25 mL) and EtOAc (40 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 column chromatography (silica gel: 100-200 mesh), compound was collected at 70 % EtOAc in pet ether to obtain (4*S*)-7-(6-(piperidin-1-yl)pyridin-3-yl)-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (150 mg, 0.336 mmol, 35.3 % yield) as a pale yellow solid. (TLC eluent: 100% EtOAc in pet ether, R_f: 0.4, UV active)., LCMS (*m/z*): 442.3 $[M+H]^+$,

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 13.71 (s, 1 H), 8.80 (d, *J*=2.63 Hz, 1 H), 8.54 (dd, *J*=8.99, 2.63 Hz, 1 H), 8.37 (dt, *J*=4.93, 0.82 Hz, 1 H), 8.18 (d, *J*=8.33 Hz, 1 H), 7.78 - 7.59 (m, 1 H), 7.51 (d, *J*=8.11 Hz, 1 H), 7.30 - 7.25 (m, 1 H), 6.97 (ddd, *J*=7.23, 4.82, 0.88 Hz, 1 H), 6.79 (d, *J*=8.99 Hz, 1 H), 5.68 (dd, *J*=5.92, 3.29 Hz, 1 H), 3.70 - 3.59 (m, 4 H), 3.09 - 3.32 (m, 3 H), 3.09 - 2.84 (m, 1 H), 2.31 (d, *J*=1.97 Hz, 1 H), 2.17 - 1.95 (m, 1 H), 1.68 (br s, 6 H).

Example 283

Synthesis of (4*S*)-*N*-(tert-butyl)-7-(6-methylpyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

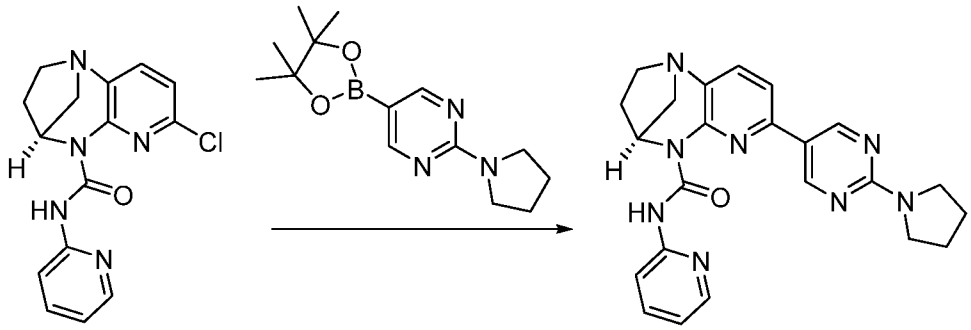


DIPEA (1.038 mL, 5.94 mmol) followed by triphosgene (353 mg, 1.189 mmol) were added to a solution of (4*S*)-7-(6-methylpyridin-3-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*] [1,4] diazepine (500 mg, 1.982 mmol) in Tetrahydrofuran (15 mL) at RT and stirred it for 30 min. Then 2-methylpropan-2-amine (217 mg, 2.97 mmol) was added and heated to 75 °C for 16 h. The reaction mixture was cooled to 28 °C and was partitioned between water (25 mL) and EtOAc (60 mL). The separated organic layer was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to obtain the crude compound. The crude mixture was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 2% MeOH in DCM) to afford the (4*S*)-N-(tert-butyl)-7-(6-methylpyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*] [1,4] diazepine-5(2*H*)-carboxamide (185 mg, 0.525 mmol, 26.5 % yield) as an off white solid(TLC eluent: 5% MeOH in DCM, R_f: 0.3; UV active), LCMS (*m/z*): 352.34 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$-*d*): δ ppm 10.4 (s, 1H), 8.90 (d, *J* = 2 Hz, 1H),7.95 (dd, *J* = 2.4 Hz, 8 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 8Hz, 1H), 7.17 (d, *J* = 8 Hz, 1H), 5.64 - 5.61 (m, 1H), 3.28 -3.12 (m, 2H), 3.10 -3.05 (m, 1H), 2.96 -2.91 (m, 1H), 2.61 (s, 3H), 2.30 - 2.21 (m, 1H), 2.06 – 1.97(m, 1H,), 1.43 (s, 9 H).

Example 284

Synthesis of (4*S*)-*N*-(pyridin-2-yl)-7-(2-(pyrrolidin-1-yl)pyrimidin-5-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

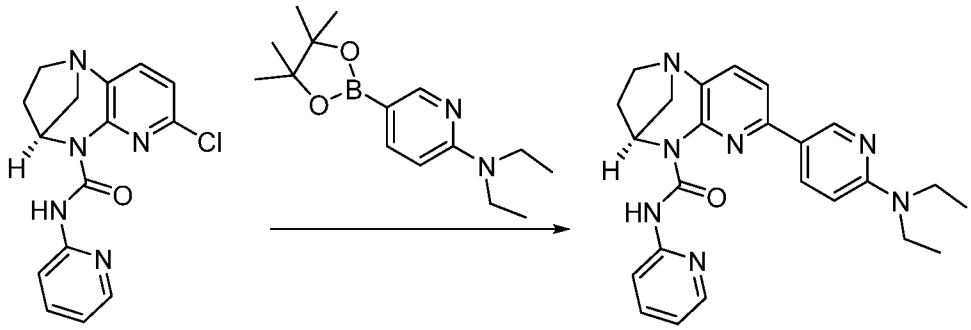


2-(pyrrolidin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (288 mg, 1.045 mmol) followed by K_3PO_4 (605 mg, 2.85 mmol) were added to a stirred solution of (4*S*)-7-chloro-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (300 mg, 0.950 mmol) in 1-Butanol (10 mL) at RT and degassed for 20 min. Then $Pd_2(dba)_3$ (43.5 mg, 0.048 mmol) and X-phos (45.3 mg, 0.095 mmol) were added to the reaction mixture and the reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was cooled to room temperature and was partitioned between water (25 mL) and EtOAc (40 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 column chromatography (silica gel: 100-200 mesh), compound was collected at 70 % EtOAc in pet ether to obtain (4*S*)-*N*-(pyridin-2-yl)-7-(2-(pyrrolidin-1-yl)pyrimidin-5-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (170 mg, 0.377mmol, 39.7 % yield) as a yellow solid. (TLC eluent: 100% EtOAc in pet ether, R_f: 0.4, UV active), LCMS (*m/z*): 429.6 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 13.57 (s, 1 H), 9.09 (s, 2 H), 8.51 - 8.26 (m, 1 H), 8.14 (d, *J*=8.33 Hz, 1 H), 7.67 (td, *J*=7.84, 1.86 Hz, 1 H), 7.54 (m, *J*=8.11 Hz, 1 H), 7.26 (s, 1 H), 6.97 (ddd, *J*=7.29, 4.88, 0.99 Hz, 1 H), 5.68 (dd, *J*=5.81, 3.18 Hz, 1 H), 3.75 - 3.60 (m, 4 H), 3.35 - 3.09 (m, 3 H), 2.99 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.32 (m, 1 H), 1.98 - 2.13 (m, 5 H)

Example 285

Synthesis of (4*S*)-7-(6-(diethylamino)pyridin-3-yl)-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

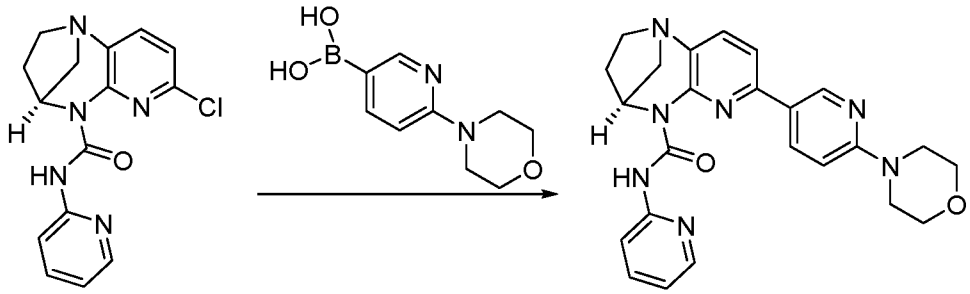


N,*N*-diethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (289 mg, 1.045 mmol) followed by K_3PO_4 (605 mg, 2.85 mmol) were added to a stirred solution of (4*S*)-7-chloro-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (300 mg, 0.950 mmol) in 1-Butanol (10 mL) at RT and degassed for 20 min. Then $Pd_2(dba)_3$ (43.5 mg, 0.048 mmol) and X-phos (45.3 mg, 0.095 mmol) were added to the reaction mixture and the reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was cooled to room temperature and was partitioned between water (25 mL) and EtOAc (40 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 column chromatography (silica gel: 100-200 mesh), compound was collected at 70 % EtOAc in pet ether to obtain (4*S*)-7-(6-(diethylamino)pyridin-3-yl)-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (120 mg, 0.271 mmol, 28.5 % yield) as an off-white solid. (TLC eluent: 100% EtOAc in pet ether, R_f: 0.4, UV active), LCMS (*m/z*): 430.3 $[M+H]^+$.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 13.77 (s, 1 H), 8.78 (d, *J*=2.41 Hz, 1 H), 8.64 - 8.43 (m, 1 H), 8.43 - 8.28 (m, 1 H), 8.18 (d, *J*=8.55 Hz, 1 H), 7.75 - 7.59 (m, 1 H), 7.51 (d, *J*=8.11 Hz, 1 H), 7.39 - 7.15 (m, 1 H), 6.97 (ddd, *J*=7.34, 4.93, 0.88 Hz, 1 H), 6.62 (d, *J*=8.99 Hz, 1 H), 5.68 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.69 - 3.50 (m, 4 H), 3.34 - 3.08 (m, 3 H), 3.08 – 2.89 (m, 1 H), 2.39 - 2.19 (m, 1 H), 2.08 (dt, *J*=13.87, 6.77 Hz, 1 H), 1.24 (t, *J*=7.02 Hz, 6 H)

Example 286

Synthesis of (4*S*)-7-(6-morpholinopyridin-3-yl)-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

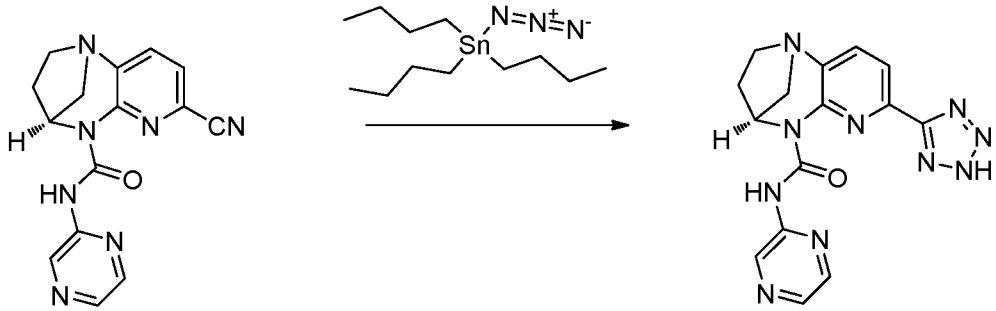


(6-morpholinopyridin-3-yl)boronic acid (296 mg, 1.425 mmol) followed by K_3PO_4 (605 mg, 2.85 mmol) were added to a stirred solution of (4*S*)-7-chloro-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (300 mg, 0.950 mmol) in 1-Butanol (10 mL) at RT and degassed for 20 min. Then $Pd_2(dba)_3$ (43.5 mg, 0.048 mmol) and X-phos (45.3 mg, 0.095 mmol) were added to the reaction mixture and the reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was cooled to room temperature and was partitioned between water (25 mL) and EtOAc (40 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 column chromatography (silica gel: 100-200 mesh), compound was collected at 70 % EtOAc in pet ether to obtain (4*S*)-7-(6-morpholinopyridin-3-yl)-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (110 mg, 0.245 mmol, 25.8 % yield) as an off-white solid. (TLC eluent: 100% EtOAc in pet ether, R_f: 0.4, UV active), LCMS (*m/z*): 444.3 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 13.68 (s, 1 H), 8.85 (s, 1 H), 8.56 - 8.64 (m, 1 H), 8.36 (d, *J*=3.73 Hz, 1 H), 8.19 (d, *J*=8.33 Hz, 1 H), 7.68 (t, *J*=7.13 Hz, 1 H), 7.54 (d, *J*=8.11 Hz, 1 H), 7.32 (s, 1 H), 7.02- 6.95 (m, 1 H), 6.78 (d, *J*=8.99 Hz, 1 H), 5.68 (dd, *J*=5.70, 3.07 Hz, 1 H), 3.91-3.83 (m, 4 H), 3.70- 3.60 (m, 4 H), 3.34 - 3.14 (m, 3 H), 2.99 (dd, *J*=11.95, 3.18 Hz, 1 H), 2.42 - 2.26 (m, 1 H), 2.08 (dt, *J*=13.87, 7.21 Hz, 1 H).

Example 287

***Synthesis* of (4S)-N-(pyrazin-2-yl)-7-(2H-tetrazol-5-yl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-b][1, 4] diazepine-5(2H)-carboxamide**



Azidotributylstannane (1.297 g , 3.90 mmol) was added to a stirred solution of (4*S*)-7-cyano-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (0.4 g, 1.302 mmol) in tetrahydrofuran (25 mL) and heated to 80-90 °C for 48 h in sealed tube. The reaction mixture was cooled to room temperature. Tetrahydrofuran was concentrated under reduced pressure to obtain residue. The residue was diluted with dichloromethane (100 mL).The organic layer was washed with 50 mL of 0.5M HCl, water (50 mL) and brine (50 mL).The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to obtain crude (TLC eluent: 10% MeOH in DCM; UV active; R_f ~0.3). The crude compound was triturated with diethyl ether and filtered to afford (4*S*)-N-(pyrazin-2-yl)-7-(2H-tetrazol-5-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (0.13g, 0.369 mmol, 28.4 % yield) as white solid, LCMS (*m/z*): 351.24 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 14.75 (br s, 1H), 9.47 (d, *J* = 1.32 Hz, 1H), 8.48 - 8.40 (m, 2H), 8.02 (d, *J* = 7.89 Hz, 1H), 7.77 (d, *J* = 7.89 Hz, 1 H), 5.57 (dd, *J* = 5.92, 3.07 Hz, 1H), 3.37 - 3.27 (m, 2H), 3.22 - 3.17 (m, 1H), 3.24 - 3.04 (m, 1H), 2.39 (ddt, *J* = 14.36, 8.88, 5.48, 5.48 Hz, 1H), 2.18 - 2.05 (m, 1H)

Example 288

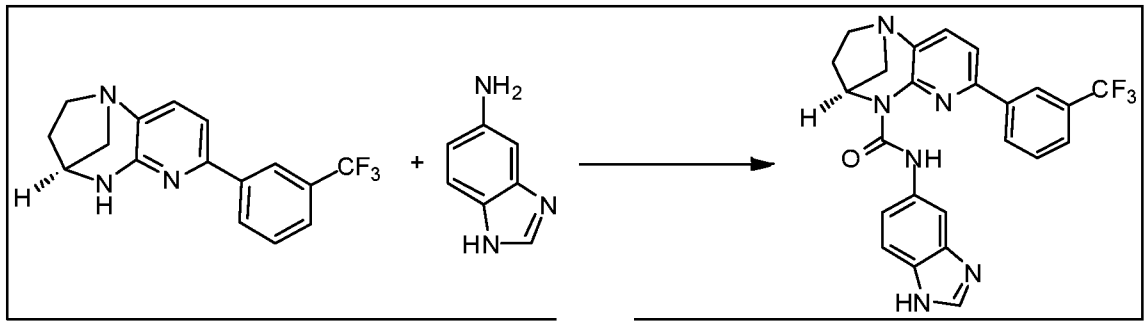
Synthesis of (4*S*)-N-(1*H*-benzo[d]imidazol-5-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

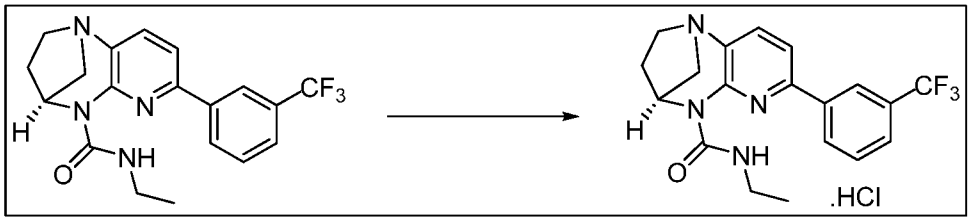
To a solution of (4*S*)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 0.983 mmol) in THF (20 mL) at RT was added Et_3N (0.822 mL, 5.90 mmol), tri-phosgene (292 mg, 0.983 mmol) and stirred for 1 h. then 1H-benzo[d]imidazol-5-amine (393 mg, 2.95 mmol) was added 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 (30 mL) and DCM (50 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: 70% ethyl acetate in hexane) to afford the desired product (4*S*)-N-(1*H*-benzo[*d*]imidazol-5-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (215 mg, 0.461 mmol, 47.0 % yield) as an off-white solid. LCMS (*m/z*): 465.09 $[M+H]^+$, R_t = 1.77 min

^{1}H NMR (400 MHz, DMSO-d_6): δppm 13.02 - 12.63 (m, 1 H), 12.34 (br s, 1 H), 8.30 - 8.20 (m, 2 H), 8.16 - 8.10 (m, 1 H), 8.06 (s, 1 H), 7.92 - 7.77 (m, 2 H), 7.73 - 7.67 (m, 1 H), 7.67 - 7.60 (m, 1 H), 7.52 - 7.37 (m, 1 H), 7.18 – 6.91 (m, 1 H), 5.53 (dd, *J*=5.70, 3.07 Hz, 1 H), 3.22 (br t, *J*=9.21 Hz, 1 H), 3.16 - 3.05 (m, 2 H), 2.97 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.35 - 2.19 (m, 1 H), 1.95 (dt, *J*=13.37, 6.69 Hz, 1 H).

Example 289

Synthesis of (4*S*)-N-ethyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide hydrochloride



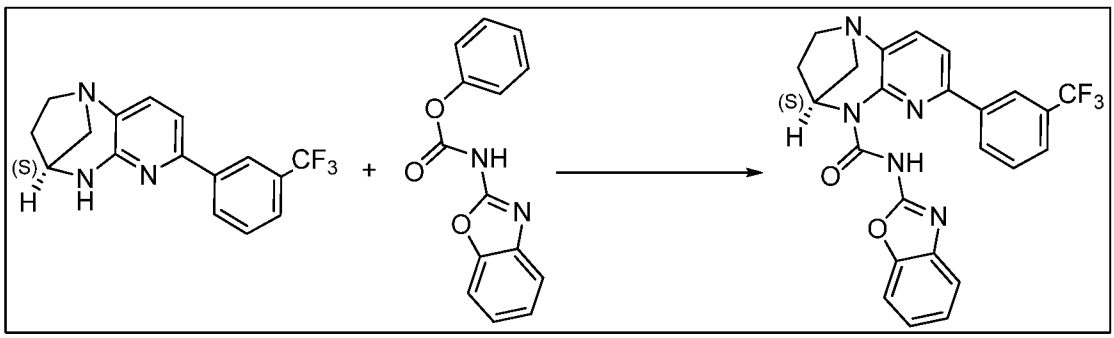


To a stirred solution of (4*S*)-N-ethyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (200 mg, 0.531 mmol) in 1,4-Dioxane (10 mL) was added 4M HCl in 1,4-Dioxane (5.31 mL, 21.26 mmol) and stirred at RT for 3 h. (TLC: Eluent: 5%MeOH in DCM, Rf: 0.3). The reaction mixture was concentrated *in vacuo* and the resultant salt was triturated with diethylether (10 mL) to afford the desired product (4*S*)-N-ethyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide hydrochloride (130 mg, 0.307 mmol, 57.7 % yield) as an off white solid. LCMS (*m/z*): 377.07 $[M+H]^+$, Rt = 2.35min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.01 (br s, 1 H), 8.21 (d, *J*=7.67 Hz, 1 H), 8.15 (s, 1 H), 7.96 (br d, *J*=7.89 Hz, 1 H), 7.85 - 7.90 (m, 1 H), 7.77 - 7.84 (m, 1 H), 7.73 (d, *J*=8.11 Hz, 1 H), 5.53 (dd, *J*=5.70, 3.07 Hz, 1 H), 3.40 - 3.64 (m, 4 H), 3.27 - 3.37 (m, 2 H), 2.33 - 2.46 (m, 1 H), 2.02 - 2.14 (m, 1 H), 1.18 (t, *J*=7.23 Hz, 3 H).

Example 290

Synthesis of (4*S*)-N-(benzo[d]oxazol-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



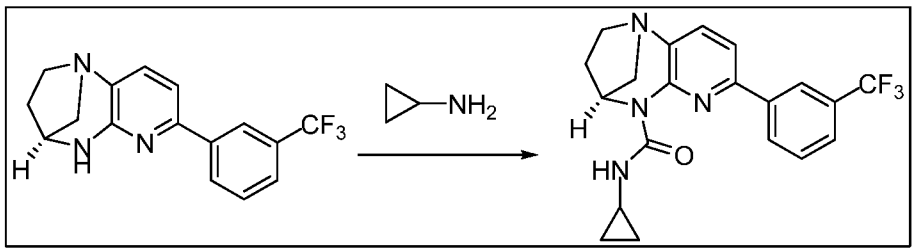
To a solution of (4*S*)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 0.983 mmol) in THF (15 mL) at 0 °C was added NaH (118 mg, 2.95 mmol), phenyl benzo[d]oxazol-2-yl-carbamate (749 mg, 2.95 mmol) and stirred at 90 °C in microwave for 1 h. (TLC eluent:100% Ethyl acetate, R_f = 0.4; UV active). The reaction mixture was cooled to room temperature, quenched with ice water and extracted into ethyl acetate (2x60 mL). The combined organic extracts were

dried over anhydrous sodium sulphate, filtered and concentrated. The crude compound was purified by column chromatography (neutral alumina, eluent: 65% ethyl acetate in hexane) to afford the desired product (4*S*)-N-(benzo[d]oxazol-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (150 mg, 0.316 mmol, 32.2 % yield) as an off-white solid. LCMS (*m/z*): 466.10 $[M+H]^+$, R_t = 2.58 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 14.60 (s, 1 H), 8.26 (s, 1 H), 8.11 (d, *J*=7.89 Hz, 1 H), 7.74 - 7.81 (m, 1 H), 7.72-7.61 (m, 3 H), 7.44 (d, *J*=8.11 Hz, 2 H), 7.50 -7.40 (m, 1 H), 7.31-7.16 (m, 1 H), 5.76 (dd, *J*=6.03, 3.18 Hz, 1 H), 3.34-3.14 (m, 3 H), 3.04 (dd, *J*=12.17, 3.18 Hz, 1 H), 2.43-2.28 (m, 1 H), 2.12 (dt, *J*=14.20, 7.04 Hz, 1 H).

Example 291

Synthesis of (4*S*)-N-cyclopropyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



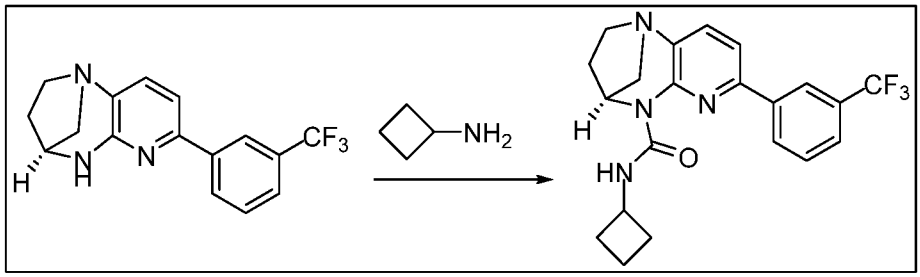
To a solution of (4*S*)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (250 mg, 0.819 mmol) in THF (20 mL) under nitrogen was added triethylamine (0.685 mL, 4.91 mmol), triphosgene (243 mg, 0.819 mmol) and stirred at RT for 30 min. then added cyclopropanamine (140 mg, 2.457 mmol) and the reaction was heated at 65 °C for 16 h. (TLC eluent: 100% Ethyl acetate; R_f = 0.3; UV active). The solvent was removed under reduced pressure, diluted with water (20 mL) and extracted with ethyl acetate (2x40 mL). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated. The crude compound was purified by column chromatography (neutral alumina, eluent: 20% ethyl acetate in hexane). Collected fractions were concentrated under reduced pressure to afford pure (4*S*)-N-cyclopropyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (170 mg, 0.437 mmol, 53.4 % yield) as an off-white solid. LCMS (*m/z*): 389.10 $[M+H]^+$, R_t = 2.34 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 10.54 (br s, 1 H), 8.02 (s, 1 H), 7.92 (d, *J*=7.89 Hz, 1 H), 7.71 - 7.65 (m, 1 H), 7.64 - 7.57 (m, 1 H), 7.54 (d, *J*=7.89 Hz, 1 H), 7.31 - 7.26 (s, 1

H), 5.66 (dd, *J*=6.03, 3.18 Hz, 1 H), 3.29 - 3.04 (m, 3 H), 2.95 (dd, *J*=11.84, 3.29 Hz, 1 H), 2.85 (tq, *J*=7.07, 3.62 Hz, 1 H), 2.27 (dddd, *J*=14.11, 9.95, 5.97, 3.95 Hz, 1 H), 2.07 - 1.96 (m, 1 H), 0.84 - 0.74 (m, 2 H), 0.61 - 0.53 (m, 2 H).

Example 292

Synthesis of (4*S*)-N-cyclobutyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

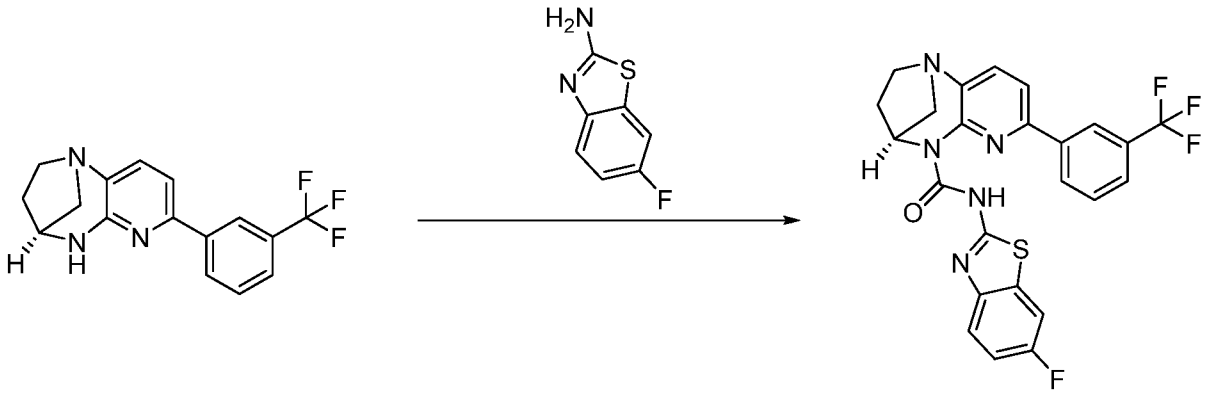


To a solution of (4*S*)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (250 mg, 0.819 mmol) in THF (20 mL) under nitrogen was added triethylamine (0.685 mL, 4.91 mmol), triphosgene (243 mg, 0.819 mmol) and stirred at RT for 30 min. then added Cyclobutanamine (175 mg, 2.457 mmol) and the reaction was heated at 65 °C for 16 h. (TLC eluent: 100% Ethyl acetate: R_f=0.3; UV active). The solvent was removed under reduced pressure, diluted with water (20 mL) and extracted in to ethyl acetate (2x40 mL). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated. The crude compound was purified by preparative HPLC (Conditions- Column: XBridge C18 (75X4.6 mm, 3.5µ); Mobile Phase- A: 0.01M Ammoniumbicarbonate B: Acetionitrile; 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 the desired product (4*S*)-N-cyclobutyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (174 mg, 0.432 mmol, 52.8 % yield) as an off white solid. LCMS (*m/z*): 403.11 $[M+H]^+$, R_t = 2.56 min.

^{1}H NMR (400 MHz, $CDCl_3$): δppm 10.62 (br d, *J*=6.58 Hz, 1 H), 8.10 (s, 1 H), 7.98 (d, *J*=7.67 Hz, 1 H), 7.73 - 7.65 (m, 1 H), 7.64 - 7.59 (m, 1 H), 7.55 (d, *J*=7.89 Hz, 1 H), 7.28 (s, 1 H), 5.63 (dd, *J*=6.03, 3.18 Hz, 1 H), 4.43 (dq, *J*=16.25, 7.96 Hz, 1 H), 3.30 -3.02 (m, 3 H), 2.94 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.46 - 2.34 (m, 2 H), 2.25 (dddd, *J*=14.03, 9.98, 6.03, 3.95 Hz, 1 H), 2.09 - 1.86 (m, 3 H), 1.85 - 1.63 (m, 2 H).

Example 293

Synthesis of (4*S*)-*N*-(6-fluorobenzo[d]thiazol-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

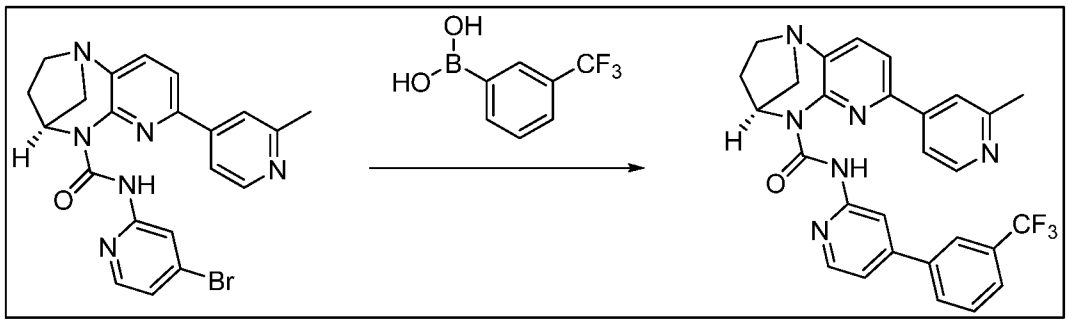


To a stirred solution of (4*S*)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (400 mg, 1.310 mmol) in Tetrahydrofuran (15 mL) were added Et_3N (1.096 mL, 7.86 mmol) and tri-phosgene (389 mg, 1.310 mmol) at 25 °C and stirred for 1h then 6-fluorobenzo[d]thiazol-2-amine (441 mg, 2.62 mmol) (solid) was added and heated at 70 °C for 15 h. (TLC system: neat ethyl acetate, R_f: 0.3). The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the residue was partitioned between water (40 mL) and EtOAc (80 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 (100-200 silica gel, eluent: 80% ethyl acetate in hexane) to afford the desired product (4*S*)-*N*-(6-fluorobenzo[*d*]thiazol-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (170 mg, 0.333 mmol, 25.4 % yield) as an off white solid. LCMS (*m/z*): 500.01 $[M+H]^+$, Rt = 3.10 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 14.75 (s, 1 H), 8.42 (s, 2 H), 7.94 - 7.75 (m, 5 H), 7.68 (dd, *J*=8.77, 4.82 Hz, 1 H), 7.31 (td, *J*=9.10, 2.85 Hz, 1 H), 5.50 (dd, *J*=6.03, 3.18 Hz, 1 H), 3.27 - 3.09 (m, 3 H), 2.99 (dd, *J*=11.73, 3.18 Hz, 1 H), 2.35 - 2.22 (m, 1 H), 2.10 - 1.96 (m, 1 H).

Example 294

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-N-(4-(3-(trifluoromethyl)phenyl)pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

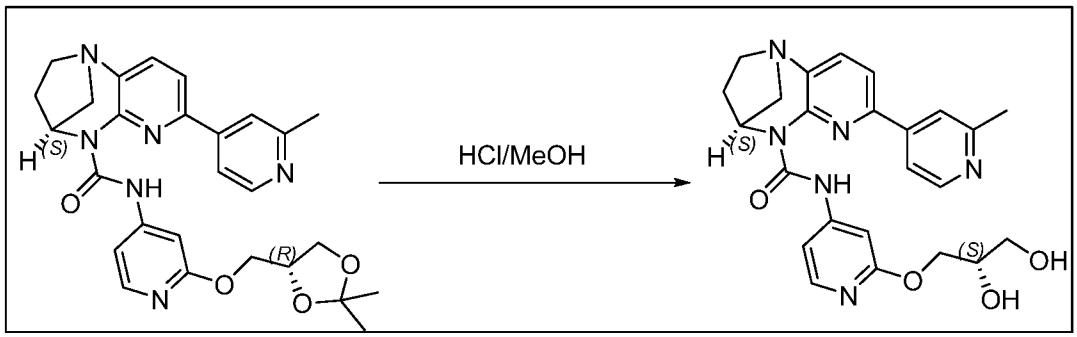


To a degassed solution of (4*S*)-N-(4-bromopyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (300 mg, 0.665 mmol), (3-(trifluoromethyl)phenyl)boronic acid (189 mg, 0.997 mmol) and Potassium phosphate tri basic (423 mg, 1.994 mmol) in 1,4-Dioxane (18 mL) and Water (4.50 mL) were added x-phos (19.20 mg, 0.133 mmol) and $Pd_2(dba)_3$ (60.9 mg, 0.066 mmol). The reaction mixture was stirred at 100 °C for 16 h. (TLC System: 5% MeOH in EtOAc, R_f: 0.5). The reaction mixture was allowed to cool to room temperature and 1,4 dioxane solvent was evaporated under reduced pressure, the obtained residue was diluted with water (50 ml) and extracted with ethyl acetate (2x 100 ml). The combined organic layer was washed with water, brine, dried over sodium sulphate and solvent was evaporated under reduced pressure to obtain the crude product. The crude product was purified by flash column chromatography using (silica gel 100-200 mesh: Elutent: Neat Ethyl acetate) to afford the desird product (4*S*)-7-(2-methylpyridin-4-yl)-N-(4-(3-(trifluoromethyl)phenyl)pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4] diazepine-5(2*H*)-carboxamide (70 mg, 0.135 mmol, 20.34 % yield) as an off white solid. LCMS (*m/z*): 517.11 $[M+H]^+$, R_t = 2.16 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.70 (s, 1 H), 8.64 (d, *J*=5.26 Hz, 1 H), 8.57 - 8.53 (m, 1 H), 8.45 (d, *J*=5.04 Hz, 1 H), 8.22 (s, 1 H), 7.85 - 7.99 (m, 2 H), 7.76 - 7.57 (m, 4 H), 7.50 (d, *J*=7.89 Hz, 1 H), 7.27 - 7.20 (m, 1 H), 5.72 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.34 - 3.13 (m, 3 H), 3.04 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.77 (s, 3 H), 2.46 - 2.29 (m, 1 H), 2.21 - 2.02 (m, 1 H).

Example 295

Synthesis of (4*S*)-N-(2-((S)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide.

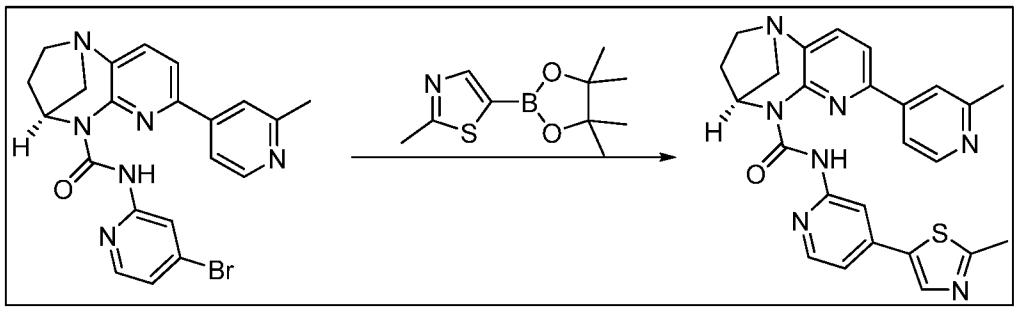


To a stirred solution of (4*S*)-N-(2-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (150 mg, 0.298 mmol) in Methanol (10 mL) was added hydrochloric acid (5 mL, 165 mmol) at 0 °C over a period of 5min. Then the reaction mixture was stirred at 30° C for 2 h. (TLC eluent: 5% MeOH in DCM: R_f-0.5; UV active), solvent evaporated and neutralized the reaction mixture with sodium bicarbonate solution, extracted with DCM and dried over anhydrous sodium sulphate and evaporated to get solid compound, filtered and washed with *n*-pentane (2 x 20 mL) to afford the desired product (4*S*)-N-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyr ido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (110 mg, 0.238 mmol, 80 % yield) as an off-white solid. LCMS (*m/z*): 463.15 $[M+H]^+$, R_t = 1.20 min.

^{1}H NMR (400 MHz, CDCl3): δ ppm 13.28 (s, 1 H), 8.68 (d, *J*=5.26 Hz, 1 H), 7.96 (d, *J*=5.70 Hz, 1 H), 7.65 (d, *J*=7.89 Hz, 1 H), 7.58 (s, 1 H), 7.48 (dd, *J*=5.15, 1.21 Hz, 1 H), 7.38 (d, *J*=7.89 Hz, 1 H), 7.13 -7.05 (m, 2 H), 5.67 (dd, *J*=6.03, 3.18 Hz, 1 H), 4.46 (dd, *J*=4.71, 1.21 Hz, 2 H), 4.35 (d, *J*=5.48 Hz, 1 H), 3.99 (dq, *J*=9.95, 4.94 Hz, 1 H), 3.73 - 3.61 (m, 2 H), 3.33 -3.12 (m, 3 H), 3.03 (dd, *J*=12.17, 3.18 Hz, 1 H), 2.89 (t, *J*=6.58 Hz, 1 H), 2.69 (s, 3 H), 2.35 (qd, *J*=9.94, 4.17 Hz, 1 H), 2.08 (dt, *J*=14.14, 6.96 Hz, 1 H).

Example 296

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-N-(4-(2-methylthiazol-5-yl)pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

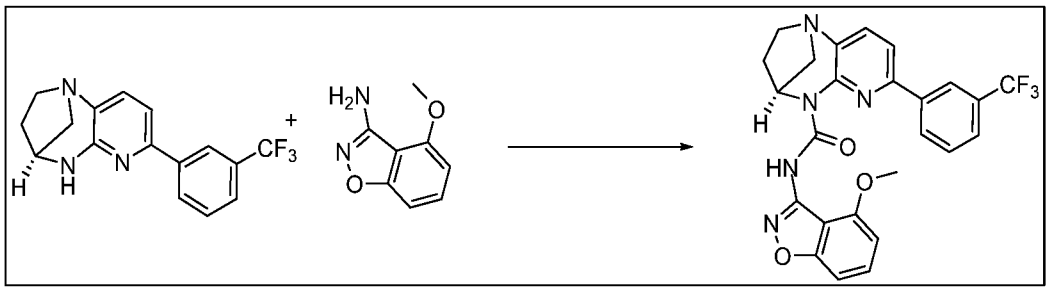


To a degassed solution of (4*S*)-N-(4-bromopyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (250 mg, 0.554 mmol), 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole (249 mg, 1.108 mmol) and Potassium phosphate tri basic (353 mg, 1.662 mmol) in 1,4-Dioxane (18 mL) and Water (4.50 mL) was added $PdCl_2(dppf)$-CH_2Cl_2 adduct (45.2 mg, 0.055 mmol). The reaction mixture was stirred at 90 °C for 16 h. (TLC: SiO2; 10% MeOH/DCM TLC: SiO2; 10% MeOH/DCM). The reaction mixture was allowed to cool to room temperature and diluted with water (50 mL), extracted with ethyl acetate (2x 50 mL). The combined organic layer was washed with water (50 mL), dried over anhydrous sodium sulphate and evaporated *in vacuo* to obtain the crude product as a brown solid. The crude product was purified by combi flash chromatography (120 g Reverse phase: 100% methanol) to afford the desired product (4*S*)-7-(2-methylpyridin-4-yl)-N-(4-(2-methylthiazol-5-yl)pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (67 mg, 0.142 mmol, 25.6 % yield) as a pale green solid. LCMS (*m/z*): 470.09 $[M+H]^+$, R_t = 1.63 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.65 (s, 1 H), 8.63 (d, *J*=5.26 Hz, 1 H), 8.45 (dd, *J*=1.53, 0.66 Hz, 1 H), 8.35 (dd, *J*=5.15, 0.77 Hz, 1 H), 8.18 (d, *J*=1.53 Hz, 1 H), 8.05 (s, 1 H), 7.72 (dd, *J*=5.37, 1.43 Hz, 1 H), 7.63 (d, *J*=7.89 Hz, 1 H), 7.49 (d, *J*=7.89 Hz, 1 H), 7.14 (dd, *J*=5.26, 1.75 Hz, 1 H), 5.72 (dd, *J*=6.03, 3.18 Hz, 1 H), 3.40 - 3.14 (m, 3 H), 3.03 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.75 (d, *J*=6.58 Hz, 6 H), 2.36 (dddd, *J*=14.11, 9.95, 6.08, 4.06 Hz, 1 H), 2.10 (dt, *J*=14.25, 6.91 Hz, 1 H).

Example 297

Synthesis of (4*S*)-N-(4-methoxybenzo[*d*]isoxazol-3-yl)-7-(3-(trifluoromethyl) phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

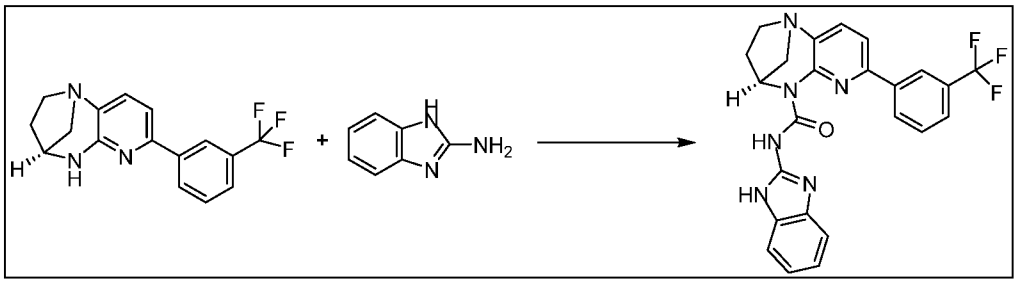


To a stirred solution of (4*S*)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (350.0 mg, 1.146 mmol) in tetrahydrofuran (20 mL) was added triethylamine (0.799 mL, 5.73 mmol) and triphosgene (340 mg, 1.146 mmol) at 25°C and stirred for 45 min then 4-methoxybenzo[d]isoxazol-3-amine (565 mg, 3.44 mmol) was added and heated the reaction mixture at 72 °C for 6 h. (TLC eluent system: 100% EtOAc,R_f-0.4,UV active). The reaction mixture was cooled to RT, the precipitated solid was filtered and filtrate was washed with water (10 ml) and extracted into ETOAc. 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 prep HPLC (Conditions: column XBridge C18 (250X30 mm, 5µ); Mobile Phase- A: 5 mM Ammonium Bicarbonate B: Acetionitrile; Gradient-Time/%B: 0/10,10/50,11.5/100,15/100,15.1/10; Column Temp:Ambient; Flow Rate: 20 ml/min: Diluent: THF+MEOH+ACN) to afford desired product (4*S*)-N-(4-methoxybenzo[d]isoxazol-3-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (106.5 mg, 0.211 mmol, 18.38 % yield) as a white solid LCMS (*m/z*): 496.05 $[M+H]^+$, R_t =2.43 min

^{1}HNMR (400 MHz, $CDCl_3$): δ ppm 12.97 (s, 1 H), 8.06 (s, 1 H), 7.99 (d, *J*=7.89 Hz, 1 H), 7.62 - 7.68 (m, 2 H), 7.45 (t, *J*=7.78 Hz, 1 H), 7.35 - 7.41 (m, 2 H), 7.10 (d, *J*=8.11 Hz, 1 H), 6.34 (d, *J*=7.89 Hz, 1 H), 5.77 (dd, *J*=5.81, 3.18 Hz, 1 H), 3.18 - 3.35 (m, 3 H), 3.03 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.90 (s, 3 H), 2.30 - 2.41 (m, 1 H), 2.16 (dt, *J*=14.03, 7.02 Hz, 1 H)

Example 298

Synthesis of (4*S*)-N-(1H-benzo[*d*]imidazol-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide:

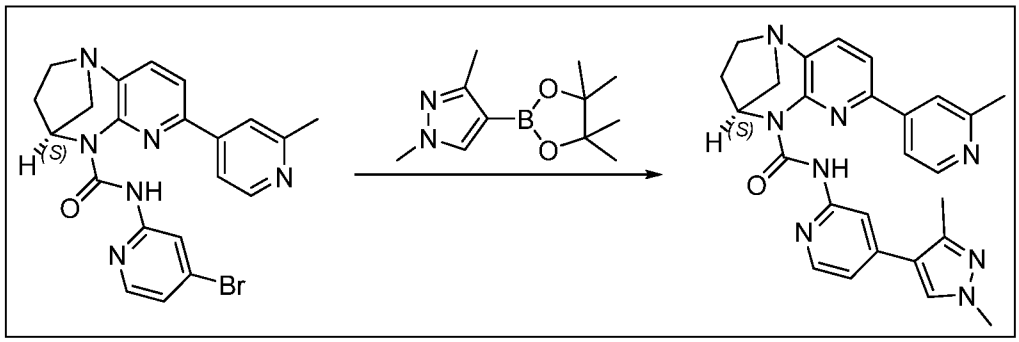


To a stirred solution of (4*S*)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (300 mg, 0.983 mmol) in tetrahydrofuran (40 mL) was added TEA (0.685 mL, 4.91 mmol) and triphosgene (292 mg, 0.983 mmol) at RT and stirred for 30 min. then 1H-benzo[d]imidazol-2-amine (393 mg, 2.95 mmol) was added and reaction mixture was heated to 60 °C for 16 h. solid (TLC eluting system: 10% MeOH in DCM; R_f-0.3; UV active). The reaction mixture was cooled to room temperature and quenched with water (15 mL) and extracted into EtOAc (2x15 mL). Organic layer was separated, dried over anhydrous sodium sulphate, filtered and filtrate was evaporated to get crude compound. The crude was purified by chromatography (GRACE using C-18 reserval column, Mobile phase A: 0.1% Formic Acid in water; B: MeOH, eluent 75% B in A). Combined fractions were evaporated and basified with saturated $NaHCO_3$ solution. The aqueous layer was extracted with DCM, DCM layer was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford (4*S*)-N-(1H-benzo[d]imidazol-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (26 mg, 0.053 mmol, 5.43 % yield) as an off white LCMS (*m/z*): 465.05 $[M+H]^+$, R_t =2.32 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 14.16 (s, 1 H), 11.99 (s, 1 H), 8.40 - 8.50 (m, 2 H), 7.86 - 7.92 (m, 1 H), 7.79 - 7.86 (m, 2 H), 7.74 - 7.78 (m, 1 H), 7.46 - 7.51 (m, 1 H), 7.38 (d, *J*=7.45 Hz, 1 H), 7.08 (td, *J*=7.73, 1.43 Hz, 2 H), 5.53 (dd, *J*=5.81, 2.96 Hz, 1 H), 3.09 - 3.27 (m, 3 H), 3.00 (dd, *J*=11.95, 3.40 Hz, 1 H), 2.23 - 2.35 (m, 1 H), 2.03 (dt, *J*=13.98, 7.15 Hz, 1 H)

Example 299

Synthesis of (4*S*)-N-(4-(1, 3-dimethyl-1H-pyrazol-4-yl) pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-*b*][1,4]diazepine-5(2*H*)-carboxamide

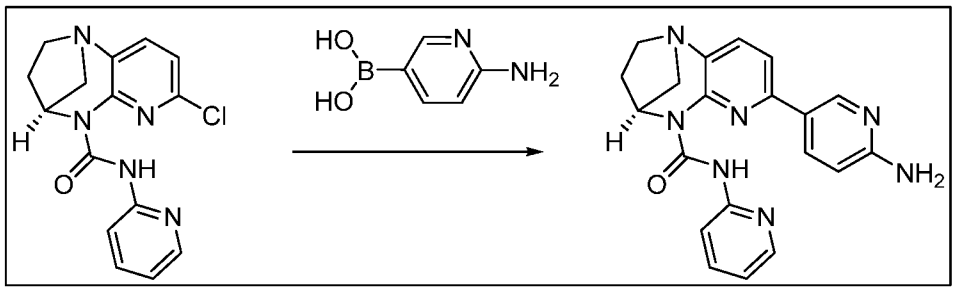


To a degassed solution of (4*S*)-N-(4-bromopyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2H)-carboxamide (250 mg, 0.554 mmol), 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (135 mg, 0.609 mmol) and sodium carbonate (176 mg, 1.662 mmol) in 1,4-Dioxane (7 mL):Water (3 mL) was added $Pd(P(Ph)_3)_4$ (32.0 mg, 0.028 mmol) and stirred the reaction mixture at 80 °C for 15 h. (TLC system:5% Méthanol in Ethyl Acetate. R_f value: 0.3.). Then allowed to cool to room temperature and diluted with water (30 mL), extracted with ethyl acetate (2X50mL). The combined organic layer was washed with brine solution (20 mL) and dried over anhydrous sodium sulphate, filtered and concentrated to afford crude compound. The crude compound was purified by flash column chromatography (silica gel: 100-200 mesh, Eluent: 2% of MeOH in Ethyl acetate) to afford the desired product (4*S*)-N-(4-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (150 mg, 0.321 mmol, 57.9 % yield) as an off white solid. LCMS (*m/z*): 467.18 $[M+H]^+$, R_t =1.47 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.56 (s, 1 H), 8.62 (d, *J*=5.26 Hz, 1 H), 8.37 - 8.28 (m, 2 H), 8.23 (s, 1 H), 7.73 (d, *J*=1.32 Hz, 1 H), 7.67 (s, 1 H), 7.63 (s, 1 H), 7.49 (d, *J*=7.89 Hz, 1 H), 7.09 - 7.04 (m, 1 H), 5.71 (dd, *J*=5.81, 3.18 Hz, 1 H), 3.89 (s, 3 H), 3.32 - 3.15 (m, 3 H), 3.02 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.75 (s, 3 H), 2.52 (s, 3 H), 2.38 - 2.30 (m, 1 H), 2.15 - 2.05 (m, 1 H).

Example 300

Synthesis of (4*S*)-7-(6-aminopyridin-3-yl)-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide

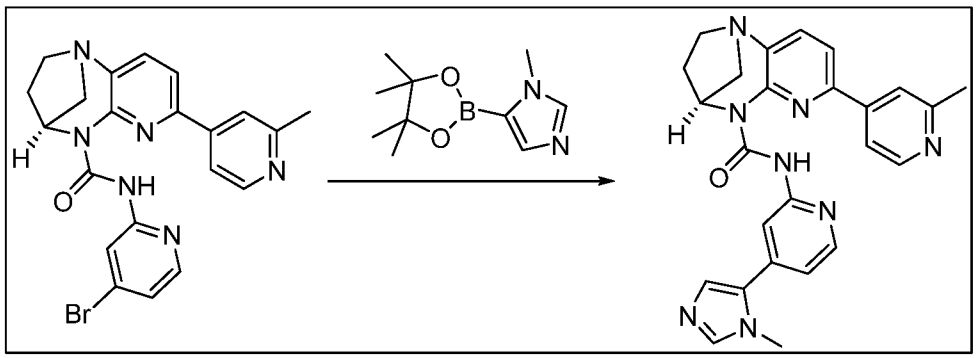


To a degassed solution of (4*S*)-7-chloro-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido [2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (350 mg, 1.108 mmol), (6-aminopyridin-3-yl)boronic acid (229 mg, 1.663 mmol) and Potasium phosphate tribasic (235 mg, 1.108 mmol) in 1,4-Dioxane (18 mL): Water (4.50 mL) were added $Pd_2(dba)_3$ (50.8 mg, 0.055 mmol) and x-phos (52.8 mg, 0.111 mmol). The reaction mixture was stirred at 100 °C for 3 h. (TLC: 10% MeOH in EtOAc R_f: 0.3). The 1,4 dioxane solvent was evaporated under reduced pressure, the obtained residue was diluted with water (50 ml) and extracted with ethylacetate (2x 100 ml). The combined organic layer was washed with water, brine, dried over sodium sulphate and solvent was evaporated under reduced pressure to obtain the crude product. The crude product was purified by flash column chromatography ((silica gel 100-200 mesh: elutent: 2% MeOH/ DCM) to afford semi pure compound and again purified by prep HPLC (Prep HPLC conditions: MP-A 5mM Ammomium Acetate (Aq)) MP-B : MeOH + ACN Column : XBRIDGE250X30 Method: - T/%B = 0/20,10/50,11/100 Flow: 28 ml/min Solubility : THF+MeOH) to afford the desired product (4*S*)-7-(6-aminopyridin-3-yl)-*N*-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (210 mg, 0.562 mmol, 50.7 % yield) as an off white solid. LCMS (*m/z*): 374.19 $[M+H]^+$, Rt = 1.32 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.64 (s, 1 H), 8.75 (d, *J*=2.41 Hz, 1 H), 8.50 (dd, *J*=8.77, 2.41 Hz, 1 H), 8.38 - 8.34 (m, 1 H), 8.18 (dt, *J*=8.55, 0.88 Hz, 1 H), 7.68 (td, *J*=7.89, 1.97 Hz, 1 H), 7.54 (d, *J*=8.11 Hz, 1 H), 7.29 (d, *J*=8.11 Hz, 1 H), 7.02 - 6.94 (m, 1 H), 6.67 (dd, *J*=8.55, 0.66 Hz, 1 H), 5.68 (dd, *J*=5.92, 3.29 Hz, 1 H), 4.65 (br s, 2 H), 3.32 - 3.12 (m, 3 H), 2.99 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.31 (dddd, *J*=13.95, 9.95, 6.03, 3.84 Hz, 1 H), 2.12 - 2.03 (m, 1 H).

Example 301

Synthesis of (4*S*)-*N*-(4-(1-methyl-1*H*-imidazol-5-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

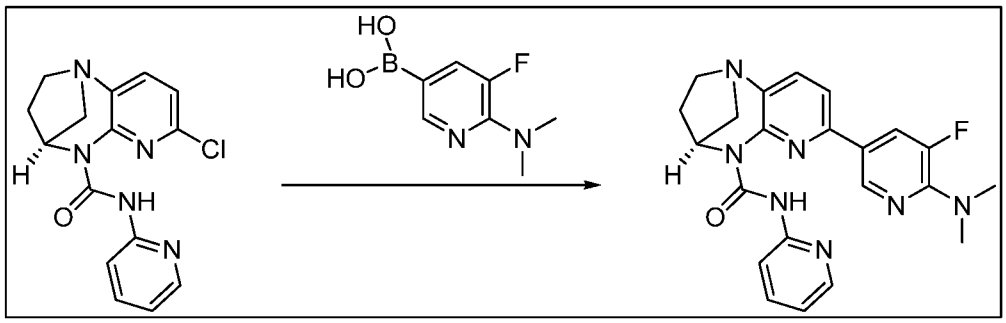


To a degassed solution of 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-imidazole (138 mg, 0.665 mmol) in 1,4-Dioxane (8 mL) : Water (2 mL) were added (4*S*)-*N*-(4-bromopyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4] diazepine-5(2*H*)-carboxamide (200 mg, 0.443 mmol), Na_2CO_3 (47.0 mg, 0.443 mmol). Then $Pd(Ph_3P)_4$ (512 mg, 0.443 mmol) was added to the reaction mixture at RT and again degassed for 5 min. Then the reaction mixture was stirred at 80 °C for 16 h. (TLC system: (10% MeOH/ DCM, R_f: 0.5) and the reaction mixture was cooled to RT and the organic solvents were evaporated, and diluted it with water followed by extracted it with ethylacetate (3X 20 mL). The combined organic layer was washed brine (2x5 mL) and dried over anhydrous sodium sulphate, filtered and concentrated to obtain crude compound. The crude compound was purified by flash column chromatography (100-200 mesh, neat ethyl acetate - 2% DCM/ MeOH) to afford the desired product (4*S*)-*N*-(4-(1-methyl-1*H*-imidazol-5-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (70 mg, 0.154 mmol, 34.7 % yield) as a yellow solid. LCMS (*m/z*): 453.14 $[M+H]^+$, Rt = 1.18 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.63 (s, 1 H), 8.60 (d, *J*=5.26 Hz, 1 H), 8.42 (d, *J*=5.26 Hz, 1 H), 8.33 (s, 1 H), 8.23 (s, 1 H), 7.94 (d, *J*=4.60 Hz, 1 H), 7.86 - 7.77 (m, 2 H), 7.75 - 7.68 (m, 1 H), 7.39 -7.27 (m, 2 H), 5.52 (br d, *J*=2.41 Hz, 1 H), 3.83 (s, 3 H), 3.45 - 2.93 (m, 4 H), 2.64 (s, 3 H), 2.35 - 2.15 (m, 1 H), 2.09 - 1.86 (m, 1 H).

Example 302

Synthesis of (4*S*)-7-(6-(dimethylamino)-5-fluoropyridin-3-yl)-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

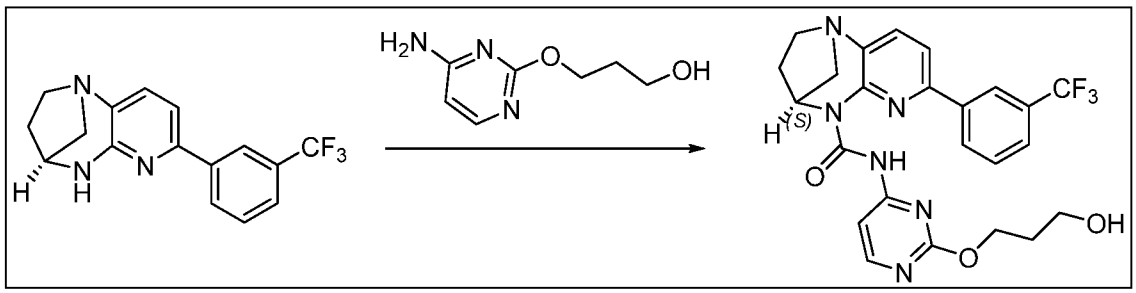


To a degassed solution of (4*S*)-7-chloro-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (3.2 g, 10.13 mmol), (6-(dimethylamino)-5-fluoropyridin-3-yl)boronicacid (2.051 g, 11.15 mmol) and sodium carbonate (3.22 g, 30.4 mmol) in 1,4-Dioxane (18 mL): Water (4.50 mL) was added $Pd(PPh_3)_4$ (0.586 g, 0.507 mmol) and stirred at 100 °C for 3 h. (TLC system: Neat Ethyl acetate, R_f: 0.4). The 1,4-dioxane solvent was evaporated under reduced pressure, the obtained residue was diluted with water (50 ml) and extracted with ethylacetate (2x 100 ml). The combined organic layer was washed with water, brine, dried over sodium sulphate and solvent was evaporated under reduced pressure to obtain the crude product. The crude product was purified by flash column chromatography (silica gel 100-200 mesh: elutent: 70 % Ethyl acetate) to afford the desired product (4S)-7-(6-(dimethylamino)-5-fluoropyridin-3-yl)-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide (1.58 g, 3.76 mmol, 37.1 % yield) as an off white solid. LCMS (*m/z*): 420.1 $[M+H]^+$, *Rt* = 2.25 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.76 (s, 1 H), 8.60 (d, *J*=1.97 Hz, 1 H), 8.56 (s, 1 H), 8.38 (dd, *J*=4.82, 1.10 Hz, 1 H), 8.16 (d, *J*=8.55 Hz, 1 H), 7.77 - 7.64 (m, 1 H), 7.53 (d, *J*=8.11 Hz, 1 H), 7.31 (d, *J*=8.11 Hz, 1 H), 7.02 - 6.91 (m, 1 H), 5.67 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.25 (s, 3 H), 3.23 (s, 3 H), 3.22- 3.02 (m, 3 H), 2.98 (dd, *J*=11.84, 3.29 Hz, 1 H), 2.31 (dddd, *J*=14.06, 9.95, 6.03, 3.95 Hz, 1 H), 2.07 (dt, *J*=13.98, 6.93 Hz, 1 H).

Example 303

Synthesis of (4*S*)-N-(2-(3-hydroxypropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

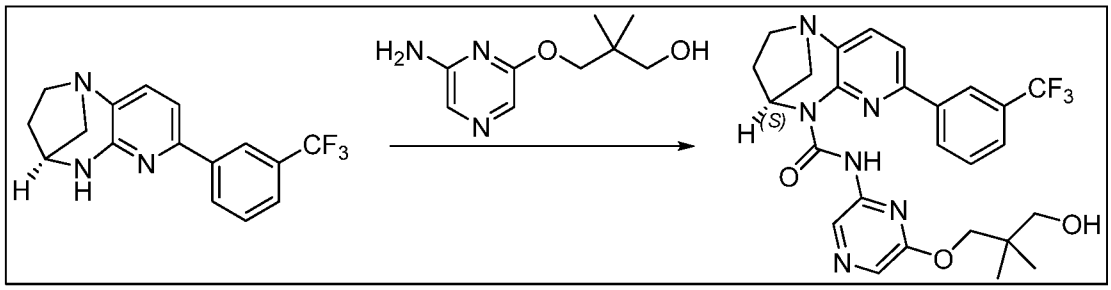


To a stirred solution of (4S)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (300 mg, 0.983 mmol) in THF (15 mL) were added triphosgene (175 mg, 0.590 mmol) and triethylamine (0.822 mL, 5.90 mmol) at room temperature, and stirred for 30 min. Then, 3-((4-aminopyrimidin-2-yl)oxy)propan-1-ol (332 mg, 1.965 mmol) was added and stirred at 80 °C for 15 h. (TLC System: R_f- 0.2, 5% MeOH/ EtOAc). The reaction mixture was allowed to cool to room temperature and diluted with water (25 mL), extracted with EtOAc (2x 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: 2% methanol in ethylacetate) to afford the desired product (4*S*)-N-(2-(3-hydroxypropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methano pyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (80 mg, 0.152 mmol, 15.46 % yield) as an off-white solid. LCMS (*m/z*): 501.24 $[M+H]^+$, R_t = 2.19 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.65 (s, 1 H), 8.46 (dd, *J*=4.17, 2.85 Hz, 1 H), 8.36 (d, *J*=5.70 Hz, 1 H), 8.06 (s, 1 H), 7.79 (d, *J*=5.48 Hz, 1 H), 7.73 (s, 2 H), 7.65 (d, *J*=8.11 Hz, 1 H), 7.43 (d, *J*=7.89 Hz, 1 H), 5.66 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.45 - 4.40 (m, 2 H), 3.76 (q, *J*=5.19 Hz, 2 H), 3.36 - 3.14 (m, 3 H), 3.02 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.50 - 2.28 (m, 1 H), 2.14 - 1.88 (m, 4 H).

