MRGPRX2 INHIBITORS AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Application Nos. 63/462,418, filed on April 27, 2023; 63/546,090, filed on October 27, 2023; and 63/614,730, filed on December 26, 2023; each of which is hereby incorporated by reference in its entirety.

BACKGROUND

Mature mammalian mast cells ordinarily reside near blood vessels or nerves, beneath or within epithelia, within airways, gastrointestinal and genitourinary tracts, and near smooth muscle and mucus-producing glands. Classically, mast cells are activated by IgE antibodies, secreting a wide range of substances with local and systemic effects, including histamine, serotonin, proteases, chemokines, and cytokines. Indeed, mast cells are implicated in the progression and/or maintenance of many diseases.

Recent work has emphasized the role of the Mas-related G protein-coupled receptor (MRGPR) family, specifically, Mrgprb2, in mast cell activation. Mrgprb2 is the mouse receptor for several cationic molecules, collectively called basic secretagogues, and the ortholog of the human receptor MRGPRX2). To date, Mrgprb2 and MRGPRX2 have been reported to be expressed only on certain populations of mast cells. This knowledge provides an opportunity to target mast cell degranulation in a very precise manner.

Natural endogenous ligands of Mrgprb2/MRGPRX2 have been reported and are mostly neuropeptides, including substance P (SP), vasoactive intestinal polypeptide (VIP), Cortistatin-14, and pituitary adenylate cyclase activating polypeptide (PACAP). Others include P-defensin, cathelicidin (LL-37), and proadrenomedullin N-terminal 20 peptide (PAMP[9-20]). Given the close proximity between mast cells and sensory nerves in various pathological conditions, it follows that neuropeptide-activated MRGPRX2 could contribute to symptoms of neurogenic inflammation including pain, swelling and pruritus. Various observations using knock-out (KO) mice are consistent with the Mrgprb2/MRGPRX2 receptors playing a role in mast cell-mediated neurogenic inflammation. For instance, Mrgprb2/MRGPRX2 agonists induce various symptoms such as flushing, swelling and itch in wild type mice, but not in Mrgprb2-deficient mice. Mrgprb2-deficent mice have also demonstrated significant reductions in inflammation (leukocyte infiltration, including mast cells), swelling, pain and overall clinical score in various disease models. An important and relevant observation was the demonstration that Substance P injection could stimulate the infiltration of leukocytes in wild type and NKR1 (canonical Substance P receptor) KO mice

whereas the response was substantially blunted in Mrgprb2 null mice. This observation extends the role of Mrgprb2/MRGPRX2 as a key receptor in mediating Substance P-induced inflammatory responses, including pain. Indeed, a Substance P / Mrgprb2 sensory cluster was demonstrated to be critical in driving the clinical score of a severe preclinical model of atopic dermatitis.

In addition to the various reports using Mrgprb2-deficient mice, further evidence suggests a role for various ligands of MRGPRX2 in human disease. For example, in addition to the number of MRGPRX2-expressing mast cells being significantly increased in severe chronic urticaria, PACAP nerve fibres were demonstrated to be in close proximity to tryptase-positive mast cells, providing the morphological basis for increased mast cell - sensory interactions. In support of this, patients with urticaria exhibit enhanced wheal reactions vs healthy individuals to MRGPRX2 agonists (e.g., Substance P) when injected intradermally. In addition, PACAP and the antimicrobial peptide, LL-37, which is implicated in cutaneous inflammation, were both demonstrated to be upregulated in rosacea. Indeed, mast cell-deficient mice do not develop inflammation/flushing following LL-37 injection thus inferring a role for Mrgprb2.

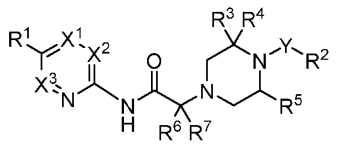
In addition to skin disorders, mast cell involvement has been highlighted for inflammatory bowel disease (IBD) and arthritis as well as asthma and migraine. In patients with rheumatoid arthritis (RA), the number of degranulated mast cells is increased in synovial tissue and is correlated with disease activity, as it is for patients with IBD. A positive correlation between serum Substance P levels and chronic pain intensity has been noted in both osteoarthritic and RA patients and a recent article suggested that the SP- MRGPRX2 axis may play a role in the pathogenesis of RA, especially in the regulation of inflammation and pain. Finally, there is a growing body of evidence for a role of PACAP in migraine pathogenesis and that it is mediated via activation of mast cells.

Accordingly, there is a need for small-molecule agonists of MRGPRX2 that block IgE-independent mast cell de-granulation, which are expected to provide therapeutic benefit in mast-cell driven pathologies including skin disorders such as urticaria, atopic dermatitis and rosacea as well as additional indications like inflammatory bowel disease, arthritis and migraine. Accordingly, there is a need in the art to provide small molecule therapeutics that modulate MRGPRX2.

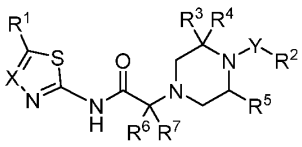
SUMMARY

One aspect of the invention provides compounds that are antagonists of MRGPRX2, compositions comprising them, and methods useful for preventing or treating MRGPRX2-mediated diseases or disorders.

Accordingly, provided herein in some embodiments is a compound having the structure of Formula (Ia) or (Ib):



(Ia)



(Ib)

or a pharmaceutical salt thereof; wherein:

X is N or CR^x;

X^1, X^2, and X^3 are each independently N or CR^x;

R^x is independently for each occurrence hydrogen, fluoro, or chloro;

Y is C(=O), $C(=O)CH_2$, CH_2, or a bond;

R^1 is $-OR^{1a}$ or $–CH_2R^{1a}$; wherein R^{1a} is phenyl, $(C_1\text{-}C_6)$alkyl, 5- to 6-membered heteroaryl, or $(C_3\text{-}C_8)$cycloalkyl$(C_1\text{-}C_6)$alkyl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, and $(C_1\text{-}C_6)$alkoxy;

R^2 is 4-, 5- or 6- membered heterocycloalkyl, 9- or 10-membered bicyclic heterocycloalkyl, 5- or 6- membered heteroaryl, 9- or 10-membered bicyclic heteroaryl, $(C_3\text{-}C_8)$cycloalkyl, or phenyl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, cyano, hydroxy, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkenyl, $-C(=O)NH_2$, $-NH_2$, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$hydroxyalkyl, $(C_1\text{-}C_6)$halohydroxyalkyl, $(C_1\text{-}C_6)$hydroxyalkoxy, $(C_1\text{-}C_6)$carboxyalkyl $(C_1\text{-}C_6)$haloalkoxy, $(C_3\text{-}C_8)$cycloalkyl, and 4- to 7-membered heterocycloalkyl; wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with phenyl, 4- to 7-membered heterocycloalkyl,and $–NHR^{2a}$; or R^2 is $(C_1\text{-}C_6)$alkyl;

R^{2a} is $C(=O)R^{2b}$, $(C_1\text{-}C_6)$alkyl, or $(C_3\text{-}C_8)$cycloalkyl, wherein $(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_8)$cycloalkyl is optionally substituted with one or more independent instances of halo;

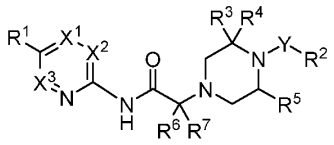
R^{2b} is $(C_1\text{-}C_6)$alkyl;

R^3 and R^4 are each independently hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxyalkyl, or (C_1-C_6)haloalkyl; or taken together with the carbon atom to which they are attached form a (C_3-C_6)cycloalkyl;

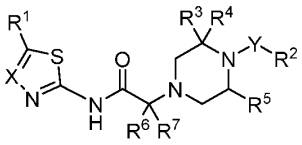
R^5 is hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxyalkyl, or (C_1-C_6)haloalkyl; or R^5 taken together with R^3 or R^4 forms $–(CH_2)_n–$; wherein n is 1, 2, or 3; and

R^6 and R^7 are independently for each occurrence hydrogen or (C_1-C_6)alkyl; or R^6 and R^7 taken together with the carbon atom to which they are attached form a (C_3-C_6)cycloalkyl.

In some embodiments, provided here in is a compound of Formula (Ia) or (Ib):



(Ia)



(Ib)

or a pharmaceutical salt thereof; wherein:

X is N or CR^x;

X^1, X^2, and X^3 are each independently N or CR^x;

R^x is independently for each occurrence hydrogen, fluoro, or chloro;

Y is C(=O), $C(=O)CH_2$, CH_2, or a bond;

R^1 is $-OR^{1a}$ or $–CH_2R^{1a}$; wherein R^{1a} is phenyl, 5- to 6-membered heteroaryl, or (C_3-C_8)cycloalkyl(C_1-C_6)alkyl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy;

R^2 is 5- or 6- membered heterocycloalkyl, 9- or 10-membered bicyclic heterocycloalkyl (e.g., indoline, octahydroindole, tetrahydroquinoline, or decahydroquinoline), 5- or 6- membered heteroaryl, 9- or 10-membered bicyclic heteroaryl, or phenyl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, cyano, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, $-C(=O)NH_2$, (C_1-C_6)alkoxy, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, and (C_1-C_6)haloalkoxy; wherein (C_1-C_6)alkyl is optionally substituted with phenyl or $–NHR^{2a}$;

R^{2a} is or (C_3-C_8)cycloalkyl, optionally substituted with one or more independent instances of halo;

R^3 and R^4 are each independently hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxyalkyl, or (C_1-C_6)haloalkyl; or taken together with the carbon atom to which they are attached form a (C_3-C_6)cycloalkyl;

R^5 is hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxyalkyl, or (C_1-C_6)haloalkyl; or R^5 taken together with R^3 or R^4 forms $–(CH_2)_n–$; wherein n is 1, 2, or 3; and

R^6 and R^7 are independently for each occurrence hydrogen or (C_1-C_6)alkyl; or R^6 and R^7 taken together with the carbon atom to which they are attached form a (C_3-C_6)cycloalkyl.

Also provided herein are pharmaceutical compositions comprising a compound of Formula (Ia) or (Ib); and at least one pharmaceutically acceptable excipient.

Additionally, methods of preventing or treating an MRGPRX2-mediated disease or disorder, comprise administering to a subject in need thereof a therapeutically effective amount of the compound of Formula (Ia) or (Ib). For example, an MRGPRX2-mediated disease or disorder may be chronic spontaneous urticaria, prurigo nodularis, irritable bowel syndrome, chronic inducible urticaria, atopic dermatitis, osteoarthritis, rosacea, migraine, pseudo-analphylaxis, mast cell activation syndrome, mastocytosis, pruritus, neurodermatitis, contact urticaria, allergic rhinitis, asthma, acute contact dermatitis, ulcerative colitis, crohns disease, idiopathic chronic cough, rheumatoid arthritis, multiple sclerosis, geographic atrophy, endometriosis, seborrheic dermatitis, psoriasis, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, neuropathic itch, periodontitis, autism, abdominal aortic aneurysms, deep vein thrombosis, amyotrophic lateral sclerosis, interstitial cystitis, coronary artery disease, cancer, sickle cell disease, obesity, or ulcers.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Other features, objects, and advantages of the invention will be apparent from the detailed description, and from the claims.

DETAILED DESCRIPTION

Definitions

For convenience, before further description of the present invention, certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and as understood by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

In order for the present invention to be more readily understood, certain terms and phrases are defined below and throughout the specification.

The articles "a" and "an" are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

The phrase "and/or," as used herein in the specification and in the claims, should be understood to mean "either or both" of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Multiple elements listed with "and/or" should be construed in the same fashion, i.e., "one or more" of the elements so conjoined. Other elements may optionally be present other than the elements specifically identified by the "and/or" clause, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, a reference to "A and/or B", when used in conjunction with open-ended language such as "comprising" can refer, in one embodiment, to A only (optionally including elements other than B); in another embodiment, to B only (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

As used herein in the specification and in the claims, "or" should be understood to have the same meaning as "and/or" as defined above. For example, when separating items in a list, "or" or "and/or" shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as "only one of" or "exactly one of," or, when used in the claims, "consisting of," will refer to the inclusion of exactly one element of a number or list of elements. In general, the term "or" as used herein shall only be interpreted as indicating exclusive alternatives (i.e., "one or the other but not both") when preceded by terms of exclusivity, such as "either," "one of," "only one of," or

"exactly one of." "Consisting essentially of," when used in the claims, shall have its ordinary meaning as used in the field of patent law.

As used herein in the specification and in the claims, the phrase "at least one," in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase "at least one" refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, "at least one of A and B" (or, equivalently, "at least one of A or B," or, equivalently "at least one of A and/or B") can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

It should also be understood that, unless clearly indicated to the contrary, in any methods claimed herein that include more than one step or act, the order of the steps or acts of the method is not necessarily limited to the order in which the steps or acts of the method are recited.

In the claims, as well as in the specification above, all transitional phrases such as "comprising," "including," "carrying," "having," "containing," "involving," "holding," "composed of," and the like are to be understood to be open-ended, i.e., to mean including but not limited to. Only the transitional phrases "consisting of" and "consisting essentially of" shall be closed or semi-closed transitional phrases, respectively, as set forth in the United States Patent Office Manual of Patent Examining Procedures, Section 2111.03.

Certain compounds contained in compositions of the present invention may exist in particular geometric or stereoisomeric forms. In addition, polymers of the present invention may also be optically active. 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.

"Geometric isomer" means isomers that differ in the orientation of substituent atoms in relationship to a carbon-carbon double bond, to a cycloalkyl ring, or to a bridged bicyclic system. Atoms (other than H) on each side of a carbon- carbon double bond may be in an E (substituents are on opposite sides of the carbon- carbon double bond) or Z (substituents are oriented on the same side) configuration. "R," "S," "S*," "R*," "E," "Z," "cis," and "trans," indicate configurations relative to the core molecule. Certain of the disclosed compounds may exist in "atropisomeric" forms or as "atropisomers." Atropisomers are stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers. The compounds of the invention may be prepared as individual isomers by either isomer-specific synthesis or resolved from a mixture of isomers. Conventional resolution techniques include forming the salt of a free base of each isomer of an isomeric pair using an optically active acid (followed by fractional crystallization and regeneration of the free base), forming the salt of the acid form of each isomer of an isomeric pair using an optically active amine (followed by fractional crystallization and regeneration of the free acid), forming an ester or amide of each of the isomers of an isomeric pair using an optically pure acid, amine or alcohol (followed by chromatographic separation and removal of the chiral auxiliary), or resolving an isomeric mixture of either a starting material or a final product using various well known chromatographic methods.

If, for instance, a particular enantiomer of compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

Percent purity by mole fraction is the ratio of the moles of the enantiomer (or diastereomer) or over the moles of the enantiomer (or diastereomer) plus the moles of its optical isomer. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least about 60%, about 70%, about 80%, about 90%, about 99% or about 99.9% by mole fraction pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at

least about 60%, about 70%, about 80%, about 90%, about 99% or about 99.9% by mole fraction pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least about 60%, about 70%, about 80%, about 90%, about 99% or about 99.9% by mole fraction pure.

When a disclosed compound is named or depicted by structure without indicating the stereochemistry, and the compound has at least one chiral center, it is to be understood that the name or structure encompasses either enantiomer of the compound free from the corresponding optical isomer, a racemic mixture of the compound or mixtures enriched in one enantiomer relative to its corresponding optical isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry and has two or more chiral centers, it is to be understood that the name or structure encompasses a diastereomer free of other diastereomers, a number of diastereomers free from other diastereomeric pairs, mixtures of diastereomers, mixtures of diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s) or mixtures of diastereomers in which one or more diastereomer is enriched relative to the other diastereomers. The invention embraces all of these forms.

Structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds produced by the replacement of a hydrogen with deuterium or tritium, or of a carbon with a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

The term “prodrug” as used herein encompasses compounds that, under physiological conditions, are converted into therapeutically active agents. A common method for making a prodrug is to include selected moieties that are hydrolyzed under physiological conditions to reveal the desired molecule. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal.

The phrase “pharmaceutically acceptable excipient” or “pharmaceutically acceptable carrier” as used herein means 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 the subject chemical from one organ or portion of the body, to another organ or portion of the body. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation, not injurious to the patient, and substantially non-pyrogenic. Some examples of materials which can 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. In certain embodiments, pharmaceutical compositions of the present invention are non-pyrogenic, i.e., do not induce significant temperature elevations when administered to a patient.

The term "pharmaceutically acceptable salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of the compound(s). These salts can be prepared in situ during the final isolation and purification of the compound(s), or by separately reacting a purified compound(s) in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts, and the like. (See, for example, Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19.)

In other cases, the compounds useful in the methods of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. The term "pharmaceutically acceptable salts" in these instances refers to the relatively non-toxic inorganic and organic base addition salts of a compound(s). These salts can likewise be prepared in situ during the final isolation and purification of the compound(s), or by separately reacting the purified compound(s) in its free acid form with a suitable base, such as the hydroxide, carbonate, or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts, and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, and the like (see, for example, Berge et al., *supra*).

The term "pharmaceutically acceptable cocrystals" refers to solid coformers that do not form formal ionic interactions with the small molecule.

A "therapeutically effective amount" (or "effective amount") of a compound with respect to use in treatment, refers to an amount of the compound in a preparation which, when administered as part of a desired dosage regimen (to a mammal, preferably a human) alleviates a symptom, ameliorates a condition, or slows the onset of disease conditions according to clinically acceptable standards for the disorder or condition to be treated or the cosmetic purpose, e.g., at a reasonable benefit/risk ratio applicable to any medical treatment.

The term "prophylactic or therapeutic" treatment is art-recognized and includes administration to the host of one or more of the subject compositions. 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 it is administered after manifestation of the unwanted condition, the treatment is therapeutic, (i.e., it is intended to diminish, ameliorate, or stabilize the existing unwanted condition or side effects thereof).

The term "patient" or "subject" refers to a mammal in need of a particular treatment. In certain embodiments, a patient is a primate, canine, feline, or equine. In certain embodiments, a patient is a human.

An aliphatic chain comprises the classes of alkyl, alkenyl and alkynyl defined below. A straight aliphatic chain is limited to unbranched carbon chain moieties. As used herein, the term "aliphatic group" refers to a straight chain, branched-chain, or cyclic aliphatic hydrocarbon group and includes saturated and unsaturated aliphatic groups, such as an alkyl group, an alkenyl group, or an alkynyl group.

"Alkyl" refers to a fully saturated cyclic or acyclic, branched or unbranched carbon chain moiety having the number of carbon atoms specified, or up to 30 carbon atoms if no specification is made. For example, alkyl of 1 to 8 carbon atoms refers to moieties such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, and octyl, and those moieties which are positional isomers of these moieties. Alkyl of 10 to 30 carbon atoms includes decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, eicosyl, heneicosyl, docosyl, tricosyl and tetracosyl. In certain embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C_1-C_{30} for straight chains, C_3-C_{30} for branched chains), and more preferably 20 or fewer. Alkyl goups may be substituted or unsubstituted.

As used herein, the term “heteroalkyl” refers to an alkyl moiety as hereinbefore defined which contain one or more oxygen, sulfur, nitrogen, phosphorus, or silicon atoms in place of carbon atoms.

As used herein, the term “haloalkyl” refers to an alkyl group as hereinbefore defined substituted with at least one halogen.

As used herein, the term “haloalkoxy” refers to an alkoxy group as defined herein substituted with at least one halogen atom. For example, haloalkoxy groups include fluoroalkoxy groups, such as trifluoromethoxy, difluoromethoxy, and the like.

As used herein, the term “hydroxyalkyl” refers to an alkyl group as hereinbefore defined substituted with at least one hydroxyl.

As used herein, the term “alkylene” refers to an alkyl group having the specified number of carbons, for example from 2 to 12 carbon atoms, that contains two points of attachment to the rest of the compound on its longest carbon chain. Non-limiting examples of alkylene groups include methylene -(CH_2)-, ethylene -(CH_2CH_2)-, n-propylene -($CH_2CH_2CH_2$)-, isopropylene -($CH_2CH(CH_3)$)-, and the like. Alkylene groups can be cyclic or acyclic, branched or unbranched carbon chain moiety, and may be optionally substituted with one or more substituents.

"Cycloalkyl" means mono- or bicyclic or bridged or spirocyclic, or polycyclic saturated carbocyclic rings, each having from 3 to 12 carbon atoms. Preferred cycloalkyls have from 3-10 carbon atoms in their ring structure, and more preferably have 3-6 carbons in the ring structure. Cycloalkyl groups may be substituted or unsubstituted.

“1,2-Disubstituted cyclohexyl” as used herein refers to a cyclohexane ring that contains points of attachment at the 1 and 2 positions of the cyclohexane ring to the rest of the compound. Similarly, “1,2-disubstituted cyclopentyl” as used herein refers to a cyclopentane ring that contains points of attachment at the 1 and 2 positions of the cyclopentane ring to the rest of the compound. 1,2-Disubstituted cyclohexyl and 1,2-disubstituted cyclopentyl can also be referred to as 1,2-cyclohexylene and 1,2-cyclopentylene, respectively.

As used herein, the term “halocycloalkyl” refers to a cycloalkyl group as hereinbefore defined substituted with at least one halogen.

"Cycloheteroalkyl" refers to an cycloalkyl moiety as hereinbefore defined which contain one or more oxygen, sulfur, nitrogen, phosphorus, or silicon atoms in place of carbon atoms. Preferred cycloheteroalkyls have from 4-8 carbon atoms and heteroatoms in their ring

structure, and more preferably have 4-6 carbons and heteroatoms in the ring structure. Cycloheteroalkyl groups may be substituted or unsubstituted.

Unless the number of carbons is otherwise specified, "lower alkyl," as used herein, means an alkyl group, as defined above, but having from one to ten carbons, more preferably from one to six carbon atoms in its backbone structure such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, and tert-butyl. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths. Throughout the application, preferred alkyl groups are lower alkyls. In certain embodiments, a substituent designated herein as alkyl is a lower alkyl.

"Alkenyl" refers to any cyclic or acyclic, branched or unbranched unsaturated carbon chain moiety having the number of carbon atoms specified, or up to 26 carbon atoms if no limitation on the number of carbon atoms is specified; and having one or more double bonds in the moiety. Alkenyl of 6 to 26 carbon atoms is exemplified by hexenyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, dodenyl, tridecenyl, tetradecenyl, pentadecenyl, hexadecenyl, heptadecenyl, octadecenyl, nonadecenyl, eicosenyl, heneicosoenyl, docosenyl, tricosenyl, and tetracosenyl, in their various isomeric forms, where the unsaturated bond(s) can be located anywhere in the moiety and can have either the (Z) or the (E) configuration about the double bond(s).

"Alkynyl" refers to hydrocarbyl moieties of the scope of alkenyl, but having one or more triple bonds in the moiety.

The term "aryl" as used herein includes 3- to 12-membered substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon (i.e., carbocyclic aryl) or where one or more atoms are heteroatoms (i.e., heteroaryl). Preferably, aryl groups include 5- to 12-membered rings, more preferably 6- to 10-membered rings The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Carboycyclic aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline, and the like. Heteroaryl groups include substituted or unsubstituted aromatic 3- to 12-membered ring structures, more preferably 5- to 12-membered rings, more preferably 5- to 10-membered rings, whose ring structures include one to four heteroatoms. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine, pyrimidine, indazole, quinoline, benzofuran, and the like. Aryl and heteroaryl can be monocyclic, bicyclic, or polycyclic.

The term "halo", "halide", or "halogen" as used herein means halogen and includes, for example, and without being limited thereto, fluoro, chloro, bromo, iodo and the like, in both radioactive and non-radioactive forms. In a preferred embodiment, halo is selected from the group consisting of fluoro, chloro and bromo.The terms "heterocyclyl" or "heterocyclic group" or "heterocycloalkyl" refer to 3- to 12-membered ring structures, more preferably 5- to 12-membered rings, more preferably 5- to 10-membered rings, whose ring structures include one to four heteroatoms. Heterocycles can be monocyclic, bicyclic, spirocyclic, or polycyclic. Heterocyclyl groups include, for example, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxathiin, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. Heterocycloalkyl groups can be fully saturated or partially saturated. Heterocycloalkyl groups include, for example, bicyclic ring systems having either or both constituent rings saturated (e.g., 2,3-dihydroindole, 4,5,6,7-tetrahydro-benzofuran, decahydroquinoline, and the like) or partially saturated (e.g., octahydroquinoline and the like).

The heterocyclic ring can be substituted at one or more positions with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphate, phosphonate, phosphinate, carbonyl, carboxyl, silyl, sulfamoyl, sulfinyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, $-CF_3$, -CN, and the like.

The term "substituted" refers to moieties having substituents replacing a hydrogen on one or more carbons of the backbone. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds.

The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxy, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. In preferred embodiments, the substituents on substituted alkyls are selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, carbonyl, cyano, or hydroxyl. In more preferred embodiments, the substituents on substituted alkyls are selected from fluoro, carbonyl, cyano, or hydroxyl. It will be understood by those skilled in the art that substituents can themselves be substituted, if appropriate. Unless specifically stated as "unsubstituted," references to chemical moieties herein are understood to include substituted variants. For example, reference to an "aryl" group or moiety implicitly includes both substituted and unsubstituted variants.

As used herein, the definition of each expression, e.g., alkyl, m, n, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

As used herein, "small molecules" refers to small organic or inorganic molecules of molecular weight below about 3,000 Daltons. In general, small molecules useful for the invention have a molecular weight of less than 3,000 Daltons (Da). The small molecules can be, e.g., from at least about 100 Da to about 3,000 Da (e.g., between about 100 to about 3,000 Da, about 100 to about 2500 Da, about 100 to about 2,000 Da, about 100 to about 1,750 Da, about 100 to about 1,500 Da, about 100 to about 1,250 Da, about 100 to about 1,000 Da, about 100 to about 750 Da, about 100 to about 500 Da, about 200 to about 1500, about 500 to about 1000, about 300 to about 1000 Da, or about 100 to about 250 Da).

In some embodiments, a "small molecule" refers to an organic, inorganic, or organometallic compound typically having a molecular weight of less than about 1000. In some embodiments, a small molecule is an organic compound, with a size on the order of 1 nm. In some embodiments, small molecule drugs of the invention encompass oligopeptides and other biomolecules having a molecular weight of less than about 1000.

An "effective amount" is an amount sufficient to effect beneficial or desired results. For example, a therapeutic amount is one that achieves the desired therapeutic effect. This amount can be the same or different from a prophylactically effective amount, which is an amount necessary to prevent onset of disease or disease symptoms. An effective amount can be administered in one or more administrations, applications or dosages. A therapeutically effective amount of a composition depends on the composition selected. The compositions can be administered from one or more times per day to one or more times per week; including once every other day. The skilled artisan will appreciate that certain factors may influence the dosage and timing required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of the compositions described herein can include a single treatment or a series of treatments.

The terms "decrease," "reduce," "reduced", "reduction", "decrease," and "inhibit" are all used herein generally to mean a decrease by a statistically significant amount relative to a reference. However, for avoidance of doubt, "reduce," "reduction" or "decrease" or "inhibit" typically means a decrease by at least 10% as compared to a reference level and can include, for example, a decrease by at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, up to and including, for example, the complete absence of the given entity or parameter ascompared to the reference level, or any decrease between 10-99% as compared to the absence of a given treatment.

The terms "increased", "increase" or "enhance" or "activate" are all used herein to generally mean an increase by a statically significant amount; for the avoidance of any doubt, the terms "increased", "increase" or "enhance" or "activate" means an increase of at least 10% as compared to a reference level, for example an increase of at least about 20%, or at least about 30%, or at least about 40%, or at least about 50%, or at least about 60%, or at least about 70%, or at least about 80%, or at least about 90% or up to and including a 100% increase or any increase between 10-100% as compared to a reference level, or at least about a 2-fold, or at least about a 3-fold, or at least about a 4-fold, or at least about a 5-fold or at least about a 10-fold increase, or any increase between 2-fold and 10-fold or greater as compared to a reference level.

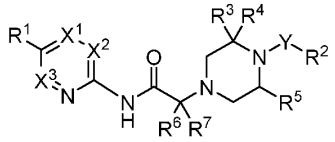
As used herein, the term "modulate" includes up-regulation and down-regulation, e.g., enhancing or inhibiting a response.

A "radiopharmaceutical agent," as defined herein, refers to a pharmaceutical agent which contains at least one radiation-emitting radioisotope. Radiopharmaceutical agents are routinely used in nuclear medicine for the diagnosis and/or therapy of various diseases. The radiolabelled pharmaceutical agent, for example, a radiolabelled antibody, contains a radioisotope (RI) which serves as the radiation source. As contemplated herein, the term "radioisotope" includes metallic and non-metallic radioisotopes. The radioisotope is chosen based on the medical application of the radiolabeled pharmaceutical agents. When the radioisotope is a metallic radioisotope, a chelator is typically employed to bind the metallic radioisotope to the rest of the molecule. When the radioisotope is a non-metallic radioisotope, the non-metallic radioisotope is typically linked directly, or via a linker, to the rest of the molecule.

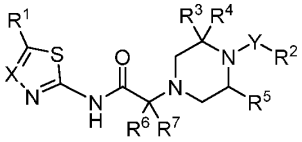
For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover.

Compounds of the Invention

In some embodiments, provided here in is a compound of Formula (Ia) or (Ib):



(Ia)



(Ib)

or a pharmaceutical salt thereof; wherein:

X is N or CR^x;

X^1, X^2, and X^3 are each independently N or CR^x;

R^x is independently for each occurrence hydrogen, fluoro, or chloro;

Y is C(=O), $C(=O)CH_2$, CH_2, or a bond;

R^1 is $-OR^{1a}$ or $-CH_2R^{1a}$; wherein R^{1a} is phenyl, $(C_1\text{-}C_6)$alkyl, 5- to 6-membered heteroaryl, or $(C_3\text{-}C_8)$cycloalkyl$(C_1\text{-}C_6)$alkyl; each of which is optionally substituted with one

or more substituents independently selected from the group consisting of fluoro, chloro, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy;

R^2 is 4-, 5- or 6- membered heterocycloalkyl, 9- or 10-membered bicyclic heterocycloalkyl, 5- or 6- membered heteroaryl, 9- or 10-membered bicyclic heteroaryl, (C_3-C_8)cycloalkyl, or phenyl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, cyano, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, -C(=O)NH_2, -NH_2, (C_1-C_6)alkoxy, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)hydroxyalkoxy, (C_1-C_6)carboxyalkyl (C_1-C_6)haloalkoxy, (C_3-C_8)cycloalkyl, and 4- to 7-membered heterocycloalkyl; wherein (C_1-C_6)alkyl is optionally substituted with phenyl, 4- to 7-membered heterocycloalkyl,and –NHR^{2a}; or R^2 is (C_1-C_6)alkyl;

R^{2a} is C(=O)R^{2b}, (C_1-C_6)alkyl, or (C_3-C_8)cycloalkyl, wherein (C_1-C_6)alkyl or (C_3-C_8)cycloalkyl is optionally substituted with one or more independent instances of halo;

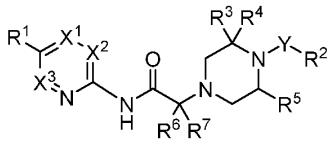
R^{2b} is (C_1-C_6)alkyl;

R^3 and R^4 are each independently hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxyalkyl, or (C_1-C_6)haloalkyl; or taken together with the carbon atom to which they are attached form a (C_3-C_6)cycloalkyl;

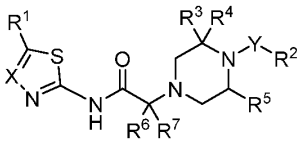
R^5 is hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxyalkyl, or (C_1-C_6)haloalkyl; or R^5 taken together with R^3 or R^4 forms –$(CH_2)_n$–; wherein n is 1, 2, or 3; and

R^6 and R^7 are independently for each occurrence hydrogen or (C_1-C_6)alkyl; or R^6 and R^7 taken together with the carbon atom to which they are attached form a (C_3-C_6)cycloalkyl.

In some embodiments, provided here in is a compound of Formula (Ia) or (Ib):



(Ia)



(Ib)

or a pharmaceutical salt thereof; wherein:

X is N or CR^x;

X^1, X^2, and X^3 are each independently N or CR^x;

R^x is independently for each occurrence hydrogen, fluoro, or chloro;

Y is C(=O), C(=O)CH_2, CH_2, or a bond;

R^1 is -OR^{1a} or –CH_2R^{1a}; wherein R^{1a} is phenyl, 5- to 6-membered heteroaryl, or (C_3-C_8)cycloalkyl(C_1-C_6)alkyl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy;

R^2 is 5- or 6- membered heterocycloalkyl, 9- or 10-membered bicyclic heterocycloalkyl (e.g., indoline, octahydroindole, tetrahydroquinoline, or decahydroquinoline), 5- or 6- membered heteroaryl, 9- or 10-membered bicyclic heteroaryl, or phenyl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, cyano, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, -C(=O)NH_2, (C_1-C_6)alkoxy, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, and (C_1-C_6)haloalkoxy; wherein (C_1-C_6)alkyl is optionally substituted with phenyl or –NHR^{2a};

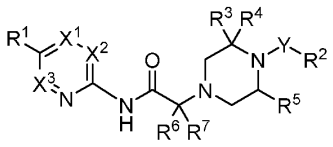
R^{2a} is (C_3-C_8)cycloalkyl, optionally substituted with one or more independent instances of halo;

R^3 and R^4 are each independently hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxyalkyl, or (C_1-C_6)haloalkyl; or taken together with the carbon atom to which they are attached form a (C_3-C_6)cycloalkyl;

R^5 is hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxyalkyl, or (C_1-C_6)haloalkyl; or R^5 taken together with R^3 or R^4 forms –$(CH_2)_n$–; wherein n is 1, 2, or 3; and

R^6 and R^7 are independently for each occurrence hydrogen or (C_1-C_6)alkyl; or R^6 and R^7 taken together with the carbon atom to which they are attached form a (C_3-C_6)cycloalkyl.

In some embodiments, the compound is



(Ia).

In certain embodiments of the compound of formula (Ia), X^1 is N, while in other embodiments, X^1 is CH.

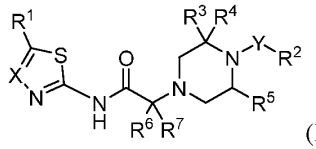
In some embodiments, X^2 is CH.

In some embodiments, X^3 is CH.

In some embodiments, X^1 is N; X^2 is CH; and X^3 is CH.

In some embodiments, X^1 is CH; X^2 is CH; and X^3 is CH.

In other embodiments, the compound is:



(Ib).

In certain embodiments of the compound of Formula (Ib), X is CH.

In some embodiments of the compound of Formula (Ia) or (Ib), Y is C(=O).

In some preferred embodiments, R^1 is $-OR^{1a}$.

In some embodiments, R^{1a} is phenyl optionally substituted with one or two instances of fluoro or chloro. In certain preferred embodiments, R^{1a} is 4-fluorophenyl, while in other embodimetns, R^{1a} is 2,4-difluorophenyl or 4-chlorophenyl.

In some embodiments, R^{1a} is 6-membered heteroaryl optionally substituted with one or two instances of fluoro or chloro. In some embodiments, R^{1a} is pyridyl optionally substituted with one or two fluoro or chloro. More particularly, in some embodiments, R^{1a} is 4-fluoropyridyl.

In some embodiments, R^{1a} is $(C_3\text{-}C_8)$cycloalkyl$(C_1\text{-}C_6)$alkyl. In some embodiments, R^{1a} is cyclopropylmethyl.

In some embodiments, R^2 is 9- or 10-membered bicyclic heteroaryl optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, cyano, hydroxy, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkenyl, $-C(=O)NH_2$, $-NH_2$, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$hydroxyalkyl, $(C_1\text{-}C_6)$halohydroxyalkyl, $(C_1\text{-}C_6)$hydroxyalkoxy, $(C_1\text{-}C_6)$carboxyalkyl $(C_1\text{-}C_6)$haloalkoxy, $(C_3\text{-}C_8)$cycloalkyl, and 4- to 7-membered heterocycloalkyl; wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with phenyl, 4- to 7-membered heterocycloalkyl, and $–NHR^{2a}$.

In more particular embodiments, R^2 is [1,2,4]triazolo[4,3-a]pyridine, [1,2,4]triazolo[1,5-a]pyridine, [1,2,4]triazolo[1,5-a]pyrazine, [1,2,4]triazolo[1,5-a]pyrimidine, [1,2,4]triazolo[4,3-a]pyrimidine, [1,2,4]triazolo[1,5-b]pyridazine, 1H-pyrazolo[3,4-b]pyridine 7-oxide, 3H-imidazo[4,5-b]pyridine 4-oxide, benzo[d]oxazole, 1H-benzo[d]imidazole, benzo[d]thiazole, 1H-benzo[d][1,2,3]triazole, [1,2,3]oxadiazolo[4,5-

b]pyridine, oxazolo[4,5-b]pyridine, 1H-indazole, 1H-pyrazolo[3,4-b]pyridine, or oxoisoindolin-1-yl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, cyano, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, -C(=O)NH_2, -NH_2, (C_1-C_6)alkoxy, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)hydroxyalkoxy, (C_1-C_6)carboxyalkyl (C_1-C_6)haloalkoxy, (C_3-C_8)cycloalkyl, and 4- to 7-membered heterocycloalkyl; wherein (C_1-C_6)alkyl is optionally substituted with phenyl, 4- to 7-membered heterocycloalkyl, or –NHR^{2a}.

In other embodiments, R^2 is 9- or 10-membered bicyclic heterocycloalkyl optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, cyano, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, -C(=O)NH_2, -NH_2, (C_1-C_6)alkoxy, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)hydroxyalkoxy, (C_1-C_6)carboxyalkyl (C_1-C_6)haloalkoxy, (C_3-C_8)cycloalkyl, and 4- to 7-membered heterocycloalkyl; wherein (C_1-C_6)alkyl is optionally substituted with phenyl, 4- to 7-membered heterocycloalkyl, or –NHR^{2a}.

In more particular embodiments, R^2 is 6,7-dihydro-5H-cyclopenta[b]pyridine 1-oxide, 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine, 4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridine, 4,5,6,7-tetrahydro-1H-benzo[d]imidazole, 4,5,6,7-tetrahydrobenzo[d]oxazole, 4,5,6,7-tetrahydro-1l2-benzo[d][1,2,3]triazole, 6,7-dihydro-5H-[1,2,4]triazolo[5,1-b][1,3]oxazine, 4,5,6,7-tetrahydro-2H-benzo[d][1,2,3]triazole, isoindolin-1-one, or 7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidine, each of which is optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, cyano, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, -C(=O)NH_2, -NH_2, (C_1-C_6)alkoxy, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)hydroxyalkoxy, (C_1-C_6)carboxyalkyl (C_1-C_6)haloalkoxy, (C_3-C_8)cycloalkyl, and 4- to 7-membered heterocycloalkyl; wherein (C_1-C_6)alkyl is optionally substituted with phenyl, 4- to 7-membered heterocycloalkyl, or –NHR^{2a}.

In some embodiments, R^2 is pyridin-2(1H)-one, pyridine oxide, pyrimidine oxide, 1,5-dihydro-2H-pyrrol-2-one, phenyl, isoindolin-1-one, 1H-indazole, tetrahydro-2H-pyran, pyridine, 1H-pyrazole, 2-oxo-2,3-dihydro-1H-imidazole, 5-oxomorpholine, tetrahydropyrimidin-2(1H)-one, piperidin-2-one, pyrimidin-2(1H)-one, pyridazin-3(2H)-one, or pyrazin-2(1H)-one; each of which is optionally substituted with one or more substituents

independently selected from the group consisting of fluoro, chloro, cyano, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, -C(=O)NH_2, (C_1-C_6)alkoxy, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, and (C_1-C_6)haloalkoxy; wherein (C_1-C_6)alkyl is optionally substituted with phenyl or –NHR^{2a}.

In some embodiments, R^2 is pyridin-2(1H)-one, pyridine oxide, pyrimidine oxide, 1,5-dihydro-2H-pyrrol-2-one, phenyl, isoindolin-1-one, 1H-indazole, tetrahydro-2H-pyran, pyridine, or 1H-pyrazole; each of which is optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, cyano, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, -C(=O)NH_2, (C_1-C_6)alkoxy, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, and (C_1-C_6)haloalkoxy; wherein (C_1-C_6)alkyl is optionally substituted with phenyl or –NHR^{2a}. Preferably, R^2 is pyridin-2(1H)-one or pyridine oxide; each of which is optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, cyano, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, -C(=O)NH_2, (C_1-C_6)alkoxy, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, and (C_1-C_6)haloalkoxy; wherein (C_1-C_6)alkyl is optionally substituted with phenyl or –NHR^{2a}. In some preferred embodiments, R^2 is unsubstituted pyridin-2(1H)-one or pyridine oxide. In other preferred embodiments, R^2 is unsubstituted pyridin-2(1H)-one or pyridine oxide.

In some embodiments, R^{2a} is methyl. In other embodiments, R^{2a} is cyclobutyl optionally substituted with at least one fluoro.

In some embodiments, R^{2b} is methyl.

In some embodiments, R^3 and R^4 are each hydrogen.

In other embodiments, R^3 and R^4 are each independently (C_1-C_6)alkyl, preferably R^3 and R^4 are each methyl.

In some embodiments, one of R^3 and R^4 is hydrogen.

In some embodiments, one of R^3 and R^4 is (C_1-C_6)fluoroalkyl, preferably trifluoromethyl.

In other embodiments, R^3 and R^4 taken together with the carbon atom to which they are attached form a (C_3-C_6)cycloalkyl. In some embodiments, R^3 and R^4 taken together with the carbon atom to which they are attached form cyclopropyl, while in other embodiments, R^3 and R^4 taken together with the carbon atom to which they are attached form cyclobutyl.

In some embodiments, R^5 is hydrogen.

In other embodiments, R^5 taken together with one of R^3 or R^4 forms $–(CH_2)_n–$, preferably wherein n is 2.

In some embodiments, one of R^6 or R^7 is hydrogen.

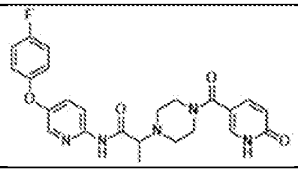
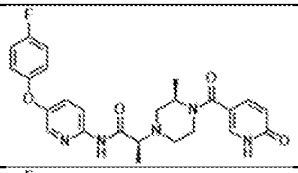
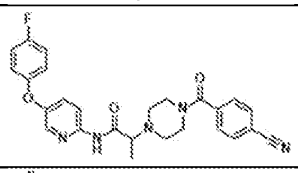
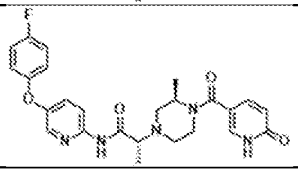
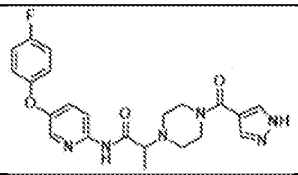
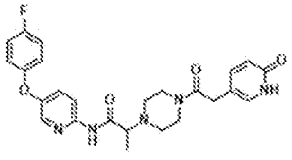
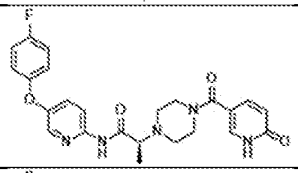
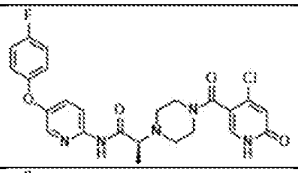
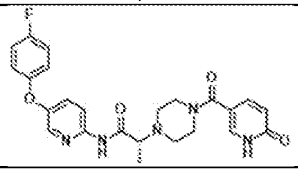
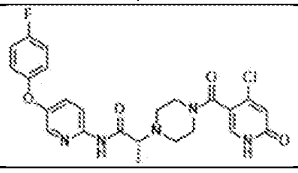
In other embodiments, one of R^6 or R^7 is $(C_1\text{-}C_6)$alkyl, preferably one of R^6 or R^7 is methyl. In other embodiments, one of R^6 or R^7 is ethyl.

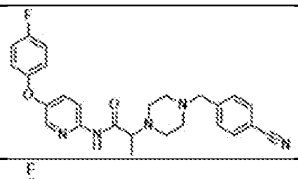
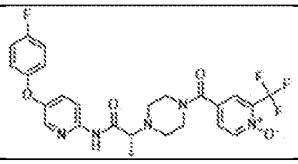
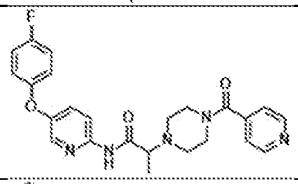
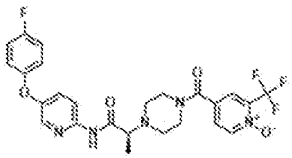
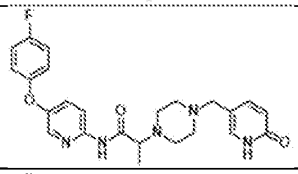
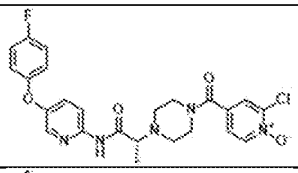
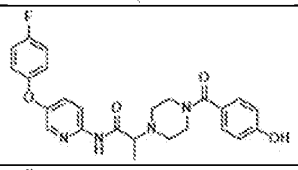
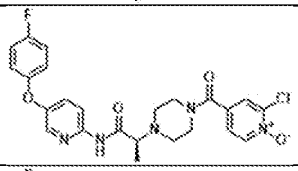
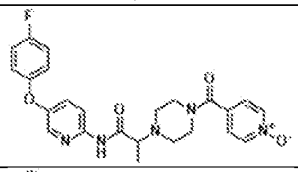
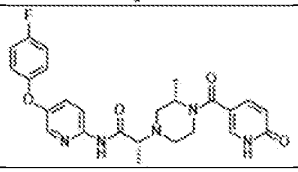
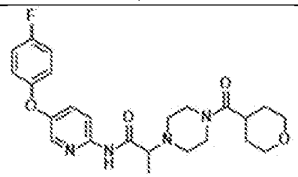
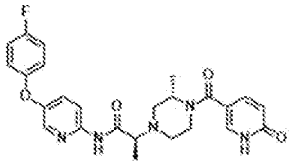
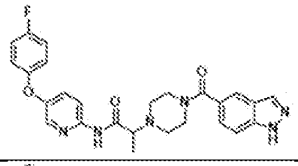
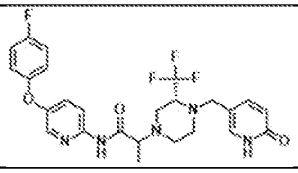
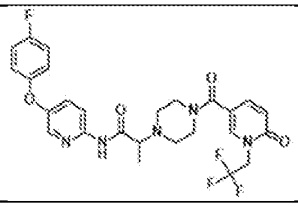
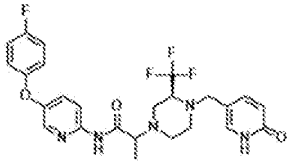
In some embodiments, R^6 and R^7 are each hydrogen.

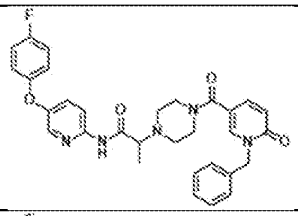
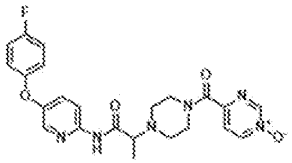
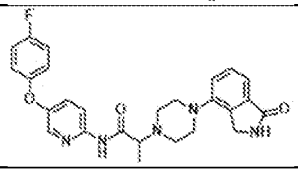
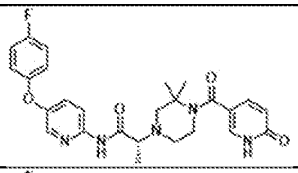
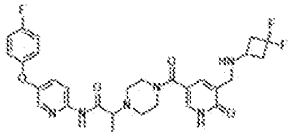
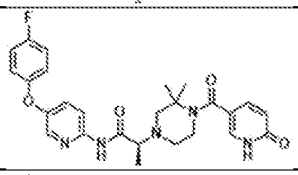
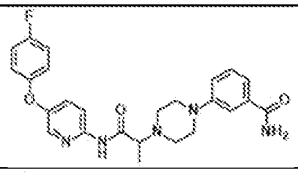
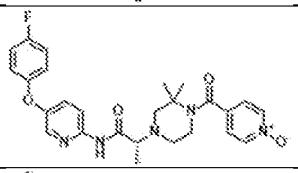
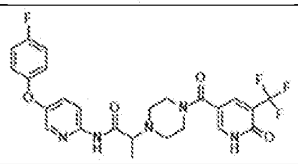
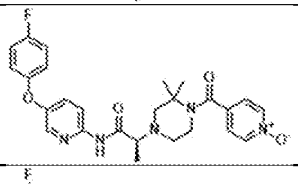
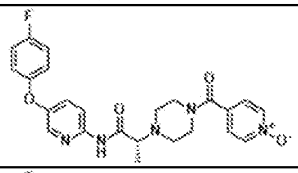
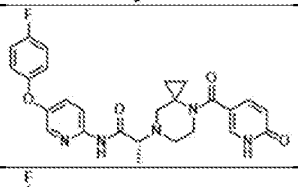
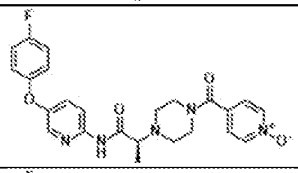
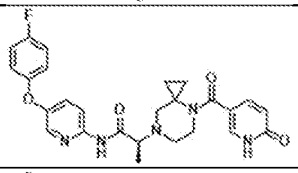
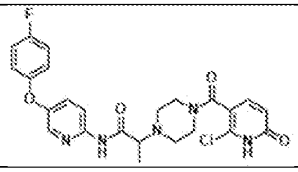
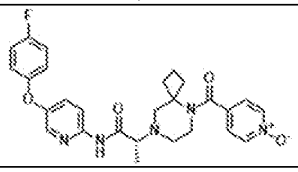
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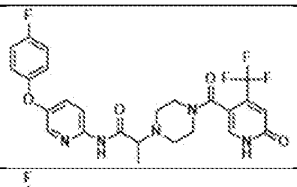
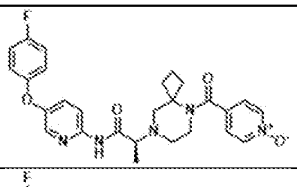
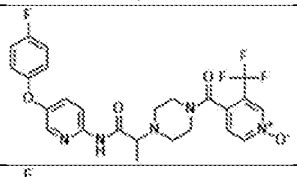
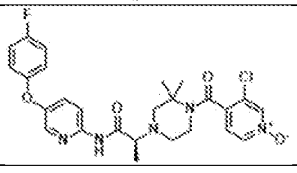
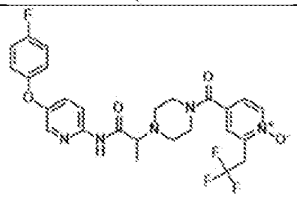
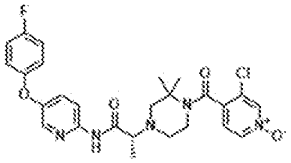
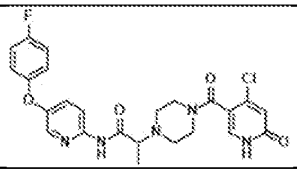
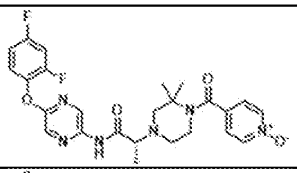
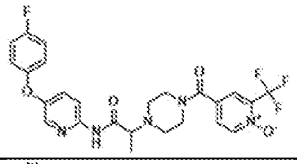
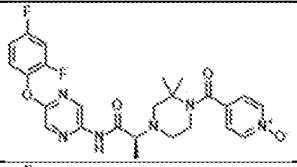
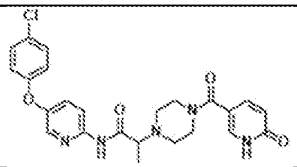
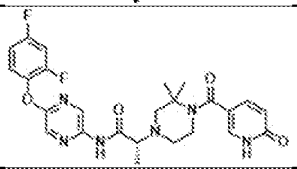
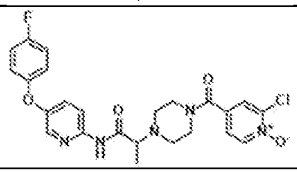
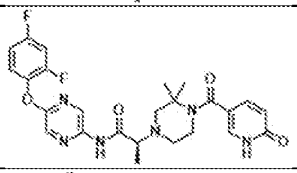
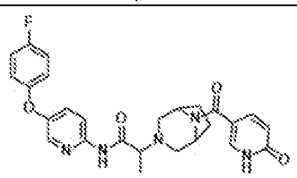
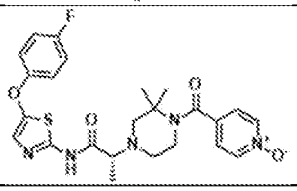
In other embodiments, R^6 and R^7 taken together with the carbon atom to which they are attached form a $(C_3\text{-}C_6)$cycloalkyl, preferably a cyclopropyl.

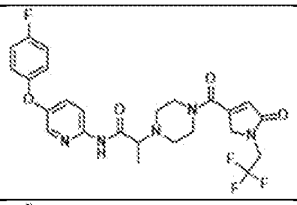
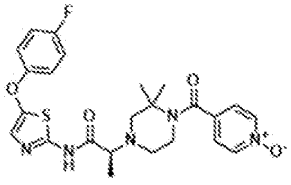
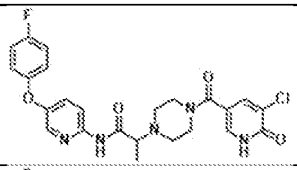
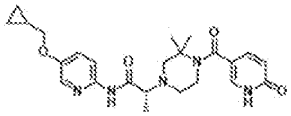
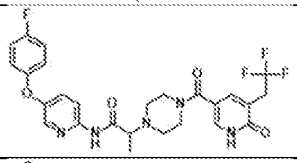
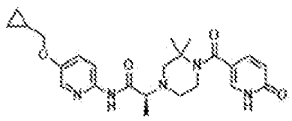
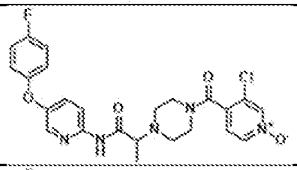
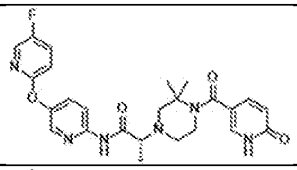
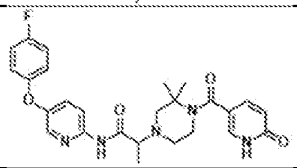
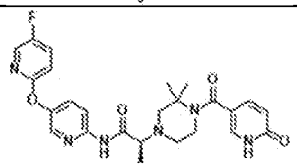
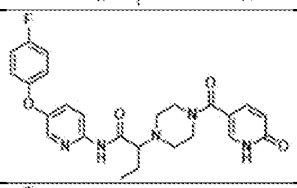
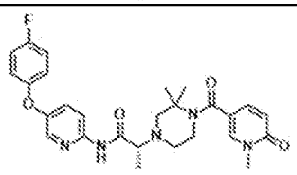
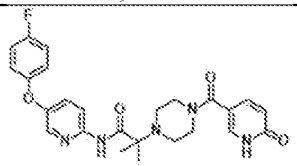
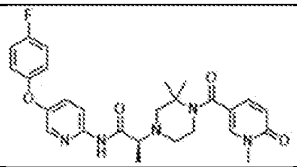
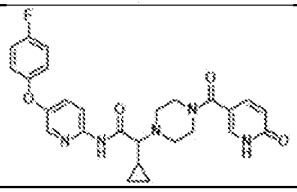
In more particular embodiments, a compound of the invention has the structure:

Structure	Example	Structure	Example
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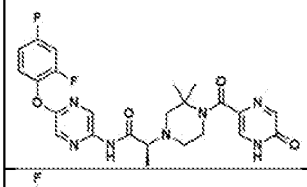
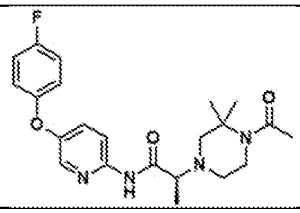
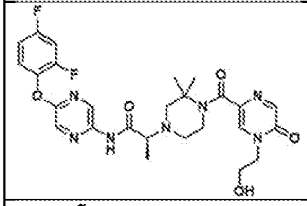
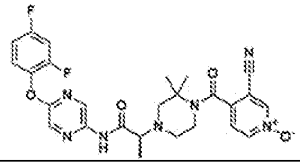
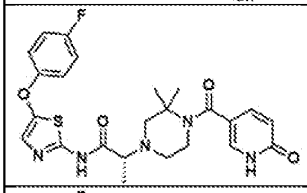
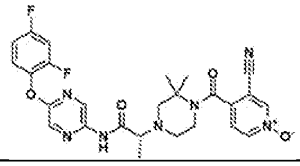
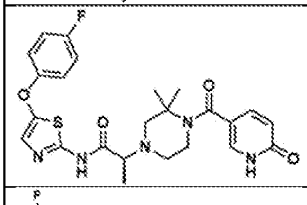
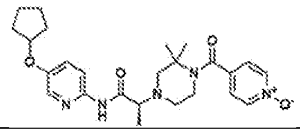
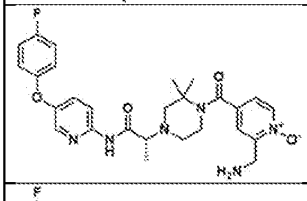
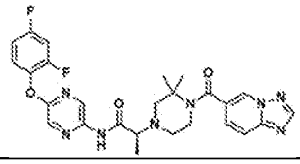
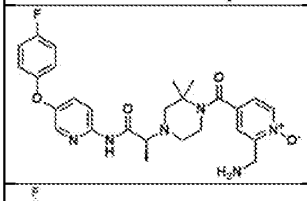
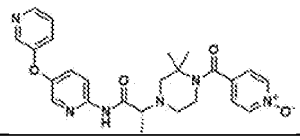
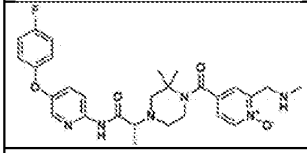
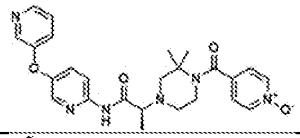
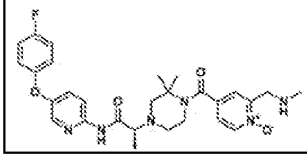
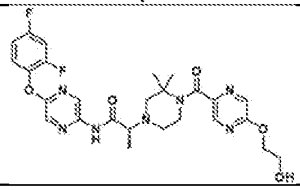
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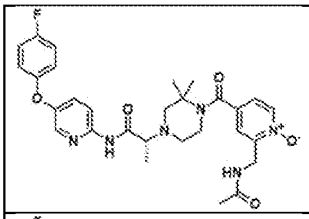
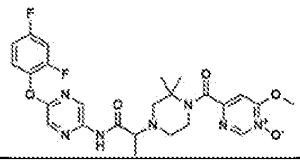
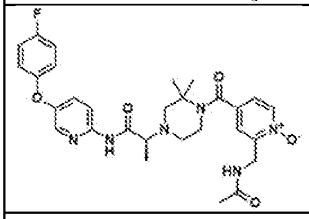
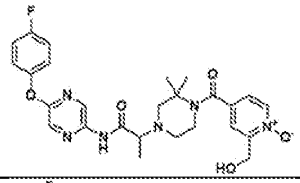
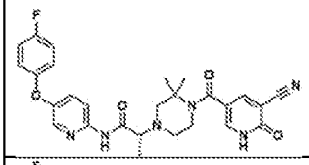
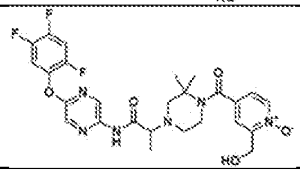
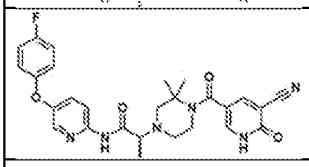
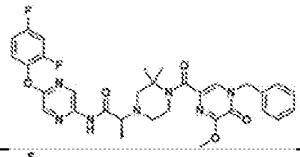
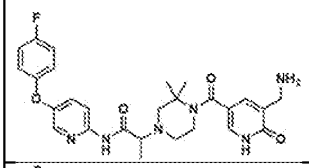
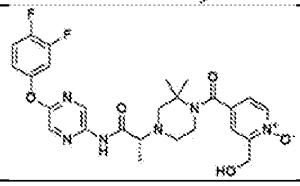
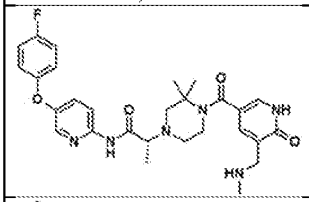
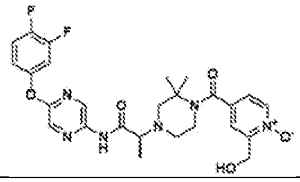
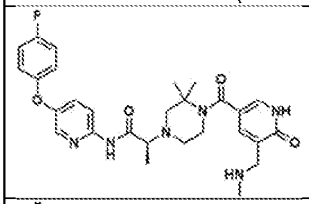
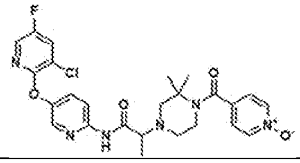
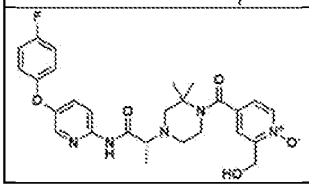
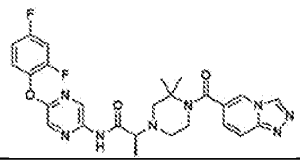
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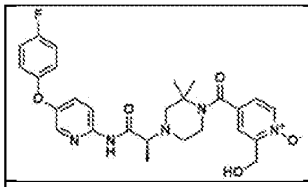
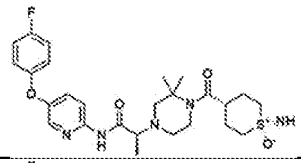
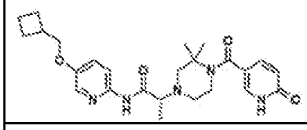
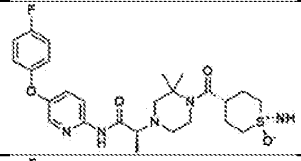
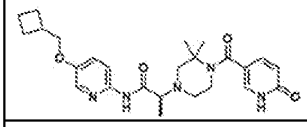
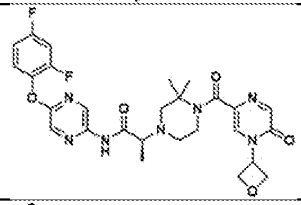
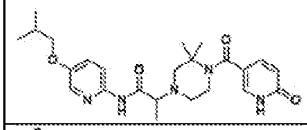
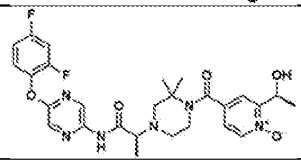
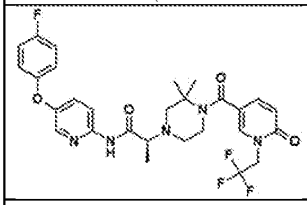
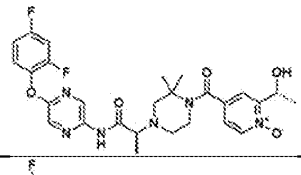
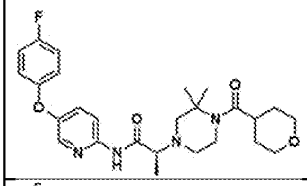
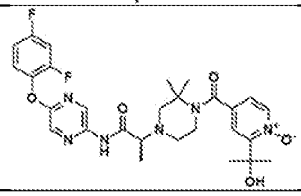
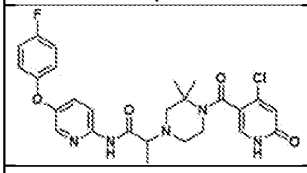
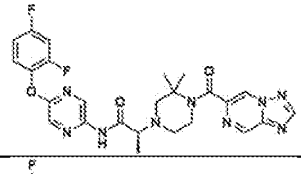
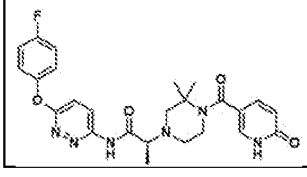
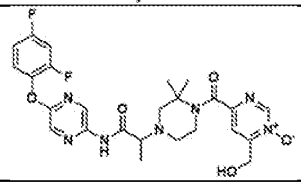
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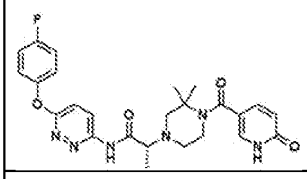
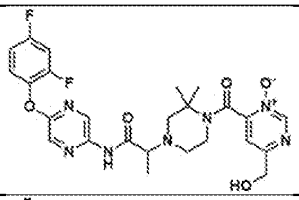
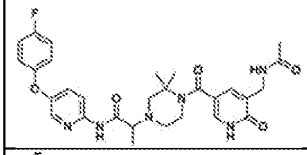
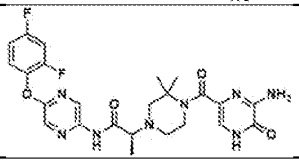
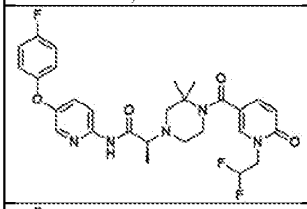
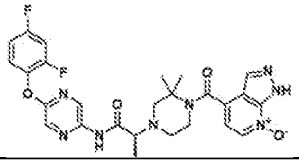
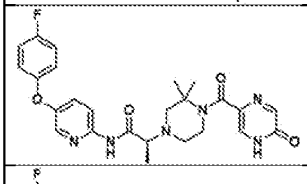
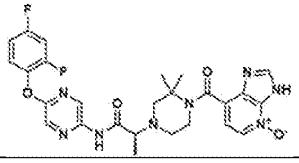
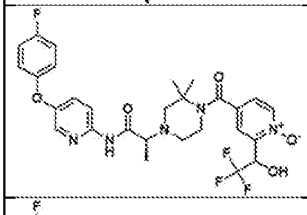
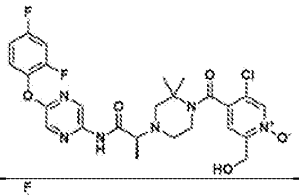
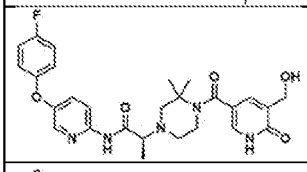
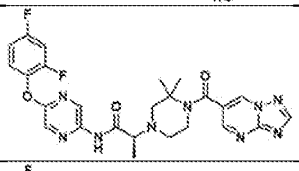
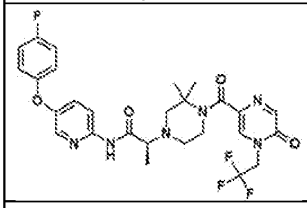
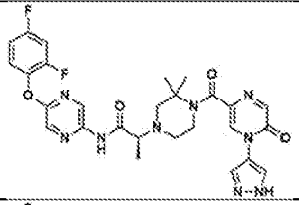
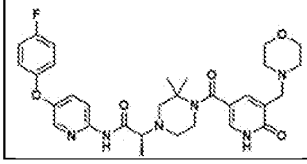
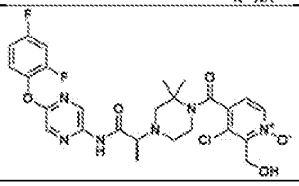
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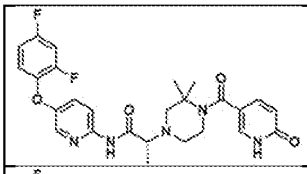
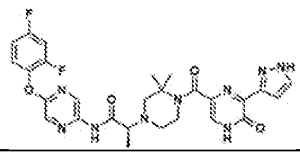
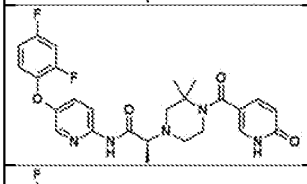
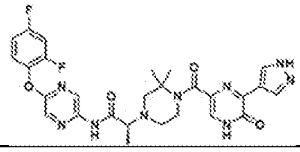
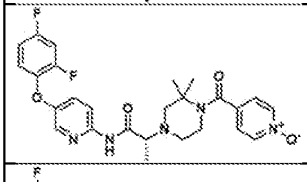
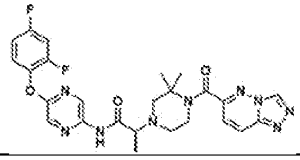
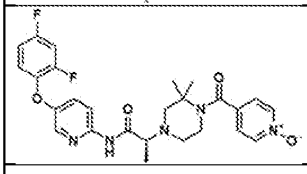
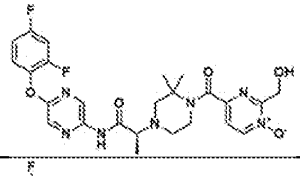
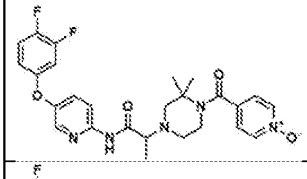
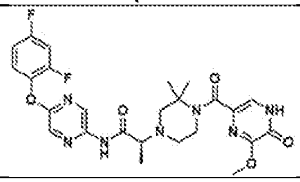
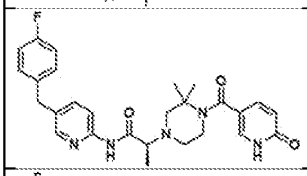
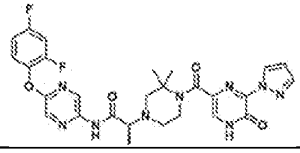
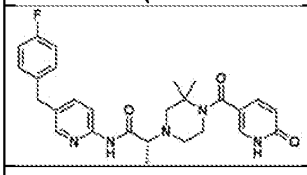
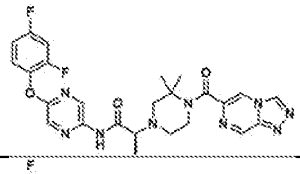
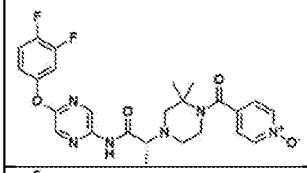
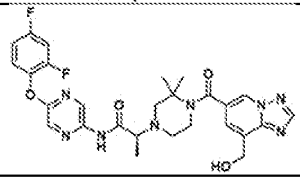
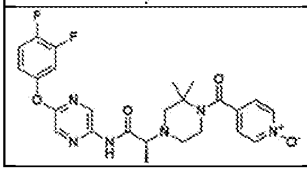
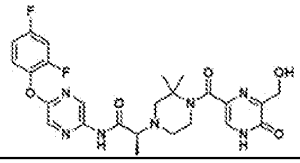
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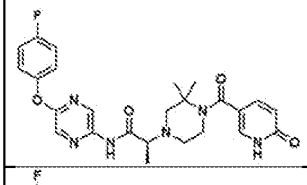
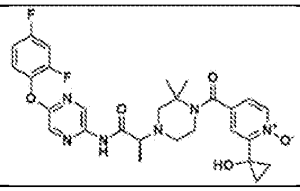
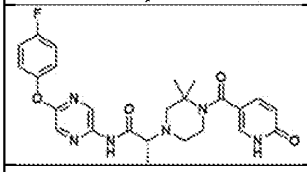
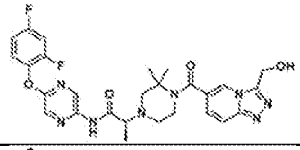
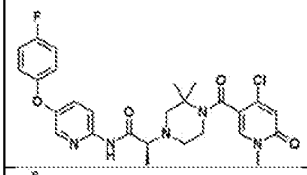
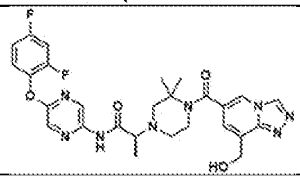
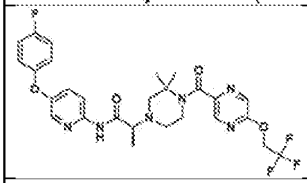
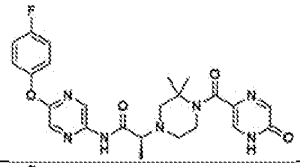
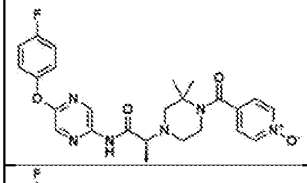
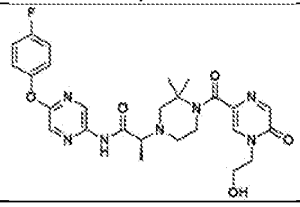
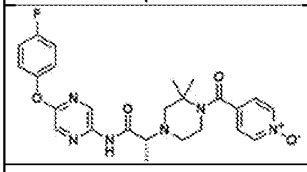
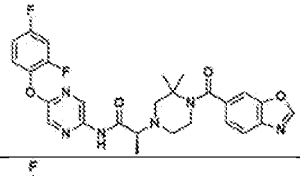
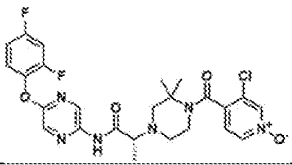
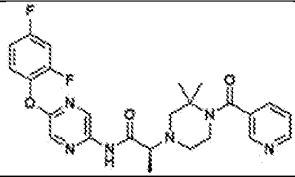
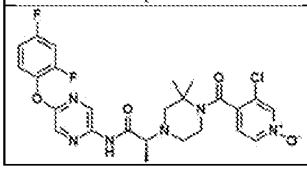
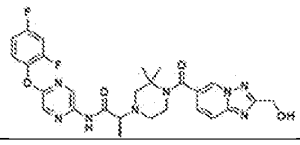
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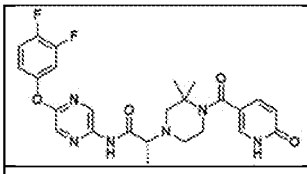
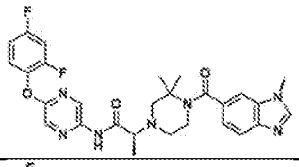
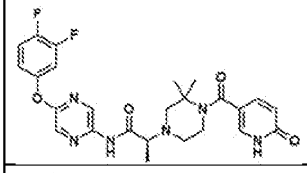
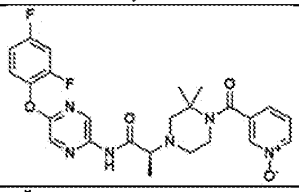
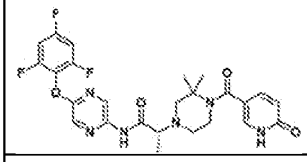
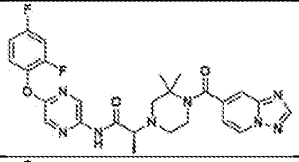
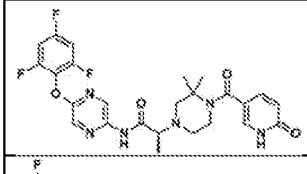
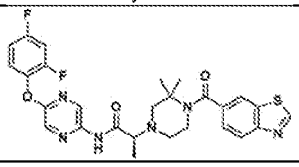
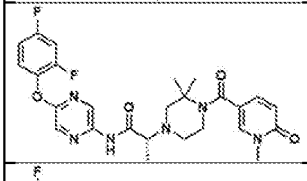
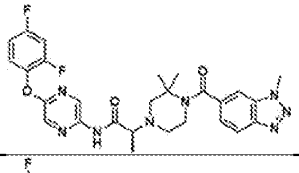
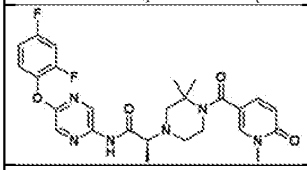
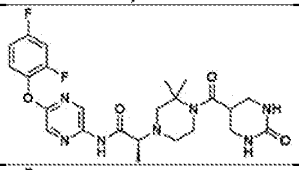
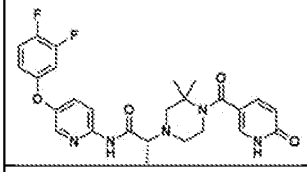
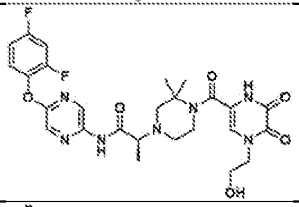
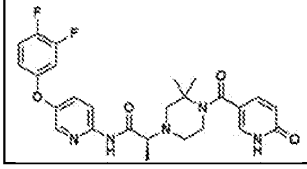
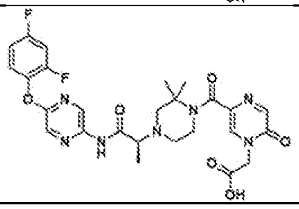
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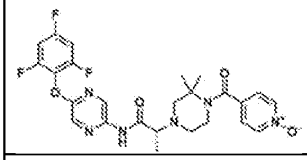
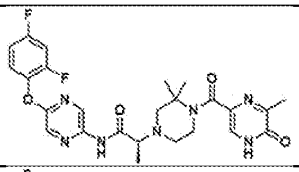
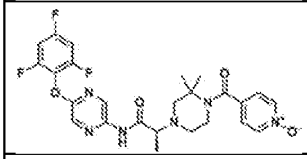
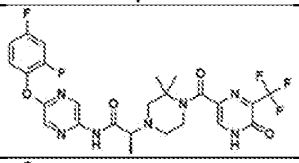
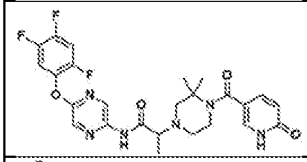
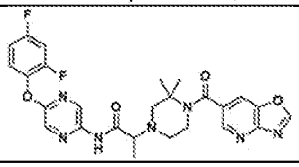
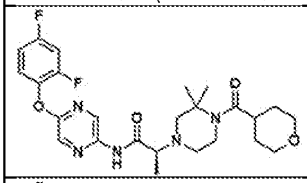
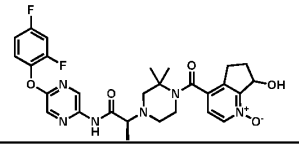
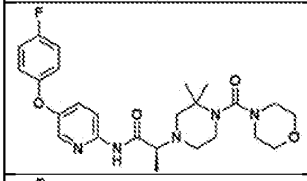
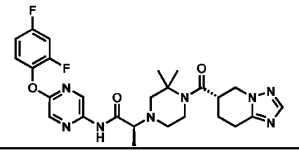
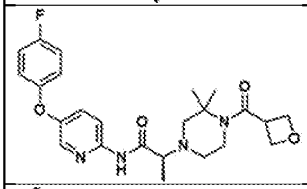
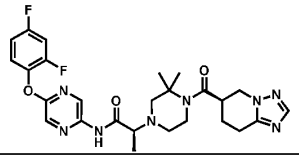
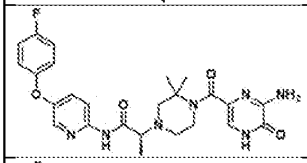
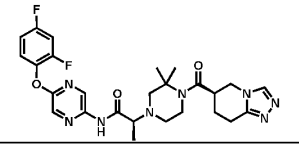
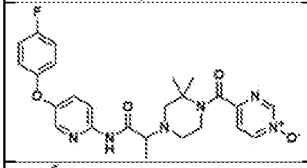
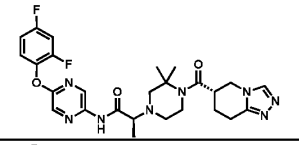
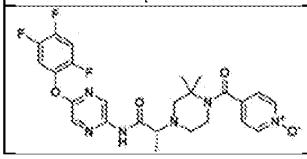
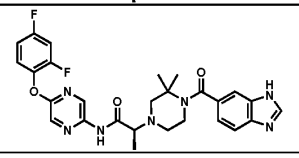
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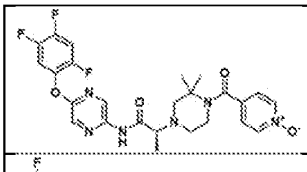
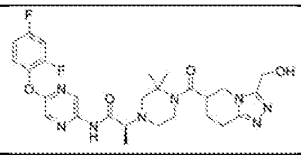
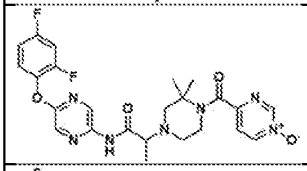
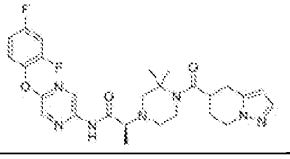
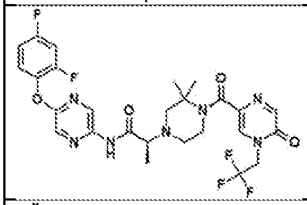
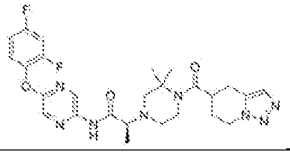
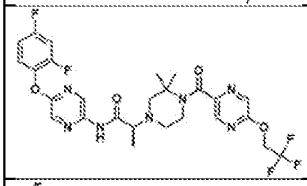
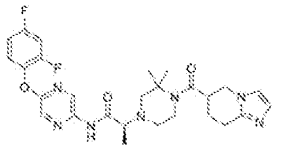
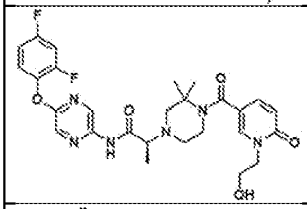
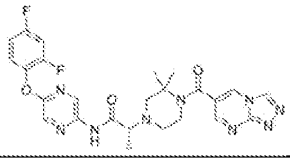
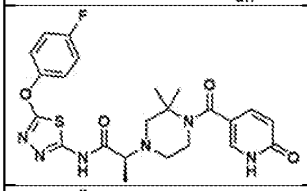
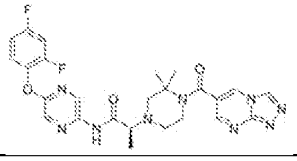
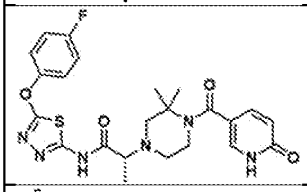
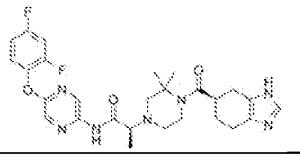
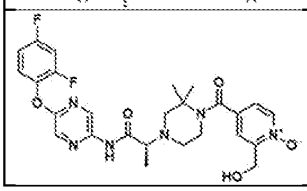
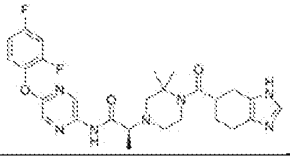
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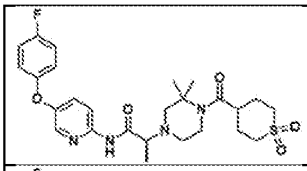
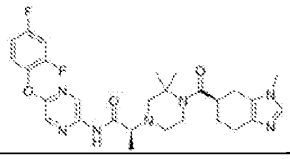
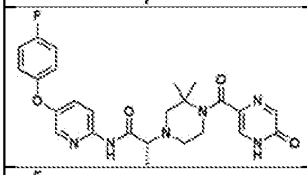
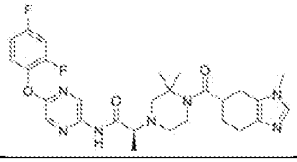
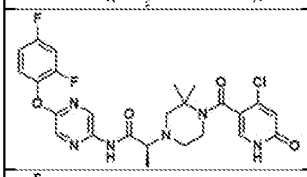
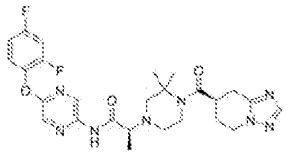
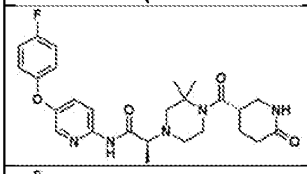
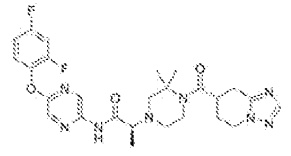
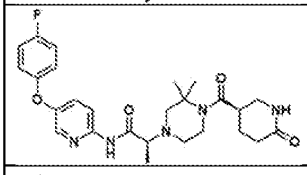
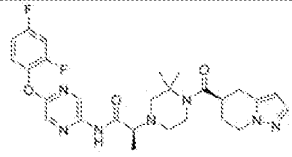
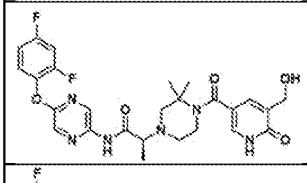
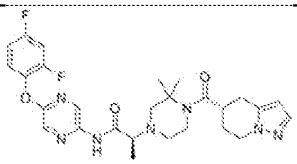
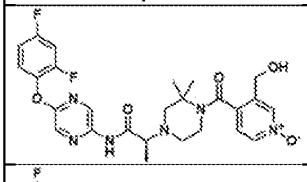
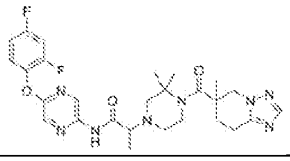
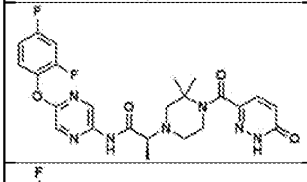
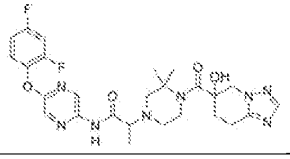
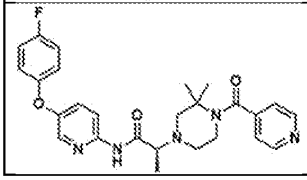
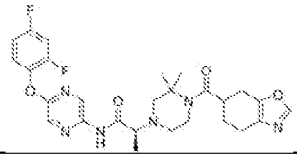
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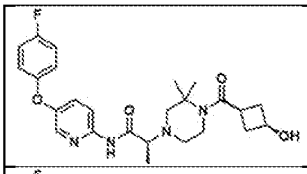
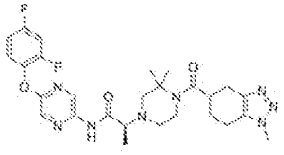
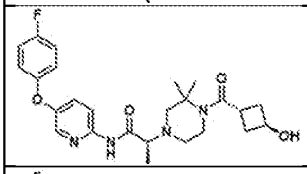
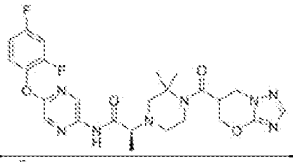
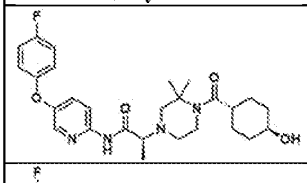
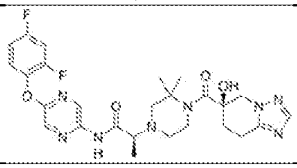
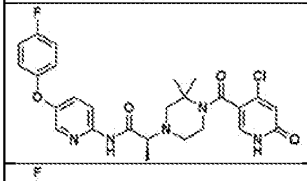
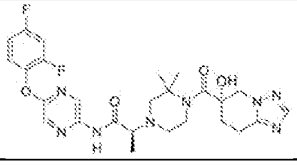
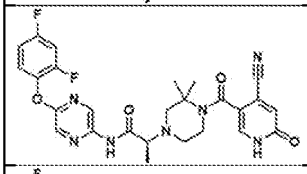
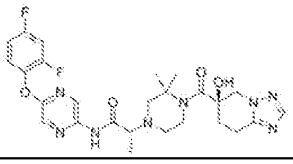
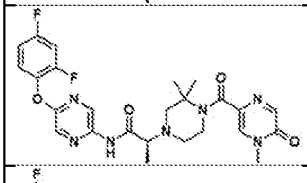
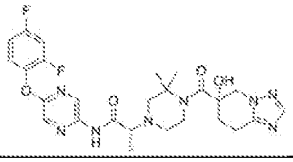
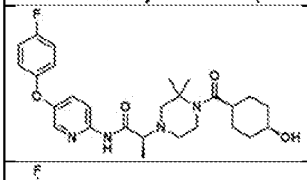
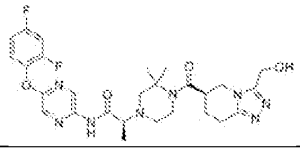
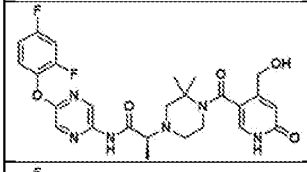
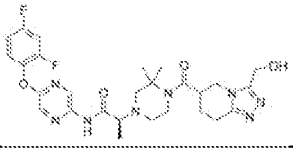
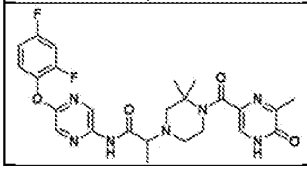
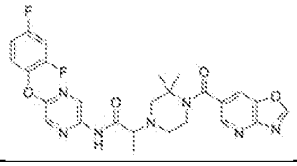
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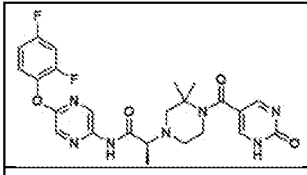
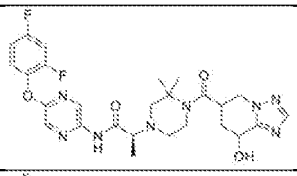
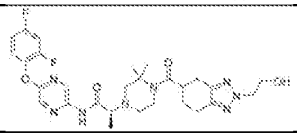
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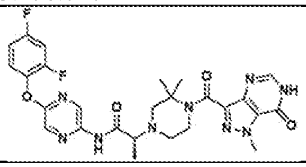
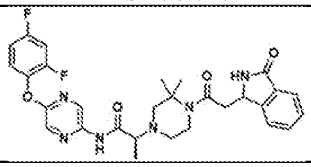
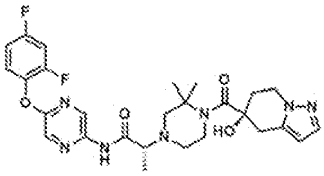
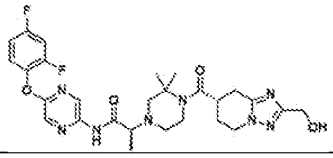
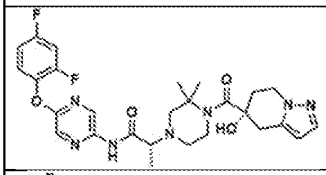
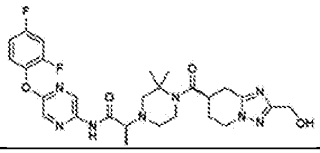
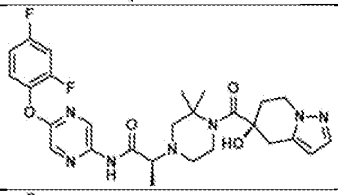
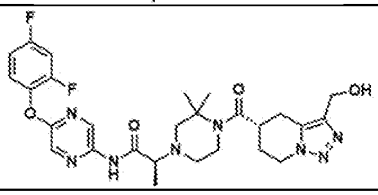
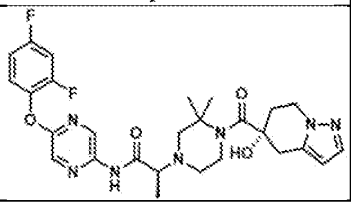
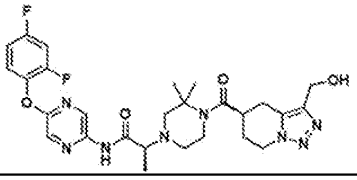
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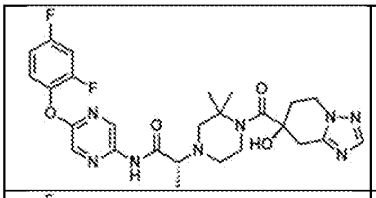
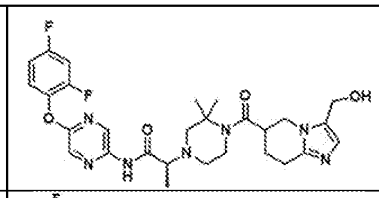
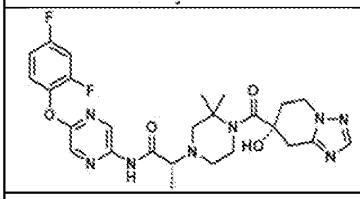
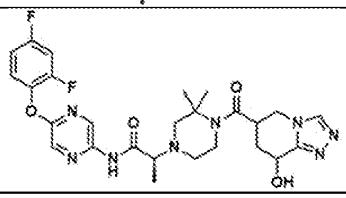
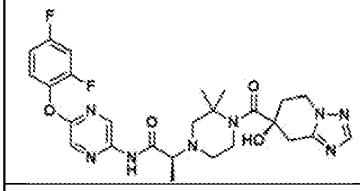
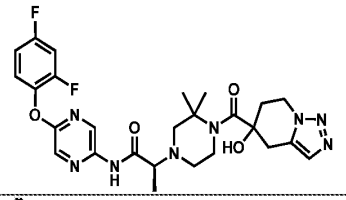
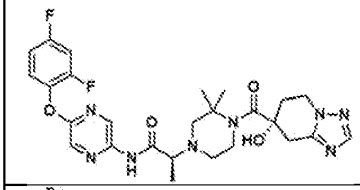
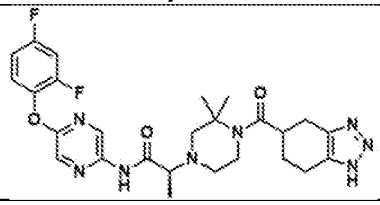
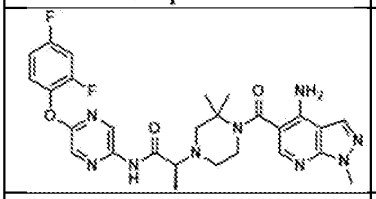
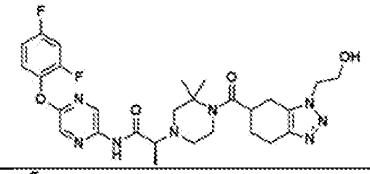
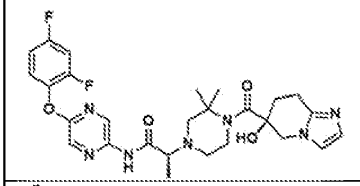
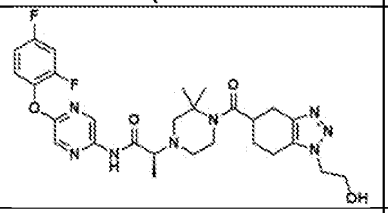
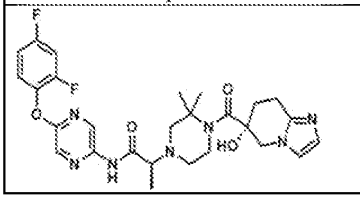
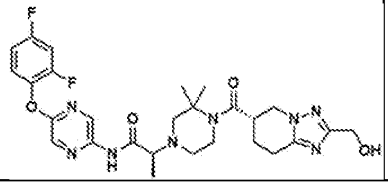
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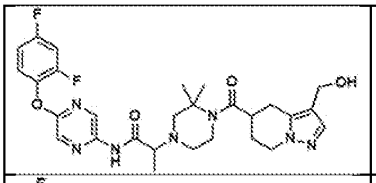
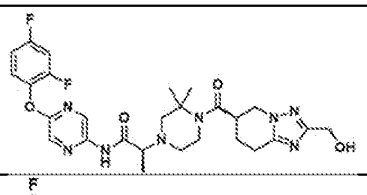
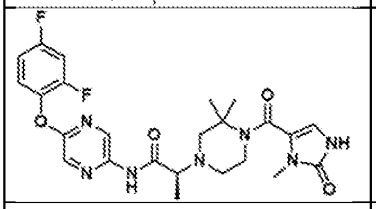
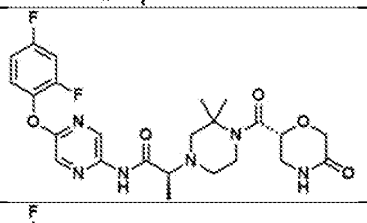
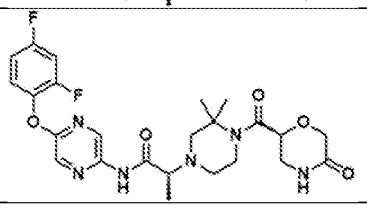
	166		259
			260

or a pharmaceutically acceptable salt thereof.

In other embodiments, a compound of the invention has the structure:

Structure	Ex.	Structure	Ex.
	261		275
	262		276
	263		277
	264		278
	265		279

	**266**		**280**
	**267**		**281**
	**268**		**282**
	**269**		**283**
	**270**		**284**
	**271**		**285**
	**272**		**286**

	273		287
	274		288
			289

or a pharmaceutically aceeptable salt thereof.

In certain embodiments, the compounds are atropisomers. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds produced by the replacement of a hydrogen with deuterium or tritium, or of a carbon with a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention. For example, in the case of variable R^1, the $(C_1\text{-}C_4)$alkyl or the -O-$(C_1\text{-}C_4)$alkyl can be suitably deuterated (*e.g.*, $-CD_3$, or $-OCD_3$, respectively).

Any compound of the invention can also be radiolabed for the preparation of a radiopharmaceutical agent.

Methods of Treatment

One aspect of the invention provides compounds, compositions, and methods useful for preventing or treating a disease Additionally, methods of preventing or treating an MRGPRX2-mediated disease or disorder, comprise administering to a subject in need thereof a therapeutically effective amount of the compound of Formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof. For example, an MRGPRX2-mediated disease or disorder may be chronic spontaneous urticaria, prurigo nodularis, irritable bowel syndrome, chronic inducible urticaria, atopic dermatitis, osteoarthritis, rosacea, migraine, pseudo-

analphylaxis, mast cell activation syndrome, mastocytosis, pruritus, neurodermatitis, contact urticaria, allergic rhinitis, asthma, acute contact dermatitis, ulcerative colitis, crohns disease, idiopathic chronic cough, rheumatoid arthritis, multiple sclerosis, geographic atrophy, endometriosis, seborrheic dermatitis, psoriasis, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, neuropathic itch, periodontitis, autism, abdominal aortic aneurysms, deep vein thrombosis, amyotrophic lateral sclerosis, interstitial cystitis, coronary artery disease, cancer, sickle cell disease, obesity, or ulcers.

In certain embodiments, the compound is administered orally to the subject.

In certain embodiments, the compound is administered parenterally to the subject.

In certain embodiments, the disease is prevented. In other embodiments, the disease is treated.

Pharmaceutical Compositions, Routes of Administration, and Dosing

In certain embodiments, the invention is directed to a pharmaceutical composition, comprising a compound of the invention, e.g. a compound of Formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In certain embodiments, the invention is directed to a pharmaceutical composition, comprising a compound of any of the disclosed embodiments, and a pharmaceutically acceptable carrier.

In certain embodiments, the pharmaceutical composition comprises a plurality of compounds of the invention and a pharmaceutically acceptable carrier.

Pharmaceutical compositions of the invention can be prepared by combining one or more compounds of the invention with a pharmaceutically acceptable carrier and, optionally, one or more additional pharmaceutically active agents.

As stated above, an "effective amount" refers to any amount that is sufficient to achieve a desired biological effect. Combined with the teachings provided herein, by choosing among the various active compounds and weighing factors such as potency, relative bioavailability, patient body weight, severity of adverse side-effects and mode of administration, an effective prophylactic or therapeutic treatment regimen can be planned which does not cause substantial unwanted toxicity and yet is effective to treat the particular subject. The effective amount for any particular application can vary depending on such factors as the disease or condition being treated, the particular compound of the invention being administered, the size of the subject, or the severity of the disease or condition. One of

ordinary skill in the art can empirically determine the effective amount of a particular compound of the invention and/or other therapeutic agent without necessitating undue experimentation. A maximum dose may be used, that is, the highest safe dose according to some medical judgment. Multiple doses per day may be contemplated to achieve appropriate systemic levels of compounds. Appropriate systemic levels can be determined by, for example, measurement of the patient's peak or sustained plasma level of the drug. "Dose" and "dosage" are used interchangeably herein.

In certain embodiments, intravenous administration of a compound may typically be from 0.1 mg/kg/day to 20 mg/kg/day. In one embodiment, intravenous administration of a compound may typically be from 0.1 mg/kg/day to 2 mg/kg/day. In one embodiment, intravenous administration of a compound may typically be from 0.5 mg/kg/day to 5 mg/kg/day. In one embodiment, intravenous administration of a compound may typically be from 1 mg/kg/day to 20 mg/kg/day. In one embodiment, intravenous administration of a compound may typically be from 1 mg/kg/day to 10 mg/kg/day.

Generally, daily oral doses of a compound will be, for human subjects, from about 0.01 milligrams/kg per day to 1000 milligrams/kg per day. It is expected that oral doses in the range of 0.5 to 50 milligrams/kg, in one or more administrations per day, will yield therapeutic results. Dosage may be adjusted appropriately to achieve desired drug levels, local or systemic, depending upon the mode of administration. For example, it is expected that intravenous administration would be from one order to several orders of magnitude lower dose per day. In the event that the response in a subject is insufficient at such doses, even higher doses (or effective higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits. Multiple doses per day are contemplated to achieve appropriate systemic levels of the compound.

For any compound described herein the therapeutically effective amount can be initially determined from animal models. A therapeutically effective dose can also be determined from human data for compounds which have been tested in humans and for compounds which are known to exhibit similar pharmacological activities, such as other related active agents. Higher doses may be required for parenteral administration. The applied dose can be adjusted based on the relative bioavailability and potency of the administered compound. Adjusting the dose to achieve maximal efficacy based on the methods described above and other methods as are well-known in the art is well within the capabilities of the ordinarily skilled artisan.

The formulations of the invention can be administered in pharmaceutically acceptable solutions, which may routinely contain pharmaceutically acceptable concentrations of salt, buffering agents, preservatives, compatible carriers, adjuvants, and optionally other therapeutic ingredients.

For use in therapy, an effective amount of the compound can be administered to a subject by any mode that delivers the compound to the desired surface. Administering a pharmaceutical composition may be accomplished by any means known to the skilled artisan. Routes of administration include but are not limited to intravenous, intramuscular, intraperitoneal, intravesical (urinary bladder), oral, subcutaneous, direct injection (for example, into a tumor or abscess), mucosal (e.g., topical to eye), inhalation, and topical.

For intravenous and other parenteral routes of administration, a compound of the invention can be formulated as a lyophilized preparation, as a lyophilized preparation of liposome-intercalated or -encapsulated active compound, as a lipid complex in aqueous suspension, or as a salt complex. Lyophilized formulations are generally reconstituted in suitable aqueous solution, e.g., in sterile water or saline, shortly prior to administration.

For oral administration, the compounds can be formulated readily by combining the active compound(s) with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject to be treated. Pharmaceutical preparations for oral use can be obtained as solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. Optionally the oral formulations may also be formulated in saline or buffers, e.g., EDTA for neutralizing internal acid conditions or may be administered without any carriers.

Also specifically contemplated are oral dosage forms of the above component or components. The component or components may be chemically modified so that oral delivery of the derivative is efficacious. Generally, the chemical modification contemplated is the attachment of at least one moiety to the component molecule itself, where said moiety

permits (a) inhibition of acid hydrolysis; and (b) uptake into the blood stream from the stomach or intestine. Also desired is the increase in overall stability of the component or components and increase in circulation time in the body. Examples of such moieties include: polyethylene glycol, copolymers of ethylene glycol and propylene glycol, carboxymethyl cellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone and polyproline. Abuchowski and Davis, "Soluble Polymer-Enzyme Adducts", In: Enzymes as Drugs, Hocenberg and Roberts, eds., Wiley-Interscience, New York, N.Y., pp. 367-383 (1981); Newmark et al., *J Appl Biochem* 4:185-9 (1982). Other polymers that could be used are poly-1,3-dioxolane and poly-1,3,6-tioxocane. For pharmaceutical usage, as indicated above, polyethylene glycol moieties are suitable.

For the component (or derivative) the location of release may be the stomach, the small intestine (the duodenum, the jejunum, or the ileum), or the large intestine. One skilled in the art has available formulations which will not dissolve in the stomach, yet will release the material in the duodenum or elsewhere in the intestine. Preferably, the release will avoid the deleterious effects of the stomach environment, either by protection of the compound of the invention (or derivative) or by release of the biologically active material beyond the stomach environment, such as in the intestine.

To ensure full gastric resistance a coating impermeable to at least pH 5.0 is essential. Examples of the more common inert ingredients that are used as enteric coatings are cellulose acetate trimellitate (CAT), hydroxypropylmethylcellulose phthalate (HPMCP), HPMCP 50, HPMCP 55, polyvinyl acetate phthalate (PVAP), Eudragit L30D, Aquateric, cellulose acetate phthalate (CAP), Eudragit L, Eudragit S, and shellac. These coatings may be used as mixed films.

A coating or mixture of coatings can also be used on tablets, which are not intended for protection against the stomach. This can include sugar coatings, or coatings which make the tablet easier to swallow. Capsules may consist of a hard shell (such as gelatin) for delivery of dry therapeutic (e.g., powder); for liquid forms, a soft gelatin shell may be used. The shell material of cachets could be thick starch or other edible paper. For pills, lozenges, molded tablets or tablet triturates, moist massing techniques can be used.

The therapeutic can be included in the formulation as fine multi-particulates in the form of granules or pellets of particle size about 1 mm. The formulation of the material for capsule administration could also be as a powder, lightly compressed plugs or even as tablets. The therapeutic could be prepared by compression.

Colorants and flavoring agents may all be included. For example, the compound of the invention (or derivative) may be formulated (such as by liposome or microsphere encapsulation) and then further contained within an edible product, such as a refrigerated beverage containing colorants and flavoring agents.

One may dilute or increase the volume of the therapeutic with an inert material. These diluents could include carbohydrates, especially mannitol, α-lactose, anhydrous lactose, cellulose, sucrose, modified dextrans and starch. Certain inorganic salts may ~~be~~ also be used as fillers including calcium triphosphate, magnesium carbonate and sodium chloride. Some commercially available diluents are Fast-Flo, Emdex, STA-Rx 1500, Emcompress and Avicell.

Disintegrants may be included in the formulation of the therapeutic into a solid dosage form. Materials used as disintegrates include but are not limited to starch, including the commercial disintegrant based on starch, Explotab. Sodium starch glycolate, Amberlite, sodium carboxymethylcellulose, ultramylopectin, sodium alginate, gelatin, orange peel, acid carboxymethyl cellulose, natural sponge and bentonite may all be used. Another form of the disintegrants are the insoluble cationic exchange resins. Powdered gums may be used as disintegrants and as binders and these can include powdered gums such as agar, Karaya or tragacanth. Alginic acid and its sodium salt are also useful as disintegrants.

Binders may be used to hold the therapeutic agent together to form a hard tablet and include materials from natural products such as acacia, tragacanth, starch and gelatin. Others include methyl cellulose (MC), ethyl cellulose (EC) and carboxymethyl cellulose (CMC). Polyvinyl pyrrolidone (PVP) and hydroxypropylmethyl cellulose (HPMC) could both be used in alcoholic solutions to granulate the therapeutic.

An anti-frictional agent may be included in the formulation of the therapeutic to prevent sticking during the formulation process. Lubricants may be used as a layer between the therapeutic and the die wall, and these can include but are not limited to; stearic acid including its magnesium and calcium salts, polytetrafluoroethylene (PTFE), liquid paraffin, vegetable oils and waxes. Soluble lubricants may also be used such as sodium lauryl sulfate, magnesium lauryl sulfate, polyethylene glycol of various molecular weights, Carbowax 4000 and 6000.

Glidants that might improve the flow properties of the drug during formulation and to aid rearrangement during compression might be added. The glidants may include starch, talc, pyrogenic silica and hydrated silicoaluminate.

To aid dissolution of the therapeutic into the aqueous environment a surfactant might be added as a wetting agent. Surfactants may include anionic detergents such as sodium lauryl sulfate, dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate. Cationic detergents which can be used and can include benzalkonium chloride and benzethonium chloride. Potential non-ionic detergents that could be included in the formulation as surfactants include lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 50 and 60, glycerol monostearate, polysorbate 40, 60, 65 and 80, sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose. These surfactants could be present in the formulation of the compound of the invention or derivative either alone or as a mixture in different ratios.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Microspheres formulated for oral administration may also be used. Such microspheres have been well defined in the art. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For topical administration, the compound may be formulated as solutions, gels, ointments, creams, suspensions, etc. as are well-known in the art. Systemic formulations include those designed for administration by injection, e.g., subcutaneous, intravenous, intramuscular, intrathecal or intraperitoneal injection, as well as those designed for transdermal, transmucosal oral or pulmonary administration.

For administration by inhalation, compounds for use according to the present invention 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.

Also contemplated herein is pulmonary delivery of the compounds disclosed herein (or salts thereof). The compound is delivered to the lungs of a mammal while inhaling and traverses across the lung epithelial lining to the blood stream. Other reports of inhaled molecules include Adjei et al., *Pharm Res* 7:565-569 (1990); Adjei et al., *Int J Pharmaceutics* 63:135-144 (1990) (leuprolide acetate); Braquet et al., *J Cardiovasc Pharmacol* 13(suppl. 5):143-146 (1989) (endothelin-1); Hubbard et al., *Annal Int Med* 3:206-212 (1989) (□1-antitrypsin); Smith et al., 1989, *J Clin Invest* 84:1145-1146 (a-1-proteinase); Oswein et al., 1990, "Aerosolization of Proteins", Proceedings of Symposium on Respiratory Drug Delivery II, Keystone, Colorado, March, (recombinant human growth hormone); Debs et al., 1988, *J Immunol* 140:3482-3488 (interferon-gamma and tumor necrosis factor alpha) and Platz et al., U.S. Pat. No. 5,284,656 (granulocyte colony stimulating factor; incorporated by reference). A method and composition for pulmonary delivery of drugs for systemic effect is described in U.S. Pat. No. 5,451,569 (incorporated by reference), issued Sep. 19, 1995 to Wong et al.

Contemplated for use in the practice of this invention are mechanical devices designed for pulmonary delivery of therapeutic products, including but not limited to nebulizers, metered dose inhalers, and powder inhalers, all of which are familiar to those skilled in the art.

Some specific examples of commercially available devices suitable for the practice of this invention are the Ultravent nebulizer, manufactured by Mallinckrodt, Inc., St. Louis, Mo.; the Acorn II nebulizer, manufactured by Marquest Medical Products, Englewood, Colo.; the Ventolin metered dose inhaler, manufactured by Glaxo Inc., Research Triangle Park, North Carolina; and the Spinhaler powder inhaler, manufactured by Fisons Corp., Bedford, Mass.

All such devices require the use of formulations suitable for the dispensing of the compounds of the invention. Typically, each formulation is specific to the type of device employed and may involve the use of an appropriate propellant material, in addition to the usual diluents, adjuvants and/or carriers useful in therapy. Also, the use of liposomes, microcapsules or microspheres, inclusion complexes, or other types of carriers is contemplated. Chemically modified compound of the invention may also be prepared in different formulations depending on the type of chemical modification or the type of device employed.

Formulations suitable for use with a nebulizer, either jet or ultrasonic, will typically comprise a compound of the invention (or derivative) dissolved in water at a concentration of about 0.1 to 25 mg of biologically active compound of the invention per mL of solution. The

formulation may also include a buffer and a simple sugar (e.g., for inhibitor stabilization and regulation of osmotic pressure). The nebulizer formulation may also contain a surfactant, to reduce or prevent surface induced aggregation of the compound of the invention caused by atomization of the solution in forming the aerosol.

Formulations for use with a metered-dose inhaler device will generally comprise a finely divided powder containing the compound of the invention (or derivative) suspended in a propellant with the aid of a surfactant. The propellant may be any conventional material employed for this purpose, such as a chlorofluorocarbon, a hydrochlorofluorocarbon, a hydrofluorocarbon, or a hydrocarbon, including trichlorofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethanol, and 1,1,1,2-tetrafluoroethane, or combinations thereof. Suitable surfactants include sorbitan trioleate and soya lecithin. Oleic acid may also be useful as a surfactant.

Formulations for dispensing from a powder inhaler device will comprise a finely divided dry powder containing a compound of the invention (or derivative) and may also include a bulking agent, such as lactose, sorbitol, sucrose, or mannitol in amounts which facilitate dispersal of the powder from the device, e.g., 50 to 90% by weight of the formulation. The compound of the invention (or derivative) should advantageously be prepared in particulate form with an average particle size of less than 10 micrometers (μm), most preferably 0.5 to 5 μm, for most effective delivery to the deep lung.

Nasal delivery of a pharmaceutical composition of the present invention is also contemplated. Nasal delivery allows the passage of a pharmaceutical composition of the present invention to the blood stream directly after administering the therapeutic product to the nose, without the necessity for deposition of the product in the lung. Formulations for nasal delivery include those with dextran or cyclodextran.

For nasal administration, a useful device is a small, hard bottle to which a metered dose sprayer is attached. In one embodiment, the metered dose is delivered by drawing the pharmaceutical composition of the present invention solution into a chamber of defined volume, which chamber has an aperture dimensioned to aerosolize and aerosol formulation by forming a spray when a liquid in the chamber is compressed. The chamber is compressed to administer the pharmaceutical composition of the present invention. In a specific embodiment, the chamber is a piston arrangement. Such devices are commercially available.

Alternatively, a plastic squeeze bottle with an aperture or opening dimensioned to aerosolize an aerosol formulation by forming a spray when squeezed is used. The opening is

usually found in the top of the bottle, and the top is generally tapered to partially fit in the nasal passages for efficient administration of the aerosol formulation. Preferably, the nasal inhaler will provide a metered amount of the aerosol formulation, for administration of a measured dose of the drug.

The compounds, when it is desirable to deliver them systemically, 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.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethylcellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active compounds 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 or vaginal 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 above, a compound may also be formulated as a depot preparation. Such long acting formulations 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.

The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

Suitable liquid or solid pharmaceutical preparation forms are, for example, aqueous or saline solutions for inhalation, microencapsulated, encochleated, coated onto microscopic

gold particles, contained in liposomes, nebulized, aerosols, pellets for implantation into the skin, or dried onto a sharp object to be scratched into the skin. The pharmaceutical compositions also include granules, powders, tablets, coated tablets, (micro)capsules, suppositories, syrups, emulsions, suspensions, creams, drops or preparations with protracted release of active compounds, in whose preparation excipients and additives and/or auxiliaries such as disintegrants, binders, coating agents, swelling agents, lubricants, flavorings, sweeteners or solubilizers are customarily used as described above. The pharmaceutical compositions are suitable for use in a variety of drug delivery systems. For a brief review of methods for drug delivery, see Langer R, *Science* 249:1527-33 (1990).

The compound of the invention and optionally other therapeutics may be administered *per se* (neat) or in the form of a pharmaceutically acceptable salt or cocrystal. When used in medicine the salts or cocrystals should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts or cocrystals may conveniently be used to prepare pharmaceutically acceptable salts or cocrystals thereof. Such salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, acetic, salicylic, p-toluene sulphonic, tartaric, citric, methane sulphonic, formic, malonic, succinic, naphthalene-2-sulphonic, and benzene sulphonic. Also, such salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts of the carboxylic acid group.

Suitable buffering agents include: acetic acid and a salt (1-2% w/v); citric acid and a salt (1-3% w/v); boric acid and a salt (0.5-2.5% w/v); and phosphoric acid and a salt (0.8-2% w/v). Suitable preservatives include benzalkonium chloride (0.003-0.03% w/v); chlorobutanol (0.3-0.9% w/v); parabens (0.01-0.25% w/v) and thimerosal (0.004-0.02% w/v).

Pharmaceutical compositions of the invention contain an effective amount of a compound as described herein and optionally therapeutic agents included in a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier" means one or more compatible solid or liquid filler, diluents or encapsulating substances which are suitable for administration to a human or other vertebrate animal. The term "carrier" denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The components of the pharmaceutical compositions also are capable of being commingled with the compounds of the present invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficiency.

The therapeutic agent(s), including specifically but not limited to a compound of the invention, may be provided in particles. Particles as used herein means nanoparticles or microparticles (or in some instances larger particles) which can consist in whole or in part of the compound of the invention or the other therapeutic agent(s) as described herein. The particles may contain the therapeutic agent(s) in a core surrounded by a coating, including, but not limited to, an enteric coating. The therapeutic agent(s) also may be dispersed throughout the particles. The therapeutic agent(s) also may be adsorbed into the particles. The particles may be of any order release kinetics, including zero-order release, first-order release, second-order release, delayed release, sustained release, immediate release, and any combination thereof, etc. The particle may include, in addition to the therapeutic agent(s), any of those materials routinely used in the art of pharmacy and medicine, including, but not limited to, erodible, nonerodible, biodegradable, or nonbiodegradable material or combinations thereof. The particles may be microcapsules which contain the compound of the invention in a solution or in a semi-solid state. The particles may be of virtually any shape.

Both non-biodegradable and biodegradable polymeric materials can be used in the manufacture of particles for delivering the therapeutic agent(s). Such polymers may be natural or synthetic polymers. The polymer is selected based on the period of time over which release is desired. Bioadhesive polymers of particular interest include bioerodible hydrogels described in Sawhney H S et al. (1993) *Macromolecules* 26:581-7, the teachings of which are incorporated herein. These include polyhyaluronic acids, casein, gelatin, glutin, polyanhydrides, polyacrylic acid, alginate, chitosan, poly(methyl methacrylates), poly(ethyl methacrylates), poly(butylmethacrylate), poly(isobutyl methacrylate), poly(hexylmethacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), and poly(octadecyl acrylate).

The therapeutic agent(s) may be contained in controlled release systems. The term "controlled release" is intended to refer to any drug-containing formulation in which the manner and profile of drug release from the formulation are controlled. This refers to immediate as well as non-immediate release formulations, with non-immediate release formulations including but not limited to sustained release and delayed release formulations. The term "sustained release" (also referred to as "extended release") is used in its conventional sense to refer to a drug formulation that provides for gradual release of a drug over an extended period of time, and that preferably, although not necessarily, results in

substantially constant blood levels of a drug over an extended time period. The term "delayed release" is used in its conventional sense to refer to a drug formulation in which there is a time delay between administration of the formulation and the release of the drug there from. "Delayed release" may or may not involve gradual release of drug over an extended period of time, and thus may or may not be "sustained release."

Use of a long-term sustained release implant may be particularly suitable for treatment of chronic conditions. "Long-term" release, as used herein, means that the implant is constructed and arranged to deliver therapeutic levels of the active ingredient for at least 7 days, and preferably 30-60 days. Long-term sustained release implants are well-known to those of ordinary skill in the art and include some of the release systems described above.

It will be understood by one of ordinary skill in the relevant arts that other suitable modifications and adaptations to the compositions and methods described herein are readily apparent from the description of the invention contained herein in view of information known to the ordinarily skilled artisan, and may be made without departing from the scope of the invention or any embodiment thereof. Having now described the present invention in detail, the same will be more clearly understood by reference to the following examples, which are included herewith for purposes of illustration only and are not intended to be limiting of the invention.

EXAMPLES

The invention is further described in the following examples, which do not limit the scope of the invention described in the claims.

Abbreviations

AIBN: Azobisisobutyronitrile

DCC: N,N′-Dicyclohexylcarbodiimide

DCM: Dichloromethane

DIEA: N,N-diisopropylethylamine

DMA: N,N-dimethylacetamide

DMAP: 4-dimethylaminopyridine

DME: Dimethoxyethane

DMF: N.N-dimethylformamide

DMSO: Dimethylsulfoxide

EA: Ethyl acetate

EDCI: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

HATU: 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate

m-CPBA: Meta-chloroperbenzoic acid

MTBE: Methyl tert-butyl ether

NBS: N-bromosuccinimide

PE: Petroleum ether

Py: Pyridine

PTSA: Para-toluenesulfonic acid

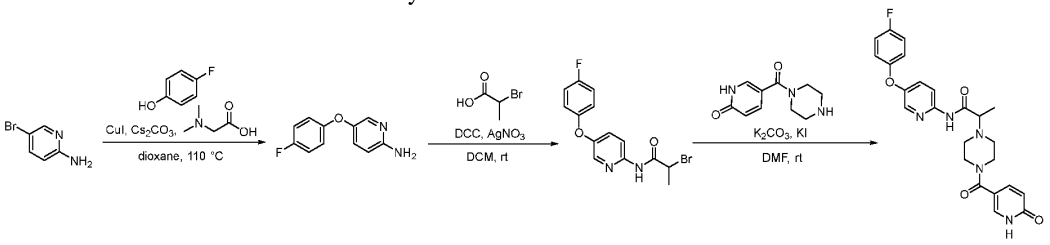
RuPhos-Pd: 2-Dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate

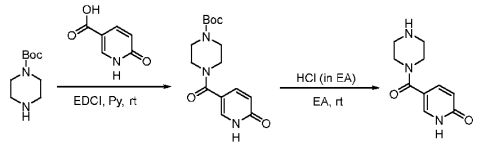
TEA: Triethylamine

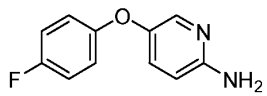
Experimental Procedures

Example 1: N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

Synthetic Scheme

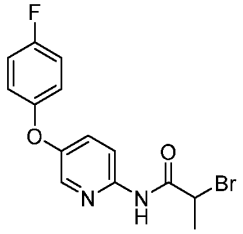






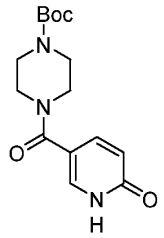
5-(4-fluorophenoxy)pyridin-2-amine

To a stirred solution of 5-bromopyridin-2-amine (3 g, 17.340 mmol, 1.0 equiv) in dioxane was added 4-fluorophenol (2.33 g, 20.808 mmol, 1.2 equiv), dimethylglycine (0.18 g, 1.734 mmol, 0.1 equiv), Cs_2CO_3 (8.47 g, 26.010 mmol, 1.5 equiv) and CuI (0.66 g, 3.468 mmol, 0.2 equiv) at room temperature. The reaction mixture was stirred at 110 °C for a period of overnight under N_2. After cooling to room temperature, the reaction mixture was quenched by addition of water (50 mL). The aqueous layer was extracted with ethyl acetate (100 mL x 3). The combined organic phase was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-60% PE/EA) to afford 5-(4-fluorophenoxy)pyridin-2-amine (450 mg, 12.69%). MS (ESI): mass calcd. For $C_{11}H_9FN_2O$: 204.07 m/z, found: 205.10 $[M+H]^+$.



2-bromo-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

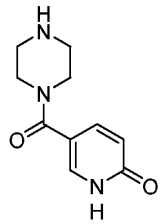
To a stirred solution of 5-(4-fluorophenoxy)pyridin-2-amine (500 mg, 2.45 mmol, 1.0 equiv) in anhydrous DCM (15 mL) was added 2-bromopropanoic acid (450 mg, 2.94 mmol, 1.2 equiv) and DCC (610 mg, 2.94 mmol, 1.2 equiv) and $AgNO_3$ (60 mg, 0.37 mmol, 0.15 equiv) at room temperature. After completion of reaction, the reaction mixture was quenched by addition of water (50 mL). The aqueous layer was extracted with DCM (100 mL x 3). The combined organic phase was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-80% PE/EA) to afford 2-bromo-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (581 mg, 70.00%). MS (ESI): mass calcd. For $C_{14}H_{12}BrFN_2O_2$: 338.01 m/z, found: 339.05 $[M+H]^+$.



tert-butyl 4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazine-1-carboxylate

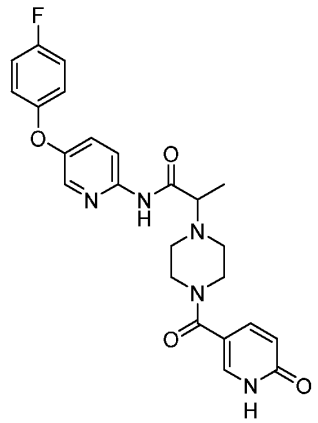
To a stirred solution of tert-butyl piperazine-1-carboxylate (600 mg, 3.221 mmol, 1.0 equiv) in pyridine (2 mL) was added 6-oxo-1,6-dihydropyridine-3-carboxylic acid (582 mg,

4.187 mmol, 1.3 equiv) and EDCI (83 mg, 0.435 mmol, 1.5 equiv) at room temperature. The reaction mixture was stirred at room temperature for a period of overnight. After completion of reaction, the reaction mixture was quenched by addition of water (20 mL). The aqueous layer was extracted with ethyl acetate (30 mL). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-60% PE/EA) to afford tert-butyl 4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazine-1-carboxylate (140 mg, 13.07%) as a white solid. MS (ESI): mass calcd. for $C_{15}H_{21}N_3O_4$: 307.15 m/z, found: 308.15 $[M+H]^+$.



5-(piperazine-1-carbonyl)pyridin-2(1H)-one

To a stirred solution of tert-butyl 4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazine-1-carboxylate (140 mg, 0.456 mmol, 1.0 equiv) in EA (5 mL) was added HCl (4 M in EA, 5 mL). The reaction mixture was stirred at room temperature for 1 h. The product was precipitated by the addition of diethyl ether. The product was obtained (90 mg, 54.24%) by filtration and drying of the HCl salt and used without further purification. MS (ESI): mass calcd. for $C_{10}H_{13}N_3O_2$: 207.10, m/z, found: 208.15 $[M+H]^+$.

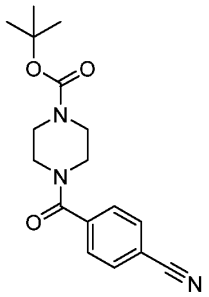


N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

To a stirred solution of 5-(piperazine-1-carbonyl)pyridin-2(1H)-one (90 mg, 0.483 mmol, 1.0 equiv) in DMF was added K_2CO_3 (67 mg, 0.483 mmol, 1.0 equiv) and KI (240 mg,

1.449 mmol, 3.0 equiv) at room temperature. The reaction mixture was stirred at room temperature for 0.5 h. To the above mixture was added 2-bromo-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (176 mg, 0.531 mmol, 1.1 equiv) at room temperature. The resulting mixture was stirred for 5 h at room temperature. After completion of reaction, the reaction mixture was quenched by addition of water (5 mL). The aqueous layer was extracted with ethyl acetate (20 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) and Prep-HPLC using a Column: XSelect CSH C18 Column, 30*150 mm, 5μm (eluent: 20% to 50% (v/v) CH_3CN and H_2O, 0.1% FA) to afford N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (20.9 mg, 8.32%) as a white solid. MS (ESI): mass calcd. for $C_{24}H_{24}FN_5O_4$: 465.18, m/z, found: 466.05 $[M+H]^+$, ^1H NMR (300 MHz, DMSO-d_6) δ 11.84 (s, 1H), 10.25 (s, 1H), 8.13 (dd, J = 6.0, 2.9 Hz, 2H), 7.43 – 7.60 (m, 3H), 7.16 – 7.29 (m, 2H), 7.02 – 7.15 (m, 2H), 6.33 (d, J = 9.4 Hz, 1H), 3.44 – 3.58 (m, 5H), 2.58 (tt, J = 9.3, 4.9 Hz, 4H), 1.19 (d, J = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.85.

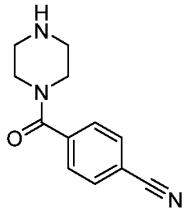
Example 2: 2-(4-(4-cyanobenzoyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide



tert-butyl 4-(4-cyanobenzoyl)piperazine-1-carboxylate

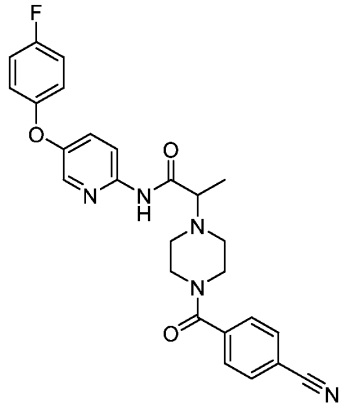
To a stirred solution of tert-butyl piperazine-1-carboxylate (500 mg, 2.684 mmol, 1.0 equiv) in pyridine (3 mL) was added 4-cyanobenzoic acid (513 mg, 3.489 mmol, 1.3 equiv) and EDCI (711 mg, 4.00 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for a period of 5 h. The reaction was quenched by water (20 mL) and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% PE/EA) to afford tert-butyl 4-(4-

cyanobenzoyl)piperazine-1-carboxylate (700 mg, 82.68%). MS (ESI): mass calcd. for: $C_{17}H_{21}N_3O_3$:315.16 m/z, found: 260.05 $[M+H]^+$.



4-(piperazine-1-carbonyl)benzonitrile

To a stirred solution of tert-butyl 4-(4-cyanobenzoyl)piperazine-1-carboxylate (600 mg, 1.903 mmol, 1.0 equiv) in EA (5 mL) was added 4 N HCl (in EA, 5 mL). The reaction mixture was stirred at room temperature for a period of 2 h. The product was precipitated by the addition of diethyl ether to afford 4-(piperazine-1-carbonyl)benzonitrile (400 mg, 95.11%) as an HCl salt and used without further purification. MS (ESI): mass calcd. for: $C_{12}H_{13}N_3O$: 215.11 m/z, found: 216.05$[M+H]^+$.



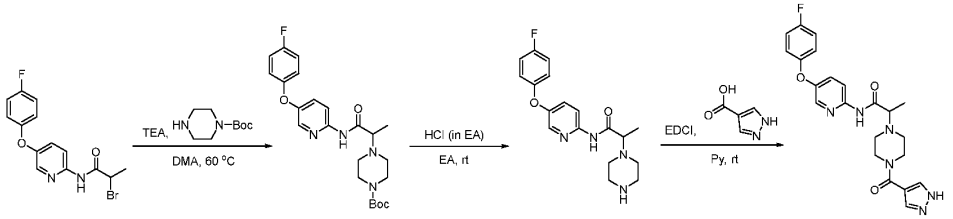
2-(4-(4-cyanobenzoyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

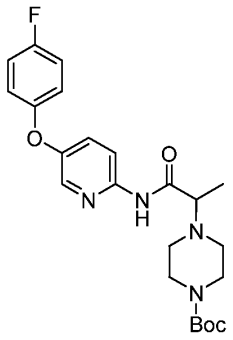
To a stirred solution of 4-(piperazine-1-carbonyl)benzonitrile (150 mg, 0.697 mmol, 1.0 equiv) in DMF was added 2-bromo-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (260 mg, 0.767 mmol, 1.1 equiv) and TEA (211 mg, 2.091 mmol, 3.0 equiv) at room temperature. The reaction mixture was stirred for 3 h at 60 °C. After cooling to room temperature, the reaction was quenched by water (20 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was further purified by silica gel chromatography (0-20% DCM/MeOH) & C18 column to afford 2-[4-(4-

cyanobenzoyl)piperazin-1-yl]-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (20.9 mg, 6.30%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{24}FN_5O_3$: 473.19 m/z, found: 474.05 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.23 (s, 1H), 8.13 (dd, J = 6.0, 2.9 Hz, 2H), 7.92 (d, J = 7.9 Hz, 2H), 7.58 (d, J = 7.9 Hz, 2H), 7.52 (dd, J = 9.1, 2.9 Hz, 1H), 7.23 (t, J = 8.8 Hz, 2H), 7.08 (dd, J = 9.1, 4.4 Hz, 2H), 3.67 (s, 2H), 3.52 (d, J = 6.9 Hz, 3H), 2.51 – 2.79 (m, 4H), 1.19 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.856.

Example 3: 2-(4-(1H-pyrazole-4-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

Synthetic Scheme

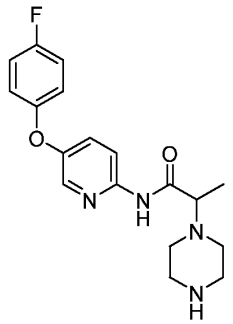




tert-butyl 4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carboxylate

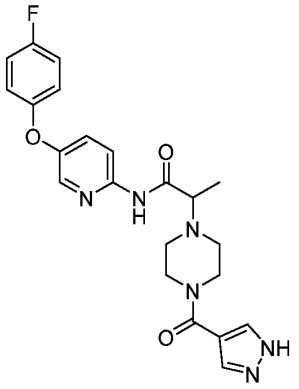
To a solution of tert-butyl piperazine-1-carboxylate (0.91 g, 4.886 mmol, 1.1 equiv) in DMA (10 mL) was added 2-bromo-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (1.5 g, 4.423 mmol, 1.0 equiv) and TEA (1.34 g, 13.269 mmol, 3.0 equiv) at rt. The resulting mixture was stirred for 3 h at 60 °C. After cooling to room temperature, the reaction was quenched by water (20 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed

with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue obtained was purified by silica gel chromatography (0-60% PE/EA) to afford tert-butyl 4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carboxylate (1.0 g, 50.23%) as yellow oil. MS (ESI): mass calcd. For $C_{23}H_{29}FN_4O_4$: 444.22 m/z, found: 445.20 $[M+H]^+$.



N-[5-(4-fluorophenoxy)pyridin-2-yl]-2-(piperazin-1-yl)propanamide hydrochloride

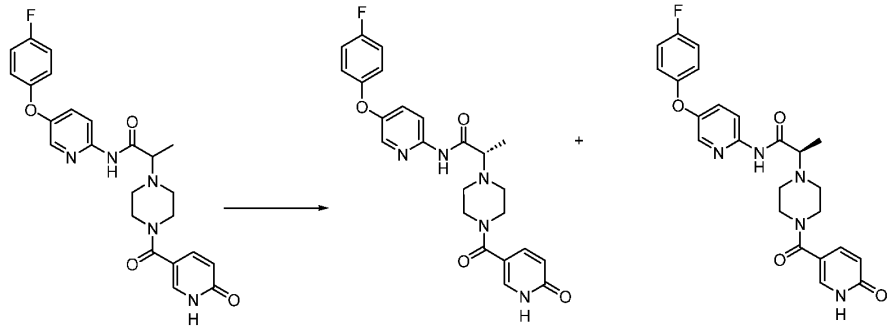
To a solution of tert-butyl 4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carboxylate (2.0 g, 4.499 mmol, 1.0 equiv) in EA (15 mL) was added 4N HCl (in EA, 15 mL) at 0 °C. The resulting mixture was stirred for 2 h at rt. The product was precipitated by the addition of anhydrous ether to afford N-[5-(4-fluorophenoxy)pyridin-2-yl]-2-(piperazin-1-yl)propanamide hydrochloride (1.7 g, crude) which was used without further purification. MS (ESI): mass calcd. For $C_{18}H_{21}FN_4O_2$: 344.16 m/z, found: 345.15 $[M+H]^+$



2-(4-(1H-pyrazole-4-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

To a solution of N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(piperazin-1-yl)propanamide (100 mg, 0.290 mmol, 1 equiv) in pyridine (3 mL) was added 1H-pyrazole-4-carboxylic acid (36 mg, 0.319 mmol, 1.1 equiv) and EDCI (111 mg, 0.580 mmol, 2 equiv) at rt. The resulting mixture was stirred for 2 h at rt. The reaction was quenched with water (10 mL). The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) and Prep-HPLC using a column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 26% to 56% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford 2-(4-(1H-pyrazole-4-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (14.3 mg, 11.30%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{23}FN_6O_3$: 438.18 m/z, found: 439.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 13.17 (s, 1H), 10.24 (s, 1H), 8.14 (dd, J = 5.9, 2.9 Hz, 2H), 8.06 (s, 1H), 7.72 (s, 1H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.16 – 7.31 (m, 2H), 7.04 – 7.16 (m, 2H), 3.64 (t, J = 4.9 Hz, 4H), 3.51 (q, J = 6.8 Hz, 1H), 2.51 – 2.66 (m, 4H), 1.20 (d, J = 6.8 Hz, 3H).

Example 4: (S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide and Example 5 (SPT-0009347): (R)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

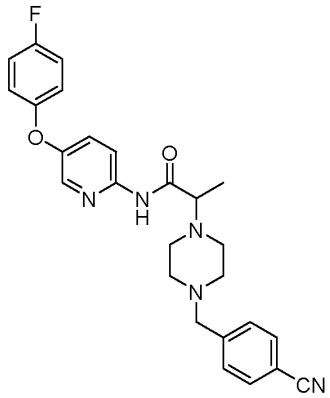


(S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide and (R)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide was separated by Chiral-Prep-HPLC (CHIRALPAK IF 2*25 cm, 5 μm; Mobile Phase A: MTBE (0.5% 2M NH_3-MeOH)-HPLC, Mobile Phase B: EtOH-HPLC; Flow rate: 15 mL/min; Gradient: isocratic 50; Wave Length: 220/254 nm) to afford (S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-

carbonyl)piperazin-1-yl)propanamide (2.0 mg), MS (ESI): mass calcd. for $C_{24}H_{24}FN_5O_4$: 465.18 m/z, found: 466.10 $[M+H]^+$, ^1H NMR (300 MHz, DMSO-d_6) δ 11.84 (s, 1H), 10.25 (s, 1H), 8.13 (dd, J = 6.0, 2.9 Hz, 2H), 7.42 – 7.60 (m, 3H), 7.17 – 7.29 (m, 2H), 7.02 – 7.16 (m, 2H), 6.33 (d, J = 9.4 Hz, 1H), 3.45 – 3.59 (m, 5H), 2.50 – 2.67 (m, 4H), 1.19 (d, J = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.37, -105.68, -119.86. and (R)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (2.6 mg). MS (ESI): mass calcd. for $C_{24}H_{24}FN_5O_4$: 465.18 m/z, found: 466.15 $[M+H]^+$, ^1H NMR (300 MHz, DMSO-d_6) δ 11.84 (s, 1H), 10.25 (s, 1H), 8.13 (dd, J = 6.0, 2.9 Hz, 2H), 7.42 – 7.60 (m, 3H), 7.17 – 7.29 (m, 2H), 7.02 – 7.17 (m, 2H), 6.33 (d, J = 9.4 Hz, 1H), 3.44 – 3.59 (m, 5H), 2.50 – 2.67 (m, 4H), 1.21 (d, J = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -27.14, -30.73, -119.85, -167.23.

Example 6 : 2-(4-(4-cyanobenzyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

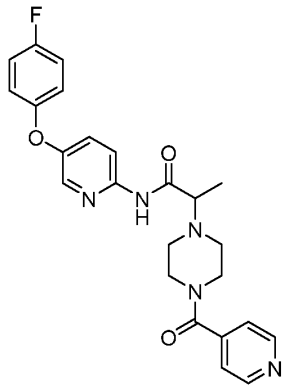


2-(4-(4-cyanobenzyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

To a solution of N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(piperazin-1-yl)propanamide (120 mg, 0.348 mmol, 1.0 equiv) in DMF (3 mL) was added K_2CO_3 (97 mg, 0.696 mmol, 2.0 equiv) and 4-(bromomethyl)benzonitrile (102 mg, 0.522 mmol, 1.5 equiv) at rt. The resulting mixture was stirred for 2 hours at 100 °C. After cooling to room temperature the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 45% to 75% CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford 2-(4-(4-cyanobenzyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (17.2 mg,

10.75%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{26}FN_5O_2$: 459.525 m/z, found 460.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.09 – 8.18 (m, 2H), 7.84 – 7.75 (m, 2H), 7.58 – 7.47 (m, 3H), 7.30 – 7.16 (m, 2H), 7.15 – 7.02 (m, 2H), 3.58 (s, 2H), 3.42 (q, J = 6.8 Hz, 1H), 2.53 – 2.61 (m, 4H), 2.40 – 2.46 (m, 4H), 1.18 (d, J = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.896.

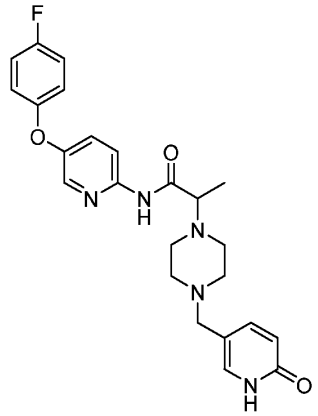
Example 7: N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-isonicotinoylpiperazin-1-yl)propanamide



N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-isonicotinoylpiperazin-1-yl)propanamide

To a solution of N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(piperazin-1-yl)propanamide (80 mg, 0.232 mmol, 1.0 equiv) in pyridine (3mL) was added isonicotinic acid (43 mg, 0.348 mmol, 1.5 equiv) and EDCI (89 mg, 0.464 mmol, 2.0 equiv) at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (10 mL x 3). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and Prep-HPLC using a column: Column: XBridge Prep OBD C18 Column, 30*150 mm (eluent: 27% to 57% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-isonicotinoylpiperazin-1-yl)propanamide (27.5 mg, 25.96%) as a white solid. MS (ESI): mass calcd. for $C_{24}H_{24}FN_5O_3$: 449.19 m/z, found 450.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.62 – 8.70 (m, 2H), 8.09 – 8.18 (m, 2H), 7.52 (dd, J = 9.1, 2.9 Hz, 1H), 7.34 – 7.42 (m, 2H), 7.16 – 7.31 (m, 2H), 7.03 – 7.15 (m, 2H), 3.64 – 3.69 (m, 2H), 3.52 (d, J = 7.0 Hz, 1H), 3.26 – 3.36 (m, 2H), 3.53 – 3.68 (m, 4H), 1.19 (d, J = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.84.

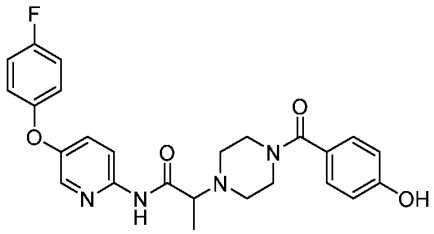
Example 8: N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-((6-oxo-1,6-dihydropyridin-3-yl)methyl)piperazin-1-yl)propanamide



N-[5-(4-fluorophenoxy)pyridin-2-yl]-4-[(6-oxo-1H-pyridin-3-yl)methyl]-1,4-diazepane-1-carboxamide

To a solution of N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(piperazin-1-yl)propanamide (150 mg, 0.436 mmol, 1.0 equiv) in DCM (5 mL) was added 6-oxo-1,6-dihydropyridine-3-carbaldehyde (100 mg, 0.812 mmol, 1.8 equiv) and TEA (88 mg, 0.872 mmol, 2.0 equiv) at rt. The resulting mixture was stirred for 1 h at rt. $NaBH(OAc)_3$ (369 mg, 1.744 mmol, 4.0 equiv) was added the mixture at 0 °C. The resulting mixture was stirred for 12 h at rt. The reaction mixture was quenched by water (10 mL) and extracted with DCM/MeOH (4:1) (10 mL x 3). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) to afford crude product as a yellow oil, and then purified by Prep-HPLC using a Column: XBridge C18 5 μm (eluent: 33% to 63% CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford N-[5-(4-fluorophenoxy)pyridin-2-yl]-4-[(6-oxo-1H-pyridin-3-yl)methyl]-1,4-diazepane-1-carboxamide as a white solid. MS (ESI): mass calcd: For $C_{24}H_{26}FN_5O_3$: 451.20 m/z, found: 452.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.46 (s, 1H), 10.11 (s, 1H), 8.10 – 8.17 (m, 2H), 7.49 – 7.57 (m, 1H), 7.33 – 7.40 (m, 1H), 7.18 – 7.29 (m, 3H), 7.04 – 7.14 (m, 2H), 6.29 (d, J = 9.4 Hz, 1H), 3.36 – 3.45 (m, 1H), 3.17 – 3.22 (m, 2H), 2.52 – 2.57 (m, 4H), 2.37 – 2.41 (m, 4H), 1.17 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -119.90.

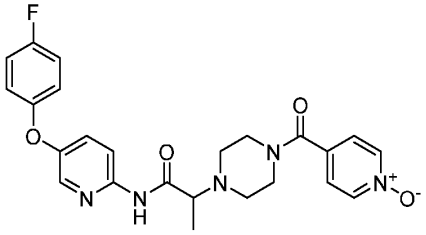
Example 9: N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(4-hydroxybenzoyl)piperazin-1-yl)propanamide



N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(4-hydroxybenzoyl)piperazin-1-yl)propanamide

To a solution of N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(piperazin-1-yl)propanamide (90 mg, 0.261 mmol, 1.0 equiv) in pyridine (2 mL) was added 4-hydroxybenzoic acid (54 mg, 0.392 mmol, 1.5 equiv) and EDCI (100 mg, 0.522 mmol, 2.0 equiv) at rt. The resulting mixture was stirred for 2 h at rt. The reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and Prep-HPLC using a Column: XBridge Shield RP 18 OBD Column, 30*150 mm, 5μm (eluent: 30% to 60% CH_3CN and H_2O with 10 mmol/L NH_4HCO_3+0.1% $NH_3{\cdot}H_2O$) to afford N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(4-hydroxybenzoyl)piperazin-1-yl)propanamide (5.6 mg, 4.62%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{25}FN_4O_4$: 464.19 m/z, found 465.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.23 (s, 1H), 9.83 (s, 1H), 8.10 – 8.17 (m, 2H), 7.49 – 7.55 (m, 1H), 7.18 – 7.28 (m, 4H), 7.05 – 7.17 (m, 2H), 6.74 – 6.81 (m, 2H), 3.43 – 3.60(m, 5H), 2.50 – 2.64 (m, 4H), 1.19 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -119.873.

Example 10: 4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide

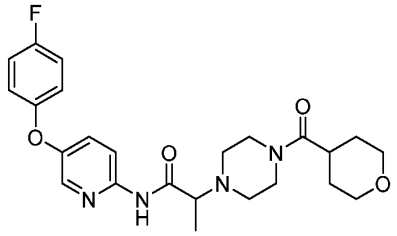


4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide

To a solution of N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(piperazin-1-yl)propanamide (80 mg, 0.232 mmol, 1.0 equiv) in pyridine (2 mL) was added 4-carboxypyridine-1-oxide (48 mg, 0.348 mmol, 1.5 equiv) and EDCI (89 mg, 0.464 mmol, 2.0 equiv) at rt. The resulting

mixture was stirred for 2 h at rt. The reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and Prep-HPLC using a Column: XBridge Shield RP 18 OBD Column, 30*150 mm, 5μm; (eluent: 23% to 53% CH_3CN and H_2O with 10 mmol/L NH_4HCO_3+0.1% $NH_3{\cdot}H_2O$) to afford 4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide (22.7 mg, 21.29%) as a white solid. MS (ESI): mass calcd. for $C_{24}H_{24}FN_5O_4$: 465.18 m/z, found 466.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.24 (d, J = 6.6 Hz, 2H), 8.11 – 8.16 (m, 2H), 7.49 – 7.55 (m, 1H), 7.45 (d, J = 6.5 Hz, 2H), 7.19 – 7.22 (m, 2H), 7.05 – 7.14 (m, 2H), 3.40 – 3.65 (m, 5H), 2.45 – 2.65 (m, 4H), 1.19 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -119.856.