Example 304

Synthesis of (4*S*)-N-(6-(3-hydroxy-2,2-dimethylpropoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

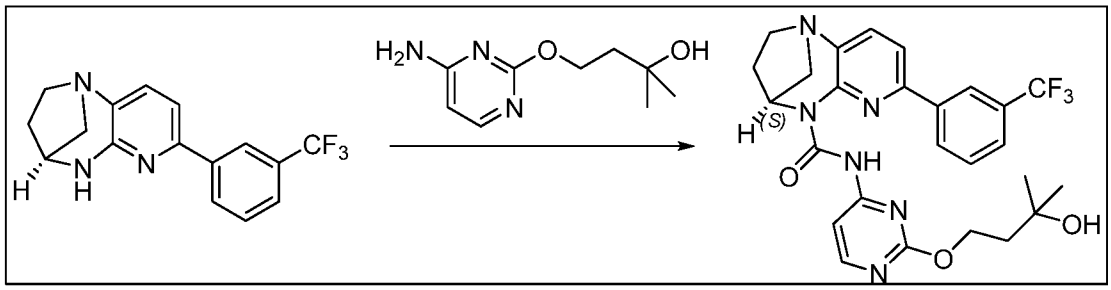


To a stirred solution of (4*S*)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 0.983 mmol) in THF (15 mL) were added triphosgene (175 mg, 0.590 mmol) and triethylamine (0.822 mL, 5.90 mmol) at room temperature, and stirred for 30 min. Then, 3-((6-aminopyrazin-2-yl)oxy)-2,2-dimethylpropan-1-ol (388 mg, 1.965 mmol) was added and stirred at 80 °C for 15 h. (TLC System: R_f- 0.4, 5% MeOH/ EtOAc). The reaction mixture was allowed to cool to room temperature and diluted with water (25 mL), extracted with EtOAc (2x 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: 1 % methanol in ethylacetate) to afford the desired product (4*S*)-N-(6-(3-hydroxy-2,2-dimethylpropoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide (130 mg, 0.240 mmol, 24.40 % yield) as an off-white solid. LCMS (*m/z*): 529.17 $[M+H]^+$, R_t = 2.52 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.24 (s, 1 H), 8.99 (s, 1 H), 8.24 - 8.18 (m, 1 H), 8.05 (s, 1 H), 7.94 (s, 1 H), 7.71 - 7.66 (m, 2 H), 7.64 (d, *J*=7.89 Hz, 1 H), 7.38 (d, *J*=7.89 Hz, 1 H), 5.71 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.89 (s, 2 H), 3.35 - 3.13 (m, 5 H), 3.02 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.40 - 2.29 (m, 1 H), 2.14 - 1.99 (m, 2 H), 0.88 (d, *J*=2.41 Hz, 6 H).

Example 305

Synthesis of (4S)-N-(2-(3-hydroxy-3-methylbutoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

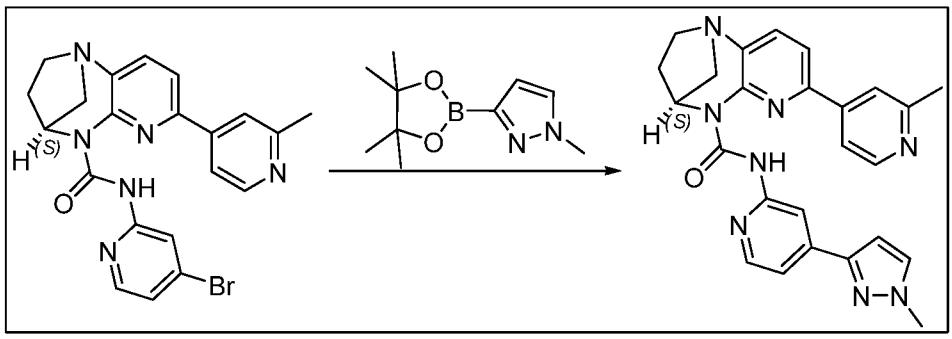


To a stirred solution of (4S)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (300 mg, 0.983 mmol) in THF (15 mL) were added triphosgene (175 mg, 0.590 mmol) and triethylamine (0.822 mL, 5.90 mmol) at RT, and stirred for 30 min. Then, 4-((4-aminopyrimidin-2-yl)oxy)-2-methylbutan-2-ol (388 mg, 1.965 mmol) was added and stirred at 80 °C for 15 h. (TLC System: R_f- 0.3, 5% MeOH/ EtOAc). The reaction mixture was allowed to cool to room temperature and diluted with water (25 mL), extracted with EtOAc (2x 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: 1% methanol in ethylacetate) to afford the desired product (4S)-N-(2-(3-hydroxy-3-methylbutoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (115 mg, 0.217 mmol, 22.04 % yield) as an off-white solid. LCMS (*m/z*): 529.25 $[M+H]^+$, R_t = 2.37 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.62 (s, 1 H), 8.54 - 8.46 (m, 1 H), 8.37 (d, *J*=5.70 Hz, 1 H), 8.04 (s, 1 H), 7.80 (d, *J*=5.70 Hz, 1 H), 7.75 - 7.69 (m, 2 H), 7.64 (d, *J*=8.11 Hz, 1 H), 7.43 (d, *J*=8.11 Hz, 1 H), 5.66 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.49 - 4.39 (m, 2 H), 3.37 - 3.14 (m, 3 H), 3.02 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.40 - 2.29 (m, 1 H), 2.17 - 2.01 (m, 2 H), 1.97 (t, *J*=6.47 Hz, 2 H), 1.28 (s, 6 H).

Example 306

Synthesis of (4*S*)-N-(4-(1-methyl-1H-pyrazol-3-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

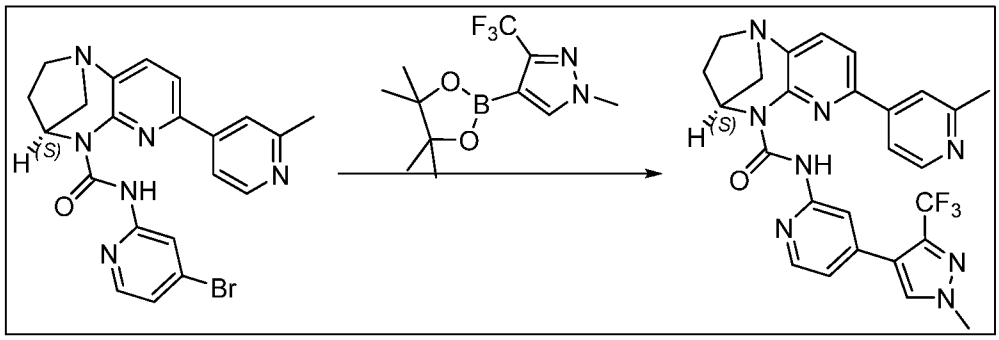


To a degassed solution of (4*S*)-N-(4-bromopyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (200 mg, 0.443 mmol), 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (138 mg, 0.665 mmol) and K_3PO_4 (282 mg, 1.329 mmol) in 1,4-Dioxane (8 mL):Water (2 mL) was added $PdCl_2$(dppf) (64.9 mg, 0.089 mmol) at room temperature and the reaction mixture was stirred at 100 °C for 6 h. (TLC system: 5% Methanol in dichloro methane, R_f: 0.2). The reaction mixture was poured in to cold water (10 mL) and extracted with ethyl acetate (2x50 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 alumina, 2% Methanol in DCM) to afford the desired product (4*S*)-N-(4-(1-methyl-1H-pyrazol-3-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazep ine-5(2*H*)-carboxamide (110 mg, 0.241 mmol, 54.3 % yield) as an off white solid. LCMS (*m/z*): 453.14 $[M+H]^+$, R_t = 1.49 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.56 (s, 1 H), 8.67 - 8.58 (m, 2 H), 8.37 (d, *J*=5.26 Hz, 1 H), 8.23 (s, 1 H), 7.72 (dd, *J*=5.15, 1.43 Hz, 1 H), 7.62 (d, *J*=7.89 Hz, 1 H), 7.55 - 7.46 (m, 2 H), 7.41 (d, *J*=2.19 Hz, 1 H), 6.74 (d, *J*=2.19 Hz, 1 H), 5.73 (dd, *J*=5.92, 3.29 Hz, 1 H), 3.98 (s, 3 H), 3.14 - 3.37 (m, 3 H), 3.03 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.76 (s, 3 H), 2.41 - 2.29 (m, 1 H), 2.19 - 2.03 (m, 1 H).

Example 307

Synthesis of (4*S*)-N-(4-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

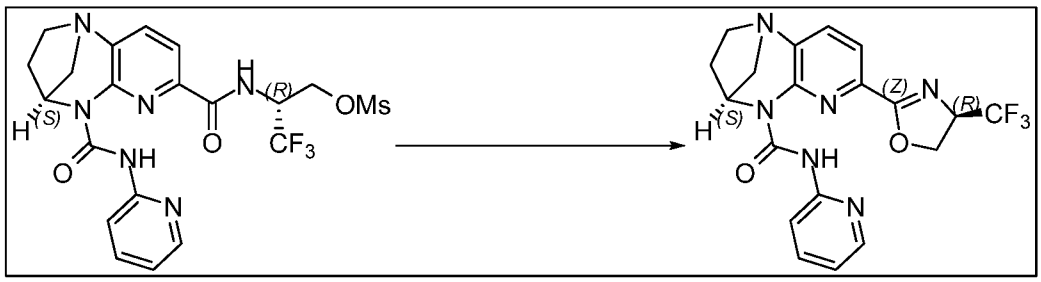


To a degassed solution of (4*S*)-N-(4-bromopyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (200 mg, 0.443 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)-1H-pyrazole (184 mg, 0.665 mmol) and K_3PO_4 (282 mg, 1.329 mmol) in 1,4-Dioxane (8 mL): Water (2 mL) was added $PdCl_2$(dppf) (32.4 mg, 0.044 mmol) at room temperature and the reaction mixture was stirred at 100 °C for 6 h. (TLC system: Neat ethyl acetate, R_f: 0.3). The reaction mixture was poured in to cold water (10 mL) and extracted with ethyl acetate (2x50 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 (silicagel: 100-200 Mesh, Eluent: 2% methanol in DCM) to afford the desired product (4*S*)-N-(4-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diaze pine-5(2*H*)-carboxamide (60 mg, 0.115 mmol, 25.9 % yield) as a pale yellow solid. LCMS (*m/z*): 521.14 $[M+H]^+$, Rt = 1.75 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.64 (s, 1 H), 8.63 (d, *J*=5.48 Hz, 1 H), 8.38 (d, *J*=5.04 Hz, 1 H), 8.32 (s, 1 H), 8.21 (s, 1 H), 7.77 - 7.70 (m, 2 H), 7.63 (d, *J*=7.89 Hz, 1 H), 7.49 (d, *J*=7.89 Hz, 1 H), 7.12 (d, *J*=5.04 Hz, 1 H), 5.70 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.00 (s, 3 H), 3.37 - 3.14 (m, 3 H), 3.02 (dd, *J*=12.28, 3.29 Hz, 1 H), 2.76 (s, 3 H), 2.41 - 2.26 (m, 1 H), 2.17 - 2.02 (m, 1 H).

Example 308

Synthesis of (4*S*)-N-(pyridin-2-yl)-7-((*R*)-4-(trifluoromethyl)-4,5-dihydrooxazol-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide:

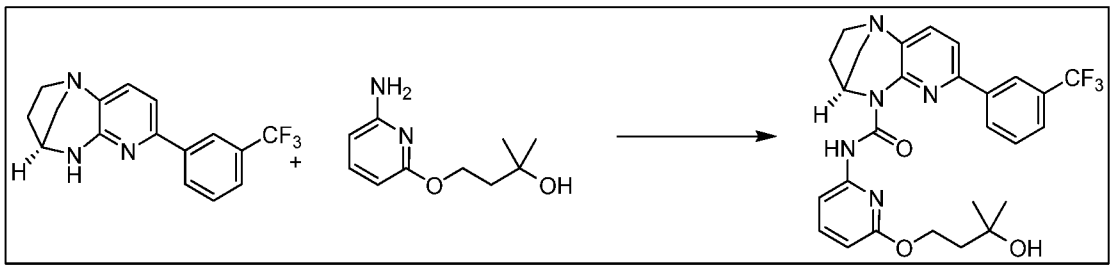


To a solution of (2*R*)-3,3,3-trifluoro-2-((4S)-5-(pyridin-2-ylcarbamoyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-7-carboxamido)propyl methanesulfonate (300 mg, 0.583 mmol) in DMSO (5 mL) under nitrogen at RT was added sodium azide (190 mg, 2.92 mmol) and stirred at 90 °C for 1 h. (TLC system: 5% Methanol in DCM. Rf value: 0.5). The reaction mixture was diluted with ice water (25 ml), and extracted with EtOAc (2x50 mL). The combined organic layers were washed with brine (25 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure to get crude compound. The crude material was purified by combiflash chromatography (using silica gel column, 5% MeOH in DCM) to afford (4*S*)-N-(pyridin-2-yl)-7-((*R*)-4-(trifluoromethyl)-4,5-dihydrooxazol-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (70 mg, 0.164 mmol, 28.1 % yield) as an off white solid. LC-MS (*m/z*): 419.04 $[M+H]^+$, Rt =1.61 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.03 (s, 1 H), 8.34 (dd, *J*=4.82, 1.10 Hz, 1 H), 8.08 (d, *J*=8.55 Hz, 1 H), 7.56 - 7.77 (m, 3 H), 6.98 (ddd, *J*=7.34, 4.93, 0.88 Hz, 1 H), 5.69 (dd, *J*=6.03, 3.18 Hz, 1 H), 4.90 (dquin, *J*=10.02, 7.31, 7.31, 7.31, 7.31 Hz, 1 H), 4.59 - 4.78 (m, 2 H), 3.08 - 3.30 (m, 3 H), 2.92 - 3.06 (m, 1 H), 2.19 - 2.39 (m, 1 H), 1.93 - 2.17 (m, 1 H).

Example 309

Synthesis of (4*S*)-N-(6-(3-hydroxy-3-methylbutoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide:

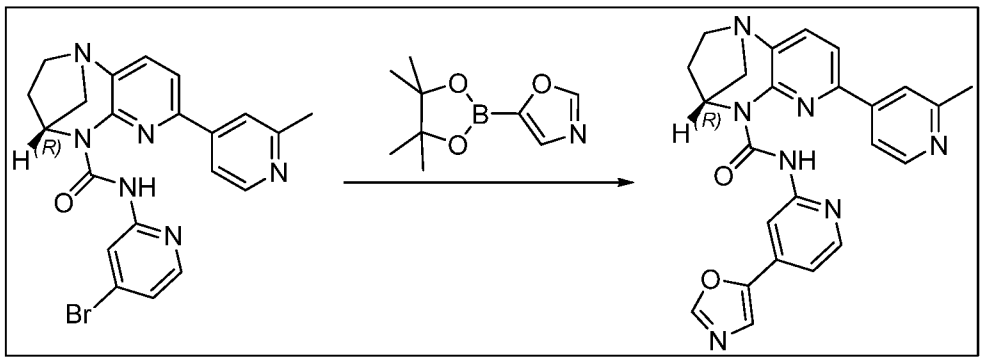


To a stirred solution of (4S)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (500 mg, 1.638 mmol) in THF (25 mL) at RT was added TEA (1.141 mL, 8.19 mmol), triphosgene (292 mg, 0.983 mmol) stirred for 30 min then 4-((6-aminopyridin-2-yl)oxy)-2-methylbutan-2-ol (643 mg, 3.28 mmol) was added and reaction mixture was stirred for at 100 °C for 16 h. (TLC eluent system: 100% EtOAc,Rf-0.4,UV active). The reaction mixture was cooled to room temperature and was partitioned between water (25 mL) and EtOAc (2x25 mL). Organic layer was separated, dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude. The crude compound was purified by chromatography (neutral alumina, eluent: 20% ethyl acetate in hexane) to afford (4S)-N-(6-(3-hydroxy-3-methylbutoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (120 mg, 0.225 mmol, 13.72 % yield) as an off-white solid LCMS (*m/z*): 528.20 $[M+H]^+$, R_t =2.64 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.97 (s, 1 H), 8.31 (br d, *J*=7.23 Hz, 1 H), 8.04 (s, 1 H), 7.73 (d, *J*=7.89 Hz, 1 H), 7.55 - 7.70 (m, 4 H), 7.36 (d, *J*=7.89 Hz, 1 H), 6.42 (d, *J*=8.11 Hz, 1 H), 5.70 (dd, *J*=5.70, 3.07 Hz, 1 H), 4.18 (td, *J*=6.14, 1.97 Hz, 2 H), 3.11 - 3.37 (m, 3 H), 3.01 (dd, *J*=12.06, 3.07 Hz, 1 H), 2.25 - 2.40 (m, 1 H), 2.03 - 2.15 (m, 2 H), 1.81 (t, *J*=6.25 Hz, 2 H), 1.18 (d, *J*=1.32 Hz, 6 H).

Example 310

Synthesis of (4R)-7-(2-methylpyridin-4-yl)-N-(4-(oxazol-5-yl)pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

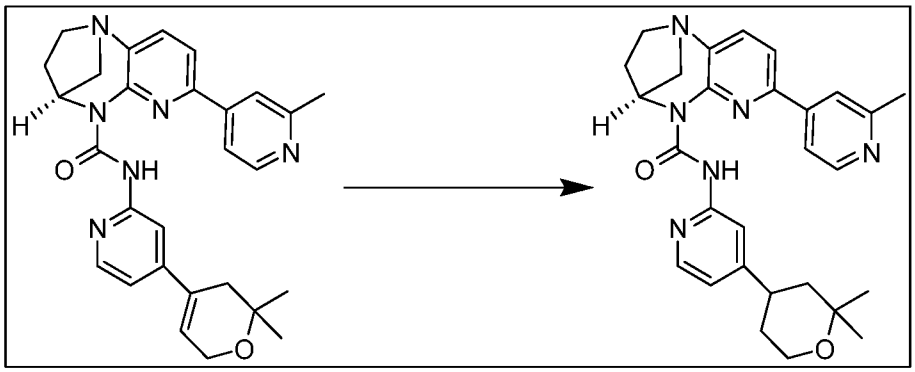


To a degassed solution of (4*R*)-N-(4-bromopyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (400 mg, 0.886 mmol), K_3PO_4 (564 mg, 2.66 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (259 mg, 1.329 mmol) in 1,4-Dioxane (12 mL) and Water (3 mL) was added $PdCl_2$(dppf)-CH_2Cl_2 (36.2 mg, 0.044 mmol). The reaction mixture was degassed again for 5 min. Then the reaction mixture was stirred at 80 °C for 16 h. (TLC system: (10% MeOH/ DCM, Rf: 0.4) and was allowed to cool to room temperature, diluted with water and extracted with ethyl acetate (3X 50 mL). The combined organic layer was washed with brine (2x 5 mL) and dried over anhydrous sodium sulphate, filtered and concentrated to obtain crude residue. The crude compound was purified by flash column chromatography (100-200 mesh, neat ethyl acetate - 2% DCM/ MeOH) to afford the desired product(4*R*)-7-(2-methylpyridin-4-yl)-N-(4-(oxazol-5-yl)pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (270 mg, 0.613 mmol, 69.2 % yield) as a yellow solid. LCMS (*m/z*): 440.18 $[M+H]^+$, Rt: 1.46 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.69 (s, 1 H), 8.63 (d, *J*=5.48 Hz, 1 H), 8.56 (s, 1 H), 8.42 (d, *J*=5.04 Hz, 1 H), 8.18 (s, 1 H), 7.99 (s, 1 H), 7.72 (dd, *J*=5.15, 1.43 Hz, 1 H), 7.66 - 7.61 (m, 2 H), 7.50 (d, *J*=8.11 Hz, 1 H), 7.27 (s, 1 H), 5.72 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.37 -3.15 (m, 3 H), 3.04 (dd, *J*=12.17, 3.40 Hz, 1 H), 2.75 (s, 3 H), 2.44 - 2.30 (m, 1 H), 2.19 - 2.06 (m, 1 H).

Example 311

Synthesis of (4*S*)-N-(4-(2,2-dimethyltetrahydro-2*H*-pyran-4-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

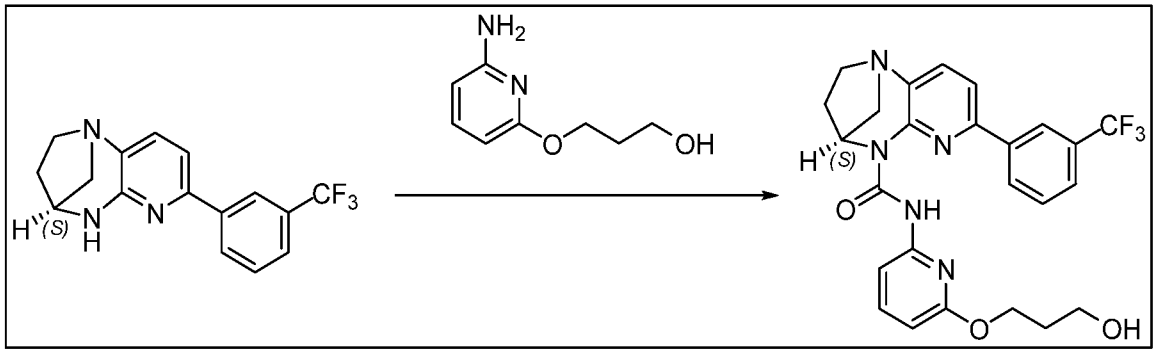


To a stirred solution of (4*S*)-N-(4-(2,2-dimethyl-3,6-dihydro-2H-pyran-4-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (220 mg, 0.456 mmol) and ammonium formate (287 mg, 4.56 mmol) in methanol (30 mL) at RT was added 10% Pd-C (48.5 mg, 0.046 mmol) and stirred at 65 °C for 16 h. (TLC eluent:5% MeOH in DCM: R_f-0.3; UV active). The reaction mixture was cooled and solids were filtered through celite and filtrate was concentrated to get crude product. The crude product was triturated with pentane (5 ml) and diethylether (5 ml) to afford desired (4*S*)-N-(4-(2,2-dimethyltetrahydro-2*H*-pyran-4-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (57 mg, 0.117 mmol, 25.7 % yield) as an off-white solid. LCMS (*m/z*): 485.25 $[M+H]^+$, R_t = 1.67 min

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.54 (s, 1 H), 8.61 (d, *J*=5.26 Hz, 1 H), 8.29 (d, *J*=5.26 Hz, 1 H), 8.20 (s, 1H), 8.14 (s, 1 H), 7.71 (dd, *J*=5.26, 1.53 Hz, 1 H), 7.62 (d, *J*=7.89 Hz, 1 H), 7.48 (d, *J*=8.11 Hz, 1 H), 6.89 (dd, *J*=5.04, 1.32 Hz, 1 H), 5.71 (dd, *J*=5.81, 3.18 Hz, 1 H), 3.90 - 3.74 (m, 2 H), 3.36 - 3.14 (m, 3 H), 3.06 - 2.92 (m, 2 H), 2.74 (s, 3 H), 2.40 - 2.30 (m, 1 H), 2.09 (dt, *J*=14.14, 6.96 Hz, 1 H), 1.84 - 1.63 (m, 3 H), 1.59 (s, 1 H), 1.30 (d, *J*=13.81 Hz, 6 H)

Example 312

Synthesis of (4*S*)-N-(6-(3-hydroxypropoxy) pyridin-2-yl)-7-(3-(trifluoromethyl) phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

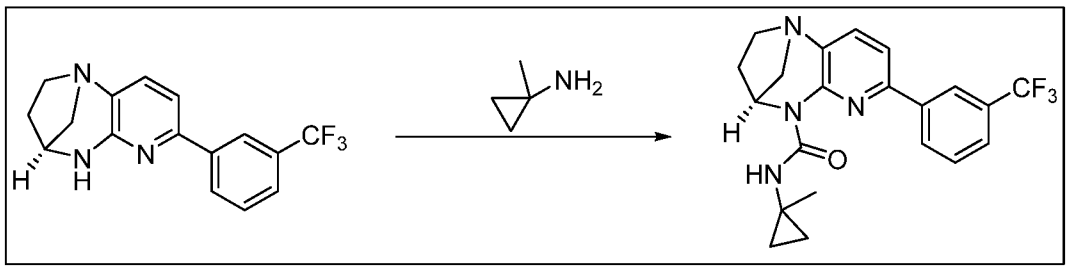


To a stirred solution of (4*S*)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (0.4 g, 1.310 mmol) in THF (50 mL) under nitrogen at RT was added Et_3N (0.913 mL, 6.55 mmol), triphosgene (0.389 g, 1.310 mmol) and stirred for 1 h. then 3-((6-aminopyridin-2-yl)oxy)propan-1-ol (0.331 g, 1.965 mmol) was added and reaction mixture was heated at 65 °C for 16 h. (TLC eluent:100% EtOAc: R_f-0.3; UV active). The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the residue was partitioned between water (30 mL) and EtOAc (50 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: 70% ethyl acetate in hexane) to afford (4*S*)-N-(6-(3-hydroxypropoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (0.115 g, 0.226 mmol, 17.25% yield) as an off white solid. LCMS (*m/z*): 500.12 $[M+H]^+$, R_t = 2.41 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.01 (s, 1 H), 8.28 (d, *J* = 7.45 Hz, 1 H), 8.04 (s, 1 H),7.66 - 7.70 (m, 2 H), 7.62 - 7.65 (m, 1 H), 7.59 - 7.61 (m, 1 H), 7.55 - 7.58 (m, 1 H), 7.34 (d, *J* = 7.89 Hz, 1 H), 6.42 (dd, *J* = 7.89, 0.66 Hz, 1 H), 5.70 (dd, *J* = 5.81, 3.18 Hz, 1 H), 4.21 - 4.15 (m, 2 H), 3.65 (q, *J* = 5.85 Hz, 2 H), 3.36 - 3.12 (m, 3 H), 3.01 (dd, *J* = 12.06, 3.29 Hz, 1 H), 2.33 (dddd, *J* = 14.09, 9.87, 5.86, 4.17 Hz, 1 H), 2.16 - 2.01 (m, 2 H), 1.82 (quin, *J* = 5.92 Hz, 2 H).

Example 313

Synthesis of (4*S*)-*N*-(1-methylcyclopropyl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide Hydrochloride:

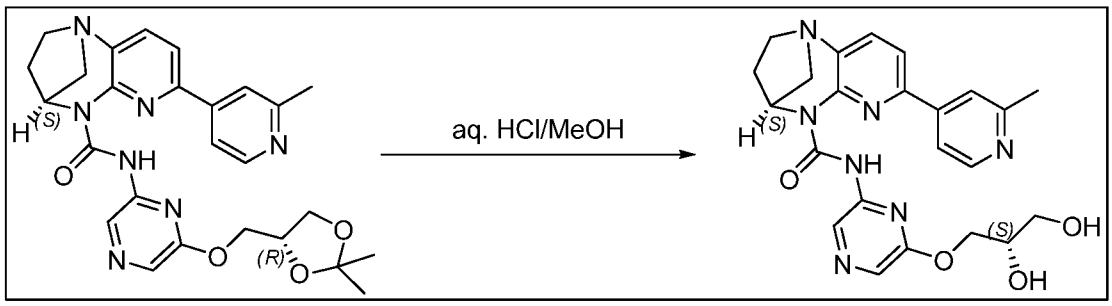


To a solution of (4*S*)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 0.983 mmol) in Tetrahydrofuran (20 mL) were added Triethylamine (0.822 mL, 5.90 mmol) and tri-phosgene (292 mg, 0.983 mmol) at RT and stirred for 30 min. Then 1-methylcyclopropanamine (140 mg, 1.965 mmol) was added and heated at 80 °C for 15 h. (TLC system: 5% MeOH in DCM, Rf: 0.4) The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the residue was partitioned between water (25 mL) and EtOAc (70 mL). Organic layer was separated and dried over anhydrous sodium sulphate, filtered and filtrate was evaporated to get crude compound. The crude material was purified by flash column chromatography (100-200 silicagel, eluent: 4% methanol in dichloromethane) to afford gummy substance. The gummy substance was dissolved in diethyl ether (10 mL) and added 2.0 M HCl (3 mL) in diethyl ether. The reaction mixture was stirred for 2 h at RT and concentrated. Resulting solid was washed with diethyl ether to afford the desired product (4*S*)-*N*-(1-methylcyclopropyl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide Hydrochloride (170 mg, 0.369 mmol, 37.6 % yield) as an off-white solid. LCMS (*m/z*): 403.13, $[M+H]^+$, Rt = 2.49 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.44 (s, 1 H), 8.21 (d, *J*=7.89 Hz, 1 H), 8.14 (s, 1 H), 8.00 – 7.75 (m, 2 H), 7.71 (d, *J*=8.11 Hz, 1 H), 5.50 (dd, *J*=5.81, 2.96 Hz, 1 H), 5.15 – 4.87 (m, 1 H), 4.87 - 4.63 (m, 1 H), 3.56 - 3.29 (m, 4 H), 2.43 - 2.21 (m, 1 H), 2.19 – 1.94 (m, 1 H), 1.39 (s, 3 H), 0.79 - 0.59 (m, 2 H), 0.08 - 0.07 (m, 2H).

Example 314

Synthesis of (4*S*)-N-(6-((*S*)-2, 3-dihydroxypropoxy) pyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-*b*] [1, 4] diazepine-5(2*H*)-carboxamide

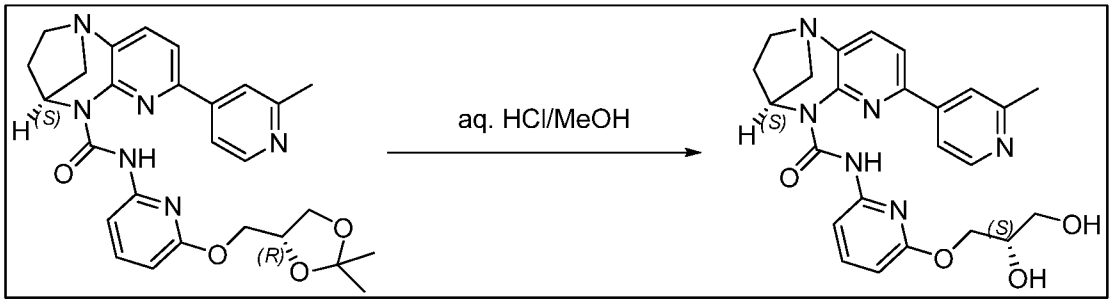


To a stirred solution of (4*S*)-N-(6-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (150 mg, 0.298 mmol) in Methanol (3 mL) was added hydrochloric acid (1 mL, 32.9 mmol) drop wise over a period of 5 min at 0 °C and stirred for 2 h. (TLC system:5% Methanol in DCM. R_f value: 0.3) at room temperature, 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: 2% MeOH in CH_2Cl_2) to afford the desired product (4*S*)-*N*-(6-((*S*)-2,3-dihydroxypropoxy)pyrazin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (90 mg, 0.193 mmol, 64.9 % yield) as a pale brown solid. LCMS (*m/z*): 464.15 $[M+H]^+$, Rt =1.26 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.14 (s, 1 H), 8.97 (s, 1 H), 8.65 (d, *J*=5.04 Hz, 1 H), 8.02 (s, 1 H), 7.90 - 7.70 (m, 4 H), 5.52 (dd, *J*=5.59, 2.74 Hz, 1 H), 4.99 (d, *J*=4.82 Hz, 1 H), 4.65 (t, *J*=5.59 Hz, 1 H), 4.27 - 4.10 (m, 2 H), 3.87 - 3.71 (m, 1 H), 3.41 (d, *J*=11.40 Hz, 2 H), 3.25 - 3.03 (m, 3 H), 2.97 (dd, *J*=12.06, 3.07 Hz, 1 H), 2.57 (s, 3 H), 2.36 - 2.17 (m, 1 H), 2.04 - 1.85 (m, 1 H).

Example 315

Synthesis of (4*S*)-N-(6-((*S*)-2, 3-dihydroxypropoxy) pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-*b*] [1, 4] diazepine-5(2*H*)-carboxamide

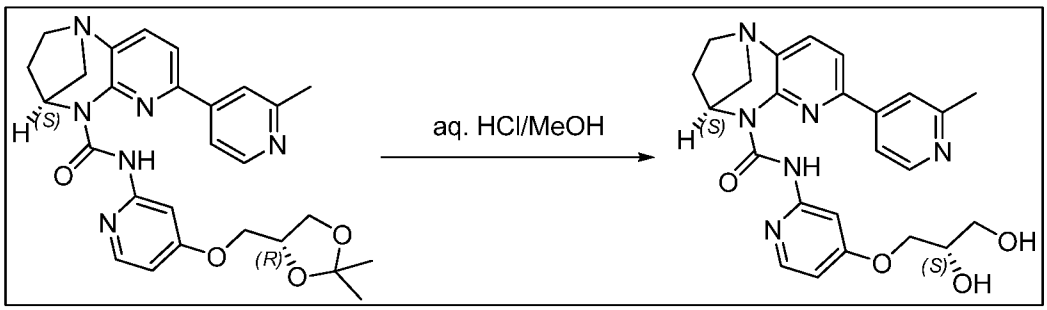


To a stirred solution of (4*S*)-N-(6-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (350 mg, 0.696 mmol) in Methanol (10 mL) was added hydrochloric acid (2 mL, 65.8 mmol) drop wise over a period 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, neutralized with Sodium bicarbonate solution, the obtained solid was filtered and washed with water, dried to get crude compound. The crude compound was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 2% methanol in DCM) to afford the desired compound (4*S*)-N-(6-((*S*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (210 mg, 0.451 mmol, 64.8 % yield) as a pale yellow solid. LCMS (*m/z*): 463.11 $[M+H]^+$, Rt = 1.38 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.82 (s, 1 H), 8.65 (d, *J*=5.26 Hz, 1 H), 7.92 (dd, *J*=5.26, 1.32 Hz, 1 H), 7.85 (s, 1 H), 7.79 - 7.63 (m, 4 H), 6.60 - 6.43 (m, 1 H), 5.57 - 5.46 (m, 1 H), 4.88 (br s, 1 H), 4.58 (br s, 1 H), 4.18 - 3.99 (m, 2 H), 3.83 - 3.67 (m, 1 H), 3.38 (t, *J*=5.37 Hz, 2 H), 3.25 - 3.03 (m, 3 H), 2.95 (dd, *J*=11.95, 3.18 Hz, 1 H), 2.57 (s, 3 H), 2.23 - 2.23 (m, 1 H), 1.84 - 2.02 (m, 1 H).

Example 316

Synthesis of (4*S*)-N-(4-((*S*)-2, 3-dihydroxypropoxy) pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-*b*] [1, 4] diazepine-5(2*H*)-carboxamide

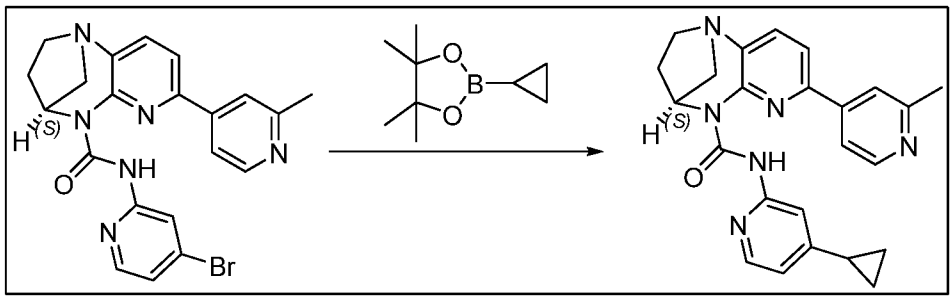


To a stirred solution of (4*S*)-N-(4-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (200 mg, 0.398 mmol) in Methanol (5 mL) was added hydrochloric acid (1 mL, 32.9 mmol) drop wise over a period 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-0.2) and evaporated the solvent, neutralized with sodium bicarbonate solution, the obtained solid was filtered and washed with water, dried to afford 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 product (4*S*)-N-(6-((*S*)-2,3-dihydroxypropoxy)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (210 mg, 0.451 mmol, 64.8 % yield) as a pale yellow solid. LCMS (*m/z*): 463.18 $[M+H]^+$, Rt = 1.13 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.48 (s, 1 H), 8.58 (s, 1 H), 8.31 - 8.16 (m, 2 H), 7.95 (d, *J*=4.82 Hz, 1 H), 7.83 - 7.65 (m, 3 H), 6.74 (dd, *J*=5.70, 2.19 Hz, 1 H), 5.56 - 5.44 (m, 1 H), 5.07 - 4.97 (m, 1 H), 4.71 (br s, 1 H), 4.19 - 4.04 (m, 1 H), 3.97 (dd, *J*=9.87, 6.36 Hz, 1 H), 3.84 (br s, 1 H), 3.47 (brs, 2 H), 3.03 - 3.39 (m, 3 H), 2.96 (dd, *J*=11.84, 2.85 Hz, 1 H), 2.6 (s, 3 H), 2.33 - 2.12 (m, 1 H), 2.01 - 1.85 (m, 1 H).

Example 317

Synthesis of (4*S*)-N-(4-cyclopropylpyridin-2-yl)-7-(2-methylpyridin-4-yl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-*b*] [1, 4] diazepine-5(2*H*)-carboxamide

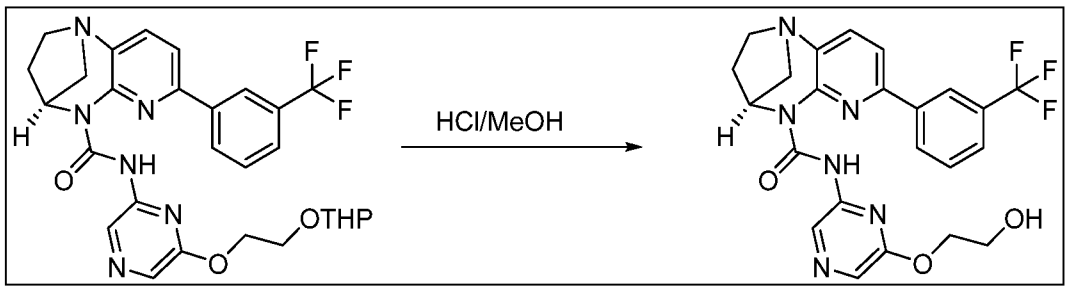


To a degassed solution of (4*S*)-N-(4-bromopyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (200 mg, 0.485 mmol), 2-cyclopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (122 mg, 0.727 mmol) and potassium phosphate tri basic (308 mg, 1.455 mmol) in 1,4-Dioxane (4 mL) and Water (1 mL) was added $PdCl_2$(dppf) (35.5 mg, 0.048 mmol). The reaction mixture was stirred at 80 °C for 16 h. (TLC eluent: 5% MeOH in DCM: R_f-0.3). The reaction mixture was diluted with water and extracted with ethyl acetate (2x10 mL). The combined organic layer was washed with brine (10 mL) solution and dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get crude compound. The crude compound was purified by flash column chromatography (silica-gel: 100-200 mesh, eluent: 2% MeOH in ethylacetate) to afford the desired product (4*S*)-N-(4-cyclopropylpyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (70 mg, 0.169 mmol, 34.8 % yield) as an off white solid. LCMS (*m/z*): 413.14 $[M+H]^+$, Rt = 1.57 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.46 (s, 1 H), 8.61 (d, *J*=5.48 Hz, 1 H), 8.20 (d, *J*=5.92 Hz, 2 H), 7.95 (s, 1 H), 7.71 (dd, *J*=5.26, 1.53 Hz, 1 H), 7.61 (d, *J*=7.89 Hz, 1 H), 7.47 (d, *J*=7.89 Hz, 1 H), 6.71 (dd, *J*=5.15, 1.64 Hz, 1 H), 5.70 (dd, *J*=5.81, 3.18 Hz, 1 H), 3.42 - 3.09 (m, 3 H), 3.07 - 2.91 (m, 1 H), 2.67 (s, 3 H) 2.42 - 2.23 (m, 1 H), 2.09 (dt, *J*=14.03, 6.80 Hz, 1 H), 1.99 - 1.79 (m, 1 H), 1.15 - 0.95 (m, 2 H), 0.93 - 0.72 (m, 2 H).

Example 318

Synthesis of (4*S*)-*N*-(6-(2-hydroxyethoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

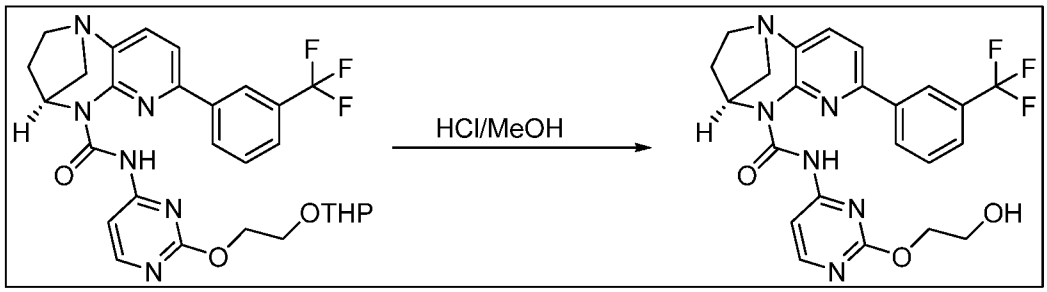


To a stirred solution of (4*S*)-*N*-(6-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (200 mg, 0.351 mmol) in Tetrahydrofuran (15 mL) was added HCl (1 mL, 2.74 mmol) at 0 °C and stirred at 28 °C 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 filtered the obtained solid, washed with water (20 mLx3) and n-pentane (10 mLx2) to afford the (4*S*)-*N*-(6-(2-hydroxyethoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanobpyrid-o[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (98 mg, 0.201 mmol, 57.4 % yield) as an off white solid. LCMS (*m/z*): 487.12 $[M+H]^+$, Rt = 2.15 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.20 (s, 1 H), 9.04 (s, 1 H), 8.20 (d, *J*=7.67 Hz, 1 H), 8.04 (s, 1 H), 7.97 (s, 1 H), 7.72 - 7.68 (m, 1 H), 7.66 - 7.60 (m, 2 H), 7.37 (d, *J*=7.89 Hz, 1 H), 5.71 (dd, *J*=5.92, 3.29 Hz, 1 H), 4.18 (td, *J*=4.60, 1.75 Hz, 2 H), 3.87 - 3.80 (m, 2 H), 3.34 - 3.14 (m, 3 H), 3.03 (dd, *J*=12.17, 3.18 Hz, 1 H), 2.35 (dddd, *J*=14.17, 9.95, 5.92, 4.17 Hz, 1 H), 2.14 - 2.00 (m, 2 H).

Example 319

Synthesis of (4*S*)-*N*-(2-(2-hydroxyethoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

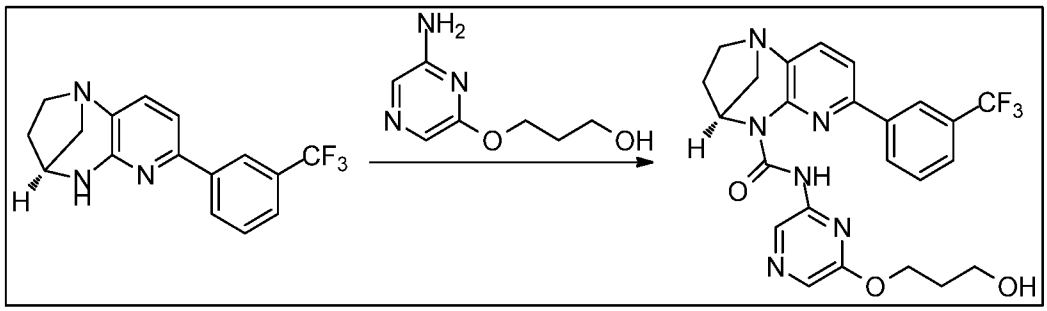


To a stirred solution of (4*S*)-*N*-(2-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (200 mg, 0.351 mmol) in THF (15 mL) was added HCl (1 mL, 2.74 mmol) at 0 °C and stirred at RT for 1 h. (TLC system: neat ethyl acetate, R_f: 0.2). The reaction mixture was concentrated *in vacuo* and the residue was filtered and washed with water (20 mLx3) and n-pentane (10 mlx2) to afford the desired product (4*S*)-*N*-(2-(2-hydroxyethoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (150 mg, 0.305 mmol, 87 % yield) as an off white solid. LCMS (*m/z*): 487.12 $[M+H]^+$, Rt = 2.15 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.64 (s, 1 H), 8.40 (d, *J*=6.80 Hz, 1 H), 8.36 (d, *J*=5.70 Hz, 1 H), 8.08 (s, 1 H), 7.82 (d, *J*=5.70 Hz, 1 H), 7.74 - 7.64 (m, 3 H), 7.42 (d, *J*=8.11 Hz, 1 H), 5.67 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.40 - 4.37 (m, 2 H), 3.94 - 3.90 (m, 2 H), 3.34 - 3.15 (m, 3 H), 3.02 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.74 (s, 1 H), 2.40 - 2.30 (m, 1 H), 2.08 (dt, *J*=14.14, 6.96 Hz, 1 H).

Example 320

Synthesis of (4*S*)-*N*-(6-(3-hydroxypropoxy) pyrazin-2-yl)-7-(3-(trifluoromethyl) phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

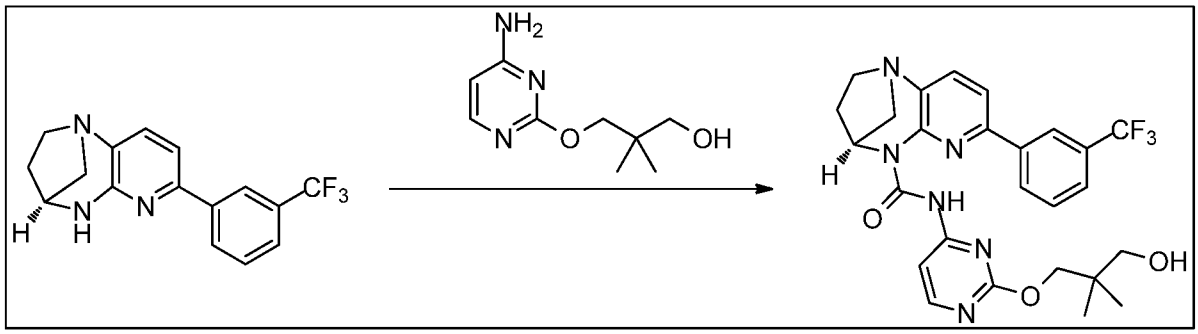


To a stirred solution of ((4*S*)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 0.983 mmol) in Tetrahydrofuran (20 mL) was added triphosgene (146 mg, 0.491 mmol) under nitrogen at room temperature and stirred for 30 min. To this reaction mixture triethylamine (0.685 mL, 4.91 mmol) and 3-((6-aminopyrazin-2-yl) oxy) propan-1-ol (216 mg, 1.277 mmol) were added and stirred at 80 °C for 15 h. (TLC system: 5% Methanol in Ethyl acetae. R*f* value: 0.5.). The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (2x50 ml). The combined organic layer was washed with brine solution (20 mL), 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 15% of MeOH in CH_2Cl_2) to afford the desired product (4*S*)-*N*-(6-(3-hydroxypropoxy)pyrazin-2-yl)-7-(3-(trifluoromethyl) phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (110 mg, 0.212 mmol, 21.56 % yield) as an off white solid. LCMS (*m/z*): 501.16 $[M+H]^+$, Rt =2.22 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.19 (s, 1 H), 9.01 (s, 1 H), 8.22 (d, *J*=7.67 Hz, 1 H), 8.03 (s, 1 H), 7.93 (s, 1 H), 7.73 - 7.58 (m, 3 H), 7.37 (d, *J*=8.11 Hz, 1 H), 5.71 (dd, *J*=5.92, 3.29 Hz, 1 H), 4.27 - 4.14 (m, 2 H), 3.72 (q, *J*=5.70 Hz, 2 H), 3.36 - 3.13 (m, 3 H), 3.03 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.41 - 2.29 (m, 1 H), 2.10 (dt, *J*=14.25, 6.91 Hz, 1 H), 1.90 (quin, *J*=5.97 Hz, 2 H), 1.69 (t, *J*=5.26 Hz, 1 H).

Example 321

Synthesis of (4*S*)-*N*-(2-(3-hydroxy-2,2-dimethylpropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

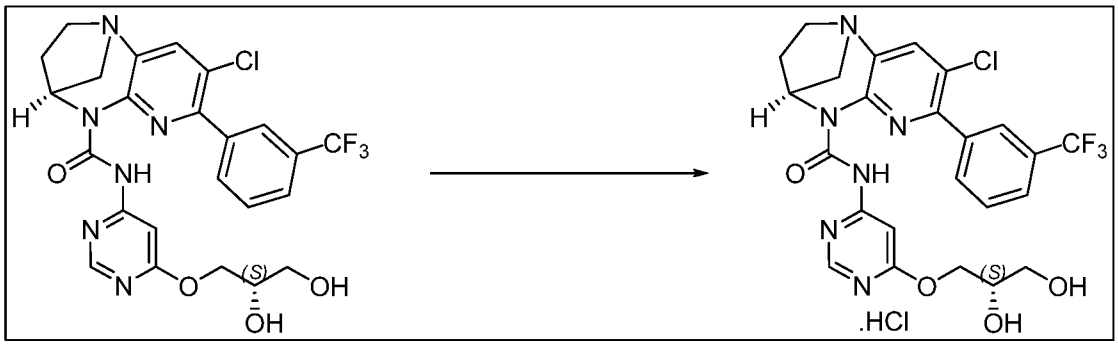


To a solution of (4*S*)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (400 mg, 1.310 mmol) in Tetrahydrofuran (20 mL), triphosgene (194 mg, 0.655 mmol) and TEA (0.913 mL, 6.55 mmol) were added under nitrogen and stirred for 30 min at room temperature. Then, 3-((4-aminopyrimidin-2-yl) oxy)-2,2-dimethylpropan-1-ol (336 mg, 1.703 mmol) was added to this reaction mixture and stirred at 80 °C for 15 h. (TLC system: Ethyl acetae. R*f* value: 0.4).The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (2x50 ml). The combined organic layer was washed with brine solution (20 mL), 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 0-15% of Methanol in DCM) to afford the desired compound (4*S*)-*N*-(2-(3-hydroxy-2,2-dimethylpropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*) carboxamide (60 mg, 0.112 mmol, 8.55 % yield) as an off-white solid. LCMS (*m/z*): 529.25 $[M+H]^+$, Rt =2.47 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.74 (s, 1 H), 8.53 (br d, *J*=7.02 Hz, 1 H), 8.34 (d, *J*=5.70 Hz, 1 H), 8.06 (s, 1 H), 7.78 - 7.69 (m, 3 H), 7.65 (d, *J*=7.89 Hz, 1 H), 7.45 (d, *J*=8.11 Hz, 1 H), 5.66 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.15 (s, 2 H), 3.50 - 3.44 (m, 3 H), 3.36 (s, 3 H), 3.02 (dd, *J*=12.17, 3.18 Hz, 1 H), 2.40 - 2.28 (m, 1 H), 2.07 (dt, *J*=14.47, 7.45 Hz, 1 H), 1.07 (s, *J*=16.50, 9.50 Hz, 6 H).

Example 322

Synthesis of (4*S*)-8-chloro-N-(6-((*S*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide, Hydrochloride

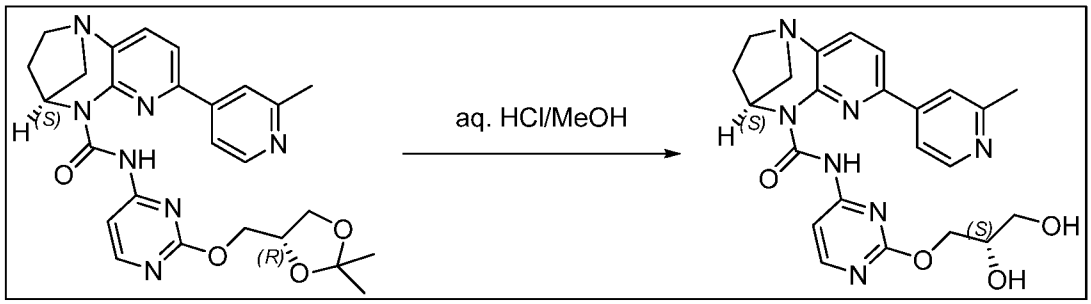


To a suspension of (4*S*)-8-chloro-N-(6-((*S*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide (150 mg, 0.272 mmol) in diethylether (2 mL) at 0 °C was added 2 M HCl in diethylether (2 mL, 65.8 mmol) and the resulting mixture was stirred at RT for 3 h. Reaction mass stand for 5 min, the solid material settled down and solvent was decanted. Obtained solid triturated with diethyl ether, filtered and dired in *vacuo* to to afford (4*S*)-8-chloro-N-(6-((*S*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide, Hydrochloride (145 mg, 0.243 mmol, 89 % yield) as a white solid. LCMS (m/z): 551.05 $[M+H]^+$, Rt = 2.36 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.00 (s, 1 H), 8.31 (d, *J*=0.88 Hz, 1 H), 8.09 - 8.18 (m, 2 H), 7.97 (s, 1 H), 7.90 (d, *J*=7.67 Hz, 1 H), 7.77 - 7.85 (m, 1 H), 7.38 (d, *J*=0.88 Hz, 1 H), 5.48 (dd, *J*=5.81, 3.18 Hz, 1 H), 4.30 - 4.39 (m, 1 H), 4.20 (dd, *J*=10.85, 6.47 Hz, 1 H), 3.73 - 3.86 (m, 1 H), 3.30 - 3.49 (m, 3 H), 3.16 - 3.28 (m, 2 H), 3.10 (dd, *J*=11.95, 3.18 Hz, 1 H), 2.23 - 2.37 (m, 1 H), 1.96 - 2.10 (m, 1 H).

Example 323

Synthesis of (4*S*)-N-(2-((*S*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide.

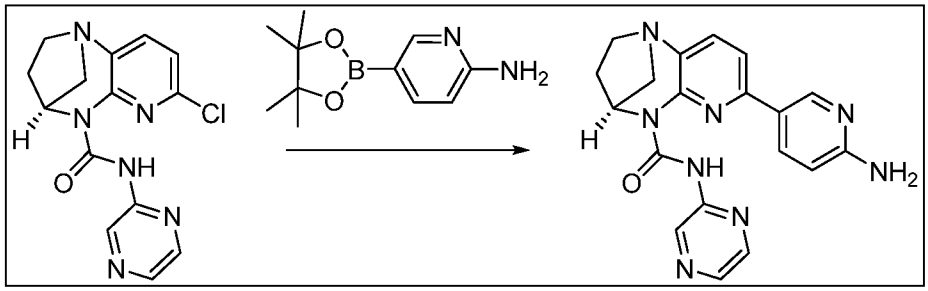


To a stirred solution of (4*S*)-N-(2-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide (300 mg, 0.596 mmol) in Methanol (10 mL) was added HCl (4 mL, 132 mmol) at 0 °C then stirred at RT for 2 h. (TLC system: 5% MeOH in DCM, R_f: 0.5). 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 (2x10 mL) to afford the desired product (4*S*)-N-(2-((*S*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide (83 mg, 0.175 mmol, 29.4 % yield) as an off white solid. LCMS (*m/z*): 464.12 $[M+H]^+$, Rt: 1.28 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.67 (s, 1 H), 8.68 (d, *J*=5.26 Hz, 1 H), 8.36 (d, *J*=5.70 Hz, 1 H), 7.85 (d, *J*=5.70 Hz, 1 H), 7.79 -7.74 (m, 2 H), 7.65 (d, *J*=7.89 Hz, 1 H), 7.46 (d, *J*=7.89 Hz, 1 H), 5.66 (dd, *J*=5.59, 2.96 Hz, 1 H), 4.44 -4.31 (m, 2 H), 4.14 -4.02 (m, 1 H), 3.77 -3.63 (m, 2 H), 3.44 -3.12 (m, 5 H), 3.02 (dd, *J*=12.17, 3.18 Hz, 1 H), 2.72 (s, 3 H), 2.41 -2.29 (m, 1 H), 2.07 (dt, *J*=14.25, 7.34 Hz, 1 H).

Example 324

Synthesis of (4*S*)-7-(6-aminopyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methano pyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide.

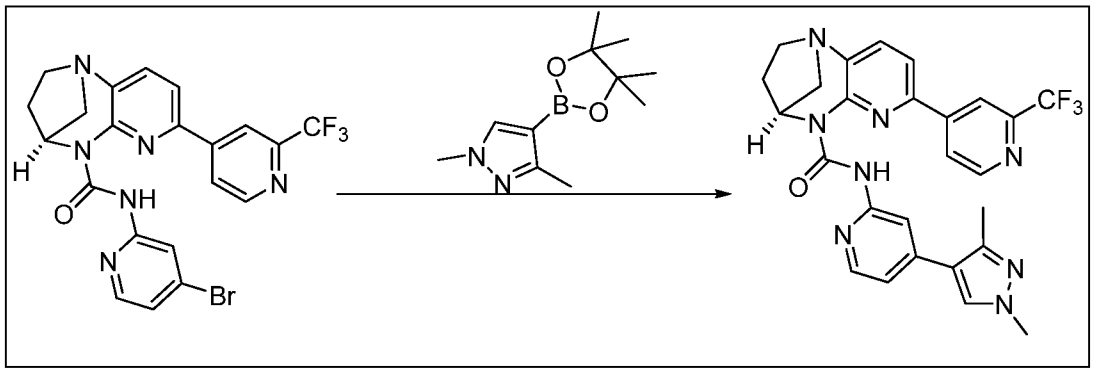


To a degassed solution of (4*S*)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide (20 g, 63.1 mmol), K_3PO_4 (40.2 g, 189 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (16.68 g, 76 mmol) in 1,4-Dioxane (400 mL)/Water (133 mL) were added $Pd_2(dba)_3$ (2.89 g, 3.16 mmol) and X-phos (3.01 g, 6.31 mmol). The reaction mixture again degassed for 10 min and stirred at 110 °C for 16 h. (TLC system: 5% MeOH in Ethyl acetate, R_f: 0.3). The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the residue was diluted with water (500 mL) and extracted with EtOAc (2x 400 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and filtrate was evaporated to obtain crude compound. The crude product was purified by flash column chromatography (100-200 silica gel, eluent: neat ethyl acetate) to afford the desired product (4*S*)-7-(6-aminopyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide (14.3 g, 38.2 mmol, 60.5 % yield) as an off white solid. LCMS (*m/z*): 375.12 $[M+H]^+$, Rt = 1.27 min.

^{1}H NMR (400 MHz, DMSO-d6): δ ppm 13.80 (s, 1 H), 9.40 (d, *J*=1.31 Hz, 1 H), 8.72 (d, *J*=2.41 Hz, 1 H), 8.41- 8.31 (m, 2 H), 8.17 (dd, *J*=8.77, 2.63 Hz, 1 H), 7.59 (d, *J*=8.11 Hz, 1 H), 7.49 (d, *J*=8.11 Hz, 1 H), 6.58 (d, *J*=8.77 Hz, 1 H), 6.35 (s, 2 H), 5.50 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.24 -3.01 (m, 3 H), 2.93 (dd, *J*=11.95, 3.18 Hz, 1 H), 2.23 (dddd, *J*=13.59, 9.81, 5.97, 3.73 Hz, 1 H), 1.95 (td, *J*=14.25, 7.23 Hz, 1 H).

Example 325

Synthesis of (4*S*)-*N*-(4-(1,3-dimethyl-1*H*-pyrazol-4-yl)pyridin-2-yl)-7-(2-(trifluoromethyl)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



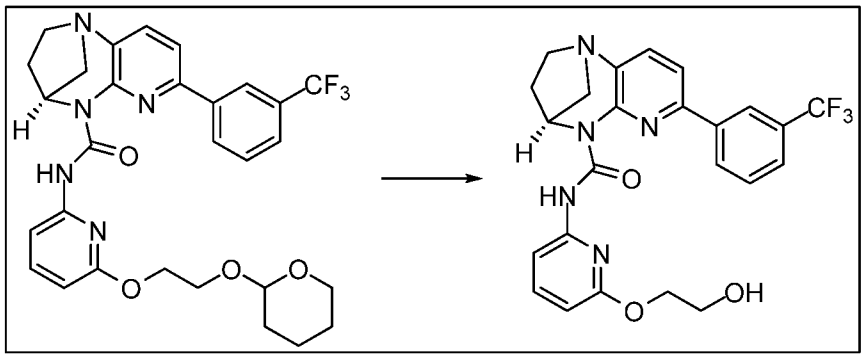
To a degassed solution of (4*S*)-*N*-(4-bromopyridin-2-yl)-7-(2-(trifluoromethyl)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide (500 mg, 0.990 mmol) in 1,4-Dioxane (16.0 mL) and Water (2.0 mL) were added 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (330 mg, 1.484 mmol), potassium phosphate tribasic (315 mg, 1.484 mmol) and $PdCl_2$(dppf)-DCM (81 mg, 0.099 mmol). Then the reaction mixture was stirred at 110 °C for 16 h. (TLC eluent: 100% ethylacetate R_f : 0.1; UV active), then the reaction mixture was cooled to room temperature and diluted with water (50 mL), extracted with ethylacetate (2 x 50 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated to obtain crude compound. The crude compound was purified by flash column chromatography (silica-gel: 100-200 mesh: Eluent: 80% ethylacetate in petether) and followed by prep HPLC (Prep HPLC conditions: MP-A: 10 Mm Ammonium bi carbonate(Aq) MP-B: Acetonitrile Column: Kinetex c8(150*30)mm,5um Method:50:50 Flow: 30ml/min Solubility: THF+ACN+MEOH) to afford the desired product (4*S*)-N-(4-(1,3-dimethyl-1*H*-pyrazol-4-yl)pyridin-2-yl)-7-(2-(trifluoromethyl)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (180 mg, 0.342 mmol, 34.6 % yield) as a pale brown solid. LCMS (*m/z*): 521.1 $[M+H]^+$, R_t = 3.75 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.38 (s, 1 H), 8.87 (d, *J*=5.04 Hz, 1 H), 8.48 (s, 1 H), 8.33 - 8.25 (m, 3 H), 7.70 - 7.65 (m, 2 H), 7.52 (d, *J*=7.89 Hz, 1 H), 7.06 (dd, *J*=5.26, 1.53 Hz, 1 H), 5.72 (dd, *J*=6.03, 3.18 Hz, 1 H), 3.89 (s, 3 H), 3.32 - 3.15 (m, 3 H), 3.04 (dd,

J=12.06, 3.29 Hz, 1 H), 2.52 (s, 3 H), 2.40 - 2.31 (m, 1 H), 2.11 (dt, *J*=14.09, 7.10 Hz, 1 H).

Example 326

Synthesis of (4*S*)-N-(6-(2-hydroxyethoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

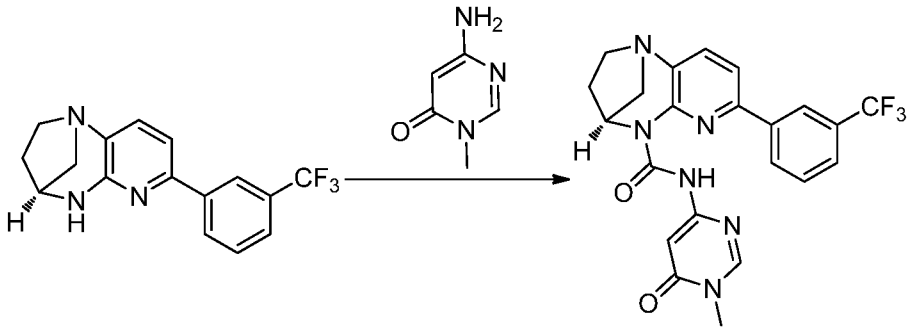


To a solution of (4*S*)-N-(6-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (250 mg, 0.439 mmol) in methanol (10 mL) at 0 °C was added aq. HCl (0.6 mL, 19.75 mmol, 36 %) and stirred for 1 h. (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) and solvent was evaporated under reduced pressure. The residue was diluted with water (10 mL) and extracted into dichloromethane (2x20 mL). Combined organic extracts were dried over anhydrous sodium sulphate, filtered and filtrate was evaporated to give the crude compound. The crude was triturated with 10% ethyl acetate in hexane and dried under reduced pressure to afford (4*S*)-N-(6-(2-hydroxyethoxy)pyridin-2-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (195 mg, 0.401 mmol, 91 % yield) as an off white solid. LCMS (*m/z*): 486.12 $[M+H]^+$, R_t = 2.33 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.99 (s, 1 H), 8.26 (d, *J*=7.67 Hz, 1 H), 8.04 (s, 1 H), 7.74 - 7.53 (m, 5 H), 7.34 (d, *J*=7.89 Hz, 1 H), 6.46 (d, *J*=7.89 Hz, 1 H), 5.70 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.20 - 4.07 (m, 2 H), 3.75 (br s, 2 H), 3.35 - 3.12 (m, 3 H), 3.02 (dd, *J*=12.06, 3.07 Hz, 1 H), 2.43 - 2.19 (m, 2 H), 2.10 (dt, *J*=14.03, 7.02 Hz, 1 H).

Example 327

Synthesis of (4*S*)-*N*-(1-methyl-6-oxo-1,6-dihydropyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

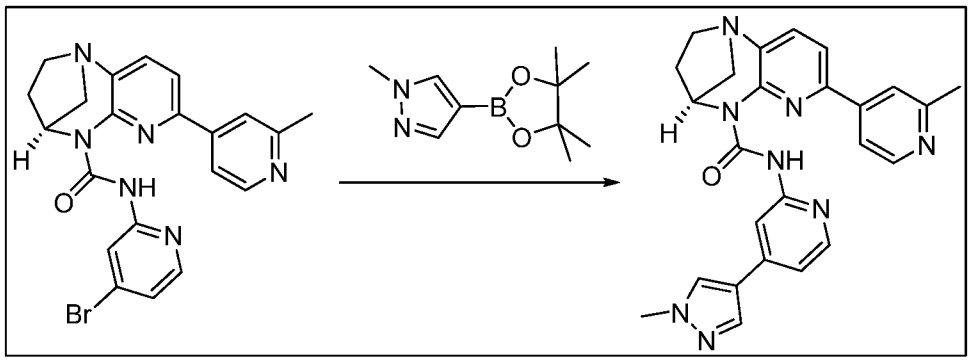


To a solution of (4*S*)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (500 mg, 1.638 mmol), in THF (20 mL) under nitrogen at RT was added triphosgene (340 mg, 1.146 mmol) and DIPEA (0.858 mL, 4.91 mmol) and stirred for 30 min, then added 6-amino-3-methylpyrimidin-4(3H)-one (246 mg, 1.965 mmol) and the reaction mixture was stirred at RT for 24 h. (TLC eluent: 10% methanol in DCM, Rf: 0.4). The reaction mixture was partitioned between water (50 mL) and EtOAc (100 mL) and the organic layer was separated and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get crude compound. The crude material was purified by combiflash chromatography (Silica gel column, 5% MeOH in DCM) to afford (4*S*)-*N*-(1-methyl-6-oxo-1,6-dihydropyrimidin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (170 mg, 0.369 mmol, 22.53 % yield) as an off white sold. LCMS (*m/z*): 457.13 $[M+H]^+$, Rt = 2.12 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.37 (s, 1 H), 8.42 (s, 1 H), 8.14 (m, *J*=7.89 Hz, 1 H), 7.92 (s, 1 H), 7.70 (br d, *J*=7.67 Hz, 1 H), 7.57 - 7.67 (m, 2 H), 7.28 - 7.46 (m, 1 H), 7.23 (s, 1 H), b5.68 (dd, *J*=5.92, 3.29 Hz, 1 H), 3.49 (s, 3 H), 3.09 - 3.34 (m, 3 H), 3.00 (dd, *J*=12.06, 3.07 Hz, 1 H), 2.20 - 2.44 (m, 1 H), 1.94 - 2.19 (m, 1 H).

Example 328

Synthesis of (4*S*)-*N*-(4-(1-methyl-1*H*-pyrazol-4-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide

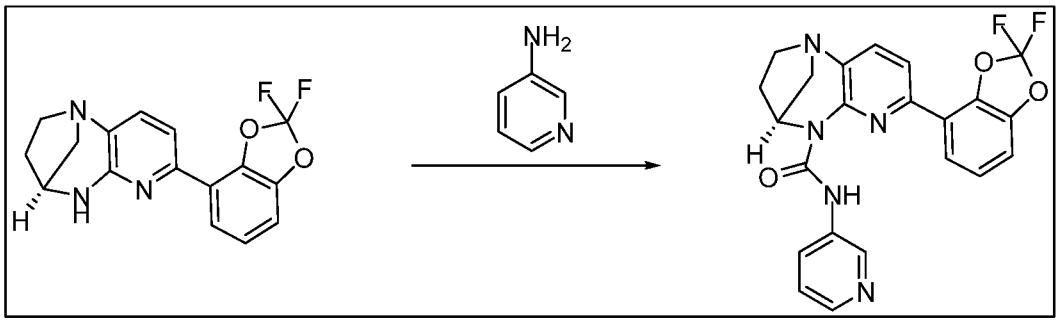


To a degassed solution of (4*S*)-*N*-(4-bromopyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (200 mg, 0.443 mmol), K_3PO_4 (282 mg, 1.329 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (138 mg, 0.665 mmol) in 1,4-Dioxane (8 mL) and water (2 mL), was added $PdCl_2$(dppf) (32.4 mg, 0.044 mmol) at RT. Then reaction mixture was degassed again for 5 min and stirred at 80 °C for 16 h. (TLC system: (10% MeOH/ DCM, R_f: 0.3), Reaction mixture was allowed to cool to room temperature and diluted with water. Then compound was extracted with ethylacetate (3X 20 mL). The combined organic layer was washed with brine (2x5 mL) and dried over anhydrous sodium sulphate, filtered and concentrated. The compound was purified by flash column chromatography (100-200 mesh, eluent: neat ethyl acetate - 2% DCM/ MeOH) and further purified by Prep HPLC (Mobilile Phase : 5mM Ammonium bicarbonate B: ACN MeTHOD : 0/10-2/25/10/55 Solubulity : MeOH,THF) to afford the desired product (4*S*)-*N*-(4-(1-methyl-1*H*-pyrazol-4-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (60 mg, 0.131 mmol, 29.5 % yield) as a yellow solid. LCMS (*m/z*): 453.17 $[M+H]^+$, Rt = 1.41 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.56 (s, 1 H), 8.62 (d, *J*=5.48 Hz, 1 H), 8.37 (d, *J*=0.66 Hz, 1 H), 8.31 (d, *J*=5.04 Hz, 1 H), 8.22 (s, 1 H), 7.91 (d, *J*=0.66 Hz, 1 H), 7.82 (s, 1 H), 7.72 (dd, *J*=5.37, 1.43 Hz, 1 H), 7.63 (d, *J*=7.89 Hz, 1 H), 7.49 (d, *J*=7.89 Hz, 1 H), 7.11 (dd, *J*=5.15, 1.64 Hz, 1 H), 5.71 (dd, *J*=6.03, 3.18 Hz, 1 H), 3.96 (s, 3 H), 3.35 - 3.16 (m, 3 H), 3.03 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.75 (s, 3 H), 2.41 - 2.31(m, 1 H), 2.17 - 2.05 (m, 1 H).

Example 329

Synthesis of (4S)-7-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide.

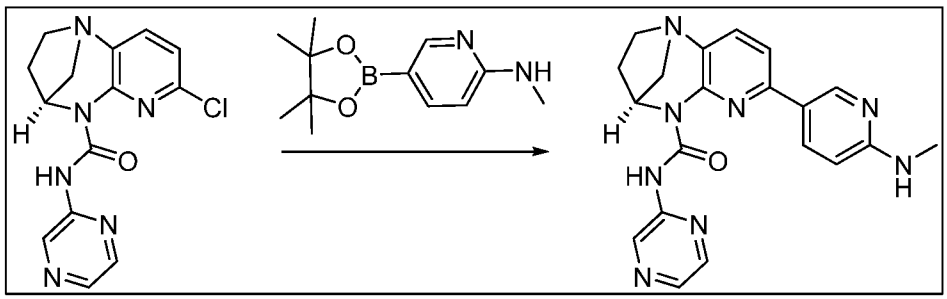


To a solution of (4*S*)-7-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (0.4 g, 1.261 mmol) in Tetrahydrofuran (THF) (15 mL) triethylamine (1.054 mL, 7.56 mmol) and triphosgene (0.374 g, 1.261 mmol) were added under nitrogen at 0 °C and stirred for 1 h at RT. To this reaction mixture pyridin-3-amine (0.237 g, 2.52 mmol) was added and stirred at 90 °C for 16 h. (TLC system: 100% Ethyl Acetate. Rf value: 0.5). The reaction mixture was diluted with water and extracted with ethyl acetate (2x30 ml). The combined organic layer was washed with brine solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford crude compound. The crude product was purified by flash column chromatography (100-200 silicagel eluted with 50% of Ethyl Acetate in PetEther) to afford the desired product (4*S*)-7-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-*N*-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2H)-carboxamide (210 mg, 0.474 mmol, 37.6 % yield) as a pale brown solid. LCMS (*m/z*): 438.13 $[M+H]^+$, Rt =1.95 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.25 (s, 1 H), 8.53 (d, *J*=2.19 Hz, 1 H), 8.27 (dd, *J*=4.71, 1.42 Hz, 1 H), 8.05 - 7.87 (m, 1 H), 7.80 - 7.66 (m, 2 H), 7.57 - 7.47 (m, 2 H), 7.43 - 7.30 (m, 2 H), 5.49 (dd, *J*=5.81, 2.96 Hz, 1 H), 3.16 - 3.07 (m, 3 H), 2.97 (dd, *J*=11.95, 3.18 Hz, 1 H), 2.25 (*J*=13.67, 9.89, 5.92, 3.84 Hz, 1 H), 1.96 (dt, *J*=14.03, 7.02 Hz, 1 H).

Example 330

Synthesis of (4S)-7-(6-(methylamino)pyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide.

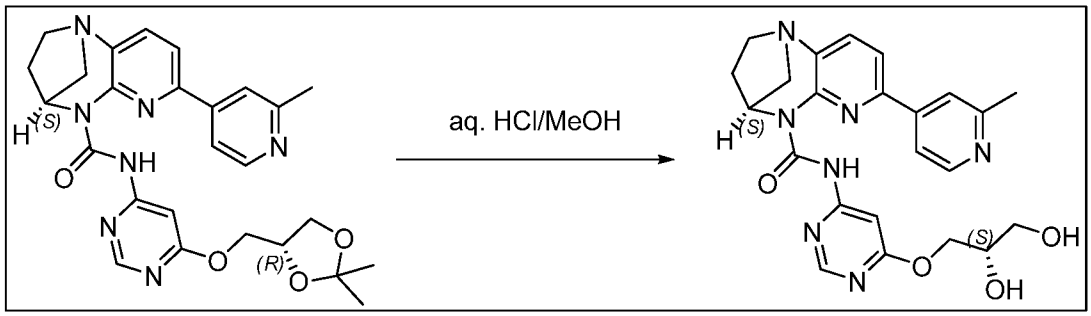


To a degassed solution of (4S)-7-chloro-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (4.2 g, 13.26 mmol), N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (3.41 g, 14.59 mmol) and Na_2CO_3 (4.22 g, 39.8 mmol) in 1,4-Dioxane (18 mL): Water (4.50 mL) was added $Pd(PPh_3)_4$ (0.766 g, 0.663 mmol). The reaction mixture was stirred at 110 °C for 16 h. (TLC system: 5% methanol in ethylacetate, R_f: 0.3). The reaction mixture was allowed to cool to room temperature and 1,4-dioxane solvent was evaporated under reduced pressure, the obtained residue was diluted with water (50 mL) and extracted with ethylacetate (2x 100 ml). The combined organic layer was washed with water, brine, dried over sodium sulphate and solvent was evaporated under reduced pressure to obtain the crude product. The crude product was purified by flash column chromatography (silica gel 100-200 mesh: elutent: Neat Ethyl acetate) to afford the desired product (4S)-7-(6-(methylamino)pyridin-3-yl)-N-(pyrazin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (2.50 g, 6.40 mmol, 48.3 % yield) as a white solid. LCMS (*m/z*): 389.16 $[M+H]^+$, *Rt* = 1.31 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.90 (s, 1 H), 9.54 (d, *J*=1.53 Hz, 1 H), 8.75 (d, *J*=2.63 Hz, 1 H), 8.36 - 8.29 (m, 3 H), 8.28 (s, 1 H), 7.55 (d, *J*=7.89 Hz, 1 H), 6.53 (d, *J*=8.77 Hz, 1 H), 5.69 (dd, *J*=6.03, 3.18 Hz, 1 H), 4.78 (d, *J*=4.82 Hz, 1 H), 3.33 - 3.13 (m, 3 H), 3.07 - 2.97 (m, 4 H), 2.35 - 2.26 (m, 1 H), 2.13 - 2.03 (m, 1 H).

Example 331

Synthesis of (4*S*)-N-(6-((*S*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide

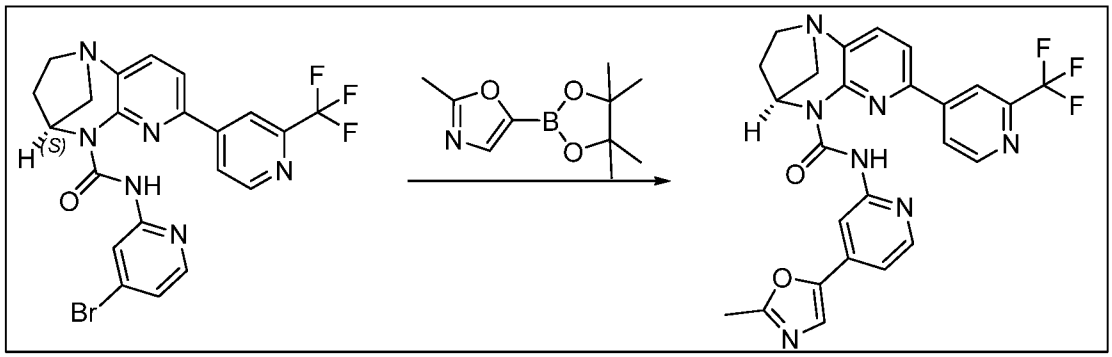


To a stirred solution of (4*S*)-N-(6-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (50 mg, 0.099 mmol) in Methanol (3 mL) at 0 °C was added hydrochloric acid (1 mL, 32.9 mmol), drop wise over a period of 5 min. Then, the reaction mixture was stirred at 28 °C for 30 min. (TLC eluent: 10% MeOH in DCM : R_f-0.2; UV active).The reaction mixture was neutralized with sodium bicarbonate solution and filtered the obtained solid, washed with water and titurated with 50% diethylether in pentane to afford the desired compound (4*S*)-N-(6-((*S*)-2,3-dihydroxypropoxy)pyrimidin-4-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido [2,3-b][1,4]diazepine-5(2H)-carboxamide (80 mg, 0.165 mmol, 167 % yield) as a yellow solid. LCMS (*m/z*): 464.15 $[M+H]^+$, R_t: 1.26 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.72 (s, 1 H), 8.62 - 8.54 (m, 2 H), 8.15 (s, 1 H), 7.93 (s, 1 H), 7.82 (d, *J*=7.45 Hz, 1 H), 7.74 (d, *J*=7.23 Hz, 1 H), 7.47 (s, 1 H), 5.49 (s, 1 H), 4.98 (d, *J*=4.38 Hz, 1 H), 4.67 (s, 1 H), 4.38 (d, *J*=8.55 Hz, 1 H), 4.26 - 4.18 (m, 1 H), 3.82 (s, 1 H), 3.45 (s, 2 H), 3.29 (s, 3 H), 3.14 - 2.91 (m, 1 H), 2.63 (s, 3 H), 2.24 (s, 1 H), 1.96 (s, 1 H).

Example 332

Synthesis of (4*S*)-*N*-(4-(2-methyloxazol-5-yl)pyridin-2-yl)-7-(2-(trifluoromethyl)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



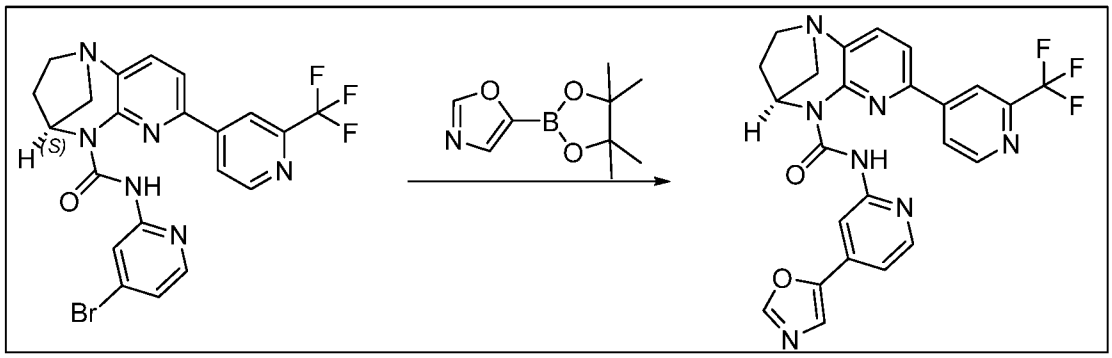
To a degassed solution of (4*S*)-*N*-(4-bromopyridin-2-yl)-7-(2-(trifluoromethyl)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (500 mg, 0.990 mmol) in 1,4-Dioxane (20 mL): Water (5 mL) were added K_3PO_4 (630 mg, 2.97 mmol), 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (310 mg, 1.484 mmol)and $PdCl_2(dppf)$-CH_2Cl_2 adduct (81 mg, 0.099 mmol)) at RT and stirred the reaction mixture at 85 ^oC for 16 h. (TLC System: R_f - 0.2, EtOAc). The reaction mixture was cool to room temperature and diluted with water (120 mL), extracted with Ethyl acetate (2x250 mL), washed with brine (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 (silica-gel: 100-200 mesh, eluent: 95% ethyl acetate in hexane) and it was again purified by Prep HPLC (Conditions: Mobile phaseA:10.0mM Ammonium Bi Carbonate Mobile phaseB:Acetonitrile isocratic:50:50(A:B) Column: Xbridge C18(250*30)mm,10um solubility: Acetonitrile+ excess volume of THF+MeoH Flow:30 ml/min) to afford the desired product (4*S*)-*N*-(4-(2-methyloxazol-5-yl)pyridin-2-yl)-7-(2-(trifluoromethyl)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (240 mg, 0.473 mmol, 47.8 % yield) as an off white solid. LCMS (*m/z*): 508.1$[M+H]^+$, Rt =2.37 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.48 (s, 1 H), 8.87 (d, *J*=5.26 Hz, 1 H), 8.46 (d, *J*=12.72 Hz, 2 H), 8.36 (d, *J*=5.26 Hz, 1 H), 8.23 (dd, *J*=5.04, 1.32 Hz, 1 H), 7.68 (d, *J*=7.89 Hz, 1 H), 7.53 (d, *J*=8.11 Hz, 1 H), 7.46 (s, 1 H), 7.21 (dd, *J*=5.15, 1.43 Hz, 1 H),

5.73 (dd, *J*=5.81, 3.18 Hz, 1 H), 3.35 -3.14 -(m, 3 H), 3.06 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.56 (s, 3 H), 2.47- 2.28 (m, 1 H), 2.12 (dt, *J*=14.20, 7.04 Hz, 1 H).

Example 333

Synthesis of (4*S*)-*N*-(4-(oxazol-5-yl)pyridin-2-yl)-7-(2-(trifluoromethyl)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



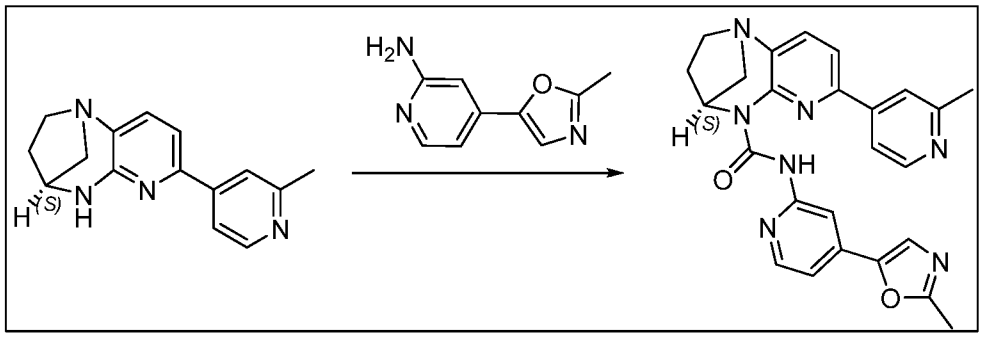
To a degassed solution of (4*S*)-*N*-(4-bromopyridin-2-yl)-7-(2-(trifluoromethyl)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (500 mg, 0.990 mmol) 1,4-Dioxane (20 mL):Water (5 mL) were added K_3PO_4 (630 mg, 2.97 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (289 mg, 1.484 mmol) and $PdCl_2(dppf)$-CH_2Cl_2 adduct (81 mg, 0.099 mmol) at RT and stirred the reaction mixture at 85 °C for 16 h. (TLC System: R_f - 0.2, EtOAc). The reaction mixture allowed to cool to RT and diluted with water (120 mL), extracted with Ethyl acetate (2x 250 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: 90% ethyl acetate in hexane) and it was again purified by Prep HPLC (Conditions: MP-A: 10mm Ammonium bicarbonate MP-B: Acetonitrile Column: Xterra(150*19mm, 10u) sun Method: T/%B 0/25,1/25, 6/65,13/65,13.10/100,16/100,16.10/25, 19/25 Flow: 17ml/min Solubility: ACN+ THF+MEOH) to afford the desired product (4*S*)-N-(4-(oxazol-5-yl)pyridin-2-yl)-7-(2-(trifluoromethyl)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (210 mg, 0.423 mmol, 42.7 % yield) as an off white solid. LCMS (*m/z*): 494.1 $[M+H]^+$, Rt =8.46 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.53 (s, 1 H), 8.89 (d, *J*=5.04 Hz, 1 H), 8.54- 8.47 (m, 2 H), 8.41 (d, *J*=5.26 Hz, 1 H), 8.22 (dd, *J*=5.15, 1.43 Hz, 1 H), 8.00 (s, 1 H), 7.70 (d,

J=8.11 Hz, 1 H), 7.62 (s, 1 H), 7.54 (d, *J*=7.89 Hz, 1 H), 7.32- 7.27 (m, 1 H), 5.74 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.37 -3.16 (m, 3 H), 3.07 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.46 -2.32 (m, 1 H), 2.13 (dt, *J*=14.09, 6.88 Hz, 1 H).

Example 334

Synthesis of (4*S*)-N-(4-(2-methyloxazol-4-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



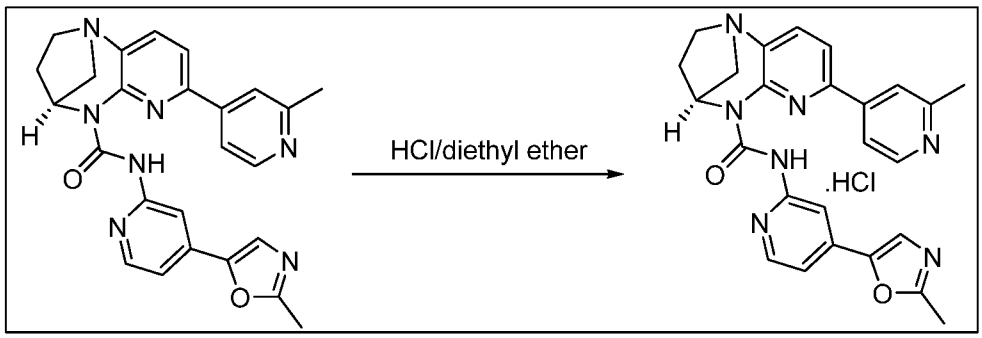
To a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (8 g, 31.7 mmol) in Tetrahydrofuran (600 mL) were added triphosgene (5.65 g, 19.02 mmol) and DIPEA (28 mL, 159 mmol) at 0 °C under nitrogen and stirred at room temperature for 30 min. then, 4-(2-methyloxazol-5-yl)pyridin-2-amine (8.33 g, 47.6 mmol) was added and stirred at 80 °C for 16 h. (TLC: 10% MeOH/ ethyl acetate, Rf: 0.3). The reaction mixture was allowed to cool to room temperature and poured in to the cold water (150 mL), extracted with ethyl acetate (2x 300 mL). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain crude compound. The crude compound was purified by flash column chromatography (Neutral alumina, 65% Ethyl acetate in pet ether) to afford the desired product (6 g). This was taken in ethyl acetate (800 mL) and Silicycle palladium scavenger (3 g) was added and stirred at 50 °C for 4 h. The mixture was filtered through celite pad and washed with hot ethyl acetate (50 ml), the obtained filtrate was concentrated under reduced pressure to afford Pd free (4*S*)-N-(4-(2-methyloxazol-4-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxa mide (5.5 g, 12.12 mmol, 38.2 % yield) as a yellow solid. LCMS (*m/z*): 454.22 $[M+H]^+$, R_t = 1.53 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.65 (s, 1 H), 8.62 (d, *J*=5.26 Hz, 1 H), 8.47 - 8.52 (m, 1 H), 8.38 (dd, *J*=5.26, 0.66 Hz, 1 H), 8.17 - 8.23 (m, 1 H), 7.72 (dd, *J*=5.15, 1.64 Hz,

1 H), 7.63 (d, *J*=7.89 Hz, 1 H), 7.43 - 7.52 (m, 2 H), 7.20 (dd, *J*=5.26, 1.53 Hz, 1 H), 5.72 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.15 - 3.37 (m, 3 H), 3.03 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.75 (s, 3 H), 2.56 (s, 3 H), 2.36 (dddd, *J*=14.00, 9.89, 5.92, 3.95 Hz, 1 H), 2.05 - 2.16 (m, 1 H).

Example 335

Synthesis of (4S)-N-(4-(2-methyloxazol-5-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide, Hydrochloride

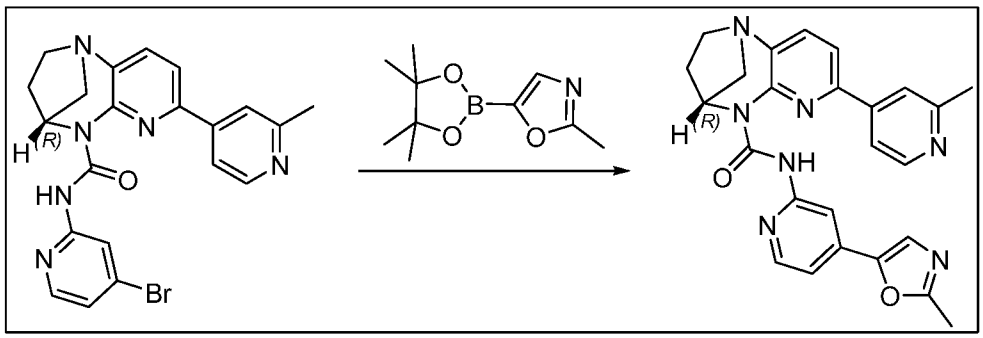


To a stirred solution of (4S)-N-(4-(2-methyloxazol-5-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (100 mg, 0.221 mmol) in Diethyl ether (10 mL) at 0 °C was added 2M HCl in Ether (2.5 mL, 0.221 mmol) drop wise over a period of 2 min. Then the reaction mixture was stirred at 30 °C for 2 h. (TLC: 10% MeOH/ DCM, R_f: 0.2). and evaporated the solvent under reduced pressure, obtained solid compound was washed with *n*-pentane (2 x20 mL) to afford the desired compound (4*S*)-N-(4-(2-methyloxazol-5-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide, Hydrochloride (84 mg, 0.171 mmol, 78 % yield) as a pale yellow solid. LCMS (*m/z*): 454.22 $[M+H]^+$, R_t = 1.52 min.

^{1}H NMR (400 MHz, CD_3OD): δ ppm 8.93 (d, *J*=6.14 Hz, 1 H), 8.69 (s, 1 H), 8.59 (d, *J*=5.92 Hz, 1 H), 8.45 (d, *J*=6.14 Hz, 1 H), 8.32 (d, *J*=8.11 Hz, 1 H), 8.14 (d, *J*=8.11 Hz, 1 H), 8.04 (s, 1 H), 7.96 (s, 1 H), 7.78 (d, *J*=6.14 Hz, 1 H), 5.88 (d, *J*=5.70 Hz, 1 H), 4.06 - 3.98 (m, 4 H), 2.95 (s, 3 H), 2.84 - 2.71 (m, 2 H), 2.67 (s, 3 H), 2.59 (dt, *J*=14.31, 6.99 Hz, 1 H).

Example 336

Synthesis of (4*R*)-N-(4-(2-methyloxazol-5-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

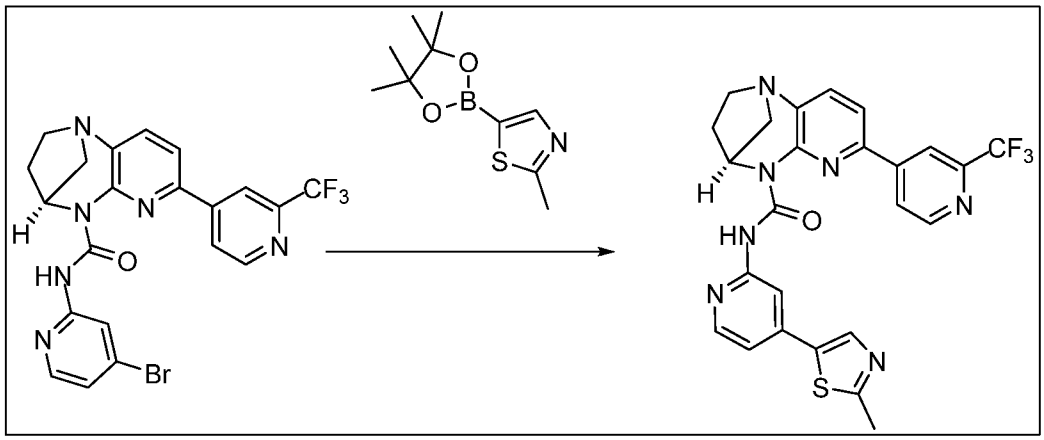


To a degassed solution of (4*R*)-N-(4-bromopyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (450 mg, 0.997 mmol), 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (313 mg, 1.496 mmol) and K_3PO_4 (635 mg, 2.99 mmol) in 1,4-Dioxane (16 mL):Water (4 mL) was added $PdCl_2$(dppf) (73.0 mg, 0.100 mmol). The reaction mixture was stirred at 90 °C for 16 h. (TLC: 10% MeOH in EtOAc R_f: 0.7). The 1,4-dioxane solvent was evaporated under reduced pressure, the obtained residue was diluted with water (50 mL) and extracted with ethylacetate (2x 100 mL). The combined organic layer was washed with water, brine, dried over sodium sulphate and solvent was evaporated under reduced pressure to obtain the crude product. The crude product was purified by flash column chromatography ((silica gel 100-200 mesh: elutent: 2% MeOH/ DCM) to afford the desired product (4*R*)-N-(4-(2-methyloxazol-5-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (250 mg, 0.550 mmol, 55.1 % yield) as a white solid. LCMS (*m/z*): 454.22 $[M+H]^+$, R_t = 1.52 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.66 (s, 1 H), 8.63 (d, *J*=5.26 Hz, 1 H), 8.49 (s, 1 H), 8.38 (d, *J*=5.26 Hz, 1 H), 8.19 (d, *J*=1.32 Hz, 1 H), 7.72 (dd, *J*=5.26, 1.75 Hz, 1 H), 7.63 (d, *J*=7.89 Hz, 1 H), 7.52 - 7.45 (m, 2 H), 7.21 (dd, *J*=5.26, 1.53 Hz, 1 H), 5.72 (dd, *J*=5.92, 3.29 Hz, 1 H), 3.36 - 3.14 (m, 3 H), 3.04 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.75 (s, 3 H), 2.56 (s, 3 H), 2.42 - 2.30 (m, 1 H), 2.11 (dt, *J*=14.09, 7.10 Hz, 1 H).

Example 337

Synthesis of (4*S*)-*N*-(4-(2-methylthiazol-5-yl)pyridin-2-yl)-7-(2-(trifluoromethyl)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



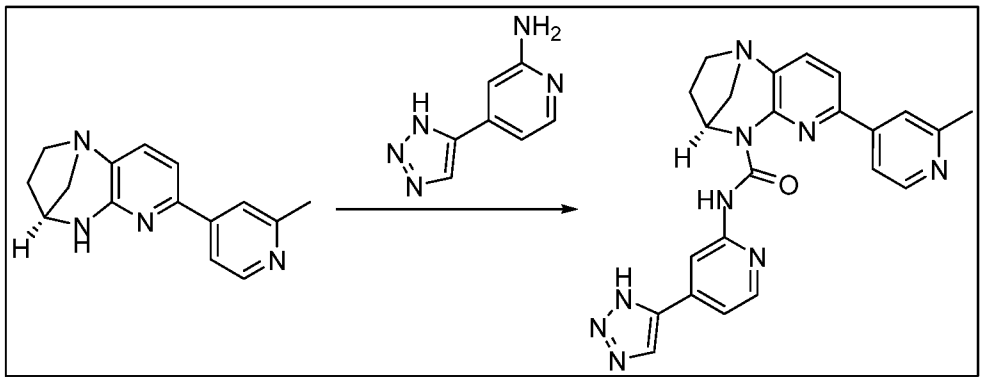
To a degassed solution of (4*S*)-N-(4-bromopyridin-2-yl)-7-(2-(trifluoromethyl)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (500mg, 0.990 mmol) in 1,4-Dioxane (20.0 mL) and water (5.0 mL) were added 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole (334 mg, 1.484 mmol), Na_2CO_3 (315 mg, 2.97 mmol) and $Pd(TPP)_4$ (57.2 mg, 0.049 mmol) and the reaction mixture was stirred at 110 °C for 16 h.(TLC system: 100% Ethylacetate, Rf value: 0.3).Reaction mixture was cooled to RT, diluted with water (30 mL) and extracted with ethylacetate (2 x 20 mL). Combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated. Crude compound was purified by flash column chromatography (silica-gel 100-200 mesh, eluted with 40% ethyl acetate in pet ether) followed by preparative HPLC (Column: Xbridge C18 (50x19 mm)5µ; mobile phase-A:10M Ammonium Bicarbonate; mobile phase-B: Acetonitrile;Method(T/%B): 0/20,/10/55; Flow: 17 ml/min; Solubility: Acetonitrile+MeOH +THF+TFA)to afford(4*S*)-N-(4-(2-methylthiazol-5-yl)pyridin-2-yl)-7-(2-(trifluoromethyl)pyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (195 mg, 0.372 mmol, 37.6 % yield)as an off-white solid. LCMS (*m/z*): 524.13$[M+H]^+$, *Rt* = 2.54 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.47 (s, 1 H), 8.87 (d, *J*=5.26 Hz, 1 H), 8.48 (s, 1 H), 8.41 (d, *J*=0.88 Hz, 1 H), 8.33 (d, *J*=5.26 Hz, 1 H), 8.22 (dd, *J*=5.15, 1.64 Hz, 1 H), 8.05 (s, 1 H), 7.68 (d, *J*=7.89 Hz, 1 H), 7.53 (d, *J*=7.89 Hz, 1 H), 7.14 (dd, *J*=5.26, 1.53 Hz, 1

H), 5.73 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.36 - 3.15 (m, 3 H), 3.05 (dd, *J*=12.17, 3.18 Hz, 1 H), 2.76 (s, 3 H), 2.37 (qd, *J*=9.90, 4.28 Hz, 1 H), 2.12 (dt, *J*=14.14, 7.18 Hz, 1 H).

Example 338

Synthesis of (4*S*)-N-(4-(1*H*-1,2,3-triazol-5-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



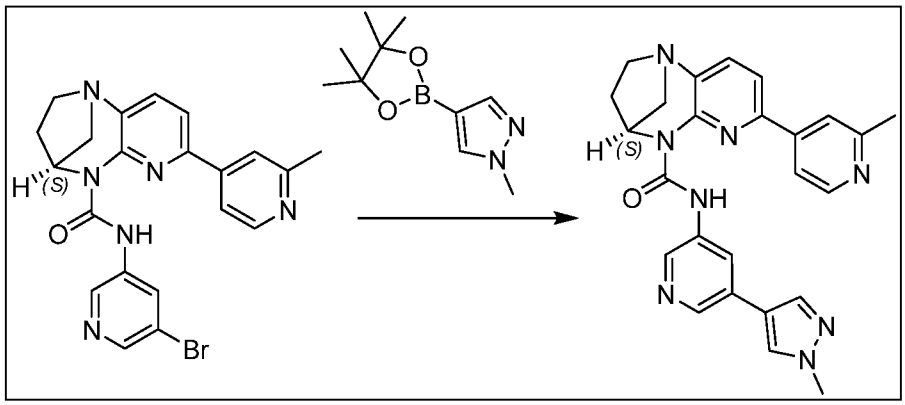
To a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 1.189 mmol) in Tetrahydrofuran (10 mL, sealed tube) were added TEA (0.829 mL, 5.94 mmol) and triphosgene (353 mg, 1.189 mmol) at room temperature and stirred for 45 min. Then 4-(1H-1,2,3-triazol-5-yl)pyridin-2-amine (287 mg, 1.783 mmol) was added to the reaction mixture at room temperature and stirred at 80 °C for 16 h. (TLC system: 5% MeOH\DCM. R_f value: 0.3, UV). Reaction mixture was cooled to RT, diluted with water (15mL), extracted with ethyl acetate (5X20 mL). The combined organic layer was washed with saturated brine solution (10 mL) and dried over anhydrous sodium sulphate, filtered and concentrated to afford crude compound. The crude compound was purified by Prep HPLC (Conditions: MP-A: 10 Mm Ammonium bi carbonate (Aq), MPB: Acetonitrile, Column: Atlantis T3 (250*19mm*5u), Method: 0/35, 11/35, 11.1/100, 15/100, 15.1/35, 19/35, Flow:16ml/min, Solubility: ACN+THF+MeOH+DMSO) to afford the desired product (4*S*)-N-(4-(1H-1,2,3-triazol-5-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*) carboxamide (60 mg, 0.133 mmol, 11.15 % yield) as an off white solid. LCMS (*m/z*): 440.21 $[M+H]^+$, R_t = 1.42 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.57 (s, 1 H), 8.66 (s, 1 H), 8.60 (d, *J*=5.26 Hz, 1 H), 8.49 - 8.39 (m, 2 H), 8.25 (s, 1 H), 7.96 (dd, *J*=5.26, 1.53 Hz, 1 H), 7.85 - 7.79 (m, 2 H), 7.72 (d, *J*=7.89 Hz, 1 H), 7.56 (dd, *J*=5.15, 1.43 Hz, 1 H), 5.54 (dd, *J*=5.70, 3.07 Hz, 1

H), 3.17 - 3.06 (m, 3 H), 2.98 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.64 (m, 3 H), 2.36 - 2.20 (m, 1 H), 1.98 (dt, *J*=13.70, 6.96 Hz, 1 H).

Example 339

Synthesis of (4*S*)-N-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

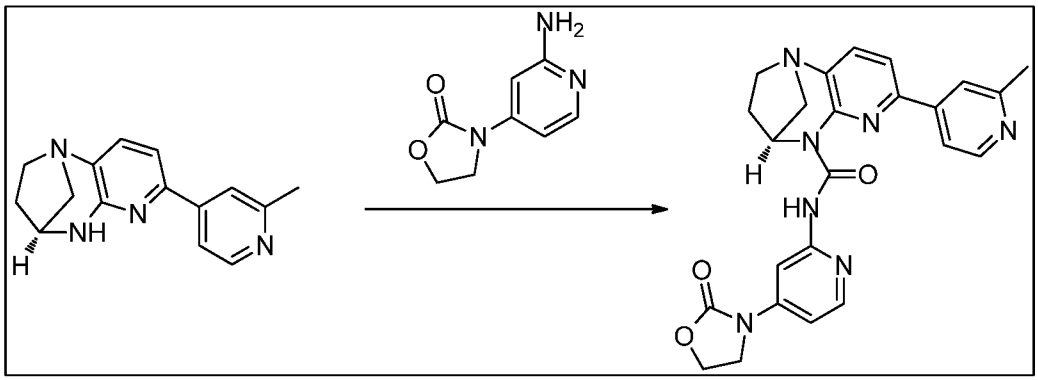


To a degassed solution of (4*S*)-N-(5-bromopyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (400 mg, 0.886 mmol), Na_2CO_3 (282 mg, 2.66 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (277 mg, 1.329 mmol) in 1,4-Dioxane (28 mL) and Water (7.00 mL) was added $Pd(Ph_3P)_4$ (51.2 mg, 0.044 mmol) at room temperature and the reaction mixture was stirred at 75 °C for 16 h. (TLC System 10% MeOH/ Ethyl acetate, Rf: 0.2). The reaction mixture was diluted with water and extracted with ethyl acetate (2x100 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated to obtain crude compound. The crude product was purified by flash column chromatography (neutral alumina, Eluent: 2% MeOH/EtOAc) to afford the desired product (4*S*)-N-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (120 mg, 0.262 mmol, 29.6 % yield) as a white solid. LCMS (*m/z*): 453.29 $[M+H]^+$, R_t = 1.34 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.13 (s, 1 H), 8.68 (d, *J*=5.04 Hz, 1 H), 8.46 (d, *J*=1.75 Hz, 1 H), 8.38 (q, *J*=2.41 Hz, 2 H), 7.81 (d, *J*=0.66 Hz, 1 H), 7.67 (d, *J*=7.02 Hz, 1 H), 7.60 (s, 1 H), 7.54 - 7.48 (m, 2 H), 7.38 (d, *J*=7.89 Hz, 1 H), 5.70 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.96 (s, 3 H), 3.35 - 3.16 (m, 3 H), 3.04 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.67 (s, 3 H), 2.28 - 2.44 (m, 1 H), 2.11 (dt, *J*=14.09, 6.88 Hz, 1 H).

Example 340

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-N-(4-(2-oxooxazolidin-3-yl)pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2*H*)-carboxamide



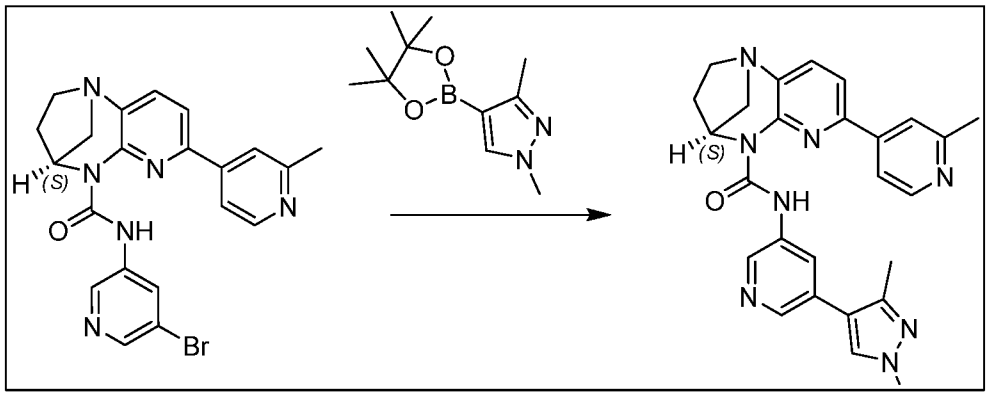
To a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (350 mg, 1.387 mmol) in Tetrahydrofuran (10 mL, sealed tube) were added TEA (0.967 mL, 6.94 mmol), triphosgene (412 mg, 1.387 mmol) at room temperature and stirred for 45 min. Then 3-(2-aminopyridin-4-yl)oxazolidin-2-one (373 mg, 2.081 mmol) was added to the reaction mixture at room temperature and stirred at 80 °C for 16 h. (TLC system: 5% MeOH\DCM. R_f value: 0.3, UV). Reaction mixture was allowed to cool to room temperature and diluted with water (15mL), extracted with ethyl acetate (5X20 mL). The combined organic layer was washed with saturated brine solution (10 mL) and dried over anhydrous sodium sulphate, filtered and the filtrate was concentrated under reduced pressure to afford crude compound. The crude compound was purified by Prep HPLC (Conditions: MP A: 10mM Ammonium Bicarbonate (Aq), MP B: Acetonitrile,Column: Kromosil C18 (250*21.2) mm 10 u, method: T/%B = 0/40, 12/40, 12.5/100, 16/100, 16.5/40, Flow:20ml/min, Solubility: Acetonitrile + THF + Water) to afford the desired product (4*S*)-7-(2-methylpyridin-4-yl)-N-(4-(2-oxooxazolidin-3-yl)pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (54 mg, 0.117 mmol, 8.47 % yield) as an off white solid. LCMS (*m/z*): 458.26 $[M+H]^+$, R_t = 1.48 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.65 (s, 1 H), 8.62 (d, *J*=5.26 Hz, 1 H), 8.30 (d, *J*=5.70 Hz, 1 H), 8.20 (s, 1 H), 8.06 (d, *J*=1.75 Hz, 1 H), 7.80 (dd, *J*=5.81, 2.08 Hz, 1 H), 7.71 (d, *J*=4.17 Hz, 1 H), 7.63 (d, *J*=7.89 Hz, 1 H), 7.49 (d, *J*=7.89 Hz, 1 H), 5.68 (dd, *J*=5.70, 3.29 Hz, 1 H), 4.53 (t, *J*=8.00 Hz, 2 H), 4.15 (t, *J*=8.00 Hz, 2 H), 3.40 - 3.13 (m, 3

H), 3.02 (dd, *J*=11.95, 3.18 Hz, 1 H), 2.74 (s, 3 H), 2.44 - 2.21 (m, 1 H), 2.09 (dt, *J*=13.98, 6.71 Hz, 1 H).

Example 341

Synthesis of (4*S*)-N-(5-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



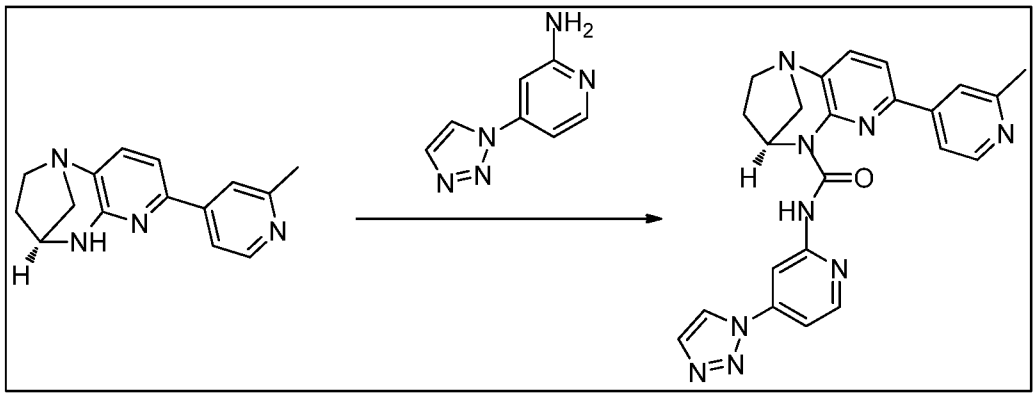
To a degassed solution of (4*S*)-N-(5-bromopyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (400 mg, 0.886 mmol), Na_2CO_3 (282 mg, 2.66 mmol), 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (295 mg, 1.329 mmol) in 1,4-Dioxane (20 mL) and Water (5 mL) was added $Pd(Ph_3P)_4$ (51.2 mg, 0.044 mmol) at RT and again degassed for 5 min. Then the reaction mixture was stirred at 80 °C for 15 h. (TLC system: 10 % Methanol in dichloro methane, R_f: 0.2). Reaction mixture was cooled to RT and evaporated the dioxane solvent from reaction mixture to obtain the residue, was diluted with water and extracted with ethylacetate (3X 50 mL). The combined organic layer was washed with brine (2x20 mL) and dried over anhydrous sodium sulphate, filtered and concentrated to obtain crude compound. The crude material was purified by flash column chromatography (silicagel: 100-200 Mesh, Eluent: 90% Ethyl acetate in pet ether) to afford the desired product (4*S*)-N-(5-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (195 mg, 0.417 mmol, 47.1 % yield) as an off white solid. LCMS (*m/z*): 467.1 $[M+H]^+$, R_t = 3.27.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.12 (s, 1 H), 8.66 (d, *J*=5.04 Hz, 1 H), 8.42 (d, *J*=2.41 Hz, 1 H), 8.38 (d, *J*=1.97 Hz, 1 H), 8.31 (t, *J*=2.08 Hz, 1 H), 7.65 (d, *J*=7.89 Hz, 1 H), 7.60 (s, 1 H), 7.53 - 7.49 (m, 2 H), 7.38 (d, *J*=7.89 Hz, 1 H), 5.70 (dd, *J*=5.81, 3.18 Hz,

1 H), 3.89 (s, 3 H), 3.34 - 3.15 (m, 3 H), 3.04 (dd, *J*=12.17, 3.18 Hz, 1 H), 2.66 (s, 3 H), 2.42 (s, 3 H), 2.40 - 2.31 (m, 1 H), 2.11 (dt, *J*=14.31, 7.43 Hz, 1 H).

Example 342

Synthesis of (4*S*)-N-(4-(1H-1,2,3-triazol-1-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



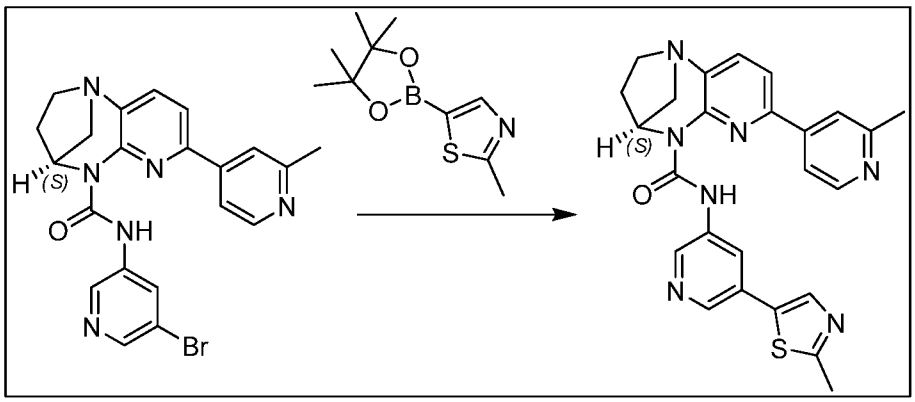
To a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (450 mg, 1.783 mmol) in Tetrahydrofuran (10 mL, sealed tube) were added TEA (1.243 mL, 8.92 mmol) and triphosgene (529 mg, 1.783 mmol) at room temperature and stirred for 45 min. Then 4-(1H-1,2,3-triazol-1-yl)pyridin-2-amine (345 mg, 2.140 mmol) was added to the reaction mixture at 28 °C and stirred at 80 °C for 4 h. (TLC system: 5% MeOH\DCM. R_f value: 0.3, UV). Reaction mixture was allowed to cool to room temperature and diluted with water (15mL), extracted with ethyl acetate (5X20 mL). The combined organic layer was washed with saturated brine solution (10 mL) and dried over anhydrous sodium sulphate, filtered and concentrated to afford crude compound. The crude compound was purified by Prep HPLC (Conditions: MP-A: 10mM Ammonium bicarbonate (aq) MP-B: Acetonitrile, Column: kromasil (2150*21.1mm) 5µ, Method :0/10, 1/10, 10/55, Flow: 17ml/min, Solubility: CAN + MeOH) to afford the desired product (4*S*)-N-(4-(1H-1,2,3-triazol-1-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (175 mg, 0.398 mmol, 22.32 % yield) as an off white solid. LCMS (*m/z*): 440.22 $[M+H]^+$, R_t = 1.60 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 13.83 (s, 1 H), 9.03 (d, *J*=1.10 Hz, 1 H), 8.81 (d, *J*=1.53 Hz, 1 H), 8.61 (t, *J*=5.81 Hz, 2 H), 8.21 (s, 1 H), 8.07 (d, *J*=1.32 Hz, 1 H), 7.95 (dd, *J*=5.26, 1.53 Hz, 1 H), 7.87 - 7.79 (m, 1 H), 7.79 - 7.62 (m, 1 H), 5.54 (dd, *J*=5.92, 3.07

Hz, 1 H), 3.28 - 3.19 (m, 1 H), 3.18 - 3.06 (m, 3 H), 2.99 (dd, *J*=11.95, 3.18 Hz, 1 H), 2.62 (s, 3 H), 2.48 - 2.20 (m, 1 H), 2.09 - 1.85 (m, 1 H).

Example 343

Synthesis of (4S)-7-(2-methylpyridin-4-yl)-N-(5-(2-methylthiazol-5-yl)pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

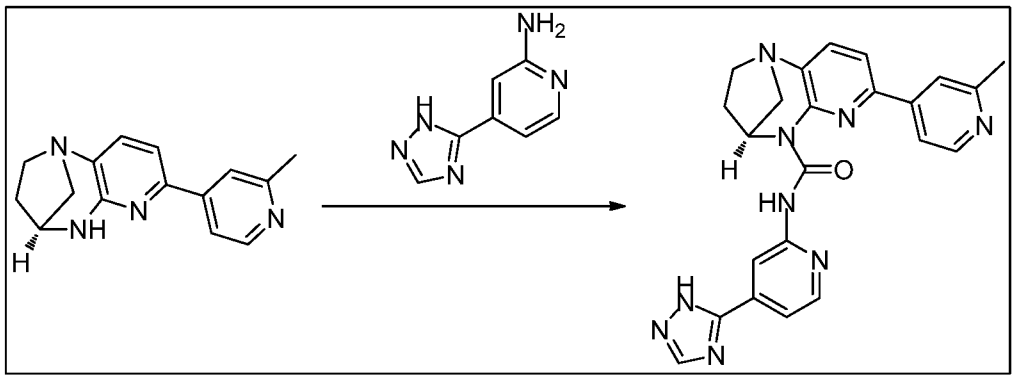


To a degassed solution of (4*S*)-N-(5-bromopyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (500 mg, 1.108 mmol), K_3PO_4 (705 mg, 3.32 mmol), 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole (374 mg, 1.662 mmol) in 1,4-Dioxane (16 mL) and Water (4 mL) was added $PdCl_2$(dppf)-CH_2Cl_2 adduct (136 mg, 0.166 mmol) at room temperature and the reaction mixture again degassed for 5 min. and stirred at 80 °C for 15 h. (TLC system: 10% MeOH/ DCM, Rf: 0.2). Reaction mixture was cooled to RT and evaporated the reaction mixture to obtain the crude. The crude compound was purified by flash column chromatography (Neutral alumina, 80% Ethyl acetate in pet ether) to afford the desired product (4*S*)-7-(2-methylpyridin-4-yl)-N-(5-(2-methylthiazol-5-yl)pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (190 mg, 0.393 mmol, 35.4 % yield) as a brown solid. LCMS (*m/z*): 470.24 $[M+H]^+$, R_t = 1.59 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.21 (s, 1 H), 8.69 (d, *J*=5.04 Hz, 1 H), 8.52 - 8.43 (m, 3 H), 7.88 (s, 1 H), 7.66 (d, *J*=7.89 Hz, 1 H), 7.58 (s, 1 H), 7.51 (dd, *J*=5.15, 1.21 Hz, 1 H), 7.39 (d, *J*=7.89 Hz, 1 H), 5.70 (dd, *J*=5.81, 3.18 Hz, 1 H), 3.15 - 3.36 (m, 3 H), 3.04 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.76 (s, 3 H), 2.67 (s, 3 H), 2.36 (qd, *J*=10.01, 4.17 Hz, 1 H), 2.11 (dt, *J*=13.98, 6.93 Hz, 1 H).

Example 344

Synthesis of (4*S*)-N-(4-(1H-1,2,4-triazol-5-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

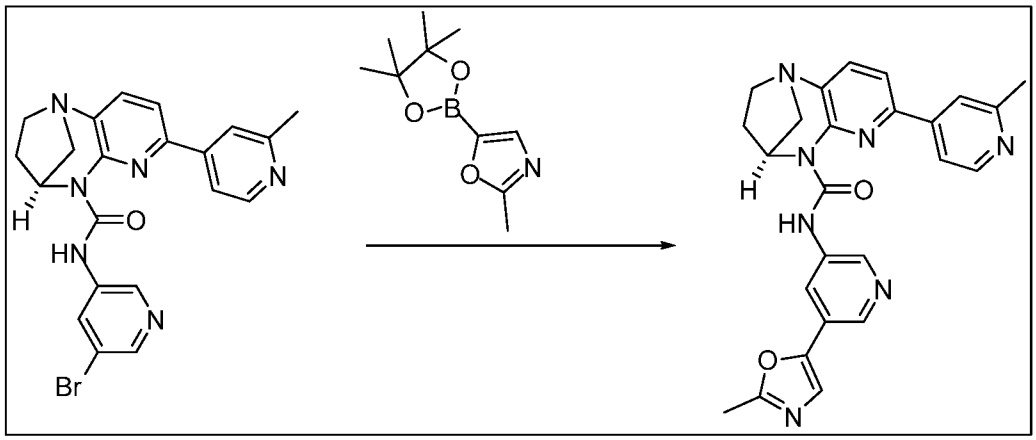


To a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (450 mg, 1.783 mmol) in Tetrahydrofuran (10 mL, sealed tube) were added TEA (1.243 mL, 8.92 mmol) and triphosgene (529 mg, 1.783 mmol) at room temperature and stirred at RT for 45 min. Then 4-(1H-1,2,4-triazol-5-yl)pyridin-2-amine (345 mg, 2.140 mmol) was added to the reaction mixture at room temperature and stirred at 80 °C for 16 h. (TLC system: 5% MeOH\DCM. R_f value: 0.3, UV). Reaction mixture was allowed to cool to room temperature and diluted with water (15mL), extracted with ethyl acetate (5X20 mL). The combined organic layer was washed with saturated brine solution (10 mL) and dried over anhydrous Na_2SO_4, filtered and filtrate was concentrated under reduced pressure to afford crude compound. The crude compound was purified by Prep HPLC (Prep HPLC Method: MP-A: 10mM Ammonium Bicarbonate (aq) MP-B: Acetonitrile, Column: kinetex C8 (150*30) mm, 5u, Method:0/10, 1/10, 8/40, 12/40, 12.1/100, 15/100, 15.1/10, Flow: 30ml/min, Solubility: Acetonitrile + THF + Methanol + DMSO + DMSO + Formic Acid) to afford the desired product (4*S*)-*N*-(4-(1H-1,2,4-triazol-5-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b] [1,4] diazepine-5(2H)-carboxamide (102 mg, 0.221 mmol, 12.38 % yield) as an off white solid. LCMS (*m/z*): 440.2 $[M+H]^+$, R_t = 3.71min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 14.52 (s, 1 H), 13.63 (s, 1 H), 8.84 (d, *J*=0.88 Hz, 1 H), 8.70 - 8.55 (m, 1 H), 8.54 - 8.38 (m, 1 H), 8.37 - 8.35 (d, 1 H) 8.25 (s, 1 H), 7.95 (dd, *J*=5.37, 1.43 Hz, 1 H), 7.86 - 7.77 (m, 1 H), 7.77 - 7.64 (m, 2 H), 5.54 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.18 - 3.05 (m, 3 H), 2.98 (dd, *J*=11.95, 3.18 Hz, 1 H), 2.78 - 2.52 (m, 3 H), 2.48 - 2.36 (m, 1 H), 2.07 (s, 1 H).