Example 11: N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(tetrahydro-2H-pyran-4-carbonyl)piperazin-1-yl)propanamide

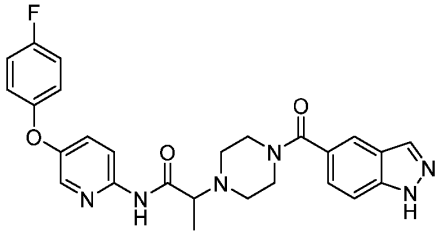


N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(tetrahydro-2H-pyran-4-carbonyl)piperazin-1-yl)propanamide

To a solution of N-[5-(4-fluorophenoxy)pyridin-2-yl]-2-(piperazin-1-yl)propanamide hydrochloride (80 mg, 0.232 mmol, 1 equiv) in pyridine (2mL) was added tetrahydro-2H-pyran-4-carboxylic acid (36 mg, 0.278 mmol, 1.2 equiv) and EDCI (89 mg, 0.464 mmol, 2.0 equiv) at rt. The resulting mixture was stirred for 3 h at rt. The reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; (eluent: 24% to 54% CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(tetrahydro-2H-pyran-4-carbonyl)piperazin-1-yl)propanamide (17.2 mg, 16.03%) as a white solid. MS (ESI): mass calcd. for $C_{24}H_{29}FN_4O_4$: 456.22 m/z, found 457.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 8.10 – 8.17 (m, 2H), 7.53 (dd, J = 8.9, 3.0 Hz,

1H), 7.19 – 7.31 (m, 2H), 7.04 – 7.14 (m, 2H), 3.79 – 3.87 (m, 2H), 3.44 – 3.58 (m, 5H), 3.31 – 3.41 (m, 2H), 2.80 – 2.90 (m, 1H), 2.66 – 2.69 (m, 2H), 2.32 – 2.35 (m, 2H) 1.46 – 1.51 (m, 4H), 1.18 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -119.859.

Example 12: 2-(4-(1H-indazole-5-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

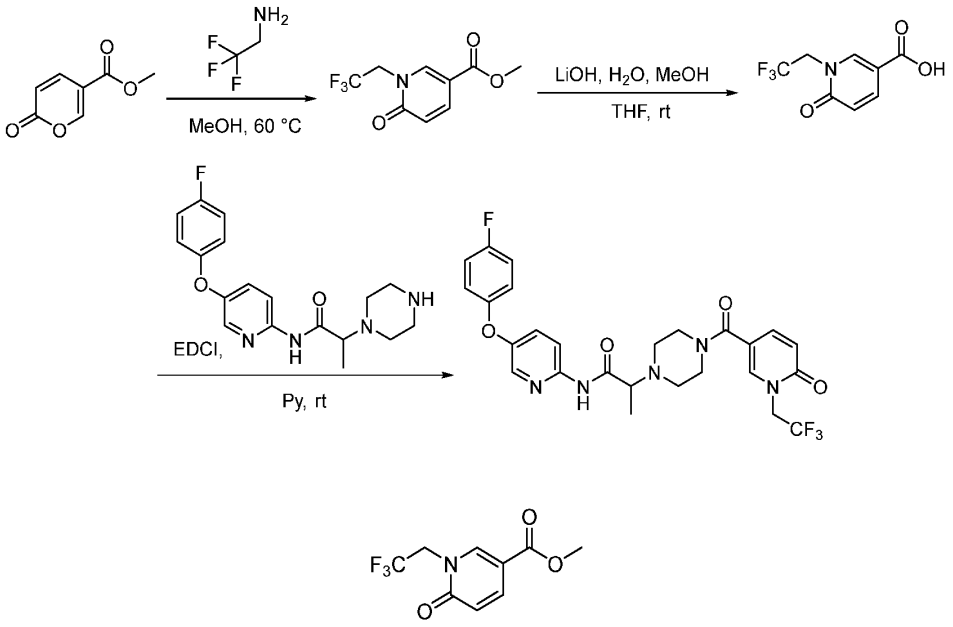


2-(4-(1H-indazole-5-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

To a solution of N-[5-(4-fluorophenoxy)pyridin-2-yl]-2-(piperazin-1-yl)propanamide hydrochloride (80 mg, 0.232 mmol, 1 equiv) in pyridine (3 mL) was added 1H-indazole-5-carboxylic acid (45 mg, 0.278 mmol, 1.2 equiv) and EDCI (66 mg, 0.348 mmol, 1.5 equiv). The mixture was stirred at room temperature for 2 h. The mixture was concentrated to dryness under reduced pressure to provide the crude product, which was purified by Prep-HPLC using for a Column: XBridge Shield RP 18 OBD Column, 30*150 mm, 5μm (eluent: 31% to 61% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3 + 0.1% $NH_3{\cdot}H_2O$) to afford 2-(4-(1H-indazole-5-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (14.5 mg, 12.77%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{25}FN_6O_3$: 488.20 m/z, found: 489.10 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.26 (s, 1H), 10.27 (s, 1H), 8.12 – 8.18 (m, 3H), 7.85 (s, 1H), 7.49 – 7.62 (m, 2H), 7.38 (dd, J = 8.6, 1.5 Hz, 1H), 7.24 (t, J = 8.8 Hz, 2H), 7.04 – 7.14 (m, 2H), 3.43 – 3.58 (m, 4H), 2.62 (s, 1H), 2.41 – 2.61 (m, 4H), 1.20 (d, J = 6.8 Hz, 3H).

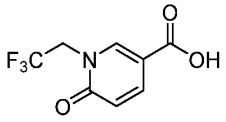
Example 13: N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

Synthetic Scheme



6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridine-3-carboxylic acid

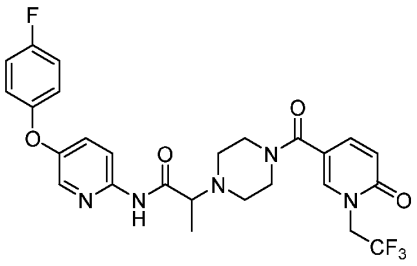
To a solution of methyl 6-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carboxylate (251 mg, 1.067 mmol, 1.0 equiv) in methanol (1 mL), tetrahydrofuran (2 mL) and water (1 mL) was added LiOH (128 mg, 5.335 mmol, 5 equiv) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The mixture was acidified pH = 5 with HCl (1N). The aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford 6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridine-3-carboxylic acid (220 mg, 95.65%) as a white solid. MS (ESI): mass calcd. for $C_8H_6F_3NO_3$: 221.14 m/z, found 222.05 $[M+H]^+$.



6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridine-3-carboxylic acid

To a solution of methyl 6-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carboxylate (251 mg, 1.067 mmol, 1.0 equiv) in methanol (1 mL), tetrahydrofuran (2 mL) and water (1 mL) was added LiOH (128 mg, 5.335 mmol, 5 equiv) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The mixture was acidified pH = 5 with HCl (1N). The

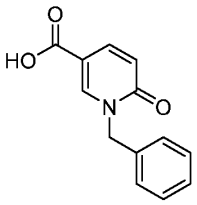
aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford 6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridine-3-carboxylic acid (220 mg, 95.65%) as a white solid. MS (ESI): mass calcd. for $C_8H_6F_3NO_3$: 221.14 m/z, found 222.05 $[M+H]^+$.



N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

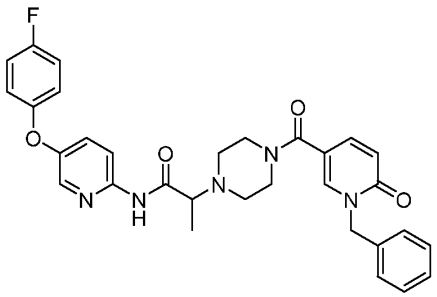
To a solution of 6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridine-3-carboxylic acid (60 mg, 0.271 mmol, 1.0 equiv) in pyridine (3 mL) was added N-[5-(4-fluorophenoxy)pyridin-2-yl]-2-(piperazin-1-yl)propanamide hydrochloride (93 mg, 0.271 mmol, 1.0 equiv) and EDCI (78 mg, 0.407 mmol, 1.5 equiv) at rt. The resulting mixture was stirred for 5 h at rt. The reaction was quenched with H_2O (10 mL) at rt. The resulting mixture was extracted with EA (20 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. The resulting mixture was filtered. The filtrate was concentrated and purified by flash chromatography (0-20% DCM/MeOH) & Prep-HPLC using a column: XBridge C18 5 m, 19 mm X 250 mm, 30*150 mm, 5μm (eluent: 35% to 60% CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (31.3 mg, 21.08%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{25}F_4N_5O_4$: 547.18 m/z, found 548.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.13 (dd, J = 6.0, 2.9 Hz, 2H), 7.97 (d, J = 2.5 Hz, 1H), 7.47 – 7.61 (m, 2H), 7.16 – 7.31 (m, 2H), 7.02 – 7.15 (m, 2H), 6.51 (d, J = 9.5 Hz, 1H), 4.89 (q, J = 9.1 Hz, 2H), 3.46 – 3.58 (m, 5H), 2.52 – 2.68 (m, 4H), 1.19 (d, J = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -69.44, -119.86.

Example 14: 2-(4-(1-benzyl-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide



1-benzyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid

To a solution of 6-oxo-1H-pyridine-3-carboxylic acid (400 mg, 2.875 mmol, 1.0 equiv) in methanol (10 mL) and water (2 mL) was added KOH (564 mg, 10.063 mmol, 3.5 equiv). The resulting solution was heated at reflux for 5 minutes and then benzyl bromide (983 mg, 5.750 mmol, 2.0 equiv) was added. Heating was continued for an additional 90 minutes, the reaction was then cooled to room temperature and the methanol removed under reduced pressure. The aqueous phase was acidified with 2 M HCl, and the resulting white precipitate was isolated by vacuum filtration, washed with water and air dried to give a white solid (410 mg, 56.60%) as a white solid. MS (ESI): mass calcd. for $C_{13}H_{11}NO_3$: 229.07 m/z, found 230.15 $[M+H]^+$.

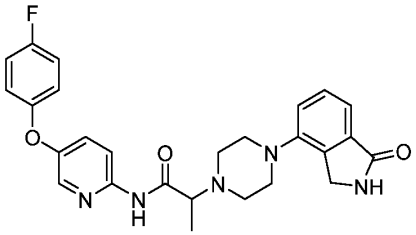


2-(4-(1-benzyl-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

To a solution of 1-benzyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid (60 mg, 0.262 mmol, 1.0 equiv) in pyridine (5 mL) was added N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(piperazin-1-yl)propanamide (90 mg, 0.262 mmol, 1.00 equiv) and EDCI (75 mg, 0.393 mmol, 1.5 equiv). The mixture was stirred at room temperature for 2 h. The mixture was concentrated to dryness under reduced pressure to provide the crude product, which was purified by Column: XBridge Shield RP 18 OBD Column, 30*150 mm, 5μm (eluent: 35% to 65% CH_3CN and H_2O with 10 mmol/L NH_4HCO_3 + 0.1%$NH_3{\cdot}H_2O$) to afford 2-(4-(1-benzyl-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (11.7 mg, 8.03%) as a white solid. MS (ESI): mass calcd. for $C_{31}H_{30}FN_5O_4$: 555.23 m/z, found 556.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H), 8.15 (dd,

J = 6.1, 2.9 Hz, 2H), 8.10 (d, *J* = 2.6 Hz, 1H), 7.46 – 7.56 (m, 2H), 7.26 – 7.39 (m, 4H), 7.24 (t, *J* = 8.7 Hz, 2H), 7.09 (dd, *J* = 9.0, 4.5 Hz, 2H), 6.45 (d, *J* = 9.3 Hz, 1H), 5.14 (s, 2H), 3.53 (t, *J* = 6.1 Hz, 5H), 2.43 – 2.67 (m, 4H), 1.19 (d, *J* = 6.8 Hz, 3H).

Example 15: N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(1-oxoisoindolin-4-yl)piperazin-1-yl)propanamide

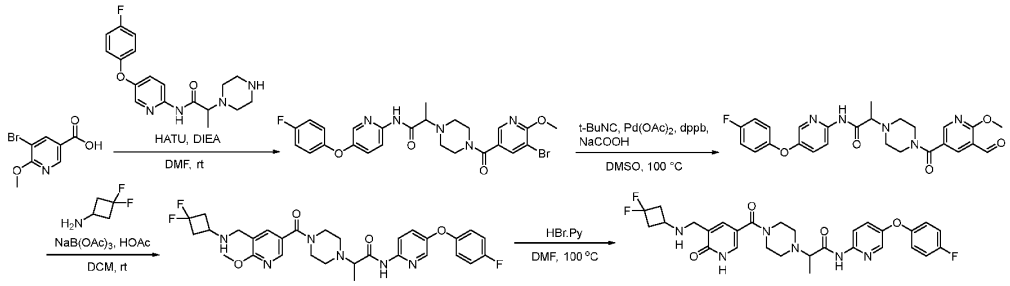


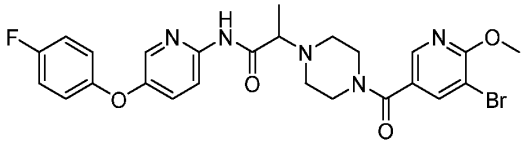
N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(1-oxoisoindolin-4-yl)piperazin-1-yl)propanamide

To a stirring solution 4-iodoisoindolin-1-one (92 mg, 0.436 mmol, 1.0 equiv) in 1,4-dioxane (2 mL) was added a solution of N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(piperazin-1-yl)propanamide (150 mg, 0.436 mmol, 1.0 equiv) and Cs_2CO_3 (425 mg, 1.308 mmol, 3.0 equiv) and (SP-4-1)-[1,3-Bis[2,6-bis(1-ethylpropyl)phenyl]-4,5-dichloro-1,3-dihydro-2H-imidazol-2-ylidene]dichloro(2-methylpyridine)palladium (36 mg, 0.0436 mmol, 0.1 equiv). The mixture was stirred at 100 °C for 5 h under N_2. The mixture was concentrated to dryness under reduced pressure to provide the crude product, which was purified by C18 column (eluent: CH_3CN and H_2O) and Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; (eluent: 33% to 63% CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(1-oxoisoindolin-4-yl)piperazin-1-yl)propanamide (6.8 mg, 3.22%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{26}FN_5O_3$: 475.20 m/z, found 476.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 8.57 (s, 1H), 8.12 – 8.20 (m, 2H), 7.50 – 7.58 (m, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.19 – 7.30 (m, 3H), 7.05 – 7.17 (m, 3H), 4.36 (s, 2H), 3.09 – 3.13 (m, 4H), 2.66 – 2.80 (m, 4H), 1.24 (d, *J* = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -119.87.

Example 16: 2-(4-(5-(((3,3-difluorocyclobutyl)amino)methyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

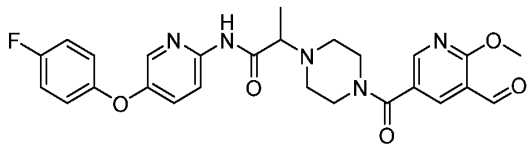
Synthetic Scheme





2-(4-(5-bromo-6-methoxynicotinoyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

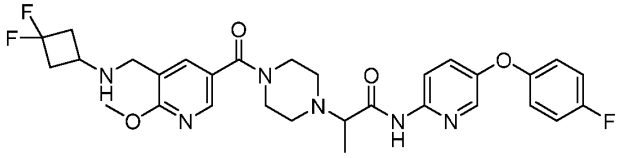
To a stirring solution 5-bromo-6-methoxynicotinic acid (337 mg, 1.452 mmol, 1.0 equiv) in DMF (5 mL) was added a solution of N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(piperazin-1-yl)propanamide (500 mg, 1.452 mmol, 1.0 equiv), HATU (828 mg, 2.178 mmol, 1.5 equiv) and DIEA (563 mg, 4.356 mmol, 3.0 equiv). The resulting mixture was stirred at room temperature for 6 h. After completion of reaction, the reaction mixture was quenched by addition of water (20 mL). The aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford 2-(4-(5-bromo-6-methoxynicotinoyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (500 mg, 61.67%). MS (ESI): mass calcd. for $C_{25}H_{25}BrFN_5O_4$: 557.11 m/z, found: 558.20 $[M+H]^+$.



N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(5-formyl-6-methoxynicotinoyl)piperazin-1-yl)propanamide

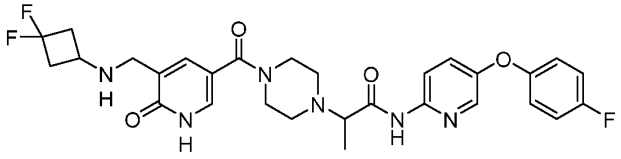
To a stirring solution 2-(4-(5-bromo-6-methoxynicotinoyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (500 mg, 0.895 mmol, 1.0 equiv) in DMSO (7 mL) was added a solution of tert-butyl isocyanide (112 mg, 1.343 mmol, 1.5 equiv), (acetyloxy)palladio acetate (20 mg, 0.090 mmol, 0.1 equiv), sodium formate (91 mg, 1.343

mmol, 1.5 equiv) and dppb (38 mg, 0.090 mmol, 0.1 equiv). The resulting mixture was maintained under nitrogen and stirred at 100 °C for 5 h. After cooled to room temperature, the reaction was quenched by water (20 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(5-formyl-6-methoxynicotinoyl)piperazin-1-yl)propanamide (350 mg, 77.02%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{26}FN_5O_5$: 507.19 m/z, found: 508.15 $[M+H]^+$.



2-(4-(5-(((3,3-difluorocyclobutyl)amino)methyl)-6-methoxynicotinoyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

To a stirring solution N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(5-formyl-6-methoxynicotinoyl)piperazin-1-yl)propanamide (350 mg, 0.690 mmol, 1.0 equiv) in DCM (3 mL) was added 3,3-difluorocyclobutan-1-amine (74 mg, 0.690 mmol, 1.0 equiv) and HOAc (12 mg, 0.207 mmol, 0.3 equiv). The reaction was stirred for 0.5 h at rt. $NaBH(OAc)_3$ (292 mg, 1.380 mmol, 2.0 equiv) was added into the solution. The resulting mixture was stirred at room temperature for 5 h. After completion of reaction, the reaction mixture was quenched by addition of water (20 mL). The aqueous layer was extracted with DCM (30 mL x 3). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford 2-(4-(5-(((3,3-difluorocyclobutyl)amino)methyl)-6-methoxynicotinoyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (170 mg, 41.18%). MS (ESI): mass calcd. for $C_{30}H_{33}F_3N_6O_4$: 598.25 m/z, found: 599.15 $[M+H]^+$.



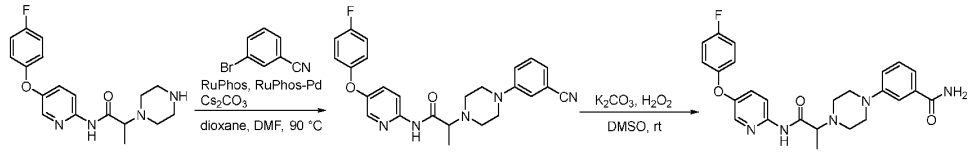
2-(4-(5-(((3,3-difluorocyclobutyl)amino)methyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

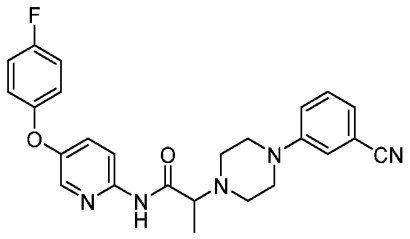
To a stirring solution 2-(4-(5-(((3,3-difluorocyclobutyl)amino)methyl)-6-methoxynicotinoyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (170

mg, 0.284 mmol, 1.0 equiv) in DMF (2 mL) was added a solution of HBr·Py (454 mg, 2.840 mmol, 10 equiv). After cooled to room temperature, the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5.0 μm (eluent: 28% to 58% CH_3CN and H_2O with 10 mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford 2-(4-(5-(((3,3-difluorocyclobutyl)amino)methyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (6.1 mg, 3.63%) as a white solid. MS (ESI): mass calcd. for $C_{29}H_{31}F_3N_6O_4$: 584.24 m/z, found: 585.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.84 (s, 1H), 10.28 (s, 1H), 8.14 (dd, J = 6.1, 2.9 Hz, 2H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.47 (q, J = 2.5 Hz, 2H), 7.24 (t, J = 8.8 Hz, 2H), 7.04 – 7.17 (m, 2H), 3.54 (t, J = 5.2 Hz, 5H),3.38 – 3.51(m,2H) 3.08 – 3.18 (m, 1H), 2.67 – 2.79 (m, 2H), 2.52 – 2.64 (m, 5H), 2.22 – 2.40 (m, 2H), 1.16 – 1.26 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -80.25, -94.97, -119.86.

Example 17: 3-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazin-1-yl)benzamide

Synthetic Scheme

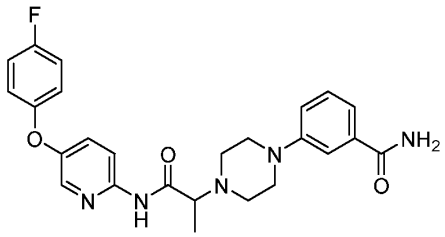




2-(4-(3-cyanophenyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

To a solution of N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(piperazin-1-yl)propanamide (hydrogen chloride salt, 100 mg, 0.26 mmol, 1.0 equiv) in 1,4-dioxane (3 mL) was added Cs_2CO_3 (170 mg, 0.52 mmol, 2.0 equiv) at rt. To the mixture was added 3-bromobenzonitrile (57 mg, 0.31 mmol, 1.2 equiv), RuPhos (13 mg, 0.026 mmol, 0.1 equiv), RuPhos-Pd (21 mg, 0.026 mmol, 1.2 equiv) and DMF (0.5 mL). The reaction was stirred for 16 h at 90 °C under

N_2. After cooled to room temperature, The reaction mixture was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield a crude product which was directly purified by flash chromatographyto (0-20% DCM/MeOH) afford 2-(4-(3-cyanophenyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (70 mg, 60.3%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{24}FN_5O_2$: 445.19 m/z, found: 446.15 $[M+H]^+$.

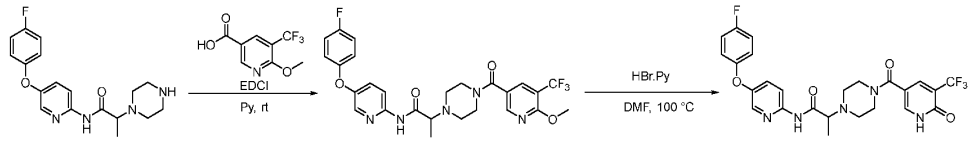


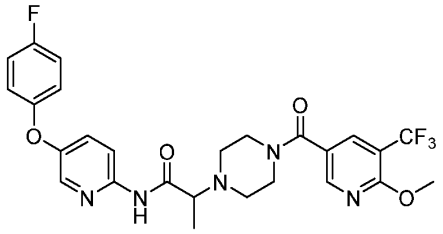
3-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazin-1-yl)benzamide

To a solution of 2-(4-(3-cyanophenyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (70 mg, 0.157 mmol, 1.0 equiv) in DMSO (2 mL) was added K_2CO_3 (65 mg, 0.471 mmol, 3.0 equiv) and 30% H_2O_2 (2 mL) at rt. The resulting mixture was stirred for 2 h at rt. After completion of reaction, the reaction was quenched by ice water (10 mL) and extracted with EA (20 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 31% to 67% CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford 3-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazin-1-yl)benzamide (2.7 mg, 3.69%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{26}FN_5O_3$: 463.20 m/z, found: 464.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.11 – 8.20 (m, 2H), 7.92 (s, 1H), 7.54 (dd, J = 9.0, 3.0 Hz, 1H), 7.16 – 7.32 (m, 5H), 7.04 – 7.16 (m, 3H), 3.52 (q, J = 6.8 Hz, 1H), 3.22 (d, J =5.1Hz, 4H), 2.61 – 2.79 (m, 4H), 1.24 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ – 119.1390.

Example 18: N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-5-(trifluoromethyl)-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

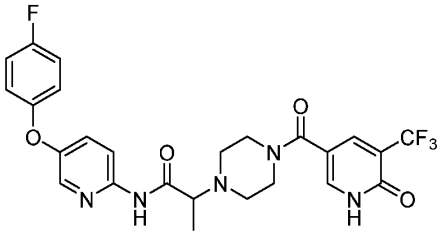
Synthetic Scheme





N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-methoxy-5-(trifluoromethyl)nicotinoyl)piperazin-1-yl)propanamide

To a solution of N-[5-(4-fluorophenoxy)pyridin-2-yl]-2-(piperazin-1-yl)propanamide hydrochloride (200 mg, 0.581 mmol, 1.0 equiv) in pyridine (10 mL) was added 6-methoxy-5-(trifluoromethyl)nicotinic acid (154 mg, 0.697 mmol, 1.2 equiv) and EDCI (167 mg, 0.871 mmol, 1.5 equiv) at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (20 mL x 3). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to give N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-methoxy-5-(trifluoromethyl)nicotinoyl)piperazin-1-yl)propanamide (180 mg, 52.65%) as a yellow solid. MS (ESI): mass calcd. for $C_{26}H_{25}F_4N_5O_4$: 547.18 m/z, found: 548.25 $[M+H]^+$.

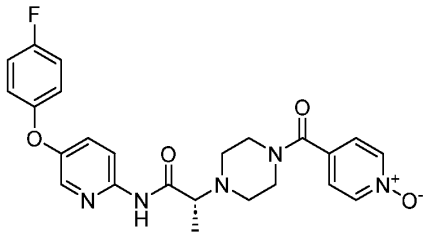


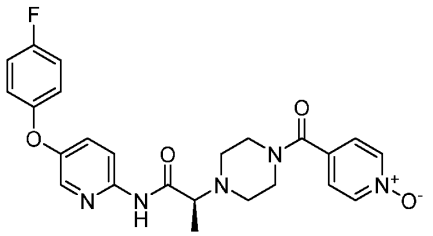
N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-5-(trifluoromethyl)-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

To a solution of N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-methoxy-5-(trifluoromethyl)nicotinoyl)piperazin-1-yl)propanamide (200 mg, 0.365 mmol, 1.0 equiv) in DMF (7 mL) the mixture was added HBr·Py (880 mg, 3.650 mmol, 10 equiv). The mixture was stirred at 100 °C for 2 h. After cooled to room temperature, the reaction was quenched by

water (10 mL) and extracted with 5:1 DCM/MeOH (10 mL x 3). The combined organic extracts were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and Prep-HPLC using a column: XBridge Shield RP 18 OBD Column, 30*150 mm, 5μm; (eluent: 5% to 20% CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-5-(trifluoromethyl)-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (61.9 mg, 31.70%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{23}F_4N_5O_4$: 533.17, found: 534.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.25 (br, 1H), 10.27 (s, 1H), 8.11 – 8.18 (m, 2H), 7.88 – 7.92 (m, 2H), 7.52 (dd, J = 9.0, 3.0 Hz, 1H), 7.19-7.23 (m , 2H), 7.08 (dd, J = 9.0, 4.5 Hz, 2H), 3.39-3.57 (m , 5H), 2.58 (tq, J = 11.7, 5.9, 5.2 Hz, 4H), 1.19 (d, J = 6.8 Hz, 3H).

Example 19: (R)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide and Example 20: (S)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide



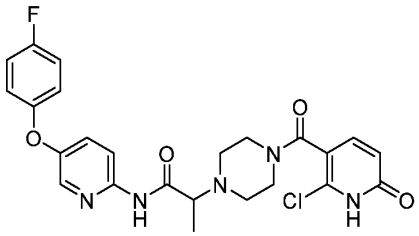


(R)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide and (S)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide

4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide was separated by Chiral-Prep-HPLC Column (CHIRALPAK ID, 2*25 cm, 5 μm; Mobile Phase A: MtBE(0.5% 2M NH_3-MeOH)-HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 50; Wave Length: 220/254 nm) to afford (R)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide (6.1 mg, first peak), MS (ESI): mass calcd. for $C_{24}H_{24}FN_5O_4$: 465.18 m/z, found: 466.10 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 8.21 – 8.28 (m, 2H), 8.10 – 8.17 (m, 2H), 7.53 (dd, J = 9.2, 2.9 Hz, 1H), 7.42 – 7.48 (m, 2H), 7.24 (t, J = 8.8 Hz, 2H), 7.05 – 7.14 (m, 2H), 3.42 – 3.63 (m, 5H), 2.53 – 2.68 (m, 4H), 1.20 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -119.856. and (S)-4-(4-(1-((5-(4-

fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide (2.8 mg, second peak), MS (ESI): mass calcd. for $C_{24}H_{24}FN_5O_4$: 465.18 m/z, found: 466.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 8.21 – 8.28 (m, 2H), 8.10 – 8.17 (m, 2H), 7.53 (dd, J = 9.2, 2.9 Hz, 1H), 7.42 – 7.48 (m, 2H), 7.24 (t, J = 8.8 Hz, 2H), 7.05 – 7.14 (m, 2H), 3.42 – 3.63 (m, 5H), 2.53 – 2.68 (m, 4H), 1.20 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -119.856.

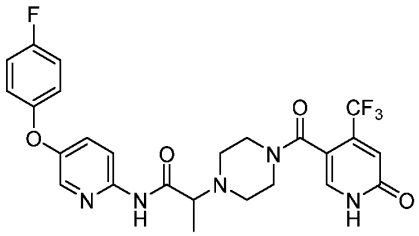
Example 21: 2-(4-(2-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide



2-(4-(2-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

To a solution of N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(piperazin-1-yl)propanamide (119 mg, 0.346 mmol, 1.2 equiv) in Py (3 mL) was added 2-chloro-6-oxo-1,6-dihydropyridine-3-carboxylic acid (50 mg, 0.288 mmol, 1.0 equiv) and EDCI (83 mg, 0.432 mmol, 1.5 equiv). The mixture was stirred at room temperature for 5 h. The reaction mixture was quenched by water (10 mL) and extracted with 5:1 DCM/MeOH (10 mL x 3). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and Prep-HPLC using a column: Column: XBridge Shield RP 18 OBD Column, 30*150 mm, 5.0 μm (eluent: 21% to 51% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$) to afford 2-(4-(2-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (21.5 mg, 14.90%) as a white solid. MS (ESI): mass calcd. for $C_{24}H_{23}ClFN_5O_4$: 499.14 m/z, found: 500.05 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-$d6$) δ 10.28 (s, 1H), 8.10 – 8.17 (m, 2H), 7.61 (d, J = 8.2 Hz, 1H), 7.53 (dd, J = 9.0, 3.0 Hz, 1H), 7.19 – 7.29 (m, 2H), 7.04 – 7.14 (m, 2H), 6.62 (d, J = 8.3 Hz, 1H), 3.58 – 3.64 (m, 2H), 3.46 – 356 (m, 1H), 3.17 – 3.42 (m,2H), 2.52 – 2.71 (m, 4H), 1.18 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -119.86.

Example 22: N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

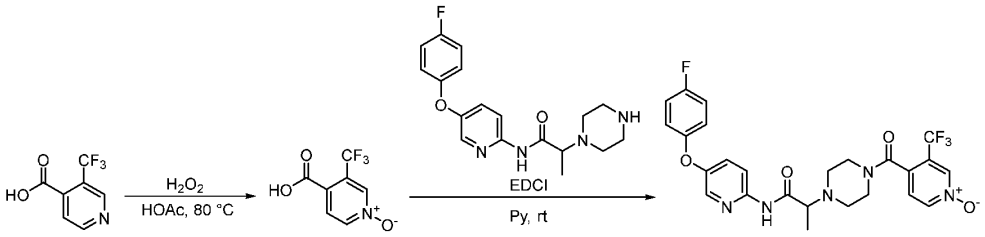


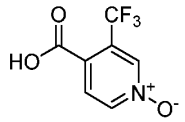
N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

To a solution of N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(piperazin-1-yl)propanamide (100 mg, 0.289 mmol, 1.2 equiv) in Py (3 mL) was added a solution of 6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carboxylic acid (50 mg, 0.241 mmol, 1.0 equiv) and EDCI (69 mg, 0.361 mmol, 1.5 equiv). The mixture was stirred at room temperature for 3 h. The reaction mixture was quenched by water (10 mL) and extracted with 5:1 DCM/MeOH (10 mL x 3). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) and Prep-HPLC using a column: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 26% to 56% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (32.7 mg, 25.31%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{23}F_4N_5O_4$: 533.17 m/z, found: 534.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.34 (s, 1H), 10.27 (s, 1H), 8.10 – 8.17 (m, 2H), 7.70 (s, 1H), 7.53 (dd, J = 8.9, 3.0 Hz, 1H), 7.19 – 7.30 (m, 2H), 7.04 – 7.14 (m, 2H), 6.79 (s, 1H), 3.66 – 3.70 (m, 1H), 3.51 (q, J = 6.8 Hz, 1H), 3.32 – 3.43 (m, 3H), 2.54 – 2.76 (m, 4H), 1.18 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -62.26, -119.86.

Example 23: 4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)-3-(trifluoromethyl)pyridine 1-oxide

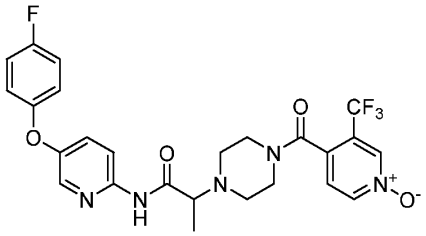
Synthetic Scheme





4-carboxy-3-(trifluoromethyl)pyridine 1-oxide

To a solution of 3-(trifluoromethyl)isonicotinic acid (300 mg, 0.244 mmol, 1.0 equiv) in HOAc (3 mL) was added 30% H_2O_2 (0.6 mL) at 0 °C. The resulting mixture was stirred for 4 h at 80 °C. After cooled to room temperature, the mixture was purified by C18 column to afford 4-carboxy-3-(trifluoromethyl)pyridine 1-oxide as a white solid. MS (ESI): mass calcd. for $C_7H_4F_3NO_3$: 207.108 m/z, found: 208.00 $[M+H]^+$.

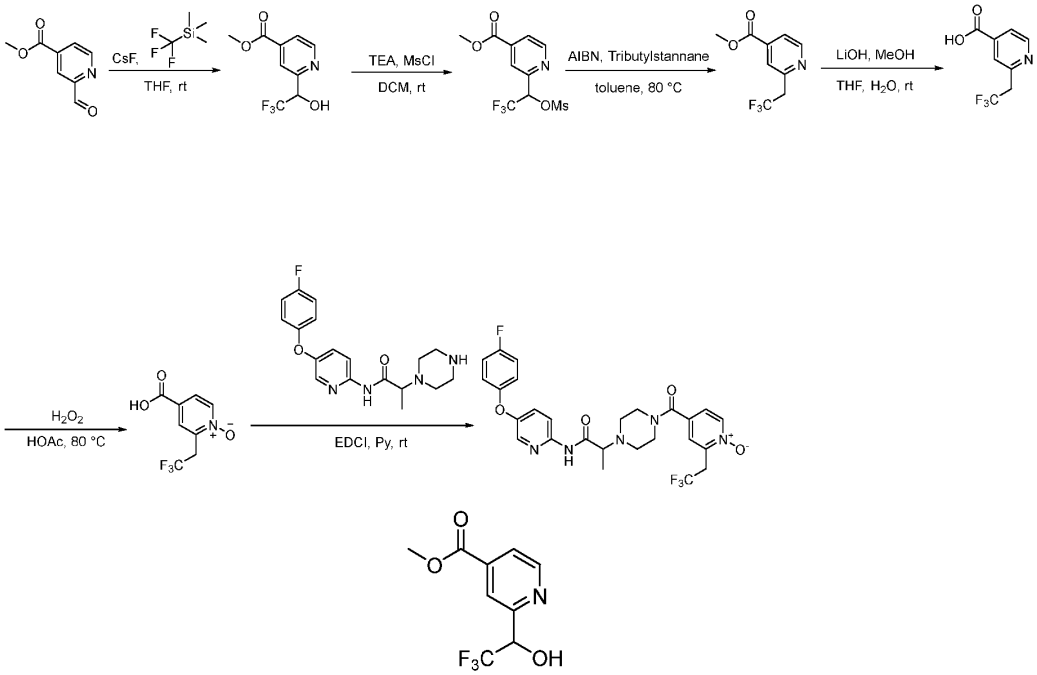


4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)-3-(trifluoromethyl)pyridine 1-oxide

To a solution of 4-carboxy-3-(trifluoromethyl)pyridine 1-oxide (100 mg, 0.483 mmol, 1.0 equiv) in Py (3 mL) was added N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(piperazin-1-yl)propanamide (166 mg, 0.483 mmol, 1.0 equiv) and EDCI (138 mg, 0.724 mmol, 1.5 equiv) at rt. The resulting mixture was stirred for 3 h at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield a crude product which was directly purified by C18 column to afford 4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)-3-(trifluoromethyl)pyridine 1-oxide as a white solid. MS (ESI): mass calcd. for $C_{25}H_{23}F_4N_5O_4$: 533.484 m/z, found 534.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.75 (d, J = 1.7 Hz, 1H), 8.48 – 8.55 (m, 1H), 8.09 – 8.17 (m, 2H), 7.50 – 7.62 (m, 2H), 7.19 – 7.30 (m, 2H), 7.04 – 7.14 (m, 2H), 3.71 (s, 1H), 3.48 - 3.59 (m, 2H), 3.25 – 3.27 (m, 2H), 2.65 – 2.75 (m, 2H), 2.30 - 2.39 (m, 2H), 1.15 – 1.21 (m, 3H).^{19}F NMR (376 MHz, DMSO-d_6) δ -59.64, -119.85.

Example 24: 4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)-2-(2,2,2-trifluoroethyl)pyridine 1-oxide

Synthetic Scheme



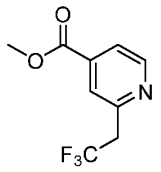
methyl 2-(2,2,2-trifluoro-1-hydroxyethyl)isonicotinate

To a solution of methyl 2-formylisonicotinate (1.0 g, 6.06 mmol, 1.0 equiv) in THF (15 mL) was added trimethyl(trifluoromethyl)silane (1.7 g, 12.12 mmol, 2.0 equiv) and CsF (1.8 g, 12.12 mmol, 2.0 equiv) at 0 °C. The resulting mixture was stirred for 16 h at rt under N_2. The reaction mixture was quenched by water (30 mL) and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford crude product as a white solid. MS (ESI): mass calcd. for $C_9H_8F_3NO_3$: 235.162 m/z, found 236.15 $[M+H]^+$.

methyl 2-(2,2,2-trifluoro-1-((methylsulfonyl)oxy)ethyl)isonicotinate

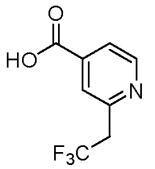
To a solution of methyl 2-(2,2,2-trifluoro-1-hydroxyethyl)isonicotinate (400 mg, 1.701 mmol, 1.0 equiv) in DCM (5 mL) was added TEA (516 mg, 5.103 mmol, 3.0 equiv) and methanesulfonylmethanesulfonylmethane (439 mg, 2.551 mmol, 1.5 equiv) at rt. The

resulting mixture was stirred for overnight rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (5-60% PE/EA) to afford methyl 2-(2,2,2-trifluoro-1-((methylsulfonyl)oxy)ethyl)isonicotinate as yellow oil. MS (ESI): mass calcd. for $C_{10}H_{10}F_3NO_5S$: 313.25 m/z, found 314.10 $[M+H]^+$.



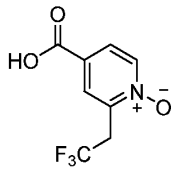
methyl 2-(2,2,2-trifluoroethyl)isonicotinate

To a solution of methyl 2-(2,2,2-trifluoro-1-((methylsulfonyl)oxy)ethyl)isonicotinate (160 mg, 0.511 mmol, 1.0 equiv) in toluene (5 mL) was added AIBN (17 mg, 0.102 mmol, 0.2 equiv) and tributylstannane (223 mg, 0.766 mmol, 1.5 equiv) at rt. The resulting mixture was stirred for 5 h at 80 °C. After cooled to room temperature, the reaction mixture was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield a crude product which was directly purified by flash chromatographyto (5-60% PE/EA) to afford methyl 2-(2,2,2-trifluoroethyl)isonicotinate as a white solid. MS (ESI): mass calcd. For: $C_9H_8F_3NO_2$: 219.163 m/z, found: 220.15 $[M+H]^+$.



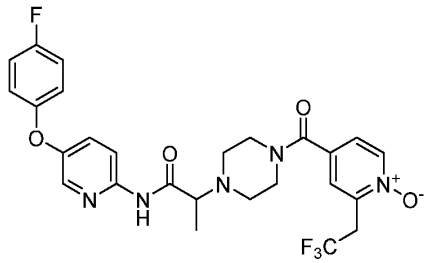
2-(2,2,2-trifluoroethyl)isonicotinic acid

To a solution of methyl 2-(2,2,2-trifluoroethyl)isonicotinate (60 mg, 0.274 mmol, 1.0 equiv) in THF/MeOH/H_2O (1 mL/1 mL/1 mL) was added LiOH (65 mg, 2.740 mmol, 10.0 equiv) at rt. The mixture was stirred for 3 h at rt. The mixture was adjusted to pH 4~5 with 2N HCl. The resulting solution was extracted with EA (30 mL x 3) and concentrated under vacuum. The crude product was used in the next step directly without further purification. MS (ESI): mass calcd. for $C_8H_6F_3NO_2$: 205.136 m/z, found: 206.00 $[M+H]^+$.



4-carboxy-2-(2,2,2-trifluoroethyl)pyridine 1-oxide

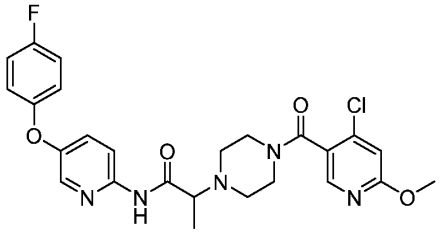
To a solution of 2-(2,2,2-trifluoroethyl)isonicotinic acid (50 mg, 0.244 mmol, 1.0 equiv) in HOAc (2 mL) was added 30% H_2O_2 (0.4 mL) at rt . The resulting mixture was stirred for 3 h at 80 °C. After cooled to room temperature, the reaction was concentrated under vacuum and purified by C18 column to afford 4-carboxy-2-(2,2,2-trifluoroethyl)pyridine 1-oxide as a white solid. MS (ESI): mass calcd. For: $C_8H_6F_3NO_3$: 221.14 m/z, found: 222.05 $[M+H]^+$.



4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)-2-(2,2,2-trifluoroethyl)pyridine 1-oxide

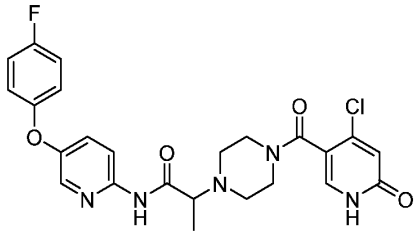
To a solution of 4-carboxy-2-(2,2,2-trifluoroethyl)pyridine 1-oxide (50 mg, 0.226 mmol, 1.0 equiv) in Py (3 mL) was added N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(piperazin-1-yl)propanamide (78 mg, 0.226 mmol, 1 equiv) and EDCI (87 mg, 0.452 mmol, 2.0 equiv) at rt .The resulting mixture was stirred for 3 h at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography & C18 column to afford 4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)-2-(2,2,2-trifluoroethyl)pyridine 1-oxide as a white solid. MS (ESI): mass calcd. for $C_{26}H_{25}F4N_5O_4$: 547.511 m/z, found: 548.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 8.39 (d, J = 6.7 Hz, 1H), 8.10 – 8.17 (m, 2H), 7.67 (d, J = 2.4 Hz, 1H), 7.45 – 7.56 (m, 2H), 7.18 – 7.28 (m, 2H), 7.05 – 7.12 (m, 2H), 4.02 - 4.05 (m, 2H), 3.32 - 3.68 (m, 5H), 2.52 – 2.68 (s, 4H), 1.19 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -62.54, -119.86.

Example 25: 2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide



2-(4-(4-chloro-6-methoxynicotinoyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

To a solution of N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(piperazin-1-yl)propanamide (100 mg, 0.290 mmol, 1.0 equiv) in Py (3 mL) was added 4-chloro-6-methoxynicotinic acid (54 mg, 0.290 mmol, 1.0 equiv) and EDCI (111 mg, 0.580 mmol, 2.0 equiv) at rt. The resulting mixture concentrated under vacuum and purified by silica gel column to afford 2-(4-(4-chloro-6-methoxynicotinoyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide as a white solid. MS (ESI): mass calcd. for $C_{25}H_{25}ClFN_5O_4$: 513.95 m/z, found: 514.20 $[M+H]^+$.

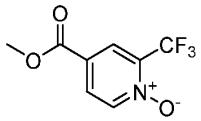


2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

To a solution of 2-(4-(4-chloro-6-methoxynicotinoyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (190 mg, 0.370 mmol, 1.0 equiv) in DMF (5 mL) was added Pyridine hydrobromide (591 mg, 3.700 mmol, 10.0 equiv) at rt. The resulting mixture was stirred for 3 h at 100 °C. After cooled to room temperature, the reaction mixture was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield a crude product which was directly purified by C18 column to afford 2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (60 mg, 32.43%)as a white solid. MS (ESI): mass calcd. for $C_{24}H_{23}ClFN_5O_4$: 499.93 m/z, found: 500.05 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-

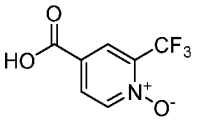
d_6) δ 12.08 (s, 1H), 10.27 (s, 1H), 8.09 – 8.18 (m, 2H), 7.60 (s, 1H), 7.49 – 7.56 (m, 1H), 7.17 – 7.31 (m, 2H), 7.03 – 7.16 (m, 2H), 6.56 (s, 1H), 3.62 (s, 2H), 3.48 – 3.56 (m, 1H), 3.48 – 3.40 (m, 2H), 2.53 – 2.56 (m, 4H), 1.19 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.85.

Example 26: 4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)-2-(trifluoromethyl)pyridine 1-oxide



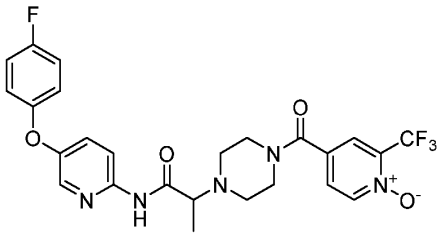
4-(methoxycarbonyl)-2-(trifluoromethyl)pyridine 1-oxide

In a 50-mL round bottom flask, to a solution of methyl 2-(trifluoromethyl)isonicotinate (500 mg, 2.437 mmol, 1.0 equiv) in HOAc (8 mL) was added H_2O_2 (2 mL) at rt. The resulting mixture was stirred for 2 hours at 80 °C. After cooled to room temperature, the reaction was quenched with water (10 mL) and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-10% DCM/MeOH) to afford 4-(methoxycarbonyl)-2-(trifluoromethyl)pyridine 1-oxide (150 mg, 27.83%) as a yellow solid. MS (ESI): mass calcd. for $C_8H_6F_3NO_3$: 221.11 m/z, found: 222.00 $[M+H]^+$.



4-carboxy-2-(trifluoromethyl)pyridine 1-oxide

In a 50-mL round bottom flask, to a solution of 4-(methoxycarbonyl)-2-(trifluoromethyl)pyridine 1-oxide (150 mg, 0.678 mmol, 1.0 equiv) in MeOH (1 mL), THF (3 mL) and H_2O (1 mL) was added LiOH (48 mg, 2.034 mmol, 3.0 equiv) at rt. The reaction mixture was stirred for 4 h at rt. The mixture was acidified to pH = 5 with 4 N HCl. The mixture was concentrated under vacuum and purified by C18 Column (Mobile Phase A: Water (0.05% HCOOH), Mobile Phase B: ACN; Gradient: 5% B to 70% B) to afford 4-carboxy-2-(trifluoromethyl)pyridine 1-oxide (80 mg, 56.95%) as a yellow solid. MS (ESI): mass calcd. for:$C_8H_6F_3NO_3$: 221.11 m/z, found: 222.00 $[M+H]^+$.

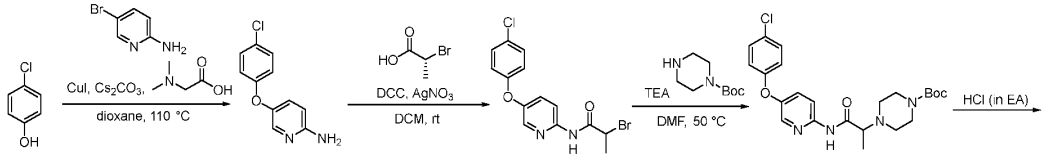


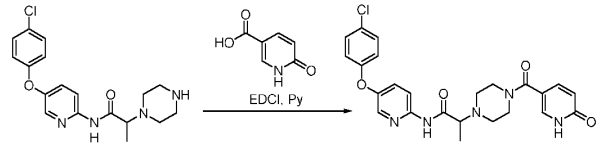
4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)-2-(trifluoromethyl)pyridine 1-oxide

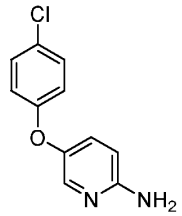
To a solution of 4-carboxy-2-(trifluoromethyl)pyridine 1-oxide (100 mg, 0.483 mmol, 1.0 equiv) in Pyridine (5 mL) was added N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(piperazin-1-yl)propanamide (166 mg, 0.483 mmol, 1.0 equiv) and EDCI (139 mg, 0.724 mmol, 1.5 equiv) at rt. The resulting mixture was stirred for 2 h at rt. The reaction was quenched with H_2O (10 mL) at rt. The resulting mixture was extracted with EA (30 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue obtained was purified by flash chromatography (0-20% DCM/MeOH) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 26% to 56% CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford 4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)-2-(trifluoromethyl)pyridine 1-oxide (22.4 mg, 8.67%) as a white solid. MS (ESI): mass calcd. for: $C_{25}H_{23}F_4N_5O_4$: 533.14 m/z, found: 534.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 8.48 (d, J = 6.7 Hz, 1H), 8.13 (dd, J = 6.0, 2.9 Hz, 2H), 7.97 (d, J = 2.4 Hz, 1H), 7.73 (dd, J = 6.7, 2.5 Hz, 1H), 7.52 (dd, J = 9.1, 2.9 Hz, 1H), 7.18 – 7.29 (m, 2H), 7.04 – 7.13 (m, 2H), 3.30 – 3.67 (m, 5H), 2.59 – 2.64 (m, 4H), 1.19 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -67.708, -119.860.

Example 27: N-(5-(4-chlorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

Synthetic Scheme

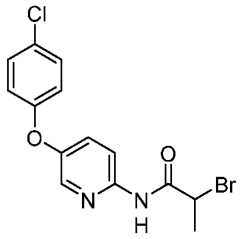






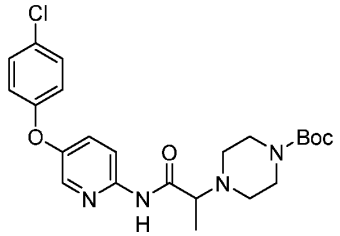
5-(4-chlorophenoxy)pyridin-2-amine

To a stirred solution of 4-chlorophenol (2 g, 15.557 mmol, 1.2 equiv) in dioxane (70 mL) was added dimethylglycine (0.13 g, 1.296 mmol, 0.1 equiv) and 5-bromopyridin-2-amine (2.24 g, 12.964 mmol, 1.0 equiv) and Cs_2CO_3 (6.34 g, 19.446 mmol, 1.5 equiv) followed by catalytic amount of CuI (0.49 g, 2.593 mmol, 0.2 equiv) at room temperature. The reaction mixture was stirred at 110 °C overnight under N_2. After cooled to room temperature, the reaction was quenched by water (50 mL) and extracted with EA (70 mL x 3). The combined organic extracts were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (35-50% PE/EA) to afford 5-(4-chlorophenoxy)pyridin-2-amine (1 g, 22.72%) as a yellow solid. MS (ESI): mass calcd. for: $C_{11}H_9ClN_2O$: 220.04 m/z, found: 221.15 $[M+H]^+$.



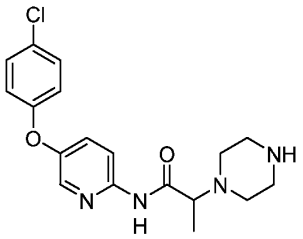
2-bromo-N-(5-(4-chlorophenoxy)pyridin-2-yl)propanamide

To a stirred solution of 5-(4-chlorophenoxy)pyridin-2-amine (1 g, 4.532 mmol, 1.0 equiv) in DCM (20 mL) was added 2-bromopropanoic acid (0.83 g, 5.438 mmol, 1.2 equiv), DCC (1.12 g, 5.438 mmol, 1.2 equiv) and $AgNO_3$ (0.12 g, 0.680 mmol, 0.15 equiv). The reaction mixture was stirred at room temperature for a period of overnight. After completion of reaction, the reaction was quenched by water (20 mL) and extracted with DCM (30 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% PE/EA) to afford 2-bromo-N-(5-(4-chlorophenoxy)pyridin-2-yl)propanamide (1.1 g, 67.56%) as a pink solid. MS (ESI): mass calcd. for: $C_{14}H_{12}BrClN_2O_2$: 353.98 m/z, found: 355.05 $[M+H]^+$.



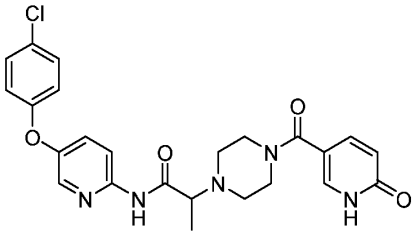
tert-butyl 4-(1-((5-(4-chlorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carboxylate

To a stirred solution of 2-bromo-N-[5-(4-chlorophenoxy)pyridin-2-yl]propanamide (520 mg, 1.462 mmol, 1.0 equiv) in anhydrous DMF (5 mL) was added tert-butyl piperazine-1-carboxylate (326 mg, 1.754 mmol, 1.2 equiv) and TEA (888 mg, 8.772 mmol, 6.0 equiv). The reaction mixture was stirred at 50 °C for 5 h. After cooled to room temperature the reaction was quenched by water (30 mL) and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (30-50% PE/EA) to afford tert-butyl 4-(1-{[5-(4-chlorophenoxy)pyridin-2-yl]carbamoyl}ethyl)piperazine-1-carboxylate (570 mg, 84.07%) as a colorless oil. MS (ESI): mass calcd. for:$C_{23}H_{29}ClN_4O_4$: 460.19 m/z, found: 461.30 $[M+H]^+$.



N-(5-(4-chlorophenoxy)pyridin-2-yl)-2-(piperazin-1-yl)propanamide

To a stirred solution of tert-butyl 4-(1-{[5-(4-chlorophenoxy)pyridin-2-yl]carbamoyl}ethyl)piperazine-1-carboxylate (520 mg, 1.128 mmol, 1.0 equiv) in anhydrous EA (6 mL) was added hydrogen chloride (4M in EA, 1.0 mL). The reaction mixture was stirred at room temperature for 1 h. The resulting mixture was concentrated under reduced pressure to afford N-(5-(4-chlorophenoxy)pyridin-2-yl)-2-(piperazin-1-yl)propanamide (400 mg, 97.32%). MS (ESI): mass calcd. for: $C_{18}H_{21}ClN_4O_2$: 360.14 m/z, found: 361.20 $[M+H]^+$.

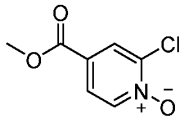


N-(5-(4-chlorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

To a stirred solution of N-[5-(4-chlorophenoxy)pyridin-2-yl]-2-(piperazin-1-yl)propanamide (100 mg, 0.277 mmol, 1.0 equiv) in pyridine (2 mL) was added 6-oxo-1H-pyridine-3-carboxylic acid (46 mg, 0.332 mmol, 1.2 equiv) and EDCI (80 mg, 0.416 mmol, 1.5 equiv) at room temperature. The reaction mixture was stirred at room temperature overnight. After completion of reaction, the reaction was quenched by water (20 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (5-60% PE/EA) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 29% to 59% CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford N-(5-(4-chlorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (9.1 mg, 6.81%) as a white solid. MS (ESI): mass calcd. for:$C_{24}H_{24}ClN_5O_4$: 482.15 m/z, found: 482.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 11.85 (s, 1H), 10.30 (s, 1H), 8.12 – 8.22 (m, 2H), 7.54 – 7.64 (m, 2H),

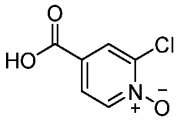
7.38 – 7.52 (m, 3H), 7.00 – 7.11 (m, 2H), 6.34 (d, *J* = 9.4 Hz, 1H), 3.50 – 3.55 (m, 5H), 2.55 – 2.59 (m, 4H), 1.19 (d, *J* = 6.8 Hz, 3H).

Example 28: 2-chloro-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide



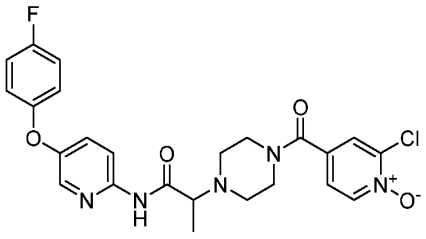
2-chloro-4-(methoxycarbonyl)pyridine 1-oxide

To a solution of methyl 2-chloroisonicotinate (500 mg, 2.914 mmol, 1.0 equiv) in DCM (5 mL) was added m-CPBA (1.51 g, 8.742 mmol, 3.0 equiv) at 0 °C. The resulting mixture was stirred for 3 h at rt. After completion of reaction, the reaction mixture was quenched by addition of water (10 mL). The aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford 2-chloro-4-(methoxycarbonyl)pyridine 1-oxide (370 mg, 67.69%) as yellow oil. MS (ESI): mass calcd. for $C_7H_6ClNO_3$: 187.00 m/z, found: 188.00 $[M+H]^+$.



4-carboxy-2-chloropyridine 1-oxide

To a solution of 2-chloro-4-(methoxycarbonyl)pyridine 1-oxide (180 mg, 0.960 mmol, 1.0 equiv) in tetrahydrofuran (1 mL), water (1 mL) and methanol (1 mL) was added LiOH (69 mg, 2.880 mmol, 3.0 equiv). The resulting mixture was stirred for 2 h at rt. The mixture was acidified pH = 5 with HCl (1N). The resulting mixture was concentrated under vacuum and purified by C18 column to afford (120 mg, 72.06%) as a yellow solid. MS (ESI): mass calcd. for $C_6H_4ClNO_3$: 172.99 m/z, found: 174.10 $[M+H]^+$.

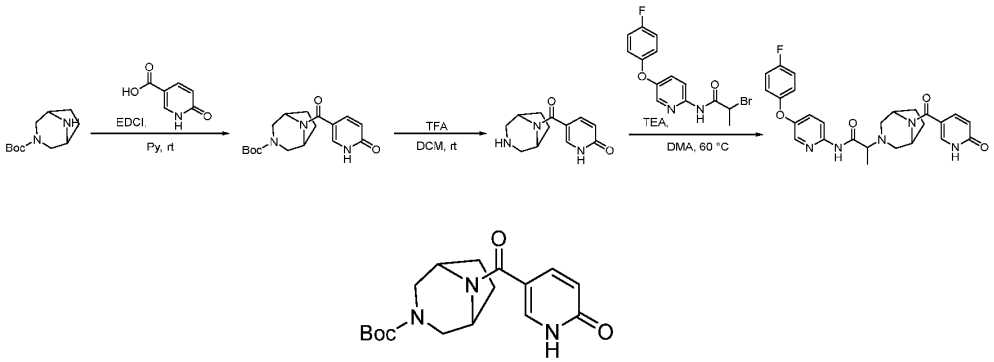


2-chloro-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide

To a solution of 4-carboxy-2-chloropyridine 1-oxide (150 mg, 0.864 mmol, 1.0 equiv) in pyridine (5 mL) in Py (3 mL) was added N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(piperazin-1-yl)propanamide (149 mg, 0.432 mmol, 0.5 equiv) and EDCI (331 mg, 1.728 mmol, 2.0 equiv) at rt. The resulting mixture was stirred for 2 h at rt. The resulting mixture was purified by C18 column & Prep-HPLC using for a Column: YMC Triart C18 ExRs Column, 30*150mm, 5μm (eluent: 27% to 57% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford 2-chloro-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide (13.4 mg, 6.20%) as a white solid. MS (ESI): mass calcd. for $C_{24}H_{23}ClFN_5O_4$: 499.14 m/z, found: 500.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.28 (s, 1H), 8.47 (d, J = 6.7 Hz, 1H), 8.14 (dd, J = 6.0, 2.9 Hz, 2H), 7.89 (d, J = 2.4 Hz, 1H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.45 (dd, J = 6.7, 2.4 Hz, 1H), 7.17 – 7.30 (m, 2H), 7.02 – 7.16 (m, 2H), 3.34 – 3.68 (m, 5H), 2.54 – 2.65 (4H), 1.19 (d, J = 6.8 Hz, 3H). ^{19}H NMR (282 MHz, DMSO-d_6) δ -119.847.

Example 29: N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(8-(6-oxo-1,6-dihydropyridine-3-carbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)propanamide

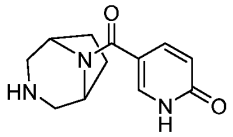
Synthetic Scheme



tert-butyl 8-(6-oxo-1,6-dihydropyridine-3-carbonyl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

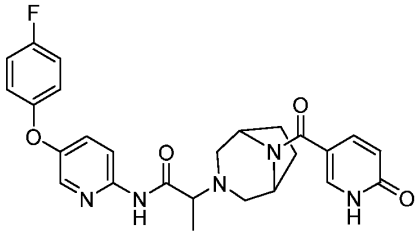
To a solution of tert-butyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate (500 mg, 2.355 mmol, 1.0 equiv) in pyridine (5 mL) the mixture was added 6-oxo-1H-pyridine-3-carboxylic acid (327 mg, 2.355 mmol, 1.0 equiv) and EDCI (677 mg, 3.532 mmol, 1.5 equiv) at rt. The resulting mixture was stirred for 3 h at rt. The reaction mixture was quenched by water (30 mL) and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine

(10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield a crude product which was directly purified by silica gel column (0-80% PE/EA) to afford tert-butyl 8-(6-oxo-1,6-dihydropyridine-3-carbonyl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate as yellow oil. MS (ESI): mass calcd. for $C_{17}H_{23}N_3O_4$: 333.17 m/z, found: 334.25 $[M+H]^+$.



5-(3,8-diazabicyclo[3.2.1]octane-8-carbonyl)pyridin-2(1H)-one

To a solution of tert-butyl 8-(6-oxo-1,6-dihydropyridine-3-carbonyl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (200 mg, 0.600 mmol, 1.0 equiv) in DCM (10 mL) was added TFA (10 mL). The resulting mixture was stirred for 2 hours at rt. The solvent was removed to give 5-(3,8-diazabicyclo[3.2.1]octane-8-carbonyl)pyridin-2(1H)-one as yellow solid. MS (ESI): mass calcd. for $C_{12}H_{15}N_3O_2$: 233.12 m/z, found: 234.20 $[M+H]^+$.

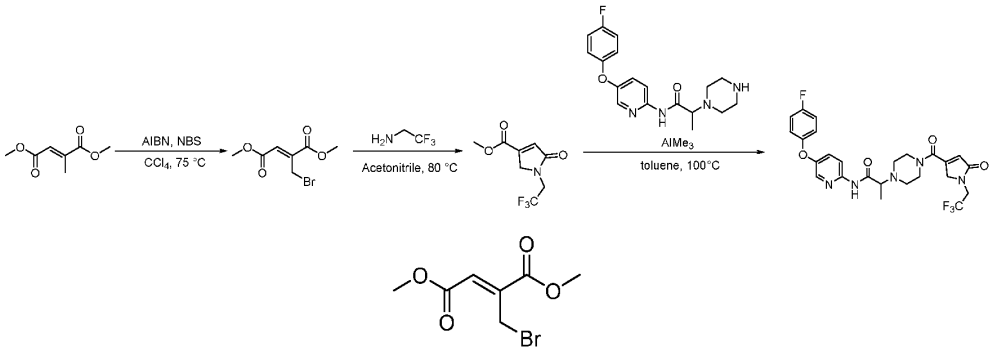


N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(8-(6-oxo-1,6-dihydropyridine-3-carbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)propanamide

To a solution of 5-(3,8-diazabicyclo[3.2.1]octane-8-carbonyl)pyridin-2(1H)-one (100 mg, 0.429 mmol, 1.0 equiv) in DMA (10 mL) was added 2-bromo-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (145 mg, 0.429 mmol, 1.0 equiv) and TEA (130 mg, 1.287 mmol, 3.0 equiv) at rt. The resulting mixture was stirred for 2 hours at 60 °C. The reaction mixture was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield a crude product which was directly purified by Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10mmol/L NH_4HCO_3+0.05%NH_3H_2O), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 29% B to 45% B in 10 min to afford N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(8-(6-oxo-1,6-dihydropyridine-3-carbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)propanamide (18.7 mg, 8.79%) as a white solid. MS: mass calcd. for $C_{26}H_{26}FN_5O_4$: 491.20, found: 492.10

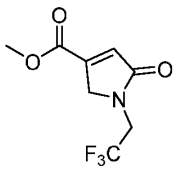
$[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H), 10.16 (s, 1H), 8.19 – 8.10 (m, 2H), 7.63 (d, J = 2.5 Hz, 1H), 7.54 (ddd, J = 9.0, 7.9, 2.8 Hz, 2H), 7.28 – 7.19 (m, 2H), 7.13 – 7.05 (m, 2H), 6.35 (d, J = 9.5 Hz, 1H), 4.34 – 4.38 (m, 2H), 3.44 (d, J = 7.1 Hz, 1H), 2.68 – 2.76 (m, 2H), 2.51 – 2.58 (m, 2H), 1.89 – 1.98 (m, 2H), 1.78 – 1.85 (m, 2H), 1.17 (d, J = 6.9 Hz, 3H).

Example 30: N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(5-oxo-1-(2,2,2-trifluoroethyl)-2,5-dihydro-1H-pyrrole-3-carbonyl)piperazin-1-yl)propanamide



dimethyl 2-(bromomethyl)fumarate

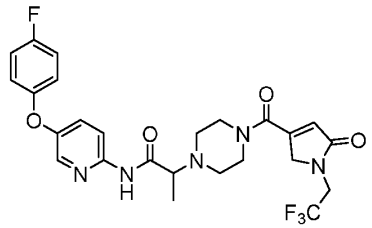
To a solution of dimethyl 2-methylfumarate (1 g, 6.323 mmol, 1.0 equiv) in carbon tetrachloride (20 mL) was added NBS (1.68 g, 9.485 mmol, 1.5 equiv) and AIBN (21 mg, 0.126 mmol, 0.02 equiv). The mixture was stirred at 75 °C for 4 h. After cooled to room temperature, the mixture was filtered and the filtrate was concentrated in vacuo. The resulting residue was purified by silica gel chromatography (0-10% PE/EA) to give dimethyl 2-(bromomethyl)fumarate (1.2 g, 80.06%) as colorless oil.



methyl 5-oxo-1-(2,2,2-trifluoroethyl)-2,5-dihydro-1H-pyrrole-3-carboxylate

To a solution of dimethyl 2-(bromomethyl)fumarate (100 mg, 0.422 mmol, 1.0 equiv) in CH_3CN (10 mL) was added 2,2,2-trifluoroethan-1-amine hydrochloride (68 mg, 0.506 mmol, 1.2 equiv) and DIEA (82 mg, 0.633 mmol, 1.5 equiv). The reaction was stirred at 80 °C for 6 h. After cooled to room temperature, the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained

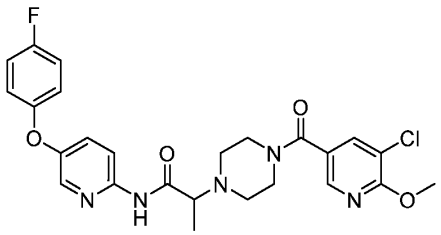
was purified by silica gel chromatography (0-30% PE/EA) to afford methyl 5-oxo-1-(2,2,2-trifluoroethyl)-2,5-dihydro-1H-pyrrole-3-carboxylate (60 mg, 63.74%) as a pink solid. MS (ESI): mass calcd. for $C_8H_8F_3NO_3$: 223.05 m/z, found: 224.15 $[M+H]^+$.



N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(5-oxo-1-(2,2,2-trifluoroethyl)-2,5-dihydro-1H-pyrrole-3-carbonyl)piperazin-1-yl)propanamide

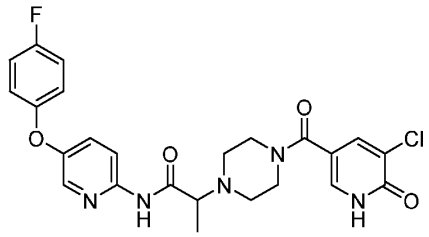
To a solution of methyl 5-oxo-1-(2,2,2-trifluoroethyl)-2,5-dihydro-1H-pyrrole-3-carboxylate (60 mg, 0.269 mmol, 1.0 equiv) in toluene (10 mL) was added trimethylaluminium (2M, in toluene, 0.538 mmol, 2 equiv) at 0 °C. The reaction was stirred at 100 °C for 4 h. After cooled to room temperature the reaction, the reaction was quenched by ice water (5 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-25% DCM/MeOH) and Prep-HPLC using a Column: YMC Triart C18 ExRs Column, 30*150mm, 5μm; (eluent: 31% to 61% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(5-oxo-1-(2,2,2-trifluoroethyl)-2,5-dihydro-1H-pyrrole-3-carbonyl)piperazin-1-yl)propanamide (14.7 mg, 6.10%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{25}F_4N_5O_4$: 535.18 m/z, found: 536.15 $[M+H]^+$, ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.28 (d, J = 3.3 Hz, 1H), 8.14 (dd, J = 5.9, 2.9 Hz, 2H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.32 – 7.17 (m, 2H), 7.09 – 7.15 (m, 2H), 6.34 – 6.41 (m, 1H), 4.27 – 4.44(m,2H), 4.21 (t, J = 9.7 Hz, 1H), 3.39 – 3.63 (m, 6H) , 2.59 (dt, J = 9.4, 5.2 Hz, 4H), 1.19 (d, J = 6.8 Hz, 3H).

Example 31: 2-(4-(5-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide



2-(4-(5-chloro-6-methoxynicotinoyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

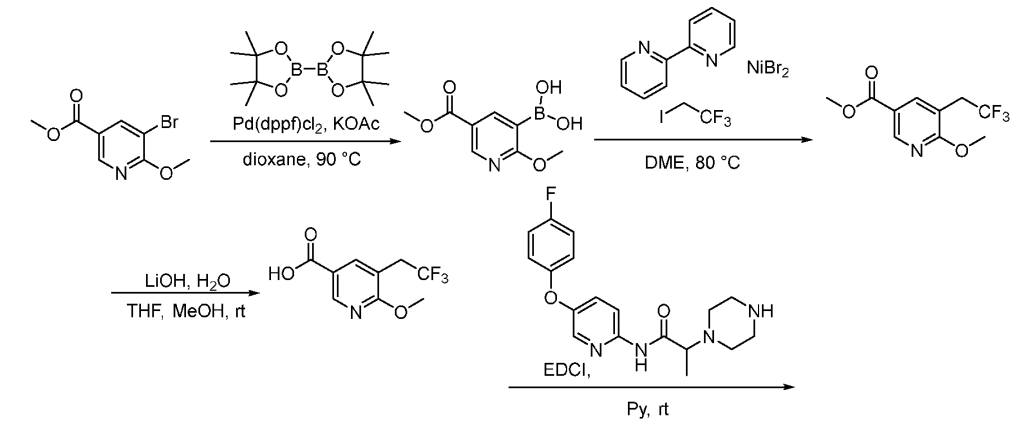
To a solution of N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(piperazin-1-yl)propanamide (120 mg, 0.348 mmol, 1.0 equiv) in Py (3 mL) was added 5-chloro-6-methoxynicotinic acid (65 mg, 0.348 mmol, 1.0 equiv) and EDCI (133 mg, 0.696 mmol, 2.0 equiv) at rt. The resulting mixture was stirred for 3 h at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield a crude product which was directly purified by flash chromatographyto (0-20% DCM/MeOH) afford 2-(4-(5-chloro-6-methoxynicotinoyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide as a white solid. MS (ESI): mass calcd. for $C_{25}H_{25}ClFN_5O_4$: 513.95 m/z, found: 514.20 $[M+H]^+$.

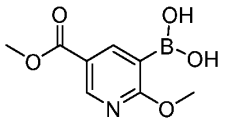


To a solution of 2-(4-(5-chloro-6-methoxynicotinoyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (180 mg, 0.350 mmol, 1.0 equiv) in DMF (5 mL) was added Pyridine hydrobromide (560 mg, 3.50 mmol, 10.0 equiv) at rt .The resulting mixture was stirred for 3 h at 100 °C. The reaction mixture was quenched by water (10 mL) and extracted with 5:1 DCM/MeOH (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield a crude product which was directly purified by silica gel column & C18 column to afford 2-(4-(5-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide as a white solid. MS (ESI): mass calcd. for $C_{24}H_{23}ClFN_5O_4$: 499.93 m/z, found: 500.05 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 12.40 (s, 1H), 10.27 (s, 1H), 8.10 - 8.18 (m, 2H), 7.79 (d, J = 2.3 Hz, 1H), 7.58 – 7.63 (m, 1H), 7.49 – 7.56 (m, 1H), 7.17 – 7.31 (m, 2H), 7.02 – 7.16 (m, 2H), 3.45 – 3.60(m, 5H), 2.50 – 2.65 (m, 4H), 1.19 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.85.

Example 32: N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-5-(2,2,2-trifluoroethyl)-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

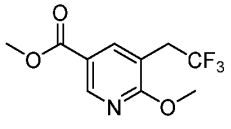
Synthetic Scheme



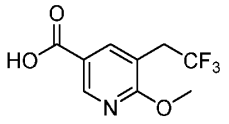


(2-methoxy-5-(methoxycarbonyl)pyridin-3-yl)boronic acid

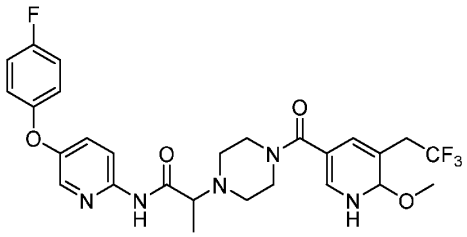
In a 40-mL round bottom flask, to a solution of methyl 5-bromo-6-methoxynicotinate (2.0 g, 8.128 mmol, 1.0 equiv) in dioxane (20 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.27 g, 8.941 mmol, 1.1 equiv), $Pd(dppf)Cl_2$ (0.59 g, 0.813 mmol, 0.1 equiv) and potassium acetate (2.39 g, 24.384 mmol, 3.0 equiv) at room temprature under. The reaction mixture was stirred at 90 °C for 2 h under N_2. After completion of reaction, the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) to afford 2-methoxy-5-(methoxycarbonyl)pyridin-3-ylboronic acid (1.6 g, 86.77%). MS (ESI): mass calcd. for $C_8H_{10}BNO_5$: 210.98 m/z. found 212.20 $[M+H]^+$.



In a 40-mL round bottom flask, to a solution of (2-methoxy-5-(methoxycarbonyl)pyridin-3-yl)boronic acid (1 g, 4.740 mmol, 1.0 equiv) in DME (20 mL) was added 2,2'-bipyridine (1.11 g, 7.110 mmol, 1.5 equiv), 1,1,1-trifluoro-2-iodoethane (1.49 g, 7.110 mmol, 1.5 equiv) and $NiBr_2$ (2.07 g, 9.480 mmol, 2.0 equiv) at rt. The reaction mixture was stirred at 80 °C for 1 h under N_2. After cooled to room temperature, the methanol removed under reduced pressure. The reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% EA/PE) to afford desired compound methyl 6-methoxy-5-(2,2,2-trifluoroethyl)nicotinate (53 mg, 4.49%). MS (ESI): mass calcd. for: $C_8H_{10}BNO_5$: 210.98 m/z. found: 250.00 $[M+H]^+$.



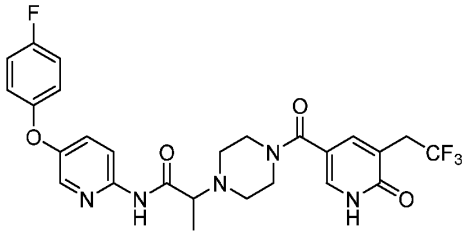
To a stirred solution of methyl 6-methoxy-5-(2,2,2-trifluoroethyl)nicotinate (50 mg, 0.201 mmol, 1.0 equiv) and LiOH (48 mg, 2.010 mmol, 10.0 equiv) in methanol (1 mL), H_2O (1 mL) and THF (1 mL) at room temperature. The reaction mixture was stirred at room temperature for a period of 3 h. The mixture was concentrated to dryness under reduced pressure to provide the crude product, which was purified by C18 column (0-20% H_2O/ACN) to afford 6-methoxy-5-(2,2,2-trifluoroethyl)pyridine-3-carboxylic acid (30 mg, 63.58%). MS (ESI): mass calcd. for $C_9H_8F_3NO_3$: 235.162 m/z. found 236.20 $[M+H]^+$.



N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-methoxy-5-(2,2,2-trifluoroethyl)-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

To a stirred solution of 6-methoxy-5-(2,2,2-trifluoroethyl)pyridine-3-carboxylic acid (30 mg, 0.128 mmol, 1.0 equiv) in pyridine (5 mL) was added N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(piperazin-1-yl)propanamide (66 mg, 0.192 mmol, 1.5 equiv) and EDCI (73 mg, 0.384 mmol, 3.0 equiv) at room temperature. The reaction mixture was stirred at room temperature for a period of 3 h. The reaction was quenched by water (10 mL) and extracted with EA (10

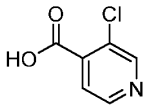
mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% EA/PE) to afford N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-methoxy-5-(2,2,2-trifluoroethyl)-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (30 mg, 41.73%).



N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-5-(2,2,2-trifluoroethyl)-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

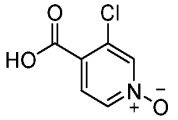
To a stirred solution of N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-methoxy-5-(2,2,2-trifluoroethyl)-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (30 mg, 0.053 mmol, 1.0 equiv) in DMF (5 mL) was added pyridine hydrobromide (85 mg, 0.530 mmol, 10.0 equiv) at room temperature. The reaction mixture was stirred at 90 °C for a period of 3 h. After cooled to room temperature, the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and Prep-HPLC using a Column: XBridge Shield RP 18 OBD Column, 30*150 mm, 5μm (eluent: 32% to 62% CH_3CN and H_2O with 10 mmol/L NH_4HCO_3+0.1% $NH_3.H_2O$) to afford N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-5-(2,2,2-trifluoroethyl)-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (1.7 mg, 7.23%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{25}F_4N_5O_4$: 547.51 m/z found: 548.10 $[M+H]^+$. ^1H NMR (400 MHz, Acetonitrile-d_3) δ 8.18 (d, J = 9.1 Hz, 1H), 8.09 (d, J = 2.6 Hz, 1H), 7.62 (s, 1H), 7.55 (d, J = 2.4 Hz, 1H), 7.44 (dd, J = 9.0, 2.7 Hz, 1H), 7.03 – 7.15 (m,4H), 3.64 – 3.71 (m, 4H), 3.33 – 3.67 (m, 3H), 3.26 (s, 2H), 2.54 – 2.76 (m, 3H), 2.61 (s, 2H),1.27 (d, J = 7.3 Hz, 3H). ^{19}F NMR (376 MHz, Acetonitrile-d_3) δ -66.28, -121.48 (d, J = 4.0 Hz).

Example 33: 3-chloro-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide



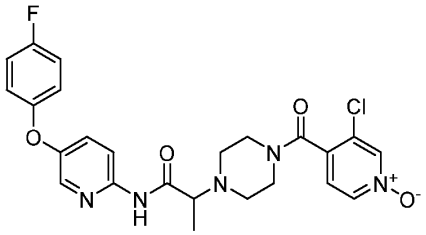
3-chloroisonicotinic acid

To a solution of methyl 3-chloropyridine-4-carboxylate (500 mg, 2.914 mmol, 1.0 equiv) in tetrahydrofuran (4 mL), water (2 mL) and methanol (2 mL) was added LiOH (349 mg, 14.570 mmol, 5.0 equiv) at rt. The resulting mixture was stirred for 1 h at rt. The resulting mixture was concentrated under vacuum. The resulting mixture was acidified pH = 6 with HCl (1N). The aqueous layer was extracted with EA (3 X 20 mL), concentrated under reduced pressure to afford 3-chloroisonicotinic acid (160 mg, 34.85%) as yellow oil. MS (ESI): mass calcd. for: $C_6H_4ClNO_2$: 156.99 m/z, found:158.05 $[M+H]^+$.



4-carboxy-3-chloropyridine 1-oxide

To a solution of 3-chloroisonicotinic acid (74 mg, 0.47. mmol, 1.0 equiv) in HOAc (1 mL) was added 30% H_2O_2 (0.2 mL) at rt. The resulting mixture was stirred for 3 h at 90 °C. After cooled to room temperature, the residue was purified by C18 column to afford 4-carboxy-3-chloropyridine 1-oxide (60 mg, 73.18%) as a yellow solid. MS (ESI): mass calcd. for: $C_6H_4ClNO_3$: 172.99 m/z, found: 174.15 $[M+H]^+$.



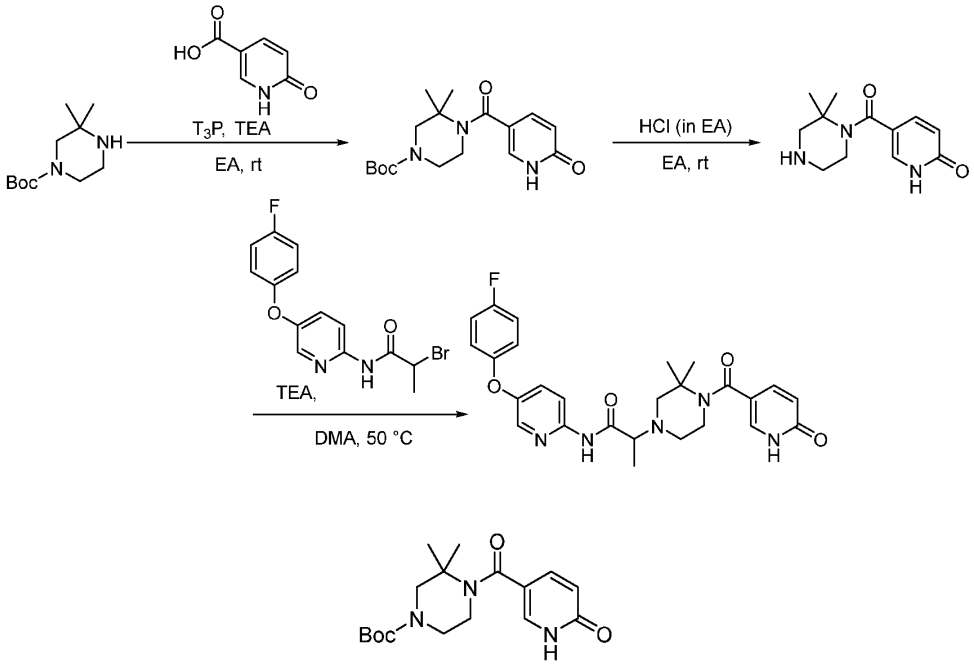
N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-5-(2,2,2-trifluoroethyl)-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

To a solution of 4-carboxy-3-chloropyridine 1-oxide (60 mg, 0.346 mmol, 1.0 equiv) in pyridine (4 mL) was added N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(piperazin-1-yl)propanamide (119 mg, 0.346 mmol, 1.0 equiv) and EDCI (132 mg, 0.692 mmol, 2.0 equiv) at rt. The resulting mixture was stirred for 3 h at rt. The reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to afford product

which was directly purified by flash chromatography (0-100% PE/EA) & C18 column to afford N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-5-(2,2,2-trifluoroethyl)-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (28.2 mg, 16.21%) as a white solid. MS (ESI): mass calcd. for: $C_{24}H_{23}ClFN_5O_4$: 499.14 m/z, found: 500.05 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 8.60 (d, J = 1.7 Hz, 1H), 8.23 – 8.28 (m, 1H), 8.09 – 8.16 (m, 2H), 7.45 – 7.56 (m, 2H), 7.18 – 7.28 (m, 2H), 7.05 – 7.14 (m, 2H), 3.54 (q, J = 6.8 Hz, 1H), 3.49 – 3.58 (m, 2H), 3.24 – 3.31 (m, 2H), 2.53 – 2.60 (m, 4H), 1.19 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -119.853.

Example 34: 2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

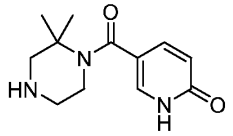
Synthetic Scheme



tert-butyl 3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazine-1-carboxylate

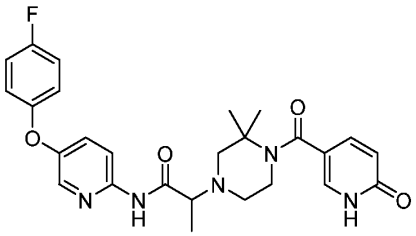
To a solution of tert-butyl 3,3-dimethylpiperazine-1-carboxylate (500 mg, 2.333 mmol, 1.0 equiv) in EA (5 mL) was added 6-oxo-1,6-dihydropyridine-3-carboxylic acid (324 mg, 2.333 mmol, 1.0 equiv), T_3P (1.48 g, 4.666 mmol, 2.0 equiv) and TEA (944 mg, 9.332 mmol, 4.0 equiv) at rt. The resulting mixture was at room temperature for 6 h. The reaction mixture was quenched by addition of water (20 mL). The aqueous layer was extracted with ethyl acetate

(30 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give crude product which was further purified by column chromatography (0-15% DCM/MeOH) to afford tert-butyl 3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazine-1-carboxylate (95 mg, 12.14%). MS (ESI): mass calcd. for $C_{17}H_{25}N_3O_4$: 335.18 m/z, found 336.20 $[M+H]^+$.



5-(2,2-dimethylpiperazine-1-carbonyl)pyridin-2(1H)-one

To a solution of tert-butyl 3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazine-1-carboxylate (95 mg, 0.283 mmol, 1.0 equiv) in EA (2 mL) was added 4N HCl (in EA, 2 mL). The resulting mixture was at room temperature for 2 h. After the reaction is complete, the product is precipitated with ethyl ether to afford 5-(2,2-dimethylpiperazine-1-carbonyl)pyridin-2(1H)-one (60 mg, 90.03%). MS (ESI): mass calcd. for $C_{12}H_{17}N_3O_2$: 235.13 m/z, found 236.05 $[M+H]^+$.

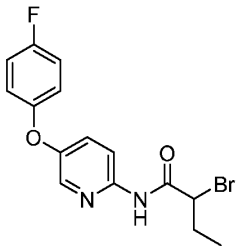


2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

To a solution of 5-(2,2-dimethylpiperazine-1-carbonyl)pyridin-2(1H)-one (50 mg, 0.213 mmol, 1.0 equiv) in DMA (2 mL) was added a solution of 2-bromo-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (86 mg, 0.256 mmol, 1.2 equiv) and TEA (86 mg, 0.852 mmol, 4.0 equiv). The mixture was stirred at 50 °C for 3 h. After cooled to room temperature, the reaction mixture was quenched by water (10 mL) and extracted with EA (50 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield a crude product which was directly purified by flash chromatographyto (0-20% DCM/MeOH) & Prep-HPLC using a Column: XBridge Prep OBD C18 Column,30*150mm 5.0 μm (eluent: 33% to 55% CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford 2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (16.1 mg,

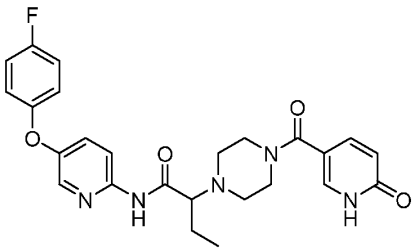
15.28%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{28}FN_5O_4$: 493.21 m/z, found: 494.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.84 (s, 1H), 10.19 (s, 1H), 8.16 (d, J = 8.6 Hz, 2H), 7.44 – 7.59 (m, 3H), 7.14 – 7.20 (m, 4H), 6.32 (d, J = 9.6 Hz, 1H), 3.46 – 3.52 (m, 1H), 2.73 (s, 2H), 2.41 (s, 4H), 1.41 (s, 6H), 1.18 – 1.24 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -119.84.

Example 35: N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)butanamide



2-bromo-N-(5-(4-fluorophenoxy)pyridin-2-yl)butanamide

To a stirred solution of 5-(4-fluorophenoxy)pyridin-2-amine (200 mg, 0.979 mmol, 1.0 equiv) in anhydrous DCM (20 mL) was added 2-bromobutyric acid (196 mg, 1.175 mmol, 1.2 equiv) and DCC (242 mg, 1.175 mmol, 1.2 equiv) and $AgNO_3$ (25 mg, 0.147 mmol, 0.15 equiv). The reaction mixture was stirred at room temperature overnight. After completion of reaction, the reaction was quenched by water (20 mL) and extracted with DCM (20 mL x 3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% PE/EA) to afford 2-bromo-N-[5-(4-fluorophenoxy)pyridin-2-yl]butanamide (250 mg, 71.48%) as a pink solid. MS (ESI): mass calcd. for: $C_{15}H_{14}BrFN_2O_2$: 352.02 m/z, found: 353.10 $[M+H]^+$.

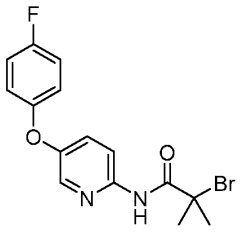


N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)butanamide

To a stirred solution of 5-(piperazine-1-carbonyl)pyridin-2(1H)-one (100 mg, 0.483 mmol, 1.0 equiv) in anhydrous DMA (2 mL) was added TEA (293 mg, 2.898 mmol, 6.0 equiv)

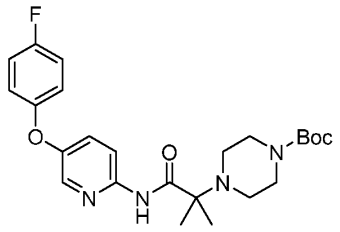
and 2-bromo-N-[5-(4-fluorophenoxy)pyridin-2-yl]butanamide (170 mg, 0.483 mmol, 1.0 equiv). The reaction mixture was stirred at 60 °C for a period of 3 h. After cooled to room temperature, the reaction was quenched by water (20 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) and Prep-HPLC using a column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; (eluent: 31% to 61% CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)butanamid as a white solid. MS (ESI): mass calcd. for $C_{25}H_{26}FN_5O_4$: 479.20 m/z, found: 480.15$[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.51 (s, 1H), 8.10 – 8.21 (m, 2H), 7.45 – 7.57 (m, 3H), 7.24 (t, J = 8.8 Hz, 2H), 7.04 – 7.16 (m, 2H), 6.33 (d, J = 9.5 Hz, 1H), 3.44 – 3.57 (m, 5H), 2.61 (dd, J = 11.2, 5.3 Hz, 4H), 1.69 – 1.79 (m, 1H), 1.54 – 1.64 (m, 1H), 0.87 (t, J = 7.3 Hz, 3H).

Example 36: N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-methyl-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide



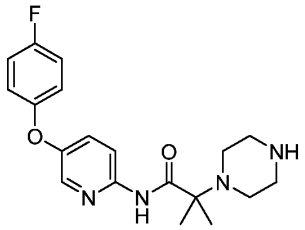
2-bromo-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-methylpropanamide

To a solution of 5-(4-fluorophenoxy)pyridin-2-amine (1.0 g, 4.9 mmol, 1.0 equiv) in DCM (15 mL) was added 2-bromo-2-methylpropanoic acid (981 mg, 5.9 mmol, 1.2 equiv), $AgNO_3$ (125 mg, 0.7 mmol, 0.15 equiv) and DCC (1.2 g, 5.9 mmol, 1.2 equiv) at 0 °C. The reaction was stirred at room temperature for 3 h. Quenched with water (50 mL) and extracted with DCM (50 mL x 3). The combined extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with PE/EA (0-100%) to give 2-bromo-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-methylpropanamide as yellow oil.



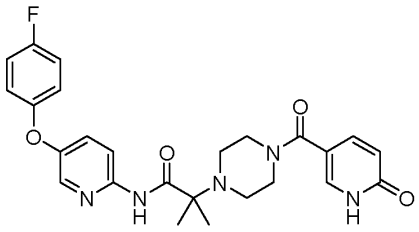
tert-butyl 4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-2-methyl-1-oxopropan-2-yl)piperazine-1-carboxylate

To a solution of 2-bromo-N-[5-(4-fluorophenoxy)pyridin-2-yl]-2-methylpropanamide (500 mg, 1.416 mmol, 1.0 equiv) in DMF (5 mL) was added tert-butyl piperazine-1-carboxylate (263 mg, 1.416 mmol, 1.0 equiv) and K_2CO_3 (591 mg, 4.248 mmol, 3.0 equiv) at rt. The resulting mixture was stirred for 2 hours at 50 °C. After cooled to room temperature, the reaction was quenched by water (20 mL) and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to give tert-butyl 4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-2-methyl-1-oxopropan-2-yl)piperazine-1-carboxylate (279 mg, 43.15%) as a yellow solid. MS (ESI): mass calcd. for $C_{24}H_{31}FN_4O_4$: 458.23 m/z, found: 459.30 $[M+H]^+$.



N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-methyl-2-(piperazin-1-yl)propanamide

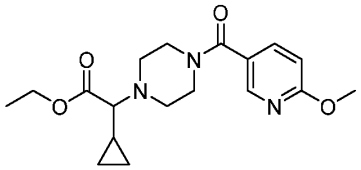
To a solution of tert-butyl 4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-2-methyl-1-oxopropan-2-yl)piperazine-1-carboxylate (0.2 g, 0.436 mmol, 1.0 equiv) in EA (3 mL) was added 4N HCl (in EA, 3 mL). The mixture was stirred at room temperature for 2 h. The mixture was concentrated to dryness under reduced pressure to provide the N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-methyl-2-(piperazin-1-yl)propanamide as a white solid. MS (ESI): mass calcd. for $C_{19}H_{23}FN_4O_2$: 358.18 m/z, found: 359.25 $[M+H]^+$.



N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-methyl-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

To a solution of N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-methyl-2-(piperazin-1-yl)propanamide (100 mg, 0.279 mmol, 1.0 equiv) in pyridine (5 mL) was added 6-oxo-1,6-dihydropyridine-3-carboxylic acid (39 mg, 0.279 mmol, 1.0 equiv) and EDCI (80.23 mg, 0.419 mmol, 1.5 equiv) at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (10 mL x 3). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and Prep-HPLC using a column: Column: XBridge Prep OBD C18 Column, 19*250 mm, 5μm (eluent: 35% to 65% CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-methyl-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (10 mg, 7.46%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{26}FN_5O_4$: 479.20, found: 480.10 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 9.85 (s, 1H), 8.07 – 8.18 (m, 2H), 7.47 – 7.62 (m, 3H), 7.24 (t, J = 8.8 Hz, 2H), 7.04 – 7.14 (m, 2H), 6.34 (d, J = 9.5 Hz, 1H), 3.46 – 3.80 (s, 4H), 2.49 (d, J = 4.1 Hz, 4H), 1.22 (s, 6H).

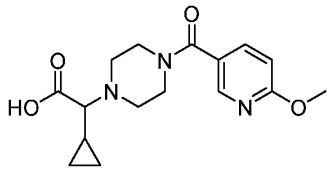
Example 37: 2-cyclopropyl-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)acetamide



ethyl 2-cyclopropyl-2-(4-(6-methoxynicotinoyl)piperazin-1-yl)acetate

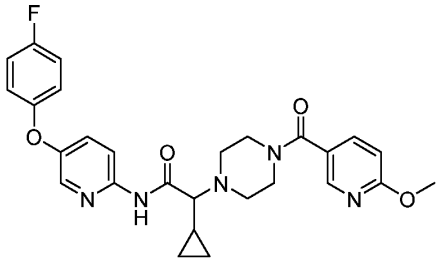
To a stirred solution of 1-(6-methoxypyridine-3-carbonyl)piperazine (200 mg, 0.904 mmol, 1.0 equiv) in DMA (3 mL) was added ethyl 2-bromo-2-cyclopropylacetate (187 mg, 0.904 mmol, 1.0 equiv) and TEA (548 mg, 5.424 mmol, 6.0 equiv). The reaction mixture was stirred at 50 °C for 5 h. After cooled to room temperature, the reaction was quenched by water (20 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with

brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-80% PE/EA) to afford ethyl 2-cyclopropyl-2-(4-(6-methoxynicotinoyl)piperazin-1-yl)acetate (50 mg, 15.92%) as a white solid. MS (ESI): mass calcd. for $C_{18}H_{25}N_3O_4$: 347.18 m/z, found: 348.30 $[M+H]^+$.



2-cyclopropyl-2-(4-(6-methoxynicotinoyl)piperazin-1-yl)acetic acid

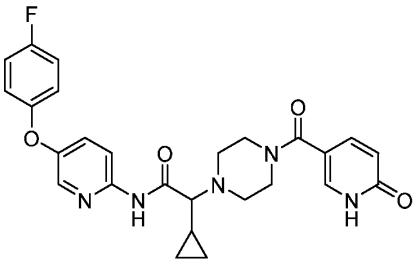
To a stirred solution of ethyl 2-cyclopropyl-2-[4-(6-methoxypyridine-3-carbonyl)piperazin-1-yl]acetate (35 mg, 0.101 mmol, 1.0 equiv) in anhydrous MeOH (0.2 mL) and THF (0.8 mL) and H_2O (0.2 mL) was added LiOH (12 mg, 0.505 mmol, 5.0 equiv). The reaction mixture was stirred at 40 °C for 1 h. After cooled to room temperature, the reaction was quenched by water (2 mL) then adjusted to pH 4~5 with 2N HCl. The resulting solution was extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated to afford 2-cyclopropyl-2-(4-(6-methoxynicotinoyl)piperazin-1-yl)acetic acid (30 mg, 83.92%) as a white solid. MS (ESI): mass calcd. for $C_{16}H_{21}N_3O_4$: 319.15 m/z, found: 320.10 $[M+H]^+$.



2-cyclopropyl-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-methoxynicotinoyl)piperazin-1-yl)acetamide

To a solution of 2-cyclopropyl-2-(4-(6-methoxynicotinoyl)piperazin-1-yl)acetic acid (27 mg, 0.085 mmol, 1.0 equiv) in pyridine (1 mL) was added 5-(4-fluorophenoxy)pyridin-2-amine (20 mg, 0.102 mmol, 1.2 equiv) and EDCI (24 mg, 0.128 mmol, 1.5 equiv). The mixture was stirred at rt for 2 h. After completion of reaction, the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-25% DCM/MeOH) to afford 2-

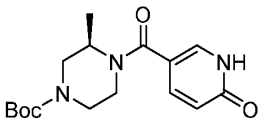
cyclopropyl-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-methoxynicotinoyl)piperazin-1-yl)acetamide (27 mg, 58.49%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{28}FN_5O_4$: 505.21 m/z, found 506.20 $[M+H]^+$.



2-cyclopropyl-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)acetamide

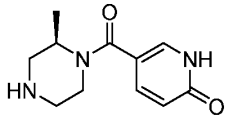
To a stirred solution of 2-cyclopropyl-N-[5-(4-fluorophenoxy)pyridin-2-yl]-2-[4-(6-methoxypyridine-3-carbonyl)piperazin-1-yl]acetamide (27 mg, 0.053 mmol, 1.0 equiv) in DMF was added LiCl (11 mg, 0.265 mmol, 5.0 equiv) and PTSA (46 mg, 0.265 mmol, 5.0 equiv). The reaction mixture was stirred at 80 °C for 5 h. After cooled to room temperature, the crude product was purified by Prep-HPLC using a column: XBridge Shield RP 18 OBD Column, 30*150 mm, 5μm; (eluent: 28% to 58% CH_3CN and H_2O with 10 mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$) to afford 2-cyclopropyl-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)acetamide (6.2 mg, 23.53%) as a white solid. MS (ESI): mass calcd. for: $C_{26}H_{26}FN_5O_4$: 491.20 m/z, found: 492.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 11.71 (s, 1H), 10.20 (s, 1H), 8.10 – 8.20 (m, 2H), 7.40 – 7.66 (m, 3H), 7.17 – 7.30 (m, 2H), 7.04 – 7.16 (m, 2H), 6.34 (d, J = 9.5 Hz, 1H), 3.43 – 3.54 (m, 5H), 2.71 – 2.82 (m, 2H), 2.28 – 2.32 (m, 1H), 2.19 – 2.23 (m, 1H), 1.10 (d, J = 8.1 Hz, 1H), 0.66 (d, J = 8.8 Hz, 1H), 0.46 (d, J = 8.8 Hz, 1H), 0.33 (d, J = 4.0 Hz, 2H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -45.65, -119.88, -120.39.

Example 38: (S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((R)-3-methyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide and Example 39: (R)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((R)-3-methyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide



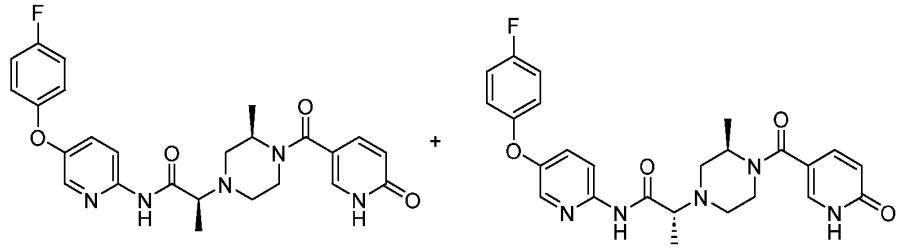
tert-butyl (R)-3-methyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazine-1-carboxylate

To a solution of tert-butyl (R)-3-methylpiperazine-1-carboxylate (500 mg, 2.496 mmol, 1.0 equiv) in Pyridine (20 mL) was added 6-oxo-1H-pyridine-3-carboxylic acid (347 mg, 2.496 mmol, 1.0 equiv) and EDCI (718 mg, 3.744 mmol, 1.5 equiv) at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (10 mL x 3). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) to give tert-butyl (R)-3-methyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazine-1-carboxylate (600 mg, 73.44%) as yellow oil. MS (ESI): mass calcd. for $C_{16}H_{23}N_3O_4$: 321.17 m/z, found: 344.10 $[M+Na]^+$.



(R)-5-(2-methylpiperazine-1-carbonyl)pyridin-2(1H)-one

To a solution of tert-butyl (R)-3-methyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazine-1-carboxylate (200 mg, 0.622 mmol, 1.0 equiv) in DCM (15 mL) was added TFA (3 mL) at rt. The resulting mixture was stirred for 2 hours at rt. The solvent was removed to give (R)-5-(2-methylpiperazine-1-carbonyl)pyridin-2(1H)-one (120 mg, 87.15%) as a yellow solid. MS (ESI): mass calcd. for $C_{11}H_{15}N_3O_2$: 221.12 m/z, found: 222.10 $[M+H]^+$.

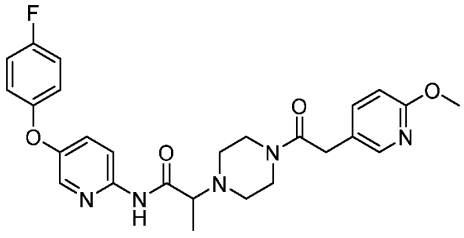


(S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((R)-3-methyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide and (R)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((R)-3-methyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

To a solution of (R)-5-(2-methylpiperazine-1-carbonyl)pyridin-2(1H)-one (100 mg, 0.452 mmol, 1.0 equiv) in DMA (20 mL) was added 2-bromo-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (153 mg, 0.452 mmol, 1.0 equiv) and TEA (137 mg, 1.356 mmol, 3.0 equiv) at rt. The resulting mixture was stirred for 2 hours at 50 °C. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3).

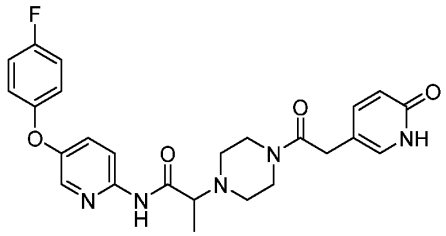
The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) to give N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((R)-3-methyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide as a white solid. The product was separated by Chiral-Prep-HPLC (CHIRALPAK IF 2*25 cm, 5 μm; Mobile Phase A: (HEX: DCM=3: 1)(0.05% 2M NH_3-MeOH), Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: isocratic 20; Wave Length: 220/254 nm; RT1(min): 9.91; RT2(min): 14.786; Sample Solvent: EtOH; Injection Volume: 1.5 mL to afford (S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((R)-3-methyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (13.9 mg, 6.34%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{26}FN_5O_4$: 479.20 m/z, found: 480.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 10.19 (s, 1H), 8.11 – 8.18 (m, 2H), 7.50 – 7.57 (m, 2H), 7.46 (dd, J = 9.4, 2.6 Hz, 1H), 7.24 (t, J = 8.8 Hz, 2H), 7.04 – 7.17 (m, 2H), 6.34 (d, J = 9.4 Hz, 1H), 4.34 (s, 1H), 3.83 (d, J = 12.9 Hz, 1H), 3.38 – 3.47 (m,1H), 3.35 (s,1H), 3.24 (t, J = 12.6 Hz, 1H), 2.84 (d, J = 11.1 Hz, 1H), 2.72 (d, J = 11.5 Hz, 1H), 2.22 (td, J = 11.6, 3.3 Hz, 1H), 1.31 (d, J = 6.7 Hz, 3H), 1.19 (d, J = 7.0 Hz, 3H). And (R)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((R)-3-methyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (7.4 mg, 3.32%) as a white solid MS (ESI): mass calcd. for $C_{25}H_{26}FN_5O_4$: 479.20 m/z, found: 480.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 10.16 (s, 1H), 8.14 (dd, J = 6.0, 2.9 Hz, 2H), 7.43 – 7.58 (m, 3H), 7.18 – 7.29 (m, 2H), 7.04 – 7.14 (m, 2H), 6.34 (d, J = 9.5 Hz, 1H), 4.33 (s, 1H), 3.85 (d, J = 13.0 Hz, 1H), 3.54 (q, J = 6.8 Hz, 1H), 3.21 – 3.32 (m, 1H), 2.85 (d, J = 11.4 Hz, 1H), 2.58 (d, J = 11.4 Hz, 1H), 2.36 – 2.48 (m, 2H), 1.31 (d, J = 6.7 Hz, 3H), 1.16 (d, J = 6.9 Hz, 3H).

Example 40: N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(2-(6-oxo-1,6-dihydropyridin-3-yl)acetyl)piperazin-1-yl)propanamide



N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(2-(6-methoxypyridin-3-yl)acetyl)piperazin-1-yl)propanamide

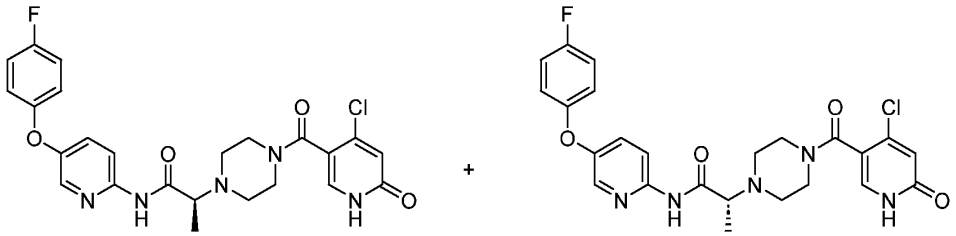
To a solution of N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(piperazin-1-yl)propanamide (100 mg, 0.290 mmol, 1.0 equiv) in pyridine (5 mL) was added 2-(6-methoxypyridin-3-yl)acetic acid (48 mg, 0.290 mmol, 1.0 equiv) and EDCI (111 mg, 0.580 mmol, 2.0 equiv) was added at rt. The resulting mixture was stirred for 2 h at rt. The resulting mixture concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20% DCM/MeOH) to afford N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(2-(6-methoxypyridin-3-yl)acetyl)piperazin-1-yl)propanamide (40 mg, 27.91%) as a white solid. MS (ESI): $C_{26}H_{28}FN_5O_4$: 493.21 m/z, found: 494.15 $[M+H]^+$.



N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(2-(6-oxo-1,6-dihydropyridin-3-yl)acetyl)piperazin-1-yl)propanamide

To a solution of N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(2-(6-methoxypyridin-3-yl)acetyl)piperazin-1-yl)propanamide (40 mg, 0.081 mmol, 1.0 equiv) in DMF (2 mL) was added lithium chloride (17 mg, 0.405 mmol, 5.0 equiv) and PTSA (70 mg, 0.405 mmol, 5.0 equiv) at rt. The resulting mixture was stirred for 12 h at 80 °C. The residue was purified by C18 column to afford N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(2-(6-oxo-1,6-dihydropyridin-3-yl)acetyl)piperazin-1-yl)propanamide (9.6 mg, 24.66%) as a white solid. MS (ESI): mass calcd. for: $C_{25}H_{26}FN_5O_4$: 479.20 m/z, found: 480.10 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.38 (s, 1H), 10.25 (s, 1H), 8.09 – 8.17 (m, 2H), 7.53 (dd, J = 9.0, 3.0 Hz, 1H), 7.15 – 7.32 (m, 4H), 7.04 – 7.15 (m, 2H), 6.26 (d, J = 9.3 Hz, 1H), 3.41 – 3.57 (m, 7H), 2.56 – 2.58 (m, 3H), 2.46 – 2.49 (m, 1H), 1.14 – 1.27 (m, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.866.

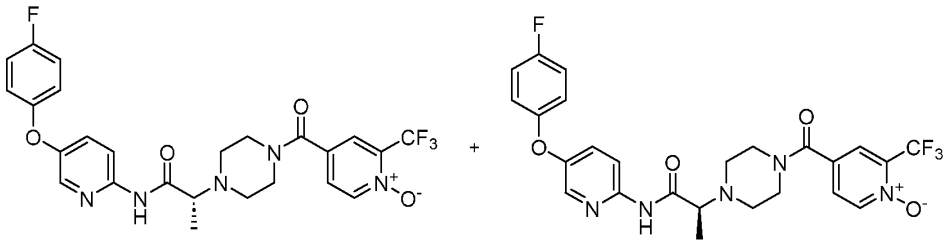
Example 41: (S)-2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide and Example 42: (R)-2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide



(S)-2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide and (R)-2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide was separated by Chiral-HPLC (Column: CHIRALPAK IA, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min) to afford (S)-2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (25.0 mg, 13.51%). MS (ESI): mass calcd. for $C_{24}H_{23}ClFN_5O_4$: 499.93 m/z, found: 500.05 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 12.08 (s, 1H), 10.27 (s, 1H), 8.09 – 8.18 (m, 2H), 7.60 (s, 1H), 7.49 – 7.56 (m, 1H), 7.17 – 7.31 (m, 2H), 7.03 – 7.16 (m, 2H), 6.56 (s, 1H), 3.62 (s, 2H), 3.48 – 3.56 (m, 1H), 3.48 – 3.40 (m, 2H), 2.53 – 2.56 (m, 4H), 1.19 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.85. And (R)-2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (25.0 mg, 13.51%). MS (ESI): mass calcd. for C24H23ClFN5O4: 499.93 m/z, found: 500.05 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 12.08 (s, 1H), 10.27 (s, 1H), 8.09 – 8.18 (m, 2H), 7.60 (s, 1H), 7.49 – 7.56 (m, 1H), 7.17 – 7.31 (m, 2H), 7.03 – 7.16 (m, 2H), 6.56 (s, 1H), 3.62 (s, 2H), 3.48 – 3.56 (m, 1H), 3.48 – 3.40 (m, 2H), 2.53 – 2.56 (m, 4H), 1.19 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.85.

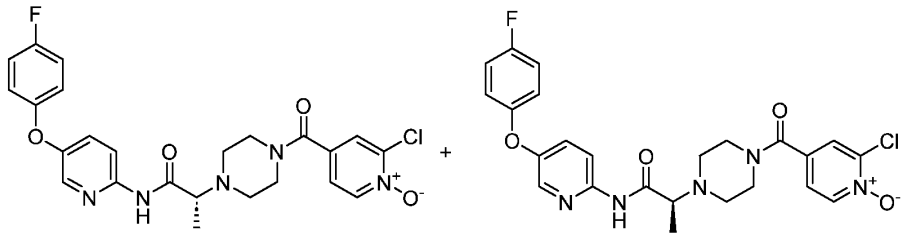
Example 43: (R)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)-2-(trifluoromethyl)pyridine 1-oxide and Example 44: (S)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)-2-(trifluoromethyl)pyridine 1-oxide



(R)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)-2-(trifluoromethyl)pyridine 1-oxide and (S)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)-2-(trifluoromethyl)pyridine 1-oxide

4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)-2-(trifluoromethyl)pyridine 1-oxide was separated by Chiral-HPLC (Column: CHIRALPAK IA 5*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min) to afford (R)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)-2-(trifluoromethyl)pyridine 1-oxide (9.9 mg, 7.67%, first peak) as a white solid, MS (ESI): mass calcd. for $C_{25}H_{23}F_4N_5O_4$: 533.11 m/z, found 534.05 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.27 (s, 1H), 8.49 (d, J = 6.7 Hz, 1H), 8.09 – 8.18 (m, 2H), 7.97 (d, J = 2.4 Hz, 1H), 7.74 (dd, J = 6.7, 2.5 Hz, 1H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.02 – 7.16 (m, 2H), 3.61 – 3.64 (m, 2H), (s, 2H), 3.47 – 3.60 (m, 2H), 3.37 – 3.46 (m, 2H), 2.62 (s, 3H), 1.20 (d, J = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -67.702, -119.850. And (S)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)-2-(trifluoromethyl)pyridine 1-oxide (10.8 mg, 8.38%, second peak) as a white solid, MS (ESI): mass calcd. for $C_{25}H_{23}F_4N_5O_4$: 533.11 m/z, found 534.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.27 (s, 1H), 8.49 (d, J = 6.7 Hz, 1H), 8.09 – 8.18 (m, 2H), 7.97 (d, J = 2.4 Hz, 1H), 7.74 (dd, J = 6.7, 2.5 Hz, 1H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.02 – 7.16 (m, 2H), 3.61 – 3.64 (m, 2H), 3.47 – 3.60 (m, 2H), 3.37 – 3.46 (m, 2H), 2.62 (s, 3H), 1.20 (d, J = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -67.702, -119.850.

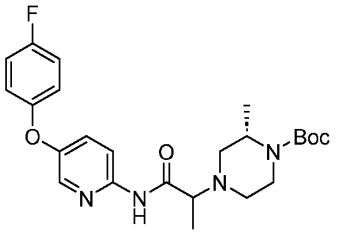
Example 45: (R)-2-chloro-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide and Example 46: (S)-2-chloro-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide



(R)-2-chloro-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide and (S)-2-chloro-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide

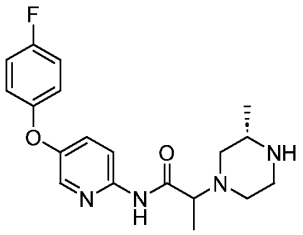
2-chloro-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide was separated by Chiral-HPLC to afford (R)-2-chloro-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide (2.0 mg). MS (ESI): mass calcd. for $C_{24}H_{23}ClFN_5O_4$: 499.14 m/z, found: 500.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.27 (s, 1H), 8.47 (d, J = 6.7 Hz, 1H), 8.14 (dd, J = 6.0, 2.9 Hz, 2H), 7.89 (d, J = 2.3 Hz, 1H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.44 (dd, J = 6.7, 2.4 Hz, 1H), 7.31 – 7.17 (m, 2H), 7.16 – 7.02 (m, 2H), 3.39 – 3.67 (m, 5H), 2.51 – 2.64 (m, 4H), 1.19 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.855. And (S)-2-chloro-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide (2.0 mg). MS (ESI): mass calcd. for $C_{24}H_{23}ClFN_5O_4$: 499.14 m/z, found: 500.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.27 (s, 1H), 8.47 (d, J = 6.7 Hz, 1H), 8.14 (dd, J = 6.0, 2.9 Hz, 2H), 7.89 (d, J = 2.3 Hz, 1H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.44 (dd, J = 6.7, 2.4 Hz, 1H), 7.31 – 7.17 (m, 2H), 7.16 – 7.02 (m, 2H), 3.39 – 3.67 (m, 5H), 2.51 – 2.64 (m, 4H), 1.19 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.859.

Example 47: (R)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((S)-3-methyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide and Example 48: (S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((S)-3-methyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide



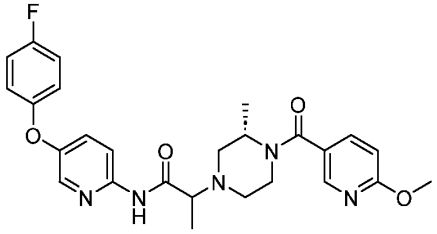
tert-butyl (2S)-4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2-methylpiperazine-1-carboxylate

To a solution of tert-butyl (S)-2-methylpiperazine-1-carboxylate (200 mg, 0.999 mmol, 1.0 equiv) in DMA (5 mL) was added TEA (303 mg, 2.997 mmol, 3.0 equiv) and 2-bromo-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (339 mg, 0.999 mmol, 1.0 equiv) at rt. The mixture was stirred for overnight at 60 °C. After cooled to room temperature, the reaction was quenched by water (15 mL) and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-80% PE/EA) to afford tert-butyl (2S)-4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2-methylpiperazine-1-carboxylate (180 mg, 39.31%) as a yellow solid. MS (ESI): mass calcd. for:$C_{24}H_{31}FN_4O_4$: 458.23 m/z, found: 459.20 $[M+H]^+$.



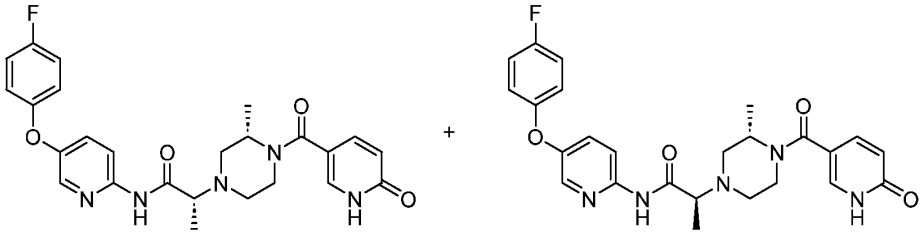
N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((S)-3-methylpiperazin-1-yl)propanamide

To a solution of tert-butyl (2S)-4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2-methylpiperazine-1-carboxylate (180 mg, 0.393 mmol, 1.0 equiv) in EA (3 mL) as added HCl (4M, in EA, 3 mL) at rt. The mixture was stirred for 3 h at rt. The reaction mixture was concentrated under vacuum to yield a crude product N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((S)-3-methylpiperazin-1-yl)propanamide (120 mg, 85.29%) as a yellow solid. MS (ESI): mass calcd. for: $C_{19}H_{23}FN_4O_2$: 358.11 m/z, found: 359.25 $[M+H]^+$.



N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((S)-4-(6-methoxynicotinoyl)-3-methylpiperazin-1-yl)propanamide

To a solution of N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((S)-3-methylpiperazin-1-yl)propanamide (150 mg, 0.419 mmol, 1.0 equiv) in DCM (5 mL) was added TEA (127 mg, 1.257 mmol, 3.0 equiv) and 6-methoxynicotinoyl chloride (107 mg, 0.628 mmol, 1.5 equiv) at rt. The mixture was stirred for 4 h at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20% DCM/MeOH) to afford N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((S)-4-(6-methoxynicotinoyl)-3-methylpiperazin-1-yl)propanamide (100 mg, 48.41%) as a yellow solid. MS (ESI): mass calcd. for: $C_{26}H_{28}FN_5O_4$: 493.23 m/z, found: 494.20 $[M+H]^+$.

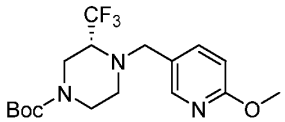


(R)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((S)-3-methyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide and (S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((S)-3-methyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

To a solution of N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((S)-4-(6-methoxynicotinoyl)-3-methylpiperazin-1-yl)propanamide (90 mg, 0.182 mmol, 1.0 equiv) in DMF (3 mL) was added LiCl (39 mg, 0.910 mmol, 5.0 equiv), TsOH (157 mg, 0.910 mmol, 5.0 equiv) at rt. The resulting mixture was stirred for overnight at 80 °C. After cooled to room temperature, the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20% DCM/MeOH) & C18 column to afford racemic product as a white solid. The racemic product was separated by Chiral-HPLC (column, CHIRALPAK IA 5*25 cm, 5 μm, Mobile Phase A: Hex: DCM=3: 1(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min) to afford (R)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((S)-3-methyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-propanamide (17.1 mg, 19.52%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{26}FN_5O_4$ 479.11 m/z, found 480.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 11.80 (s, 1H), 10.18 (s, 1H), 8.10 – 8.19 (m, 2H), 7.48 – 7.58 (m, 2H), 7.46 (dd, J = 9.4, 2.6 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.03 – 7.16 (m, 2H),

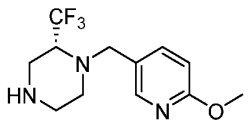
6.34 (d, *J* = 9.4 Hz, 1H), 4.34 (s, 1H), 3.84 (d, *J* = 13.2 Hz, 1H), 3.42 (q, *J* = 6.9 Hz, 1H), 3.24 (t, *J* = 12.4 Hz, 1H), 2.84 (d, *J* = 11.1 Hz, 1H), 2.72 (d, *J* = 11.3 Hz, 1H), 2.53 (s, 1H), 2.22 (t, *J* = 11.1 Hz, 1H), 1.31 (d, *J* = 6.7 Hz, 3H), 1.15 – 1.27 (m, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.867. And (S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((S)-3-methyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (25.0 mg, 28.51%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{26}FN_5O_4$ 479.11m/z, found 480.10 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.81 (s, 1H), 10.15 (s, 1H), 8.14 (dd, *J* = 6.0, 2.9 Hz, 2H), 7.48 – 7.58 (m, 2H), 7.47 (dd, *J* = 9.4, 2.6 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.03 – 7.16 (m, 2H), 6.34 (d, *J* = 9.4 Hz, 1H), 4.29 – 4.37 (m, 1H), 3.85 (d, *J* = 13.0 Hz, 1H), 3.54 (q, *J* = 6.7 Hz, 1H), 2.85 (d, *J* = 11.1 Hz, 1H), 2.58 (d, *J* = 11.4 Hz, 1H), 2.35 – 2.50 (m, 2H), 1.32 (d, *J* = 6.7 Hz, 3H), 1.16 (d, *J* = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.867.

Example 49: N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((R)-4-((6-oxo-1,6-dihydropyridin-3-yl)methyl)-3-(trifluoromethyl)piperazin-1-yl)propanamide



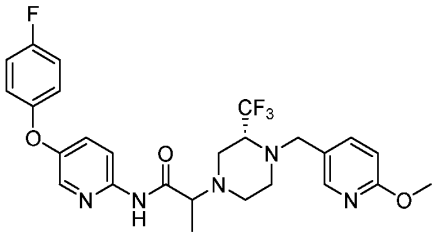
tert-butyl (R)-4-((6-methoxypyridin-3-yl)methyl)-3-(trifluoromethyl)piperazine-1-carboxylate

To a stirred solution of tert-butyl (R)-3-(trifluoromethyl)piperazine-1-carboxylate (100 mg, 0.393 mmol, 1.0 equiv) in DCM (3 mL) was added 6-methoxypyridine-3-carbaldehyde (108 mg, 0.786 mmol, 2.0 equiv) and HOAc (20 mg). The reaction was stirred for 0.5 h at rt. STAB (125 mg, 0.590 mmol, 1.5 equiv) was added into the solution. The reaction mixture was stirred at room temperature for a period of 5 h. After completion of reaction, the reaction mixture was quenched by addition of water (10 mL). The aqueous layer was extracted with DCM (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give crude product which was further purified by column chromatography (0-50% PE/EA) to afford desired compound tert-butyl (R)-4-((6-methoxypyridin-3-yl)methyl)-3-(trifluoromethyl)piperazine-1-carboxylate (30 mg, 20.32%) as colorless oil. MS (ESI): mass calcd. for: $C_{17}H_{24}F_3N_3O_3$: 375.18 m/z, found: 376.15 $[M+H]^+$.



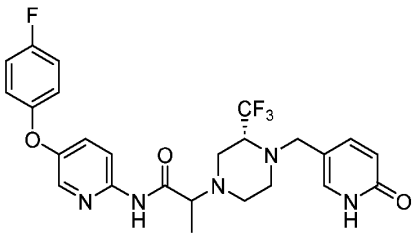
(R)-1-((6-methoxypyridin-3-yl)methyl)-2-(trifluoromethyl)piperazine

To a stirred solution of tert-butyl (R)-4-((6-methoxypyridin-3-yl)methyl)-3-(trifluoromethyl)piperazine-1-carboxylate (28 mg, 0.075 mmol, 1.0 equiv) in EA (1 mL) was added 4N HCl (10 in EA, 1 mL). The reaction mixture was stirred at room temperature for a period of 1 h. The resulting mixture was concentrated under reduced pressure to afford (R)-1-((6-methoxypyridin-3-yl)methyl)-2-(trifluoromethyl)piperazine (30 mg, crude) as a white solid. The crude product mixture was used in the next step directly without further purification. MS (ESI): mass calcd. for $C_{12}H_{16}F_3N_3O_3$: 275.12 m/z, found 276.10 $[M+H]^+$.



N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((R)-4-((6-methoxypyridin-3-yl)methyl)-3-(trifluoromethyl)piperazin-1-yl)propanamide

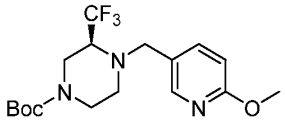
To a solution of (R)-1-((6-methoxypyridin-3-yl)methyl)-2-(trifluoromethyl)piperazine (28 mg, 0.102 mmol, 1.0 equiv) in DMA (1 mL) was added TEA (62 mg, 0.612 mmol, 6.0 equiv) and 2-bromo-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (41 mg, 0.122 mmol, 1.2 equiv) at rt. The resulting mixture was stirred for 3 hours at 50 °C. After cooled to room temperature, the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-80% PE/EA) to afford N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((R)-4-((6-methoxypyridin-3-yl)methyl)-3-(trifluoromethyl)piperazin-1-yl)propanamide (20 mg, 35.18%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{27}F_4N_5O_3$: 533.21 m/z, found 534.20 $[M+H]^+$.



N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((R)-4-((6-oxo-1,6-dihydropyridin-3-yl)methyl)-3-(trifluoromethyl)piperazin-1-yl)propanamide

To a stirred solution of N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((R)-4-((6-methoxypyridin-3-yl)methyl)-3-(trifluoromethyl)piperazin-1-yl)propanamide (20 mg, 0.036 mmol, 1.0 equiv) in DMF (1 mL) was added LiCl (8 mg, 0.180 mmol, 5.0 equiv) and PTSA (31 mg, 0.180 mmol, 5.0 equiv). The reaction mixture was stirred at 80 °C for a period of 5 h. After cooled to room temperature, the reaction was purified by Prep-HPLC using a Column: YMC Triart C18 ExRs Column, 20*250mm, 5μm(eluent: 43% to 73% CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((R)-4-((6-oxo-1,6-dihydropyridin-3-yl)methyl)-3-(trifluoromethyl)piperazin-1-yl)propanamide (3.1 mg, 15.48%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{25}F4N_5O_3$: 519.19 m/z, found 520.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 11.33 (s, 1H), 10.07 (d, J = 18.4 Hz, 1H), 8.10 – 8.18 (m, 2H), 7.43 – 7.57 (m, 1H), 7.39 (dd, J = 9.5, 2.3 Hz, 1H), 7.17 – 7.31 (m, 3H), 7.03 – 7.16 (m, 2H), 6.32 (d, J = 9.4 Hz, 1H), 3.36 – 3.68 (m, 5H), 2.78 – 3.02 (m, 2H), 2.53 – 2.73 (m, 2H), 2.32 (d, J = 18.5 Hz, 1H), 1.17 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -62.90, -63.24, -119.82, -119.88.

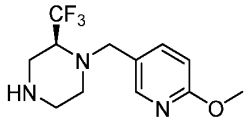
Example 50: N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((S)-4-((6-oxo-1,6-dihydropyridin-3-yl)methyl)-3-(trifluoromethyl)piperazin-1-yl)propanamide



tert-butyl (S)-4-((6-methoxypyridin-3-yl)methyl)-3-(trifluoromethyl)piperazine-1-carboxylate

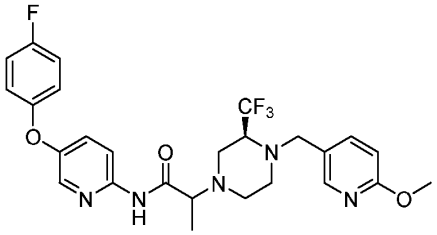
To a stirred solution of tert-butyl (S)-3-(trifluoromethyl)piperazine-1-carboxylate (100 mg, 0.393 mmol, 1.0 equiv) in DCM (3 mL) was added 6-methoxypyridine-3-carbaldehyde (108 mg, 0.786 mmol, 2.0 equiv) and HOAc (20 mg). The reaction was stirred for 0.5 h at rt. STAB (125 mg, 0.590 mmol, 1.5 equiv) was was added into the solution. The reaction mixture was stirred at room temperature for a period of 5 h. After completion of reaction, the reaction mixture was quenched by addition of water (10 mL). The aqueous layer was extracted with DCM (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give crude product which was further purified by column chromatography (0-50% PE/EA) to afford desired compound tert-butyl (S)-4-((6-methoxypyridin-3-yl)methyl)-3-

(trifluoromethyl)piperazine-1-carboxylate (30 mg, 20.32%) as colorless oil. MS (ESI): mass calcd. for: $C_{17}H_{24}F_3N_3O_3$: 375.18 m/z, found: 376.30 $[M+H]^+$.



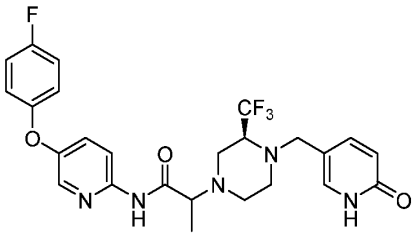
(S)-1-((6-methoxypyridin-3-yl)methyl)-2-(trifluoromethyl)piperazine

To a stirred solution of tert-butyl (S)-4-((6-methoxypyridin-3-yl)methyl)-3-(trifluoromethyl)piperazine-1-carboxylate (28 mg, 0.075 mmol, 1.0 equiv) in EA (1 mL) was added 4N HCl (10 in EA, 1 mL). The reaction mixture was stirred at room temperature for a period of 1 h. The resulting mixture was concentrated under reduced pressure to afford (S)-1-((6-methoxypyridin-3-yl)methyl)-2-(trifluoromethyl)piperazine (30 mg, crude) as a white solid. The crude product mixture was used in the next step directly without further purification. MS (ESI): mass calcd. for $C_{12}H_{16}F_3N_3O_3$: 275.12 m/z, found 276.10 $[M+H]^+$.



N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((S)-4-((6-methoxypyridin-3-yl)methyl)-3-(trifluoromethyl)piperazin-1-yl)propanamide

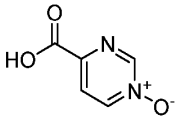
To a solution of (S)-1-((6-methoxypyridin-3-yl)methyl)-2-(trifluoromethyl)piperazine (28 mg, 0.102 mmol, 1.0 equiv) in DMA (1 mL) was added TEA (61 mg, 0.612 mmol, 6.0 equiv) and 2-bromo-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (41 mg, 0.122 mmol, 1.2 equiv) at rt. The resulting mixture was stirred for 3 hours at 50 °C. After the reaction cooled to room temperature, which was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((S)-4-((6-methoxypyridin-3-yl)methyl)-3-(trifluoromethyl)piperazin-1-yl)propanamide (20 mg, 35.18%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{27}F_4N_5O_3$: 533.21 m/z, found 534.20 $[M+H]^+$.



N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((S)-4-((6-oxo-1,6-dihydropyridin-3-yl)methyl)-3-(trifluoromethyl)piperazin-1-yl)propanamide

To a stirred solution of N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((S)-4-((6-methoxypyridin-3-yl)methyl)-3-(trifluoromethyl)piperazin-1-yl)propanamide (20 mg, 0.036 mmol, 1.0 equiv) in anhydrous DMF (1 mL) was added LiCl (8 mg, 0.180 mmol, 5 equiv) and PTSA (31 mg, 0.180 mmol, 5 equiv). The reaction mixture was stirred at 80 °C for a period of 5 h. After the reaction cooled to room temperature, the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) and Prep-HPLC using a Column: XBridge Prep Phenyl OBD C18 Column, 19*250 mm, 5μm(eluent: 50% to 80% CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((S)-4-((6-oxo-1,6-dihydropyridin-3-yl)methyl)-3-(trifluoromethyl)piperazin-1-yl)propanamide (3.1 mg, 15.25%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{25}F4N_5O_3$: 519.19 m/z, found 520.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 11.43 (s, 1H), 10.07 (d, J = 18.4 Hz, 1H), 8.11 – 8.18 (m, 2H), 7.43 – 7.57 (m, 1H), 7.39 (dd, J = 9.5, 2.3 Hz, 1H), 7.18 – 7.29 (m, 3H), 7.03 – 7.14 (m, 2H), 6.32 (d, J = 9.4 Hz, 1H), 3.36 – 3.68 (m, 4H), 2.77 – 3.01 (m, 2H), 2.52 – 2.71 (m, 2H), 2.32 (d, J = 18.5 Hz, 1H), 1.17 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -62.90, -63.24, -119.82, -119.88.

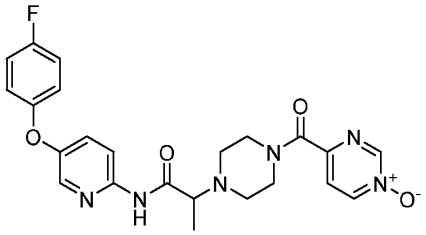
Example 51: 4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyrimidine 1-oxide



4-carboxypyrimidine 1-oxide

To a solution of pyrimidine-4-carboxylic acid (500 mg, 4.029 mmol, 1.0 equiv) in DCM (3 mL) was added m-CPBA (2.1 g, 12.087 mmol, 3.0 equiv) at 0 °C. The resulting mixture was stirred for 3 h at rt. The combined organic extracts were concentrated under

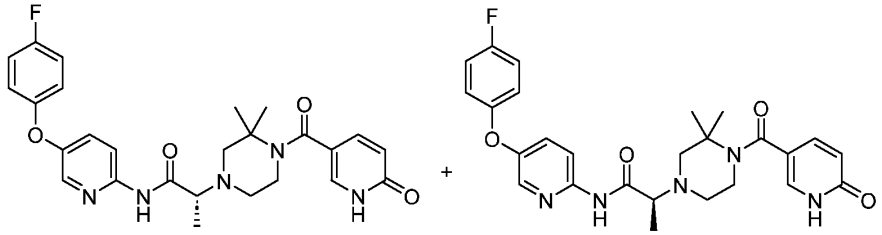
vacuum and purified by C18 column to afford 4-carboxypyrimidine 1-oxide as a white solid. MS (ESI): mass calcd. for $C_5H_4N_2O_3$ 140.09 m/z, found 141.10 $[M+H]^+$.



4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyrimidine 1-oxide

To a solution of 4-carboxypyrimidine 1-oxide (100 mg, 0.714 mmol, 1.0 equiv) in Py (3 mL) was added N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(piperazin-1-yl)propanamide (246 mg, 0.714 mmol, 1.0 equiv) and EDCI (410 mg, 2.142 mmol, 3.0 equiv) at rt. The resulting mixture was stirred for 3 h at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield a crude product which was directly purified by C18 column to afford 4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyrimidine 1-oxide (52 mg, 15.6%) as a white solid. MS (ESI): mass calcd. for $C_{23}H_{23}FN_6O_4$: 466.473 m/z, found: 467.05 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 12.62 (s, 1H), 10.28 (s, 1H), 8.22 (d, J = 1.1 Hz, 1H), 8.09 – 8.18 (m, 2H), 7.48 – 7.55 (m, 1H), 7.17 – 7.31 (m, 2H), 7.03 – 7.13 (m, 2H), 6.36 (d, J = 1.1 Hz, 1H), 3.49 – 3.63 (m, 3H), 3.27 – 3.41 (m, 2H), 2.52 – 2.64 (m, 4H), 1.19 (d, J = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.874.

Example 52: (R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide and Example 53: (S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

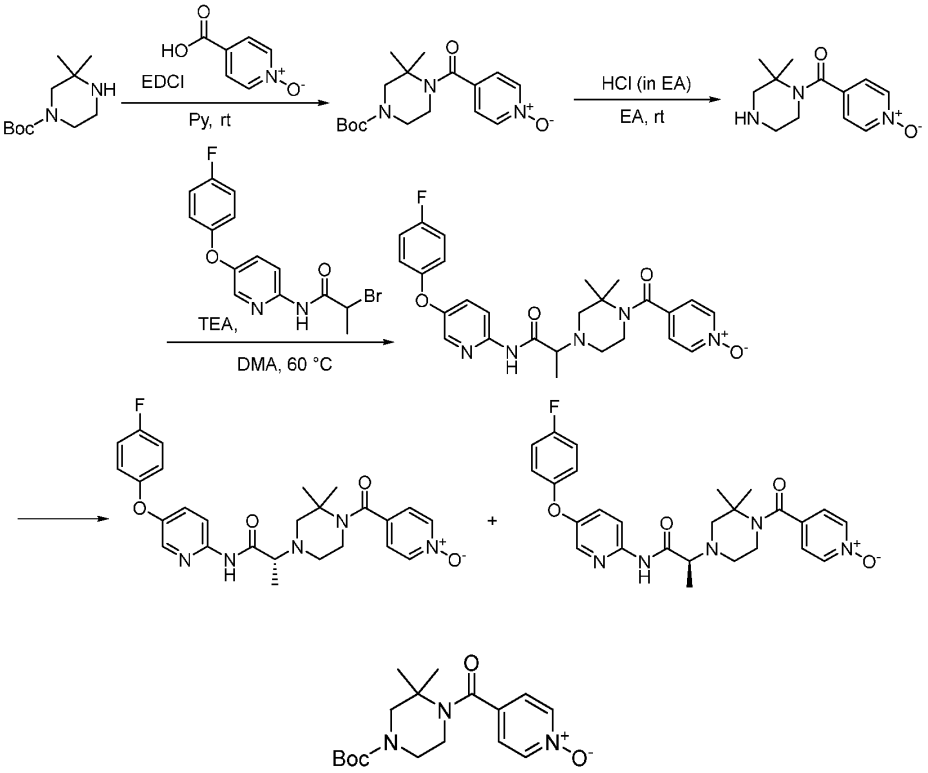


(R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide and (S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide was separated by Chiral-HPLC (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: (HEX: DCM=3: 1)(0.5% 2M NH_3-MeOH), Mobile Phase B: IPA; Flow rate: 18 mL/min; Gradient: isocratic 50; Wave Length: 220/254 nm) to afford (R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (21.1 mg) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{28}FN_5O_4$: 493.21 found: 494.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 11.84 (s, 1H), 10.18 (s, 1H), 8.11 – 8.20 (m, 2H), 7.40 – 7.60 (m, 3H), 7.17 – 7.31 (m, 2H), 7.03 – 7.16 (m, 2H), 6.32 (d, J = 9.5 Hz, 1H), 3.49 (q, J = 6.8 Hz, 1H), 3.34 – 3.40 （m,2H), 2.68 – 2.79 (m, 1H), 2.57 – 2.67 (m, 1H), 2.41 (s, 2H), 1.41 (d, J = 2.0 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.82. And (S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (77.3 mg) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{28}FN_5O_4$: 493.21 found: 494.05 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 11.84 (s, 1H), 10.18 (s, 1H), 8.11 – 8.20 (m, 2H), 7.40 – 7.60 (m, 3H), 7.17 – 7.31 (m, 2H), 7.03 – 7.16 (m, 2H), 6.32 (d, J = 9.5 Hz, 1H), 3.49 (q, J = 6.8 Hz, 1H), 3.34 – 3.40 （m, 2H), 2.68 – 2.79 (m, 1H), 2.57 – 2.67 (m, 1H), 2.41 (s, 2H), 1.41 (d, J = 2.0 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.82.

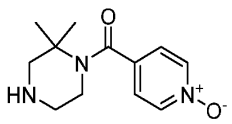
Example 54: (R)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide and Example 55: (S)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

Synthetic Scheme



4-(4-(tert-butoxycarbonyl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

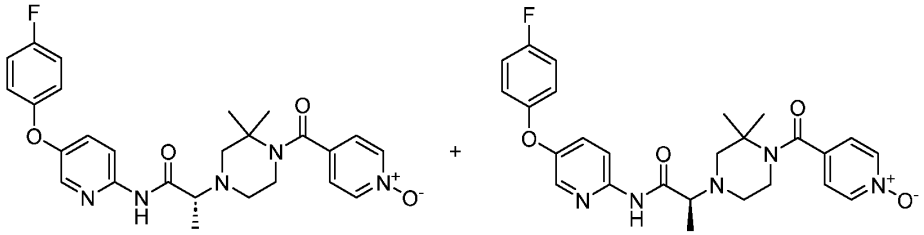
To a solution of tert-butyl 3,3-dimethylpiperazine-1-carboxylate (800 mg, 3.733 mmol, 1.0 equiv) in Py (10 mL) was added 4-carboxypyridine 1-oxide (519 mg, 3.733 mmol, 1.0 equiv) and EDCI (1.4 g, 7.466 mmol, 2.0 equiv) at rt. The resulting mixture was stirred for 3 h at rt. The reaction mixture was quenched by water and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% PE/EA) to afford 4-(4-(tert-butoxycarbonyl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (814 mg, 65.12%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{25}N_3O_4$: 355.18 m/z, found: 336.15 $[M+H]^+$.



4-(2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

To a solution of 4-(4-(tert-butoxycarbonyl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (670 mg, 1.998 mmol, 1.0 equiv) in EA (10 mL), was added 4N

HCl (in EA, 10 mL). The resulting mixture was stirred for 2 h at rt. The product was precipitated by the addition of anhydrous ether. The precipitated solids were collected by filtration to afford 4-(2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (0.4 g, 85.32%) as a white solid. MS (ESI): mass calcd. for $C_{12}H_{17}N_3O_2$: 235.13 m/z, found: 236.25 $[M+H]^+$.

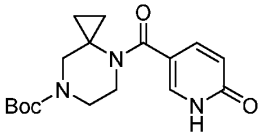


(R)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide and (S)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

To a solution of 4-(2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (150 mg, 0.638 mmol, 1.0 equiv) in DMF (3 mL) was added 2-bromo-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (216 mg, 0.638mmol, 1.0 equiv) and TEA (193 mg, 1.914 mmol, 3.0 equiv) at rt. The resulting mixture was stirred for 3 h at 60 °C. After cooled to room temperature, the reaction mixture was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield a crude product which was purified by silica gel chromatography (0-100% PE/EA) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 29% to 59% (v/v) CH_3CN and H_2O, 10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford 4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide as a white solid. The product was separated by Chiral-Prep-HPLC (Mobile Phase A: Hex: DCM=3: 1(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 15 mL/min; Gradient: isocratic 50; Wave Length: 220/254 nm) to afford (R)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (15.8 mg, first peak) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{28}FN_5O_4$: 493.53 m/z, found: 494.05 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H), 8.19 – 8.26 (m, 2H), 8.12 – 8.19 (m, 2H), 7.53 (dd, J = 9.0, 3.1 Hz, 1H), 7.40 – 7.47 (m, 2H), 7.19 – 7.30 (m, 2H), 7.05 – 7.14 (m, 2H), 3.51 (q, J = 6.9 Hz, 1H), 2.67 – 2.76 (m, 1H), 2.57 – 2.65 (m, 1H), 2.41 – 2.49 (m, 4H), 1.46 (d, J = 3.8 Hz, 6H), 1.18 – 1.26 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -

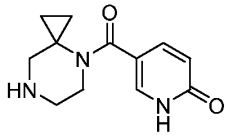
119.826. And (S)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (25.5 mg, second peak) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{28}FN_5O_4$: 493.53 m/z, found: 494.05 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H), 8.19 – 8.26 (m, 2H), 8.12 – 8.19 (m, 2H), 7.53 (dd, J = 9.0, 3.1 Hz, 1H), 7.40 – 7.47 (m, 2H), 7.19 – 7.30 (m, 2H), 7.05 – 7.14 (m, 2H), 3.51 (q, J = 6.9 Hz, 1H), 2.67 – 2.76 (m, 1H), 2.57 – 2.65 (m, 1H), 2.41 – 2.49 (m, 4H), 1.46 (d, J = 3.8 Hz, 6H), 1.18 – 1.26 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -119.826.