Example 345

Synthesis of (4*S*)-N-(5-(2-methyloxazol-5-yl)pyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide



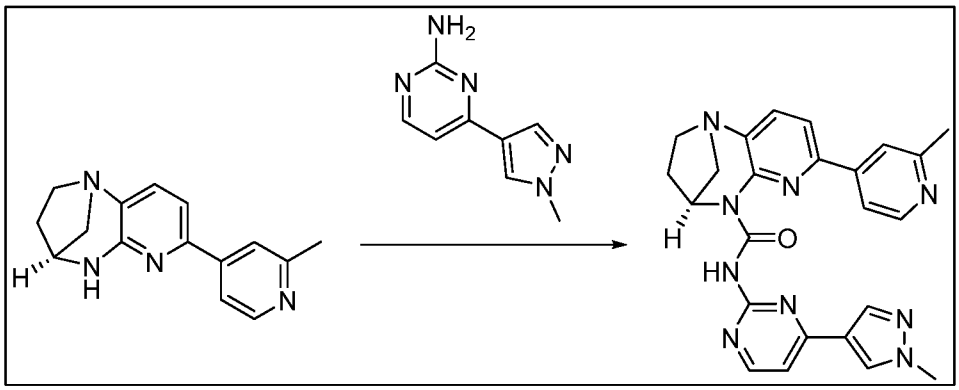
To a degassed solution (4*S*)-N-(5-bromopyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (350 mg, 0.776 mmol), Na_2CO_3 (247 mg, 2.327 mmol) and 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (243 mg, 1.163 mmol) in 1,4-Dioxane (20 mL) and Water (4 mL) at RT was added $Pd(Ph_3P)_4$ (44.8 mg, 0.039 mmol) and again degassed for 5 min. Then the resulted reaction mixture was stirred to 80 °C for 15 h. (TLC system: 10 % MeOH/ DCM, Rf: 0.3) and the reaction mixture was allowed to cool to RT, evaporated the organic solvent from reaction mixture and the obtained residue was diluted with water, extracted with ethylacetate (3X 20 mL). The combined organic layer was washed with saturated brine solution (2x5 mL), dried over anhydrous sodium sulphate, filtered and concentrated to obtain crude material. The crude compound was purified by Prep HPLC (conditions: MP-A: 10mM Ammonium Bicarbonate (aq) MP-B: Acetonitrile Column: sunfire C8(150*19)mm,10u Method :-0/10, 1/10, 10/45 Flow : 18ml/min Solubility: methanol + CAN + THF) to afford the desired product (4*S*)-N-(5-(2-methyloxazol-5-yl)pyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (68 mg, 0.149 mmol, 19.17 % yield) as an off white solid. LCMS (*m/z*): 454.1 $[M+H]^+$, *Rt* = 3.39 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.24 (s, 1 H), 8.69 (d, *J*=5.26 Hz, 1 H), 8.58 (d, *J*=1.75 Hz, 1 H), 8.52 (d, *J*=2.19 Hz, 1 H), 8.48 - 8.44 (m, 1 H), 7.66 (d, *J*=7.89 Hz, 1 H), 7.59 (s, 1 H), 7.52 (d, *J*=5.26 Hz, 1 H), 7.39 (d, *J*=7.89 Hz, 1 H), 7.33 (s, 1 H), 5.71 (dd,

J=5.81, 3.18 Hz, 1 H), 3.37 - 3.15 (m, 3 H), 3.05 (dd, *J*=12.17, 3.40 Hz, 1 H), 2.68 (s, 3 H), 2.56 (s, 3 H), 2.37 (qd, *J*=9.79, 4.38 Hz, 1 H), 2.11 (dt, *J*=14.36, 7.07 Hz, 1 H).

Example 346

Synthesis of (4*S*)-N-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

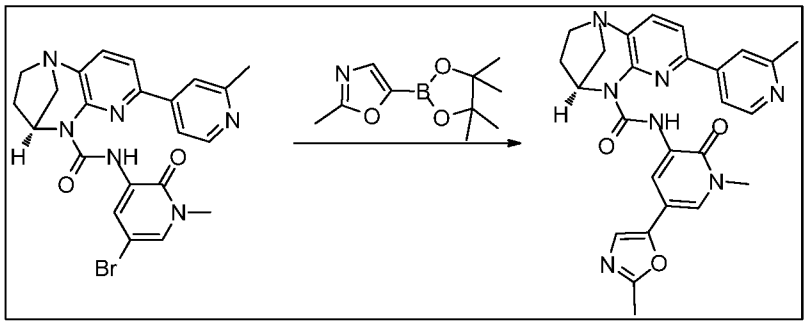


To a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (350 mg, 1.387 mmol) in Tetrahydrofuran (25 mL), were added triphosgene (247 mg, 0.832 mmol), DIPEA (1.211 mL, 6.94 mmol) under nitrogen atmosphere at room temperature in sealed tube and stirred at RT for 30 min. To this 4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (365 mg, 2.081 mmol) was added and stirred at 75 °C for 16 h. (TLC System 10% MeOH/ Ethyl acetate, *Rf*: 0.1). The reaction mixture was allowed to cool to room temperature and diluted with water (100 mL), extracted with ethylacetate (2x100 mL). The combined organic layer was washed with saturated brine solution (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to obtain crude compound. The crude product was purified by flash column chromatography (neutral alumina, Eluent: 50% EtOAc/petetether) to afford the desired product (4*S*)-N-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (140 mg, 0.307 mmol, 22.11 % yield) as a yellow solid. LCMS (*m/z*): 454.19 $[M+H]^+$, *Rt* = 1.44 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.75 (s, 1 H), 8.59 (dd, *J*=12.06, 5.26 Hz, 2 H), 7.95 (s, 1 H), 7.90 - 7.84 (m, 2 H), 7.76 (dd, *J*=5.15, 1.43 Hz, 1 H), 7.64 (d, *J*=7.89 Hz, 1 H), 7.45 (d, *J*=7.89 Hz, 1 H), 7.08 (d, *J*=5.26 Hz, 1 H), 5.78 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.95 (s, 3 H), 3.34 - 3.13 (m, 3 H), 3.02 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.61 (s, 3 H), 2.43 - 2.26 (m, 1 H), 2.11 (dt, *J*=14.03, 7.02 Hz, 1 H).

Example 347

Synthesis of (4*S*)-N-(1-methyl-5-(2-methyloxazol-5-yl)-2-oxo-1,2-dihydropyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



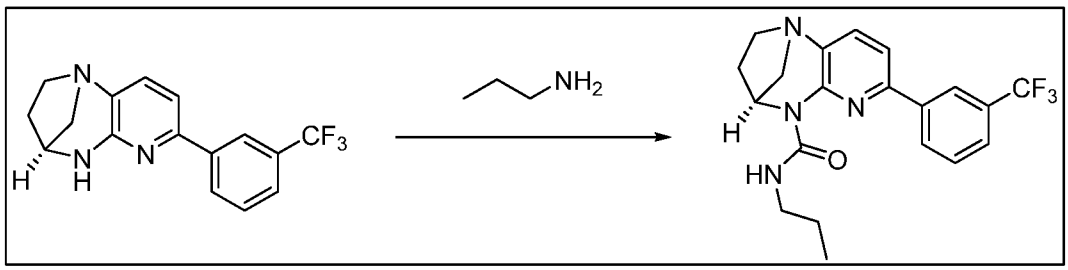
To a stirred solution of (4*S*)-N-(5-bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (700 mg, 1.454 mmol) and 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (456 mg, 2.181 mmol) in 1,4-Dioxane (24 mL) and Water (6 mL) was added K_3PO_4 (926 mg, 4.36 mmol). The resulting reaction mixture was degassed for 15 min with nitrogen. Then $PdCl_2$(dppf) (106 mg, 0.145 mmol) was added to the reaction mixture and again degassed for 5 min. The resulting reaction mixture was stirred at 100 °C for 18 h. (TLC system: 10% MeOH in DCM, R_f: 0.6). The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (3x30 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 column chromatography (silica gel: 100-200 mesh Eluent: 4% MeOH in DCM), to obtain sticky solid. The sticky solid was washed with EtOH (1 mL) and diethyl ether (15 mL), filtered and dried well to afford the desired product (4*S*)-N-(1-methyl-5-(2-methyloxazol-5-yl)-2-oxo-1,2-dihydropyridin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (95 mg, 0.188 mmol, 12.94 % yield) as an off-white solid. LCMS (*m/z*): 484.24 $[M+H]^+$, R_t=1.51 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ 12.46 (s, 1 H), 8.61 – 8.53 (m, 2 H), 8.09 (dt, *J* = 1.9, 0.8 Hz, 1 H), 7.69 – 7.65. (d, *J* = 5.6 Hz, 1 H), 7.61 - 7.59 (d, *J* = 7.9 Hz, 1 H), 7.43 – 7.31 (m, 2 H), 7.07 (s, 1 H), 5.70 (dd, *J* = 6.0, 3.2 Hz, 1 H), 3.64 (s, 3 H), 3.35 – 3.13 (m, 3 H), 3.00

(dd, *J* = 12.1, 3.3 Hz, 1 H), 2.69 (s, 3 H), 2.49 (s, 3 H), 2.39-2.34 (dddd, *J* = 13.9, 10.0, 6.0, 4.0 Hz, 1 H), 2.16-2.05 (dt, *J* = 14.2, 7.3 Hz, 1 H).

Example 348

Synthesis of (4*S*)-*N*-propyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyri do[2,3-b][1,4]diazepine-5(2H)-carboxamide.

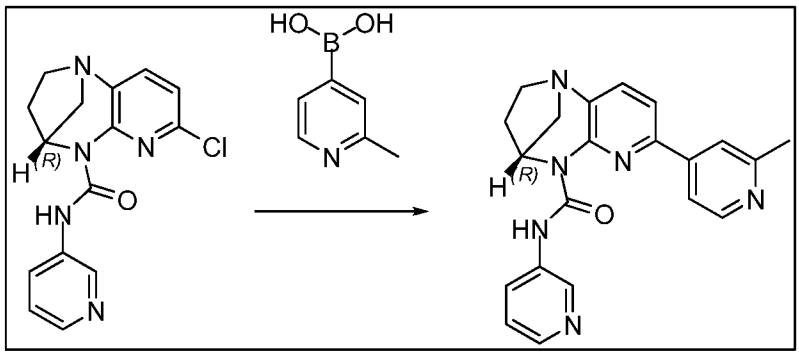


To a solution of (4*S*)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (200 mg, 0.655 mmol) in Tetrahydrofuran (20 mL) were added Triethylamine (0.548 mL, 3.93 mmol) and tri-phosgene (194 mg, 0.655 mmol) at RT and stirred for 30 min. Then propan-1-amine (77 mg, 1.310 mmol) was added and heated at 80 °C for 15 h. (TLC system: 5% MeOH in DCM R_f: 0.5). The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the residue was partitioned between water (25 mL) and EtOAc (70 mL). The organic layer was separated and dried over anhydrous sodium sulphate, filtered and filtrate was evaporated to get crude compound. The crude material was purified by flash column chromatography (100-200 silicagel, eluent: 3% methanol in dichloro methane) to afford the desired product (4*S*)-*N*-propyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carbox amide (130 mg, 0.322 mmol, 49.1 % yield) as an off white solid. LCMS (*m/z*): 391.07 $[M+H]^+$, Rt = 2.47 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 10.67 - 10.20 (m, 1 H), 8.04 (s, 1 H), 7.94 (d, *J*=7.67 Hz, 1 H), 7.69 - 7.65 (m, 1 H), 7.62 - 7.52 (m, 2 H), 7.27 (s, 1 H), 5.65 (dd, *J*=5.92, 3.29 Hz, 1 H), 3.41 (m, 2 H), 3.30 (m, 3 H), 2.95 (dd, *J*=11.84, 3.29 Hz, 1 H), 2.45 (m, 1 H), 2.09 (m, 1 H), 1.76- 1.74 (m, 2 H), 0.94 (t, *J*=7.45 Hz, 3 H).

Example 349

Synthesis of (4*R*)-7-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

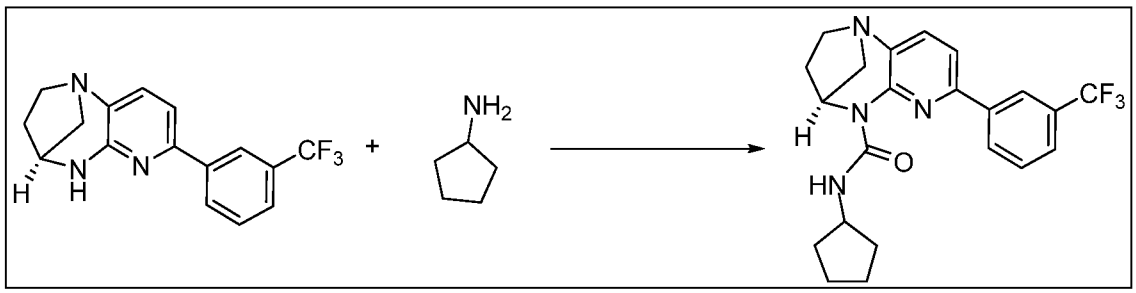


To a stirred and degassed solution of (4*R*)-7-chloro-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (3 g, 9.50 mmol) in 1,4-Dioxane (80 mL); Water (20 mL) were added (2-methylpyridin-4-yl)boronic acid (1.952 g, 14.25 mmol) and K_3PO_4 (6.05 g, 28.5 mmol) at room temperature. Then the reaction mixture was stirred for 15 min. and again degassed with Argon for 15 min. followed by x-phos (1.812 g, 3.80 mmol) and $Pd_2(dba)_3$ (1.740 g, 1.900 mmol) was added and stirred at 110 °C for 3 h. (TLC system: Neat EtOAc, R*f*: 0.2). Then the reaction mixture was allowed to cool to room temperature and poured in ice water(100 mL), extracted with EtOAc (2 x 300 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 material was purified by flash column chromatography (silica gel: 100-200 mesh, Eluent: 2% MeOH in DCM) to afford the desired product (4*R*)-7-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine -5(2*H*)-carboxamide (2 g, 5.37 mmol, 56.5 % yield) as an off white solid. LCMS (*m/z*): 373.07 $[M+H]^+$, R_t =1.14 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.07 (s, 1 H), 8.70 - 8.62 (m, 2 H), 8.32 (dd, *J*=4.71, 1.43 Hz, 1 H), 8.20 - 8.09 (m, 1 H), 7.65 (d, *J*=7.89 Hz, 1 H), 7.59 (s, 1 H), 7.50 (dd, *J*=5.26, 1.32 Hz, 1 H), 7.38 (d, *J*=7.89 Hz, 1 H), 7.30 - 7.23 (m, 1 H), 5.70 (dd, *J*=5.92, 3.29 Hz, 1 H), 3.34 - 3.16 (m, 3 H), 3.03 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.68 (s, 3 H), 2.35 (dddd, *J*=14.14, 9.92, 5.86, 4.06 Hz, 1 H), 2.15 - 2.05 (m, 1 H).

Example 350

Synthesis of (4*S*)-N-cyclopentyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide:



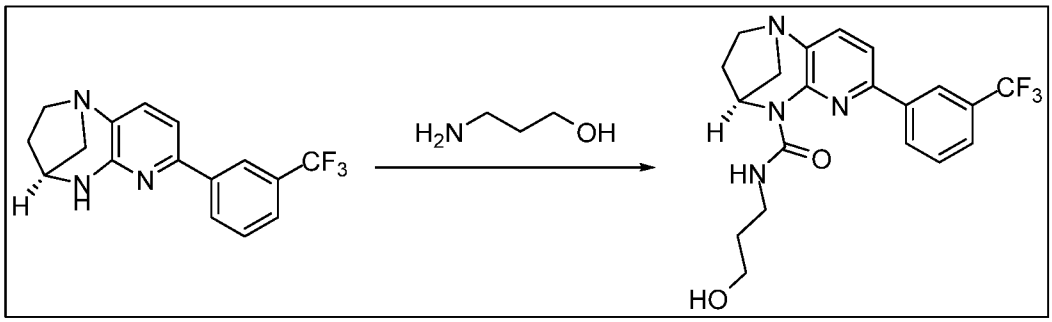
To a stirred solution of (4*S*)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (300.0 mg, 0.983 mmol) in THF (20 mL) at RT was added TEA (0.685 mL, 4.91 mmol), triphosgene (292 mg, 0.983 mmol) and stirred for 45 min. then added cyclopentanamine (0.291 mL, 2.95 mmol) and the reaction mixture was heated to 75 °C for 9 h. (TLC eluting system: 100% EtOAc; R_f-0.4; UV active). The reaction mixture was cooled to RT, solid was filtered and filtrate was washed with water (5 mL) and extracted into EtOAc (2x15 mL). Organic layer was separated, dried over anhydrous sodium sulphate, filtered and filtrate was evaporated to get crude compound. The crude was purified by chromatography (neutral alumina, eluent: 20-30% ethyl acetate in hexane) to afford (4*S*)-N-cyclopentyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (138.4 mg, 0.331 mmol, 33.7 % yield) as a pale yellow solid. LCMS (*m/z*): 417.24 $[M+H]^+$, R_t =2.66 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 10.37 (br d, *J*=6.14 Hz, 1 H), 8.02 (s, 1 H), 7.94 (d, *J*=7.89 Hz, 1 H), 7.70 - 7.65 (m, 1 H), 7.62 - 7.52 (m, 2 H), 7.23 (d, *J*=7.89 Hz, 1 H), 5.66 (dd, *J*=6.03, 3.18 Hz, 1 H), 4.23 (sxt, *J*=6.88 Hz, 1 H), 3.30 - 3.06 (m, 3 H), 2.94 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.26 (dddd, *J*=13.98, 9.98, 5.97, 4.06 Hz, 1 H), 2.10-1.99 (m, 3 H), 1.59 - 1.72 (m, 4 H), 1.56 - 1.44 (m, 2 H).

Example 351

GSK3493927A

Synthesis of (4*S*)-N-(3-hydroxypropyl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

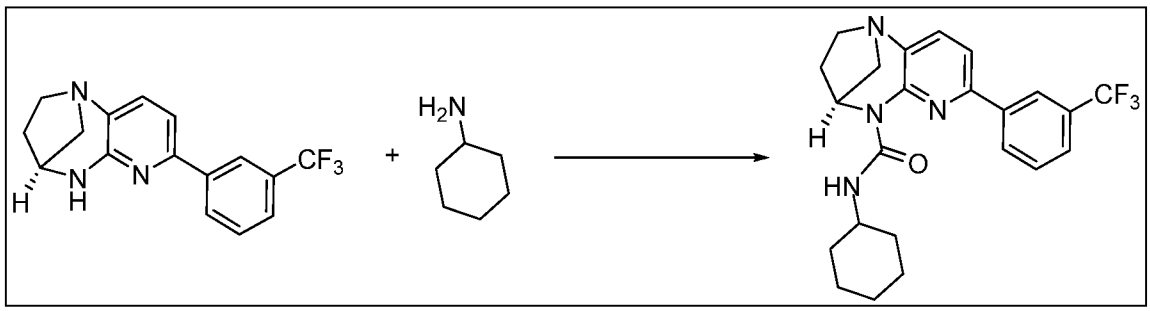


To a suspension of (4*S*)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (500 mg, 1.638 mmol) in Tetrahydrofuran (20 mL) were added TEA (1.370 mL, 9.83 mmol) and triphosgene (486 mg, 1.638 mmol) at 0 °C under Nitrogen atmosphere and the reaction mixture was stirred at RT for 1 h. To this resulted reaction mixture was added a solution of 3-aminopropan-1-ol (246 mg, 3.28 mmol) in THF (5mL) at RT. After this addition the reaction mixture was stirred at 70 °C for 16 h. (TLC: 5% MeOH-DCM, R_f value: 0.5). The reaction mixture was cooled to RT and diluted with water (50 mL), extracted with EtOAc (3x30 mL). The combined organic layer was washed with brine solution (2x30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to obtain crude compound. The crude product was purified by flash column chromatography (silica gel: 100-200 Mesh, Eluent: 2% MeOH-DCM) to afford the desired product (4*S*)-N-(3-hydroxypropyl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (180 mg, 0.437 mmol, 26.7 % yield) as an off white solid. LCMS (*m/z*): 407.09 $[M+H]^+$, R_t = 1.95 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.38 - 10.13 (m, 1 H), 8.23-8.13 (m, 2 H), 7.88 - 7.68 (m, 2 H), 7.66 - 7.54 (m, 2 H), 5.41 (dd, *J*=5.81, 2.96 Hz, 1 H), 4.43 (t, *J*=5.15 Hz, 1 H), 3.51 - 3.31 (m, 4 H), 3.20 - 3.02 (m, 2 H), 2.99 - 2.87 (m, 2 H), 2.18 (dddd, *J*=13.73, 9.95, 5.92, 3.73 Hz, 1 H), 1.82 (dt, *J*=13.98, 7.15 Hz, 1 H), 1.69 (quin, *J*=6.69 Hz, 2 H).

Example 352

Synthesis of (4*S*)-N-cyclohexyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide:

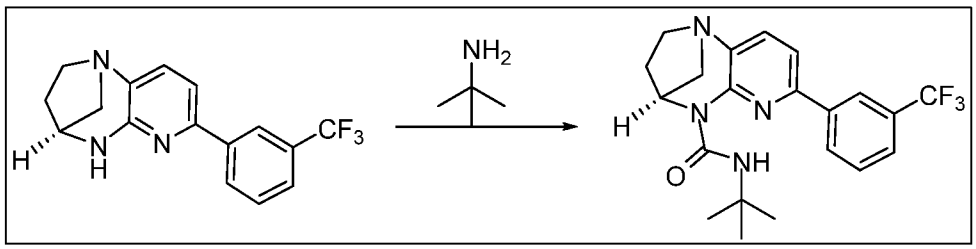


To a stirred solution of (4*S*)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-b][1,4]diazepine (300.0 mg, 0.983 mmol) in THF (20.0 mL) at RT was added TEA (0.685 mL, 4.91 mmol), triphosgene (292 mg, 0.983 mmol) and stirred for 45 min. then added cyclohexanamine (0.339 mL, 2.95 mmol) and the reaction mixture was heated to 75 °C for 6 h. (TLC eluting system: 100% EtOAc; R_f-0.4; UV active). The reaction mixture was cooled to RT, solid was filtered and filtrate was washed with water (5 mL) and extracted into EtOAc (2 x 10 mL). Organic layer was separated, dried over anhydrous sodium sulphate, filtered and filtrate was evaporated to get crude compound. The crude was purified by chromatography (neutral alumina, eluent: 20-30% ethyl acetate in hexane) to afford (4*S*)-N-cyclohexyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (221.9 mg, 0.515 mmol, 52.4 % yield) as a pale yellow solid. LCMS (*m/z*): 431.25 $[M+H]^+$, R_t =2.82 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 10.32 (br d, *J*=7.23 Hz, 1 H), 8.05 (s, 1 H), 7.94 (d, *J*=7.89 Hz, 1 H), 7.70 - 7.66 (m, 1 H), 7.62 - 7.52 (m, 2 H), 7.28 - 7.25 (m, 1 H), 5.65 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.80-3.72 (m, 1 H), 3.30 - 3.06 (m, 3 H), 2.94 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.40- 2.26 (m, 1 H), 2.09 - 1.98 (m, 3 H), 1.77 - 1.62 (m, 3 H), 1.44 - 1.31 (m, 3 H), 1.29 - 1.10 (m, 2 H).

Example 353

Synthesis of (4*S*)-N-(tert-butyl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methano pyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

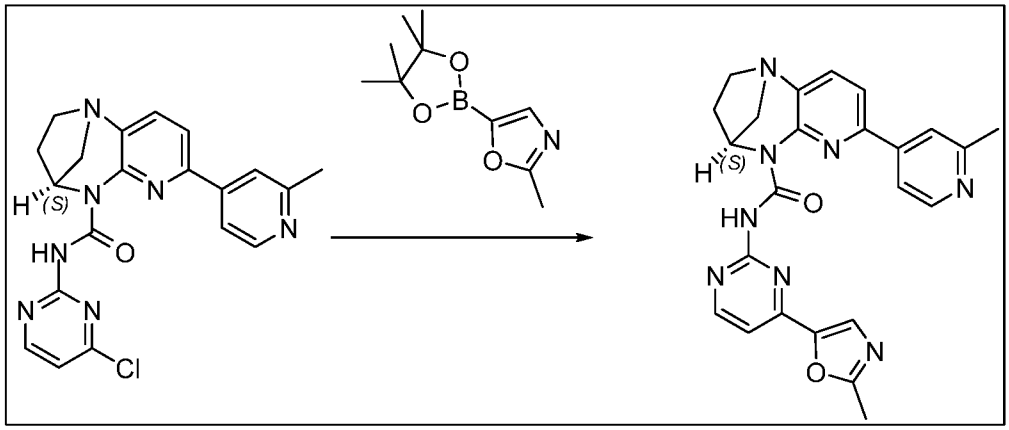


To a solution of (4*S*)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (0.4 g, 1.310 mmol) in Tetrahydrofuran (10 mL) was added triethylamine (1.096 mL, 7.86 mmol), triphosgene (0.389 g, 1.310 mmol) at 0 ºC and stirred the reaction mixture at room temperature for 1 h. and 2-methylpropan-2-amine (0.275 mL, 2.62 mmol) was added, stirred the reaction mixture at 80 °C for 16 h. (TLC System: Neat EtOAc. R_f value: 0.5) and the reaction mixture was cooled to RT, extracted with ethylacetate (2x30 mL). The combined organic layer was washed with brine solution (2x20 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated to get the crude compound. The crude product purified by flash column chromatography (silica gel:100-200 mesh, Eluent: 5% MeOH/CH_2Cl_2) to afford the desired product (4*S*)-N-(tert-butyl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (180 mg, 0.436 mmol, 33.3 % yield) as a yellow solid. LCMS (*m/z*): 405.11 $[M+H]^+$, *Rt* = 2.67 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.17 (s, 1 H), 8.08 - 8.16 (m, 2 H), 7.70 - 7.83 (m, 2 H), 7.60 (d, *J*=7.89 Hz, 1 H), 7.50 (d, *J*=7.89 Hz, 1 H), 5.41 (dd, *J*=5.81, 2.96 Hz, 1 H), 3.01 - 3.16 (m, 2 H), 2.86 - 2.97 (m, 2 H), 2.12 - 2.21 (m, 1 H), 1.75 - 1.85 (m, 1 H), 1.28 (s, 9 H).

Example 354

Synthesis of (4*S*)-*N*-(4-(2-methyloxazol-5-yl)pyrimidin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

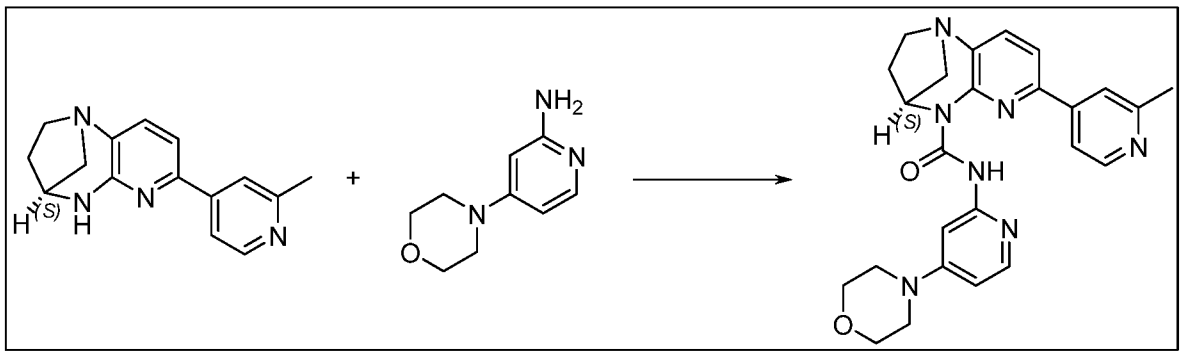


To a degassed solution of (4*S*)-*N*-(4-chloropyrimidin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (700 mg, 1.716 mmol), in 1,4-Dioxane (25 mL) and Water (5.00 mL) were added $PdCl_2(dppf)$-CH_2Cl_2 adduct (70.1 mg, 0.086 mmol), K_3PO_4 (1093 mg, 5.15 mmol) and 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (466 mg, 2.231 mmol) and stirred at 70 °C for 3 h. (TLC system: 10% methanol in DCM, Rf value: 0.4). To the reaction mixture was added water (10.0 mL), and extracted with ethylacetate (3 x 30 mL). Combined organic layer was separated, dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude product. Crude compound was purified by preparative HPLC (Column: KROMASIL PHENYL (150*25) mm*10u; MP-A: 10mM Ammonium Bicarbonate (aq), MP-B: Acetonitrile; Method: 00/30,13.5/30,14/100,18/100,18.5/30; Flow: 25 ml/min; Temperature: Ambient; Solubility: Acetonitrile+THF+water) to afford (4*S*)-*N*-(4-(2-methyloxazol-5-yl)pyrimidin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (120 mg, 0.258 mmol, 15.04 % yield) as a pale yellow solid. LCMS (*m/z*): 455.19$[M+H]^+$, *Rt* = 1.35 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm: 13.87 (s, 1 H), 8.69 (d, *J*=5.04 Hz, 1 H), 8.63 (d, *J*=5.26 Hz, 1 H), 7.89 (s, 1 H), 7.81 - 7.76 (m, 1 H), 7.71 (s, 1 H), 7.64 (d, *J*=7.89 Hz, 1 H), 7.48 (d, *J*=7.89 Hz, 1 H), 7.23 (d, *J*=5.04 Hz, 1 H), 5.79 (dd, *J*=5.92, 3.07 Hz, 1 H), 3.33 - 3.13 (m, 3 H), 3.02 (dd, *J*=12.17, 3.18 Hz, 1 H), 2.65 (s, 3 H), 2.59 (s, 3 H), 2.39 - 2.30 (m, 1 H), 2.11 (dt, *J*=14.47, 7.45 Hz, 1 H).

Example 355

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-N-(4-morpholinopyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

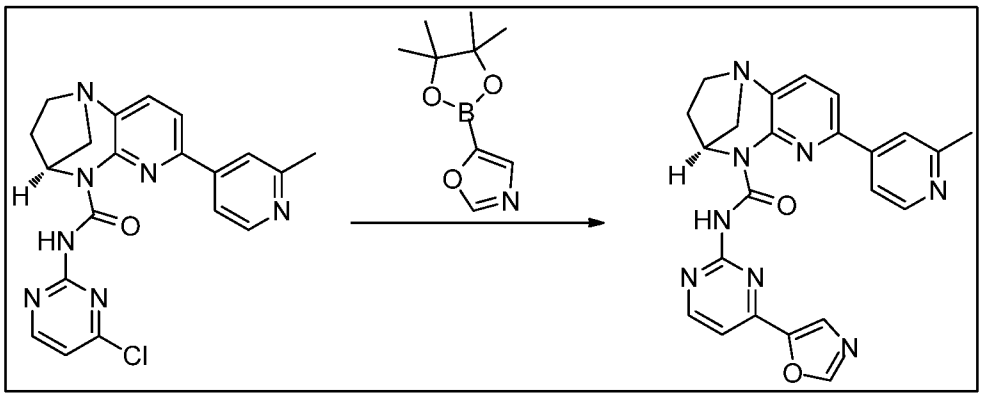


To a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 1.189 mmol) in Tetrahydrofuran (30 mL) were added triethylamine (0.829 mL, 5.94 mmol) and triphosgene (353 mg, 1.189 mmol) under nitrogen atmosphere at room temperature and stirred at rt for 1 h. Then 4-morpholinopyridin-2-amine (320 mg, 1.783 mmol) was added to the reaction mixture and stirred at 70 °C for 16 h. (TLC System: 10% MeOH in DCM, R_f-0.4; UV active). The reaction mixture was cooled to rt and partitioned between water (30 mL) and EtOAc (3X30 mL). The combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude. The crude compound was purified by column chromatography (Silica gel: Neutral alumina, Eluent: 20% EtOAc in Pet ether) to afford the desired product (4*S*)-7-(2-methylpyridin-4-yl)-N-(4-morpholinopyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (145 mg, 0.312 mmol, 26.3 % yield) as an off white solid. LCMS (*m/z*): 458.29 $[M+H]^+$, R_t = 1.23 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.40 (s, 1 H), 8.61 (d, *J* = 5.2 Hz, 1 H), 8.24 (d, *J* = 1.8 Hz, 1 H), 8.09 (d, *J* = 6.0 Hz, 1 H), 7.79 (d, *J* = 2.4 Hz, 1 H), 7.75 - 7.68 (m, 1 H), 7.61 (d, *J* = 8.0 Hz, 1 H), 7.48 (d, *J* = 7.9 Hz, 1 H), 6.45 (dd, *J* = 6.0, 2.5 Hz, 1 H), 5.68 (dd, *J* = 6.0, 3.2 Hz, 1 H), 3.88 - 3.80 (m, 4 H), 3.40 - 3.32 (m, 4 H), 3.32 - 3.20 (m, 2 H), 3.24 - 3.13 (m, 1 H), 3.01 (dd, *J* = 12.1, 3.3 Hz, 1 H), 2.73 (s, 3 H), 2.40 - 2.26 (m, 1 H), 2.08 (dt, *J* = 14.9, 7.7 Hz, 1 H).

Example 356

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-N-(4-(oxazol-5-yl)pyrimidin-2-yl)-3,4-dihydro -1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

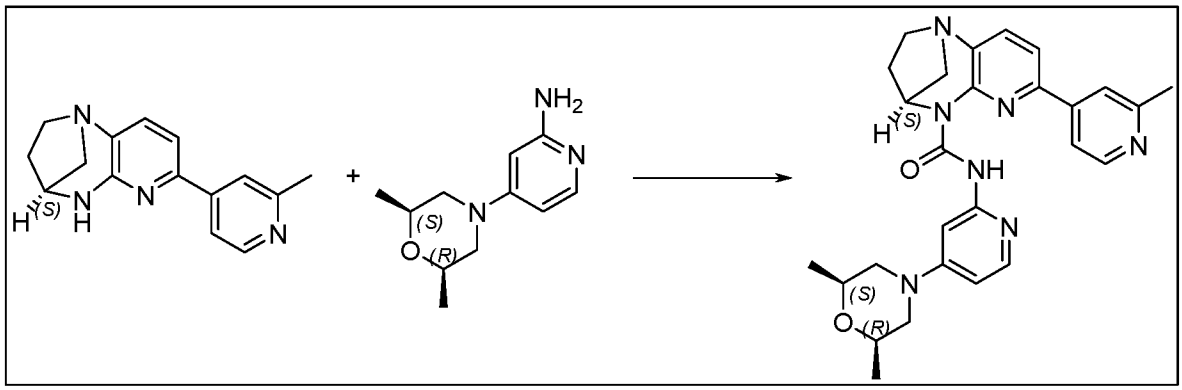


To a degassed solution of (4*S*)-N-(4-chloropyrimidin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (600 mg, 1.471 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (430 mg, 2.207 mmol) and K_3PO_4 (937 mg, 4.41 mmol) in 1,4-Dioxane (30.00 mL), Water (7.50 mL) was added $PdCl_2(dppf)$-CH_2Cl_2 adduct (120 mg, 0.147 mmol) and degassed again for 5 min. Then the reaction mixture was stirred at 80 °C for 15 h. (TLC system: 10% Methanol in DCM. R_f value: 0.2). The reaction was allowed to cool to RT and evaporated the organic solvent, diluted with water (50 mL) and extracted with Ethyl acetate (3x 50 ml). The combined organic layer was washed with saturated brine solution and dried over anhydrous sodium sulphate, filtered and evaporated in vacuum to give the crude product. The crude compound was purified by flash column chromatography (Neutral alumina, Eluent: 2% methanol in Ethyl acetate) to afford (4*S*)-7-(2-methylpyridin-4-yl)-N-(4-(oxazol-5-yl)pyrimidin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (320 mg, 0.710 mmol, 48.3 % yield) as an off- white solid. LCMS (*m/z*): 441.23 $[M+H]^+$, *Rt* = 1.30 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.91 (s, 1 H), 8.74 (dd, *J* = 5.1, 0.6 Hz, 1 H), 8.64 (d, *J* = 5.2 Hz, 1 H), 8.05 (d, *J* = 0.5 Hz, 1 H), 7.90 - 7.76 (m, 2 H), 7.65 (dd, *J* = 8.0, 0.6 Hz, 1 H), 7.48 (dd, *J* = 8.0, 0.6 Hz, 1 H), 7.33 - 7.24 (m, 2 H), 5.79 (dd, *J* = 6.0, 3.2 Hz, 1 H), 3.35 - 3.12 (m, 3 H), 3.03 (dd, *J* = 12.1, 3.3 Hz, 1 H), 2.65 (s, 3 H), 2.35 (dddd, *J* = 14.1, 9.9, 6.0, 4.0 Hz, 1 H), 2.11 (dt, *J* = 14.6, 7.4 Hz, 1 H).

Example 357

Synthesis of (4*S*)-N-(4-((2*S*,6*R*)-2,6-dimethylmorpholino)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



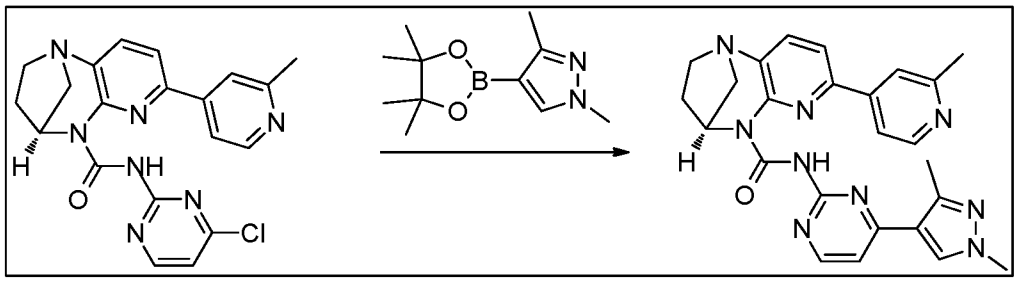
To a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 1.189 mmol) in Tetrahydrofuran (THF) (30 mL) were added triethylamine (0.829 mL, 5.94 mmol) and triphosgene (353 mg, 1.189 mmol) under nitrogen at room temperature and stirred at rt for 4 h. Then 4-((2*S*,6*R*)-2,6-dimethylmorpholino)pyridin-2-amine (493 mg, 2.378 mmol) was added to the reaction mixture and the resulted reaction mixture was stirred at 70 °C for 16 h. (TLC System: 10% MeOH in DCM, R_f-0.4; UV active). The reaction mixture was cooled to RT, partitioned between water (30 mL) and EtOAc (3X30 mL). The combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to give crude compound. The crude compound was purified by flash column chromatography (Silica gel: Neutral alumina, Eluent: 25% EtOAc in pet ether) to afford the desired product (4*S*)-N-(4-((2*S*,6*R*)-2,6-dimethylmorpholino)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methano pyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (200 mg, 0.410 mmol, 34.5 % yield) as an off white solid. LCMS (*m/z*): 486.33 $[M+H]^+$, R_t = 1.37 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.40 (s, 1 H), 8.60 (d, *J* = 5.3 Hz, 1 H), 8.25 (d, *J* = 1.8 Hz, 1 H), 8.07 (d, *J* = 6.0 Hz, 1 H), 7.78 - 7.68 (m, 2 H), 7.61 (d, *J* = 7.9 Hz, 1 H), 7.48 (d, *J* = 8.0 Hz, 1 H), 6.45 (dd, *J* = 6.0, 2.5 Hz, 1 H), 5.69 (dd, *J* = 6.0, 3.2 Hz, 1 H), 3.81 - 3.64 (m, 4 H), 3.32 - 3.12 (m, 3 H), 3.01 (dd, *J* = 12.1, 3.3 Hz, 1 H), 2.73 (s, 3 H), 2.61 - 2.51

(m, 2 H), 2.34 (dddd, *J* = 13.9, 10.0, 6.0, 4.0 Hz, 1 H), 2.09 (dt, *J* = 14.3, 7.8 Hz, 1 H), 1.28 (d, *J* = 6.2 Hz, 6 H).

Example 358

Synthesis of (4*S*)-N-(4-(1,3-dimethyl-1*H*-pyrazol-4-yl)pyrimidin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



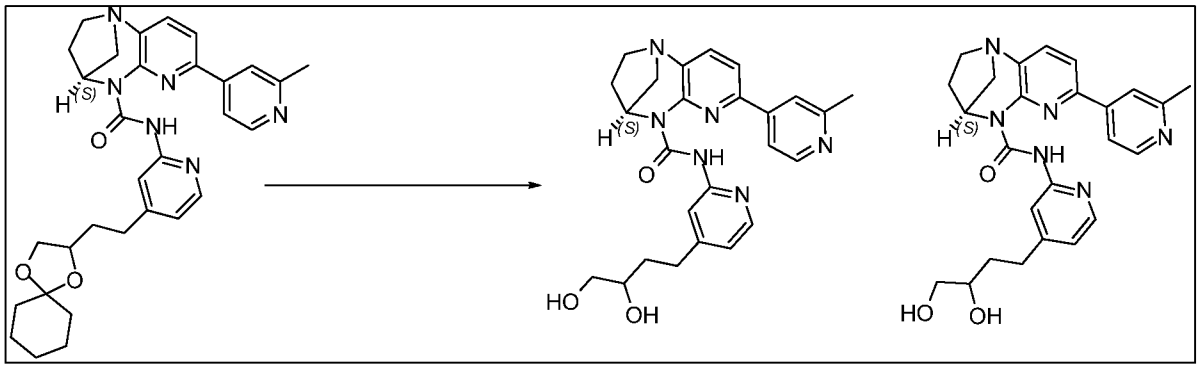
To a degassed solution of (4*S*)-N-(4-chloropyrimidin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (200 mg, 0.490 mmol), 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (109 mg, 0.490 mmol) and K_3PO_4 (104 mg, 0.490 mmol) in 1,4-Dioxane (30.00 mL),Water (7.50 mL) was added $PdCl_2$(dppf)-CH_2Cl_2 adduct (400 mg, 0.490 mmol) and again degassed for 5 min. Then the reaction mixture was stirred at 80 °C for 15 h. (TLC system: 10% Methanol in DCM. R_f value: 0.2). The reaction was cooled to RT and evaporated the organic solvent, diluted with water (50 mL) and extracted with Ethyl acetate (3x 50 ml). The combined organic layer was washed with saturated brine solution and dried over anhydrous sodium sulphate and evaporated in vacuo to obtain the crude product. The crude compound was purified by flash column chromatography (Neutral alumina, Eluent: 4% methanol in Ethyl acetate) to afford the desired product (4*S*)-N-(4-(1,3-dimethyl-1H-pyrazol-4-yl)pyrimidin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (120 mg, 0.256 mmol, 52.2 % yield) as an off white solid. LCMS (*m/z*): 468.30 $[M+H]^+$, R_t = 1.36 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.68 (s, 1 H), 8.58 (dd, *J* = 6.6, 5.3 Hz, 1 H), 7.95 (s, 1 H), 7.85 (s, 1 H), 7.79 (s, 1 H), 7.65 (d, *J* = 8.0 Hz, 1 H), 7.46 (d, *J* = 7.9 Hz, 1 H), 7.26 (s, 1 H), 7.09 (d, *J* = 5.2 Hz, 1 H), 5.79 (dd, *J* = 6.0, 3.1 Hz, 1 H), 3.88 (s, 3 H), 3.32 - 3.12 (m, 3 H), 3.02 (dd, *J* = 12.0, 3.3 Hz, 1 H), 2.64 (s, 3 H), 2.54 (s, 3 H), 2.35 (ddt, *J* = 14.3, 10.0, 4.7 Hz, 1 H), 2.11 (dt, *J* = 14.8, 7.8 Hz, 1 H).

Example 359, 360

Peak-I: Synthesis of (4*S*)-N-(4-(3, 4-dihydroxybutyl) pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-*b*] [1, 4] diazepine-5(2*H*)-carboxamide

Peak-II: Synthesis of (4*S*)-N-(4-(3, 4-dihydroxybutyl) pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-*b*] [1, 4] diazepine-5(2*H*)-carboxamide



To a stirred solution of (4*S*)-N-(4-(2-(1,4-dioxaspiro[4.5]decan-2-yl)ethyl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (850 mg, 1.572 mmol) in Methanol (10 mL) was added HCl (2 mL, 24.00 mmol) at room temperature. The resulting reaction mixture was stirred at room temperature for 6 h. (TLC system: 10% MeOH in DCM, R_f: 0.5) and evaporated the solvent, obtained residue was neutralized with $NaHCO_3$ solution and extracted with DCM (3 x 30 mL). The combined organic layer was washed with brine solution (20 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 (silica gel: 100-200 mesh, Eluent: 6% MeOH in DCM) to afford racemic compound (400 mg). The racemic compound was purified by Chiral SFC (Conditions: Column/dimensions: LuxAmylose-2(250 X30)mm, 5µ, % CO2 solvent: 50.0%, % CO solvent: 50.0% (100% IPA), Total Flow: 90.0 g/min, Back Pressure: 100.0 bar, UV: 218 nm, Stack time: 7.5 min, Load/inj: 20.0 mg, *Solubility: IPA+DCM*, Instrument details: Make/Model: Thar SFC-200 (NEW-2)) peak-I: (4*S*)-N-(4-(3,4-dihydroxybutyl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (163 mg, 0.353 mmol, 22.48 % yield) as an off white solid. LCMS(*m/z*):

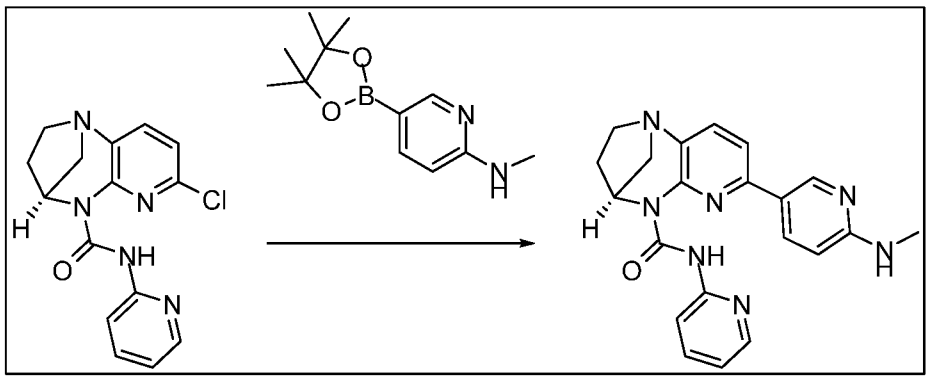
461.35[M+H]$^+$, *Rt* = 1.25 min. and Peak-II: (4*S*)-N-(4-(3,4-dihydroxybutyl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (67 mg, 0.142 mmol, 9.03 % yield) as a yellow sticky solid. LCMS (*m/z*): 461.31[M+H]$^+$, *Rt* = 1.25 min.

Peak-I:^{1}H NMR (400 MHz, $CDCl_3$): δ 13.52 (s, 1 H), 8.61 (d, *J* = 5.3 Hz, 1 H), 8.26 (dd, *J* = 5.0, 0.8 Hz, 1 H), 8.20 (d, *J* = 1.8 Hz, 1 H), 8.13 (s, 1 H), 7.71 (dd, *J* = 5.4, 1.8 Hz, 1 H), 7.62 (d, *J* = 8.0 Hz, 1 H), 7.48 (d, *J* = 8.0 Hz, 1 H), 6.89 (dd, *J* = 5.1, 1.5 Hz, 1 H), 5.69 (dd, *J* = 6.0, 3.2 Hz, 1 H), 3.81 - 3.64 (m, 2 H), 3.49 (dd, *J* = 11.0, 7.4 Hz, 1 H), 3.35 - 3.13 (m, 3 H), 3.02 (dd, *J* = 12.0, 3.3 Hz, 1 H), 2.92 - 2.74 (m, 2 H), 2.73 (s, 3 H), 2.34 (ddt, *J* = 14.5, 10.0, 5.1 Hz, 1 H), 2.09 (dt, *J* = 14.5, 7.4 Hz, 1 H), 1.88 - 1.77 (m, 2 H).

Peak-II:^{1}H NMR (400 MHz, $CDCl_3$): δ 13.52 (s, 1 H), 8.61 (d, *J* = 5.3 Hz, 1 H), 8.26 (dd, *J* = 5.0, 0.8 Hz, 1 H), 8.20 (d, *J* = 1.8 Hz, 1 H), 8.13 (s, 1 H), 7.71 (dd, *J* = 5.4, 1.8 Hz, 1 H), 7.62 (d, *J* = 8.0 Hz, 1 H), 7.48 (d, *J* = 8.0 Hz, 1 H), 6.89 (dd, *J* = 5.1, 1.5 Hz, 1 H), 5.69 (dd, *J* = 6.0, 3.2 Hz, 1 H), 3.81 - 3.64 (m, 2 H), 3.49 (dd, *J* = 11.0, 7.4 Hz, 1 H), 3.35 - 3.13 (m, 3 H), 3.02 (dd, *J* = 12.0, 3.3 Hz, 1 H), 2.92 - 2.74 (m, 2 H), 2.73 (s, 3 H), 2.34 (ddt, *J* = 14.5, 10.0, 5.1 Hz, 1 H), 2.09 (dt, *J* = 14.5, 7.4 Hz, 1 H), 1.88 - 1.77 (m, 2 H).

Example 361

Synthesis of (4*S*)-7-(6-(methylamino) pyridin-3-yl)-N-(pyridin-2-yl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-*b*] [1, 4] diazepine-5(2*H*)-carboxamide



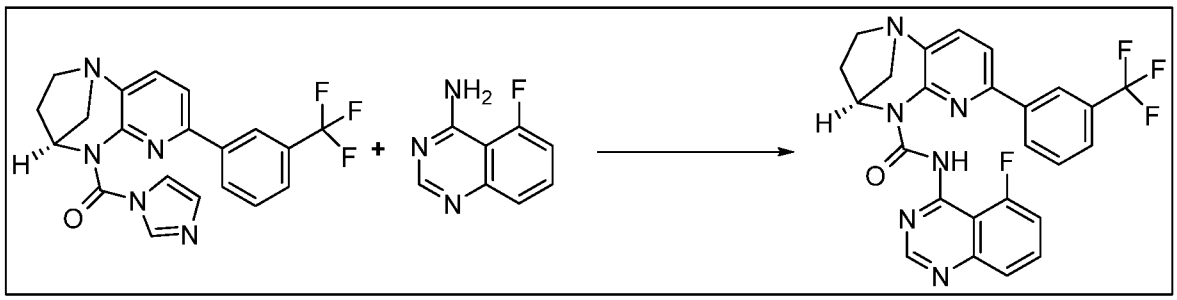
To a stirred solution of (4*S*)-7-chloro-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (3 g, 9.50 mmol) in 1,4-Dioxane (70 mL) and Water (24 mL) were added N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (2.447 g, 10.45 mmol) and K_3PO_4 (6.05 g, 28.5 mmol) and degassed for 20 min. Then $Pd_2(dba)_3$ (0.435 g, 0.475 mmol) and X-phos (0.453 g,

0.950 mmol) were added to the reaction mixture and again degassed for another 10 min. The reaction mixture was stirred at 100 °C for 16 h. (TLC eluent: Neat Ethyl acetate: R_f-0.4; UV active). Reaction mixture was cooled to room temp and diluted with water, extracted with ethyl acetate (2X70 mL), combined organic layer was washed with brine solution (50 mL) and dried over anhydrous sodium sulphate, filtered and concentrated to get crude compound. The crude product was purified by flash column chromatography (using 100-200 silica gel, compound eluted at 70% ethyl acetate in n-hexane) to afford the desired product (4*S*)-7-(6-(methylamino)pyridin-3-yl)-N-(pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (1.47 g, 3.78 mmol, 39.8 % yield) as a white solid. LCMS (*m/z*): 388.13 $[M+H]^+$, R_t = 1.38 min

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.69 (s, 1 H), 8.75 (d, *J*=2.19 Hz, 1 H), 8.52 (dd, *J*=8.77, 2.63 Hz, 1 H), 8.43 - 8.29 (m, 1 H), 8.29 - 8.06 (m, 1 H), 7.68 (t, *J*=7.84 Hz, 1 H), 7.52 (d, *J*=7.89 Hz, 1 H), 7.33 - 7.19 (m, 1 H), 6.97 (ddd, *J*=7.23, 4.82, 0.88 Hz, 1 H), 6.55 (d, *J*=8.99 Hz, 1 H), 5.68 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.77 (d, *J*=4.60 Hz, 1 H), 3.33 - 3.08 (m, 3 H), 3.06 - 2.94 (m, 4 H), 2.31 (dddd, *J*=14.03, 9.92, 5.97, 3.84 Hz, 1 H), 2.17 - 1.93 (m, 1 H).

Example 362

Synthesis of (4*S*)-N-(5-fluoroquinazolin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide:



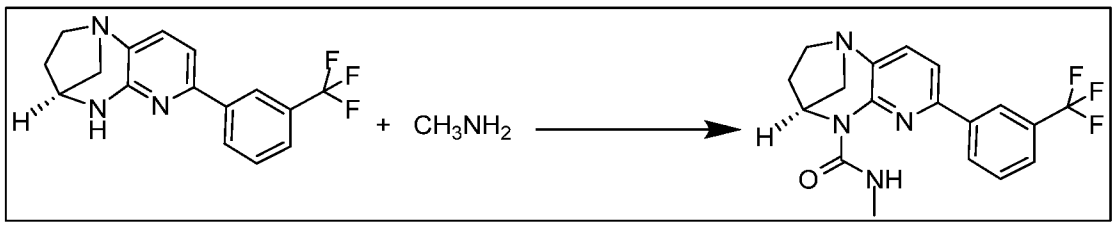
To a stirred solution of 5-fluoroquinazolin-4-amine (250 mg, 1.532 mmol) in THF (10 mL) at 0 °C was added NaH (201 mg, 4.60 mmol) and stirred for 10 min. then added (1H-imidazol-1-yl)((4S)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepin-5(2H)-yl)methanone (612 mg, 1.532 mmol) and the reaction was stirred at 60 °C for 12 h.(TLC eluting system: 10% MeOH in EtOAc; R_f-0.3; UV active). The reaction mixture was cooled to RT, quenched with water (10 mL) and extracted into

EtOAc (25 mL). Organic layer was separated and dried over anhydrous sodiumsulphate, filtered and filtrate was evaporated to get crude compound. The crude was purified by chromatography (GRACE using C-18 reserval column, Mobile phase A: 0.1% Formic Acid in water; B: MeOH, eluent 65% B in A). Combined fractions were concentrated basified with saturated $NaHCO_3$ solution. The aqueous layer was extracted with DCM and separated DCM layer was dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to afford (4*S*)-N-(5-fluoroquinazolin-4-yl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (190 mg, 0.380 mmol, 24.77 % yield) as a white solid. LCMS (*m/z*): 495.08 $[M+H]^+$, R_t = 2.19 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.86 (br d, *J*=4.60 Hz, 1 H), 9.13 (s, 1 H), 7.95 (s, 1 H), 7.76 - 7.88 (m, 2 H), 7.68 - 7.75 (m, 1 H), 7.66 (d, *J*=7.89 Hz, 1 H), 7.60 (d, *J*=7.89 Hz, 1 H), 7.32 - 7.42 (m, 2 H), 6.75 - 6.84 (m, 1 H), 5.78 (dd, *J*=5.92, 3.29 Hz, 1 H), 3.17 - 3.38 (m, 3 H), 3.05 (dd, *J*=12.28, 3.29 Hz, 1 H), 2.31 - 2.43 (m, 1 H), 2.13 - 2.24 (m, 1 H).

Example 363

Synthesis of (4*S*)-N-methyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



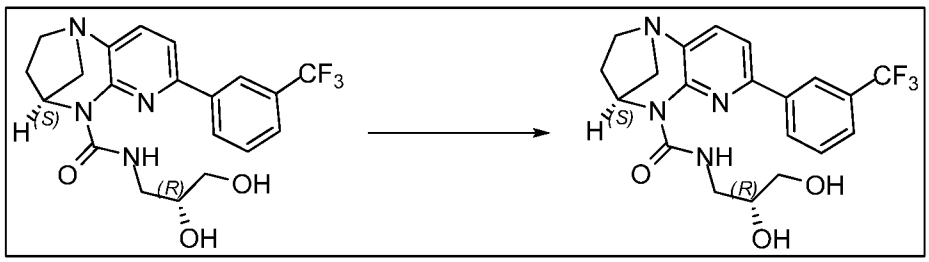
To a stirred solution of (4*S*)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (500 mg, 1.638 mmol) in THF (25 mL) at RT was added triethylamine (1.370 mL, 9.83 mmol) followed by triphosgene (486 mg, 1.638 mmol) and stirred for 1 h. then added 2M methanamine in THF (2.457 mL, 4.91 mmol,) and the reaction was heated at 65 °C for 16 h. (TLC eluent:50% EtOAc in Hexane: R_f-0.3; UV active). The reaction mixture was cooled to RT, concentrated *in vacuo* and the residue was partitioned between water (30 mL) and EtOAc (2x35 mL). Organic layer was separated and dried over anhydrous sodiumsulphate, filtered and filtrate was evaporated to get crude compound. The crude product was purified by flash column chromatography (neutral alumina, eluent: 50% ethyl acetate in hexane) to afford (4*S*)-N-methyl-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-

carboxamide (161 mg, 0.444 mmol, 27.1 % yield) as a white solid. LCMS (*m/z*): 362.99 $[M+H]^+$, R_t = 2.19 min

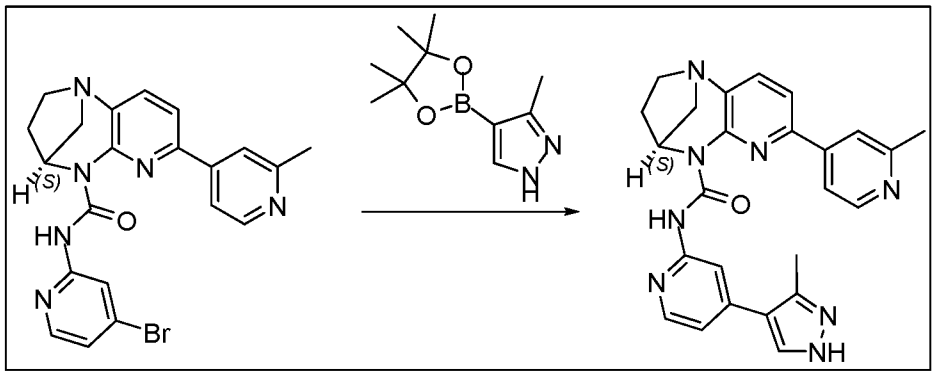
^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 10.38 (br d, *J*=3.51 Hz, 1 H), 8.06 (s, 1 H), 7.94 (d, *J*=7.67 Hz, 1 H), 7.70 - 7.66 (m, 1 H), 7.63 - 7.58 (m, 1 H), 7.55 (d, *J*=7.89 Hz, 1 H), 7.28 (d, *J*=7.89 Hz, 1 H), 5.65 (dd, *J*=6.03, 3.18 Hz, 1 H), 3.28 - 3.07 (m, 3 H), 3.01 - 2.92 (m, 4 H), 2.27 (dddd, *J*=13.98, 9.92, 6.03, 4.06 Hz, 1 H), 2.08 - 1.97 (m, 1 H).

Example 364

Synthesis of (4*S*)-N-((*R*)-2,3-dihydroxypropyl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide, Hydrochloride



Synthesis of (4*S*)-N-(4-(3-methyl-1H-pyrazol-4-yl) pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-*b*] [1, 4] diazepine-5(2*H*)-carboxamide



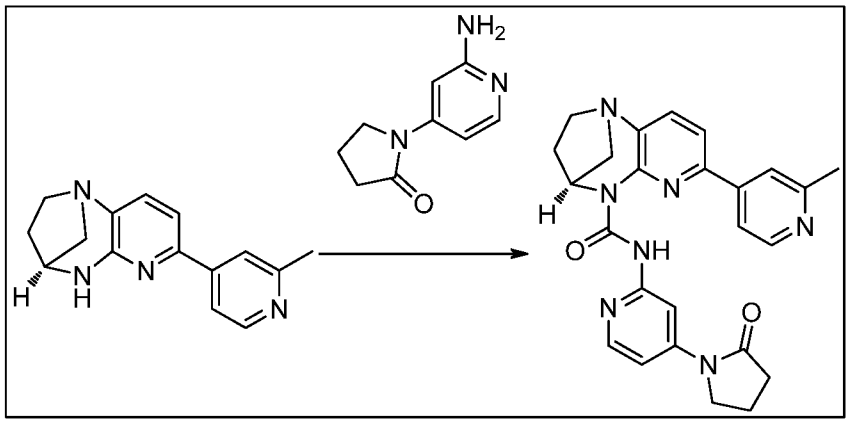
To a stirred solution of (4*S*)-N-(4-bromopyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (300 mg, 0.665 mmol) in 1,4-Dioxane (40 mL) and Water (10 mL) were added 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (207 mg, 0.997 mmol) and K_3PO_4 (423 mg, 1.994 mmol) at RT and degassed for 15 min. Then $Pd_2(dba)_3$ (60.9 mg, 0.066 mmol) and x-phos (63.4 mg, 0.133 mmol) were added to the reaction mixture again degassed for 10 min, then the reaction mixture was stirred at 80 °C for 16 h. (TLC System: 10% methanol in DCM, R_f-0.2; UV active). The reaction mixture was cooled to RT and

partitioned between water and ethyl acetate (3x30 mL). The combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude compound. The crude compound was purified by flash column chromatography (using neutral alumina and eluted at 20% ethyl acetate in Pet ether) to afford the desired compound (4*S*)-N-(4-(3-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (139 mg, 0.304 mmol, 45.7 % yield) as a pale brown solid. LCMS (*m/z*): 453.21 $[M+H]^+$, R_t = 1.36 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.59 (s, 1 H), 10.35 (br s, 1 H), 8.63 (d, *J*=5.26 Hz, 1 H), 8.44 - 8.16 (m, 3 H), 7.87 (s, 1 H), 7.73 (d, *J*=3.95 Hz, 1 H), 7.63 (d, *J*=8.11 Hz, 1 H), 7.49 (d, *J*=7.89 Hz, 1 H), 7.10 (dd, *J*=5.15, 1.43 Hz, 1 H), 5.72 (dd, *J*=5.70, 3.07 Hz, 1 H), 3.36 - 3.16 (m, 3 H), 3.02 (dd, *J*=12.06, 3.07 Hz, 1 H), 2.76 (s, 3 H), 2.59 (s, 3 H), 2.42 - 2.29 (m, 1 H), 2.10 (dt, *J*=14.03, 7.02 Hz, 1 H).