Example 56: (R)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)-4,7-diazaspiro[2.5]octan-7-yl)propanamide and Example 57: (S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)-4,7-diazaspiro[2.5]octan-7-yl)propanamide



tert-butyl 4-(6-oxo-1H-pyridine-3-carbonyl)-4,7-diazaspiro[2.5]octane-7-carboxylate

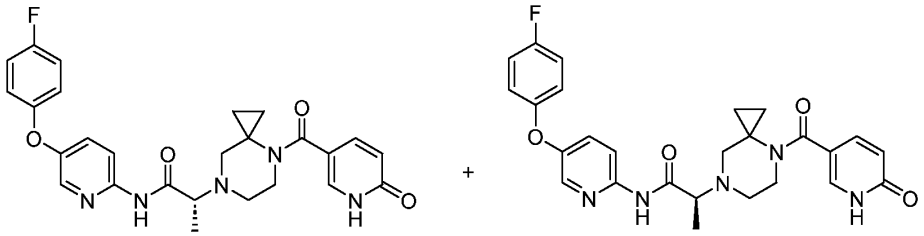
To a solution of tert-butyl 4,7-diazaspiro[2.5]octane-7-carboxylate (1.0 g, 4.710 mmol, 1.0 equiv) in Py (10 mL) was added 6-oxo-1,6-dihydropyridine-3-carboxylic acid (0.66 g, 4.710 mmol, 1.0 equiv) and EDCI (1.35 g, 7.065 mmol, 1.5 equiv). The mixture was stirred at room temperature for 2 h. The reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford tert-butyl 4-(6-oxo-1,6-dihydropyridine-3-carbonyl)-4,7-diazaspiro[2.5]octane-7-carboxylate (1.1 g, 68.78%) as a yellow oil. MS (ESI): mass calcd. for $C_{17}H_{23}N_3O_4$: 333.16 m/z, found: 334.10 $[M+H]^+$.



5-(4,7-diazaspiro[2.5]octane-4-carbonyl)pyridin-2(1H)-one

To a solution of tert-butyl 4-(6-oxo-1H-pyridine-3-carbonyl)-4,7-diazaspiro[2.5]octane-7-carboxylate (500 mg, 1.500 mmol, 1.0 equiv) in DCM (6 mL) was added TFA (2 mL). The mixture was stirred at room temperature for 2 h. The mixture was concentrated to dryness under reduced pressure to afford 5-(4,7-diazaspiro[2.5]octane-4-

carbonyl)pyridin-2(1H)-one (275 mg, 78.71%) as a yellow solid. (MS (ESI): mass calcd. for $C_{12}H_{15}N_3O_2$: 233.11 m/z, found: 234.25 $[M+H]^+$.

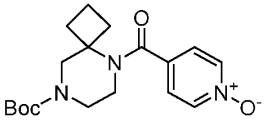


(R)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)-4,7-diazaspiro[2.5]octan-7-yl)propanamide and (S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)-4,7-diazaspiro[2.5]octan-7-yl)propanamide

To a solution of 5-(4,7-diazaspiro[2.5]octane-4-carbonyl)pyridin-2(1H)-one (100 mg, 0.429 mmol, 1.0 equiv) in DMF (5 mL) the mixture was added 2-bromo-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (145 mg, 0.429 mmol, 1.0 equiv) and TEA (130 mg, 1.287 mmol, 3.0 equiv). The mixture was stirred for 3 h at 60 °C. After cooled to room temperature, the reaction was quenched by water (20 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) to afford N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)-4,7-diazaspiro[2.5]octan-7-yl)propanamide as a white solid. The product was separated by Chiral-HPLC (CHIRALPAKIE3; Mobile Phase A: (Hex: DCM=3: 1)(0.1%DEA): EtOH=50: 50; Flow rate: 1mL/min; Gradient: isocratic ; Injection Volume: 3L mL) to afford (R)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)-4,7-diazaspiro[2.5]octan-7-yl)propanamide (8.3 mg, 3.91%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{26}FN_5O_4$: 491.20 m/z, found: 492.05 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.78 (s, 1H), 10.21 (s, 1H), 8.10 – 8.18 (m, 2H), 7.60 (d, J = 2.6 Hz, 1H), 7.52 (ddd, J = 9.6, 6.5, 2.8 Hz, 2H), 7.18 – 7.29 (m, 2H), 7.04 – 7.14 (m, 2H), 6.33 (d, J = 9.5 Hz, 1H), 3.50 – 3.92 (m, 2H), 3.45 (d, J = 6.8 Hz, 1H), 2.56 – 2.69 (m, 4H), 1.18 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 17.9 Hz, 4H). And (S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)-4,7-diazaspiro[2.5]octan-7-yl)propanamide (13.1 mg, 6.19%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{26}FN_5O_4$: 491.20 m/z, found: 492.05 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.78 (s, 1H), 10.21 (s, 1H), 8.10 – 8.18 (m, 2H), 7.60 (d, J = 2.6 Hz, 1H), 7.52 (ddd, J = 9.6,

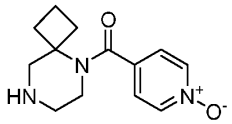
6.5, 2.8 Hz, 2H), 7.18 – 7.29 (m, 2H), 7.04 – 7.14 (m, 2H), 6.33 (d, *J* = 9.5 Hz, 1H), 3.50 – 3.92 (m, 2H), 3.45 (d, *J* = 6.8 Hz, 1H), 2.56 – 2.69 (m, 4H), 1.18 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 17.9 Hz, 4H).

Example 58: (R)-4-(8-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-5,8-diazaspiro[3.5]nonane-5-carbonyl)pyridine 1-oxide and Example 59: (S)-4-(8-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-5,8-diazaspiro[3.5]nonane-5-carbonyl)pyridine 1-oxide



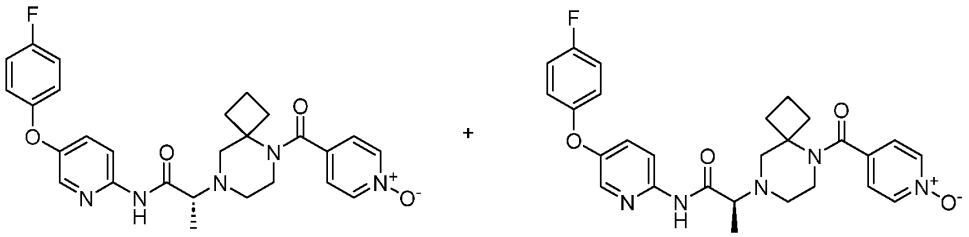
4-(8-(tert-butoxycarbonyl)-5,8-diazaspiro[3.5]nonane-5-carbonyl)pyridine 1-oxide

To a solution of tert-butyl 5,8-diazaspiro[3.5]nonane-8-carboxylate (300 mg, 1.326 mmol, 1.0 equiv) in Pyridine (6 mL) was added isonicotinic acid N-oxide (184 mg, 1.326 mmol, 1 equiv), EDCI (381 mg, 1.989 mmol, 1.5 equiv) at rt, the mixture was stirred for 5 h at rt. The reaction was quenched by water (30 mL) and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to afford a crude product which was directly purified by flash chromatography (0-80% PE/EA) to afford 4-(8-(tert-butoxycarbonyl)-5,8-diazaspiro[3.5]nonane-5-carbonyl)pyridine 1-oxide (300 mg, 65.14%) as a yellow solid. MS (ESI): mass calcd. for: $C_{18}H_{25}N_3O_4$: 347.23 m/z, found: 348.20 $[M+H]^+$.



4-(5,8-diazaspiro[3.5]nonane-5-carbonyl)pyridine 1-oxide

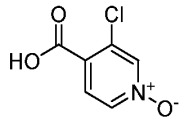
To a solution of 4-(8-(tert-butoxycarbonyl)-5,8-diazaspiro[3.5]nonane-5-carbonyl)pyridine 1-oxide (150 mg, 0.432 mmol, 1.0 equiv) in EA (3 mL) was added HCl (4 M, in EA, 3 mL) at rt, the mixture was stirred for 2 h at rt . The mixture was concentrated under vacuum to afford 4-(5,8-diazaspiro[3.5]nonane-5-carbonyl)pyridine 1-oxide (100 mg, 93.66%) as a yellow solid. MS (ESI): mass calcd. for: $C_{13}H_{17}N_3O_2$: 247.11 m/z, found: 248.25 $[M+H]^+$.



(R)-4-(8-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-5,8-diazaspiro[3.5]nonane-5-carbonyl)pyridine 1-oxide and (S)-4-(8-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-5,8-diazaspiro[3.5]nonane-5-carbonyl)pyridine 1-oxide

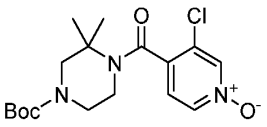
To a solution of 4-(5,8-diazaspiro[3.5]nonane-5-carbonyl)pyridine 1-oxide (100 mg, 0.404 mmol, 1.0 equiv) in DMA (5 mL) was added 2-bromo-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (137 mg, 0.404 mmol, 1.0 equiv), TEA (122 mg, 1.212 mmol, 3.0 equiv) at rt. The resulting mixture was stirred for 3 h at 60 °C. After cooled to room temperature, the reaction was quenched by water (20 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue obtained was purified by silica gel chromatography (0-25% DCM/MeOH) and separated by Chiral-HPLC (Column: CHIRAL Amylose-SA, 4.6*150 mml. D.S-5um; Mobile Phase A: Hex: DCM=3: 1 (0.5% 2M NH3-MeOH)-HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 17 mL/min; Gradient: isocratic 50; Wave Length: 220/254 nm) to afford (R)-4-(8-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-5,8-diazaspiro[3.5]nonane-5-carbonyl)pyridine 1-oxide (15.4 mg, 7.51%, first peak) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{28}FN_5O_4$: 505.11 m/z, found 506.05 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.20 – 8.27 (m, 2H), 8.10 – 8.17 (m, 2H), , 7.18 – 7.29 (m, 2H), 7.09 (ddd, J = 6.7, 5.4, 3.0 Hz, 2H), 3.51 (q, J = 6.9 Hz, 1H), 2.75 (s, 2H), 2.35 – 2.47 (m, 4H), 2.14 – 2.28 (m, 4H), 1.59 – 1.69 (m, 2H), 1.18 (d, J = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.837. And (S)-4-(8-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-5,8-diazaspiro[3.5]nonane-5-carbonyl)pyridine 1-oxide (18.8 mg, 9.17%, second peak) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{23}F_4N_5O_4$: 505.11 m/z, found 506.05 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 10.25 (s, 1H), 8.20 – 8.27 (m, 2H), 8.10 – 8.17 (m, 2H), 7.44 – 7.52 (m, 3H), 7.18 – 7.29 (m, 2H), 7.04 – 7.14 (m, 2H), 3.51 (q, J = 6.9 Hz, 1H), 2.75 (s, 2H), 2.35 – 2.47 (m, 4H), 2.14 – 2.28 (m, 4H), 1.59 – 1.69 (m, 2H), 1.18 (d, J = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.902.

Example 60: (S)-3-chloro-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide and Example 61: (R)-3-chloro-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide



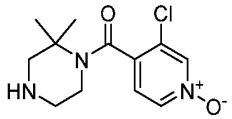
4-carboxy-3-chloropyridine 1-oxide

To a solution of 3-chloroisonicotinic acid (300 mg, 1.904 mmol, 1.0 equiv) in HOAc (5 mL) was added 30% H_2O_2 (1 mL) at 0 °C. The resulting mixture was stirred for 4 h at 80 °C. After cooled to room temperature, the mixture was purified by C18 column to afford 4-carboxy-3-chloropyridine 1-oxide (0.3 g, 91.0%) as a white solid. MS (ESI): mass calcd. for $C_6H_4ClNO_3$: 172.99 m/z, found: 174.05 $[M+H]^+$.



4-(4-(tert-butoxycarbonyl)-2,2-dimethylpiperazine-1-carbonyl)-3-chloropyridine 1-oxide

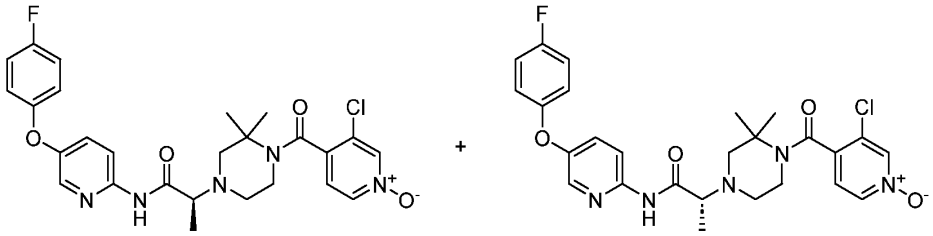
To a solution of 4-carboxy-3-chloropyridine 1-oxide (300 mg, 1.729 mmol, 1.0 equiv) in Py (10 mL) was added tert-butyl 3,3-dimethylpiperazine-1-carboxylate (370 mg, 1.729 mmol, 1.0 equiv), HATU (986 mg, 2.594 mmol, 1.5 equiv) and DIEA (335 mg, 2.594 mmol, 1.5 equiv) at rt. The resulting mixture was stirred for 3 h at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% PE/EA) to afford 4-(4-(tert-butoxycarbonyl)-2,2-dimethylpiperazine-1-carbonyl)-3-chloropyridine 1-oxide (439 mg, 68.70%) as a white solid. MS (ESI): mass calcd. for: $C_{17}H_{24}ClN_3O_4$: 369.15 m/z, found: 370.10 $[M+H]^+$.



3-chloro-4-(2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

To a solution of 4-(4-(tert-butoxycarbonyl)-2,2-dimethylpiperazine-1-carbonyl)-3-chloropyridine 1-oxide (400 mg, 1.08 mmol, 1.0 equiv) in EA (5 mL) was added 4N HCl (in

EA, 5 mL) at 0 °C. The resulting mixture was stirred for 3 h at rt. The product was precipitated by the addition of anhydrous ether. The precipitated solids were collected by filtration to afford 3-chloro-4-(2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (233 mg, 80.0%) as a white solid. MS (ESI): mass calcd. for: $C_{12}H_{16}ClN_3O$ 269.09 m/z, found: 270.10 $[M+H]^+$.



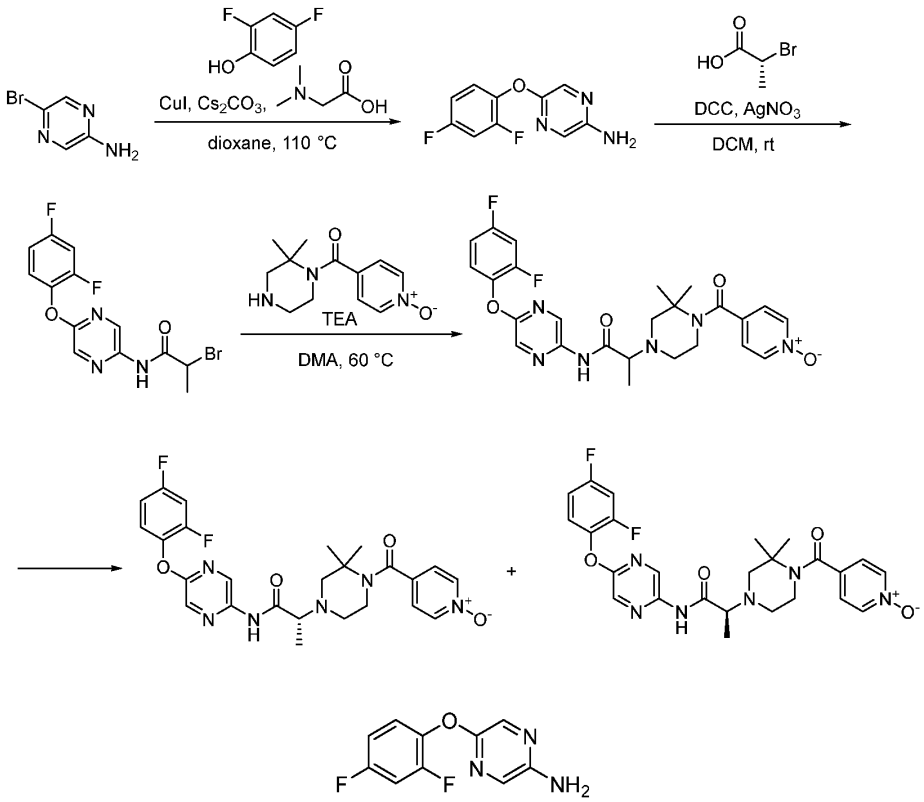
(S)-3-chloro-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide and (R)-3-chloro-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

To a solution of 3-chloro-4-(2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (100 mg, 0.371 mmol, 1 equiv) in DMA (3 mL) was added 2-bromo-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (126 mg, 0.371 mmol, 1.0 equiv) and TEA (112 mg, 1.113 mmol, 3.0 equiv) at rt. The resulting mixture was stirred for 3 h at 50 °C. After cooled to room temperature, the reaction mixture was quenched by water (10 mL) and extracted with 5:1 DCM/MeOH (20 mL x 3). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by C18 column to afford 3-chloro-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide as a white solid. The product was separated by Chiral-HPLC (Column: SA 2cm MTBE(0.5% 2M NH3-MeOH): ETOH=70: 30; Mobile Phase A: CHIRALPAK SA 2*25 cm, 5 μm, Mobile Phase B: EtOH--HPLC; Flow rate: MTBE(0.5% 2M NH3-MeOH)--HPLC mL/min; Gradient: isocratic 20; Wave Length: 70 nm) to afford (S)-3-chloro-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (9.9 mg) as a white solid. MS (ESI): mass calcd. for: $C_{26}H_{27}ClFN_5O_4$: 527.98 m/z, found: 528.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.57 (d, J = 1.7 Hz, 1H), 8.23 (dd, J = 6.7, 1.7 Hz, 1H), 8.09 – 8.18 (m, 2H), 7.52 (dd, J = 9.1, 3.0 Hz, 1H), 7.42 (d, J = 6.7 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.03 – 7.16 (m, 2H), 3.50 (q, J = 6.8 Hz, 1H), 3.22 – 3.31 (m, 2H), 2.60 – 2.70 (m, 2H), 2.42 – 2.48 (m, 2H), 1.43 – 1.55 (m, 6H), 1.14 – 1.27 (m, 3H). And (R)-3-chloro-4-(4-(1-((5-(4-

fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (3.7 mg) as a white solid. MS (ESI): mass calcd. for: $C_{26}H_{27}ClFN_5O_4$: 527.98 m/z, found: 528.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.57 (d, J = 1.7 Hz, 1H), 8.23 (dd, J = 6.7, 1.7 Hz, 1H), 8.09 – 8.18 (m, 2H), 7.52 (dd, J = 9.1, 3.0 Hz, 1H), 7.42 (d, J = 6.7 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.03 – 7.16 (m, 2H), 3.50 (q, J = 6.8 Hz, 1H), 3.22 – 3.31 (m, 2H), 2.60 – 2.70 (m, 2H), 2.42 – 2.48 (m, 2H), 1.43 – 1.55 (m, 6H), 1.14 – 1.27 (m, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.83.

Example 62: (R)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide and Example 63: (S)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

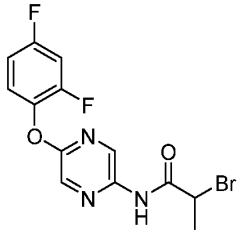
Synthetic Scheme



5-(2,4-difluorophenoxy)pyrazin-2-amine

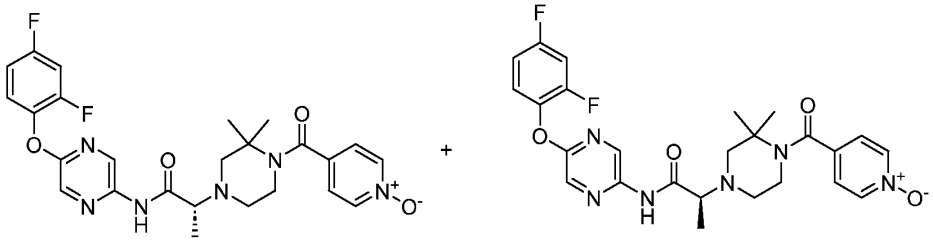
To a solution of 5-bromopyrazin-2-amine (3 g, 17.241 mmol, 1.0 equiv) in dioxane (30 mL) was added 2,4-difluorophenol (2.24 g, 17.241 mmol, 1.0 equiv), dimethylglycine (0.71 g,

6.896 mmol, 0.4 equiv), CuI (0.66 g, 3.448 mmol, 0.2 equiv) and Cs_2CO_3 (11.24 g, 34.482 mmol, 2.0 equiv) at room temperature. The mixture was stirred at 110 °C for overnight under N_2. After cooled to room temperature, the reaction mixture was quenched by addition of water (50 mL). The aqueous layer was extracted with ethyl acetate (100 mL x 3). The combined organic phase was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-60% PE/EA) to afford 5-(2,4-difluorophenoxy)pyrazin-2-amine (2 g, 51.98%) as a yellow solid. MS (ESI): mass calcd for $C_{10}H_7F_2N_3O$: 223.183 m/z, found: 224.10 $[M+H]^+$.



2-bromo-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

To a solution of 5-(2,4-difluorophenoxy)pyrazin-2-amine (1 g, 4.481 mmol, 1.0 equiv) in DCM (10 mL) was added 2-bromopropanoic acid (0.82 g, 5.377 mmol, 1.2 equiv), DCC (1.11 g, 5.377 mmol, 1.2 equiv) and $AgNO_3$ (0.08 g, 0.448 mmol, 0.1 equiv) at room temperature. The mixture was stirred at room temperature for 3 h. After completion of reaction, the reaction mixture was quenched by addition of water (20 mL). The aqueous layer was extracted with ethyl acetate (50 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-60% PE/EA) to afford 2-bromo-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (800 mg, 49.85%) as a yellow solid. MS (ESI): mass calcd for $C_{13}H_{10}BrF_2N_3O_2$: 356.99 m/z, found: 357.95 $[M+H]^+$.

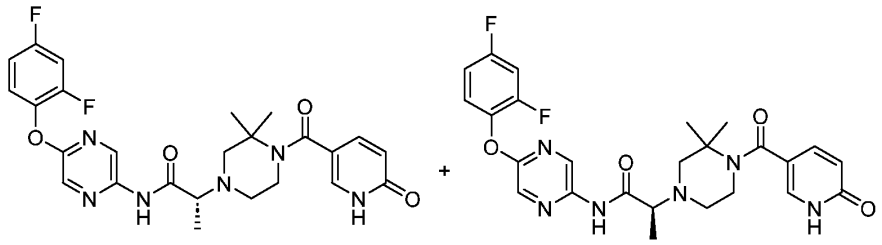


(R)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide and (S)-4-(4-(1-((5-(2,4-

difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

To a solution of 2-bromo-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (200 mg, 0.558 mmol, 1.0 equiv) in DMA (5 mL) was added 4-(2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (131 mg, 0.558 mmol, 1.0 equiv) and TEA (169 mg, 1.67 mmol, 3.0 equiv) at rt. The resulting mixture was stirred for 3 h at 60 °C. After cooled to room temperature, the reaction mixture was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by C18 column to afford 4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide as a white solid. The compound was separated by preparative Chiral-HPLC (Column: CHIRALPAK IK, 4.6*150mm, 5μm; Mobile Phase A: Hex: DCM=3: 1(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 18 mL/min; Gradient: isocratic 50; Wave Length: 220/254 nm; RT1(min): 23.918; RT2(min): 33.652; Sample Solvent: EtOH--HPLC) to afford (R)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (22.2 mg) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{26}F_2N_6O_4$: 512.518 m/z, found: 513.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.44 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.17 – 8.27 (m, 2H), 7.38 – 7.56 (m, 4H), 7.11 – 7.24 (m, 1H), 3.54 (q, J = 6.8 Hz, 1H), 3.27 – 3.34 (m, 2H), 2.67 – 2.75 (m, 1H), 2.57 – 2.66 (m, 1H), 2.37 – 3.48 (m, 2H), 1.45 (d, J = 3.0 Hz, 6H), 1.16 – 1.26 (m, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.42, -124.21. And (S)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (42.3 mg) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{26}F_2N_6O_4$: 512.518 m/z, found: 513.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.44 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.17 – 8.27 (m, 2H), 7.38 – 7.56 (m, 4H), 7.11 – 7.24 (m, 1H), 3.54 (q, J = 6.8 Hz, 1H), 3.27 – 3.34 (m, 2H), 2.67 – 2.75 (m, 1H), 2.57 – 2.66 (m, 1H), 2.37 – 3.48 (m, 2H), 1.45 (d, J = 3.0 Hz, 6H), 1.16 – 1.26 (m, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.42, -124.21.

Example 64: (R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide and Example 65: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide



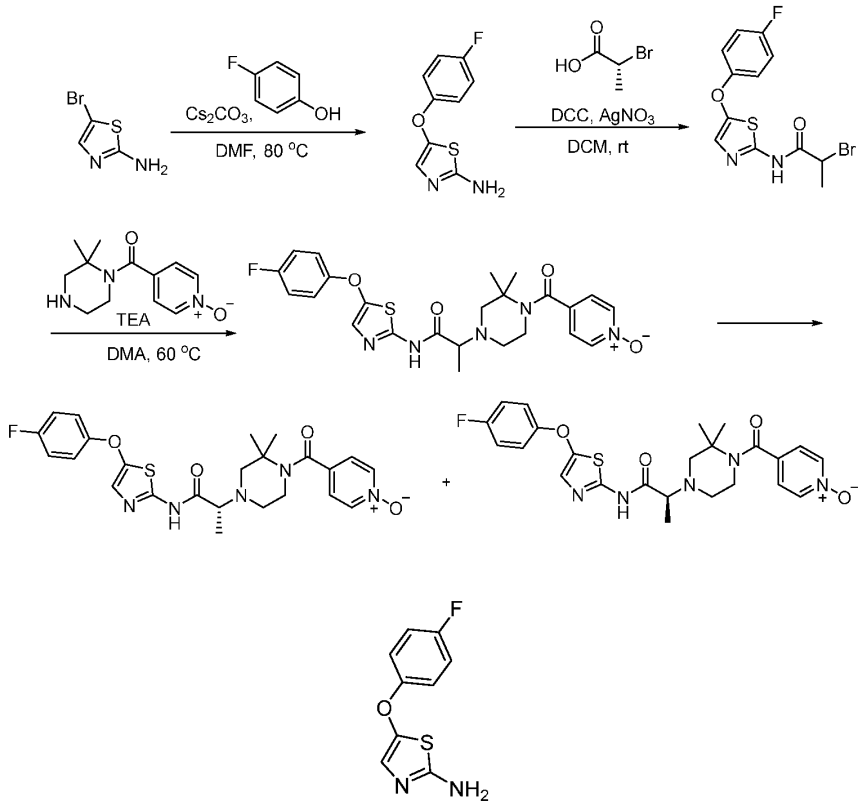
(R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide and (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

To a solution of 2-bromo-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (100 mg, 0.279 mmol, 1.0 equiv) in DMA was added 5-(2,2-dimethylpiperazine-1-carbonyl)pyridin-2(1H)-one (65 mg, 0.279 mmol, 1.0 equiv) and TEA (113 mg, 1.116 mmol, 4.0 equiv) at room temperature. The reaction mixture was stirred for 3 h at 50 °C. After completion of reaction, the reaction mixture was quenched by addition of water (5 mL). The aqueous layer was extracted with ethyl acetate (20 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and Prep-HPLC using a Column: Kinetex EVO C18 Column, 21.2*250 mm, 5μm (eluent: 34% to 64% (v/v) CH_3CN and H_2O, NH_4HCO_3+0.1%$NH_3.H_2O$) to afford N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide as a white solid. The product was separated by Chiral-Prep-HPLC (CHIRALPAK IF 2*25 cm, 5 μm; Mobile Phase A: MtBE (0.1%DEA)-HPLC, Mobile Phase B: EtOH-HPLC; Flow rate: 15 mL/min; Gradient: isocratic 50; Wave Length: 220/254 nm) to afford (R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (5.6 mg). MS (ESI): mass calcd. for $C_{25}H_{26}F_2N_6O$: 512.20 m/z, found: 513.20 $[M+H]^+$, ^1H NMR (300 MHz, DMSO-d_6) δ 11.81 (s, 1H), 10.40 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.56 (d, J = 2.5 Hz, 1H), 7.39 – 7.54 (m, 3H), 7.17 (tdd, J = 9.1, 3.0, 1.6 Hz, 1H), 6.32 (d, J = 9.4 Hz, 1H), 3.52 (t, J = 6.9 Hz, 1H),3.33 – 3.40 (m,2H), 2.67 – 2.78(m,1H), 2.58 – 2.67 (m, 1H), 2.40 (d, J = 2.1 Hz, 2H), 1.40 (d, J = 2.8 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.44, -124.22. And (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (9.9 mg). MS (ESI): mass calcd. for $C_{25}H_{26}F_2N_6O$: 512.20 m/z, found: 513.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 11.82 (s,

1H), 10.40 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.56 (d, J = 2.6 Hz, 1H), 7.39 – 7.54(m, 3H), 7.11 – 7.24 (m, 1H), 6.32 (d, J = 9.4 Hz, 1H), 3.52 (t, J = 6.9 Hz, 1H), 3.34 – 3.38 (m, 2H), 2.68 – 2.78 (m, 1H), 2.58 – 2.68 (m, 1H), 2.33 – 2.48 (m, 2H), 1.40 (d, J = 2.7 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.43, -124.22.

Example 66: (R)-4-(4-(1-((5-(4-fluorophenoxy)thiazol-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide and Example 67: (S)-4-(4-(1-((5-(4-fluorophenoxy)thiazol-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

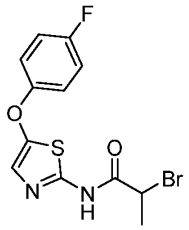
Synthetic Scheme



5-(4-fluorophenoxy)-1,3-thiazol-2-amine

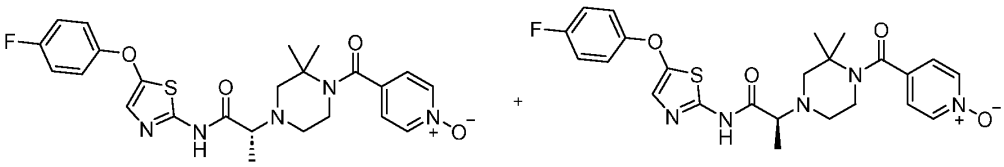
To a solution of 5-bromothiazol-2-amine (2.0 g, 11.171 mmol, 1.0 equiv) in acetonitrile (30 mL) was added 4-fluorophenol (2.5 g, 22.342 mmol, 2.0 equiv) and Cs_2CO_3 (10.9 g, 33.513 mmol, 3.0 equiv) at rt. The resulting mixture was stirred for 2 h at 80 °C under nitrogen atmosphere. After cooled to room temperature, the reaction mixture was quenched by water (50 mL) and extracted with EA (50 mL x 3). The combined organic extracts

were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield a crude product which was directly purified by silica gel chromatography (0-60% PE/EA) to afford 5-(4-fluorophenoxy)-1,3-thiazol-2-amine (500 mg, 21.29%) as a yellow solid. MS (ESI): mass calcd. for $C_9H_7FN_2OS$: 210.2 m/z, found: 211.00 $[M+H]^+$.



2-bromo-N-(5-(4-fluorophenoxy)thiazol-2-yl)propanamide

To a solution of 5-(4-fluorophenoxy)thiazol-2-amine (470 mg, 2.236 mmol, 1.0 equiv) in CH_2Cl_2 (45 mL) was added 2-bromopropanoic acid (684 mg, 4.472 mmol, 2.0 equiv), DCC (692 mg, 3.354 mmol, 1.5 equiv) and $AgNO_3$ (57 mg, 0.335 mmol, 0.15 equiv)at rt. The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched by water (10 mL) and extracted with DCM (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% PE/EA) to afford 2-bromo-N-[5-(4-fluorophenoxy)-1,3-thiazol-2-yl]propanamide (620 mg, 80.34%) as a yellow solid. MS (ESI): mass calcd. for $C_{12}H_{10}BrFN_2O_2S$: 344.1 m/z, found: 345.10 $[M+H]^+$.



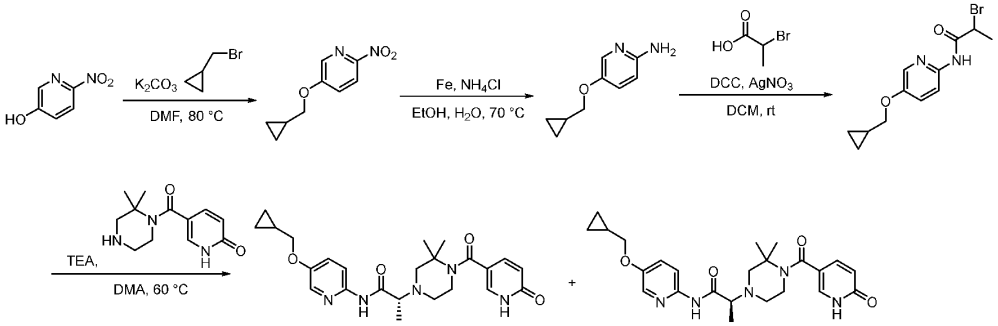
(R)-4-(4-(1-((5-(4-fluorophenoxy)thiazol-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide and (S)-4-(4-(1-((5-(4-fluorophenoxy)thiazol-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

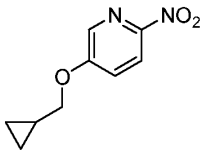
To a solution of 2-bromo-N-[5-(4-fluorophenoxy)-1,3-thiazol-2-yl]propanamide (320 mg, 0.927 mmol, 1.5 equiv) in DMA (5 mL) was added 4-(2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (145 mg, 0.618 mmol, 1.0 equiv), TEA (125 mg, 1.236 mmol, 2.0 equiv) at rt. The resulting mixture was stirred for 2 h at 60 °C. After cooled to room temperature, the reaction mixture was quenched by water (10 mL) and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous

Na_2SO_4, filtered and concentrated under vacuum to yield a crude product which was directly purified by silica gel column (0-50% PE/EA) & Prep-HPLC (a XBridge Shield RP18 OBD 250 mm x 19 mm x 10 μm column (eluent: 55% to 65% (v/v) MeOH and H2O with 0.05% NH_4HCO_3) to afford 4-(4-(1-((5-(4-fluorophenoxy)thiazol-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide as a white solid. The product was separated by Chiral-HPLC (CHIRAL ART Amylose-SA, 5*25 cm, 5 μm column (eluent: 40% to 40%(v/v): EtOH and Hex (0.5% 2M NH_3-MeOH)) to afford (R)-4-(4-(1-((5-(4-fluorophenoxy)thiazol-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (2.2 mg) as a white solid. MS (ESI): mass calcd. for $C_{24}H_{26}FN_5O_4S$: 499.17 m/z, found: 500.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.95 (s, 1H), 8.17 – 8.25 (m, 2H), 7.38 – 7.46 (m, 2H), 7.15 – 7.30 (m, 5H), 3.54 (q, J = 6.9 Hz, 1H), 3.29 (d, J = 5.3 Hz, 2H), 2.69 (dt, J = 10.3, 4.8 Hz, 1H), 2.59 (dt, J = 10.8, 5.2 Hz, 1H), 2.37 – 2.49 (m, 2H), 1.43 (d, J = 4.8 Hz, 6H), 1.26 – 1.18 (m, 3H). And (S)-4-(4-(1-((5-(4-fluorophenoxy)thiazol-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (2.2 mg) as a white solid. MS (ESI): mass calcd. for $C_{24}H_{26}FN_5O4_S$: 499.17 m/z, found: 500.25 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.95 (s, 1H), 8.17 – 8.25 (m, 2H), 7.38 – 7.46 (m, 2H), 7.15 – 7.30 (m, 5H), 3.54 (q, J = 6.9 Hz, 1H), 3.29 (d, J = 5.3 Hz, 2H), 2.69 (dt, J = 10.3, 4.8 Hz, 1H), 2.59 (dt, J = 10.8, 5.2 Hz, 1H), 2.37 – 2.49 (m, 2H), 1.43 (d, J = 4.8 Hz, 6H), 1.26 – 1.18 (m, 3H).

Example 68: (R)-N-(5-(cyclopropylmethoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide and Example 69: (S)-N-(5-(cyclopropylmethoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

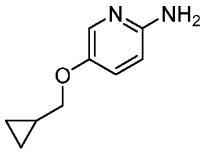
Synthetic Scheme





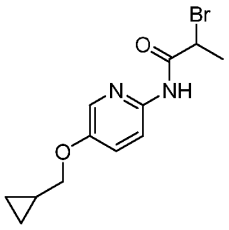
5-(cyclopropylmethoxy)-2-nitropyridine

To a solution of 6-nitropyridin-3-ol (600 mg, 4.283 mmol, 1.0 equiv) in DMF (8 mL) was added (bromomethyl)cyclopropane (578 mg, 4.283 mmol, 1.0 equiv) and K_2CO_3 (1.2 g, 8.565 mmol, 2.0 equiv) at room temperature. The mixture was stirred at 80 °C for 3 h. After cooled to room temperature, the reaction was quenched by water (20 mL). The aqueous layer was extracted with ethyl acetate (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% PE/EA) to afford 5-(cyclopropylmethoxy)-2-nitropyridine (700 mg, 84.17%) as a yellow solid. MS (ESI): mass calcd for $C_9H_{10}N_2O_3$: 194.19 m/z, found 195.05 $[M+H]^+$.



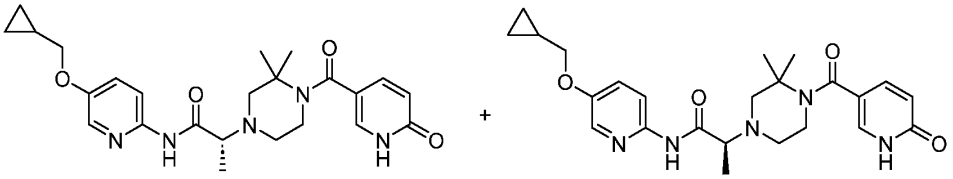
5-(cyclopropylmethoxy)pyridin-2-amine

To a solution of 5-(cyclopropylmethoxy)-2-nitropyridine (400 mg, 2.060 mmol, 1.0 equiv) in EtOH (20 mL) and H_2O (5 mL) was added NH_4Cl (1.3 g, 24.72 mmol, 12.0 equiv) and Fe (690 mg, 12.36 mmol, 6.0 equiv) at room temperature. The mixture was stirred at 70 °C for 4 h. After cooled to room temperature, the reaction was completed by filtration. The filter cake was rinsed with dichloromethane. The mixture was extracted with dichloromethane (50 mL × 3). The organic phases were combined and washed with saturated brine (20 mL). It was dried over sodium sulfate, filtered with suction, and the filtrate was concentrated under reduced pressure to obtain the crude product. The crude product was purified by silica gel chromatography (0-80% PE/EA) to afford 5-(cyclopropylmethoxy)pyridin-2-amine (150 mg, 44.35%) as a yellow solid. MS (ESI): mass calcd for $C_9H_{12}N_2O$: 164.20 m/z, found 165. 15$[M+H]^+$.



2-bromo-N-(5-(cyclopropylmethoxy)pyridin-2-yl)propanamide

To a solution of 5-(cyclopropylmethoxy)pyridin-2-amine (135 mg, 0.822 mmol, 1.0 equiv) in DCM (3mL) was added 2-bromopropanoic acid (150 mg, 0.986 mmol, 1.2 equiv), $AgNO_3$ (28 mg, 0.16 mmol, 0.2 equiv) and DCC (203 mg, 0.986 mmol, 1.2 equiv) at rt. The mixture was stirred at rt for 3 h. After completion of reaction, the reaction mixture was quenched by addition of water (20 mL). The aqueous layer was extracted with DCM (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% PE/EA) to afford 2-bromo-N-(5-(cyclopropylmethoxy)pyridin-2-yl)propanamide (180 mg, 73.18%) as a yellow solid. MS (ESI): mass calcd for $C_{12}H_{15}BrN_2O_2$: 299.168 m/z, found 299.05 $[M+H]^+$.



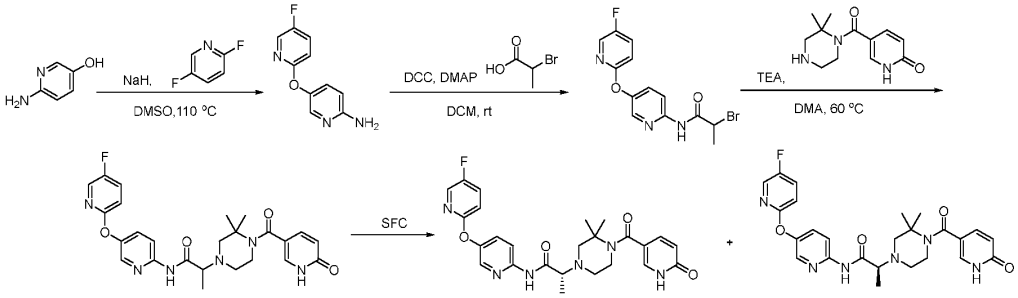
(R)-N-(5-(cyclopropylmethoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide and (S)-N-(5-(cyclopropylmethoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

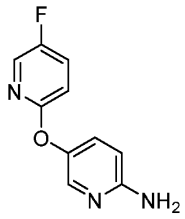
To a solution of 5-(2,2-dimethylpiperazine-1-carbonyl)pyridin-2(1H)-one (100 mg, 0.425 mmol, 1.0 equiv) in DMA (3 mL) was added TEA (257 mg, 2.55 mmol, 6.0 equiv) and 2-bromo-N-(5-(cyclopropylmethoxy)pyridin-2-yl)propanamide (127 mg, 0.425 mmol, 1.0 equiv) at rt. The resulting mixture was stirred for 3 h at 60 °C. After cooled to room temperature, the reaction mixture was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and Prep-HPLC using a Column: XSelect CSH C18 Column, 30*150 mm, 5μm (eluent: 20% to 50% (v/v) CH_3CN and H_2O, 0.1% FA) to afford 30

mg of N-(5-(cyclopropylmethoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide as a white solid. The product was separated by Chiral-Prep-HPLC (Column: CHIRALPAK IA, 2*25 cm, 5 μm; Mobile Phase A: HEX(0.5% 2M NH_3-MeOH), Mobile Phase B: IPA; Flow rate: 20 mL/min) to afford (R)-N-(5-(cyclopropylmethoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (8.5 mg, 5.10%, first peak), MS (ESI): mass calcd. for $C_{24}H_{31}N_5O_4$ 453.543 m/z, found 454.25 $[M+H]^+$, ^1H NMR (300 MHz, DMSO-d_6) δ 11.83 (s, 1H), 9.96 (s, 1H), 7.99 – 8.09 (m, 2H), 7.56 (d, J = 2.6 Hz, 1H), 7.38 – 7.50 (m, 2H), 6.32 (d, J = 9.5 Hz, 1H), 3.87 (d, J = 7.0 Hz, 2H), 3.40 – 3.52 (m, 1H), 3.32 – 3.39 (m, 2H), 2.68 – 2.77 (m, 1H), 2.56 – 2.65 (m, 1H), 2.40 (s, 2H), 1.41 (d, J = 1.9 Hz, 6H), 1.23 – 1.28 (m, 1H), 1.14 – 1.22 (m, 3H), 0.52 – 0.64 (m, 2H), 0.27 – 0.38 (m, 2H), and (S)-N-(5-(cyclopropylmethoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (9.9 mg, 5.94%, second peak) as a white solid, MS (ESI): mass calcd. for $C_{24}H_{31}N_5O_4$ 453.543 m/z, found 454.25 $[M+H]^+$, ^1H NMR (300 MHz, DMSO-d_6) δ 11.83 (s, 1H), 9.96 (s, 1H), 7.99 – 8.09 (m, 2H), 7.56 (d, J = 2.6 Hz, 1H), 7.38 – 7.50 (m, 2H), 6.32 (d, J = 9.5 Hz, 1H), 3.87 (d, J = 7.0 Hz, 2H), 3.40 – 3.52 (m, 1H), 3.32 – 3.39 (m, 2H), 2.68 – 2.77 (m, 1H), 2.56 – 2.65 (m, 1H), 2.40 (s, 2H), 1.41 (d, J = 1.9 Hz, 6H), 1.23 – 1.28 (m, 1H), 1.14 – 1.22 (m, 3H), 0.52 – 0.64 (m, 2H), 0.27 – 0.38 (m, 2H).

Example 70: (R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-((5-fluoropyridin-2-yl)oxy)pyridin-2-yl)propanamide and Example 71: (S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-((5-fluoropyridin-2-yl)oxy)pyridin-2-yl)propanamide

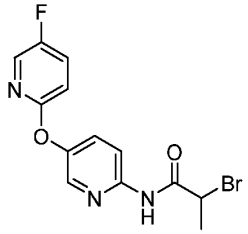
Synthetic Scheme





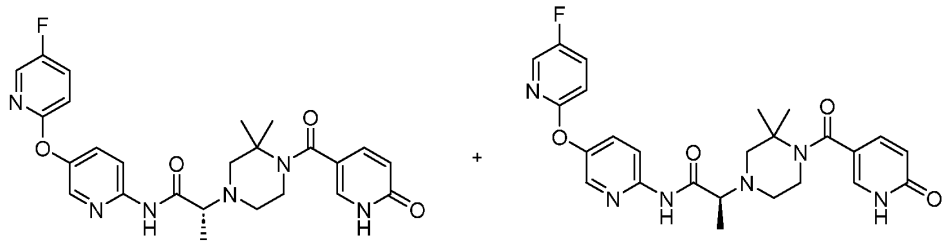
5-((5-fluoropyridin-2-yl)oxy)pyridin-2-amine

To a stirred solution of NaH (1.09 g, 27.243 mmol, 3.0 equiv) in anhydrous DMSO (10 mL) was added 6-aminopyridin-3-ol (2 g, 9.081 mmol, 1.0 equiv). After 15 min, 2,5-difluoropyridine (1.57 g, 13.621 mmol, 1.5 equiv) was added, and the reaction was heated to 110 °C for 90 min. After cooled to room temperature, the reaction was quenched by water (50 mL) and extracted with EA (100 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford 5-((5-fluoropyridin-2-yl)oxy)pyridin-2-amine (2 g, 26.68%). MS (ESI): mass calcd. for $C_{10}H_8FN_3O$: 205.07 m/z, found 206.10 $[M+H]^+$.



2-bromo-N-(5-((5-fluoropyridin-2-yl)oxy)pyridin-2-yl)propanamide

To a stirred solution of 5-((5-fluoropyridin-2-yl)oxy)pyridin-2-amine (660 mg, 3.216 mmol, 1.0 equiv) in DCM was added (R)-2-bromopropanoic acid (590 mg, 3.859 mmol, 1.2 equiv) and DCC (995 mg, 4.824 mmol, 1.5 equiv) followed by catalytic amount of DMAP (39 mg, 0.322 mmol, 0.1 equiv) at room temperature. The reaction mixture was stirred at room temperature for a period of 2.5 h. After completion of reaction, the reaction was quenched by water (10 mL) and extracted with DCM (50 mL x 3). The combined organic extracts were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (5-25% PE/EA) to afford desired compound 2-bromo-N-(5-((5-fluoropyridin-2-yl)oxy)pyridin-2-yl)propanamide (570 mg, 51.86%) as a light yellow solid. MS (ESI): mass calcd. for $C_{13}H_{11}BrFN_3O_2$: 339.00 m/z, found 339.90 $[M+H]^+$.

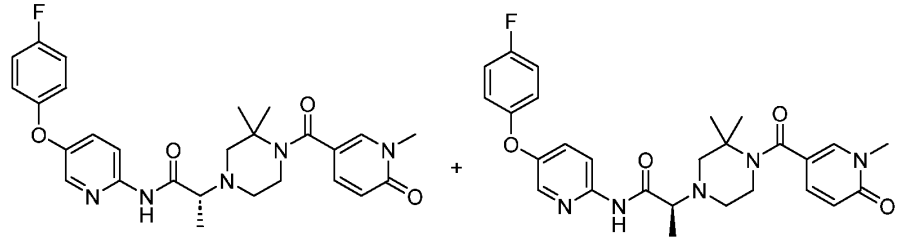


(R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-((5-fluoropyridin-2-yl)oxy)pyridin-2-yl)propanamide and (S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-((5-fluoropyridin-2-yl)oxy)pyridin-2-yl)propanamide

To a stirred solution of 2-bromo-N-(5-((5-fluoropyridin-2-yl)oxy)pyridin-2-yl)propanamide (144 mg, 0.425 mmol, 1.0 equiv) in anhydrous DMA (2 mL) was added 5-(2,2-dimethylpiperazine-1-carbonyl)pyridin-2(1H)-one (100 mg, 0.425 mmol, 1.0 equiv) and TEA (258 mg, 2.550 mmol, 6.0 equiv) at room temperature. The reaction mixture was stirred at 60 °C for a period of 3 h. After cooled to room temperature, the reaction was quenched by water (10 mL) and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-25% DCM/MeOH) and Prep-HPLC using a Column: YMC Triart C18 ExRs Column, 20*250mm, 5μm (eluent: 35% to 65% CH_3CN and H_2O, 10mmol/L NH4HCO3) to afford 2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-((5-fluoropyridin-2-yl)oxy)pyridin-2-yl)propanamide as a white solid. The product was separated by Chiral-Prep-HPLC (CHIRALPAK IF 2*25 cm, 5 μm; Mobile Phase A: HEX(0.5% 2M NH3-MeOH), Mobile Phase B: IPA; Flow rate: 14 mL/min; Gradient: isocratic 50; Wave Length: 220/254 nm) to afford (R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-((5-fluoropyridin-2-yl)oxy)pyridin-2-yl)propanamide (19.5 mg, first peak). MS (ESI): mass calcd. for $C_{25}H_{27}FN_6O_4$: 494.21 m/z, found: 495.15 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6) δ 11.84 (s, 1H), 10.18 (s, 1H), 8.15 – 8.24 (m, 3H), 7.86 (td, J = 8.5, 3.1 Hz, 1H), 7.62 – 7.71 (m, 1H), 7.57 (d, J = 2.6 Hz, 1H), 7.47 (dd, J = 9.4, 2.6 Hz, 1H), 7.20 (dd, J = 9.0, 3.6 Hz, 1H), 6.32 (d, J = 9.4 Hz, 1H), 3.50 (q, J = 6.9, 6.3 Hz, 1H), 2.70 – 2.77 (m, 1H), 2.63 (d, J = 5.7 Hz, 1H), 2.48 – 2.53 (m, 2H), 2.33 – 2.46 (m, 2H), 1.41 (d, J = 2.9 Hz, 6H), 1.23 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ – 135.83, – 135.88, – 136.28. And (S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-((5-fluoropyridin-2-yl)oxy)pyridin-2-yl)propanamide (19.2 mg, second peak). MS (ESI): mass calcd. for

$C_{25}H_{27}FN_6O_4$: 494.21 m/z, found: 495.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.84 (s, 1H), 10.18 (s, 1H), 8.15 – 8.24 (m, 3H), 7.86 (td, J = 8.5, 3.1 Hz, 1H), 7.62 – 7.71 (m, 1H), 7.57 (d, J = 2.6 Hz, 1H), 7.47 (dd, J = 9.4, 2.6 Hz, 1H), 7.20 (dd, J = 9.0, 3.6 Hz, 1H), 6.32 (d, J = 9.4 Hz, 1H), 3.50 (q, J = 6.9, 6.3 Hz, 1H), 2.70 – 2.77 (m, 1H), 2.63 (d, J = 5.7 Hz, 1H), 2.48 – 2.53 (m, 2H), 2.33 – 2.46 (m, 2H), 1.41 (d, J = 2.9 Hz, 6H), 1.23 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -135.88.

Example 72: (R)-2-(3,3-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide and Example 73: (S)-2-(3,3-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide



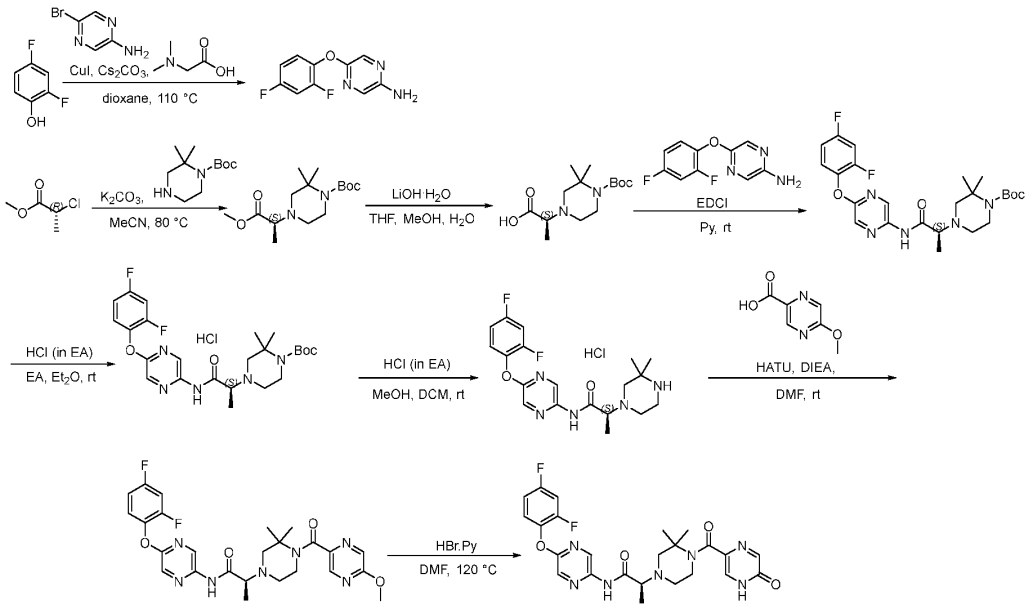
(R)-2-(3,3-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide and (S)-2-(3,3-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

To a solution of 1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid (30 mg, 0.196 mmol, 1.0 equiv) in DMF (2 mL) was added 2-(3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (73 mg, 0.196 mmol, 1.0 equiv), HATU (71 mg, 0.294 mmol, 1.5 equiv) and DIEA (76 mg, 0.588 mmol, 3.0 equiv). The reaction was stirred at room temperature for 3 h. The mixture was quenched with water (10 mL) extracted with EA (3 x 20 mL). The organic layer were dried and filtered then concentrated to dryness under reduced pressure to provide the crude product. The crude product was purified C18 column then separated by chiral-HPLC (column: CHIRALPAK IA, 2*25 cm, 5 μm column: Mobile Phase A: MtBE(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: IPA: DCM=1: 1--HPLC; Flow rate: 20 mL/min) to afford (R)-2-(3,3-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (12.7 mg) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{30}FN_5O_4$: 507.23 m/z, found: 508.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.17 (s, 1H), 8.11 – 8.20 (m, 2H), 7.99 (d, J = 2.5 Hz, 1H),

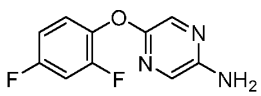
7.53 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.46 (dd, *J* = 9.4, 2.5 Hz, 1H), 7.17 – 7.32 (m, 2H), 7.04 – 7.16 (m, 2H), 6.38 (d, *J* = 9.3 Hz, 1H), 3.46 – 3.56 (m, 1H), 3.46 (s, 3H), 3.32 (s, 2H), 2.70 – 2.82 (m, 1H), 2.59 – 2.70 (m, 1H), 2.43 (s, 2H), 1.43 (s, 6H), 1.22 (d, *J* = 6.9 Hz, 3H). And (S)-2-(3,3-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (16.4 mg) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{30}FN_5O_4$: 507.23, found: 508.20 $[M+H]^+$, ^1H NMR (300 MHz, DMSO-d_6) δ 10.17 (s, 1H), 8.11 – 8.21 (m, 2H), 7.99 (d, *J* = 2.5 Hz, 1H), 7.53 (dd, *J* = 8.9, 3.1 Hz, 1H), 7.46 (dd, *J* = 9.3, 2.6 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.03 – 7.16 (m, 2H), 6.38 (d, *J* = 9.3 Hz, 1H), 3.46 – 3.55 (m, 1H), 3.46 (s, 3H), 3.34 – 3.42 (m, 2H), 2.71 – 2.81 (m, 1H), 2.59 – 2.71 (m, 1H), 2.43 (s, 2H), 1.43 (s, 6H), 1.22 (d, *J* = 6.8 Hz, 3H).

Example 74: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide

Synthetic Scheme



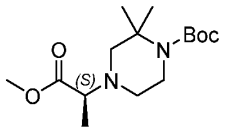
5-(2,4-difluorophenoxy)pyrazin-2-amine



To a stirring solution of 2,4-difluorophenol (18.0 g, 137.930 mmol, 1.2 equiv) in dioxane (200 mL) was added dimethylglycine (1.2 g, 11.494 mmol, 0.1 equiv), 5-

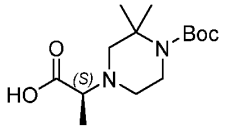
bromopyrazin-2-amine (20.0 g, 114.942 mmol, 1.0 equiv), Cs_2CO_3 (56.2 g, 172.413 mmol, 1.5 equiv) and CuI (4.4 g, 22.988 mmol, 0.2 equiv) at room temperature. The reaction mixture was stirred at 110 °C for 5h. After cooling to room temperature, the reaction was filtered and the filter cake was washed with EA (200 mL). The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography (20-40% PE/EA) to afford 5-(2,4-difluorophenoxy)pyrazin-2-amine (20.0 g, 77.83%) as a yellow solid. MS (ESI): mass calcd. for: $C_{10}H_7F_2N_3O$: 223.05 m/z, found: 224.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 7.92 (d, J = 1.4 Hz, 1H), 7.46 (d, J = 1.4 Hz, 1H), 7.35 – 7.45 (m, 1H), 7.21 – 7.35 (m, 1H), 7.00 – 7.14 (m, 1H), 6.17 (s, 2H).

Tert-butyl (S)-4-(1-methoxy-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carboxylate



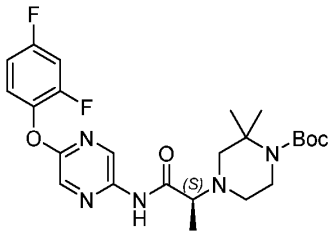
To a stirring solution of tert-butyl 2,2-dimethylpiperazine-1-carboxylate (15.0 g, 69.992 mmol, 1.0 equiv) in MeCN (200 mL) was added methyl (R)-2-chloropropanoate (17.2 g, 139.984 mmol, 2.0 equiv) and K_2CO_3 (29.0 g, 209.976 mmol, 3.0 equiv). The reaction stirred overnight at 80 °C. The reaction was subsequently cooled to ambient temperature and concentrated under reduced pressure. Water (100 mL) was added and the contents were extracted with EA (200 mL x 3). The combined organic extracts were washed with water (100 mL x 4), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (5-20% PE/EA) to afford tert-butyl (S)-4-(1-methoxy-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carboxylate (15.0 g, 71.34%) as light-yellow oil. MS (ESI): mass calcd. for: $C_{15}H_{28}N_2O_4$: 300.20 m/z, found: 300.95 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4) δ 4.09 (q, J = 7.1 Hz, 1H), 3.68 (s, 3H), 3.38 – 3.46 (m, 1H), 3.33 (q, J = 7.1 Hz, 1H), 2.56 – 2.65 (m, 2H), 2.37 – 2.44 (m, 1H), 2.30 (d, J = 11.6 Hz, 1H), 1.44 (s, 9H), 1.36 (d, J = 7.7 Hz, 6H), 1.26 (d, J = 7.1 Hz, 3H).

(S)-2-(4-(tert-butoxycarbonyl)-3,3-dimethylpiperazin-1-yl)propanoic acid



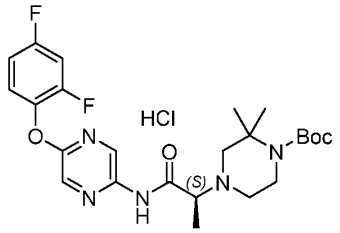
To a stirring solution of tert-butyl (S)-4-(1-methoxy-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carboxylate (15.0 g, 49.934 mmol, 1.0 equiv) in THF (90 mL), MeOH (30 mL) and H_2O (30 mL) was added $LiOH{\cdot}H_2O$ (3.1 g, 74.901 mmol, 1.5 equiv) at room temperature. After stirring the reaction at room temperature for a period of 4h, the mixture was acidified to a pH = 6 with HCl (*aq.*, 1N). The low boiling point solvent removed under reduced pressure. The residue was extracted with MeOH/DCM=1/4 (100 mL x 4), dried over anhydrous sodium sulfate, filtered and concentrated to afford (S)-2-(4-(tert-butoxycarbonyl)-3,3-dimethylpiperazin-1-yl)propanoic acid (15.0 g, 94.41%) as light yellow oil. MS (ESI): mass calcd. for : $C_{14}H_{26}N_2O_4$: 286.19 m/z, found: 287.25 $[M+H]^+$.

Tert-butyl (S)-4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carboxylate



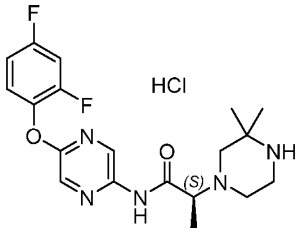
To a stirring solution of (S)-2-(4-(tert-butoxycarbonyl)-3,3-dimethylpiperazin-1-yl)propanoic acid (15.0 g, 52.379 mmol, 1.0 equiv) in pyridine (150 mL) was added 5-(2,4-difluorophenoxy)pyrazin-2-amine (15.2 g, 68.093 mmol, 1.3 equiv) and EDCI (20.1 g, 104.758 mmol, 2.0 equiv) at room temperature. The reaction mixture was stirred at room temperature for 4h then quenched by the addition of water (100 mL) and extracted with EA (200 mL x 3). The combined organic extracts were washed with water (100 mL x 4), dried over anhydrous sodium sulfate, filtered and concentrated. Purification by silica gel chromatography (5-20% PE/EA) to afforded tert-butyl (S)-4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carboxylate (10.0 g, 37.91%, ~90% *ee*) as yellow oil. MS (ESI): mass calcd. for: $C_{24}H_{31}F_2N_5O_4$: 491.23 m/z, found: 491.80 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 8.83 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.41 – 7.54 (m, 2H), 7.12 – 7.22 (m, 1H), 3.47 (q, J = 6.8 Hz, 1H), 3.31 – 3.36 (m, 2H), 2.63 (dt, J = 10.9, 5.2 Hz, 1H), 2.51 – 2.56 (m, 1H), 2.31 (s, 2H), 1.39 (s, 9H), 1.33 (d, J = 1.8 Hz, 6H), 1.18 (d, J = 6.9 Hz, 3H).

Tert-butyl (S)-4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carboxylate (hydrochloride)



To a stirring solution of tert-butyl (S)-4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carboxylate (10.0 g, 20.344 mmol, 1.0 equiv) in EA (50 mL) and Et_2O (100 mL) was added 4N HCl (in EA, ~15 mL). A precipitate formed which was filtered and washed with ether. The precipitate was dried to afford tert-butyl (S)-4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carboxylate (hydrochloride) (~90% *ee*). The solid was dissolved with CH_3CN (~400 mL) at 90 °C. The solution was allowed to cool to room temperature. The precipitate was filtered and dried under reduced pressure to afford tert-butyl (S)-4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carboxylate (hydrochloride) (8.0 g, >99% *ee*) as a white solid. MS (ESI): mass calcd. for: $C_{24}H_{31}F_2N_5O_4$: 491.23 m/z, found: 491.80 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ^1H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 8.82 (s, 1H), 8.50 (d, J = 1.4 Hz, 1H), 7.42 – 7.55 (m, 2H), 7.13 – 7.23 (m, 1H), 3.93 – 4.35 (m, 3H), 3.47 – 3.57 (m, 2H), 2.08 (s, 2H), 1.59 – 1.64 (m, 3H), 1.47 (d, J = 9.1 Hz, 6H), 1.41 (s, 9H).

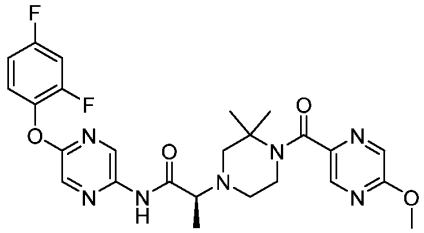
(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (hydrochloride)



To a stirring solution of tert-butyl (S)-4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carboxylate (hydrochloride) (8 g, 15.152 mmol, 1.0 equiv) in MeOH (20 mL) and DCM (60 mL) was added 4N HCl (in EA, 80

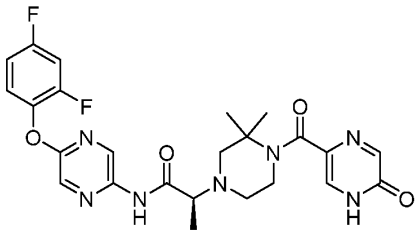
mL). The reaction stirred at room temperature for 2 h and subsequently concentrated under reduced pressure. MeOH (~10 mL) was added to the residue and the mixture was added to Et_2O (~200 mL). The solids were filtered and the filter cake was washed with ether and dried under reduced pressure to obtain (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (hydrochloride) (6 g, >99% *ee*). MS (ESI): mass calcd. for: $C_{19}H_{23}F_2N_5O_2$: 391.18 m/z, found: 392.25 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4) δ 8.87 (s, 1H), 8.30 (s, 1H), 7.33 (td, J = 8.9, 5.5 Hz, 1H), 7.09 – 7.19 (m, 1H), 6.98 – 7.08 (m, 1H), 4.37 (q, J = 6.9 Hz, 1H), 3.82 – 3.90 (m, 1H), 3.69 – 3.72 (m, 2H), 3.59 – 3.65 (m, 3H) , 1.75 (d, J = 6.9 Hz, 3H), 1.65 (d, J = 25.8 Hz, 6H).

(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-methoxypyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide



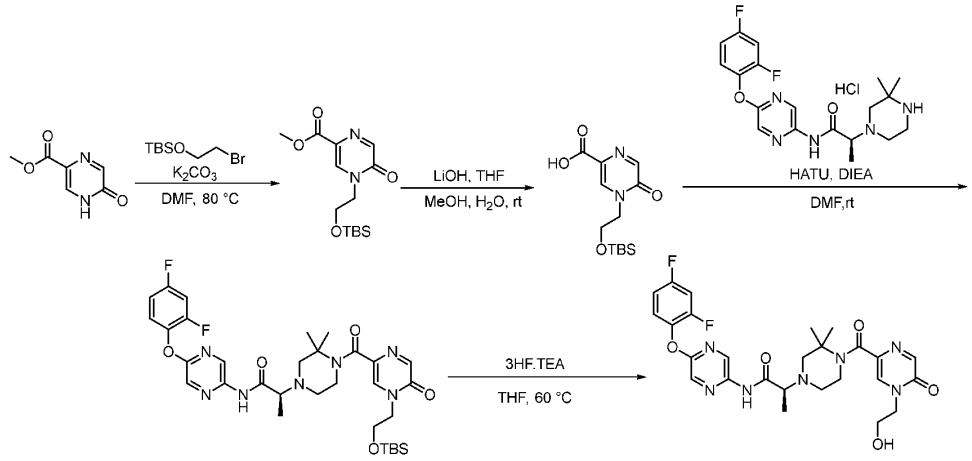
To a stirring solution of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (hydrochloride) (7.0 g, 16.35 mmol, 1.0 equiv) in DMF (100 mL) was added 5-methoxypyrazine-2-carboxylic acid (3.3 g, 21.25 mmol, 1.3 equiv), HATU (9.3 g, 24.52 mmol, 1.5 equiv) and DIEA (20.0 mL, 114.45 mmol, 7.0 equiv) at rt. The reaction stirred for 5 h at rt. The reaction mixture was quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined organic extracts were washed with brine (3 x 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (0-20% DCM/MeOH) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-methoxypyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (5.6 g, 65.1%) as a yellow oil. MS (ESI): mass calcd. for $C_{25}H_{27}F_2N_7O_4$: 527.21, found: 528.40 $[M+H]^+$.

(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-methoxypyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

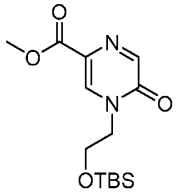


To a solution of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-methoxypyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (4.0 g, 7.57 mmol, 1.0 equiv) in DMF (80 mL) was added pyridinium hydrobromide (1.2 g, 45.42 mmol, 6.0 equiv) at rt. The resulting mixture was stirred for 12 h at 120 °C. The reaction was subsequently cooled to room temperature and quenched with water (100 mL). The mixture was extracted with EA (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by C18 column (eluent: 30% to 60% ACN and H_2O (0.01 % FA) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide (2.0 g, 51.3%) as a yellow solid. The solid was dissolved in toluene (~40 mL) at reflux and the resulting solution was allowed to cool to ambient temperature. The precipitate was filtered and dried under reduced pressure to afford 1.6 g of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide as a yellow solid. MS (ESI): mass calcd. for $C_{24}H_{25}F_2N_7O_4$: 513.19, found: 514.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.60 (s, 1H), 10.39 (s, 1H), 8.85 (s, 1H), 8.46 (d, J = 1.5 Hz, 1H), 7.91 (s, 1H), 7.75 (s, 1H), 7.51 – 7.39 (m, 2H), 7.20 – 7.10 (m, 1H), 3.56 - 3.45 (m, 3H), 2.77 - 2.68 (m, 1H), 2.65 - 2.56 (m, 1H), 2.47 - 2.35 (m, 2H), 1.44 – 1.39 (m, 6H), 1.20 (d, J = 6.9 Hz, 3H).

Example 75: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(4-(2-hydroxyethyl)-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

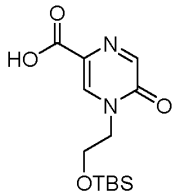


Synthesis of methyl 4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-oxo-4,5-dihydropyrazine-2-carboxylate



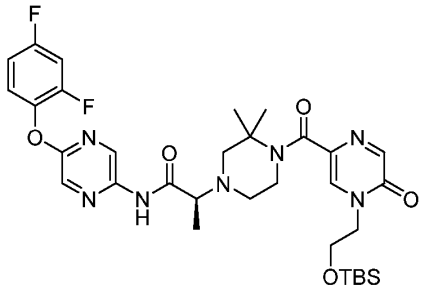
To a solution of methyl 5-oxo-4,5-dihydropyrazine-2-carboxylate (10 g, 64.882 mmol, 1.0 equiv) in DMF (100 mL) was added K_2CO_3 (27.1 g, 194.646 mmol, 3.0 equiv) and (2-bromoethoxy)(tert-butyl)dimethylsilane (31.0 g, 129.764 mmol, 2 equiv) at rt. The reaction stirred for 3 h at 80 °C. The reaction was then cooled to room temperature and quenched with water (100 mL). The resulting mixture was extracted with EA (3 x 200 mL). The combined organic layers were washed with brine (3 x 60 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude was purified by silica gel column (0-30% PE/EA) to afford methyl 4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-oxo-4,5-dihydropyrazine-2-carboxylate (15 g, 73.99%, large polar isomer) as a yellow solid. MS (ESI): mass calcd. for $C_{14}H_{24}N_2O_4Si$: 312.15, found: 313.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.39 (d, J = 1.1 Hz, 1H), 8.02 (d, J = 1.0 Hz, 1H), 4.09 (dd, J = 5.6, 4.5 Hz, 2H), 3.81 (dd, J = 5.6, 4.5 Hz, 2H), 3.78 (s, 3H), 0.76 (s, 9H), -0.11 (s, 6H).

Synthesis of 4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-oxo-4,5-dihydropyrazine-2-carboxylic acid



To a solution of methyl 4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-oxo-4,5-dihydropyrazine-2-carboxylate (10.0 g, 32.006 mmol, 1 equiv) in THF (100 mL), methanol (10 mL) and water (10 mL) was added LiOH (1.15 g, 48.009 mmol, 1.5 equiv) at rt. The resulting mixture was stirred for 1 h at rt then concentrated under vacuum. To the residue was added ice-water and the mixture was acidified to pH 5~6 with 3 N HCl. The precipitate was collected by filtration and washed with H_2O (50 mL) to afford 4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-oxo-4,5-dihydropyrazine-2-carboxylic acid (7.5 g, 78.53%) as a yellow solid. MS (ESI): mass calcd. for $C_{13}H_{22}N_2O_4Si$: 298.13, found: 299.10 $[M+H]^+$.

Synthesis of (S)-2-(4-(4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

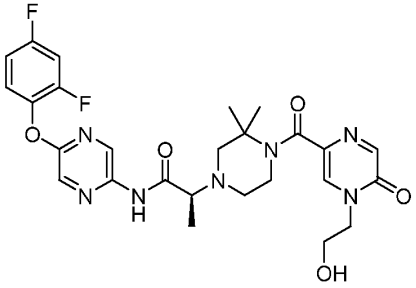


To a solution of ((S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (hydrochloride) (5.0 g, 11.68 mmol, 1.0 equiv) in DMF (80 mL) was added 4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-oxo-4,5-dihydropyrazine-2-carboxylic acid (5.2 g, 17.5 mmol, 1.5 equiv), HATU (6.65 g, 17.5 mmol, 1.5 equiv), DIEA (12.2 mL, 70.08 mmol, 6.0 equiv). The resulting mixture was stirred for 2 h at rt. The reaction was subsequently quenched with water (80 mL) and extracted with EA (3 x 100 mL). The combined organic extracts were washed with brine (3 x 50 mL), dried over anhydrous

Na_2SO_4 and concentrated under vacuum. The crude was purified by silica gel column (0-10% MeOH/DCM) to afford (S)-2-(4-(4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-

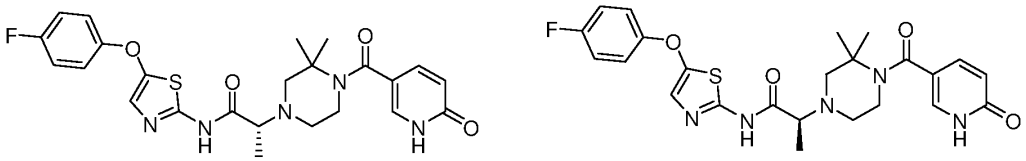
difluorophenoxy)pyrazin-2-yl)propanamide (6 g, 76.9%) as a white solid. MS (ESI): mass calcd. for $C_{32}H_{43}F_2N_7O_5Si$: 671.30 m/z, found 672.20 $[M+H]^+$.

Synthesis of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(4-(2-hydroxyethyl)-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

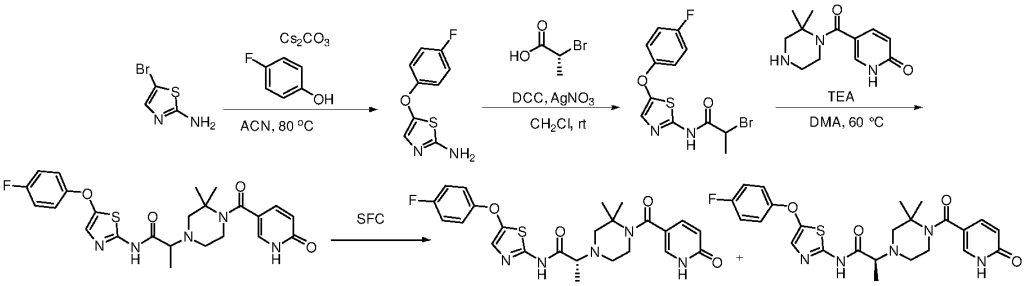


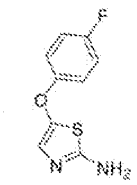
To a solution of (S)-2-(4-(4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (6 g, 8.931 mmol, 1 equiv) in THF (100 mL) was added TEA·3HF (5 mL). The resulting mixture was stirred for 1 h at 60 °C. The reaction was then cooled to room temperature. The reaction mixture was diluted with water (60 mL) and extracted with EA (3 x 100 mL). The combined organic extracts were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by C18 column (eluent: 30% to 65% ACN and H_2O) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(4-(2-hydroxyethyl)-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (3.2 g, 64.3%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{29}F_2N_7O_5$: 557.22 m/z, found 558.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.85 (d, J = 1.5 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.97 (d, J = 1.1 Hz, 1H), 7.93 (d, J = 1.0 Hz, 1H), 7.55 - 7.39 (m, 2H), 7.24 - 7.11 (m, 1H), 4.96 (t, J = 5.6 Hz, 1H), 4.02 – 3.92 (m, 2H), 3.69 – 3.58 (m, 2H), 3.55 – 3.44 (m, 3H), 2.79 - 2.69 (m, 1H), 2.67 - 2.57 (m, 1H), 2.49 - 2.35 (m, 2H), 1.46 – 1.40 (m, 6H), 1.21 (d, J = 6.9 Hz, 3H).

Example 76: (2R)-2-[3,3-dimethyl-4-(6-oxo-1H-pyridine-3-carbonyl)piperazin-1-yl]-N-[5-(4-fluorophenoxy)-1,3-thiazol-2-yl]propanamide and Example 77: (2S)-2-[3,3-dimethyl-4-(6-oxo-1H-pyridine-3-carbonyl)piperazin-1-yl]-N-[5-(4-fluorophenoxy)-1,3-thiazol-2-yl]propanamide



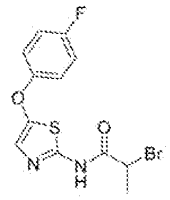
Synthetic Scheme





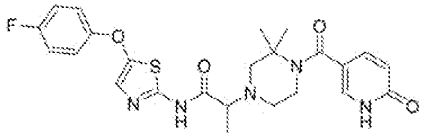
Synthesis of 5-(4-fluorophenoxy)-1,3-thiazol-2-amine

To a stirred mixture of 5-bromo-1,3-thiazol-2-amine (2.0g, 11.171 mmol, 1 equiv) and 4-fluorophenol (2.5 g, 22.342 mmol, 2 equiv) in acetonitrile (20 mL) was added Cs_2CO_3 (10.9 g, 33.513 mmol, 3 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at 80 °C under nitrogen atmosphere. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:2) to afford 5-(4-fluorophenoxy)-1,3-thiazol-2-amine (500 mg, 21.29 %) as a yellow solid. MS (ESI): mass calcd. for $C_9H_7FN_2OS$: 210.0 m/z, found: 211.00 $[M+H]^+$.



2-bromo-N-[5-(4-fluorophenoxy)-1,3-thiazol-2-yl]propanamide

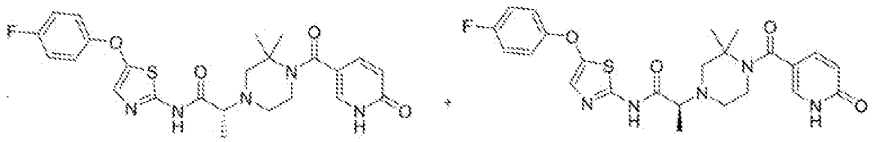
To a stirred mixture of 5-(4-fluorophenoxy)-1,3-thiazol-2-amine (470 mg, 2.236 mmol, 1 equiv) and (2R)-2-bromopropanoic acid (684.00 mg, 4.472 mmol, 2 equiv) in CH_2Cl_2 (5 mL) were added DCC (691.93 mg, 3.354 mmol, 1.5 equiv) and $AgNO_3$ (56.97 mg, 0.335 mmol, 0.15 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at room temperature under air atmosphere. The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 2-bromo-N-[5-(4-fluorophenoxy)-1,3-thiazol-2-yl]propanamide (620 mg, 80.34 %) as a yellow solid. MS (ESI): mass calcd. for $C_{12}H_{10}BrFN_2O_2S$: 344.0 m/z, found: 345.0 $[M+H]^+$.



2-[3,3-dimethyl-4-(6-oxo-1H-pyridine-3-carbonyl)piperazin-1-yl]-N-[5-(4-fluorophenoxy)-1,3-thiazol-2-yl]propanamide

To a stirred mixture of 2-bromo-N-[5-(4-fluorophenoxy)-1,3-thiazol-2-yl]propanamide (320 mg, 0.927 mmol, 1.5 equiv) and 5-(2,2-dimethylpiperazine-1-carbonyl)-1H-pyridin-2-one (145.41 mg, 0.618 mmol, 1 equiv) in DMA (5 mL) was added TEA (125.08 mg, 1.236 mmol, 2 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 1.5 h at 60 °C under air atmosphere. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (3 x10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced

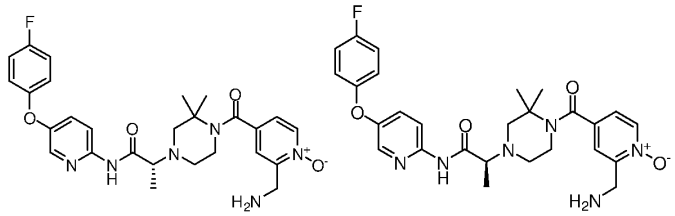
pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:4) to afford 2-[3,3-dimethyl-4-(6-oxo-1H-pyridine-3-carbonyl)piperazin-1-yl]-N-[5-(4-fluorophenoxy)-1,3-thiazol-2-yl]propanamide (60 mg, 19.43 %) as a yellow solid. MS (ESI): mass calcd. for $C_{24}H_{26}FN_5O_4S$:499.2 m/z, found:500.20 $[M+H]^+$.



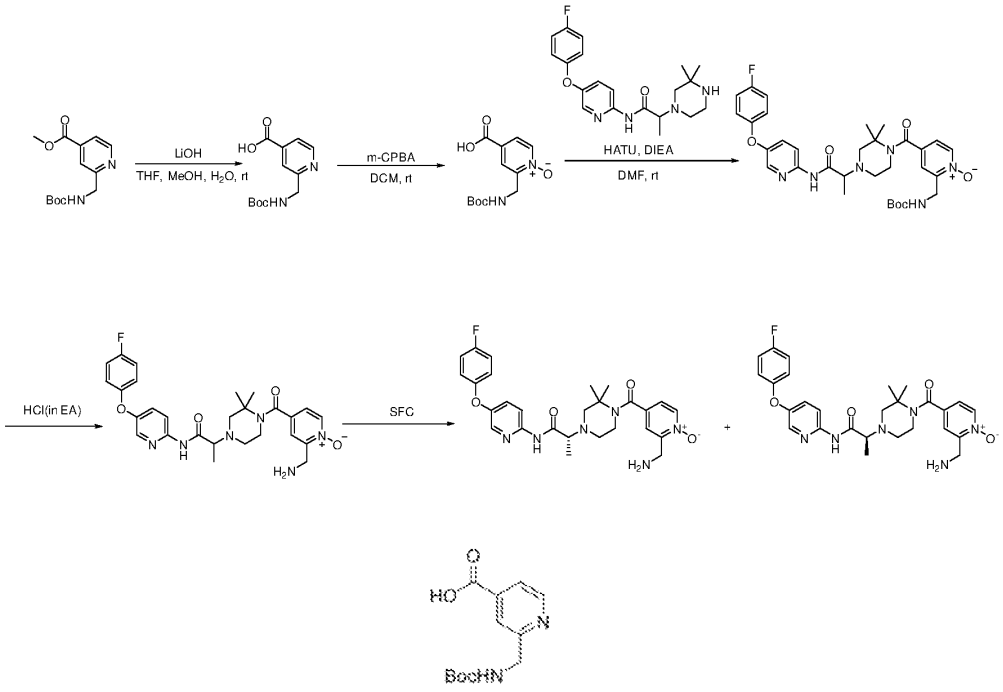
(2R)-2-[3,3-dimethyl-4-(6-oxo-1H-pyridine-3-carbonyl)piperazin-1-yl]-N-[5-(4-fluorophenoxy)-1,3-thiazol-2-yl]propanamide and (2S)-2-[3,3-dimethyl-4-(6-oxo-1H-pyridine-3-carbonyl)piperazin-1-yl]-N-[5-(4-fluorophenoxy)-1,3-thiazol-2-yl]propanamide

2-[3,3-dimethyl-4-(6-oxo-1H-pyridine-3-carbonyl)piperazin-1-yl]-N-[5-(4-fluorophenoxy)-1,3-thiazol-2-yl]propanamide (30 mg) was purified by chiral-HPLC using a CHIRAL ART Amylose-SA, 5*25 cm, 5 μm column (eluent: 40% (v/v) Hex: DCM=3: 1(0.5% 2M NH_3-MeOH) and EtOH) to afford (2S)-2-[3,3-dimethyl-4-(6-oxo-1H-pyridine-3-carbonyl)piperazin-1-yl]-N-[5-(4-fluorophenoxy)-1,3-thiazol-2-yl]propanamide (6.4 mg, 21.19 %) as a white solid. MS (ESI): mass calcd. for $C_{24}H_{26}FN_5O_4S$:499.2 m/z, found: 500.20 $[M+H]^+$. ^1H NMR (400 MHz, Acetonitrile-d_3) δ 7.55 – 7.65 (m, 1H), 7.47 – 7.55 (m, 1H), 7.13 – 7.21 (m, 4H), 7.06 – 7.13 (m, 1H), 6.37 (d, J = 9.5 Hz, 1H),3.40 – 3.57 (m, 3H), 2.74 – 2.88 (m, 1H), 2.60 – 2.73 (m, 1H), 2.36 – 2.48 (m, 2H), 1.50 (d, J = 4.2 Hz, 6H), 1.31 – 1.32 (m, 3H). ^{19}F NMR (376 MHz, CD_3CN) δ -121.32. And (2R)-2-[3,3-dimethyl-4-(6-oxo-1H-pyridine-3-carbonyl)piperazin-1-yl]-N-[5-(4-fluorophenoxy)-1,3-thiazol-2-yl]propanamide (4.8 mg, 15.92 %) as a white solid. MS (ESI): mass calcd. for $C_{24}H_{26}FN_5O_4S$: 499.2 m/z, found: 500.25 $[M+H]^+$. ^1H NMR (400 MHz, Acetonitrile-d_3) 7.57 – 7.68 (m, 1H), 7.47 – 7.57 (m, 1H), 7.22 – 7.38 (m, 4H), 7.06 – 7.14 (m, 1H), 6.39 (d, J = 9.4, 0.7 Hz, 1H), 3.40 – 3.55 (m, 3H), 2.70 – 2.85 (m, 1H), 2.60 – 2.70 (m, 1H), 2.33 – 2.48 (m, 2H), 1.50 (d, J = 4.3 Hz, 6H), 1.24 – 1.32 (m, 3H). ^{19}F NMR (376 MHz, CD_3CN) δ -121.35.

Example 78: 2-(aminomethyl)-4-{4-[(1R)-1-{[5-(4-fluorophenoxy)pyridin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}pyridin-1-ium-1-olate and Example 79: 2-(aminomethyl)-4-{4-[(1S)-1-{[5-(4-fluorophenoxy)pyridin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}pyridin-1-ium-1-olate

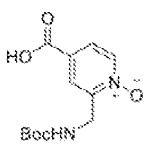


Synthetic Scheme



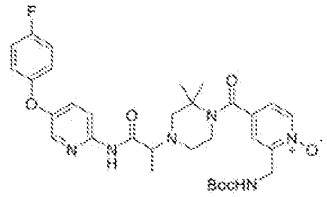
2-{[(tert-butoxycarbonyl)amino]methyl}pyridine-4-carboxylic acid

To a solution of methyl 2-{[(tert-butoxycarbonyl)(methyl)amino]methyl}pyridine-4-carboxylate (260 mg, 0.927 mmol, 1 equiv) in THF/MeOH/H_2O (4:2:2 mL) was added LiOH (222.14 mg, 9.270 mmol, 10 equiv) at rt. The crude product mixture was used in the next step directly without further purification 2-{[(tert-butoxycarbonyl)amino]methyl}pyridine-4-carboxylic acid (300 mg, crude). MS (ESI): mass calcd. for $C_{12}H_{16}N_2O_4$ 252.11 m/z, found 253.10 $[M+H]^{+.}$



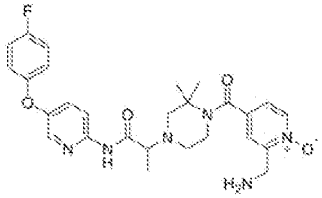
2-{[(tert-butoxycarbonyl)amino]methyl}-4-carboxypyridin-1-ium-1-olate

To a solution of 2-{[(tert-butoxycarbonyl)amino]methyl}pyridine-4-carboxylic acid (290 mg, 1.150 mmol, 1 equiv) in DCM (5 mL) was added m-CPBA (595.11 mg, 3.450 mmol, 3 equiv) at 0 degrees C .The resulting mixture was stirred for 3h at rt. The reaction mixture was quenched by water and extracted with EA (3*20 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography by C18 to afford product as 2-{[(tert-butoxycarbonyl)amino]methyl}-4-carboxypyridin-1-ium-1-olate (200 mg, 64.85%) a white solid. MS (ESI): mass calcd. for $C_{12}H_{16}N_2O_5$ 268.11 m/z, found 269.15 $[M+H]^+$.



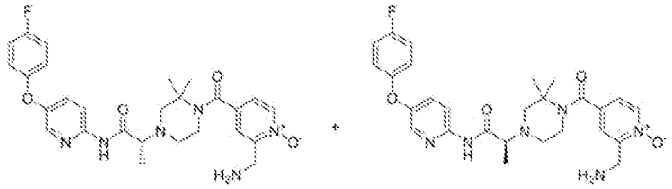
2-{[(tert-butoxycarbonyl)amino]methyl}-4-[4-(1-{[5-(4-fluorophenoxy)pyridin-2-yl] carbamoyl}ethyl)-2,2-dimethylpiperazine-1-carbonyl]pyridin-1-ium-1-olate

To a solution of 2-{[(tert-butoxycarbonyl)amino]methyl}-4-carboxypyridin-1-ium-1-olate (190 mg, 0.708 mmol, 1 equiv) in DMF (3mL) was added 2-(3,3-dimethylpiperazin-1-yl)-N-[5-(4-fluorophenoxy) pyridine-2-yl]propanamide (263.78 mg, 0.708 mmol, 1 equiv) and HATU (403.95 mg, 1.062 mmol, 1.5 equiv) and DIEA (183.08 mg, 1.416 mmol, 2 equiv) at rt .The resulting mixture was stirred for 3h at rt. The reaction mixture was quenched by water and extracted with EA (3*20 mL). The combined organic extracts were washed with brine (10mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford product 2-{[(tert-butoxycarbonyl)amino] methyl}-4-[4-(1-{[5-(4-fluorophenoxy)pyridin-2-yl]carbamoyl}ethyl)-2,2-dimethylpiperazine-1-carbonyl] pyridin-1-ium-1-olate (140 mg, 31.74%) as a white solid. MS (ESI): mass calcd. for $C_{32}H_{39}FN_6O_6$ 622.29 m/z, found 623.20 $[M+H]^+$.

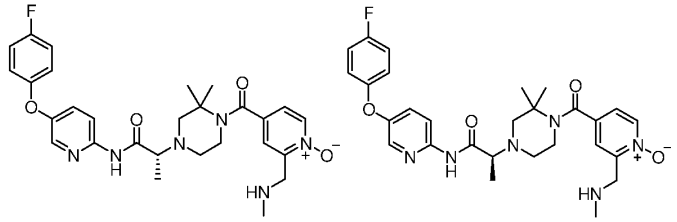


2-(aminomethyl)-4-{4-[(1R)-1-{[5-(4-fluorophenoxy)pyridin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}pyridin-1-ium-1-olate

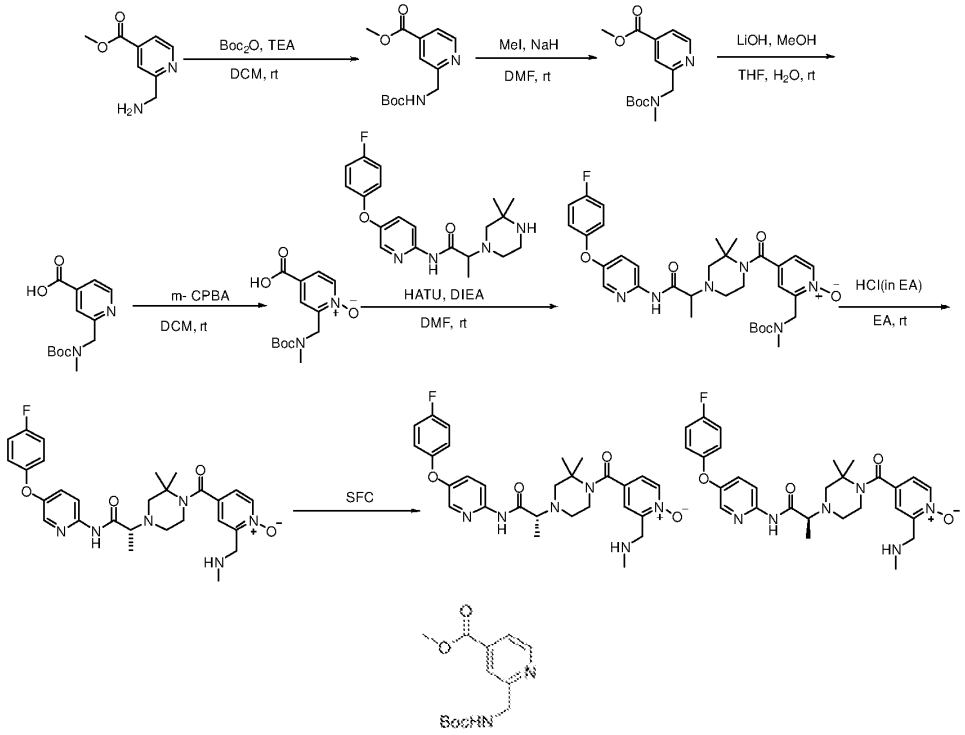
To a solution of 2-{[(tert-butoxycarbonyl)amino]methyl}-4-[4-(1-{[5-(4-fluorophenoxy)pyridin-2-yl] carbamoyl}ethyl)-2,2-dimethylpiperazine-1-carbonyl]pyridin-1-ium-1-olate (70 mg, 0.112 mmol, 1 equiv) in EA (1 mL) was added hydrochloric acid (in EA) (2 mL) at 0 °C. The resulting mixture was stirred for 2 h at rt. The product was precipitated by the addition of anhydrous ether. The precipitated solids were collected by filtration and washed with anhydrous ether to afford crude product. The crude product was separated by chiral-HPLC using a CHIRALPAK IF Column, 2*25 cm*5 μm column (eluent: 60% (v/v) Hex: DCM=3: 1(0.5% 2M NH_3-MeOH) and EtOH) to afford 2-(aminomethyl)-4-{4-[(1R)-1-{[5-(4-fluorophenoxy)pyridin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl} pyridine -1-ium-1-olate (4.9 mg, 31.74%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{31}FN_6O_4$ 522.24 m/z, found: 523.35[M+H]$^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.24 (d, J = 6.5 Hz, 1H), 8.11 – 8.19 (m, 2H), 7.61 (d, J = 2.5 Hz, 1H), 7.49 – 7.57 (m, 1H), 7.29 – 7.37 (m, 1H), 7.19 – 7.28 (m, 2H), 7.09 – 7.14 (m, 2H), 3.79 (s, 2H), 3.43 – 3.55 (m, 1H), 2.67 – 2.77 (m, 2H), 2.59 – 2.64 (m, 2H), 2.45 – 2.50 (m, 2H),1.48 (d, J = 2.4 Hz, 6H), 1.17 – 1.27 (m, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.83. And 2-(aminomethyl)-4-{4-[(1S)-1-{[5-(4-fluorophenoxy)pyridin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}pyridin-1-ium-1-olate (4.8 mg, 31.74%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{31}FN_6O_4$ 522.24 m/z, found: 523.35 [M+H]$^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.24 (d, J = 6.6 Hz, 1H), 8.11 – 8.19 (m, 2H), 7.61 (d, J = 2.5 Hz, 1H), 7.49 – 7.57 (m, 1H), 7.29 – 7.37 (m, 1H), 7.19 – 7.28 (m, 2H), 7.03 – 7.16 (m, 2H), 3.78 (s, 2H), 3.45 – 3.58 (m, 1H), 2.67 – 2.78 (m, 2H), 2.57 – 2.66 (m, 2H), 2.43– 2.52 (m, 2H), 1.48 (d, J = 2.4 Hz, 6H), 1.17 – 1.28 (m, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -119.83.



Example 80: 4-{4-[(1R)-1-{[5-(4-fluorophenoxy)pyridin-2-yl]carbamoyl} ethyl]-2,2-dimethylpiperazine-1-carbonyl}-2-[(methylamino)methyl]pyridin-1-ium-1-olate and Example 81: 4-{4-[(1S)-1-{[5-(4-fluorophenoxy)pyridin-2-yl]carbamoyl} ethyl]-2,2-dimethylpiperazine-1-carbonyl}-2-[(methylamino)methyl]pyridin-1-ium-1-olate



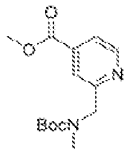
Synthetic Scheme



methyl 2-{[(tert-butoxycarbonyl)amino]methyl}pyridine-4-carboxylate

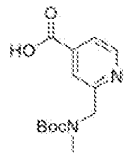
To a solution of methyl 2-(aminomethyl)pyridine-4-carboxylate (350 mg, 2.106 mmol, 1 equiv) in DCM (5 mL) was added TEA (639.38 mg, 6.318 mmol, 3 equiv) and Boc_2O (919.33 mg, 4.212 mmol, 2 equiv). The mixture was stirred at rt for 3 h. After completion of

reaction, the reaction mixture was quenched by addition of water (10 mL). The aqueous layer was extracted with ethyl acetate (50 mL). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) to afford methyl 2-{[(tert-butoxycarbonyl)amino]methyl}pyridine-4-carboxylate (350 mg, 62.40%) as a yellow solid. MS (ESI): mass calcd for $C_{13}H_{18}N_2O_4$ 266.13 m/z, found 267.15 $[M+H]^+$



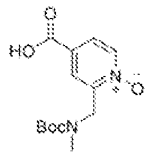
methyl 2-{[(tert-butoxycarbonyl)(methyl)amino]methyl}pyridine-4-carboxylate

To a solution of methyl 2-{[(tert-butoxycarbonyl)amino]methyl}pyridine-4-carboxylate (350 mg, 1.314 mmol, 1 equiv) in DMF (5 mL) was added NaH (78.85 mg, 3.285 mmol, 2.5 equiv) at 0 °C .The resulting mixture was stirred for 0.5h at rt. Then the resulting mixture was added MeI (373.11 mg, 2.628 mmol, 2 equiv) at 0 °C. The resulting mixture was stirred for 4 h at rt. After completion of reaction, the reaction mixture was quenched by addition of water (10 mL). The aqueous layer was extracted with ethyl acetate (2*50 mL). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100%) PE/EA to afford methyl 2-{[(tert-butoxycarbonyl)(methyl)amino]methyl}pyridine-4-carboxylate (270 mg, 73.28%) as a white solid. MS (ESI): mass calcd for $C_{14}H_{20}N_2O_4$ 280.14 m/z, found 281.15 $[M+H]^+$.



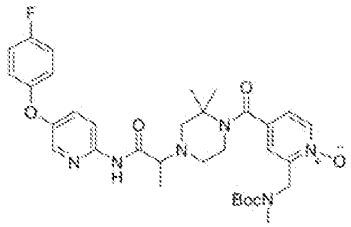
2-{[(tert-butoxycarbonyl)(methyl)amino]methyl}pyridine-4-carboxylic acid

To a solution of methyl 2-{[(tert-butoxycarbonyl)(methyl)amino]methyl}pyridine-4-carboxylate (260 mg, 0.927 mmol, 1 equiv) in THF: MeOH : H_2O (2:1:1 mL) was added LiOH (222.14 mg, 9.270 mmol, 10 equiv) at rt .The crude product/ resulting mixture was used in the next step directly without further purification to afford 2-{[(tert-butoxycarbonyl)(methyl)amino]methyl}pyridine-4-carboxylic acid (90 mg, 23.58%) as a yellow oil. MS (ESI): mass calcd. for $C_{13}H_{18}N_2O_4$ 266.13 m/z, found 267.05 $[M+H]^+$.



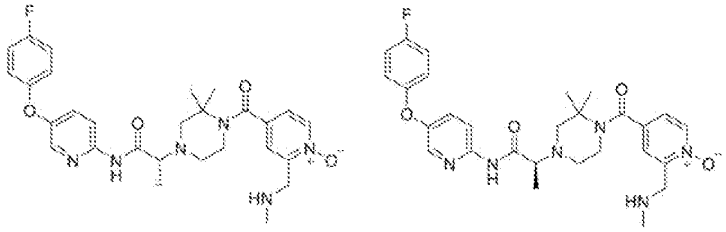
2-{[(tert-butoxycarbonyl)(methyl)amino]methyl}-4-carboxypyridin-1-ium-1-olate

To a solution of methyl 2-(2,2,2-trifluoroethyl)pyridine-4-carboxylate (90 mg, 0.411 mmol, 1 equiv)in DCM (3 mL) was added m-CPBA (207.36 mg, 1.202 mmol, 2 equiv) at 0 ° C. The resulting mixture was stirred for 3 h at rt. The reaction mixture was quenched by water and extracted with EA (3*20 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography by C18 to afford product as 2-{[(tert-butoxycarbonyl)(methyl)amino]methyl}-4-carboxypyridin-1-ium-1-olate (40 mg, 23.58%) a white solid. MS (ESI): mass calcd. for $C_{13}H_{18}N_2O_5$ 282.12 m/z, found 283.10 $[M+H]^+$.



2-{[(tert-butoxycarbonyl)(methyl)amino]methyl}-4-[4-(1-{[5-(4-fluorophenoxy)pyridin-2-yl]carbamoyl}ethyl)-2,2-dimethylpiperazine-1-carbonyl]pyridin-1-ium-1-olate

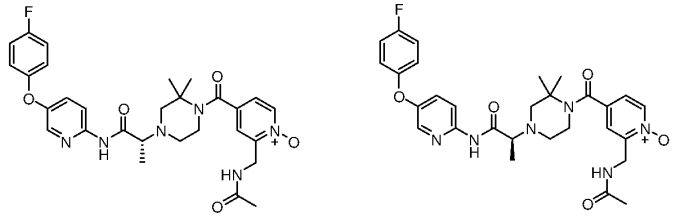
To a solution of 2-{[(tert-butoxycarbonyl)(methyl)amino]methyl}pyridine-4-carboxylic acid (35 mg, 0.131 mmol, 1 equiv) in DMF (10mL) was added 2-(3,3-dimethylpiperazin-1-yl)-N-[5-(4-fluorophenoxy) pyridin-2-yl]propanamide (48.95 mg, 0.131 mmol, 1 equiv) and HATU (99.95 mg, 0.262 mmol, 2 equiv) and DIEA (67.95 mg, 0.524 mmol, 4 equiv) at rt .The resulting mixture was stirred for 3h at rt. The reaction mixture was quenched by water and extracted with EA (3*20 mL).The combined organic extracts were washed with brine (10mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography(0-20% DCM/MeOH) to afford product 2-{[(tert-butoxycarbonyl)(methyl)amino]methyl}-4-[4-(1-{[5-(4-fluorophenoxy)pyridin-2-yl]carbamoyl}ethyl)-2,2-dimethylpiperazine-1-carbonyl]pyridin-1-ium-1-olate (45 mg, 53.77%) as a white solid. MS (ESI): mass calcd for $C_{33}H_{41}FN_6O_6$ 636.31 m/z, found 637.10 $[M+H]^+$.



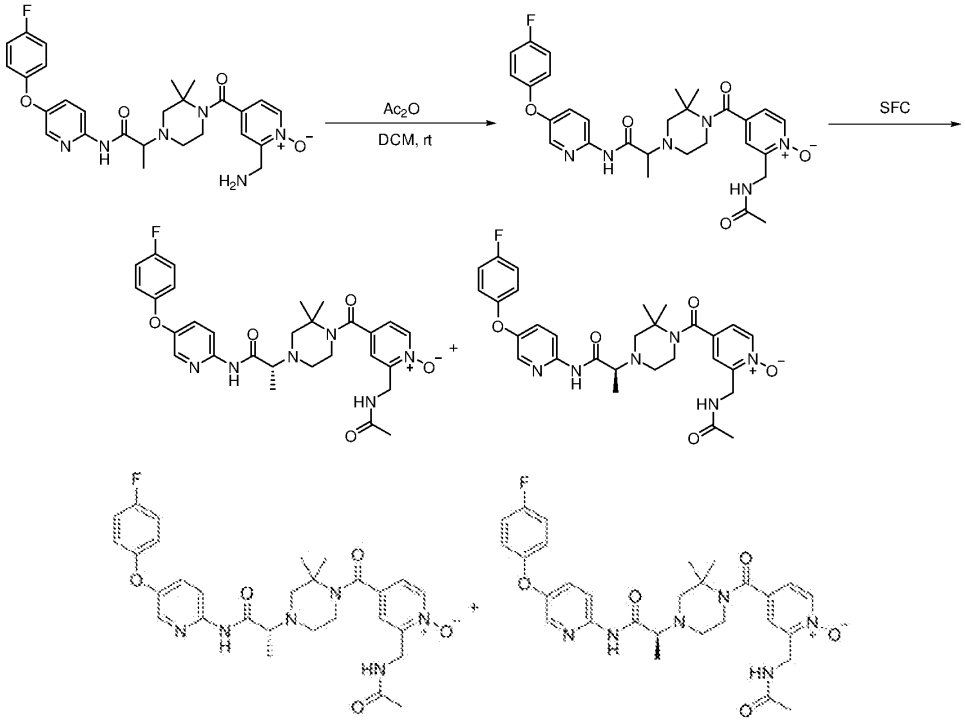
4-{4-[(1R)-1-{[5-(4-fluorophenoxy)pyridin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}-2-[(methylamino)methyl]pyridin-1-ium-1-olate and 4-{4-[(1S)-1-{[5-(4-fluorophenoxy)pyridin-2-yl]carbamoyl} ethyl]-2,2-dimethylpiperazine-1-carbonyl}-2-[(methylamino)methyl]pyridin-1-ium-1-olate

To a solution of 2-{[(tert-butoxycarbonyl)(methyl)amino]methyl}-4-[4-(1-{[5-(4-fluorophenoxy) pyridin-2-yl]carbamoyl}ethyl)-2,2-dimethylpiperazine-1-carbonyl]pyridin-1-ium-1-olate (45 mg, 0.071 mmol, 1 equiv) in EA(1 mL), was added hydrochloric acid (4N, in EA) (2 mL) at rt. The resulting mixture was stirred for 2h at rt. The product was precipitated by the addition of anhydrous ether. The precipitated solids were collected by filtration and washed with anhydrous ether to afford crude product. The crude product was separated by chiral-HPLC using a CHIRALPAK IF Column, 2*25 cm*5 μm column (eluent: 50% (v/v) Hex: DCM=3: 1(0.5% 2M NH_3-MeOH) and EtOH) to afford 4-{4-[(1R)-1-{[5-(4-fluorophenoxy)pyridin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}-2-[(methylamino)methyl]pyridin-1-ium-1-olate (1.9 mg) as a white solid. MS (ESI): mass calcd. for $C_{28}H_{33}FN_6O_4$, 536.25 found: 537.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.27 (d, J = 6.6 Hz, 1H), 8.11 – 8.20 (m, 2H), 7.48 – 7.58 (m, 2H), 7.30 – 7.38 (m, 1H), 7.17 – 7.30 (m, 2H), 7.04 – 7.16 (m, 2H), 3.75 (s, 2H), 2.68 – 2.78 (m, 1H), 2.58 – 2.65 (m, 1H), 2.42 – 2.50 (m, 4H), 2.26 – 2.33 (m, 3H),1.47 (d, J = 2.4 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -119.82. And 4-{4-[(1S)-1-{[5-(4-fluorophenoxy)pyridin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}-2-[(methylamino)methyl]pyridin-1-ium-1-olate (2.0 mg) as a white solid. MS (ESI): mass calcd. for $C_{28}H_{33}FN_6O_4$, 536.25 found: 537.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.27 (d, J = 6.6 Hz, 1H), 8.11 – 8.22 (m, 2H), 7.48 – 7.57 (m, 2H), 7.30 – 7.39 (m, 1H), 7.17 – 7.31 (m, 2H), 7.04 – 7.16 (m, 2H), 3.76 (s, 2H), 3.51 (q, J = 6.8 Hz, 1H), 2.67– 2.77 (m, 1H), 2.55 – 2.63 (m, 1H), 2.45 – 2.48(m, 4H), 2.26 – 2.33 (m, 3H), 1.47 (d, J = 2.4 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -119.82.

Example 82: 2-(acetamidomethyl)-4-{4-[(1R)-1-{[5-(4-fluorophenoxy)pyridin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}pyridin-1-ium-1-olate and Example 83: 2-(acetamidomethyl)-4-{4-[(1S)-1-{[5-(4-fluorophenoxy)pyridin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}pyridin-1-ium-1-olate



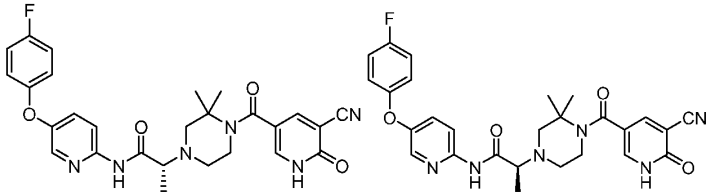
Synthetic Scheme



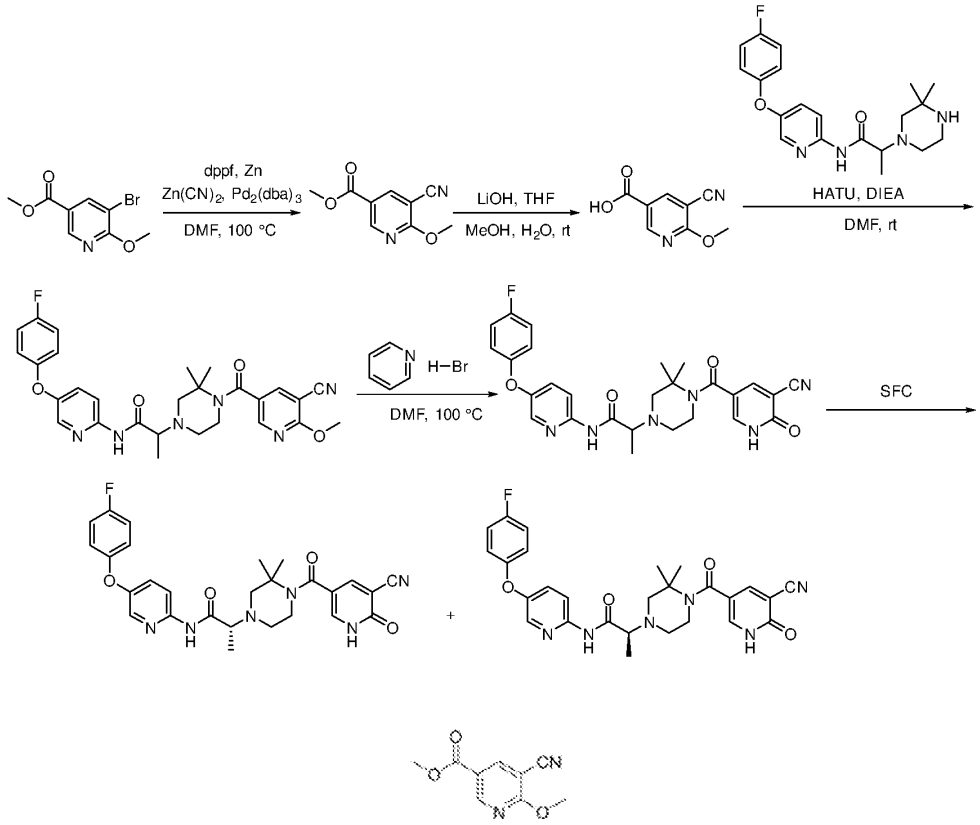
2-(acetamidomethyl)-4-{4-[(1R)-1-{[5-(4-fluorophenoxy)pyridin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}pyridin-1-ium-1-olate AND 2-(acetamidomethyl)-4-{4-[(1S)-1-{[5-(4-fluorophenoxy)pyridin-2-yl]carbamoyl}ethyl]-2,2 -dimethylpiperazine-1-carbonyl}pyridin-1-ium-1-olate

To a solution of 2-(aminomethyl)-4-[4-(1-{[5-(4-fluorophenoxy)pyridin-2-yl]carbamoyl}ethyl)-2,2-dimethylpiperazine-1-carbonyl]pyridin-1-ium-1-olate (55 mg, 0.105 mmol, 1 equiv) in DCM (1 mL), was added Ac_2O (0.2 mL) at rt. The resulting mixture was stirred for 4 h at rt. The product was precipitated by the addition of anhydrous ether. The precipitated solids were collected by filtration and washed with anhydrous ether. The crude is separated by chiral-HPLC using a chiral-HPLC using a CHIRALPAK IG, 2*25 cm, 5 μm column (eluent: 60% (v/v) Hex: DCM=3: 1(0.5% 2M NH3-MeOH) and EtOH) to afford 2-(acetamidomethyl)-4-{4-[(1R)-1-{[5-(4-fluorophenoxy)pyridin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}pyridin-1-ium-1-olate (8.3 mg) as a white solid. MS (ESI): mass calcd. for $C_{29}H_{33}FN_6O_5$, 564.25 found: 656.30 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.23 (s, 1H), 8.47 (t, J = 6.0 Hz, 1H), 8.30 (d, J = 6.6 Hz, 1H), 8.11 – 8.20 (m, 2H), 7.53 (dd, J = 9.0, 3.1 Hz, 1H), 7.38 (dd, J = 6.6, 2.5 Hz, 1H), 7.17 – 7.32 (m, 3H), 7.03 – 7.16 (m, 2H), 4.32 (d, J = 5.9 Hz, 2H), 3.53 (q, J = 6.6 Hz, 1H), 2.56– 2.77 (m, 2H), 2.50 – 2.54 (m, 2H), 2.45 – 2.48(m, 2H), 1.91 (s, 3H), 1.46 (d, J = 3.7 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -119.83. And 2-(acetamidomethyl)-4-{4-[(1S)-1-{[5-(4-fluorophenoxy)pyridin-2-yl]carbamoyl}ethyl]-2,2 -dimethylpiperazine-1-carbonyl}pyridin-1-ium-1-olate (8.8 mg). MS (ESI): mass calcd. for $C_{29}H_{33}FN_6O_5$, 564.25 m/z found: 656.30 $[M+H]^+$.^1H NMR (300 MHz, DMSO-d_6) δ 10.23 (s, 1H), 8.47 (t, J = 5.9 Hz, 1H), 8.30 (d, J = 6.6 Hz, 1H), 8.11 – 8.20 (m, 2H), 7.53 (dd, J = 8.9, 3.1 Hz, 1H), 7.38 (dd, J = 6.6, 2.5 Hz, 1H), 7.17 – 7.32 (m, 3H), 7.04 – 7.16 (m, 2H), 4.32 (d, J = 5.9 Hz, 2H), 3.53 (q, J = 6.7 Hz, 1H), 2.56 – 2.76 (m, 2H), 2.50 – 2.54 (m, 2H), 2.45 – 2.48(m, 2H), 1.91 (s, 3H), 1.46 (d, J = 3.7 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ-119.83.

Example 84: (R)-2-(4-(5-cyano-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propenamide and Example 85: (S)-2-(4-(5-cyano-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide



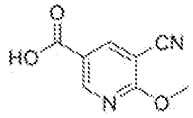
Synthetic Scheme



methyl 5-cyano-6-methoxynicotinate

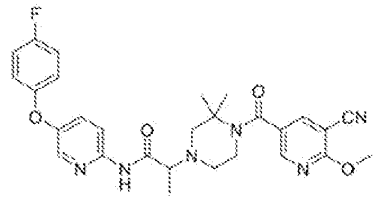
To a solution of methyl 5-bromo-6-methoxypyridine-3-carboxylate (300 mg, 1.219 mmol, 1 equiv) in dimethylformamide (10 mL) the mixture was added zinc cyanide (286.32 mg, 2.438 mmol, 2 equiv) $Pd_2(dba)_3$ (66.99 mg, 0.073 mmol, 0.06 equiv) dppf (80.82 mg, 0.146 mmol, 0.12 equiv) and Zn (2.39 mg, 0.037 mmol, 0.03 equiv). The mixture was stirred at 100 °C for 2 h under N_2. After completion of reaction, the mixture was quenched with water (30 mL) extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% EA/PE) to afford

methyl 5-cyano-6-methoxynicotinate (130 mg, 55.48%) as a yellow solid. MS (ESI): mass calcd. for $C_9H_8N_2O_3$: 192.05, found: 193.10 $[M+H]^+$.



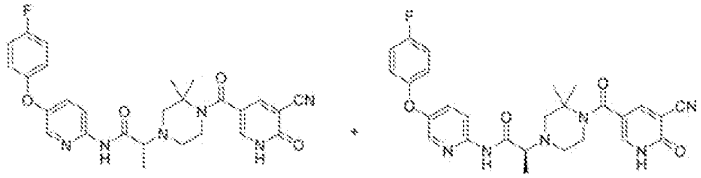
5-cyano-6-methoxynicotinic acid

To a solution of methyl 5-cyano-6-methoxypyridine-3-carboxylate (130 mg, 0.676 mmol, 1 equiv) in THF (2 mL) MeOH (1 mL) and H_2O (1 mL). The mixture was stirred at room temperature for 2 h. After completion of reaction, the mixture was acidified to pH=3 with (2 N HCl) extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated to afford 5-cyano-6-methoxynicotinic acid (102 mg, 84.64%) as a yellow solid. MS (ESI): mass calcd. for $C_8H_6N_2O_3$: 178.04, found: 179.10 $[M+H]^+$.



2-(4-(5-cyano-6-methoxynicotinoyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

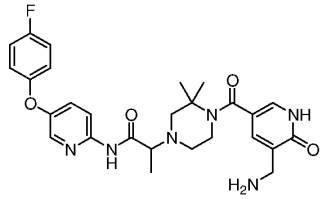
To a solution of 5-cyano-6-methoxypyridine-3-carboxylic acid (100 mg, 0.561 mmol, 1 equiv) in N,N-dimethylformamide (5 mL) the mixture was added 2-(3,3-dimethylpiperazin-1-yl)-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (209.07 mg, 0.561 mmol, 1.0 equiv), HATU (320.16 mg, 0.842 mmol, 1.5 equiv) then added DIEA (217.65 mg, 1.683 mmol, 3.0 equiv). The mixture was stirred at room temperature for 2 h. After completion of reaction the mixture was quenched with water (10 mL) extracted with ethyl acetate (3 x 10 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford 2-(4-(5-cyano-6-methoxynicotinoyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (160 mg, 53.52%) as a yellow solid. MS (ESI): mass calcd. for $C_{28}H_{29}FN_6O_4$: 532.22, found: 533.05 $[M+H]^+$.



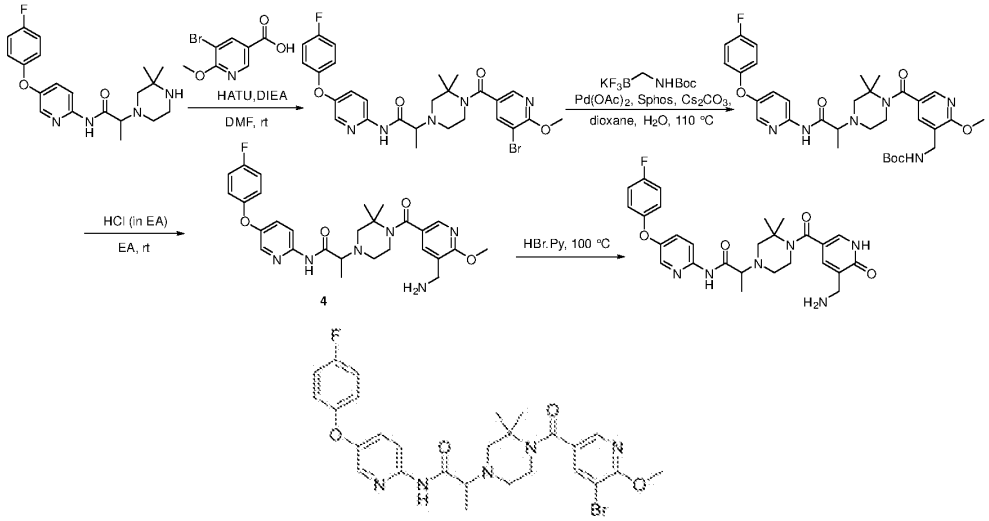
(R)-2-(4-(5-cyano-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide and (S)-2-(4-(5-cyano-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

To a solution of 2-[4-(5-cyano-6-methoxypyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl]-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (100 mg, 0.188 mmol, 1 equiv) in N,N-dimethylformamide(DMF) (2 mL) the mixture was added Pyridine hydrobromide (150.22 mg, 0.940 mmol, 5.0 equiv). The reaction was stirred at 100°C for 3 h. The mixture was concentrated to dryness under reduced pressure to provide the crude product, which was purified by chiral-HPLC using a CHIRALPAK IA, 2*25 cm, 5 μm column (eluent: 40% (v/v) MtBE (0.5% 2M NH_3-MeOH) and IPA: DCM=1: 1 to afford (R)-2-(4-(5-cyano-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (13.0 mg, 12.82%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{27}FN_6O_4$: 518.21, found: 519.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 11.98 – 12.70 (br, 1H), 10.18 (s, 1H), 8.11 – 8.20 (m, 3H), 7.93 (d, J = 2.6 Hz, 1H), 7.53 (dd, J = 9.0, 3.1 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.02 – 7.16 (m, 2H), 3.50 (q, J = 6.8 Hz, 1H), 3.32 – 3.42 (m, 2H), 2.69 – 2.81 (m, 1H), 2.57 – 2.69 (m, 1H), 2.35 – 2.50 (m, 2H), 1.42 (d, J = 2.3 Hz, 6H), 1.14 – 1.27 (m, 3H). And (S)-2-(4-(5-cyano-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (21.5 mg, 21.91%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{27}FN_6O_4$: 518.21, found: 519.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 11.79 – 12.52 (br, 1H), 10.18 (s, 1H), 8.11 – 8.20 (m, 3H), 7.93 (d, J = 2.6 Hz, 1H), 7.53 (dd, J = 9.0, 3.1 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.02 – 7.16 (m, 2H), 3.50 (q, J = 6.8 Hz, 1H), 3.32 – 3.42 (m, 2H), 2.69 – 2.81 (m, 1H), 2.59 – 2.69 (m, 1H), 2.35 – 2.49 (m, 2H), 1.42 (d, J = 2.3 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H).

Example 86: 2-(4-(5-(aminomethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

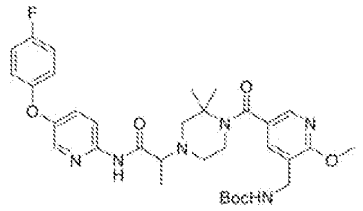


Synthetic Scheme



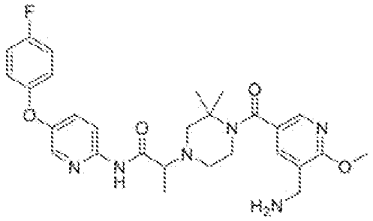
2-(4-(5-bromo-6-methoxynicotinoyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

To a solution of 2-(3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (1 g, 2.685 mmol, 1 equiv) in DMF (20 mL) the mixture was added 5-bromo-6-methoxynicotinic acid (623 mg, 2.685 mmol, 1 equiv), HATU (1.83 g, 4.027 mmol, 1.5 equiv), and N,N-diisopropylethylamine (1.39 g, 10.740 mmol, 4 equiv) at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenche d by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to give 2-(4-(5-bromo-6-methoxynicotinoyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (600 mg, 35.06%) a white solid. MS (ESI): mass calcd. for $C_{27}H_{29}BrFN_5O_4$: 585.13, found: 586.20 $[M+H]^+$.



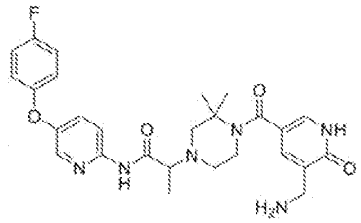
tert-butyl ((5-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-methoxypyridin-3-yl)methyl)carbamate

In a 40-mL round bottom flask, to a solution of 2-(4-(5-bromo-6-methoxynicotinoyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (600 mg, 35.06%) (1 g, 1.705 mmol, 1 equiv) in dioxane (20 mL) and H_2O (2 mL) was added tert-butyl N-[(trifluoro-lambda4-boranyl)methyl]carbamate potassium (0.81 g, 3.410 mmol, 2 equiv), $Pd(OAc)_2$ (0.04 g, 0.171 mmol, 0.1 equiv), Cs_2CO_3 (1.11 g, 3.410 mmol, 2 equiv) and Sphos (0.07 g, 0.171 mmol, 0.1 equiv) at room temprature under. The reaction mixture was stirred at 110 °C for 3 h under N_2. After completion of reaction, the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% EA/PE) to afford tert-butyl ((5-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-methoxypyridin-3-yl)methyl)carbamate (120 mg, 71.19%). MS (ESI): mass calcd. for $C_{33}H_{41}FN_6O_6$: 636.30 m/z. found 637.15 $[M+H]^+$.



2-(4-(5-(aminomethyl)-6-methoxynicotinoyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

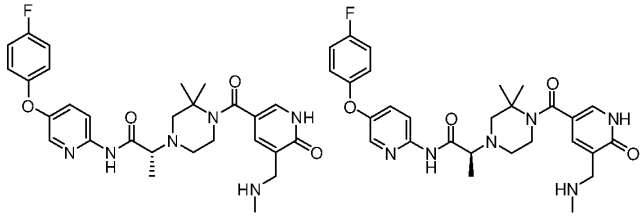
To a stirred solution of 2-(4-(5-(aminomethyl)-6-methoxynicotinoyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (200 mg, 0.314 mmol, 1 equiv) in EA (5 mL) was added HCl (4 M in EA, 5 mL). The reaction mixture was stirred at room temperature for 1 h. The product was precipitated by the addition of diethyl ether. The product is obtained (120 mg, 71.19%) by filtration and drying. MS (ESI): mass calcd. for $C_{28}H_{33}FN_6O_4$: 536.25, m/z, found: 537.15 $[M+H]^+$.



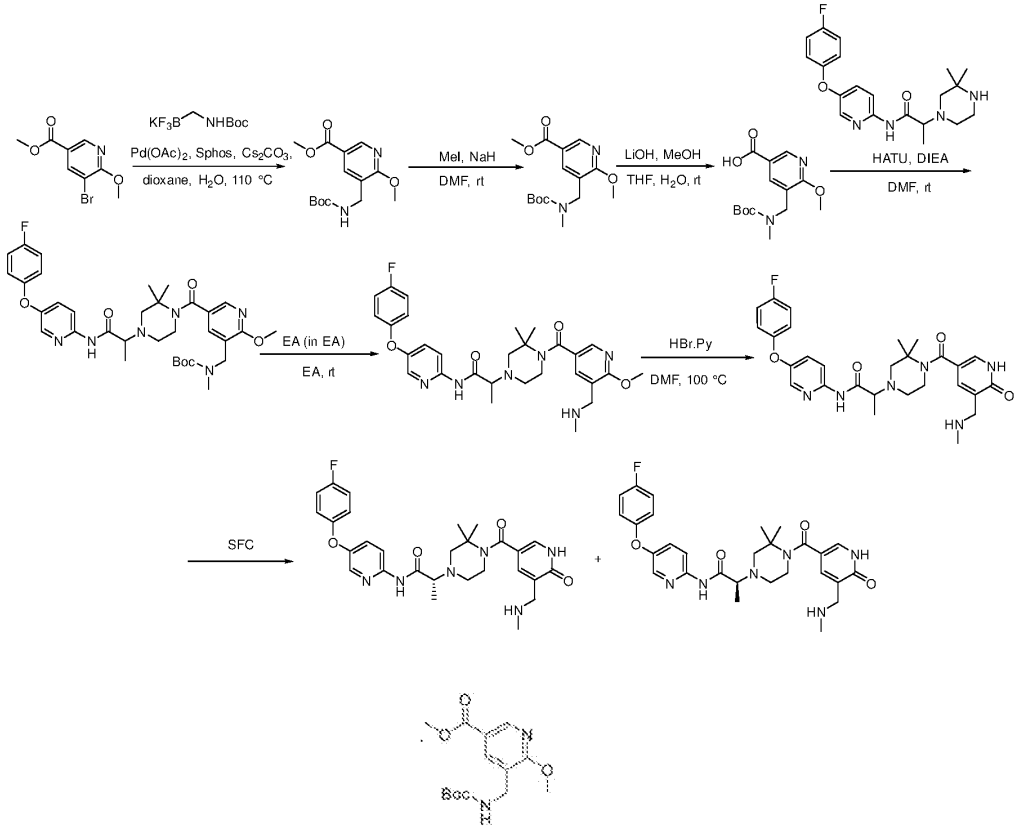
2-(4-(5-(aminomethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

To a solution of 2-(4-(5-(aminomethyl)-6-methoxynicotinoyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (100 mg, 0.186 mmol, 1 equiv) in DMF (5 mL) the mixture was added pyridine hydrobromide (149.10 mg, 0.930 mmol, 5 equiv) . The mixture was stirred at 100°C for 2h. The mixture was concentrated to dryness under reduced pressure to provide the crude product, which was purified by C18 Column (CH_3CN & H_2O with 10 mmol/L NH_4HCO_3) to afford 2-(4-(5-(aminomethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide as a white solid. MS (ESI): mass calcd. for $C_{27}H_{31}FN_6O_4$: 522.24, found: 523.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H), 8.12 – 8.19 (m, 2H), 7.44 – 7.57 (m, 3H), 7.19 – 7.32 (m, 2H), 7.05 – 7.15 (m, 2H), 3.44 – 3.54 (m, 3H), 3.34 – 3.42 (m, 1H), 2.56 – 2.78 (m, 3H), 2.42 (s, 2H), 1.42 (d, J = 2.2 Hz, 6H), 1.18 – 1.27 (m, 3H).

Example 87: (R)-2-(3,3-dimethyl-4-(5-((methylamino)methyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide and Example 88: (S)-2-(3,3-dimethyl-4-(5-((methylamino)methyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

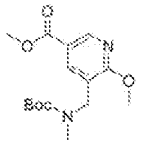


Synthetic Scheme



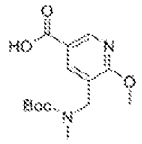
Synthesis of methyl 5-(((tert-butoxycarbonyl)amino)methyl)-6-methoxynicotinate

In a 40-mL round bottom flask, to a solution of methyl 5-bromo-6-methoxypyridine-3-carboxylate (800 mg, 3.251 mmol, 1 equiv) in dioxane (20 mL) and H_2O (2 mL) was added tert-butyl N-[(trifluoro-lambda4-boranyl)methyl]carbamate potassium (1541.54 mg, 6.502 mmol, 2 equiv), $Pd(OAc)_2$ (72.99 mg, 0.325 mmol, 0.1 equiv), Cs_2CO_3 (2125.19 mg, 6.502 mmol, 2 equiv) and Sphos (133.48 mg, 0.325 mmol, 0.1 equiv) at room temprature. The reaction mixture was stirred at 110 °C for 3 h under N_2. After completion of reaction, the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% EA/PE) to afford methyl 5-(((tert-butoxycarbonyl)amino)methyl)-6-methoxynicotinate (600 mg, 56.67%). MS (ESI): mass calcd. for $C_{14}H_{20}N_2O_5$: 296.13 m/z. found 297.20 [M+H]+.



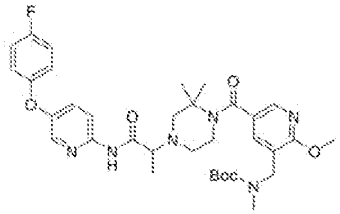
methyl 5-(((tert-butoxycarbonyl)(methyl)amino)methyl)-6-methoxynicotinate

To a solution of methyl 5-(((tert-butoxycarbonyl)amino)methyl)-6-methoxynicotinate (500 mg, 1.687 mmol, 1 equiv) in dimethylformamide (5 mL) was treated with sodium hydride (60.74 mg, 2.530 mmol, 1.5 equiv) for 30 min at 0 °C under nitrogen atmosphere followed by the addition of methyl iodide (359.25 mg, 2.530 mmol, 1.5 equiv) dropwise in at rt. The resulting mixture was stirred for 2 hours at rt. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% PE/EA) to give methyl 5-(((tert-butoxycarbonyl)(methyl)amino)methyl)-6-methoxynicotinate (400 mg, 71.04%) as a white solid. MS (ESI): mass calcd. for $C_{15}H_{22}N_2O_5$: 310.15, found: 311.15$[M+H]^+$.



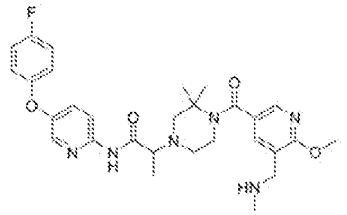
5-(((tert-butoxycarbonyl)(methyl)amino)methyl)-6-methoxynicotinic acid

To a stirred solution of methyl 5-{[(tert-butoxycarbonyl)(methyl)amino]methyl}-6-methoxypyridine-3-carboxylate (400 mg, 1.611 mmol, 1 equiv) in methanol (3 mL), H_2O (3 mL) and THF (6 mL) was added LiOH (92 mg, 3.87 mmol, 3 equiv) at room temperature. The reaction mixture was stirred at room temperature for a period of 3 h. The mixture was concentrated to dryness under reduced pressure to provide the crude product, which was purified by C18 column (0-20% H_2O/ACN) to afford 5-(((tert-butoxycarbonyl)(methyl)amino)methyl)-6-methoxynicotinic acid (300 mg, 78.7%). MS (ESI): mass calcd. for $C_{14}H_{20}N_2O_5$: 296.13 m/z. found 297.15 $[M+H]^+$.



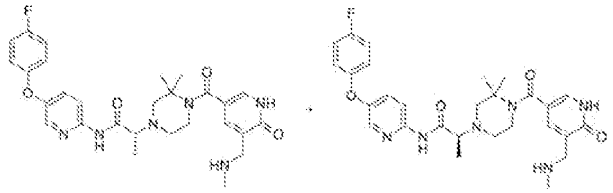
tert-butyl ((5-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-methoxypyridin-3-yl)methyl)(methyl)carbamate

To a solution of 5-{[(tert-butoxycarbonyl)(methyl)amino]methyl}-6-methoxypyridine-3-carboxylic acid (200 mg, 0.675 mmol, 1 equiv) in DMF (10 mL) the mixture was added2-(3,3-dimethylpiperazin-1-yl)-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (251.38 mg, 0.675 mmol, 1 equiv) , [(dimethylamino)({[1,2,3] triazolo[4,5-b]pyridin-3-yloxy})methylidene]dimethylazanium; hexafluoro-lambda5-phosphanuide (384.95 mg, 1.013 mmol, 1.5 equiv) and N,N-diisopropylethylamine (348.94 mg, 2.700 mmol, 4 equiv) at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to give tert-butyl ((5-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-methoxypyridin-3-yl)methyl)(methyl)carbamate (210 mg, 47.81%) a white solid. MS (ESI): mass calcd. for $C_{34}H_{43}FN_6O_6$: 650.33, found: 651.20[M+H]$^+$.



N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-methoxy-5-((methylamino)methyl)nicotinoyl)-3,3-dimethylpiperazin-1-yl)propanamide

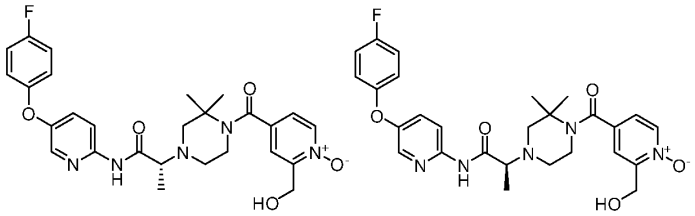
To a stirred solution of tert-butyl N-({5-[4-(1-{[5-(4-fluorophenoxy)pyridin-2-yl]carbamoyl}ethyl)-2,2-dimethylpiperazine-1-carbonyl]-2-methoxypyridin-3-yl}methyl)-N-methylcarbamate (200 mg, 0.307 mmol, 1 equiv) in EA (3 mL) was added HCl (4 M in EA, 3 mL). The reaction mixture was stirred at room temperature for 1 h. The product was precipitated by the addition of diethyl ether. The product is obtained (150 mg, 51.24%) by filtration and drying. MS (ESI): mass calcd. for $C_{29}H_{35}FN_6O_4$: 550.27m/z, found: 551.20 [M+H +.



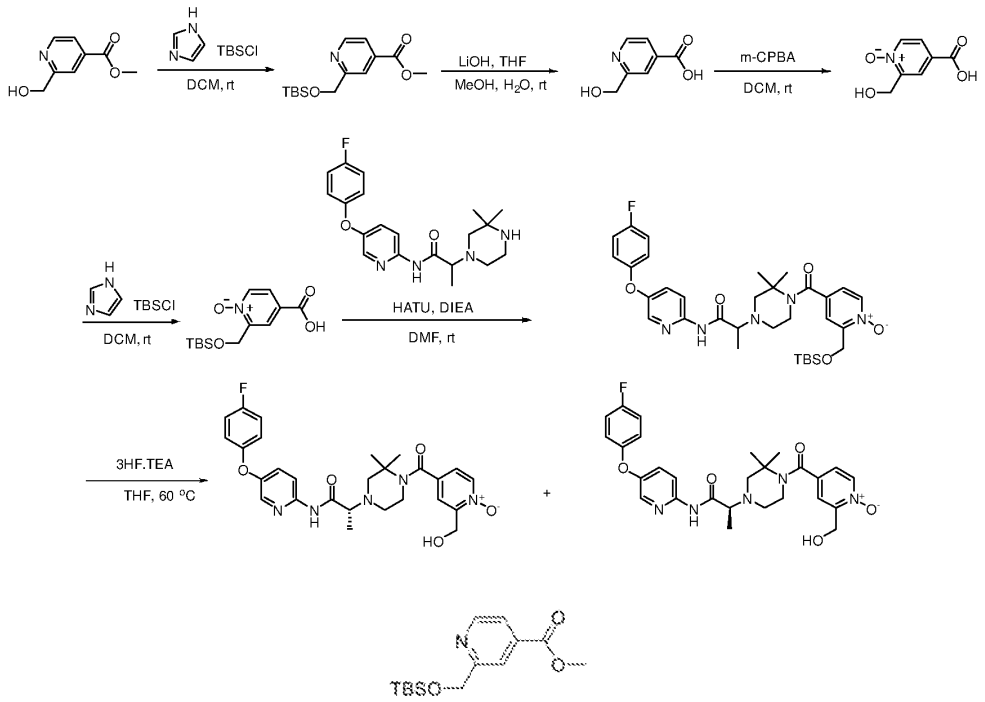
(R)-2-(3,3-dimethyl-4-(5-((methylamino)methyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propenamide and (S)-2-(3,3-dimethyl-4-(5-((methylamino)methyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

To a solution of N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-methoxy-5-((methylamino)methyl)nicotinoyl)-3,3-dimethylpiperazin-1-yl)propanamide (100 mg, 0.182 mmol, 1 equiv) in DMF (10 mL) the mixture was added pyridine hydrobromide (145.30 mg, 0.910 mmol, 5 equiv) . The mixture was stirred at 100 °C for 2h. The mixture was concentrated to dryness under reduced pressure to provide the crude product, which was purified by chiral-HPLC using a CHIRALPAK IG, 2*25 cm, 5 μm column (eluent: 50% (v/v) EtOH and MTBE with 0.1% DEA) to afford (R)-2-(3,3-dimethyl-4-(5-((methylamino)methyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (14.2 mg, 14.19%) as a white solid. MS(ESI): mass calcd. for $C_{28}H_{33}FN_6O_4$: 536.25, found: 537.30 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6) δ 10.18 (s, 1H), 8.12 – 8.18 (m, 2H), 7.41 – 7.57 (m, 3H), 7.19 – 7.29 (m, 2H), 7.06 – 7.15 (m, 2H), 3.49 (d, J = 6.9 Hz, 1H), 3.43 (s, 2H), 3.35 – 3.41 (m, 2H), 2.73 (d, J = 5.5 Hz, 1H), 2.63 (d, J = 5.4 Hz, 1H), 2.42 (s, 2H), 2.27 (s, 3H), 1.42 (d, J = 2.4 Hz, 6H), 1.18 – 1.27 (m, 3H) And (S)-2-(3,3-dimethyl-4-(5-((methylamino)methyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (18.5 mg, 18.70%) as a white solid. MS (ESI): mass calcd. for $C_{28}H_{33}FN_6O_4$: 536.25, found: 537.30 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.18 (s, 1H), 8.12 – 8.19 (m, 2H), 7.41 – 7.57 (m, 3H), 7.19 – 7.29 (m, 2H), 7.05 – 7.15 (m, 2H), 3.44 – 3.54 (m, 1H), 3.43 (s, 2H),3.36 – 3.40 (m, 2H), 2.70 – 2.78 (m, 1H), 2.58 – 2.66 (m, 1H), 2.42 (s, 2H), 2.27 (s, 3H), 1.42 (d, J = 2.4 Hz, 6H), 1.18 – 1.26 (m, 3H).

Example 89: (R)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide and Example 90: (S)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide



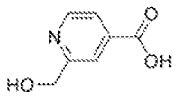
Synthetic Scheme



methyl 2-(((tert-butyldimethylsilyl)oxy)methyl)isonicotinate

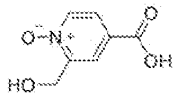
To a solution of methyl 2-(hydroxymethyl)pyridine-4-carboxylate (1 g, 5.982 mmol, 1 equiv) in DCM (10 mL) was added imidazole (1.22 g, 17.946 mmol, 3 equiv), t-butyldimethylchlorosilane (1.35 g, 8.973 mmol, 1.5 equiv) at rt , the mixture was stirred for overnight at rt , the reaction mixture was quenched by water and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford methyl 2-(((tert-

butyldimethylsilyl)oxy)methyl)isonicotinate (1.2 g, 71.28%) as a yellow solid. MS (ESI): mass calcd. for $C_{14}H_{23}NO_3Si$: 281.10 m/z, found: 282.15$[M+H]^+$.



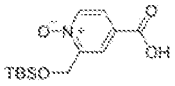
2-(hydroxymethyl)isonicotinic acid

To a solution of methyl 2-(((tert-butyldimethylsilyl)oxy)methyl)isonicotinate (600 mg, 2.132 mmol, 1 equiv) in MeOH (3 mL), THF (10 mL), H_2O (3 mL) was added LiOH (102.12 mg, 4.264 mmol, 2 equiv) at rt , the mixture was stirred for overnight at rt , the reaction mixture was concentrated under vacuumwas added water and the mixture was acidified to pH = 5 with 4N HCl, extracted with EA (3*30 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 2-(hydroxymethyl)isonicotinic acid (300 mg, 91.89%) as a yellow solid. MS (ESI): mass calcd. for $C_7H_7NO_3$:153.10 m/z, found: 154.10 $[M+H]^+$.



4-carboxy-2-(hydroxymethyl)pyridine 1-oxide

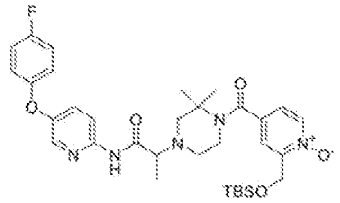
To a solution of 2-(hydroxymethyl)isonicotinic acid (300 mg, 1.959 mmol, 1 equiv) in DCM (6.00 mL, 94.385 mmol, 48.18 equiv) was added m-CPBA (676.10 mg, 3.918 mmol, 2 equiv), the mixture was stirred for 2 h at rt. the reaction mixture was quenched by water and extracted with EA (3*30 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 4-carboxy-2-(hydroxymethyl)pyridine 1-oxide (150 mg, 45.27%) as a yellow solid. MS (ESI): mass calcd. for $C_7H_7NO_4$:169.10 m/z, found: 170.15 $[M+H]^+$.



2-(((tert-butyldimethylsilyl)oxy)methyl)-4-carboxypyridine 1-oxide

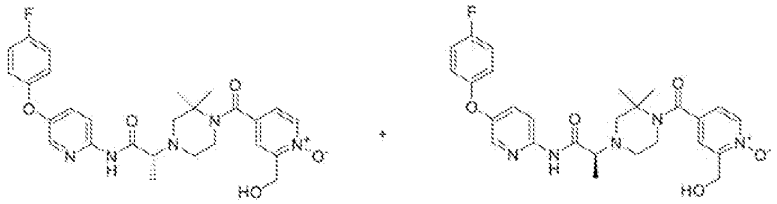
To a solution of 4-carboxy-2-(hydroxymethyl)pyridine 1-oxide (150 mg, 0.887 mmol, 1 equiv) in DCM (3 mL) was added imidazole (181.13 mg, 2.661 mmol, 3 equiv) t-

butyldimethylchlorosilane (267.34 mg, 1.774 mmol, 2 equiv), t-butyldimethylchlorosilane (35.64 mg, 0.236 mmol, 2 equiv), the mixture was stirred for 2 h at rt. the reaction mixture was quenched by water and extracted with EA (3*30 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 2-(((tert-butyldimethylsilyl)oxy)methyl)-4-carboxypyridine 1-oxide (100 mg, 39.79%) as a yellow solid. MS (ESI): mass calcd. for $C_{13}H_{21}NO_4Si$: 283.10 m/z, found: 284.15 $[M+H]^+$.



2-(((tert-butyldimethylsilyl)oxy)methyl)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

To a solution of 2-(((tert-butyldimethylsilyl)oxy)methyl)-4-carboxypyridine 1-oxide (50 mg, 0.176 mmol, 1 equiv) in dimethylformamide (2 mL) was added 2-(3,3-dimethylpiperazin-1-yl)-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (65.71 mg, 0.176 mmol, 1 equiv), HATU (100.63 mg, 0.264 mmol, 1.5 equiv), DIEA (45.61 mg, 0.352 mmol, 2 equiv), the mixture was stirred for 2 h at rt. the reaction mixture was quenched by water and extracted with EA (3*30 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 2-(((tert-butyldimethylsilyl)oxy)methyl)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (50 mg, 44.43%) as a yellow solid. MS (ESI): mass calcd. for $C_{33}H_{44}FN_5O_5Si$: 637.10 m/z, found: 638.15 $[M+H]^+$.

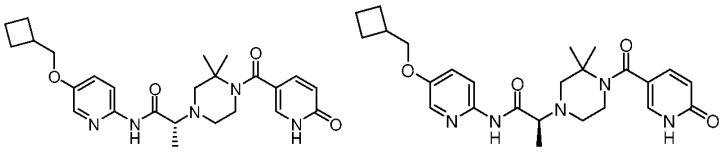


(R)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide and (S)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide

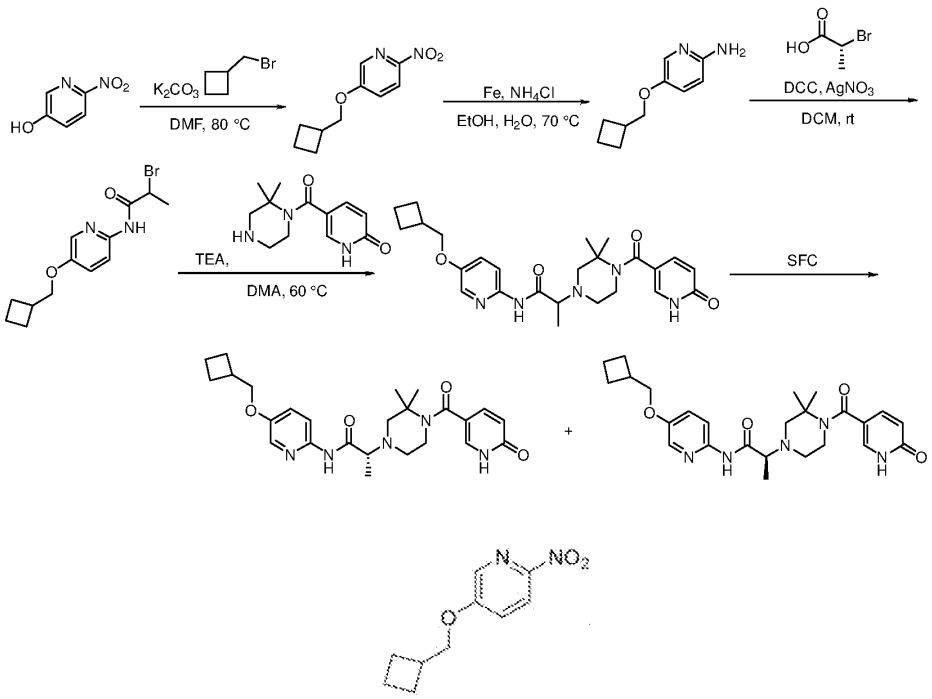
To a solution of 2-(((tert-butyldimethylsilyl)oxy)methyl)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (50 mg, 0.078 mmol, 1 equiv) in tetrahydrofuran (2 mL) with Triethylamine trihydrofluoride (0.5 mL).The resulting mixture was stirred for 3 h at 60°C. After cooled to room temperature the reaction reaction mixture was quenched by water and extracted with EA (3*20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 30 mg crude product as a white solid. The compound was separated by chiral-HPLC using a CHIRAL Amylose-SA, 4.6*150 mml.D.S-5um column (eluent: 50% (v/v) Hex: DCM=3: 1(0.5% 2M NH_3-MeOH) and EtOH) to afford (R)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide (2.1 mg, 5.10%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{30}FN_5O_5$ 523.22 m/z, found 524.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.26 (d, J = 6.6 Hz, 1H), 8.11 – 8.20 (m, 2H), 7.48 – 7.58 (m, 2H), 7.35 – 7.38 (m, J = 6.6, 2.5 Hz, 1H), 7.18 – 7.30 (m, 2H), 7.07 – 7.13 (m, 2H), 5.66 (t, J = 5.8 Hz, 1H), 4.58 (d, J = 5.7 Hz, 2H), 3.51 (q, J = 7.0 Hz, 1H), 3.30 – 3.37 (m, 2H), 2.49 – 2.54 (m, 2H), 2.48 (s, 2H), 1.48 (d, J = 2.0 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.831. And (S)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide (2.1 mg, 5.08%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{30}FN_5O_5$ 523.11m/z, found 524.30 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.26 (d, J = 6.6 Hz, 1H), 8.11 – 8.20 (m, 2H), 7.48 – 7.58 (m, 2H), 7.36 (dd, J = 6.6, 2.6 Hz, 1H), 7.17 – 7.30 (m, 2H), 7.10 (ddd, J = 6.7, 5.4, 3.1 Hz, 2H), 5.66 (t, J = 5.8 Hz, 1H), 4.58 (d, J = 5.7 Hz, 2H), 3.51 (q, J = 6.7 Hz, 1H), 3.30 – 3.37 (m, 2H), 2.49 – 2.54 (m, 2H), 2.48 (s, 2H), 1.48 (d, J = 2.0 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.831.

Example 91: (R)-N-(5-(cyclobutylmethoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide and Example 92: (S)-N-(5-

(cyclobutylmethoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

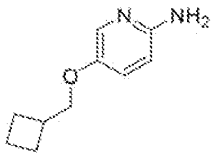


Synthetic Scheme



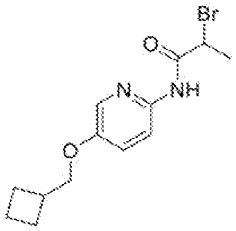
5-(cyclobutylmethoxy)-2-nitropyridine

To a solution of 6-nitropyridin-3-ol (600 mg, 4.283 mmol, 1 equiv) in DMF (5 mL). (bromomethyl)cyclobutane (638.26 mg, 4.283 mmol, 1 equiv) and K_2CO_3 (1.19 g, 8.566 mmol, 2 equiv) was added at rt. The resulting mixture was stirred for 12h at 80 °C. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% PE/EA) to afford 5-(cyclobutylmethoxy)-2-nitropyridine (680 mg, 76.26%) as a yellow oli. MS (ESI): mass calcd. for $C_{10}H_{12}N_2O_3$: 208.08, found:209.15 $[M+H]^+$.



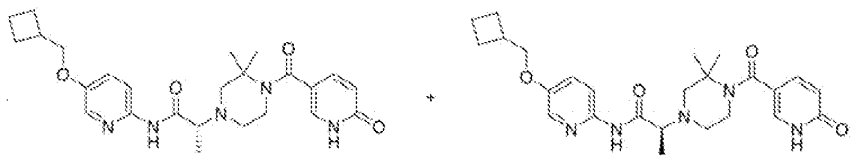
5-(cyclobutylmethoxy)-2-nitropyridine

To a solution of 5-(cyclobutylmethoxy)-2-nitropyridine (400 mg, 1.921 mmol, 1 equiv) in EtOH (8ml) and H_2O (2 mL). Iron (536.41 mg, 9.605 mmol, 5 equiv) and NH_4Cl (513.79 mg, 9.605 mmol, 5 equiv) was added at rt. The resulting mixture was stirred for 12 h at 70 °C. The resulting mixture was concentrated under vacuum, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% PE/EA) to afford 5-(cyclobutylmethoxy)-2-nitropyridine (680 mg, 76.26%) as a yellow oli. MS (ESI): mass calcd. for $C_{10}H_{14}N_2O$:178.11, found:179.10 $[M+H]^+$.



2-bromo-N-(5-(cyclobutylmethoxy)pyridin-2-yl)propanamide

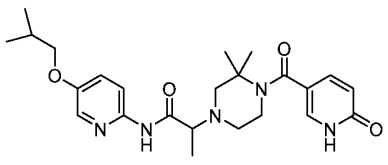
To a solution of 5-(cyclobutylmethoxy)pyridin-2-amine (230 mg, 1.290 mmol, 1 equiv) in DCM (5ml). $AgNO_3$ (32.88 mg, 0.194 mmol, 0.15 equiv), (2R)-2-bromopropanoic acid (236.88 mg, 1.548 mmol, 1.2 equiv) and DCC (319.51 mg, 1.548 mmol, 1.2 equiv) was added at 0 °C. The resulting mixture was stirred for 3h at rt. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% PE/EA) to afford 2-bromo-N-(5-(cyclobutylmethoxy)pyridin-2-yl)propanamide (680 mg, 76.26%) as a yellow oli. MS (ESI): mass calcd. for $C_{13}H_{17}BrN_2O_2$:312.05, found:313.05 $[M+H]^+$.



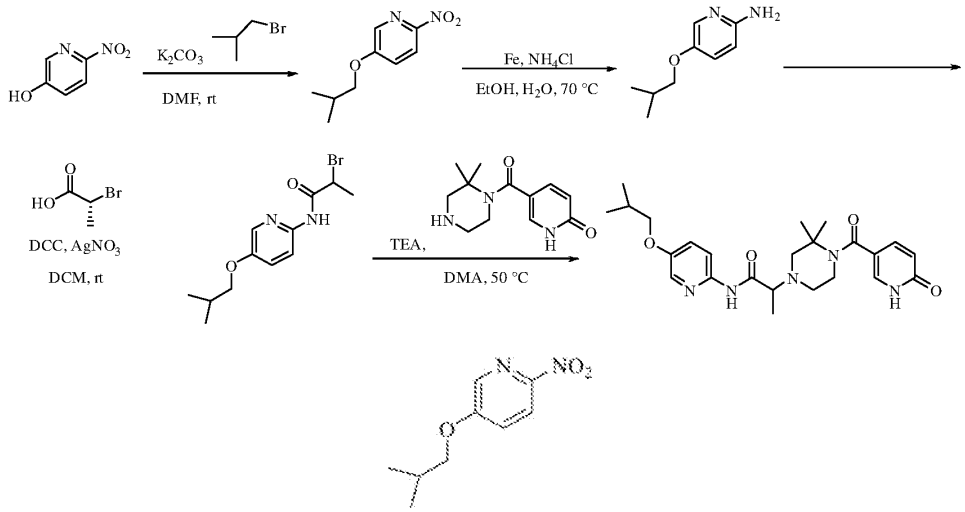
(R)-N-(5-(cyclobutylmethoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propenamide and (S)-N-(5-(cyclobutylmethoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

To a solution of 2-bromo-N-(5-(cyclobutylmethoxy)pyridin-2-yl)propanamide (80 mg, 0.255 mmol, 1 equiv) in DMA (5 mL). 5-(2,2-dimethylpiperazine-1-carbonyl)-1H-pyridin-2-one (60.10 mg, 0.255 mmol, 1 equiv) and TEA (77.54 mg, 0.765 mmol, 3 equiv) was added at rt. The resulting mixture was stirred for 3h at 60 °C. The resulting mixture was extracted with EA (3*100 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-15% DCM/MeOH) and Chiral-HPLC using a CHIRALPAK IG, 2*25 cm, 5 μm column (eluent: 50% (v/v) Hex: DCM=3: 1(0.5% 2M NH3-MeOH) and IPA) to afford (R)-N-(5-(cyclobutylmethoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (14.9 mg, 12.01%). MS (ESI): mass calcd. for $C_{25}H_{33}N_5O_4$: 467.25, found: 468.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 9.97 (s, 1H), 8.01 – 8.01 (m, 2H), 7.56 (d, J = 2.6 Hz, 1H), 7.41 – 7.51 (m, 2H), 6.32 (d, J = 9.5 Hz, 1H), 4.00 (d, J = 6.7 Hz, 2H), 3.41 – 3.50 (m, 1H), 3.32 – 3.41 (m, 2H), 2.67 – 2.77 (m, 2H), 2.56 – 2.66 (m, 1H), 2.40 (d, J = 2.4 Hz, 2H), 2.01 – 2.13 (m, 4H), 1.76 – 2.00 (m, 4H), 1.41 (d, J = 2.5 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H). And (S)-N-(5-(cyclobutylmethoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (16.6 mg, 13.85%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{33}N_5O_4$: 467.25, found: 468.20$[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 9.97 (s, 1H), 8.01 – 8.01 (m, 2H), 7.56 (d, J = 2.6 Hz, 1H), 7.41 – 7.51 (m, 2H), 6.32 (d, J = 9.5 Hz, 1H), 4.00 (d, J = 6.7 Hz, 2H), 3.41 – 3.50 (m, 1H), 3.32 – 3.41 (m, 2H), 2.67 – 2.77 (m, 2H), 2.56 – 2.66 (m, 1H), 2.40 (d, J = 2.4 Hz, 2H), 2.01 – 2.13 (m, 4H), 1.76 – 2.00 (m, 4H), 1.41 (d, J = 2.5 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H). Stereochemistry of example 91 and example 92 was arbitrarily assigned.

Example 93: 2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-isobutoxypyridin-2-yl)propanamide

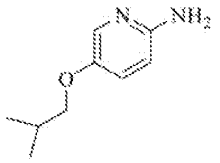


Synthetic Scheme



5-isobutoxy-2-nitropyridine

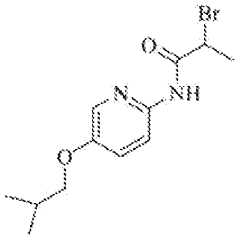
To a stirred solution of 6-nitropyridin-3-ol (800 mg, 5.710 mmol, 1 equiv) in anhydrous DMF (5 mL) was added K_2CO_3 (1589.89 mg, 11.420 mmol, 2 equiv) and isobutyl bromide (782.42 mg, 5.710 mmol, 1 equiv) at room temperature. The reaction mixture was stirred at room temperature for 5h. After completion of reaction, the reaction was quenched by water (50 mL) and extracted with EA (100 mL x 3). The combined organic extracts were washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to 5-isobutoxy-2-nitropyridine (80 mg, 7.93%). MS (ESI): mass calcd. for $C_9H_{12}N_2O_3$: 196.08 m/z, found 197.10 $[M+H]^+$.



5-isobutoxypyridin-2-amine

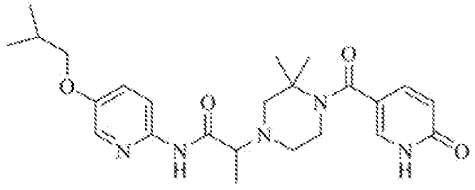
To a stirred solution of 5-isobutoxy-2-nitropyridine (260 mg, 1.325 mmol, 1 equiv) in anhydrous EtOH (4 mL) and H_2O (1 mL) was added Fe (740.02 mg, 13.250 mmol, 10 equiv) and NH_4Cl (708.82 mg, 13.250 mmol, 10 equiv) at room temperature. The reaction mixture was stirred at 70°C for a period of 3 h. The mixture was allowed to cool down to room

temperature. The resulting mixture was filtered, the filter cake was washed with EtOH (3x10 mL). The filtrate was concentrated under reduced pressure. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford 5-isobutoxypyridin-2-amine (190 mg, 35.81%) as a yellow solid. MS (ESI): mass calcd. for $C_9H_{14}N_2O$: 166.11 m/z, found 167.10 $[M+H]^+$.



2-bromo-N-(5-isobutoxypyridin-2-yl)propanamide

To a stirred solution of 5-isobutoxypyridin-2-amine (180 mg, 1.083 mmol, 1 equiv) in anhydrous DCM was added (R)-2-bromopropanoic acid (115.96 mg, 0.758 mmol, 0.7 equiv) and DCC (335.15 mg, 1.624 mmol, 1.5 equiv) followed by catalytic amount of $AgNO_3$ (18.40 mg, 0.108 mmol, 0.1 equiv) at room temperature. The reaction mixture was stirred at room temperature for a period of overnight. After completion of reaction, the reaction was quenched by water (50 mL) and extracted with EA (100 mL x 3). The combined organic extracts were washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford 2-bromo-N-(5-isobutoxypyridin-2-yl)propanamide (110 mg, 33.58%) as a yellow solid. MS (ESI): mass calcd. for $C_{12}H_{17}BrN_2O_2$: 300.05 m/z, found 301.00 $[M+H]^+$.

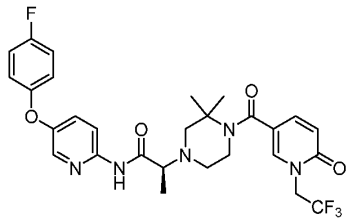


2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-isobutoxypyridin-2-yl)propanamide

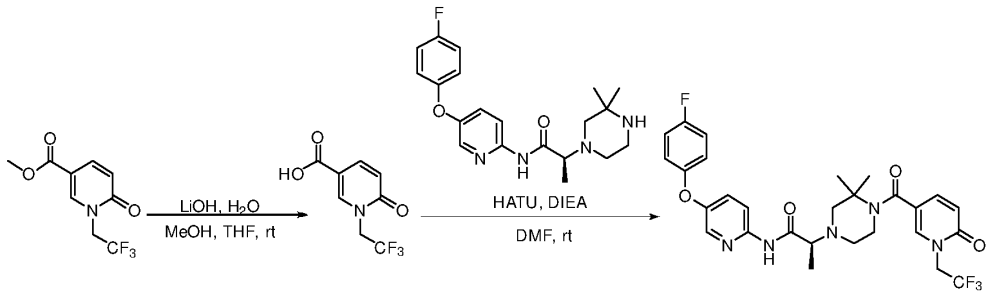
To a stirred solution of 2-bromo-N-(5-isobutoxypyridin-2-yl)propanamide (50 mg, 0.083 mmol, 1 equiv) in anhydrous DMA was added 5-(2,2-dimethylpiperazine-1-carbonyl)pyridin-2(1H)-one (19.53 mg, 0.083 mmol, 1 equiv) and TEA (25.20 mg, 0.249 mmol, 3 equiv) . The reaction mixture was stirred at 50 °C for a period of 5h. After completion of reaction, the reaction mixture was quenched by addition of water 20mL. The

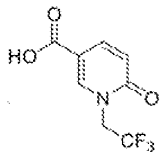
aqueous layer was extracted with ethyl acetate (10*3mL). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude product which was further purified by silica gel column chromatography (MeOH & DCM =1:10) to afford desired compound crude product. The residue was purified by The residue was purified by preparative HPLC using a XBridge Prep OBD 150 mm x 30 mm x 5 μm column (eluent: 29% to 59% (v/v) CH_3CN and H_2O with NH_4HCO_3+0.05%NH_3H_2O) to afford 2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-isobutoxypyridin-2-yl)propanamide (6.9 mg, 18.21%) as a white solid. MS (ESI): mass calcd. for $C_{24}H_{33}N_5O_4$: 455.25 m/z, found: 456.25 $[M+H]^+$.^{1}H NMR (300 MHz, DMSO-d_6) δ 11.82 (s, 1H), 9.97 (s, 1H), 8.00 – 8.10 (m, 2H), 7.56 (d, J = 2.6 Hz, 1H), 7.36 – 7.45 (m, 2H), 6.32 (d, J = 9.5 Hz, 1H), 3.79 (d, J = 6.5 Hz, 2H), 3.45 (q, J = 6.8 Hz, 1H), 3.34 – 3.39 (m, 2H), 2.73 (s, 1H), 2.61 (d, J = 11.6 Hz, 1H), 2.40 (s, 2H), 1.92 – 2.11 (m, 1H), 1.41 (d, J = 1.9 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.7 Hz, 6H).

Example 94: (2S)-2-{3,3-dimethyl-4-[6-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carbonyl]piperazin-1-yl}-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide



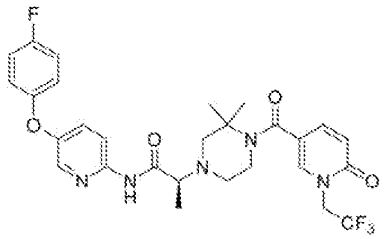
Synthetic Scheme





6-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carboxylic acid

To a solution ofmethyl 6-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carboxylate (100 mg, 0.043 mmol, 1 equiv) in THF (3 mL) MeOH (1 mL), H_2O (1 mL) was added LiOH (50.9 mg, 0.215 mmol, 5 equiv) at rt. The resulting mixture was stirred for 2 h at rt. The reaction was quenched with H_2O (10 mL) at rt. The resulting mixture was extracted with EA (3*30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. The resulting mixture was filtered. The filtrate was concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20% DCM/MeOH) to afford crude product was purified by Prep-HPLC using a Column: Xselect CSH C18 OBD Column, 30*150 mm, 5μm; (eluent: 5% to 25% ACN and Water(0.1% FA) to afford6-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carboxylic acid (150 mg, 63.81%) as a yellow solid. MS (ESI): mass calcd. for $C_8H_6F_3NO_3$: 221.03, found: 222.15 $[M+H]^+$.

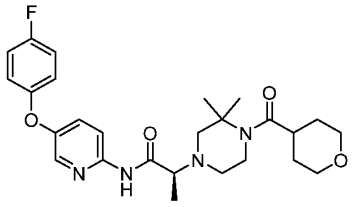


(2S)-2-{3,3-dimethyl-4-[6-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carbonyl]piperazin-1-yl}-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide

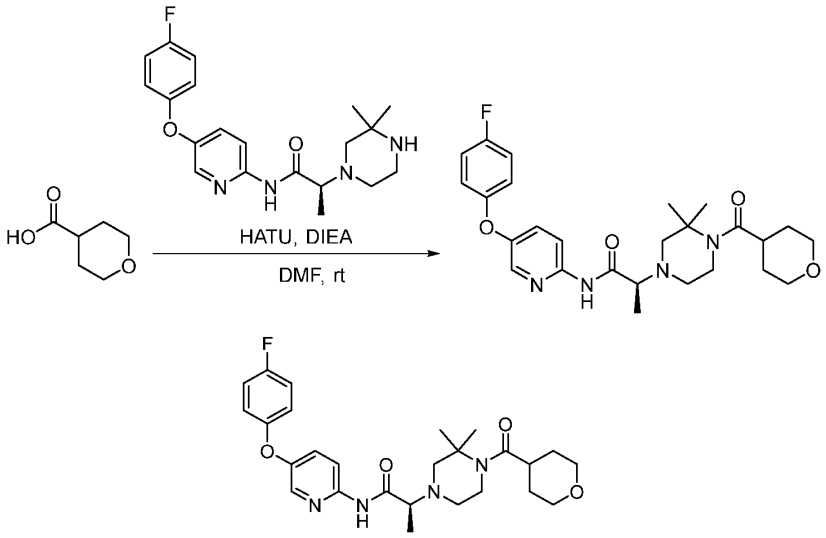
To a solution of (2S)-2-(3,3-dimethylpiperazin-1-yl)-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (50 mg, 0.134 mmol, 1.00 equiv) in dimethylformamide (3 mL) was added 6-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carboxylic acid (29.69 mg, 0.134 mmol, 1.00 equiv), HATU (76.57 mg, 0.201 mmol, 1.5 equiv), DIEA (52.05 mg, 0.402 mmol, 3 equiv) at rt. The resulting mixture was stirred for 2 h at rt. The reaction was quenched with H_2O (10 mL) at rt. The resulting mixture was extracted with EA (3*30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. The resulting mixture was filtered. The filtrate was concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20% DCM/MeOH) to afford crude product was purified by Prep-HPLC using a Column: Xselect CSH C18 OBD Column, 30*150 mm, 5μm;

(eluent: 5% to 25% ACN and Water (0.1% FA) to afford (2S)-2-{3,3-dimethyl-4-[6-oxo-1-(2,2,2-trifluoroethyl)pyridine-3-carbonyl]piperazin-1-yl}-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (16.5 mg, 21.32%) as a white solid. MS (ESI): mass calcd. for $C_{28}H_{29}F_4N_5O_4$: 575.22, found: 576.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.18 (s, 1H), 8.11 – 8.20 (m, 2H), 8.00 (s, 1H), 7.48 – 7.58 (m, 2H), 7.18 – 7.30 (m, 2H), 7.04 – 7.15 (m, 2H), 6.50 (d, J = 9.4 Hz, 1H), 4.92 (q, J = 9.1 Hz, 2H), 3.49 – 3.56 (m, 1H), 3.35 – 3.40 (m,1H), 2.63 – 2.69 (m, 1H), 2.44 (s, 2H), 1.43 (d, J = 2.5 Hz, 6H), 1.18 – 1.28(m, 5H). ^{19}F NMR (282 MHz, DMSO-d_6) δ-69.50, -119.82.

Example 95: (S)-2-(3,3-dimethyl-4-(tetrahydro-2H-pyran-4-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide



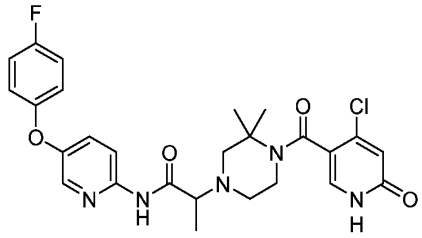
Synthetic Scheme



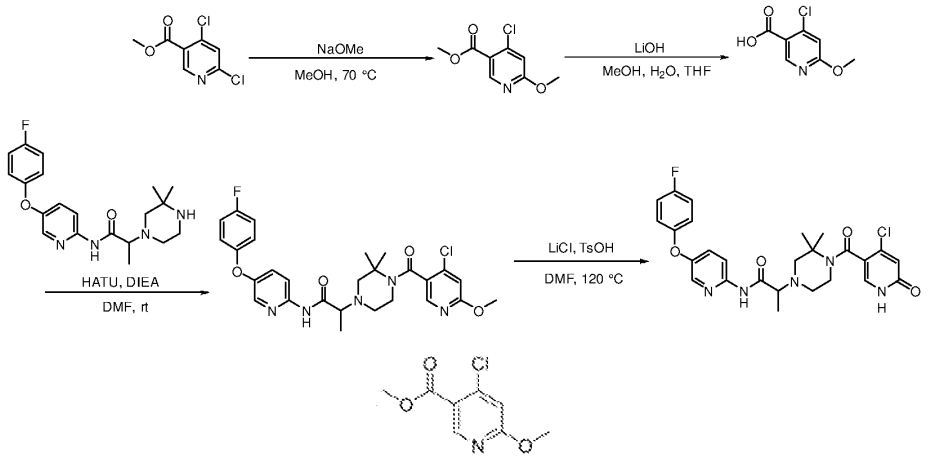
(S)-2-(3,3-dimethyl-4-(tetrahydro-2H-pyran-4-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

To a solution of (2S)-2-(3,3-dimethylpiperazin-1-yl)-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (50 mg, 0.134 mmol, 1.00 equiv) in dimethylformamide (3 mL) was added HATU (76.57 mg, 0.201 mmol, 1.5 equiv), DIEA (52.05 mg, 0.402 mmol, 3 equiv), oxane-4-carboxylic acid (26.21 mg, 0.201 mmol, 1.5 equiv) at rt. The resulting mixture was stirred for 2 h at rt. The reaction was quenched with H_2O (10 mL) at rt. The resulting mixture was extracted with EA (3*30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. The resulting mixture was filtered. The filtrate was concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20% DCM/MeOH) to afford crude product. The residue was purified by preparative HPLC using a Xselect CSH C18 OBD 150 mm x 30 mm x 5 μm column (eluent: 5% to 25% (v/v) CH_3CN and H_2O with 0.1% FA) to afford (S)-2-(3,3-dimethyl-4-(tetrahydro-2H-pyran-4-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (13.5 mg, 20.63%) as a white solid. MS (ESI): mass calcd. for $C_{18}H_{18}ClN_5O$: 484.24, found: 485.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.14 (s, 1H), 8.14 (dd, J = 6.0, 2.9 Hz, 2H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.03 – 7.16 (m, 2H), 3.82 (dt, J = 11.1, 3.3 Hz, 2H), 3.49 (s, 2H), 3.43 – 3.51 (m, 1H), 3.31 – 3.46 (m, 1H), 3.37 (s, 1H), 2.50 – 2.52 (m, 4H), 2.33 (s, 1H), 1.53 (td, J = 9.2, 8.2, 3.7 Hz, 4H), 1.37 (d, J = 2.4 Hz, 6H), 1.15 – 1.27 (m, 4H). ^{19}F NMR (282 MHz, DMSO-d_6) δ-119.841.

Example 96: 2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

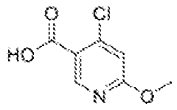


Synthetic Scheme



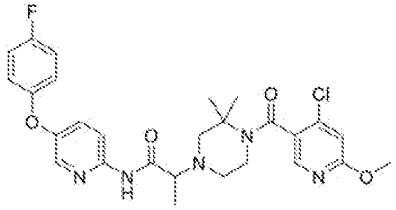
methyl 4-chloro-6-methoxynicotinate

To a stirring solution methyl 4,6-dichloropyridine-3-carboxylate (3 g, 14.562 mmol, 1 equiv) in methanol (40 mL) was added a solution of sodium methoxide (0.71 g, 13.106 mmol, 0.9 equiv). The mixture was stirred at 70 °C for 8 h under N_2. After cooled to room temperature, the reaction was dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% PE/EA) to afford methyl 4-chloro-6-methoxynicotinate (300 mg, 10.22%) as a white solid. MS (ESI): mass calcd. for $C_8H_8ClNO_3$: 201.12 m/z, found 202.05 $[M+H]^+$.



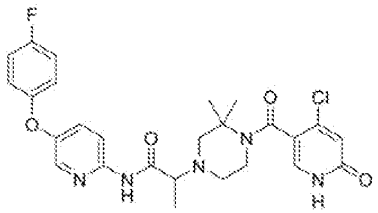
4-chloro-6-methoxynicotinic acid

To a solution of methyl 4-chloro-6-methoxypyridine-3-carboxylate (600 mg, 2.976 mmol, 1 equiv) in methanol (5 mL) and water (5 mL) was added LiOH (712.76 mg, 29.760 mmol, 10 equiv) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The mixture was acidified pH = 5 with HCl (1N). The aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by C18 (0-100% H_2O/ACN) to afford 4-chloro-6-methoxynicotinic acid (307 mg, 54.99%) as a white solid. MS (ESI): mass calcd. for $C_7H_6ClNO_3$: 187.00 m/z, found 188.05 $[M+H]^+$.



2-(4-(4-chloro-6-methoxynicotinoyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

To a stirred solution of 4-chloro-6-methoxypyridine-3-carboxylic acid (100 mg, 0.533 mmol, 1 equiv) in dimethylformamide (5 mL) was added 2-(3,3-dimethylpiperazin-1-yl)-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (198.55 mg, 0.533 mmol, 1 equiv), HATU (192.75 mg, 0.800 mmol, 1.5 equiv) and DIEA (206.71 mg, 1.599 mmol, 3 equiv) at room temperature. The reaction mixture was stirred at room temperature for a period of overnight. After completion of reaction, the reaction mixture was quenched by water (10 mL) and extracted with EA (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-60% PE/EA) to afford 2-(4-(4-chloro-6-methoxynicotinoyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (90 mg, 31.15%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{29}ClFN_5O_4$: 541.19 m/z, found: 542.15 $[M+H]^+$.

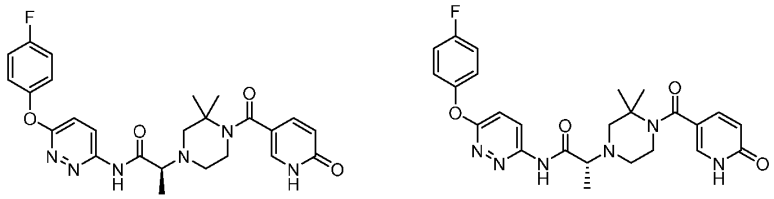


2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

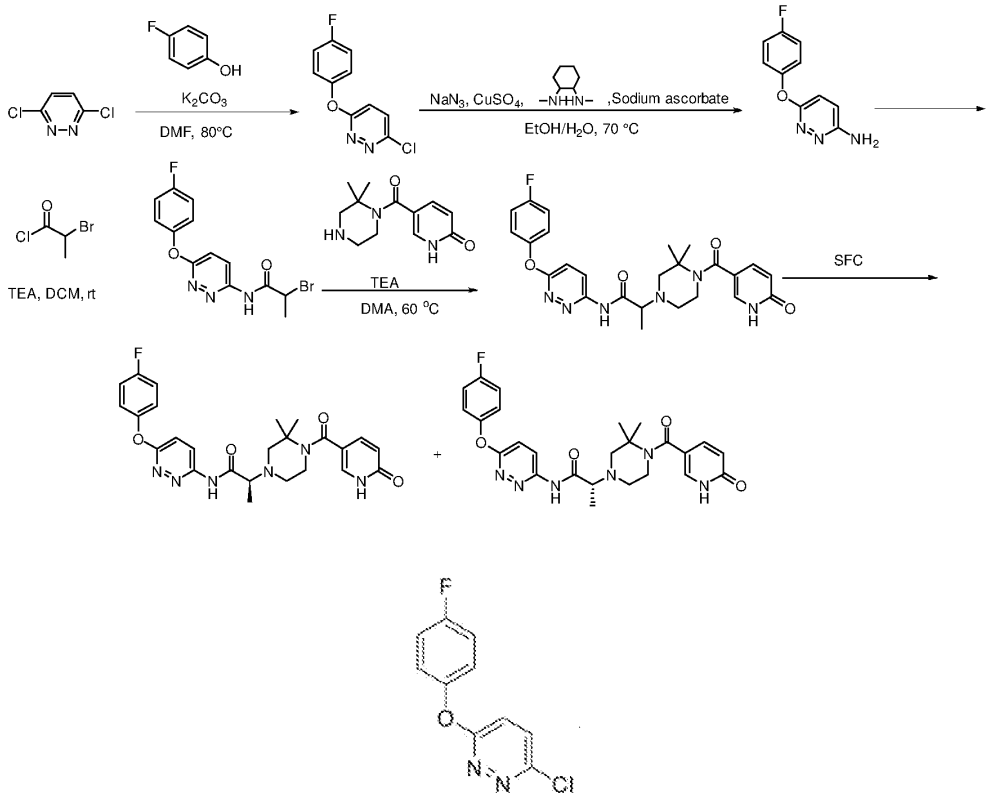
To a solution of 2-(4-(4-chloro-6-methoxynicotinoyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (80 mg, 0.148 mmol, 1 equiv) in dimethylformamide (3 mL) was added LiCl (31.28 mg, 0.740 mmol, 5 equiv) and TsOH (127.08 mg, 0.740 mmol, 5 equiv). The resulting solution was heated at 120 °C for 8 h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over

anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% H_2O/ACN) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 20% to 50% CH_3CN and H_2O with 60 mmol/L NH_4HCO_3) to afford 2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (6.7 mg, 8.57%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{26}FN_5O_2$: 527.17 m/z, found 528.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.10-8.19 (m, 2H), 7.90 (s, 1H), 7.52 (dd, J = 9.1, 2.9 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.04 – 7.16 (m, 2H), 6.66 (s, 1H), 3.40 – 3.55 (m, 2H), 3.27 (s, 2H), 2.61-2.67 (m, 2H), 2.42 (s, 2H), 1.48 (d, J = 2.8 Hz, 6H), 1.14 – 1.27 (m, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.85.

Example 97: (2S)-2-[3,3-dimethyl-4-(6-oxo-1H-pyridine-3-carbonyl)piperazin-1-yl]-N-[6-(4-fluorophenoxy)pyridazin-3-yl]propanamide and Example 98: (2R)-2-[3,3-dimethyl-4-(6-oxo-1H-pyridine-3-carbonyl)piperazin-1-yl]-N-[6-(4-fluorophenoxy)pyridazin-3-yl]propanamide

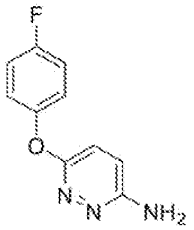


Synthetic Scheme



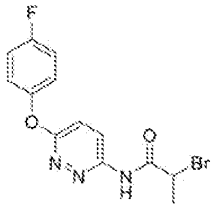
3-chloro-6-(4-fluorophenoxy)pyridazine

To a stirred solution of 3,6-dichloropyridazine (2 g, 13.426 mmol, 1 equiv) and K_2CO_3 (1.89 g, 13.560 mmol, 1.01 equiv) in DMF (10 mL) were added 4-fluorophenol (1.51 g, 13.426 mmol, 1 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 3 h at 80 °C under air atmosphere. Desired product could be detected by LCMS. The reaction was quenched with water (20 mL). The resulting mixture was extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 3-chloro-6-(4-fluorophenoxy)pyridazine (2 g, 66.32 %) as a yellow oil. MS (ESI): mass calcd. for $C_{10}H_6ClFN_2O$: 224.0 m/z, found: 225.15 $[M+H]^+$.



6-(4-fluorophenoxy)pyridazin-3-amine

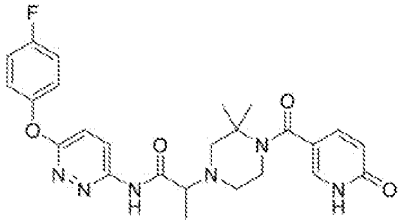
To a stirred solution of 3-chloro-6-(4-fluorophenoxy)pyridazine (2 g, 8.904 mmol, 1 equiv) and N1,N2-dimethylcyclohexane-1,2-diamine (0.76 g, 5.342 mmol, 0.6 equiv) in EtOH (8 mL)/H_2O (2 mL) were added NaN_3 (1.74 g, 26.712 mmol, 3 equiv), Sodium ascorbate (3.55 g, 17.808 mmol, 2 equiv) and $CuSO_4$ (1.42 g, 8.904 mmol, 1 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 3h at 70 °C under nitrogen atmosphere. Desired product could be detected by LCMS. After cooling down to rt, the reaction was quenched with water (10 mL). The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:2) to afford 6-(4-fluorophenoxy)pyridazin-3-amine (1.5 g, 82.10 %) as a yellow solid. MS (ESI): mass calcd. for $C_{10}H_8FN_3O$: 205.1 m/z, found: 206.05 $[M+H]^+$.



2-bromo-N-[6-(4-fluorophenoxy)pyridazin-3-yl]propanamide

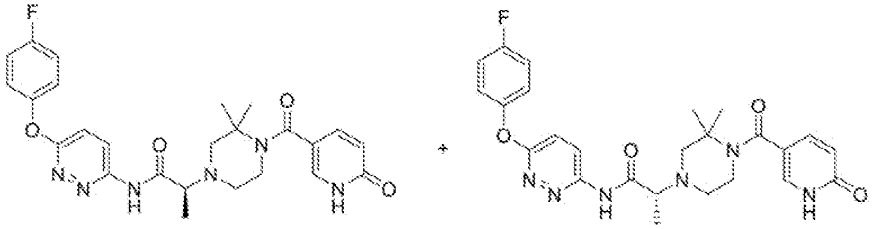
To a stirred solution of 6-(4-fluorophenoxy)pyridazin-3-amine (460 mg, 2.242 mmol, 1 equiv) and TEA (680.56 mg, 6.726 mmol, 3 equiv) in DCM (5 mL) were added 2-bromo-propionyl chloride (384.29 mg, 2.242 mmol, 1 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at room temperature under air atmosphere. Desired product could be detected by LCMS. The reaction was quenched with water (10 mL). The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted

with PE / EA (1:1) to afford 2-bromo-N-[6-(4-fluorophenoxy)pyridazin-3-yl]propanamide (450 mg, 59.01 %) as a yellow oil. MS (ESI): mass calcd. for $C_{13}H_{11}BrFN_3O_2$: 339.0 m/z, found: 340.05 $[M+H]^+$.



2-[3,3-dimethyl-4-(6-oxo-1H-pyridine-3-carbonyl)piperazin-1-yl]-N-[6-(4-fluorophenoxy)pyridazin-3-yl]propanamide

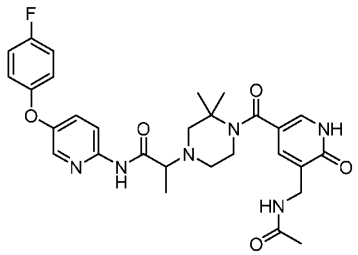
To a stirred solution of 2-bromo-N-[6-(4-fluorophenoxy)pyridazin-3-yl]propanamide (150 mg, 0.441 mmol, 1 equiv) in DMA (4 mL) were added 5-(2,2-dimethylpiperazine-1-carbonyl)-1H-pyridin-2-one (103.76 mg, 0.441 mmol, 1 equiv) and TEA (133.87 mg, 1.323 mmol, 3 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at 60°C under air atmosphere. Desired product could be detected by LCMS. After cooling down to rt, the reaction was quenched with water (10 mL). The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 2-[3,3-dimethyl-4-(6-oxo-1H-pyridine-3-carbonyl)piperazin-1-yl]-N-[6-(4-fluorophenoxy)pyridazin-3-yl]propanamide (150 mg, 68.78 %) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{27}FN_6O_4$: 494.2 m/z, found: 495.20 $[M+H]^+$.



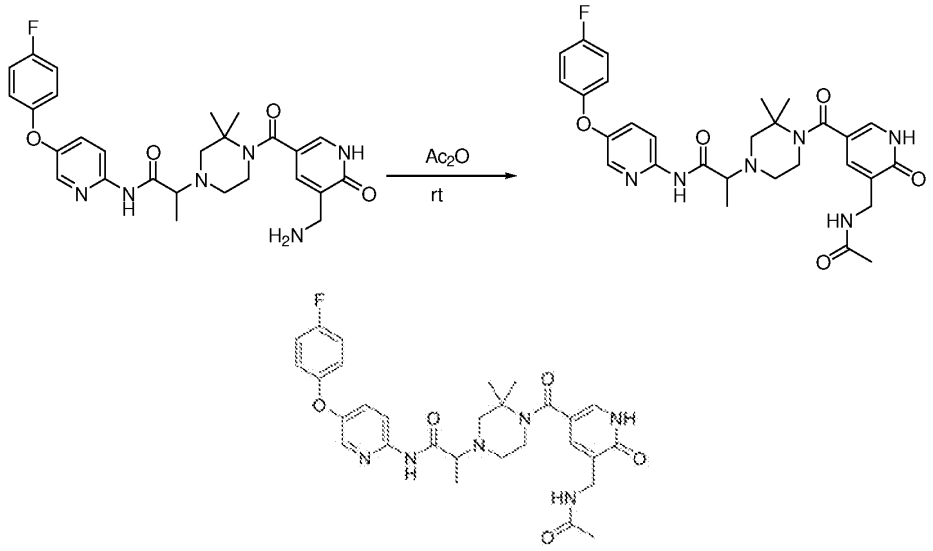
(2S)-2-[3,3-dimethyl-4-(6-oxo-1H-pyridine-3-carbonyl)piperazin-1-yl]-N-[6-(4-fluorophenoxy)pyridazin-3-yl]propanamide and (2R)-2-[3,3-dimethyl-4-(6-oxo-1H-pyridine-3-carbonyl)piperazin-1-yl]-N-[6-(4-fluorophenoxy)pyridazin-3-yl]propanamide

The crude product (60 mg) was purified chiral-HPLC using a CHIRALPAK IA, 5*25 cm, 5 μm column (eluent: 10% (v/v) Hex: DCM=3: 1(0.5% 2M NH3-MeOH) and EtOH) to afford (2S)-2-[3,3-dimethyl-4-(6-oxo-1H-pyridine-3-carbonyl)piperazin-1-yl]-N-[6-(4-fluorophenoxy)pyridazin-3-yl]propanamide (25.8 mg, 42.88 %) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{27}FN_6O_4$: 494.2 m/z, found: 495.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.84 (s, 1H), 10.66 (s, 1H), 8.43 (d, J = 9.5 Hz, 1H), 7.50 – 7.59 (m, 3H), 7.21 – 7.33 (m, 4H), 6.32 (d, J = 9.5 Hz, 1H), 3.56 (q, J = 6.8 Hz, 1H), 3.35 – 3.40 (m, 2H), 2.70 – 2.80 (m, 1H), 2.60 – 2.70 (m, 1H), 2.36 – 2.47 (m, 2H), 1.40 (d, J = 3.4 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H). And afford (2R)-2-[3,3-dimethyl-4-(6-oxo-1H-pyridine-3-carbonyl)piperazin-1-yl]-N-[6-(4-fluorophenoxy)pyridazin-3-yl]propanamide (26.3 mg, 43.72 %) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{27}FN_6O_4$: 494.2 m/z, found: 495.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.84 (s, 1H), 10.66 (s, 1H), 8.43 (d, J = 9.5 Hz, 1H), 7.50 – 7.59 (m, 3H), 7.21 – 7.33 (m, 4H), 6.32 (d, J = 9.5 Hz, 1H), 3.56 (q, J = 6.8 Hz, 1H), 3.35 – 3.42 (m, 2H), 2.70 – 2.80 (m, 1H), 2.60 – 2.70 (m, 1H), 2.36 – 2.47 (m, 2H), 1.40 (d, J = 3.4 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H). Stereochemistry of example 97 and example 98 was arbitrarily assigned.

Example 99: 2-(4-(5-(acetamidomethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide



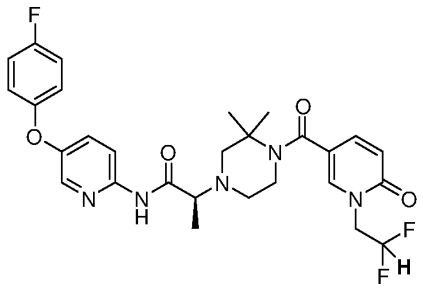
Synthetic Scheme



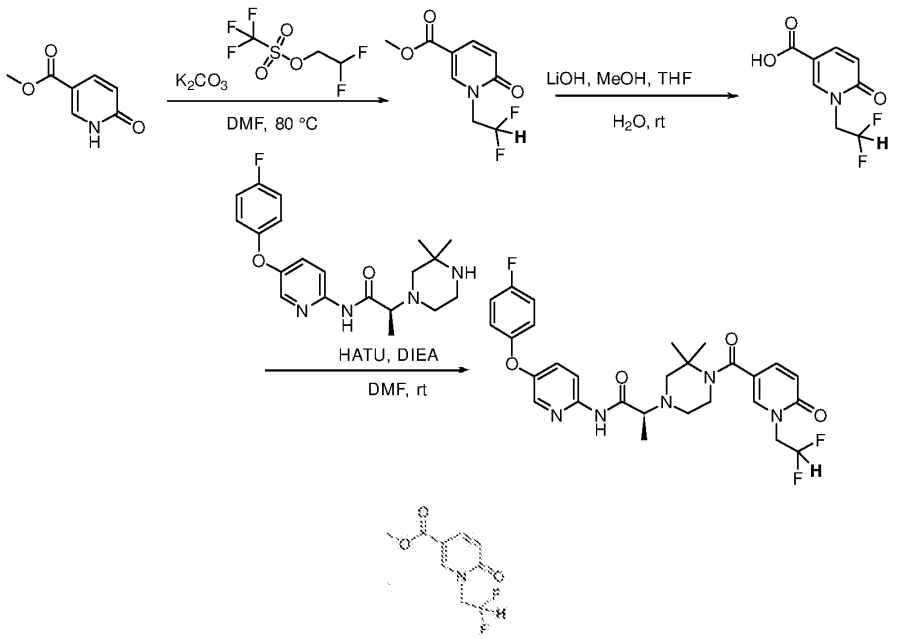
2-(4-(5-(acetamidomethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

To a solution of 2-(4-(5-(aminomethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (40 mg, 0.077 mmol, 1 equiv) in acetic anhydride (5 mL). The mixture was stirred at room temperature for 2h. Quenched with water (100 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with PE/EA (0-100%) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; (eluent: 27% to 57% ACN and Water (10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to give 2-(4-(5-(acetamidomethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propenamide (15.9 mg, 36.67%) as a white solid. MS (ESI): mass calcd. for $C_{29}H_{33}FN_6O_5$: 564.24, found: 565.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 10.21 (s, 1H), 8.12 – 8.26 (m, 3H), 7.49 – 7.57 (m, 2H), 7.19 – 7.30 (m, 3H), 7.04 – 7.14 (m, 2H), 3.99 (d, J = 5.8 Hz, 2H), 3.52 (q, J = 6.9 Hz, 1H), 2.56 – 2.76 (m, 2H), 2.47 – 2.50 (m, 2H), 2.36 – 2.47 (m, 2H), 1.86 (s, 3H), 1.41 (d, J = 4.5 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H).

Example 100: (S)-2-(4-(1-(2,2-difluoroethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide



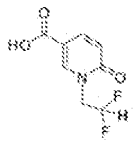
Synthetic Scheme



methyl 1-(2,2-difluoroethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate

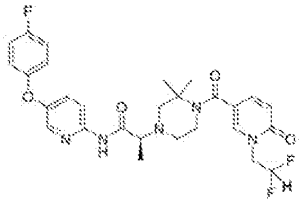
To a solution of methyl methyl 6-oxo-1H-pyridine-3-carboxylate (1 g, 6.530 mmol, 1 equiv) in DMF (15 mL). 2,2-difluoroethyl trifluoromethanesulfonate (2.80 g, 13.060 mmol, 2 equiv) and potassium methaneperoxoate potassium (2.73 g, 19.590 mmol, 3 equiv) added at rt. The resulting mixture was stirred for 2h at 80 °C. The resulting mixture was extracted with EA (3*100 mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% PE/EA) to afford methyl 1-(2,2-

difluoroethyl)-6-oxopyridine-3-carboxylate (730 mg, 51.48%) as a white solid, MS (ESI): mass calcd. for $C_9H_9F_2NO_{33}$: 217.06, found:218.10 $[M+H]^+$.



1-(2,2-difluoroethyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid

To a solution of methyl 1-(2,2-difluoroethyl)-6-oxopyridine-3-carboxylate (50 mg, 0.046 mmol, 1 equiv) in THF (3 mL). water (0.25 mL, 0.014 mmol, 0.30 equiv), methanol (0.25 mL, 0.008 mmol, 0.17 equiv) and LiOH (5.51 mg, 0.230 mmol, 5 equiv) added at rt. The resulting mixture was stirred for 2h at rt. The resulting mixture was concentrated under vacuum. Water (5ml) was added at the resulting mixture. The mixture was acidified to pH 6-7. The precipitated solids were collected by filtration and washed with H_2O (5 mL) to afford 1-(2,2-difluoroethyl)-6-oxopyridine-3-carboxylic acid (130 mg, 69.49%) as a white solid. MS (ESI): mass calcd. for $C_8H_7F_2NO$: 203.04, found:204.05 $[M+H]^+$.

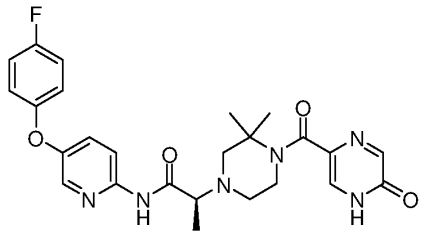


(S)-2-(4-(1-(2,2-difluoroethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

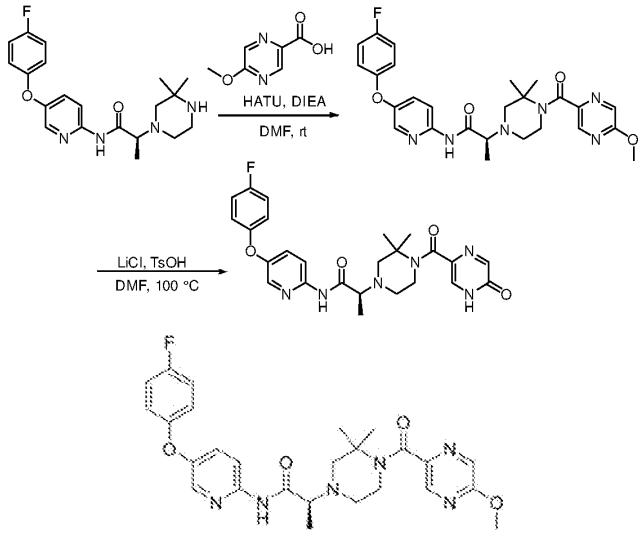
To a solution of (2S)-2-(3,3-dimethylpiperazin-1-yl)-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (50 mg, 0.134 mmol, 1 equiv) in DMF (2 mL). 1-(2,2-difluoroethyl)-6-oxopyridine-3-carboxylic acid (27.27 mg, 0.134 mmol, 1 equiv) DIEA (34.70 mg, 0.268 mmol, 2 equiv) and HATU (48.54 mg, 0.201 mmol, 1.5 equiv) was added at rt. The resulting mixture was stirred at rt for 2 h. The resulting mixture was extracted with EA (3*100 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% PE/EA) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; (eluent: 32% to 53% ACN and Water(10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-2-(4-(1-(2,2-difluoroethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-

yl)propanamide (18.0 mg, 24.03%) as a white solid. MS (ESI): mass calcd. for $C_{28}H_{30}F_3N_5O_4$: 557.22, found: 558.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.12 – 8.19 (m, 2H), 7.99 (d, J = 2.7 Hz, 1H), 7.48 – 7.57 (m, 2H), 7.19 – 7.30 (m, 2H), 7.05 – 7.14 (m, 2H), 6.46 (d, J = 9.4 Hz, 2H), 4.39 – 4.52 (m, 2H), 3.46 – 3.56 (m, 1H), 3.34 – 3.41 (m, 2H), 2.60 – 2.81 (m, 2H), 2.38 – 2.48 (m, 2H), 1.43 (d, J = 3.6 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -119.81, -122.80.

Example 101: (S)-2-(3,3-dimethyl-4-(5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

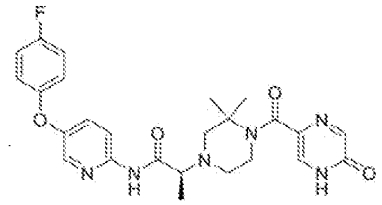


Synthetic Scheme



(S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(5-methoxypyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

To a solution of (S)-2-(3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (50 mg, 0.134 mmol, 1 equiv) in dimethylformamide (2 mL) was added 5-methoxypyrazine-2-carboxylic acid (24.83 mg, 0.161 mmol, 1.2 equiv), HATU (76.57 mg, 0.201 mmol, 1.5 equiv), DIEA (34.70 mg, 0.268 mmol, 2 equiv), the mixture was stirred for 2 h at rt. the reaction mixture was quenched by water and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford (S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(5-methoxypyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (50 mg, 73.24%) as a yellow solid. MS (ESI):$C_{26}H_{29}FN_6O_4$: 508.10 m/z, found: 509.15$[M+H]^+$.

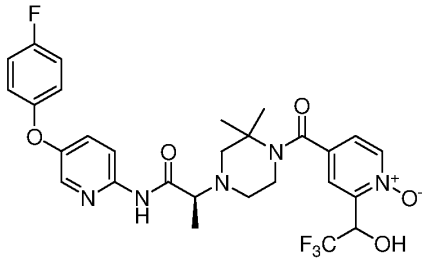


(S)-2-(3,3-dimethyl-4-(5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

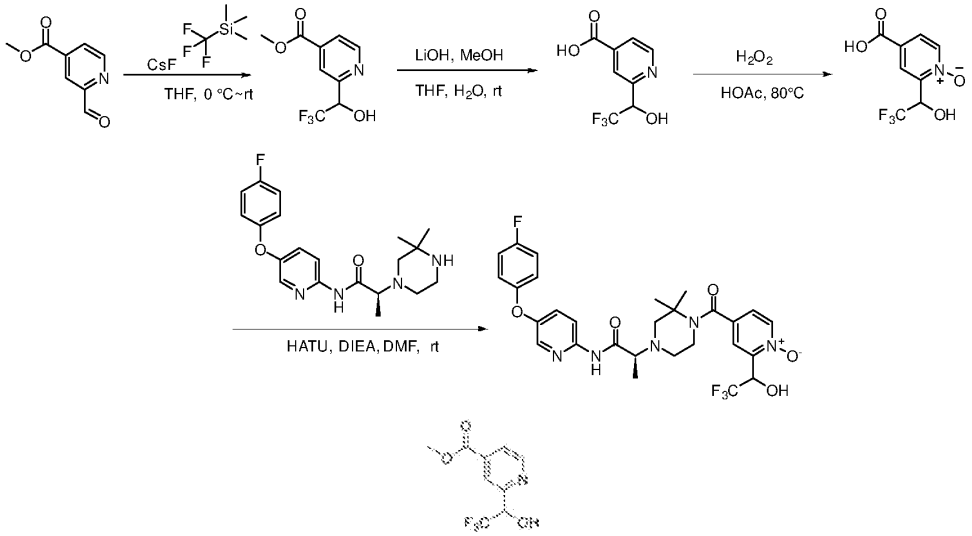
To a solution of (S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(5-methoxypyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (50 mg, 0.098 mmol, 1 equiv) in dimethylformamide (2 mL) was added LiCl (20.84 mg, 0.490 mmol, 5 equiv), TsOH (84.65 mg, 0.490 mmol, 5 equiv).The resulting mixture was stirred for overnight at 100°C. The reaction was quenched with H_2O (10 mL) at rt. The resulting mixture was extracted with EA (3 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. The resulting mixture was filtered. The filtrate was concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20% DCM/MeOH) to afford crude product. The residue was purified by preparative HPLC using a XBridge Prep OBD150 mm x 30 mm x 5 μm column (eluent: 17% to 37% (v/v) CH_3CN and H_2O (10mmol/L NH_4HCO_3+0.05%NH_3H_2O)) to afford (S)-2-(3,3-dimethyl-4-(5-oxo-4,5-dihydropyrazine-2-carbonyl) piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (8.6 mg, 17.67%) as a white solid. MS (ESI): mass

calcd. for $C_{25}H_{27}FN_6O_4$ 494.11m/z, found 495.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 12.55 (s, 1H), 10.18 (s, 1H), 8.11 – 8.20 (m, 2H), 7.89 (d, J = 1.3 Hz, 1H), 7.75 (s, 1H), 7.53 (dd, J = 9.0, 3.0 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.03 – 7.16 (m, 2H), 3.41 – 3.52 (m, 3H), 2.68 – 2.78 (m, 1H), 2.60 (d, J = 4.9 Hz, 1H), 2.42 (d, J = 2.9 Hz, 2H), 1.44 (d, J = 1.9 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.911.

Example 102: 4-(4-((S)-1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(2,2,2-trifluoro-1-hydroxyethyl)pyridine 1-oxide



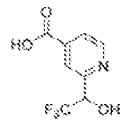
Synthetic Scheme



methyl 2-(2,2,2-trifluoro-1-hydroxyethyl)isonicotinate

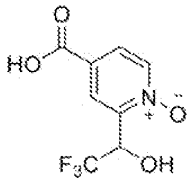
To a solution of trimethyl(trifluoromethyl)silane (1.36 g, 9.564 mmol, 1.05 equiv) in THF (20 mL) at rt. The resulting mixture was stirred for 0.1 h at 0 °C. To the above mixture was added methyl 2-formylisonicotinate (1.5 g, 9.083 mmol, 1 equiv) and cesium fluoride (2.07 g, 13.625 mmol, 1.5 equiv) dropwise at 0 °C. The resulting mixture was stirred for

additional overnight at rt. The reaction mixture was quenched by water and extracted with EA (3*100 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography DCM/MeOH (0-20%) to afford product methyl 2-(2,2,2-trifluoro-1-hydroxyethyl)isonicotinate (1.5 g, 77.3%) as a white solid. MS (ESI): mass calcd. for $C_9H_8F_3NO_3$ 235.16 m/z, found 236.10 $[M+H]^+$.



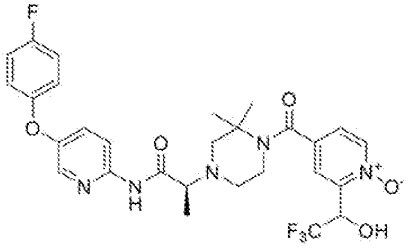
2-(2,2,2-trifluoro-1-hydroxyethyl)isonicotinic acid

To a solution of methyl 2-(2,2,2-trifluoro-1-hydroxyethyl)isonicotinate (500 mg, 2.126 mmol, 1 equiv) in THF: MeOH : H_2O (6:3:3 mL) was added LiOH (509.22 mg, 21.260 mmol, 10 equiv) at rt. The resulting mixture was stirred for 2h at rt. The crude product was used in the next step directly without further purification 2-(2,2,2-trifluoro-1-hydroxyethyl)pyridine-4-carboxylic acid (210 mg, 44.6%). MS (ESI): mass calcd. for $C_8H_6F_3NO_3$ 221.13 m/z, found 222.00 $[M+H]^+$.



4-carboxy-2-(2,2,2-trifluoro-1-hydroxyethyl)pyridine 1-oxide

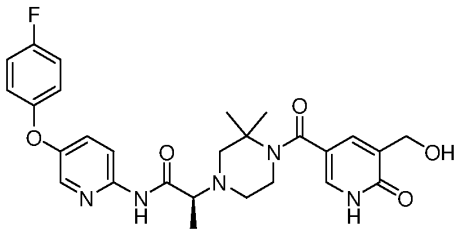
To a solution of 2-(2,2,2-trifluoro-1-hydroxyethyl)pyridine-4-carboxylic acid (200 mg, 0.904 mmol, 1 equiv) in HOAc (5 mL, 87.258 mmol, 96.48 equiv) was added H_2O_2 (1 mL, 42.924 mmol, 47.46 equiv) at 0 °C.The resulting mixture was stirred for 4 h at 80 °C. The reaction mixture concentrated under vacuum to yield a crude product which was directly purified by flash C18 to afford product 4-carboxy-2-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-1-ium-1-olate (150 mg, 69.9%) as a white solid. MS (ESI): mass calcd. for $C_8H_6F_3NO_4$ 237.13 m/z, found 238.05 $[M+H]^+$.



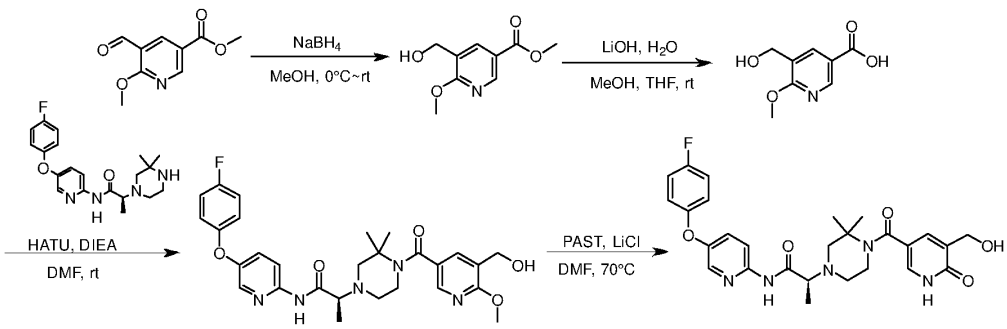
4-(4-((S)-1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(2,2,2-trifluoro-1-hydroxyethyl)pyridine 1-oxide

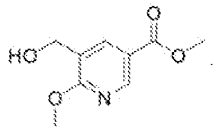
To a solution of 4-carboxy-2-(2,2,2-trifluoro-1-hydroxyethyl)pyridine 1-oxide (38.20 mg, 0.161 mmol, 1.2 equiv) in DMF (2 mL) was added (S)-2-(3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (50 mg, 0.134 mmol, 1.00 equiv) and HATU (76.57 mg, 0.201 mmol, 1.5 equiv) and DIEA (34.70 mg, 0.268 mmol, 2 equiv) at rt . The mixture was stirred at rt for 2 h. After completion of reaction, the reaction mixture was quenched by addition of water (10 mL). The aqueous layer was extracted with ethyl acetate (50 mL). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH). The residue was purified by preparative HPLC using a XBridge Prep OBD 150 mm x 30 mm x 5 μm column (eluent: 37% to 50% (v/v) CH_3CN and H_2O (10mmol/LNH_4HCO_3+0.05%NH_3H_2O)) to afford 4-(4-((S)-1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(2,2,2-trifluoro-1-hydroxyethyl)pyridine 1-oxide (2.7 mg, 3.40%) as a white solid. MS (ESI): mass calcd for $C_{28}H_{29}F_4N_5O_5$ 591.21 m/z, found 592.30 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.82 (s, 1H), 10.19 (s, 1H), 8.12 – 8.19 (m, 2H), 7.44 – 7.49 (m, 3H), 7.19 – 7.30 (m, 2H), 7.05 – 7.15 (m, 2H), 5.14 (t, J = 5.6 Hz, 1H), 4.29 (d, J = 5.5 Hz, 2H), 3.50 (q, J = 6.8 Hz, 1H), 3.34 – 3.42 (m, 2H), 2.68 – 2.78 (m, 1H), 2.57 – 2.67 (m, 1H), 2.42 (s, 2H), 1.42 (d, J = 1.9 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -119.83.

Example 103: (S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(5-(hydroxymethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)propenamide



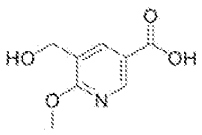
Synthetic Scheme





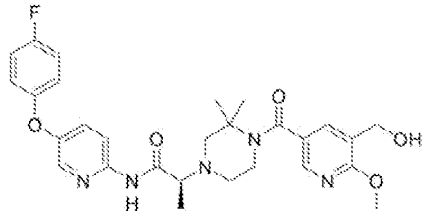
methyl 5-(hydroxymethyl)-6-methoxynicotinate

To a solution of methyl 5-formyl-6-methoxynicotinate (200 mg, 1.025 mmol, 1 equiv) in MeOH (3mL) was added $NaBH_4$ (116.30 mg, 3.075 mmol, 3 equiv) at 0°C. The resulting mixture was stirred for 3h at rt. The reaction mixture was quenched by water and extracted with EA (3*20 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford product. MS (ESI): mass calcd. for $C_9H_{11}NO_4$ 197.19 m/z, found 198.05$[M+H]^+$.



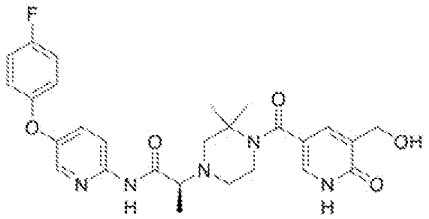
5-(hydroxymethyl)-6-methoxynicotinic acid

To a solution of methyl 5-(hydroxymethyl)-6-methoxynicotinate (160 mg, 0.811 mmol, 1 equiv) in THF: MeOH: H_2O (2:1:1 mL) was added LiOH (194.33 mg, 8.110 mmol, 10 equiv) at rt.The resulting mixture was stirred for 2h at rt. The crude product/ resulting mixture was used in the next step directly without further purification. MS (ESI): mass calcd. for $C_8H_9NO_4$ 183.16 m/z, found 184.05M+H]$^+$.



(S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(5-(hydroxymethyl)-6-methoxynicotinoyl)-3,3-dimethylpiperazin-1-yl)propanamide

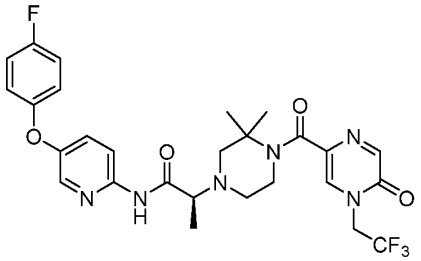
To a solution of 5-(hydroxymethyl)-6-methoxynicotinic acid (50 mg, 0.273 mmol, 1 equiv) in DMF (3mL) was added (S)-2-(3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (101.67 mg, 0.273 mmol, 1 equiv) and HATU (155.70 mg, 0.410 mmol, 1.5 equiv) and DIEA (352.82 mg, 2.730 mmol, 10 equiv) at rt. The resulting mixture was stirred for 3h at rt. The reaction mixture was quenched by water and extracted with EA (3*20 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (DCM/MeOH =10:1) to afford (S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(5-(hydroxymethyl)-6-methoxynicotinoyl)-3,3-dimethylpiperazin-1-yl)propanamide (80 mg, 54.7%) as a white solid. MS (ESI): mass calcd. for $C_{28}H_{32}FN_5O_5$ 537.59 m/z, found 538.30[M+H]$^+$.



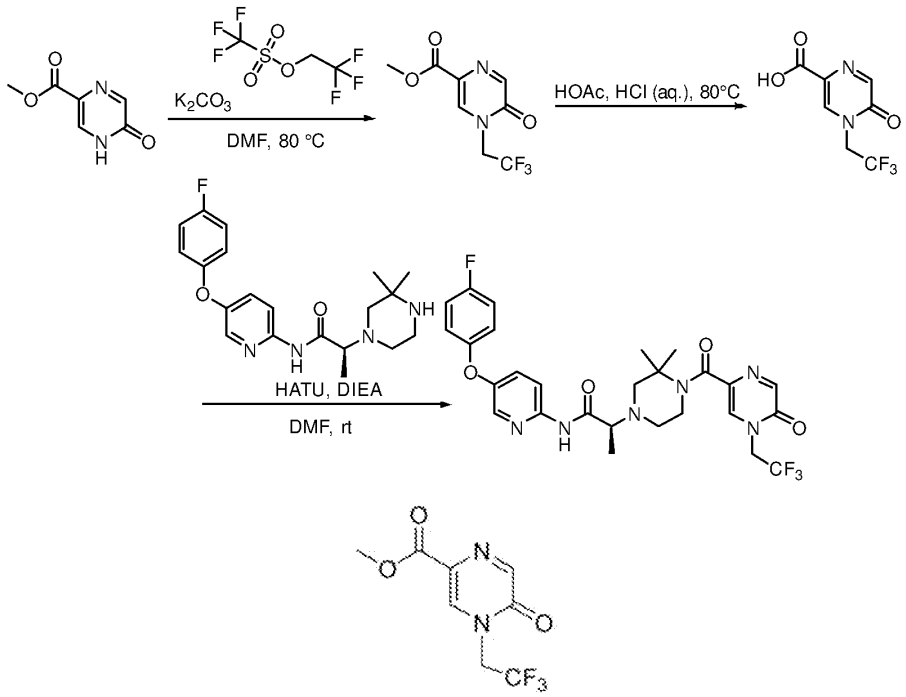
(S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(5-(hydroxymethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

To a solution of (S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(5-(hydroxymethyl)-6-methoxynicotinoyl)-3,3-dimethylpiperazin-1-yl)propanamide (80 mg, 0.149 mmol, 1 equiv) in DMF (3 mL) was added PTSA (128.13 mg, 0.745 mmol, 5 equiv) and LiCl (31.54 mg, 0.745 mmol, 5 equiv) at room temperature. The mixture was stirred at 70 °C for 3h. After completion of reaction, the reaction mixture was quenched by addition of water (10 mL). The aqueous layer was extracted with ethyl acetate (50 mL). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH). The residue was purified by preparative HPLC using a YMC Triart C18 ExRs 250 mm x 20 mm x 5 μm column (eluent: 37% to 50% (v/v) CH_3CN and H_2O (10mmol/L NH_4HCO_3)) to afford (S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(5-(hydroxymethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (5.2 mg, 6.61%) as a white solid. MS (ESI): mass calcd for $C_{27}H_{30}FN_5O_5$ 523.56 m/z, found 524.25 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.82 (s, 1H), 10.19 (s, 1H), 8.12 – 8.19(m, 2H), 7.44 – 7.49(m, 3H), 7.19 – 7.30 (m, 2H), 7.05 – 7.15 (m, 2H), 5.14 (t, J = 5.6 Hz, 1H), 4.29 (d, J = 5.5 Hz, 2H), 3.50 (q, J = 6.8 Hz, 1H), 3.34 – 3.42 (m, 2H), 2.68 – 2.78 (m, 1H), 2.57 – 2.67 (m, 1H), 2.42 (s, 2H), 1.42 (d, J = 1.9 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H).^{19}F NMR (376 MHz, DMSO-d_6) δ -119.83.

Example 104: (S)-2-(3,3-dimethyl-4-(5-oxo-4-(2,2,2-trifluoroethyl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

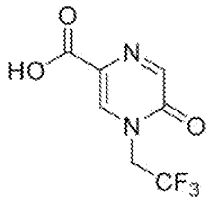


Synthetic Scheme



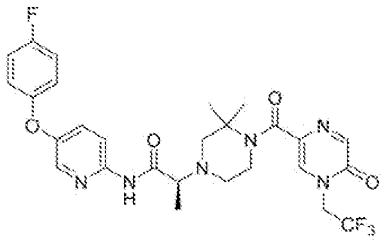
methyl 5-oxo-4-(2,2,2-trifluoroethyl)-4,5-dihydropyrazine-2-carboxylate

To a solution of methyl methyl 5-oxo-4H-pyrazine-2-carboxylate (500 mg, 3.244 mmol, 1 equiv) in DMF (1 mL). 2,2,2-trifluoroethyl trifluoromethanesulfonate (1.51 g, 6.488 mmol, 2 equiv) and K_2CO_3 (1.35 g, 9.732 mmol, 3 equiv) added at rt. The resulting mixture was stirred for 2h at 80 °C. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% PE/EA) to afford methyl 5-oxo-4-(2,2,2-trifluoroethyl)-4,5-dihydropyrazine-2-carboxylate (large polarity, 300 mg, 39.16%) as a yellow oil. MS (ESI): mass calcd. for $C_8H_7F_3N_2O_3$: 236.04, found: 237.15 $[M+H]^+$. And methyl 5-(2,2,2-trifluoroethoxy)pyrazine-2-carboxylate (small polarity, 150 mg, 19.58%) as a yellow oli, MS (ESI): mass calcd. for $C_8H_7F_3N_2O_3$: 236.04, found: 237.15$[M+H]^+$.



5-oxo-4-(2,2,2-trifluoroethyl)-4,5-dihydropyrazine-2-carboxylic acid

To a solution of methyl 5-oxo-4-(2,2,2-trifluoroethyl)pyrazine-2-carboxylate (100 mg, 0.42 mmol, 1 equiv) in acetic acid (6 mL) and concentrated HCl (3 mL) was heated under 80 °C in a hood for 1.5 hours.The reaction was quenched with ice-cold at rt. The resulting mixture was extracted with EA (3*50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% PE/EA) to afford 5-oxo-4-(2,2,2-trifluoroethyl)-4,5-dihydropyrazine-2-carboxylic acid as a white solid, MS (ESI): mass calcd. for $C_7H_5F_3N_2O_3$: 222.03, found: 221.10$[M-H]^-$.

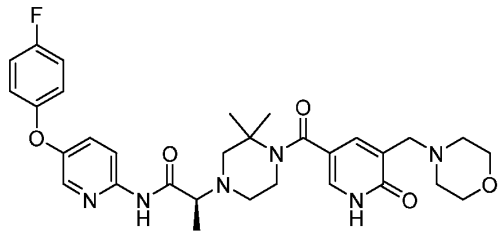


methyl (S)-2-(3,3-dimethyl-4-(5-oxo-4-(2,2,2-trifluoroethyl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

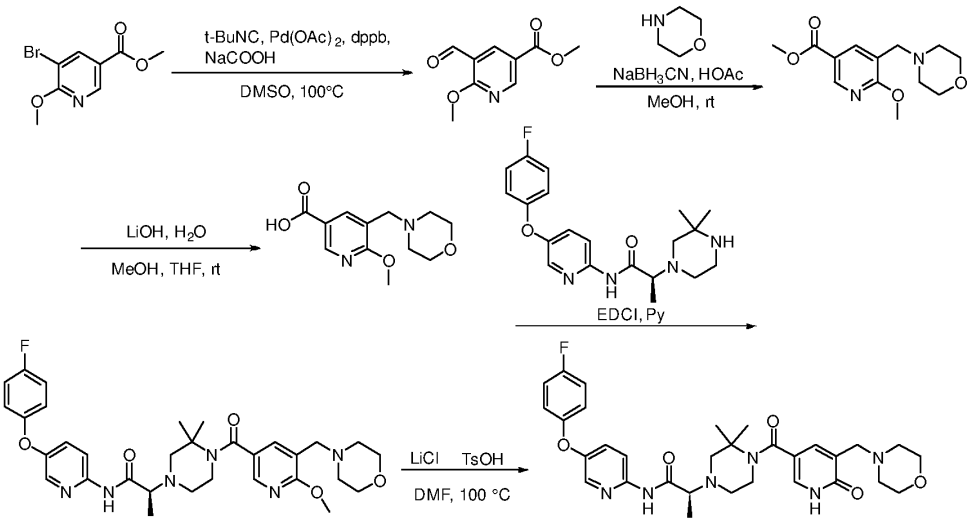
To a solution of (2S)-2-(3,3-dimethylpiperazin-1-yl)-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (35 mg, 0.094 mmol, 1 equiv) in DMF (3 mL). HATU (33.98 mg, 0.141 mmol, 1.5 equiv), 5-oxo-4-(2,2,2-trifluoroethyl)pyrazine-2-carboxylic acid (20.87 mg, 0.094 mmol, 1 equiv) and DIEA (24.29 mg, 0.188 mmol, 2 equiv) was added at rt. The resulting mixture was stirred for 2h at rt under weak alkali environment (PH~7.5). The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, , and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20% DCM/MeOH) to afford (S)-2-(3,3-dimethyl-4-(5-oxo-4-(2,2,2-trifluoroethyl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 42% to 60% CH_3CN and H_2O with (10mmol/L

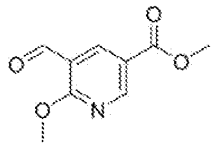
NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-2-(3,3-dimethyl-4-(5-oxo-4-(2,2,2-trifluoroethyl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (15.4 mg, 28.27%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{28}F_4N_6O_4$: 576.21,found:577.25 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.05 – 8.19 (m, 4H), 7.53 (dd, J = 8.9, 3.1 Hz, 1H), 7.19 – 7.30 (m, 2H), 7.05 – 7.15 (m, 2H), 4.86 – 4.97 (m, 2H), 3.42 – 3.57 (m, 3H), 2.56 – 2.79 (m, 2H), 2.38 – 2.49 (m, 2H), 1.45 (d, J = 3.1 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -69.0937, -119.8364.

Example 105: (S)-2-(3,3-dimethyl-4-(5-(morpholinomethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide



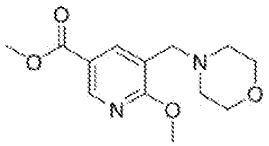
Synthetic Scheme





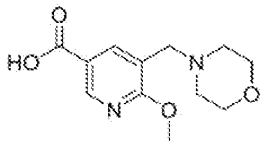
methyl 5-formyl-6-methoxynicotinate

To a solution of methyl 5-bromo-6-methoxynicotinate (1 g, 4.064 mmol, 1 equiv) in DMSO (10 mL) was added $Pd(OAc)_2$ (91.24 mg, 0.406 mmol, 0.1 equiv), 2-isocyano-2-methylpropane (506.78 mg, 6.096 mmol, 1.5 equiv), DPPB (173.32 mg, 0.406 mmol, 0.1 equiv), Sodium formate (414.58 mg, 6.096 mmol, 1.5 equiv), the mixture was stirred for 2 h at 100 °C under N_2 atmosphere. After cooled to room temperature the reaction mixture was quenched by water and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford methyl 5-formyl-6-methoxypyridine-3-carboxylate (500 mg, 63.04%) as a yellow solid. MS (ESI): $C_9H_9NO_4$:195.10 m/z, found: 196.10$[M+H]^+$.



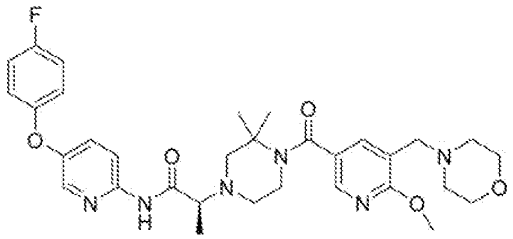
methyl 6-methoxy-5-(morpholinomethyl)nicotinate

To a solution of methyl 5-formyl-6-methoxypyridine-3-carboxylate (200 mg, 1.025 mmol, 1 equiv) in methanol (3 mL) was added morpholine (89.28 mg, 1.025 mmol, 1 equiv), $NaBH_3CN$ (193.18 mg, 3.075 mmol, 3 equiv), HOAc (123.07 mg, 2.050 mmol, 2 equiv), the mixture was stirred for 2 h at rt. The reaction mixture was quenched by water and extracted with EA (3*30 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford methyl 6-methoxy-5-(morpholin-4-ylmethyl)pyridine-3-carboxylate (150 mg, 54.97%) as a yellow solid. MS (ESI):$C_{13}H_{18}N_2O_4$: 266.29 m/z, found: 267.15$[M+H]^+$.



6-methoxy-5-(morpholinomethyl)nicotinic acid

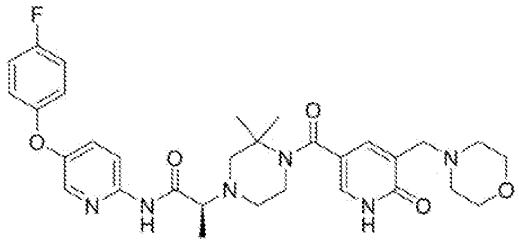
To a solution of methyl 6-methoxy-5-(morpholin-4-ylmethyl)pyridine-3-carboxylate (150 mg, 0.563 mmol, 1 equiv) in H_2O (1 mL, 55.509 mmol, 98.55 equiv) MeOH (1 mL, 24.699 mmol, 43.85 equiv) THF (3 mL, 37.028 mmol, 65.74 equiv) was added LiOH (4.50 mg, 0.190 mmol, 5 equiv), the mixture was stirred for 2 h at rt. the reaction mixture was concentrated under vacuumwas added water and the mixture was acidified to pH = 5 with 4N HCl, extracted with EA (3*30 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 6-methoxy-5-(morpholin-4-ylmethyl)pyridine-3-carboxylic acid (80 mg, 56.30%) as a yellow solid. MS (ESI): $C_{12}H_{16}N_2O_4$: 252.10 m/z, found: 253.10 $[M+H]^+$.



(S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-methoxy-5-(morpholinomethyl)nicotinoyl)-3,3-dimethylpiperazin-1-yl)propanamide

To a solution of 6-methoxy-5-(morpholin-4-ylmethyl)pyridine-3-carboxylic acid (80 mg, 0.317 mmol, 1 equiv) in dimethylformamide (3 mL) was added (2S)-2-(3,3-dimethylpiperazin-1-yl)-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (118.11 mg, 0.317 mmol, 1 equiv), HATU (180.87 mg, 0.476 mmol, 1.5 equiv), DIEA (81.97 mg, 0.634 mmol, 2 equiv), the mixture was stirred for 2 h at rt. the reaction mixture was quenched by water and extracted with EA (3*30 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether)

to afford S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-methoxy-5-(morpholinomethyl)nicotinoyl)-3,3-dimethylpiperazin-1-yl)propanamide (50 mg, 25.99%) as a yellow solid. MS (ESI):$C_{32}H_{39}FN_6O_5$: 606.29 m/z, found: 607.15 $[M+H]^+$.

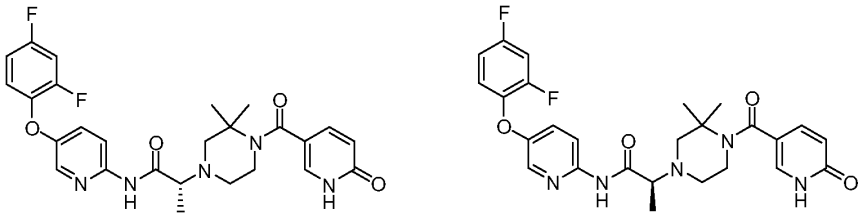


(S)-2-(3,3-dimethyl-4-(5-(morpholinomethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

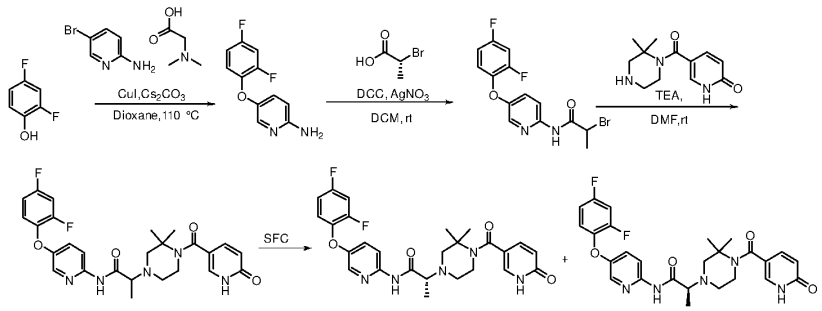
To a solution of S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-methoxy-5-(morpholinomethyl)nicotinoyl)-3,3-dimethylpiperazin-1-yl)propanamide (50 mg, 0.082 mmol, 1 equiv) in dimethylformamide (3 mL) was added LiCl (17.47 mg, 0.410 mmol, 5 equiv) TsOH (70.96 mg, 0.410 mmol, 5 equiv).The resulting mixture was stirred for overnight at 100 °C. After cooled to room temperature the reaction was quenched with H_2O (10 mL) at rt. The resulting mixture was extracted with EA (3 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. The resulting mixture was filtered. The filtrate was concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20% DCM/MeOH) to afford crude product. The residue was purified by preparative HPLC using a XBridge Prep C18 OBD 250 mm x 19 mm x 5 μm column (eluent: 37% to 67% (v/v) CH_3CN and H_2O(10mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$)) to afford (S)-2-(3,3-dimethyl-4-(5-(morpholinomethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (8.0 mg, 16.36%) as a white solid. MS (ESI): mass calcd. for $C_{31}H_{37}FN_6O_5$ 592.11m/z, found 593.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 11.86 (s, 1H), 10.22 (s, 1H), 8.11 – 8.21 (m, 2H), 7.47 – 7.58 (m, 2H), 7.45 (d, J = 2.5 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.04 – 7.16 (m, 2H), 3.46 – 3.60 (m, 5H), 3.34 – 3.40 (m, 2H), 3.25 – 3.29(m, 2H), 2.69 – 2.78 (m, 1H), 2.57 – 2.64 (m, 1H),2.40 (dt, J = 9.4, 4.4 Hz, 6H), 1.42 (d, J = 3.2 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.861.

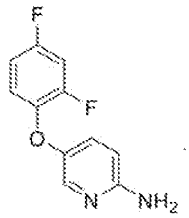
Example 106: (R)-N-(5-(2,4-difluorophenoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide and Example 107: (S)-N-(5-

(2,4-difluorophenoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide



Synthetic Scheme

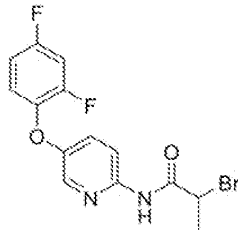




5-(2,4-difluorophenoxy)pyridin-2-amine

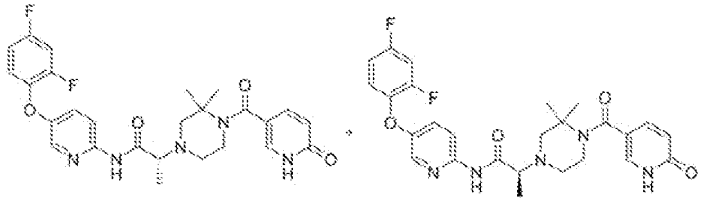
To a stirring solution 2,4-difluorophenol (1.80 g, 13.872 mmol, 1.2 equiv) in 1,4-Dioxane (30 mL) was added a solution of dimethylglycine (119.21 mg, 1.156 mmol, 0.1 equiv) and 5-bromopyridin-2-amine (2 g, 11.560 mmol, 1.00 equiv) and CuI (440.31 mg, 2.312 mmol, 0.2 equiv) and Cs_2CO_3 (5.65 g, 17.340 mmol, 1.5 equiv). The resulting mixture under N_2 was stirred at 110 °C for 6 h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and

concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford 5-(2,4-difluorophenoxy)pyridin-2-amine (1.5 g, 58.40%) MS (ESI): mass calcd. for $C_{11}H_8F_2N_2O$: 222.06 m/z found: 223.05 $[M+H]^+$.



2-bromo-N-(5-(2,4-difluorophenoxy)pyridin-2-yl)propanamide

To a stirring solution 5-(2,4-difluorophenoxy)pyridin-2-amine (1 g, 4.501 mmol, 1 equiv) in DCM (20 mL) was added a solution of (R)-2-bromopropanoic acid (0.83 g, 5.401 mmol, 1.2 equiv) and $AgNO_3$ (0.11 g, 0.675 mmol, 0.15 equiv) and DCC (1.86 g, 9.002 mmol, 2 equiv). The resulting mixture was stirred at room temperature for 6h. The reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford (R)-2-bromo-N-(5-(2,4-difluorophenoxy)pyridin-2-yl)propanamide (270 mg) MS (ESI): mass calcd. for $C_{14}H_{11}BrF_2N_2O_2$: 356.00 found: 357.05 $[M+H]^+$

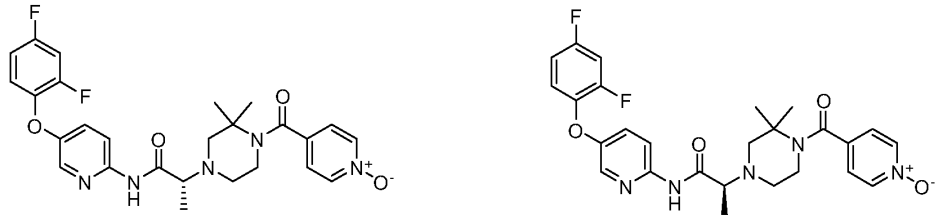


(R)-N-(5-(2,4-difluorophenoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide and (S)-N-(5-(2,4-difluorophenoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

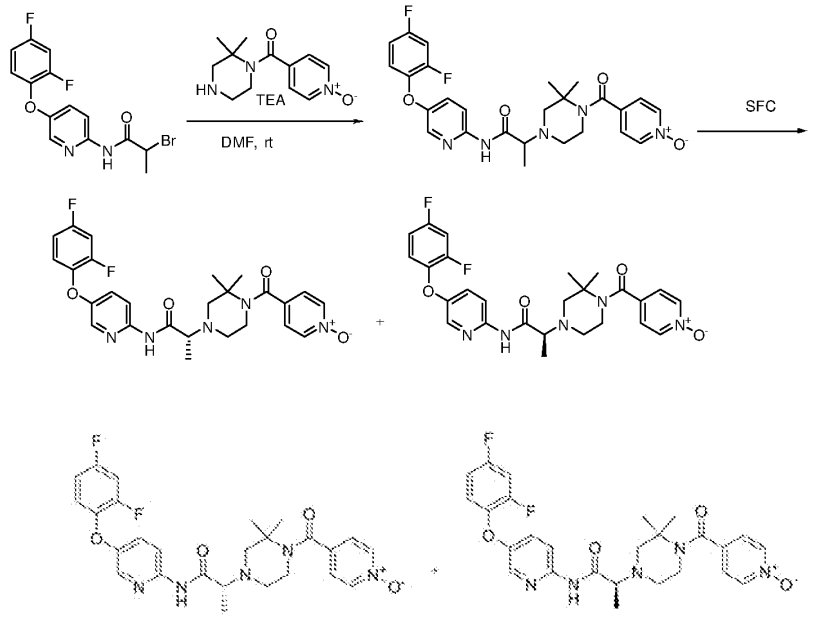
To a stirred solution of (R)-2-bromo-N-(5-(2,4-difluorophenoxy)pyridin-2-yl)propanamide (50 mg, 0.140 mmol, 1 equiv) in DMF (1 mL) was added 5-(2,2-dimethylpiperazine-1-carbonyl)-1H-pyridin-2-one (164.70 mg, 0.700 mmol, 5 equiv) and TEA (85.00 mg, 0.840 mmol, 6 equiv) at room temperature. The reaction mixture was stirred at room temperature for 3 h. The resulting mixture was stirred for additional overnight at

room temperature. After completion of reaction, the reaction mixture was quenched by addition of water (5 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and Prep-HPLC using a Column: YMC Triart C18 ExRs Column, 20*250mm, 5μm (eluent: 40% to 70% (v/v) CH_3CN and H_2O, NH_4HCO_3) to afford N-(5-(2,4-difluorophenoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (20 mg, 25%) as a white solid. The product was separated by Chiral-HPLC using a CHIRALPAK IF 2*25 cm, 5 μm column (eluent: 50% (v/v) EtOH and MTBE with 0.1% DEA) to afford (R)-N-(5-(2,4-difluorophenoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (2.9 mg, 3.97%), MS (ESI): mass calcd. for $C_{26}H_{27}F_2N_5O_4$: 511.20 m/z, found: 512.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 11.78 (s, 1H), 10.18 (s, 1H), 8.09 – 8.19 (m, 2H), 7.42 – 7.59 (m, 4H), 7.30 (td, J = 9.2, 5.6 Hz, 1H), 7.13 (tdd, J = 9.1, 3.0, 1.6 Hz, 1H), 6.32 (d, J = 9.5 Hz, 1H), 3.49 (q, J = 6.8 Hz, 1H), 3.36 (d, J = 6.1 Hz, 2H), 2.73 (t, J = 5.9 Hz, 1H), 2.5 – 2.66 (m, 1H), 2.40 (s, 2H), 1.40 (d, J = 2.2 Hz, 6H), 1.21 (t, J = 7.3 Hz, 3H). And (S)-N-(5-(2,4-difluorophenoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (6.7 mg, 9.36%). MS (ESI): mass calcd. for $C_{26}H_{27}F_2N_5O_4$: 511.20 m/z, found: 512.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 11.72 (s, 1H), 10.18 (s, 1H), 8.09 – 8.19 (m, 2H), 7.41 – 7.60 (m, 4H),7.30 (td, J = 9.2, 5.6 Hz, 1H), 7.13 (tdd, J = 9.1, 3.0, 1.6 Hz, 1H), 6.32 (d, J = 9.5 Hz, 1H), 3.49 (q, J = 6.9 Hz, 1H), 3.36 – 3.39(s, 2H), 2.72 (q, J = 5.6, 5.0 Hz, 1H), 2.53 – 2.64(m, 1H) 2.40 (s, 2H), 1.40 (d, J = 2.2 Hz, 6H), 1.21 (t, J = 7.3 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -114.56 (d, J = 4.6 Hz), -126.77 (d, J = 4.7 Hz).

Example 108: (R)-4-(4-(1-((5-(2,4-difluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide and Example 109: (S)-4-(4-(1-((5-(2,4-difluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide



Synthetic Scheme

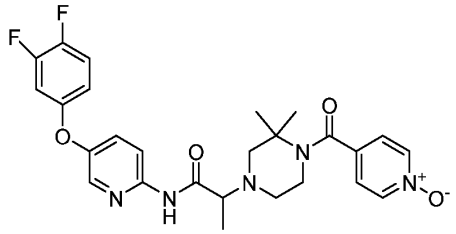


(R)-4-(4-(1-((5-(2,4-difluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide and (S)-4-(4-(1-((5-(2,4-difluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

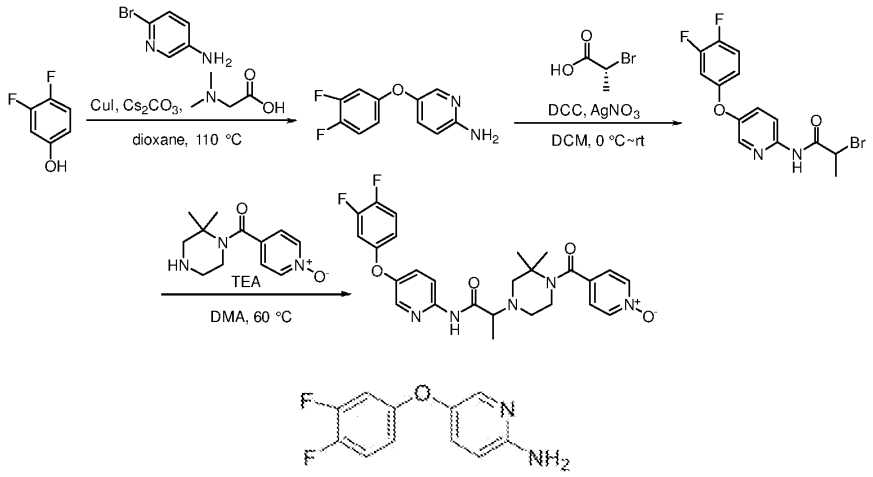
To a stirred solution of 2-bromo-N-[5-(2,4-difluorophenoxy)pyridin-2-yl]propanamide (50 mg, 0.140 mmol, 1 equiv) in DMF (1 mL) was added 4-(2,2-dimethylpiperazine-1-carbonyl)pyridin-1-ium-1-olate (164.70 mg, 0.700 mmol, 5 equiv) and TEA (85.00 mg, 0.840 mmol, 6 equiv) at room temperature. The reaction mixture was stirred at room temperature for 3 h. The resulting mixture was stirred for additional overnight at room temperature. After completion of reaction, the reaction mixture was quenched by addition of water (5 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was

washed with brine (10 mL), dried over anhydrous sodium sulfate filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150mm, 5μm (eluent: 27% to 47% (v/v) CH_3CN and H_2O, NH_4HCO_3+0.05%NH_3H_2O) to afford 4-(4-(1-((5-(2,4-difluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (50 mg, 65%) as a white solid. The product was separated by Chiral-HPLC using a CHIRALPAK IF 2*25 cm, 5 μm column (eluent: 50% (v/v) EtOH and MTBE with 0.1% DEA) to afford (R)-4-(4-(1-((5-(2,4-difluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (6.3 mg, 8.71%). MS (ESI): mass calcd. for $C_{26}H_{27}F_2N_5O_4$: 511.20 m/z, found: 512.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.21 (s, 1H), 8.17 – 8.27 (m, 2H), 8.09 – 8.23 (m, 2H), 7.38 – 7.58 (m, 4H), 7.30 (td, J = 9.3, 5.6 Hz, 1H), 7.13 (ddd, J = 9.3, 8.1, 3.0 Hz, 1H), 3.50 (q, J = 6.8 Hz, 1H), 3.32 (s, 2H), 2.71 (d, J = 5.3 Hz, 1H), 2.61 (q, J = 5.5 Hz, 1H), 2.38 – 2.48 (m, 2H), 1.45 (d, J = 3.0 Hz, 6H), 1.21 (t, J = 7.6 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -114.55 (d, J = 4.6 Hz), -126.77 (d, J = 4.8 Hz). And (S)-4-(4-(1-((5-(2,4-difluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (9.9 mg, 13.55%), MS (ESI): mass calcd. for $C_{26}H_{27}F_2N_5O_4$: 511.20 m/z, found: 512.25 $[M+H]^+$,^1H NMR (300 MHz, DMSO-d_6) δ 10.21 (s, 1H), 8.09 – 8.27 (m, 4H), 7.38 – 7.58 (m, 4H), 7.30 (td, J = 9.2, 5.6 Hz, 1H), 7.13 (ddd, J = 9.3, 8.1, 3.0 Hz, 1H), 3.50 (q, J = 6.8 Hz, 1H),3.32 (s, 2H), 2.71 (d, J = 5.4 Hz, 1H), 2.61 (q, J = 5.6 Hz, 1H), 2.38 – 2.48 (m, 2H), 1.45 (d, J = 3.0 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -114.55 (d, J = 4.8 Hz), -126.77 (d, J = 4.7 Hz).

Example 110: 4-(4-(1-((5-(3,4-difluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

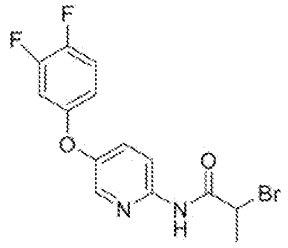


Synthetic Scheme



5-(3,4-difluorophenoxy)pyridin-2-amine

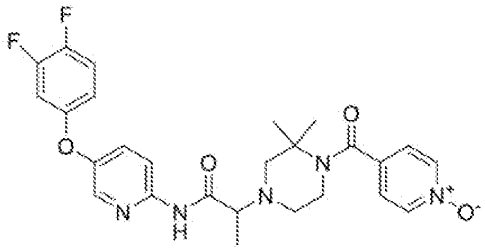
To a solution of 3,4-difluorophenol (5 g, 38.434 mmol, 1 equiv) in dioxane (15 mL) was added dimethylglycine (1.59 g, 15.374 mmol, 0.4 equiv) and 6-bromopyridin-3-amine (6.65 g, 38.434 mmol, 1 equiv) and CuI (1.46 g, 7.687 mmol, 0.2 equiv) and Cs_2CO_3 (18.78 g, 57.651 mmol, 1.5 equiv) at rt .The resulting mixture was stirred for overnight at 110 °C The reaction mixture was quenched by water and extracted with EA (3*100 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford product 5-(3,4-difluorophenoxy)pyridin-2-amine(4 g). MS (ESI): mass calcd. for $C_{11}H_8F_2N_2O$ 222.06 m/z, found 223.05 $[M+H]^+$.



2-bromo-N-[5-(3,4-difluorophenoxy)pyridin-2-yl]propanamide

To a solution of 5-(3,4-difluorophenoxy)pyridin-2-amine (700 mg, 3.150 mmol, 1 equiv) (2R)-2-bromopropanoic acid (722.90 mg, 4.725 mmol, 1.5 equiv) in DCM (5 mL) was added DCC (780.03 mg, 3.780 mmol, 1.2 equiv)at 0 °C. The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water and extracted with EA (3*20

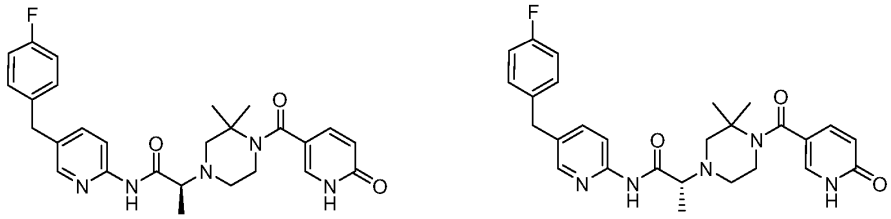
mL).The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford product 2-bromo-N-[5-(3,4-difluorophenoxy)pyridin-2-yl]propenamide (240 mg). MS (ESI): mass calcd. for $C_{14}H_{11}BrF_2N_2O_2$ 356.00 m/z, found 357.15 $[M+H]^+$.



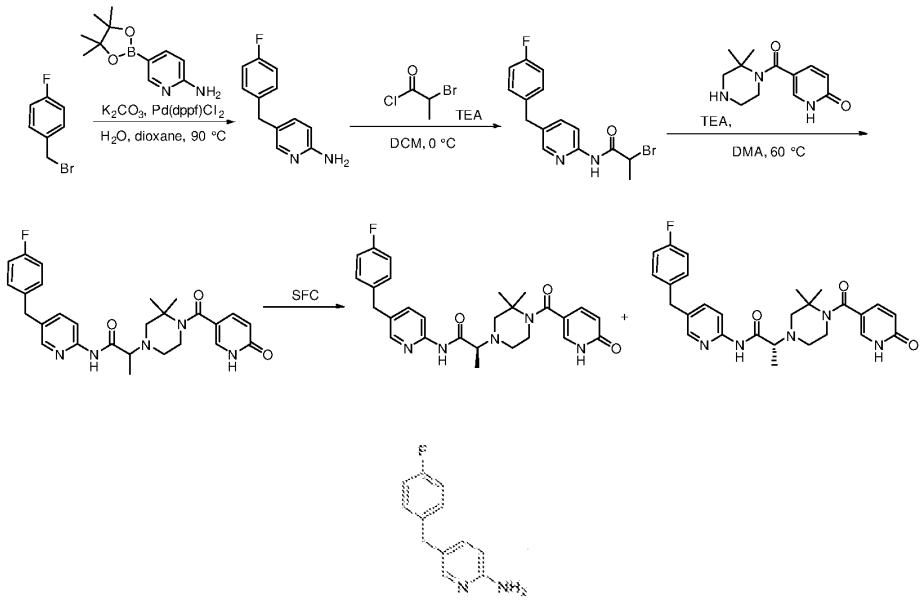
4-(4-(1-((5-(3,4-difluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

To a solution of 2-bromo-N-[5-(3,4-difluorophenoxy)pyridin-2-yl]propanamide (180 mg, 0.504 mmol, 1 equiv) in DMA (3 mL) was added 4-(2,2-dimethylpiperazine-1-carbonyl)pyridin-1-ium-1-olate (118.58 mg, 0.504 mmol, 1 equiv) and TEA (153.00 mg, 1.512 mmol, 3 equiv) at rt .The resulting mixture was stirred for 3h at 60 °C. The reaction mixture was quenched by water and extracted with EA (3*20 mL).The combined organic extracts were washed with brine (10mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatographyto afford product as a white solid. The residue was purified by preparative HPLC using a XBridge Prep OBD 150 mm x 30 mm x 5 μm column (eluent: 31% to 47% (v/v) CH_3CN and H_2O (10mmol/L NH_4HCO_3+0.05%NH_3H_2O)) to afford product 4-(4-(1-((5-(3,4-difluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide as a white solid. (3.1 mg, 1.19%). MS (ESI): mass calcd. for $C_{26}H_{27}F_2N_5O_4$ 511.20 m/z, found 512.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.22 (s, 1H), 8.11 – 8.24 (m, 4H), 7.57 (dd, J = 9.0, 3.0 Hz, 1H), 7.37 – 7.52 (m, 3H), 7.17 – 7.30 (m, 1H), 6.80 – 6.92 (m, 1H), 3.49 (dd, J = 7.7, 5.9 Hz, 1H), 3.34 – 3.40 (m, 2H),2.70 (q, J = 5.6, 5.1 Hz, 1H), 2.60 (q, J = 5.7 Hz, 1H), 2.35 – 2.45 (m, 2H), 1.44 (d, J = 2.8 Hz, 6H), 1.13 – 1.22 (m, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -135.05 (d, J = 22.7 Hz), -144.98 (d, J = 22.8 Hz).

Example 111: (S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorobenzyl)pyridin-2-yl)propanamide and Example 112: (R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorobenzyl)pyridin-2-yl)propanamide



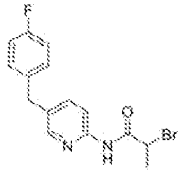
Synthetic Scheme



5-(4-fluorobenzyl)pyridin-2-amine

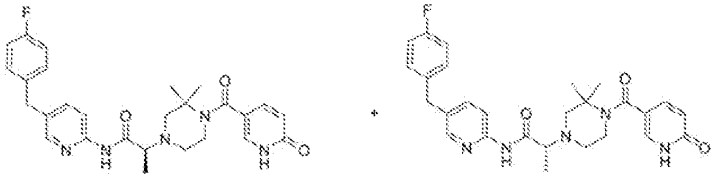
In a 40-mL round bottom flask, to a solution of 1-(bromomethyl)-4-fluorobenzene (1 g, 5.290 mmol, 1 equiv) in dioxane (15 mL) and H_2O (1.5 mL) was added 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (1.40 g, 6.348 mmol, 1.2 equiv), $Pd(dppf)Cl_2$ (0.39 g, 0.529 mmol, 0.1 equiv) and K_2CO_3 (2.21 g, 15.870 mmol, 3 equiv) at rt. The reaction mixture was stirred at 90 °C for 2 h under N_2. After completion of reaction, the

reaction was quenched by water (50 mL) and extracted with EA (50 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% EA/PE) to afford 5-(4-fluorobenzyl)pyridin-2-amine (350 mg, 30.10%). MS (ESI): mass calcd. for $C_{12}H_{11}FN_2$: 202.09 m/z. found 203.20 $[M+H]^+$.



2-bromo-N-(5-(4-fluorobenzyl)pyridin-2-yl)propanamide

To a stirred mixture of 5-(4-fluorobenzyl)pyridin-2-amine (300 mg, 1.483 mmol, 1 equiv) and TEA (450.34 mg, 4.449 mmol, 3 equiv) in DCM (10 mL) were added 2-bromopropanoyl chloride (254.29 mg, 1.483 mmol, 1 equiv) at 0 °C. After completion of reaction, the reaction mixture was quenched by addition of water (30 mL). The aqueous layer was extracted with DCM (20 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford 2-bromo-N-(5-(4-fluorobenzyl)pyridin-2-yl)propanamide (200 mg, 37.58%). MS (ESI): mass calcd. for $C_{15}H_{14}BrFN_2O$: 337.19 m/z, found: 338.05 $[M+H]^+$.

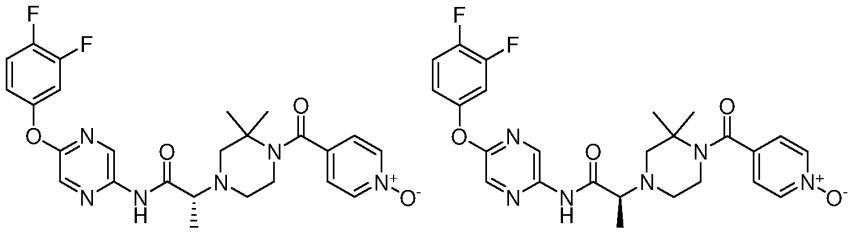


(S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorobenzyl)pyridin-2-yl)propanamide and (R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorobenzyl)pyridin-2-yl)propanamide

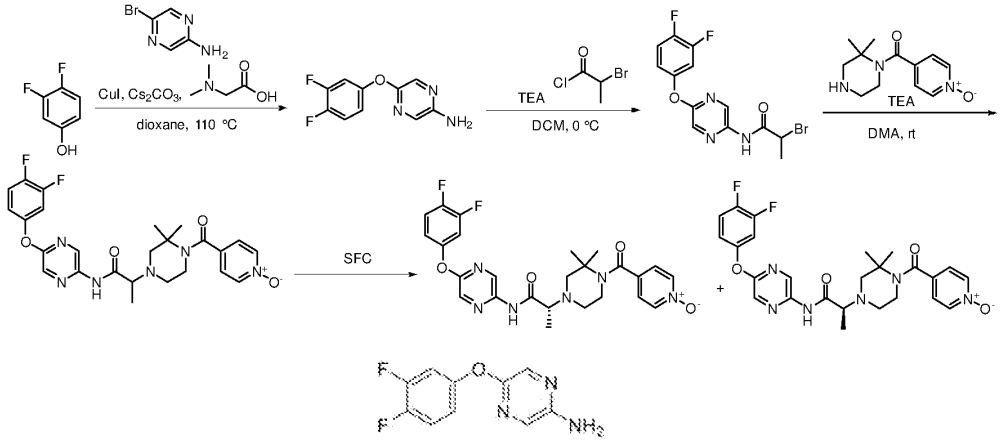
To a solution of 2-bromo-N-(5-(4-fluorobenzyl)pyridin-2-yl)propanamide (100 mg, 0.297 mmol, 1 equiv) in DMA (10 mL, 129.215 mmol, 435.70 equiv) the mixture was added 5-(2,2-dimethylpiperazine-1-carbonyl)-1H-pyridin-2-one (69.78 mg, 0.297 mmol, 1

equiv) and TEA (90.03 mg, 0.891 mmol, 3 equiv) at rt. The resulting mixture was stirred for 2 hours at 60 °C. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to give 2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorobenzyl)pyridin-2-yl)propanamide as a white solid. The product was purified by chiral-HPLC using a CHIRALPAK IF 25 cm x 2 cm x 5 μm column (eluent: 50% (v/v) EtOH and (HEX: DCM=3: 1)(0.05% 2M NH_3-MeOH)) to afford (S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorobenzyl)pyridin-2-yl)propanamide (12.5 mg, 8.56%) (13.9 mg, 6.34%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{30}FN_5O_3$: 491.23, found: 492.25 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.75 (s, 1H), 10.07 (s, 1H), 8.24 (d, J = 2.3 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.65 (dd, J = 8.5, 2.4 Hz, 1H), 7.56 (d, J = 2.6 Hz, 1H), 7.47 (dd, J = 9.5, 2.7 Hz, 1H), 7.24 – 7.33 (m, 2H), 7.07 – 7.18 (m, 2H), 6.32 (d, J = 9.4 Hz, 1H), 3.92 (s, 2H), 3.48 (dt, J = 13.8, 6.7 Hz, 1H), 2.72 (dt, J = 10.5, 4.6 Hz, 1H), 2.60 (dt, J = 10.5, 4.6 Hz, 1H), 2.51 – 2.53 (m, 2H), 2.33 – 2.44 (m, 2H), 1.40 (d, J = 3.0 Hz, 6H), 1.19 (d, J = 7.0 Hz, 3H). (R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorobenzyl)pyridin-2-yl)propanamide (15.7mg, 10.75%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{30}FN_5O_3$: 491.23, found: 492.30$[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 10.07 (s, 1H), 8.24 (d, J = 2.4 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.65 (dd, J = 8.5, 2.4 Hz, 1H), 7.56 (d, J = 2.6 Hz, 1H), 7.47 (dd, J = 9.5, 2.6 Hz, 1H), 7.24 – 7.33 (m, 2H), 7.07 – 7.18 (m, 2H), 6.32 (d, J = 9.4 Hz, 1H), 3.92 (s, 2H), 3.48 (dt, J = 13.9, 6.6 Hz, 1H),2.73 (dd, J = 11.1, 4.8 Hz, 1H), 2.56 – 2.65 (m, 1H), 2.51 – 2.53 (m, 2H), 2.33 – 2.44 (m, 2H), 1.40 (d, J = 3.0 Hz, 6H), 1.19 (d, J = 6.9 Hz, 3H).

Example 113 : (R)-4-(4-(1-((5-(3,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide and Example 114: (S)-4-(4-(1-((5-(3,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

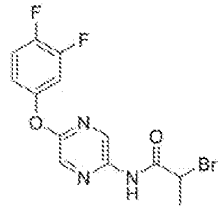


Synthetic Scheme



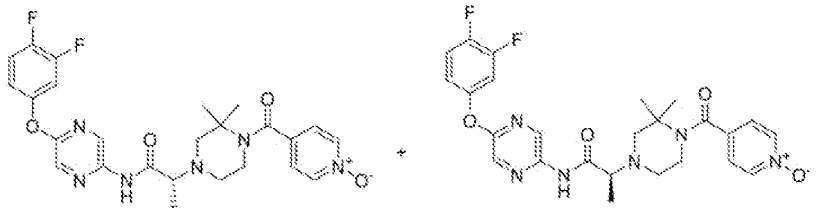
5-(3,4-difluorophenoxy)pyrazin-2-amine

To a stirred solution of 3,4-difluorophenol (1 g, 7.687 mmol, 1 equiv) in anhydrous dioxane (20 mL) was added dimethylglycine (0.08 g, 0.769 mmol, 0.1 equiv) and 5-bromopyrazin-2-amine (1.61 g, 9.224 mmol, 1.2 equiv) and Cs_2CO_3 (3.76 g, 11.530 mmol, 1.5 equiv) followed by catalytic amount of CuI (0.29 g, 1.537 mmol, 0.2 equiv) at room temperature. The reaction mixture was stirred at 110 °C for 3h. After cooled to room temperature the reaction was quenched by water (50 mL) and extracted with EA (100 mL x 3). The combined organic extracts were washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford 5-(3,4-difluorophenoxy)pyrazin-2-amine (700 mg, 38.49%) as a yellow solid. MS (ESI): mass calcd. for $C_{10}H_7F_2N_3O$: 223.06 m/z, found 224.15 $[M+H]^+$.



2-bromo-N-(5-(3,4-difluorophenoxy)pyrazin-2-yl)propanamide

To a stirred solution of 5-(3,4-difluorophenoxy)pyrazin-2-amine (400 mg, 1.792 mmol, 1 equiv) in anhydrous DCM was added TEA (544.09 mg, 5.376 mmol, 3 equiv) at room temperature. The reaction mixture was stirred at 0 °C for 5min. To a stirred mixture was added 2-bromopropanoyl chloride (245.78 mg, 1.434 mmol, 0.8 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 40 min. After completion of reaction, the reaction was quenched by water (20 mL) and extracted with DCM (50 mL x 3). The combined organic extracts were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford 2-bromo-N-(5-(3,4-difluorophenoxy)pyrazin-2-yl)propanamide (300 mg, 46.59%) as a pink solid. MS (ESI): mass calcd. for:$C_{13}H_{10}BrF_2N_3O_2$: 357.01 m/z, found: 358.10$[M+H]^+$.

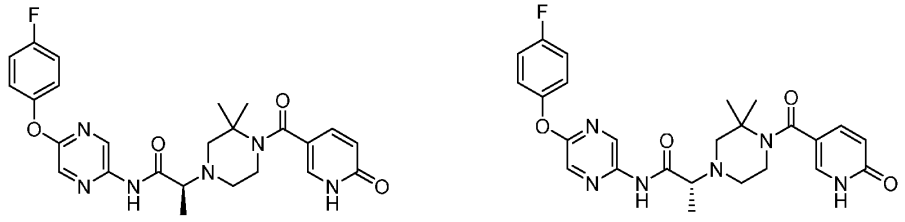


(R)-4-(4-(1-((5-(3,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide and (S)-4-(4-(1-((5-(3,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

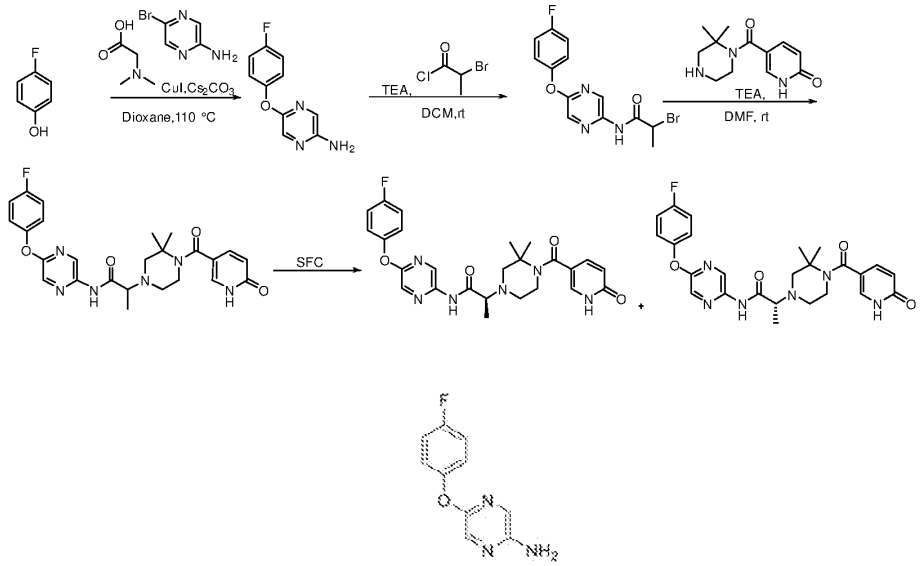
To a stirred solution of 2-bromo-N-(5-(3,4-difluorophenoxy)pyrazin-2-yl)propanamide (304.43 mg, 0.850 mmol, 1 equiv) in anhydrous DMA (3 mL) was added 4-(2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (200 mg, 0.850 mmol, 1.00 equiv) and TEA (258.05 mg, 2.550 mmol, 3 equiv) at room temperature. The reaction mixture was stirred at room temperature for 3 h. After completion of reaction, the reaction was quenched by water

(20 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (5-80% PE/EA) and by preparative HPLC using a XBridge Prep OBD 150 mm x 30 mm x 5 μm column (eluent: 30% to 44% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford 4-(4-(1-((5-(3,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide as a white solid. The residue was purified by chiral-HPLC using a CHIRALPAK IF 25 cm x 2 cm x 5 μm column (eluent: 50% (v/v) Hex: DCM=1: 1(0.5% 2M NH3-MeOH and IPA) and ETOH) to affordto afford (R)-4-(4-(1-((5-(3,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (21.0 mg, first peak). MS (ESI): mass calcd. for $C_{25}H_{26}F_2N_6O_4$: 512.20 m/z, found 513.15 $[M+H]^+$.^{1}H NMR (300 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.92 (d, J = 1.4 Hz, 1H), 8.35 (d, J = 1.5 Hz, 1H), 8.21 (d, J = 6.9 Hz, 2H), 7.46 (dd, J = 24.0, 8.3 Hz, 4H), 7.03 – 7.13 (m, 1H), 3.54 (t, J = 7.2 Hz, 1H), 2.57 – 2.67 (m, 3H), 2.45 (s, 3H), 1.45 (d, J = 2.6 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H). And (S)-4-(4-(1-((5-(3,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (21.6 mg, second peak). MS (ESI): mass calcd. for $C_{25}H_{26}F_2N_6O_4$: 512.20 m/z, found 513.15 $[M+H]^+$.^{1}H NMR (300 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.92 (d, J = 1.4 Hz, 1H), 8.35 (d, J = 1.4 Hz, 1H), 8.21 (d, J = 6.5 Hz, 2H), 7.37 – 7.58 (m, 4H), 7.08 (dd, J = 9.0, 4.4 Hz, 1H), 3.48 – 3.58 (m, 1H), 2.57 – 2.67 (m, 3H), 2.38 – 2.49 (m, 3H), 1.45 (d, J = 2.6 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H).

Example 115: (S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)propanamide and Example 116: (R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)propanamide

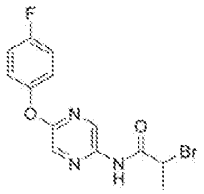


Synthetic Scheme



5-(4-fluorophenoxy)pyrazin-2-amine

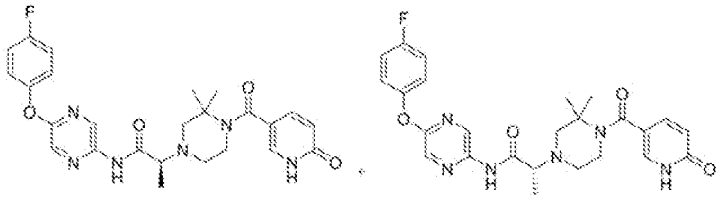
To a stirring solution 4-fluorophenol (1 g, 8.920 mmol, 1 equiv) in 1,4-Dioxane (20 mL) was added a solution of dimethylglycine (0.09 g, 0.892 mmol, 0.1 equiv) and 5-bromopyrazin-2-amine (1.55 g, 8.920 mmol, 1 equiv) and CuI (0.34 g, 1.784 mmol, 0.2 equiv) and Cs_2CO_3 (4.36 g, 13.380 mmol, 1.5 equiv) .The resulting mixture under N_2 was stirred at 110 °C for 6h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford 5-(4-fluorophenoxy)pyrazin-2-amine (350 mg, 19.12%) MS (ESI): mass calcd. for $C_{10}H_8FN_3O$: 205.07 found: 206.05 [$M+H^+$]



2-bromo-N-(5-(4-fluorophenoxy)pyrazin-2-yl)propanamide

To a stirring solution 5-(4-fluorophenoxy)pyrazin-2-amine (300 mg, 1.462 mmol, 1 equiv) in DCM (5 mL) was added a solution of 2-bromo-propionyl chloride (375.94 mg, 2.193 mmol, 1.5 equiv) and TEA (443.85 mg, 4.386 mmol, 3 equiv). The resulting mixture

was stirred at room temperature for 6h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford 2-bromo-N-(5-(4-fluorophenoxy)pyrazin-2-yl)propanamide (300 mg, 60.32%). MS (ESI): mass calcd. for $C_{13}H_{11}BrFN_3O_2$: 339.00 found: 340.05 $[M+H]^+$

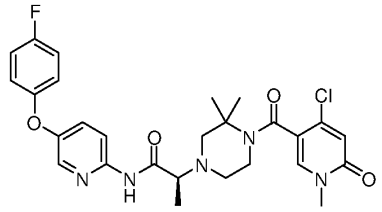


(R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)propanamide and (S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)propanamide

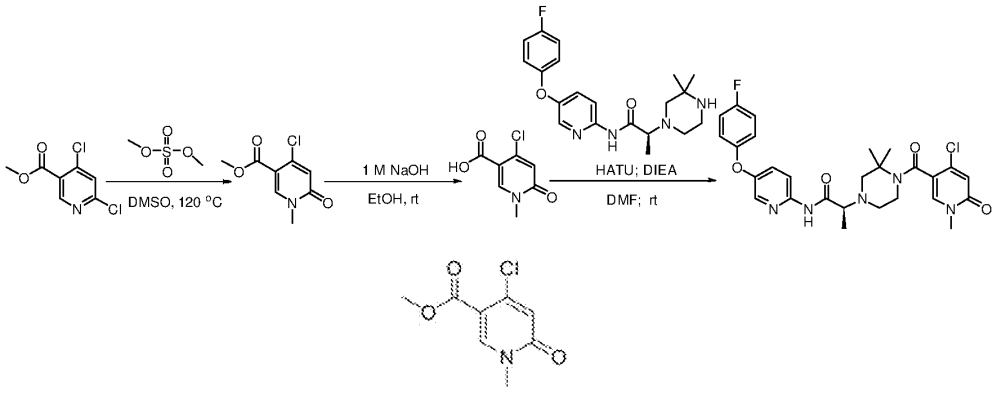
To a stirred solution of 2-bromo-N-(5-(4-fluorophenoxy)pyrazin-2-yl)propanamide (100 mg, 0.294 mmol, 1 equiv) in dimethylformamide (2 mL) was added 4-(2,2-dimethylpiperazine-1-carbonyl)pyridin-1-ium-1-olate (207.51 mg, 0.882 mmol, 3 equiv) and TEA (148.75 mg, 1.470 mmol, 5 equiv) at room temperature. The reaction mixture was stirred at room temperature for 3 h. The resulting mixture was stirred for additional overnight at room temperature. After completion of reaction, the reaction mixture was quenched by addition of water (5 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150mm, 5μm (eluent: 28% to 58% (v/v) CH_3CN and H_2O, NH_4HCO_3+0.05%NH_3H_2O) to afford 2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)propanamide (50 mg, 30%) as a white solid. The product was separated by Chiral-HPLC using a CHIRALPAK IF 2*25 cm, 5 μm column (eluent: 50% (v/v) EtOH and MTBE with 0.1% DEA) to afford (R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)propanamide (15 mg, 10.25%), MS (ESI): mass calcd. for

$C_{25}H_{27}FN_6O_4$: 494.21 m/z, found: 495.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.89 (d, J = 1.4 Hz, 1H), 8.33 (d, J = 1.4 Hz, 1H), 8.17 – 8.27 (m, 2H), 7.38 – 7.48 (m, 2H), 7.17 – 7.33 (m, 4H), 3.54 (q, J = 6.8 Hz, 1H), 3.31 (s, 2H), 2.71 (q, J = 5.6, 5.1 Hz, 1H), 2.57 – 2.67 (m, 1H), 2.45 (d, J = 2.5 Hz, 2H), 1.45 (d, J = 2.8 Hz, 6H), 1.06 – 1.27 (m, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -118.36. And (S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)propanamide (13 mg, 8.88%), MS (ESI): mass calcd. for $C_{25}H_{27}FN_6O_4$: 494.21 m/z, found: 512.25 $[M+H]^+$, ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.89 (d, J = 1.4 Hz, 1H), 8.33 (d, J = 1.4 Hz, 1H), 8.17 – 8.28 (m, 2H), 7.38 – 7.48 (m, 2H), 7.17 – 7.34 (m, 4H), 3.54 (q, J = 6.8 Hz, 1H), 3.31 (s, 2H), 2.68 – 2.79 (m, 1H), 2.56 – 2.68 (m, 1H),2.45 (d, J = 2.5 Hz, 2H), 1.45 (d, J = 2.8 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H).

Example 117: (S)-2-(4-(4-chloro-1-methyl-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide



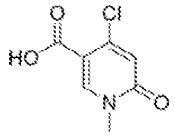
Synthetic Scheme



methyl 4-chloro-1-methyl-6-oxopyridine-3-carboxylate

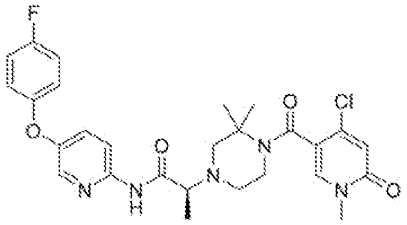
Compound methyl 4,6-dichloropyridine-3-carboxylate (3.19 g, 15.484 mmol, 1 equiv) and dimethyl sulfate (6 mL) were combined in a thick-walled glass tube. The tube was sealed

and heated in a 120 °C sand bath. After 5 h, the reaction was cooled to RT and diluted with acetonitrile (100 mL) and saturated aq $NaHCO_3$ solution (100 mL). The reaction mixture was stirred vigorously for 18 h. This mixture was further diluted with water and was extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with brine (200 mL) and dried (Na_2SO_4) and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford product methyl 4-chloro-1-methyl-6-oxopyridine-3-carboxylate (1.7 g). MS (ESI): mass calcd. for $C_8H_8ClNO_3$ 201.02 m/z, found 202.00 $[M+H]^+$.



4-chloro-1-methyl-6-oxopyridine-3-carboxylic acid

Compound methyl 4-chloro-1-methyl-6-oxopyridine-3-carboxylate (280 mg, 1.389 mmol, 1 equiv) was suspended in EtOH (20mL), to which was added 1 M NaOH (20mL). This mixture was stirred at rt for 1.5 h and then diluted with 1 M HCl and the resulting precipitate extracted into EtOAc (2 × 10 mL). The combined EtOAc fractions were dried (Na_2SO_4) and filtered. The crude product/ resulting mixture was used in the next step directly without further purification. MS (ESI): mass calcd. for $C_7H_6ClNO_3$ 187.00 m/z, found 188.00 $[M+H]^+$.

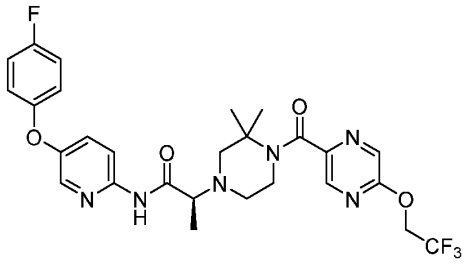


(S)-2-(4-(4-chloro-1-methyl-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

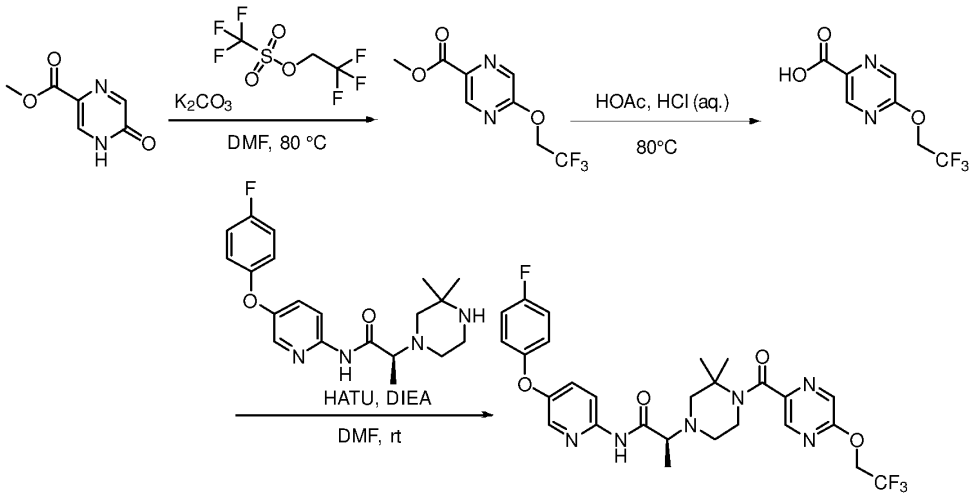
To a solution of 4-chloro-1-methyl-6-oxopyridine-3-carboxylic acid (80 mg, 0.426 mmol, 1 equiv) in DMF (3 mL) was added (2S)-2-(3,3-dimethylpiperazin-1-yl)-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (158.84 mg, 0.426 mmol, 1 equiv) and HATU (243.25 mg, 0.639 mmol, 1.5 equiv) and DIEA (110.24 mg, 0.852 mmol, 2 equiv) at rt . The mixture was stirred at rt for 3 h. After completion of reaction, the reaction mixture was quenched by addition of water (10 mL). The aqueous layer was extracted with ethyl acetate

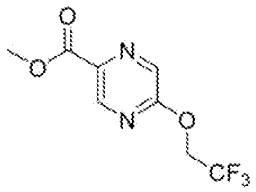
(50 mL). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH). The residue was purified by preparative HPLC using a YMC Triart C18 ExRs 250 mm x 20 mm x 5 μm column (eluent: 47% to 77% (v/v) CH_3CN and H_2O with 0.05% TFA) to afford (S)-2-(4-(4-chloro-1-methyl-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (20.8 mg, 9.00%) as a white solid. MS (ESI): mass calcd for $C_{27}H_{29}ClFN_5O_4$ 541.19 m/z, found 542.25 $[M+H]^+$.

Example 118: (S)-2-(3,3-dimethyl-4-(5-(2,2,2-trifluoroethoxy)pyrazine-2-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide



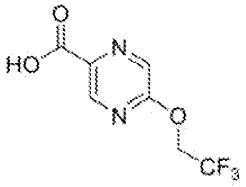
Synthetic Scheme





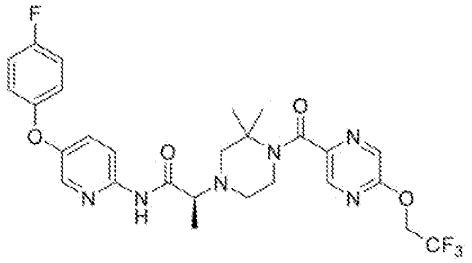
methyl 5-(2,2,2-trifluoroethoxy)pyrazine-2-carboxylate

To a solution of methyl 5-oxo-4H-pyrazine-2-carboxylate (500 mg, 3.244 mmol, 1 equiv) in DMF (1 mL). 2,2,2-trifluoroethyl trifluoromethanesulfonate (1.51 g, 6.488 mmol, 2 equiv) and potassium methaneperoxoate potassium (1.35 g, 9.732 mmol, 3 equiv) added at rt. The resulting mixture was stirred for 2h at 80 degrees. After cooled to room temperature the resulting mixture was extracted with EA (3*100 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% PE/EA) to afford afford methyl 5-oxo-4-(2,2,2-trifluoroethyl)-4,5-dihydropyrazine-2-carboxylate (large polarity, 300 mg, 39.16%) as a yellow oil. MS (ESI): mass calcd. for $C_8H_7F_3N_2O_3$: 236.04, found: 237.15 $[M+H]^+$. And methyl 5-(2,2,2-trifluoroethoxy)pyrazine-2-carboxylate (small polarity, 150 mg, 19.58%) as a yellow oli, MS (ESI): mass calcd. for $C_8H_7F_3N_2O_3$: 236.04, found: 237.15$[M+H]^+$.



5-(2,2,2-trifluoroethoxy)pyrazine-2-carboxylic acid

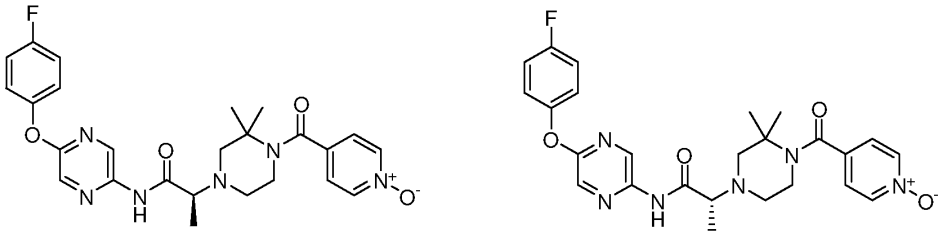
To a solution of methyl 5-oxo-4-(2,2,2-trifluoroethyl)pyrazine-2-carboxylate (10 mg, 0.042 mmol, 1 equiv) in acetic acid (0.6 mL) and concentrated hydrogen chloride (0.3 mL) was heated under 80 °C for 1.5 hours. The reaction was quenched with ice-cold at rt. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% PE/EA) to afford 5-(2,2,2-trifluoroethoxy)pyrazine-2-carboxylic acid as a white solid, MS (ESI): mass calcd. for $C_7H_5F_3N_2O_3$: 222.03, found: 221.10 $[M-H]^-$.



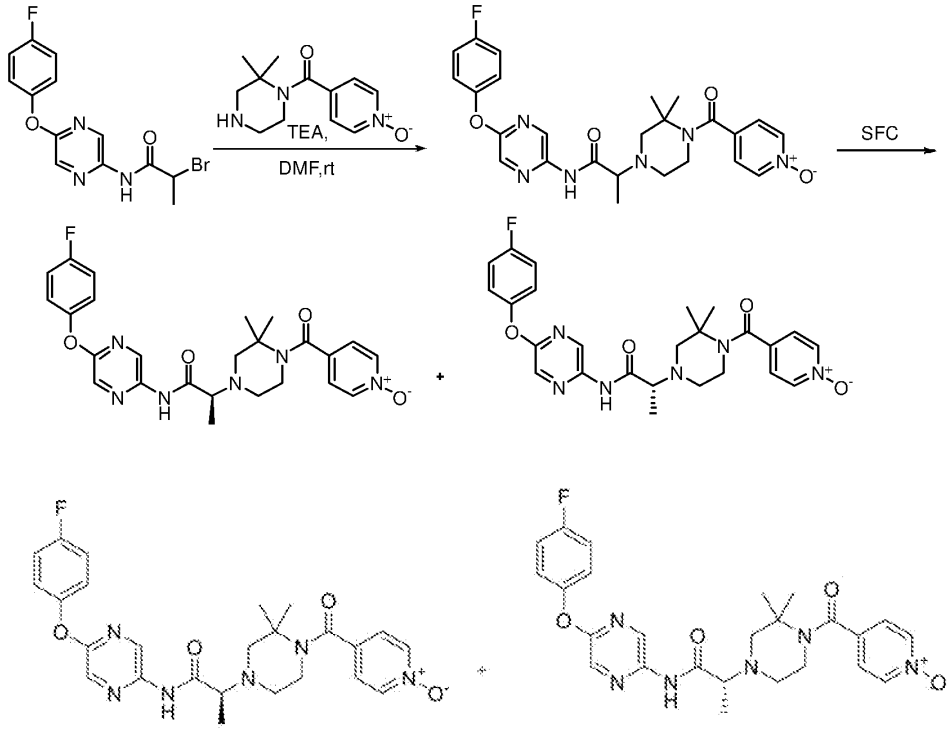
(S)-2-(3,3-dimethyl-4-(5-(2,2,2-trifluoroethoxy)pyrazine-2-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

To a solution of 5-(2,2,2-trifluoroethoxy)pyrazine-2-carboxylic acid (40 mg, 0.180 mmol, 1 equiv) in DMF (10 mL). (2S)-2-(3,3-dimethylpiperazin-1-yl)-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (67.07 mg, 0.180 mmol, 1 equiv), HATU (136.95 mg, 0.360 mmol, 2 equiv) and DIEA (34.91 mg, 0.270 mmol, 1.5 equiv) added at rt. The resulting mixture was stirred for 2h at rt. After cooled to room temperature the resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% PE/EA) to afford (2S)-2-{3,3-dimethyl-4-[5-(2,2,2-trifluoroethoxy)pyrazine-2-carbonyl]piperazin-1-yl}-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide as a yellow oli and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 50% to 70% CH_3CN and H_2O with10mmol/L NH_4HCO_3+0.05%H_2O) to afford (S)-2-(3,3-dimethyl-4-(5-(2,2,2-trifluoroethoxy)pyrazine-2-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (2.0 mg, 1.89%) as a white solid, MS (ESI): mass calcd. for $C_{27}H_{28}F_4N_6O_4$:576.21, found:577.30$[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.17 (s, 1H), 8.40 – 8.48 (m, 2H), 8.08 – 8.18 (m, 2H), 7.51 (dd, J = 9.1, 2.9 Hz, 1H), 7.15 – 7.29 (m, 2H), 7.01 – 7.14 (m, 2H), 4.99 – 5.14 (m, 2H), 3.41 – 3.54 (m, 1H), 3.35 – 3.41 (m, 2H), 2.63 – 2.74 (m, 1H), 2.50 – 2.63 (m, 1H), 2.38 – 2.48 (m. 2H), 1.47 (d, J = 2.4 Hz, 6H), 1.18 (d, J = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -72.186, -119.844.

Example 119: ((S)-4-(4-(1-((5-(4-fluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide and Example 120: ((R)-4-(4-(1-((5-(4-fluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide



Synthetic Scheme

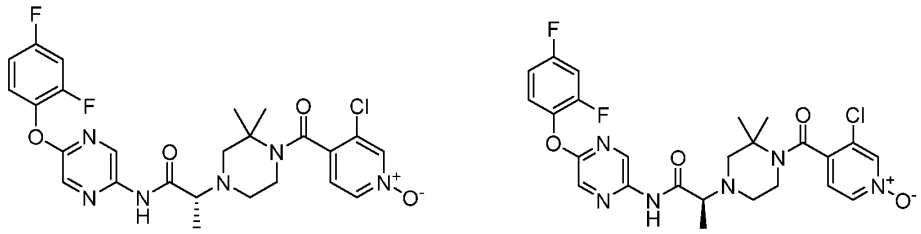


(S)-4-(4-(1-((5-(4-fluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide and (R)-4-(4-(1-((5-(4-fluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

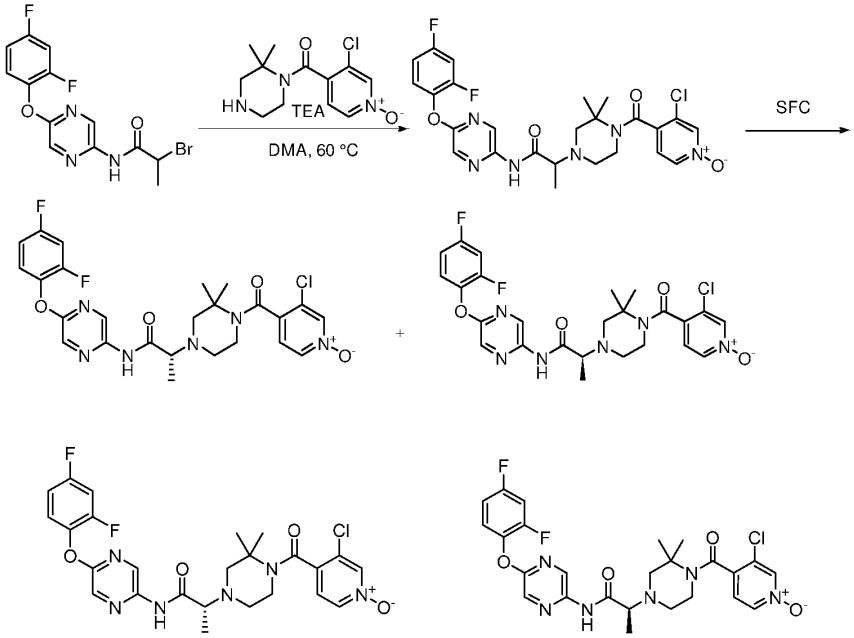
To a stirred solution of 2-bromo-N-(5-(4-fluorophenoxy)pyrazin-2-yl)propanamide (100 mg, 0.294 mmol, 1 equiv) in dimethylformamide (2 mL) was added 4-(2,2-dimethylpiperazine-1-carbonyl)pyridin-1-ium-1-olate (207.51 mg, 0.882 mmol, 3 equiv) and TEA (148.75 mg, 1.470 mmol, 5 equiv) at room temperature. The reaction mixture was stirred at room temperature for 3 h. The resulting mixture was stirred for additional overnight

at room temperature. After completion of reaction, the reaction mixture was quenched by addition of water (5 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150mm, 5μm (eluent: 28% to 58% (v/v) CH_3CN and H_2O, NH_4HCO_3+0.05%NH_3H_2O) to afford 2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)propanamide (50 mg, 30%) as a white solid. The product was separated by Chiral-HPLC using a CHIRALPAK IF 2*25 cm, 5 μm column (eluent: 50% (v/v) EtOH and MTBE with 0.1% DEA) to afford (S)-4-(4-(1-((5-(4-fluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (15 mg, 10.25%) ,MS (ESI): mass calcd. for $C_{25}H_{27}FN_6O_4$: 494.21 m/z, found: 495.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.89 (d, J = 1.4 Hz, 1H), 8.33 (d, J = 1.4 Hz, 1H), 8.17 – 8.27 (m, 2H), 7.38 – 7.48 (m, 2H), 7.17 – 7.33 (m, 4H), 3.54 (q, J = 6.8 Hz, 1H), 3.31 (s, 2H), 2.71 (q, J = 5.6, 5.1 Hz, 1H), 2.57 – 2.67 (m, 1H), 2.45 (d, J = 2.5 Hz, 2H), 1.45 (d, J = 2.8 Hz, 6H), 1.06 – 1.27 (m, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -118.36. And (R)-4-(4-(1-((5-(4-fluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (13 mg, 8.88%), MS (ESI): mass calcd. for $C_{25}H_{27}FN_6O_4$: 494.21 m/z, found: 512.25 $[M+H]^+$, ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.89 (d, J = 1.4 Hz, 1H), 8.33 (d, J = 1.4 Hz, 1H), 8.17 – 8.28 (m, 2H), 7.38 – 7.48 (m, 2H), 7.17 – 7.34 (m, 4H), 3.54 (q, J = 6.8 Hz, 1H), 3.31 (s, 2H), 2.68 – 2.79 (m, 1H), 2.56 – 2.68 (m, 1H),2.45 (d, J = 2.5 Hz, 2H), 1.45 (d, J = 2.8 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -118.43.