Example 365

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-N-(4-(2-oxopyrrolidin-1-yl) pyridin-2-yl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-*b*] [1, 4] diazepine-5(2*H*)-carboxamide



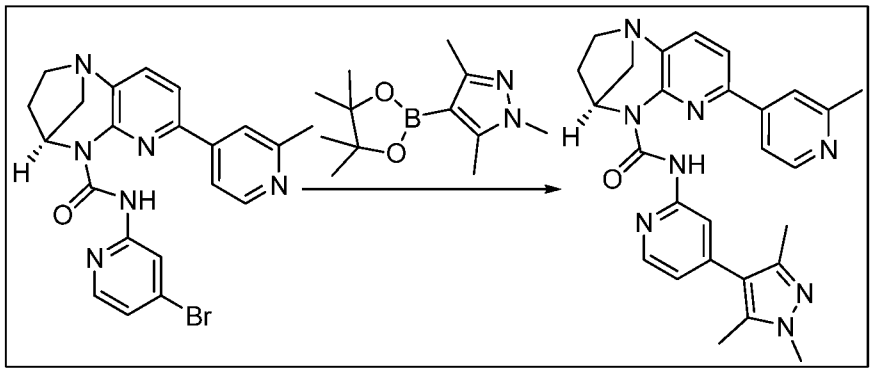
To a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2, 3, 4,5-tetrahydro-1,4-methanopyrido [2,3-*b*][1,4]diazepine (400 mg, 1.585 mmol) in THF (40 mL) were added triethylamine (1.105 mL, 7.93 mmol) and triphosgene (470 mg, 1.585 mmol) under nitrogen atmosphere and stirred at RT for 1 h. To this 1-(2-aminopyridin-4-yl)pyrrolidin-2-one (562 mg, 3.17 mmol) was added and stirred at 70 °C for 16 h. (TLC eluent: 10% MeOH in DCM, R_f:0.3, UV active). The reaction mixture was cooled to RT, partitioned between water and ethyl acetate (3X40 mL). The combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and was evaporated to get crude compound. The crude compound was purified by flash column chromatography (using neutral alumina

and eluted at 25% ethyl acetate in pet ether) to afford the desired compound (4*S*)-7-(2-methylpyridin-4-yl)-N-(4-(2-oxopyrrolidin-1-yl)pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (287 mg, 0.625 mmol, 39.5 % yield) as an off white solid. LCMS (*m/z*): 456.20 $[M+H]^+$, R_t = 1.40 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.59 (s, 1 H), 8.62 (d, *J*=5.26 Hz, 1 H), 8.29 (d, *J*=5.92 Hz, 1 H), 8.21 (s, 1 H), 8.12 (d, *J*=1.97 Hz, 1 H), 7.92 (dd, *J*=5.70, 2.19 Hz, 1 H), 7.71 (dd, *J*=5.26, 1.53 Hz, 1 H), 7.62 (d, *J*=7.89 Hz, 1 H), 7.48 (d, *J*=8.11 Hz, 1 H), 5.69 (dd, *J*=6.03, 3.18 Hz, 1 H), 3.96 (t, *J*=7.13 Hz, 2 H), 3.35 - 3.13 (m, 3 H), 3.02 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.74 (s, 3 H), 2.65 (t, *J*=8.11 Hz, 2 H), 2.40 - 2.28 (m, 1 H), 2.19 (quin, *J*=7.62 Hz, 2 H), 2.13 - 2.02 (m, 1 H).

Example 366

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-N-(4-(1,3,5-trimethyl-1H-pyrazol-4-yl)pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



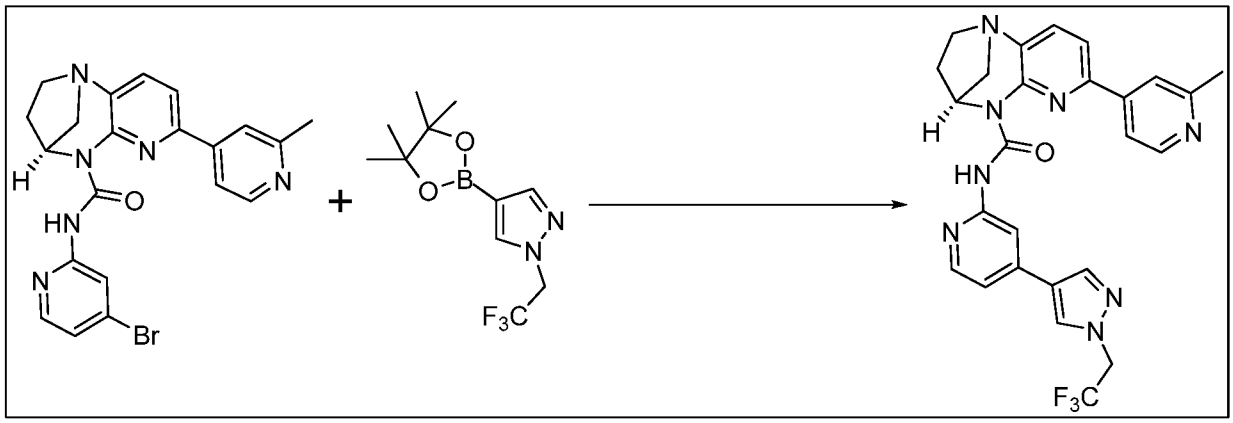
To a stirred solution of (4*S*)-N-(4-bromopyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (300 mg, 0.665 mmol) in 1,4-Dioxane (30 mL) and Water (6 mL) were added 1,3,5-trimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (235 mg, 0.997 mmol) and K_3PO_4 (423 mg, 1.994 mmol) at RT, degassed for 10 min. Then $PdCl_2(dppf)$-CH_2Cl_2 adduct (54.3 mg, 0.066 mmol) was added to the reaction mixture and again degassed for 5 min. The reaction mixture was stirred to 80 °C for 16 h. (TLC eluent: 10% methanol in DCM, R_f: 0.3; UV active). The reaction mixture was cooled to RT, partitioned between water and ethyl acetate (3X30 mL). The combined organic layer was washed with saturated brine solution and dried over anhydrous Na_2SO_4, filtered concentrated under reduced pressure to get crude compound. The crude compound was purified by flash column chromatography

(using neutral alumina and eluted at 30% ethyl acetate in pet ether) to afford pure compound (4*S*)-7-(2-methylpyridin-4-yl)-N-(4-(1,3,5-trimethyl-1H-pyrazol-4-yl)pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (238 mg, 0.494 mmol, 74.2 % yield) as an off white solid. LCMS (*m/z*): 481.22 $[M+H]^+$, R_t = 1.55 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.57 (s, 1 H), 8.63 (d, *J*=5.26 Hz, 1 H), 8.37 (dd, *J*=5.04, 0.66 Hz, 1 H), 8.24 (s, 1 H), 8.16 (d, *J*=0.66 Hz, 1 H), 7.73 (dd, *J*=5.26, 1.53 Hz, 1 H), 7.62 (d, *J*=7.89 Hz, 1 H), 7.49 (d, *J*=7.89 Hz, 1 H), 6.93 (dd, *J*=5.26, 1.53 Hz, 1 H), 5.71 (dd, *J*=5.92, 3.29 Hz, 1 H), 3.79 (s, 3 H) 3.36 - 3.13 (m, 3 H), 3.01 (dd, *J*=12.06, 3.29 Hz, 1 H), 2.76 (s, 3 H), 2.36 (d, *J*=7.67 Hz, 7 H), 2.09 (dt, *J*=14.25, 7.34 Hz, 1 H).

Example 367

Synthesis (4*S*)-7-(2-methylpyridin-4-yl)-*N*-(4-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



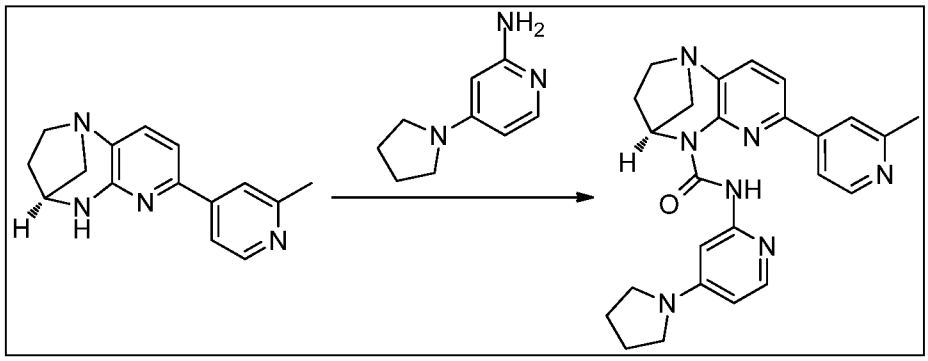
To a degassed solution of (4*S*)-*N*-(4-bromopyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (450 mg, 0.997 mmol), in 1,4-Dioxane (50 mL) and Water (10 mL) under argon, was added K_3PO_4 (635 mg, 2.99 mmol) 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole (358 mg, 1.296 mmol) and stirred at RT for 10 min. then added $PdCl_2$(dppf)-CH_2Cl_2 adduct (81 mg, 0.100 mmol) and stirred at 80 °C for 3 h. (TLC system: 10% methanol in DCM, Rf value: 0.4). Water (100 mL) was added to the reaction mixture and extracted with ethylacetate (3x100 mL). Combined extracts were washed with brine solution (100 mL), dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude compound. Crude product was purified by preparative HPLC (Column: XBridge C-18 (150*19)mm,5µ; Mobile phase-A: 0.1% Formic acid; Mobile phase-B: Acetonitrile;

Flow:15 mL/min; Method: 0.1/37,1/37,10/37; Solubility: Acetonitrile+THF+MeOH) to afford (4*S*)-7-(2-methylpyridin-4-yl)-*N*-(4-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (155 mg, 0.297 mmol, 29.8% yield) as an off white solid. LCMS (*m/z*): 521.22 $[M+H]^+$, *Rt* =1.74 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.61 (s, 1 H), 8.63 (d, *J*=5.48 Hz, 1 H), 8.41 (s, 1 H), 8.35 (d, *J*=5.04 Hz, 1 H), 8.21 (s, 1 H), 8.00 (s, 1 H), 7.96 (s, 1 H), 7.73 (br d, *J*=4.38 Hz, 1 H), 7.63 (d, *J*=7.89 Hz, 1 H), 7.49 (d, *J*=7.89 Hz, 1 H), 7.13 (d, *J*=3.95 Hz, 1 H), 5.71 (dd, *J*=5.70, 3.07 Hz, 1 H), 4.75 (q, *J*=8.26 Hz, 2 H), 3.36 - 3.12 (m, 3 H), 3.03 (dd, *J*=12.06, 3.07 Hz, 1 H), 2.75 (s, 3 H), 2.36 (qd, *J*=9.83, 4.49 Hz, 1 H), 2.11 (dt, *J*=14.20, 7.26 Hz, 1 H).

Example 368

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-N-(4-(pyrrolidin-1-yl) pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



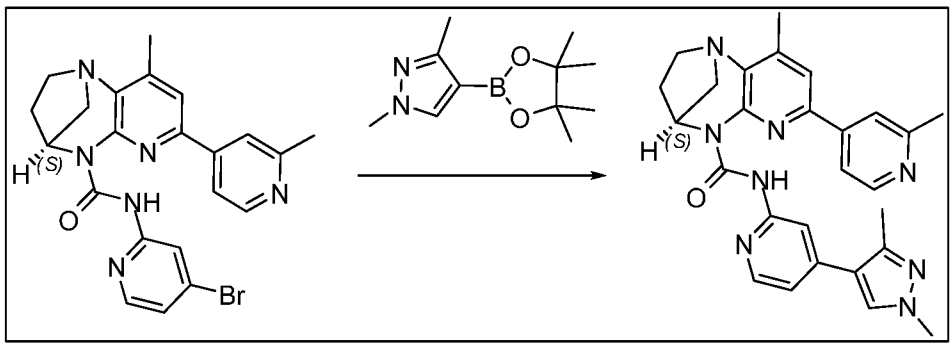
To a stirred solution of (4*S*)-7-(2-methylpyridin-4-yl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (300 mg, 1.189 mmol in THF (30 mL)) were added triethylamine (0.829 mL, 5.94 mmol) and triphosgene (353 mg, 1.189 mmol) under nitrogen, stirred at RT for 1 h. To this 4-(pyrrolidin-1-yl)pyridin-2-amine (388 mg, 2.378 mmol) was added and stirred at 70 °C for 16 h. (TLC eluent: 10% MeOH in DCM, R_f:0.4, UV active). The reaction mixture was cooled to rt, partitioned between water and ethyl acetate (3X30 mL). The combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude compound. The crude compound was purified by flash column chromatography (using neutral alumina and eluted at 20% EtOAc in pet ether) to afford the desired product (4*S*)-7-(2-methylpyridin-4-yl)-N-(4-(pyrrolidin-1-yl)pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (251 mg, 0.561 mmol, 47.2 % yield) as an off white

solid. LCMS (*m/z*): 442.3 $[M+H]^+$, R_t = 4.78 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.27 (s, 1 H), 8.60 (d, *J* = 5.3 Hz, 1 H), 8.28 (s, 1 H), 8.00 (d, *J* = 5.9 Hz, 1 H), 7.72 (dd, *J* = 5.5, 1.8 Hz, 1 H), 7.59 (d, *J* = 7.9 Hz, 1 H), 7.50 - 7.38 (m, 2 H), 6.19 (dd, *J* = 5.9, 2.3 Hz, 1 H), 5.70 (dd, *J* = 6.0, 3.2 Hz, 1 H), 3.39 (q, *J* = 6.2, 4.8 Hz, 3 H), 3.26 (s, 1 H), 3.27 - 3.12 (m, 3 H), 3.00 (dd, *J* = 12.0, 3.3 Hz, 1 H), 2.74 (s, 3 H), 2.32 (dddd, *J* = 14.0, 10.0, 6.2, 4.2 Hz, 1 H), 2.15 - 1.97 (m, 5 H).

Example 369

Synthesis of (4*S*)-N-(4-(1, 3-dimethyl-1H-pyrazol-4-yl) pyridin-2-yl)-9-methyl-7-(2-methylpyridin-4-yl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-*b*] [1, 4] diazepine-5(2*H*)-carboxamide

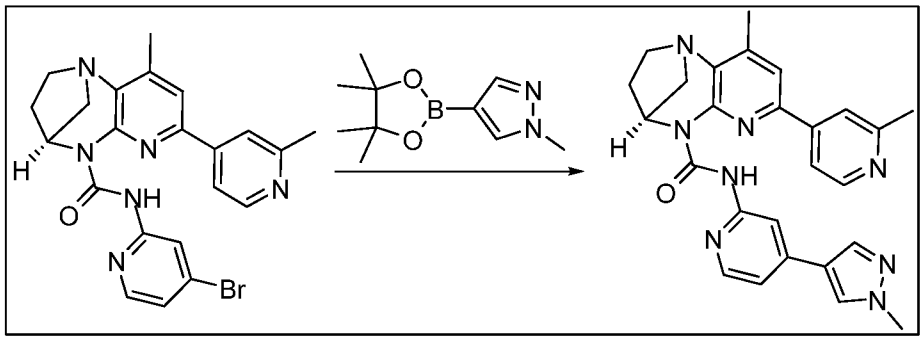


To a stirred solution of (4*S*)-N-(4-bromopyridin-2-yl)-9-methyl-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (300 mg, 0.645 mmol) in 1,4-Dioxane (40 mL) and Water (10 mL) were added 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (215 mg, 0.967 mmol) and K_3PO_4 (411 mg, 1.934 mmol) at RT and degassed for 15 min. Then added $PdCl_2$ (dppf)-CH_2Cl_2 adduct (52.6 mg, 0.064 mmol) and degassed for 5 min and stirred at 80 °C for 16 h. (TLC eluent: Neat ethyl acetate: R_f:0.3; UV active). The reaction was cooled to RT and poured in ice water and extracted with ethyl acetate (2x100 ml). The combined organic layer was washed with saturated brine (50 mL) solution and dried over anhydrous sodium sulphate and evaporated in vacuo to get the crude product. The crude compound was purified by flash column chromatography (using neutral alumina, column eluented at 60% ethyl acetate in pet ether) to afford pure compound (4*S*)-N-(4-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-2-yl)-9-methyl-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (101 mg, 0.208 mmol, 32.3 % yield) as an off white solid. LCMS (*m/z*): 481.33 $[M+H]^+$, R_t = 1.70 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.72 (s, 1 H), 8.61 (d, *J* = 5.3 Hz, 1 H), 8.36 - 8.29 (m, 2 H), 8.22 (d, *J* = 1.7 Hz, 1 H), 7.76 - 7.70 (m, 1 H), 7.67 (s, 1 H), 7.38 (d, *J* = 0.7 Hz, 1 H), 7.06 (dd, *J* = 5.2, 1.7 Hz, 1 H), 5.71 (dd, *J* = 6.1, 3.1 Hz, 1 H), 3.88 (s, 3 H), 3.22 - 3.07 (m, 3 H), 3.02 (dd, *J* = 12.0, 3.2 Hz, 1 H), 2.75 (s, 3 H), 2.51 (d, *J* = 2.8 Hz, 6 H), 2.33 (m, 1 H), 2.13 - 2.00 (m, 1 H).

Example 370

Synthesis of (4*S*)-9-methyl-N-(4-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



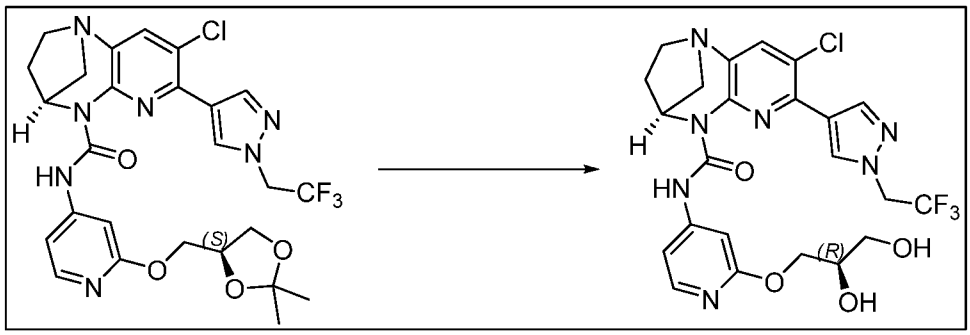
To a stirred solution of (4*S*)-N-(4-bromopyridin-2-yl)-9-methyl-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (300 mg, 0.645 mmol) in 1,4-Dioxane (40 mL) and Water (10 mL) were added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (201 mg, 0.967 mmol) and K_3PO_4 (411 mg, 1.934 mmol) at RT and degassed for 15 min. Then added $PdCl_2$(dppf)-CH2Cl2 adduct (52.6 mg, 0.064 mmol) and degassed for another 5 min and stirred at 80 °C for 16 h. (TLC eluent: Neat ethyl acetate: R_f:0.3; UV active). The reaction was cooled to RT and poured in ice water and extracted with ethyl acetate (2x100 ml). The combined organic layer was washed with saturated brine (50 mL) solution, dried over anhydrous sodium sulphate and evaporated in vacuo to get the crude product. The crude compound was purified by flash column chromatography (using neutral alumina, column eluented at 60% ethyl acetate in petether) to afford pure compound (4*S*)-9-methyl-N-(4-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (126 mg, 0.269 mmol, 41.8 % yield) as a white solid. LCMS (*m/z*): 467.29 $[M+H]^+$; R_t = 1.63 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.72 (s, 1 H), 8.64 - 8.57 (m, 1 H), 8.37 (dd, *J* = 1.6, 0.8 Hz, 1 H), 8.30 (dd, *J* = 5.2, 0.8 Hz, 1 H), 8.21 (d, *J* = 1.5 Hz, 1 H), 7.91 (d, *J* = 0.8 Hz, 1

H), 7.85 - 7.80 (m, 1 H), 7.76 - 7.70 (m, 1 H), 7.41 - 7.36 (m, 1 H), 7.10 (dd, *J* = 5.2, 1.6 Hz, 1 H), 5.70 (dd, *J* = 6.0, 3.1 Hz, 1 H), 3.96 (s, 3 H), 3.22 - 3.08 (m, 3 H), 3.03 (dd, *J* = 12.0, 3.2 Hz, 1 H), 2.75 (s, 3 H), 2.51 (s, 3 H), 2.34 (dq, *J* = 13.3, 6.5 Hz, 1 H), 2.08 (dt, *J* = 14.4, 7.9 Hz, 1 H).

Example 371

Synthesis of (4*S*)-8-chloro-*N*-(2-((*R*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

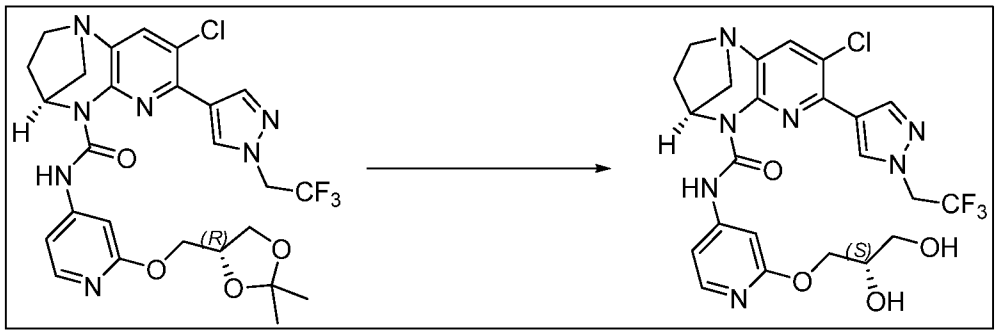


To a stirred solution of (4*S*)-8-chloro-N-(2-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (270 mg, 0.455 mmol) in methanol (5 mL) at 0 °C was added aq. HCl (0.5 ml, 6.00 mmol) and stirred at RT for 1 h. (TLC system: 10%MeOH in DCM, R_f value: 0.3). The reaction mixture was basified with saturated aqueous $NaHCO_3$ solution and extracted with 10% MeOH in DCM (2x50 mL). The combined organic layers were dried over sodiumsulphate and concentrated. The crude compound was purified by chromatography (Grace instrument, C-18 reserval column, Mobile phase A: 0.1% Formic acid in water; B: Acetonitrile, the product was eluted at 60-65% B in A) to afford (4*S*)-8-chloro-N-(2-((*R*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (220 mg, 0.393 mmol, 86 % yield) as a white solid. LCMS (*m/z*): 554.23 $[M+H]^+$, *Rt* = 1.84 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.67 (s, 1 H), 8.14 (d, *J*=9.21 Hz, 2 H), 7.96 (d, *J*=5.70 Hz, 1 H), 7.62 (s, 1 H), 7.13 (d, *J*=1.75 Hz, 1 H), 6.95 (dd, *J*=5.81, 1.86 Hz, 1 H), 5.63 (dd, *J*=5.81, 2.96 Hz, 1 H), 4.82 (q, *J*=8.33 Hz, 2 H), 4.47- 4.43 - (m, 2 H), 4.27 (br d, *J*=5.48 Hz, 1 H), 3.95 - 4.01 (m, 1 H), 3.62 - 3.69 (m, 2 H), 3.08 - 3.32 (m, 3 H), 3.03 - 2.96 - (m, 2 H), 2.38 -2.26 - (m, 1 H), 2.09 -2.00 - (m, 1 H).

Example 372

Synthesis of (4*S*)-8-chloro-N-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

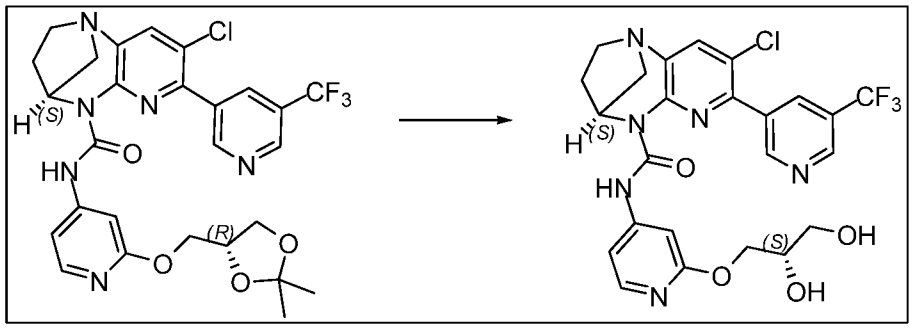


To a stirred solution of (4*S*)-8-chloro-N-(2-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (250 mg, 0.421 mmol) in methanol (5 mL) at 0 °C, was added aqueous HCL (0.5 ml, 6.00 mmol) and stirred at RT for 1 h. (TLC system: 10%MeOH in DCM, R_f value: 0.3). The reaction mixture was basified with saturated $NaHCO_3$ solution and extracted with 10% MeOH in DCM (2x50 mL). The combined organic layers were dried over sodiumsulphate and concentrated. The crude compound was purified by chromatography (Grace instrument, C-18 reserval column, Mobile phase A: 0.1% Formic acid in water; B: Acetronitrile ; the product was eluted at 59-64% B in A) to afford (4*S*)-8-chloro-*N*-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (210 mg, 0.374 mmol, 89 % yield) as a white solid. LCMS (*m/z*): 554.23 $[M+H]^+$, *Rt* =1.84 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.67 (s, 1 H), 8.14 (d, *J*=10.30 Hz, 2 H), 7.96 (d, *J*=5.92 Hz, 1 H), 7.62 (s, 1 H), 7.12 (d, *J*=1.75 Hz, 1 H), 6.95 (dd, *J*=5.81, 1.86 Hz, 1 H), 5.63 (dd, *J*=5.92, 3.07 Hz, 1 H), 4.82 (q, *J*=8.33 Hz, 2 H), 4.40 - 4.51 (m, 2 H), 4.45 (dd, *J*=4.82, 1.75 Hz, 1 H), 3.99 (t, *J*=4.71 Hz, 1 H), 3.59 - 3.75 (m, 2 H), 3.15 - 3.32 (m, 2 H), 3.07 - 3.14 (m, 1 H), 2.86 - 3.03 (m, 2 H), 2.25 - 2.39 (m, 1 H), 2.05 (dt, *J*=14.52, 7.54 Hz, 1 H).

Example 373

Synthesis of (4*S*)-8-chloro-*N*-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(5-(trifluoromethyl)pyridin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide:

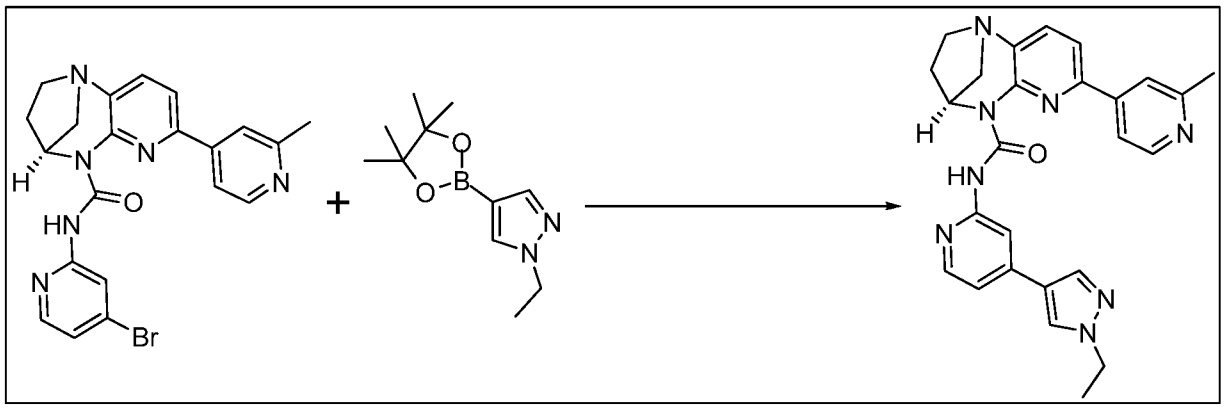


To a stirred solution of (4*S*)-8-chloro-*N*-(2-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)pyridin-4-yl)-7-(6-(trifluoromethyl)pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (60 mg, 0.102 mmol) in methanol (10 mL) at 0 °C was added aq. HCL (1 mL, 32.9 mmol) and stirred at RT for 2 h. (TLC system: 10%MeOH in DCM, Rf value: 0.25). The reaction mixture was basified with saturated aq. $NaHCO_3$ solution and extracted with ethyl acetate (3x30 mL). The combined organic layer was dried over anhydrous sodiumsulphate, filtered and concentrated. The crude compound was purified by coloumn chromatography (Grace instrument, reversal C-18 column, eluted with 27% acetonitrile in 1% Aqueous formic acid) to afford (4*S*)-8-chloro-*N*-(2-((*S*)-2,3-dihydroxypropoxy)pyridin-4-yl)-7-(6-(trifluoromethyl)pyridin-2-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (32 mg, 0.058 mmol, 57.0 % yield) as an off white solid. LCMS (*m/z*): 551.20 $[M+H]^+$, *Rt* =1.99 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.74 (s, 1 H), 8.08 (t, *J*=7.78 Hz, 1 H), 7.98 (d, *J*=7.89 Hz, 1 H), 7.91 - 7.80 (m, 2 H), 7.69 (s, 1 H), 7.24 -7.03 (m, 1 H), 6.81 (dd, *J*=5.92, 1.97 Hz, 1 H), 5.65 (dd, *J*=5.81, 3.18 Hz, 1 H), 4.43 (d, *J*=4.82 Hz, 2 H), 4.29 (d, *J*=5.92 Hz, 1 H), 3.96 (br d, *J*=5.26 Hz, 1 H), 3.70-3.46 (m, 2 H), 3.25 (br dd, *J*=9.65, 6.80 Hz, 2 H), 3.08 - 3.18 (m, 1 H), 3.07 -2.94 (m, 1 H), 2.86 (dd, *J*=7.02, 6.14 Hz, 1 H), 2.29 - 2.39 (m, 1 H), 2.07 (dt, *J*=14.47, 7.02 Hz, 1 H)

Example 374

Synthesis of (4*S*)-*N*-(4-(1-ethyl-1*H*-pyrazol-4-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

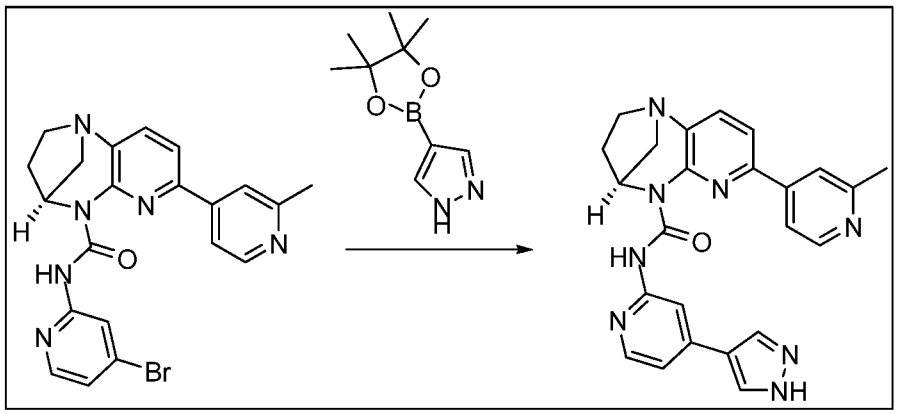


To a degassed solution of (4*S*)-*N*-(4-bromopyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (500 mg, 1.108 mmol), in 1,4-Dioxane (50 mL) and Water (10 mL) under argon, was added K_3PO_4 (705 mg, 3.32 mmol), 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (320 mg, 1.440 mmol) and stirred at RT for 10 min. then added $PdCl_2(dppf)$-CH_2Cl_2 adduct (90 mg, 0.111 mmol) and stirred at 80 °C for 3 h. (TLC system: 10% methanol in DCM, R*f* value: 0.5). Water (100 mL) was added to the reaction mixture and extracted with ethylacetate (3x100 mL). Combined extracts were washed with brine solution (100 mL), dried over anhydrous Na_2SO_4, filtered and filtrate was evaporated to get crude compound. Crude product was purified by chromatography (neutral alumina, eluted in DCM) to afford (4*S*)-*N*-(4-(1-ethyl-1*H*-pyrazol-4-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (300 mg, 0.641 mmol, 57.9 % yield) as an off white solid. LCMS (*m/z*): 467.25 $[M+H]^+$, *Rt* =1.57 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.56 (s, 1 H), 8.62 (d, *J*=5.26 Hz, 1 H), 8.38 (dd, *J*=1.43, 0.77 Hz, 1 H), 8.31 (dd, *J*=5.26, 0.66 Hz, 1 H), 8.26 - 8.15 (m, 1 H), 7.92 (d, *J*=0.66 Hz, 1 H), 7.86 (s, 1 H), 7.72 (dd, *J*=5.26, 1.32 Hz, 1 H), 7.63 (d, *J*=8.11 Hz, 1 H), 7.49 (d, *J*=8.11 Hz, 1 H), 7.25 - 7.03 (m, 1 H), 5.71 (dd, *J*=5.81, 3.18 Hz, 1 H), 4.23 (q, *J*=7.38 Hz, 2 H), 3.35 - 3.16 (m, 3 H), 3.03 (dd, *J*=12.28, 3.29 Hz, 1 H), 2.75 (s, 3 H), 2.44 - 2.24 (m, 1 H), 2.11 (dt, *J*=14.31, 7.43 Hz, 1 H), 1.59 - 1.53 (m, 3 H).

Example 375

Synthesis of (4*S*)-N-(4-(1H-pyrazol-4-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihy dro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide

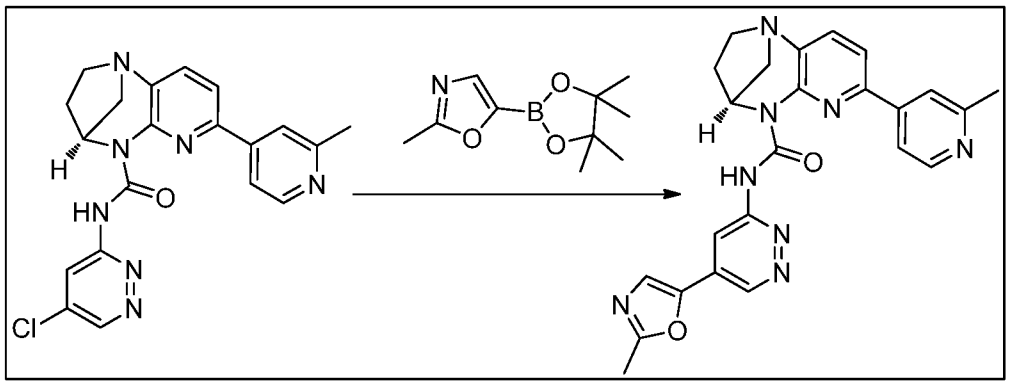


To a degassed solution of (4*S*)-N-(4-bromopyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (650 mg, 1.440 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (419 mg, 2.160 mmol) and Na_2CO_3 (458 mg, 4.32 mmol) in 1,4-Dioxane (24 mL) and Water (6 mL) was added $Pd(Ph_3P)_4$ (166 mg, 0.144 mmol) and stirred at 80 °C for 16 h. (TLC eluent: 10% MeOH in ethyl acetate, R_f - 0.4, UV active). 1, 4-dioxane was evaporated under reduced pressure, the obtained residue was diluted with water (50 ml) and extracted with ethyl acetate (2x 100 ml). The combined organic layer was washed with brine solution (30 mL), dried over anhydrous sodium sulphate and evaporated under reduced pressure to obtain crude product. The crude product was purified by flash column chromatography (using neutral Alumina, eluted at 5% Methanol in ethyl acetate) to afford the desired product (4*S*)-N-(4-(1H-pyrazol-4-yl)pyridin-2-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (150 mg, 0.333 mmol, 23.09 % yield) as an off white solid. LCMS (*m/z*): 439.21 $[M+H]^+$, R_t = 1.33 min.

^{1}H NMR (400 MHz, DMSO-d6): δ ppm 13.50 (s, 1 H), 13.20 (br s, 1 H), 8.59 (d, J=5.26 Hz, 1 H), 8.42 – 8.31 (m, 3 H), 8.25 (s, 1 H), 8.06 - 7.93 (m, 2 H), 7.81 (d, J=8.11 Hz, 1 H), 7.75 - 7.66 (m, 1 H), 7.37 (dd, J=5.15, 1.43 Hz, 1 H), 5.54 (dd, J=5.59, 2.96 Hz, 1 H), 3.25 - 3.09 (m, 3 H), 2.98 (dd, J=11.95, 3.18 Hz, 1 H), 2.64 (s, 3 H), 2.35 - 2.18 (m, 1 H), 2.06 - 1.89 (m, 1 H).

Example 376

Synthesis of (4*S*)-N-(5-(2-methyloxazol-5-yl) pyridazin-3-yl)-7-(2-methylpyridin-4-yl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-*b*] [1, 4] diazepine-5(2*H*)-carboxamide



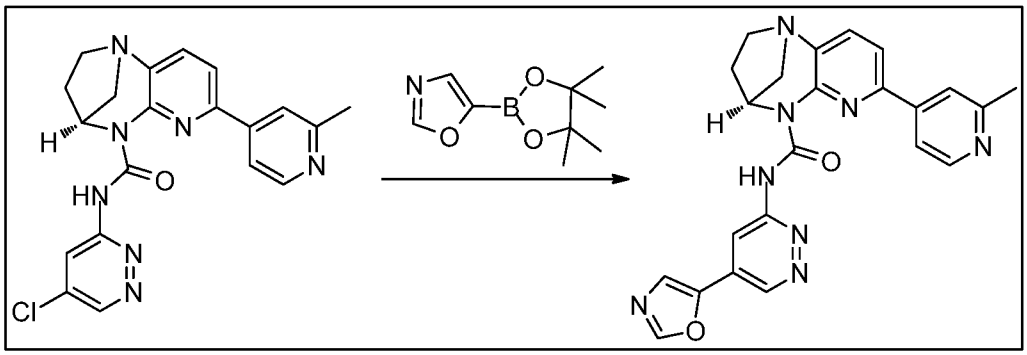
To a stirred solution of (4*S*)-N-(5-chloropyridazin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-b][1,4]diazepine-5(2H)-carboxamide (400 mg, 0.981 mmol) in 1,4-Dioxane (16 mL) and Water (4 mL) were added 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (308 mg, 1.471 mmol) and K_3PO_4 (625 mg, 2.94 mmol). The resulting reaction mixture was degassed for 15 min with Argon gas. To this Pd $(Ph_3P)_4$ (113 mg, 0.098 mmol) was added and again degassed for 5 min. The resulting reaction mixture was stirred at 100 °C for 18 h. (TLC eluent: 10% MeOH in DCM, R_f - 0.6, UV active). Reaction mixture was diluted with water and extracted with ethyl acetate (3 X 30 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 obtain crude compound. The crude compound was purified by flash column chromatography (100-200 silica gel, eluted at 4% MeOH in DCM) and followed by Prep-HPLC (Prep-HPLC Condition: MP-A: 10m m Ammonium Bicarbonate (aq) MP-B: Acetonitrile Column: Kinetex C8 (150*30) mm*5u Method: % of 'B':0/10, 9/50, 9.5/100, 13/100, 13.5/50, 15/50 Flow: 30 ml/min Solubility: ACN +THF +MeoH Temperature: Ambient) to afford the desired compound (4*S*)-N-(5-(2-methyloxazol-5-yl)pyridazin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (124 mg, 0.271 mmol, 27.6 % yield) as an off white solid. LCMS (*m/z*): 455.19 $[M+H]^+$, R_t = 1.38 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.65 (s, 1 H), 9.01 (d, *J*=2.63 Hz, 1 H), 8.74 (d, *J*=5.26 Hz, 1 H), 8.28 (d, *J*=2.63 Hz, 1 H), 7.79 (s, 1 H), 7.70 (d, *J*=7.89 Hz, 1 H), 7.57 (s, 1 H), 7.51 (d, *J*=5.26 Hz, 1 H),7.42 (d, *J*=7.89 Hz, 1 H), 5.68 (dd, *J*=5.92, 3.29 Hz, 1 H),

3.33 - 3.16 (m, 3 H), 3.06 (dd, *J*=12.28, 3.29 Hz, 1 H), 2.72 (s, 3 H), 2.60 (s, 3 H), 2.45 - 2.29 (m, 1 H), 2.17 - 2.03 (m, 1 H)

Example 377

Synthesis of (4*S*)-7-(2-methylpyridin-4-yl)-N-(5-(oxazol-5-yl) pyridazin-3-yl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-*b*] [1, 4] diazepine-5(2*H*)-carboxamide



To a stirred solution of (4*S*)-N-(5-chloropyridazin-3-yl)-7-(2-methylpyridin-4-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (500 mg, 1.226 mmol) in 1,4-Dioxane (16 mL) and Water (4 mL) were added 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (359 mg, 1.839 mmol) and K_3PO_4 (781 mg, 3.68 mmol). The resulting reaction mixture was degassed for 15 min with Argon gas. To this Pd $(Ph_3P)_4$ (142 mg, 0.123 mmol) was added and again degassed for 5 min. The resulting reaction mixture was stirred at 100 °C for 18 h. (TLC eluent: 10% MeOH in DCM, R_f - 0.6, UV active). Reaction mixture was diluted with water and extracted with ethyl acetate (3 X 30 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 obtain crude compound. The crude compound was purified by flash column chromatography (100-200 silica gel, eluted at 4% MeOH in DCM) and followed by Prep-HPLC (Prep-HPLC Condition: MP-A: 10 mm Ammonium Bicarbonate (aq) MP-B: Acetonitrile Column: Kinetex C8 (150*30) mm*5u Method: % of 'B':0/10, 9/50, 9.5/100, 13/100, 13.5/50, 15/50 Flow: 30 ml/min Solubility: ACN +THF +MeOH Temperature: Ambient) to afford the desired product (4*S*)-7-(2-methylpyridin-4-yl)-N-(5-(oxazol-5-yl)pyridazin-3-yl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (49 mg, 0.111 mmol, 9.02 % yield) as an off-white solid. LCMS (*m/z*): 441.23$[M+H]^+$, R_t = 1.32 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 13.68 (s, 1 H), 9.07 (d, *J*=2.41 Hz, 1 H), 8.75 (d, *J*=5.04 Hz, 1 H), 8.35 (d, *J*=2.41 Hz, 1 H), 8.05 (s, 1 H), 7.96 (s, 1 H), 7.70 (d, *J*=7.89 Hz,

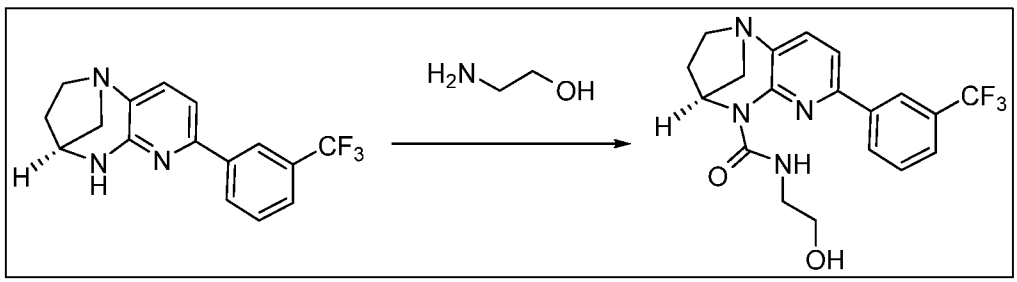
1 H), 7.57 (s, 1 H), 7.51 (d, *J*=5.04 Hz, 1 H), 7.42 (d, *J*=7.89 Hz, 1 H), 5.69 (dd, *J*=6.03, 2.96 Hz, 1 H), 3.39 - 3.13 (m, 3 H), 3.07 (dd, *J*=12.28, 3.07 Hz, 1 H), 2.72 (s, 3 H), 2.50 - 2.29 (m, 1 H), 2.11 (dt, *J*=14.25, 7.13 Hz, 1 H).

To a stirred suspension of (4*S*)-N-((R)-2,3-dihydroxypropyl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (135 mg, 0.320 mmol) in Diethyl ether (10 mL) was added HCl in diethyl ether (2M) (0.160 mL, 0.320 mmol) at 0 ^{o}C and stirred at RT for 1 h. (TLC eluent: 10% Methanol in DCM: R_f-0.1; UV active). Then the reaction mixture was concentrated under reduced pressure, nitrogen atmosphere to get solid compound. The solid compound was dissolved in 10 ml of water and acetonitrile (1:1), concentrated under reduced pressure to afford pure compound (4*S*)-N-((*R*)-2,3-dihydroxypropyl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide, Hydrochloride (120 mg, 0.256 mmol, 80 % yield) as an off white solid. LCMS (*m/z*): 423.04 $[M+H]^+$, R_t = 1.76 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.12 (t, *J*=5.04 Hz, 1 H), 8.38 (d, *J*=7.67 Hz, 1 H), 8.21 (s, 1 H), 7.97 (d, *J*=7.89 Hz, 1 H), 7.89 - 7.71 (m, 3 H), 5.59 (m, 1 H), 3.68 - 3.27 (m, 8 H), 3.26 - 3.15 (m, 1 H), 2.47 - 2.30 (m, 1 H), 2.19 - 2.02 (m, 1 H)

Example 378

Synthesis of (4*S*)-N-(2-hydroxyethyl)-7-(3-(trifluoromethyl) phenyl)-3, 4-dihydro-1, 4-methanopyrido [2, 3-*b*] [1, 4] diazepine-5(2*H*)-carboxamide



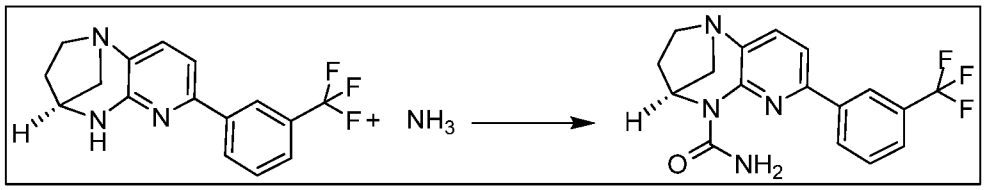
To a stirred solution of (4*S*)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (0.3 g, 0.983 mmol) in THF (10 mL) were added triethyl amine (0.822 mL, 5.90 mmol) and triphosgene (0.292 g, 0.983 mmol) at 0 °C, then stirred for 1 h at RT and 2-aminoethanol (0.172 mL, 1.965 mmol) was added and the reaction mixture stirred at 80°C for 16 h. (TLC eluent: Neat ethyl acetate: R_f-0.5; UV active). Reaction mixture was allowed to room temp and diluted with water, extracted with

ethyl acetate (2x30 mL). The combined organic layer was washed with brine solution (2x20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to get the crude compound. The crude compound was purified by column chromatography (100-200 silicagel eluted with 5% of Methanol in DCM) to afford the desired compound (4*S*)-N-(2-hydroxyethyl)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (186 mg, 0.467 mmol, 47.5 % yield) as a pale green gummy liquid. LCMS (*m/z*): 393.08 $[M+H]^+$, R_t = 1.89 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.34 (d, *J*=10.52 Hz, 1 H), 8.31 (s, 1 H), 8.17 (s, 1 H), 7.84 - 7.76 (m, 1 H), 7.76 - 7.59 (m, 3 H), 5.48 - 5.40 (m, 1 H), 3.63 - 3.47 (m, 2 H), 3.45 - 3.30 (m, 2 H), 3.28 - 2.89 (m, 4 H), 2.30 - 2.08 (m, 1 H), 1.95 - 1.75 (m, 1 H).

Example 379

Synthesis of (4*S*)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide



To a solution of (4*S*)-7-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine (250 mg, 0.819 mmol) in THF (25 mL) at RT was added triethylamine (0.685 ml, 4.91 mmol) followed by triphosgene (243 mg, 0.819 mmol) and stirred for 30 min. then added 2M ammonia in THF (1.228 mL, 2.457 mmol) and the reaction was heated at 65 °C for 16 h. (TLC eluent:70% EtOAc in Hexane: R_f-0.3; UV active). The reaction mixture was cooled to RT, concentrated *in vacuo* and the residue was partitioned between water (30 mL) and EtOAc (2x35 mL). Organic layer was separated and dried over anhydrous sodiumsulphate, filtered and filtrate was evaporated to get crude compound. The crude product was purified by flash column chromatography (neutral alumina, eluent: 50% ethyl acetate in hexane) to afford (4*S*)-7-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1,4-methanopyrido[2,3-*b*][1,4]diazepine-5(2*H*)-carboxamide (225 mg, 0.644 mmol, 79 % yield) as a white solid. LCMS (*m/z*): 349.08 $[M+H]^+$, R_t = 1.97 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 10.23 - 10.02 (m, 1 H), 8.00 (s, 1 H), 7.94 (d, *J*=7.89 Hz, 1 H), 7.69 - 7.65 (m, 1 H), 7.62 - 7.54 (m, 2 H), 7.29 (d, *J*=7.89 Hz, 1 H), 5.63 (dd,

J=6.03, 3.18 Hz, 1 H), 5.23 (br s, 1 H), 3.31 - 3.08 (m, 3 H), 2.96 (dd, *J*=11.84, 3.29 Hz, 1 H), 2.28 (dddd, *J*=14.03, 9.98, 6.03, 3.95 Hz, 1 H), 2.10 - 2.00 (m, 1 H)

Example 380. Full-length SIRT1production

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 382. SIRT1 deacetylation reactions

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 x g for 10

minutes to precipitate protein before being analyzed with an Agilent RapidFire 200 High-Throughput Mass Spectrometry System (Agilent, Wakefield, MA) 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)-GQSTSSHSK(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

$$\frac{v_x}{v_0} = b + \frac{RV_{max} - b}{1 + \frac{EC_{50}}{[X]}} \quad \textbf{(Eq.1)}$$

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_0.

Example 283. Biochemical Activity

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).

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.

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. 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).

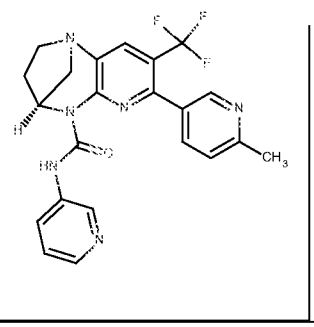
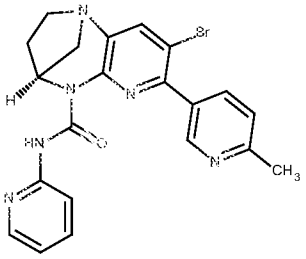
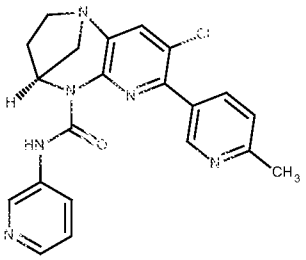
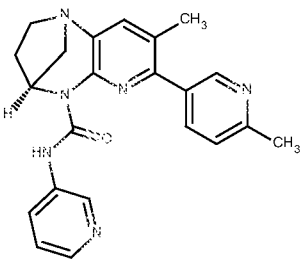
A control for inhibition of sirtuin activity was conducted by adding 1 μL of 500 mM nicotinamide as a negative control at the start of the reaction (e.g., permits determination of maximum sirtuin inhibition). A control for activation of sirtuin activity was conducted using 10 nM of sirtuin protein, with 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.

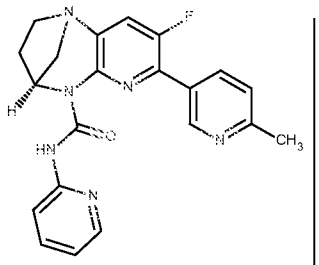
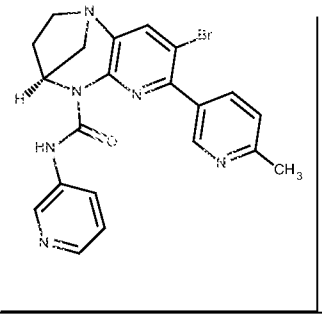
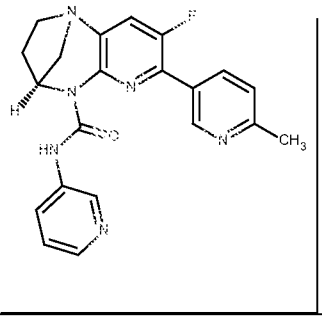
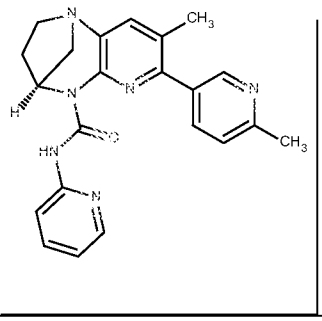
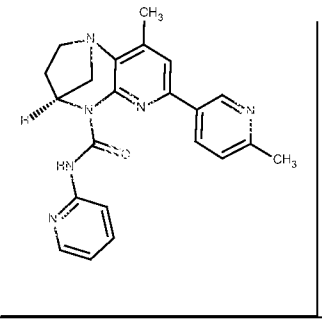
For the above assay, SIRT1 protein was expressed and purified as follows. The SirT1 gene was cloned into a T7-promoter containing vector and transformed into BL21(DE3). The protein was expressed by induction with 1 mM IPTG as an N-terminal His-tag fusion protein at 18°C overnight and harvested at 30,000 x 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.

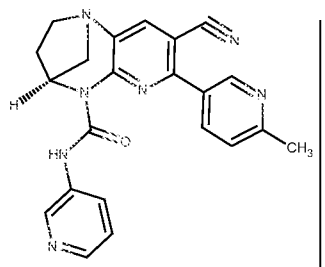
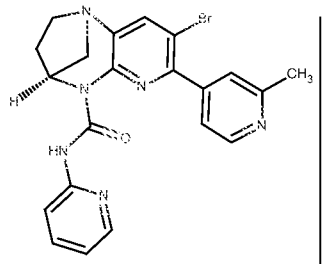
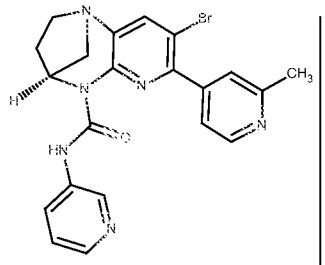
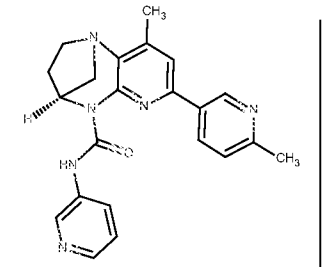
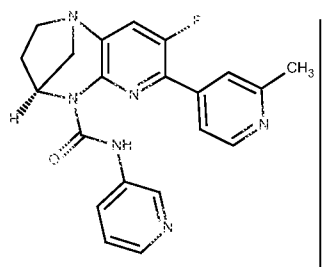
Sirtuin-modulating compounds of Formula (I) that activated SIRT1 were identified using the assay described above and are shown below in Table 1. The $EC_{1.5}$ values represent the concentration of test compounds that result in 150% activation of SIRT1. The $EC_{1.5}$ values for the activating compounds 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 Figure 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)).

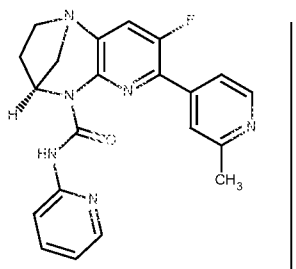
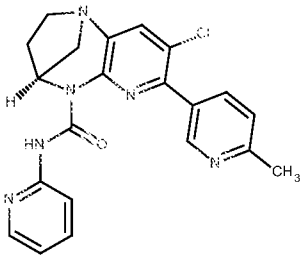
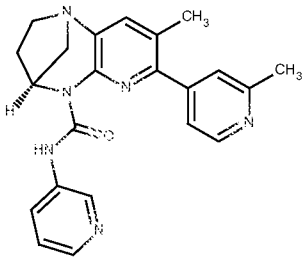
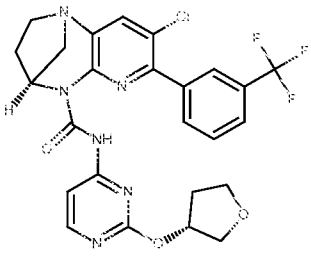
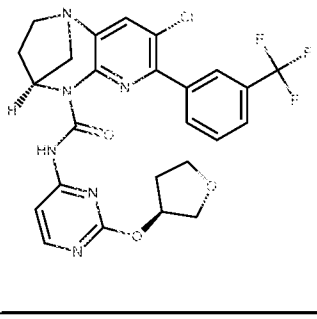
It is noted that compounds of the present invention have been named by two different chemical nomenclature conventions as generated by two different chemical drawing and/or chemical naming computer programs, i.e., generated by Chem Axon (JChem-Excel) and Cambridge Soft (ChemDraw®) , respective companies.

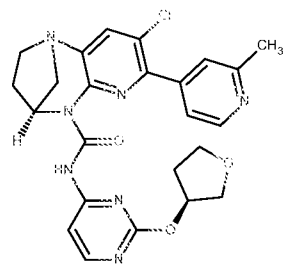
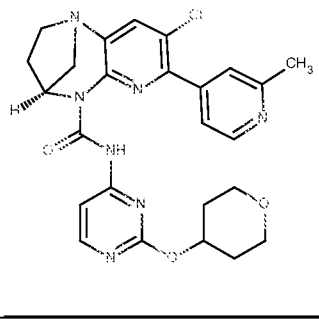
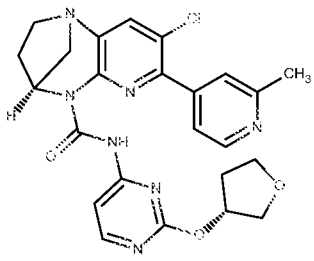
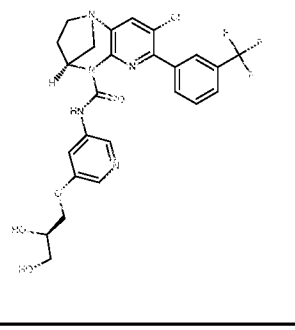
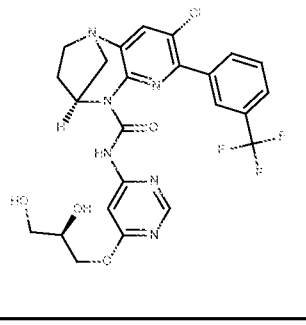
TABLE 1

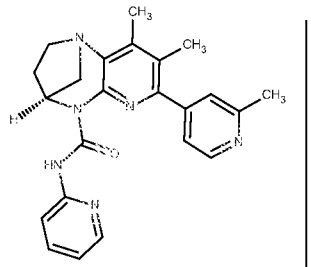
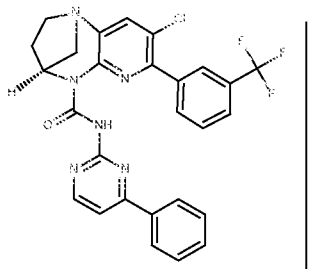
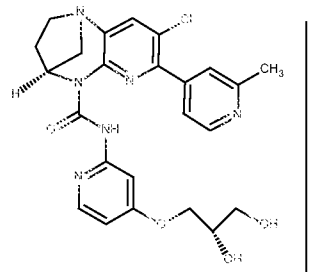
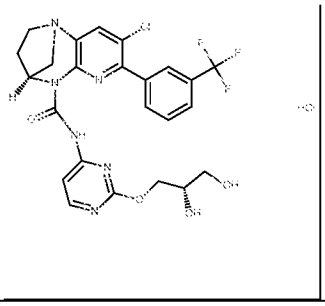
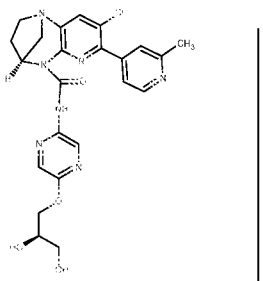
Example No.	Structure	Chemical Name: Generated by CHemAxon	TRP Activity	TRP MAX RESP
1		(9S)-5-(6-methylpyridin-3-yl)-N-(pyridin-3-yl)-4-(trifluoromethyl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	C	B
2		(9S)-4-bromo-5-(6-methylpyridin-3-yl)-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
3		(9S)-4-chloro-5-(6-methylpyridin-3-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
4		(9S)-4-methyl-5-(6-methylpyridin-3-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

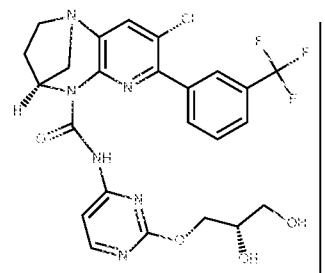
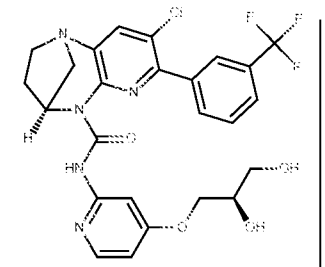
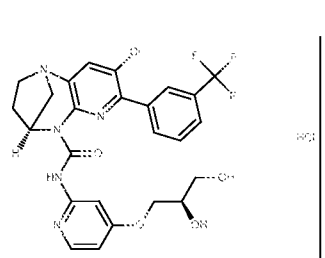
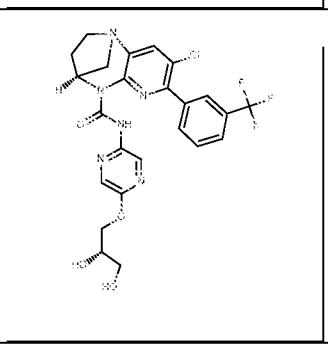
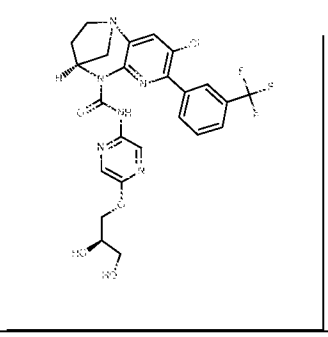
5		(9S)-4-fluoro-5-(6-methylpyridin-3-yl)-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
6		(9S)-4-bromo-5-(6-methylpyridin-3-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
7		(9S)-4-fluoro-5-(6-methylpyridin-3-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
8		(9S)-4-methyl-5-(6-methylpyridin-3-yl)-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
9		(9S)-3-methyl-5-(6-methylpyridin-3-yl)-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A

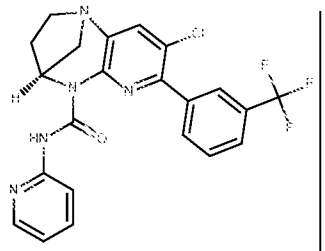
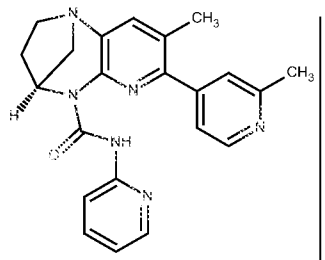
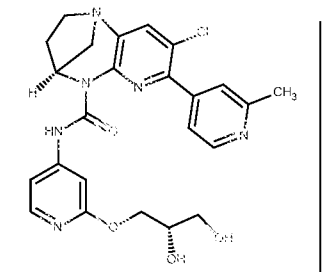
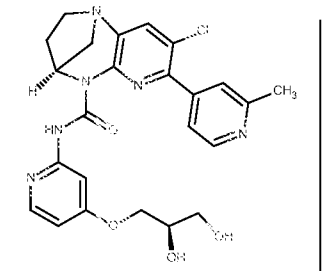
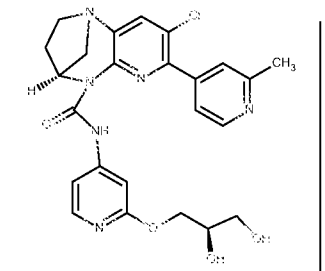
10		(9S)-4-cyano-5-(6-methylpyridin-3-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
11		(9S)-4-bromo-5-(2-methylpyridin-4-yl)-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
12		(9S)-4-bromo-5-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
13		(9S)-3-methyl-5-(6-methylpyridin-3-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
14		(9S)-4-fluoro-5-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

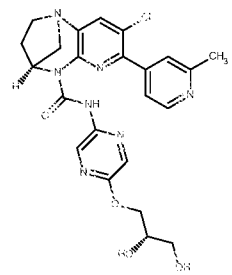
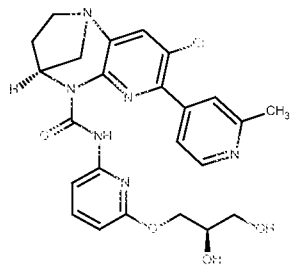
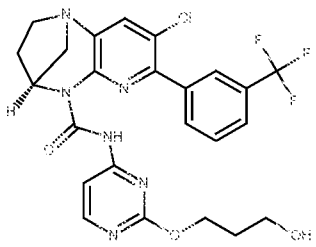
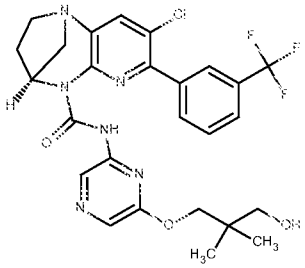
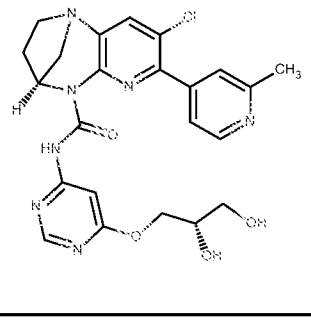
15		(9S)-4-fluoro-5-(2-methylpyridin-4-yl)-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
16		(9S)-4-chloro-5-(6-methylpyridin-3-yl)-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
17		(9S)-4-methyl-5-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
18		(9S)-4-chloro-N-{2-[(3R)-oxolan-3-yloxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
19		(9S)-4-chloro-N-{2-[(3S)-oxolan-3-yloxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A

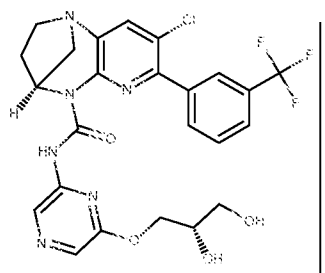
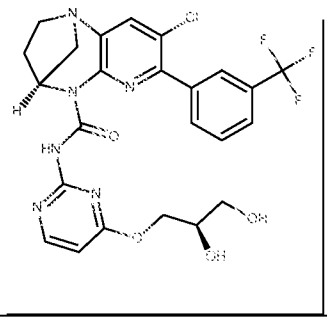
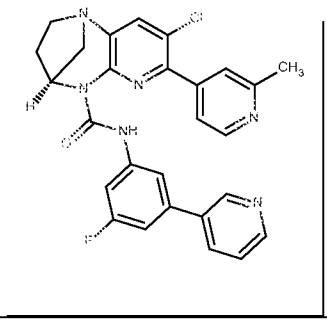
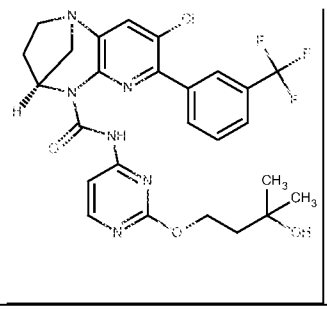
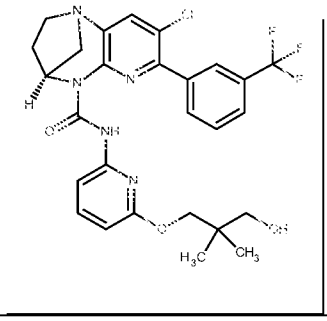
20		(9S)-4-chloro-5-(2-methylpyridin-4-yl)-N-{2-[(3S)-oxolan-3-yloxy]pyrimidin-4-yl}-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	C	A
21		(9S)-4-chloro-5-(2-methylpyridin-4-yl)-N-[2-(oxan-4-yloxy)pyrimidin-4-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	C	B
22		(9S)-4-chloro-5-(2-methylpyridin-4-yl)-N-{2-[(3R)-oxolan-3-yloxy]pyrimidin-4-yl}-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	C	B
23		(9S)-4-chloro-N-{5-[(2R)-2,3-dihydroxypropoxy]pyridin-3-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
24		(9S)-4-chloro-N-{6-[(2R)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A

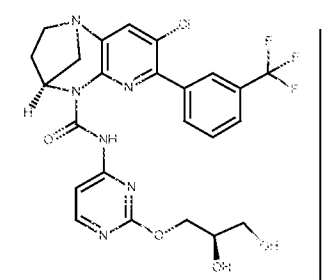
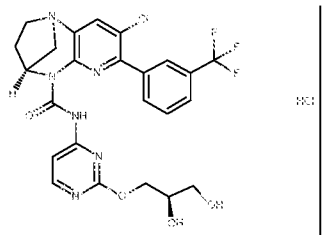
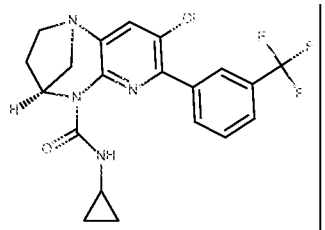
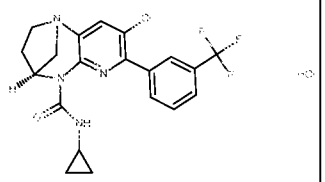
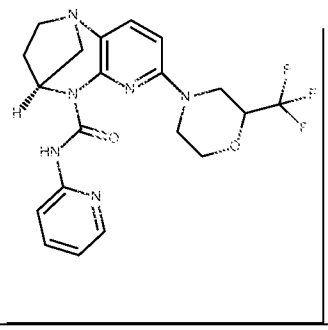
25		(9S)-3,4-dimethyl-5-(2-methylpyridin-4-yl)-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
26		(9S)-4-chloro-N-(4-phenylpyrimidin-2-yl)-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A
27		(9S)-4-chloro-N-{4-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
28		(9S)-4-chloro-N-{2-[(2S)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide hydrochloride	A	A
29		(9S)-4-chloro-N-{5-[(2R)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

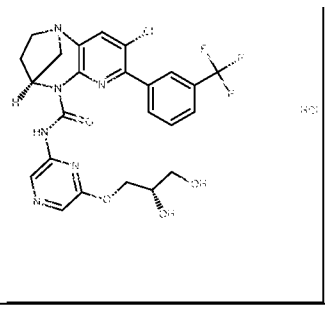
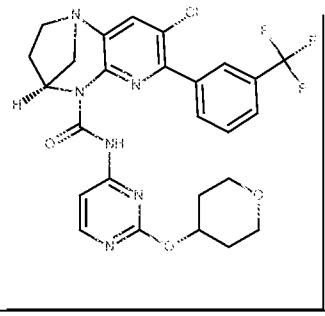
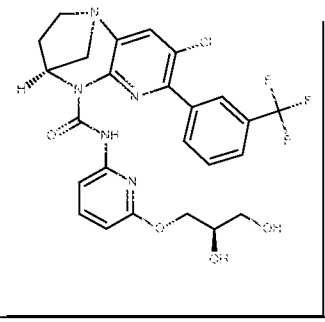
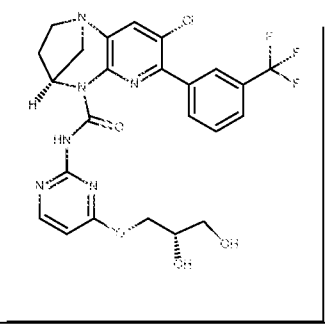
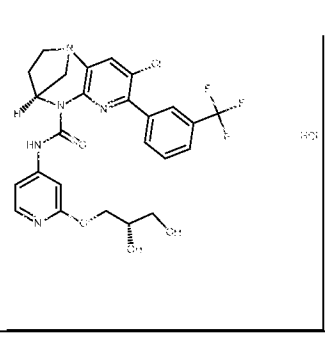
30		(9S)-4-chloro-N-{2-[(2S)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
31		(9S)-4-chloro-N-{4-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
32		(9S)-4-chloro-N-{4-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide hydrochloride	B	A
33		(9S)-4-chloro-N-{5-[(2S)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
34		(9S)-4-chloro-N-{5-[(2R)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A

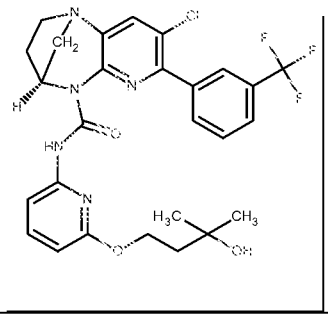
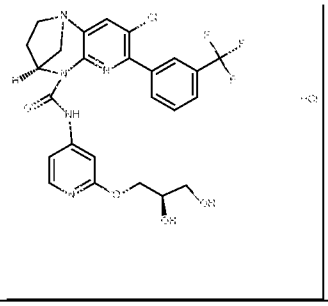
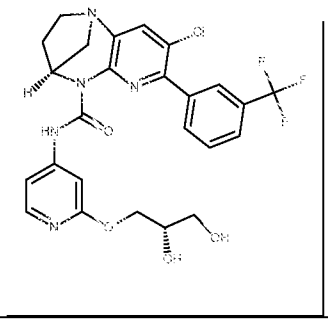
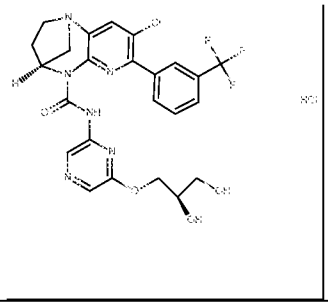
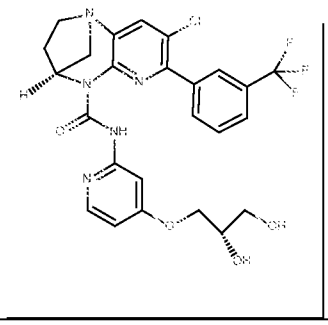
35		(9S)-4-chloro-N-(pyridin-2-yl)-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
36		(9S)-4-methyl-5-(2-methylpyridin-4-yl)-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
37		(9S)-4-chloro-N-{2-[(2S)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
38		(9S)-4-chloro-N-{4-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
39		(9S)-4-chloro-N-{2-[(2R)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A

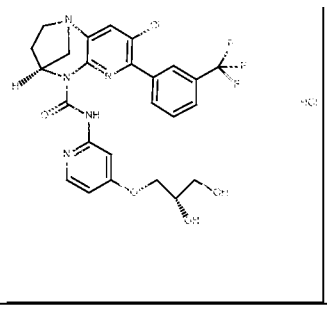
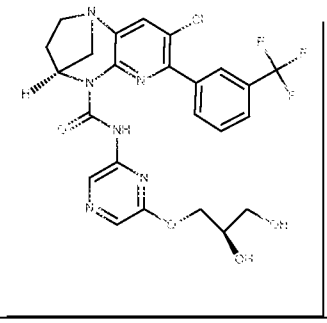
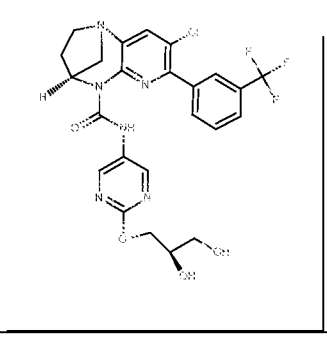
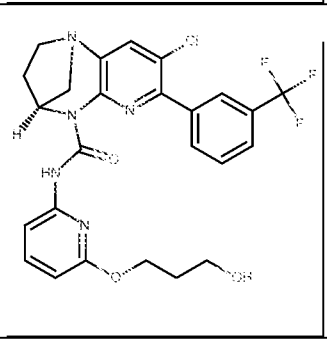
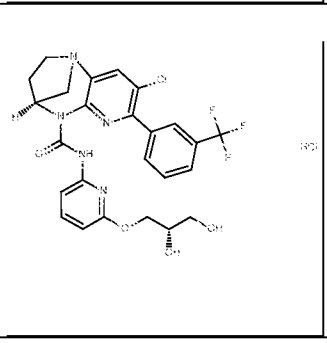
40		(9S)-4-chloro-N-{5-[(2S)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
41		(9S)-4-chloro-N-{6-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
42		(9S)-4-chloro-N-[2-(3-hydroxypropoxy)pyrimidin-4-yl]-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
43		(9S)-4-chloro-N-[6-(3-hydroxy-2,2-dimethylpropoxy)pyrazin-2-yl]-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
44		(9S)-4-chloro-N-{6-[(2S)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	C	B

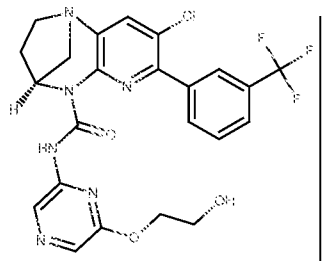
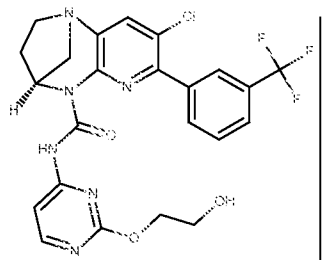
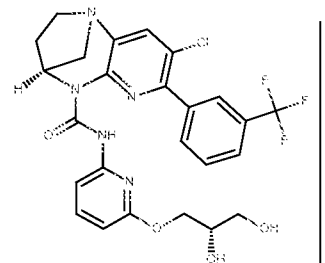
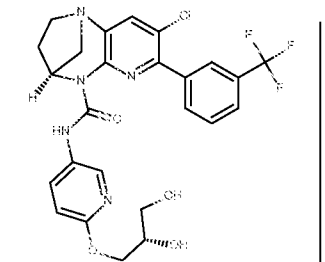
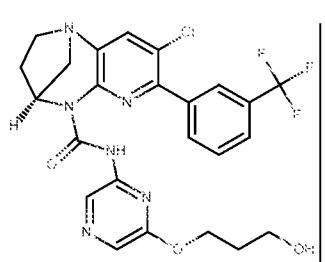
45		(9S)-4-chloro-N-{6-[(2S)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
46		(9S)-4-chloro-N-{4-[(2R)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
47		(9S)-4-chloro-N-[3-fluoro-5-(pyridin-3-yl)phenyl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
48		(9S)-4-chloro-N-[2-(3-hydroxy-3-methylbutoxy)pyrimidin-4-yl]-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
49		(9S)-4-chloro-N-[6-(3-hydroxy-2,2-dimethylpropoxy)pyridin-2-yl]-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

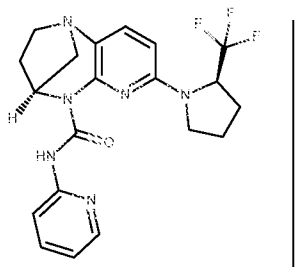
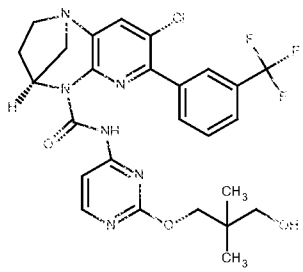
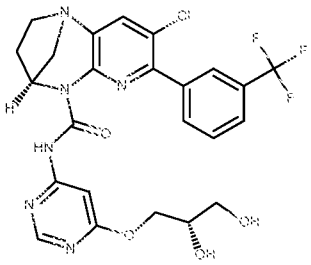
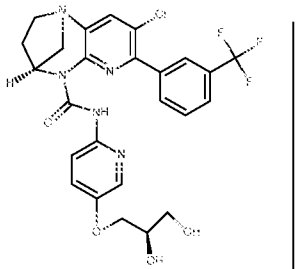
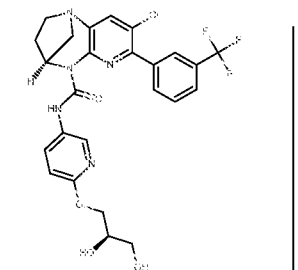
50		(9S)-4-chloro-N-{2-[(2R)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
51		(9S)-4-chloro-N-{2-[(2R)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide hydrochloride	A	A
52		(9S)-4-chloro-N-cyclopropyl-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A
53		(9S)-4-chloro-N-cyclopropyl-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide hydrochloride	A	A
54		(9S)-N-(pyridin-2-yl)-5-[2-(trifluoromethyl)morpholin-4-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

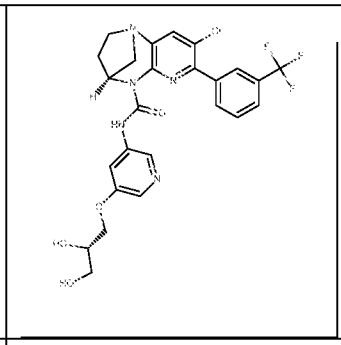
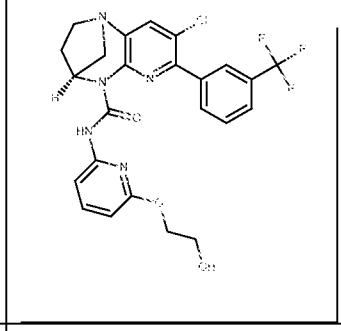
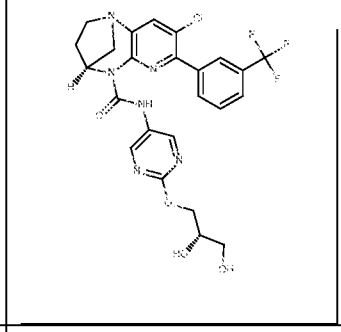
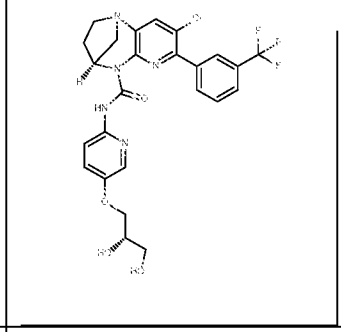
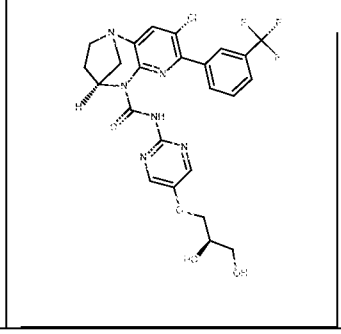
54		(9S)-4-chloro-N-{6-[(2S)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide hydrochloride	A	A
55		(9S)-4-chloro-N-[2-(oxan-4-yloxy)pyrimidin-4-yl]-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
56		(9S)-4-chloro-N-{6-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A
57		(9S)-4-chloro-N-{4-[(2S)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
58		(9S)-4-chloro-N-{2-[(2S)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide hydrochloride	A	A

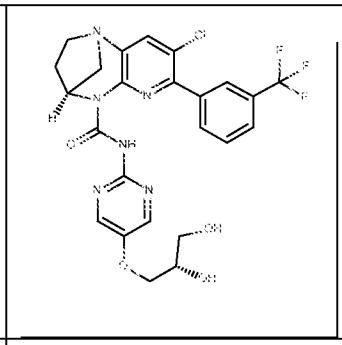
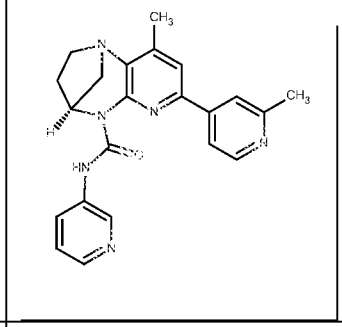
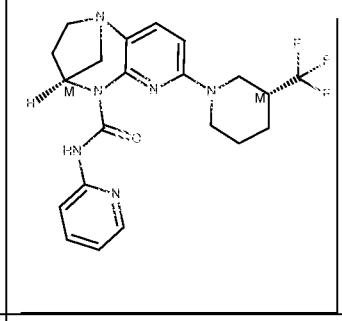
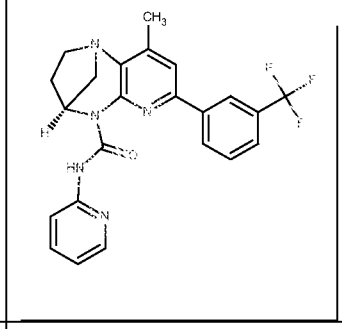
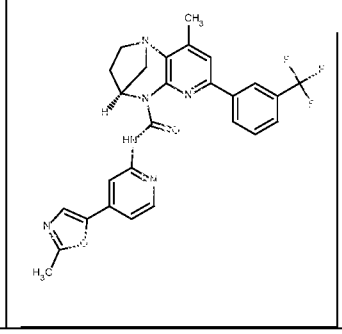
59		(9S)-4-chloro-N-[6-(3-hydroxy-3-methylbutoxy)pyridin-2-yl]-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
60		(9S)-4-chloro-N-{2-[(2R)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide hydrochloride	A	A
61		(9S)-4-chloro-N-{2-[(2S)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
62		(9S)-4-chloro-N-{6-[(2R)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide hydrochloride	A	A
63		(9S)-4-chloro-N-{4-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A

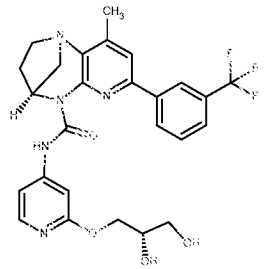
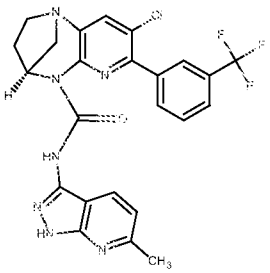
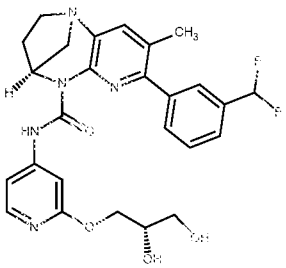
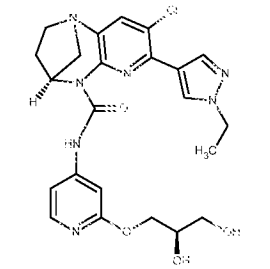
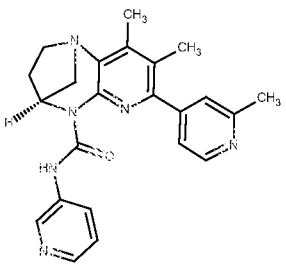
64		(9S)-4-chloro-N-{4-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide hydrochloride	B	A
65		(9S)-4-chloro-N-{6-[(2R)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A
66		(9S)-4-chloro-N-{2-[(2R)-2,3-dihydroxypropoxy]pyrimidin-5-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
67		(9S)-4-chloro-N-[6-(3-hydroxypropoxy)pyridin-2-yl]-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
68		(9S)-4-chloro-N-{6-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide hydrochloride	A	A

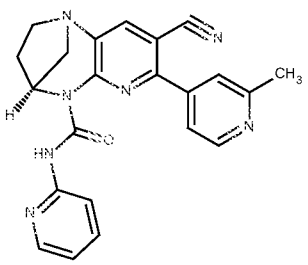
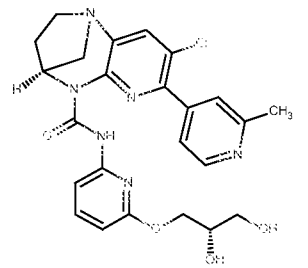
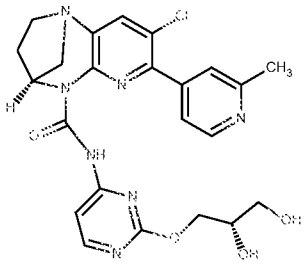
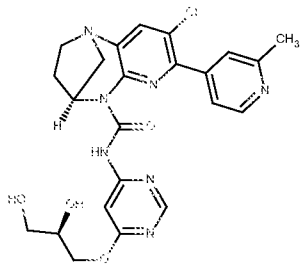
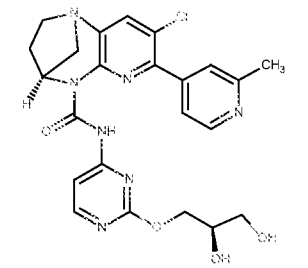
69		(9S)-4-chloro-N-[6-(2-hydroxyethoxy)pyrazin-2-yl]-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
70		(9S)-4-chloro-N-[2-(2-hydroxyethoxy)pyrimidin-4-yl]-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
71		(9S)-4-chloro-N-{6-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A
72		(9S)-4-chloro-N-{6-[(2S)-2,3-dihydroxypropoxy]pyridin-3-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
73		(9S)-4-chloro-N-[6-(3-hydroxypropoxy)pyrazin-2-yl]-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A

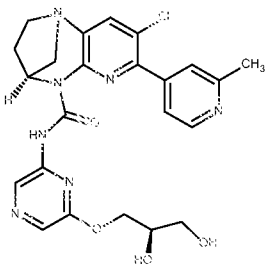
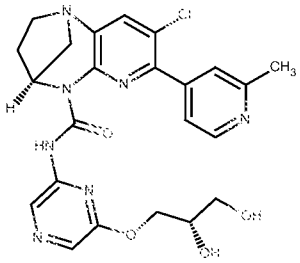
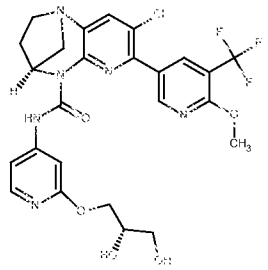
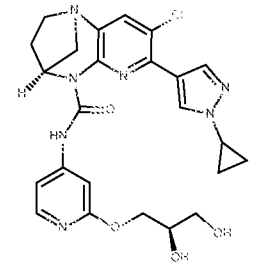
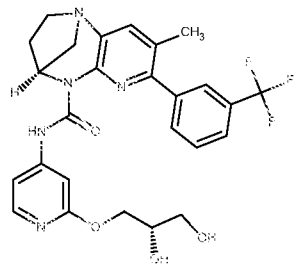
74		(9S)-N-(pyridin-2-yl)-5-[(2R)-2-(trifluoromethyl)pyrrolidin-1-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
74		(9S)-4-chloro-N-[2-(3-hydroxy-2,2-dimethylpropoxy)pyrimidin-4-yl]-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
75		(9S)-4-chloro-N-{6-[(2S)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
76		(9S)-4-chloro-N-{5-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A
77		(9S)-4-chloro-N-{6-[(2R)-2,3-dihydroxypropoxy]pyridin-3-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A

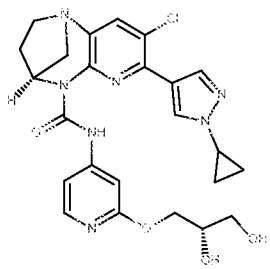
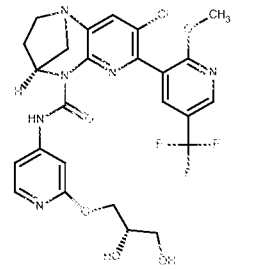
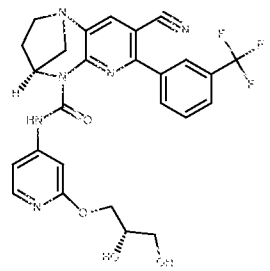
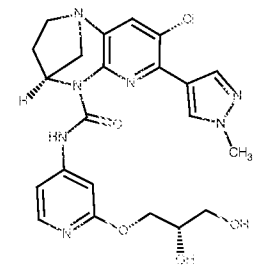
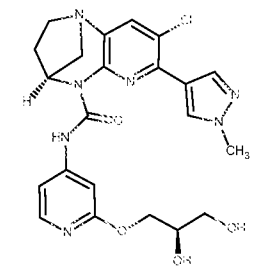
78		(9S)-4-chloro-N-{5-[(2S)-2,3-dihydroxypropoxy]pyridin-3-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
79		(9S)-4-chloro-N-[6-(2-hydroxyethoxy)pyridin-2-yl]-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
80		(9S)-4-chloro-N-{2-[(2S)-2,3-dihydroxypropoxy]pyrimidin-5-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
81		(9S)-4-chloro-N-{5-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
82		(9S)-4-chloro-N-{5-[(2R)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A

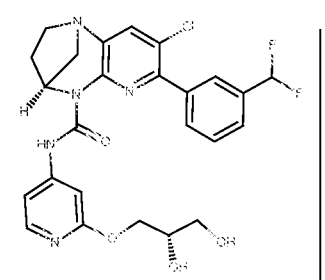
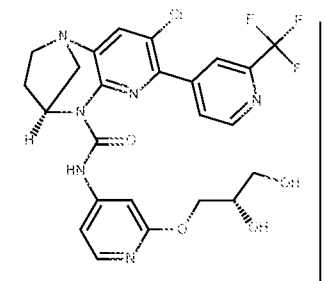
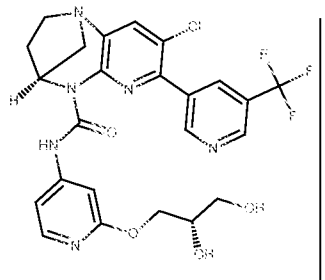
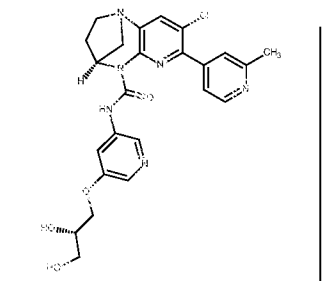
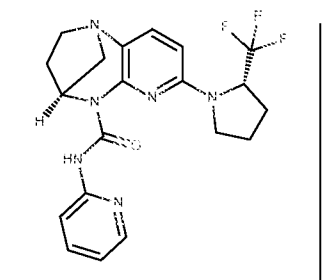
83		(9S)-4-chloro-N-{5-[(2S)-2,3-dihydroxypropoxy]pyrimidin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
84		(9S)-3-methyl-5-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
85		(9S)-N-(pyridin-2-yl)-5-[(3R)-3-(trifluoromethyl)piperidin-1-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
85		(9S)-3-methyl-N-(pyridin-2-yl)-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
86		(9S)-3-methyl-N-[4-(2-methyl-1,3-oxazol-5-yl)pyridin-2-yl]-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A

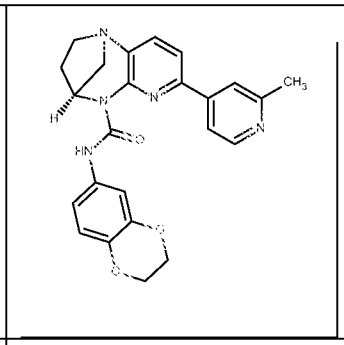
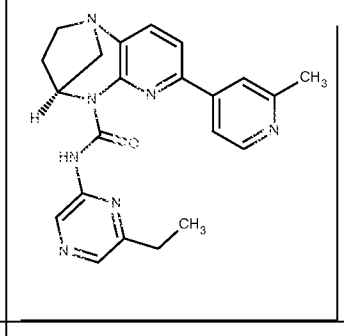
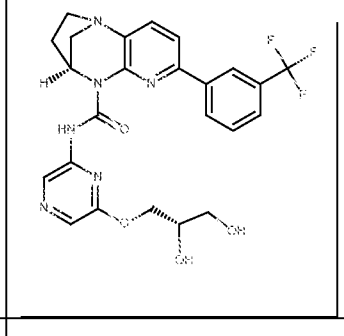
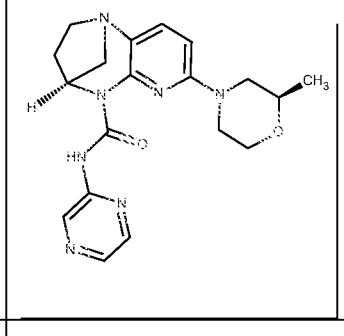
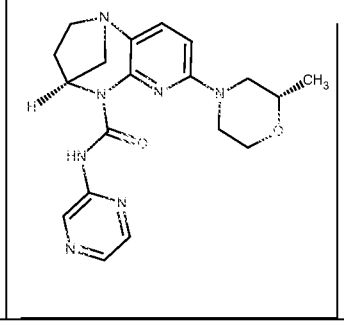
87		(9S)-N-{2-[(2S)-2,3-dihydroxypropoxy]pyridin-4-yl}-3-methyl-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
88		(9S)-4-chloro-N-{6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
89		(9S)-5-[3-(difluoromethyl)phenyl]-N-{2-[(2S)-2,3-dihydroxypropoxy]pyridin-4-yl}-4-methyl-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
90		(9S)-4-chloro-N-{2-[(2R)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-(1-ethyl-1H-pyrazol-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
91		(9S)-3,4-dimethyl-5-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A

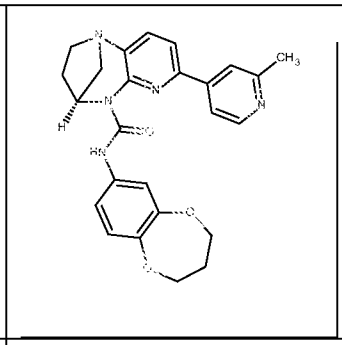
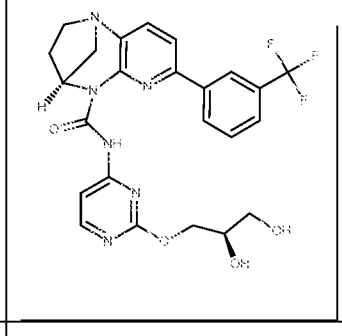
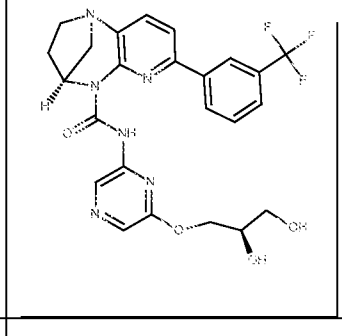
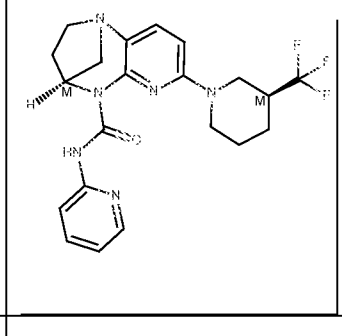
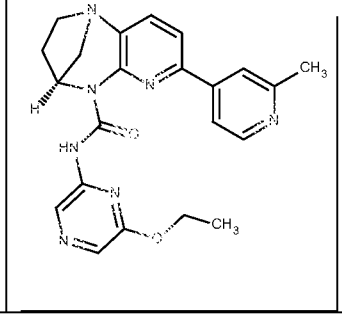
92		(9S)-4-cyano-5-(2-methylpyridin-4-yl)-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
93		(9S)-4-chloro-N-{6-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
94		(9S)-4-chloro-N-{2-[(2S)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	C	B
95		(9S)-4-chloro-N-{6-[(2R)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	C	B
96		(9S)-4-chloro-N-{2-[(2R)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	C	B

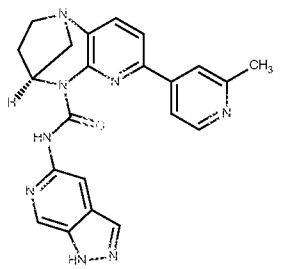
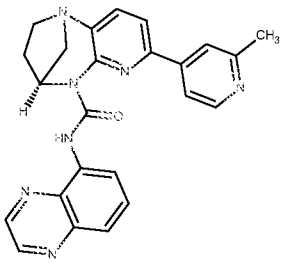
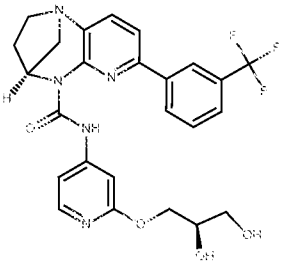
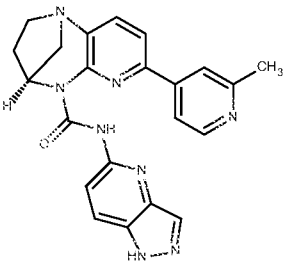
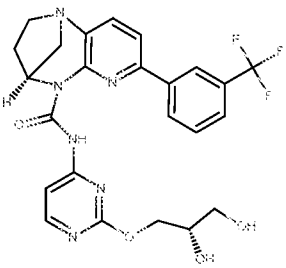
97		(9S)-4-chloro-N-{6-[(2R)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	C	B
98		(9S)-4-chloro-N-{6-[(2S)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	C	B
99		(9S)-4-chloro-N-{2-[(2S)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-[6-methoxy-5-(trifluoromethyl)pyridin-3-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
100		(9S)-4-chloro-5-(1-cyclopropyl-1H-pyrazol-4-yl)-N-{2-[(2R)-2,3-dihydroxypropoxy]pyridin-4-yl}-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
101		(9S)-N-{2-[(2S)-2,3-dihydroxypropoxy]pyridin-4-yl}-4-methyl-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A

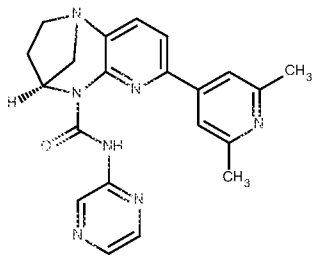
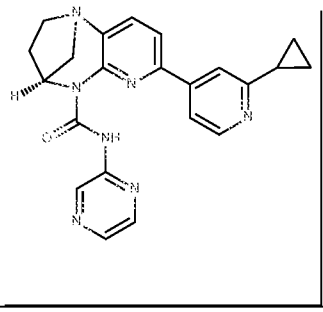
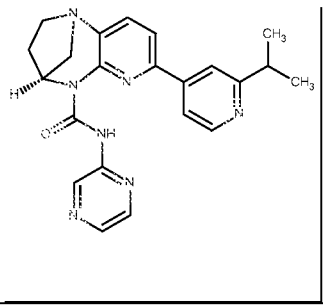
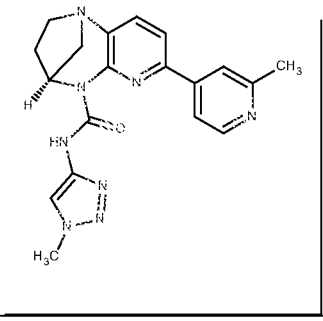
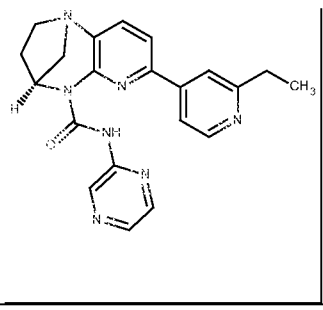
102		(9S)-4-chloro-5-(1-cyclopropyl-1H-pyrazol-4-yl)-N-{2-[(2S)-2,3-dihydroxypropoxy]pyridin-4-yl}-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
103		(9S)-4-chloro-N-{2-[(2S)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-[2-methoxy-5-(trifluoromethyl)pyridin-3-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
104		(9S)-4-cyano-N-{2-[(2S)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A
105		(9S)-4-chloro-N-{2-[(2S)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-(1-methyl-1H-pyrazol-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
106		(9S)-4-chloro-N-{2-[(2R)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-(1-methyl-1H-pyrazol-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

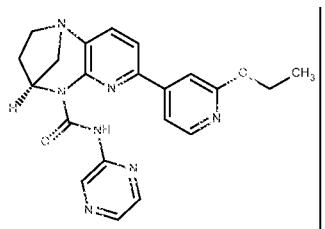
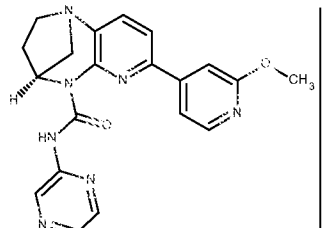
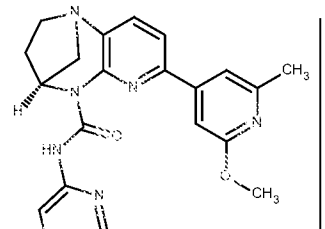
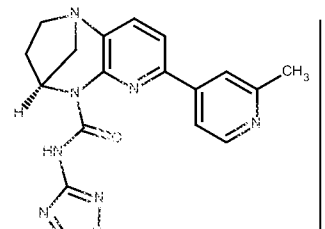
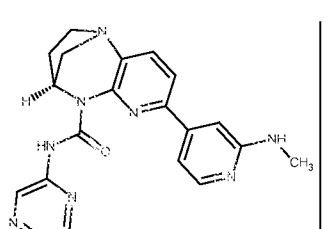
107		(9S)-4-chloro-5-[3-(difluoromethyl)phenyl]-N-{2-[(2S)-2,3-dihydroxypropoxy]pyridin-4-yl}-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
108		(9S)-4-chloro-N-{2-[(2S)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-[2-(trifluoromethyl)pyridin-4-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
109		(9S)-4-chloro-N-{2-[(2S)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-[5-(trifluoromethyl)pyridin-3-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
110		(9S)-4-chloro-N-{5-[(2S)-2,3-dihydroxypropoxy]pyridin-3-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
120		(9S)-N-(pyridin-2-yl)-5-[(2S)-2-(trifluoromethyl)pyrrolidin-1-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

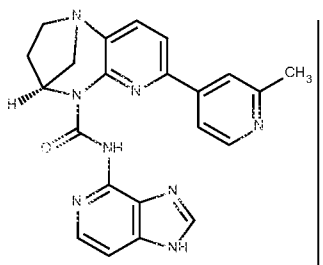
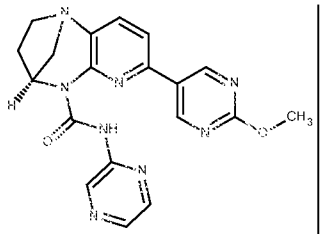
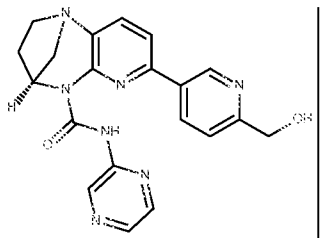
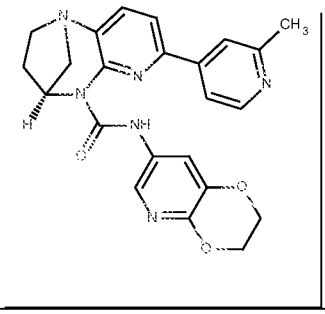
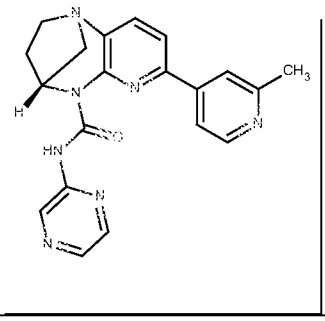
121		(9S)-N-(2,3-dihydro-1,4-benzodioxin-6-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
122		(9S)-N-(6-ethylpyrazin-2-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
123		(9S)-N-{6-[(2S)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
124		(9S)-5-[(2R)-2-methylmorpholin-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
125		(9S)-5-[(2S)-2-methylmorpholin-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A

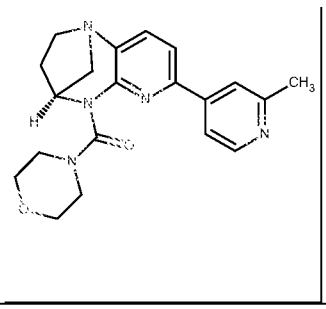
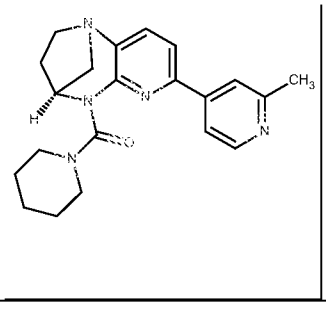
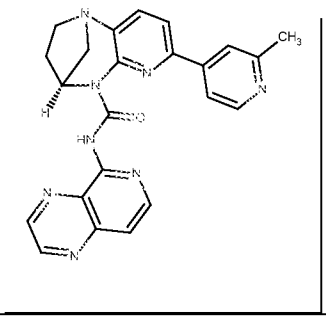
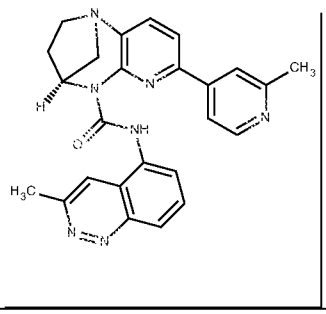
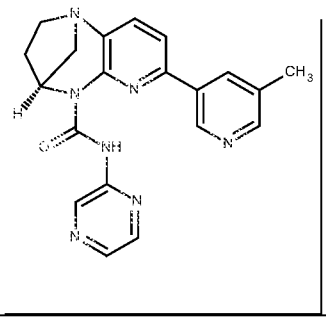
126		(9S)-N-(3,4-dihydro-2H-1,5-benzodioxepin-7-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A
127		(9S)-N-{2-[(2R)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
128		(9S)-N-{6-[(2R)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
129		(9S)-N-(pyridin-2-yl)-5-[(3S)-3-(trifluoromethyl)piperidin-1-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
129		(9S)-N-(6-ethoxypyrazin-2-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A

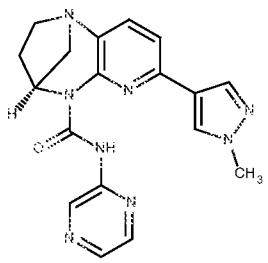
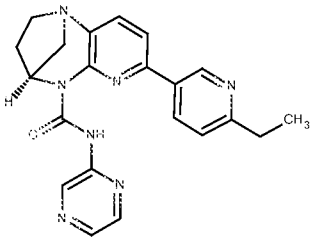
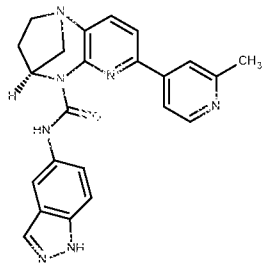
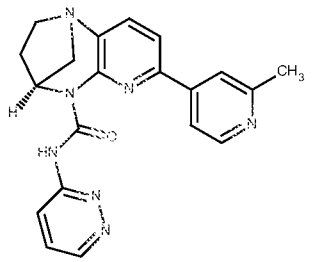
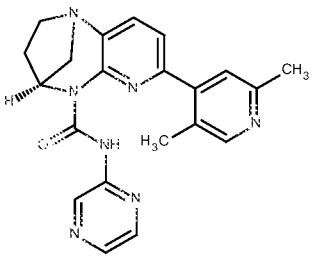
130		(9S)-5-(2-methylpyridin-4-yl)-N-{1H-pyrazolo[3,4-c]pyridin-5-yl}-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
131		(9S)-5-(2-methylpyridin-4-yl)-N-(quinoxalin-5-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
132		(9S)-N-{2-[(2R)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
133		(9S)-5-(2-methylpyridin-4-yl)-N-{1H-pyrazolo[4,3-b]pyridin-5-yl}-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
134		(9S)-N-{2-[(2S)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A

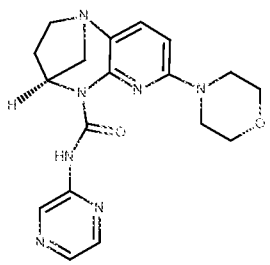
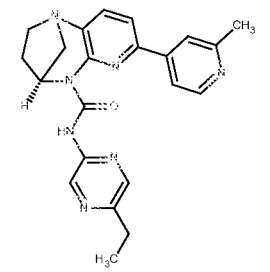
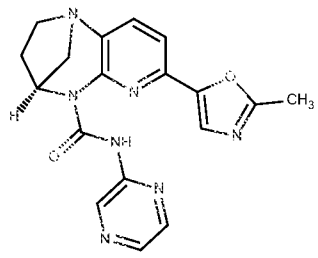
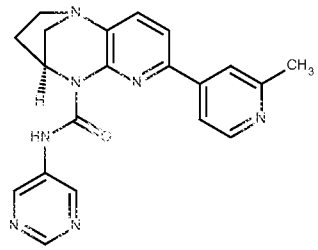
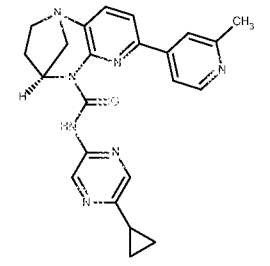
135		(9S)-5-(2,6-dimethylpyridin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
136		(9S)-5-(2-cyclopropylpyridin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A
137		(9S)-5-[2-(propan-2-yl)pyridin-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A
138		(9S)-N-(1-methyl-1H-1,2,3-triazol-4-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
139		(9S)-5-(2-ethylpyridin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A

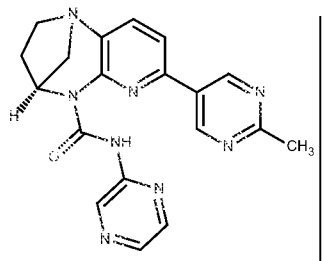
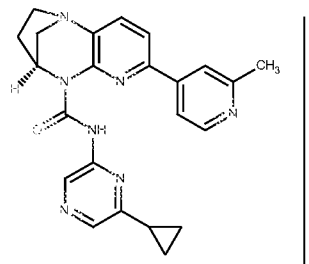
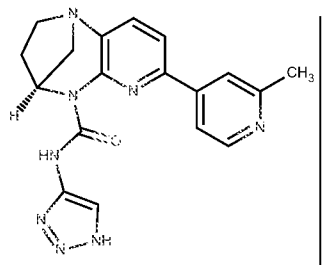
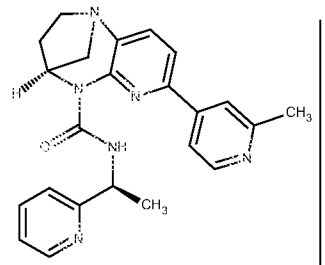
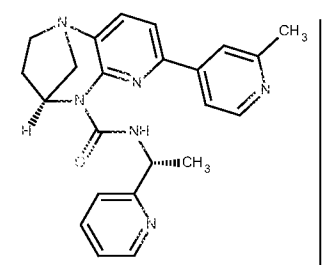
140		(9S)-5-(2-ethoxypyridin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
141		(9S)-5-(2-methoxypyridin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
142		(9S)-5-(2-methoxy-6-methylpyridin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
143		(9S)-N-(1-methyl-1H-1,2,4-triazol-3-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
144		(9S)-5-[2-(methylamino)pyridin-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

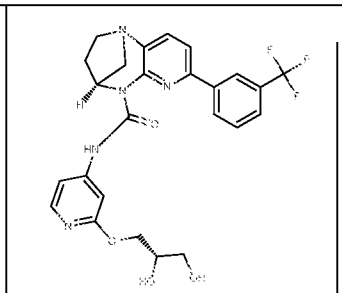
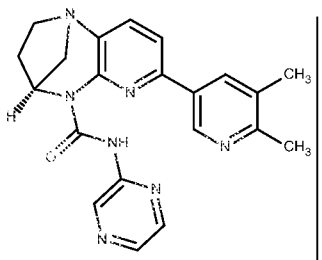
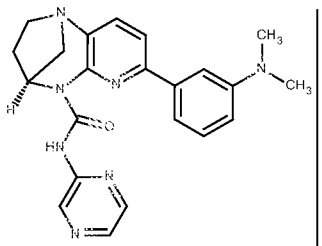
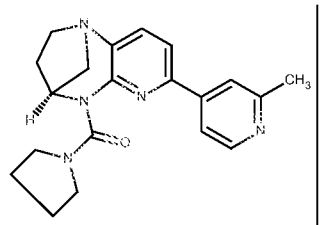
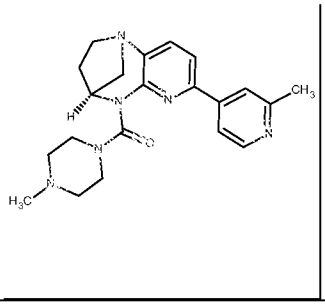
145		(9S)-N-{1H-imidazo[4,5-c]pyridin-4-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
146		(9S)-5-(2-methoxypyrimidin-5-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
147		(9S)-5-[6-(hydroxymethyl)pyridin-3-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
148		(9S)-N-{2H,3H-[1,4]dioxino[2,3-b]pyridin-7-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
149		(9R)-5-(2-methylpyridin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

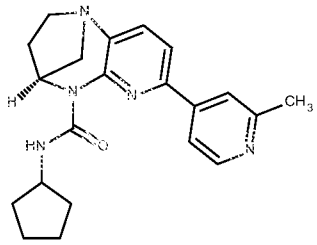
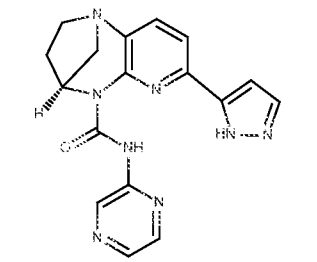
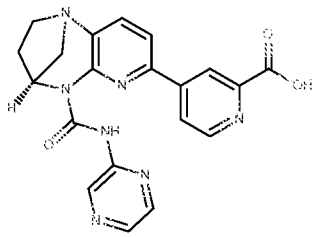
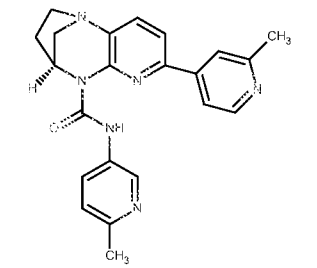
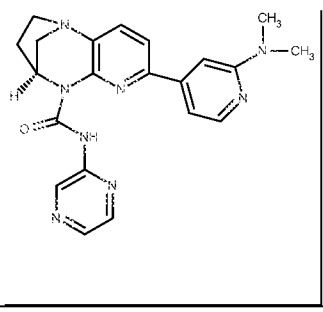
150		(9S)-5-(2-methylpyridin-4-yl)-8-(morpholine-4-carbonyl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene	C	B
151		(9S)-5-(2-methylpyridin-4-yl)-8-(piperidine-1-carbonyl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene	C	B
152		(9S)-5-(2-methylpyridin-4-yl)-N-{pyrido[3,4-b]pyrazin-5-yl}-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
153		(9S)-N-(3-methylcinnolin-5-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
154		(9S)-5-(5-methylpyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

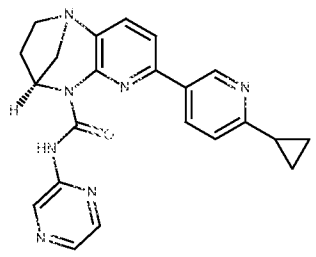
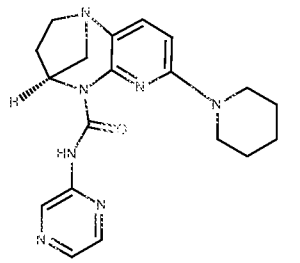
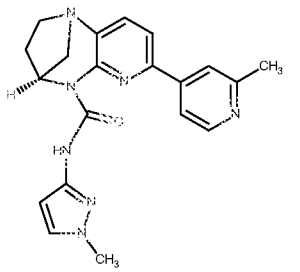
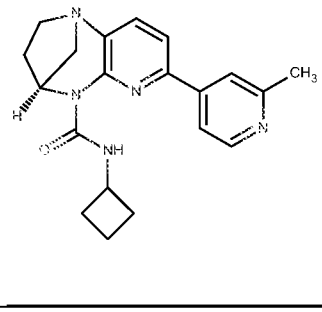
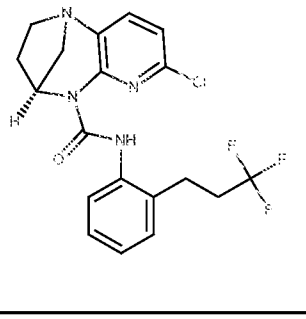
155		(9S)-5-(1-methyl-1H-pyrazol-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
156		(9S)-5-(6-ethylpyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
157		(9S)-N-(1H-indazol-5-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
158		(9S)-5-(2-methylpyridin-4-yl)-N-(pyridazin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
159		(9S)-5-(2,5-dimethylpyridin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A

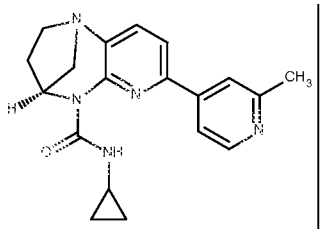
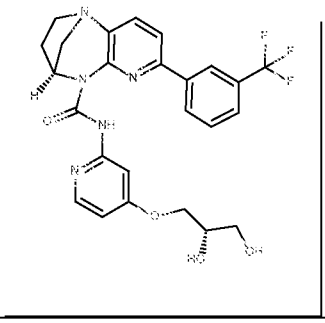
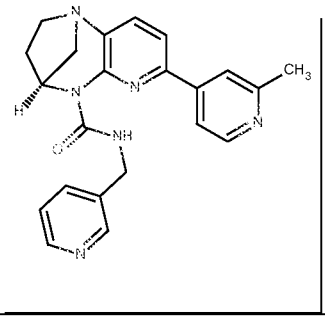
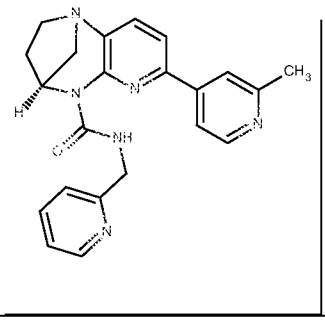
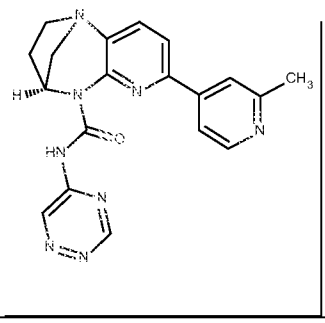
160		(9S)-5-(morpholin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
161		(9S)-N-(5-ethylpyrazin-2-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
162		(9S)-5-(2-methyl-1,3-oxazol-5-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
163		(9S)-5-(2-methylpyridin-4-yl)-N-(pyrimidin-5-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	C	A
164		(9S)-N-(5-cyclopropylpyrazin-2-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

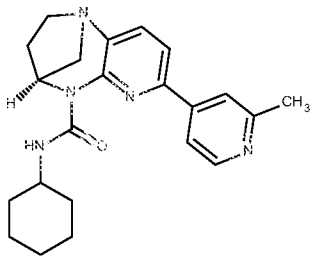
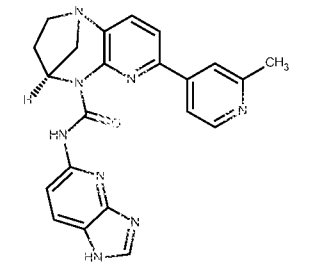
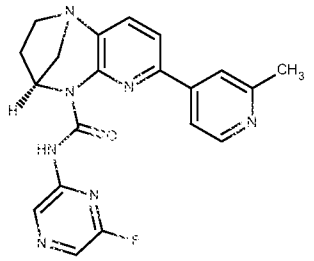
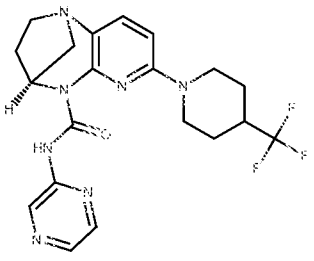
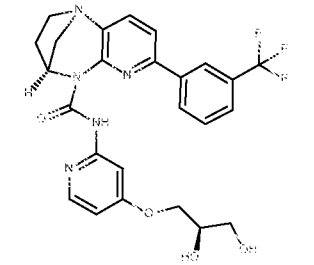
165		(9S)-5-(2-methylpyrimidin-5-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
166		(9S)-N-(6-cyclopropylpyrazin-2-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
167		(9S)-5-(2-methylpyridin-4-yl)-N-(1H-1,2,3-triazol-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
168		(9S)-5-(2-methylpyridin-4-yl)-N-[(1S)-1-(pyridin-2-yl)ethyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	C	B
169		(9S)-5-(2-methylpyridin-4-yl)-N-[(1R)-1-(pyridin-2-yl)ethyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	C	B

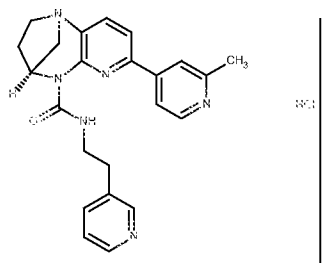
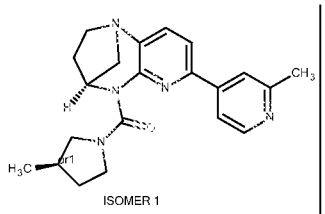
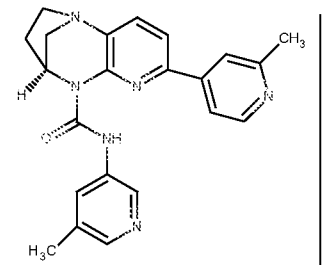
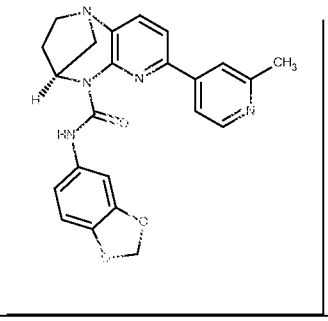
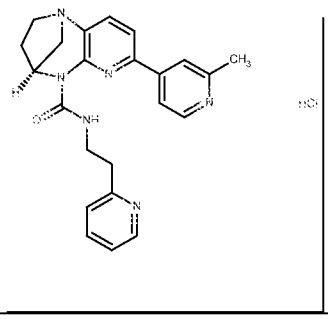
170		(9S)-N-{2-[(2S)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A
171		(9S)-5-(5,6-dimethylpyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
172		(9S)-5-[3-(dimethylamino)phenyl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
173		(9S)-5-(2-methylpyridin-4-yl)-8-(pyrrolidine-1-carbonyl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene	C	B
174		(9S)-8-(4-methylpiperazine-1-carbonyl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene	C	B