Example 121: (R)-3-chloro-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide and Example 122: (S)-3-chloro-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide



Synthetic Scheme

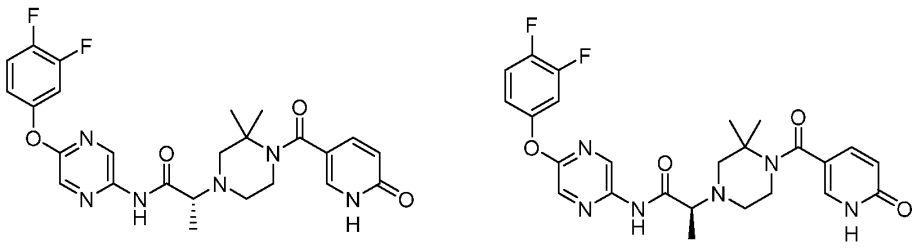


(R)-3-chloro-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide and (S)-3-chloro-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

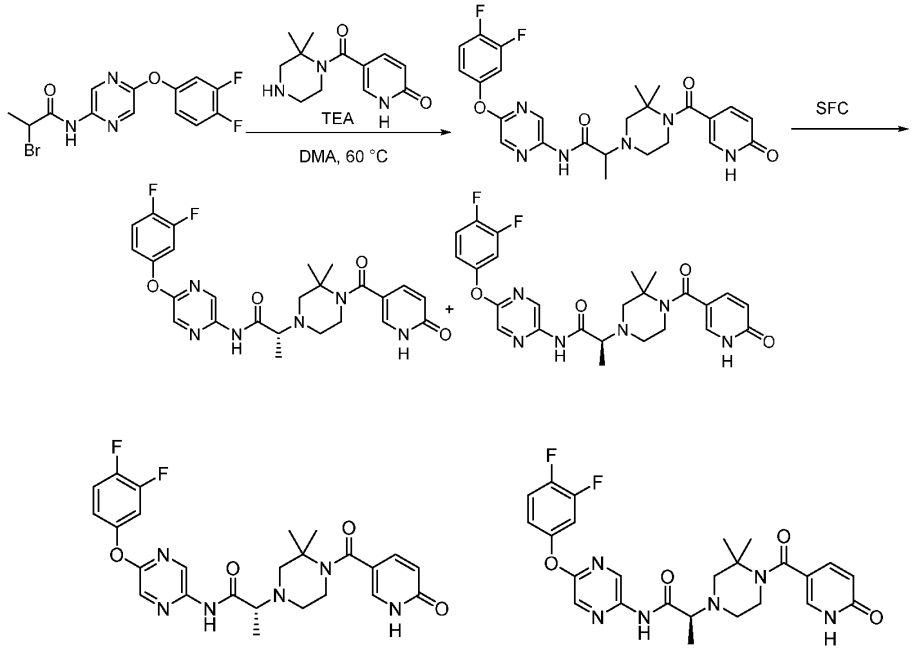
To a solution of 2-bromo-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (200 mg, 0.558 mmol, 1 equiv) in DMA (5 mL) was added 3-chloro-4-(2,2-dimethylpiperazine-1-carbonyl)pyridin-1-ium-1-olate (150.63 mg, 0.558 mmol, 1 equiv) and TEA (169.53 mg, 1.674 mmol, 3 equiv) at rt. The resulting mixture was stirred for 3 hours at 60 °C. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over

anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-15% DCM/MeOH). The product was purified by chiral-HPLC using a CHIRAL ART Cellulose-SC 25 cm x 2 cm x 5 μm column (eluent: 50% (v/v) EtOH and Hex: DCM=3: 1(0.5% 2M NH3-MeOH)) to afford (R)-3-chloro-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (12.7 mg, 4.14%) MS (ESI): mass calcd. for $C_{25}H_{25}ClF_2N_6O_4$: 546.16 m/z, found: 547.15 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 2H), 8.83 (d, J = 1.4 Hz, 2H), 8.57 (d, J = 1.7 Hz, 2H), 8.45 (d, J = 1.4 Hz, 2H), 8.22 (dd, J = 6.6, 1.8 Hz, 2H), 7.54 – 7.39 (m, 7H), 7.25 – 7.13 (m, 3H), 3.58 – 3.48 (m, 3H), 2.69 – 2.61 (m, 3H), 2.56 (dd, J = 10.8, 5.1 Hz, 12H), 2.45 (d, J = 3.0 Hz, 4H), 1.50 (s, 11H), 1.24 (s, 1H), 1.19 (d, J = 6.9 Hz, 6H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -113.4362, -124.2292. And (S)-3-chloro-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (18.9 mg, 6.17%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{25}ClF_2N_6O_4$: 546.16 m/z, found: 547.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 2H), 8.83 (d, J = 1.4 Hz, 2H), 8.57 (d, J = 1.7 Hz, 2H), 8.45 (d, J = 1.4 Hz, 2H), 8.22 (dd, J = 6.6, 1.8 Hz, 2H), 7.54 – 7.39 (m, 7H), 7.25 – 7.13 (m, 3H), 3.58 – 3.48 (m, 3H), 2.69 – 2.61 (m, 3H), 2.56 (dd, J = 10.8, 5.1 Hz, 12H), 2.45 (d, J = 3.0 Hz, 4H), 1.50 (s, 11H), 1.24 (s, 1H), 1.19 (d, J = 6.9 Hz, 6H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -113.4361, -124.2260.

Example 123: (R)-N-(5-(3,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide and Example 124: (S)-N-(5-(3,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide



Synthetic Scheme

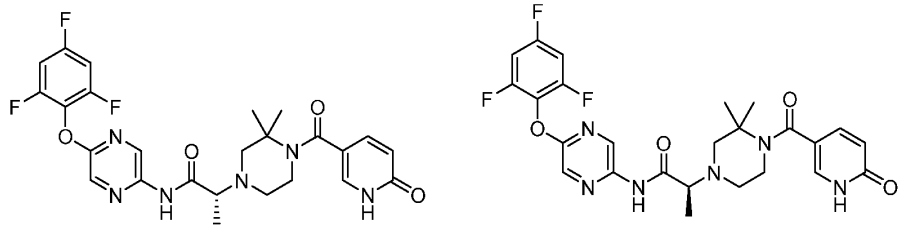


(R)-N-(5-(3,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide and (S)-N-(5-(3,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

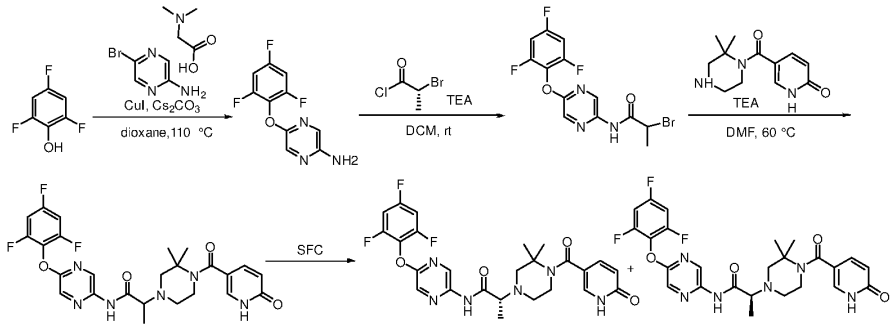
To a stirred solution of 2-bromo-N-(5-(3,4-difluorophenoxy)pyrazin-2-yl)propanamide (152.22 mg, 0.425 mmol, 1 equiv) in anhydrous dimethylformamide (2 mL) was added 5-(2,2-dimethylpiperazine-1-carbonyl)pyridin-2(1H)-one (99 mg, 0.425 mmol, 1.00 equiv) and TEA (129.02 mg, 1.275 mmol, 3 equiv) at room temperature. The reaction mixture was stirred at 60 ℃ for 3 h. After completion of reaction, the reaction was quenched by water (20 mL) and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (5-80% PE/EA) and Prep-HPLC using a XBridge Prep OBD C18 Column, 30 x 150 mm x 5μm Column (eluent: 30% to 44% CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford N-(5-(3,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide as a white solid. The residue was purified by Chiral-HPLC using a CHIRALPAK IF 25 cm x 2 cm x 5 μm column (eluent: 50% (v/v) HEX (0.5% 2M NH_3-MeOH) and IPA) to afford (R)-

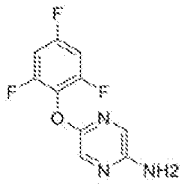
N-(5-(3,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (1.9 mg, first peak). MS (ESI): mass calcd. for $C_{25}H_{26}F_2N_6O_4$: 512.20 m/z, found 513.15 $[M+H]^+$.^{1}H NMR (300 MHz, Acetonitrile-d_3) δ 9.33 (s, 1H), 8.87 (d, J = 1.4 Hz, 1H), 8.10 – 8.22 (m, 1H), 7.83 (d, J = 2.4 Hz, 1H), 7.53 (dd, J = 9.4, 2.4 Hz, 1H), 7.26 – 7.38 (m, 1H), 7.11 – 7.24 (m, 1H), 7.00 (dd, J = 9.0, 4.3 Hz, 1H), 6.47 (d, J = 9.4 Hz, 1H), 5.59 (q, J = 7.2 Hz, 1H), 3.33 (q, J = 4.6 Hz, 2H), 2.86 (t, J = 5.2 Hz, 2H), 2.67 (s, 2H), 1.72 (d, J = 7.3 Hz, 3H), 1.44 (s, 6H). And (S-N-(5-(3,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (2.4 mg, second peak). MS (ESI): mass calcd. for $C_{25}H_{26}F_2N_6O_4$: 512.20 m/z, found 513.15 $[M+H]^+$. ^{1}H NMR (300 MHz, Acetonitrile-d_3) δ 9.33 (s, 1H), 8.87 (d, J = 1.4 Hz, 1H), 8.10 – 8.22 (m, 1H), 7.83 (d, J = 2.4 Hz, 1H), 7.53 (dd, J = 9.4, 2.4 Hz, 1H), 7.26 – 7.38 (m, 1H), 7.11 – 7.24 (m, 1H), 7.00 (dd, J = 9.0, 4.3 Hz, 1H), 6.47 (d, J = 9.4 Hz, 1H), 5.59 (q, J = 7.2 Hz, 1H), 3.33 (q, J = 4.6 Hz, 2H), 2.86 (t, J = 5.2 Hz, 2H), 2.67 (s, 2H), 1.72 (d, J = 7.3 Hz, 3H), 1.44 (s, 6H).

Example 125: (R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(2,4,6-trifluorophenoxy)pyrazin-2-yl)propanamide and Example 126 (S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(2,4,6-trifluorophenoxy)pyrazin-2-yl)propanamide



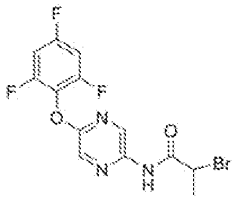
Synthetic Scheme





5-(2,4,6-trifluorophenoxy)pyrazin-2-amine

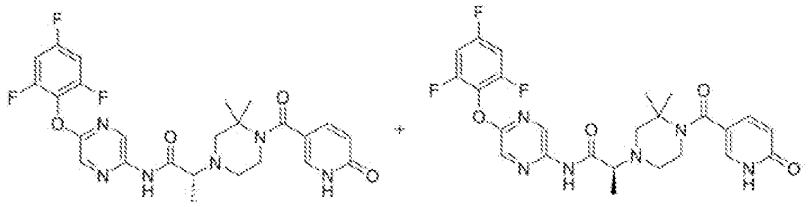
To a stirred solution of 2,4,6-trifluorophenol (1.5 g, 10.129 mmol, 1 equiv) in dioxane was added 5-bromopyrazin-2-amine (2.12 g, 12.155 mmol, 1.2 equiv), dimethylglycine (0.10 g, 1.013 mmol, 0.1 equiv), Cs_2CO_3 (4.97 g, 15.194 mmol, 1.5 equiv) and copper(I) iodide (0.39 g, 2.026 mmol, 0.2 equiv) at room temperature. The reaction mixture was stirred at 110 °C for a period of overnight under N2. After cooled to room temperature, the reaction mixture was quenched by addition of water (50 mL). The aqueous layer was extracted with ethyl acetate (100 mL x 3). The combined organic phase was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-60% PE/EA) to afford 5-(2,4,6-trifluorophenoxy)pyrazin-2-amine (800 mg, 30.13%) . MS (ESI): mass calcd. For $C_{10}H_6F_3N_3O$: 241.17 m/z, found: 242.10 $[M+H]^+$.



2-bromo-N-(5-(2,4,6-trifluorophenoxy)pyrazin-2-yl)propanamide

To a stirred mixture of 5-(2,4,6-trifluorophenoxy)pyrazin-2-amine (500 mg, 2.073 mmol, 1 equiv) and TEA (629.38 mg, 6.219 mmol, 3 equiv) in DCM (10 mL) were added

(R)-2-bromopropanoyl chloride (355.39 mg, 2.073 mmol, 1 equiv) at 0 °C . After completion of reaction, the reaction mixture was quenched by addition of water (50 mL). The aqueous layer was extracted with DCM (100 mL x 3). The combined organic phase was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford 2-bromo-N-(5-(2,4,6-trifluorophenoxy)pyrazin-2-yl)propanamide (500 mg, 67.62%). MS (ESI): mass calcd. for $C_{13}H_9BrF_3N_3O_2$: 375.13 m/z, found: 376.20 $[M+H]^+$.

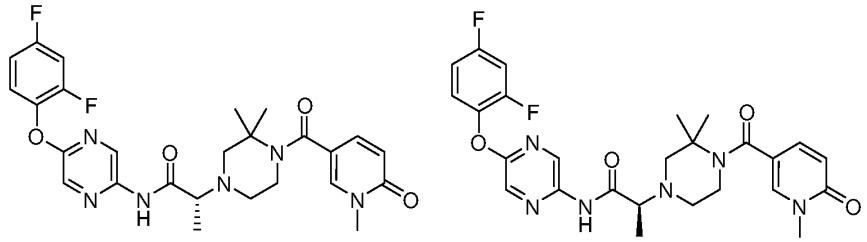


(R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(2,4,6-trifluorophenoxy)pyrazin-2-yl)propanamide and (S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(2,4,6-trifluorophenoxy)pyrazin-2-yl)propanamide

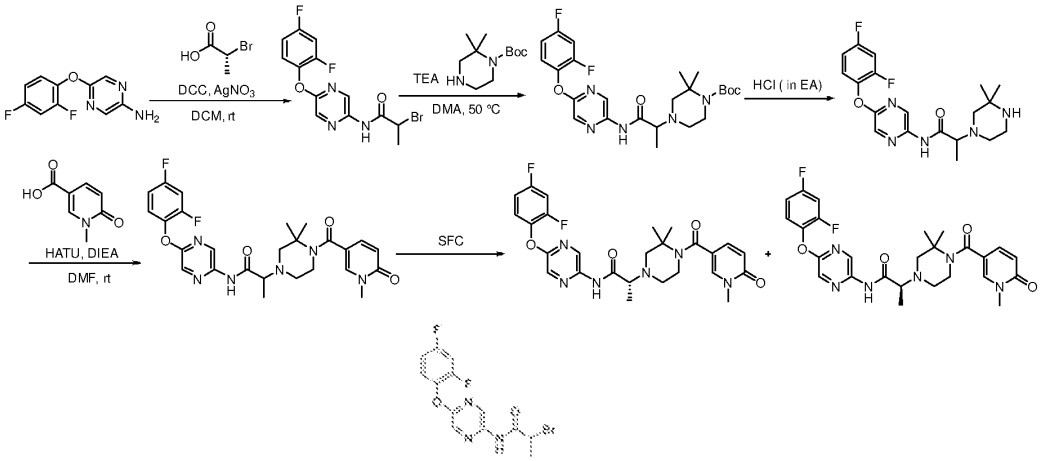
To a solution of 2-bromo-N-(5-(2,4,6-trifluorophenoxy)pyrazin-2-yl)propanamide(100 mg, 0.266 mmol, 1 equiv) in dimethylformamide (10 mL) the mixture was added 5-(2,2-dimethylpiperazine-1-carbonyl)-1H-pyridin-2-one (62.55 mg, 0.266 mmol, 1 equiv) and TEA (80.71 mg, 0.798 mmol, 3 equiv) at rt. The resulting mixture was stirred for 2 hours at 60 °C. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to give crude product. The product was purified by chiral-HPLC using a Chiral-Prep-HPLC Enanticel C9-3 50 mm x 4.6 mm x 3 μm (eluent: 50% (v/v) EtOH and Hex(0.5% 2M NH3-MeOH) to afford (R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(2,4,6-trifluorophenoxy)pyrazin-2-yl)propanamide (30.7 mg, 21.68%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{25}F_3N_6O_4$: 530.19, found: 531.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.82 (s, 1H), 10.46 (s, 1H), 8.86 (d, J = 1.4 Hz, 1H), 8.58 (d, J = 1.4 Hz, 1H), 7.56 (d, J = 2.6 Hz, 1H), 7.42 -7.53 (m, 3H), 6.32 (d, J = 9.5 Hz, 1H), 3.48 – 3.58 (m, 1H), 3.32 – 3.39 (m, 2H), 2.67 – 2.77 (m, 1H), 2.59 – 2.66 (m, 1H), 2.34 – 2.46 (m, 2H), 1.40 (d, J = 4.2 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H).^{19}F NMR (376 MHz, DMSO-d_6) δ -110.79 (t, J = 4.0 Hz), -

123.77 (d, J = 4.0 Hz) and (S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(2,4,6-trifluorophenoxy)pyrazin-2-yl)propanamide (33.5 mg, 23.63%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{25}F_3N_6O_4$: 530.19, found: 531.20[M+H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.78 (s, 1H), 10.46 (s, 1H), 8.86 (d, J = 1.4 Hz, 1H), 8.58 (d, J = 1.4 Hz, 1H), 7.56 (d, J = 2.5 Hz, 1H), 7.43 – 7.52 (m, 3H), 6.32 (d, J = 9.5 Hz, 1H), 3.53 (d, J = 7.1 Hz, 1H), 3.34 – 3.42(m, 2H) ,2.69 – 2.77 (m, 1H), 2.59 – 2.66 (m, 1H), 2.34 – 2.46 (m, 2H), 1.40 (d, J = 4.2 Hz, 6H), 1.17 – 1.26 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -110.79 (t, J = 4.0 Hz), -123.77 (d, J = 4.0 Hz).

Example 127: (R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide and Example 128 : (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

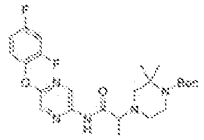


Synthetic Scheme



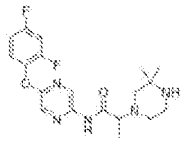
2-bromo-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

To a solution of 5-(2,4-difluorophenoxy)pyrazin-2-amine (1.1 g, 4.929 mmol, 1 equiv) in DCM (20 mL). (2R)-2-bromopropanoic acid (1.13 g, 7.394 mmol, 1.5 equiv), $AgNO_3$ (125.59 mg, 0.739 mmol, 0.15 equiv) and DCC (1.22 g, 5.915 mmol, 1.2 equiv) added at rt. The resulting mixture was stirred for 2h at rt. Theresulting mixture was extracted with EA (3*100 mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% PE/EA) to afford 2-bromo-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (1 g, 56.65%) as a yellow oil. MS (ESI): mass calcd. for $C_{13}H_{10}BrF_2N_3O_2$:356.99 m/z, found 358.10 $[M+H]^+$.



tert-butyl 4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carboxylate

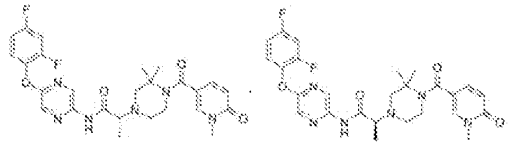
To a solution of 2-bromo-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (1 g, 2.792 mmol, 1 equiv) in DMA (12 mL) was added tert-butyl 2,2-dimethylpiperazine-1-carboxylate (0.60 g, 2.792 mmol, 1 equiv) and TEA (TEA (0.85 g, 8.376 mmol, 3 equiv)) at rt. The resulting mixture was stirred for 3 hours at 60 °C. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford tert-butyl 4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carboxylate (800 mg, 58.29%) as a white solid. MS (ESI): mass calcd. for $C_{24}H_{31}F_2N_5O_4$: 491.23 m/z, found: 492.25 $[M+H]^+$.



N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide

To a solution of tert-butyl 4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carboxylate (800 mg, 1.628 mmol, 1 equiv) in EA (0.5ml) was added hydrogen chloride (0.5 mL, 0.027 mmol, 0.57 equiv) at rt. The

resulting mixture was stirred for 2h at rt. The resulting mixture was washed with 50 mL of Diethyl ether. The precipitated solids were collected by filtration and washed with Diethyl ether (10 mL). The resulting mixture was concentrated under vacuum to afford N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (400 mg, 62.79%) as a yellow solid. MS (ESI): mass calcd. for $C_{19}H_{23}F_2N_5O_2$:391.18 m/z, found 392.10 $[M+H]^+$.

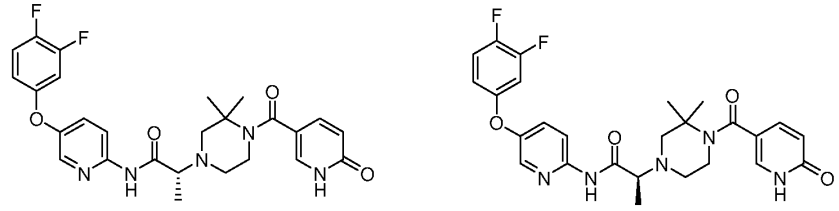


Synthesis of (R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide and (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

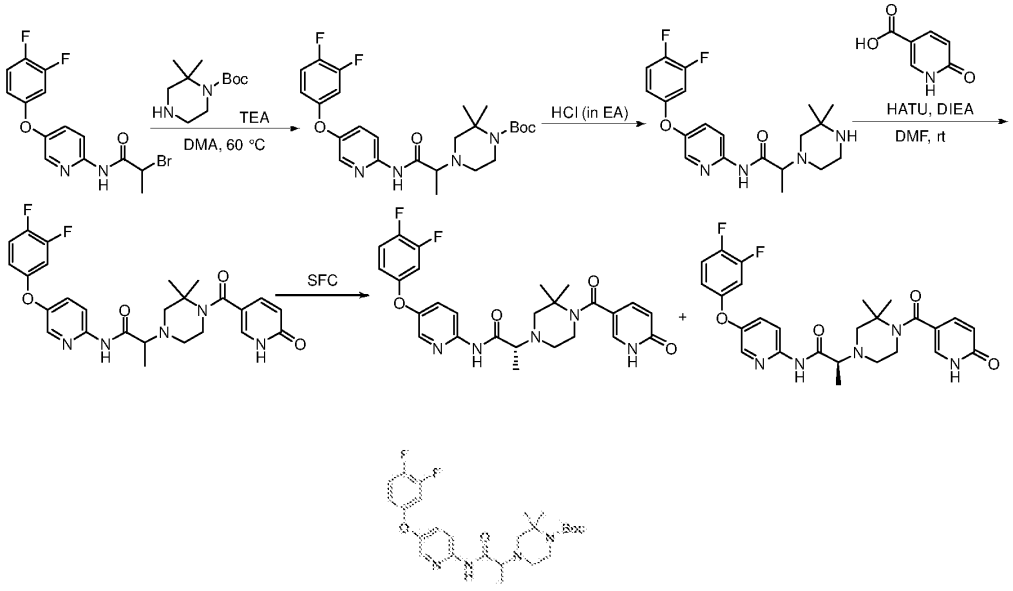
To a solution of N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (50 mg, 0.128 mmol, 1 equiv) in DMF (5 mL) was added 1-methyl-6-oxopyridine-3-carboxylic acid (19.56 mg, 0.128 mmol, 1 equiv), DIEA (33.02 mg, 0.256 mmol, 2 equiv) and HATU (72.86 mg, 0.192 mmol, 1.5 equiv) at rt. The resulting mixture was stirred for 3 hours at rt. The reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH). The product was purified by chiral-HPLC using a CHIRALPAK IK 25 cm x 2 cm x 5 μm column (eluent: 50% (v/v) EtOH and Hex: DCM=3: 1(0.5% 2M NH3-MeOH)) to afford (R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (13 mg, 19.08%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{28}F_2N_6O_4$: 526.21 m/z, found: 527.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.99 (d, J = 2.5 Hz, 1H), 7.39 – 7.55 (m, 3H), 7.11 – 7.24 (m, 1H), 6.37 (d, J = 9.3 Hz, 1H), 3.48 – 3.59 (m, 1H), 3.45 (s, 3H), 3.32 – 3.42 (m, 2H), 2.70 – 2.80 (m, 1H), 2.59 – 2.69 (m, 1H), 2.34 – 2.48 (m, 2H), 1.41 (d, J = 3.0 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.437, -124.225, and (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (19.3 mg, 28.62%) as a white solid.

MS (ESI): mass calcd. for $C_{26}H_{28}F_2N_6O_4$: 526.21 m/z, found: 527.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.99 (d, J = 2.5 Hz, 1H), 7.39 – 7.55 (m, 3H), 7.11 – 7.24 (m, 1H), 6.37 (d, J = 9.3 Hz, 1H), 3.48 – 3.59 (m, 1H), 3.45 (s, 3H), 3.32 – 3.42 (m, 2H), 2.70 – 2.80 (m, 1H), 2.59 – 2.69 (m, 1H), 2.34 – 2.48 (m, 2H), 1.41 (d, J = 3.0 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.434, -124.218.

Example 129 : (R)-N-(5-(3,4-difluorophenoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide and Example 130: (S)-N-(5-(3,4-difluorophenoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

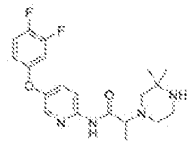


Synthetic Scheme



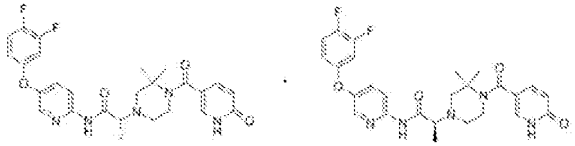
tert-butyl 4-(1-((5-(3,4-difluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carboxylate

To a solution of 2-bromo-N-(5-(3,4-difluorophenoxy)pyridin-2-yl)propanamide (300 mg, 0.840 mmol, 1 equiv) in DMA (5 mL) the mixture was added tert-butyl 2,2-dimethylpiperazine-1-carboxylate (198.01 mg, 0.924 mmol, 1.1 equiv) and TEA (255.00 mg, 2.520 mmol, 3 equiv) at rt. The resulting mixture was stirred for 2 hours at 60 °C. After cooled to room temperature e the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% EA/PE) to give tert-butyl 4-(1-((5-(3,4-difluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carboxylate (250 mg, 60.67%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{32}F_2N_4O_4$: 490.24, found: 491.20 $[M+H]^+$.



N-(5-(3,4-difluorophenoxy)pyridin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide

To a stirred solution of tert-butyl 4-(1-((5-(3,4-difluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carboxylate (200 mg, 0.408 mmol, 1 equiv) in EA (3 mL) was added HCl (4 M in EA, 3 mL). The reaction mixture was stirred at room temperature for 1 h. The product was precipitated by the addition of diethyl ether. The product is obtained (110 mg, 68.75%) by filtration and drying. MS (ESI): mass calcd. for $C_{20}H_{24}F_2N_4O_2$: 390.18, m/z, found: 391.20 $[M+H]^+$.

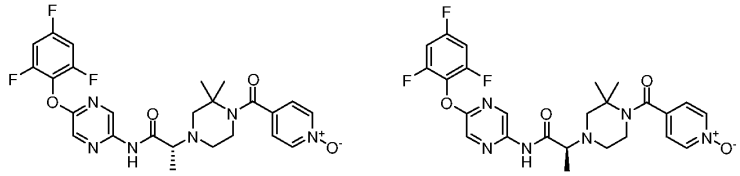


(R)-N-(5-(3,4-difluorophenoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide and (S)-N-(5-(3,4-difluorophenoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

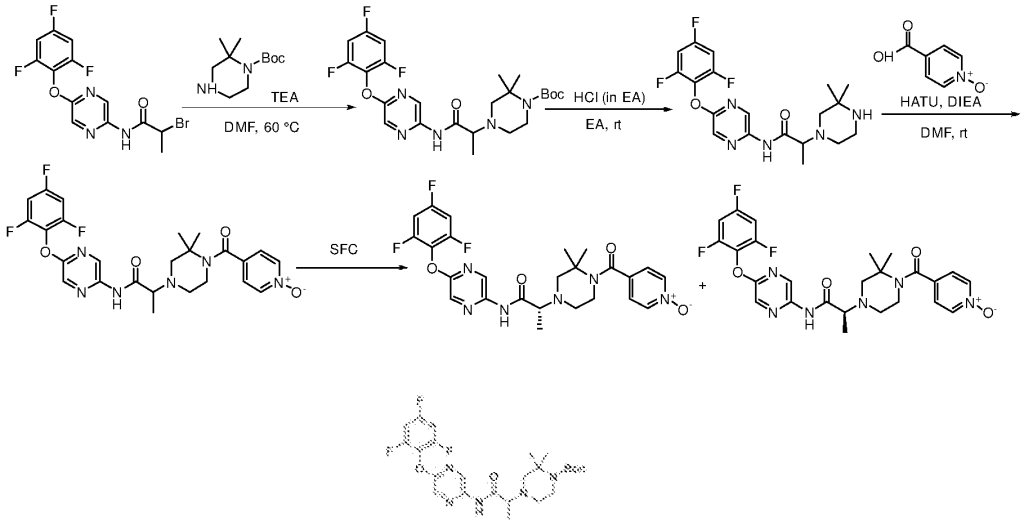
To a solution of N-(5-(3,4-difluorophenoxy)pyridin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide

(100 mg, 0.256 mmol, 1 equiv) in DMF (10 mL) the mixture was added 6-oxo-1H-pyridine-3-carboxylic acid (35.63 mg, 0.256 mmol, 1 equiv), HATU (146.08 mg, 0.384 mmol, 1.5 equiv) and N,N-diisopropylethylamine (132.41 mg, 1.024 mmol, 4 equiv) at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to give crude N-(5-(3,4-difluorophenoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide. The crude product was purified by chiral-HPLC using a CHIRALPAK IF 25 cm x 2 cm x 5 μm column (eluent: 50% (v/v) EtOH and(HEX: DCM=3: 1) (0.05% 2M NH_3-MeOH)) to afford (R)-N-(5-(3,4-difluorophenoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (6.8 mg, 5.11%) as a white solid. MS: mass calcd. for $C_{26}H_{27}F_2N_5O_4$: 511.20, found: 512.25 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 10.22 (s, 1H), 8.14 – 8.22 (m, 2H), 7.54 – 7.64 (m, 2H), 7.41 – 7.53 (m, 2H), 7.26 (ddd, J = 11.8, 6.7, 3.0 Hz, 1H), 6.85 -6.93 (m, 1H), 6.32 (d, J = 9.5 Hz, 1H), 3.45 – 3.55 (m, 1H), 3.35 – 3.40 (m, 2H), 2.70 – 2.78 (m, 1H), 2.58 – 2.65 (m, 1H), 2.41 (s, 2H), 1.41 (d, J = 3.0 Hz, 6H), 1.18 – 1.26 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -135.03, -135.09, -144.96, -145.02. And (S)-N-(5-(3,4-difluorophenoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide (11.2 mg, 8.53%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{27}F_2N_5O_4$: 511.20, found: 512.25 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.77 (s, 1H), 10.22 (s, 1H), 8.14 – 8.22 (m, 2H), 7.54 – 7.64 (m, 2H), 7.41 – 7.53 (m, 2H), 7.26 (ddd, J = 10.9, 6.7, 2.9 Hz, 1H), 6.85 – 6.92 (m, 1H), 6.32 (d, J = 9.5 Hz, 1H), 3.47 – 3.54 (m, 1H), 3.35 – 3.40 (m, 2H), 2.58 – 2.78 (m, 2H), 2.41 (s, 2H), 1.41 (d, J = 2.9 Hz, 6H), 1.18 – 1.26 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -135.03, -135.09, -144.96, -145.02.

Example 131: (R)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(2,4,6-trifluorophenoxy)pyrazin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide and Example 132: (S)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(2,4,6-trifluorophenoxy)pyrazin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide

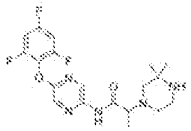


Synthetic Scheme



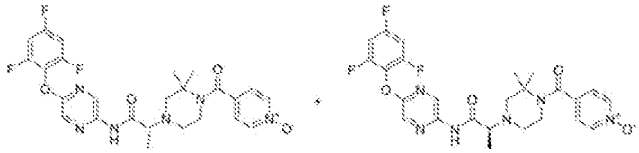
tert-butyl 2,2-dimethyl-4-(1-oxo-1-((5-(2,4,6-trifluorophenoxy)pyrazin-2-yl)amino)propan-2-yl)piperazine-1-carboxylate

To a solution of 2-bromo-N-(5-(2,4,6-trifluorophenoxy)pyrazin-2-yl)propanamide (300 mg, 0.798 mmol, 1 equiv) in dimethylformamide (5 mL) the mixture was added tert-butyl 2,2-dimethylpiperazine-1-carboxylate (188.02 mg, 0.878 mmol, 1.1 equiv) and TEA (242.13 mg, 2.394 mmol, 3 equiv) at rt. The resulting mixture was stirred for 2 hours at 60 °C. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% EA/PE) to give tert-butyl 2,2-dimethyl-4-(1-oxo-1-((5-(2,4,6-trifluorophenoxy)pyrazin-2-yl)amino)propan-2-yl)piperazine-1-carboxylate (250 mg, 58.44%) as a white solid. MS (ESI): mass calcd. for $C_{24}H_{30}F_3N_5O_4$: 509.22 m/z found: 510.20 $[M+H]^+$.



2-(3,3-dimethylpiperazin-1-yl)-N-(5-(2,4,6-trifluorophenoxy)pyrazin-2-yl)propanamide

To a stirred solution of tert-butyl 2,2-dimethyl-4-(1-oxo-1-((5-(2,4,6-trifluorophenoxy)pyrazin-2-yl)amino)propan-2-yl)piperazine-1-carboxylate (200 mg, 0.393 mmol, 1 equiv) , 1 equiv) in EA (5 mL) was added HCl (4 M in EA, 5 mL). The reaction mixture was stirred at room temperature for 1 h. The product was precipitated by the addition of diethyl ether. The product is obtained (100 mg, 62.5%) by filtration and drying. MS (ESI): mass calcd. for $C_{19}H_{22}F_3N_5O_2$: 409.17 m/z found: 410.20 $[M+H]^+$.

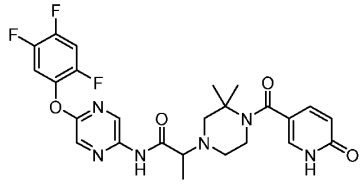


(R)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(2,4,6-trifluorophenoxy)pyrazin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide and (S)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(2,4,6-trifluorophenoxy)pyrazin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide

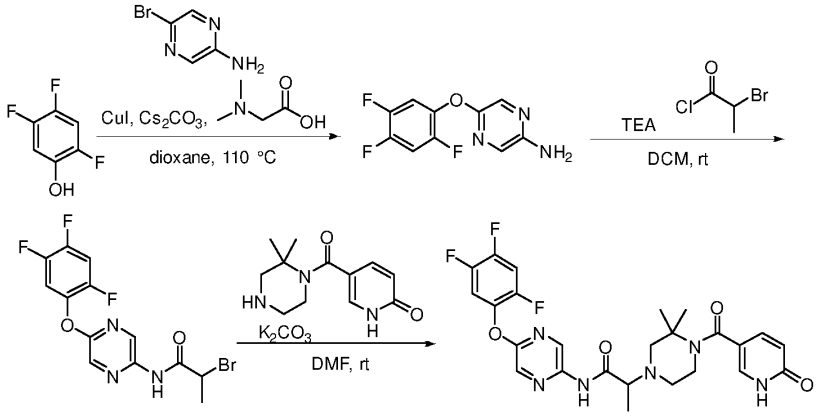
To a stirring solution 2-(3,3-dimethylpiperazin-1-yl)-N-[5-(2,4,6-trifluorophenoxy)pyrazin-2-yl]propanamide (100 mg, 0.244 mmol, 1 equiv) in dimethylformamide (10 mL) the mixture was added isonicotinic acid N-oxide (33.98 mg, 0.244 mmol, 1 equiv), HATU (139.31 mg, 0.366 mmol, 1.5 equiv) and N,N-diisopropylethylamine (126.28 mg, 0.976 mmol, 4 equiv) at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to give N-(5-(3,4-difluorophenoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamideas a white solid. The product was purified by chiral-HPLC using a CHIRALPAK IF 25 cm x 2 cm x 5 μm column (eluent: 50% (v/v) EtOH and (HEX: DCM=3: 1)(0.05% 2M NH3-MeOH)) to afford (R)-4-(2,2-dimethyl-4-(1-oxo-1-((5-

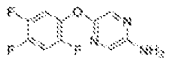
(2,4,6-trifluorophenoxy)pyrazin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide (12.4 mg, 9.53%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{25}F_3N_6O_4$: 530.21 m/z found: 531.20 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 8.83 – 8.88 (m, 1H), 8.58 (d, J = 1.5 Hz, 1H), 8.22 (d, J = 6.8 Hz, 2H), 7.36 – 7.53 (m, 4H), 3.49 – 3.60 (m, 1H), 3.25 – 3.34 (m, 2H), 2.68 – 2.76 (m, 1H), 2.58 – 2.67 (m, 1H), 2.39 – 2.51 (m, 2H), 1.45 (d, J = 4.6 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H).^{19}F NMR (376 MHz, DMSO-d_6) δ -110.78 (t, J = 3.9 Hz), -123.77 (d, J = 4.0 Hz) and (S)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(2,4,6-trifluorophenoxy)pyrazin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide (14.5 mg, 11.16%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{25}F_3N_6O_4$: 530.21 m/z found: 531.20 $[M+H]^+$.^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 8.86 (d, J = 1.4 Hz, 1H), 8.58 (d, J = 1.4 Hz, 1H), 8.18 – 8.27 (m, 2H), 7.39 – 7.53 (m, 4H), 3.49 – 3.59 (m, 1H), 2.39 – 2.48 (m, 2H), 2.66 – 2.76 (m, 1H), 2.58 – 2.67 (m, 1H), 2.39 – 2.51 (m, 2H), 1.45 (d, J = 4.5 Hz, 6H), 1.17 – 1.23 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -69.18, -71.06, -110.78 (t, J = 3.8 Hz), -123.77 (d, J = 4.0 Hz).

Example 133: 2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(2,4,5-trifluorophenoxy)pyrazin-2-yl)propanamide



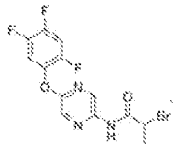
Synthetic Scheme





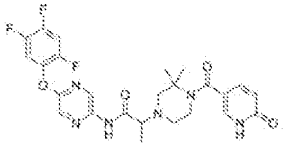
5-(2,4,5-trifluorophenoxy)pyrazin-2-amine

To a stirring solution 2,4,5-trifluorophenol (1 g, 6.753 mmol, 1 equiv) in dioxane (20 mL) was added a solution of dimethylglycine (0.07 g, 0.675 mmol, 0.1 equiv) and 5-bromopyrazin-2-amine (1.41 g, 8.104 mmol, 1.2 equiv) and CuI (0.26 g, 1.351 mmol, 0.2 equiv) and Cs_2CO_3 (4.40 g, 13.506 mmol, 2 equiv). The resulting mixture under N_2 was stirred at 110 °C for 6 h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford 5-(2,4,5-trifluorophenoxy)pyrazin-2-amine (800 mg, 49.12%) MS (ESI): mass calcd. for $C_{10}H_6F_3N_3O$: 241.05 found: 242.05 [M+H$^+$]



2-bromo-N-(5-(2,4,5-trifluorophenoxy)pyrazin-2-yl)propanamide

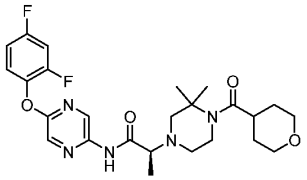
To a stirring solution 5-(2,4,5-trifluorophenoxy)pyrazin-2-amine (500 mg, 2.073 mmol, 1 equiv) in DCM (5 mL) was added a solution of 2-bromo-propionyl chloride (533.08 mg, 3.109 mmol, 1.5 equiv) and TEA (303 mg, 3.109 mmol, 1.5 equiv). The resulting mixture under N_2 was stirred at room temperature for 6h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford 2-bromo-N-(5-(2,4,5-trifluorophenoxy)pyrazin-2-yl)propanamide (300 mg, 38.47%) MS (ESI): mass calcd. for $C_{13}H_9BrF_3N_3O_2$: 374.98 found: 375.95 [M+H$^+$]



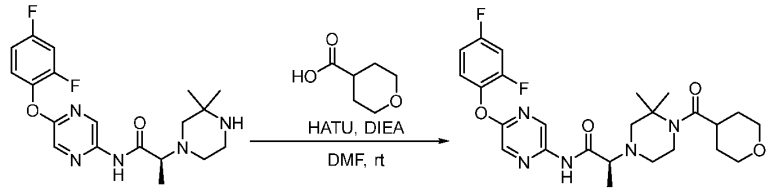
2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(2,4,5-trifluorophenoxy)pyrazin-2-yl)propanamide

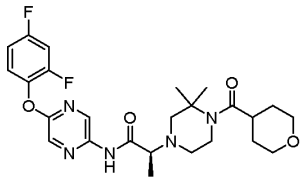
To a stirred solution of 2-bromo-N-[5-(2,4,5-trifluorophenoxy)pyrazin-2-yl]propanamide (100 mg, 0.266 mmol, 1 equiv) in DMF (2 mL) was added 5-(2,2-dimethylpiperazine-1-carbonyl)pyridin-2(1H)-one (125.11 mg, 0.532 mmol, 2 equiv) and K_2CO_3 (122 mg, 0.798 mmol, 3 equiv) at room temperature. The reaction mixture was stirred at room temperature for 3 h. The resulting mixture was stirred for additional overnight at room temperature. After completion of reaction, the reaction mixture was quenched by addition of water (5 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150mm, 5μm (eluent: 28% to 58% (v/v) CH_3CN and H_2O (NH_4HCO_3+0.05%NH_3H_2O) to afford 2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(2,4,5-trifluorophenoxy)pyrazin-2-yl)propanamid (11.8 mg, 8.34%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{25}F_3N_6O_4$: 530.19 m/z, found: 531.25 $[M^+H]^+$, ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.80 (s, 1H), 10.43 (s, 1H), 8.87 (d, J = 1.5 Hz, 1H), 8.47 (d, J = 1.4 Hz, 1H), 7.67 – 7.90 (m, 2H), 7.56 (d, J = 2.6 Hz, 1H), 7.47 (dd, J = 9.5, 2.6 Hz, 1H), 6.32 (d, J = 9.5 Hz, 1H), 3.53 (d, J = 7.1 Hz, 1H), 3.35 – 3.38 (s, 2H), 2.69 – 2.78 (m, 1H), 2.64 (q, J = 5.3 Hz, 1H), 2.40 (s, 2H), 1.40 (d, J = 2.7 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -129.76 (d, J = 13.8 Hz), -137.93, -140.56 (dd, J = 23.1, 13.8 Hz).

Example 134: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(tetrahydro-2H-pyran-4-carbonyl)piperazin-1-yl)propanamide



Synthetic Scheme



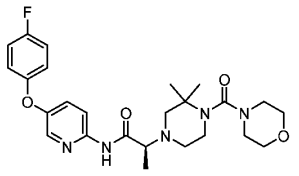


(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(tetrahydro-2H-pyran-4-carbonyl)piperazin-1-yl)propanamide

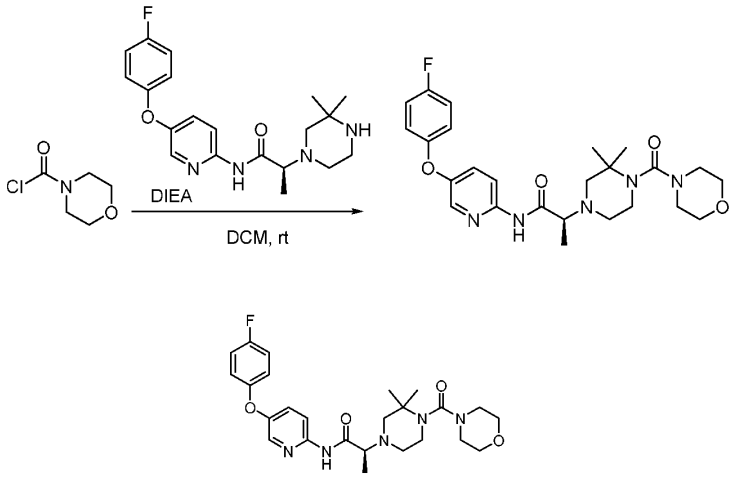
To a stirred solution of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (50 mg, 0.128 mmol, 1 equiv) in dimethylformamide (1 mL) was added [(dimethylamino)({3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy})methylidene]dimethylazanium (46.19 mg, 0.192 mmol, 1.5 equiv) and tetrahydro-2H-pyran-4-carboxylic acid (24.94 mg, 0.192 mmol, 1.5 equiv) and DIEA (49.53 mg, 0.384 mmol, 3 equiv) at room temperature. The reaction mixture was stirred at room temperature for 3 h. The resulting mixture was stirred for additional overnight at room temperature. After completion of reaction, the reaction mixture was quenched by addition of water (5 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and the residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30 x 150mm x 5μm (eluent: 28% to 58% (v/v) CH_3CN and H_2O with NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(tetrahydro-2H-pyran-4-carbonyl)piperazin-1-yl)propanamide (17.2 mg, 26.65%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{31}F_2N_5O_4$: 503.23 m/z, found: 504.30 $[M+H]^+$, ^1H NMR (300 MHz, DMSO-d_6) δ 10.38 (s, 1H), 8.83 (d, J = 1.5 Hz, 1H), 8.45 (d, J = 1.3 Hz, 1H), 7.48 (qd, J = 8.8, 4.3 Hz, 2H), 7.11 – 7.24 (m, 1H), 3.81 (dt, J = 11.0, 3.3 Hz, 2H), 3.49 (dt, J = 8.1, 4.7 Hz, 3H), 3.38 (d, J = 6.1 Hz, 1H), 2.81 (q, J = 6.9, 6.2 Hz, 1H), 2.75 – 2.87 (m, 2H), 2.55 – 2.75 (m, 1H), 2.32 (s, 2H), 1.50 (dd, J = 8.0, 3.4 Hz, 4H), 1.35 (d, J = 2.0 Hz, 6H), 1.19 (d, J

= 6.9 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -113.43 (d, J = 5.2 Hz), -124.23 (d, J = 5.3 Hz)..

Example 135: (S)-2-(3,3-dimethyl-4-(morpholine-4-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide



Synthetic Scheme

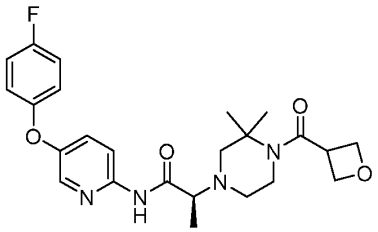


(S)-2-(3,3-dimethyl-4-(morpholine-4-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

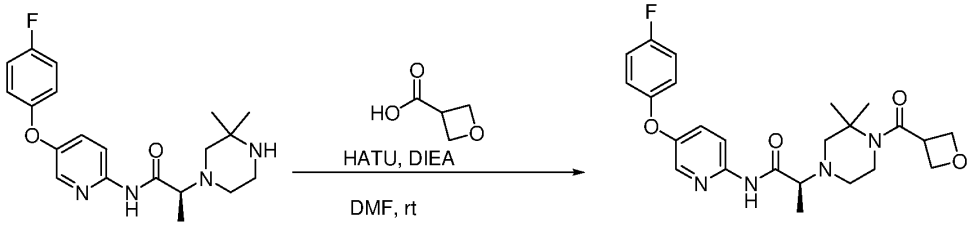
To a stirred solution of (S)-2-(3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (249.01 mg, 0.669 mmol, 1 equiv) and DIEA (172.82 mg, 1.338 mmol, 2 equiv) in DCM (5 mL) was added morpholine-4-carbonyl chloride (100 mg, 0.669 mmol, 1 equiv) at room temperature. The reaction mixture was stirred at room temperature for 2 h After completion of reaction, the reaction mixture was quenched by water (10 mL) and extracted with EA (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and

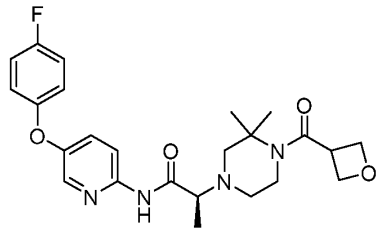
concentrated. The residue obtained was purified by silica gel chromatography (0-60% PE/EA) and by preparative HPLC using a XBridge Prep OBD 150 mm x 30 mm x 5μm column (eluent: 39% to 69% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-2-(3,3-dimethyl-4-(morpholine-4-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (22.2 mg, 6.84%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{32}FN_5O_4$: 485.24 m/z, found: 486.25 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.15 (dd, J = 6.0, 2.9 Hz, 2H), 7.52 (dd, J = 9.1, 2.9 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.04 – 7.16 (m, 2H), 3.53 (t, J = 4.5 Hz, 4H), 3.45 (d, J = 6.9 Hz, 1H), 3.21 (t, J = 4.7 Hz, 4H), 3.11 (s, 2H), 2.63 – 2.73 (m, 1H), 2.57 (d, J = 5.3 Hz, 1H), 2.27 (s, 2H), 1.30 (d, J = 2.8 Hz, 6H), 1.18 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ-120.35.

Example 136: (S)-2-(3,3-dimethyl-4-(oxetane-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide



Synthetic Scheme

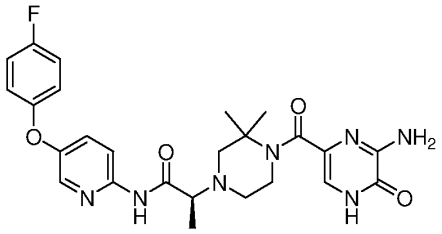




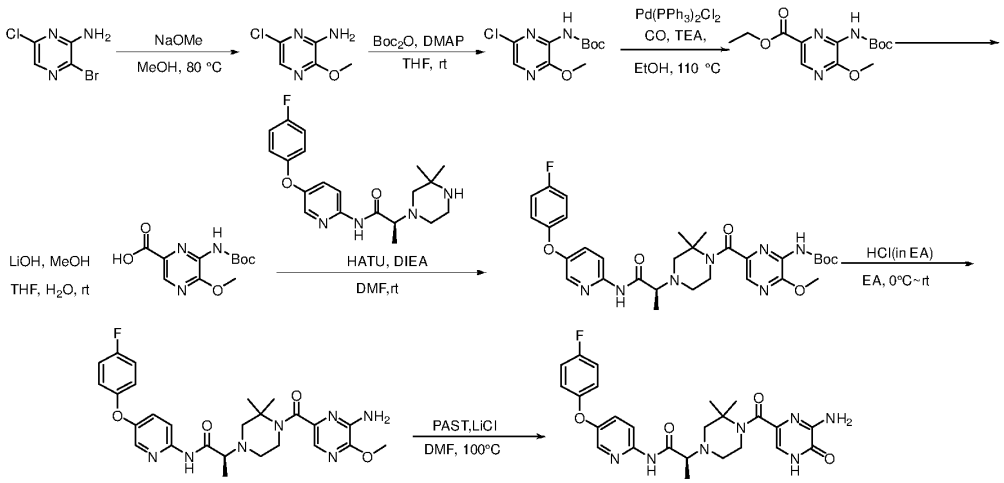
(S)-2-(3,3-dimethyl-4-(oxetane-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

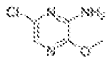
To a solution of (2S)-2-(3,3-dimethylpiperazin-1-yl)-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (100 mg, 0.268 mmol, 1 equiv) in DMF (2 mL). oxetane-3-carboxylic acid (27.41 mg, 0.268 mmol, 1 equiv), HATU (153.14 mg, 0.402 mmol, 1.5 equiv) and DIEA (69.40 mg, 0.536 mmol, 2 equiv) added at rt. The resulting mixture was stirred for 2h at rt degrees. The resulting mixture was extracted with EA 3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-15% DCM/MeOH) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 50% to 70% v/vCH_3CN and H_2O NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-2-(3,3-dimethyl-4-(oxetane-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (9.3 mg, 7.54%) as a white solid, MS (ESI): mass calcd. for$C_{24}H_{29}FN_4O_4$:456.22, found:457.20$[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.18 – 8.09 (m, 2H), 7.52 (dd, J = 9.1, 2.9 Hz, 1H), 7.31 – 7.17 (m, 2H), 7.16 – 7.02 (m, 2H), 4.69 – 4.54 (m, 4H), 4.03 (tt, J = 8.5, 6.9 Hz, 1H), 3.47 (p, J = 6.9, 6.2 Hz, 1H), 3.09 (t, J = 5.4 Hz, 2H), 2.71 – 2.51 (m, 4H), 2.34 (s, 2H), 1.42 (d, J = 2.6 Hz, 6H), 1.18 (d, J = 6.8 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -119.83.

Example 137: (S)-2-(4-(6-amino-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide



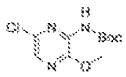
Synthetic Scheme





6-chloro-3-methoxypyrazin-2-amine

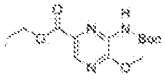
To a solution of 3-bromo-6-chloropyrazin-2-amine (100 mg, 0.480 mmol, 1 equiv) in MeOH (1mL) was added sodium methoxide (25.92 mg, 0.480 mmol, 1 equiv) at rt. The resulting mixture was stirred for overnight at 80 °C. The resulting mixture was stirred for 3h at rt. The reaction mixture was quenched by water and extracted with EA (2*30 mL). The combined organic extracts were washed with brine (10mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford product 6-chloro-3-methoxypyrazin-2-amine (80 mg, crude). MS (ESI): mass calcd. for $C_5H_6ClN_3O$ 159.02 m/z, found 160.10 $[M+H]^+$.



tert-butyl (6-chloro-3-methoxypyrazin-2-yl)carbamate

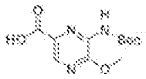
To a solution of 6-chloro-3-methoxypyrazin-2-amine (700 mg, 4.387 mmol, 1 equiv) in THF (10mL) was added Boc_2O (1914.82 mg, 8.774 mmol, 2 equiv), DMAP (107.19 mg, 0.877 mmol, 0.2 equiv) at rt. The resulting mixture was stirred for overnight at rt. The resulting mixture was stirred for 3h at rt. The reaction mixture was quenched by water and extracted with EA (2*30 mL). The combined organic extracts were washed with brine

(10mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford product.



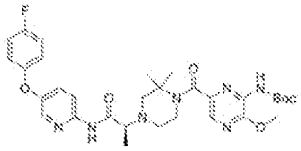
ethyl 6-((tert-butoxycarbonyl)amino)-5-methoxypyrazine-2-carboxylate

To a solution of tert-butyl (6-chloro-3-methoxypyrazin-2-yl)carbamate (700 mg, 2.696 mmol, 1 equiv) and TEA (818.30 mg, 8.088 mmol, 3 equiv) and in 25 mL EtOH was added $Pd(PPh_3)_2Cl_2$ (189.20 mg, 0.270 mmol, 0.1 equiv) in a pressure tank. The mixture was purged with nitrogen for 5 min and then was pressurized to 50 atm with carbon monoxide at 110 °C for overnight. The reaction mixture was cooled to room temperature and filtered to remove insoluble solids. The resulting mixture was concentrated under reduced pressure. The combined organic extracts was directly purified by flash chromatography to afford product ethyl 6-((tert-butoxycarbonyl)amino)-5-methoxypyrazine-2-carboxylate (300 mg, 37.5%). MS (ESI): mass calcd. for $C_{12}H_{17}N_3O_5$ 283.28 m/z, found.284.20 $[M+H]^+$.



6-((tert-butoxycarbonyl)amino)-5-methoxypyrazine-2-carboxylic acid

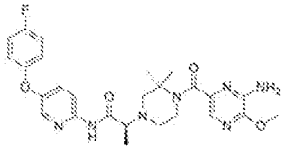
To a solution of ethyl 6-((tert-butoxycarbonyl)amino)-5-methoxypyrazine-2-carboxylate (300 mg, 10.5mmol, 1 equiv) in THF (4 mL) : MeOH (2mL) : H_2O (2mL)was added LiOH (407 mg, 21.0 mmol, 2 equiv) at rt. The resulting mixture was stirred for 3 h at rt. Desired product could be detected by LCMS .The mixture was acidified to pH 4 with 2 N HCl (aq.).The resulting mixture was filtered, the filter cake was washed with H_2O (2 x 6 mL). The filtrate was concentrated under reduced pressure to afford 6-((tert-butoxycarbonyl)amino)-5-methoxypyrazine-2-carboxylic acid (150 mg, 47.3%) as a yellow oil.



(S)-(6-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-3-methoxypyrazin-2-yl)carbamate

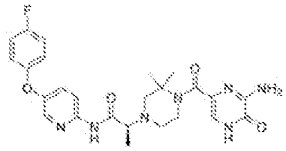
To a solution of 6-((tert-butoxycarbonyl)amino)-5-methoxypyrazine-2-carboxylic acid (350 mg, 1.3 mmol, 1 equiv) in DMF (5 mL) was added (S)-2-(3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (484.1 mg, 1.3 mmol, 1 equiv), HATU

(741.4 mg, 1.95 mmol, 1.5 equiv) DIEA (336 mg, 2.6 mmol, 2 equiv) at rt .The resulting mixture was stirred for 3h at rt. The reaction mixture was quenched by water and extracted with EA (3*20 mL). The combined organic extracts were washed with brine (10mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford product tert-butyl (S)-(6-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-3-methoxypyrazin-2-yl)carbamate (160 mg, 19.7%) as a white solid. MS (ESI): mass calcd. for $C_{31}H_{38}FN_7O_6$ 623.68 m/z, found 624.40 $[M+H]^+$.



(S)-2-(4-(6-amino-5-methoxypyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

To a solution of tert-butyl (S)-(6-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-3-methoxypyrazin-2-yl)carbamate (100 mg, 1.6 mmol, 1 equiv) in EA (1mL) was added HCI in (EA) (2 mL) at 0 °C. The resulting mixture was stirred for 1h at rt. The residue was washed with diethyl ether (2x10 mL). The precipitated solids were collected by filtration and washed with diethyl ether (3x5 mL). The crude product mixture was used in the next step directly without further purification. MS (ESI): mass calcd. for $C_{26}H_{30}FN_7O_4$ 523.56 m/z, found 524.40 $[M+H]^+$.

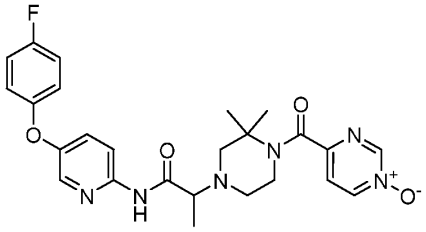


Synthesis of (S)-2-(4-(6-amino-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

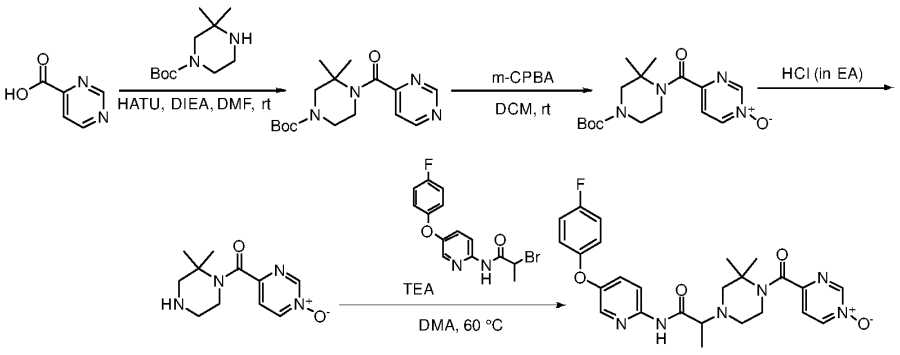
To a solution of (S)-2-(4-(6-amino-5-methoxypyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (15 mg, 0.029 mmol, 1 equiv) in DMF (2mL) was added PAST (24.67 mg, 0.145 mmol, 5 equiv) and LiCl (6.07 mg, 0.145 mmol, 5 equiv) at rt. The resulting mixture was stirred for 48 h at 100 °C. The reaction mixture was quenched by water and extracted with EA (2*30 mL). The combined organic extracts were washed with brine (10mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash

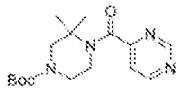
chromatography DCM/MeOH (0-20%). The residue was purified by preparative HPLC using a YMC-Actus Triart C18 ExRS 250 mm x 19 mm x 5 μm column (eluent: 28% to 58% (v/v) CH_3CN and H_2O (10mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$)) to afford (S)-2-(4-(6-amino-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (3.7 mg, 1.96%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{28}FN_7O_4$ 509.54 m/z, found 510.25$[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.14 (s, 1H), 8.11 – 8.20 (m, 2H), 7.48 – 7.57 (m, 1H), 7.24 (t, J = 8.8 Hz, 1H), 7.04 – 7.15 (m, 3H), 7.05 (d, J = 16.1 Hz, 1H), 3.49 – 3.66 (m, 1H). 3.40 – 3.49 (m, 2H), 2.59 – 2.68 (m, 2H),2.38 (d, J = 3.3 Hz, 2H), 1.43 (s, 6H), 1.10 – 1.27(m, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ-119.867.

Example 138: 4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyrimidine 1-oxide



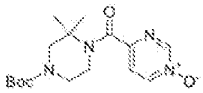
Synthetic Scheme





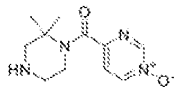
tert-butyl 3,3-dimethyl-4-(pyrimidine-4-carbonyl)piperazine-1-carboxylate

To a solution of pyrimidine-4-carboxylic acid (2 g, 16.116 mmol, 1 equiv) in DMF (30 mL). tert-butyl 3,3-dimethylpiperazine-1-carboxylate (3.45 g, 16.116 mmol, 1 equiv), HATU (9.19 g, 24.174 mmol, 1.5 equiv) and DIEA (4.17 g, 32.232 mmol, 2 equiv) was added at rt. The resulting mixture was stirred for 2h at rt. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20% DCM/MeOH) to afford tert-butyl 3,3-dimethyl-4-(pyrimidine-4-carbonyl)piperazine-1-carboxylate (5 g, 96.83%) as a yellow oil. MS (ESI): mass calcd. for $C_{16}H_{24}N_4O_3$:320.18 found: 321.10 $[M+H]^+$.



4-(4-(tert-butoxycarbonyl)-2,2-dimethylpiperazine-1-carbonyl)pyrimidine 1-oxide

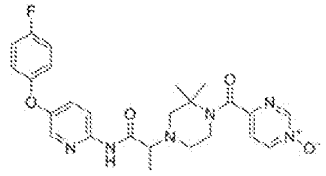
To a solution of tert-butyl 3,3-dimethyl-4-(pyrimidine-4-carbonyl)piperazine-1-carboxylate (5 g, 15.606 mmol, 1 equiv) in DCM (60 mL). m-CPBA (5.39 g, 31.212 mmol, 2 equiv) was added at rt. The resulting mixture was stirred for 24h at rt. The resulting mixture was extracted with DCM/MeOH (4:1) (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20% DCM/MeOH) to afford tert-butyl 3,3-dimethyl-4-(pyrimidine-4-carbonyl)piperazine-1-carboxylate (5 g, 96.83%) as a yellow oil. MS (ESI): mass calcd. for $C_{16}H_{24}N_4O$:336.18, found:337.15 $[M+H]^+$.



4-(2,2-dimethylpiperazine-1-carbonyl)pyrimidine 1-oxide

To a solution of tert-butyl 3,3-dimethyl-4-(pyrimidine-4-carbonyl)piperazine-1-carboxylate (5 g, 0.015 mmol, 1 equiv) in EA (20 mL) and HCl (in EA) (25 mL) was added at rt .The resulting mixture was stirred for 2h at rt. The resulting mixture was washed

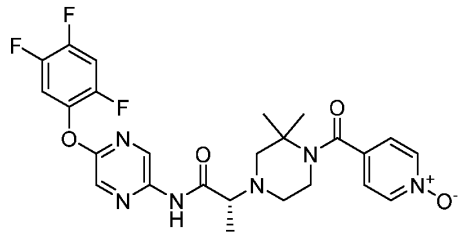
with 3x10 (ml) diethyl ether. The resulting mixture was filtered, the filter cake was washed with diethyl ether (10 mL). The filtrate was concentrated under reduced pressure to afford 4-(2,2-dimethylpiperazine-1-carbonyl)pyrimidine 1-oxide (4g, 86.83%) as a yellow oil. MS (ESI): mass calcd. for $C_{11}H_{16}N_4O_2$:236.13, found:237.10 [M+H]+.

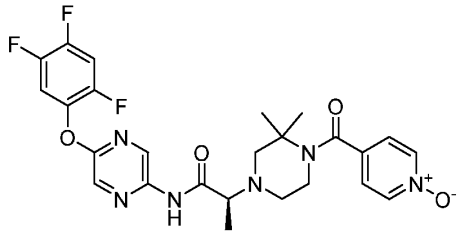


4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyrimidine 1-oxide

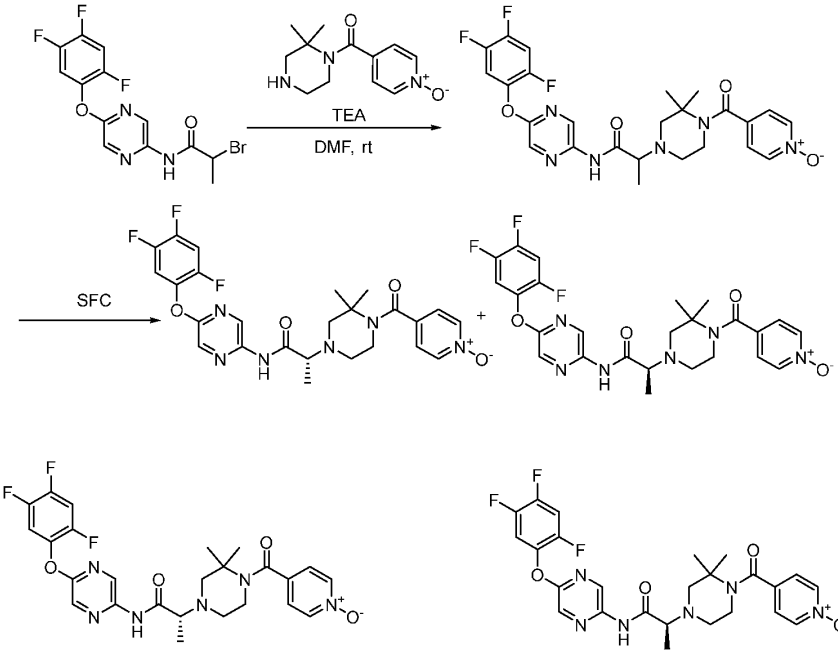
To a solution of 4-(2,2-dimethylpiperazine-1-carbonyl)pyrimidin-1-ium-1-olate (100 mg, 0.423 mmol, 1 equiv) in DMA (5 mL). 2-bromo-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (143.55 mg, 0.423 mmol, 1 equiv) and TEA (64.24 mg, 0.634 mmol, 1.5 equiv) added at rt. The resulting mixture was stirred for 2 h at 60 degrees. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-15% DCM/MeOH). The residue was purified by preparative HPLC using a XSelect CSH Fluoro Pheny 250 mm x 19 mm x 5 μm column (eluent: 22% to 47% (v/v) CH_3CN and H_2O (0.1% FA)) to afford 4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyrimidine 1-oxide (9.8 mg, 4.60%) as a white solid, MS (ESI): mass calcd. for $C_{25}H_{27}FN_6O_4$:494.21, found:495.30 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.19 (s, 1H), 9.03 (d, J = 2.0 Hz, 1H), 8.61 (dd, J = 6.8, 2.1 Hz, 1H), 8.15 (dd, J = 6.0, 2.9 Hz, 2H), 7.66 (d, J = 6.8 Hz, 1H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.24 (t, J = 8.8 Hz, 2H), 7.04 – 7.16 (m, 2H), 3.47 – 3.55 (m, 5H), 2.53 – 2.66 (m, 2H), 1.48 (d, J = 2.5 Hz, 6H), 1.30 (s, 1H), 1.21 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.833.

Example 139: (R)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(2,4,5-trifluorophenoxy)pyrazin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide and Example 140: (S)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(2,4,5-trifluorophenoxy)pyrazin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide





Synthetic Scheme

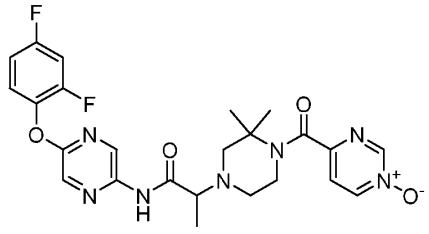


(R)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(2,4,5-trifluorophenoxy)pyrazin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide and (S)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(2,4,5-trifluorophenoxy)pyrazin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide

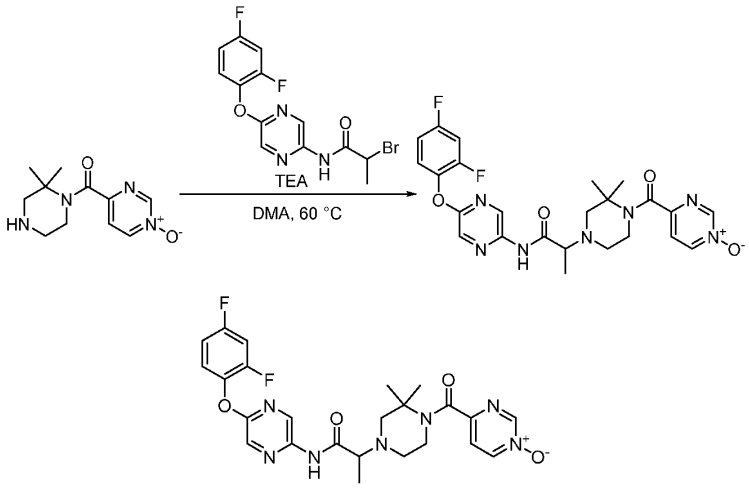
To a stirred solution of (2R)-2-bromo-N-[5-(2,4,5-trifluorophenoxy)pyrazin-2-yl]propanamide (60 mg, 0.160 mmol, 1 equiv) in DMF (2 mL) was added 4-(2,2-dimethylpiperazine-1-carbonyl)pyridin-1-ium-1-olate (187.66 mg, 0.800 mmol, 5 equiv) and TEA (96.85 mg, 0.960 mmol, 6 equiv) at room temperature. The reaction mixture was stirred at room temperature for 3 h. The resulting mixture was stirred for additional overnight at room temperature. After completion of reaction, the reaction mixture was quenched by

addition of water (5 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150mm, 5μm (eluent: 28% to 58% (v/v) CH_3CN and H_2O, NH_4HCO_3+0.05%NH_3H_2O) to afford 2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)propanamide (50 mg, 30%) as a white solid. The product was separated by Chiral-HPLC using a CHIRALPAK IF 2*25 cm, 5 μm column (eluent: 50% (v/v) EtOH and MTBE with 0.1% DEA) to afford (R)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(2,4,5-trifluorophenoxy)pyrazin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide (8.7 mg, 10.28%) , MS (ESI): mass calcd. for $C_{25}H_{25}F_3N_6O_4$: 530.19 m/z, found: 531.25 $[M+H]^+$, ^1H NMR (300 MHz, DMSO-d_6) δ 10.46 (s, 1H), 8.87 (d, J = 1.4 Hz, 1H), 8.47 (d, J = 1.4 Hz, 1H), 8.18 – 8.27 (m, 2H), 7.78 (ddt, J = 20.5, 11.0, 7.6 Hz, 2H), 7.39 – 7.48 (m, 2H), 3.55 (q, J = 6.8 Hz, 1H), 3.34 (s, 2H), 2.72 (q, J = 5.4, 5.0 Hz, 1H), 2.62 (dt, J = 10.8, 4.9 Hz, 1H), 2.46 (d, J = 2.8 Hz, 2H), 1.45 (d, J = 2.7 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H). And (S)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(2,4,5-trifluorophenoxy)pyrazin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide (9.9 mg, 11.70%). MS (ESI): mass calcd. for $C_{25}H_{25}F_3N_6O_4$: 530.19 m/z, found: 531.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.46 (s, 1H), 8.87 (d, J = 1.4 Hz, 1H), 8.47 (d, J = 1.4 Hz, 1H), 8.17 – 8.26 (m, 2H), 7.78 (ddt, J = 20.4, 11.0, 7.7 Hz, 2H), 7.38 – 7.48 (m, 2H), 3.55 (q, J = 6.8 Hz, 1H), 3.34 (s, 2H), 2.68 – 2.79 (m, 1H), 2.57 – 2.68 (m, 1H), 2.46 (d, J = 2.8 Hz, 2H), 1.45 (d, J = 2.7 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H).

Example 141: 4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyrimidine 1-oxide



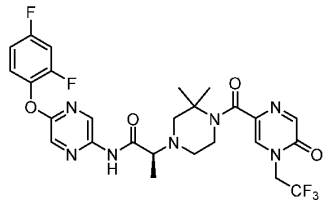
Synthetic Scheme



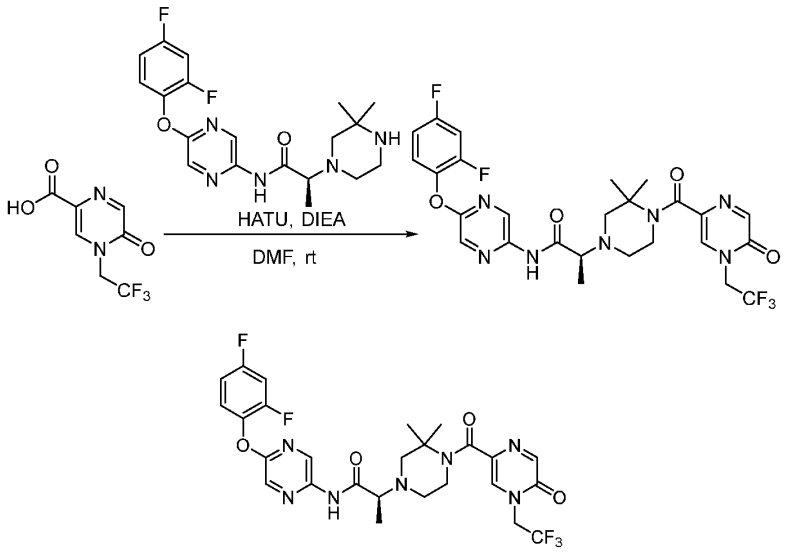
4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyrimidine 1-oxide

To a solution of 4-(2,2-dimethylpiperazine-1-carbonyl)pyrimidin-1-ium-1-olate (100 mg, 0.423 mmol, 1 equiv) in DMA (5 mL). 2-bromo-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (151.58 mg, 0.423 mmol, 1 equiv) and TEA (64.24 mg, 0.634 mmol, 1.5 equiv) added at rt. The resulting mixture was stirred for 2h at 60 °C. After cooled to room temperature, the resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-15% DCM/MeOH). The residue was purified by preparative HPLC using a XSelect CSH Fluoro Pheny 250 mm x 19 mm x 5 μm column (eluent: 22% to 47% (v/v) CH_3CN and H_2O with 0.05% TFA) to afford 4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyrimidine 1-oxide (12.2 mg, 5.40%) as a white solid, MS (ESI): mass calcd. for $C_{24}H_{25}F_2N_7O_4$:513.19, found:514.20$[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 9.01 (dd, J = 2.1, 1.0 Hz, 1H), 8.82 (d, J = 1.4 Hz, 1H), 8.59 (dd, J = 6.8, 2.0 Hz, 1H), 8.43 (d, J = 1.4 Hz, 1H), 7.64 (dd, J = 6.8, 1.0 Hz, 1H), 7.37 – 7.54 (m, 2H), 7.09 – 7.22 (m, 1H), 3.48 – 3.56 (m, 1H), 3.36 – 3.45 (m, 2H), 2.63 – 2.75 (m, 1H), 2.55 – 2.63 (m, 1H), 2.40 – 2.48 (m, 2H), 1.44 (d, J = 2.2 Hz, 6H), 1.14 – 1.25 (m, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -73.425, -113.448, -124.247.

Example 142: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-4-(2,2,2-trifluoroethyl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide



Synthetic Scheme

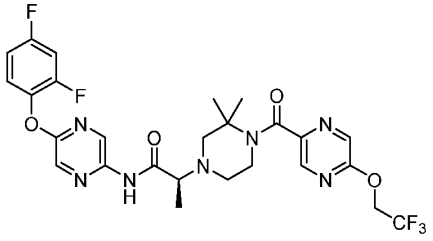


methyl (S)-2-(3,3-dimethyl-4-(5-oxo-4-(2,2,2-trifluoroethyl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

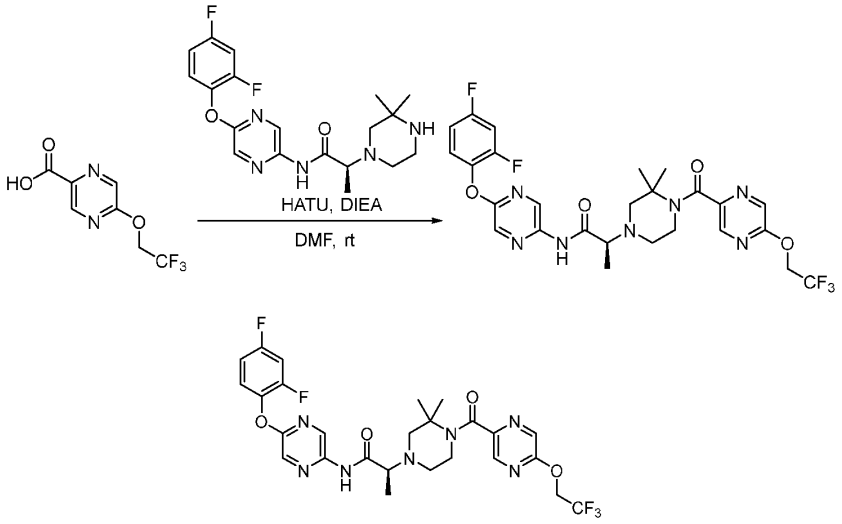
To a solution of 5-oxo-4-(2,2,2-trifluoroethyl)pyrazine-2-carboxylic acid (50 mg, 0.225 mmol, 1 equiv) in DMF (3 mL). (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (88.11 mg, 0.225 mmol, 1 equiv) ,HATU (128.39 mg, 0.338 mmol, 1.5 equiv) and DIEA (58.19 mg, 0.450 mmol, 2 equiv) added at rt. The resulting mixture was stirred for 2h at rt. The resulting mixture was extracted with EA (3*100 mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-15% DCM/MeOH). The residue was purified by preparative

HPLC using a Xselect CSH OBD 150 mm x 30 mm x 5 μm column (eluent: 43% to 73% (v/v) CH_3CN and H_2O (10mmol/L NH_4HCO_3+0.05%NH_3H_2O)) to afford (S)-2-(3,3-dimethyl-4-(5-oxo-4-(2,2,2-trifluoroethyl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (14.0 mg, 10.41%) as a white solid, MS (ESI): mass calcd. for $C_{26}H_{26}F_5N_7O_4$: 595.20, found: 596.30 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 8.05 – 8.13 (m, 2H), 7.39 – 7.55 (m, 2H), 7.10 – 7.24 (m, 1H), 4.84 – 4.99 (m, 2H), 3.45 – 3.60 (m, 3H), 2.68 – 2.79 (m, 1H), 2.60 – 2.68 (m, 1H), 2.43 (d, J = 3.0 Hz, 2H), 1.44 (d, J = 2.0 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -69.087, -113.469, -124.262.

Example 143: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-(2,2,2-trifluoroethoxy)pyrazine-2-carbonyl)piperazin-1-yl)propanamide



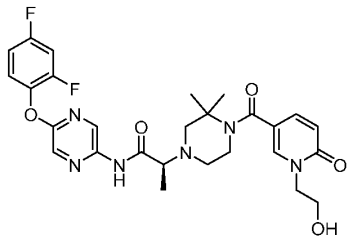
Synthetic Scheme



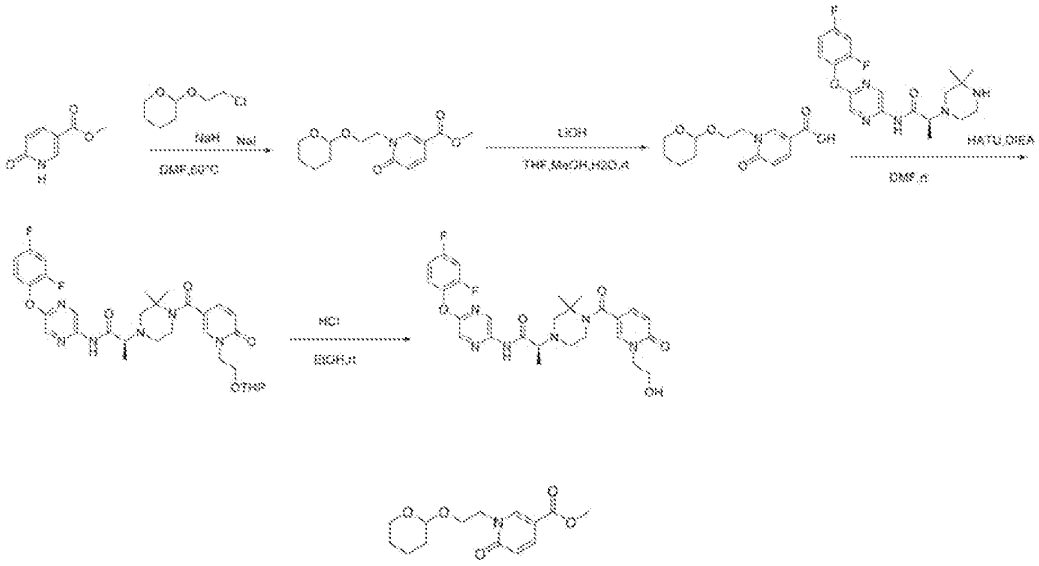
(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-(2,2,2-trifluoroethoxy)pyrazine-2-carbonyl)piperazin-1-yl)propanamide

To a solution of 5-(2,2,2-trifluoroethoxy)pyrazine-2-carboxylic acid (50 mg, 0.225 mmol, 1 equiv) (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (88.11 mg, 0.225 mmol, 1 equiv) in DMF (2 mL) was added HATU (128.39 mg, 0.338 mmol, 1.5 equiv) and DIEA (145.47 mg, 1.126 mmol, 5.00 equiv) at rt .The resulting mixture was stirred for 2h at rt. The reaction mixture was quenched by water and extracted with EA (3*20 mL). The combined organic extracts were washed with brine (10mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography and by HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10mmol/L NH_4HCO_3+0.05%NH_3H_2O), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 50% B to 80% B in 7min; Wave Length: 254nm/220nm nm; RT1(min): 6.42) to afford product (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-(2,2,2-trifluoroethoxy)pyrazine-2-carbonyl)piperazin-1-yl)propanamide (6.3 mg, 4.69%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{26}F_5N_7O_4$ 595.20 m/z, found 596.25$[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.42 – 8.49 (m, 3H), 7.41 – 7.54 (m, 2H), 7.18 (ddt, J = 11.0, 8.6, 2.2 Hz, 1H), 5.09 (q, J = 8.9 Hz, 2H), 3.53 (q, J = 6.9 Hz, 1H), 3.39 (t, J = 5.4 Hz, 2H), 2.72 (dd, J = 11.1, 5.2 Hz, 1H), 2.59 (dt, J = 10.9, 5.3 Hz, 1H), 2.46 (d, J = 5.1 Hz, 2H), 1.48 (d, J = 3.0 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H).^{19}F NMR (376 MHz, DMSO-*d6*) δ -72.18, -113.43 (d, J = 5.3 Hz), -124.23 (d, J = 5.4 Hz).

Example 144: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(1-(2-hydroxyethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

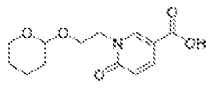


Synthetic Scheme



methyl 6-oxo-1-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-1,6-dihydropyridine-3-carboxylate

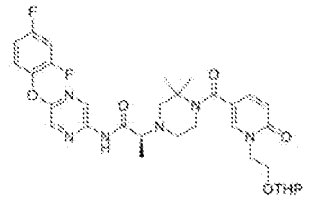
To a solution of methyl 6-oxo-1H-pyridine-3-carboxylate (1 g, 6.530 mmol, 1 equiv) in DMF (10 mL) was added sodium hydride (60% in oil, 0.5 g) at 0 °C. The mixture was stirred for 15 min. 2-(2-chloroethoxy)oxane (3.23 g, 19.590 mmol, 3 equiv) and iodosodium (0.20 g, 1.306 mmol, 0.2 equiv) was added and the mixture was allowed to warm to 60 °C and stirred for 2h. After completion of reaction, the reaction mixture was quenched by addition of water (20 mL). The aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford methyl 6-oxo-1-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-1,6-dihydropyridine-3-carboxylate (1.2 g, 65.32%). MS (ESI): mass calcd. for $C_{14}H_{19}NO_5$: 281.02 m/z, found: 282.20 $[M+H]^+$.



6-oxo-1-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-1,6-dihydropyridine-3-carboxylic acid

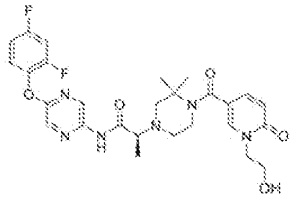
To a stirred solution of methyl 6-oxo-1-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-1,6-dihydropyridine-3-carboxylate (800 mg, 2.844 mmol, 1 equiv) and LiOH (681.10 mg, 28.440 mmol, 10 equiv) in methanol (5 mL), H_2O (5 mL) and THF (10 mL) at room temperature.

The reaction mixture was stirred at room temperature for a period of 3 h. The mixture was concentrated to dryness under reduced pressure to provide the crude product, which was purified by C18 column (0-20% H_2O/ACN) to afford 6-oxo-1-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-1,6-dihydropyridine-3-carboxylic acid (600 mg, 71.83%). MS (ESI): mass calcd. for $C_{13}H_{17}NO_5$: 267.10 m/z. found 266.20 $[M-H]^-$.



(2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

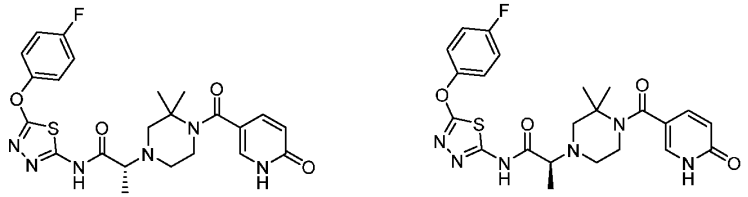
To a stirring solution6-oxo-1-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-1,6-dihydropyridine-3-carboxylic acid (300 mg, 1.122 mmol, 1 equiv) in DMF (5 mL) was added a solution of (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (439.34 mg, 1.122 mmol, 1 equiv), HATU (640.17 mg, 1.683 mmol, 1.5 equiv) and DIEA (580.27 mg, 4.488 mmol, 4 equiv). The resulting mixture was stirred at room temperature for 6 h. After completion of reaction, the reaction mixture was quenched by addition of water (20 mL). The aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethyl-4-{1-[2-(oxan-2-yloxy)ethyl]-6-oxopyridine-3-carbonyl}piperazin-1-yl)propanamide (400 mg, 55.62%). MS (ESI): mass calcd. for $C_{32}H_{38}F_2N_6O_6$: 640.15 m/z, found: 641.20 $[M+H]^+$.



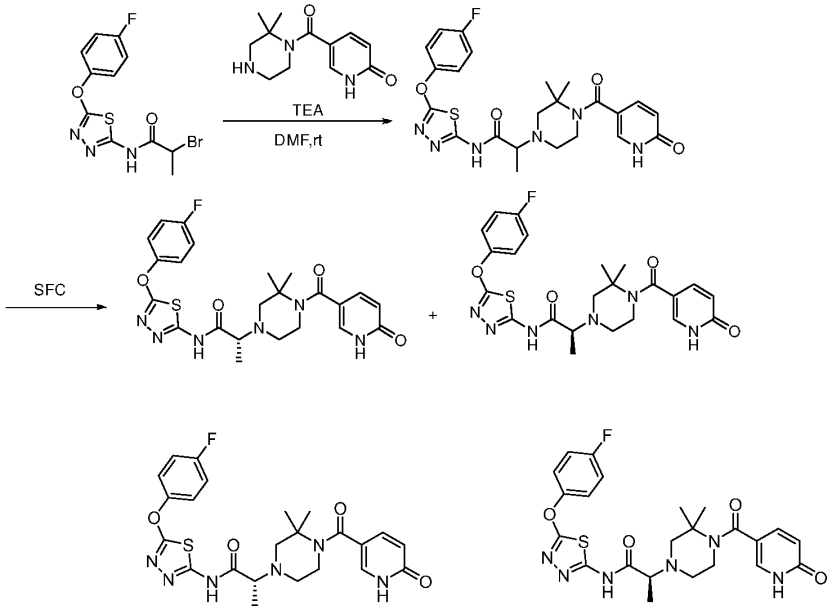
(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(1-(2-hydroxyethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

To a stirred solution of (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propenamide (100 mg, 0.156 mmol, 1 equiv) in ethyl alcohol (3 mL) was added HCl (2 M, 3 mL). The reaction mixture was stirred at room temperature for 1 h. The product was precipitated by the addition of diethyl ether. The residue was purified by column chromatography on silica gel with DCM/MeOH (0-10%) and Prep-HPLC using a column: Column: XBridge Prep OBD C_{18} Column, 30*150 mm, 5μm; Mobile Phase A: Water(10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to give (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(1-(2-hydroxyethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (27.8 mg, 31.88%) as a white solild. MS (ESI): mass calcd. for $C_{27}H_{30}F_2N_6O_5$: 556.20, found: 557.25 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ10.42 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.5 Hz, 1H), 7.86 (d, J = 2.5 Hz, 1H), 7.42 – 7.55 (m, 3H), 7.13 – 7.23 (m, 1H), 6.38 (d, J = 9.3 Hz, 1H), 4.92 (t, J = 5.4 Hz, 1H), 3.98 (t, J = 5.2 Hz, 2H), 3.48 – 3.65 (m, 3H), 3.37 – 3.42 (m, 2H), 2.70 – 2.78 (m, 1H), 2.59 – 2.69 (m, 1H), 2.41 (s, 2H), 1.41 (d, J = 4.4 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H).^{19}F NMR (376 MHz, DMSO-d_6) δ-113.41 (d, J = 5.3 Hz), -124.20 (d, J = 5.2 Hz).

Example 145: (R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)-1,3,4-thiadiazol-2-yl)propanamide and Example 146: (S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)-1,3,4-thiadiazol-2-yl)propenamide



Synthetic Scheme

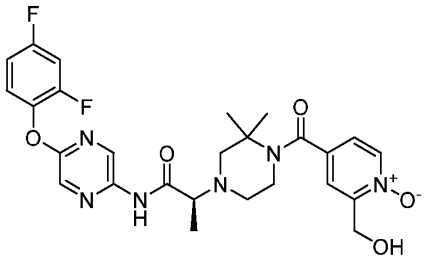


(R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)-1,3,4-thiadiazol-2-yl)propanamide and (S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)-1,3,4-thiadiazol-2-yl)propanamide

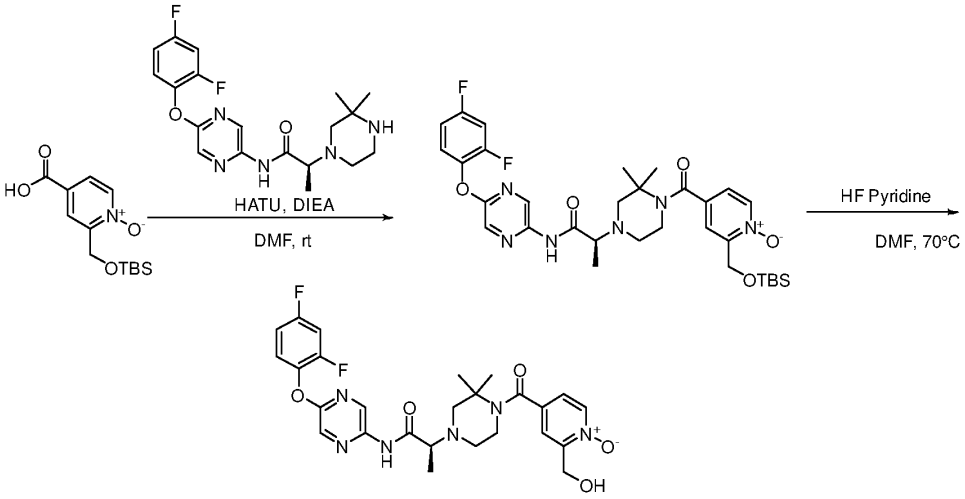
To a stirred solution of 2-bromo-N-(5-(4-fluorophenoxy)-1,3,4-thiadiazol-2-yl)propanamide (200 mg, 0.058 mmol, 1 equiv) in anhydrous DMF (5 mL) was added 5-(2,2-dimethylpiperazine-1-carbonyl)pyridin-2(1H)-one (163.1 mg, 0.070 mmol, 1.2 equiv) and TEA (175.4 mg, 0.174 mmol, 3 equiv) at room temperature. The reaction mixture was stirred at rt for 3 h. After completion of reaction, the reaction was quenched by water (20 mL) and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (5-80% PE/EA) and by preparative HPLC using a XBridge Prep OBD 150 mm x 30 mm x 5 μm column (eluent: 21% to 51% (v/v) ACN and H_2O with 10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford 2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)-1,3,4-thiadiazol-2-yl)propanamide as a white solid. The residue was purified by chiral-HPLC using a CHIRALPAK IF 25 mm x 2 mm x 5 μm column (eluent: 50% to 50% (v/v) HEX(0.5% 2M NH3-MeOH) and IPA) to afford (R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)-1,3,4-thiadiazol-2-yl)propanamide (7.0 mg, first peak). MS (ESI): mass calcd. for $C_{23}H_{25}FN_6O_4S$: 500.16 m/z, found 501.15 $[M+H]^+$.^1H

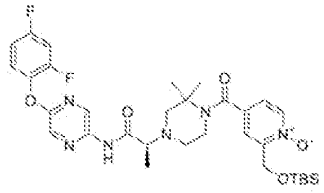
NMR (300 MHz, DMSO-d_6) δ 12.42 (s, 1H), 8.17 – 8.25 (m, 2H), 7.36 – 7.51 (m, 4H), 7.28 – 7.35 (m, 2H), 3.53 (t, J = 6.9 Hz, 1H), 3.21 – 3.25 (m, 2H), 2.56 – 2.63 (m, 2H), 2.33 – 2.50 (m, 2H), 1.42 (d, J = 2.9 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ-116.41. And (S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)-1,3,4-thiadiazol-2-yl)propanamide (16.8 mg, second peak). MS (ESI): mass calcd. for $C_{23}H_{25}FN_6O_4S$: 500.16 m/z, found 501.15 $[M+H]^+$.^{1}H NMR (300 MHz, DMSO-d_6) δ 12.42 (s, 1H), 8.17 – 8.25 (m, 2H), 7.36 – 7.51 (m, 4H), 7.28 – 7.35 (m, 2H), 3.55 (d, J = 7.0 Hz, 1H), 3.27 (s, 2H), 2.58 – 2.73 (m, 2H), 2.40 (t, J = 11.0 Hz, 2H), 1.42 (d, J = 2.9 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -116.40.

Example 147: 4-{4-[(1S)-1-{[5-(2,4-difluorophenoxy)pyrazin-2-yl] carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}-2-(hydroxymethyl)pyridin-1-ium-1-olate



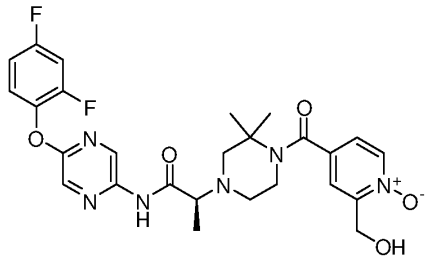
Synthetic Scheme





2-{[(tert-butyldimethylsilyl)oxy]methyl}-4-{4-[(1S)-1-{[5-(2,4-difluorophenoxy)pyrazin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}pyridin-1-ium-1-olate

To a solution of 2-{[(tert-butyldimethylsilyl)oxy]methyl}-4-carboxypyridin-1-ium-1-olate (70 mg, 0.247 mmol, 1 equiv) in DMF (3mL) was added (2S)-1-{[5-(2,4-difluorophenoxy)piperazin-2-yl]amino}-2-(3,3-dimethylpiperazin-1-yl)propan-1-ol (98.67 mg, 0.247 mmol, 1 equiv) and HATU (140.88 mg, 0.370 mmol, 1.5 equiv) and DIEA (95.77 mg, 0.741 mmol, 3 equiv) at rt .The resulting mixture was stirred for 2h at rt. The reaction mixture was quenched by water and extracted with EA (3*30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford 2-{[(tert-butyldimethylsilyl)oxy]methyl}-4-{4-[(1S)-1-{[5-(2,4-difluorophenoxy)pyrazin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}pyridin-1-ium-1-olate (80 mg, 50.0%)as a white solid. MS (ESI): mass calcd. for $C_{32}H_{42}F_2N_6O_5Si$ 656.80 m/z, found 657.25 $[M+H]^+$.

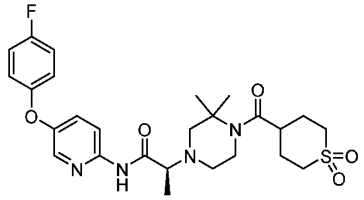


4-{4-[(1S)-1-{[5-(2,4-difluorophenoxy)pyrazin-2-yl]carbamoyl}ethyl]-2,2-dimethyl piperazine-1-carbonyl}-2-(hydroxymethyl)pyridin-1-ium-1-olate

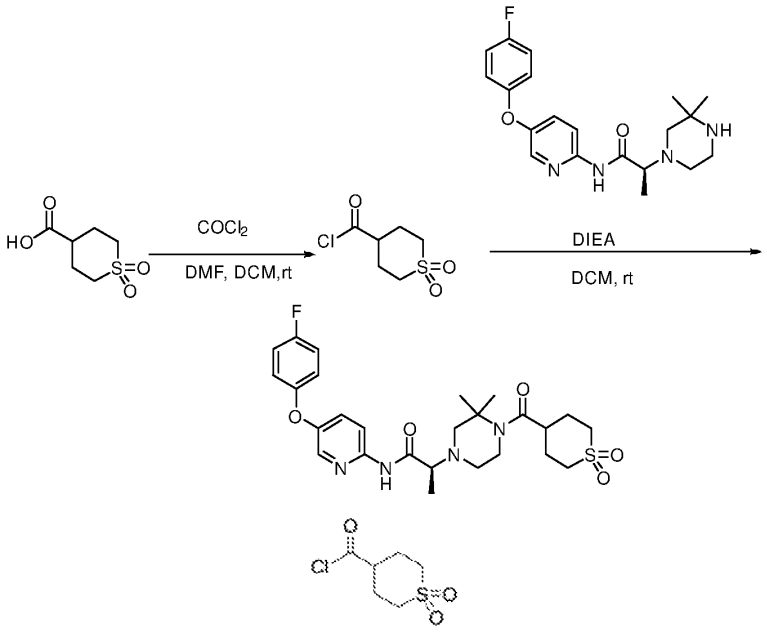
To a solution of 2-{[(tert-butyldimethylsilyl)oxy]methyl}-4-{4-[(1S)-1-{[5-(2,4-difluorophenoxy) pyrazin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}pyridin-1-ium-1-olate (300 mg, 0.457 mmol, 1 equiv) in DMF (3mL) was added HF Pyridine (5 mL, 55.495 mmol, 121.50 equiv) at rt .The resulting mixture was stirred for 3 h at 70 °C. The reaction mixture was quenched by water and extracted with EA (2*30 mL). The combined

organic extracts were washed with brine (10mL), dried over anhydrous Na2SO4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography and by HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford product 4-{4-[(1S)-1-{[5-(2,4-difluorophenoxy)pyrazin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}-2-(hydroxymethyl)pyridin-1-ium-1-olate (59.6 mg, 23.72%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{28}F_2N_6O_5$ 542.54 m/z, found 543.30$[M+H]^+$.^{1}H NMR (400 MHz, DMSO-d_6) δ 10.44 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.26 (d, J = 6.6 Hz, 1H), 7.42 – 7.55 (m, 3H), 7.36 (dd, J = 6.7, 2.6 Hz, 1H), 7.18 (ddt, J = 11.2, 9.1, 2.3 Hz, 1H), 5.68 (t, J = 5.8 Hz, 1H), 4.57 (d, J = 5.7 Hz, 2H), 3.54 (q, J = 7.0 Hz, 1H), 3.35 (s, 2H), 2.56 – 2.79 (m, 2H), 2.46 (d, J = 2.5 Hz, 2H), 1.46 (d, J = 2.9 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H).^{19}F NMR (376 MHz, DMSO-d_6) δ -113.42 (d, J = 5.1 Hz), -124.22 (d, J = 5.4 Hz).

Example 148: (2S)-2-[4-(1,1-dioxo-1lambda6-thiane-4-carbonyl)-3,3-dimethyl piperazin-1-yl]-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide

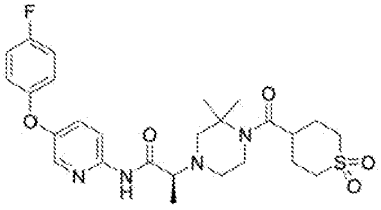


Synthetic Scheme



1,1-dioxo-1lambda6-thiane-4-carbonyl chloride

To a solution of 1,1-dioxo-1lambda6-thiane-4-carboxylic acid (150 mg, 0.842 mmol, 1 equiv) in DCM (2 mL) was added $COCl_2$ (218.57 mg, 1.684 mmol, 2 equiv) and DMF at 0 °C. The resulting mixture was stirred for 2 at rt. The resulting mixture was concentrated under reduced pressure afford 0.1 g crude 1,1-dioxo-1lambda6-thiane-4-carbonyl chloride as yellow oil.

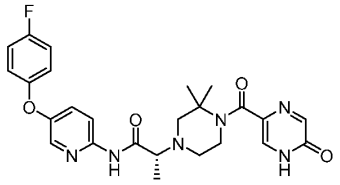


(2S)-2-[4-(1,1-dioxo-1lambda6-thiane-4-carbonyl)-3,3-dimethylpiperazin-1-yl]-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide

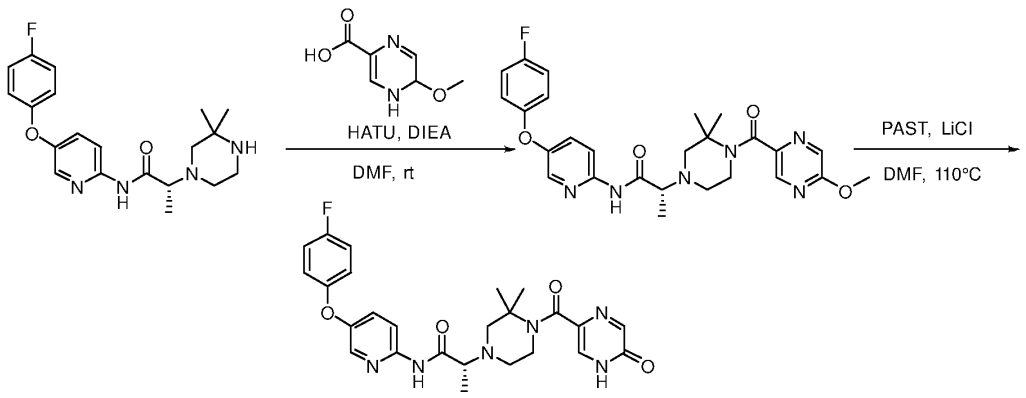
To a solution of1,1-dioxo-1lambda6-thiane-4-carbonyl chloride (0.1 g, crude) (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (88.11 mg, 0.225 mmol, 1 equiv) in DCM (3 mL) was added (2S)-2-(3,3-dimethylpiperazin-1-yl)-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (142.05 mg, 0.381 mmol, 1 equiv) and DIEA (246.47 mg, 1.905 mmol, 5 equiv) at rt. The resulting mixture was stirred for 3h at rt. The reaction mixture was quenched by water and extracted with EA (3*20 mL). The combined

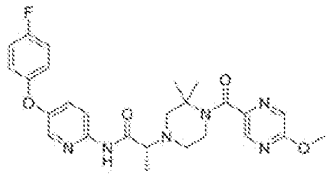
organic extracts were washed with brine (10mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography DCM/MeOH (0-20%) to afford product (2S)-2-[4-(1,1-dioxo-1lambda6-thiane-4-carbonyl)-3,3-dimethylpiperazin-1-yl]-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (9.3 mg, 4.56%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{33}FN_4O_5S$ 532.22 m/z, found 533.30 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.17 (s, 1H), 8.14 (dd, J = 6.0, 2.9 Hz, 2H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.04 – 7.16 (m, 2H), 3.42 – 3.52 (m, 3H), 3.10 – 3.25 (m, 2H), 2.93 – 3.09 (m, 3H), 2.67 – 2.79 (m, 1H), 2.56 – 2.66 (m, 1H), 2.26 – 2.38 (m, 2H), 1.82 – 2.03 (d, J = 5.8 Hz, 4H), 1.37 (d, J = 3.0 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ-119.826.

Example 149: (R)-2-(3,3-dimethyl-4-(5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propenamide



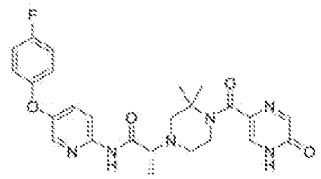
Synthetic Scheme





(R)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(5-methoxypyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

To a solution of 5-methoxy-4,5-dihydropyrazine-2-carboxylic acid (150 mg, 0.973 mmol, 1 equiv) in DMF (3 mL) was added (R)-2-(3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (362.48 mg, 0.973 mmol, 1 equiv) and HATU (555.09 mg, 1.460 mmol, 1.5 equiv) and DIEA (628.94 mg, 4.865 mmol, 5 equiv). The resulting mixture was stirred for 2 h at rt. The reaction mixture was quenched by water (20 mL) and extracted with EA (3*30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford product (R)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(5-methoxypyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (200 mg, 98.0%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{29}FN_6O_4$ 508.22 m/z, found 508.80 $[M+H]^+$.

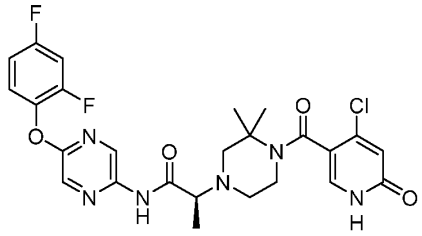


(R)-2-(3,3-dimethyl-4-(5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

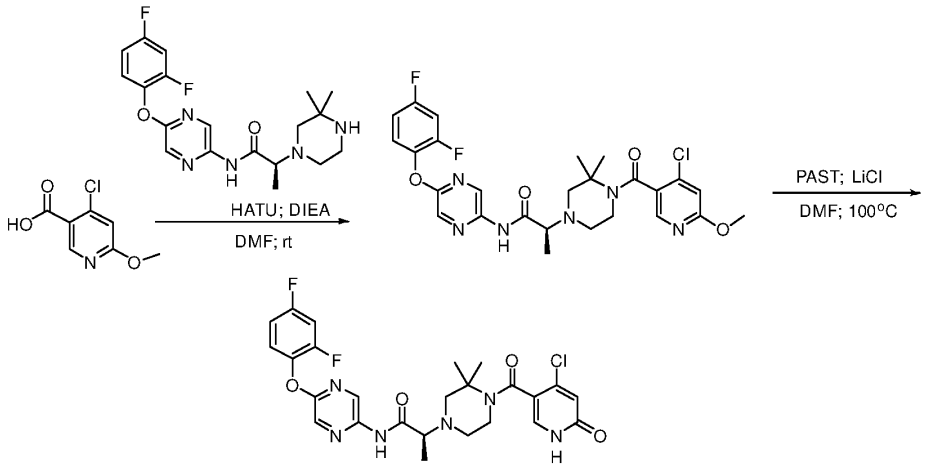
To a solution of (R)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(5-methoxypyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (100 mg, 0.197 mmol, 1 equiv) in DMF (3mL) was added PAST (338.61 mg, 1.970 mmol, 10 equiv) and LiCl (83.35 mg, 1.970 mmol, 10 equiv). The resulting mixture was stirred for overnight at 110 °C. The reaction mixture was quenched by water and extracted with EA (2*30 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20% DCM/MeOH). The residue was purified by preparative HPLC using a XBridge Shield RP 18 OBD 250 mm x 19 mm x 5 μm column (eluent: 28% to 58% (v/v) CH_3CN and H_2O (10mmol/L NH_4HCO_3)) to afford (R)-2-(3,3-dimethyl-4-(5-oxo-4,5-dihydropyrazine-2-

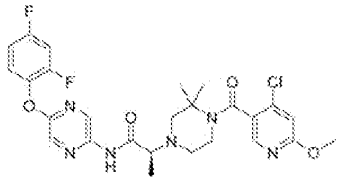
carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (15.3 mg, 15.69%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{27}FN_6O_4$ 494.21 m/z, found 495.25 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.62 (s, 1H), 10.19 (s, 1H), 8.12 – 8.19 (m, 2H), 7.85 (s, 1H), 7.77 (s, 1H), 7.53 (dd, J = 8.9, 3.1 Hz, 1H), 7.18 – 7.29 (m, 2H), 7.05 – 7.14 (m, 2H), 3.49 (tt, J = 8.9, 5.4 Hz, 3H), 2.57 – 2.75 (m, 2H), 2.35 – 2.47 (m, 2H), 1.44 (d, J = 2.6 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H).^{19}F NMR (376 MHz, DMSO-d_6) δ -119.85.

Example 150: (S)-2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide



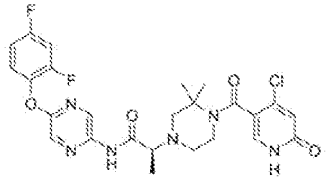
Synthetic Scheme





2-[4-(4-chloro-6-methoxypyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl]-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide

To a solution of 4-chloro-6-methoxypyridine-3-carboxylic acid (100 mg, 0.533 mmol, 1 equiv) in DMF (5mL) was added N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (208.67 mg, 0.533 mmol, 1 equiv) and HATU (304.06 mg, 0.800 mmol, 1.5 equiv) and DIEA (137.80 mg, 1.066 mmol, 2 equiv) at rt. The resulting mixture was stirred for 3 h at rt. The reaction mixture was quenched by water and extracted with EA (2*30 mL). The combined organic extracts were washed with brine (10mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford product 2-[4-(4-chloro-6-methoxypyridine-3-carbonyl)-3,3-dimethyl piperazin-1-yl]-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propenamide (0.2 g). MS (ESI): mass calcd. for $C_{26}H_{27}ClF_2N_6O_4$ 560.18 m/z, found 561.30 $[M+H]^+$.

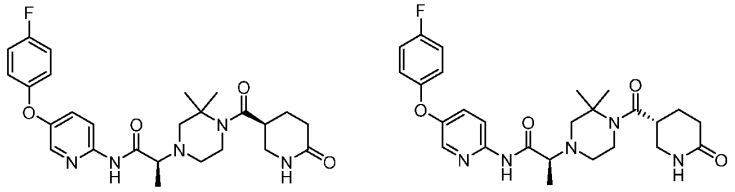


(S)-2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

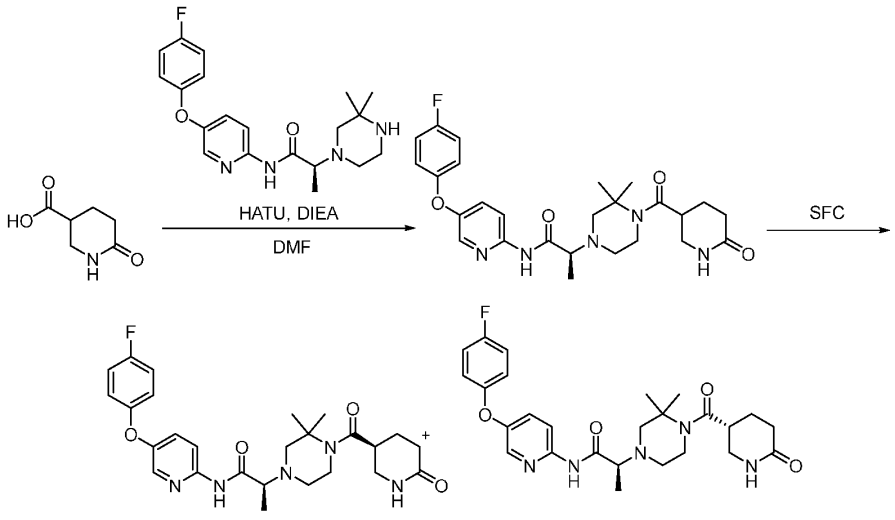
To a solution of (2S)-2-[4-(4-chloro-6-methoxypyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl]-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (200 mg, 0.357 mmol, 1 equiv) in DMF (3mL) was added PAST (613.91 mg, 3.570 mmol, 10 equiv) and LiCl (151.13 mg, 3.570 mmol, 10 equiv) at rt .The resulting mixture was stirred for 12 h at 100 °C. The reaction mixture was quenched by water and extracted with EA (2*30 mL).The combined organic extracts were washed with brine (10mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford product. The residue was purified by preparative HPLC using a YMC-ActusTriart C18 ExRS 150 mm x 30 mm x 5 μm column (eluent: 31% to 61%

(v/v) CH_3CN and H_2O(10mmol/L NH4HCO3+0.05%NH3H2O)) to afford (S)-2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (45 mg, 22.59%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{26}ClF_2N_6O_4$ 546.16 m/z, found 547.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.01 (s, 1H), 10.42 (s, 1H), 8.81 – 8.85 (m, 1H), 8.45 (d, J = 1.5 Hz, 1H), 7.41 – 7.55 (m, 3H), 7.12 – 7.22 (m, 1H), 6.52 (s, 1H), 3.52 (q, J = 6.9 Hz, 1H), 2.50 – 2.71 (m, 2H), 2.56 (dt, J = 11.1, 5.2 Hz, 2H), 2.35 – 2.48 (m, 2H), 1.45 (s, 6H), 1.19 (d, J = 6.9 Hz, 3H).^{19}F NMR (376 MHz, DMSO-d_6) δ -113.42 (d, J = 5.1 Hz), -124.20 (d, J = 5.4 Hz).

Example 151: (S)-2-(3,3-dimethyl-4-((S)-6-oxopiperidine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide and Example 152: (S)-2-(3,3-dimethyl-4-((R)-6-oxopiperidine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propenamide



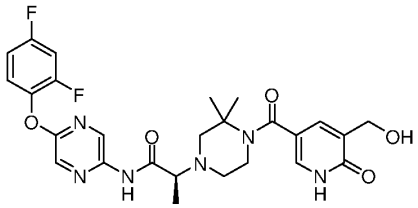
Synthetic Scheme



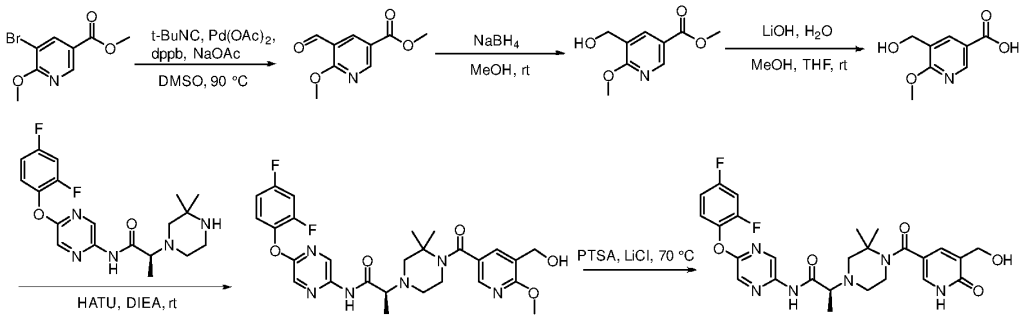
(S)-2-(3,3-dimethyl-4-((S)-6-oxopiperidine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propenamide and (S)-2-(3,3-dimethyl-4-((R)-6-oxopiperidine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

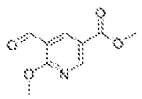
To a solution of (2S)-2-(3,3-dimethylpiperazin-1-yl)-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (70 mg, 0.188 mmol, 1.00 equiv) in dimethylformamide (4 mL) was added HATU (142.93 mg, 0.376 mmol, 2 equiv), DIEA (121.46 mg, 0.940 mmol, 5 equiv) at rt. The resulting mixture was stirred for 2 h at rt. The reaction was quenched with H_2O (10 mL) at rt. The resulting mixture was extracted with EA (3*30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. The resulting mixture was filtered. The filtrate was concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20% DCM/MeOH) to afford crude product; The product was separated by Chiral-HPLC using a Column: CHIRALPAK IA, 5*25 cm, 5 μm column (eluent: 10% (v/v)Mobile Phase A: Hex: DCM=3: 1(0.5% 2M NH3-MeOH) to afford (S)-2-(3,3-dimethyl-4-((S)-6-oxopiperidine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (1.8 mg, 1.91%), as a white solid. MS (ESI): mass calcd. for $C_{26}H_{32}FN_5O_4$: 497.24, found: 498.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.14 (dd, J = 6.1, 2.9 Hz, 2H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.41 (s, 1H), 7.17 – 7.31 (m, 2H), 7.04 – 7.16 (m, 2H), 5.07 (s, 2H), 4.35 (s, 6H), 3.45 – 3.55(m, 4H), 3.16 – 3.25 (m, 2H), 2.98 (s, 1H), 2.55 – 2.63 (m, 2H), 2.34 (d, J = 3.1 Hz, 2H), 2.12 – 2.26 (m, 1H), 1.70 – 1.90 (m, 2H), 1.37 (d, J = 3.3 Hz, 6H), 1.16 – 1.27 (m, 3H). And (S)-2-(3,3-dimethyl-4-((R)-6-oxopiperidine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (1.3 mg, 1.39%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{32}FN_5O_4$: 497.24, found: 498.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.14 (dd, J = 6.0, 2.9 Hz, 2H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.41 (s, 1H), 7.18 – 7.30 (m, 2H), 7.04 – 7.16 (m, 2H), 3.51 (s, 3H), 3.48 (d, J = 6.9 Hz, 1H), 3.16 (d, J = 10.4 Hz, 2H), 2.70-2.80 (m, 1H), 2.60 – 2.69 (m, 1H), 2.34 (s, 2H), 2.05 – 2.29 (m, 2H), 1.80-1.90 (m, 1H), 1.37 (d, J = 1.5 Hz, 6H), 1.27 – 1.15 (m, 4H). Stereochemistry of example 151 and example 152 was arbitrarily assigned.

Example 153: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-(hydroxymethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide



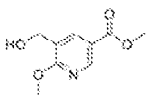
Synthetic Scheme





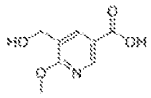
methyl 5-formyl-6-methoxynicotinate

To a stirring solution methyl 5-bromo-6-methoxypyridine-3-carboxylate (2 g, 8.128 mmol, 1 equiv) in DMSO (30 mL) was added a solution of NaOAc (0.83 g, 12.192 mmol, 1.5 equiv) and dppb (0.35 g, 0.813 mmol, 0.1 equiv) and $Pd(OAc)_2$ (0.18 g, 0.813 mmol, 0.1 equiv) and 2-isocyano-2-methylpropane (1.01 g, 12.192 mmol, 1.5 equiv). The resulting mixture under N_2 was stirred at 90 °C for 6h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford methyl 5-formyl-6-methoxynicotinate (1.1 g, 69.34%). MS (ESI): mass calcd. for $C_9H_9NO_4$: 195.05 found: 196.05[$M+H^+$]



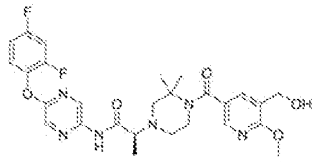
methyl 5-(hydroxymethyl)-6-methoxynicotinate

To a stirring solution methyl methyl 5-formyl-6-methoxynicotinate (500 mg, 2.562 mmol, 1 equiv) in methanol (5 mL) was added at 0°C a solution of borane sodium (141.49 mg, 3.843 mmol, 1.5 equiv). The resulting mixture was stirred at room temperature for 6h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford methyl 5-(hydroxymethyl)-6-methoxynicotinate (480 mg, 95.02%). MS (ESI): mass calcd. for $C_9H_{11}NO_4$: 197.05found: 198.15[M+H$^+$]



5-(hydroxymethyl)-6-methoxynicotinic acid

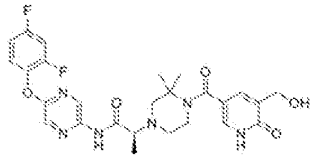
To a stirring solution methyl 5-(hydroxymethyl)-6-methoxynicotinate (250 mg, 1.268 mmol, 1 equiv) in methanol (1 mL) and tetrahydrofuran (2 mL) and water (1 mL) was added a solution of lithiumol (151.82 mg, 6.340 mmol, 5 equiv) .The resulting mixture was stirred at room temperature for 6h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% H_2O/ACN) to afford 5-(hydroxymethyl)-6-methoxynicotinic acid (200 mg, 86.13%) as a yellow oil. MS (ESI): mass calcd. for $C_8H_9NO_4$: 183.05found: 184.05[M+H$^+$]



(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-(hydroxymethyl)-6-methoxynicotinoyl)-3,3-dimethylpiperazin-1-yl)propanamide

To a stirring solution 5-(hydroxymethyl)-6-methoxynicotinic acid (140.38 mg, 0.765 mmol, 3 equiv) in dimethylformamide (2 mL) was added a solution of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (100 mg, 0.255 mmol, 1.00 equiv) and HATU(194.28 mg, 0.510 mmol, 2 equiv) and DIEA (165.10 mg, 1.275 mmol, 5 equiv) .The resulting mixture was stirred at room temperature for 6h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with

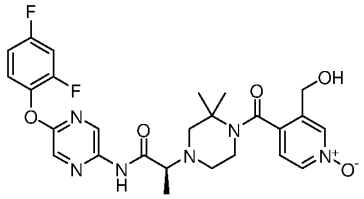
EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-(hydroxymethyl)-6-methoxynicotinoyl)-3,3-dimethylpiperazin-1-yl)propanamide (50 mg, 35.16%) MS (ESI): mass calcd. for $C_{27}H_{30}F_2N_6O_5$: 556.22found: 557.25[M+H$^+$]



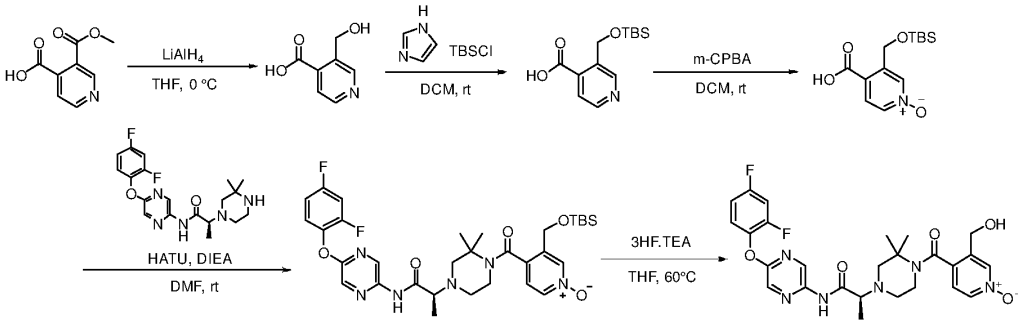
(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-(hydroxymethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

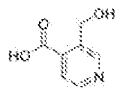
To a stirred solution of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-(hydroxymethyl)-6-methoxynicotinoyl)-3,3-dimethylpiperazin-1-yl)propanamide (50 mg, 0.090 mmol, 1 equiv) in dimethylformamide (1 mL) was added lithium chloride (19.04 mg, 0.450 mmol, 5 equiv) and PTSA (77.35 mg, 0.450 mmol, 5 equiv) at room temperature . The reaction mixture was stirred at 70 °C for 3 h. The resulting mixture was stirred for additional overnight at room temperature. After completion of reaction, the reaction mixture was quenched by addition of water (5 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and the residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30 x150mm x5μm (eluent: 28% to 58% (v/v) CH_3CN and H_2O with NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-(hydroxymethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (2 mg, 4.07%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{28}F_2N_6O_5$: 542.21 m/z, found: 543.30 [M+H]$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.78 (s, 1H), 10.42 (s, 1H), 8.85 (s, 1H), 8.46 (s, 1H), 7.48 (qd, J = 9.9, 9.1, 4.5 Hz, 4H), 7.13 – 7.23 (m, 1H), 5.16 (s, 1H), 4.28 (s, 2H), 3.49 – 3.57 (m, 3H), 2.72 (dt, J = 10.5, 4.9 Hz, 1H), 2.63 (q, J = 5.8, 5.3 Hz, 1H), 2.41 (s, 2H), 1.41 (d, J = 2.8 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H).^{19}F NMR (376 MHz, DMSO-d_6) δ -113.42 (d, J = 5.0 Hz), -124.21 (d, J = 5.0 Hz).

Example 154: (S)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-3-(hydroxymethyl)pyridine 1-oxide



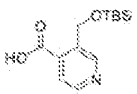
Synthetic Scheme





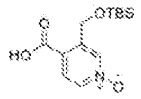
3-(hydroxymethyl)isonicotinic acid

To a solution of 3-(methoxycarbonyl)pyridine-4-carboxylic acid (1 g, 5.520 mmol, 1 equiv) in tetrahydrofuran (10 mL) was added $LiAlH_4$ (419.00 mg, 11.040 mmol, 2 equiv) at 0 °C, the mixture was stirred for 1h at rt. the reaction mixture was quenched by water and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 3-(hydroxymethyl)pyridine-4-carboxylic acid (150 mg, 17.74%) as a yellow solid. MS (ESI):$C_7H_7NO_3$: 153.29 m/z, found: 154.15 $[M+H]^+$.



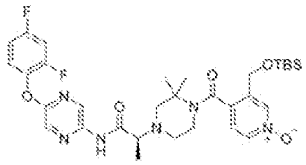
3-(((tert-butyldimethylsilyl)oxy)methyl)isonicotinic acid

To a solution of 3-(hydroxymethyl)pyridine-4-carboxylic acid (150 mg, 0.980 mmol, 1 equiv) in DCM(3 mL) was added imidazole (200.05 mg, 2.940 mmol, 3 equiv) t-butyldimethylchlorosilane (221.45 mg, 1.470 mmol, 1.5 equiv), the mixture was stirred for 2 h at rt. the reaction mixture was quenched by water and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 3-{[(tert-butyldimethylsilyl)oxy]methyl}pyridine-4-carboxylic acid (120 mg, 45.82%) as a yellow solid. MS (ESI):$C_{13}H_{21}NO_3Si$:267.29 m/z, found: 268.05$[M+H]^+$.



3-(((tert-butyldimethylsilyl)oxy)methyl)-4-carboxypyridine 1-oxide

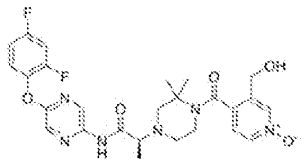
To a solution of 3-{[(tert-butyldimethylsilyl)oxy]methyl}pyridine-4-carboxylic acid (100 mg, 0.374 mmol, 1 equiv) in DCM (3 mL) was added m-CPBA (129.07 mg, 0.748 mmol, 2 equiv), the mixture was stirred for 2 h at rt. the reaction mixture was quenched by water and extracted with EA (3*30 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 3-{[(tert-butyldimethylsilyl)oxy]methyl}-4-carboxypyridin-1-ium-1-olate (60 mg, 56.61%) as a yellow solid. MS (ESI):$C_{13}H_{21}NO_4Si$: 283.29 m/z, found: 284.05$[M+H]^+$.



(S)-3-(((tert-butyldimethylsilyl)oxy)methyl)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

To a solution of 3-{[(tert-butyldimethylsilyl)oxy]methyl}-4-carboxypyridin-1-ium-1-olate (50 mg, 0.176 mmol, 1 equiv) in dimethylformamide (3 mL) was added (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (69.06 mg, 0.176

mmol, 1 equiv), HATU (100.63 mg, 0.264 mmol, 1.5 equiv), DIEA (45.61 mg, 0.352 mmol, 2 equiv), the mixture was stirred for 2 h at rt. the reaction mixture was quenched by water and extracted with EA (3*30 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 3-{[(tert-butyldimethylsilyl)oxy]methyl}-4-{4-[(1S)-1-{[5-(2,4-difluorophenoxy)pyrazin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}pyridin-1-ium-1-olate (30 mg, 25.89%) as a yellow solid. MS (ESI):$C_{32}H_{42}F_2N_6O_5Si$: 656.29 m/z, found: 657.05$[M+H]^+$.

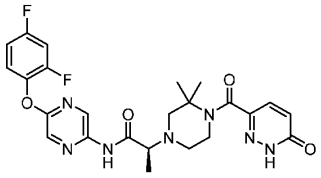


(S)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-3-(hydroxymethyl)pyridine 1-oxide

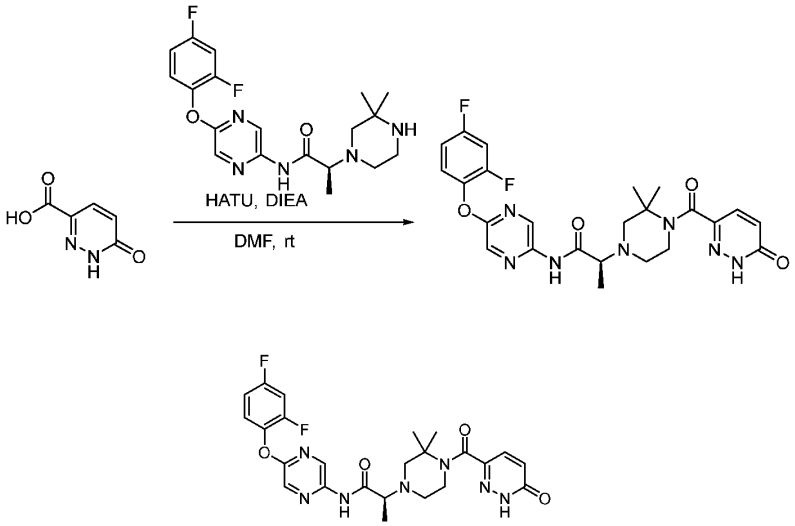
To a solution of 3-{[(tert-butyldimethylsilyl)oxy]methyl}-4-{4-[(1S)-1-{[5-(2,4-difluorophenoxy)pyrazin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}pyridin-1-ium-1-olate (30 mg, 0.046 mmol, 1 equiv) in tetrahydrofuran (2 mL) with Triethylamine trihydrofluoride (0.5 mL).The resulting mixture was stirred for 3 h at 60°C. After cooled to room temperature the reaction mixture was quenched by water and extracted with EA (3 x 20 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 20 mg crude product as a white solid.The compound was separated by HPLC (Column: XBridge Prep C_{18} OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water(10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 25 mL/min mL/min; Gradient: 34% B to 64% B in7min; Wave Length: 254nm nm; RT1(min): 6.33) to afford 4-{4-[(1S)-1-{[5-(2,4-difluorophenoxy)pyrazin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}-3-(hydroxymethyl)pyridin-1-ium-1-olate (2 mg, 7.99%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{28}F_2N_6O_5$: 542.22m/z, found 543.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.83 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 8.08 – 8.21 (m, 2H), 7.40 – 7.56 (m, 2H), 7.24 (d, J = 6.5 Hz, 1H), 7.12 – 7.24 (m, 1H), 5.49 (t, J = 5.5 Hz, 1H), 4.45 (d, J = 5.3 Hz, 2H), 3.53 (d, J = 6.7 Hz, 1H), 3.21 (s, 2H), 2.63 (d, J = 5.4 Hz, 2H), 2.40 – 2.47

(m, 2H), 1.48 (d, J = 2.0 Hz, 6H), 1.19 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.43, -124.23.

Example 155: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridazine-3-carbonyl)piperazin-1-yl)propanamide



Synthetic Scheme

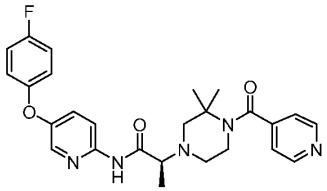


(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridazine-3-carbonyl)piperazin-1-yl)propanamide

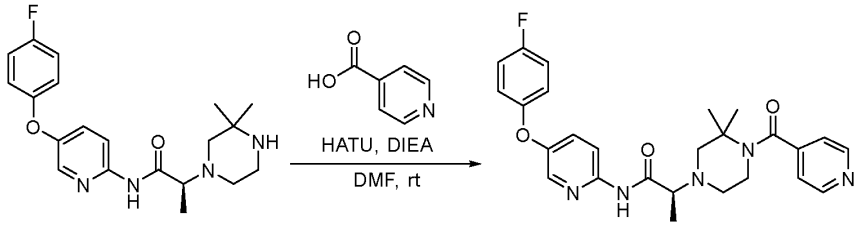
To a solution of (S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (50 mg, 0.128 mmol, 1 equiv) in DMF (2 mL). 6-oxo-1H-pyridazine-3-carboxylic acid (53.69 mg, 0.384 mmol, 3 equiv), HATU (72.86 mg, 0.192 mmol, 1.5 equiv) and DIEA (82.55 mg, 0.640 mmol, 5 equiv) added at rt. The resulting mixture was stirred for 2h at rt. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and

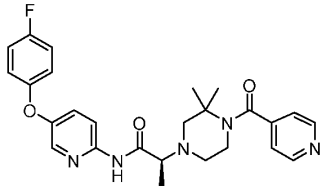
concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-15% DCM/MeOH) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 28% to 46% ACN and H2O (10mmol/L NH_4HCO_3+0.05%NH_3H_2O)) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridazine-3-carbonyl)piperazin-1-yl)propanamide (13.9 mg, 21.12%) as a white solid, MS (ESI): mass calcd. for $C_{24}H_{25}F_2N_7O_4$:513.19, found:514.20[M+H]$^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.12 (s, 1H), 10.43 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.5 Hz, 1H), 7.39 – 7.45 (m, 3H), 7.10 – 7.24 (m, 1H), 6.91 (d, J = 9.8 Hz, 1H), 3.42 – 3.59 (m, 3H), 2.65 – 2.78 (m, 1H), 2.53 – 2.65 (m, 1H), 2.40 – 2.47 (m, 2H), 1.43 (d, J = 2.3 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.422, -124.216.

Example 156: (S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-isonicotinoyl-3,3-dimethylpiperazin-1-yl)propanamide



Synthetic Scheme

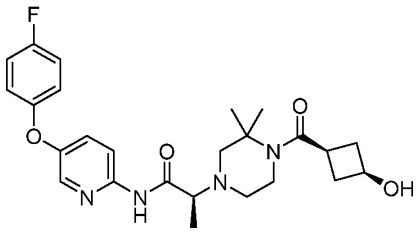




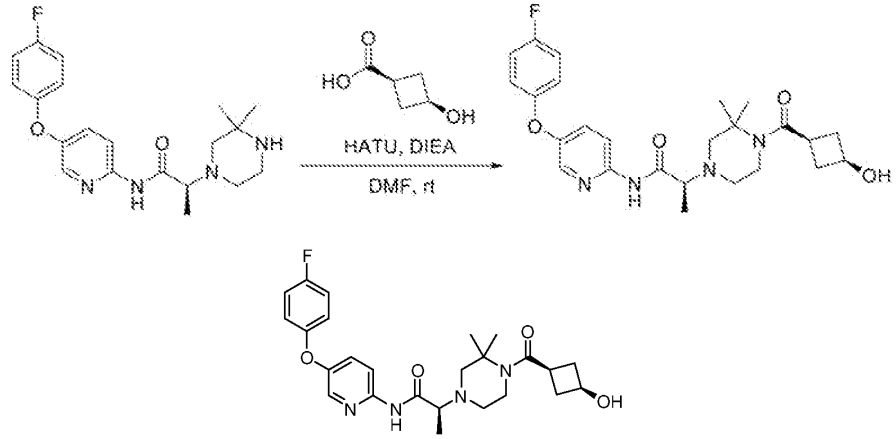
(S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-isonicotinoyl-3,3-dimethylpiperazin-1-yl)propanamide

To a solution of (2S)-2-(3,3-dimethylpiperazin-1-yl)-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (50 mg, 0.134 mmol, 1 equiv) in DMF (2 mL). isonicotinic acid (49.58 mg, 0.402 mmol, 3 equiv, HATU (76.57 mg, 0.201 mmol, 1.5 equiv) and DIEA (86.76 mg, 0.670 mmol, 5 equiv) added at rt. The resulting mixture was stirred for 2h at rt. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-15% DCM/MeOH) and Prep-HPLC using a Column: YMC-ActusTriart C18 ExRS, 150*30.0mml.D.S-5μm, 8nm (eluent: 40% to 70% ACN and H_2O (10mmol/L NH_4HCO_3+0.05%NH_3H_2O)) to afford (S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-isonicotinoyl-3,3-dimethylpiperazin-1-yl)propanamide (13 mg, 20.15%) as a white solid, MS (ESI): mass calcd. for $C_{26}H_{28}FN_5O_3$:477.22, found:478.25[M+H]$^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.64 (d, J = 4.9 Hz, 2H), 8.10 – 8.19 (m, 2H), 7.52 (dd, J = 9.1, 3.0 Hz, 1H), 7.36 (d, J = 5.3 Hz, 2H), 7.24 (t, J = 8.7 Hz, 2H), 7.09 (dd, J = 9.1, 4.3 Hz, 2H), 3.43 – 3.56 (m, 1H), 3.26 (d, J = 5.4 Hz, 2H), 2.64 – 2.73 (m, 1H), 2.53 – 2.63 (m, 1H), 2.4 – 2.49 (m, 2H), 1.49 (d, J = 2.7 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.828.

Example 157: (S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-((1s,3R)-3-hydroxycyclobutane-1-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide



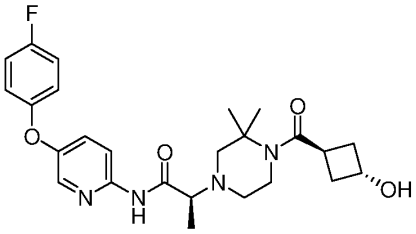
Synthetic Scheme



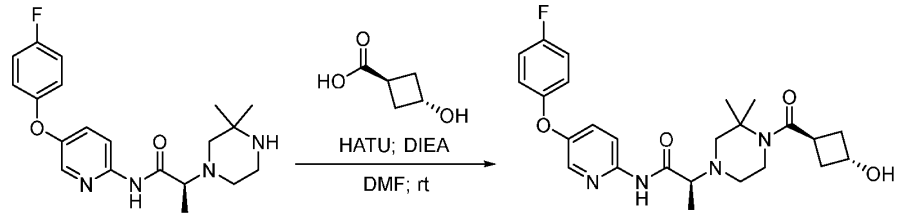
(S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-((1s,3R)-3-hydroxycyclobutane-1-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

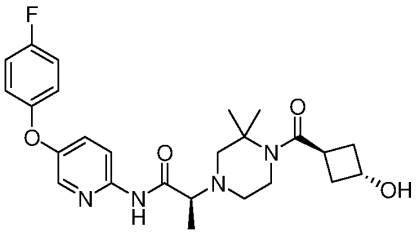
To a solution of (2S)-2-(3,3-dimethylpiperazin-1-yl)-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (50 mg, 0.134 mmol, 1 equiv) in DMF (2 mL). (1s,3s)-3-hydroxycyclobutane-1-carboxylic acid (77.94 mg, 0.670 mmol, 5 equiv), HATU (76.57 mg, 0.201 mmol, 1.5 equiv) and DIEA (86.76 mg, 0.670 mmol, 5 equiv) added at rt. The resulting mixture was stirred for 12h at rt. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-15% DCM/MeOH) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm (eluent: 32% to 62% ACN and H_2O (10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-((1s,3R)-3-hydroxycyclobutane-1-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (4.5 mg, 7.03%) as a white solid, MS (ESI): mass calcd. for $C_{25}H_{31}FN_4O_4$:470.23, found:471.30$[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.09 – 8.18 (m, 2H), 7.47 – 7.58 (m, 1H), 7.17 – 7.30 (m, 2H), 7.17 – 7.02 (m, 2H), 5.02 (dd, J = 7.0, 1.2 Hz, 1H), 3.82 – 4.01 (m, 1H), 3.39 – 3.51 (m, 1H), 3.23 – 3.32 (m, 2H), 2.60 – 2.70 (m, 3H), 2.21 – 2.34 (m, 4H), 1.81 – 1.97 (m, 2H), 1.34 – 1.41 (m, 6H), 1.18 (d, J = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.834

Example 158: (2S)-2-{3,3-dimethyl-4-[(1r,3r)-3-hydroxycyclobutanecarbonyl] piperazin-1-yl}-N-[5-(4-fluorophenoxy)pyridin-2-yl]propenamide



Synthetic Scheme



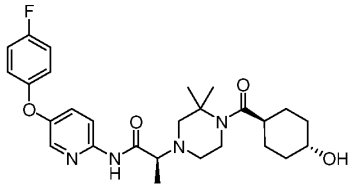


(2S)-2-{3,3-dimethyl-4-[(1r,3r)-3-hydroxycyclobutanecarbonyl]piperazin-1-yl}-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide

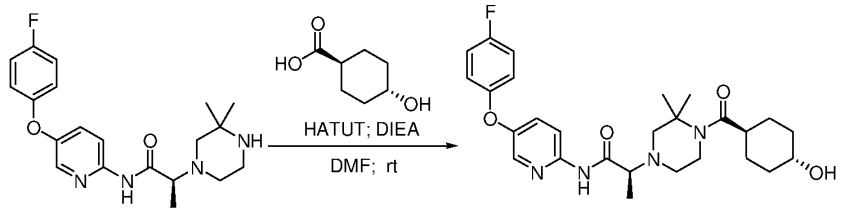
To a solution of (2S)-2-(3,3-dimethylpiperazin-1-yl)-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (50 mg, 0.134 mmol, 1 equiv) in DMF (3mL) was added (1r,3r)-3-hydroxycyclobutane-1-carboxylic acid (23.38 mg, 0.201 mmol, 1.5 equiv) and HATU (76.57 mg, 0.201 mmol, 1.5 equiv) and DIEA (86.76 mg, 0.670 mmol, 5 equiv) at rt .The resulting mixture was stirred for 3h at rt. The reaction mixture was quenched by water and extracted with EA (3*20 mL). The combined organic extracts were washed with brine (10mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography DCM/MeOH (0-20%) to afford product (2S)-2-{3,3-dimethyl-4-[(1r,3r)-3-hydroxycyclobutanecarbonyl] piperazin-1-yl}-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (4.1 mg, 6.47%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{31}FN_4O_4$ 470.23 m/z, found 471.30$[M+H]^+$.^{1}H NMR (400 MHz, DMSO-d_6) δ

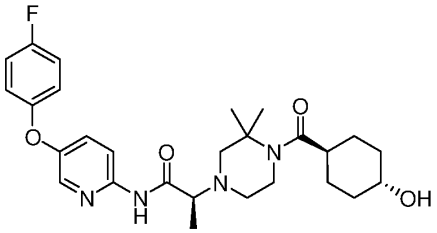
10.15 (s, 1H), 8.10 – 8.17 (m, 2H), 7.52 (dd, *J* = 9.1, 2.9 Hz, 1H), 7.18 – 7.29 (m, 2H), 7.04 – 7.14 (m, 2H), 5.03 (d, *J* = 5.9 Hz, 1H), 4.05 (h, *J* = 6.6 Hz, 1H), 3.44 (q, *J* = 6.9 Hz, 1H), 13.26 (s, 2H), 3.10 (dq, *J* = 9.5, 4.8 Hz, 1H), 2.64 (q, *J* = 5.8 Hz, 1H), 2.55 (t, *J* = 5.6 Hz, 1H), 2.26 – 2.37 (m, 4H), 1.97 (tdd, *J* = 9.7, 6.4, 2.5 Hz, 2H), 1.38 (d, *J* = 3.0 Hz, 6H), 1.18 (d, *J* = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ-119.84.

Example 159: (2S)-2-{3,3-dimethyl-4-[(1r,4r)-4-hydroxycyclohexanecarbonyl] piperazin-1-yl}-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide



Synthetic Scheme



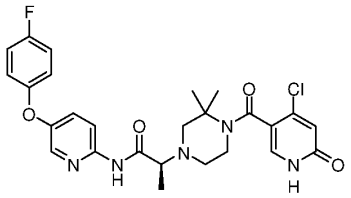


(2S)-2-{3,3-dimethyl-4-[(1r,4r)-4-hydroxycyclohexanecarbonyl]piperazin-1-yl}-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide

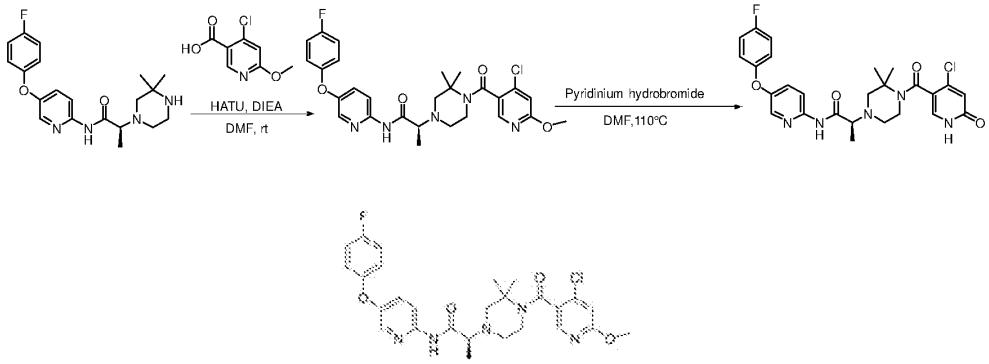
To a solution of (2S)-2-(3,3-dimethylpiperazin-1-yl)-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (50 mg, 0.134 mmol, 1 equiv) in DMF (3mL) was adde (1r,4r)-4-hydroxycyclohexane-1-carboxylic acid (29.03 mg, 0.201 mmol, 1.5 equiv) and DIEA (86.76 mg, 0.670 mmol, 5 equiv) and HATU (76.57 mg, 0.201 mmol, 1.5 equiv) at rt. The resulting

mixture was stirred for 3h at rt. The reaction mixture was quenched by water and extracted with EA (3*20 mL). The combined organic extracts were washed with brine (10mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography DCM/MeOH (0-20%) to afford product (2S)-2-{3,3-dimethyl-4-[(1r,4r)-4-hydroxycyclohexanecarbonyl] piperazin-1-yl}-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (2.9 mg, 4.32%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{35}FN_4O_4$ 498.29 m/z, found 499.35$[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.14 (dd, J = 6.0, 2.9 Hz, 2H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.03 – 7.13 (m, 2H), 4.53 (d, J = 4.3 Hz, 1H), 3.46 (d, J = 7.1 Hz, 3H), 2.64 – 2.75 (m, 1H), 7.54 – 2.64 (m, 1H), 7.03 – 7.13 (m, 2H), 2.35 – 1.47 (m, 2H), 2.31 (s, 2H), 1.81 (dd, J = 12.4, 4.1 Hz, 2H), 1.61 (d, J = 12.8 Hz, 2H), 1.38 – 1.22 (m, 7H), 1.07 – 1.22 (m, 6H).^{19}F NMR (282 MHz, DMSO-d_6) δ -119.84.

Example 160: (S)-2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

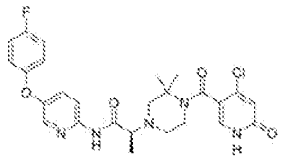


Synthetic Scheme



(S)-2-(4-(4-chloro-6-methoxynicotinoyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

To a solution of 2-(3,3-dimethylpiperazin-1-yl)-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (100 mg, 0.268 mmol, 1 equiv) in DMF (3 mL). 4-chloro-6-methoxypyridine-3-carboxylic acid (151.09 mg, 0.804 mmol, 3 equiv), HATU (153.14 mg, 0.402 mmol, 1.5 equiv) and DIEA (104.11 mg, 0.804 mmol, 3 equiv) added at rt. The resulting mixture was stirred for 4h at rt. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-15% DCM/MeOH) to afford (S)-2-(4-(4-chloro-6-methoxynicotinoyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (100 mg, 68.7%) as a yellow oil. MS (ESI): mass calcd. for $C_{27}H_{29}ClFN_5O_4$:541.19 m/z, found:542.35 $[M+H]^+$.

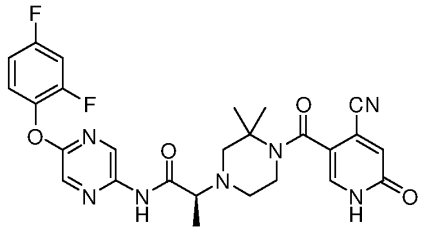


(S)-2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

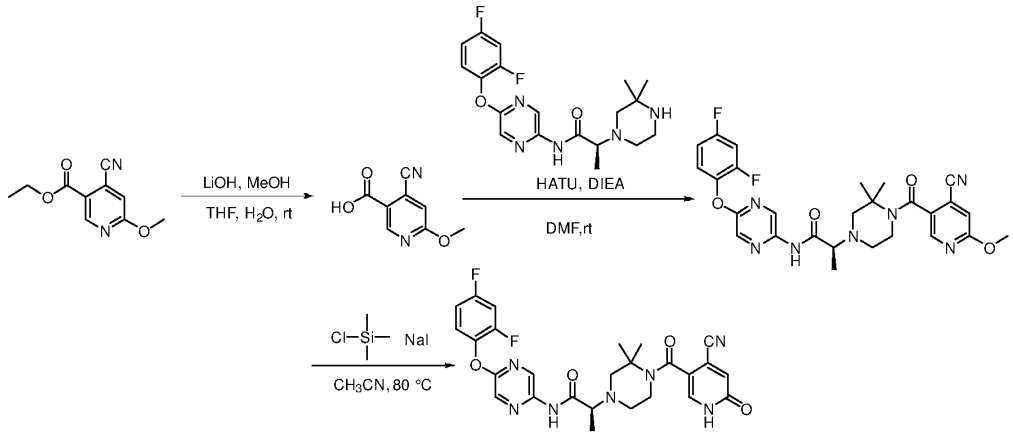
To a solution of (S)-2-(4-(4-chloro-6-methoxynicotinoyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (150 mg, 0.277 mmol, 1 equiv) in DMF (3 mL). Pyridinium hydrobromide added at rt. The resulting mixture was stirred for 10h at 100 °C. The resulting mixture was extracted with EA (3*100 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash C18 (ACN:H_2O(0.1FA%)) and Prep-HPLC using a Column: YMC Triart C18 ExRs Column, 20*250mm, 5μm (eluent: 43% to 73% ACN and H_2O (10mmol/L NH_4HCO_3) to afford (S)-2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (36.2 mg, 24.33%)) as a white solid, MS (ESI): mass calcd. for $C_{26}H_{27}ClFN_5O_4$: 527.17 m/z, found: 528.25 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.94 (s, 1H), 10.19 (s, 1H), 8.14 (dd, J = 6.1, 3.0 Hz, 2H), 7.49 – 7.56 (m, 2H), 7.24 (t, J = 8.8 Hz, 2H), 7.04 – 7.14 (m, 2H), 6.53 (s, 1H), 3.44 – 3.53 (m, 1H), 3.20 – 3.30

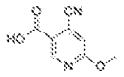
(m, 2H), 2.62 – 2.72 (m, 1H), 2.52 – 2.60 (m, 1H), 2.42 (s, 2H), 1.47 (d, J = 2.9 Hz, 6H), 1.19 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -119.8256.

Example 161: (2S)-2-[4-(4-cyano-6-oxo-1H-pyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl]-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide



Synthetic Scheme

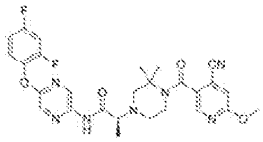




4-cyano-6-methoxypyridine-3-carboxylic acid

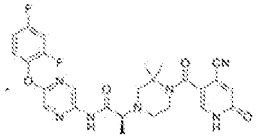
To a stirred solution of ethyl 4-cyano-6-methoxypyridine-3-carboxylate (200 mg, 0.970 mmol, 1 equiv) in MeOH/THF/H_2O (1:1:1, 3 mL) was added LiOH (46.46 mg, 1.940 mmol, 2 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at room temperature under air atmosphere.The reaction was monitored by LCMS. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The

residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water, 10% to 50% gradient in 10 min; detector, UV 254 nm. This resulted in 4-cyano-6-methoxypyridine-3-carboxylic acid (140 mg, 81.02%) as a white solid. MS (ESI): mass calcd. for $C_8H_6N_2O_3$:178.0 m/z, found:179.10 $[M+H]^+$.



(2S)-2-[4-(4-cyano-6-methoxypyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl]-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide

To a stirred solution of 4-cyano-6-methoxypyridine-3-carboxylic acid (60 mg, 0.337 mmol, 1 equiv) and HATU (192.10 mg, 0.506 mmol, 1.5 equiv) in DMF (2 Ml) were added DIEA (87.06 mg, 0.674 mmol, 2 equiv) and (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (131.83 mg, 0.337 mmol, 1 equiv) in portions at room temperature under 0°C. The resulting mixture was stirred for 2 h at room temperature under air atmosphere. The reaction was monitored by LCMS. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford (2S)-2-[4-(4-cyano-6-methoxypyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl]-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (100 mg, 53.83%) as a light yellow solid. MS (ESI): mass calcd. for $C_{27}H_{27}F_2N_7O_4$:551.2 m/z, found:552.20 $[M+H]^+$.

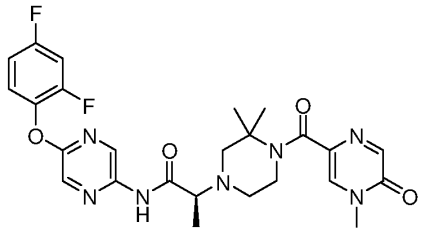


(2S)-2-[4-(4-cyano-6-oxo-1H-pyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl]-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide

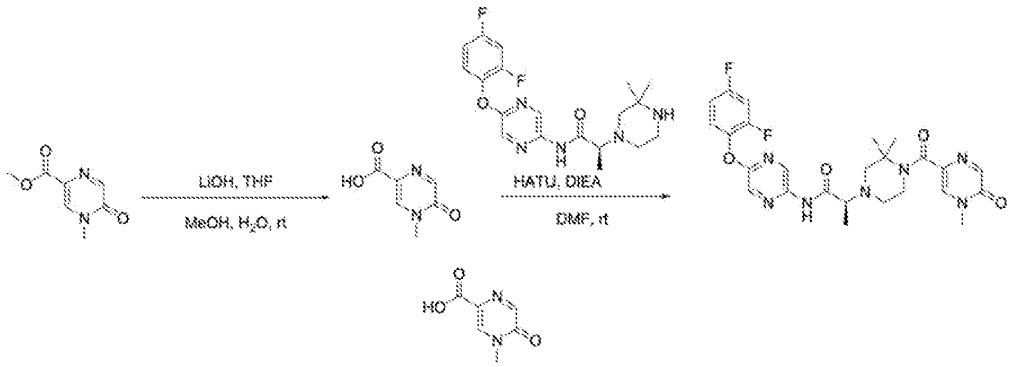
To a stirred solution of (2S)-2-[4-(4-cyano-6-methoxypyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl]-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (40 mg, 0.073 mmol, 1 equiv) in MeCN (1 mL) were added chlorotrimethylsilane (23.64 mg, 0.219 mmol, 3 equiv) and iodosodium (32.61 mg, 0.219 mmol, 3 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at 80 °C under nitrogen

atmosphere. The reaction was monitored by LCMS. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by Prep-HPLC using a X Bridge Prep OBD C18 150 mm x 30 mm x 5 μm column (eluent: 27% to 45% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford (2S)-2-[4-(4-cyano-6-oxo-1H-pyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl]-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (13.2 mg, 33.25%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{25}F_2N_7O_4$:537.2 m/z, found:538.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.42 (s, 1H), 8.83 (d, *J* = 1.2 Hz, 1H), 8.45 (d, *J* = 1.2 Hz, 1H), 7.71 (s, 1H), 7.50 – 7.45 (m, 2H), 7.21 – 7.16 (m, 1H), 6.99 (s, 1H), 3.52 (d, *J* = 7.1 Hz, 1H), 2.70 (s, 1H), 2.63 (s, 1H), 2.51 – 2.42 (m, 2H), 1.43 (d, *J* = 2.1 Hz, 6H), 1.19 (d, *J* = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.42 (d, *J* = 6.3 Hz), -124.21 (d, *J* = 6.2 Hz).

Example 162: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(4-methyl-5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide

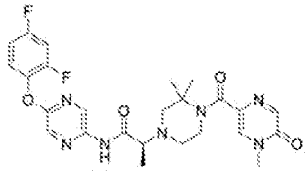


Synthetic Scheme



4-methyl-5-oxo-4,5-dihydropyrazine-2-carboxylic acid

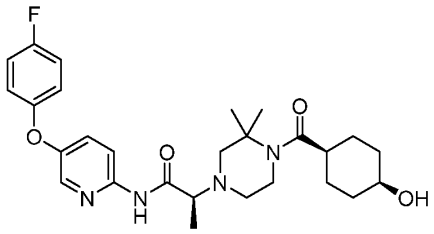
To a solution of methyl 4-methyl-5-oxopyrazine-2-carboxylate (500 mg, 2.974 mmol, 1 equiv) in THF (5 mL). methanol (2.5 mL, 0.078 mmol, 0.03 equiv) and water (2.5 mL, 0.139 mmol, 0.05 equiv) added at rt. The resulting mixture was stirred for 2h at rt. The resulting mixture was concentrated under vacuum. The residue was acidified to pH 2~3 with 3N HCl. The precipitated solids were collected by filtration and washed with H_2O (5 mL) to afford 4-methyl-5-oxopyrazine-2-carboxylic acid (280 mg, 61.10%) as a yellow solid. MS (ESI): mass calcd. for $C_6H_6N_2O_3$:154.04m/z, found:155.10[M+H$^+$.



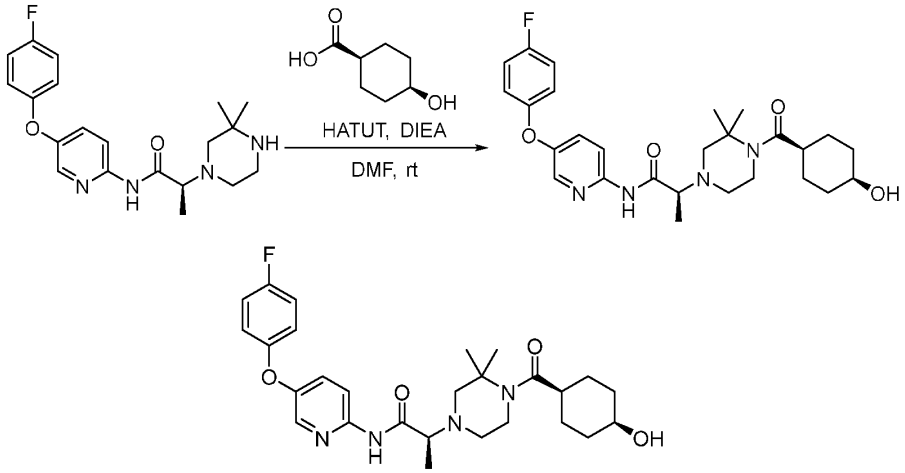
(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(4-methyl-5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide

To a solution of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (50 mg, 0.128 mmol, 1 equiv) in DMF (5 mL). methyl 4-methyl-5-oxopyrazine-2-carboxylate (21.48 mg, 0.128 mmol, 1 equiv), HATU (72.86 mg, 0.192 mmol, 1.5 equiv) and DIEA (33.02 mg, 0.256 mmol, 2 equiv) added at rt. The resulting mixture was stirred for 2h at rt. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-15% DCM/MeOH) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 32% to 62% ACN and H_2O (10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (14.9 mg, 21.98%) as a white solid, MS (ESI): mass calcd. for $C_{25}H_{27}F_2N_7O_4$:527.21m/z, found:528.30[M+H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.12 (s, 1H), 7.91 (d, J = 1.0 Hz, 1H), 7.41 – 7.54 (m, 2H), 7.12 – 7.22 (m, 1H), 3.45 – 3.57 (m, 6H), 2.56 – 2.78 (m, 2H), 2.36 – 2.47 (m, 2H), 1.44 (d, J = 2.8 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -113.4369, -124.2187.

Example 163: (S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-((1s,4R)-4-hydroxycyclohexane-1-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide



Synthetic Scheme

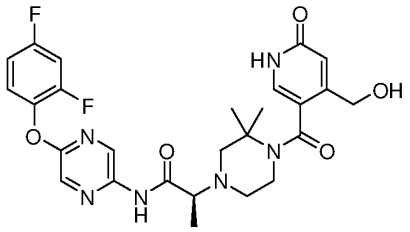


(S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-((1s,4R)-4-hydroxycyclohexane-1-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

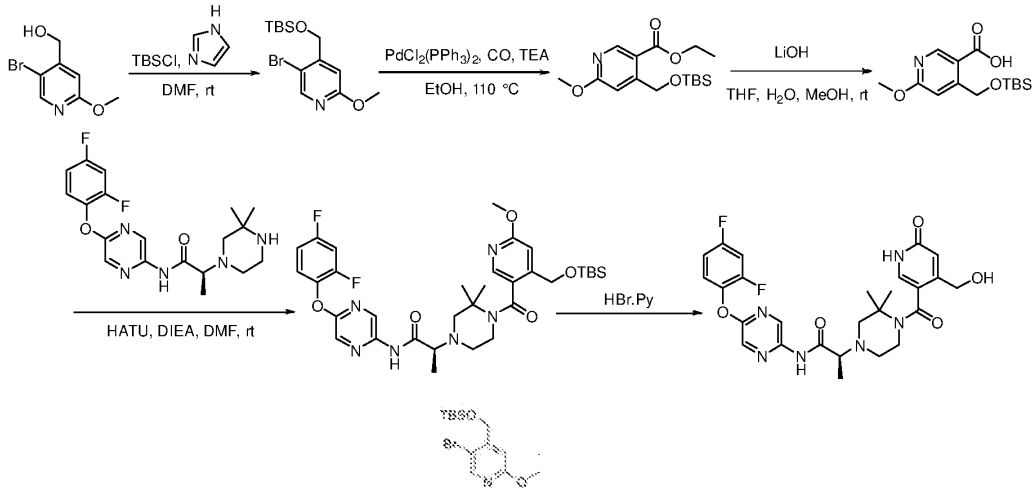
To a solution of (S)-2-(3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (50 mg, 0.134 mmol, 1 equiv) in DMF (2 mL). (1s,4s)-4-hydroxycyclohexane-1-carboxylic acid (96.77 mg, 0.670 mmol, 5 equiv), HATU (76.57 mg, 0.201 mmol, 1.5 equiv) and DIEA (86.76 mg, 0.670 mmol, 5 equiv) added at rt. The resulting mixture was stirred for 12h at rt. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-15% DCM/MeOH) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 36% to 66% ACN and H_2O (10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-((1s,4R)-4-hydroxycyclohexane-1-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (8.1 mg, 12.02%) as a white solid, MS (ESI): mass calcd. for $C_{27}H_{35}FN_4O_4$:498.26m/z, found:499.30$[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.14 (dd, J = 6.0, 2.9

Hz, 2H), 7.53 (dd, *J* = 9.1, 2.9 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.02 – 7.16 (m, 2H), 4.27 (d, *J* = 3.0 Hz, 1H), 3.74 (d, *J* = 4.7 Hz, 1H), 3.39 – 3.54 (m, 3H), 2.63 – 2.75 (m, 1H), 2.51 – 2.63 (m, 1H), 2.44 – 2.48 (m, 1H), 2.31 (s, 2H), 1.54 – 1.79 (m, 4H), 1.26 – 1.50 (m, 10H), 1.19 (d, *J* = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -119.839.

Example 164: (*S*)-*N*-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(4-(hydroxymethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide



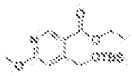
Synthetic Scheme



5-bromo-4-(((tert-butyldimethylsilyl)oxy)methyl)-2-methoxypyridine

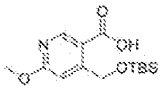
To a stirred solution of (5-bromo-2-methoxypyridin-4-yl)methanol (2 g, 9.172 mmol, 1 equiv) in DMF (15 mL) was added t-butyldimethylchlorosilane (2.07 g, 13.758 mmol, 1.5 equiv) and imidazole (1.87 g, 27.516 mmol, 3 equiv) at room temperature. The reaction mixture was stirred at room temperature for a period of overnight. After completion of reaction, the reaction mixture was quenched by water (30 mL) and extracted with EA (100 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel

chromatography (0-20% PE/EA) to afford 5-bromo-4-{[(tert-butyldimethylsilyl)oxy]methyl}-2-methoxypyridine (2.1 g, 68.90%) as a white solid. MS (ESI): mass calcd. for $C_{13}H_{22}BrNO_2Si$: 332.313 m/z, found: 333.10[M+H]$^+$.



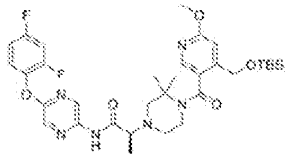
ethyl 4-(((tert-butyldimethylsilyl)oxy)methyl)-6-methoxynicotinate

To a stirring solution 5-bromo-4-{[(tert-butyldimethylsilyl)oxy]methyl}-2-methoxypyridine (0.5 g, 1.505 mmol, 1 equiv) in EtOH (30 mL) was added a solution of TEA (0.46 g, 4.515 mmol, 3 equiv) and Bis(triphenylphosphine)palladium(II) chloride,Dichlorobis(triphenylphosphine)palladium(II) (0.06 g, 0.090 mmol, 0.06 equiv). The mixture was stirred at 110 °C for 18 h under CO. The mixture was concentrated to dryness under reduced pressure to provide the crude product, which was purified by silica gel chromatography (0-80% PE/EA) to afford ethyl ethyl 4-(((tert-butyldimethylsilyl)oxy)methyl)-6-methoxynicotinate (1 g, 63.81%) as a yellow oil. MS (ESI): mass calcd. for $C_{16}H_{27}NO_4Si$: 325.48 m/z, found: 326.25 [M+H]$^+$.



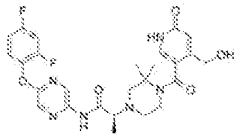
4-(((tert-butyldimethylsilyl)oxy)methyl)-6-methoxynicotinic acid

To a solution of ethyl 4-(((tert-butyldimethylsilyl)oxy)methyl)-6-methoxynicotinate (1 g, 3.072 mmol, 1 equiv) in water (2 mL) , methanol (2 mL) and tetrahydrofuran (4 mL) was added lithiumol (0.07 g, 3.072 mmol, 1 equiv) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The mixture was acidified pH = 5 with HCl (1N). The aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) to afford 4-(((tert-butyldimethylsilyl)oxy)methyl)-6-methoxynicotinic acid (80 mg, 8.75%) as a white solid. MS (ESI): mass calcd. for $C_{14}H_{23}NO_4Si$:297.426 m/z, found 298.20 [M+H]$^+$.



(*S*)-2-(4-(4-(((tert-butyldimethylsilyl)oxy)methyl)-6-methoxynicotinoyl)-3,3-dimethylpiperazin-1-yl)-*N*-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

To a stirred solution of 4-(((tert-butyldimethylsilyl)oxy)methyl)-6-methoxynicotinic acid (100 mg, 0.336 mmol, 1 equiv) in DMF (1 mL) was added (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (197.41 mg, 0.504 mmol, 1.5 equiv) and HATU (191.76 mg, 0.504 mmol, 1.5 equiv) and DIEA (86.91 mg, 0.672 mmol, 2 equiv). The reaction mixture was stirred at room temperature for a period of overnight. After completion of reaction, the reaction mixture was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford (S)-2-(4-(4-(((tert-butyldimethylsilyl)oxy)methyl)-6-methoxynicotinoyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (30 mg, 13.30%) as a white solid. MS (ESI): mass calcd. for $C_{33}H_{44}F_2N_6O_5Si$: 670.834 m/z, found: 693.50 $[M+H]^+$.

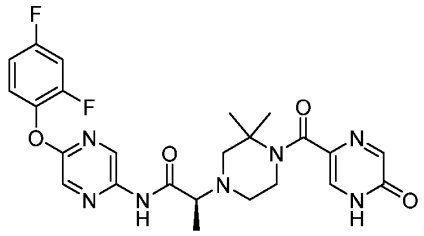


(*S*)-*N*-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(4-(hydroxymethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

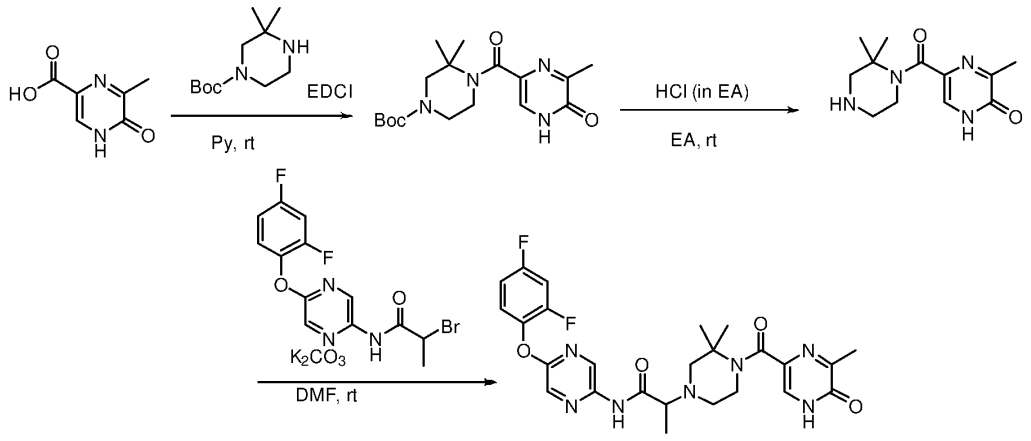
To a solution of (S)-2-(4-(4-(((tert-butyldimethylsilyl)oxy)methyl)-6-methoxynicotinoyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (80 mg, 0.119 mmol, 1 equiv) in dimethylformamide (5 mL) was added pyridine hydrobromide (95.41 mg, 0.595 mmol, 5 equiv) at rt. The resulting mixture was stirred for 2 hours at 80 °C. After cooled to room temperature, the reaction was quenched by EA (10 mL) and extracted with water (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) and by

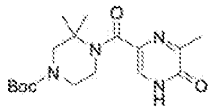
preparative HPLC using a XBridge Prep OBD 150 mm x 30 mm x 5 μm column (eluent: 21% to 51% (v/v) ACN and H_2O with 10 mmol/L NH_4HCO_3) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(4-(hydroxymethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (34.9 mg, 53.85%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{28}F_2N_6O_5$: 542.544 m/z, found 543.30 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 11.46 (s, 1H), 10.39 (s, 1H), 8.83 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.39 – 7.55 (m, 2H), 7.26 (s, 1H), 7.10 – 7.23 (m, 1H), 6.39 (s, 1H), 5.29 (t, J = 5.5 Hz, 1H), 4.32 (d, J = 5.5 Hz, 2H), 3.51 (q, J = 6.8 Hz, 1H),3.33(s, 2H), 2.60 – 2.69(m, 1H), 2.55 (s, 1H), 2.39 (s, 2H), 1.42 (d, J = 1.9 Hz, 6H), 1.18 (d, J = 6.9 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -113.43 (d, J = 5.2 Hz), -124.22 (d, J = 5.4 Hz).

Example 165: N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-methyl-5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide



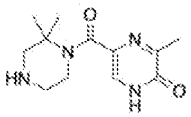
Synthetic Scheme





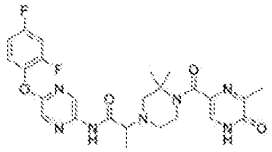
tert-butyl 3,3-dimethyl-4-(6-methyl-5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazine-1-carboxylate

To a solution of 6-methyl-5-oxo-4,5-dihydropyrazine-2-carboxylic acid (100 mg, 0.065 mmol, 1 equiv) in pyridine (1ml). tert-butyl 3,3-dimethylpiperazine-1-carboxylate (13.90 mg, 0.065 mmol, 1 equiv) and EDCI (24.88 mg, 0.130 mmol, 2 equiv) was added at rt. The mixture was allowed to warm to RT and stirred for 2 h.The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-15% DCM/MeOH) to afford tert-butyl 3,3-dimethyl-4-(6-methyl-5-oxo-4H-pyrazine-2-carbonyl)piperazine-1-carboxylate (110 mg, 24.19%) as a yellow oil, MS (ESI): mass calcd. for $C_{17}H_{26}N_4O_4$:350.20 m/z, found:351.15$[M+H]^+$.



5-(2,2-dimethylpiperazine-1-carbonyl)-3-methylpyrazin-2(1H)-one

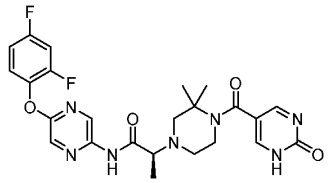
To a solution of tert-butyl 3,3-dimethyl-4-(6-methyl-5-oxo-4 H-pyrazine-2-carbonyl)piperazine-1-carboxylate (130 mg, 0.371 mmol, 1 equiv) in EA (5 mL). 4N HCl in EA (5 mL) was added at 0 °C. The mixture was allowed to warm to RT and stirred for 2 h. The resulting mixture was concentrated under vacuum. The precipitated solids were collected by filtration and washed with diethyl ether (20 mL) to afford 5-(2,2-dimethylpiperazine-1-carbonyl)-3-methylpyrazin-2(1H)-one (110 mg, 118.46%) as a yellow oil, MS (ESI): mass calcd. for $C_{12}H_{18}N_4O_2$:250.14m/z, found:251.15$[M+H]^+$.



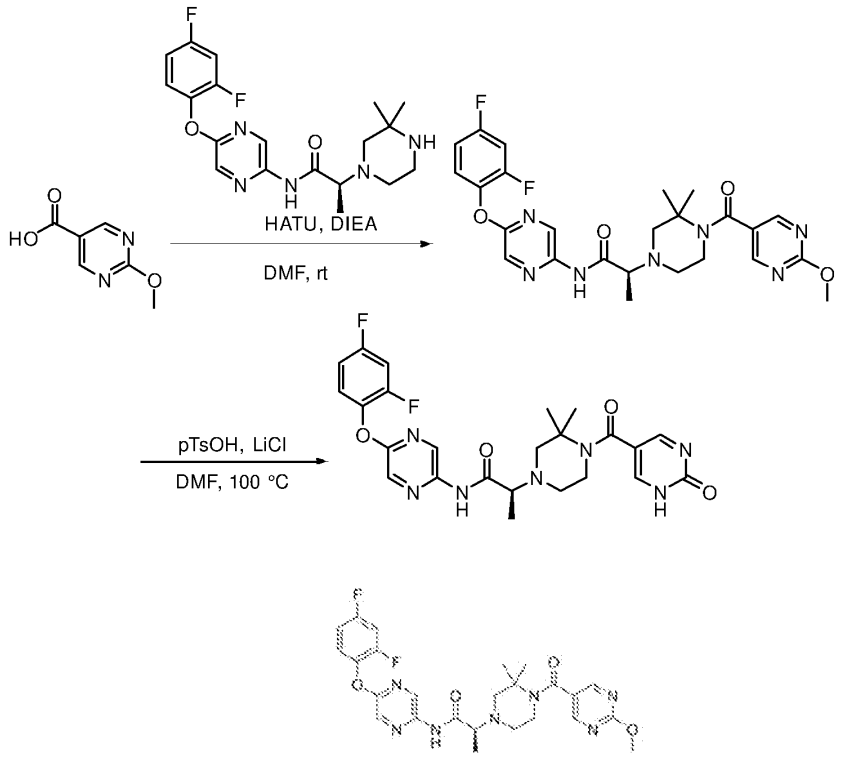
tert-butyl 3,3-dimethyl-4-(6-methyl-5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazine-1-carboxylate

To a solution of 5-(2,2-dimethylpiperazine-1-carbonyl)-3-methylpyrazin-2(1H)-one (80 mg, 0.320 mmol, 1 equiv) in DMF (3ml). potassium methaneperoxoate potassium (88.99 mg, 0.640 mmol, 2 equiv) was added at rt. After stirring for 30 min, the mixture was allowed to warm to RT and stirred for 2 h. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-15% DCM/MeOH) and Prep-HPLC using a Column: XSelect CSH C18 Column, 19*250 mm, 5μm (eluent: 17% to 42% ACN and H_2O (0.1% FA) to afford N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-methyl-5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide (2.9 mg, 1.66%) as a white solid, MS (ESI): mass calcd. for $C_{25}H_{27}F_2N_7O_4$:527.21 m/z, found:528.30 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.39 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.58 (s, 1H), 7.39 – 7.55 (m, 2H), 7.11 – 7.24 (m, 1H), 3.50 (d, J = 4.6 Hz, 4H), 2.69 – 2.79 (m, 1H), 2.58 – 2.68 (m, 1H), 2.41 (s, 2H), 2.26 (s, 3H), 1.43 (s, 6H), 1.21 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.434, -124.226.

Example 166: (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-[3,3-dimethyl-4-(2-oxo-1H-pyrimidine-5-carbonyl)piperazin-1-yl]propanamide

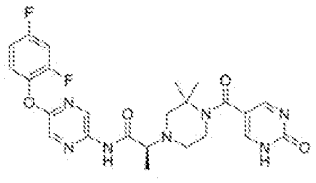


Synthetic Scheme



(2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-[4-(2-methoxypyrimidine-5-carbonyl)-3,3-dimethylpiperazin-1-yl]propanamide

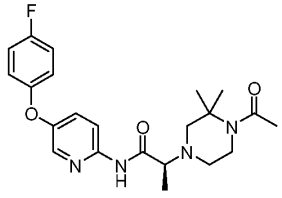
To a solution of 2-methoxypyrimidine-5-carboxylic acid (23.63 mg, 0.153 mmol, 1.00 equiv) in dimethylformamide (3 mL) was added 2-methoxypyrimidine-5-carboxylic acid (23.63 mg, 0.153 mmol, 1.00 equiv), HATU (174.86 mg, 0.459 mmol, 3 equiv), DIEA (198.12 mg, 1.530 mmol, 10 equiv) at rt. The resulting mixture was stirred for 2 h at rt. The reaction was quenched with H_2O (10 mL) at rt. The resulting mixture was extracted with EA (3*30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. The resulting mixture was filtered. The filtrate was concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20% DCM/MeOH) to afford crude product; Flow rate: 60 mL/min mL/min; Gradient: 5% B to 25% B in 7min; ct Wave Length: 254nm/220nm nm; RT1 (min): 6.43) to afford (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-[4-(2-methoxypyrimidine-5-carbonyl)-3,3-dimethylpiperazin-1-yl]propanamide) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{27}F_2N_7O_4$: 527.21, found: 528.15 $[M+H]^+$.



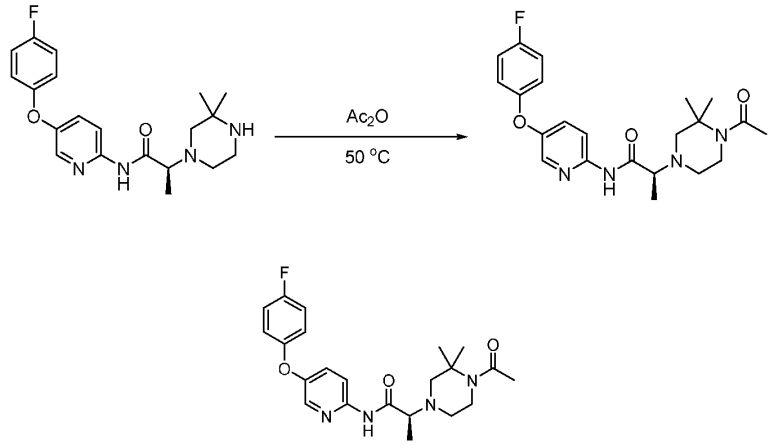
(2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-[3,3-dimethyl-4-(2-oxo-1H-pyrimidine-5-carbonyl)piperazin-1-yl]propanamide

To a solution of (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-[4-(2-methoxypyrimidine-5-carbonyl)-3,3-dimethylpiperazin-1-yl]propanamide (50 mg, 0.095 mmol, 1 equiv) in DMF (3 mL) was added 4-methylbenzenesulfonic acid (81.61 mg, 0.475 mmol, 5 equiv) lithium chloride (40.18 mg, 0.950 mmol, 10 equiv) at rt. The resulting mixture was stirred for 2 h at 100°C. The reaction was quenched with H_2O (10 mL) at rt. The resulting mixture was extracted with EA (3*30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. The resulting mixture was filtered. The filtrate was concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20% DCM/MeOH) to afford crude product ; Flow rate: 60 mL/min mL/min; Gradient: 5% B to 25% B in 7min; ct Wave Length: 254nm/220nm nm; RT1(min): 6.43) to afford(2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-[3,3-dimethyl-4-(2-oxo-1H-pyrimidine-5-carbonyl)piperazin-1-yl]propanamide (11.4 mg, 23.19%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{27}F_2N_7O_4$: 513.19, found: 514.20 $[M+H]^+$.

Example 167: (S)-2-(4-acetyl-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide



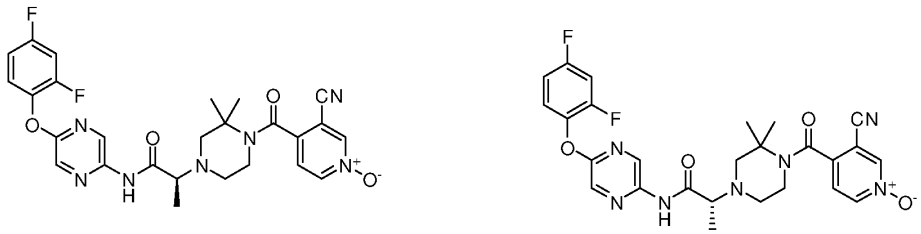
Synthetic Scheme



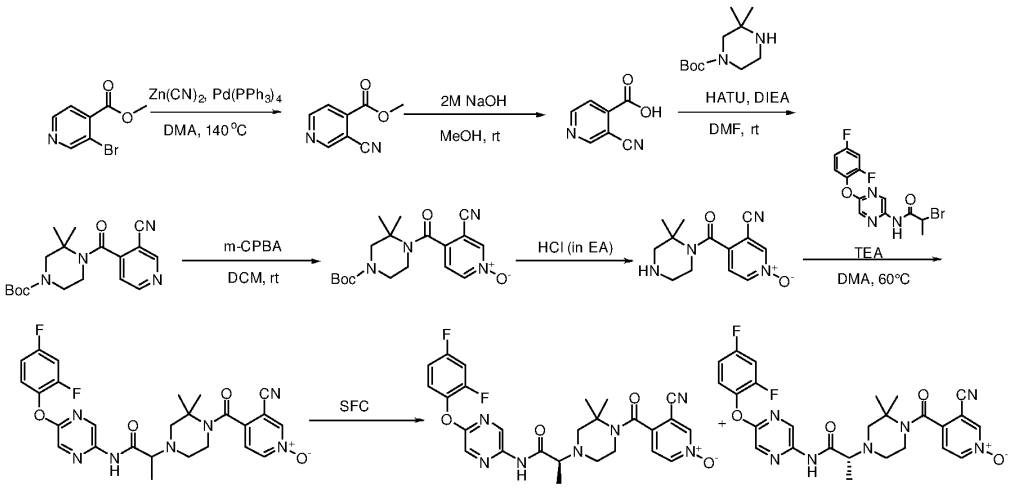
(S)-2-(4-acetyl-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

To a solution of (S)-2-(3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (50 mg, 0.134 mmol, 1 equiv) was added acetic acid (3 mL, 0.050 mmol, 0.37 equiv) at rt. The mixture was allowed to warm to 50°C and stirred for 12h. The resulting mixture was concentrated under vacuum. The residue was purified by C18 column (CH_3CN & H_2O with 0.05% FA) afford (S)-2-(4-acetyl-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (8.5 mg, 15.20%) as a white solid, MS (ESI): mass calcd. for $C_{22}H_{27}FN_4O_3$:414.21m/z, found:415.20$[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.11 – 8.17 (m, 2H), 7.52 (dd, J = 9.1, 2.9 Hz, 1H), 7.18 – 7.29 (m, 2H), 7.04 – 7.14 (m, 2H), 3.36 – 3.48 (m, 3H), 2.64 – 2.74 (m, 1H), 2.52 – 2.61 (m, 1H), 2.31 (s, 2H), 1.96 (s, 3H), 1.37 (d, J = 3.6 Hz, 6H), 1.18 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -119.82, -119.8229.

Example 168: 3-cyano-4-{4-[(1S)-1-{[5-(2,4-difluorophenoxy)pyrazin-2-yl] carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}pyridin-1-ium-1-olate and Example 169: 3-cyano-4-{4-[(1R)-1-{[5-(2,4-difluorophenoxy)pyrazin-2-yl] carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}pyridin-1-ium-1-olate



Synthetic Scheme





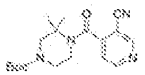
methyl 3-cyanopyridine-4-carboxylate

To a solution of methyl 3-bromopyridine-4-carboxylate (1 g, 4.629 mmol, 1 equiv) and $Zn(CN)_2$ (0.54 g, 4.629 mmol, 1 equiv) in DMA (10 mL) were added $Pd(PPh_3)_4$ (0.27 g, 0.231 mmol, 0.05 equiv). After stirring for 2 h at 140 °C under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel C18 chromatography, eluted with CH_3CN/H_2O to afford methyl 3-cyanopyridine-4-carboxylate (0.75 g, 96.6%)as a white solid. MS (ESI): mass calcd. for $C_8H_6N_2O_2$ 162.14 m/z, found 163.15 $[M+H]^+$.



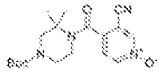
3-cyanopyridine-4-carboxylic acid

To a solution of methyl 3-cyanopyridine-4-carboxylate (600 mg, 3.700 mmol, 1 equiv) in MeOH (8 mL) were added NaOH (2 mL) at rt. After stirring for 2h at rt. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel C18 chromatography, eluted with CH_3CN/H_2O to afford 3-cyanopyridine-4-carboxylic acid (270 mg, 49.26%) as a white solid. MS (ESI): mass calcd. for $C_7H_4N_2O_2$ 148.12 m/z, found 149.05$[M+H]^+$.



tert-butyl 4-(3-cyanopyridine-4-carbonyl)-3,3-dimethylpiperazine-1-carboxylate

To a degassed solution of 3-cyanopyridine-4-carboxylic acid (740 mg, 4.996 mmol, 1 equiv) in DMF (12 mL) was added tert-butyl 3,3-dimethylpiperazine-1-carboxylate (1070.67 mg, 4.996 mmol, 1 equiv) followed by HATU (2849.43 mg, 7.494 mmol, 1.5 equiv) and DIEA (1291.41 mg, 9.992 mmol, 2 equiv) at room temperature. The reaction mixture was stirred at room temperature for 3h. After completion of the reaction, the reaction mixture was quenched with saturated sodium H_2O 30 mL. The aqueous layer was extracted with ethyl acetate (120 mL). Then, the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4. Purified by column chromatography on silica gel (Combiflash) (DCM/MeOH) to afford tert-butyl 4-(3-cyanopyridine-4-carbonyl)-3,3-dimethylpiperazine-1-carboxylate (0.7 g, 42.9%). MS (ESI): mass calcd. for $C_{18}H_{24}N_4O_3$ 344.18 m/z, found 345.10 $[M+H]^+$.



4-[4-(tert-butoxycarbonyl)-2,2-dimethylpiperazine-1-carbonyl]-3-cyanopyridin-1-ium-1-olate

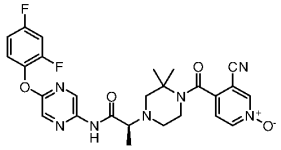
To a solution of tert-butyl 4-(3-cyanopyridine-4-carbonyl)-3,3-dimethylpiperazine-1-carboxylate (700 mg, 2.032 mmol, 1 equiv) in DCM (10 mL) was added m-CPBA (1227.51 mg, 7.112 mmol, 3.5 equiv) at 0°C. The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water and extracted with EA (3*50 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford product 4-[4-(tert-butoxycarbonyl)-2,2-dimethylpiperazine-1-

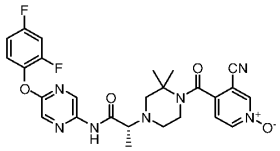
carbonyl]-3-cyanopyridin-1-ium-1-olate) (0.2 g, 30.5%) as a white solid. MS (ESI): mass calcd. for $C_{18}H_{24}N_4O_4$ 360.18 m/z, found 361.15$[M+H]^+$.



3-cyano-4-(2,2-dimethylpiperazine-1-carbonyl)pyridin-1-ium-1-olate

To a solution of 4-[4-(tert-butoxycarbonyl)-2,2-dimethylpiperazine-1-carbonyl]-3-cyanopyridin-1-ium-1-olate (200 mg, 0.555 mmol, 1 equiv) in EA (3mL) was added HCI in (EA) (6 mL) at 0 degrees C. The resulting mixture was stirred for 2h at rt. The residue was washed with diethyl ether (20 mL). The precipitated solids were collected by filtration and washed with diethyl ether (3x50 mL). The crude product mixture was used in the next step directly without further purification. MS (ESI): mass calcd. for $C_{13}H_{16}N_4O_2$ 260.13 m/z, found 261.25$[M+H]^+$.



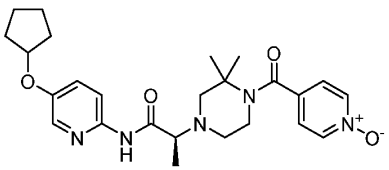


3-cyano-4-{4-[(1S)-1-{[5-(2,4-difluorophenoxy)pyrazin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}pyridin-1-ium-1-olate and 3-cyano-4-{4-[(1R)-1-{[5-(2,4-difluorophenoxy)pyrazin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}pyridin-1-ium-1-olate

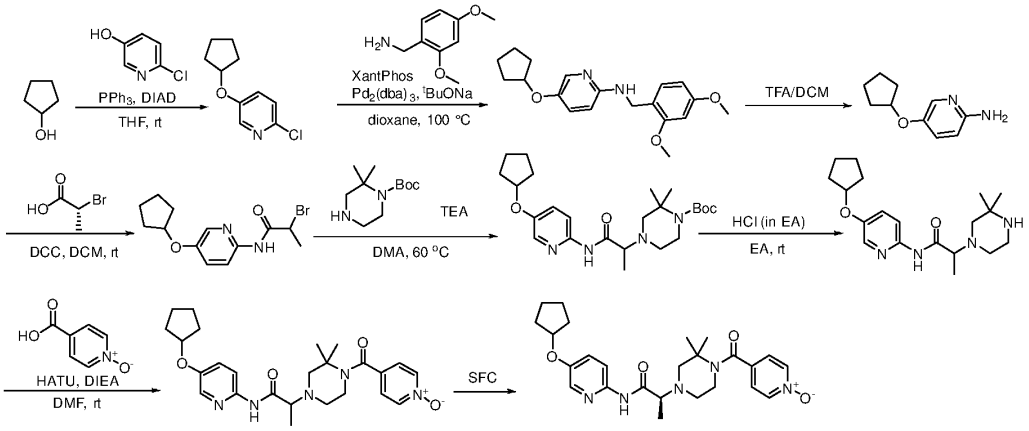
To a solution of 3-cyano-4-(2,2-dimethylpiperazine-1-carbonyl)pyridin-1-ium-1-olate (100 mg, 0.384 mmol, 1 equiv) in DMA (3 mL) was added 2-bromo-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (137.59 mg, 0.384 mmol, 1 equiv) and TEA (116.63 mg, 1.152 mmol, 3 equiv) at rt. The resulting mixture was stirred for overnight at 60 degrees C. The reaction mixture was quenched by water and extracted with EA (3*50 mL).The combined organic extracts were washed with brine (10mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20% DCM/MeOH) to afford a white solid. The compound was separated by preparative HPLC (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm ,column (eluent: 50% (v/v); Mobile Phase A: Hex: DCM=3: 1(0.5% 2M NH_3-MeOH) to afford (3-cyano-4-{4-[(1S)-1-{[5-(2,4-difluorophenoxy)pyrazin-2-yl]carbamoyl} ethyl]-2,2-dimethylpiperazine-1-carbonyl}pyridin-1-ium-1-olate (9.7 mg, 4.64%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{25}F_2N_7O_4$ 537.19 m/z, found 538.30$[M+H]^+$.^{1}H NMR (300 MHz,

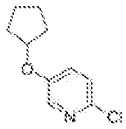
DMSO-d_6) δ 10.44 (s, 1H), 8.80 – 8.94 (m, 2H), 8.43 – 8.52 (m, 2H), 7.59 (d, J = 6.8 Hz, 1H), 7.48 (tq, J = 9.2, 6.0, 4.4 Hz, 2H), 7.18 (t, J = 8.4 Hz, 1H), 3.49 – 3.59 (m, 1H), 2.54 – 2.75 (m, 3H), 2.44 – 2.49 (m, 3H), 1.50 (d, J = 2.3 Hz, 6H), 1.18 – 1.26 (m, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -113.43 (d, J = 5.3 Hz), -124.23 (d, J = 5.2 Hz). And 3-cyano-4-{4-[(1R)-1-{[5-(2,4-difluorophenoxy)pyrazin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}pyridin-1-ium-1-olate (7.4 mg, 3.58%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{25}F_2N_7O_4$ 537.19 m/z, found 538.30 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.44 (s, 1H), 8.91 (d, J = 1.8 Hz, 1H), 8.83 (d, J = 1.5 Hz, 1H), 8.42 – 8.52 (m, 2H), 7.59 (d, J = 6.8 Hz, 1H), 7.48 (qd, J = 9.0, 4.3 Hz, 2H), 7.18 (t, J = 8.8 Hz, 1H), 3.55 (q, J = 6.1, 5.3 Hz, 1H), 2.56 – 2.74 (m, 2H), 2.41 – 2.48 (m, 4H), 1.50 (d, J = 2.4 Hz, 6H), 1.18 – 1.26 (m, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -113.44 (d, J = 5.5 Hz), -124.23 (d, J = 5.3 Hz).

Example 170: (S)-4-(4-(1-((5-(cyclopentyloxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide



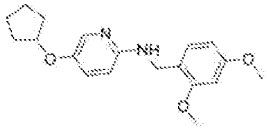
Synthetic Scheme





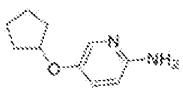
2-chloro-5-(cyclopentyloxy)pyridine

To a solution of cyclopentanol (1 g, 11.610 mmol, 1 equiv) in tetrahydrofuran (20 mL) was treated with 6-chloropyridin-3-ol (1.50 g, 11.610 mmol, 1 equiv) for 3 min at 0 °C under nitrogen atmosphere followed by the addition of triphenylphosphine (4.57 g, 17.415 mmol, 1.5 equiv) and diisopropyl azodicarboxylate (3.52 g, 17.415 mmol, 1.5 equiv) dropwise/ in portions at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (20 mL) and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to give 2-chloro-5-(cyclopentyloxy)pyridine (1.8g, 78.60%) a white solid. MS (ESI): mass calcd. for $C_{10}H_{12}ClNO$: 197.06, found: 198.10$[M+H]^+$.



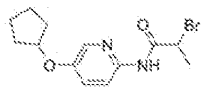
5-(cyclopentyloxy)-N-(2,4-dimethoxybenzyl)pyridin-2-amine

To a solution of 2-chloro-5-(cyclopentyloxy)pyridine (500 mg, 2.530 mmol, 1 equiv) in dioxane (10 mL) was treated with 1-(2,4-dimethoxyphenyl)methanamine (422.97 mg, 2.530 mmol, 1 equiv) under nitrogen atmosphere followed by the addition of XantPhos (608.74 mg, 1.012 mmol, 0.4 equiv), $Pd_2(dba)_3$ (463.29 mg, 0.506 mmol, 0.2 equiv) and ^{t}BuONa (369.91 mg, 5.060 mmol, 2 equiv) at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (20 mL) and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% EA/PE) to give 5-(cyclopentyloxy)-N-[(2,4-dimethoxyphenyl)methyl]pyridin-2-amine (620mg, 74.6%) a white solid. MS (ESI): mass calcd. for $C_{19}H_{24}N_2O_3$: 328.06, found: 329.10$[M+H]^+$.



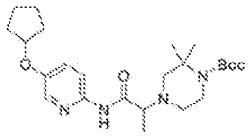
5-(cyclopentyloxy)pyridin-2-amine

To a solution of 5-(cyclopentyloxy)-N-[(2,4-dimethoxyphenyl)methyl]pyridin-2-amine (400 mg, 1.218 mmol, 1 equiv) in DCM (4 mL, 62.922 mmol, 51.66 equiv) was added TFA (1 mL) . The reaction mixture was stirred at room temperature for 1 h. The product was precipitated by the addition of diethyl ether to afford (150 mg, 69.12%) as a white solid. MS (ESI): mass calcd. for $C_{10}H_{14}N_2O$:178.20, found:179.25 $[M+H]^+$.



2-bromo-N-(5-(cyclopentyloxy)pyridin-2-yl)propanamide

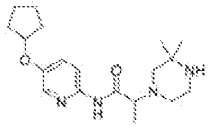
To a solution of 5-(cyclopentyloxy)pyridin-2-amine (500 mg, 2.805 mmol, 1 equiv) in anhydrous DCM (10 mL) was added (2R)-2-bromopropanoic acid (472.05 mg, 3.086 mmol, 1.1 equiv) and DCC (694.59 mg, 3.366 mmol, 1.2 equiv) at room temperature. After completion of reaction, the reaction mixture was quenched by addition of water (50 mL). The aqueous layer was extracted with DCM (100 mL x 3). The combined organic phase was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-80% PE/EA) to afford 2-bromo-N-[5-(cyclopentyloxy)pyridin-2-yl]propanamide (420 mg, 47.80%). MS (ESI): mass calcd. For $C_{13}H_{17}BrN_2O_2$: 313.19 m/z, found: 324.20 $[M+H]^+$.



tert-butyl (S)-4-(1-((5-(cyclopentyloxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carboxylate

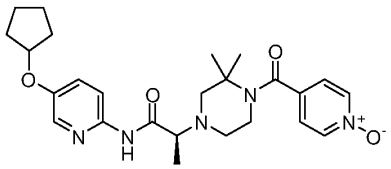
To a solution of 2-bromo-N-[5-(cyclopentyloxy)pyridin-2-yl]propanamide (400 mg, 1.277 mmol, 1 equiv) in dimethylformamide (10 mL) the mixture was added tert-butyl 2,2-dimethylpiperazine-1-carboxylate (273.71 mg, 1.277 mmol, 1 equiv) and TEA (387.72 mg, 3.831 mmol, 3 equiv) at rt. The resulting mixture was stirred for 2 hours at 60 °C. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% EA/PE) to give tert-butyl 4-[(1S)-1-{[5-(cyclopentyloxy)pyridin-2-yl]carbamoyl}

ethyl]-2,2-dimethylpiperazine-1-carboxylate (480 mg, 84.21%) as a white solid. MS (ESI): mass calcd. for $C_{24}H_{38}N_4O_4$: 446.28, found: 447.20 $[M+H]^+$.



(S)-N-(5-(cyclopentyloxy)pyridin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide

To a solution of tert-butyl 4-[(1S)-1-{[5-(cyclopentyloxy)pyridin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carboxylate (300 mg, 0.672 mmol, 1 equiv) in EA (3 mL) was added HCl (4 M in EA, 3 mL). The reaction mixture was stirred at room temperature for 1 h. The product was precipitated by the addition of diethyl ether. The product is obtained (180 mg, 78.26%) by filtration and drying. MS (ESI): mass calcd. for $C_{19}H_{30}N_4O_2$: 346.23, m/z, found: 347.20 $[M+H]^+$.

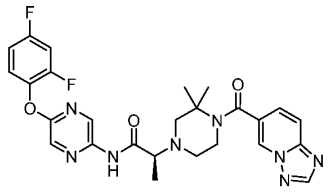


(S)-4-(4-(1-((5-(cyclopentyloxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

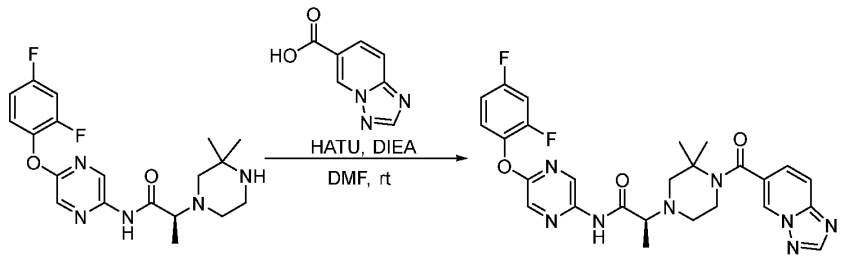
To a stirring solution N-[5-(cyclopentyloxy)pyridin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (100 mg, 0.289 mmol, 1 equiv) in dimethylformamide (10 mL) the mixture was added isonicotinic acid N-oxide (40.15 mg, 0.289 mmol, 1 equiv), HATU (164.62 mg, 0.433 mmol, 1.5 equiv) and N,N-diisopropylethylamine (149.21 mg, 1.156 mmol, 4 equiv) at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to give crude product. The product was separated by Chiral-Prep-HPLC (CHIRALPAK IG, 2*25 cm, 5 μm column (eluent: 50% (v/v) ; Mobile Phase A: MtBE(0.5% 2M NH_3-MeOH) to afford (S)-4-(4-(1-((5-(cyclopentyloxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (major isomer, 6 mg, 4.43%) as a white solidt. MS (ESI): mass calcd. for $C_{25}H_{33}N_5O_4$: 467.25, found: 468.25 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H), 8.19 – 8.25 (m, 2H), 7.96 – 8.07 (m, 2H), 7.38 – 7.46 (m, 3H), 4.85 (s, 1H), 3.48 (dd, J = 14.9, 8.4 Hz, 1H), 2.54 – 2.77 (m, 4H),

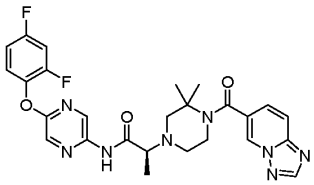
2.45 (d, *J* = 2.5 Hz, 2H), 1.88 – 1.94 (m, 2H), 1.70 (s, 4H), 1.60 (d, *J* = 9.2 Hz, 2H), 1.46 (d, *J* = 3.7 Hz, 6H), 1.16 – 1.22 (m, 3H).

Example 171: (S)-2-(4-([1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide



Synthetic Scheme



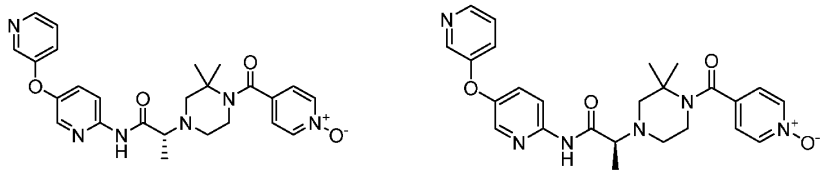


(S)-2-(4-([1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

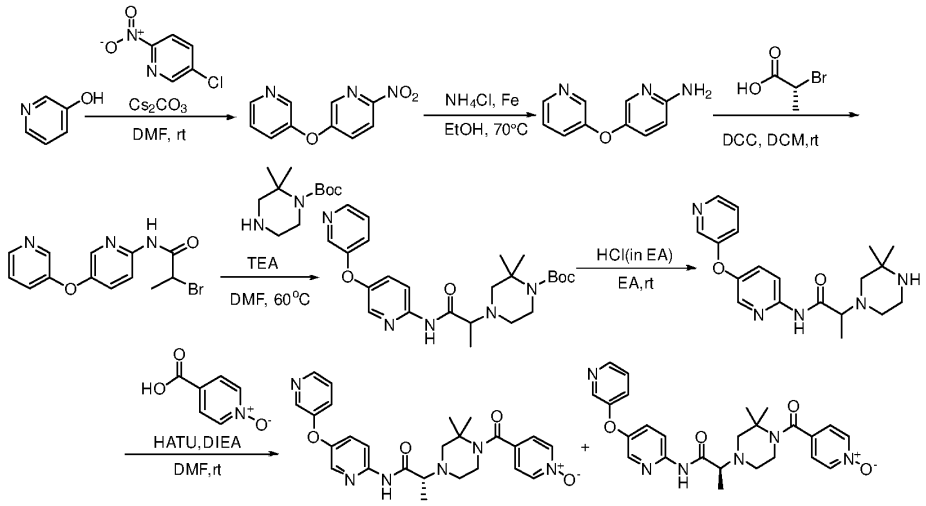
To a stirred solution of [1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid (31.26 mg, 0.192 mmol, 1.5 equiv) in DMF (1 mL) was added (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (50 mg, 0.128 mmol, 1.00 equiv) and HATU (72.86 mg, 0.192 mmol, 1.5 equiv) and DIEA (49.53 mg, 0.384 mmol, 3 equiv) at room temperature. The reaction mixture was stirred at room temperature for 3 h. The resulting

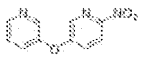
mixture was stirred for additional overnight at room temperature. After completion of reaction, the reaction mixture was quenched by addition of water (5 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) the residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30 x150mm x 5µm (eluent: 36% to 66% (v/v) CH_3CN and H_2O with NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-2-(4-([1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (21.2 mg, 30.72%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{26}F_2N_8O_3$: 536.21 m/z, found: 537.30 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6) δ 10.44 (s, 1H), 9.09 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.59 (s, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.88 (d, J = 9.1 Hz, 1H), 7.67 (dd, J = 9.2, 1.7 Hz, 1H), 7.42 – 7.55 (m, 2H), 7.18 (s, 1H), 3.56 (t, J = 6.9 Hz, 1H), 2.60 – 2.79 (m, 3H), 2.46 (d, J = 11.7 Hz, 3H), 1.49 (d, J = 4.1 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H).^{19}F NMR (376 MHz, DMSO-d_6) δ -113.41 (d, J = 5.4 Hz), -124.20 (d, J = 5.4 Hz).

Example 172: (R)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(pyridin-3-yloxy)pyridin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide and Example 173: (S)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(pyridin-3-yloxy)pyridin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide



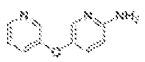
Synthetic Scheme





2-nitro-5-(pyridin-3-yloxy)pyridine

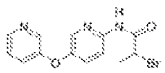
To a solution of 3-hydroxypyridine (1 g, 10.515 mmol, 1 equiv) in DMF (20 mL) the mixture was added 5-chloro-2-nitropyridine (1.67 g, 10.515 mmol, 1 equiv) and Cs_2CO_3 (6.87 g, 21.030 mmol, 2 equiv) at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (20 mL) and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% EA/PE) to give 2-nitro-5-(pyridin-3-yloxy)pyridine (1.1 g, 48.17%) a white solid. MS (ESI): mass calcd. for $C_{10}H_7N_3O_3$: 217.04, found: 218.20 $[M+H]^+$.



5-(pyridin-3-yloxy)pyridin-2-amine

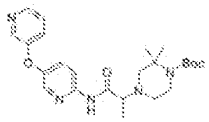
To a solution of 2-nitro-5-(pyridin-3-yloxy)pyridine (800 mg, 3.684 mmol, 1 equiv) in ethyl alcohol (10 mL) and water (2.5 mL) , the mixture was added iron (2.0 g, 36.840 mmol, 10 equiv) and NH_4Cl (1.0 g, 18.810 mmol, 10 equiv). The mixture was stirred at 70°C for 1 h. After cooled to room temperature the reaction was quenched by water (20 mL) and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue

obtained was purified by silica gel chromatography (0-100% PE/EA) to give 5-(pyridin-3-yloxy)pyridin-2-amine (600 mg, 87.01%) as a white solid. MS (ESI): mass calcd. for $C_{10}H_9N_3O$: 187.07, found: 188.20 $M+H]^+$.



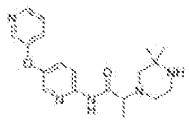
2-bromo-N-(5-(pyridin-3-yloxy)pyridin-2-yl)propanamide

To a solution of 5-(pyridin-3-yloxy)pyridin-2-amine (400 mg, 2.137 mmol, 1 equiv) in DCM (10 mL, 157.306 mmol, 73.62 equiv) the mixture was added (2R)-2-bromopropanoic acid (326.87 mg, 2.137 mmol, 1 equiv) and DCC (491.53 mg, 2.564 mmol, 1.2 equiv) at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (20 mL) and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% EA/PE) to give 2-bromo-N-[5-(pyridin-3-yloxy)pyridin-2-yl]propanamide (320 mg, 46.49%) a white solid. MS (ESI): mass calcd. for $C_{13}H_{12}BrN_3O_2$: 321.01, found: 322.10 $[M+H]^+$.



tert-butyl 2,2-dimethyl-4-(1-oxo-1-((5-(pyridin-3-yloxy)pyridin-2-yl)amino)propan-2-yl)piperazine-1-carboxylate

To a solution of 2-bromo-N-[5-(pyridin-3-yloxy)pyridin-2-yl]propanamide (300 mg, 0.931 mmol, 1 equiv) in DMF (10 mL) the mixture was added tert-butyl 2,2-dimethylpiperazine-1-carboxylate (199.57 mg, 0.931 mmol, 1 equiv) and triethylamine (282.70 mg, 2.793 mmol, 3 equiv) at rt. The resulting mixture was stirred for 2 hours at 60 °C. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% EA/PE) to give tert-butyl 2,2-dimethyl-4-(1-{[5-(pyridin-3-yloxy)pyridin-2-yl]carbamoyl}ethyl)piperazine-1-carboxylate) as a white solid. MS (ESI): mass calcd. for $C_{24}H_{33}N_5O_4$: 455.25, found: 456.20 $[M+H]^+$.



2-(3,3-dimethylpiperazin-1-yl)-N-(5-(pyridin-3-yloxy)pyridin-2-yl)propanamide

To a stirred solution of tert-butyl 2,2-dimethyl-4-(1-oxo-1-((5-(pyridin-3-yloxy)pyridin-2-yl)amino)propan-2-yl)piperazine-1-carboxylate (200 mg, 0.439 mmol, 1 equiv) in EA (3 mL) was added HCl (4 M in EA, 3 mL). The reaction mixture was stirred at room temperature for 1 h. The product was precipitated by the addition of diethyl ether. The product is obtained (142 mg, 54.24%) by filtration and drying. MS (ESI): mass calcd. for $C_{19}H_{25}N_5O2$: 355.20, m/z, found: 356.20 $[M+H]^+$.

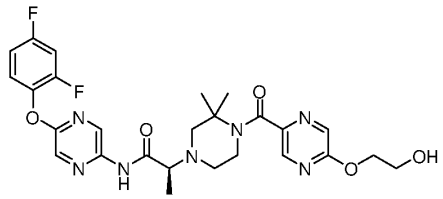


(R)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(pyridin-3-yloxy)pyridin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide and (S)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(pyridin-3-yloxy)pyridin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide

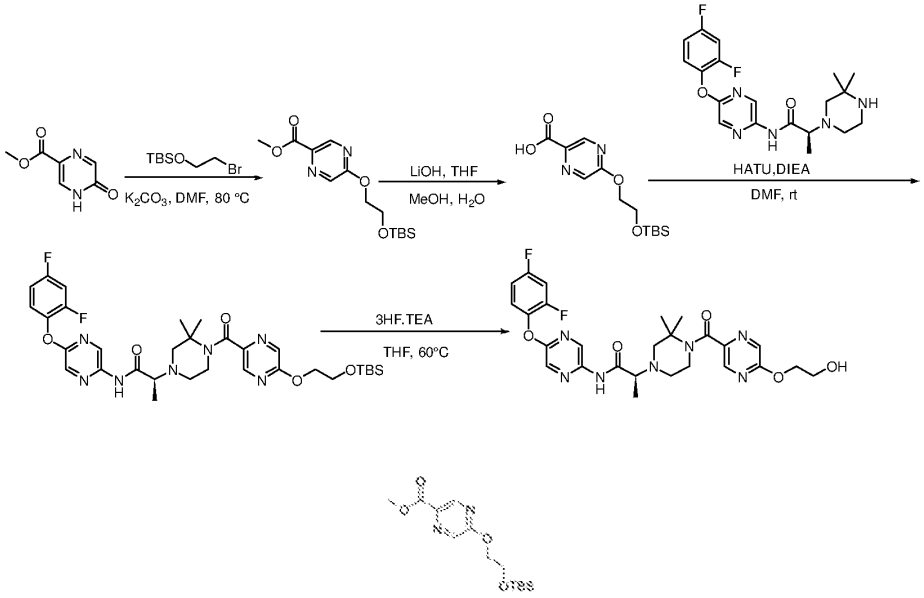
To a stirring solution 2-(3,3-dimethylpiperazin-1-yl)-N-(5-(pyridin-3-yloxy)pyridin-2-yl)propanamide (100 mg, 0.281 mmol, 1 equiv) in DMF (10 mL) the mixture was added isonicotinic acid N-oxide (39.14 mg, 0.281 mmol, 1 equiv), HATU (160.46 mg, 0.422 mmol, 1.5 equiv) and DIEA (145.45 mg, 1.124 mmol, 4 equiv) at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to give crude product as a brown solid. The product was separated by Chiral-Prep-HPLC (CHIRALPAK IE, 2*25 cm, 5 μm; column (eluent: 50% (v/v) Mobile Phase A: Hex: DCM=1: 1(0.5% 2M NH_3-MeOH) to afford (R)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(pyridin-3-yloxy)pyridin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide as a brown solid. MS (ESI): mass calcd. for $C_{25}H_{27}N_6O_4$: 476.22, found: 477.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H), 8.36 – 8.45 (m, 2H), 8.14 – 8.26 (m, 4H), 7.61 – 7.68 (m, 1H), 7.39 – 7.50 (m, 4H), 3.44 – 3.56 (m, 1H), 2.54 – 2.78 (m, 4H), 2.31 – 2.47(m, 2H), 1.48 (d, J = 4.0 Hz, 6H), 1.24 (d, J = 6.9 Hz, 3H). And (S)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(pyridin-3-yloxy)pyridin-2-yl)amino)propan-2-yl)piperazine-

1-carbonyl)pyridin-2-ylium 1-oxide as a brown solid. MS (ESI): mass calcd. for $C_{25}H_{27}N_6O_4$: 476.22, found: 477.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 8.35 – 8.45 m, 2H), 8.15 – 8.26 (m, 4H), 7.60 – 7.67 (m, 1H), 7.39 – 7.49 (m, 4H), 3.47 – 3.55 (m, 1H), 2.55 – 2.76 (m, 4H), 2.41 – 2.49 (m, 2H), 1.46 (d, J = 4.0 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H).

Example 174: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-(2-hydroxyethoxy)pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide



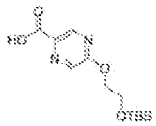
Synthetic Scheme



methyl methyl 5-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-4,5-dihydropyrazine-2-carboxylate

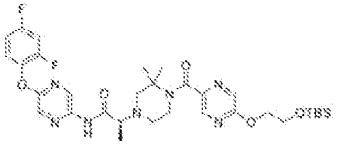
To a solution of methyl 5-oxo-4H-pyrazine-2-carboxylate (1 g, 6.488 mmol, 1 equiv) in DMF (100ml) was added potassium methaneperoxoate potassium (2.71 g, 19.464 mmol, 3

equiv) and (2-bromoethoxy)(tert-butyl)dimethylsilane (3.10 g, 12.976 mmol, 2 equiv) at rt. The mixture was allowed to warm to 80 °C and stirred for 3 h. After cooled to room temperature the resulting mixture was extracted with EA (3 x 100 mL). The combined organic layers were washed with brine (2*50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% EA/PE) to afford methyl 5-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-4,5-dihydropyrazine-2-carboxylate (small polar isomer, 0.56 g, 25.12%) as a yellow solid. MS (ESI): mass calcd. for $C_{14}H_{24}N_2O_4Si$: 312.15, found: 313.10 $[M+H]^+$.



5-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-4,5-dihydropyrazine-2-carboxylic acid

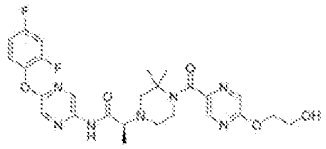
To a solution of methyl 5-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-4,5-dihydropyrazine-2-carboxylate (1 g, 3.20 mmol, 1 equiv) in THF (10 mL), methanol (1 mL), water (1 mL) was added lithiumol (115 mg, 4.81 mmol, 1.5 equiv) at rt. The resulting mixture was stirred for 1 h at rt. The resulting mixture was concentrated under vacuum. The residue was acidified to pH 5~6 with 3N HCl. The precipitated solids were collected by filtration and washed with H_2O (100 mL) to afford 5-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-4,5-dihydropyrazine-2-carboxylic acid (7.5 g, 78.53%) as a yellow solid. MS (ESI): mass calcd. for $C_{13}H_{22}N_2O_4Si$: 298.13, found: 299.10$[M+H]^+$.



(2S)-2-(4-(5-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

To a solution of (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (500 mg, 1.277 mmol, 1 equiv) in DMF (5 mL) was added 5-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-4,5-dihydropyrazine-2-carboxylic acid (572 mg, 1.916 mmol, 1.5 equiv), HATU (729 mg, 19.161 mmol, 1.5 equiv), DIEA (991 mg, 7.664 mmol, 6 equiv).The resulting mixture was stirred for 1 h at rt. The reaction mixture was

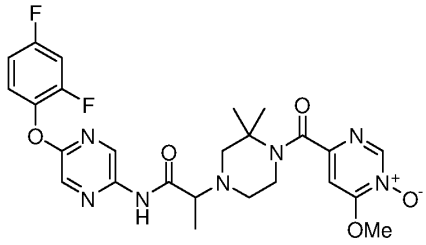
quenched by water and extracted with EA (3 x 200 mL).The combined organic extracts were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-10% MeOH/DCM) to afford (2S)-2-[4-(4-{2-[(tert-butyldimethylsilyl)oxy]ethyl}-5-oxopyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl]-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (600 mg, 69.92%) as a white solid. MS (ESI): mass calcd. for $C_{32}H_{43}F_2N_7O_5Si$: 671.30m/z, found 672.20 $[M+H]^+$.



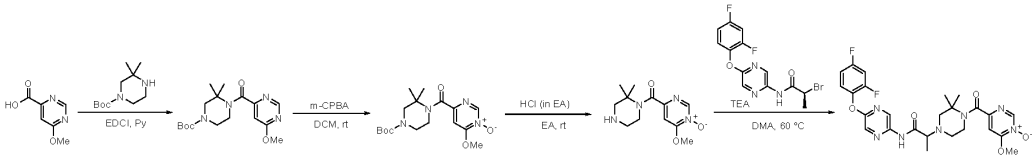
(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-(2-hydroxyethoxy)pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

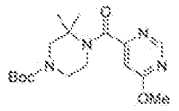
To a solution of (2S)-2-[4-(5-{2-[(tert-butyldimethylsilyl)oxy]ethoxy}pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl]-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (100 mg, 0.149 mmol, 1 equiv) in tetrahydrofuran (6 mL) with Triethylamine trihydrofluoride (1.5 mL). The resulting mixture was stirred for 3 h at 60 °C. After cooled to room temperature the reaction mixture was quenched by water and extracted with EA (3 x 20 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 20 mg crude product as a white solid.The compound was was purified by preparative HPLC using a XBridge Prep OBD 150 mm x 30 mm x 5 μm column (eluent: 35% to 51% (v/v) ACN and H2O with 10mmol/L NH4HCO3+0.05%NH3H2O) to afford (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-{4-[5-(2-hydroxyethoxy)pyrazine-2-carbonyl]-3,3-dimethylpiperazin-1-yl}propanamide (20.9 mg, 25.13%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{29}F_2N_7O_5$: 557.22 m/z, found 558.30 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.39 (s, 1H), 8.82 (d, J = 1.4 Hz, 1H), 8.44 (d, J = 1.4 Hz, 1H), 8.36 (d, J = 1.4 Hz, 1H), 8.24 (d, J = 1.3 Hz, 1H), 7.38 – 7.54 (m, 2H), 7.16 (t, J = 8.6 Hz, 1H), 4.90 (s, 1H), 4.34 (t, J = 5.0 Hz, 2H), 3.72 (d, J = 4.9 Hz, 2H), 3.51 (d, J = 7.1 Hz, 1H), 3.34 – 3.45 (m, 2H), 2.69 (d, J = 4.8 Hz, 1H), 2.59 (d, J = 5.6 Hz, 1H), 2.43 (s, 2H), 1.45 (d, J = 2.1 Hz, 6H), 1.19 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.44, -124.24.

Example 175: 4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-6-methoxypyrimidine 1-oxide



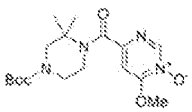
Synthetic Scheme





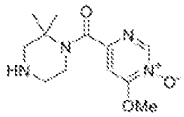
tert-butyl 4-(6-methoxypyrimidine-4-carbonyl)-3,3-dimethylpiperazine-1-carboxylate

To a solution of 6-methoxypyrimidine-4-carboxylic acid (1.5 g, 9.732 mmol, 1 equiv) in Py (20ml). tert-butyl 3,3-dimethylpiperazine-1-carboxylate (2.09 g, 9.732 mmol, 1 equiv) and EDCI (5.60 g, 29.196 mmol, 3 equiv) was added at rt. The mixture was allowed to warm to RT and stirred for 2 h. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% PE/EA) to afford tert-butyl 4-(6-methoxypyrimidine-4-carbonyl)-3,3-dimethylpiperazine-1-carboxylate (500 mg, 14.66%) as a yellow oil, MS (ESI): mass calcd. for $C_{17}H_{26}N_4O_4$:350.20 m/z, found:351.30$[M+H]^+$.



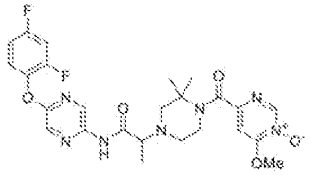
4-(4-(tert-butoxycarbonyl)-2,2-dimethylpiperazine-1-carbonyl)-6-methoxypyrimidine 1-oxide

To a solution of tert-butyl 4-(6-methoxypyrimidine-4-carbonyl)-3,3-dimethylpiperazine-1-carboxylate (450 mg, 1.284 mmol, 1 equiv) in DCM (1 mL). m-CPBA (443.20 mg, 2.568 mmol, 2 equiv) added at 0 °C. The resulting mixture was stirred for 2h at rt. The resulting mixture was extracted with DCM (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100%PE/EA) to afford 4-(4-(tert-butoxycarbonyl)-2,2-dimethylpiperazine-1-carbonyl)-6-methoxypyrimidine 1-oxide (300 mg, 63.76%) as a yellow oil, MS (ESI): mass calcd. for $C_{17}H_{26}N_4O_5$:366.19 m/z, found:367.15$[M+H]^+$.



4-(2,2-dimethylpiperazine-1-carbonyl)-6-methoxypyrimidine 1-oxide

To a solution of 4-[4-(tert-butoxycarbonyl)-2,2-dimethylpiperazine-1-carbonyl]-6-methoxypyrimidin-1-ium-1-olate (400 mg, 1.092 mmol, 1 equiv) in EA (5ml). 4N HCl in EA (5 mL) was added at 0 °C. The mixture was allowed to warm to RT and stirred for 2 h. The resulting mixture was concentrated under vacuum. The precipitated solids were collected by filtration and washed with diethyl ether (20 mL) to afford 4-(2,2-dimethylpiperazine-1-carbonyl)-6-methoxypyrimidine 1-oxide (300 mg, 103.20%) as a yellow oil, MS (ESI): mass calcd. for $C_{12}H_{18}N_4O_3$:266.14 m/z, found:267.15$[M+H]^+$.

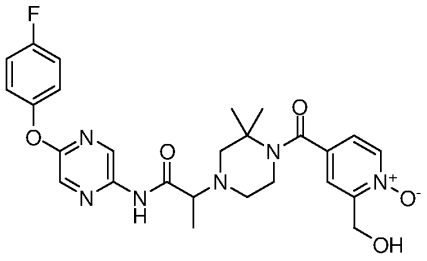


4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-6-methoxypyrimidine 1-oxide

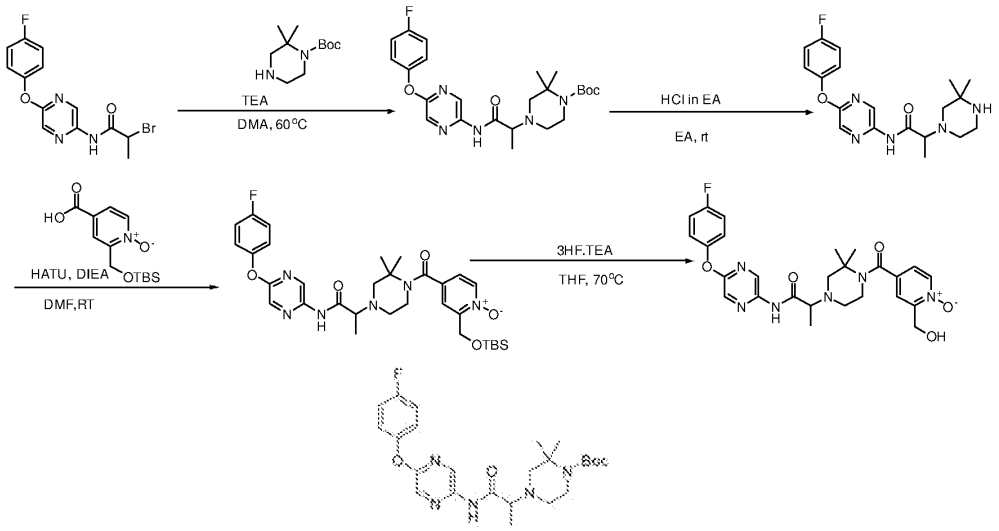
To a solution of 4-(2,2-dimethylpiperazine-1-carbonyl)-6-methoxypyrimidine 1-oxide (200 mg, 0.751 mmol, 1 equiv) in DMA (5 mL) .2-bromo-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (268.98 mg, 0.751 mmol, 1 equiv) and TEA (228.00 mg, 2.253 mmol, 3 equiv) was added at rt. The mixture was allowed to warm to 60 °C and stirred for 2 h. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash

chromatography (0-100%PE/EA) and Prep-HPLC using a Column: Kinetex 5u EVO C18 20 x 250 mm (eluent: 35% to 50% ACN and H2O (0.1% FA) to afford 4-[4-(1-{[5-(2,4-difluorophenoxy)pyrazin-2-yl]carbamoyl}ethyl)-2,2-dimethylpiperazine-1-carbonyl]-6-methoxypyrimidin-1-ium-1-olate (7.9 mg, 1.90%) as a white solid, MS (ESI): mass calcd. for $C_{25}H_{27}F_2N_7O_5$:543.20 m/z, found:544.30$[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.44 (s, 1H), 8.82 (d, J = 1.9 Hz, 2H), 8.45 (d, J = 1.4 Hz, 1H), 7.39 – 7.56 (m, 2H), 7.18 (d, J = 11.7 Hz, 2H), 3.91 (s, 3H), 3.50 -3.56 (m, 1H), 3.36 – 3.43 (m, 3H), 3.20 – 3.26 (m, 1H), 2.60 – 2.66 (m, 1H), 2.35 – 2.41 (m, 1H), 1.55 (d, J = 4.3 Hz, 3H), 1.46 (s, 3H), 1.15 – 1.21 (m, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.4477, -124.241

Example 176: 4-(4-(1-((5-(4-fluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide

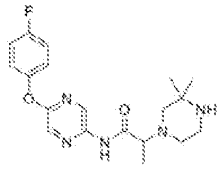


Synthetic Scheme



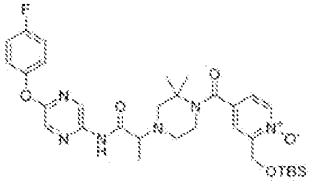
tert-butyl 4-(1-(5-(4-fluorophenoxy)pyrazin-2-ylamino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carboxylate

To a solution of 2-bromo-N-[5-(4-fluorophenoxy)pyrazin-2-yl]propanamide (100 mg, 0.294 mmol, 1 equiv) in DMA (1ml) .tert-butyl 2,2-dimethylpiperazine-1-carboxylate (63.00 mg, 0.294 mmol, 1 equiv) and TEA (0.09 g, 0.882 mmol, 3 equiv) was added at rt. The mixture was allowed to warm to 60 °C and stirred for 2 h. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100%PE/EA) to afford tert-butyl 4-(1-{[5-(4-fluorophenoxy)pyrazin-2-yl]carbamoyl}ethyl)-2,2-dimethylpiperazine-1-carboxylate (110 mg, 79.01%) as a yellow oil. MS (ESI): mass calcd. for $C_{24}H_{32}FN_5O_4$:473.24, found:474.20[M+H] $^+$.



tert-butyl 4-(1-(5-(4-fluorophenoxy)pyrazin-2-ylamino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carboxylate

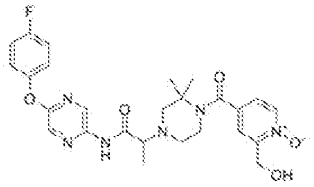
To a solution of tert-butyl 4-(1-{[5-(4-fluorophenoxy)pyrazin-2-yl]carbamoyl}ethyl)-2,2-dimethylpiperazine-1-carboxylate (100 mg, 0.211 mmol, 1 equiv) in EA (2.5ml). HCl in EA (2.5 mL) was added at 0 °C. The mixture was allowed to warm to RT and stirred for 2 h. The resulting mixture was concentrated under vacuum. The precipitated solids were collected by filtration and washed with diethyl ether (20 mL) to afford tert-butyl 4-(1-(5-(4-fluorophenoxy)pyrazin-2-ylamino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carboxylate (80 mg, 101.45%) as a yellow oil, MS (ESI): mass calcd. for $C_{19}H_{24}FN_5O_2$:373.19, found:374.15[M+H] $^+$.



2-((tert-butyldimethylsilyloxy)methyl)-4-(4-(1-(5-(4-fluorophenoxy)pyrazin-2-ylamino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

To a solution of tert-butyl 4-(1-(5-(4-fluorophenoxy)pyrazin-2-ylamino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carboxylate (100 mg, 0.268 mmol, 1 equiv) in DMF (3ml). 2-

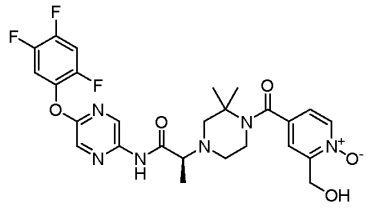
{[(tert-butyldimethylsilyl)oxy]methyl}-4-carboxypyridin-1-ium-1-olate (75.89 mg, 0.268 mmol, 1 equiv) , HATU (152.73 mg, 0.402 mmol, 1.5 equiv) and DIEA (103.83 mg, 0.804 mmol, 3 equiv) was added at rt. The mixture was allowed to warm to room temperature and stirred for 2 h. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100%PE/EA) to afford 2-((tert-butyldimethylsilyloxy)methyl)-4-(4-(1-(5-(4-fluorophenoxy)pyrazin-2-ylamino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (80 mg, 46.77%) as a yellow oil, MS (ESI): mass calcd. for $C_{32}H_{43}FN_6O_5Si$:638.30, found:639.20$[M+H]^+$.



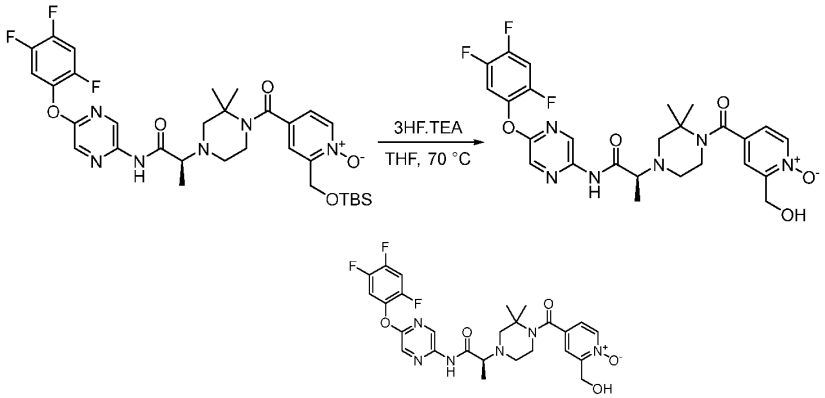
4-(4-(1-(5-(4-fluorophenoxy)pyrazin-2-ylamino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide

To a solution of 2-((tert-butyldimethylsilyloxy)methyl)-4-(4-(1-(5-(4-fluorophenoxy)pyrazin-2-ylamino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (40 mg, 0.063 mmol, 1 equiv) in THF (5ml) and Triethylamine trihydrofluoride (1.25 mL, 0.008 mmol, 0.12 equiv). The mixture was allowed to warm to 70 °C and stirred for 2 h. After cooled to room temperature, the resulting mixture was concentrated under reduced pressure and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 28% to 44% ACN and H_2O (10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford 4-(4-(1-(5-(4-fluorophenoxy)pyrazin-2-ylamino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide (8.2 mg, 24.91%) as a white solid, MS (ESI): mass calcd. for $C_{26}H_{29}FN_6O_5$:524.22, found:525.25$[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.89 (d, J = 1.5 Hz, 1H), 8.33 (d, J = 1.4 Hz, 1H), 8.26 (d, J = 6.6 Hz, 1H), 7.50 (d, J = 2.5 Hz, 1H), 7.36 (dd, J = 6.6, 2.6 Hz, 1H), 7.19 – 7.32 (m, 4H), 5.69 (t, J = 5.8 Hz, 1H), 4.57 (d, J = 5.8 Hz, 2H), 3.50 – 3.59 (m, 1H), 3.37 – 3.40 (m, 1H), 3.29 – 3.32 (m, 1H), 2.68 – 2.75 (m, 2H), 2.58 – 2.65 (m, 2H), 1.46 (d, J = 2.8 Hz, 6H), 1.18 – 1.26 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -118.3578.

Example 177: N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-methyl-5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide



Synthetic Scheme

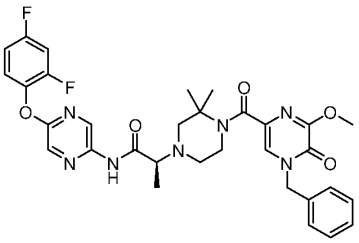


(S)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(2,4,5-trifluorophenoxy)pyrazin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide

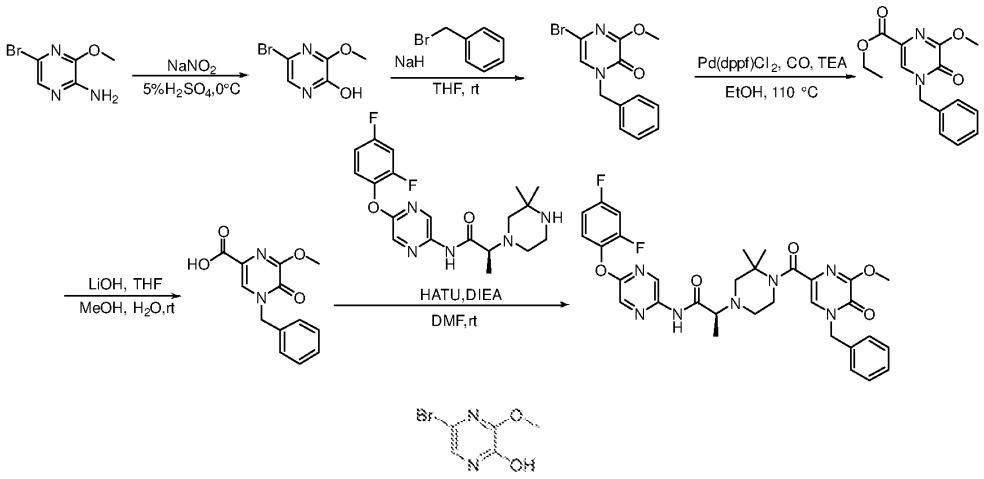
To a solution of (S)-2-(((tert-butyldimethylsilyl)oxy)methyl)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(2,4,5-trifluorophenoxy)pyrazin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide (25 mg, 0.037 mmol, 1 equiv) in THF (1ml) and Triethylamine trihydrofluoride (0.25 mL, 0.002 mmol, 0.04 equiv). The mixture was allowed to warm to 70 °C and stirred for 2 h. After cooled to room temperature, the resulting mixture was concentrated under reduced pressure and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; (eluent: 29% to 59% ACN and H_2O (10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(2,4,5-trifluorophenoxy)pyrazin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide (18.5 mg, 87.81%) as a white solid, MS (ESI): mass calcd. for $C_{26}H_{27}F_3N_6O_5$:560.20m/z, found:561.30$[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.87 (d, J = 1.4 Hz, 1H), 8.48 (d, J = 1.4 Hz, 1H), 8.26 (d, J = 6.6 Hz, 1H), 7.70 –

7.89 (m, 2H), 7.50 (d, *J* = 2.5 Hz, 1H), 7.36 (dd, *J* = 6.7, 2.6 Hz, 1H), 5.68 (t, *J* = 5.8 Hz, 1H), 4.57 (d, *J* = 5.7 Hz, 2H), 3.55 (d, *J* = 6.8 Hz, 1H), 2.68 – 2.75 (m, 1H), 2.58 – 2.66 (m, 2H), 2.46 (d, *J* = 2.7 Hz, 2H), 1.46 (d, *J* = 2.8 Hz, 6H), 1.21 (d, *J* = 6.9 Hz, 4H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -129.7534, -137.9384, -140.5446.

Example 178: (S)-2-(4-(4-benzyl-6-methoxy-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide



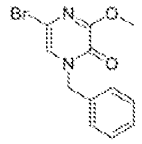
Synthetic Scheme



5-bromo-3-methoxypyrazin-2-ol

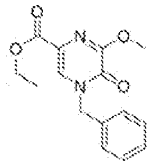
To a mixture of 5-bromo-3-methoxypyrazin-2-amine (1 g, 4.901 mmol, 1 equiv) in sulfuric acid (20 mL, 5% in water) was added a solution of sodium nitrite (0.37 g, 5.391 mmol, 1.1 equiv) in water (2 mL) at 0-5 °C. The mixture was stirred at 0-5 °C for 2 h. The mixture was extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue obtained was purified by silica gel chromatography (0-50% EA/PE) to give 5-bromo-3-

methoxypyrazin-2-ol (900 mg, 89.57%) a white solid. MS (ESI): mass calcd. for $C_5H_5BrN_2O_2$: mass calcd. for: 203.95, found: 205.20 $[M+H]^+$.



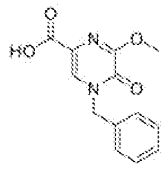
1-benzyl-5-bromo-3-methoxypyrazin-2(1H)-one

A solution of 5-bromo-3-methoxypyrazin-2-ol (800 mg, 3.902 mmol, 1 equiv) in dimethylformamide (10 mL) was treated with sodium hydride (187.29 mg, 7.804 mmol, 2 equiv) for 30 minat 0 °C under nitrogen atmosphere followed by the addition of benzyl bromide (734.17 mg, 4.292 mmol, 1.1 equiv) dropwise in at rt.The resulting mixture was stirred for 2 hours at rt. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% EA/PE) to give 1-benzyl-5-bromo-3-methoxy-2H-pyrazin-2-ol) as a white solid. MS (ESI): mass calcd. for $C_{12}H_{13}BrN_2O_2$: 294.00, found: 295.15 $[M+H]^+$.



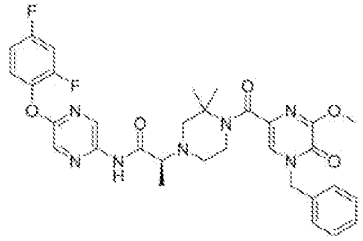
ethyl 4-benzyl-6-methoxy-5-oxo-4,5-dihydropyrazine-2-carboxylate

To a solution of 1-benzyl-5-bromo-3-methoxy-2H-pyrazin-2-ol (500 mg, 1.683 mmol, 1 equiv) in 50 mL EtOH was added $Pd(dppf)Cl_2$ (70.86 mg) and triethylamine (510.81 mg, 5.049 mmol, 3 equiv) in a pressure tank. The mixture was purged with nitrogen for 5 min and then was pressurized to 50 atm with CO at 110 °C for 24 h. The reaction mixture was cooled to room temperature and filtered to remove insoluble solids. The residue obtained was purified by silica gel chromatography (0-50% EA/PE) to give ethyl 4-benzyl-6-methoxy-5-oxo-4,5-dihydropyrazine-2-carboxylate (420 mg, 85.98%) as a white solid. MS (ESI): mass calcd. for $C_{15}H_{16}N_2O_4$: 288.11 m/z, found: 289.05$[M+H]^+$.



4-benzyl-6-methoxy-5-oxo-4,5-dihydropyrazine-2-carboxylic acid

To a stirred solution of ethyl 4-benzyl-5-hydroxy-6-methoxy-5H-pyrazine-2-carboxylate (400 mg, 1.378 mmol, 1 equiv) and LiOH (164.99 mg, 6.890 mmol, 5 equiv) in methanol (3 mL), H_2O (3 mL) and THF (6 mL) at room temperature. The reaction mixture was stirred at room temperature for a period of 3 h. The mixture was concentrated to dryness under reduced pressure to provide the crude product, which was purified by C18 column (0-20% H_2O/ACN) to afford 4-benzyl-5-hydroxy-6-methoxy-5H-pyrazine-2-carboxylic acid) (260mg, 72.22%). MS (ESI): mass calcd. for $C_{13}H_{12}N_2O_4$: 260.08 m/z. found 261.15 $[M+H]^+$.

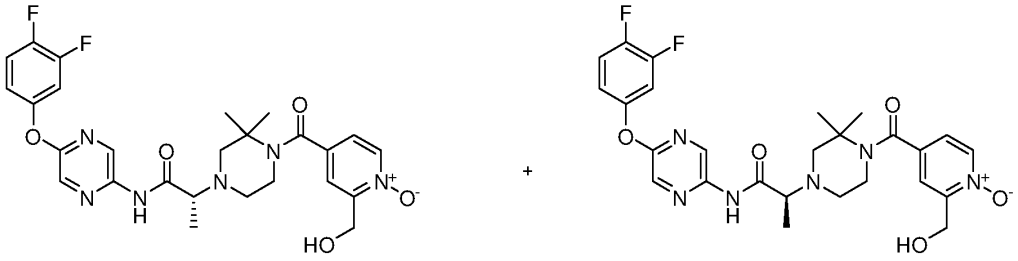


(S)-2-(4-(4-benzyl-6-methoxy-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

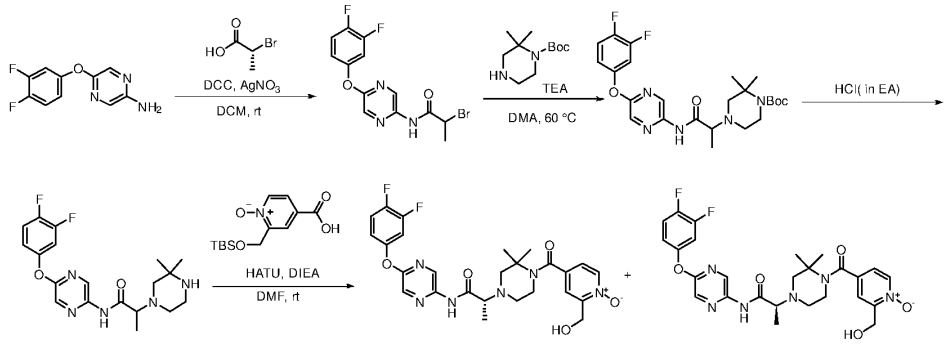
To a stirring solution (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (100 mg, 0.255 mmol, 1 equiv) in dimethylformamide (10 mL) the mixture was added 4-benzyl-6-methoxy-5-oxopyrazine-2-carboxylic acid (66.49 mg, 0.255 mmol, 1 equiv), HATU (145.71 mg, 0.383 mmol, 1.5 equiv) and N,N-diisopropylethylamine (132.08 mg, 1.020 mmol, 4 equiv) at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% EA/PE) and was purified by preparative HPLC using a XBridge Prep OBD 150 mm x 30 mm x 5 μm column (eluent: 55% to 65% (v/v) ACN and H_2O with 10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-2-(4-(4-benzyl-6-methoxy-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (30.4 mg, 18.65%) as a white solid. MS (ESI):

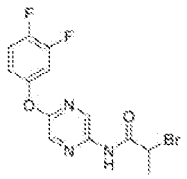
mass calcd. for $C_{32}H_{33}F_2N_7O_5$: 633.25, found: 634.35 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 8.83 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.80 (s, 1H), 7.41 – 7.54 (m, 2H), 7.27 – 7.41 (m, 5H), 7.13 – 7.22 (m, 1H), 5.12 (s, 2H), 3.84 (s, 3H), 3.45 – 3.60 (m, 3H), 2.59 – 2.79 (m, 2H), 2.35 – 2.46 (m, 2H), 1.42 (d, J = 1.8 Hz, 6H), 1.20 (d, J = 7.0 Hz, 3H).^{19}F NMR (376 MHz, DMSO-d_6) δ -113.43 (d, J = 5.4 Hz), -124.22 (d, J = 5.4 Hz).

Example 179: 4-{4-[(1R)-1-{[5-(3,4-difluorophenoxy)pyrazin-2-yl]carbamoyl} ethyl]-2,2-dimethylpiperazine-1-carbonyl}-2-(hydroxymethyl)pyridin-1-ium-1-olate and Example 180: 4-{4-[(1S)-1-{[5-(3,4-difluorophenoxy)pyrazin-2-yl]carbamoyl} ethyl]-2,2-dimethylpiperazine-1-carbonyl}-2-(hydroxymethyl)pyridin-1-ium-1-olate



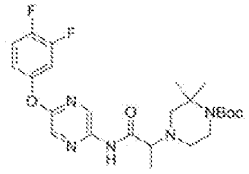
Synthetic Scheme





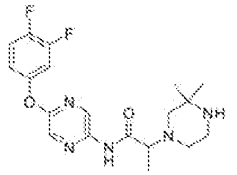
2-bromo-N-[5-(3,4-difluorophenoxy)pyrazin-2-yl]propanamide

To a solution of 5-(3,4-difluorophenoxy)pyrazin-2-amine (330 mg, 1.479 mmol, 1 equiv) in DCM (5 mL) was added (2R)-2-bromopropanoic acid (271.43 mg, 1.775 mmol, 1.2 equiv) and DCC (366.10 mg, 1.775 mmol, 1.2 equiv) at 0 °C. The resulting mixture was stirred for 2 h at rt. The reaction mixture was quenched by water and extracted with EA (3*30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford 2-bromo-N-[5-(3,4-difluorophenoxy)pyrazin-2-yl]propanamide (0.3 g, 56.8%)s a yellow solid. MS (ESI): mass calcd. for $C_{13}H_{10}BrF_2N_3O_2$ 358.14 m/z, found 359.90 $[M+H]^+$.



tert-butyl4-(1-{[5-(3,4-difluorophenoxy)pyrazin-2-yl]carbamoyl}ethyl)-2,2-dimethyl piperazine-1-carboxylate

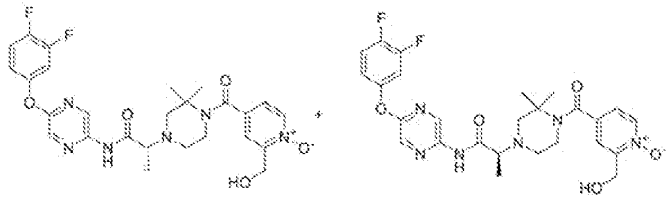
To a solution of 2-bromo-N-[5-(3,4-difluorophenoxy)pyrazin-2-yl]propanamide (360 mg, 1.005 mmol, 1 equiv) in DMA (5 mL) was added (tert-butyl 2,2-dimethylpiperazine-1-carboxylate (215.42 mg, 1.005 mmol, 1 equiv) and TEA (305.15 mg, 3.015 mmol, 3 equiv) at rt . The resulting mixture was stirred for 2h at 60°C. The reaction mixture was quenched by water and extracted with EA (3*30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford tert-butyl4-(1-{[5-(3,4-difluorophenoxy)pyrazin-2-yl]carbamoyl}ethyl)-2,2-dimethyl piperazine-1-carboxylate (0.4 g) as a yellow solid. MS (ESI): mass calcd. for $C_{24}H_{31}F_2N_5O_4$ 491.54m/z, found 492.20$[M+H]^+$.



N-[5-(3,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide

To a solution of tert-butyl 4-(1-{[5-(3,4-difluorophenoxy)pyrazin-2-yl]carbamoyl}ethyl)-2,2-dimethylpiperazine-1-carboxylate (400 mg, 0.814 mmol, 1 equiv) in

EA (3 mL) was added HCl (3 mL) at rt. The resulting mixture was stirred for 3h at rt. The product was precipitated by the addition of diethyl ether. The precipitated solids were collected by filtration and washed with diethyl ether. The resulting mixture was concentrated under reduced pressure to afford N-[5-(3,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (0.3 g, crude) as white solid. MS (ESI): mass calcd. for $C_{19}H_{23}F_2N_5O_2$ 391.22m/z, found 392.05$[M+H]^+$.

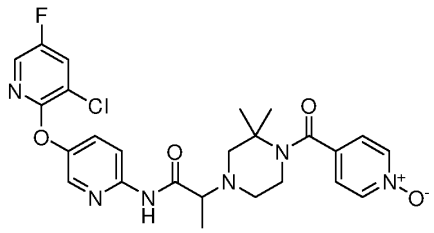


4-{4-[(1R)-1-{[5-(3,4-difluorophenoxy)pyrazin-2-yl]carbamoyl}ethyl]-2,2-dimethyl piperazine-1-carbonyl}-2-(hydroxymethyl)pyridin-1-ium-1-olate and 4-{4-[(1S)-1-{[5-(3,4-difluorophenoxy)pyrazin-2-yl]carbamoyl} ethyl]-2,2-dimethylpiperazine-1-carbonyl}-2-(hydroxymethyl)pyridin-1-ium-1-olate

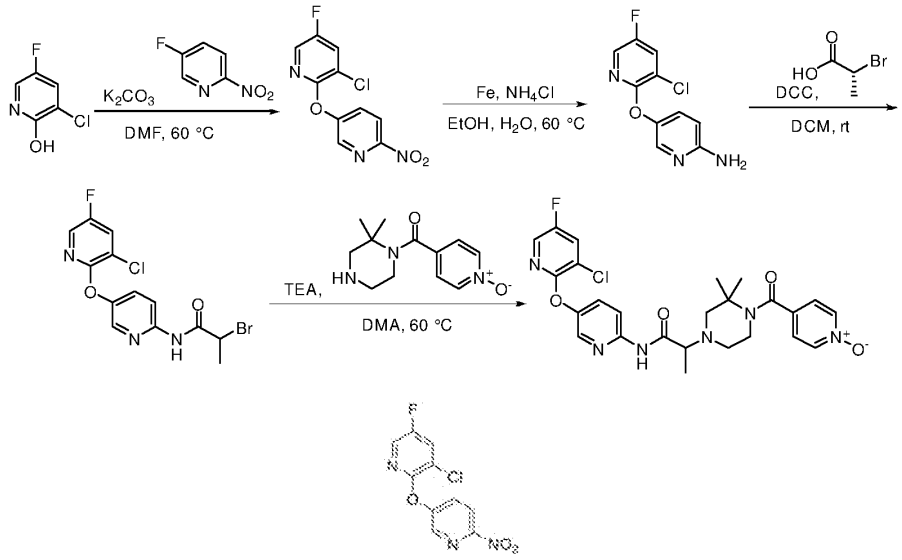
To a solution of1,1-dioxo-1lambda6-thiane-4-carbonyl chloride (75 mg, 0.381 mmol, 1 equiv) (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (88.11 mg, 0.225 mmol, 1 equiv) in DMF (3mL) was added (2S)-2-(3,3-dimethylpiperazin-1-yl)-N-[5-(4-fluorophenoxy)pyridin-2-yl]propanamide (142.05 mg, 0.381 mmol, 1 equiv) and DIEA (246.47 mg, 1.905 mmol, 5 equiv) at rt. The resulting mixture was stirred for 3h at rt. The reaction mixture was quenched by water and extracted with EA (3*20 mL). The combined organic extracts were washed with brine (10mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford solid product. The compound was purified by chiral-HPLC using a CHIRALPAK IA, 5*25 cm, 5 μm column (eluent: 30% (v/v) MtBE(0.5% 2M NH_3-MeOH) and MeOH: EtOH=1: 1) to afford 4-{4-[(1R)-1-{[5-(3,4-difluorophenoxy)pyrazin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}-2-(hydroxymethyl)pyridin-1-ium-1-olate (15.2 mg, 5.46%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{28}F_2N_6O_5$ 542.21 m/z, found 543.30 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.47 (s, 1H), 8.92 (d, J = 1.4 Hz, 1H), 8.37 (d, J = 1.4 Hz, 1H), 8.26 (d, J = 6.6 Hz, 1H), 7.39 – 7.57 (m, 3H), 7.36 (dd, J = 6.6, 2.6 Hz, 1H), 7.04 – 7.13 (m, 1H), 5.68 (t, J = 5.8 Hz, 1H), 4.57 (d, J = 5.8 Hz, 2H), 3.55 (p, J = 6.8 Hz, 1H), 2.68 – 2.76 (m, 1H), 2.58 – 2.66 (m, 1H), 2.47 (d, J = 2.3 Hz, 4H), 1.46 (d, J = 2.8 Hz, 6H), 1.18 – 1.26 (m, 3H).^{19}F NMR (376

MHz, DMSO-d_6) δ-135.64, -143.32. and 4-{4-[(1S)-1-{[5-(3,4-difluorophenoxy)pyrazin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}-2-(hydroxymethyl)pyridin-1-ium-1-olate (21 mg, 7.55%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{28}F_2N_6O_5$ 542.21m/z, found 543.30 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.47 (s, 1H), 8.92 (d, J = 1.4 Hz, 1H), 8.37 (d, J = 1.4 Hz, 1H), 8.26 (d, J = 6.6 Hz, 1H), 7.40 – 7.56 (m, 3H), 7.36 (dd, J = 6.6, 2.6 Hz, 1H), 7.08 (dtd, J = 8.9, 3.3, 1.8 Hz, 1H), 5.68 (t, J = 5.7 Hz, 1H), 4.57 (d, J = 5.8 Hz, 2H), 3.55 (p, J = 6.9 Hz, 1H), 2.58 – 2.76 (m, 2H), 2.47 (d, J = 2.3 Hz, 4H), 1.46 (d, J = 2.8 Hz, 6H), 1.18 – 1.26 (m, 3H).^{19}F NMR (376 MHz, DMSO-d_6) δ-135.58, -143.32.

Example 181: 4-(4-(1-((5-((3-chloro-5-fluoropyridin-2-yl)oxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

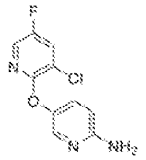


Synthetic Scheme



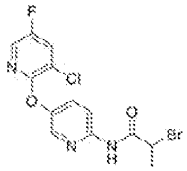
3-chloro-5-fluoro-2-((6-nitropyridin-3-yl)oxy)pyridine

To a solution of 3-chloro-5-fluoropyridin-2-ol (3 g, 20.335 mmol, 1 equiv) in DMF (50 mL) was added K_2CO_3 (4.25 g, 30.503 mmol, 1.5 equiv) and 5-fluoro-2-nitropyridine (3.47 g, 24.402 mmol, 1.2 equiv) at rt. The resulting mixture was stirred for 2 hours at 60 °C. After cooled to room temperature, the reaction was quenched by water (30 mL) and extracted with EA (100 mL x 3). The combined organic extracts were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-60% PE/EA) to afford 3-chloro-5-fluoro-2-((6-nitropyridin-3-yl)oxy)pyridine (4.1 g, 74.78%) and 3-chloro-5-fluoro-2-((6-nitropyridin-3-yl)oxy)pyridine (1.6 g, 29.18%) as a white solid. MS (ESI): mass calcd. for $C_{10}H_5ClFN_3O_3$: 269.00 m/z, found 270.05 $[M+H]^+$.



5-((3-chloro-5-fluoropyridin-2-yl)oxy)pyridin-2-amine

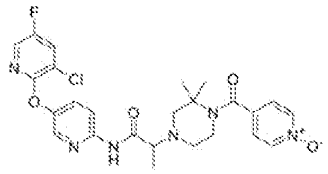
To a solution of 3-chloro-5-fluoro-2-((6-nitropyridin-3-yl)oxy)pyridine (1.8 g, 6.676 mmol, 1 equiv) in ethyl alcohol (24 mL) and water (6 mL) was added Fe (1.49 g, 26.704 mmol, 4 equiv) and NH_4Cl (1.43 g, 26.704 mmol, 4 equiv) at rt. The resulting mixture was stirred for 0.5 hours at 60 °C. After cooled to room temperature, the mixture was concentrated to dryness under reduced pressure to provide the crude product, which was purified bysilica gel chromatography (0-10% DCM/MeOH) to afford 5-((3-chloro-5-fluoropyridin-2-yl)oxy)pyridin-2-amine (1.1 g, 68.76%) as a white solid. MS (ESI): mass calcd. for $C_{10}H_7ClFN_3O$: 239.03 m/z, found 240.10 $[M+H]^+$.



2-bromo-N-(5-((3-chloro-5-fluoropyridin-2-yl)oxy)pyridin-2-yl)propanamide

To a stirred solution of 5-((3-chloro-5-fluoropyridin-2-yl)oxy)pyridin-2-amine (500 mg, 2.087 mmol, 1 equiv) in DCM (2 mL) was added (R)-2-bromopropanoic acid (383.03 mg, 2.504 mmol, 1.2 equiv) and DCC (516.63 mg, 2.504 mmol, 1.2 equiv) at room temperature. The reaction mixture was stirred at room temperature for a period of overnight. After

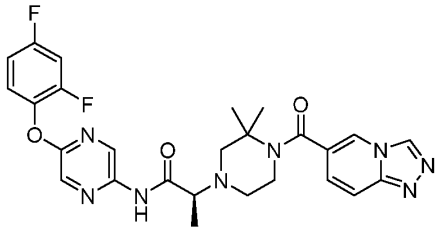
completion of reaction, the reaction mixture was quenched by water (10 mL) and extracted with EA (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-60% PE/EA) to afford 2-bromo-N-(5-((3-chloro-5-fluoropyridin-2-yl)oxy)pyridin-2-yl)propanamide (300 mg, 38.38%) as a white solid. MS (ESI): mass calcd. for $C_{13}H_{10}BrClFN_3O_2$: 372.96 m/z, found: 376.05 $[M+H]^+$.



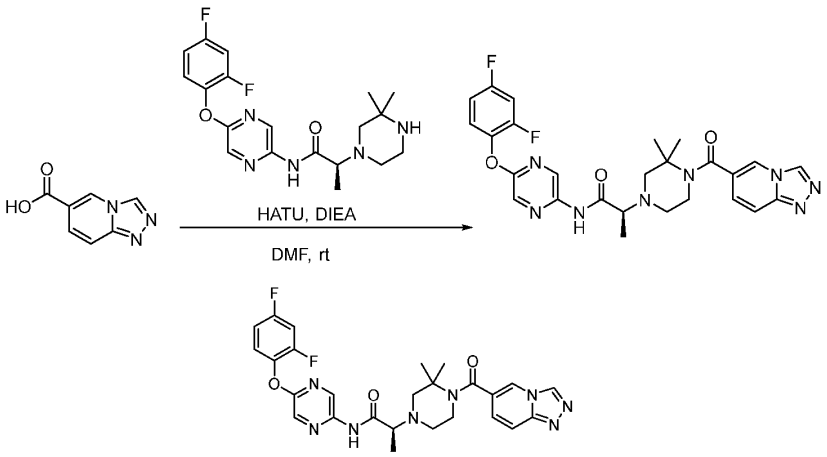
4-(4-(1-((5-((3-chloro-5-fluoropyridin-2-yl)oxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

To a solution of 4-(2,2-dimethylpiperazine-1-carbonyl)pyridin-1-ium-1-olate (94.22 mg, 0.401 mmol, 1.5 equiv) in DMA (3 mL, 32.265 mmol, 120.86 equiv) was added TEA (54.03 mg, 0.534 mmol, 2 equiv) at room temperature. The reaction mixture was stirred at 60 °C for 1 h. The mixture was added 2-bromo-N-(5-((3-chloro-5-fluoropyridin-2-yl)oxy)pyridin-2-yl)propanamide (100 mg, 0.267 mmol, 1 equiv) . The resulting mixture was stirred for 2 hours at 60 °C. After cooled to room temperature, the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-30% DCM/MeOH) and purified by preparative HPLC using a XBridge Prep OBD 150 mm x 30 mm x 5 μm column (eluent: 28% to 48% (v/v) ACN and H_2O with 10 mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford 4-(4-(1-((5-((3-chloro-5-fluoropyridin-2-yl)oxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (20.7 mg, 14.22%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{26}ClFN_6O_4$: 528.17 m/z, found 529.25 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.31 (dd, J = 7.8, 2.7 Hz, 1H), 8.26 (d, J = 2.9 Hz, 1H), 8.26 – 8.24 (m, 3H), 8.14 (d, J = 2.7 Hz, 1H), 7.72 (dd, J = 9.0, 2.9 Hz, 1H), 7.40 – 7.47 (m, 2H), 3.53 (d, J = 7.0 Hz, 1H), 3.37 (m, 2H), 2.73 (dt, J = 10.5, 5.0 Hz, 2H), 2.47 (d, J = 4.2 Hz, 2H), 1.47 (d, J = 3.8 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H).^{19}F NMR (376 MHz, DMSO-d_6) δ-132.98.

Example 182: (S)-2-(4-([1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide



Synthetic Scheme

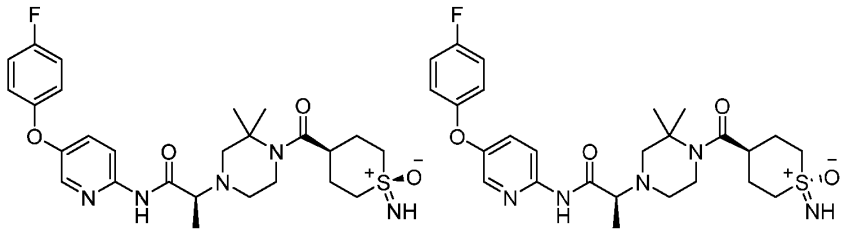


(S)-2-(4-([1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

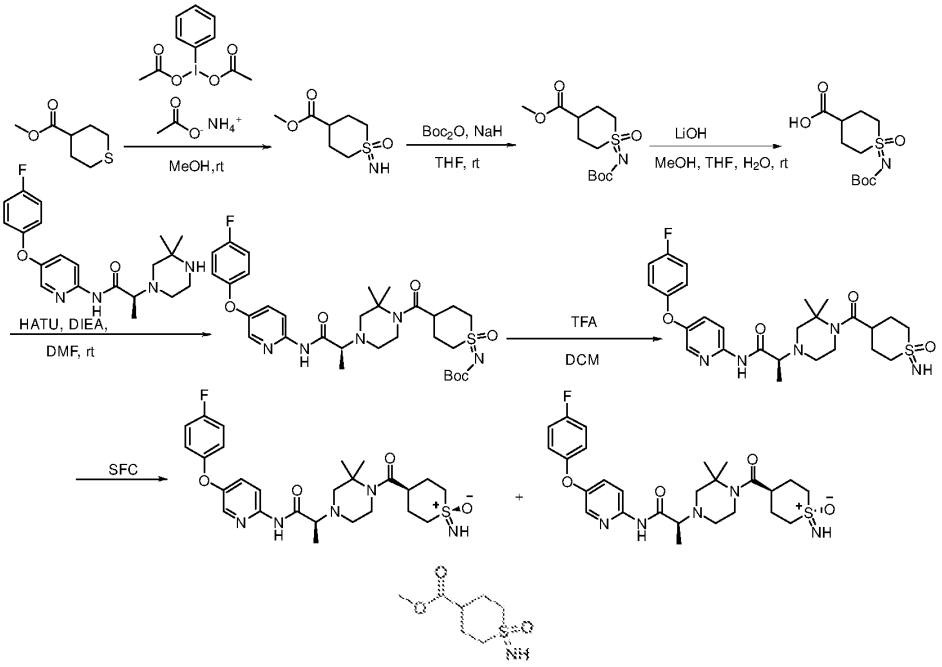
To a solution of [1,2,4]triazolo[4(S)-2-(4-([1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide,3-a]pyridine-6-carboxylic acid (80 mg, 0.490 mmol, 1 equiv) in DMF (5 mL). (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (191.95 mg, 0.490 mmol, 1 equiv), HATU (279.69 mg, 0.735 mmol, 1.5 equiv) and DIEA (126.76 mg, 0.980 mmol, 2 equiv)added at rt. The resulting mixture was stirred for 2h at rt. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na2SO4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% PE/EA) and the residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30*150

mm* 5μm column (eluent: 37% to 57% (v/v) CH_3CN and H_2O with NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-2-(4-([1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (44.7 mg, 16.81%) as a yellow solid, MS (ESI): mass calcd. for $C_{26}H_{26}F_2N_8O_3$:536.21m/z, found:537.30$[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.47 (s, 1H), 9.26 (s, 1H), 8.86 (d, J = 1.5 Hz, 1H), 8.75 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.79 (d, J = 9.4 Hz, 1H), 7.42 – 7.55 (m, 2H), 7.37 (dd, J = 9.5, 1.6 Hz, 1H), 7.13 – 7.23 (m, 1H), 3.52 – 3.62 (m, 1H), 3.41 (d, J = 10.9 Hz, 2H), 2.59 – 2.80 (m, 2H), 2.44 – 2.50 (m, 2H), 1.47 (d, J = 4.4 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -113.4004, -124.1865.

Example 183: (*S*)-*N*-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-((1*R*,4*s*)-1-imino-1-oxidohexahydro-1λ^6-thiopyran-4-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide and Example 184: (*S*)-*N*-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-((1*S*,4*r*)-1-imino-1-oxidohexahydro-1λ^6-thiopyran-4-carbonyl)-3,3-dimethylpiperazin-1-yl)propenamide

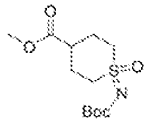


Synthetic Scheme



methyl 1-iminohexahydro-1λ⁶-thiopyran-4-carboxylate 1-oxide

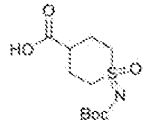
To a stirred solution of methyl thiane-4-carboxylate (1.5 g, 9.362 mmol, 1 equiv) in methanol (20 mL) was added (acetyloxy)(phenyl)-lambda3-iodanyl acetate (6332.20 mg, 19.660 mmol, 2.1 equiv) and ammonium acetate (1154.59 mg, 14.979 mmol, 1.6 equiv) at room temperature. The reaction mixture was stirred at room temperature for a period of overnight. After completion of reaction, the reaction mixture was quenched by water (50 mL) and extracted with EA (80 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (10-30% DCM/MeOH) to methyl 1-iminohexahydro-1λ⁶-thiopyran-4-carboxylate 1-oxide (1.5 g, 83.78%) as a white solid. MS (ESI): mass calcd. for $C_7H_{13}NO_3S$: 191.25 m/z, found: 192.15 $[M+H]^+$.



methyl 1-((tert-butoxycarbonyl)imino)hexahydro-1λ⁶-thiopyran-4-carboxylate 1-oxide

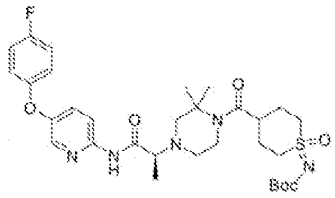
To a stirred solution of methyl 1-imino-1-oxo-1lambda6-thiane-4-carboxylate (1.5 g, 7.843 mmol, 1 equiv) in tetrahydrofuran (20 mL) was added NaH (329.38 mg, 13.725 mmol, 1.75 equiv) at 0°C. The reaction mixture was stirred at room temperature for 0.5 h. The

reaction mixture was added a solution of di-tert-butyl dicarbonate (4724.45 mg, 21.647 mmol, 2.76 equiv) at room temperature. After completion of reaction, the reaction mixture was quenched by water (10 mL) and extracted with EA (80 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to methyl 1-((tert-butoxycarbonyl)imino)hexahydro-1λ^6-thiopyran-4-carboxylate 1-oxide (1.5 g, 65.64%) as a white solid. MS (ESI): mass calcd. for $C_{12}H_{21}NO_5S$: 291.36 m/z, found: 292.20 $[M+H]^+$.



1-((*tert*-butoxycarbonyl)imino)hexahydro-1λ^6-thiopyran-4-carboxylic acid 1-oxide

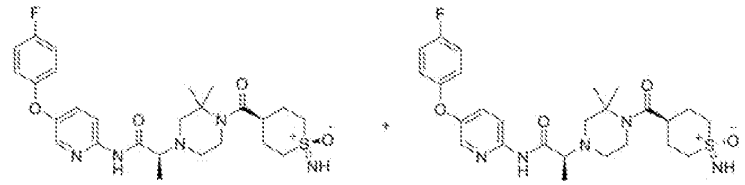
To a solution of methyl 1-((tert-butoxycarbonyl)imino)hexahydro-1λ^6-thiopyran-4-carboxylate 1-oxide (500 mg, 1.716 mmol, 1 equiv) in methanol (2 mL), tetrahydrofuran (4 mL) and water (2 mL) was added lithiumol (82.20 mg, 3.432 mmol, 2 equiv) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The mixture was acidified pH = 5 with HCl (1N). The product was precipitated by the addition of diethyl ether. The product is obtained (1-((*tert*-butoxycarbonyl)imino)hexahydro-1λ^6-thiopyran-4-carboxylic acid 1-oxide (300 mg, 63.03%)) by filtration and drying. MS (ESI): mass calcd. for $C_{11}H_{19}NO_5S$: 277.34, m/z, found: 278.15 $[M+H]^+$.



***tert*-butyl (*S*)-(4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-1-oxidotetrahydro-2*H*-1λ^6-thiopyran-1-ylidene)carbamate**

To a stirred solution of (1-((*tert*-butoxycarbonyl)imino)hexahydro-1λ^6-thiopyran-4-carboxylic acid 1-oxide (300 mg, 1.082 mmol, 1 equiv) in DMF (10 mL) was added (S)-2-(3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide (604.31 mg, 1.623 mmol, 1.5 equiv) and HATU (822.60 mg, 2.164 mmol, 2 equiv) and DIEA (279.61 mg, 2.164 mmol, 2 equiv) at room temperature. The reaction mixture was stirred at room

temperature for a period of overnight. After completion of reaction, the reaction mixture was quenched by water (10 mL) and extracted with EA (100 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford *tert*-butyl (*S*)-(4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-1-oxidotetrahydro-2*H*-1λ^6-thiopyran-1-ylidene)carbamate (200 mg, 29.27%) as a white solid. MS (ESI): mass calcd. for $C_{31}H_{42}FN_5O_6S$: 631.76 m/z, found: 632.40 $[M+H]^+$.

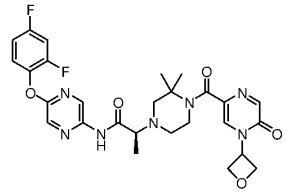


(*S*)-*N*-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-((1*R*,4*s*)-1-imino-1-oxidohexahydro-1λ^6-thiopyran-4-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide and (*S*)-*N*-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-((1*S*,4*r*)-1-imino-1-oxidohexahydro-1λ^6-thiopyran-4-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

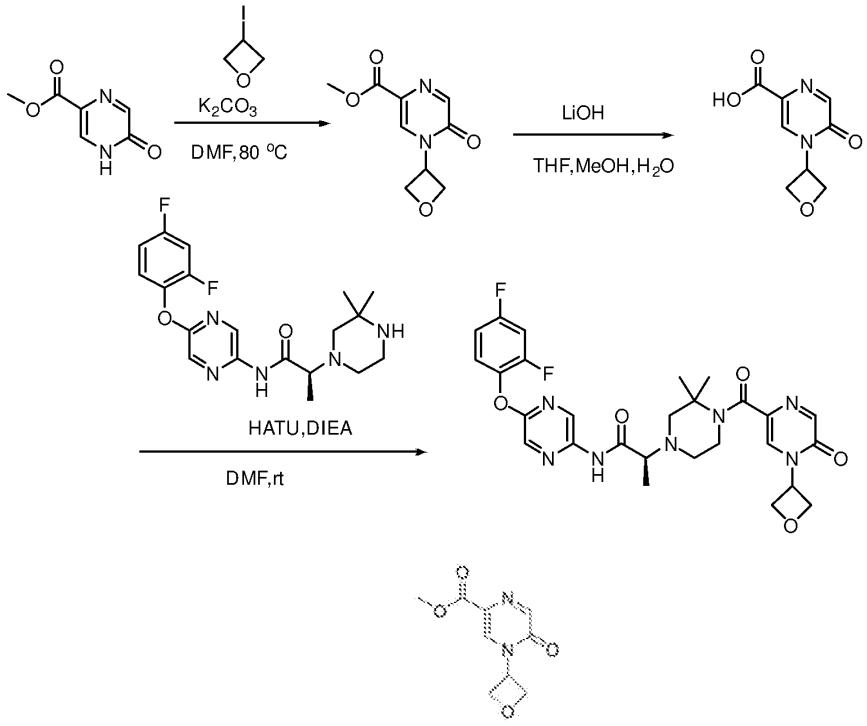
To a stirred solution of *tert*-butyl (*S*)-(4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-1-oxidotetrahydro-2*H*-1λ^6-thiopyran-1-ylidene)carbamate (260 mg, 0.412 mmol, 1 equiv) in DCM (1 mL) was added TFA (3 mL) . The reaction mixture was stirred at room temperature for 1 h. The product was precipitated by the addition of diethyl ether. The mixture was concentrated to dryness under reduced pressure to provide the crude product. The residue was purified by preparative HPLC using a Xselect CSH C18 OBD 150 mm x 30 mm x 5 μm column (eluent: 12% to 42% (v/v) ACN and H_2O with 0.1% FA) to afford (*S*)-*N*-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-((1*R*,4*s*)-1-imino-1-oxidohexahydro-1λ^6-thiopyran-4-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (12 mg, first peak) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{34}FN_5O_4S$: 531.65 m/z, found 532.25$[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.13 (dd, *J* = 6.0, 2.9 Hz, 2H), 7.52 (dd, *J* = 9.1, 2.9 Hz, 1H), 7.30 – 7.16 (m, 2H), 7.03 – 7.15 (m, 2H), 3.42 (s, 3H), 2.86 - 3.15 (m, 5H), 2.72 (d, *J* = 11.9 Hz, 2H), 2.33 (s, 2H), 1.85 – 2.04 (m, 4H), 1.36 (d, *J* = 2.8 Hz, 6H), 1.19 (d, *J* = 6.9 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ-119.798. And (*S*)-*N*-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-((1*S*,4*r*)-1-imino-1-oxidohexahydro-1λ^6-thiopyran-4-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (13.6

mg, second peak) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{34}FN_5O_4S$: 531.65 m/z, found 532.25[M+H]$^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.13 (dd, J = 6.1, 2.9 Hz, 2H), 7.52 (dd, J = 9.1, 2.9 Hz, 1H), 7.16 – 7.29 (m, 2H), 7.03 – 7.14 (m, 2H), 3.80 – 3.85(m,1H), 3.00 (d, J = 6.8 Hz, 2H), 2.86 - 3.15 (m, 5H), 2.72 (d, J = 11.9 Hz, 2H), 2.33 (s, 2H), 1.90 (d, J = 5.3 Hz, 4H), 1.36 (d, J = 2.6 Hz,6H), 1.15 – 1.26 (m, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ-119.784 (d, J = 1.6 Hz). Stereochemistry of example 183 and example 184 was arbitrarily assigned.

Example 185: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(4-(oxetan-3-yl)-5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide

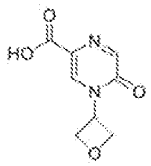


Synthetic Scheme



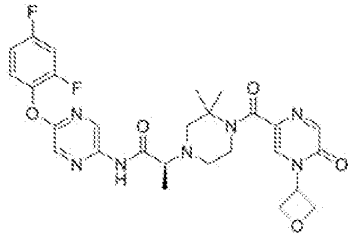
methyl 4-(oxetan-3-yl)-5-oxo-4,5-dihydropyrazine-2-carboxylate

To a solution of methyl 5-oxo-4H-pyrazine-2-carboxylate (2 g, 12.976 mmol, 1 equiv) in DMF (10 mL) was added 3-iodooxetane (4.77 g, 25.952 mmol, 2 equiv) and K_2CO_3 (5.38 g, 38.928 mmol, 3 equiv). The reaction was stirred at 80 °C for 2 h. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with PE/EA (0-100%) to afford the title compound methyl 4-(oxetan-3-yl)-5-oxo-4,5-dihydropyrazine-2-carboxylate as a white solid. MS (ESI): mass calcd. for $C_9H_{10}N_2O_4$:210.17 m/z, found:211.20 [M+H]+.



4-(oxetan-3-yl)-5-oxo-4,5-dihydropyrazine-2-carboxylic acid

To a solution of methyl 4-(oxetan-3-yl)-5-oxo-4,5-dihydropyrazine-2-carboxylate (10 mg, 0.048 mmol, 1 equiv) in THF (0.2 mL), MeOH (0.2 mL) and H_2O (0.1 mL) was added lithiumol (3.42 mg, 0.144 mmol, 3 equiv). The reaction was stirred at 25 °C for 2 h. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to afford the title compound 4-(oxetan-3-yl)-5-oxo-4,5-dihydropyrazine-2-carboxylic acid as a white solid. MS (ESI): mass calcd. for $C_8H_8N_2O_4$:196.17 m/z, found:197.20 $[M+H]^+$.

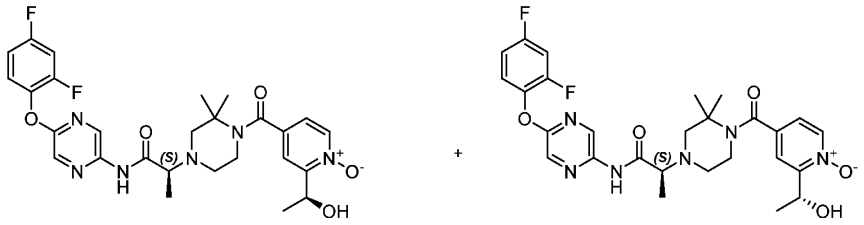


(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(4-(oxetan-3-yl)-5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide

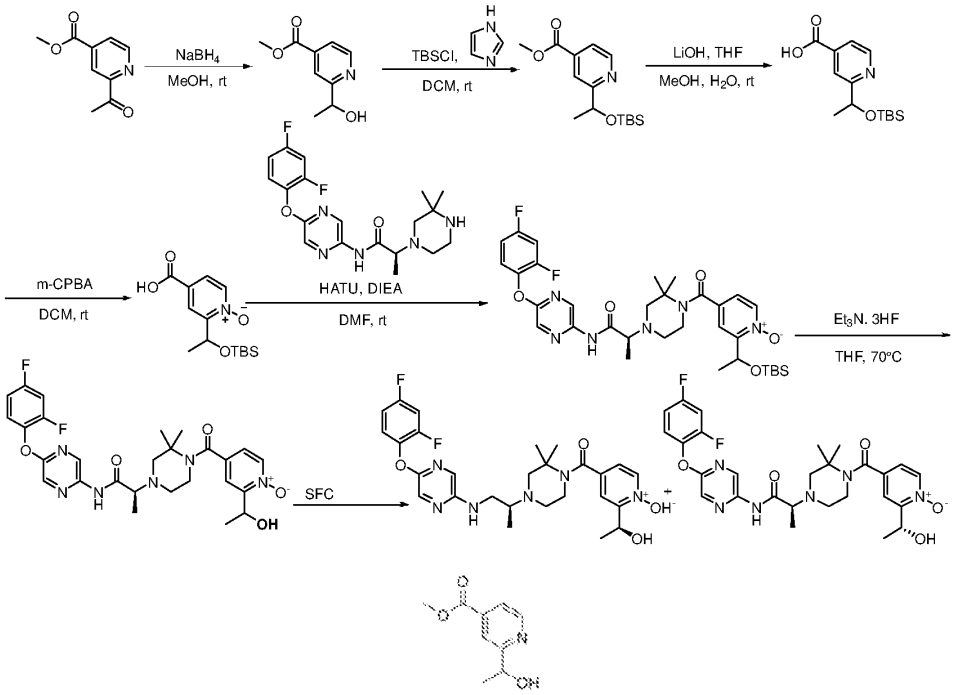
To a solution of 4-(oxetan-3-yl)-5-oxo-4,5-dihydropyrazine-2-carboxylic acid (80 mg, 0.408 mmol, 1.2 equiv) in DMF (5 mL) was added (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (133.03 mg, 0.340 mmol, 1 equiv) , HATU (193.84 mg, 0.510 mmol, 1.5 equiv) and DIEA (131.78 mg, 1.020 mmol, 3 equiv) . The reaction was

stirred at 25 °C for 2 h. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to afford the title compound (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(4-(oxetan-3-yl)-5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide (26.5 mg, 13.20%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{29}F_2N_7O_5$:569.17 m/z, found:570.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-*d6*) δ 10.42 (s, 1H), 8.85 (d, *J* = 1.4 Hz, 1H), 8.46 (d, *J* = 1.4 Hz, 1H), 8.03 (d, *J* = 1.1 Hz, 1H), 7.94 (d, *J* = 1.0 Hz, 1H), 7.41 – 7.55 (m, 2H), 7.18 – 7.23 (m, 1H), 5.45 – 5.51 (m, 1H), 4.76 – 4.87 (m, 4H), 3.49 – 3.52 (m, 1H), 3.44 – 3.47 (m, 2H), 2.68 – 2.77 (m, 2H), 2.42 – 2.48 (m, 2H), 1.47 (d, *J* = 3.0 Hz, 6H), 1.17 – 1.26 (m, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -113.43, -124.24.

Example 186: 4-(4-((S)-1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-((S)-1-hydroxyethyl)pyridine 1-oxide and Example 187: 4-(4-((S)-1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-((R)-1-hydroxyethyl)pyridine 1-oxide

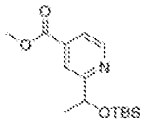


Synthetic Scheme



methyl 2-(1-hydroxyethyl)isonicotinate

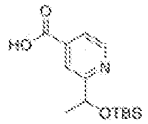
To a solution of methyl 2-acetylpyridine-4-carboxylate (1 g, 5.581 mmol, 1 equiv) in methanol (20 mL) the mixture was added $NaBH_4$ (0.23 g, 6.139 mmol, 1.1 equiv) at 0°C. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (20 mL) and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% EA/PE) to give methyl 2-(1-hydroxyethyl)isonicotinate (900 mg, 89.00%) as a white solid. MS (ESI): mass calcd. for $C_9H_{11}NO_3$: 181.07, found: 182.20 $[M+H]^+$.



methyl 2-(1-((tert-butyldimethylsilyl)oxy)ethyl)isonicotinate

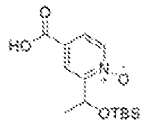
To a solution of methyl 2-(1-hydroxyethyl)isonicotinate (800 mg, 4.415 mmol, 1 equiv) in DCM (10 mL) the mixture was added t-butyldimethylchlorosilane (865.10 mg, 5.740 mmol, 1.3 equiv) and imidazole (601.17 mg, 8.830 mmol, 2 equiv) at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (20 mL)

and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% EA/PE) to give methyl 2-(1-((tert-butyldimethylsilyl)oxy)ethyl)isonicotinate (750 mg, 57.49%) a white solid. MS (ESI): mass calcd. for $C_{15}H_{25}NO_3Si$: 295.16, found: 296.20$[M+H]^+$.



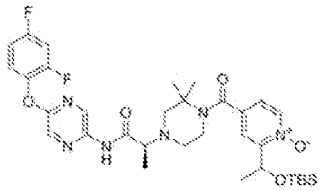
2-(1-((tert-butyldimethylsilyl)oxy)ethyl)isonicotinic acid

To a stirred solution of 2-(1-((tert-butyldimethylsilyl)oxy)ethyl)isonicotinate (600 mg, 2.031 mmol, 1 equiv) and lithiumol (243.19 mg, 10.155 mmol, 5 equiv) in methanol (3 mL), H2O (3 mL) and THF (6 mL) at room temperature. The reaction mixture was stirred at room temperature for a period of 3 h. The mixture was concentrated to dryness under reduced pressure to provide the crude product, which was purified by C18 column (0-20% H_2O/ACN) to afford 2-(1-((tert-butyldimethylsilyl)oxy)ethyl)isonicotinic acid. MS (ESI): mass calcd. for $C_{14}H_{23}NO_3Si$: 281.10 m/z. found 282.20 $[M+H]^+$.



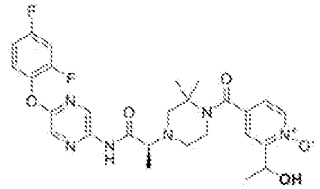
2-(1-((tert-butyldimethylsilyl)oxy)ethyl)-4-carboxypyridine 1-oxide

To a solution of 2-(1-((tert-butyldimethylsilyl)oxy)ethyl)isonicotinic acid (500 mg, 1.777 mmol, 1 equiv) in DCM (30 mL, 471.918 mmol, 265.62 equiv) the mixture was addedmcpba (1532.90 mg, 8.885 mmol, 5 equiv) at 0°C. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (20 mL) and extracted with DCM (30 mL x 3). The combined organic extracts were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by C18 chromatography (0-100% H_2O/ACN) to give 2-(1-((tert-butyldimethylsilyl)oxy)ethyl)-4-carboxypyridine 1-oxide as a white solid. MS (ESI): mass calcd. for $C_{14}H_{23}NO_4Si$: 297.13, found: 298.20$[M+H]^+$.



2-(1-((tert-butyldimethylsilyl)oxy)ethyl)-4-(4-((S)-1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

To a solution of (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (200 mg, 0.511 mmol, 1 equiv) in DMF (10 mL) the mixture was added 2-(1-((tert-butyldimethylsilyl)oxy)ethyl)-4-carboxypyridine 1-oxide (151.97 mg, 0.511 mmol, 1 equiv) , [(dimethylamino)({[1,2,3]triazolo[4,5-b]pyridin-3-yloxy})methylidene]dimethylazanium; hexafluoro-lambda5-phosphanuide (291.43 mg, 0.766 mmol, 1.5 equiv) and N,N-diisopropylethylamine (264.16 mg, 2.044 mmol, 4 equiv) at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to give 2-(1-((tert-butyldimethylsilyl)oxy)ethyl)-4-(4-((S)-1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide) as a white solid. MS (ESI): mass calcd. for $C_{33}H_{44}F_2N_6O_5Si$: 670.31, found: 671.20$[M+H]^+$.

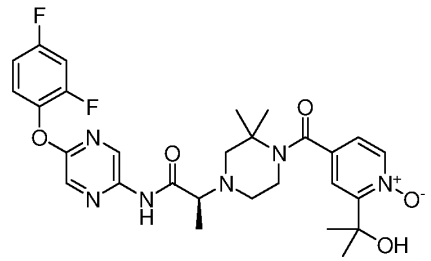


4-(4-((S)-1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-((S)-1-hydroxyethyl)pyridine 1-oxide and 4-(4-((S)-1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-((R)-1-hydroxyethyl)pyridine 1-oxide

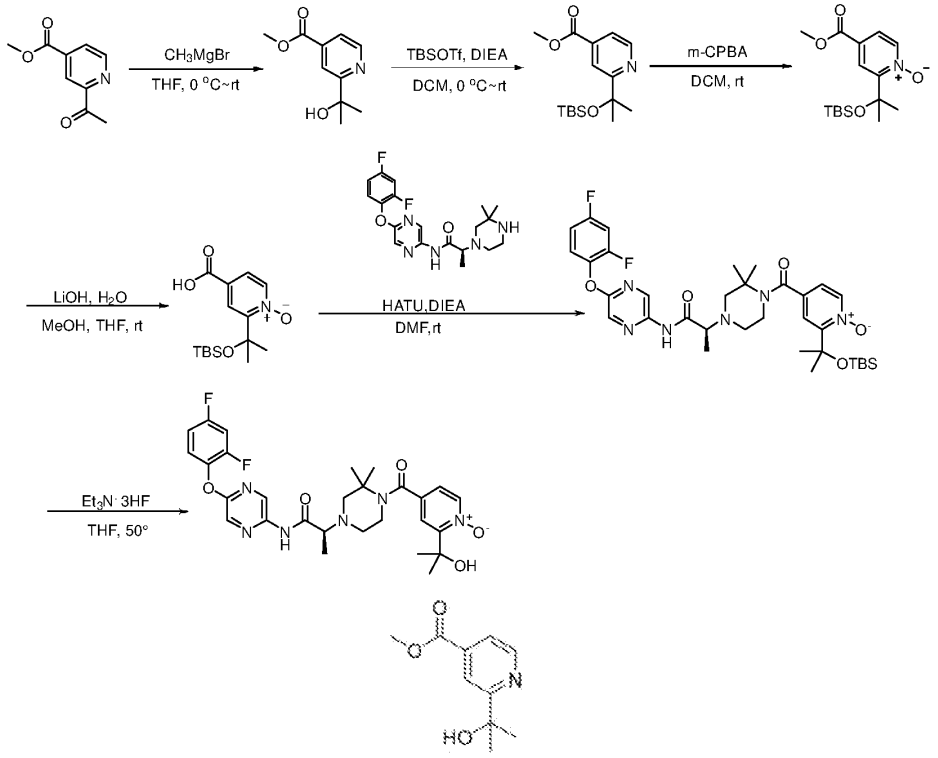
To a solution of 2-(1-((tert-butyldimethylsilyl)oxy)ethyl)-4-(4-((S)-1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (100 mg, 0.149 mmol, 1 equiv) in tetrahydrofuran (2 mL) the

mixture was added triethylamine trihydrofluoride (0.5 mL) . The mixture was stirred at 70°C for 2h. the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by chiral-HPLC using a CHIRALPAK IA, 2*25 cm, 5 μm column (eluent: 30% (v/v) MTBE (0.5% 2M NH_3-MeOH) and ETOH) to afford 4-(4-((S)-1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-((S)-1-hydroxyethyl)pyridine 1-oxide (21.0 mg, 25.10%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{30}F_2N_6O_5$: 556.22, found: 557.35 $[M+H]^+$.^{1}H NMR (400 MHz, DMSO-d_6) δ 10.45 (s, 1H), 8.85 (d, J = 1.5 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.23 (d, J = 6.6 Hz, 1H), 7.55 (d, J = 2.6 Hz, 1H), 7.41 – 7.54 (m, 2H), 7.35 (dd, J = 6.6, 2.6 Hz, 1H), 7.13 – 7.23 (m, 1H), 5.68 (d, J = 4.9 Hz, 1H), 5.00 – 5.10 (m, 1H), 3.55 (q, J = 6.8 Hz, 1H), 3.36 – 3.42 (m, 2H), 2.60 – 2.76 (m, 2H), 2.46 (s, 2H), 1.46 (s, 6H), 1.35 (d, J = 6.3 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H). And 4-(4-((S)-1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-((R)-1-hydroxyethyl)pyridine 1-oxide (21.0 mg, 25.10%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{30}F_2N_6O_5$: 556.22, found: 557.35 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.45 (s, 1H), 8.85 (d, J = 1.5 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.23 (d, J = 6.6 Hz, 1H), 7.55 (d, J = 2.6 Hz, 1H), 7.41 – 7.54 (m, 2H), 7.35 (dd, J = 6.6, 2.6 Hz, 1H), 7.13 – 7.23 (m, 1H), 5.68 (d, J = 4.9 Hz, 1H), 5.00 – 5.10 (m, 1H), 3.55 (q, J = 6.8 Hz, 1H), 3.36 – 3.42 (m, 2H), 2.60 – 2.76 (m, 2H), 2.46 (s, 2H), 1.46 (s, 6H), 1.35 (d, J = 6.3 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H). Stereochemistry of example 186 and example 187 was arbitrarily assigned.

Example 188: (S)-4-(4-(1-(5-(2,4-difluorophenoxy)pyrazin-2-ylamino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(2-hydroxypropan-2-yl)pyridine 1-oxide

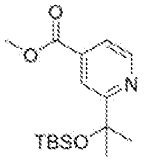


Synthetic Scheme



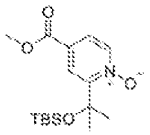
methyl 2-(2-hydroxypropan-2-yl)isonicotinate

To a solution of methyl 2-acetylpyridine-4-carboxylate (1 g, 5.581 mmol, 1 equiv) in tetrahydrofuran (10 mL) was added bromo(methyl)magnesium (0.67 g, 5.581 mmol, 1 equiv) under N_2 atmosphere at 0 °C. The reaction was stirred at 25°C for 1 h. Quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give methyl 2-(2-hydroxypropan-2-yl)pyridine-4-carboxylate (600 mg, 55.07%) as a yellow oil. MS (ESI): mass calcd. for $C_{10}H_{13}NO_3$:195.09 m/z, found:196.09 $[M+H]^+$.



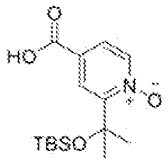
methyl 2-(2-(tert-butyldimethylsilyloxy)propan-2-yl)isonicotinate

To a solution of methyl 2-(2-hydroxypropan-2-yl)pyridine-4-carboxylate (600 mg, 3.073 mmol, 1 equiv) in DCM (10 mL) was added TBSOTf (1949.80 mg, 7.375 mmol, 2.4 equiv) and DIEA (1986.19 mg, 15.365 mmol, 5 equiv) at 0°C. The reaction was stirred at 25°C for 2 h. Quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give methyl 2-{2-[(tert-butyldimethylsilyl)oxy]propan-2-yl}pyridine-4-carboxylate (620 mg, 65.18%) as a yellow oil. TLC showed the desired product was generated.