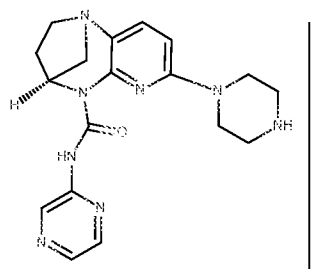
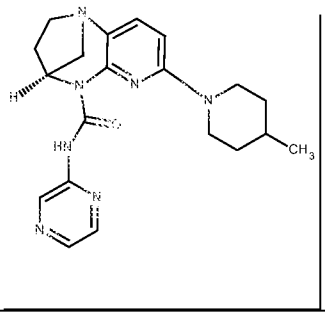
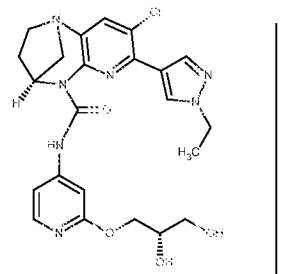
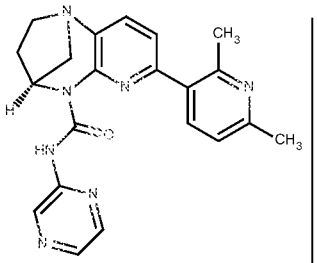
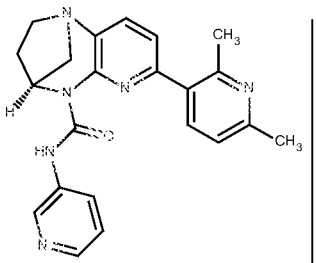
175		(9S)-N-cyclopentyl-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
176		(9S)-N-(pyrazin-2-yl)-5-(1H-pyrazol-5-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
177		4-[(9S)-8-[(pyrazin-2-yl)carbamoyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-trien-5-yl]pyridine-2-carboxylic acid	C	B
178		(9S)-N-(6-methylpyridin-3-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
179		(9S)-5-[2-(dimethylamino)pyridin-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

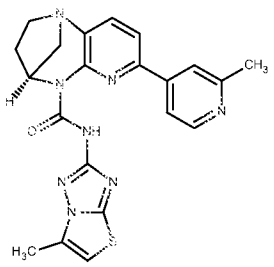
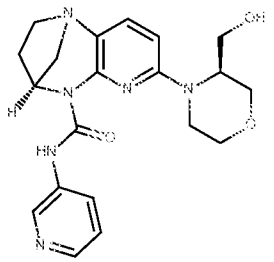
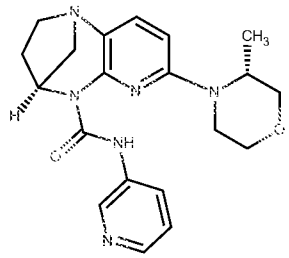
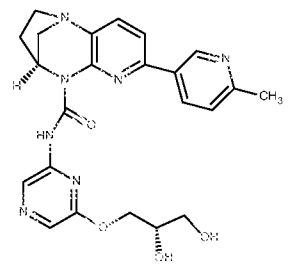
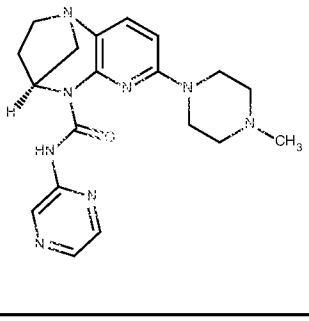
180		(9S)-5-(6-cyclopropylpyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
181		(9S)-5-(piperidin-1-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
182		(9S)-N-(1-methyl-1H-pyrazol-3-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
183		(9S)-N-cyclobutyl-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
184		(9S)-5-chloro-N-[2-(3,3,3-trifluoropropyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

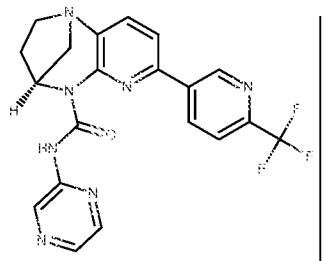
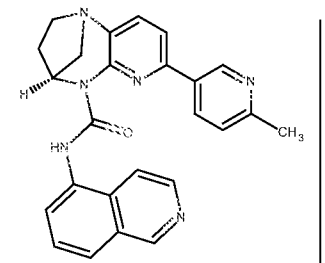
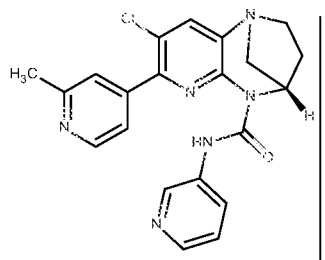
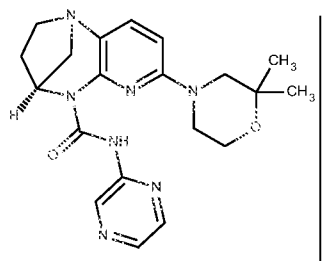
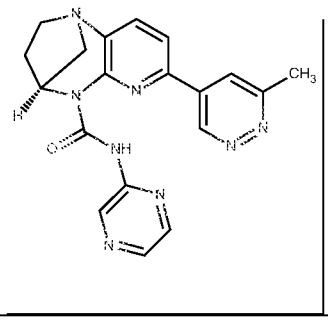
184		(9S)-N-cyclopropyl-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
185		(9S)-N-{4-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
185		(9S)-5-(2-methylpyridin-4-yl)-N-(pyridin-3-ylmethyl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	C	B
186		(9S)-5-(2-methylpyridin-4-yl)-N-(pyridin-2-ylmethyl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	C	B
187		(9S)-5-(2-methylpyridin-4-yl)-N-(1,2,4-triazin-5-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	C	B

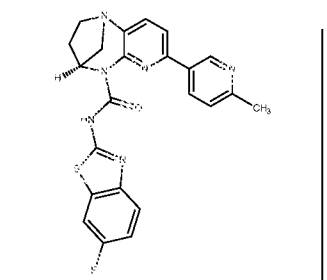
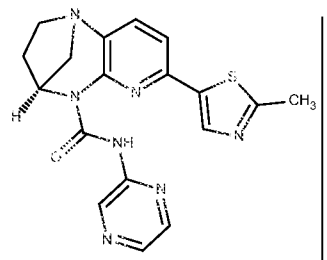
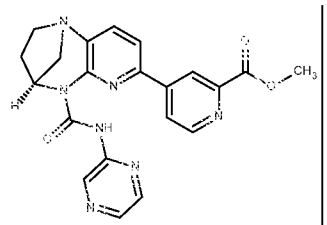
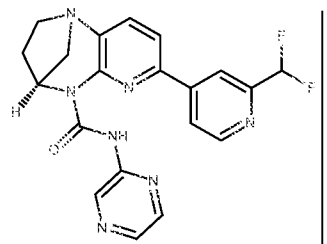
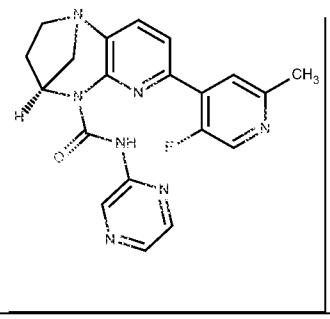
188		(9S)-N-cyclohexyl-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
189		(9S)-N-{1H-imidazo[4,5-b]pyridin-5-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
190		(9S)-N-(6-fluoropyrazin-2-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
191		(9S)-N-(pyrazin-2-yl)-5-[4-(trifluoromethyl)piperidin-1-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
192		(9S)-N-{4-[(2R)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A

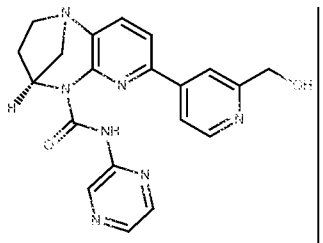
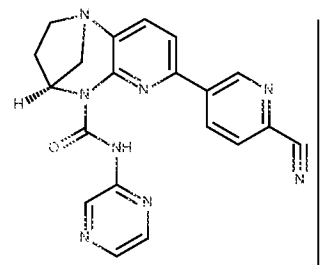
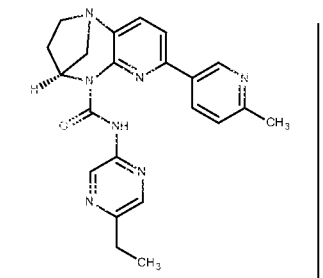
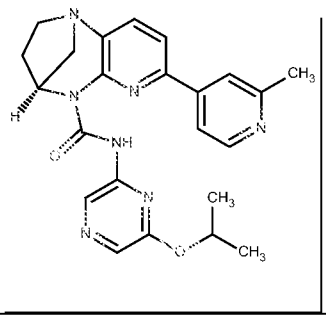
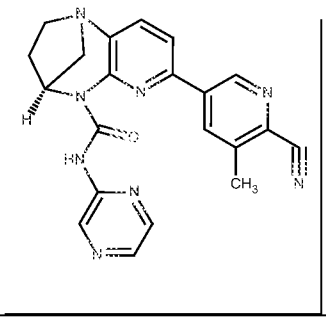
192		(9S)-5-(2-methylpyridin-4-yl)-N-[2-(pyridin-3-yl)ethyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide hydrochloride	C	B
193		(9S)-5-(2-methylpyridin-4-yl)-8-[(3R)-3-methylpyrrolidine-1-carbonyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene	C	B
194		(9S)-N-(5-methylpyridin-3-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
195		(9S)-N-(2H-1,3-benzodioxol-5-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
196		(9S)-5-(2-methylpyridin-4-yl)-N-[2-(pyridin-2-yl)ethyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide hydrochloride	C	B

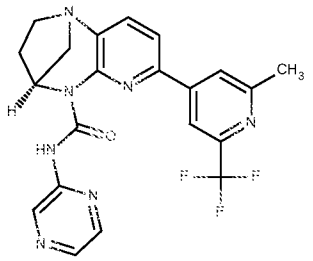
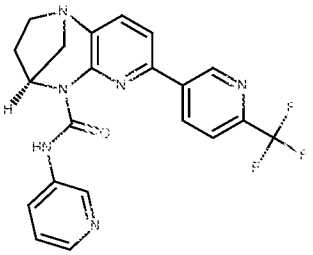
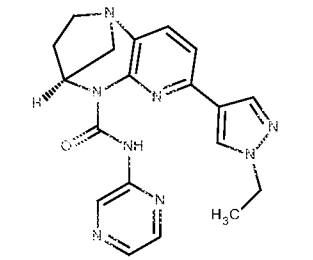
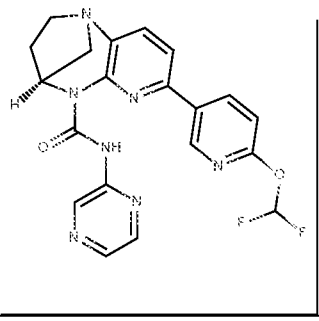
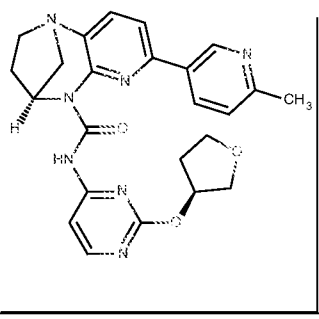
197		(9S)-5-(piperazin-1-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	C	B
198		(9S)-5-(4-methylpiperidin-1-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
199		(9S)-4-chloro-N-{2-[(2S)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-(1-ethyl-1H-pyrazol-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
200		(9S)-5-(2,6-dimethylpyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
201		(9S)-5-(2,6-dimethylpyridin-3-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

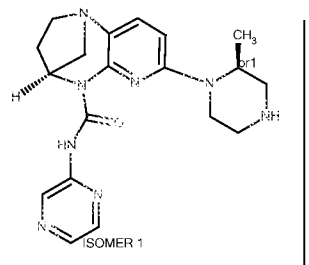
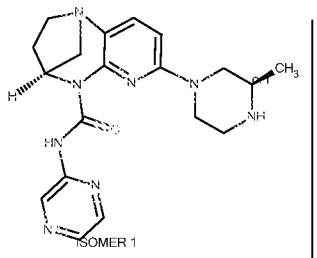
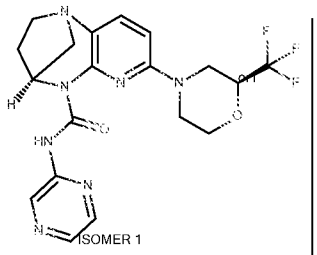
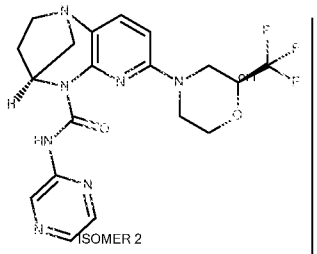
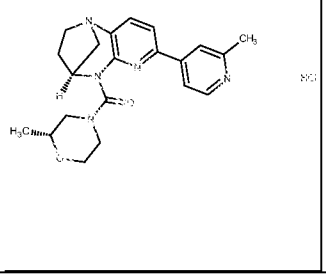
202		(9S)-N-{6-methyl-[1,2,4]triazolo[3,2-b][1,3]thiazol-2-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
203		(9S)-5-[(3S)-3-(hydroxymethyl)morpholin-4-yl]-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	C	B
204		(9S)-5-[(3R)-3-methylmorpholin-4-yl]-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
205		(9S)-N-{6-[(2S)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-(6-methylpyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
206		(9S)-5-(4-methylpiperazin-1-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

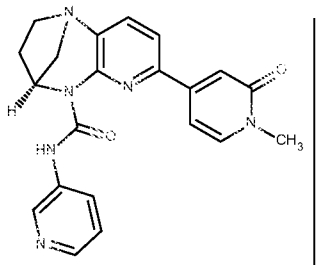
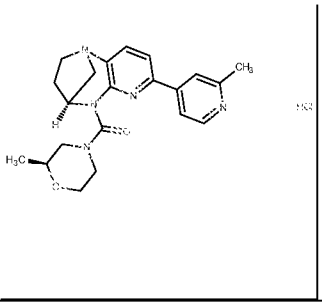
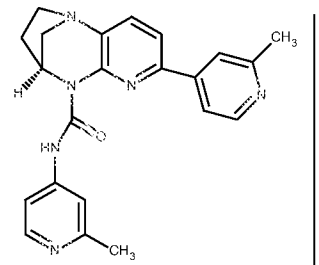
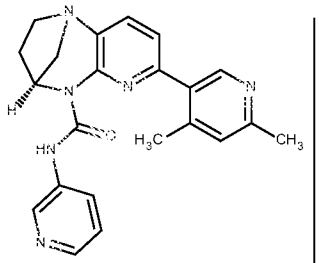
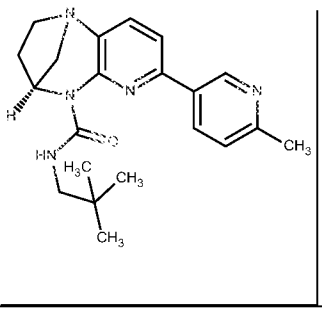
208		(9S)-N-(pyrazin-2-yl)-5-[6-(trifluoromethyl)pyridin-3-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
209		(9S)-N-(isoquinolin-5-yl)-5-(6-methylpyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
210		(9S)-4-chloro-5-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
211		(9S)-5-(2,2-dimethylmorpholin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
212		(9S)-5-(6-methylpyridazin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

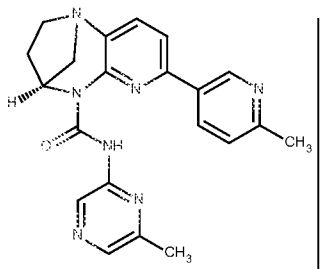
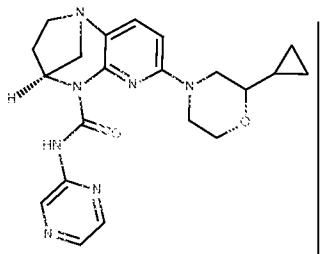
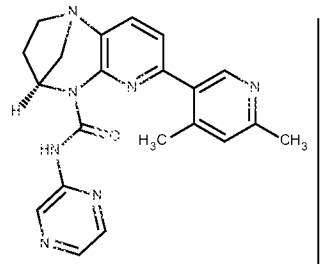
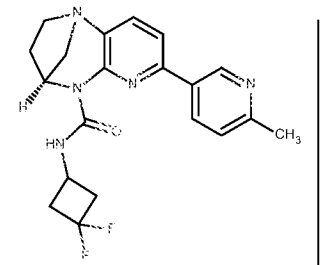
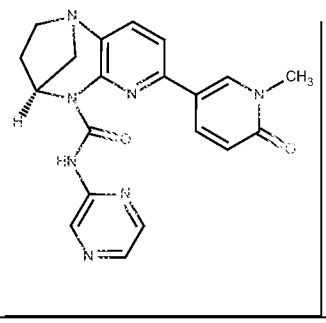
213		(9S)-N-(6-fluoro-1,3-benzothiazol-2-yl)-5-(6-methylpyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
214		(9S)-5-(2-methyl-1,3-thiazol-5-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
215		methyl 4-[(9S)-8-[(pyrazin-2-yl)carbamoyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-trien-5-yl]pyridine-2-carboxylate	B	A
216		(9S)-5-[2-(difluoromethyl)pyridin-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
217		(9S)-5-(5-fluoro-2-methylpyridin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

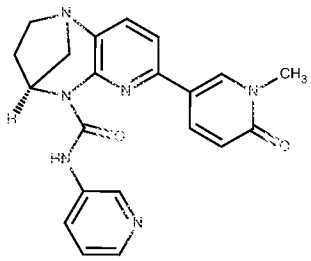
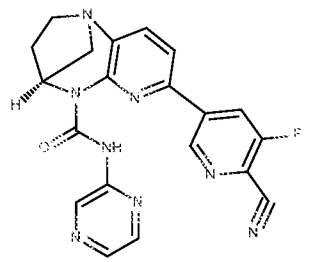
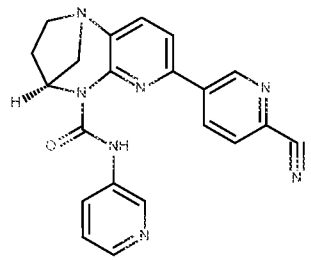
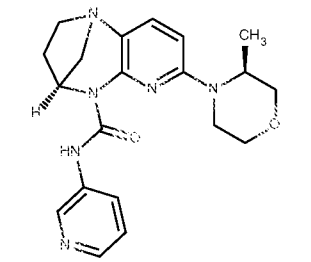
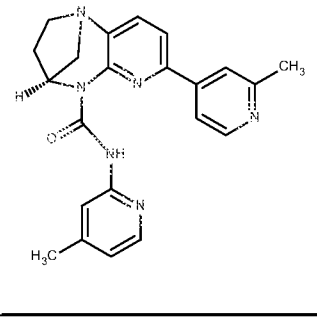
218		(9S)-5-[2-(hydroxymethyl)pyridin-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
219		(9S)-5-(6-cyanopyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	C	B
220		(9S)-N-(5-ethylpyrazin-2-yl)-5-(6-methylpyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
221		(9S)-5-(2-methylpyridin-4-yl)-N-[6-(propan-2-yloxy)pyrazin-2-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
222		(9S)-5-(6-cyano-5-methylpyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

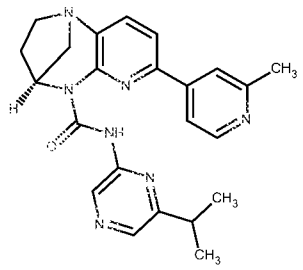
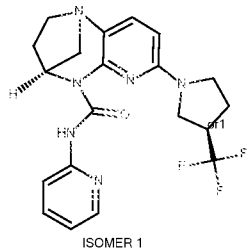
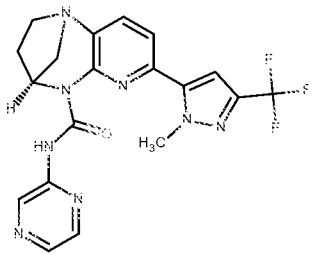
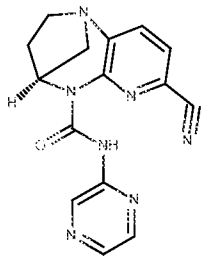
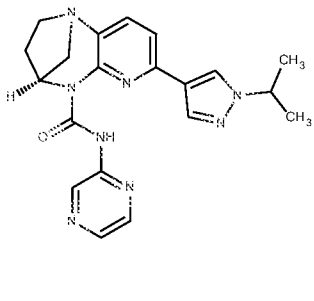
223		(9S)-5-[2-methyl-6-(trifluoromethyl)pyridin-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
224		(9S)-N-(pyridin-3-yl)-5-[6-(trifluoromethyl)pyridin-3-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
225		(9S)-5-(1-ethyl-1H-pyrazol-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
226		(9S)-5-[6-(difluoromethoxy)pyridin-3-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
227		(9S)-5-(6-methylpyridin-3-yl)-N-{2-[(3S)-oxolan-3-yloxy]pyrimidin-4-yl}-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A

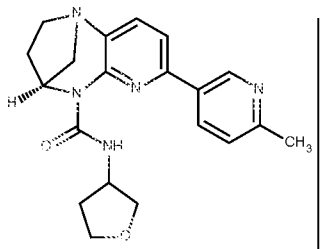
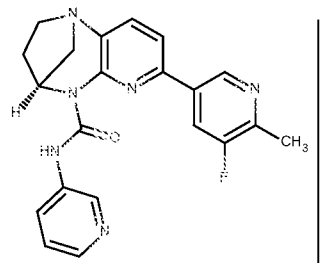
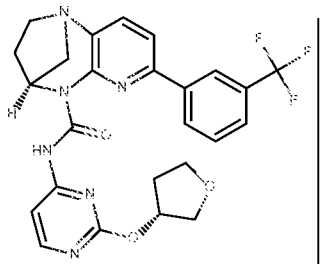
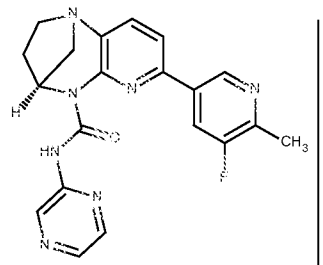
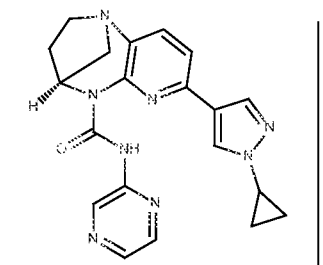
228		(9S)-5-[(2S)-2-methylpiperazin-1-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	C	B
229		(9S)-5-[(3R)-3-methylpiperazin-1-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	C	B
230		(9S)-N-(pyrazin-2-yl)-5-[(2S)-2-(trifluoromethyl)morpholin-4-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
231		(9S)-N-(pyrazin-2-yl)-5-[(2S)-2-(trifluoromethyl)morpholin-4-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
232		(9S)-8-[(2R)-2-methylmorpholine-4-carbonyl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene hydrochloride	C	B

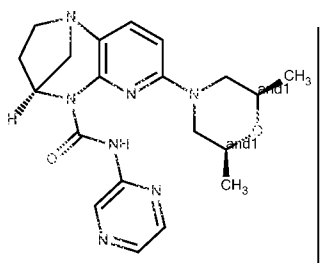
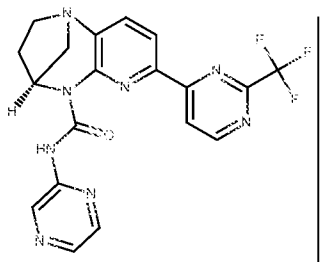
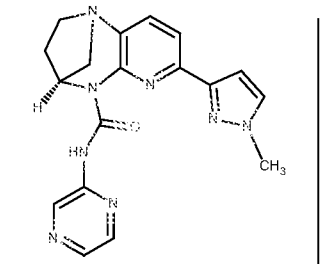
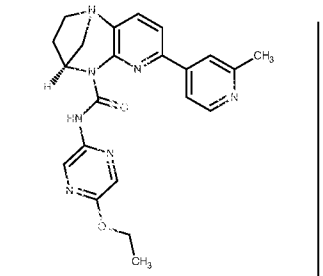
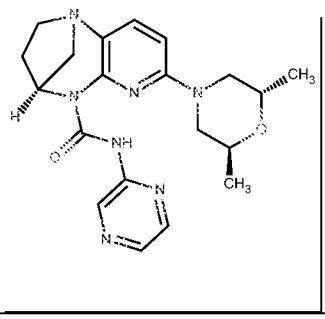
233		(9S)-5-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
234		(9S)-8-[(2S)-2-methylmorpholine-4-carbonyl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene hydrochloride	C	B
235		(9S)-N,5-bis(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
236		(9S)-5-(4,6-dimethylpyridin-3-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
237		(9S)-N-(2,2-dimethylpropyl)-5-(6-methylpyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	C	B

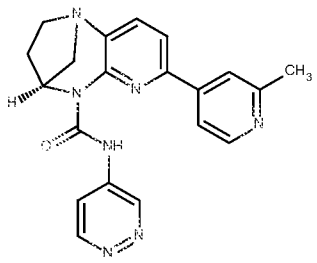
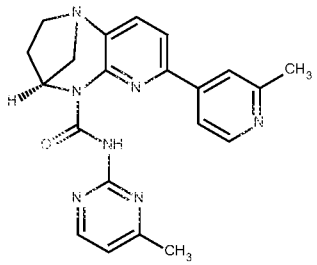
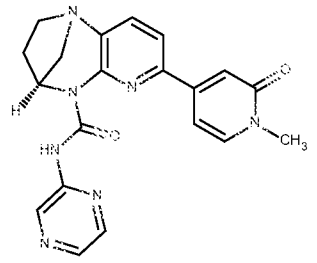
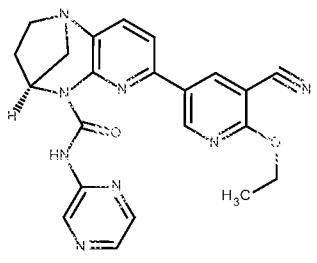
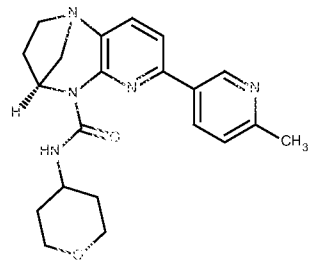
238		(9S)-N-(6-methylpyrazin-2-yl)-5-(6-methylpyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
239		(9S)-5-(2-cyclopropylmorpholin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
240		(9S)-5-(4,6-dimethylpyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	C	B
241		(9S)-N-(3,3-difluorocyclobutyl)-5-(6-methylpyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
242		(9S)-5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	C	B

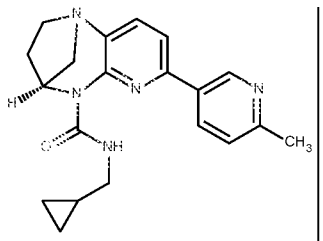
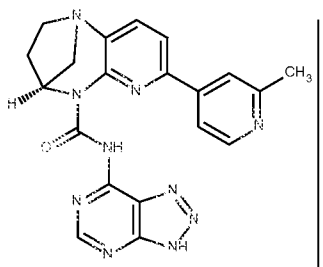
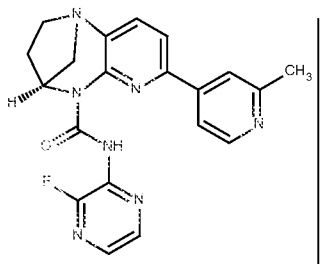
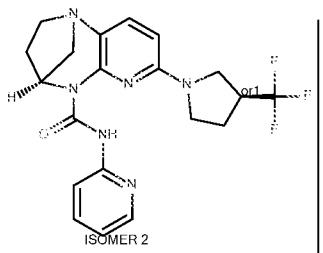
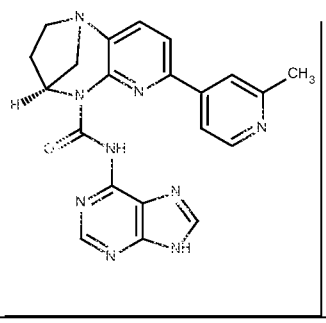
243		(9S)-5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
244		(9S)-5-(6-cyano-5-fluoropyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	C	B
245		(9S)-5-(6-cyanopyridin-3-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
246		(9S)-5-[(3S)-3-methylmorpholin-4-yl]-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
247		(9S)-N-(4-methylpyridin-2-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A

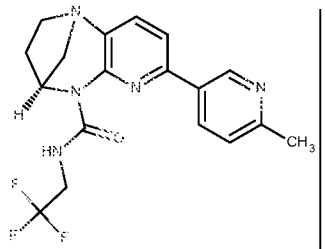
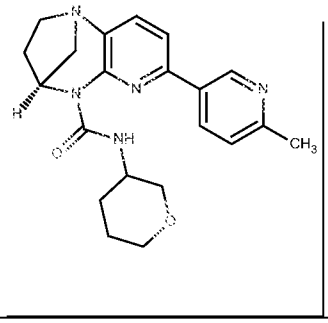
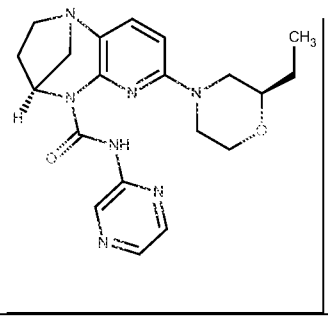
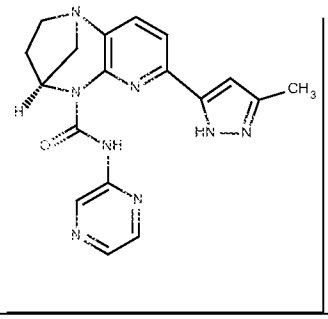
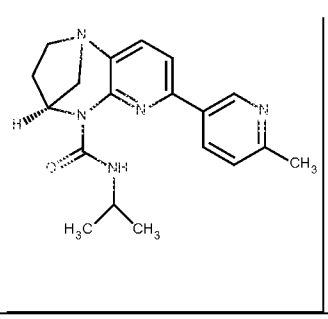
248		(9S)-5-(2-methylpyridin-4-yl)-N-[6-(propan-2-yl)pyrazin-2-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
249	 ISOMER 1	(9S)-N-(pyridin-2-yl)-5-[(3R)-3-(trifluoromethyl)pyrrolidin-1-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A
250		(9S)-5-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
251		(9S)-5-cyano-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	C	B
252		(9S)-5-[1-(propan-2-yl)-1H-pyrazol-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A

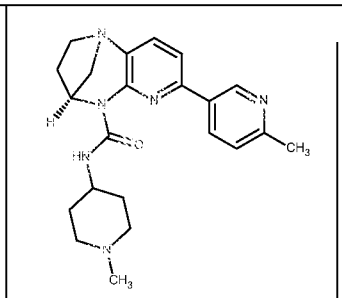
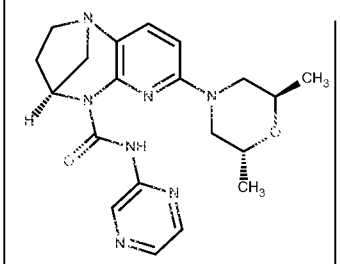
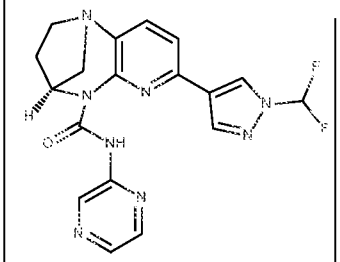
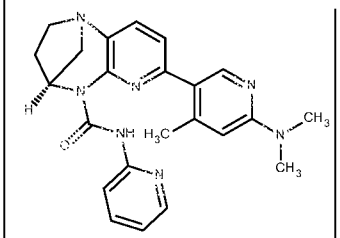
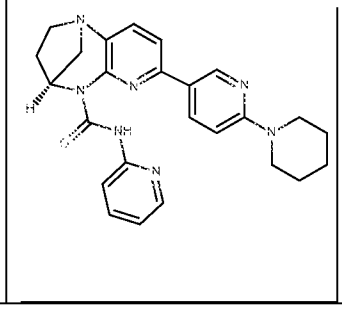
253		(9S)-5-(6-methylpyridin-3-yl)-N-(oxolan-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	C	B
254		(9S)-5-(5-fluoro-6-methylpyridin-3-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
255		(9S)-N-{2-[(3R)-oxolan-3-yloxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
255		(9S)-5-(5-fluoro-6-methylpyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
256		(9S)-5-(1-cyclopropyl-1H-pyrazol-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

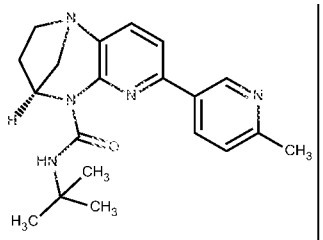
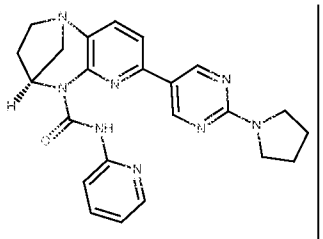
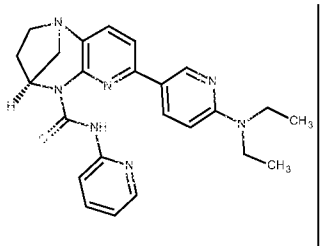
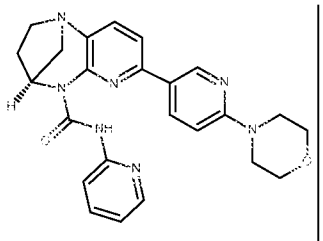
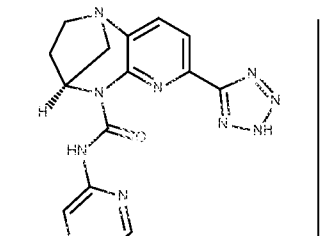
257		(9S)-5-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
258		(9S)-N-(pyrazin-2-yl)-5-[2-(trifluoromethyl)pyrimidin-4-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
259		(9S)-5-(1-methyl-1H-pyrazol-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
260		(9S)-N-(5-ethoxypyrazin-2-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
261		(9S)-5-[(2S,6S)-2,6-dimethylmorpholin-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

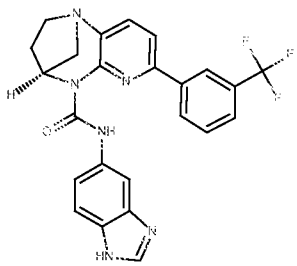
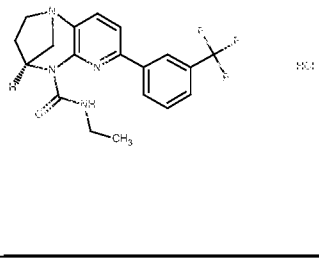
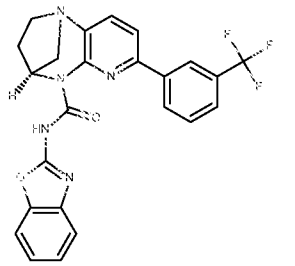
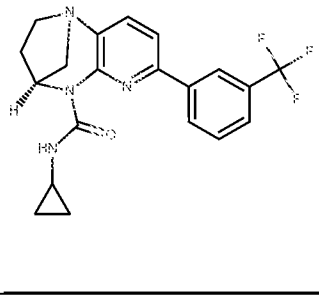
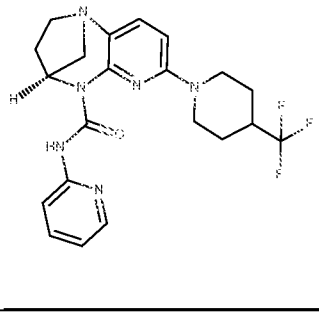
262		(9S)-5-(2-methylpyridin-4-yl)-N-(pyridazin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
263		(9S)-5-(2-methylpyridin-4-yl)-N-(4-methylpyrimidin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
264		(9S)-5-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
265		(9S)-5-(5-cyano-6-ethoxypyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	C	B
266		(9S)-5-(6-methylpyridin-3-yl)-N-(oxan-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	C	B

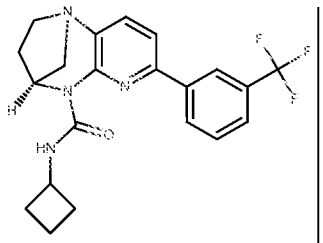
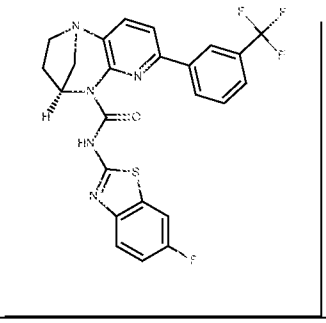
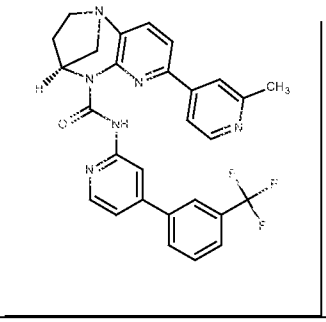
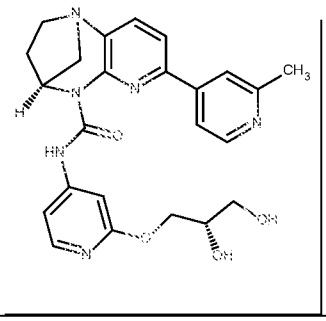
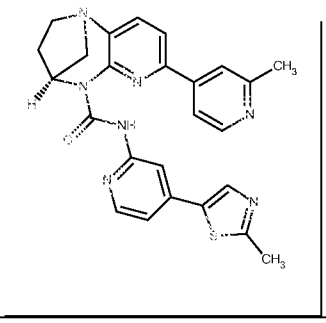
267		(9S)-N-(cyclopropylmethyl)-5-(6-methylpyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
268		(9S)-5-(2-methylpyridin-4-yl)-N-{3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl}-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	C	B
269		(9S)-N-(3-fluoropyrazin-2-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
270		(9S)-N-(pyridin-2-yl)-5-[(3S)-3-(trifluoromethyl)pyrrolidin-1-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
271		(9S)-5-(2-methylpyridin-4-yl)-N-(9H-purin-6-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A

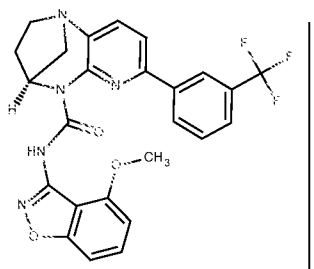
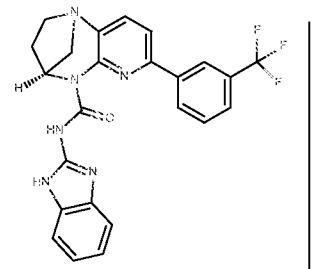
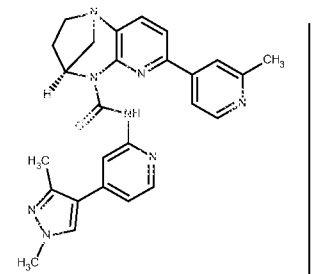
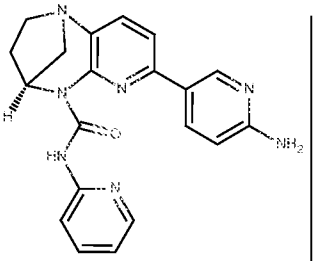
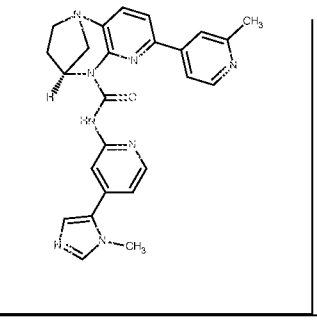
272		(9S)-5-(6-methylpyridin-3-yl)-N-(2,2,2-trifluoroethyl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
273		(9S)-5-(6-methylpyridin-3-yl)-N-(oxan-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	C	B
274		(9S)-5-[(2R)-2-ethylmorpholin-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
275		(9S)-5-(3-methyl-1H-pyrazol-5-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
276		(9S)-5-(6-methylpyridin-3-yl)-N-(propan-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A

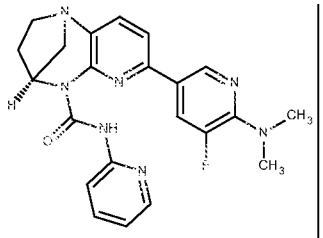
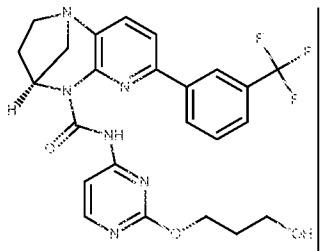
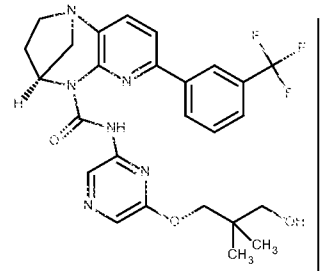
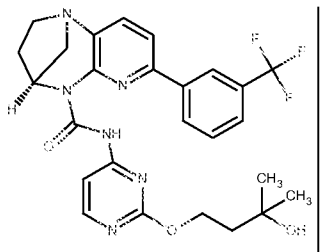
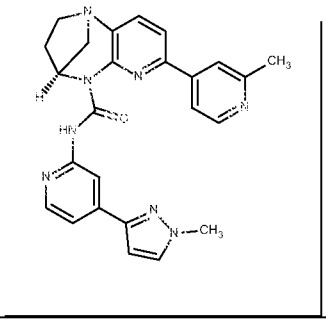
277		(9S)-N-(1-methylpiperidin-4-yl)-5-(6-methylpyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	C	B
278		(9S)-5-[(2R,6R)-2,6-dimethylmorpholin-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
279		(9S)-5-[1-(difluoromethyl)-1H-pyrazol-4-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
280		(9S)-5-[6-(dimethylamino)-4-methylpyridin-3-yl]-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
281		(9S)-5-[6-(piperidin-1-yl)pyridin-3-yl]-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

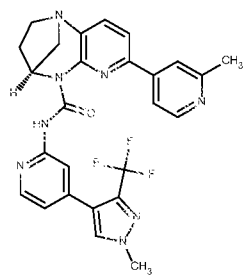
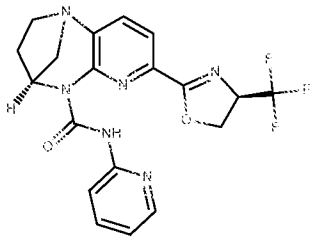
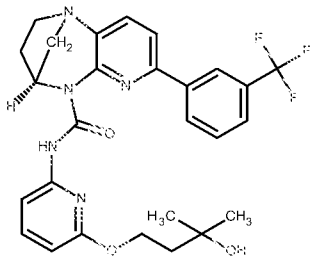
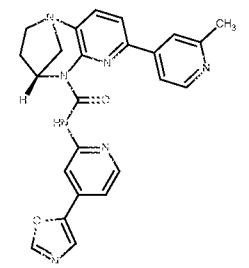
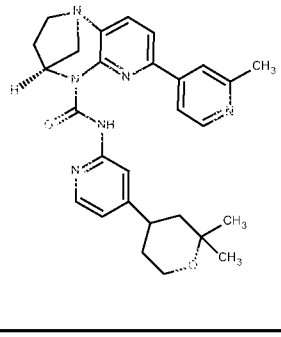
282		(9S)-N-tert-butyl-5-(6-methylpyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
283		(9S)-N-(pyridin-2-yl)-5-[2-(pyrrolidin-1-yl)pyrimidin-5-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
284		(9S)-5-[6-(diethylamino)pyridin-3-yl]-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
285		(9S)-5-[6-(morpholin-4-yl)pyridin-3-yl]-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
286		(9S)-N-(pyrazin-2-yl)-5-(2H-1,2,3,4-tetrazol-5-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	C	B

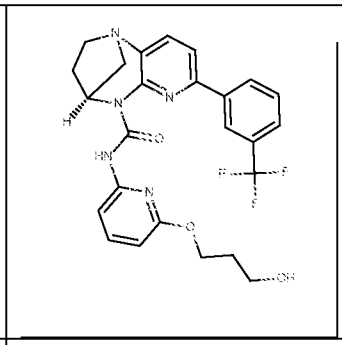
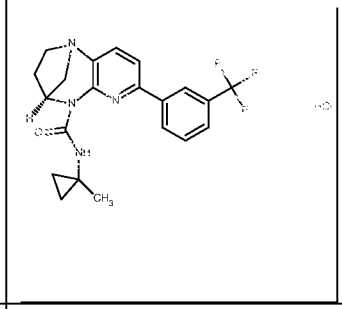
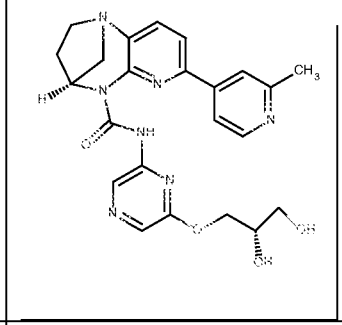
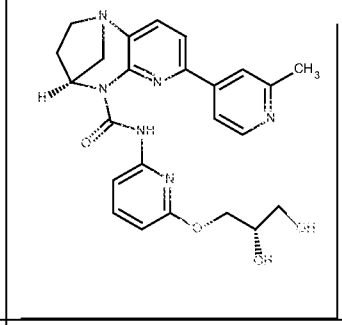
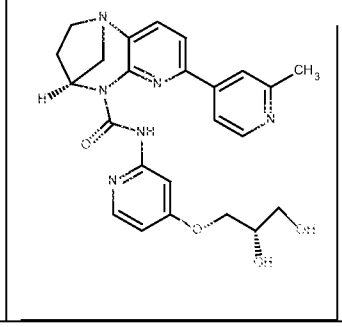
287		(9S)-N-(1H-1,3-benzodiazol-5-yl)-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A
288		(9S)-N-ethyl-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide hydrochloride	A	A
289		(9S)-N-(1,3-benzoxazol-2-yl)-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
290		(9S)-N-cyclopropyl-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
291		(9S)-N-(pyridin-2-yl)-5-[4-(trifluoromethyl)piperidin-1-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A

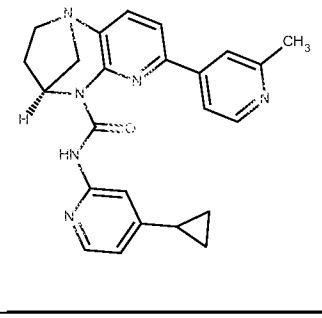
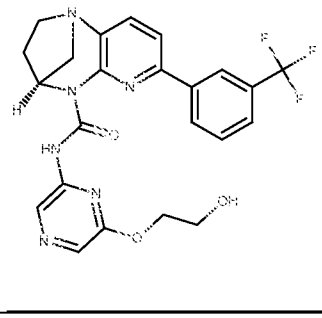
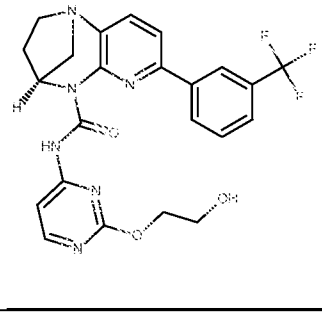
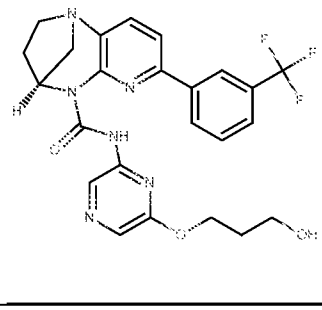
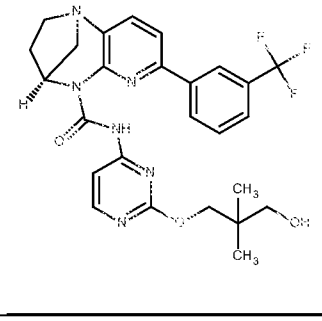
291		(9S)-N-cyclobutyl-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
292		(9S)-N-(6-fluoro-1,3-benzothiazol-2-yl)-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
293		(9S)-5-(2-methylpyridin-4-yl)-N-{4-[3-(trifluoromethyl)phenyl]pyridin-2-yl}-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
294		(9S)-N-{2-[(2S)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
295		(9S)-N-[4-(2-methyl-1,3-thiazol-5-yl)pyridin-2-yl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A

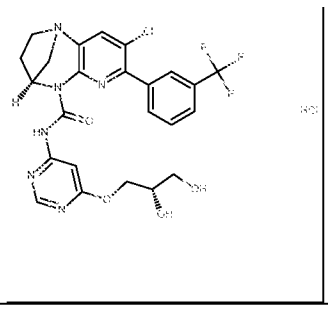
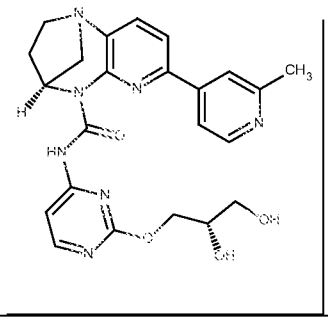
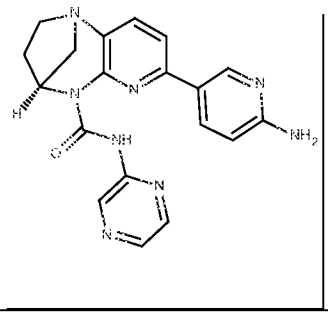
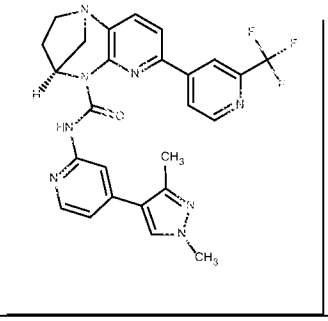
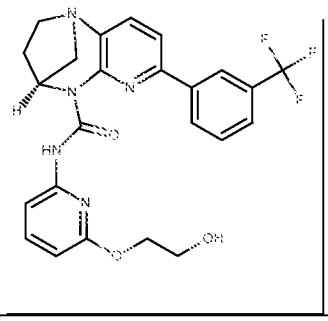
296		(9S)-N-(4-methoxy-1,2-benzoxazol-3-yl)-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A
297		(9S)-N-(1H-1,3-benzodiazol-2-yl)-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A
298		(9S)-N-[4-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-2-yl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
299		(9S)-5-(6-aminopyridin-3-yl)-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
300		(9S)-N-[4-(1-methyl-1H-imidazol-5-yl)pyridin-2-yl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

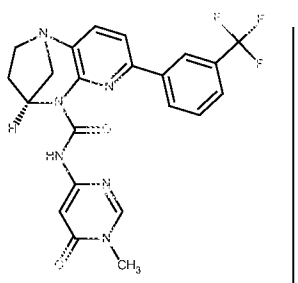
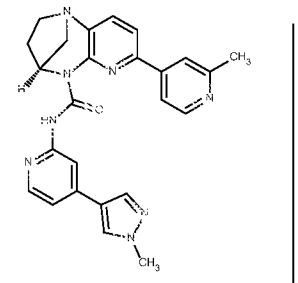
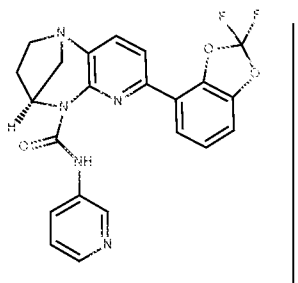
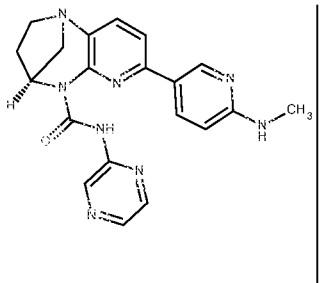
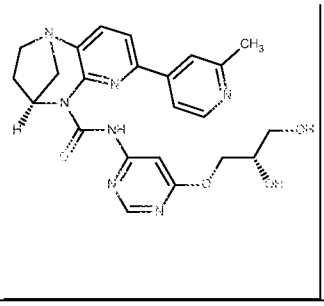
301		(9S)-5-[6-(dimethylamino)-5-fluoropyridin-3-yl]-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
302		(9S)-N-[2-(3-hydroxypropoxy)pyrimidin-4-yl]-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
303		(9S)-N-[6-(3-hydroxy-2,2-dimethylpropoxy)pyrazin-2-yl]-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
304		(9S)-N-[2-(3-hydroxy-3-methylbutoxy)pyrimidin-4-yl]-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
305		(9S)-N-[4-(1-methyl-1H-pyrazol-3-yl)pyridin-2-yl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A

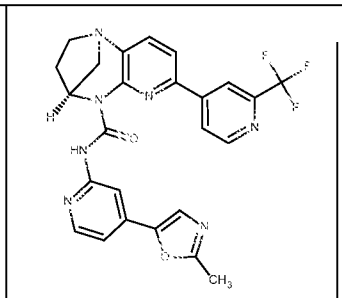
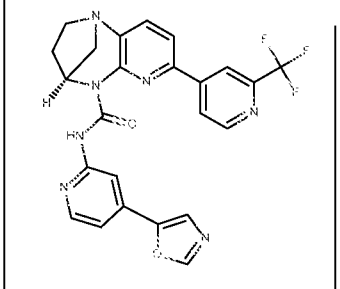
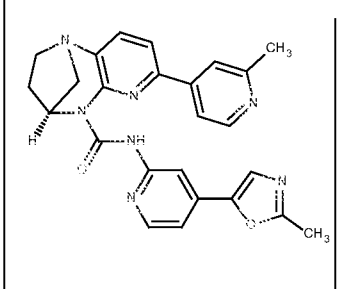
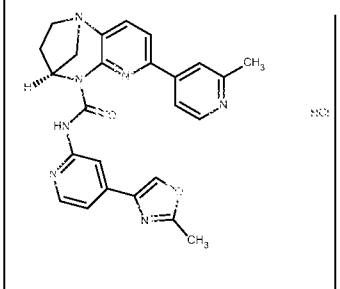
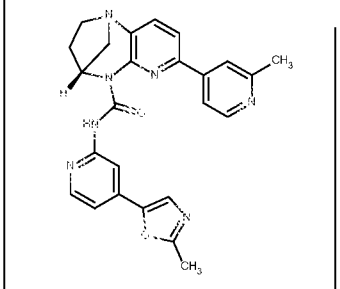
306		(9S)-N-{4-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyridin-2-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
307		(9S)-N-(pyridin-2-yl)-5-[(4R)-4-(trifluoromethyl)-4,5-dihydro-1,3-oxazol-2-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
308		(9S)-N-[6-(3-hydroxy-3-methylbutoxy)pyridin-2-yl]-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A
309		(9R)-5-(2-methylpyridin-4-yl)-N-[4-(1,3-oxazol-5-yl)pyridin-2-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
310		(9S)-N-[4-(2,2-dimethyloxan-4-yl)pyridin-2-yl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A

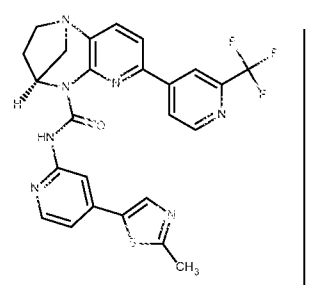
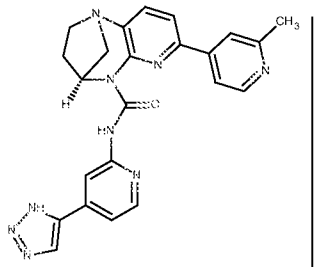
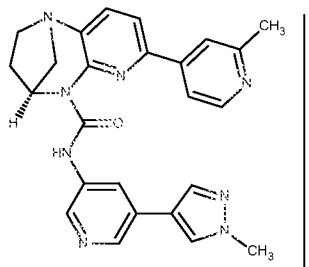
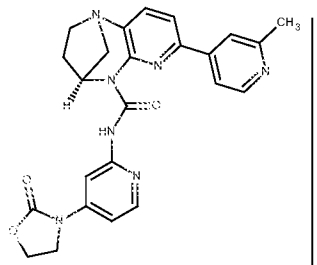
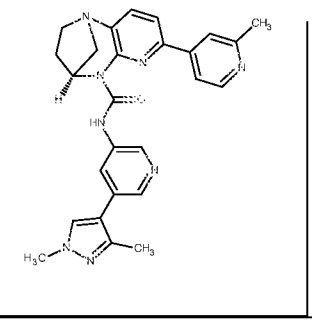
311		(9S)-N-[6-(3-hydroxypropoxy)pyridin-2-yl]-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
312		(9S)-N-(1-methylcyclopropyl)-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide hydrochloride	B	A
313		(9S)-N-{6-[(2S)-2,3-dihydroxypropoxy]pyrazin-2-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
314		(9S)-N-{6-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
315		(9S)-N-{4-[(2S)-2,3-dihydroxypropoxy]pyridin-2-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A

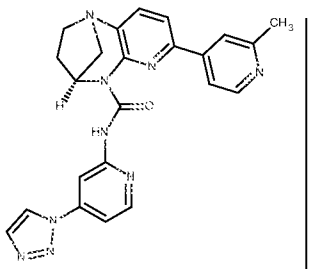
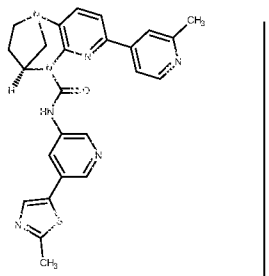
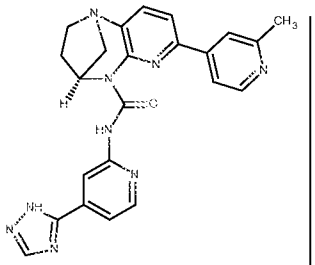
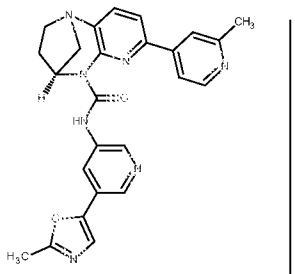
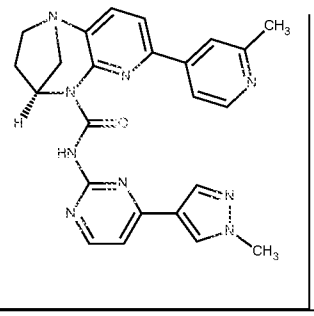
316		(9S)-N-(4-cyclopropylpyridin-2-yl)-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
317		(9S)-N-[6-(2-hydroxyethoxy)pyrazin-2-yl]-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
318		(9S)-N-[2-(2-hydroxyethoxy)pyrimidin-4-yl]-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
319		(9S)-N-[6-(3-hydroxypropoxy)pyrazin-2-yl]-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
320		(9S)-N-[2-(3-hydroxy-2,2-dimethylpropoxy)pyrimidin-4-yl]-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A

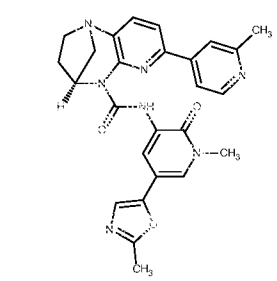
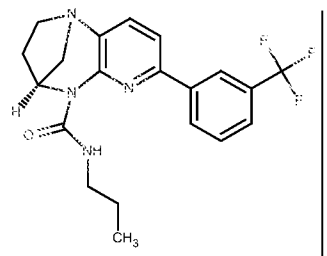
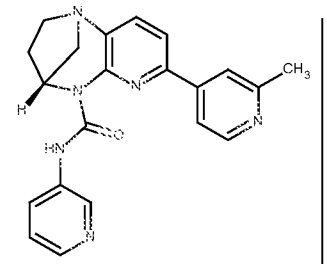
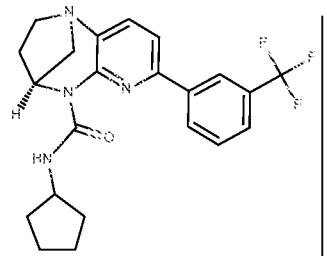
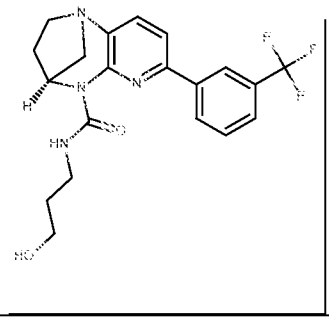
321		(9S)-4-chloro-N-{6-[(2S)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide hydrochloride	B	A
322		(9S)-N-{2-[(2S)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
323		(9S)-5-(6-aminopyridin-3-yl)-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
324		(9S)-N-[4-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-2-yl]-5-[2-(trifluoromethyl)pyridin-4-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
325		(9S)-N-[6-(2-hydroxyethoxy)pyridin-2-yl]-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A

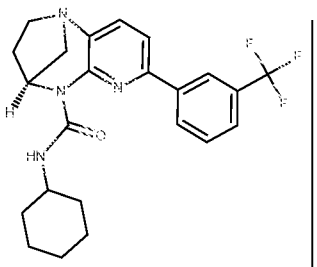
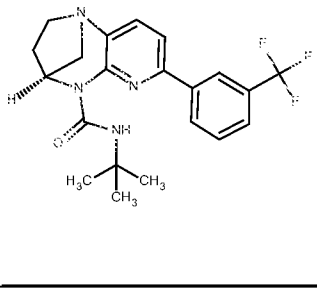
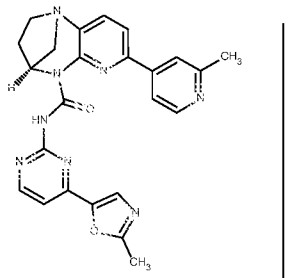
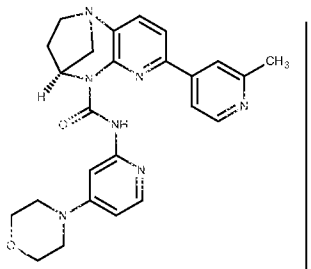
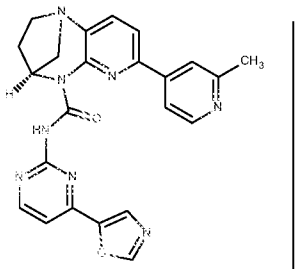
326		(9S)-N-(1-methyl-6-oxo-1,6-dihydropyrimidin-4-yl)-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
327		(9S)-N-[4-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
328		(9S)-5-(2,2-difluoro-2H-1,3-benzodioxol-4-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
329		(9S)-5-[6-(methylamino)pyridin-3-yl]-N-(pyrazin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
330		(9S)-N-{6-[(2S)-2,3-dihydroxypropoxy]pyrimidin-4-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A