2-(2-(tert-butyldimethylsilyloxy)propan-2-yl)-4-(methoxycarbonyl)pyridine 1-oxide

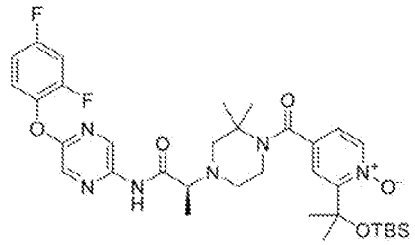
To a solution of methyl 2-{2-[(tert-butyldimethylsilyl)oxy]propan-2-yl}pyridine-4-carboxylate (640 mg, 2.068 mmol, 1 equiv) in DCM (10 mL, 1006.764 mmol) was added m-CPBA (356.85 mg, 2.068 mmol, 1 equiv). The reaction was stirred at 25°C for 2 h. Quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 2-{2-[(tert-butyldimethylsilyl)oxy]propan-2-yl}-4-(methoxycarbonyl)pyridin-1-ium-1-olate (420 mg, 62.40%) as a yellow oil. TLC showed the desired product was generated.



2-(2-(tert-butyldimethylsilyloxy)propan-2-yl)-4-carboxypyridine 1-oxide

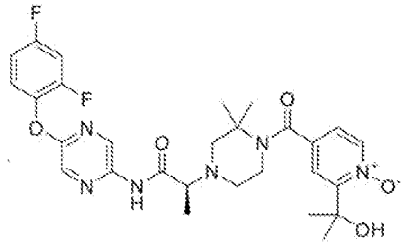
To a solution of 2-{2-[(tert-butyldimethylsilyl)oxy]propan-2-yl}-4-(methoxycarbonyl)pyridin-1-ium-1-olate (410 mg, 1.260 mmol, 1 equiv) in MeOH (5 mL) and THF (5 mL) was added LiOH (181.02 mg, 7.560 mmol, 6 equiv) and H_2O (2.5 mL). The reaction was stirred at 25°C for 1 h. The mixture was acidified to pH 3 with 2 N HCl. The precipitated solids were collected by filtration and washed with H_2O (3x5 mL). The resulting

solids was allowed to air-dry. MS (ESI): mass calcd. for $C_{15}H_{25}NO_4Si$:311.16 m/z, found:312.16 $[M+H]^+$.



(S)-2-(2-(tert-butyldimethylsilyloxy)propan-2-yl)-4-(4-(1-(5-(2,4-difluorophenoxy)pyrazin-2-ylamino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

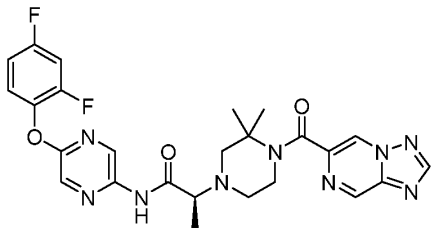
To a solution of 2-{2-[(tert-butyldimethylsilyl)oxy]propan-2-yl}-4-carboxypyridin-1-ium-1-olate (110 mg, 0.353 mmol, 1 equiv) in DMF (5 mL) was added (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (138.24 mg, 0.353 mmol, 1 equiv), HATU (134.29 mg, 0.353 mmol, 1 equiv) and DIEA (182.59 mg, 1.412 mmol, 4 equiv). The reaction was stirred at 25°C for 2 h. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (S)-2-(2-(tert-butyldimethylsilyloxy)propan-2-yl)-4-(4-(1-(5-(2,4-difluorophenoxy)pyrazin-2-ylamino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (210 mg, 86.82%) as a yellow oil. MS (ESI): mass calcd. for $C_{34}H_{46}F_2N_6O_5Si$:684.33 m/z, found:685.33 $[M+H]^+$.



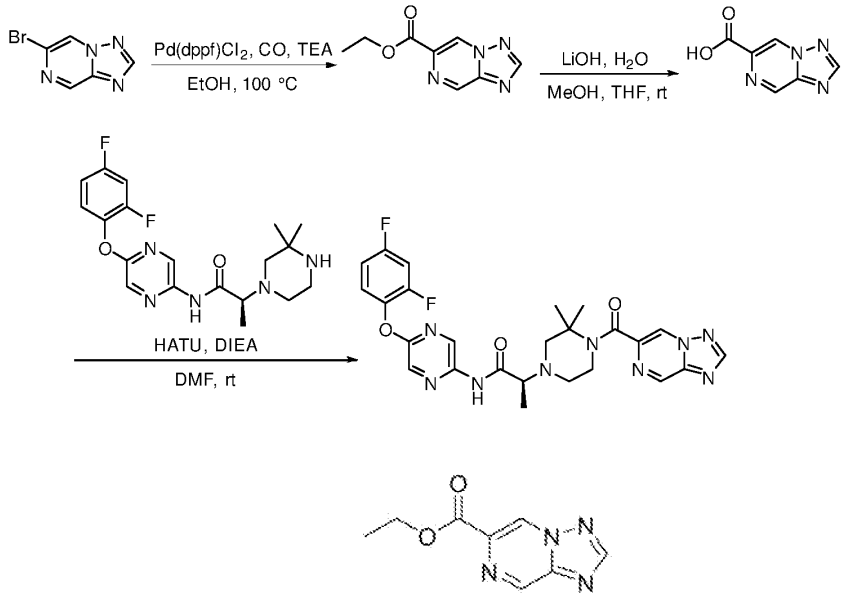
(S)-4-(4-(1-(5-(2,4-difluorophenoxy)pyrazin-2-ylamino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(2-hydroxypropan-2-yl)pyridine 1-oxide

To a solution of (S)-2-(2-(tert-butyldimethylsilyloxy)propan-2-yl)-4-(4-(1-(5-(2,4-difluorophenoxy)pyrazin-2-ylamino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (110 mg, 0.161 mmol, 1 equiv) in THF (4 mL) was added $Et_3N.3HF$ (4 mL, 28.777 mmol, 179.16 equiv) . The reaction was stirred at 50°C for 1h. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C_{18} 30*150 mm, 5μm column (eluent: 35% to 57% (v/v) ACN and H_2O with 10mmol/L NH_4HCO_3+0.05%NH_3H_2O to afford the title compound (S)-4-(4-(1-(5-(2,4-difluorophenoxy)pyrazin-2-ylamino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(2-hydroxypropan-2-yl)pyridine 1-oxide (30.5 mg, 33.05%) as a white solid. MS (ESI): mass calcd. for $C_{28}H_{32}F_2N_6O_5$:570.24 m/z, found:571.25 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 10.45 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.43 – 8.48 (m, 1H), 8.22 – 8.29 (m, 1H), 7.62 – 7.67 (m, 1H), 7.55 – 7.42 (m, 2H), 7.35 – 7.42 (m, 1H), 7.13 – 7.23 (m, 1H), 6.46 (s, 1H), 3.50 – 3.59 (m, 1H), 2.59 – 2.76 (m, 2H), 2.41 – 2.49 (m, 4H), 1.58 (s, 6H), 1.44 – 1.49 (m, 6H), 1.21 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO) δ -113.42, -124.21.

Example 189: (S)-2-(4-([1,2,4]triazolo[1,5-a]pyrazine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

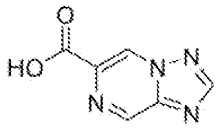


Synthetic Scheme



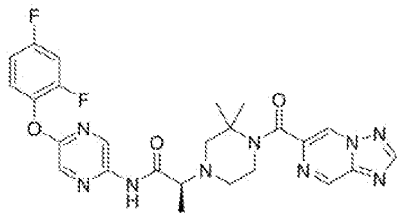
tert-butyl 3,3-dimethyl-4-(6-methyl-5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazine-1-carboxylate

To a solution of 6-bromo-[1,2,4]triazolo[1,5-a]pyrazine (1 g, 5.025 mmol, 1 equiv)in EtOH (15 mL) was added $Pd(dppf)_2Cl_2$ (352.69 mg, 0.503 mmol, 0.1 equiv) and TEA (1.53 g, 15.120 mmol, 3.01 equiv) in a pressure tank. The mixture was purged with nitrogen for 5 min and then was pressurized to 50 atm with carbon monoxide at 100 degrees for 12 h. The reaction mixture was cooled to room temperature and filtered to remove insoluble solids.The resulting mixture was allowed to warm to rt and stirred at rt for another 1h. It was quenched with Saturated sodium bicarbonate solution (5 mL), extracted with DCM (20 mL), the organic phase was dired over Na_2SO_4, filtered and concentrated. The residue was applied onto a silica gel column (40g, EtOAc/PE: 1:1) to afford ethyl [1,2,4]triazolo[1,5-a]pyrazine-6-carboxylate (500 mg, 51.78%) as a yellow oil, MS (ESI): mass calcd. for $C_8H_8N_4O_2$:192.06m/z, found:193.20$[M+H]^+$.



[1,2,4]triazolo[1,5-a]pyrazine-6-carboxylic acid

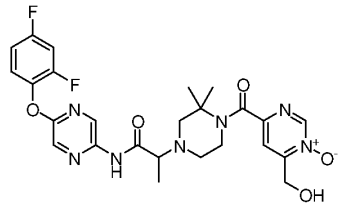
To a solution of ethyl [1,2,4]triazolo[1,5-a]pyrazine-6-carboxylate (250 mg, 1.301 mmol, 1 equiv) in THF (1 mL).methanol (0.5 mL, 0.008 mmol, 0.24 equiv), LiOH (37.39 mg, 1.561 mmol, 1.2 equiv) and water (0.5 mL, 0.014 mmol, 0.43 equiv) added at rt. The resulting mixture was stirred for 2h at rt. The resulting mixture was concentrated under vacuum. The residue was acidified to pH 2~3 with 3NHCl. The precipitated solids were collected by filtration and washed with H_2O (5mL) to afford [1,2,4]triazolo[1,5-a]pyrazine-6-carboxylic acid (150 mg, 70.26%) as a yellow oil. MS (ESI): mass calcd. for $C_6H_4N_4O_2$:164.06m/z, found:165.10$[M+H]^+$.



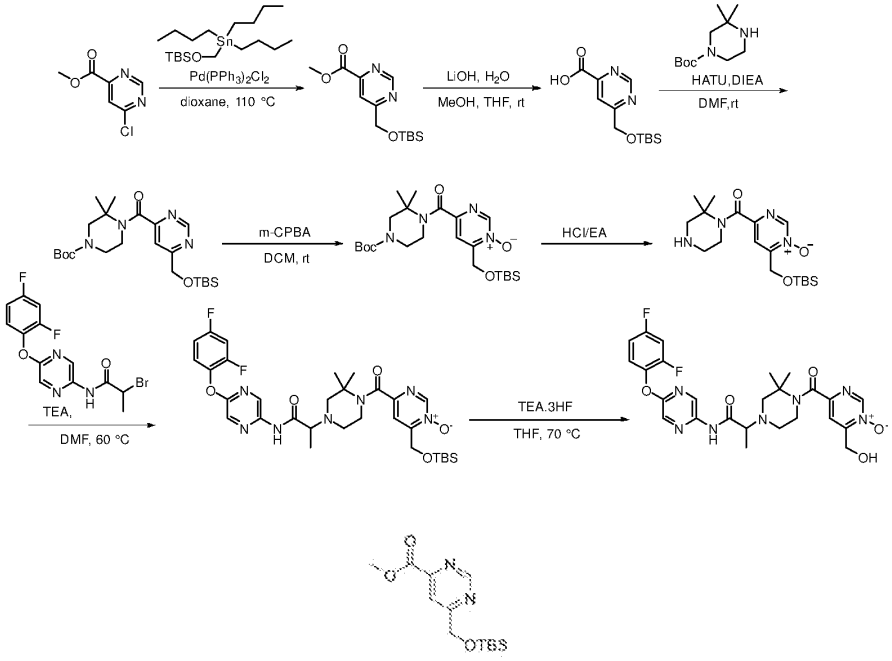
tert-butyl 3,3-dimethyl-4-(6-methyl-5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazine-1-carboxylate

To a solution of [1,2,4]triazolo[1,5-a]pyrazine-6-carboxylic acid (100 mg, 0.609 mmol, 1 equiv) in DMF (5 mL). (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (238.49 mg, 0.609 mmol, 1 equiv) ,HATU (231.68 mg, 0.609 mmol, 1 equiv) and DIEA (236.25 mg, 1.827 mmol, 3 equiv) added at rt. The resulting mixture was stirred for 2h at rt. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% PE/EA) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm (eluent: 35% to 55% ACN and H_2O (10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-2-(4-([1,2,4]triazolo[1,5-a]pyrazine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (26.4 mg, 8.04%) as a yellow solid, MS (ESI): mass calcd. for $C_{25}H_{25}F_2N_9O_3$:537.20m/z, found:538.30$[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.44 (s, 1H), 9.39 (d, J = 1.5 Hz, 1H), 9.31 (d, J = 1.4 Hz, 1H), 8.81 – 8.88 (m, 2H), 8.46 (d, J = 1.5 Hz, 1H), 7.41 – 7.54 (m, 2H), 7.12 – 7.22 (m, 1H), 3.49 – 3.59 (m, 1H), 3.45 (t, J = 5.3 Hz, 2H), 2.56 – 2.77 (m, 2H), 2.46 (d, J = 11.8 Hz, 2H), 1.51 (d, J = 3.2 Hz, 6H), 1.21 (d, J = 7.0 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -113.43, -124.22.

Example 190: 4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-6-(hydroxymethyl)pyrimidine 1-oxide



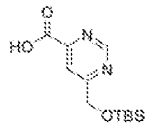
Synthetic Scheme



methyl 6-(((tert-butyldimethylsilyl)oxy)methyl)pyrimidine-4-carboxylate

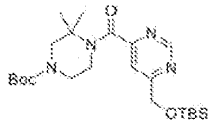
To a stirring solution methyl 6-chloropyrimidine-4-carboxylate (200 mg, 1.159 mmol, 1 equiv) in dioxane (5 mL) was added $Pd(PPh_3)_2Cl_2$ (81.35 mg, 0.116 mmol, 0.1 equiv) and tert-butyldimethyl[(tributylstannyl)methoxy]silane (605.47 mg, 1.391 mmol, 1.2 equiv). The mixture was stirred at 110 °C for 1 h under N_2. After cooled to room temperature, the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-80% PE/EA) to afford methyl 6-(((tert-

butyldimethylsilyl)oxy)methyl)pyrimidine-4-carboxylate (133 mg, 40.63%) as a yellow solid. MS (ESI): mass calcd. for $C_{13}H_{22}N_2O_3Si$: 282.415 m/z, found 283.05 $[M+H]^+$.



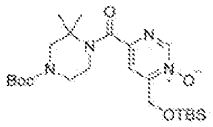
6-(((tert-butyldimethylsilyl)oxy)methyl)pyrimidine-4-carboxylic acid

To a solution of methyl 6-{[(tert-butyldimethylsilyl)oxy]methyl}pyrimidine-4-carboxylate (500 mg, 1.770 mmol, 1 equiv) in tetrahydrofuran (6 mL) methanol (3 mL) and water (3 mL) the mixture was added LiOH (84.80 mg, 3.540 mmol, 2.0 equiv). The mixture was stirred at room temperature for 2 h. After completion of reaction the mixture was acidified neutralized to (pH =3) with (4N HCl). The mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated to afford 6-(((tert-butyldimethylsilyl)oxy)methyl)pyrimidine-4-carboxylic acid (412 mg, 86.71%) as a yellow oil. MS (ESI): mass calcd. for $C_{12}H_{20}N_2O_3Si$: 268.12, found: 269.10 $[M+H]^+$.



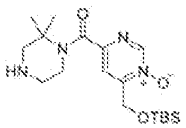
tert-butyl 4-(6-(((tert-butyldimethylsilyl)oxy)methyl)pyrimidine-4-carbonyl)-3,3-dimethylpiperazine-1-carboxylate

To a solution of 6-{[(tert-butyldimethylsilyl)oxy]methyl}pyrimidine-4-carboxylic acid (200 mg, 0.745 mmol, 1 equiv) in N,N-dimethylformamide (5 mL) the mixture was added tert-butyl 3,3-dimethylpiperazine-1-carboxylate (175.67 mg, 0.820 mmol, 1.1 equiv) HATU (425.02 mg, 1.117 mmol, 1.5 equiv) then added DIEA (288.94 mg, 2.235 mmol, 3.0 equiv). The mixture was stirred at room temperature for 2 h. After completion of reaction the mixture was quenched with water (30 mL) extracted with ethyl acetate (3 x 100 mL), the residue was washed with water (3 x 20 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% MeOH/DCM) to afford tert-butyl 4-(6-(((tert-butyldimethylsilyl)oxy)methyl)pyrimidine-4-carbonyl)-3,3-dimethylpiperazine-1-carboxylate (253 mg, 73.06%) as a yellow solid. MS (ESI): mass calcd. for $C_{23}H_{40}N_4O_4Si$: 464.28, found: 465.40 $[M+H]^+$.



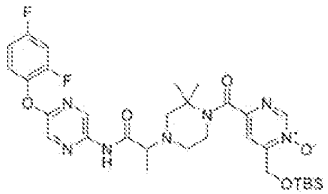
4-(4-(tert-butoxycarbonyl)-2,2-dimethylpiperazine-1-carbonyl)-6-(((tert-butyldimethylsilyl)oxy)methyl)pyrimidine 1-oxide

To a solution of tert-butyl 4-(6-{[(tert-butyldimethylsilyl)oxy]methyl}pyrimidine-4-carbonyl)-3,3-dimethylpiperazine-1-carboxylate (400 mg, 0.861 mmol, 1 equiv) in DCM (10 mL) the mixture was added m-CPBA (297.08 mg, 1.722 mmol, 2.0 equiv). The mixture was stirred at room temperature for 16 h. After completion of reaction the mixture was quenched with water (50 mL) extracted with ethyl acetate (3 x 100 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10%MeOH /DCM) to afford 4-(4-(tert-butoxycarbonyl)-2,2-dimethylpiperazine-1-carbonyl)-6-(((tert-butyldimethylsilyl)oxy)methyl)pyrimidine 1-oxide (assumed, 125 mg, 30.21%) as a yellow solid. MS (ESI): mass calcd. for $C_{23}H_{40}N_4O_5Si$: 480.28, found: 481.40 $[M+H]^+$. And 6-(4-(tert-butoxycarbonyl)-2,2-dimethylpiperazine-1-carbonyl)-4-(((tert-butyldimethylsilyl)oxy)methyl)pyrimidine 1-oxide (assumed, 113 mg, 27.31%) as a yellow solid. MS (ESI): mass calcd. for $C_{23}H_{40}N_4O_5Si$: 480.28, found: 481.40 $[M+H]^+$.



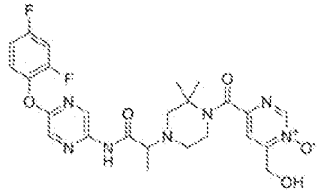
6-(((tert-butyldimethylsilyl)oxy)methyl)-4-(2,2-dimethylpiperazine-1-carbonyl)pyrimidine 1-oxide

To a solution of 4-[4-(tert-butoxycarbonyl)-2,2-dimethylpiperazine-1-carbonyl]-6-{[(tert-butyldimethylsilyl)oxy]methyl}pyrimidin-1-ium-1-olate (120 mg, 0.250 mmol, 1 equiv) in EA (2 mL) and 2N HCl in EA (2 mL). The mixture was stirred at room temperature for 2 h. After completion of reaction the mixture was concentrated basified neutralized to pH =13 with $NaHCO_3$ solution extracted with ethyl acetate (3 x 100 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated to afford 6-(((tert-butyldimethylsilyl)oxy)methyl)-4-(2,2-dimethylpiperazine-1-carbonyl)pyrimidine 1-oxide (85 mg, 89.47%) as a yellow solid.



6-(((tert-butyldimethylsilyl)oxy)methyl)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyrimidine 1-oxide

To a solution of 6-(((tert-butyldimethylsilyl)oxy)methyl)-4-(2,2-dimethylpiperazine-1-carbonyl)pyrimidine 1-oxide (80 mg, 0.210 mmol, 1 equiv) in DMF (2 mL) the mixture was added 2-bromo-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (75.29 mg, 0.210 mmol, 1.0 equiv) and TEA (63.82 mg, 0.630 mmol, 3.0 equiv). The mixture was stirred at 60 °C for 5 h. After completion of reaction the mixture was quenched with water (10 mL) extracted with ethyl acetate (3 x 50 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50%EA/PE) to afford 6-(((tert-butyldimethylsilyl)oxy)methyl)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyrimidine 1-oxide (20 mg, 14.46%) as a yellow solid.

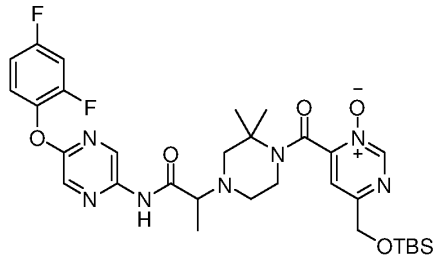


4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-6-(hydroxymethyl)pyrimidine 1-oxide

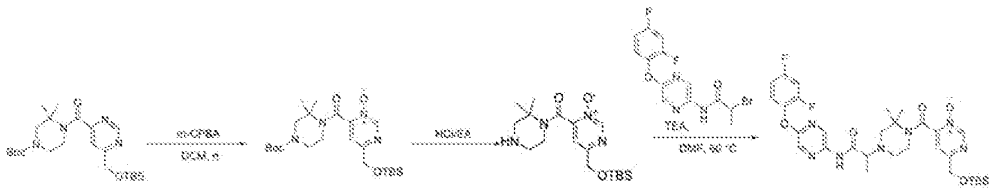
To a solution of 6-(((tert-butyldimethylsilyl)oxy)methyl)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyrimidine 1-oxide (15 mg, 0.023 mmol, 1 equiv) in tetrahydrofuran (0.4 mL) the mixture was added triethylamine trihydrofluoride (0.1 mL). The mixture was stirred at 70°C for 2 h. The reaction was quenched by water (5 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by preparative HPLC using a YMC-Actus Triart C18 ExRS 150 mm x 30 mm column (eluent: 28% to 42% (v/v) ACN and H_2O with 10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford 4-(4-(1-((5-(2,4-

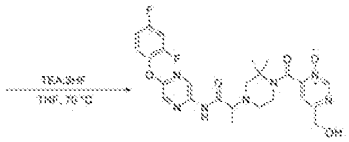
difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-6-(hydroxymethyl)pyrimidine 1-oxide (4.7 mg, 30.93%) as a light yellow solid. MS (ESI): mass calcd. for $C_{25}H_{27}F_2N_7O_5$: 543.20, found: 544.30 $[M+H]^+$. ^1H NMR (300 MHz, Methanol-d_4) δ 8.99 (s, 1H), 8.88 (s, 1H), 8.28 (s, 1H), 7.94 (s, 1H), 7.25 – 7.40 (m, 1H), 7.08 – 7.20 (m, 1H), 6.96 – 7.07 (m, 1H), 4.79 (s, 2H), 4.53 (q, J = 7.0 Hz, 1H), 3.61 – 3.84 (m, 2H), 3.30 (s, 1H), 3.12 – 3.22 (m, 1H), 3.00 – 3.10 (m, 1H), 2.92 (s, 2H), 1.65 (dd, J = 6.1, 3.0 Hz, 6H), 1.50 (d, J = 7.0 Hz, 3H).

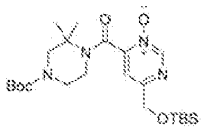
Example 191: 4-(((tert-butyldimethylsilyl)oxy)methyl)-6-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyrimidine 1-oxide



Synthetic Scheme

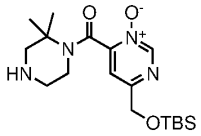






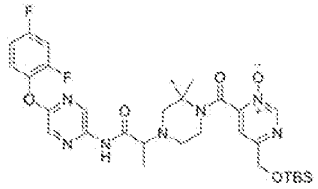
6-(4-(tert-butoxycarbonyl)-2,2-dimethylpiperazine-1-carbonyl)-4-(((tert-butyldimethylsilyl)oxy)methyl)pyrimidine 1-oxide

To a solution of tert-butyl 4-(6-{[(tert-butyldimethylsilyl)oxy]methyl}pyrimidine-4-carbonyl)-3,3-dimethylpiperazine-1-carboxylate (400 mg, 0.861 mmol, 1 equiv) in DCM (10 mL) the mixture was added m-CPBA (297.08 mg, 1.722 mmol, 2.0 equiv). The mixture was stirred at room temperature for 16 h. After completion of reaction the mixture was quenched with water (50 mL) extracted with ethyl acetate (3 x 100 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10%MeOH /DCM) to afford 4-(4-(tert-butoxycarbonyl)-2,2-dimethylpiperazine-1-carbonyl)-6-(((tert-butyldimethylsilyl)oxy)methyl)pyrimidine 1-oxide (assumed, 125 mg, 30.21%) as a yellow solid. MS (ESI): mass calcd. for $C_{23}H_{40}N_4O_5Si$: 480.28, found: 481.40 $[M+H]^+$. And 6-(4-(tert-butoxycarbonyl)-2,2-dimethylpiperazine-1-carbonyl)-4-(((tert-butyldimethylsilyl)oxy)methyl)pyrimidine 1-oxide (assumed, 113 mg, 27.31%) as a yellow solid. MS (ESI): mass calcd. for $C_{23}H_{40}N_4O_5Si$: 480.28, found: 481.40 $[M+H]^+$.



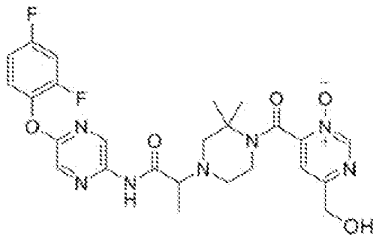
4-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-(2,2-dimethylpiperazine-1-carbonyl)pyrimidine 1-oxide

To a solution of 6-[4-(tert-butoxycarbonyl)-2,2-dimethylpiperazine-1-carbonyl]-4-{[(tert-butyldimethylsilyl)oxy]methyl}pyrimidin-1-ium-1-olate (110 mg, 0.229 mmol, 1 equiv) in EA (2 mL) and 2N HCl in EA (2 mL). The mixture was stirred at room temperature for 2 h. After completion of reaction the mixture was concentrated basified neutralized to pH =13 with $NaHCO_3$ solution extracted with ethyl acetate (3 x 100 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated to afford 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (76 mg, 87.27%) as a yellow solid.



4-(((tert-butyldimethylsilyl)oxy)methyl)-6-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyrimidine 1-oxide

To a solution of 2-(2,2-dimethylpiperazine-1-carbonyl)-4-(hydroxymethyl)pyridine 1-oxide (70 mg, 0.184 mmol, 1 equiv) in DMF (2 mL) the mixture was added 2-bromo-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (65.88 mg, 0.184 mmol, 1.0 equiv) and TEA (55.84 mg, 0.552 mmol, 3.0 equiv). The mixture was stirred at 60 °C for 5 h. After completion of reaction the mixture was quenched with water (10 mL) extracted with ethyl acetate (3 x 500 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50%EA/PE) to afford 4-(((tert-butyldimethylsilyl)oxy)methyl)-6-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyrimidine 1-oxide (18 mg, 14.88%) as a yellow solid.

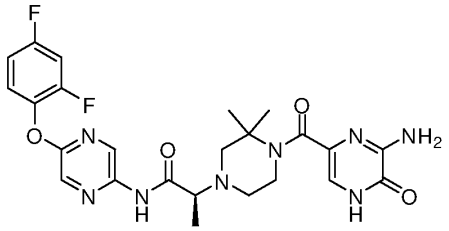


4-(((tert-butyldimethylsilyl)oxy)methyl)-6-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyrimidine 1-oxide

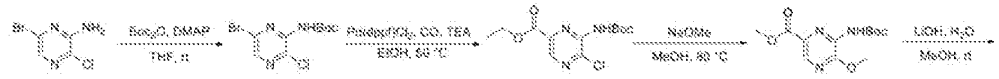
To a solution of 4-(((tert-butyldimethylsilyl)oxy)methyl)-6-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyrimidine 1-oxide (10 mg, 0.015 mmol, 1 equiv) in tetrahydrofuran (0.4 mL) the mixture was added triethylamine trihydrofluoride (0.1 mL). The mixture was stirred at 70°C for 2 h. The reaction was quenched by water (5 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by preparative HPLC using a YMC-Actus Triart C18 ExRS 150 mm x 30 mm column (eluent: 28% to 42% (v/v)

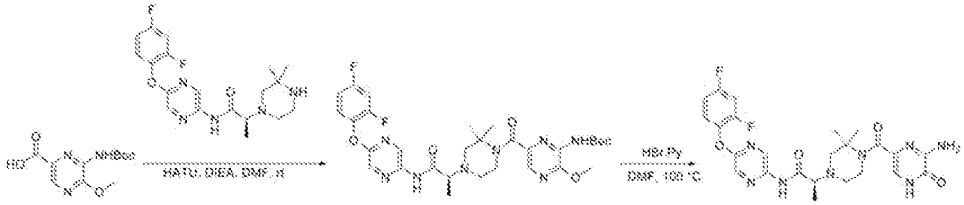
ACN and H_2O with 10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford 4-(((tert-butyldimethylsilyl)oxy)methyl)-6-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyrimidine 1-oxide (2.1 mg, 24.36%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{27}F_2N_7O_5$ 543.20, found: 544.30 $[M+H]^+$. ^1H NMR (300 MHz, Methanol-d_4) δ 9.00 (s, 1H), 8.88 (s, 1H), 8.28 (s, 1H), 7.65 (s, 1H), 7.27 – 7.41 (m, 1H), 7.09 – 7.22 (m, 1H), 6.98 – 7.09 (m, 1H), 4.70 (s, 2H), 4.61 (s, 1H), 3.44 – 3.63 (m, 2H), 2.43 – 2.90 (m, 4H), 1.69 (d, J = 4.3 Hz, 6H), 1.24-1.39 (m, 3H).

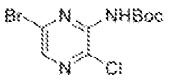
Example 192: (S)-2-(4-(6-amino-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide



Synthetic Scheme



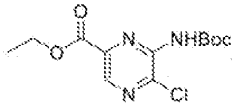




tert-butyl (6-bromo-3-chloropyrazin-2-yl)carbamate

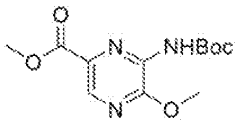
To a solution of 6-bromo-3-chloropyrazin-2-amine (1.2 g, 5.757 mmol, 1 equiv) in THF (1mL) was added Boc_2O (2512.94 mg, 11.514 mmol, 2 equiv) DMAP (140.67 mg, 1.151 mmol, 0.2 equiv) at rt .The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water and extracted with EA (2*100 mL). The combined organic

extracts were washed with brine (100mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford tert-butyl (6-bromo-3-chloropyrazin-2-yl)carbamate (1.5 g, 50.33%) as a yellow oil .MS (ESI): mass calcd. for $C_9H_{11}BrClN_3O_2$ 308.56m/z, found 253.95 $[M+H]^+$.



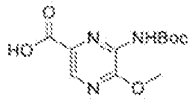
ethyl 6-((tert-butoxycarbonyl)amino)-5-chloropyrazine-2-carboxylate

To a solution of tert-butyl (6-bromo-3-chloropyrazin-2-yl)carbamate (1.6 g, 5.185 mmol, 1 equiv) in 20 mL EtOH was added $Pd(dppf)Cl_2$ (0.38 g, 0.518 mmol, 0.1 equiv) in a pressure tank. The mixture was purged with nitrogen for 1 min and then was pressurized to 30 atm with carbon monoxide at 50 °C for overnight. The reaction mixture was cooled to room temperature and filtered to remove insoluble solids. The resulting mixture was concentrated under reduced pressure. The residue/crude product was purified by reverse phase flash to afford ethyl 6-((tert-butoxycarbonyl)amino)-5-chloropyrazine-2-carboxylate (900 mg, 50.33%) as a . MS (ESI): mass calcd. for $C_{12}H_{16}ClN_3O_4$ 301.73m/z, found 302.10 $[M+H]^+$.



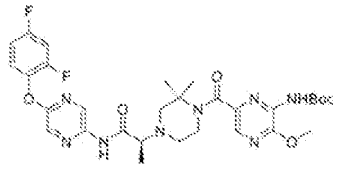
methyl 6-((tert-butoxycarbonyl)amino)-5-methoxypyrazine-2-carboxylate

To a solution of ethyl 6-[(tert-butoxycarbonyl)amino]-5-chloropyrazine-2-carboxylate (500 mg, 1.657 mmol, 1 equiv) in MeOH (1mL) was addedsodium methoxide (179.05 mg, 3.314 mmol, 2 equiv) at rt .The resulting mixture was stirred for overnight at 80 °C. The reaction mixture was quenched by water and extracted with EA (2*100 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford methyl 6-((tert-butoxycarbonyl)amino)-5-methoxypyrazine-2-carboxylate (560 mg, 50.33%) as a yellow oil. MS (ESI): mass calcd. for $C_{12}H_{17}N_3O_5$ 283.284 m/z, found 283.85$[M+H]^+$.



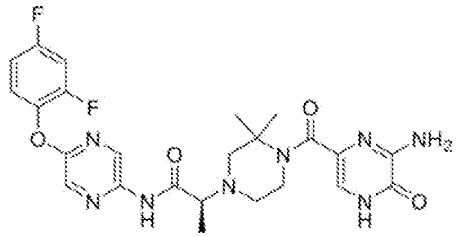
6-((tert-butoxycarbonyl)amino)-5-methoxypyrazine-2-carboxylic acid

To a solution of methyl 6-[(tert-butoxycarbonyl)amino]-5-methoxypyrazine-2-carboxylate (10 mg, 0.035 mmol, 1 equiv) in THF (4mL) : MeOH (2 mL) : H_2O(2 mL)was added LiOH (1.69 mg, 0.070 mmol, 2 equiv) at rt .The resulting mixture was stirred for 3h at rt. Desired product could be detected by LCMS .The mixture/residue was acidified/basified/neutralized to pH 4 with 2 N HCl (aq.).The resulting mixture was filtered, the filter cake was washed with H_2O (2x6 mL). The filtrate was concentrated under reduced pressure to afford 6-((tert-butoxycarbonyl)amino)-5-methoxypyrazine-2-carboxylic acid (140 mg, 29.33%) as a yellow solid, MS (ESI): mass calcd. for $C_{11}H_{15}N_3O_5$:269.27, found:270.30[M+H] $^+$.



tert-butyl (S)-(6-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-3-methoxypyrazin-2-yl)carbamate

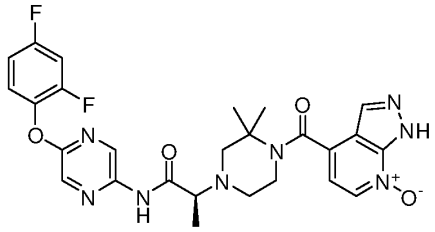
To a solution of 6-((tert-butoxycarbonyl)amino)-5-methoxypyrazine-2-carboxylic acid (200 mg, 0.743 mmol, 1 equiv) in DMF (5ml). (2S)-N- [5-(2,4-difluorophenoxy) pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl) propanamide (290.74 mg, 0.743 mmol, 1 equiv), HATU (423.65 mg, 1.115 mmol, 1.5 equiv) and DIEA (384.01 mg, 2.972 mmol, 4 equiv) was added at rt. The mixture was allowed to warm to room temperature and stirred for 2 h. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% PE/EA) to afford tert-butyl (S)-(6-(4-(1-((5-(2,4-difluorophenoxy) pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-3-methoxypyrazin-2-yl)carbamate (140 mg, 29.33%) as a yellow solid, MS (ESI): mass calcd. for $C_{30}H_{36}F_2N_8O_6$:642.27 m/z, found:542.75[M+H] $^+$.



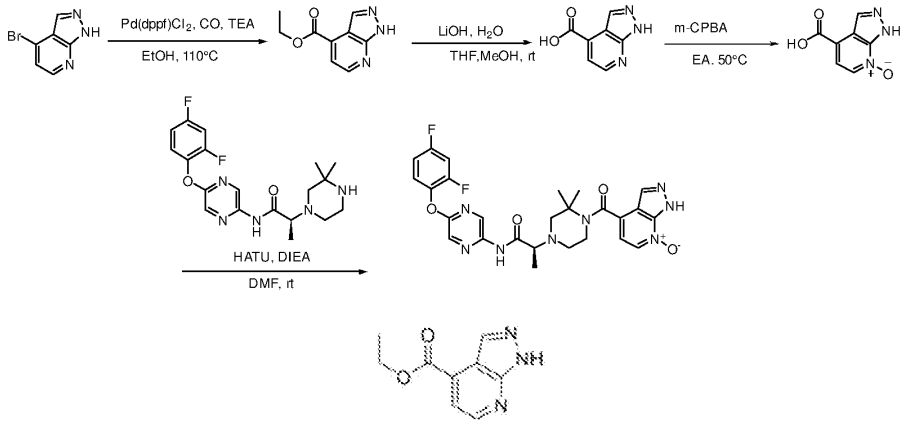
(S)-2-(4-(6-amino-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

To a solution of tert-butyl (S)-(6-(4-(1-((5-(2,4-difluorophenoxy) pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-3-methoxypyrazin-2-yl)carbamate (100 mg, 0.156 mmol, 1 equiv) in DMF (3 mL). Pyridine hydrobromide (124.49 mg, 0.780 mmol, 5 equiv) added at rt. The resulting mixture was stirred for 2 h at rt. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% PE/EA) and Prep-HPLC using a Column: YMC-Actus Triart C18 ExRS30*150 mm; (eluent: 27% to 47% ACN and H_2O (10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-2-(4-(6-amino-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (13.3 mg, 15.71%) as a white solid, MS (ESI): mass calcd. for $C_{24}H_{26}F_2N_8O_4$:528.20 m/z, found:529.25$[M+H]^+$.

Example 193: (S)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-1H-pyrazolo[3,4-b]pyridine 7-oxide

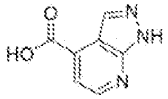


Synthetic Scheme



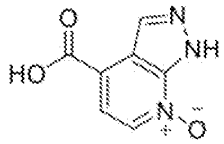
ethyl 1H-pyrazolo[3,4-b]pyridine-4-carboxylate

To a solution of 4-bromo-1H-pyrazolo[3,4-b]pyridine (1 g, 5.050 mmol, 1 equiv) in EtOH (25 mL) was added Pd(dppf)Cl_2 (0.37 g, 0.505 mmol, 0.1 equiv) and TEA (1.53 g, 15.150 mmol, 3 equiv) at rt. The autoclave was sealed, purged three times with carbon monoxide (CO), and pressurized to 50 ATM with CO. The reaction mixture was stirred at 110 °C for overnight. The autoclave was cooled to room temperature and CO was carefully released. The catalytic system was magnetically separated and the solution decanted and evaporated under vacuum in a rotary evaporator. The products were purified by column chromatography on silica gel (PE/EA = 3:1) to afford ethyl 1H-pyrazolo[3,4-b]pyridine-4-carboxylate (0.5 g, 51.8%) as a white solid. MS (ESI): mass calcd. for $C_9H_9N_3O_2$ 191.19 m/z, found 192.15 $[M+H]^+$.



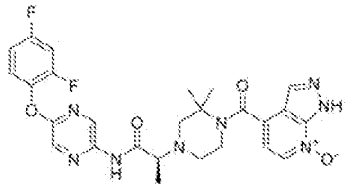
1H-pyrazolo[3,4-b]pyridine-4-carboxylic acid

To a solution of ethyl ethyl 1H-pyrazolo[3,4-b]pyridine-4-carboxylate (900 mg, 4.707 mmol, 1 equiv) in THF (10 mL) was added MeOH (5 mL, 123.494 mmol, 26.23 equiv) and H_2O (5 mL, 277.546 mmol, 58.96 equiv) and LiOH.H_2O (395.04 mg, 9.414 mmol, 2 equiv) at rt .The resulting mixture was stirred for 2h at rt. The mixture was acidified to pH 2 with 2N HCl (aq.). The precipitated solids were collected by filtration and washed with water to afford 1H-pyrazolo[3,4-b]pyridine-4-carboxylic acid (0.6 g, crude) as a yellow solid. MS (ESI): mass calcd. for $C_7H_5N_3O_2$ 163.13m/z, found 164.15M+H]$^+$.



4-carboxy-1H-pyrazolo[3,4-b]pyridine 7-oxide

To a solution of 1H-pyrazolo[3,4-b]pyridine-4-carboxylic acid (400 mg, 2.452 mmol, 1 equiv) in EA (8 mL) was added m-CPBA (1692.43 mg, 9.808 mmol, 4 equiv) at 0 °C. The resulting mixture was stirred for 4h at 50 °C. The autoclave was cooled to room temperature. The reaction mixture was quenched by water and extracted with EA (3*30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford 4-carboxy-1H-pyrazolo[3,4-b]pyridine 7-oxide (0.2 g, 45.5%) as a yellow solid. MS (ESI): mass calcd. for $C_7H_5N_3O_3$ 179.13 m/z, found 180.10M+H]$^+$.

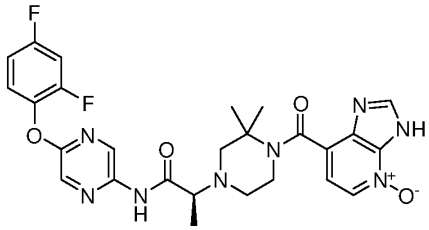


(S)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-1H-pyrazolo[3,4-b]pyridine 7-oxide

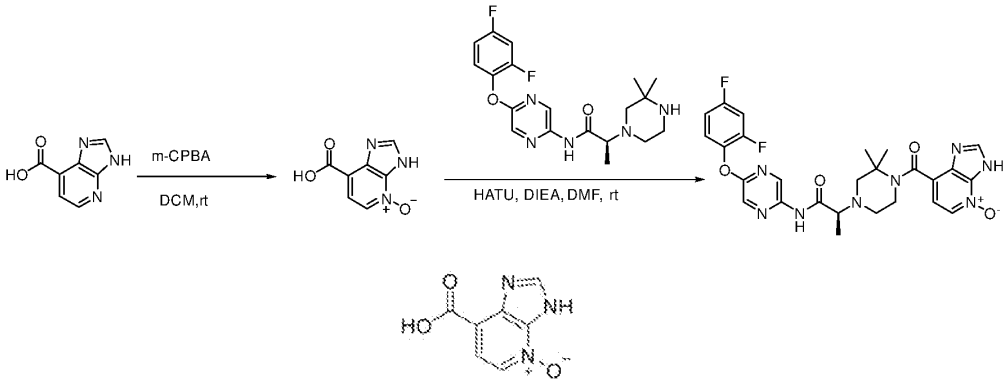
To a solution of 4-carboxy-1H-pyrazolo[3,4-b]pyridin-7-ium-7-olate (120 mg, 0.670 mmol, 1 equiv) in DMF (3mL) was added (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(piperazin-1-yl)propanamide (194.73 mg, 0.536 mmol, 0.8 equiv) and HATU (382.07 mg, 1.005 mmol, 1.5 equiv) and DIEA (519.48 mg, 4.020 mmol, 6 equiv) at rt. The resulting mixture was stirred for 3h at rt. The reaction mixture was quenched by water and extracted with EA (2*30 mL). The combined organic extracts were washed with brine (10mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography DCM/MeOH (0-20%) and purified by preparative HPLC using a XBridge Prep OBD 150 mm x 30 mm x 5 μm column (eluent: 27% to 41% (v/v) ACN and H_2O with 10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford product (S)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-1H-pyrazolo[3,4-b]pyridine 7-oxide (18.4 mg, 4.92%) as a white solid. MS

(ESI): mass calcd. for $C_{26}H_{26}F_2N_8O_4$ 552.20 m/z, found 553.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 8.34 (d, J = 6.1 Hz, 1H), 8.28 (s, 1H), 7.40 – 7.56 (m, 2H), 7.17 (dd, J = 10.5, 7.3 Hz, 2H), 3.53 (d, J = 6.9 Hz, 1H), 3.35 – 3.39 (m, 2H), 2.62 – 2.72 (m, 1H), 2.53 – 2.59 (m, 2H), 2.48 – 2.52 (m, 1H), 1.53 (s, 6H), 1.21 (d, J = 6.9 Hz, 3H).

Example 194: (S)-7-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-3H-imidazo[4,5-b]pyridine 4-oxide



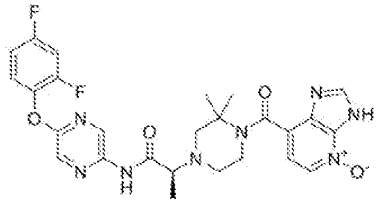
Synthetic Scheme



7-carboxy-3H-imidazo[4,5-b]pyridine 4-oxide

To a stirring solution 3H-imidazo[4,5-b]pyridine-7-carboxylic acid (400 mg, 2.452 mmol, 1 equiv) in NMP (5 mL) was added a solution of m-CPBA (2961.75 mg, 17.164 mmol, 7 equiv) .The resulting mixture was stirred at rt for 6h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford 7-carboxy-3H-imidazo[4,5-b]pyridine 4-

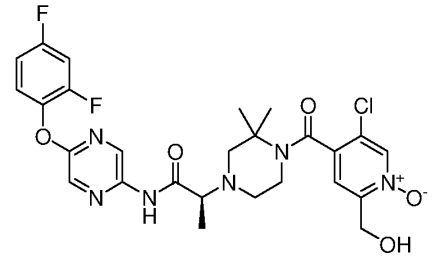
oxide (200 mg, 45.53%) MS (ESI): mass calcd. for $C_7H_5N_3O_3$: 179.13 m/z found: 180.10$[M+H]^+$.



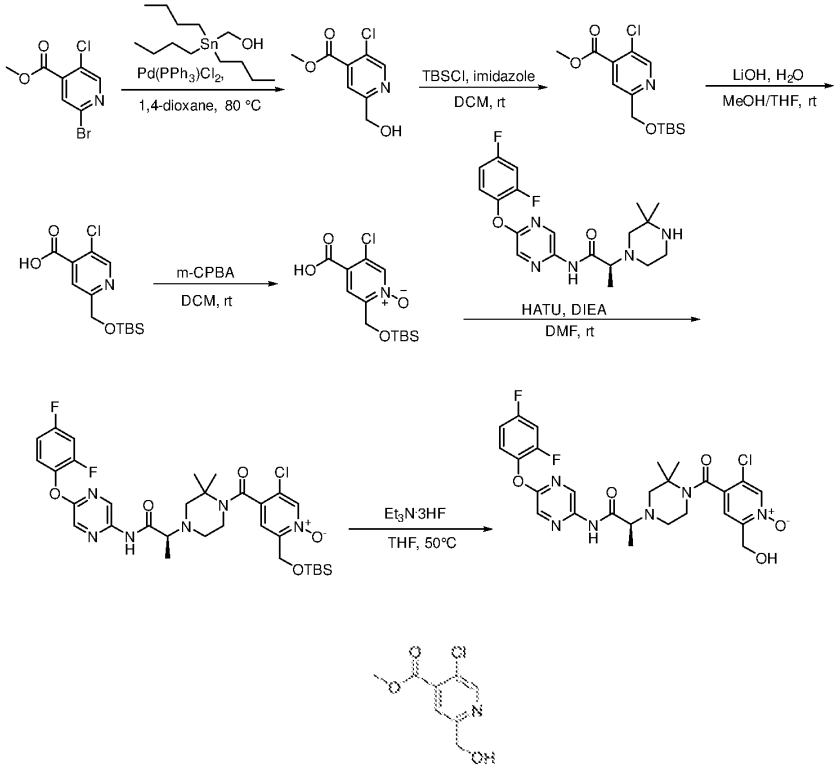
(S)-7-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-3H-imidazo[4,5-b]pyridine 4-oxide

To a stirred solution of 2-bromo-N-(5-(2,4,5-trifluorophenoxy)pyrazin-2-yl)propanamide (100 mg, 0.558 mmol, 1 equiv) in dimethylformamide (3 mL) was added (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (327.76 mg, 0.837 mmol, 1.5 equiv) and HATU (424.52 mg, 1.116 mmol, 2 equiv) and DIEA (288.60 mg, 2.232 mmol, 4 equiv) at room temperature . The reaction mixture was stirred at room temperature for 3 h. The resulting mixture was stirred for additional overnight at room temperature. After completion of reaction, the reaction mixture was quenched by addition of water (5 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and the residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30 x150mm x 5μm (eluent: 18% to 48% (v/v) CH_3CN and H_2O with NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-7-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-3H-imidazo[4,5-b]pyridine 4-oxide (11.1 mg, 3.48%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{26}F_2N_8O_4$: 552.20 m/z, found: 553.30$[M+H]^+$, ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.84 (s, 1H), 8.45 (s, 1H), 8.35 (s, 1H), 8.15 (d, J = 6.5 Hz, 1H), 7.48 (tq, J = 9.2, 6.1, 4.5 Hz, 2H), 7.17 (td, J = 8.7, 3.0 Hz, 2H), 3.53 (d, J = 7.0 Hz, 4H), 2.61 – 2.76 (m, 3H), 1.53 (s, 6H), 1.21 (d, J = 6.9 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -113.42 (d, J = 5.2 Hz), -124.21 (d, J = 5.3 Hz).

Example 195: (S)-5-chloro-4-(4-(1-(5-(2,4-difluorophenoxy)pyrazin-2-ylamino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide



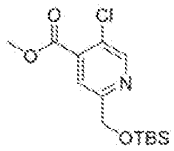
Synthetic Scheme



methyl 5-chloro-2-(hydroxymethyl)isonicotinate

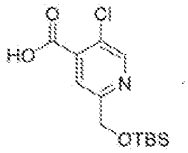
To a solution of methyl 2-bromo-5-chloropyridine-4-carboxylate (1 g, 3.992 mmol, 1 equiv) in 1,4-dioxane (10 mL) was added (tributylstannyl)methanol (2.563 g, 7.984 mmol, 2 equiv) and $Pd(PPh_3)_2Cl_2$ (280.22 mg, 0.399 mmol, 0.1 equiv). The reaction was stirred at 80°C for 2 h under N_2 atmosphere. The mixture was allowed to cool down to room temperature. Quenched with water (500 mL) and extracted with EA (3 x 300 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE

(0-100%) to give methyl 5-chloro-2-(hydroxymethyl)pyridine-4-carboxylate (320 mg, 39.76%) as a yellow oil. MS (ESI): mass calcd. for $C_8H_8ClNO_3$: 201.02 m/z, found: 202.02 $[M+H]^+$.



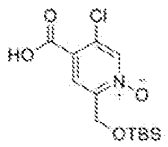
methyl 2-((tert-butyldimethylsilyloxy)methyl)-5-chloroisonicotinate

To a solution of methyl 5-chloro-2-(hydroxymethyl)pyridine-4-carboxylate (850 mg, 4.216 mmol, 1 equiv) in DCM (10 mL) was added TBSCl (762.53 mg, 5.059 mmol, 1.2 equiv) and Imidazole (2870.25 mg, 42.160 mmol, 10 equiv). The reaction was stirred at 25 °C for 2 h. Quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give methyl 2-{[(tert-butyldimethylsilyl)oxy]methyl}-5-chloropyridine-4-carboxylate (550 mg, 41.30%) as a yellow oil. MS (ESI): mass calcd. for $C_{14}H_{22}ClNO_3Si$:315.11 m/z, found: 316.11 $[M+H]^+$.



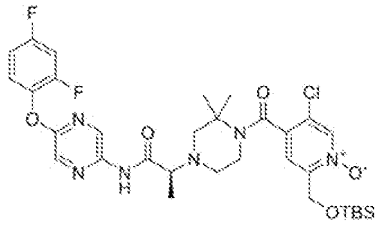
2-((tert-butyldimethylsilyloxy)methyl)-5-chloroisonicotinic acid

To a solution of methyl 2-{[(tert-butyldimethylsilyl)oxy]methyl}-5-chloropyridine-4-carboxylate (400 mg, 1.266 mmol, 1 equiv) in H_2O (2.5 mL) THF (5 mL) and MeOH (5 mL) was added LiOH (181.97 mg, 7.596 mmol, 6 equiv). The reaction was stirred at 25°C for 2 h. The mixture acidified to pH 4 with 2 M HCl. The precipitated solids were collected by filtration and washed with H_2O (3 x 5 mL). The resulting solid was dried air-dry to give 2-{[(tert-butyldimethylsilyl)oxy]methyl}-5-chloropyridine-4-carboxylic acid (160 mg, 41.86%). MS (ESI): mass calcd. for $C_{13}H_{20}ClNO_3Si$: 301.09 m/z, found: 302.09 $[M+H]^+$.



2-((tert-butyldimethylsilyloxy)methyl)-4-carboxy-5-chloropyridine 1-oxide

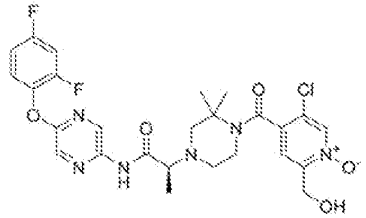
To a solution of 2-{[(tert-butyldimethylsilyl)oxy]methyl}-5-chloropyridine-4-carboxylic acid (150 mg, 0.497 mmol, 1 equiv) in DCM (8 mL) was added m-CPBA (343.02 mg, 1.988 mmol, 4 equiv). The reaction was stirred at 25°C for 2 h. Quenched with water (10 mL) and extracted with DCM (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with DCM/MeOH (0-20%) to give 2-{[(tert-butyldimethylsilyl)oxy]methyl}-4-carboxy-5-chloropyridin-1-ium-1-olate (110 mg, 69.64%) as a yellow oil. MS (ESI): mass calcd. for $C_{13}H_{20}ClNO_4Si$: 317.09 m/z, found: 318.09 $[M+H]^+$.



(S)-2-((tert-butyldimethylsilyloxy)methyl)-5-chloro-4-(4-(1-(5-(2,4-difluorophenoxy)pyrazin-2-ylamino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

To a solution of 2-{[(tert-butyldimethylsilyl)oxy]methyl}-4-carboxy-5-chloropyridin-1-ium-1-olate (90 mg, 0.283 mmol, 1 equiv) in DMF (5 mL) was added (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (110.84 mg, 0.283 mmol, 1 equiv) ,HATU (107.67 mg, 0.283 mmol, 1 equiv) and DIEA (146.39 mg, 1.132 mmol, 4 equiv). The reaction was stirred at 25°C for 2 h. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 2-{[(tert-butyldimethylsilyl)oxy]methyl}-5-chloro-4-{4-[(1S)-1-{[5-(2,4-difluorophenoxy)pyrazin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}pyridin-1-ium-1-olate (120 mg,

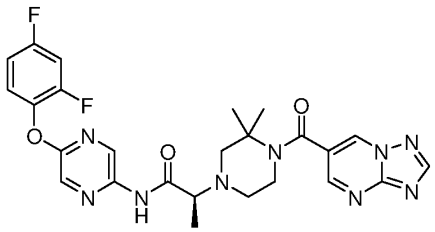
50.33%) as a yellow oil. MS (ESI): mass calcd. for $C_{32}H_{41}ClF_2N_6O_5Si$: 690.26 m/z, found: 691.26 $[M+H]^+$.



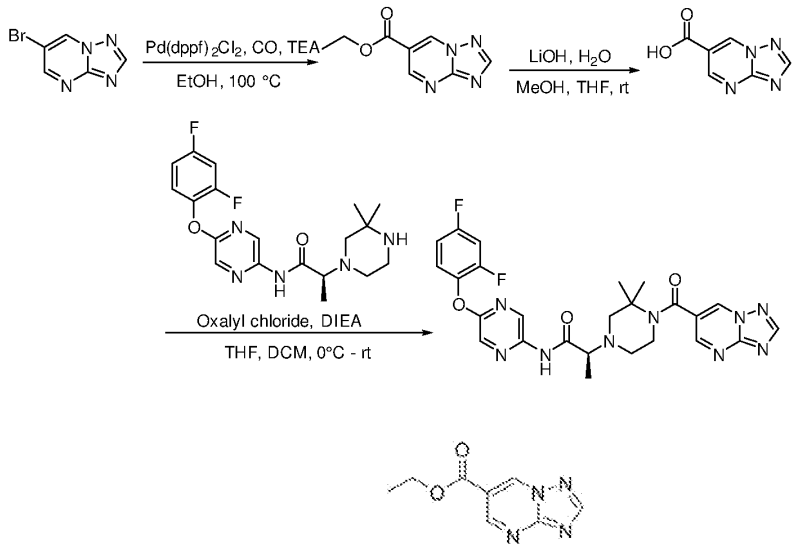
(S)-5-chloro-4-(4-(1-(5-(2,4-difluorophenoxy)pyrazin-2-ylamino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide

To a solution of 2-{[(tert-butyldimethylsilyl)oxy]methyl}-5-chloro-4-{4-[(1S)-1-{[5-(2,4-difluorophenoxy)pyrazin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazine-1-carbonyl}pyridin-1-ium-1-olate (110 mg, 0.159 mmol, 1 equiv) in THF (4 mL) was added $Et_3N.3HF$ (4 mL) . The reaction was stirred at 50°C for 1h. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a YMC-Actus Triart C_{18} ExRS 19 **x** 250mm **x** 5μm column (eluent: 40% to 70% (v/v) ACN and H_2O with 10mmol/L NH_4HCO_3 to afford the title compound (S)-5-chloro-4-(4-(1-(5-(2,4-difluorophenoxy)pyrazin-2-ylamino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide (37 mg, 40.06%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{27}ClF_2N_6O_5$: 576.17 m/z, found: 577.25 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.83 (d, J = 1.4 Hz, 1H), 8.61 (s, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.41 – 7.55 (m, 2H), 7.38 (s, 1H), 7.13 – 7.23 (m, 1H), 5.68 – 5.76 (m, 1H), 4.51 – 4.59 (m, 2H), 3.48 – 3.58 (m, 1H), 3.22 – 3.32 (m, 3H), 2.62 – 2.67 (m, 1H), 2.40 – 2.47 (m, 2H), 1.52 (s, 6H), 1.19 (d, J = 7.0 Hz, 3H).

Example 196: (S)-2-(4-([1,2,4]triazolo[1,5-a]pyrimidine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

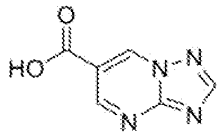


Synthetic Scheme



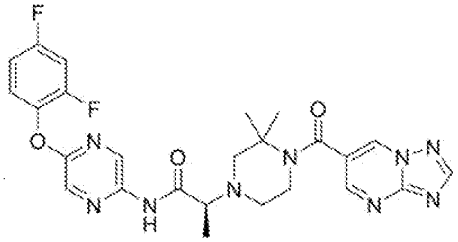
tert-butyl 3,3-dimethyl-4-(6-methyl-5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazine-1-carboxylate

To a solution of 6-bromo-[1,2,4]triazolo[1,5-a]pyrimidine (1 g, 5.025 mmol, 1 equiv)in EtOH (15 mL) was added $Pd(dppf)_2Cl_2$ (352.69 mg, 0.503 mmol, 0.1 equiv) and TEA (1.53 g, 15.120 mmol, 3.01 equiv) in a pressure tank. The mixture was purged with nitrogen for 5 min and then was pressurized to 50 atm with carbon monoxide at 100 °C for 12 h. The reaction mixture was cooled to room temperature and filtered to remove insoluble solids.The resulting mixture was allowed to warm to rt and stirred at rt for another 1h. It was quenched with Saturated sodium bicarbonate solution (5 mL), extracted with DCM (20 mL), the organic phase was dired over Na_2SO_4, filtered and concentrated. The residue was applied onto a silica gel column (40g, EtOAc/PE: 1:1) to afford ethyl [1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate (500 mg, 51.78%) as a yellow oil, MS (ESI): mass calcd. for $C_8H_8N_4O_2$:192.06 m/z, found:193.20 $[M+H]^+$.



5-(2,2-dimethylpiperazine-1-carbonyl)-3-methylpyrazin-2(1H)-one

To a solution of ethyl [1,2,4] triazolo[1,5-a]pyrimidine-6-carboxylate (250 mg, 1.301 mmol, 1 equiv) in THF (1 mL).methanol (0.5 mL, 0.008 mmol, 0.24 equiv) ,lithiumol (37.39 mg, 1.561 mmol, 1.2 equiv) and water (0.5 mL, 0.014 mmol, 0.43 equiv) added at rt. The resulting mixture was stirred for 2h at rt. The resulting mixture was concentrated under vacuum. The residue was acidified to pH 2~3 with 3NHCl. The precipitated solids were collected by filtration and washed with H_2O (5ml) to afford [1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylic acid (150 mg, 70.26%) as a yellow oil. MS (ESI): mass calcd. for $C_6H_4N_4O_2$:164.06m/z, found:165.10$[M+H]^+$.

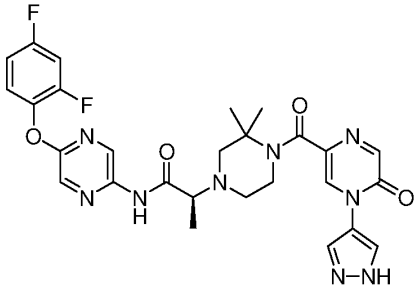


tert-butyl 3,3-dimethyl-4-(6-methyl-5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazine-1-carboxylate

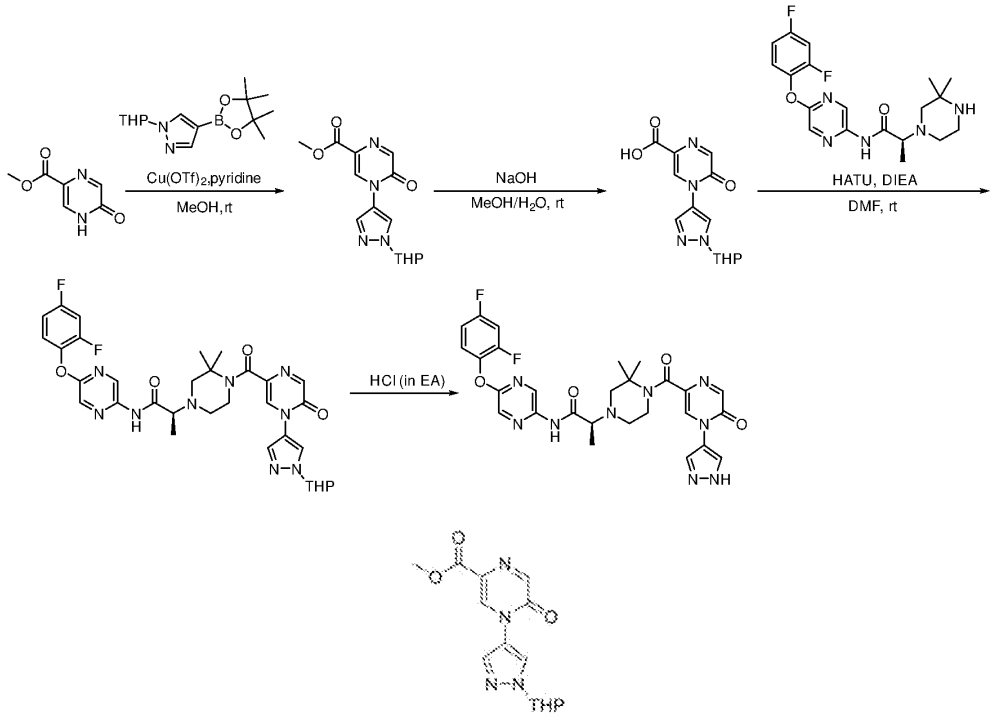
With an inert atmosphere of nitrogen, to a mixture of [1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylic acid (130 mg, 0.792 mmol, 1 equiv) in THF (3 mL) was added Oxalyl chloride (201.06 mg, 1.584 mmol, 2 equiv) at 0 °C. The mixture was stirred at rt for 1 h to give a solution of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (200 mg, 0.511 mmol, 0.65 equiv) and DIEA (204.75 mg, 1.584 mmol, 2 equiv) in DCM (3ml) over 5 min at 0 degrees. The resulting mixture was allowed to warm to rt and stirred at rt for another 1h. It was quenched with Saturated sodium bicarbonate solution (5 mL), extracted with DCM (20 mL), the organic phase was dired over Na_2SO_4, filtered and concentrated. The residue was applied onto a silica gel column (40g, EtOAc/PE: 1:1) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 29% to 59% ACN and H_2O (10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-2-(4-([1,2,4]triazolo[1,5-a]pyrimidine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (5.8 mg, 1.36%) as a white solid, MS

(ESI): mass calcd. for $C_{25}H_{25}F_2N_9O_3$:537.20m/z, found: 538.30[M+H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.45 (s, 1H), 9.57 (d, J = 2.3 Hz, 1H), 8.91 (d, J = 2.3 Hz, 1H), 8.86 (d, J = 1.4 Hz, 1H), 8.76 (s, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.2 – 7.55 (m, 2H), 7.13 – 7.23 (m, 1H), 3.49 – 3.61 (m, 1H), 3.46 (t, J = 5.3 Hz, 2H), 2.62 – 2.81 (m, 2H), 2.43 – 2.50 (m, 2H), 1.50 (d, J = 5.0 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -113.4257, -124.2089.

Example 197: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-4-(1H-pyrazol-4-yl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide

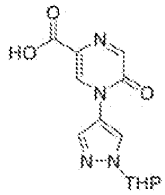


Synthetic Scheme



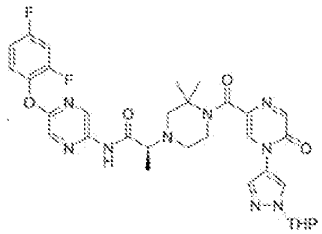
methyl 5-oxo-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-4,5-dihydropyrazine-2-carboxylate

To a solution of methyl 5-oxo-4H-pyrazine-2-carboxylate (100 mg, 0.649 mmol, 1 equiv) in methanol (10 mL) was added 1-(oxan-2-yl)pyrazol-4-ylboronic acid (127.18 mg, 0.649 mmol, 1 equiv), $Cu(OTf)_2$ (234.66 mg, 0.649 mmol, 1 equiv) and Pyridine (82.12 mg, 1.038 mmol, 1.6 equiv). The reaction was stirred at rt for 18 h. Quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with DCM/MeOH (0-20%) to give methyl 4-[1-(oxan-2-yl)pyrazol-4-yl]-5-oxopyrazine-2-carboxylate (190 mg, 45 %) as a yellow oil. MS (ESI): mass calcd. for $C_{14}H_{16}N_4O_4$:304.12 m/z, found 305.12 $[M+H]^+$.



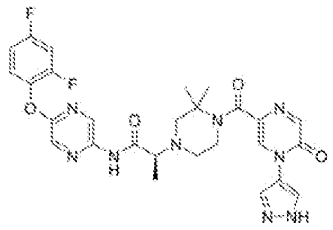
5-oxo-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-4,5-dihydropyrazine-2-carboxylic acid

To a solution of methyl 4-[1-(oxan-2-yl)pyrazol-4-yl]-5-oxopyrazine-2-carboxylate (180 mg, 0.592 mmol, 1 equiv) in MeOH (3 mL) and H_2O (3 mL, 0.017 mmol) was added NaOH (47.32 mg, 1.184 mmol, 2 equiv). The reaction was stirred at 25°C for 2 h. The mixture was acidified to pH 4 with 2 M HCl. The precipitated solids were collected by filtration and washed with H_2O (3 x 5 mL). The resulting solid was dried air-dry to give 4-[1-(oxan-2-yl)pyrazol-4-yl]-5-oxopyrazine-2-carboxylic acid (200 mg, 116.48%). MS (ESI): mass calcd. for $C_{13}H_{14}N_4O_4$: 290.10 m/z, found: 291.10 $[M+H]^+$.



(2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide

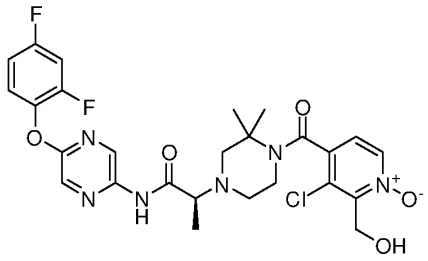
To a solution of 4-[1-(oxan-2-yl)pyrazol-4-yl]-5-oxopyrazine-2-carboxylic acid (190 mg, 0.655 mmol, 1 equiv) in dimethylformamide (5 mL) was added (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (256.20 mg, 0.655 mmol, 1 equiv), HATU (248.88 mg, 0.655 mmol, 1 equiv) and DIEA (338.39 mg, 2.620 mmol, 4 equiv). The reaction was stirred at 25°C for 2 h. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethyl-4-{4-[1-(oxan-2-yl)pyrazol-4-yl]-5-oxopyrazine-2-carbonyl}piperazin-1-yl)propanamide (150 mg, 34.53%) as a yellow oil. MS (ESI): mass calcd. for $C_{32}H_{35}F_2N_9O_5$: 663.27 m/z, found: 664.27 $[M+H]^+$.



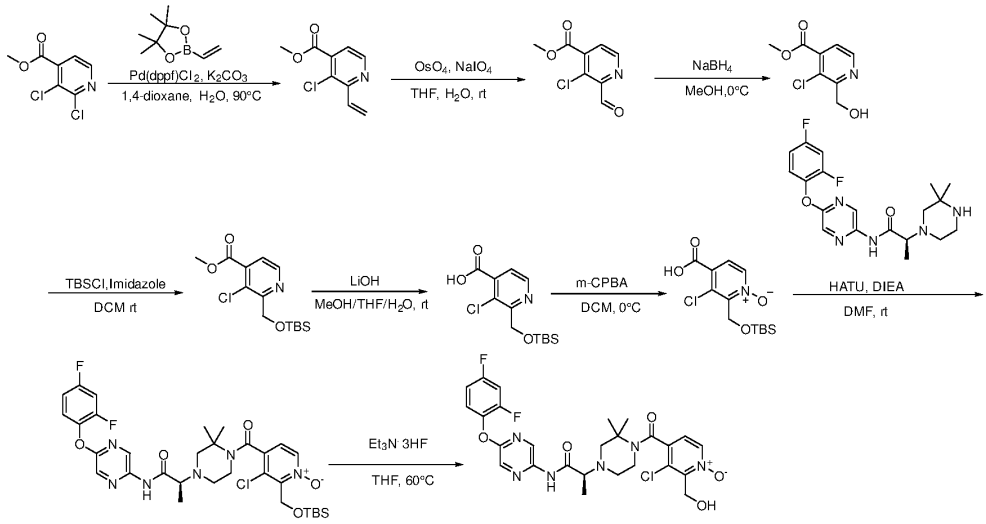
(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-4-(1H-pyrazol-4-yl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide

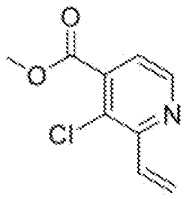
To (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethyl-4-{4-[1-(oxan-2-yl)pyrazol-4-yl]-5-oxopyrazine-2-carbonyl}piperazin-1-yl)propanamide (110 mg, 0.166 mmol, 1 equiv) was added HCl(gas) in 1,4-dioxane (4 mL). The reaction was stirred at 25°C for 1h. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a Xselect CSH Prep Fluoro-Phenyl 19*250, 5μm column eluent:20% to 48% (v/v) ACN and H_2O with 10mmol/L NH_4HCO_3 to afford the title compound (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-4-(1H-pyrazol-4-yl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide (22.4 mg, 22.20%) as a off-white solid. MS (ESI): mass calcd. for $C_{27}H_{27}F_2N_9O$:579.22 m/z, found:580.25 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.23 – 11.87 (m, 1H), 9.70 – 10.68 (m, 1H), 8.85 (s, 1H), 8.52 (s, 1H), 8.21 – 8.31 (m, 3H), 8.06 – 8.14 (m, 1H), 7.43 – 7.56 (m, 2H), 7.00 – 7.31 (m, 1H), 3.16 – 4.67 (m, 7H), 1.43 – 1.77 (m, 9H).

Example 198: (S)-3-chloro-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide



Synthetic Scheme

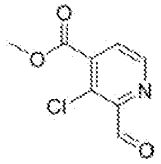




methyl 3-chloro-2-vinylisonicotinate

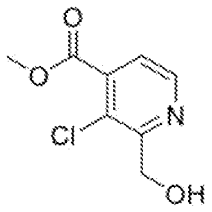
To a solution of methyl 2,3-dichloroisonicotinate (1 g, 4.854 mmol, 1 equiv) in dioxane (10 mL, 118.040 mmol, 24.32 equiv) was added 2-ethenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.12 g, 7.272 mmol, 1.50 equiv) and $Pd(dppf)Cl_2$ (0.396 g, 0.541 mmol, 0.11

equiv) and potassium methaneperoxoate potassium (1.68 g, 12.068 mmol, 2.49 equiv). The reaction was stirred at 90 °C under N_2 for 5h. After cooled to room temperature the reaction mixture was quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated.The residue was purified by column chromatography on silica gel with MeOH/DCM (0-10%) to give methyl 3-chloro-2-ethenylpyridine-4-carboxylate) as yellow oil (600 mg, 62%). MS(ESI): mass calcd. for $C_9H_8ClNO_2$:197.0 m/z, found: 198.30 $[M+H]^+$.



methyl 3-chloro-2-formylisonicotinate

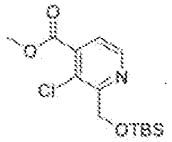
To a solution of methyl 3-chloro-2-vinylisonicotinate (600 mg, 3.036 mmol, 1 equiv) in THF (5 mL, 61.714 mmol, 20.33 equiv) and H_2O (5 mL, 277.546 mmol, 91.41 equiv) was added OsO_4 (154.39 mg, 0.607 mmol, 0.20 equiv) and $NaIO_4$ (1311.19 mg, 6.130 mmol, 2.02 equiv). The reaction was stirred at rt for 6h. After cooled to room temperature the reaction mixture was quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with MeOH/DCM (0-10%) to give methyl 3-chloro-2-formylisonicotinate as a yellow oil (310 mg,51 %). MS (ESI): mass calcd. for $C_8H_6ClNO_3$: 199.0 m/z, found:199.95 $[M+H]^+$.



methyl 3-chloro-2-(hydroxymethyl)isonicotinate

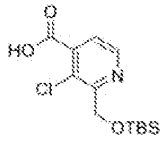
To a solution of methyl 3-chloro-2-formylisonicotinate (150 mg, 0.752 mmol, 1 equiv) in methanol (5 mL) was added $NaBH_4$ (14.21 mg, 0.376 mmol, 0.50 equiv). The reaction was stirred at 0 °C for 0.5 h. Quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated.The residue was purified by column chromatography on silica gel with MeOH/DCM (0-10%) to give methyl 3-chloro-2-(hydroxymethyl)isonicotinate as

yellow oil (120 mg). MS (ESI): mass calcd. for $C_8H_8ClNO_3$: 201.0 m/z, found: 202.05 $[M+H]^+$.



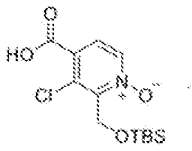
methyl 2-(((tert-butyldimethylsilyl)oxy)methyl)-3-chloroisonicotinate

To a solution of methyl 3-chloro-2-(hydroxymethyl)isonicotinate (230 mg, 1.141 mmol, 1 equiv) in DCM (5 mL, 78.653 mmol, 68.94 equiv) was added Imidazole (233.01 mg, 3.423 mmol, 3.00 equiv) and TBSCl (257.93 mg, 1.711 mmol, 1.50 equiv). The reaction was stirred at rt for 2h. Quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated.The residue was purified by column chromatography on silica gel with MeOH/DCM (0-10%) to give methyl 2-(((tert-butyldimethylsilyl)oxy)methyl)-3-chloroisonicotinate as yellow oil (300 mg). MS (ESI): mass calcd. for $C_{14}H_{22}ClNO_3Si$: 315.1 m/z, found: 315.95 $[M+H]^+$.



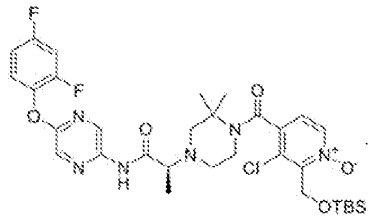
2-(((tert-butyldimethylsilyl)oxy)methyl)-3-chloroisonicotinic acid

To a solution of methyl 2-(((tert-butyldimethylsilyl)oxy)methyl)-3-chloroisonicotinate (300 mg, 0.950 mmol, 1 equiv) in MeOH (1 mL), THF (3 mL), H_2O (1 mL) was added lithiumol (34.12 mg, 1.425 mmol, 1.5 equiv) at 0 °C, the mixture was stirred for 1h at rt. the reaction mixture was concentrated under vacuumwas added water and the mixture was acidified to pH = 5 with 4N HCl, extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 2-(((tert-butyldimethylsilyl)oxy)methyl)-3-chloroisonicotinic acid (200 mg, 69.77%) as a yellow solid.MS (ESI) mass calcd. for $C_{13}H_{20}ClNO_3Si$:301.10 m/z, found: 302.10 $[M+H]^+$.



2-(((tert-butyldimethylsilyl)oxy)methyl)-4-carboxy-3-chloropyridine 1-oxide

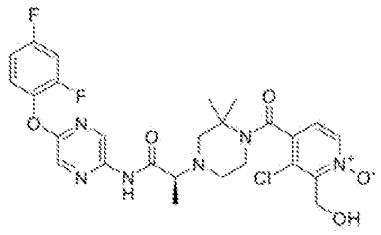
To a solution of 2-(((tert-butyldimethylsilyl)oxy)methyl)-3-chloroisonicotinic acid (200 mg, 0.663 mmol, 1 equiv) in DCM (10.00 mL, 157.403 mmol, 237.41 equiv) was added m-CPBA (228.68 mg, 1.326 mmol, 2 equiv) at 0°C, the mixture was stirred for 2h at rt. the reaction mixture was quenched by water and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 2-(((tert-butyldimethylsilyl)oxy)methyl)-4-carboxy-3-chloropyridine 1-oxide (120 mg, 56.98%) as a yellow solid.MS (ESI) mass calcd. for $C_{13}H_{20}ClNO_4Si$: 317.29 m/z, found: 318.05 $[M+H]^+$.



(S)-2-(((tert-butyldimethylsilyl)oxy)methyl)-3-chloro-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

To a solution of 2-(((tert-butyldimethylsilyl)oxy)methyl)-4-carboxy-3-chloropyridine 1-oxide (100 mg, 0.315 mmol, 1 equiv) in dimethylformamide (5 mL) was added (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (123.15 mg, 0.315 mmol, 1 equiv), HATU (179.45 mg, 0.473 mmol, 1.5 equiv), DIEA (203.32 mg, 1.575 mmol, 5 equiv), the mixture was stirred for 2h at rt. the reaction mixture was quenched by water and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford (S)-2-(((tert-butyldimethylsilyl)oxy)methyl)-3-chloro-4-(4-

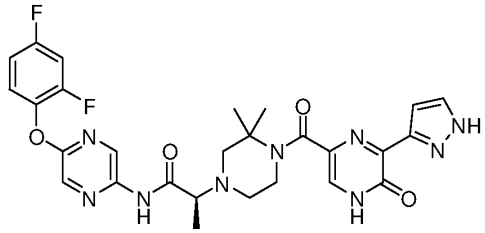
(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (100 mg, 45.98%) as a yellow solid.MS (ESI) mass calcd. for $C_{32}H_{41}ClF_2N_6O_5Si$:6 90.29 m/z, found: 691.05 $[M+H]^+$.



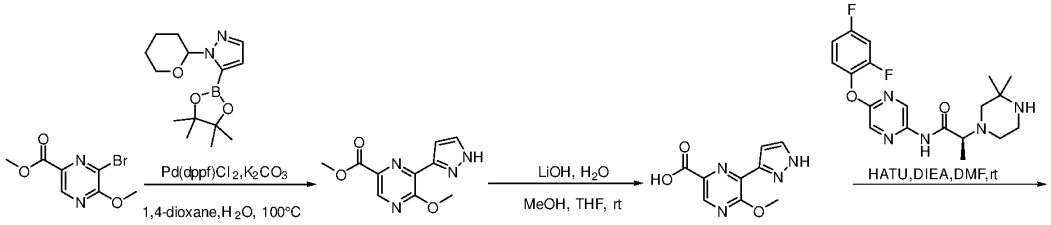
(S)-3-chloro-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide

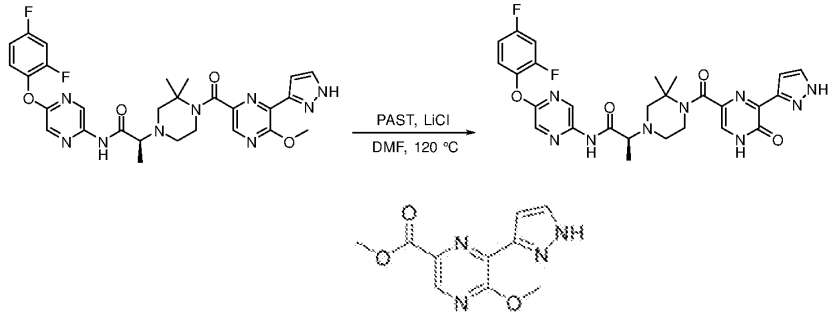
To a solution of (S)-2-(((tert-butyldimethylsilyl)oxy)methyl)-3-chloro-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (150 mg, 0.217 mmol, 1 equiv) in THF (5 mL) with Triethylamine trihydrofluoride (1 mL).The resulting mixture was stirred for 1 h at 60°C. After cooled to room temperature the reaction mixture was quenched by water and extracted with EA (3*20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 100 mg crude product as a white solid. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 30*150 mm*5μm column (eluent: 31% to 61% (v/v) CH_3CN and H_2O with NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-3-chloro-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide (73.5 mg, 58.15%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{27}ClF_2N_6O_5$: 576.22 m/z, found 577.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.83 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 8.31 (d, J = 6.7 Hz, 1H), 7.41 – 7.56 (m, 2H), 7.38 (d, J = 6.7 Hz, 1H), 7.11 – 7.24 (m, 1H), 5.44 (t, J = 6.2 Hz, 1H), 4.71 – 4.82 (m, 2H), 3.53 (q, J = 6.8 Hz, 1H), 3.18 – 3.30 (m, 2H), 2.63 (s, 2H), 2.45 (s, 2H), 1.51 (s, 6H), 1.19 (d, J = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.43, -124.22.

Example 199: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-6-(1H-pyrazol-3-yl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propenamide



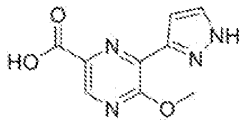
Synthetic Scheme





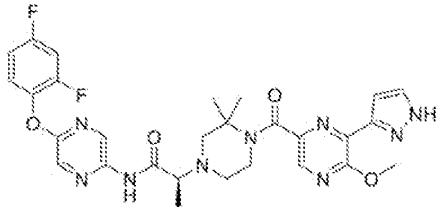
methyl 5-methoxy-6-(1H-pyrazol-3-yl)pyrazine-2-carboxylate

To a solution of methyl 6-bromo-5-methoxypyrazine-2-carboxylate (500 mg, 2.024 mmol, 1 equiv) and 1-(oxan-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (844.45 mg, 3.036 mmol, 1.5 equiv) in 1,4-dioxane (1 mL) and H_2O (5.00 mL, 277.551 mmol, 137.13 equiv) were added K_2CO_3 (559.43 mg, 4.048 mmol, 2 equiv) and $Pd(dppf)Cl_2$ (740.45 mg, 1.012 mmol, 0.5 equiv). After stirring for overnight at 100 °C under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA to afford methyl 5-methoxy-6-(1H-pyrazol-3-yl)pyrazine-2-carboxylate) (0.3 g, 63.8%) as a yellow solid. MS (ESI): mass calcd. for $C_{10}H_{10}N_4O_3$ 234.22 m/z, found 235.15 $[M+H]^+$.



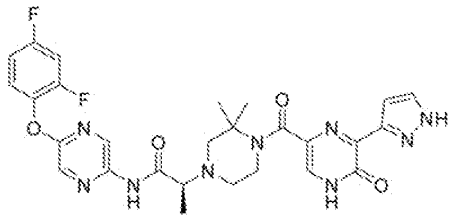
5-methoxy-6-(1H-pyrazol-3-yl)pyrazine-2-carboxylic acid

To a solution of methyl 5-methoxy-6-(1H-pyrazol-3-yl)pyrazine-2-carboxylate (700 mg, 2.99 mmol, 1 equiv) in THF (16 mL) was added MeOH (8 mL) and H_2O (8 mL) and LiOH (143 mg, 5.98 mmol, 2 equiv) at rt. The resulting mixture was stirred for 2h at rt. The mixture was acidified to pH 2 with 2N HCl (aq.). The precipitated solids were collected by filtration and washed with water. The resulting mixture was concentrated under reduced pressure to afford 5-methoxy-6-(1H-pyrazol-3-yl)pyrazine-2-carboxylic acid (0.5 g, crude) as a white solid. MS (ESI): mass calcd. for $C_9H_8N_4O_3$ 220.19 m/z, found 221.15 $[M+H]^+$.



(2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-{4-[5-methoxy-6-(1H-pyrazol-3-yl)pyra zine-2-carbonyl]-3,3-dimethylpiperazin-1-yl}propanamide

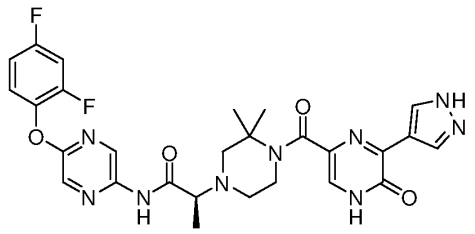
To a solution of 5-methoxy-6-(1H-pyrazol-3-yl)pyrazine-2-carboxylic acid (200 mg, 0.908 mmol, 1 equiv) in DMF (5 mL) was added (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl) propanamide (355.54 mg, 0.908 mmol, 1 equiv) and HATU (518.06 mg, 1.362 mmol, 1.5 equiv) and DIEA (352.19 mg, 2.724 mmol, 3 equiv) at rt. The resulting mixture was stirred for 2h at rt. The reaction mixture was quenched by water and extracted with EA (3*30 mL).The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-{4-[5-methoxy-6-(1H-pyrazol-3-yl)pyra zine-2-carbonyl]-3,3-dimethylpiperazin-1-yl}propanamide (0.2 g, 37.1%) as a yellow solid. MS (ESI): mass calcd. for $C_{28}H_{29}F_2N_9O_4$ 593.29 m/z, found 594.20 $[M+H]^+$.



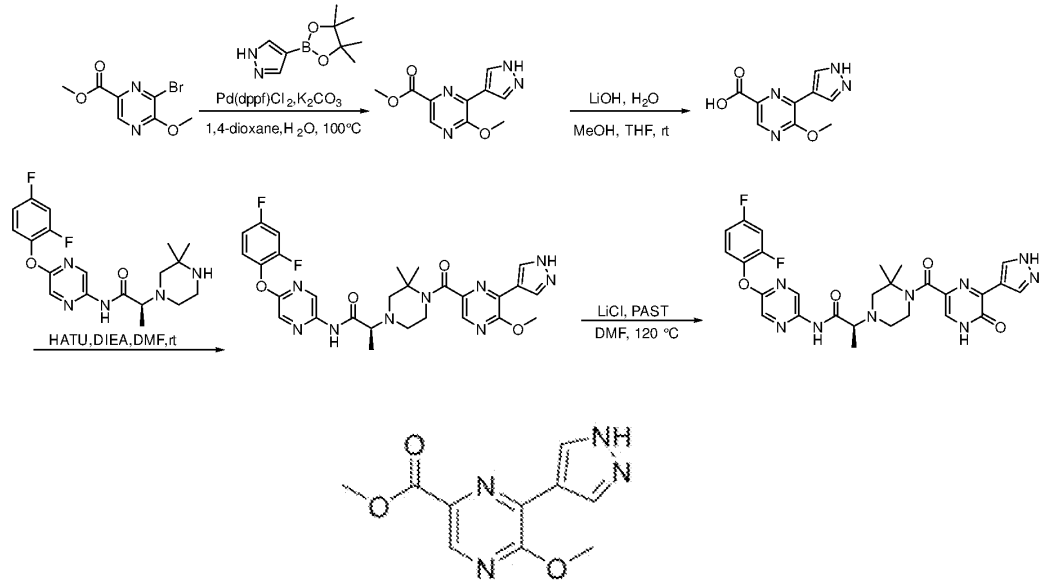
(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-6-(1H-pyrazol-3-yl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide

To a solution of 4N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-{4-[5-methoxy-6-(1H-pyrazol-3-yl) pyrazine-2-carbonyl]-3,3-dimethylpiperazin-1-yl}acetamide (200 mg, 0.345 mmol, 1 equiv) in DMF (3 mL) was added PAST (297.12 mg, 1.725 mmol, 5 equiv) and LiCl (73.14 mg, 1.725 mmol, 5 equiv) at rt .The resulting mixture was stirred for overnight at 120 °C. The reaction mixture was quenched by water and extracted with EA (2*30 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography and by preparative HPLC using a Column: Xselect CSH C18 OBD Column, 30*150 mm, 5μm; (eluent: 20% to 30% (v/v) Water(0.1% FA) to ACN and afford product 4-[4-(1-{[5-(2,4-difluorophenoxy) pyrazin-2-yl]carbamoyl}ethyl)-2,2-dimethylpiperazine-1-carbonyl]-1H-pyrazolo[3,4-b]pyridin-7-ium-7-olate (1.6 mg, 1.68%) as a light pink solid. MS (ESI): mass calcd. for $C_{27}H_{27}F_2N_9O_4$ 579.22 m/z, found 580.35$[M+H]^+$.^{1}H NMR (400 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.85 (s, 1H), 8.46 (s, 1H), 7.75 (s, 1H), 7.62 (s, 1H), 7.48 (d, J = 9.8, 9.4, 4.3 Hz, 2H), 7.17 (td, J = 8.8, 2.9 Hz, 1H), 7.05 (s, 1H), 3.47 – 3.62 (m, 3H), 2.78 – 2.86 (m, 1H), 2.67 – 2.75 (m, 1H), 2.46 (d, J = 6.7 Hz, 2H), 1.47 (d, J = 2.7 Hz, 6H), 1.23 (d, J = 6.8 Hz, 3H).^{19}F NMR (376 MHz, DMSO-d_6) δ -113.40 (d, J = 5.1 Hz), -124.19 (d, J = 5.3 Hz).

Example 200: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-6-(1H-pyrazol-4-yl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide

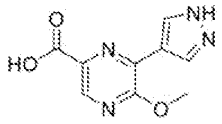


Synthetic Scheme



methyl 5-methoxy-6-(1H-pyrazol-4-yl)pyrazine-2-carboxylate

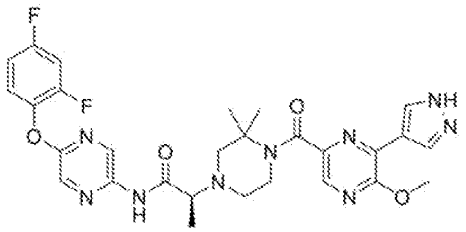
To a solution of methyl 6-bromo-5-methoxypyrazine-2-carboxylate (500 mg, 2.024 mmol, 1 equiv) and 4-(4-ethyl-4,5,5-trimethyl-1,3,2-dioxaborolan-2-yl)-1-(oxan-2-yl)pyrazole (591.36 mg, 2.024 mmol, 1 equiv) in 1,4-dioxane (10 mL) and H_2O (1 mL, 55.509 mmol, 27.43 equiv) were added K_2CO_3 (559.43 mg, 4.048 mmol, 2 equiv) and $Pd(dppf)Cl_2$ (740.45 mg, 1.012 mmol, 0.5 equiv) . After stirring for overnight at 100 °C under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA to afford methyl 5-methoxy-6-(1H-pyrazol-4-yl)pyrazine-2-carboxylate (0.2 g, 71.4%)as a yellow solid. MS (ESI): mass calcd. for C10H10N4O3 234.21m/z, found 235.15$[M+H]^+$.



5-methoxy-6-(1H-pyrazol-4-yl)pyrazine-2-carboxylic acid

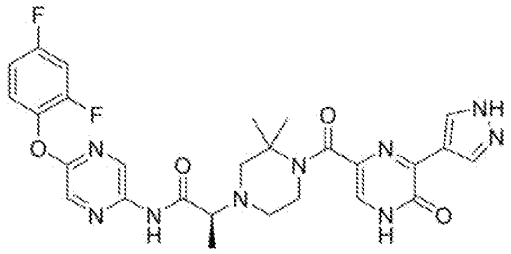
To a solution of methyl 5-methoxy-6-(1H-pyrazol-4-yl)pyrazine-2-carboxylate (500 mg, 2.135 mmol, 1 equiv) in THF (8 mL) was added MeOH (4 mL) and H_2O (4 mL) and LiOH (102.26 mg, 4.270 mmol, 2 equiv) at rt .The resulting mixture was stirred for 2 h at rt. The

mixture was acidified to pH 2 with 2N HCl (aq.). The precipitated solids were collected by filtration and washed with water. The resulting mixture was concentrated under reduced pressure to afford 5-methoxy-6-(1H-pyrazol-4-yl)pyrazine-2-carboxylic acid as a white solid (0.3 g, crude). MS (ESI): mass calcd. for $C_9H_8N_4O_3$ 220.18 m/z, found 221.15 $[M+H]^+$.



(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-methoxy-6-(1H-pyrazol-4-yl)pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

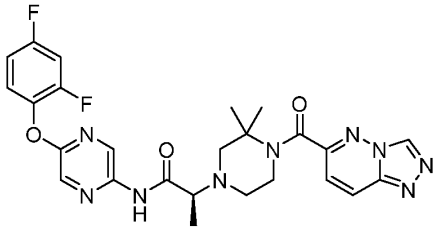
To a solution of 5-methoxy-6-(1H-pyrazol-4-yl)pyrazine-2-carboxylic acid (200 mg, 0.908 mmol, 1 equiv) in DMF (5 mL) was added (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl) propanamide (177.8 mg, 0.045 mmol, 1 equiv) and HATU (259.0 mg, 0.068 mmol, 1.5 equiv) and DIEA (176.1 mg, 0.135 mmol, 3 equiv) at rt .The resulting mixture was stirred for 2h at rt.The reaction mixture was quenched by water and extracted with EA (3*30 mL).The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-methoxy-6-(1H-pyrazol-4-yl)pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (0.3 g, 55.6%) as a yellow solid. MS (ESI): mass calcd. for $C_{28}H_{29}F_2N_9O_4$ 593.59 m/z, found 594.35 $[M+H]^+$.



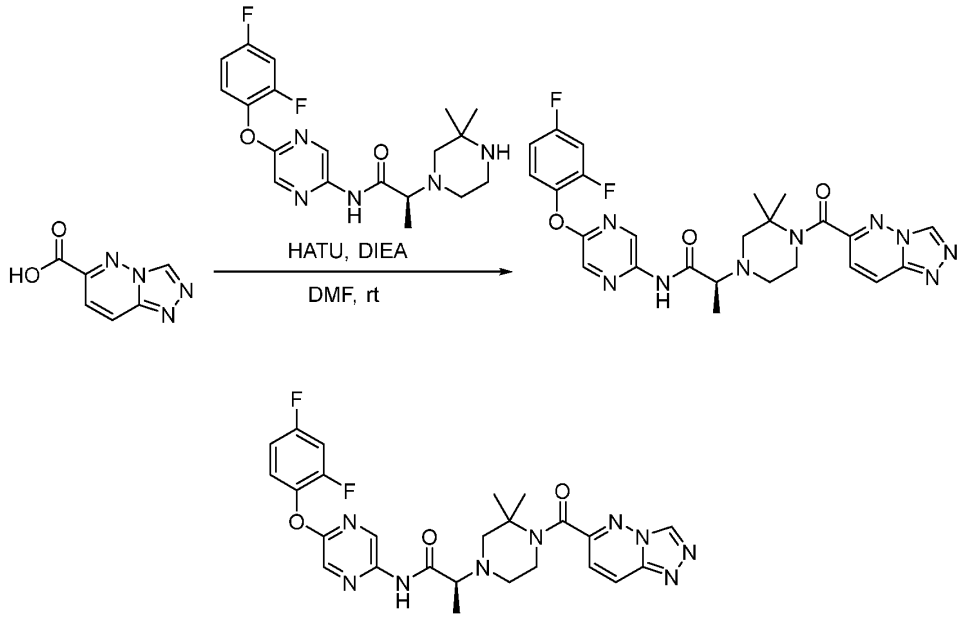
Synthesis of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-6-(1H-pyrazol-4-yl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide

To a solution of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-methoxy-6-(1H-pyrazol-4-yl)pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (300 mg, 0.505 mmol, 1 equiv) in DMF (3mL) was added LiCl (107.12 mg, 2.525 mmol, 5 equiv) and PAST (435.14 mg, 2.525 mmol, 5 equiv) at rt .The resulting mixture was stirred for overnight at 120 ° C. The reaction mixture was quenched by water and extracted with EA (2*30 mL).The combined organic extracts were washed with brine (20mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-10% DCM/MeOH) and purified by preparative HPLC using a Column: YMC-Actus Triart C18 ExRS19*250mm, 5μm; (eluent: 30% to 50% (v/v) Water(10mmol/L NH4HCO3) and CAN to afford product (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-6-(1H-pyrazol-4-yl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide (15.7 mg, 5.25%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{27}F_2N_9O_4$ 579.22 m/z, found 580.40[M+H]$^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.61 (s, 1H), 10.40 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.5 Hz, 2H), 8.11 (s, 1H), 7.60 (s, 1H), 7.40 – 7.56 (m, 2H), 7.17 (t, J = 8.8 Hz, 1H), 3.64 (s, 2H), 3.53 (d, J = 7.0 Hz, 1H), 2.84 (d, J = 6.4 Hz, 1H), 2.67 – 2.75 (m, 1H), 2.43 – 2.48 (m, 2H), 1 .46 (s, 6H), 1.28(dd, J = 20.2, 6.6 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.45 (d, J = 5.3 Hz), -124.23 (d, J = 5.4 Hz).

Example 201: (S)-2-(4-([1,2,4]triazolo[4,3-b]pyridazine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide



Synthetic Scheme

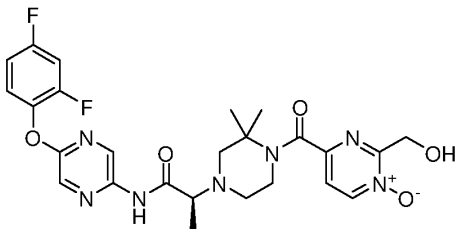


(S)-2-(4-([1,2,4]triazolo[4,3-b]pyridazine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

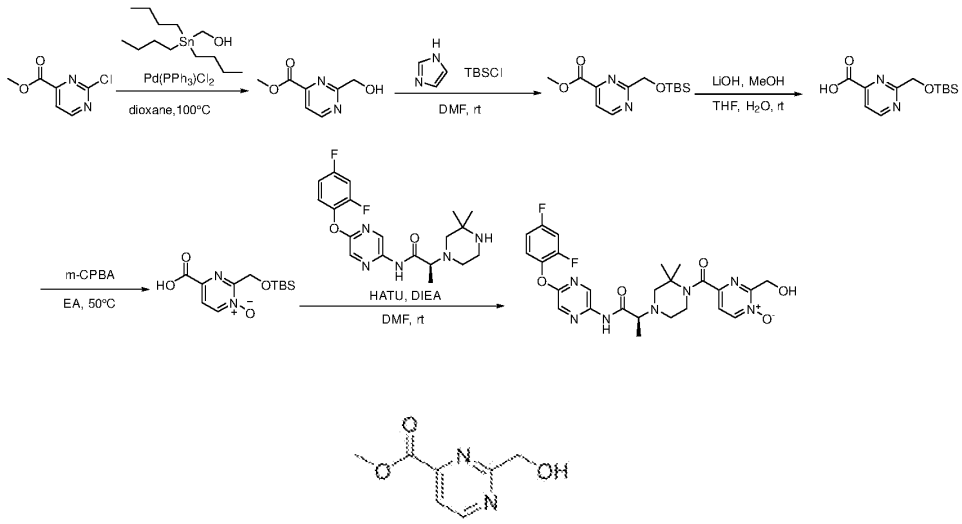
To a stirring solution (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (100 mg, 0.255 mmol, 1 equiv) in dimethylformamide (5 mL) the mixture was added [1,2,4]triazolo[4,3-b]pyridazine-6-carboxylic acid (41.93 mg, 0.255 mmol, 1 equiv), HATU (145.71 mg, 0.383 mmol, 1.5 equiv) and N,N-diisopropylethylamine (132.08 mg, 1.020 mmol, 4 equiv) at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) and purified by preparative HPLC using a Xselect CSH OBD 150 mm x 30 mm x 5μm column (eluent: 37% to 50% (v/v), CH_3CN & H_2O with 0.05% NH_4HCO_3) to afford (S)-2-(4-([1,2,4]triazolo[4,3-b]pyridazine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propenamide (80.1 mg, 57.94%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{25}F_2N_9O_3$: 537.20, found: 538.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ10.47 (s, 1H), 9.69 (d, J = 0.8 Hz, 1H), 8.84 (d, J = 1.4 Hz,1H), 8.41 - 8.50 (m, 2H), 7.37 – 7.56 (m, 3H), 7.12 – 7.24 (m, 1H), 3.49 – 3.62 (m, 1H), 3.45 (s, 2H), 2.65 – 2.75 (m, 1H), 2.54 – 2.64 (m,1H), 2.43 – 2.48 (m, 2H),1.51 (s, 6H),

1.20 (d, J = 6.9 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -113.42 (d, J = 5.3 Hz), -124.21 (d, J = 5.3 Hz).

Example 202: (S)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyrimidine 1-oxide



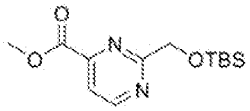
Synthetic Scheme



methyl 2-(hydroxymethyl)pyrimidine-4-carboxylate

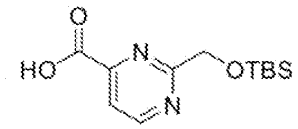
To a solution of methyl 2-chloropyrimidine-4-carboxylate (2.0 g, 11.589 mmol, 1 equiv) in dioxane (30 mL) the mixture was added (tributylstannyl)methanol (5.58 g, 17.384 mmol, 1.5 equiv) and $Pd(PPh_3)_2Cl_2$ (813 mg, 1.159 mmol, 0.1 equiv). The mixture was stirred at 100 °C for 3 h under N_2. After completion of reaction the mixture was cooled to room temperature then quenched with water (50 mL) extracted with ethyl acetate (3 x 100 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-

50%EA/PE) to afford methyl 2-(hydroxymethyl)pyrimidine-4-carboxylate (1.0 g, 51.31%) as a yellow solid.



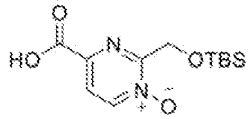
methyl 2-(((tert-butyldimethylsilyl)oxy)methyl)pyrimidine-4-carboxylate

To a solution of methyl 2-(hydroxymethyl)pyrimidine-4-carboxylate (800 mg, 4.758 mmol, 1 equiv) in N,N-dimethylformamide (20 mL) the mixture was added t-butyldimethylchlorosilane (860.48 mg, 5.710 mmol, 1.2 equiv) then added imidazole (647.79 mg, 9.516 mmol, 2.0 equiv). The mixture was stirred at room temperature for 2 h. After completion of reaction the mixture was quenched with water (30 mL) extracted with ethyl acetate (3 x 100 mL), the residue was washed with water (3x30 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% EA/PE) to afford methyl 2-(((tert-butyldimethylsilyl)oxy)methyl)pyrimidine-4-carboxylate (652 mg, 48.53%) as a yellow solid. MS (ESI): mass calcd. for $C_{13}H_{22}N_2O_3Si$: 282.14, found: 283.20 $[M+H]^+$.



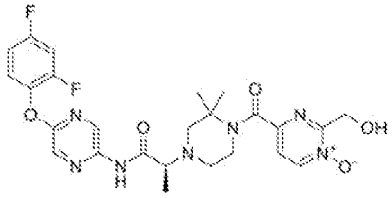
2-(((tert-butyldimethylsilyl)oxy)methyl)pyrimidine-4-carboxylic acid

To a solution of methyl 2-{[(tert-butyldimethylsilyl)oxy]methyl}pyrimidine-4-carboxylate (400 mg, 1.416 mmol, 1 equiv) in tetrahydrofuran (10 mL) methanol (5 mL) and water (5 mL) the mixture was added LiOH (50.88 mg, 2.124 mmol, 1.5 equiv). The mixture was stirred at room temperature for 2 h. After completion of reaction the mixture was acidified neutralized to (pH =3) with (4N HCl). The mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated to afford 2-(((tert-butyldimethylsilyl)oxy)methyl)pyrimidine-4-carboxylic acid (270 mg, 71.03%) as a yellow solid. MS (ESI): mass calcd. for $C_{12}H_{20}N_2O_3Si$: 268.12, found: 269.35 $[M+H]^+$.



2-(((tert-butyldimethylsilyl)oxy)methyl)-4-carboxypyrimidine 1-oxide

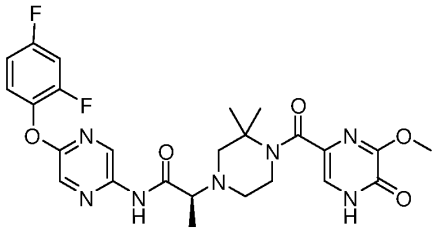
To a solution of 2-{[(tert-butyldimethylsilyl)oxy]methyl}pyrimidine-4-carboxylic acid (150 mg, 0.559 mmol, 1 equiv) in EA (5 mL) the mixture was added m-CPBA (192.88 mg, 1.118 mmol, 2 equiv). The mixture was stirred at 50°C for 3 h. After completion of reaction the mixture was cooled to room temperature then quenched with water (30 mL) extracted with ethyl acetate (3 x 100 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by C18 chromatography (0-50% ACN/H2O) to afford 2-(((tert-butyldimethylsilyl)oxy)methyl)-4-carboxypyrimidine 1-oxide (26 mg, 16.36%) as a yellow solid. MS (ESI): mass calcd. for $C_{12}H_{20}N_2O_4Si$: 284.12, found: 285.00 $[M+H]^+$.



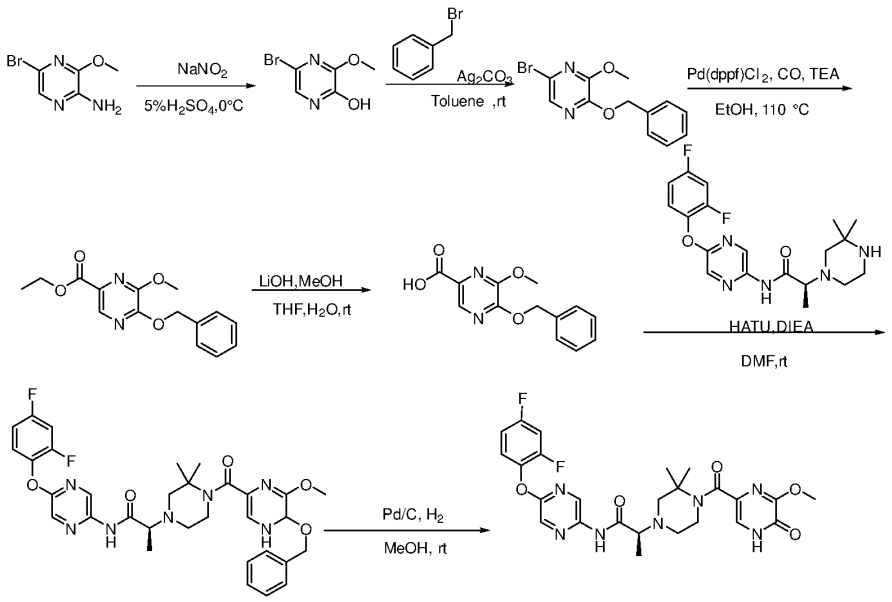
(S)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyrimidine 1-oxide

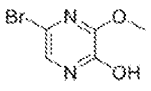
To a solution of 2-(((tert-butyldimethylsilyl)oxy)methyl)-4-carboxypyrimidine 1-oxide (20 mg, 0.070 mmol, 1 equiv)in N,N-dimethylformamide(1 mL) the mixture was added (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide mmol, 1.0 equiv) then added HATU (40.11 mg, 0.105 mmol, 1.5 equiv) and DIEA (27.27 mg, 0.210 mmol, 3.0 equiv). The mixture was stirred at room temperature for 2 h. After completion reaction the reaction was quenched by water (10 mL) then extracted with EA (3 x 30 mL). The resulting mixture was concentrated under reduced pressure was purified by preparative HPLC using a XBridge Prep OBD 150 mm x 30 mm x 5 μm column (eluent: 27% to 57% (v/v) ACN and H_2O with 10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyrimidine 1-oxide (9.6 mg, 24.80%) as a white solid MS (ESI): mass calcd. for $C_{25}H_{27}F_2N_7O_5$: 543.20, found: 544.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.42 (s, 1H), 8.80 (s, 1H), 8.43 (s, 1H), 8.33 (d, J = 4.7 Hz, 1H), 7.37 – 7.57 (m, 3H), 7.08 – 7.22 (m, 1H), 5.37 (t, J = 6.5 Hz, 1H), 4.65 – 4.74 (m, 2H), 3.43 – 3.58 (m, 2H), 3.05 – 3.19 (m, 1H), 2.56 – 2.75 (m, 2H), 2.29 – 2.42 (m, 2H), 1.40 – 1.60 (m, 6H), 1.05 – 1.21 (m, 3H).

Example 20: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(6-methoxy-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide



Synthetic Scheme

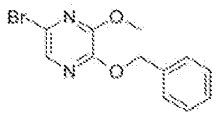




5-bromo-3-methoxypyrazin-2-ol

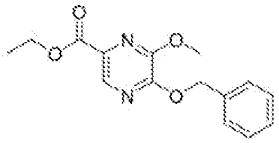
To a stirring solution 5-bromo-3-methoxypyrazin-2-amine (1 g, 4.901 mmol, 1 equiv) in H_2SO_4 (10 mL, 5%) was added a solution of sodium nitrite (676.33 mg, 9.802 mmol, 2

equiv). The resulting mixture was stirred at 0°C for 6h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford 5-bromo-3-methoxypyrazin-2-ol (1 g, 99.52%). MS (ESI): mass calcd. for $C_5H_5BrN_2O_2$: 203.95 m/zfound: 205.05[M+H$^+$]



2-(benzyloxy)-5-bromo-3-methoxypyrazine

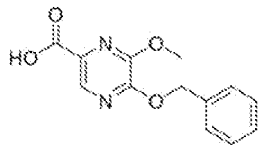
To a stirring solution 5-bromo-3-methoxypyrazin-2-ol (660 mg, 3.219 mmol, 1 equiv) in Toluene (10 mL) was added a solution of benzyl bromide (825.94 mg, 4.829 mmol, 1.5 equiv) and Ag_2CO_3 (1775.43 mg, 6.438 mmol, 2 equiv). The resulting mixture was stirred at room temperature for 16h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford 2-(benzyloxy)-5-bromo-3-methoxypyrazine (780 mg, 82.09%). MS (ESI): mass calcd. for $C_{12}H_{11}BrN_2O_2$: 294.13 m/z found: 294.95[M+H$^+$]



ethyl 5-(benzyloxy)-6-methoxypyrazine-2-carboxylate

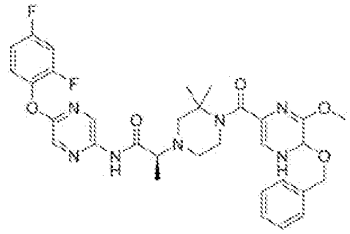
To a stirring solution 2-(benzyloxy)-5-bromo-3-methoxypyrazine (780 mg, 2.643 mmol, 1 equiv) in ethyl alcohol (15 mL) was added a solution of palladium chloride; bis(triphenylphosphine) (185.50 mg, 0.264 mmol, 0.1 equiv) and TEA (802.31 mg, 7.929 mmol, 3 equiv). The resulting mixture was under CO stirred at 110°C for 16h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford ethyl 5-(benzyloxy)-6-

methoxypyrazine-2-carboxylate (670 mg, 87.93%). MS (ESI): mass calcd. for $C_{15}H_{16}N_2O_4$: 288.11 m/z found: 289.20[M+H$^+$]



5-(benzyloxy)-6-methoxypyrazine-2-carboxylic acid

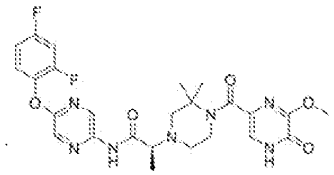
To a stirring solution ethyl 5-(benzyloxy)-6-methoxypyrazine-2-carboxylate (670 mg, 2.324 mmol, 1 equiv) in methanol (1 mL) and tetrahydrofuran (2 mL) and water (1 mL) was added a solution of lithiumol (278.29 mg, 11.620 mmol, 5 equiv). The resulting mixture was stirred at room temperature for 16h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford 5-(benzyloxy)-6-methoxypyrazine-2-carboxylic acid (200 mg, 33.07%) MS (ESI): mass calcd. for $C_{13}H_{12}N_2O_4$: 260.08 m/z found: 261.15[M+H$^+$]



(2S)-2-(4-(5-(benzyloxy)-6-methoxy-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

To a stirring solution 5-(benzyloxy)-6-methoxypyrazine-2-carboxylic acid (200 mg, 0.768 mmol, 1 equiv) in dimethylformamide (2 mL) was added a solution of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (300.81 mg, 0.768 mmol, 1 equiv) and [(dimethylamino)({3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy})methylidene]dimethylazanium (438.31 mg, 1.152 mmol, 1.5 equiv) and DIEA (397.30 mg, 3.072 mmol, 4 equiv) .The resulting mixture was stirred at room temperature for 16h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford (2S)-2-(4-(5-

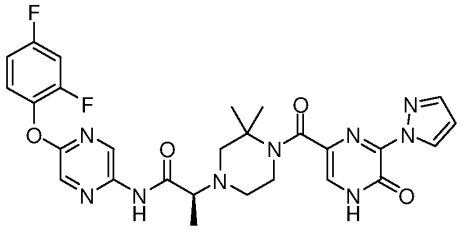
(benzyloxy)-6-methoxy-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (200 mg, 41.07%) MS (ESI): mass calcd. for $C_{32}H_{33}F_2N_7O_5$: 633.25 m/z found: 634.35[M+H$^+$]



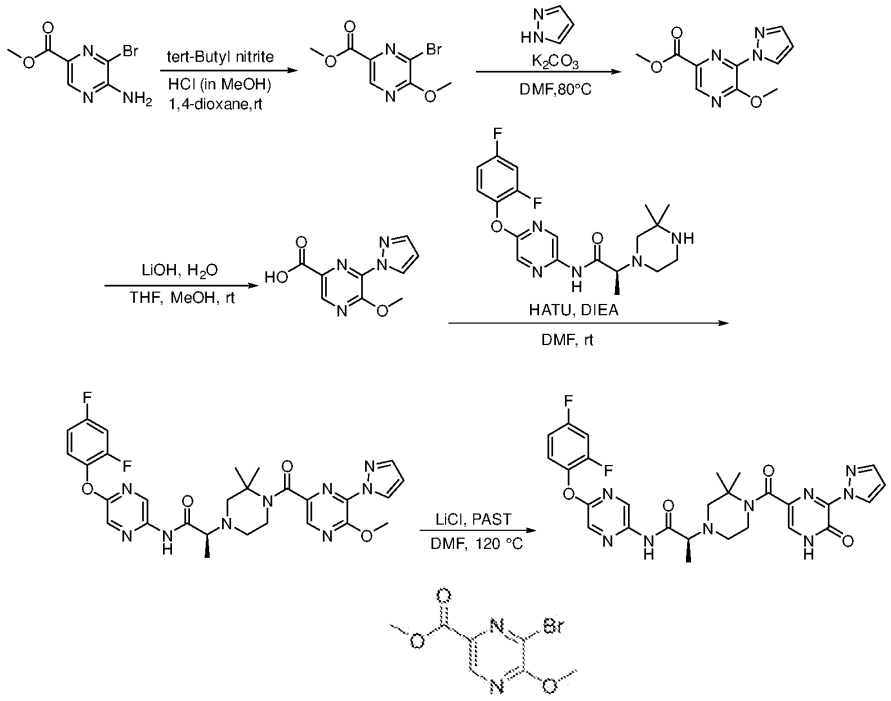
(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(6-methoxy-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

To a stirred solution of (2S)-2-(4-(5-(benzyloxy)-6-methoxy-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (200 mg, 0.316 mmol, 1 equiv) in methanol (50 mL) was added Pd/C (167.95 mg, 1.580 mmol, 5 equiv) at room temperature . The reaction mixture under H_2 was stirred at room temperature for 3 h. The resulting mixture was stirred for additional overnight at room temperature. After completion of reaction, the reaction mixture was quenched by addition of water (5 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and the residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30 x150mm x 5μm (eluent: 18% to 48% (v/v) CH_3CN and H_2O with NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(6-methoxy-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (20.4 mg, 11.82%) as a white solid. MS (ESI): mass calcd for $C_{25}H_{27}F_2N_7O_5$: 543.20 m/z, found: 544.25[M+H]$^+$, ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.36 (s, 1H), 8.83 (s, 1H), 8.45 (s, 1H), 7.47 (tt, J = 8.7, 4.8 Hz, 2H), 7.34 (s, 1H), 7.17 (s, 1H), 3.81 (s, 3H), 3.59 (d, J = 5.1 Hz, 3H), 2.66 – 2.81 (m, 2H), 2.40 (s, 2H), 1.42 (s, 6H), 1.20 (d, J = 6.8 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -113.38 (t, J = 5.2 Hz), -124.19 (t, J = 3.5 Hz).

Example 204: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-6-(1H-pyrazol-1-yl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propenamide

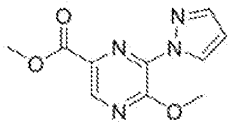


Synthetic Scheme



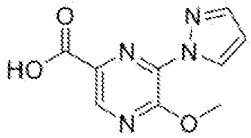
methyl 6-bromo-5-methoxypyrazine-2-carboxylate

To a solution of methyl 5-amino-6-bromopyrazine-2-carboxylate (2 g, 8.619 mmol, 1 equiv) in MeOH(20 mL), at 0 degrees, was added tert-Butyl nitrite (3.8 mL) followed by 4N hydrochloric acid in 1,4-dioxane(0.95 mL). The reaction mixture was allowed to warm to room temperature and stirred for 8 h. The reaction was quenched by the addition of ice water (5 mL) at 0 degrees. The residue was diluted with aq. $NaHCO_3$ and extracted in to DCM. The combined organic layers were dried, and the solvent was removed under reduced pressure,and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% PE/EA) to afford methyl 6-bromo-5-methoxypyrazine-2-carboxylate (1.2 g, 56.35%) as a yellow oil.MS (ESI): mass calcd. for $C_7H_7BrN_2O_3$:245.96 m/z, found:246.85$[M+H]^+$.



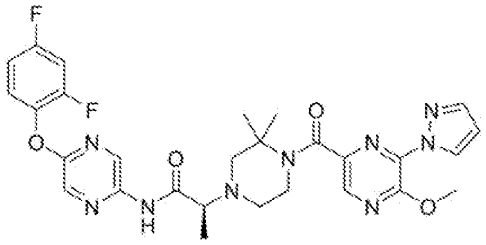
methyl 5-methoxy-6-(1H-pyrazol-1-yl)pyrazine-2-carboxylate

To a solution of methyl 6-bromo-5-methoxypyrazine-2-carboxylate (500 mg, 2.024 mmol, 1 equiv) in DMF (5ml) was wadded potassium methaneperoxoate potassium (1.69 g, 12.144 mmol, 6 equiv) and pyrazole (413.35 mg, 6.072 mmol, 3 equiv) at rt. The mixture was allowed to warm to 80 °C and stirred for 12 h. The resulting mixture was extracted with EA (3*50mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% PE/EA) to afford methyl 5-methoxy-6-(pyrazol-1-yl)pyrazine-2-carboxylate (250 mg, 52.74%) as a yellow oil, MS (ESI): mass calcd. for $C_{10}H_{10}N_4O_3$:234.08 m/z, found:235.15$[M+H]^+$.



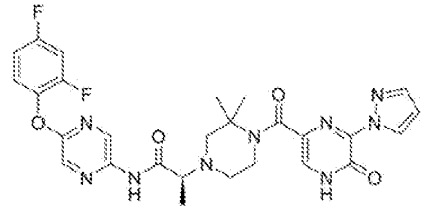
5-methoxy-6-(1H-pyrazol-1-yl)pyrazine-2-carboxylic acid

To a solution of methyl 5-methoxy-6-(pyrazol-1-yl)pyrazine-2-carboxylate (240 mg, 1.025 mmol, 1 equiv) in THF (3 mL).methanol (0.5 mL), LiOH (49.08 mg, 2.050 mmol, 2 equiv) and water (0.5 mL) added at rt. The resulting mixture was stirred for 2h at rt. The resulting mixture was concentrated under vacuum. The residue was acidified to pH 2~3 with 3NHCl. The precipitated solids were collected by filtration and washed with H_2O (5ml) to afford 5-methoxy-6-(pyrazol-1-yl)pyrazine-2-carboxylic acid)(120mg) as a yellow oil. MS (ESI): mass calcd. for $C_9H_8N_4O_3$:220.06 m/z, found:221.10$[M+H]^+$.



(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-methoxy-6-(1H-pyrazol-1-yl)pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

To a solution of 5-methoxy-6-(pyrazol-1-yl)pyrazine-2-carboxylic acid (100 mg, 0.454 mmol, 1 equiv) in DMF (3 mL). (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (177.77 mg, 0.454 mmol, 1 equiv) ,HATU (259.03 mg, 0.681 mmol, 1.5 equiv) and DIEA (352.19 mg, 2.724 mmol, 6 equiv) added at rt. The resulting mixture was stirred for 2h at rt. The resulting mixture was extracted with EA (3*50mL). The combined organic layers were washed with brine (20mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20% DCM/MeOH)to afford(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-methoxy-6-(1H-pyrazol-1-yl)pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (80 mg, 29.68%) as a yellow oil, MS (ESI): mass calcd. for $C_{28}H_{29}F_2N_9O_4$: 593.23m/z, found: 594.35 $[M+H]^+$.

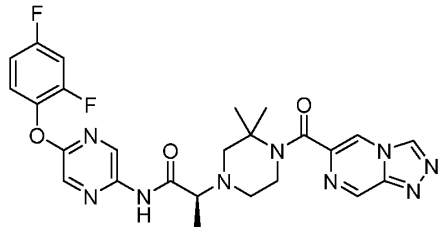


(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-6-(1H-pyrazol-1-yl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide

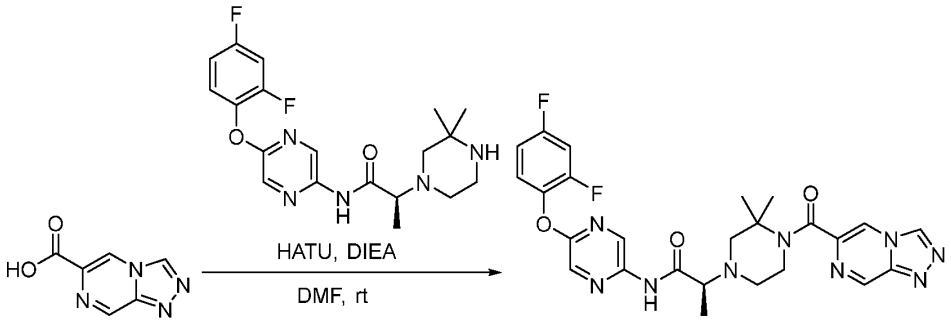
To a solution of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-methoxy-6-(1H-pyrazol-1-yl)pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (200 mg, 0.337 mmol, 1 equiv) in DMF (3 mL).lithium chloride (71.41 mg, 1.685 mmol, 5 equiv) and PAST (290.10 mg, 1.685 mmol, 5 equiv) added at rt. The resulting mixture was stirred for 2h at rt. The resulting mixture was extracted with EA (3*50mL). The combined organic layers were washed with brine (20mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% PE/EA) and Prep-HPLC using a Column: YMC-Actus Triart C18 ExRS30*150 mm; eluent:(27% to 47%v/v) ACN and H_2O (10mmol/L NH_3HCO_3+0.05%NH_3H_2O) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-6-(1H-pyrazol-1-yl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide (18.3 mg, 9.23%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{27}F_2N_9O_4$:579.22 m/z, found:580.30 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.39 (s, 1H), 8.83 (s, 1H), 8.44 (s, 1H), 7.60 – 8.02 (m, 2H), 7.45 (s,

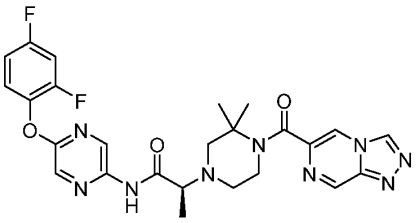
2H), 7.16 (s, 1H), 6.47 (s, 1H), 3.43 – 3.72 (m, 4H), 2.63 – 2.86 (m, 3H), 1.43 (s, 6H), 1.21 (s, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -113.442, -124.225.

Example 205: (S)-2-(4-([1,2,4]triazolo[4,3-a]pyrazine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide



Synthetic Scheme



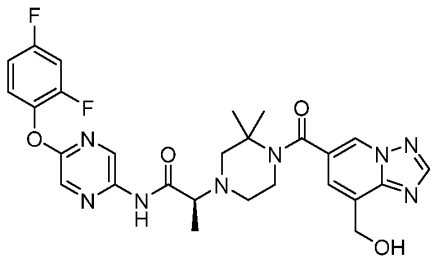


(S)-2-(4-([1,2,4]triazolo[4,3-a]pyrazine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

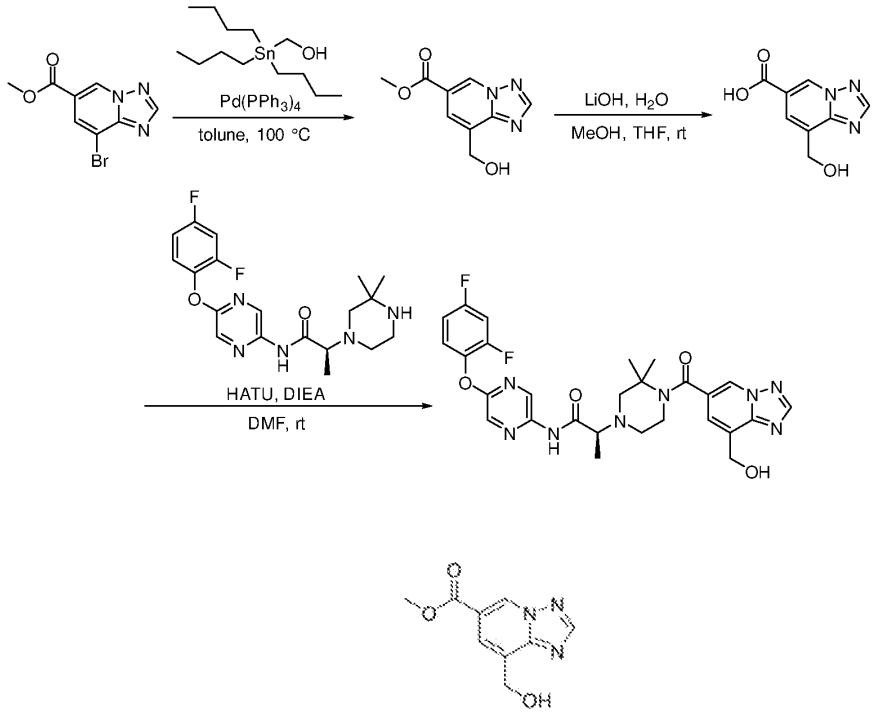
To a stirring solution (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (100 mg, 0.255 mmol, 1 equiv) in dimethylformamide (5 mL) the mixture was added [1,2,4]triazolo[4,3-a]pyrazine-6-carboxylic acid (41.93 mg, 0.255 mmol, 1 equiv), HATU (145.71 mg, 0.383 mmol, 1.5 equiv) and N,N-diisopropylethylamine (132.08 mg, 1.020 mmol, 4 equiv) at rt. The resulting mixture was

stirred for 2 hours at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) and purified by preparative HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 20% to 45% (v/v) using a Water (10mmol/L NH4HCO3+0.05%NH3H2O) and ACN; Flow rate: 60 mL/min mL/min; Gradient: 29% B to 59% B in 7min; Wave Length: 254nm/220nm nm; RT1(min): 6.27 to afford (S)-2-(4-([1,2,4]triazolo[4,3-a]pyrazine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (73.9 mg, 53.45%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{25}F_2N_9O_3$: 537.20 m/z, found: 538.25 $[M+H]^+$,^{1}H NMR (400 MHz, DMSO-d_6) δ 10.45 (s, 1H), 9.45 (d, J = 0.7 Hz, 1H), 9.39 (d, J = 1.6 Hz, 1H), 8.86 (dd, J = 3.9, 1.5 Hz, 2H), 8.46 (d, J = 1.4 Hz, 1H), 7.42 -7.55 (m, 2H), 7.13-7.23 (m, 1H), 3.49-3.59 (m, 1H), 3.45 (t, J = 5.3 Hz, 2H), 2.57-2.76 (m, 2H), 2.41 - 2.50 (m, 2H), 1.49 (d, J = 3.2 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H).^{19}F NMR (376 MHz, DMSO-d_6) δ -113.42 (d, J = 5.3 Hz), -124.22 (d, J = 5.4 Hz), -218.46.

Example 206: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(8-(hydroxymethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

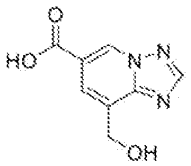


Synthetic Scheme



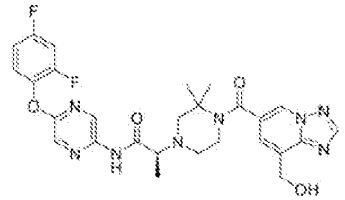
methyl 8-(hydroxymethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate

To a solution of methyl 8-bromo-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (400 mg, 1.562 mmol, 1 equiv) in toluene (10 mL) the mixture was added (tributylstannyl)methanol (752.39 mg, 2.343 mmol, 1.5 equiv) and $Pd(PPh_3)_4$ (180.52 mg, 0.156 mmol, 0.1 equiv). The mixture was stirred at 100°C for 2 h under N_2. After completion of reaction the mixture was cooled to room temperature then quenched with water (30 mL) extracted with ethyl acetate (3 x 50 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% EA/PE) to afford methyl 8-(hydroxymethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (213 mg, 65.81%) as a yellow solid. MS (ESI): mass calcd. for $C_9H_9N_3O_3$: 207.06m/z, found: 208.10 $[M+H]^+$.



8-(hydroxymethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid

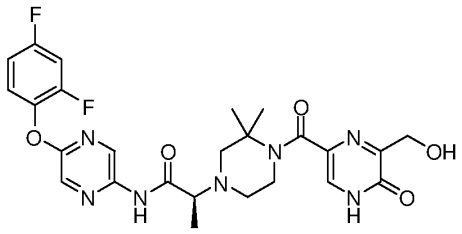
To a solution of methyl 8-(hydroxymethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (150 mg, 0.724 mmol, 1 equiv) in tetrahydrofuran (4 mL) methanol (2 mL) and water (2 mL) the mixture was added LiOH (26.01 mg, 1.086 mmol, 1.5 equiv). The mixture was stirred at room temperature for 2 h. After completion of reaction the mixture was acidified neutralized to (pH =3) with (4N HCl). The mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated to afford 8-(hydroxymethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid (96 mg, 68.65%) as a yellow solid. MS (ESI): mass calcd. for $C_8H_7N_3O_3$ 193.05 m/z, found: 194.10 $[M+H]^+$.



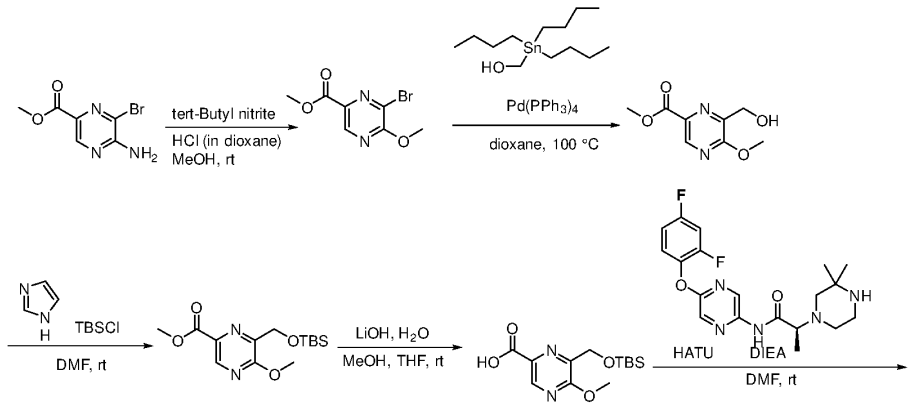
(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(8-(hydroxymethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

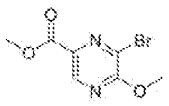
To a solution of 8-(hydroxymethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid (80 mg, 0.414 mmol, 1 equiv) in N,N-dimethylformamide (3 mL) the mixture was added (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (162.11 mg, 0.414 mmol, 1.0 equiv) then added HATU (236.21 mg, 0.621 mmol, 1.5 equiv) and DIEA (160.59 mg, 1.242 mmol, 3.0 equiv). The mixture was stirred at room temperature for 2 h. After completion reaction the reaction was quenched by water (10 mL) then extracted with EA (3 x 30 mL). The resulting mixture was concentrated under reduced pressure then purified by HPLC Column XBridge Prep Shield RP18 OBD Column, 30*150 mm*5 μm; (eluent: 15% to 30% (v/v) Water (10mmol/L NH_4HCO_3+0.05%NH_3H_2O) and ACN to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(8-(hydroxymethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (43.6 mg, 18.47%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{28}F_2N_8O_4$: 566.22 m/z, found: 567.25 $[M+H]^+$, ^1H NMR (300 MHz, DMSO-d_6) δ 10.44 (s, 1H), 8.93 – 9.00 (m, 1H), 8.86 (d, J = 1.4 Hz, 1H), 8.55 (s, 1H), 8.46 (d, J = 1.5 Hz, 1H), 7.57 – 7.65 (m, 1H), 7.40 – 7.55 (m, 2H), 7.11 – 7.24 (m, 1H), 5.65 (t, J = 5.7 Hz, 1H), 4.86 (d, J = 5.7 Hz, 2H), 3.55 (q, J = 6.8 Hz, 1H), 3.36-3.45 (m, 2H), 2.69 – 2.79 (m, 1H),2.59 – 2.69 (m, 1H), 2.42 – 2.55 (m, 2H), 1.50 (d, J = 2.2 Hz, 6H), 1.22 (d, J = 6.8 Hz, 3H).

Example 207: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(6-(hydroxymethyl)-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide



Synthetic Scheme

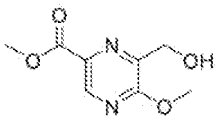




methyl 6-bromo-5-methoxypyrazine-2-carboxylate

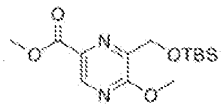
To a solution of methyl 5-amino-6-bromopyrazine-2-carboxylate (2 g, 8.619 mmol, 1 equiv) in methanol (20 mL) the mixture was cooled to 0°C then added tert-butyl nitrate (3.8 mL) and hydrogen chloride in dioxane (0.95 mL). The mixture was stirred at room temperature for 16 h. After completion of reaction the mixture was quenched with water (50

mL) basified to pH=13 with $NaHCO_3$ solution then extracted with ethyl acetate (3 x 100 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50%EA/PE) to afford methyl 6-bromo-5-methoxypyrazine-2-carboxylate (1.6 g, 75.14%) as a yellow solid.



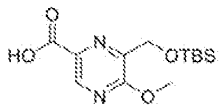
methyl 6-(hydroxymethyl)-5-methoxypyrazine-2-carboxylate

To a solution of methyl 6-bromo-5-methoxypyrazine-2-carboxylate (1.5 g, 6.072 mmol, 1 equiv) in dioxane (30 mL) the mixture was added (tributylstannyl)methanol (2.92 g, 9.108 mmol, 1.5 equiv) and $Pd(PPh_3)_4$ (0.70 g, 0.607 mmol, 0.1 equiv). The mixture was stirred at 100°C for 2 h under N_2. After completion of reaction the mixture was cooled to room temperature then quenched with water (30 mL) extracted with ethyl acetate (3 x 100 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% EA/PE) to afford methyl 6-(hydroxymethyl)-5-methoxypyrazine-2-carboxylate (423 mg, 35.15%) as a yellow solid. MS (ESI): mass calcd. for $C_8H_{10}N_2O_4$: 198.06, found: 199.25 $[M+H]^+$.



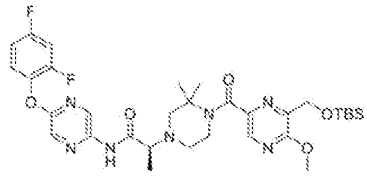
methyl 6-(((tert-butyldimethylsilyl)oxy)methyl)-5-methoxypyrazine-2-carboxylate

To a solution of methyl 6-(hydroxymethyl)-5-methoxypyrazine-2-carboxylate (312 mg, 1.574 mmol, 1 equiv) in N,N-dimethylformamide (10 mL) the mixture was added TBSCl (284.74 mg, 1.889 mmol, 1.2 equiv) then added Imidazole (214.36 mg, 3.148 mmol, 2.0 equiv). The mixture was stirred at room temperature for 2 h. After completion of reaction the mixture was quenched with water (30 mL) extracted with ethyl acetate (3 x 100 mL), the residue was washed withwater (3 x 50 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% EA/PE) to afford methyl 6-(((tert-butyldimethylsilyl)oxy)methyl)-5-methoxypyrazine-2-carboxylate (283 mg, 57.53%) as a yellow solid. MS (ESI): mass calcd. for $C_{14}H_{24}N_2O_4Si$: 312.15, found: 313.30 $[M+H]^+$.



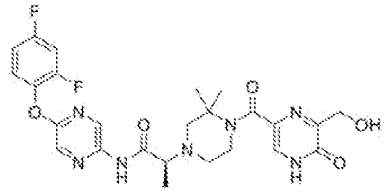
6-(((tert-butyldimethylsilyl)oxy)methyl)-5-methoxypyrazine-2-carboxylic acid

To a solution of methyl 6-{[(tert-butyldimethylsilyl)oxy]methyl}-5-methoxypyrazine-2-carboxylate (280 mg, 0.896 mmol, 1 equiv) in tetrahydrofuran (6 mL) methanol (3 mL) and water (3 mL) the mixture was added LiOH (32.19 mg, 1.344 mmol, 1.5 equiv). The mixture was stirred at room temperature for 2 h. After completion of reaction the mixture was acidified neutralized to (pH =3) with (4N HCl). The mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated to afford 6-(((tert-butyldimethylsilyl)oxy)methyl)-5-methoxypyrazine-2-carboxylic acid (180 mg, 67.31%) as a yellow solid. MS (ESI): mass calcd. for $C_{13}H_{22}N_2O_4Si$: 298.13, found: 299.00 $[M+H]^+$.



(S)-2-(4-(6-(((tert-butyldimethylsilyl)oxy)methyl)-5-methoxypyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

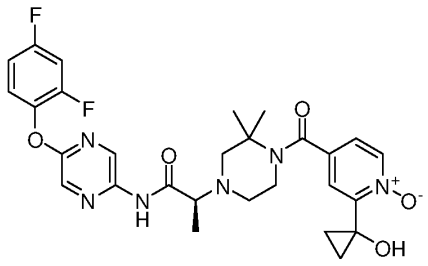
To a solution of 6-{[(tert-butyldimethylsilyl)oxy]methyl}-5-methoxypyrazine-2-carboxylic acid (100 mg, 0.335 mmol, 1 equiv) in DMF (3 mL) the mixture was added (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (131.17 mg, 0.335 mmol, 1.0 equiv) then added HATU (191.13 mg, 0.503 mmol, 1.5 equiv) and DIEA (129.93 mg, 1.005 mmol, 3.0 equiv). The mixture was stirred at room temperature for 2 h. After completion reaction the reaction was quenched by water (30 mL) then extracted with EA (3x 30 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% MeOH/DCM) to afford (S)-2-(4-(6-(((tert-butyldimethylsilyl)oxy)methyl)-5-methoxypyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (112 mg, 49.75%) as a yellow solid. MS (ESI): mass calcd. for $C_{32}H_{43}F_2N_7O_5Si$: 671.31, found: 672.10 $[M+H]^+$.



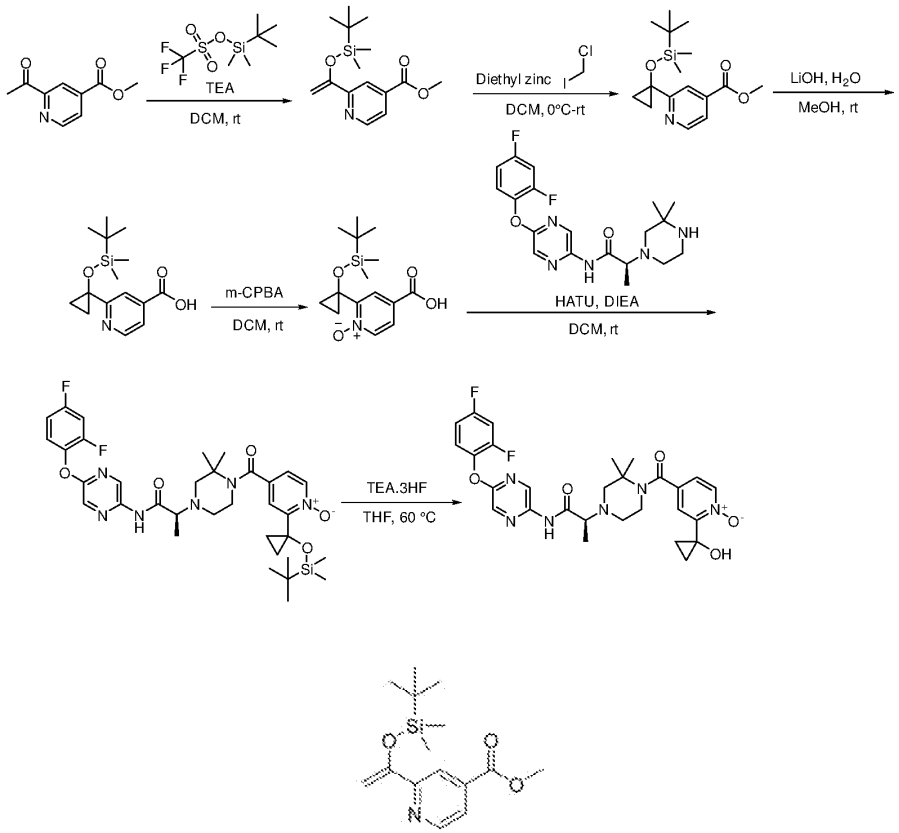
(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(6-(hydroxymethyl)-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

To a solution of (S)-2-(4-(6-(((tert-butyldimethylsilyl)oxy)methyl)-5-methoxypyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (100 mg, 0.149 mmol, 1 equiv) in DCM (5 mL) the mixture was added KI (247.09 mg, 1.490 mmol, 10 equiv) then added chlorotrimethylsilane (161.71 mg, 1.490 mmol, 10 equiv). The mixture was stirred at room temperature for 8 h. After completion reaction the reaction was quenched by water (30mL) then extracted with EA (3x30 mL). The resulting mixture was concentrated under reduced pressure then was purified by preparative HPLC using a XBridge Prep OBD 150 mm x 30 mm x 5 μm column (eluent: 20% to 50% (v/v) ACN and H_2O with 10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(6-(hydroxymethyl)-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (20.3 mg, 24.25%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{27}F_2N_7O_5$: 543.20, found: 544.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.38 (s, 1H), 8.83 (d, J = 1.4 Hz, 1H), 8.43 (d, J = 1.4 Hz, 1H), 7.64 (s, 1H), 7.38 – 7.54 (m, 2H), 7.09 – 7.22 (m, 1H), 4.42 (s, 2H), 3.43 – 3.64 (m, 4H), 2.68 – 2.80 (m, 1H), 2.55 – 2.68 (m, 2H), 2.40 (s, 2H), 1.42 (d, J = 1.6 Hz, 6H), 1.19 (d, J = 6.8 Hz, 3H).

Example 208: (S)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(1-hydroxycyclopropyl)pyridine 1-oxide

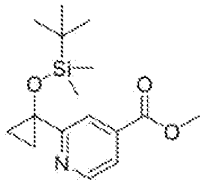


Synthetic Scheme



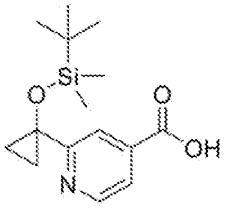
methyl 2-(1-((tert-butyldimethylsilyl)oxy)vinyl)isonicotinate

To a solution of methyl 2-acetylpyridine-4-carboxylate (4 g, 22.325 mmol, equiv) in DCM (80 mL) was added tert-butyldimethylsilyl trifluoromethanesulfonate (8.85 g, 33.487 mmol, 1.5 equiv) and TEA (6.78 g, 66.975 mmol, 3 equiv), the mixture was stirred for 2h at rt. the reaction mixture was quenched by water and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford methyl 2-(1-((tert-butyldimethylsilyl)oxy)vinyl)isonicotinate (3.2 g, 48.85%) as a yellow solid. MS (ESI): $C_{15}H_{23}NO_3Si$: 293.29 m/z, found 294.05 $[M+H]^+$.



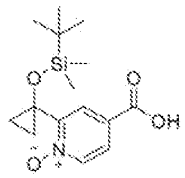
methyl 2-(1-((tert-butyldimethylsilyl)oxy)cyclopropyl)isonicotinate

To a solution of diethylzinc (20.45 mL, 20.448 mmol, 3 equiv) was dissolved in dichloromethane (50 mL), under nitrogen protection, the temperature was reduced to 0 °C, chloroiodomethane (7.21 g, 40.896 mmol, 6 equiv) was addeddropwise, and the mixture was stirred at 0 °C for 20 minutes, a solution of methyl 2-(1-((tert-butyldimethylsilyl)oxy)vinyl)isonicotinate (2 g, 6.816 mmol, 1 equiv) in dichloromethane (10 mL) was added dropwise. After the addition, the solution wasmaintained at 0 ° C. and stirred for 2 hours. TLC showed that the reaction was basically complete.The reaction solution was quenched by adding saturated ammonium chloride, extracted with ethylacetate, the organic phases were combined, washed with water, washed with saturated brine, driedover anhydrous sodium sulfate, concentrated, and purified by silica gel column chromatography to obtain the title compound methyl 2-(1-((tert-butyldimethylsilyl)oxy)cyclopropyl)isonicotinate (1.7 g, 81.12%) as an oil. MS (ESI): $C_{16}H_{25}NO_3Si$: 307.16 m/z, found: 308.05 $[M+H]^+$.