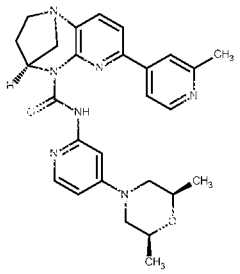
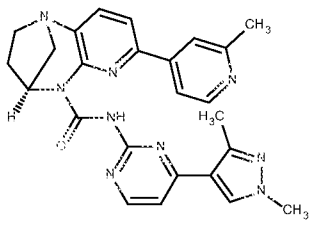
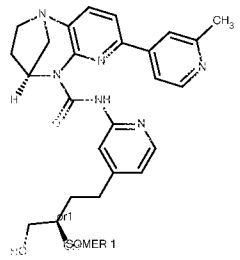
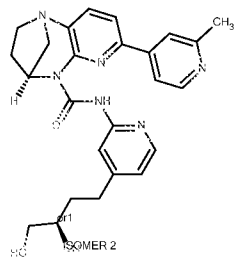
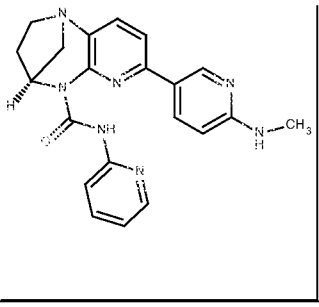
331		(9S)-N-[4-(2-methyl-1,3-oxazol-5-yl)pyridin-2-yl]-5-[2-(trifluoromethyl)pyridin-4-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
332		(9S)-N-[4-(1,3-oxazol-5-yl)pyridin-2-yl]-5-[2-(trifluoromethyl)pyridin-4-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
333		(9S)-N-[4-(2-methyl-1,3-oxazol-5-yl)pyridin-2-yl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
334		(9S)-N-[4-(2-methyl-1,3-oxazol-4-yl)pyridin-2-yl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide hydrochloride	A	A
335		(9R)-N-[4-(2-methyl-1,3-oxazol-5-yl)pyridin-2-yl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

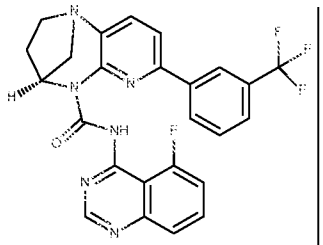
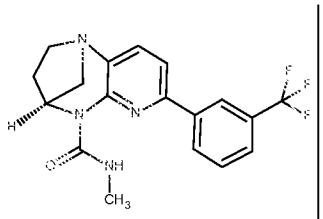
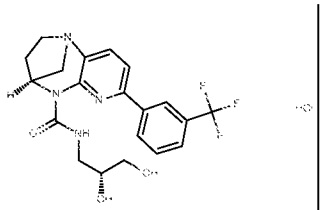
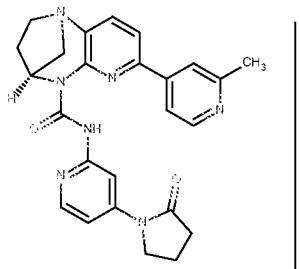
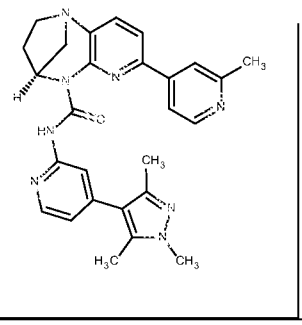
336		(9S)-N-[4-(2-methyl-1,3-thiazol-5-yl)pyridin-2-yl]-5-[2-(trifluoromethyl)pyridin-4-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
337		(9S)-5-(2-methylpyridin-4-yl)-N-[4-(1H-1,2,3-triazol-5-yl)pyridin-2-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
338		(9S)-N-[5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A
339		(9S)-5-(2-methylpyridin-4-yl)-N-[4-(2-oxo-1,3-oxazolidin-3-yl)pyridin-2-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
340		(9S)-N-[5-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A

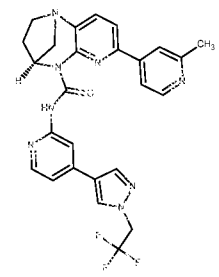
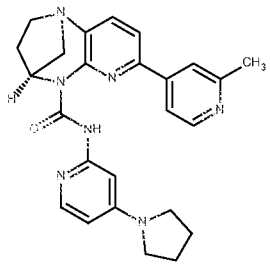
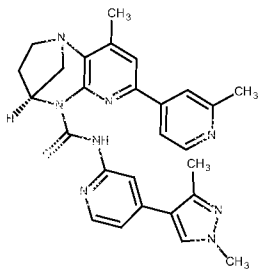
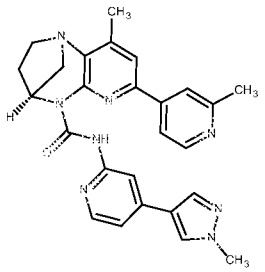
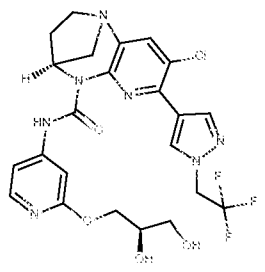
341		(9S)-5-(2-methylpyridin-4-yl)-N-[4-(1H-1,2,3-triazol-1-yl)pyridin-2-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
342		(9S)-N-[5-(2-methyl-1,3-thiazol-5-yl)pyridin-3-yl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
343		(9S)-5-(2-methylpyridin-4-yl)-N-[4-(1H-1,2,4-triazol-5-yl)pyridin-2-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
344		(9S)-N-[5-(2-methyl-1,3-oxazol-5-yl)pyridin-3-yl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
345		(9S)-N-[4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A

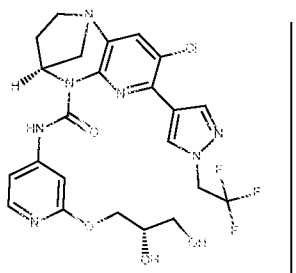
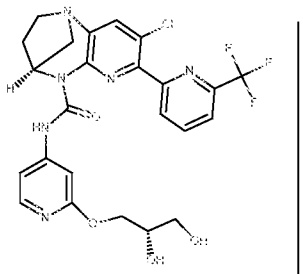
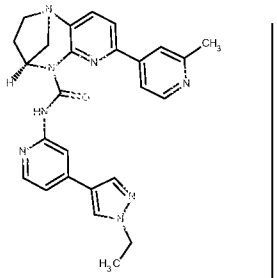
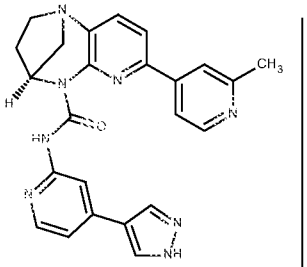
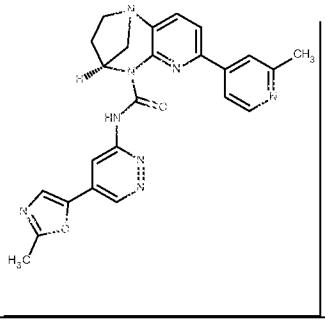
346		(9S)-N-[1-methyl-5-(2-methyl-1,3-oxazol-5-yl)-2-oxo-1,2-dihydropyridin-3-yl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
347		(9S)-N-propyl-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
348		(9R)-5-(2-methylpyridin-4-yl)-N-(pyridin-3-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
349		(9S)-N-cyclopentyl-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
350		(9S)-N-(3-hydroxypropyl)-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

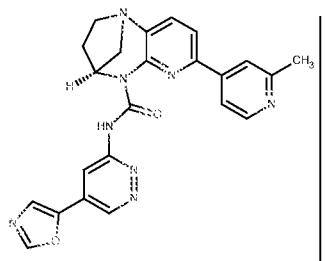
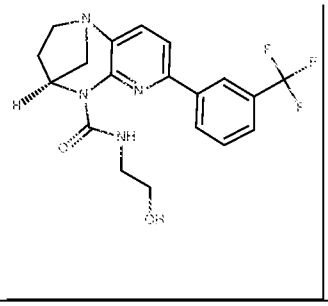
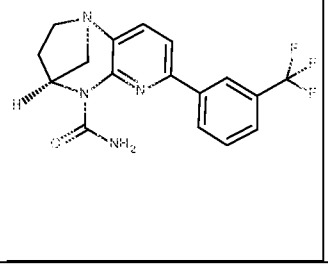
351		(9S)-N-cyclohexyl-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
352		(9S)-N-tert-butyl-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
353		(9S)-N-[4-(2-methyl-1,3-oxazol-5-yl)pyrimidin-2-yl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A
354		(9S)-5-(2-methylpyridin-4-yl)-N-[4-(morpholin-4-yl)pyridin-2-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
355		(9S)-5-(2-methylpyridin-4-yl)-N-[4-(1,3-oxazol-5-yl)pyrimidin-2-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A

356		(9S)-N-{4-[(2R,6S)-2,6-dimethylmorpholin-4-yl]pyridin-2-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
357		(9S)-N-[4-(1,3-dimethyl-1H-pyrazol-4-yl)pyrimidin-2-yl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
358		(9S)-N-{4-[(3R)-3,4-dihydroxybutyl]pyridin-2-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
359		(9S)-N-{4-[(3R)-3,4-dihydroxybutyl]pyridin-2-yl}-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
360		(9S)-5-[6-(methylamino)pyridin-3-yl]-N-(pyridin-2-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A

361		(9S)-N-(5-fluoroquinazolin-4-yl)-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A
362		(9S)-N-methyl-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
363		(9S)-N-[(2R)-2,3-dihydroxypropyl]-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide hydrochloride	B	A
364		(9S)-5-(2-methylpyridin-4-yl)-N-[4-(2-oxopyrrolidin-1-yl)pyridin-2-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
365		(9S)-5-(2-methylpyridin-4-yl)-N-[4-(trimethyl-1H-pyrazol-4-yl)pyridin-2-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

366		(9S)-5-(2-methylpyridin-4-yl)-N-{4-[1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl]pyridin-2-yl}-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
367		(9S)-5-(2-methylpyridin-4-yl)-N-[4-(pyrrolidin-1-yl)pyridin-2-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
368		(9S)-N-[4-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-2-yl]-3-methyl-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
369		(9S)-3-methyl-N-[4-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
370		(9S)-4-chloro-N-{2-[(2R)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-[1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A

371		(9S)-4-chloro-N-{2-[(2S)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-[1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	B	A
372		(9S)-4-chloro-N-{2-[(2S)-2,3-dihydroxypropoxy]pyridin-4-yl}-5-[6-(trifluoromethyl)pyridin-2-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	A	A
373		(9S)-N-[4-(1-ethyl-1H-pyrazol-4-yl)pyridin-2-yl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	A	A
374		(9S)-5-(2-methylpyridin-4-yl)-N-[4-(1H-pyrazol-4-yl)pyridin-2-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene-8-carboxamide	C	B
375		(9S)-N-[5-(2-methyl-1,3-oxazol-5-yl)pyridazin-3-yl]-5-(2-methylpyridin-4-yl)-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	C	B

376		(9S)-5-(2-methylpyridin-4-yl)-N-[5-(1,3-oxazol-5-yl)pyridazin-3-yl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	C	B
378		(9S)-N-(2-hydroxyethyl)-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	B	A
379		(9S)-5-[3-(trifluoromethyl)phenyl]-1,6,8-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-8-carboxamide	C	B

Example 375

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.

In addition to therapeutic potential, structural and biophysical studies of SIRT1 activity and activation by small molecule sirtuin modualtors 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.

Based on the foregong, 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:

1. Marcia C. Haigis and David A. Sinclair, Mammalian Sirtuins: Biological Insights and Disease Relevance, *Annu Rev Pathol*. 2010 ; 5: 253–295.

Haigis and Sinclair teach:

"Aging is accompanied by a decline in the healthy function of multiple organ systems, leading toincreased 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 thefield in the coming years (see, ABSTRACT, therein and reference)."

2. Gizem Donmez1 et. al., SIRT1 and SIRT2: emerging targets in neurodegeneration, EMBO Mol Med (2013) 5, 344–352.

Gizem Donmez1 et. al., teaches:

"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)."

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 Mar;23(3):199-201. doi: 10.1111/exd.12321.

In particular, Bracke et al. teaches

"Psoriasis is a complex inflammatory skin disease that presents a wide variety of clinical manifestations. Human β 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."

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-1a, and TNF-a,*J Immunol* 2010; 184:5263-5270.

Guilloteau et al. teaches:

"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-a, and IL-1a 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-a, and IL-1a 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 376 Description of assays:

PBMC ASSAY

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 down-regulates 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.

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

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.

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).

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).

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-1alpha, 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.

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:

Blander G, Bhimavarapu A, Mammone T, Maes D, Elliston K, Reich C, Matsui MS, Guarente L, Loureiro JJ. SIRT1 promotes differentiation of normal human keratinocytes. *J Invest Dermatol*. 2009 Jan;129(1):41-9.

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 Mar;23(3):199-201.

Guilloteau K, Paris I, Pedretti N, Boniface K, Juchaux F, Huguier V, Guillet G, Bernard FX, Lecron JC, Morel F. Skin Inflammation Induced by the Synergistic Action of IL-17A, IL-22, Oncostatin M, IL-1alpha, and TNFalpha Recapitulates Some Features of Psoriasis. *J Immunol*. 2010 Mar 24.

Jansen PA, Rodijk-Olthuis D, Hollox EJ, Kamsteeg M, Tjabringa GS, de Jongh GJ, van Vlijmen-Willems IM, Bergboer JG, van Rossum MM, de Jong EM, den Heijer M, Evers AW, Bergers M, Armour JA, Zeeuwen PL, 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.

Kamsteeg M, Jansen PA, van Vlijmen-Willems IM, van Erp PE, Rodijk-Olthuis D, van der Valk PG, Feuth T, Zeeuwen PL, Schalkwijk J. Molecular diagnostics of psoriasis, atopic dermatitis, allergic contact dermatitis and irritant contact dermatitis. *Br J Dermatol*. 2010 Mar;162(3):568-78.

Sestito R, Madonna S, Scarponi C, Cianfarani F, Failla CM, 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 Mar;25(3):916-27.

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 CK 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

Psoriasis is a chronic, relapsing, inflammatory autoimmune skin disorder with a multi-factorial pathogenesis influenced by genetic, environmental, and immunopathologic factors (Griffiths CE 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 MP N. Engl. J. Med. 352: 1899–1912).

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 DA et al, J Invest Dermatol 2013; 133:17-26).

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 IL-17 in mediating psoriasis pathogenesis.

Method (Ex Vivo Skin Assay)

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.

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).

On the first day following abdominoplasty surgery, skin explants were cultured in Cornification media and allowed to incubate overnight at 37°CSpecifically, 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 10uM 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.

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

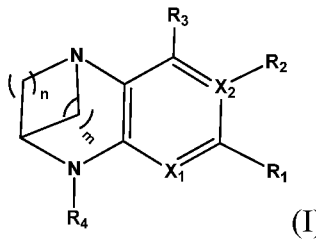
The present invention provides among other things sirtuin-modulating compounds, pharmaceutical compositions, methods or uses thereof. While specific embodiments of the

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.

CLAIMS

What is claimed is:

1. A compound of Formula (I):



(I);

wherein:

X_1 or X_2 independently is selected from -N or -C;

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 $-C(O)-NR_bR_c$;

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

R^4 is hydrogen or $-C(O)NR_bR_c$;

wherein:

when X_2 is -N, R_2 is non-existent; or

when X_2 is -C, R_2 is as defined above;

each R^1, R^2, R^3 and R^4 as defined above optionally is further substituted with one or more substituents selected from hydrogen, halogen, -OH, $-(CH_2)_xOH$,

$-C\equiv N$, $-NR_dR_e$, -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,

$-O-(CH_2)_xCH(OH)CH_2(OH)$, or $-C(O)OR_f$;

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, $-(CH_2)_xC_1.C_6$-cycloalkyl, heterocyclyl, -N-heterocyclyl, aryl, heteroaryl, or -$(CH_2)_x$heteroaryl, $-(CHR_g)_x$heteroaryl;

wherein:

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

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-$(CH_2)_xCH(OH)CH_2(OH)$, -$(CH_2)_x$-OH, or -C(O)-OH;

m is an integer from 1 to 3;

n is an integer selected from 1 to 3;

x is 0 or an integer from 1 to 6; or

a pharmaceutically salt thereof.

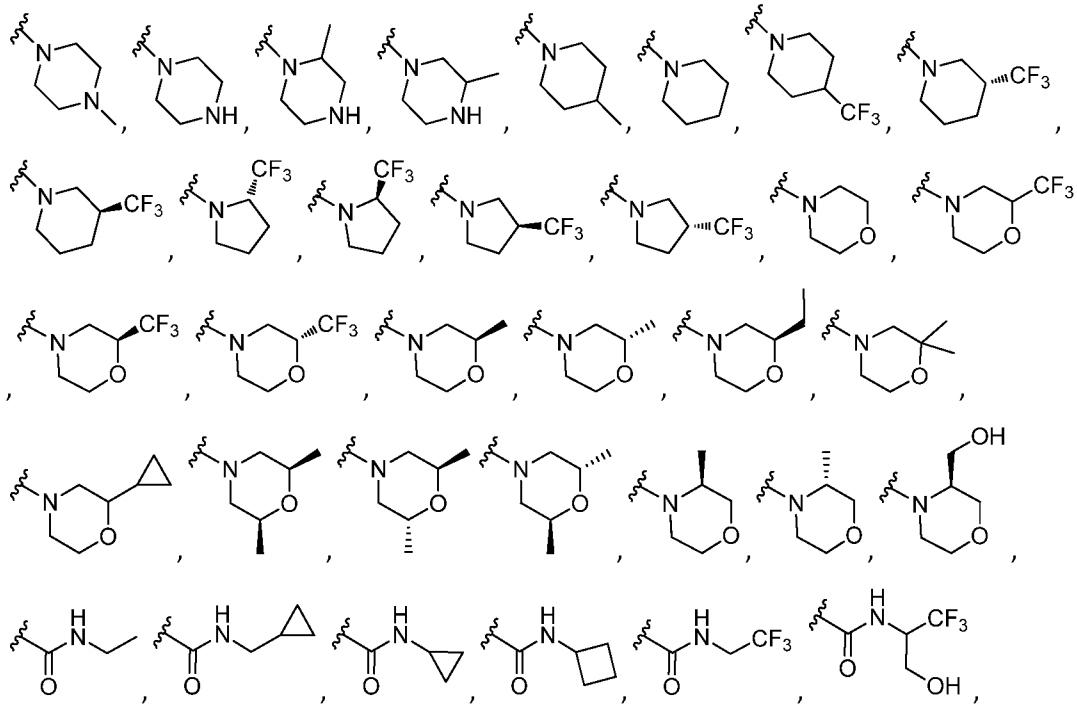
2. The compound of Formula (I) according to claim 1, wherein:

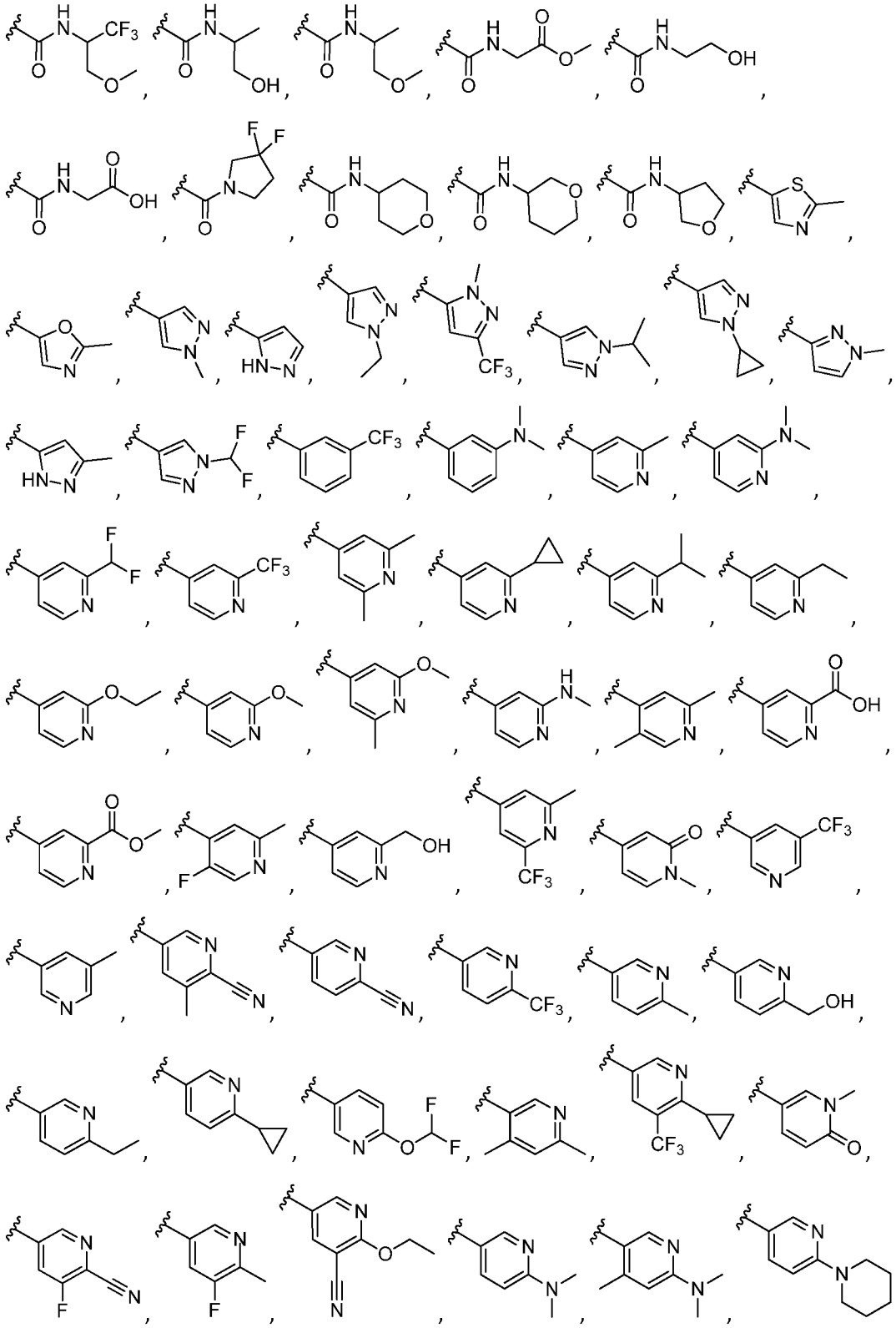
m is 1;

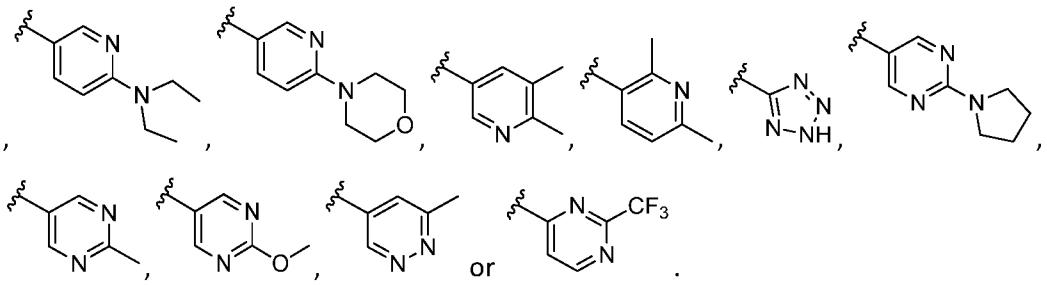
n is 2 or 3; and

R4 is –C(O)NRbRc, wherein Rb and Rc is as defined above in claim 1.

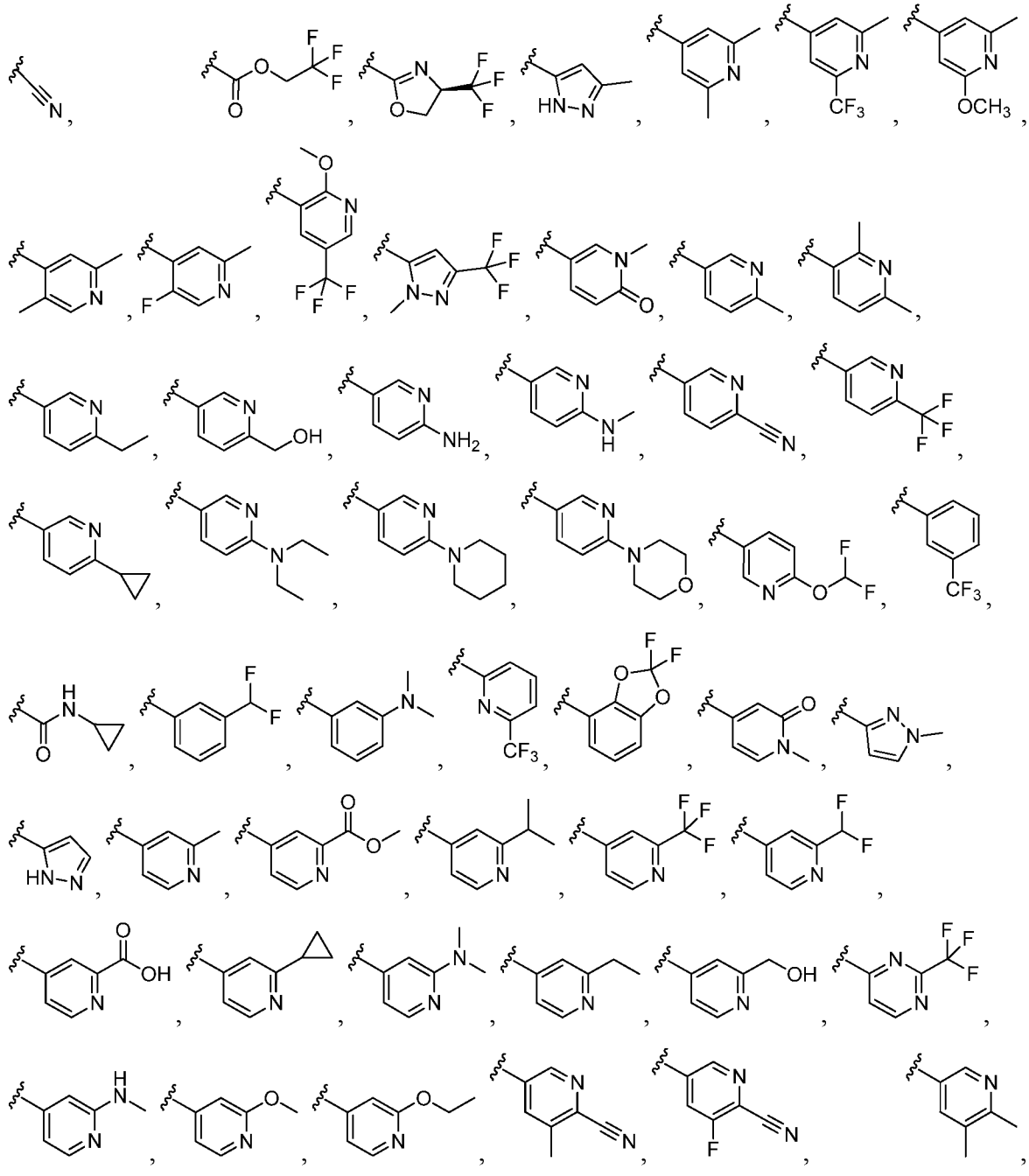
3. The compound of Formula (I) according to claim 1, wherein R^1 is selected from:

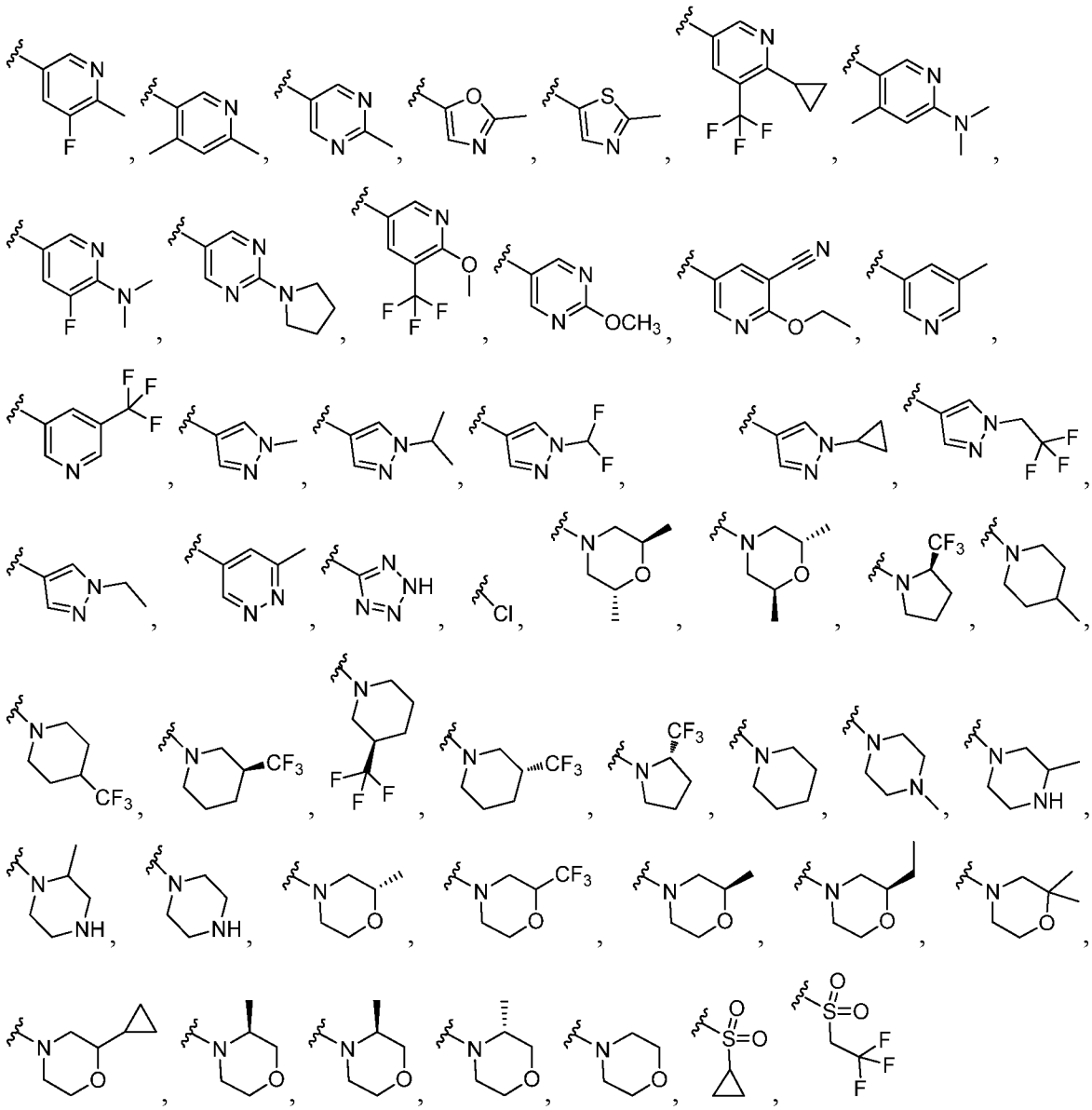




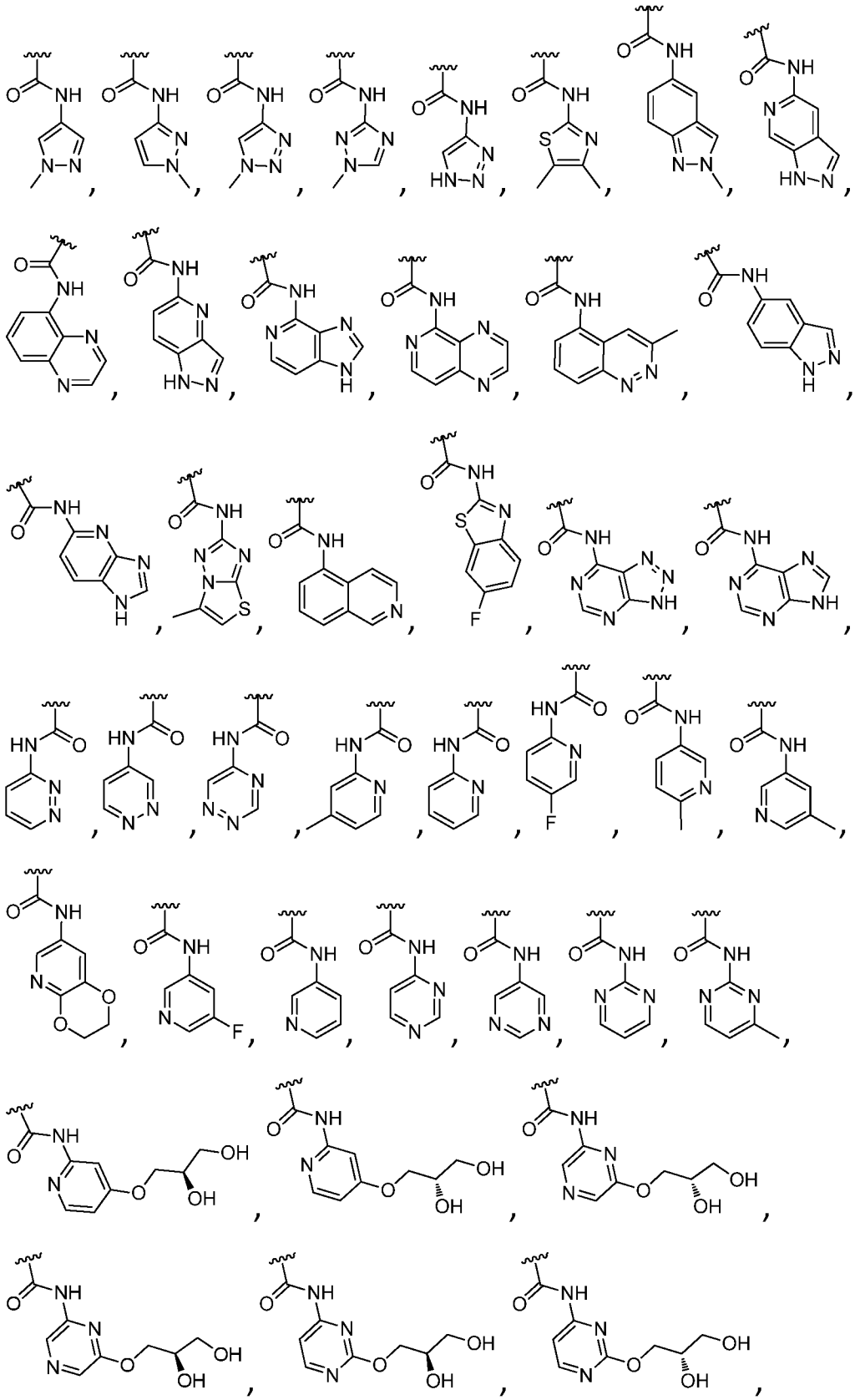


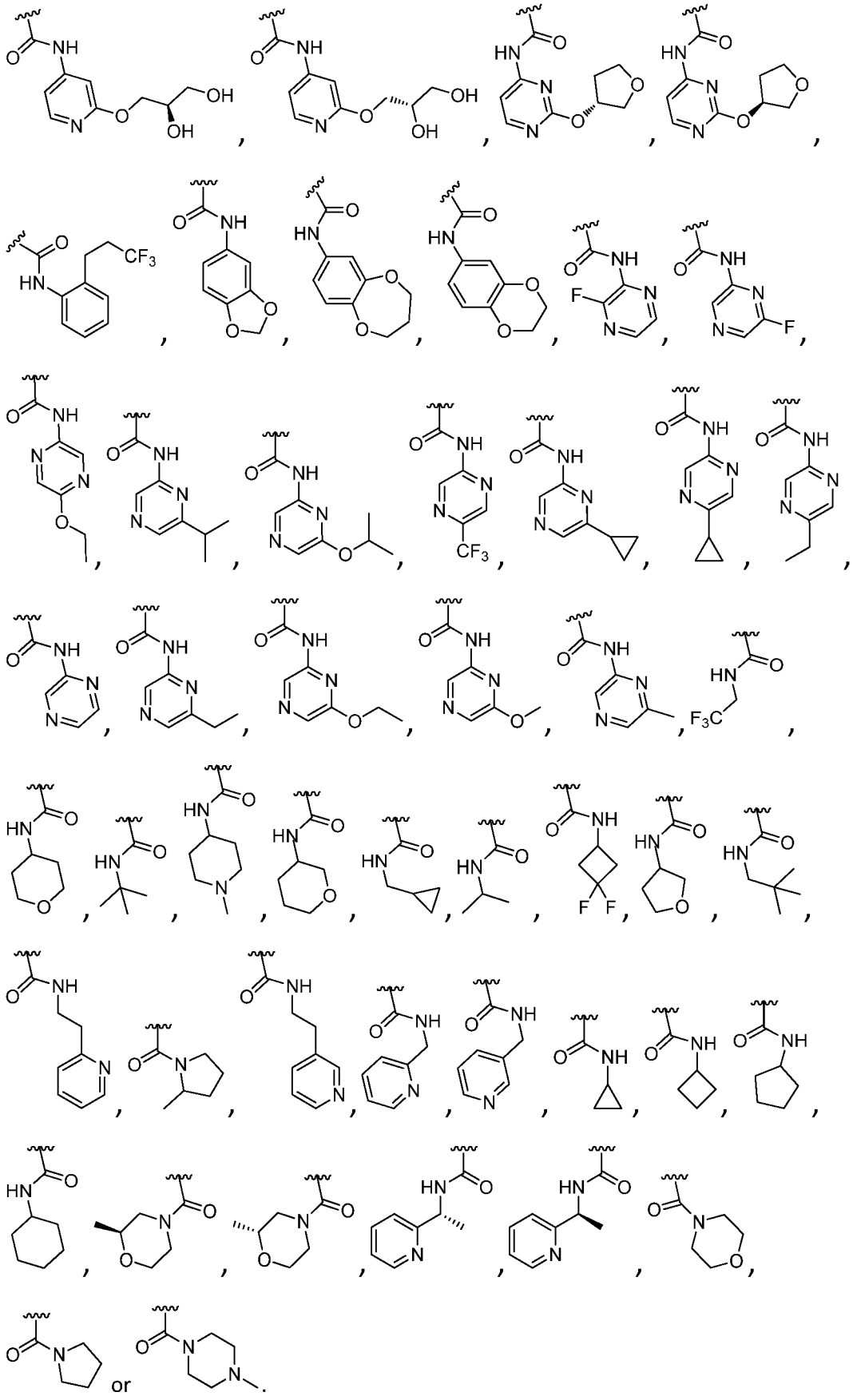
4. The compound of Formula (I) according to claim 1, wherein R^1 is selected from:



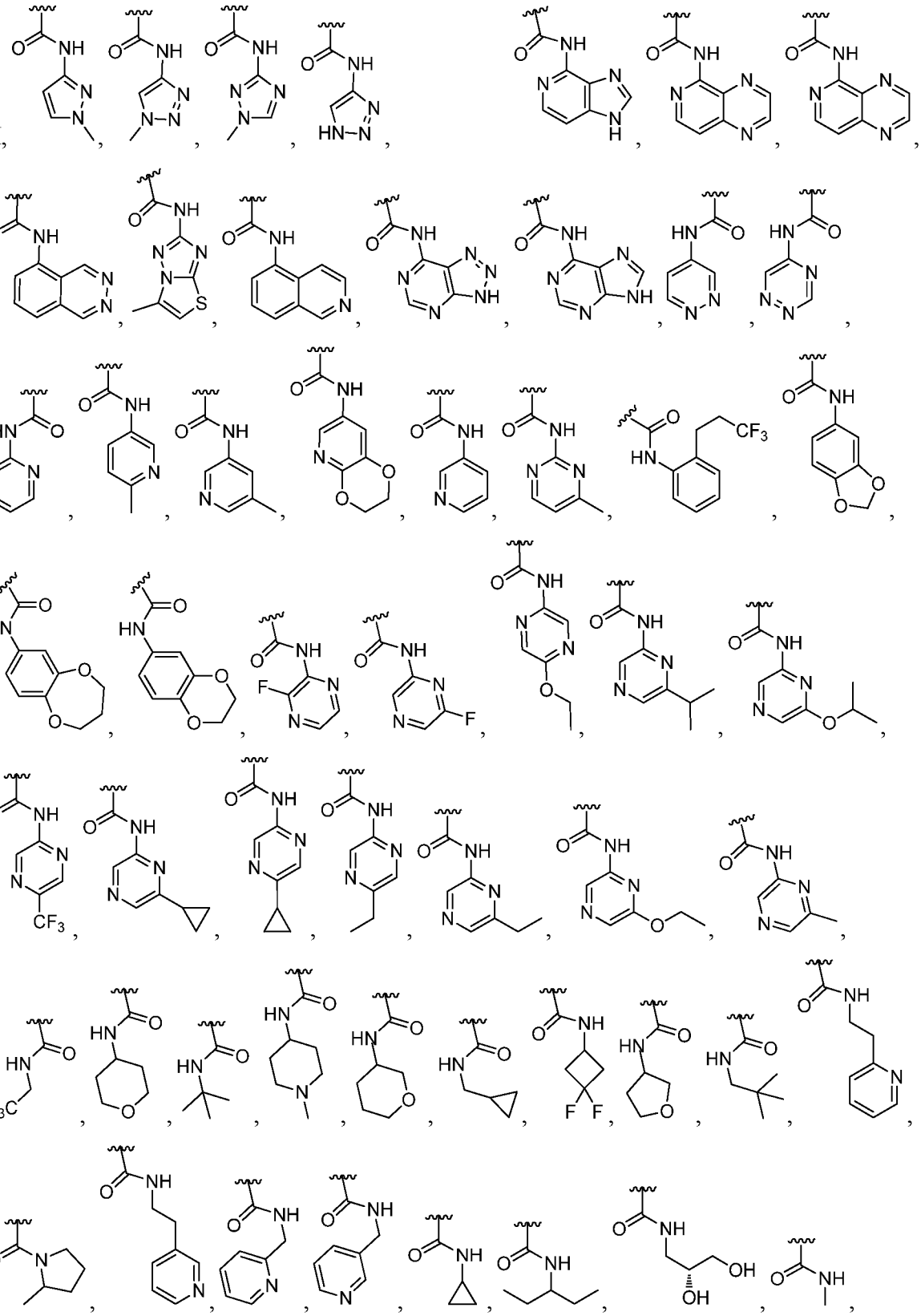


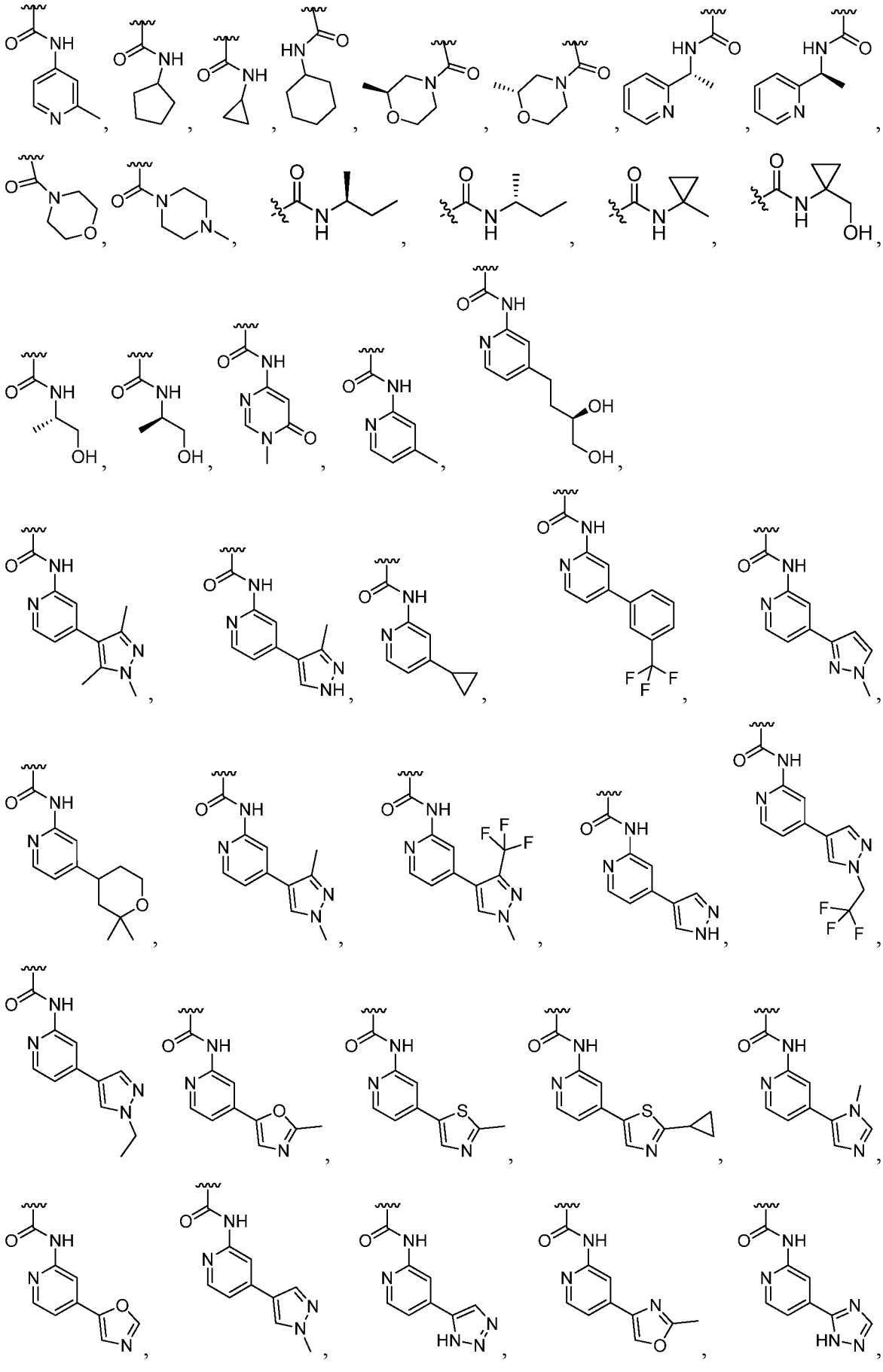
5. The compound of Formula (I) according to claim 1, wherein where R^4 is selected from:

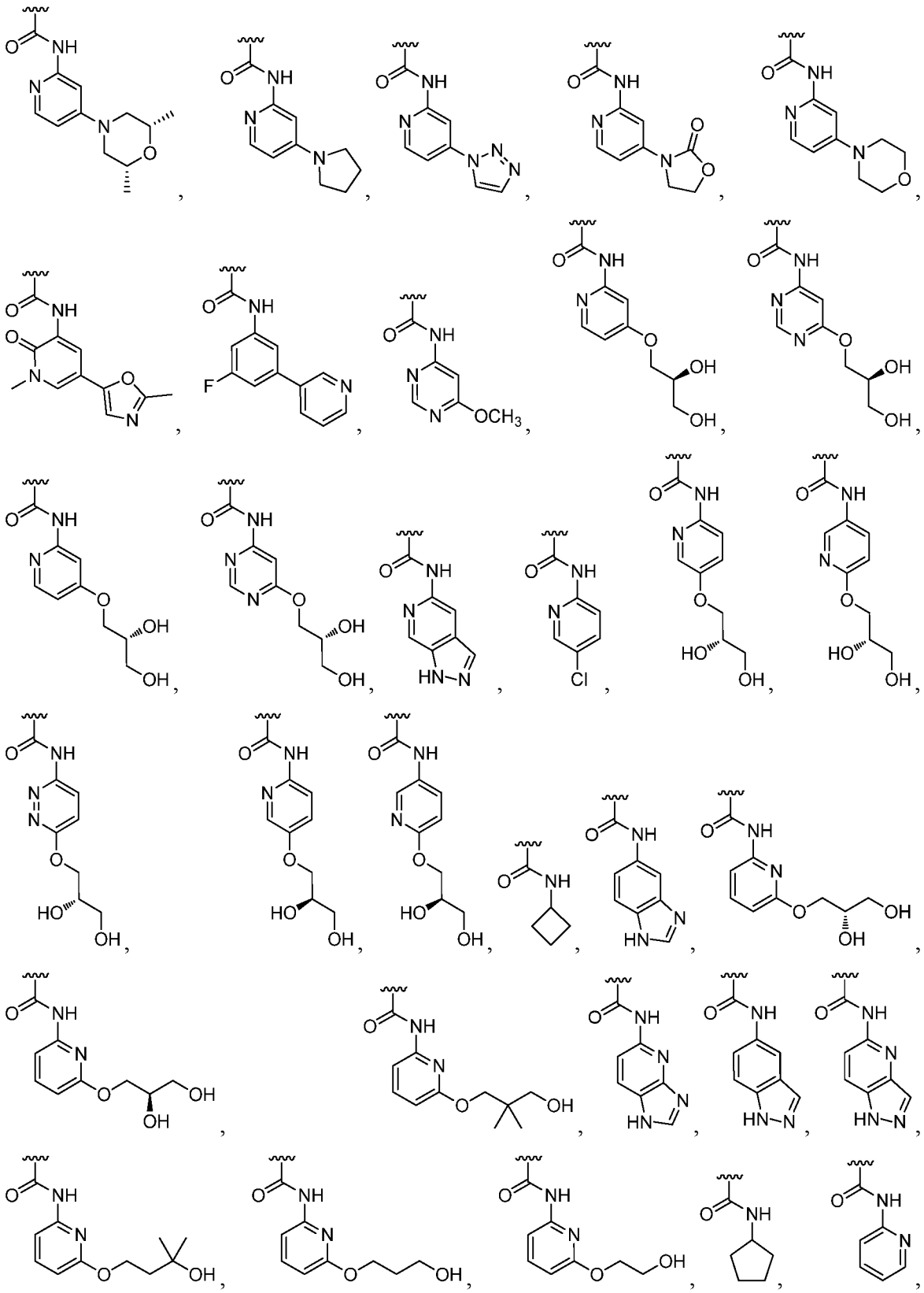


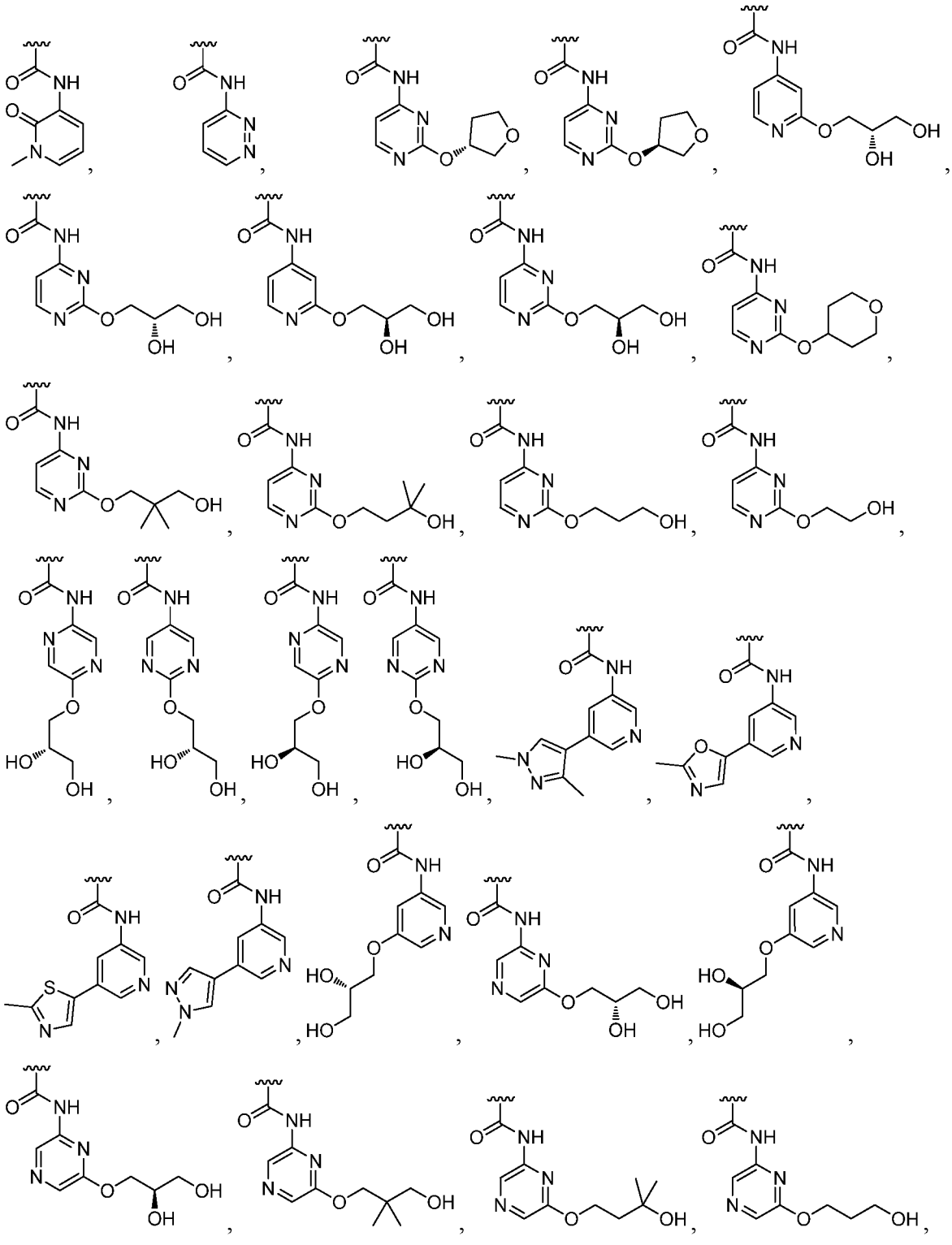


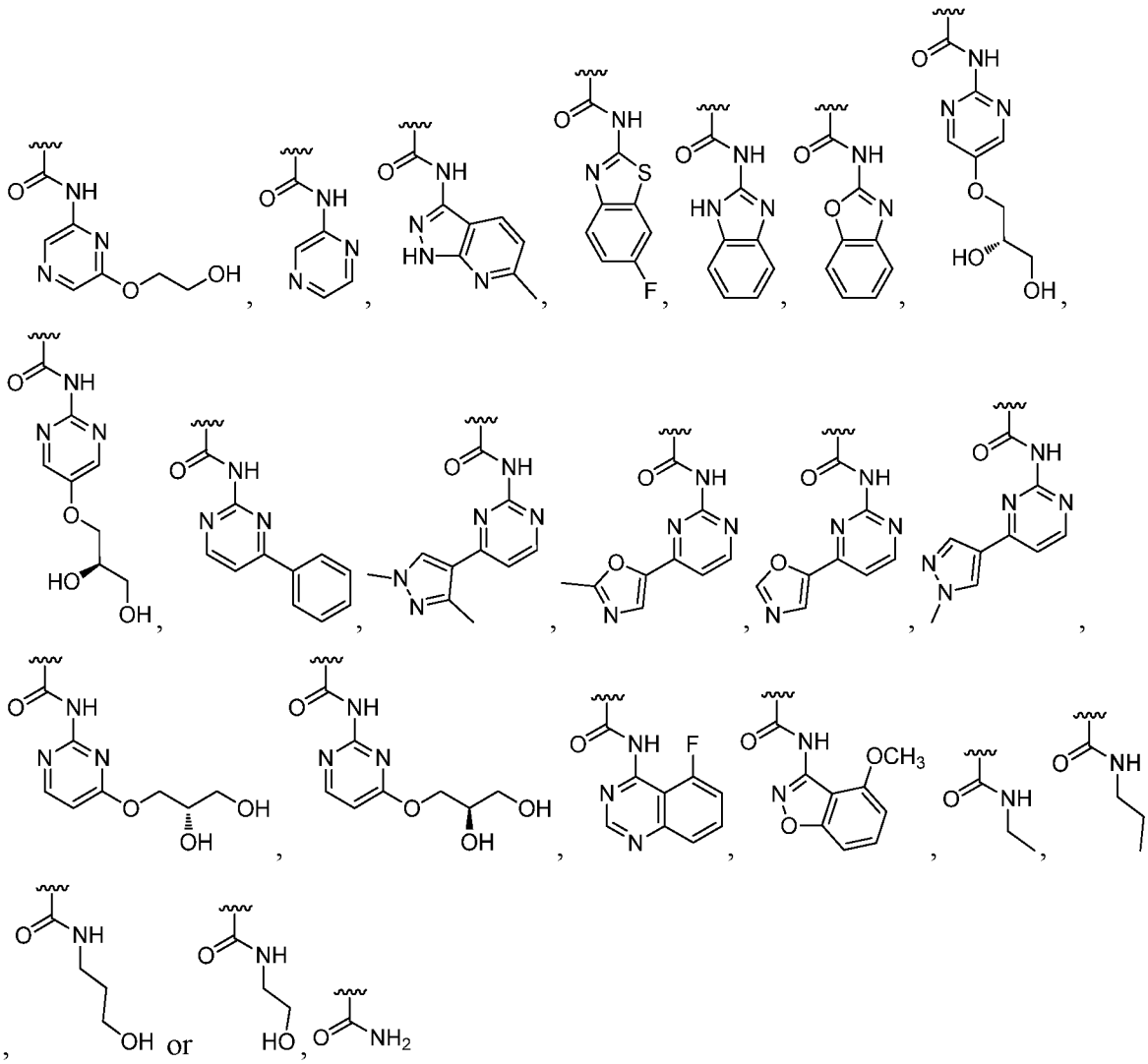
In another aspect, the present invention relates to compound(s) of Formulas (I) to (IV), respectively, where R^4 is selected from:

H, 

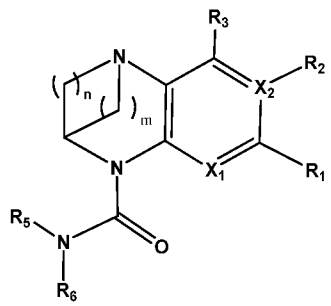








6. A compound of Formula (III):



(III);

wherein:

X_1 or X_2 independently is selected from -N or -C;

wherein:

when X_2 is -N, R_2 is non-existent; or

when X_2 is -C, R_2 is as defined above;

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 $-C(O)-NR_bR_c$;

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

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, $-(CH_2)_xC_1$.C_6cycloalkyl, heterocyclyl, -N-heterocyclyl, aryl, heteroaryl, or $-(CH_2)_x$heteroaryl, $-(CHR_g)_x$heteroaryl;

wherein:

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, $-(CH_2)_xOH$,

$-C\equiv N$, $-NR_dR_e$, -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, $-O-(CH_2)_xCH(OH)CH_2(OH)$, or $-C(O)OR_f$;

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, $-(CH_2)_xC_1$.C_6-cycloalkyl, heterocyclyl, -N-heterocyclyl, aryl, heteroaryl, or -$(CH_2)_x$heteroaryl;

wherein:

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, $-(CH_2)_xOH$, $-C\equiv N$, $-NR_hR_i$, -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, $-O-(CH_2)_xCH(OH)CH_2(OH)$, $-(CH_2)_x$-OH, or

$-C(O)OR_j$;

wherein:

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;

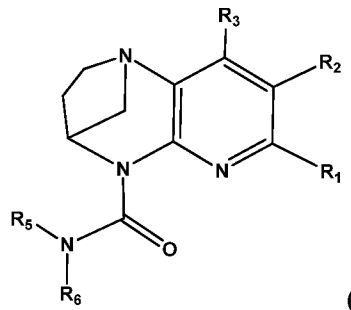
m is an integer from 1 to 3;

n is an integer selected from 2 to 3;

x is 0 or an integer from 1 to 6; or

a pharmaceutically salt thereof.

7. A compound of Formula (V):



(V);

wherein:

R^1 is hydrogen, halogen, -CN, carbocyclyl, heterocyclyl, -N-substituted heterocyclyl, aryl or heteroaryl;

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;

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

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, -$(CH_2)_xC_1$.C_6cycloalkyl, heterocyclyl, -N-heterocyclyl, aryl, heteroaryl, or -$(CH_2)_x$heteroaryl, -$(CHR_g)_x$heteroaryl;

wherein:

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;

each R_a, R_b, R_c, R_d, R_e, R_f or R_g as define 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, -$(CH_2)_xC_1$.C_6-cycloalkyl, heterocyclyl, -N-heterocyclyl, aryl, heteroaryl, or -$(CH_2)_x$heteroaryl;

wherein:

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;

wherein:

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;

m is an integer from 1 to 3;

n is an integer selected from 2 to 3;

x is 0 or an integer from 1 to 6; or

a pharmaceutically salt thereof.

8. A compound which is as set forth in Table I or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition comprising a compound of any one of claims 1 to 8 and a pharmaceutically acceptable carrier.

10. The pharmaceutical composition of claim 9, further comprising an additional active agent.

11. A method for treating insulin resistance, a metabolic syndrome, metabolic dysfunctions, diabetes, or complications thereof, or for increasing insulin sensitivity, comprising administering a **compound** according to any one of claims 1 to 8 or a pharmaceutical composition according to any one of claims 9 or 10 to a subject in need thereof.

12. 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 any one of claims 1 to 8 or a

pharmaceutical composition according to any one of claims 9 or 10 to a subject in need thereof.

13. The method according to claim 12, wherein 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.

14. The method according to claim 13, wherein 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.

15. A method for treating psoriasis, which comprises administering a compound according to any one of claims 1 to 8 or pharmaceutical composition according to claims 9 or 10 a subject in need thereof.

16. A compound as defined in claims 1 to 8 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.

17. The use of compound as defined in any one of claim 1 to 8 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.