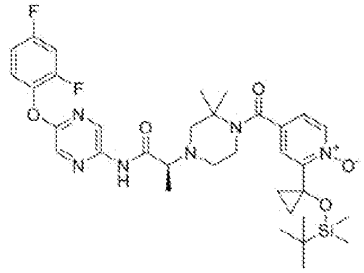
2-(1-((tert-butyldimethylsilyl)oxy)cyclopropyl)isonicotinic acid

To a solution of methyl 2-(1-((tert-butyldimethylsilyl)oxy)cyclopropyl)isonicotinate (900 mg, 2.927 mmol, 1 equiv) in MeOH (10 mL, 246.988 mmol, 84.38 equiv) THF (10 mL, 123.428 mmol, 42.17 equiv) H_2O (2 mL, 111.019 mmol, 37.93 equiv) was added LiOH (350.53 mg, 14.635 mmol, 5 equiv) at 0 °C, the mixture was stirred for 2 h at rt. The mixture was acidified to pH =5 with 4N HCl. The precipitated solids were collected by filtration to offer2-(1-((tert-butyldimethylsilyl)oxy)cyclopropyl)isonicotinic acid (600 mg, 69.85%) as a yellow solid. MS (ESI):$C_{15}H_{23}NO_3Si$: 293.29 m/z, found: 294.05 $[M+H]^+$.



2-(1-((tert-butyldimethylsilyl)oxy)cyclopropyl)-4-carboxypyridine 1-oxide

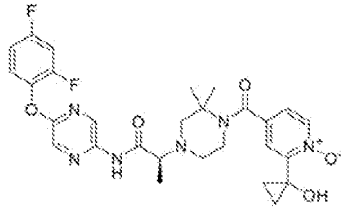
To a solution of 2-(1-((tert-butyldimethylsilyl)oxy)cyclopropyl)isonicotinic acid (600 mg, 2.045 mmol, 1 equiv) in DCM (10 mL) was added m-CPBA (705.68 mg, 4.090 mmol, 2 equiv) at 0 °C, the mixture was stirred for 2 h at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-10% MeOH/DCM) to afford 2-(1-((tert-butyldimethylsilyl)oxy)cyclopropyl)-4-carboxypyridine 1-oxide (350 mg, 55.32%) as a yellow solid. MS (ESI): mass calcd. for $C_{15}H_{23}NO_4Si$ 309.14 m/z, found 310.35 $[M+H]^+$.



(S)-2-(1-((tert-butyldimethylsilyl)oxy)cyclopropyl)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

To a solution of 2-(1-((tert-butyldimethylsilyl)oxy)cyclopropyl)-4-carboxypyridine 1-oxide (100 mg, 0.323 mmol, 1 equiv) in dimethylformamide (5 mL) was added (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (126.50 mg, 0.323 mmol, 1 equiv), HATU (184.32 mg, 0.485 mmol, 1.5 equiv), DIEA (167.07 mg, 1.292 mmol, 4 equiv), the mixture was stirred for 2h at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-10% MeOH/DCM) to afford (S)-2-(1-((tert-butyldimethylsilyl)oxy)cyclopropyl)-4-(4-(1-((5-(2,4-

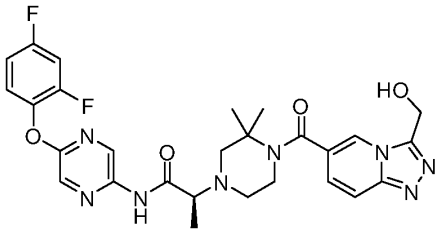
difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (100 mg, 45.32%) as a yellow solid.MS (ESI): mass calcd. for $C_{34}H_{44}F_2N_6O_5Si$: 682.14 m/z, found 683.35 $[M+H]^+$.



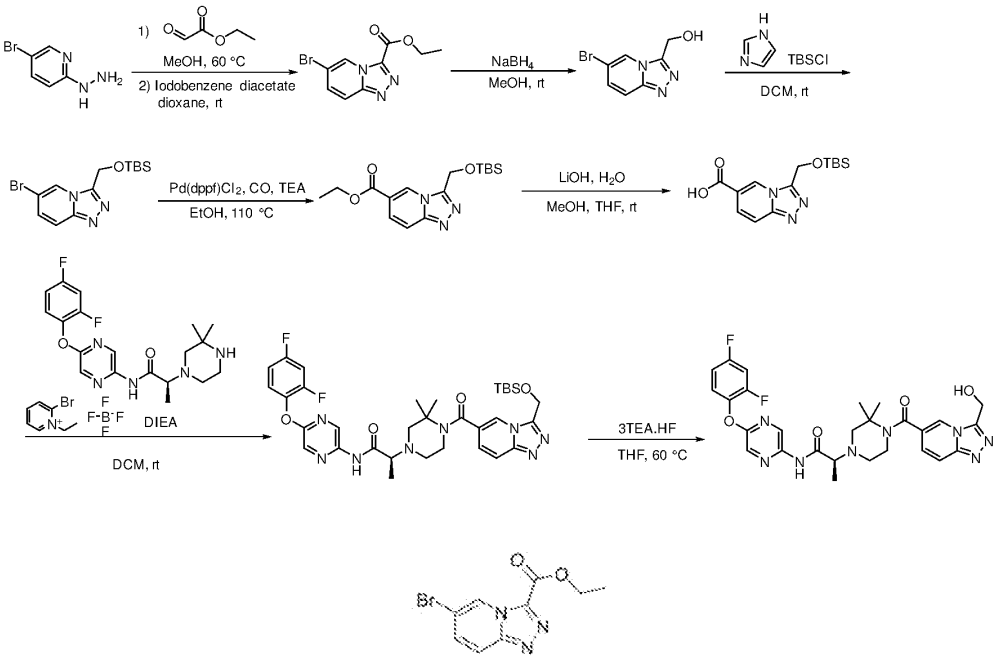
(S)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(1-hydroxycyclopropyl)pyridine 1-oxide

To a solution of (S)-2-(1-((tert-butyldimethylsilyl)oxy)cyclopropyl)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide (100 mg, 0.146 mmol, 1 equiv) in tetrahydrofuran (3 mL) with Triethylamine trihydrofluoride (0.5 mL).The resulting mixture was stirred for 1 h at 60 °C. After cooled to room temperature the reaction mixture was quenched by water and extracted with EA (3 x 20 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 100 mg crude product as a white solid. purified by preparative HPLC using Column: Xselect CSH C_{18} OBD Column, 30*150 mm, 5μm; (eluent: 27% to 40% (v/v) Water(0.1% FA) and ACN to afford (S)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(1-hydroxycyclopropyl)pyridine 1-oxide (23.4 mg, 27.29%) as a white solid. MS (ESI): mass calcd. for $C_{28}H_{30}F_2N_6O_5$: 568.22m/z, found 569.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.84 (d, J = 1.5 Hz, 1H), 8.45 (d, J = 1.5 Hz, 1H), 8.29 (d, J = 6.7 Hz, 1H), 7.47 (pd, J = 10.1, 9.0, 4.3 Hz, 3H), 7.37 (dd, J = 6.6, 2.5 Hz, 1H), 7.17 (t, J = 8.7 Hz, 1H), 6.48 (s, 1H), 3.49 – 3.56 (m, 1H), 2.57 – 2.74 (m, 3H), 2.45 (d, J = 4.1 Hz, 2H), 1.45 (d, J = 3.3 Hz, 6H), 1.34 – 1.17 (m, 6H), 1.00 (q, J = 5.1 Hz, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -113.42, -124.21.

Example 209: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(3-(hydroxymethyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide



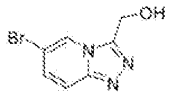
Synthetic Scheme



ethyl 6-bromo-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate

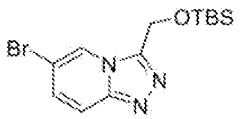
To a stirring solution 5-bromo-2-hydrazinylpyridine (1.4 g, 7.446 mmol, 1 equiv) in methanol (20 mL) was added a solution of ethyl glyoxylate (1520.25 mg, 14.892 mmol, 2 equiv). The mixture was stirred under N_2 at 60°C for 1h.The resulting mixture was concentrated under reduced pressure .The resulting mixture in dioxane (20 mL) was added a solution of Iodobenzene diacetate (2638.06 mg, 8.191 mmol, 1.1 equiv) .The mixture was stirred under N_2 at room temperature for 16h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20%

DCM/MeOH) to afford ethyl 6-bromo-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate (1.4 g, 69.62%) MS (ESI): mass calcd. for $C_9H_8BrN_3O_2$: 270.08 m/z found: 271.05[M^+H^+]



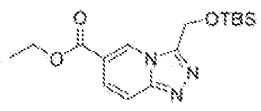
(6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methanol

To a stirring solutionethyl 6-bromo-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate (1.4 g, 5.184 mmol, 1 equiv) in methanol (20 mL) was added a solution of $NaBH_4$ (392.19 mg, 10.368 mmol, 2 equiv). The mixture was stirred at room temperature for 6h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) to afford {6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl}methanol (790 mg, 66.83%) MS (ESI): mass calcd. for $C_7H_6BrN_3O$: 226.96 m/z found: 228.05[$M+H^+$]



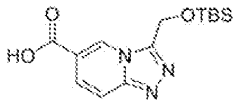
6-bromo-3-(((tert-butyldimethylsilyl)oxy)methyl)-[1,2,4]triazolo[4,3-a]pyridine

To a stirring solution {6-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl}methanol (790 mg, 3.464 mmol, 1 equiv) in DCM (10 mL) was added a solution of imidazole (707.51 mg, 10.392 mmol, 3 equiv) and t-butyldimethylchlorosilane (783.18 mg, 5.196 mmol, 1.5 equiv) at room temperature for 5h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) to afford 6-bromo-3-(((tert-butyldimethylsilyl)oxy)methyl)-[1,2,4]triazolo[4,3-a]pyridine (1 g, 84.33%) MS (ESI): mass calcd. for $C_{13}H_{20}BrN_3OSi$: 342.31 m/z found: 344.10[$M+H^+$]



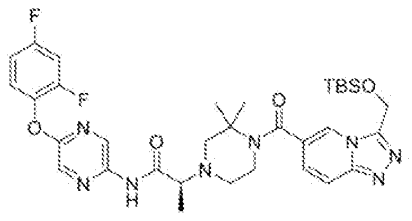
ethyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylate

To a stirring solution 6-bromo-3-(((tert-butyldimethylsilyl)oxy)methyl)-[1,2,4]triazolo[4,3-a]pyridine (1 g, 2.921 mmol, 1 equiv) in ethyl alcohol (20 mL) was added a solution of $Pd(dppf)Cl_2$ (0.21 g, 0.292 mmol, 0.1 equiv) and TEA (0.89 g, 8.763 mmol, 3 equiv) .The resulting mixture was under CO stirred at 110℃ for 6h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) to afford ethyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylate (400 mg, 40.81%) MS (ESI): mass calcd. for $C_{16}H_{25}N_3O_3Si$: 335.47 m/z found: 336.25[M+H$^+$]



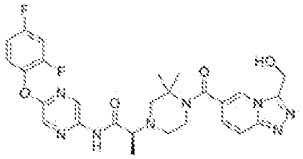
3-(((tert-butyldimethylsilyl)oxy)methyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid

To a stirring solution ethyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylate (500 mg, 1.490 mmol, 1 equiv) in methanol (1 mL) and tetrahydrofuran (2 mL) and water (1 mL) was added a solution of lithiumol (35.70 mg, 1.490 mmol, 1 equiv) .The resulting mixture was stirred at room temperature for 6h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) to afford 3-(((tert-butyldimethylsilyl)oxy)methyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid (180 mg, 39.29%). MS (ESI): mass calcd. for $C_{14}H_{21}N_3O_3Si$: 307.42 m/z found: 308.25[M+H$^+$]



(S)-2-(4-(3-(((tert-butyldimethylsilyl)oxy)methyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

To a stirring solution 3-(((tert-butyldimethylsilyl)oxy)methyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid (100 mg, 0.325 mmol, 1 equiv) in DCM (3 mL) was added a solution of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (190.98 mg, 0.488 mmol, 1.5 equiv) and DIEA (84.08 mg, 0.650 mmol, 2 equiv) and 2-bromo-1-ethylpyridin-1-ium tetrafluoroborate (133.62 mg, 0.488 mmol, 1.5 equiv) .The resulting mixture was stirred at room temperature for 6h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) to afford (S)-2-(4-(3-(((tert-butyldimethylsilyl)oxy)methyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (150 mg, 67.73%) MS (ESI): mass calcd. for $C_{33}H_{42}F_2N_8O_4Si$: 680.30 m/z found: 681.10[M+H$^+$]

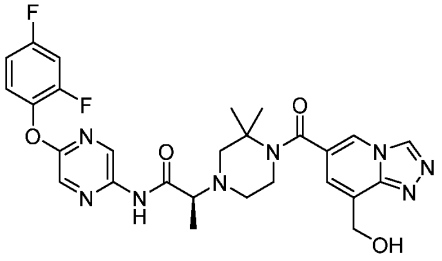


(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(3-(hydroxymethyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

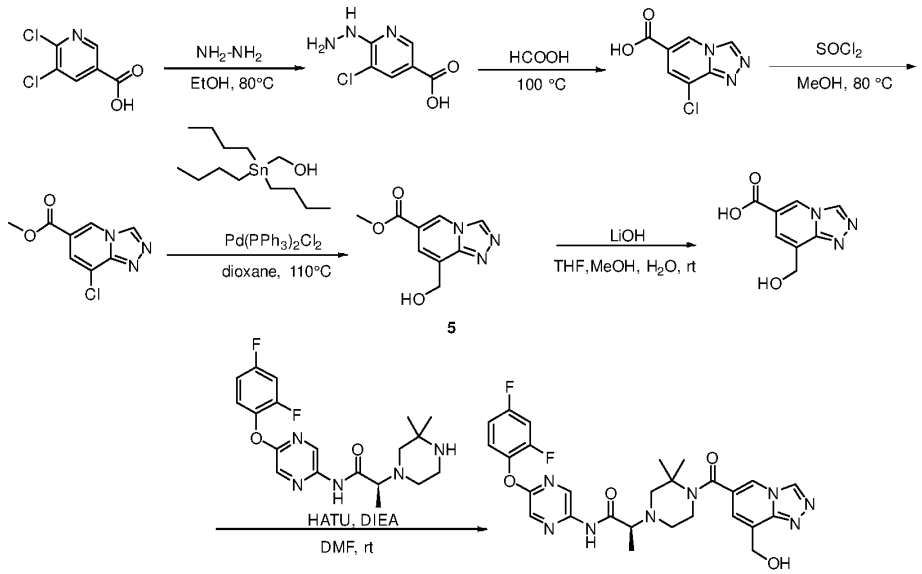
To a stirred solution of (S)-2-(4-(3-(((tert-butyldimethylsilyl)oxy)methyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (150 mg, 0.220 mmol, 1 equiv) in tetrahydrofuran (5 mL) was addedtriethylamine trihydrofluoride (1 mL) at room temperature . The reaction mixture was stirred at 60°C for 3 h. The resulting mixture was stirred for additional overnight at room temperature. After completion of reaction, the reaction mixture was quenched by addition of water (5 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and the residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30 x150mm x 5μm (eluent: 18% to 48% (v/v) CH_3CN and H_2O with NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-N-(5-(2,4-

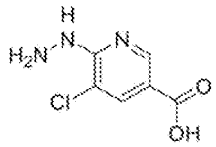
difluorophenoxy)pyrazin-2-yl)-2-(4-(3-(hydroxymethyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (9.9 mg, 7.91%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{28}F_2N_8O_4$: 566.22 m/z, found: 567.25[M+H]$^+$, ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.42 (s, 1H), 8.84 (s, 1H), 8.57 (s, 1H), 8.45 (s, 1H), 7.78 (d, J = 9.4 Hz, 1H), 7.34 – 7.55 (m, 13H), 7.17 (t, J = 8.2 Hz, 1H), 5.79 (d, J = 5.8 Hz, 1H), 5.01 (d, J = 5.8 Hz, 2H), 3.41 (s, 3H), 2.66 – 2.78 (m, 1H), 2.58 – 2.65 (m, 1H),2.44 – 2.55 (m, 2H), 1.49 (d, J = 2.3 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -113.35 (d, J = 5.3 Hz), -124.18 (d, J = 5.4 Hz).

Example 210: (*S*)-*N*-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(8-(hydroxymethyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide



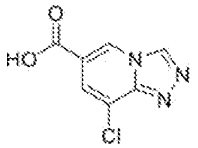
Synthetic Scheme





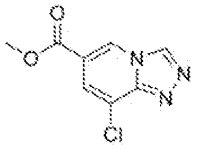
5-chloro-6-hydrazineylnicotinic acid

To a stirred solution of 5,6-dichloropyridine-3-carboxylic acid (2 g, 10.417 mmol, 1 equiv) in anhydrous EtOH (20 mL) was added hydrazine hydrate (98%) (2.61 g, 52.085 mmol, 5 equiv) at room temperature. The reaction mixture was stirred at 80°C for a period of 2h. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered. The filter cake was washed with EtOH (20 mL). The filtrate was concentrated under reduced pressure to afford 5-chloro-6-hydrazineylnicotinic acid (2 g, 99%) as a white solid. MS (ESI): mass calcd. for:$C_6H_6ClN_3O_2$: 187.01 m/z, found: 188.10 $[M+H]^+$.



8-chloro-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid

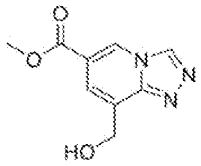
To a stirred solution of 5-chloro-6-hydrazineylnicotinic acid (1.5 g, 7.997 mmol, 1 equiv) in anhydrous formic acid (20 mL) at room temperature. The reaction mixture was stirred at 100°C for a period of 3h. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure to afford 8-chloro-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid (1 g, 59.80%) as a yellow solid. MS (ESI): mass calcd. for:$C_7H_4ClN_3O_2$: 197.00 m/z, found: 198.05 $[M+H]^+$.



methyl 8-chloro-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylate

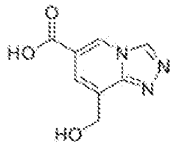
To a stirred solution of 8-chloro-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid (1 g, 5.061 mmol, 1 equiv) in anhydrous MeOH (10 mL) was added thionyl chloride (1.51 g, 12.652 mmol, 2.5 equiv) at 0°C. The reaction mixture was stirred at 80°C for a period of 3h. The mixture was allowed to cool down to room temperature. After cooled to room temperature the reaction was quenched by water (20 mL) and extracted with

MeOH/DCM=1/10 (20 mL x 3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford methyl 8-chloro-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylate (0.76 g, 70.88%) as a white solid.MS (ESI): mass calcd. for $C_8H_6ClN_3O_2$: 211.61 found: 212.05 $[M+H]^+$.



methyl 8-(hydroxymethyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylate

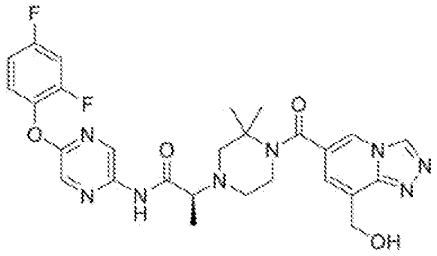
To a stirring solution methyl 8-chloro-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylate (800 mg, 3.781 mmol, 1 equiv) in dioxane (20 mL) was added a solution of $Pd(PPh_3)_2Cl_2$ (530.71 mg, 0.756 mmol, 0.2 equiv) and (tributylstannyl)methanol (1456.68 mg, 4.537 mmol, 1.2 equiv) . The mixture was stirred at 110 °C for 1 h under N_2. After cooled to room temperature, the reaction was quenched by water (10 mL) and extracted with EA (50 mL x 3). The combined organic extracts were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-80% PE/EA) to afford methyl 8-(hydroxymethyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylate (120 mg, 15.32%) as a yellow oil. MS (ESI): mass calcd. for $C_9H_9N_3O_3$: 207.189 m/z, found 207.90 $[M+H]^+$.



8-(hydroxymethyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid

To a solution of methyl 8-(hydroxymethyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylate (110 mg, 0.531 mmol, 1 equiv) in MeOH (2 mL) , tetrahydrofuran (4 mL) and water (2 mL) was added lithiumol (25.43 mg, 1.062 mmol, 2 equiv) at room temperature. The reaction mixture was stirred at room temperature for 1 h. The mixture was acidified pH = 5 with HCl (1N). The precipitated solids were collected by filtration and washed with water. The product was precipitated by the addition of diethyl ether. The product is obtained (8-

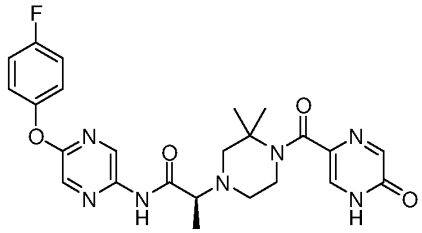
(hydroxymethyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid (70 mg, 68.26%)) as a white solid.



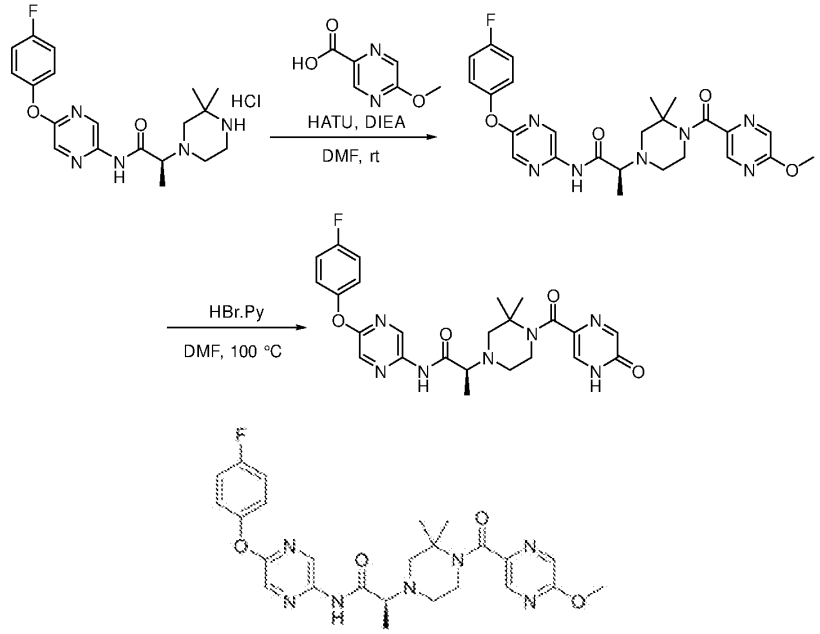
(*S*)-*N*-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(8-(hydroxymethyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

To a solution of 8-(hydroxymethyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid (60 mg, 0.311 mmol, 1 equiv) in dimethylformamide (3 mL) was added (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (145.90 mg, 0.373 mmol, 1.2 equiv) and HATU (149.75 mg, 0.622 mmol, 2 equiv) and DIEA (80.29 mg, 0.622 mmol, 2 equiv). The mixture was stirred at room temperature for 2 h. The mixture was concentrated to dryness under reduced pressure to provide the crude product. The residue was purified by preparative HPLC using a Xselect CSH C18 OBD 150 mm x 30 mm x 5 μm column (eluent: 18% to 48% (v/v) ACN and H_2O with 0.1% FA) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(8-(hydroxymethyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (1.6 mg, 0.90%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{28}F_2N_8O_4$: 566.57 m/z, found: 567.25 $[M+H]^+$.^{1}H NMR (300 MHz, Methanol-d_4) δ 9.25 (s, 1H), 8.89 (s, 1H), 8.64 (s, 1H), 8.28 (d, J = 1.5 Hz, 1H), 7.52 (d, J = 1.8 Hz, 1H), 7.34 (td, J = 8.9, 5.5 Hz, 1H), 7.15 (ddd, J = 11.0, 8.5, 2.9 Hz, 1H), 7.04 (t, J = 9.3 Hz, 1H), 5.03 (s, 2H), 3.57 (s, 2H), 3.38 - 3.51 (m, 1H), 2.78 – 2.90 (m, 1H), 2.66 – 2.76 (m, 1H), 2.58 (s, 2H), 1.63 (s, 6H), 1.28 – 1.40 (m, 3H).^{19}F NMR (282 MHz, Methanol-d_4) δ -115.47, -125.48.

Example 211: (S)-2-(3,3-dimethyl-4-(5-oxo-4,5-dihydropyrazine-2-carbonyl) piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)propanamide



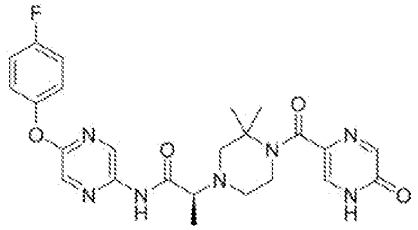
Synthetic Scheme



(S)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)-2-(4-(5-methoxypyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

To a solution of (S)-2-(3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)propanamide (500 mg, 1.20 mmol, 1 equiv) in DMF (20 mL) was added 5-methoxypyrazine-2-carboxylic acid (184 mg, 1.20 mmol, 1.0 equiv) and HATU (684 mg, 1.80 mmol, 1.5 equiv) and DIEA (464 mg, 3.60 mmol, 3 equiv) at rt .The resulting mixture was stirred for 2h at rt.The reaction mixture was quenched by water and extracted with EA (3*30 mL).The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20% DCM/MeOH) to afford (S)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)-2-(4-(5-methoxypyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-

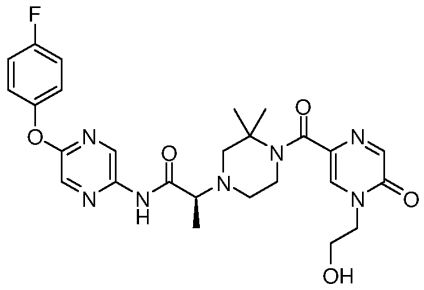
yl)propanamide (0.4 g, 58.6%) as a yellow solid. MS (ESI): mass calcd. for $C_{25}H_{28}FN_7O_4$ 509.22 m/z, found 509.80 $[M+H]^+$.



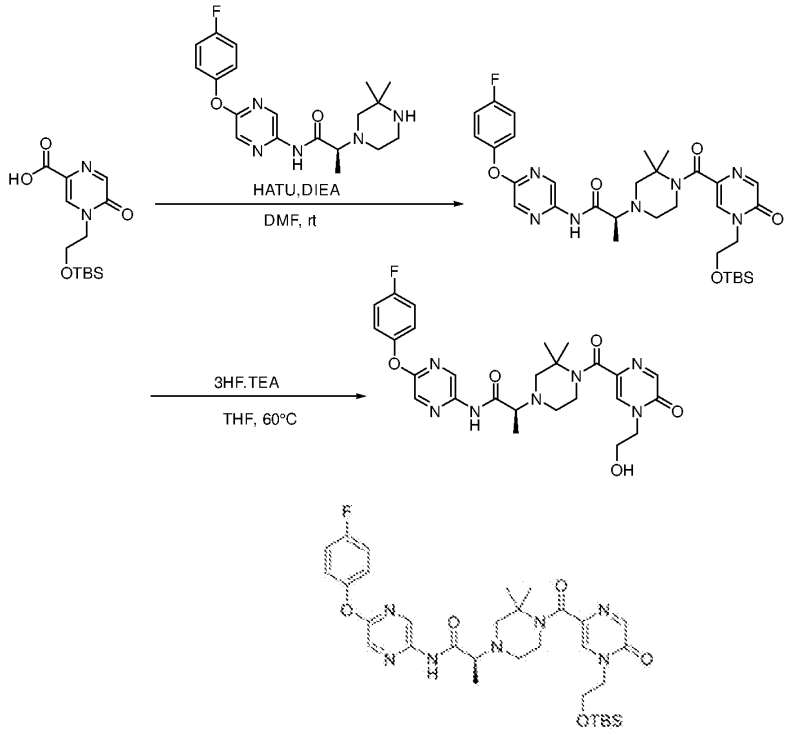
(S)-2-(3,3-dimethyl-4-(5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)propanamide

To a solution of (S)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)-2-(4-(5-methoxypyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (400 mg, 0.785 mmol, 1 equiv) in DMF (5mL) was added pyridine hydrobromide (1004.90 mg, 6.280 mmol, 8 equiv) at rt .The resulting mixture was stirred for overnight at 120 degrees C. The resulting mixture was stirred for 3h at rt. The reaction mixture was quenched by water and extracted with EA (2*30 mL).The combined organic extracts were washed with brine (20mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by HPLC Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm: (eluent: 20% to 50% (v/v)Water(10mmol/L NH_4HCO_3+0.05%NH_3H_2O) and ACN to afford (S)-2-(3,3-dimethyl-4-(5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)propanamide (98.9 mg, 25.29%) as a white soild. MS (ESI): mass calcd. for $C_{24}H_{26}FN_7O_4$ 495.20 m/z, found 496.25 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.39 (s, 1H), 8.90 (d, J = 1.4 Hz, 1H), 8.33 (d, J = 1.4 Hz, 1H), 7.87 (d, J = 1.2 Hz, 1H), 7.77 (d, J = 1.3 Hz, 1H), 7.25 (td, J = 5.9, 5.3, 3.2 Hz, 4H), 3.43 – 3.56 (m, 3H), 2.68 – 2.78 (m, 1H), 2.56 – 2.65 (m, 1H), 2.49 – 2.34 (m, 2H), 1.43 (d, J = 2.0 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -118.38.

Example 212: (S)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)-2-(4-(4-(2-hydroxyethyl)-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide



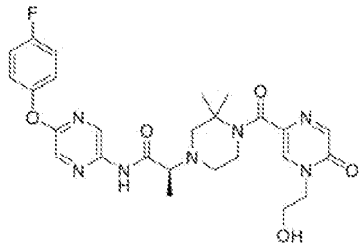
Synthetic Scheme



(2S)-2-(4-(4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-methoxy-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)propanamide

To a solution of 4-{2-[(tert-butyldimethylsilyl)oxy]ethyl}-5-oxopyrazine-2-carboxylic acid (500 mg, 17.0 mmol, 1 equiv) in DMF (10 mL) (2S)-2-(3,3-dimethylpiperazin-1-yl)-N-[5-(4-fluorophenoxy) pyrazin-2-yl]propanamide (625.5 mg, 17.0 mmol, 1 equiv)and HATU (955.5 mg, 25.5 mmol, 1.5 equiv) and DIEA (430 mg, 34 mmol, 2 equiv) added at rt. The resulting mixture was stirred for 2h at rt. The resulting mixture was extracted with EA (3*50mL). The combined organic layers were washed with brine (50mL), dried over

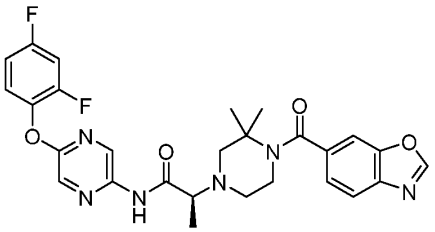
anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-15%DCM/MeOH) to afford (2S)-2-(4-(4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-methoxy-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)propanamide (500 mg, 91.28%) as a white solid, MS (ESI): mass calcd. for $C_{32}H_{44}FN_7O_5Si$ 653.32 m/z, found 653.75 $[M+H]^+$.



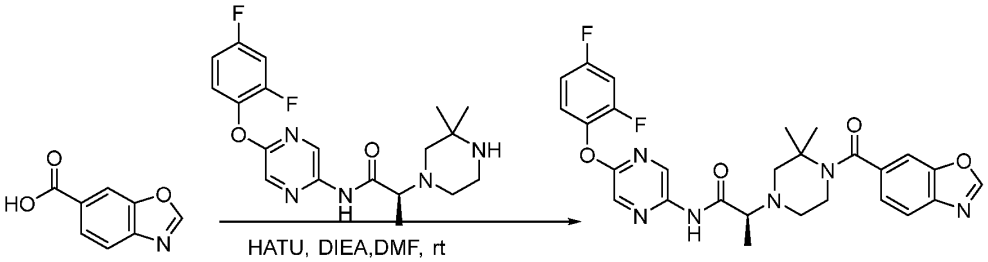
(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-6-(1H-pyrazol-1-yl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide

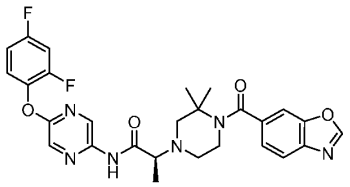
To a solution of (2S)-2-(4-(4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-methoxy-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)propanamide (200 mg, 0.306 mmol, 1 equiv) in THF (3 mL) was added Triethylamine trihydrofluoride (0.3 mL, 0.002 mmol, 0.01 equiv) at rt. The resulting mixture was stirred for 40 min at 60 degrees. The resulting mixture was concentrated under reduced pressure to yield a crude product which was directly purified by Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 28% to 28% ACN and H_2O (10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)-2-(4-(4-(2-hydroxyethyl)-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (45.6 mg, 27.56%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{30}FN_7O_5$: 539.23 m/z, found: 540.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.90 (s, 1H), 8.31 – 8.36 (m, 1H), 7.96 (d, J = 15.9 Hz, 2H), 7.19 – 7.31 (m, 4H), 4.96 (t, J = 5.6 Hz, 1H), 3.98 (t, J = 5.2 Hz, 2H), 3.60 – 3.69 (m, 2H), 3.48 – 3.57 (m, 3H), 2.54 – 2.79 (m, 2H), 2.36 – 2.48 (m, 2H), 1.44 (d, J = 3.0 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -118.3689.

Example 213: (S)-2-(4-(benzo[d]oxazole-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide



Synthetic Scheme



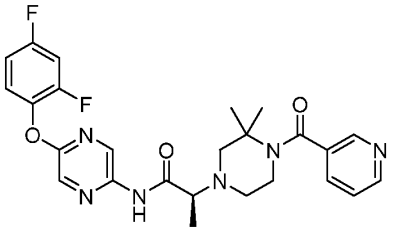


(S)-2-(4-(benzo[d]oxazole-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

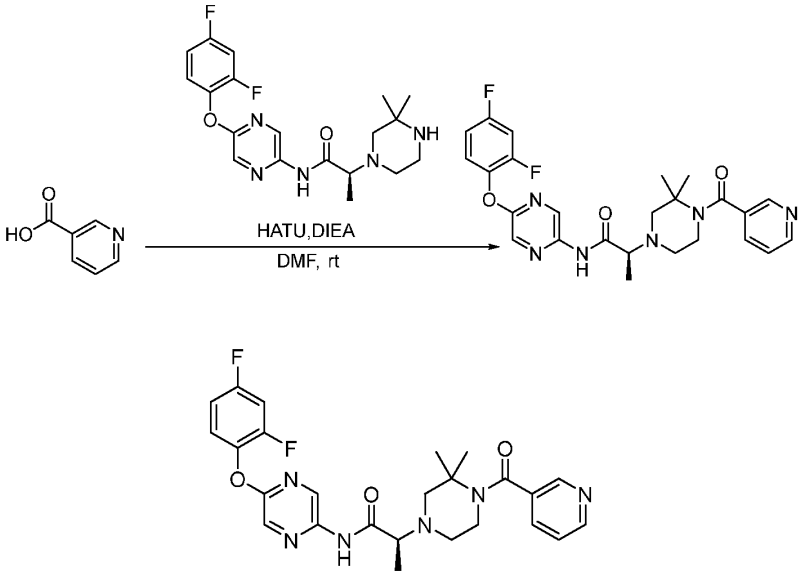
To a stirred solution of 1,3-benzoxazole-6-carboxylic acid (50 mg, 0.307 mmol, 1 equiv) in dimethylformamide (2 mL) was added (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (119.97 mg, 0.307 mmol, 1 equiv) and HATU (174.81 mg, 0.461 mmol, 1.5 equiv) and DIEA (158.46 mg, 1.228 mmol, 4 equiv) at room temperature. The reaction mixture was stirred at room temperature for 3 h. The resulting mixture was stirred for additional overnight at room temperature. After completion of reaction, the reaction mixture was quenched by addition of water (5 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) andthe residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30 x 150mm x 5μm (eluent: 18% to 48% (v/v) CH_3CN and H_2O with NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-2-(4-(benzo[d]oxazole-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-

difluorophenoxy)pyrazin-2-yl)propanamide (34.6 mg, 20.29%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{26}F_2N_6O_4$: 536.20 m/z, found: 537.30[M+H]$^+$ ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.85 (d, J = 1.8 Hz, 2H), 8.45 (d, J = 1.4 Hz, 1H), 7.84 (dd, J = 4.8, 3.3 Hz, 2H), 7.39 – 7.55 (m, 3H), 7.11 – 7.24 (m, 1H), 3.53 (q, J = 6.8 Hz, 1H), 3.32 (s, 2H), 2.71 (dt, J = 10.2, 4.8 Hz, 1H), 2.61 (q, J = 5.9, 5.4 Hz, 1H), 2.47 (d, J = 2.7 Hz, 2H), 1.49 (d, J = 2.3 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -113.43 (d, J = 5.2 Hz), -124.20 (d, J = 5.2 Hz).

Example 214: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-nicotinoylpiperazin-1-yl)propanamide



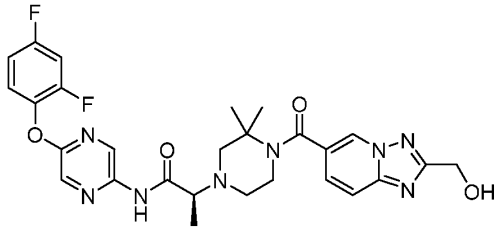
Synthetic Scheme



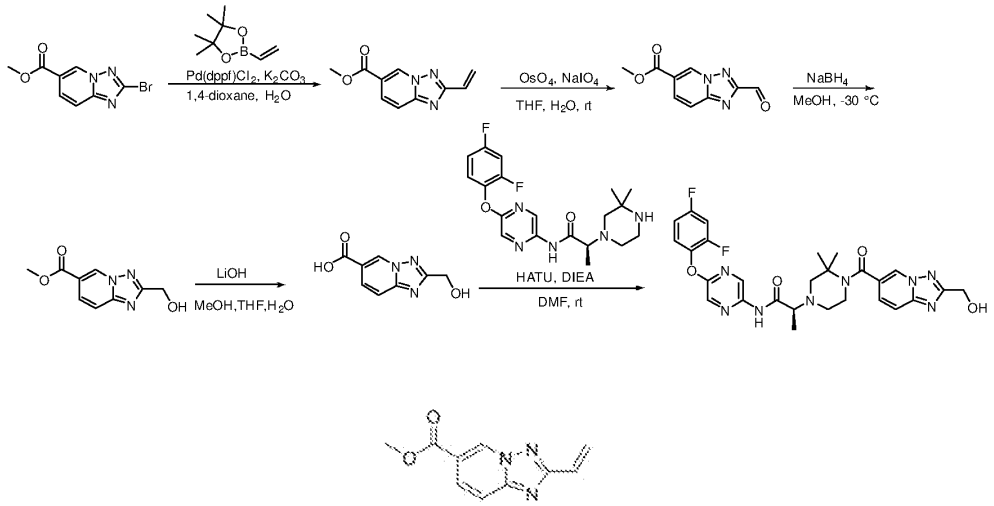
(S)-2-(4-([1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

To a solution of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (200 mg, 0.511 mmol, 1 equiv) in DMF (5 mL). niacin (94.36 mg, 0.766 mmol, 1.5 equiv) and HATU (291.43 mg, 0.766 mmol, 1.5 equiv) and DIEA (396.24 mg, 3.066 mmol, 6 equiv) added at rt. The resulting mixture was stirred for 24h at rt. The resulting mixture was extracted with EA (3*50mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-15%DCM/MeOH) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 36% to 66% ACN and H_2O (10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-nicotinoylpiperazin-1-yl)propanamide (62.7 mg, 24.71%) as a white solid, MS (ESI): mass calcd. For $C_{25}H_{26}F_2N_6O_3$:496.20 m/z, found 497.25 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.58 – 8.67 (m, 2H), 8.46 (d, J = 1.5 Hz, 1H), 7.78 – 7.85 (m, 1H), 7.41 – 7.54 (m, 3H), 7.12 – 7.22 (m, 1H), 3.48 – 3.58 (m, 1H), 3.30 (t, J = 5.3 Hz, 2H), 2.67 – 2.56 (m, 2H), 2.40 – 2.49 (m, 2H), 1.47 (d, J = 3.6 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -113.42, -124.20.

Example 215: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(2-(hydroxymethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

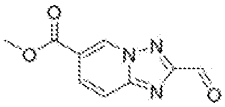


Synthetic Scheme



methyl 2-vinyl-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate

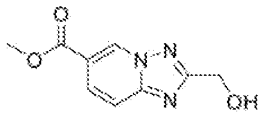
To a solution of methyl 2-bromo-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (1 g, 3.905 mmol, 1 equiv) in dioxane (10 mL) H_2O (1 mL) was added 2-ethenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.80 g, 11.715 mmol, 3 equiv), $Pd(dppf)Cl_2$ (318.14 mg, 0.391 mmol, 0.1 equiv), K_2CO_3 (1.08 g, 7.810 mmol, 2 equiv), the mixture was stirred for 2 h at 90 °C under a nitrogen atmosphere. After cooled to room temperature the reaction mixture was quenched by water and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-10% MeOH/DCM) to afford methyl 2-vinyl-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (750 mg, 94.51%) as a yellow solid. MS (ESI): mass calcd. for $C_{10}H_9N_3O_2$: 203.14 m/z, found 204.35 $[M+H]^+$.



methyl 2-formyl-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate

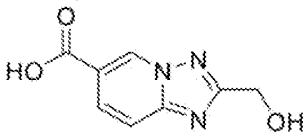
To a solution of methyl 2-vinyl-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (800 mg, 3.937 mmol, 1 equiv) in THF (10 mL, 123.428 mmol, 31.35 equiv) H_2O (10 mL, 555.093 mmol, 140.99 equiv) was added OsO_4 (1.00 g, 3.937 mmol, 1 equiv), $NaIO_4$ (3.37 g, 15.748 mmol, 4 equiv), the mixture was stirred for 2 h at 65°C. After cooled to room temperature the

reaction mixture was quenched by water and extracted with EA (3 x 20 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-10% MeOH/DCM) to afford methyl 2-formyl-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (300 mg, 37.14%) as a yellow solid.MS (ESI): mass calcd. for $C_9H_7N_3O_3$: 205.14m/z, found 206.35 $[M+H]^+$.



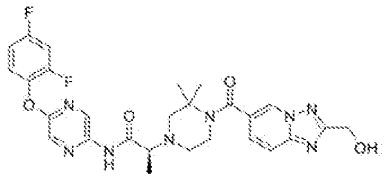
methyl 2-(hydroxymethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate

To a solution of methyl 2-formyl-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (250 mg, 1.218 mmol, 1 equiv) in MeOH (5 mL, 123.494 mmol, 101.35 equiv) was added $NaBH_4$ (46.10 mg, 1.218 mmol, 1 equiv) at -30°C, the mixture was stirred for 1 h at -30 °C. The reaction mixture was quenched by water and extracted with EA (3*20 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-10% MeOH/DCM) to afford methyl 2-(hydroxymethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (170 mg, 67.34%) as a yellow solid. MS (ESI): mass calcd. for $C_9H_9N_3O_3$: 207.14 m/z, found 208.35 $[M+H]^+$.



2-(hydroxymethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid

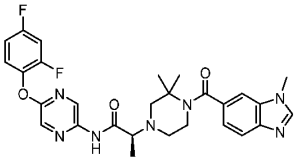
To a solution of methyl 2-(hydroxymethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (160 mg, 0.772 mmol, 1 equiv) in MeOH (4.00 mL, 98.762 mmol, 127.93 equiv) THF (4.00 mL, 49.354 mmol, 63.93 equiv) H_2O (1 mL, 55.509 mmol, 71.88 equiv) was added LiOH (36.99 mg, 1.544 mmol, 2 equiv) at 0 °C, the mixture was stirred for 2 h at rt. The mixture was acidified to pH =5 with 4N HCl. The precipitated solids were collected by filtration to offer 2-(hydroxymethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid (100 mg, 67.04%) as a yellow solid.



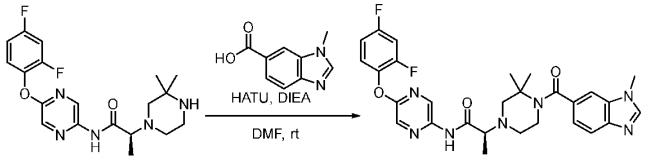
(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(2-(hydroxymethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

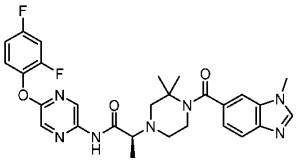
To a solution of 2-(hydroxymethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid (100 mg, 0.518 mmol, 1 equiv) in dimethylformamide (3 mL) was added (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (101.32 mg, 0.259 mmol, 0.5 equiv), HATU (295.27 mg, 0.777 mmol, 1.5 equiv), DIEA (401.47 mg, 3.108 mmol, 6 equiv).The resulting mixture was stirred for 1 h at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 100 mg crude product as a white solid.The compound was separated by HPLC (Column: XBridge Prep OBD C_{18} Column, 30*150 mm, 5μm; (eluent: 20% to 45% (v/v)Water(10mmol/L NH_4HCO_3+0.05%NH_3H_2O) and CAN to afford (S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-{4-[2-(hydroxymethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl]-3,3-dimethylpiperazin-1-yl}propanamide (33.5 mg, 11.38%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{28}F_2N_8O_4$: 566.22m/z, found 567.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H), 9.01 (t, J = 1.3 Hz, 1H), 8.85 (d, J = 1.5 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.78 (dd, J = 9.2, 0.9 Hz, 1H), 7.64 (dd, J = 9.2, 1.7 Hz, 1H), 7.41 – 7.54 (m, 2H), 7.12 – 7.22 (m, 1H), 5.50 (t, J = 6.2 Hz, 1H), 4.65 (d, J = 6.1 Hz, 2H), 3.54 (q, J = 6.9 Hz, 1H), 3.38 (d, J = 10.8 Hz, 2H), 3.30 – 3.31 (m, 1H), 2.74 (dd, J = 11.3, 5.1 Hz, 1H), 2.60 – 2.67 (m, 1H), 2.45 (d, J = 11.6 Hz, 1H), 1.48 (d, J = 4.0 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -113.43, -124.21.

Example 216: (*S*)-*N*-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-methyl-1*H*-benzo[d]imidazole-6-carbonyl)piperazin-1-yl)propanamide



Synthetic Scheme

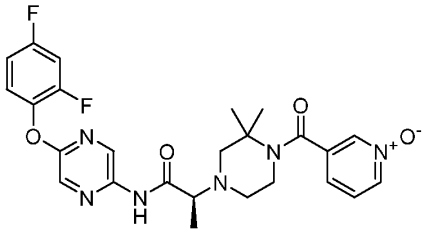




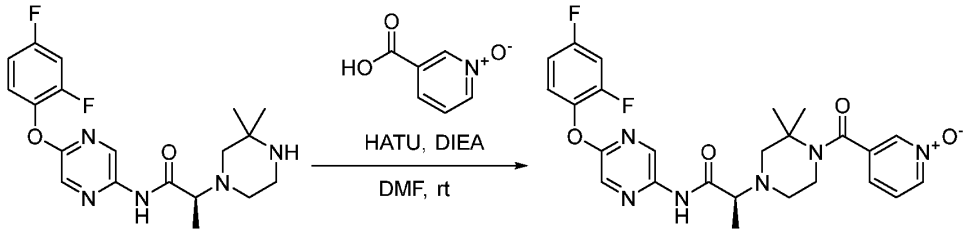
(*S*)-*N*-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-methyl-1*H*-benzo[d]imidazole-6-carbonyl)piperazin-1-yl)propanamide

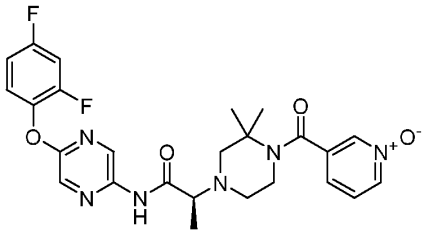
To a solution of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (80 mg, 0.204 mmol, 1 equiv) in dimethylformamide (3 mL) was added 3-methyl-1,3-benzodiazole-5-carboxylic acid (43.21 mg, 0.245 mmol, 1.2 equiv) and HATU (155.43 mg, 0.408 mmol, 2 equiv) and DIEA (52.83 mg, 0.408 mmol, 2 equiv). The mixture was stirred at room temperature for 2 h. The mixture was concentrated to dryness under reduced pressure to provide the crude product. The residue was purified by preparative HPLC using a YMC-Actus Triart OBD 250 mm x 19 mm x 5 μm column (eluent: 52% to 80% (v/v) ACN and H_2O with 10mmol/L NH_4HCO_3) to afford (*S*)-*N*-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-methyl-1*H*-benzo[d]imidazole-6-carbonyl)piperazin-1-yl)propanamide (55.6 mg, 48.92%) as an off-white solid. MS (ESI): mass calcd. for $C_{28}H_{29}F_2N_7O_3$: 549.583 m/z, found: 550.25 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.86 (d, *J* = 1.4 Hz, 1H), 8.46 (d, *J* = 1.4 Hz, 1H), 8.28 (s, 1H), 7.61 – 7.70 (m, 2H), 7.40 – 7.56 (m, 2H), 7.27 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.11 -7.23 (m, 1H), 3.87 (s, 3H), 3.53 (q, *J* = 6.8 Hz, 1H), 3.36 (s, 1H), 3.33 (s, 1H), 2.77 – 2.67 (m, 1H), 2.66 – 2.56 (m, 1H), 2.47 (s, 2H), 1.50 (d, *J* = 1.9 Hz, 6H), 1.22 (d, *J* = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.42 (d, *J* = 5.2 Hz), -124.21 (d, *J* = 5.3 Hz).

Example 217: (S)-3-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide



Synthetic Scheme



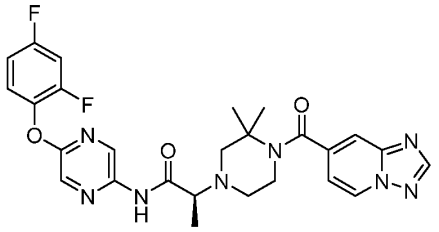


(S)-3-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

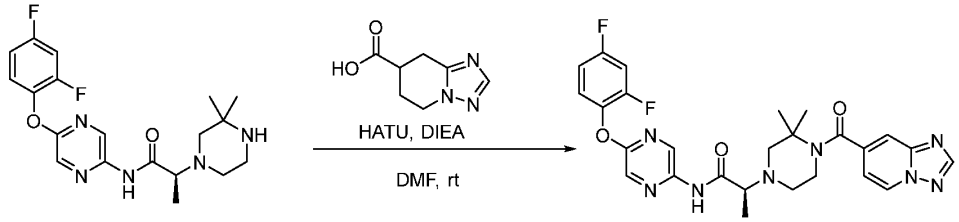
To a solution of 3-carboxypyridin-1-ium-1-olate (42.65 mg, 0.306 mmol, 1.20 equiv) in DMF (1mL) was added (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (100 mg, 0.255 mmol, 1.00 equiv) and HATU (145.71 mg, 0.383 mmol, 1.5 equiv) and DIEA (198.12 mg, 1.530 mmol, 6 equiv) at rt .The resulting mixture was stirred for 2h at rt. The reaction mixture was quenched by water and extracted with EA (3*30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography DCM/MeOH (0-20%) and Prep-HPLC using a XBridge Prep OBD C18 30*150 mm, 5μm Column (eluent: 27% to 47% (v/v) CH_3CN and H_2O, NH_4HCO_3) to afford (S)-3-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide as a white

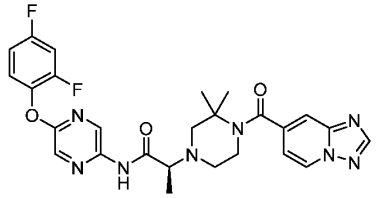
solid. MS (ESI): mass calcd. for $C_{25}H_{26}F_2N_6O_4$ 512.20 m/z, found 513.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.84 (d, J = 1.5 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.19 – 8.30 (m, 2H), 7.48 (ddd, J = 18.3, 9.4, 4.6 Hz, 3H), 7.31 (d, J = 7.8 Hz, 1H), 7.18 (t, J = 8.8 Hz, 1H), 3.54 (d, J = 7.0 Hz, 1H), 3.28 – 3.33 (m, 2H), 2.69 (d, J = 5.1 Hz, 1H), 2.55 – 2.64 (m, 1H), 2.45 (d, J = 4.1 Hz, 2H), 1.46 (d, J = 2.8 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.43 (d, J = 5.3 Hz), -124.22 (d, J = 5.2 Hz).

Example 218: (S)-2-(4-([1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide



Synthetic Scheme



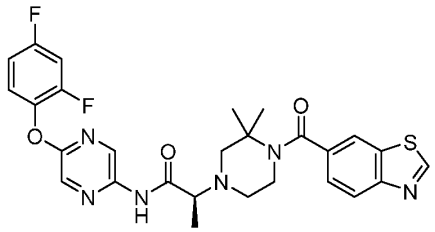


(S)-2-(4-([1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

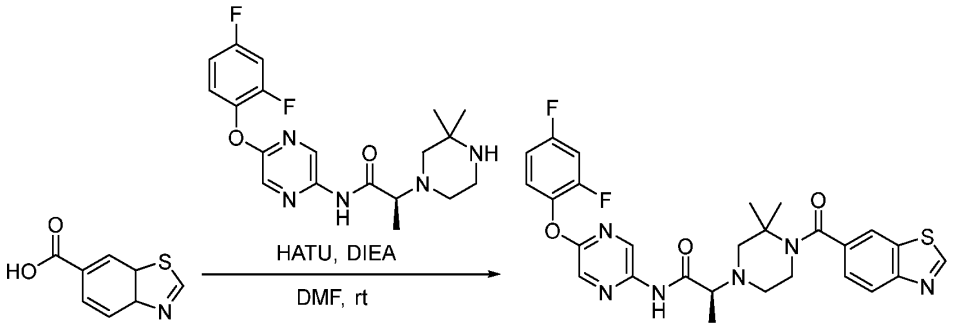
To a solution of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamideide (100 mg, 0.255 mmol, 1 equiv) in DMF (2 mL). 5H,6H,7H,8H-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylic acid (51.25 mg, 0.306 mmol, 1.2 equiv), HATU (145.71 mg, 0.383 mmol, 1.5 equiv) and DIEA (198.12 mg, 1.530 mmol, 6 equiv) added at

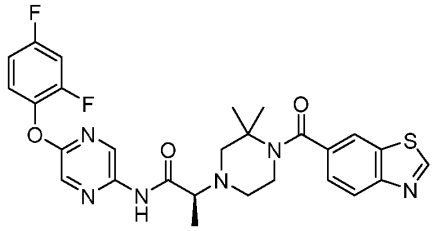
rt. The resulting mixture was stirred for 2h at rt. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-15%DCM/MeOH) and Prep-HPLC using a XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 34% to 64% ACN and H_2O (10mmol/L NH_4HCO_3+0.05%NH_3H_2O)) to afford (S)-2-(4-([1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (28.1 mg, 20.12%) as a white solid, MS (ESI): mass calcd. for$C_{26}H_{26}F_2N_8O_3$:536.21m/z, found:537.30$[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.44 (s, 1H), 9.00 (d, J = 7.0, 0.9 Hz, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.58 (s, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.86 (t, J = 1.3 Hz, 1H), 7.41 – 7.54 (m, 2H), 7.13 – 7.23 (m, 2H), 3.49 – 3.59 (m, 1H), 2.56 – 2.76 (m, 2H), 2.42 – 2.51 (m, 4H), 1.50 (d, J = 3.7 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -113.4086, -124.1935.

Example 219: (S)-2-(4-(benzo[d]thiazole-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide



Synthetic Scheme

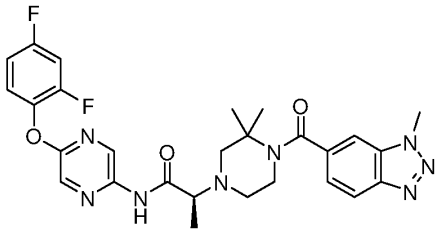




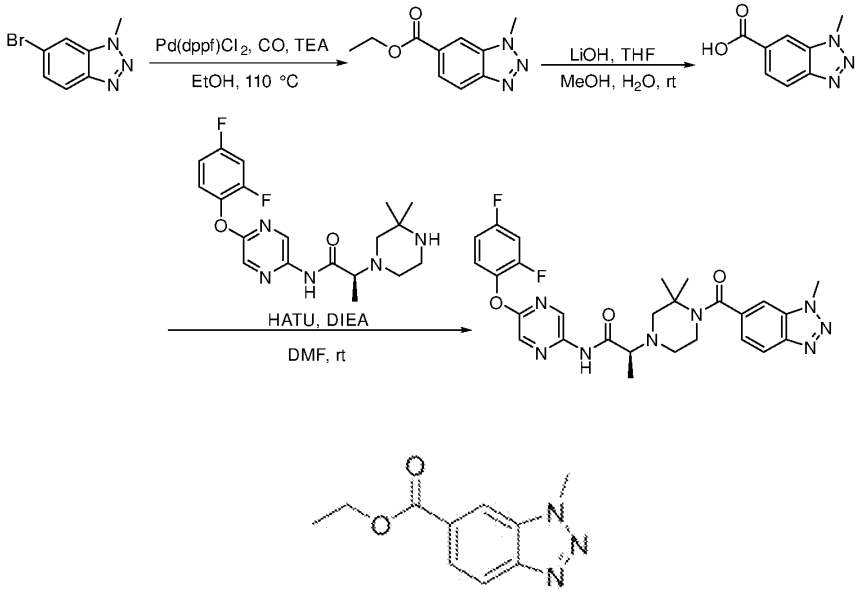
(S)-2-(4-(benzo[d]thiazole-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

To a stirring solution (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (100 mg, 0.255 mmol, 1 equiv) in dimethylformamide (10 mL) the mixture was added 3a,7a-dihydrobenzo[d]thiazole-6-carboxylic acid (46.30 mg, 0.255 mmol, 1 equiv), HATU (145.71 mg, 0.383 mmol, 1.5 equiv) and N,N-diisopropylethylamine (132.08 mg, 1.020 mmol, 4 equiv) at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (10 mL x 3) . The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% EA/PE) and Prep-HPLC using a XBridge Prep OBD C18 30*150 mm, 5μm Column (eluent: 44% to 74% (v/v) CH_3CN and Water(10mmol/L NH_4HCO_3+0.05% NH_3H_2O)) to afford (S)-2-(4-(benzo[d]thiazole-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy) pyrazin-2-yl)propanamide (53.2 mg, 37.00%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{26}F_2N_6O_3S$: 552.17, found: 553.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.42 (s, 1H), 9.49 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.28 (d, J = 1.6 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.57 (dd, J = 8.4, 1.7 Hz, 1H), 7.35 – 7.41 (m, 2H), 7.11 – 7.24 (m, 1H), 3.54 (d, J = 7.0 Hz, 1H), 3.33 – 3.38 (m, 2H), 2.67 – 2.81 (m, 1H), 2.57 – 2.66 (m, 1H), 2.46 – 2.49 (m, 2H), 1.50 (d, J = 2.3 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.43 (d, J = 5.2 Hz), -124.22 (d, J = 5.3 Hz).

Example 220: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-methyl-1H-benzo[d][1,2,3]triazole-6-carbonyl)piperazin-1-yl)propanamide

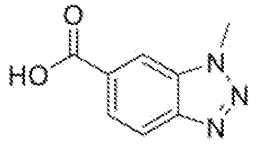


Synthetic Scheme



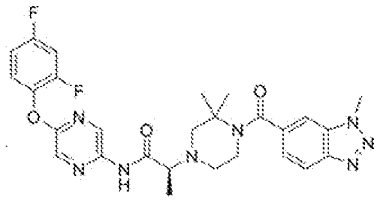
ethyl 1-methyl-1H-benzo[d][1,2,3]triazole-6-carboxylate

To a stirring solution 6-bromo-1-methyl-1,2,3-benzotriazole (500 mg, 2.358 mmol, 1 equiv) in ethyl alcohol (10 mL) was added a solution of $Pd(dppf)Cl_2$ (165.50 mg, 0.236 mmol, 0.1 equiv) and TEA (715.82 mg, 7.074 mmol, 3 equiv) .The resulting mixture was under CO stirred at 110°C for 6h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) to afford ethyl 1-methyl-1H-benzo[d][1,2,3]triazole-6-carboxylate (300 mg, 62.00%) MS (ESI): mass calcd. for $C_{10}H_{11}N_3O_2$: 205.219 m/zfound: 206.05[$M+H^+$]



1-methyl-1H-benzo[d][1,2,3]triazole-6-carboxylic acid

To a stirring solution ethyl 1-methyl-1H-benzo[d][1,2,3]triazole-6-carboxylate (300 mg, 1.462 mmol, 1 equiv) in methanol (1 mL) and tetrahydrofuran (2 mL) and water (1 mL) was added a solution of LiOH (35.01 mg, 1.462 mmol, 1 equiv) .The resulting mixture was stirred at room temperature for 6h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% ACN/H_2O) to afford 1-methyl-1H-benzo[d][1,2,3]triazole-6-carboxylic acid (250 mg, 96.53%) MS (ESI): mass calcd. for $C_8H_7N_3O_2$: 177.05 m/zfound: 176.05$[M+H]^+$

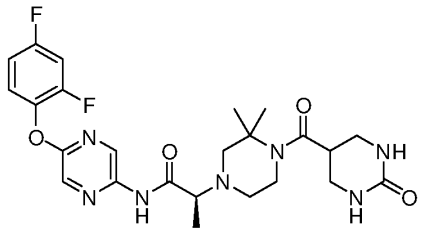


(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-methyl-1H-benzo[d][1,2,3]triazole-6-carbonyl)piperazin-1-yl)propanamide

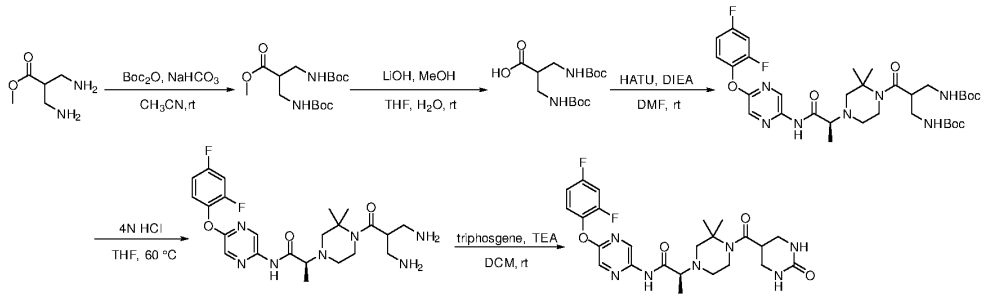
To a stirred solution of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (300 mg, 0.766 mmol, 1 equiv) in dimethylformamide (3 mL) was added 1-methyl-1H-benzo[d][1,2,3]triazole-6-carboxylic acid (296.16 mg, 1.532 mmol, 2 equiv) and HATU (582.84 mg, 1.532 mmol, 2 equiv) and DIEA (396.24 mg, 3.064 mmol, 4 equiv) at room temperature. The reaction mixture was stirred at room temperature for 3 h. The resulting mixture was stirred for additional overnight at room temperature. After completion of reaction, the reaction mixture was quenched by addition of water (5 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and the residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30 x150mm x 5μm (eluent: 40% to 70% (v/v) CH_3CN and H_2O with NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-

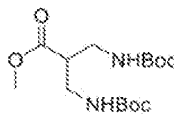
dimethyl-4-(1-methyl-1H-benzo[d][1,2,3]triazole-6-carbonyl)piperazin-1-yl)propanamide (120.4 mg, 28.07%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{28}F_2N_8O_3$: 550.23m/z, found: 551.30$[M+H]^+$ ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.40 s, 1H), 8.82 – 8.88 (m, 1H), 8.44 (d, J = 1.4 Hz, 1H), 8.05 (d, J = 8.6 Hz, 1H), 7.93 (s, 1H), 7.35 – 7.53 (m, 3H), 7.10 – 7.23 (m, 1H), 4.34 (s, 3H), 3.53 (d, J = 7.0 Hz, 1H), 3.30 (d, J = 5.3 Hz, 2H), 2.55 – 2.78 (m, 2H), 2.49 (s, 2H), 1.48 – 1.55 (m, 6H), 1.21 (d, J = 6.8 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -113.39 (d, J = 5.3 Hz), -124.15 (d, J = 5.3 Hz).

Example 221: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(2-oxohexahydropyrimidine-5-carbonyl)piperazin-1-yl)propanamide



Synthetic Scheme

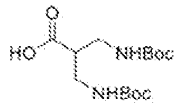




methyl 3-((tert-butoxycarbonyl)amino)-2-(((tert-butoxycarbonyl)amino)methyl)propanoate

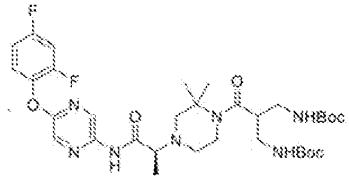
To a solution of methyl 3-amino-2-(aminomethyl)propanoate (500 mg, 3.783 mmol, 1 equiv) in acetonitrile (10mL) was added Boc_2O (1.65 g, 7.566 mmol, 2 equiv), $NaHCO_3$ (953.44 mg, 11.349 mmol, 3 equiv) at rt, the mixture was stirred for 1 h at rt. The reaction

was quenched with water/sat. (100 mL), and then the mixture was extracted with ether/EtOAc (2 x 150 mL),The aqueous layers were combined, adjusted to pH 1 with concentrated (aq) HC1, and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2S0_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to offer methyl 3-[(tert-butoxycarbonyl)amino]-2-{[(tert-butoxycarbonyl)amino]methyl}propanoate (500 mg, 39.76%) as a yellow solid. MS (ESI): mass calcd. for $C_{15}H_{28}N_2O_6$:332.14, found: 333.90 $[M+H]^+$.



3-((tert-butoxycarbonyl)amino)-2-(((tert-butoxycarbonyl)amino)methyl)propanoic acid

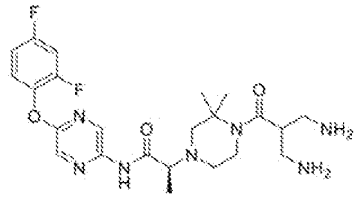
To a solution of methyl 3-[(tert-butoxycarbonyl)amino]-2-{[(tert-butoxycarbonyl)amino]methyl}propanoate (500 mg, 1.504 mmol, 1 equiv) in MeOH (5 mL, 123.494 mmol, 82.10 equiv) THF (5 mL, 61.714 mmol, 41.03 equiv) H_2O (2 mL, 111.019 mmol, 73.80 equiv) was added LiOH (180.13 mg, 7.520 mmol, 5 equiv) at 0°C, the mixture was stirred for 2 h at rt. The mixture was acidified to pH =5 with 4N HCl. The precipitated solids were collected by filtration to offer 3-[(tert-butoxycarbonyl)amino]-2-{[(tert-butoxycarbonyl)amino]methyl}propanoic acid (300 mg, 62.64%) as a yellow solid. MS (ESI): mass calcd. for $C_{14}H_{26}N_2O_6$: 318.22 m/z, found 319.25 $[M+H]^+$.



di-tert-butyl (2-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)propane-1,3-diyl)(S)-dicarbamate

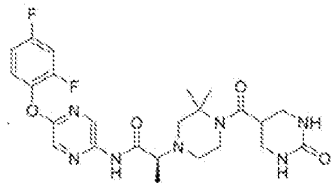
To a solution of 3-[(tert-butoxycarbonyl)amino]-2-{[(tert-butoxycarbonyl)amino]methyl}propanoic acid (300 mg, 0.942 mmol, 1 equiv) in dimethylformamide (10 mL) was added (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (368.84 mg, 0.942 mmol, 1 equiv), HATU (537.44

mg, 1.413 mmol, 1.5 equiv) and DIEA (487.16 mg, 3.768 mmol, 4 equiv), the mixture was stirred for 2 h at rt. The reaction was quenched with water/sat. (100 mL), and then the mixture was extracted with ether/EtOAc (2 x 150mL). The combined organic layers were dried over Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to offer di-tert-butyl (2-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)propane-1,3-diyl)(S)-dicarbamate (250 mg, 38.35%) as a yellow solid. MS (ESI): mass calcd. for $C_{33}H_{47}F_2N_7O_7$:691.14, found: 692.20$[M+H]^+$.



(S)-2-(4-(3-amino-2-(aminomethyl)propanoyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

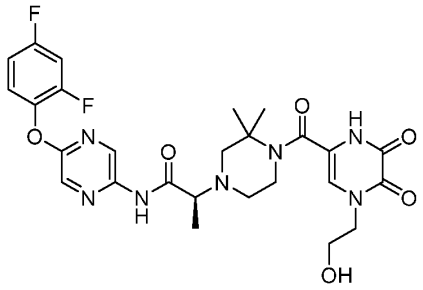
To a solution of tert-butyl N-(2-{[(tert-butoxycarbonyl)amino]methyl}-3-{4-[(1S)-1-{[5-(2,4-difluorophenoxy)pyrazin-2-yl]carbamoyl}ethyl]-2,2-dimethylpiperazin-1-yl}-3-oxopropyl)carbamate (200 mg, 0.289 mmol, 1 equiv) in tetrahydrofuran (5 mL) 4N HCl (1 mL), the mixture was stirred for 2 h at 60°C. After cooled to room temperature the reaction was quenched with water/sat. (100 mL), and then the mixture was extracted with ether/EtOAc (2 x 150mL), The combined organic layers were dried over Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to offer S)-2-(4-(3-amino-2-(aminomethyl)propanoyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (100 mg, 70.37%) as a yellow solid. MS (ESI): mass calcd. for $C_{23}H_{31}F_2N_7O_3$:491.14, found: 492.20$[M+H]^+$.



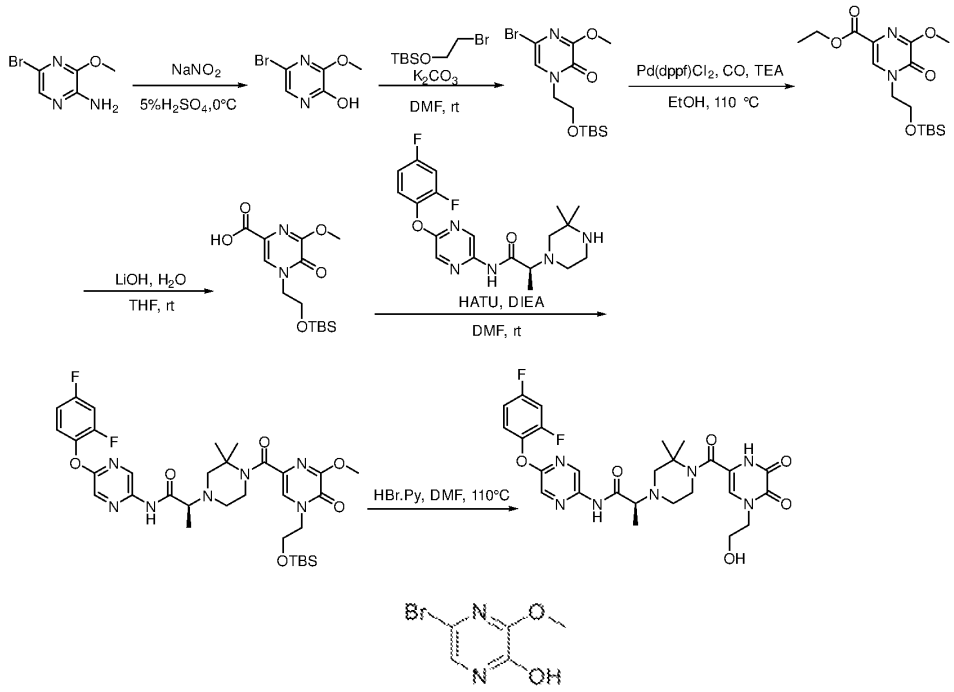
(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(2-oxohexahydropyrimidine-5-carbonyl)piperazin-1-yl)propanamide

To a solution of S)-2-(4-(3-amino-2-(aminomethyl)propanoyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (90 mg, 0.183 mmol, 1 equiv) in DCM (5 mL) was added triphosgene (17.93 mg, 0.060 mmol, 0.33 equiv), TEA (37.06 mg, 0.366 mmol, 2 equiv). The resulting mixture was stirred for 3 h at rt. The reaction mixture was quenched by water and extracted with EA (3*20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-10% MeOH/DCM) to afford 30 mg crude product as a white solid. The compound was separated by Prep-HPLC using a XBridge Prep OBD C_{18} 30*150 mm, 5μm Column (eluent: 33% to 55% (v/v) CH_3CN and Water(10mmol/L NH_4HCO_3+0.05%NH_3H_2O)) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(2-oxohexahydropyrimidine-5-carbonyl)piperazin-1-yl)propanamide (5.9 mg, 6.10%) as a yellow solid. MS (ESI): mass calcd. for $C_{24}H_{29}F_2N_7O_4$: 517.22m/z, found 518.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.39 (s, 1H), 8.83 (d, J = 1.4 Hz, 1H), 8.44 (d, J = 1.5 Hz, 1H), 7.47 (dtd, J = 11.1, 8.9, 7.9, 4.3 Hz, 2H), 7.17 (s, 1H), 6.13 (s, 2H), 3.46 – 3.55 (m, 3H), 3.01 - 3.10 (m, 5H), 2.66 – 2.76(m, 1H), 2.57 – 2.65 (m, 1H), 2.33 (s, 2H), 1.34 (d, J = 1.6 Hz, 6H), 1.19 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.44, -124.24.

Example 222: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(4-(2-hydroxyethyl)-5,6-dioxo-1,4,5,6-tetrahydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propenamide

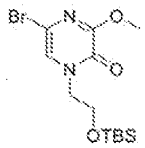


Synthetic Scheme



5-bromo-3-methoxypyrazin-2-ol

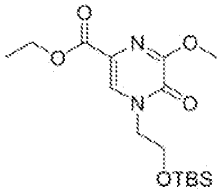
To a solution of 5-bromo-3-methoxypyrazin-2-amine (2 g, 9.803 mmol, 1 equiv) in 5% sulfuric acid (25 mL, 254.920 mmol, 26.01 equiv). Sodium nitrite (0.74 g, 10.783 mmol, 1.1 equiv) added at 0 °C. The resulting mixture was stirred for 2h at 0 °C. The reaction was quenched with H_2O (5 mL) at rt. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20%DCM/MeOH) to afford 5-bromo-3-methoxypyrazin-2-ol (1.7 g, 84.59%) as a yellow oil, MS (ESI): mass calcd. for $C_5H_5BrN_2O_2$:203.95m/z, found:204.90$[M+H]^+$.



5-bromo-1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-3-methoxypyrazin-2(1H)-one

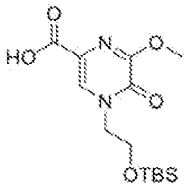
To a solution of 5-bromo-3-methoxypyrazin-2-ol (2 g, 9.756 mmol, 1 equiv) in DMF (10 mL). K_2CO_3 (4.07 g, 29.268 mmol, 3 equiv) and (2-bromoethoxy)(tert-

butyl)dimethylsilane (4.67 g, 19.512 mmol, 2 equiv) added at rt. The resulting mixture was stirred for 4h at rt. The reaction was quenched with H_2O (5 mL) at rt. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100%PE/EA) to afford 5-bromo-1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-3-methoxypyrazin-2(1H)-one (2 g, 56.43%) as a yellow oil, MS (ESI): mass calcd. for $C_{13}H_{23}BrN_2O_3Si$:362.07m/z, found:362.95$[M+H]^+$.



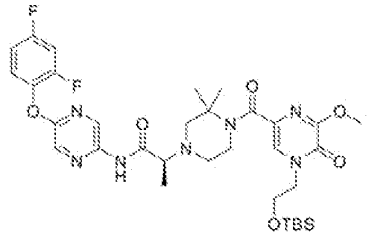
ethyl 4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6-methoxy-5-oxo-4,5-dihydropyrazine-2-carboxylate

To a solution of 5-bromo-1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-3-methoxypyrazin-2(1H)-one (2 g, 5.505 mmol, 1 equiv) in EtOH (15 mL) was added $Pd(dppf)Cl_2$ (4.03 g, 5.505 mmol, 1 equiv) and TEA (1.67 g, 16.515 mmol, 3 equiv) in a pressure tank. The mixture was purged with nitrogen for rt and then was pressurized to 50 atm with carbon monoxide at 110 °C for 12 h. The reaction mixture was cooled to room temperature and filtered to remove insoluble solids. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100%PE/EA) to afford ethyl 4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6-methoxy-5-oxo-4,5-dihydropyrazine-2-carboxylate (1 g, 50.96%) as a yellow oil, MS (ESI): mass calcd. for $C_{16}H_{28}N_2O_5Si$:356.18m/z, found:357.10$[M+H]^+$.



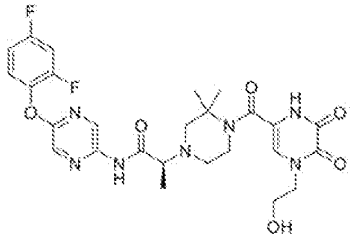
4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6-methoxy-5-oxo-4,5-dihydropyrazine-2-carboxylic acid

To a solution of ethyl 4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6-methoxy-5-oxo-4,5-dihydropyrazine-2-carboxylate (400 mg, 1.122 mmol, 1 equiv) in THF (20 mL).methanol (15 mL, 0.008 mmol, 0.24 equiv), LiOH (53.75 mg, 1.561 mmol, 2 equiv) and water (5 mL, 0.014 mmol, 0.43 equiv) added at rt. The resulting mixture was stirred for 2h at rt. The resulting mixture was concentrated under vacuum. The residue was acidified to pH 2~3 with 3N HCl. The precipitated solids were collected by filtration and washed with H_2O (5 mL) to afford 4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6-methoxy-5-oxo-4,5-dihydropyrazine-2-carboxylic acid (200 mg, 54.27%) as a yellow oil. MS (ESI): mass calcd. for $C_{12}H_{24}N_2O_5Si$: 328.15m/z, found:329.05$[M+H]^+$.



(S)-2-(4-(4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6-methoxy-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

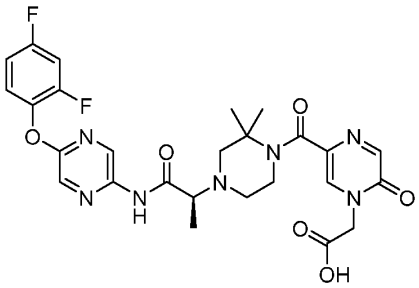
To a solution of 4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6-methoxy-5-oxo-4,5-dihydropyrazine-2-carboxylic acid (150 mg, 0.457 mmol, 1 equiv) in DMF (3 mL) . (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (178.76 mg, 0.457 mmol, 1 equiv), HATU (347.31 mg, 0.914 mmol, 2 equiv) and DIEA (472.22 mg, 3.656 mmol, 8 equiv) was added at rt. The mixture was allowed to warm to rt and stirred for 2 h. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20%DCM/MeOH) to afford (S)-2-(4-(4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6-methoxy-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (35 mg, 10.92%) as a yellow oil, MS (ESI): mass calcd. for $C_{33}H_{45}F_2N_7O_6Si$:701.32m/z, found:701.05$[M+H]^+$.



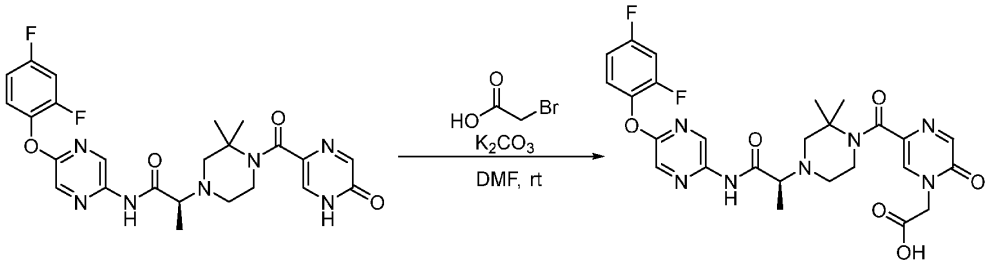
(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(4-(2-hydroxyethyl)-5,6-dioxo-1,4,5,6-tetrahydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

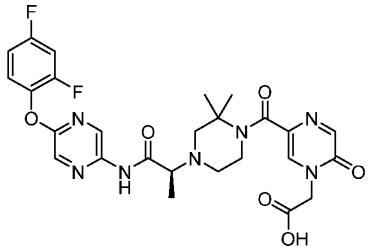
To a solution of (S)-2-(4-(4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6-methoxy-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (70 mg, 0.100 mmol, 1 equiv) in DMF (3 mL) Pyridinium hydrobromide (55.93 mg, 0.700 mmol, 7 equiv) added at rt. The resulting mixture was stirred for 4h at 110 °C. After cooled to room temperature, the resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-15%DCM/MeOH) and Prep-HPLC using a XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 23% to 53% ACN and Water(10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(4-(2-hydroxyethyl)-5,6-dioxo-1,4,5,6-tetrahydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (9.8 mg, 2.44%) as a white solid, MS (ESI): mass calcd. for $C_{26}H_{29}F_2N_7O_6$:573.21m/z, found:574.25$[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 11.25 (s, 1H), 10.32 – 10.44 (m, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.39 – 7.55 (m, 2H), 7.12 – 7.25 (m, 1H), 6.80 (s, 1H), 4.87 (t, J = 5.8 Hz, 1H), 3.78 (d, J = 5.6 Hz, 2H), 3.48 – 3.65 (m, 5H), 2.70 – 2.81 (m, 1H), 2.59 – 2.71 (m, 1H), 2.33 – 2.49 (m, 2H), 1.39 (d, J = 4.1 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.430, -124.221.

Example 223: (S)-2-(5-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-oxopyrazin-1(2H)-yl)acetic acid



Synthetic Scheme



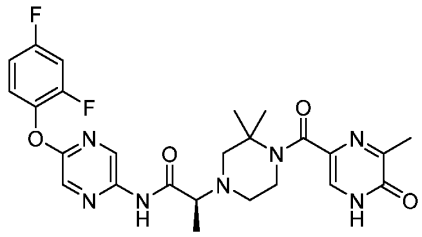


(S)-2-(5-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-oxopyrazin-1(2H)-yl)acetic acid

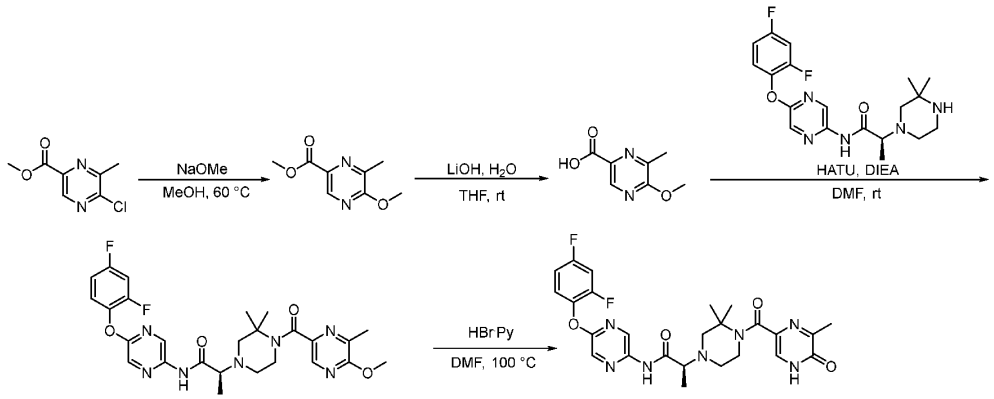
To a solution of (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-[3,3-dimethyl-4-(5-oxo-4H-pyrazine-2-carbonyl)piperazin-1-yl]propanamide (50 mg, 0.097 mmol, 1 equiv) in DMF (1 mL) the mixture was added 2-bromoacetic acid (14.88 mg, 0.107 mmol, 1.1 equiv) and K_2CO_3 (40.67 mg, 0.291 mmol, 3 equiv) at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (20 mL) and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) and Prep-HPLC using a YMC-Actus Triart C18 ExRS30*150 mm Column (eluent: 18% to 34% (v/v) CH_3CN and Water(10mmol/L

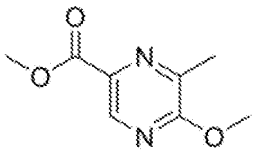
NH_4HCO_3+0.05%NH_3H_2O)) to afford (S)-2-(5-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-oxopyrazin-1(2H)-yl)acetic acid (8.6 mg, 14.78%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{27}F_2N_7O_6$: 571.15, found: 572.20 $[M+H]^+$.^{1}H NMR (300 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.89 (d, J = 10.3 Hz, 2H), 7.40 – 7.56 (m, 2H), 7.10 – 7.24 (m, 1H), 4.28 (s, 2H), 3.47 – 3.57 (m, 3H), 2.76 (d, J = 7.2 Hz, 1H), 2.63 (d, J = 5.8 Hz, 1H), 2.41 (d, J = 3.9 Hz, 2H), 1.44 (d, J = 2.0 Hz, 6H), 1.17-1.27 (m, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -113.45 (d, J = 5.2 Hz), -124.25 (d, J = 5.2 Hz).

Example 224: (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-[3,3-dimethyl-4-(6-methyl-5-oxo-4H-pyrazine-2-carbonyl)piperazin-1-yl]propenamide



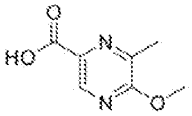
Synthetic Scheme





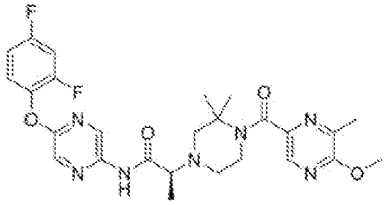
methyl 5-methoxy-6-methylpyrazine-2-carboxylate

To a solution ofmethyl 5-chloro-6-methylpyrazine-2-carboxylate (1 g, 5.359 mmol, 1 equiv) in MeOH (1mL) was added sodium methoxide (0.35 g, 6.479 mmol, 1.21 equiv) at rt .The resulting mixture was stirred for 3 h at rt. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA to afford methyl 5-methoxy-6-methylpyrazine-2-carboxylate (890 mg, 91.16%) as a solid. MS (ESI): mass calcd. for $C_8H_{10}N_2O_3$ 182.17 m/z, found 183.10$[M+H]^+$.



5-methoxy-6-methylpyrazine-2-carboxylic acid

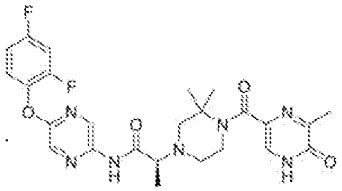
To a solution of methyl 5-methoxy-6-methylpyrazine-2-carboxylate (340 mg, 1.866 mmol, 1 equiv)) in THF (6mL)/MeOH (3 mL)/H_2O(3 mL)was added $LiOH.H_2O$ (89.40 mg, 3.732 mmol, 2 equiv) .The resulting mixture was stirred for 3 h at rt. The mixturewas acidified to pH 4 with 2 N HCl (aq.). The resulting mixture was filtered, the filter cake was washed with H_2O (2x6 mL). The filtrate was concentrated under reduced pressure 5-methoxy-6-methylpyrazine-2-carboxylic acid (180mg). MS (ESI): mass calcd. for $C_7H_8N_2O_3$ 168.15 m/z, found 169.05 $[M+H]^+$.



(2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-[4-(5-methoxy-6-methylpyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl]propanamide

To a solution of 5-methoxy-6-methylpyrazine-2-carboxylic acid (200 mg, 1.189 mmol, 1 equiv) in DMF (20mL) was added(2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (465.56 mg, 1.189 mmol, 1 equiv) and HATU (678.38

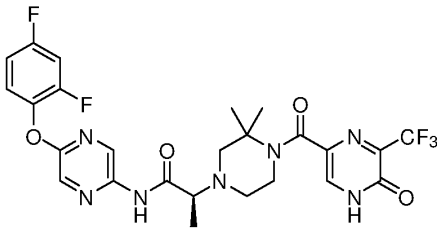
mg, 1.784 mmol, 1.5 equiv) and DIEA (922.36 mg, 7.134 mmol, 6 equiv) at rt .The resulting mixture was stirred for 5 h at rt. The reaction mixture was quenched by water and extracted with EA (3*20 mL).The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford product (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-[4-(5-methoxy-6-methylpyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl]propanamide (200 mg, 31.05%) as a yellow solid. MS (ESI): mass calcd. for $C_{26}H_{29}F_2N_7O_4$ 541.56 m/z, found 542.20$[M+H]^+$.



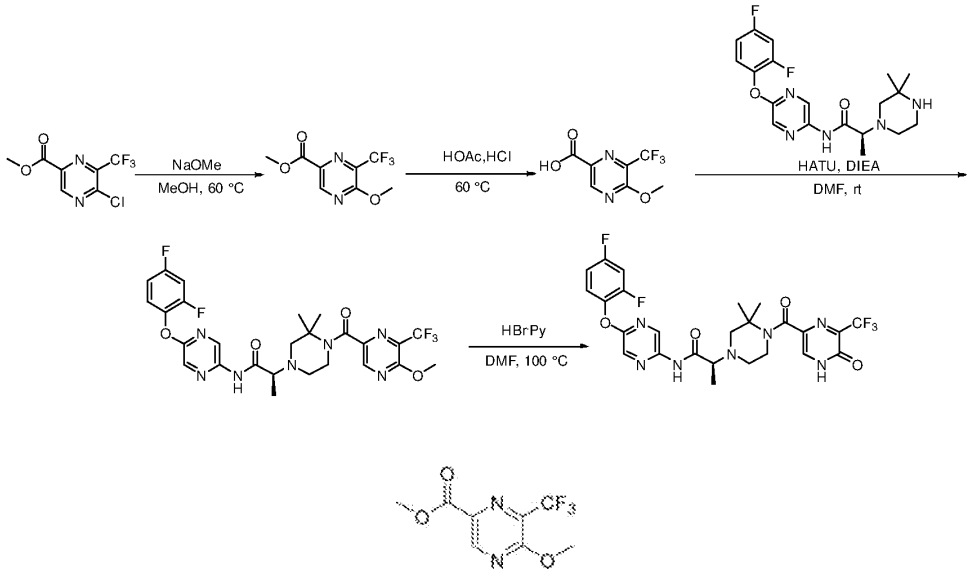
(2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-[3,3-dimethyl-4-(6-methyl-5-oxo-4H-pyrazine-2-carbonyl)piperazin-1-yl]propanamide

To a solution of 2-[4-(4-chloro-6-methoxypyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl]-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (200 mg, 0.357 mmol, 1 equiv) in DMF (3mL) was added Pyridine hydrobromide (413.65 mg, 2.583 mmol, 7 equiv) at rt .The resulting mixture was stirred for 3 h at 100 degrees C. The reaction mixture was quenched by water and extracted with EA (2*50 mL).The combined organic extracts were washed with brine (20mL), dried over anhydrous Na_2SO_4, and concentrated The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and Prep-HPLC using a XSelect CSH Pheny-Hexy, 19*250 mm, 5μm Column (eluent: 40% to 70% (v/v) CH_3CN and Water(0.1% FA)) to afford (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-[3,3-dimethyl-4-(6-methyl-5-oxo-4H-pyrazine-2-carbonyl)piperazin-1-yl]propanamide (65.9 mg, 33.30%) as a light yellow solid. MS (ESI): mass calcd. for $C_{25}H_{27}F_2N_7O_4$ 527.53 m/z, found 528.25$[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.36 (s, 1H), 10.38 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.56 (s, 1H), 7.41 – 7.53 (m, 2H), 7.12 – 7.22 (m, 1H), 3.51 (d, J = 6.0 Hz, 3H), 2.70 – 2.77 (m, 1H), 2.59 – 2.68 (m, 1H), 2.41 (s, 2H), 2.26 (s, 3H), 1.40 – 1.45 (m, 6H), 1.21 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ-113.44 (d, J = 5.2 Hz), -124.24 (d, J = 5.4 Hz).

Example 225: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-6-(trifluoromethyl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propenamide

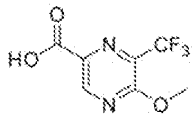


Synthetic Scheme



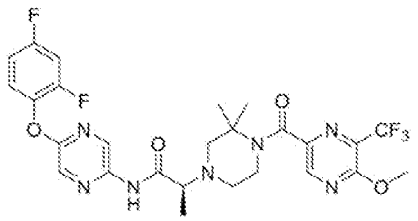
methyl 5-methoxy-6-(trifluoromethyl)pyrazine-2-carboxylate

To a stirring solution methyl 5-chloro-6-((difluoro-l3-methyl)-l2-fluoraneyl)pyrazine-2-carboxylate (800 mg, 3.325 mmol, 1 equiv) in methanol (10 mL) was added a solution of sodium methoxide (215.58 mg, 3.990 mmol, 1.2 equiv) .The resulting mixture was stirred at 60°C for 6h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford methyl 5-methoxy-6-(trifluoromethyl)pyrazine-2-carboxylate (560 mg, 71.31%) MS (ESI): mass calcd. for $C_8H_7F_3N_2O_3$: 236.04 m/z found: 237.00$[M+H]^+$



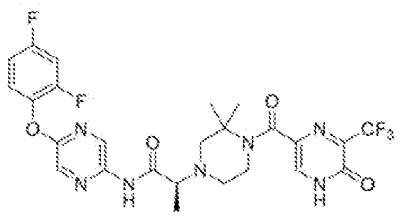
5-methoxy-6-(trifluoromethyl)pyrazine-2-carboxylic acid

To a stirring solution methyl 5-methoxy-6-(trifluoromethyl)pyrazine-2-carboxylate (200 mg, 0.847 mmol, 1 equiv) in hydrogen chloride (1 mL) and 1-holmioethanone (2 mL). The resulting mixture was stirred at 60°C for 6h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% ACN/H_2O) to afford 5-methoxy-6-(trifluoromethyl)pyrazine-2-carboxylic acid (150 mg, 79.74%) MS (ESI): mass calcd. for $C_7H_5F_3N_2O_3$: 222.03 m/z found: 221.00[M^+H^-]



4,5,6,7-tetrahydrobenzo[d]oxazole-6-carboxylic acid

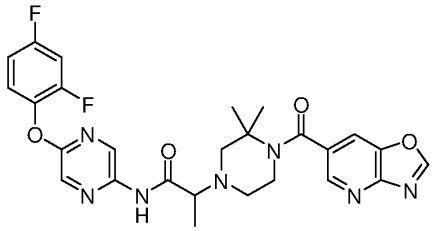
To a stirring solution 5-methoxy-6-(trifluoromethyl)pyrazine-2-carboxylic acid (150 mg, 0.675 mmol, 1 equiv) in THF (2 mL) was added a solution of (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (264.33 mg, 0.675 mmol, 1 equiv) and HATU (385.15 mg, 1.013 mmol, 1.5 equiv) and DIEA (349.12 mg, 2.700 mmol, 4 equiv) .The resulting mixture was stirred at room temperature for 6h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford 4,5,6,7-tetrahydrobenzo[d]oxazole-6-carboxylic acid (200 mg, 49.73%) MS (ESI): mass calcd. for $C_{26}H_{26}F_5N_7O_4$: 595.20 m/z found: 596.05[M+H]$^+$



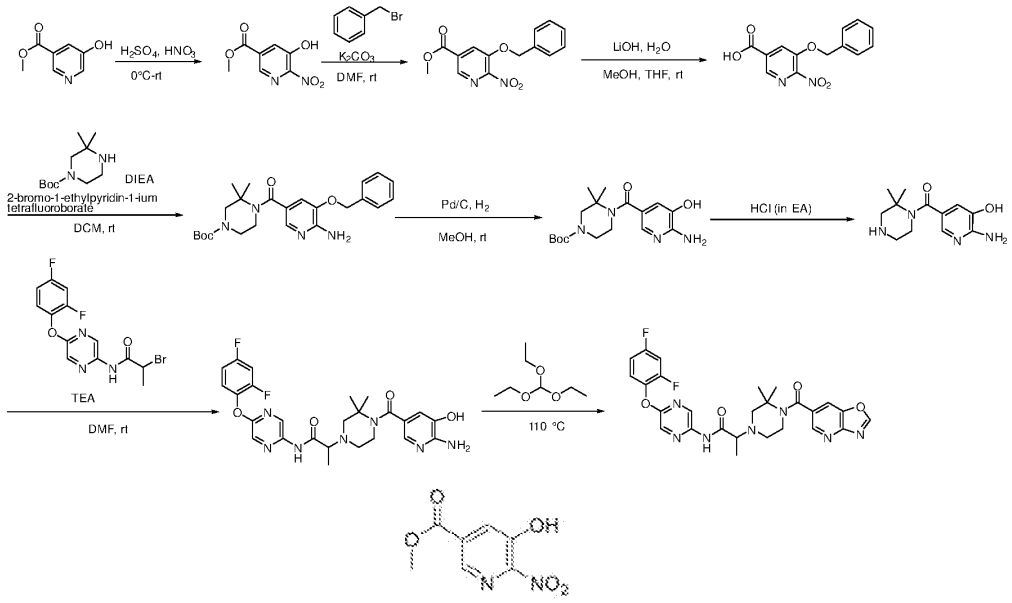
(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-6-(trifluoromethyl)- Synthesis of 4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide

To a stirred solution of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-methoxy-6-(trifluoromethyl)pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (200 mg, 0.336 mmol, 1 equiv) in dimethylformamide (2 mL) was added pyridine hydrobromide (537.38 mg, 3.360 mmol, 10 equiv) at room temperature . The reaction mixture was stirred at 100°C for 3 h. The resulting mixture was stirred for additional overnight at room temperature. After completion of reaction, the reaction mixture was quenched by addition of water (5 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and the residue was purified by preparative HPLC using XBridge Prep OBD C18 Column, 30 x150mm x5μm (eluent: 29% to 46% (v/v) CH_3CN and H_2O with NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-6-(trifluoromethyl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide (64.1 mg, 32.45%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{24}F_5N_7O_4$: 581.18m/z, found: 582.25$[M+H]^+$ ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.39 (s, 1H), 8.84 (s, 1H), 8.45 (s, 1H), 8.15 (s, 1H), 7.48 (ddt, J = 14.9, 9.3, 4.6 Hz, 2H), 7.17 (td, J = 8.5, 2.9 Hz, 1H), 3.48 – 3.57 (m, 2H), 3.17 (s, 1H), 2.69 – 2.79 (m, 1H), 2.64 (q, J = 5.2 Hz, 1H), 2.41 (s, 2H), 1.43 (s, 6H), 1.20 (d, J = 6.7 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -67.79, -113.43 (d, J = 5.2 Hz), -124.23 (d, J = 5.3 Hz).

Example 226: *N*-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(oxazolo[4,5-b]pyridine-6-carbonyl)piperazin-1-yl)propanamide

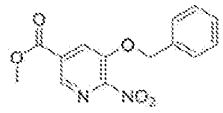


Synthetic Scheme



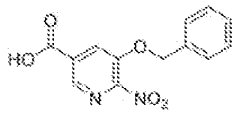
methyl 5-hydroxy-6-nitronicotinate

To a solution of methyl 5-hydroxypyridine-3-carboxylate (5 g, 32.651 mmol, 1 equiv) in H_2SO_4 (25 mL). Then HNO_3 (2.58 g, 21.596 mmol, 4 equiv) was added at 0 °C. The reaction mixture was stirred at room temperature for 0.5h. After completion of reaction, the crude product was re-crystallized from ice water to afford methyl 5-hydroxy-6-nitropyridine-3-carboxylate (5 g) as a yellow solid. The residue obtained was purified by silica gel chromatography (0-60% PE/EA) to afford methyl 5-hydroxy-6-nitronicotinate (3.5 g, 54.10%) as a white solid. MS (ESI): mass calcd. for $C_{14}H_{26}N_2O_3$: 198.03 m/z, found: 196.9 $[M-H]^-$.



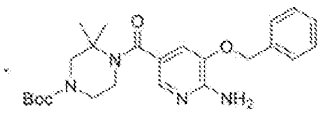
methyl 5-(benzyloxy)-6-nitronicotinate

To a solution of methyl 5-hydroxy-6-nitronicotinate (3 g, 15.141 mmol, 1 equiv) in dimethylformamide (30 mL) was added K_2CO_3 (6.32 g, 45.423 mmol, 3 equiv) and benzyl bromide (4.40 g, 25.740 mmol, 1.7 equiv) at rt. The resulting mixture was stirred for 2 hours at room temperature. After completion of reaction, the reaction mixture was quenched by water (50 mL) and extracted with EA (80 mL x 3). The combined organic phase was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-40% PE/EA) to afford methyl 5-(benzyloxy)-6-nitronicotinate (2.8 g, 64.15%) as a white solid. MS (ESI): mass calcd. for $C_{14}H_{12}N_2O_5$: 288.07 m/z, found: 289.05 $[M+H]^+$.



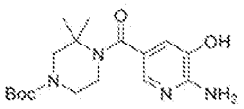
5-(benzyloxy)-6-nitronicotinic acid

To a solution of 5-(benzyloxy)-6-nitronicotinate (2.7 g, 9.367 mmol, 1 equiv) in methanol (5 mL), tetrahydrofuran (10 mL) and water (5 mL) was added LiOH (0.45 g, 18.734 mmol, 2 equiv) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated to dryness under reduced pressure to provide the mixture. The mixture was acidified pH = 5 with HCl (1N). The precipitated solids were collected by filtration and washed with water. The product was precipitated by the addition of diethyl ether. The product is obtained (5-(benzyloxy)-6-nitronicotinic acid (2 g, 77.86%)) by filtration and drying. MS (ESI): mass calcd. for $C_{13}H_{10}N_2O_5$: 274.06 m/z, found: 273.00 $[M-H]^-$.



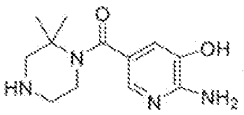
***tert*-butyl 4-(6-amino-5-(benzyloxy)nicotinoyl)-3,3-dimethylpiperazine-1-carboxylate**

To a stirred solution of (5-(benzyloxy)-6-nitronicotinic acid (1 g, 3.647 mmol, 1 equiv) in DCM (20 mL) was added tert-butyl 3,3-dimethylpiperazine-1-carboxylate (0.94 g, 4.376 mmol, 1.2 equiv) and 2-bromo-1-ethylpyridin-1-ium tetrafluoroborate (2.00 g, 7.294 mmol, 2 equiv) at room temperature. The reaction mixture was stirred at room temperature for a period of overnight. After completion of reaction, the reaction mixture was quenched by water (10 mL) and extracted with EA (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (40-100% PE/EA) to afford tert-butyl 4-(6-amino-5-(benzyloxy)nicotinoyl)-3,3-dimethylpiperazine-1-carboxylate (300 mg, 18.67%) as a white solid. MS (ESI): mass calcd. for $C_{24}H_{32}N_4O_4$: 440.24 m/z, found: 441.15 $[M+H]^+$.



***tert*-butyl 4-(6-amino-5-hydroxynicotinoyl)-3,3-dimethylpiperazine-1-carboxylate**

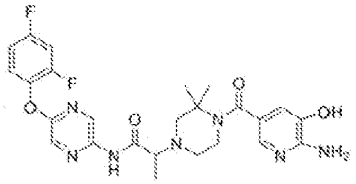
To a stirred solution of tert-butyl 4-(6-amino-5-(benzyloxy)nicotinoyl)-3,3-dimethylpiperazine-1-carboxylate (300 mg, 0.681 mmol, 1 equiv) in methanol (6 mL) was added Pd/C (7.25 mg, 0.068 mmol, 0.1 equiv) under H_2. The reaction mixture was stirred at room temperature for 1 h under H_2. The resulting mixture was filtered, the filter cake was washed with MeOH. The filtrate was concentrated under reduced pressure. The product was precipitated by the addition of diethyl ether. The product is obtained (tert-butyl 4-(6-amino-5-hydroxynicotinoyl)-3,3-dimethylpiperazine-1-carboxylate (0.2 g, 83.8%) by filtration and drying. MS (ESI): mass calcd. for $C_{17}H_{26}N_4O_4$: 350.20 m/z, found: 351.15 $[M+H]^+$.



(6-amino-5-hydroxypyridin-3-yl)(2,2-dimethylpiperazin-1-yl)methanone

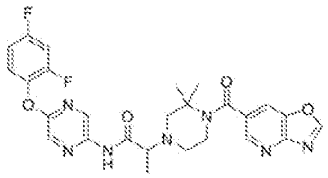
To a stirred solution of (tert-butyl 4-(6-amino-5-hydroxynicotinoyl)-3,3-dimethylpiperazine-1-carboxylate (300 mg, 0.856 mmol, 1 equiv) in EA (3 mL) was added HCl (4 M in EA, 3 mL). The reaction mixture was stirred at room temperature for 1 h. The

product was precipitated by the addition of diethyl ether. The product is obtained ((6-amino-5-hydroxypyridin-3-yl)(2,2-dimethylpiperazin-1-yl)methanone (200 mg, 93.33%)) by filtration and drying. MS (ESI): mass calcd. for $C_{12}H_{18}N_4O_2$: 250.14 m/z, found: 251.10 $[M+H]^+$.



***N*-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(oxazolo[4,5-b]pyridine-6-carbonyl)piperazin-1-yl)propanamide**

To a solution of 2-amino-5-(2,2-dimethylpiperazine-1-carbonyl)pyridin-3-ol (200 mg, 0.799 mmol, 1 equiv) in dimethylformamide (5 mL) was added TEA (242.57 mg, 2.397 mmol, 3 equiv) and 2-bromo-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (343.40 mg, 0.959 mmol, 1.2 equiv) at rt. The resulting mixture was stirred for 2 hours at room temperature. After completion of reaction, the reaction mixture was quenched by water (10 mL) and extracted with EA (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) to afford 2-[4-(6-amino-5-hydroxypyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl]-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (280 mg, 66.43%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{27}F_2N_7O_4$: 527.21 m/z, found: 528.20 $[M+H]^+$.

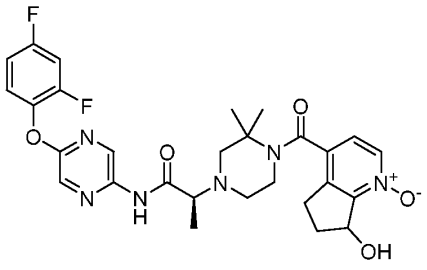


***N*-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(oxazolo[4,5-b]pyridine-6-carbonyl)piperazin-1-yl)propanamide**

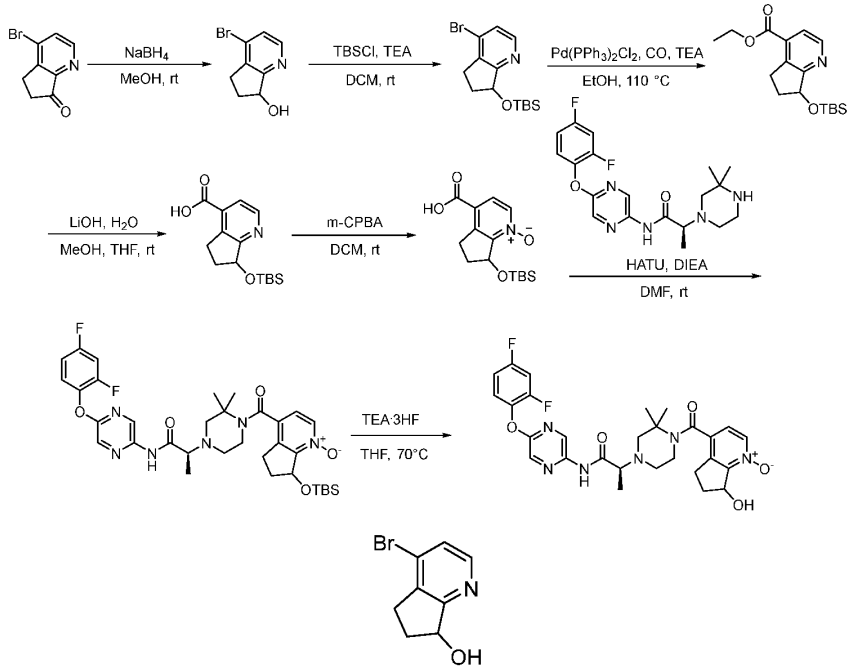
To a stirring solution ((6-amino-5-hydroxypyridin-3-yl)(2,2-dimethylpiperazin-1-yl)methanone (280 mg, 0.531 mmol, 1 equiv) in triethyl orthoformate (3 mL) . The mixture was stirred at 110 °C for 3 h. After cooled to room temperature, the reaction was

concentrated to dryness under reduced pressure to provide the crude product, which was purified by silica gel chromatography (0-5% DCM/MeOH) to afford N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(oxazolo[4,5-b]pyridine-6-carbonyl)piperazin-1-yl)propanamide (24.2 mg, 7.77%) as a yellow solid. MS (ESI): mass calcd. for $C_{26}H_{25}F_2N_7O_4$: 537.19 m/z, found: 538.25 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H), 9.14 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.61 (d, J = 1.8 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.33 (d, J = 1.8 Hz, 1H), 7.48 (dtd, J = 14.5, 9.3, 4.3 Hz, 2H), 7.17 (ddd, J = 10.6, 8.3, 2.3 Hz, 1H), 3.54 (q, J = 6.8 Hz, 1H), 3.28 – 3.40 (m,3H), 3.17 (d, J = 5.2 Hz, 1H), 2.57 – 2.78 (m, 2H), 1.50 (d, J = 3.9 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H).^{19}F NMR (376 MHz, DMSO-d_6) δ -113.43 (d, J = 5.3 Hz), -124.21 (d, J = 5.1 Hz).

Example 227: 4-(4-((S)-1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-7-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridine 1-oxide

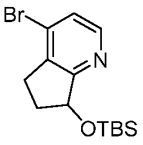


Synthetic Scheme



4-bromo-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol

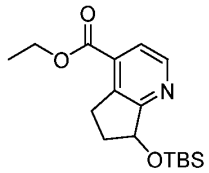
To a solution of 4-bromo-5H,6H-cyclopenta[b]pyridin-7-one (1 g, 4.716 mmol, 1 equiv) in methanol (20 mL) the mixture was added $NaBH_4$ (214.09 mg, 5.659 mmol, 1.2 equiv) at 0 °C. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (20 mL) and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% EA/PE) to give 4-bromo-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol (900 mg, 89.15%) as white solid. MS (ESI): mass calcd. for C_8H_8BrNO: 212.98, found: 214.20 $[M+H]^+$.



4-bromo-7-((tert-butyldimethylsilyl)oxy)-6,7-dihydro-5H-cyclopenta[b]pyridine

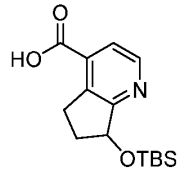
To a solution of 4-bromo-6,7-dihydro-5H-cyclopenta[b]pyridin-7-ol (700 mg, 3.270 mmol, 1 equiv) in DCM (20 mL) the mixture was added t-butyldimethylchlorosilane (591.44 mg, 3.924 mmol, 1.2 equiv) and TEA (661.82 mg, 6.540 mmol, 2 equiv) at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (20 mL)

and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% EA/PE) to give 4-bromo-7-((tert-butyldimethylsilyl)oxy)-6,7-dihydro-5H-cyclopenta[b]pyridine as white solid. MS (ESI): mass calcd. for $C_{14}H_{22}BrNOSi$: 327.07, found: 328.20 $[M+H]^+$.



ethyl 7-((tert-butyldimethylsilyl)oxy)-6,7-dihydro-5H-cyclopenta[b]pyridine-4-carboxylate

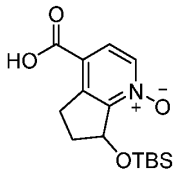
To a solution of 4-bromo-7-[(tert-butyldimethylsilyl)oxy]-5H,6H,7H-cyclopenta[b]pyridine (500 mg, 1.523 mmol, 1 equiv) in EtOH (20 mL) was added $Pd(PPh_3)_2Cl_2$ (106.89 mg, 0.152 mmol, 0.1 equiv) and triethylamine (462.31 mg, 4.569 mmol, 3 equiv) in a pressure tank. The mixture was purged with nitrogen for 5 min and then was pressurized to 50 atm with CO (gas) at 110 °C for 24 h. The reaction mixture was cooled to room temperature and filtered to remove insoluble solids. The residue obtained was purified by silica gel chromatography (0-50% EA/PE) to give ethyl 7-((tert-butyldimethylsilyl)oxy)-6,7-dihydro-5H-cyclopenta[b]pyridine-4-carboxylate as a white solid. MS (ESI): mass calcd. for $C_{17}H_{27}NO_3Si$: 321.18, found: 322.25 $[M+H]^+$.



7-((tert-butyldimethylsilyl)oxy)-6,7-dihydro-5H-cyclopenta[b]pyridine-4-carboxylic acid

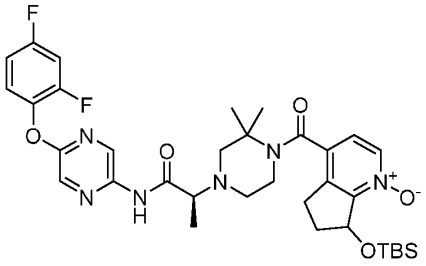
To a stirred solution of ethyl 7-((tert-butyldimethylsilyl)oxy)-6,7-dihydro-5H-cyclopenta[b]pyridine-4-carboxylate (300 mg, 0.933 mmol, 1 equiv) and LiOH (111.74 mg, 4.665 mmol, 5 equiv) in methanol (3 mL), H_2O (3 mL) and THF (6 mL) at room temperature. The reaction mixture was stirred at room temperature for a period of 3 h. The mixture was concentrated to dryness under reduced pressure to provide the crude product, which was purified by C18 column (0-20% H_2O/ACN) to afford 7-((tert-butyldimethylsilyl)oxy)-

6,7-dihydro-5H-cyclopenta[b]pyridine-4-carboxylic acid (220 mg, 80.34%) as a white solid. MS (ESI): mass calcd. for $C_{15}H_{23}NO_3Si$: 293.14 m/z. found 294.20 $[M+H]^+$.



7-((tert-butyldimethylsilyl)oxy)-4-carboxy-6,7-dihydro-5H-cyclopenta[b]pyridine 1-oxide

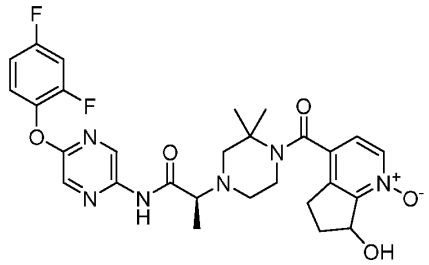
To a solution of 7-((tert-butyldimethylsilyl)oxy)-6,7-dihydro-5H-cyclopenta[b]pyridine-4-carboxylic acid (200 mg, 0.682 mmol, 1 equiv) in DCM (20 mL) the mixture was added m-CPBA (352.84 mg, 2.046 mmol, 3 equiv) at 0 °C. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (20 mL) and extracted with DCM (30 mL x 3). The combined organic extracts were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by C18 chromatography (0-100% H_2O/ACN) to give 7-((tert-butyldimethylsilyl)oxy)-4-carboxy-6,7-dihydro-5H-cyclopenta[b]pyridine 1-oxide as a white solid. MS (ESI): mass calcd. for $C_{15}H_{23}NO_4Si$: 309.14, found: 310.20 $[M+H]^+$.



7-((tert-butyldimethylsilyl)oxy)-4-(4-((S)-1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-6,7-dihydro-5H-cyclopenta[b]pyridine 1-oxide

To a solution of (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (100 mg, 0.255 mmol, 1 equiv) in DMF (20 mL) the mixture was added 7-((tert-butyldimethylsilyl)oxy)-4-carboxy-6,7-dihydro-5H-cyclopenta[b]pyridine 1-oxide (79.05 mg, 0.255 mmol,1equiv), HATU (145.71 mg, 0.383 mmol, 1.5 equiv) and N,N-diisopropylethylamine (99.06 mg, 0.765 mmol, 3 equiv) at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (10 mL x 3

). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodi um sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromat ography (0-10% DCM/MeOH) to give 7-((tert-butyldimethylsilyl)oxy)-4-(4-((S)-1-((5-(2,4-di fluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-6,7-dihydro-5H-cyclopenta[b]pyridine 1-oxide as a white solid. MS (ESI): mass calcd. for $C_{34}H_{44}F_2N_6O_5Si$: 682.31, found: 683.20 $[M+H]^+$.

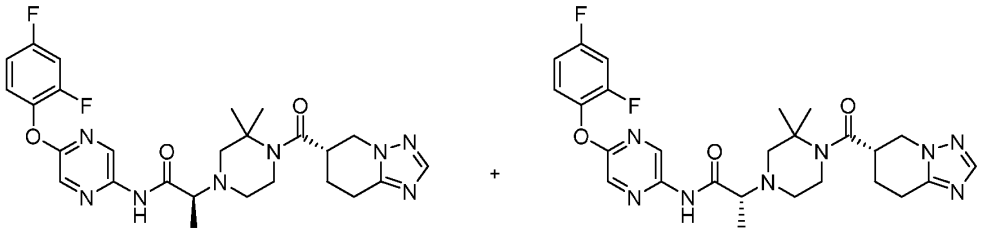


4-(4-((S)-1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-7-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridine 1-oxide

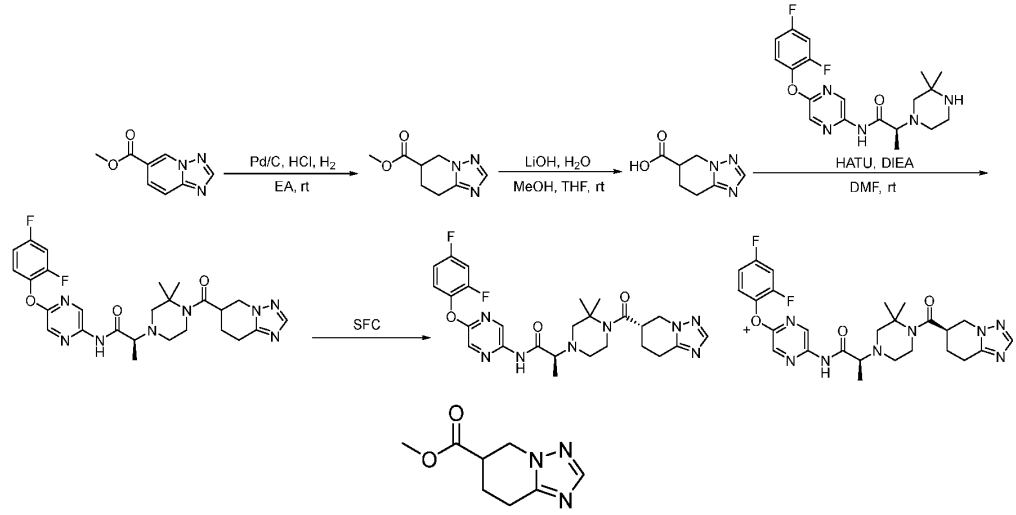
To a solution of 7-((tert-butyldimethylsilyl)oxy)-4-(4-((S)-1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-6,7-dihydro-5H-cyclopenta[b]pyridine 1-oxide (100 mg, 0.146 mmol, 1 equiv) in THF (4 mL) the mixture was added 3TEA.HF (1 mL). The mixture was stirred at 70 °C for 2 h. the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by preparative HPLC using a XBridge Prep OBD 150 mm x 30 mm x 5 μm column (eluent: 22% to 52% (v/v) ACN and H_2O with NH_4HCO_3+0.05%NH_3H_2O) to afford 4-(4-((S)-1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-7-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridine 1-oxide (24.6 mg, 29.25%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{30}F_2N_6O_5$: 556.22, found: 557.35 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.09 (d, J = 6.5 Hz, 1H), 7.41 – 7.55 (m, 2H), 7.26 (d, J = 6.5 Hz, 1H), 7.18 (s, 1H), 5.47 (d, J = 5.0 Hz, 1H), 5.21 (s, 1H), 3.49 – 3.57 (m, 1H), 3.25 (s, 2H), 3.01 (s, 1H), 2.72 – 2.82 (m, 1H), 2.55 – 2.71(m, 2H), 2.44 (d, J = 4.8 Hz, 2H), 2.26 – 2.34 (m, 1H), 1.89 (s, 1H),

1.47 (t, *J* = 1.8 Hz, 6H), 1.20 (d, *J* = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -113.42 (d, *J* = 5.2 Hz), -124.22 (d, *J* = 5.3 Hz).

Example 228: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)piperazin-1-yl)propanamide and Example 229: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)piperazin-1-yl)propanamide



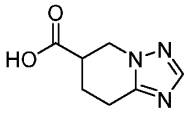
Synthetic Route:



methyl 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate

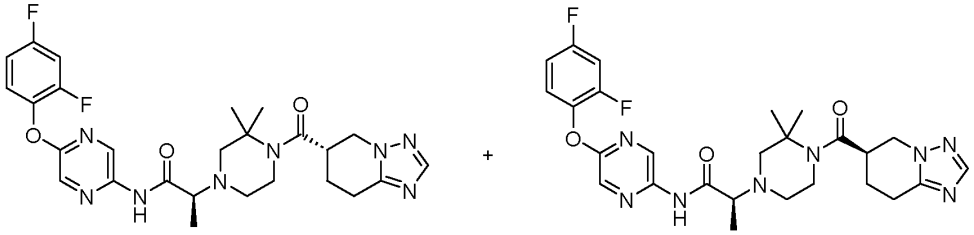
To a stirring solution of methyl [1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (2 g, 11.290 mmol, 1 equiv) in EA (30 mL) was added a solution of Pd/C (18.12 mg, 0.170 mmol, 0.1 equiv) and 4N HCl (0.1 mL). The mixture was stirred at 25 °C for 4 h under H_2. The reaction mixture was filtered through a pad of celite and concentrated under reduced pressure to afford to afford methyl 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (800 mg,

39.80%) as a white solid. MS (ESI): mass calcd. for $C_8H_{11}N_3O_2$: 181.09 m/z, found 182.05 $[M+H]^+$.



5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid

To a solution of methyl 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (1 g, 5.52 mmol, 1 equiv) in THF (5 mL), MeOH (5 mL) and H_2O (5 mL). LiOH (0.529 g, 22.08 mmol, 4 equiv) was added the mixture. The mixture was stirred at room temperature for 2 h. After completion of reaction, the mixture was acidified to pH=3 with (2 N HCl) extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated to afford 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid (0.5 g, crude) as a yellow solid. MS (ESI): mass calcd. for $C_7H_9N_3O_2$: 167.07 m/z, found 161.25 $[M+H]^+$.

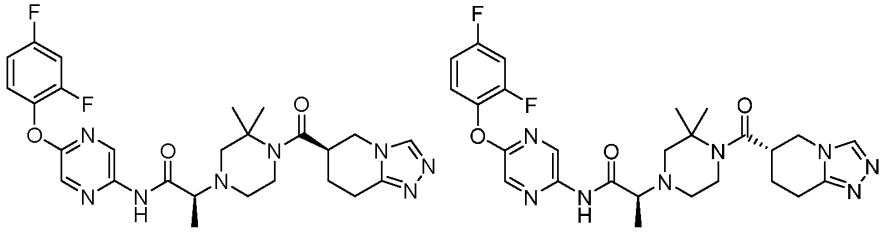


(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)piperazin-1-yl)propanamide and (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)piperazin-1-yl)propanamide

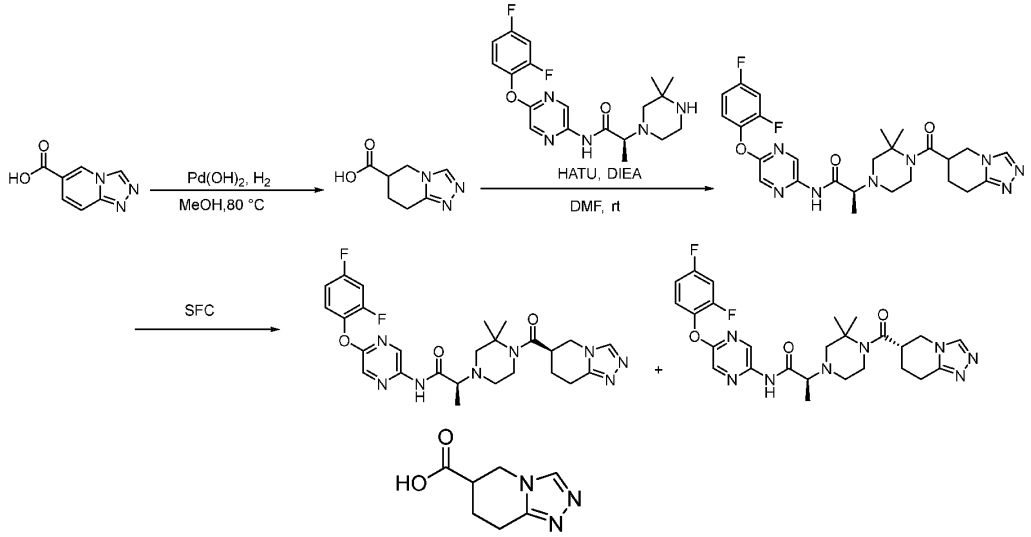
To a solution of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (100 mg, 0.255 mmol, 1 equiv) in N,N-dimethylformamide (2 mL) the mixture was added 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid (42 mg, 0.255 mmol, 1 equiv), HATU (145 mg, 0.385 mmol, 1.5 equiv), and DIEA (99 mg, 0.765 mmol, 3 equiv). The reaction was stirred at 25°C for 3 h. The reaction mixture was quenched by water (10 mL) and extracted with EA (3*10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by CHIRALPAK ID, 2*25 cm, 5 μm column (eluent: 30% (v/v) Hex: DCM=3: 1(0.5% 2M NH_3-MeOH) and IPA) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-5,6,7,8-

tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)piperazin-1yl)propanamide (18.8 mg, 13.6%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{30}F_2N_8O_3$: 540.24 m/z, found 541.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.84 (d, J =1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.83 (s, 1H), 7.39 – 7.50 (m, 2H), 7.10 – 7.24 (m, 1H), 4.02 – 4.22 (m, 2H), 3.40 – 3.63 (m, 4H), 2.69 – 2.96 (m, 3H), 2.55 – 2.65 (m, 1H), 2.29 – 2.47 (m, 2H), 2.00 – 2.11 (m, 1H), 1.80 – 1.98 (m, 1H), 1.38 (s, 6H), 1.16 – 1.27 (m, 3H). And (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)piperazin-1-yl)propanamide (23.6 mg, 17.1%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{30}F_2N_8O_3$: 540.24 m/z, found 541.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.81 – 8.88 (m, 1H), 8.42 – 8.49 (m, 1H), 7.83 (d, J = 2.0 Hz, 1H), 7.39 – 7.56 (m, 2H), 7.11 – 7.24 (m, 1H), 4.02 – 4.22 (m, 2H), 3.41 – 3.63 (m, 4H), 2.66 – 2.94 (m, 4H), 2.31 – 2.41 (m, 2H), 2.00 – 2.13 (m, 1H),1.82 – 1.98 (m, 1H), 1.38 (s, 6H), 1.16 – 1.27 (m, 3H).

Example 230: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)piperazin-1-yl)propanamide and Example 231: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)piperazin-1-yl)propanamide

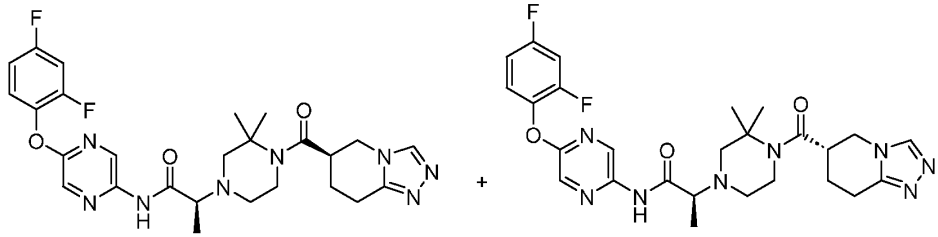


Synthetic Route:



2,3,5,6,7,8-hexahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid

To a solution of [1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid (500 mg, 3.065 mmol, 1 equiv) in MeOH (100 mL) was added $Pd(OH)_2$ (430.4 mg) in a pressure tank. The mixture was hydrogenated at 80 °C under 50 atm of hydrogen pressure for 24 h, filtered through a Celite pad and concentrated under reduced pressure. The residue was purified by C18 column (CH_3CN & H_2O with 0.05% HCl) to afford 2,3,5,6,7,8-hexahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid (300 mg, 58.55%) as a yellow oil. MS (ESI): mass calcd. For $C_7H_9N_3O_2$:167.07m/z, found: 168.05$[M+H]^+$.

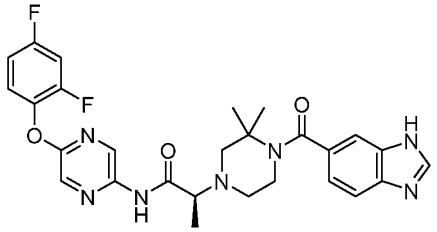


(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)piperazin-1-yl)propanamide and (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)piperazin-1-yl)propanamide

To a solution of 2,3,5,6,7,8-hexahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid (200 mg, 1.196 mmol, 1 equiv) in DMF (5 mL) was added (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (468.30 mg,

1.196 mmol, 1 equiv), and HATU (432.58 mg, 1.794 mmol, 1.5 equiv) and DIEA (927.79 mg, 7.176 mmol, 6 equiv) added at rt. The resulting mixture was stirred for 2h at rt. The resulting mixture was extracted with EA (3*50mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-15%DCM/MeOH) and Prep-HPLC using a Column: Xselect CSH C18 OBD Column, 30*150 mm, 5μm (eluent: 19% to 49% ACN and Water(0.1% FA) and by Chiral-HPLC using a CHIRALPAK IF 2*25 cm, 5 μm column (eluent: 30% (v/v) EtOH and Hex: DCM=3: 1 0.5% 2M NH_3-MeOH) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)piperazin-1-yl)propanamide (2.6 mg, 0.40%) as a white solid as a white solid, MS (ESI): mass calcd. for $C_{26}H_{30}F_2N_8O_3$: 540.24m/z, found: 541.30[M+H]$^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.84 (s, 1H), 8.32 – 8.49 (m, 2H), 7.40 – 7.71 (m, 2H), 7.18 (t, J = 8.5 Hz, 1H), 3.89 – 4.18 (m, 2H), 3.50 – 3.61 (m, 4H), 2.72 – 2.89 (m, 3H), 2.58 – 2.62 (m, 1H), 2.28 – 2.44 (m, 2H), 1.99 – 2.09 (m, 1H), 1.74 – 1.93 (m, 1H), 1.37 (s, 6H), 1.21 (d, J = 6.6 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -118.380, -124.190. And (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)piperazin-1-yl)propanamide (3.1 mg, 0.46%) as a white solid, MS (ESI): mass calcd. For $C_{26}H_{30}F_2N_8O_3$: 540.24 m/z, found: 541.30 [M+H]$^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.84 (s, 1H), 8.32 – 8.49 (m, 2H), 7.40 – 7.71 (m, 2H), 7.18 (t, J = 8.5 Hz, 1H), 3.89 – 4.18 (m, 2H), 3.50 – 3.61 (m, 4H), 2.72 – 2.89 (m, 3H), 2.58 – 2.62 (m, 1H), 2.28 – 2.44 (m, 2H), 1.99 – 2.09 (m, 1H), 1.74 – 1.93 (m, 1H), 1.37 (s, 6H), 1.21 (d, J = 6.6 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -118.380, -124.190.

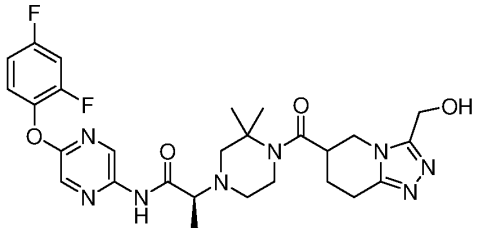
Example 232: (S)-2-(4-(1H-benzo[d]imidazole-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide



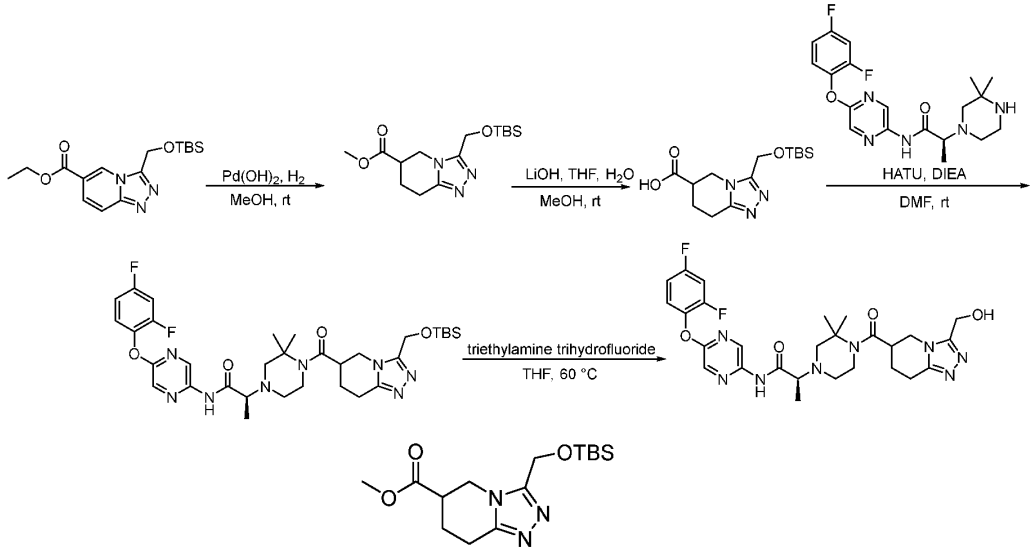
(S)-2-(4-(1H-benzo[d]imidazole-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

To a stirred solution of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (150 mg, 0.383 mmol, 1 equiv) in dimethylformamide (2 mL) was added 1H-benzo[d]imidazole-5-carboxylic acid (93.21 mg, 0.575 mmol, 1.5 equiv) and HATU (291.42 mg, 0.766 mmol, 2 equiv) and DIEA (198.12 mg, 1.532 mmol, 4 equiv) at room temperature . The reaction mixture was stirred under H_2 at room temperature for 3 h. The resulting mixture was stirred for additional overnight at room temperature. After completion of reaction, the reaction mixture was quenched by addition of water (5 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and the residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30 x 150mm x 5μm (eluent: 18% to 48% (v/v) CH_3CN and H_2O with NH_4HCO_3+0.05%NH_3H_2O) to afford (S)-2-(4-(1H-benzo[d]imidazole-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (24.3 mg, 11.37%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{27}F_2N_7O_3$: 535.21 m/z, found: 536.30 $[M+H]^+$ ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.60 (s, 1H), 10.40 (s, 1H), 8.85 (d, J = 1.5 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 8.31 (s, 1H), 7.57 - 7.73 (m, 2H), 7.39 - 7.55 (m, 2H), 7.29 (s, 1H), 7.10 - 7.24 (m, 1H), 3.53 (d, J = 7.0 Hz, 1H), 3.32 (s, 2H),2.71 (d, J = 5.2 Hz, 1H), 2.56 – 2.66 (m, 1H), 2.46 (d, J = 2.1 Hz, 2H), 1.48 (d, J = 1.8 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.41 (d, J = 5.3 Hz), -124.21 (d, J = 5.3 Hz).

Example 233: (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(3-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

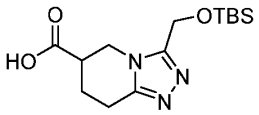


Synthetic Route:



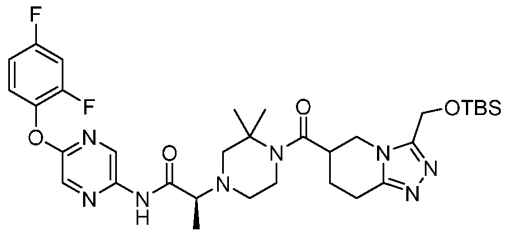
Methyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a] pyridine-6-carboxylate

To a solution of ethyl 3-{[(tert-butyldimethylsilyl)oxy]methyl}-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylate (500 mg, 1.490 mmol, 1 equiv) in 20 mL MeOH was added $Pd(OH)_2/C$ (10%, 100 mg) in a pressure tank. The mixture was hydrogenated at room temperature under 30 atm of hydrogen pressure for overnight, filtered through a Celite pad and concentrated under reduced pressure. MS (ESI): mass calcd. for $C_{16}H_{29}N_3O_3Si$ 325.18 m/z, found 325.95 $M+H]^+$.



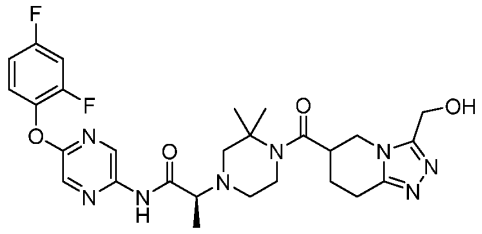
3-{[(tert-butyldimethylsilyl)oxy]methyl}-5H,6H,7H,8H-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid

To a solution ethyl 3-{[(tert-butyldimethylsilyl)oxy]methyl}-5H,6H,7H,8H-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylate (450 mg, 1.325 mmol, 1 equiv) in THF (0.5mL) was added $LiOH.H_2O$ (66.74 mg, 1.590 mmol, 1.2 equiv) and H_2O (11.25 mL, 624.274 mmol, 471.15 equiv) and MeOH (11.25 mL, 2.773 mmol, 209.64 equiv) at rt. The resulting mixture was stirred for 2 h at rt. The mixture was acidified to pH 2 with 2N HCl (aq.). The precipitated solids were collected by filtration and washed with water. The resulting mixture was concentrated under reduced pressure. MS (ESI): mass calcd. for $C_{14}H_{25}N_3O_3Si$ 311.167 m/z, found 312.10 $[M+H]^+$.



(2S)-2-[4-(3-{[(tert-butyldimethylsilyl)oxy]methyl}-5H,6H,7H,8H-[1,2,4]triazolo[4,3-a] pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl]-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl] propanamide

To a solution of 3-{[(tert-butyldimethylsilyl)oxy]methyl}-5H,6H,7H,8H-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid (90 mg, 0.289 mmol, 1 equiv) in DMF (3 mL) was added (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (113.11 mg, 0.289 mmol, 1 equiv), HATU (164.81 mg, 0.433 mmol, 1.5 equiv) and DIEA (149.39 mg, 1.156 mmol, 4 equiv) at rt. The resulting mixture was stirred for 2 h at rt. The reaction mixture was quenched by water and extracted with EA (3*30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford product as a yellow solid. This was directly purified by flash chromatography to afford product as a yellow solid.

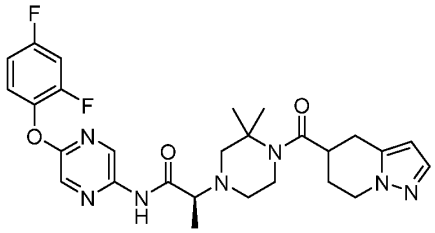


(2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-{4-[3-(hydroxymethyl)-5H,6H,7H,8H-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl]-3,3-dimethylpiperazin-1-yl}propanamide

To a solution of (2S)-2-[4-(3-{[(tert-butyldimethylsilyl)oxy]methyl}-5H,6H,7H,8H-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl]-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (50 mg, 0.073 mmol, 1 equiv) in THF (3 mL) was added Triethylamine trihydrofluoride (94.16 mg, 0.584 mmol, 8 equiv) at rt . The resulting mixture was stirred for overnight at 60 °C. The reaction mixture was quenched by water and extracted with EA (3*30 mL).The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum The residue

obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 28% to 46% (v/v) CH_3CN and H_2O, NH_4HCO_3) to afford product (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-{4-[3-(hydroxymethyl)-5H,6H,7H,8H-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl]-3,3-dimethylpiperazin-1-yl}propanamide (12.8 mg, 30.29%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{32}F_2N_8O_4$ 570.25 m/z, found 571.35 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.84 (d, J = 1.5 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.19 – 8.30 (m, 2H), 7.48 (ddd, J = 18.3, 9.4, 4.6 Hz, 3H), 7.31 (d, J = 7.8 Hz, 1H), 7.18 (t, J = 8.8 Hz, 1H), 3.54 (d, J = 7.0 Hz, 1H), 3.28 – 3.33 (m, 2H), 2.69 (d, J = 5.1 Hz, 1H), 2.55 – 2.64 (m, 1H), 2.45 (d, J = 4.1 Hz, 2H), 1.46 (d, J = 2.8 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -113.43 (d, J = 5.3 Hz), -124.22 (d, J = 5.2 Hz).

Example 234: (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)piperazin-1-yl)propanamide

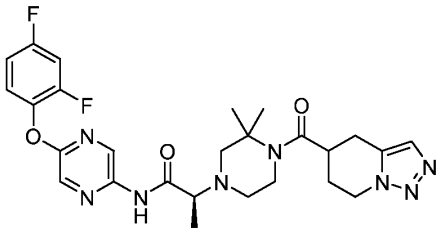


(2*S*)-*N*-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)piperazin-1-yl)propanamide

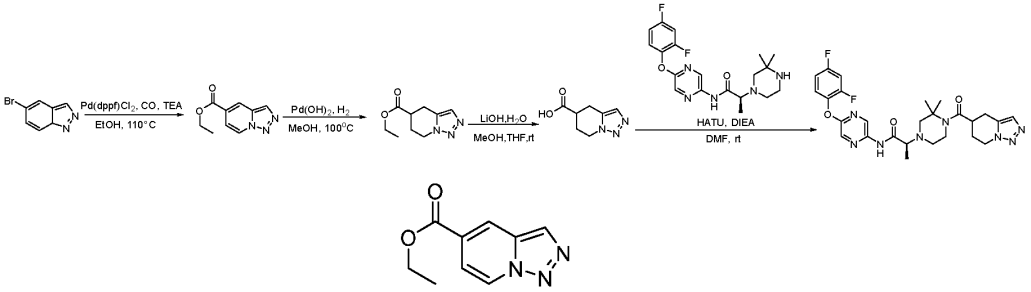
To a solution of 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carboxylic acid (80 mg, 0.481 mmol, 1 equiv) in dimethylformamide (5 mL) was added (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (188.43 mg, 0.481 mmol, 1 equiv) and HATU (366.09 mg, 0.962 mmol, 2 equiv) and DIEA (124.44 mg, 0.962 mmol, 2 equiv). The mixture was stirred at room temperature for 2 h. The mixture was concentrated to dryness under reduced pressure to provide the crude product, which was purified by Prep-HPLC using for a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 40% B to 70% (v/v) ACN and Water (10mmol/L NH_4HCO_3+0.05%NH_3H_2O)) to afford (2*S*)-*N*-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)piperazin-1-yl)propanamide (55.6 mg, 48.92%) as an off-white solid. MS (ESI): mass calcd. for $C_{27}H_{31}F_2N_7O_3$: 539.25 m/z, found: 540.20 $[M+H]^+$.^1H NMR (300 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.84 (d, J = 1.5 Hz, 1H),

8.45 (d, *J* = 1.4 Hz, 1H), 7.39 - 7.55 (m, 2H), 7.33 (d, *J* = 1.8 Hz, 1H), 7.10 - 7.24 (m, 1H), 5.98 (d, *J* = 1.8 Hz, 1H), 3.95 – 4.20 (m, 2H), 3.45 - 3.60 (m, 3H), 3.10 – 3.22 (m, 1H), 2.81 – 2.94 (m, 1H), 2.59 – 2.80 (m, 3H), 2.36 (d, *J* = 2.3 Hz, 2H), 2.04 (s, 1H), 1.83 – 2.02 (m, 1H), 1.35 – 1.42 (m, 6H), 1.20 (d, *J* = 6.9 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -113.43 (d, *J* = 5.3 Hz), -124.22 (d, *J* = 5.3 Hz).

Example 235: (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carbonyl)piperazin-1-yl)propanamide

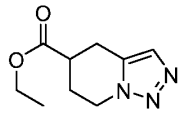


Synthetic Route:



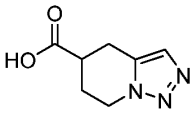
Ethyl [1,2,3]triazolo[1,5-a]pyridine-5-carboxylate

To a stirring solution5-bromo-[1,2,3]triazolo[1,5-a]pyridine (500 mg, 2.525 mmol, 1 equiv) in ethyl alcohol (20 mL) was added a solution of Pd(dppf)Cl_2 (177.23 mg, 0.253 mmol, 0.1 equiv) and TEA (766.52 mg, 7.575 mmol, 3 equiv) .The resulting mixture was under CO stirred at 110°C for 6h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) to afford ethyl [1,2,3]triazolo[1,5-a]pyridine-5-carboxylate (480 mg, 99.43%) MS (ESI): mass calcd. for $C_9H_9N_3O_2$: 191.109 m/zfound: 192.00[M+H^+]



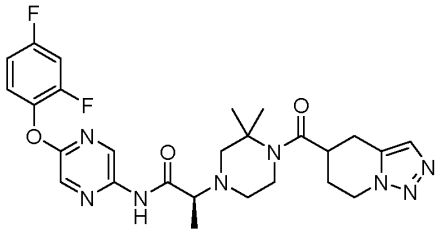
Ethyl 4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylate

To a stirring solution ethyl [1,2,3]triazolo[1,5-a]pyridine-5-carboxylate (400 mg, 2.092 mmol, 1 equiv) in methanol (200 mL) was added a solution of $Pd(OH)_2$ (881.41 mg, 6.276 mmol, 3 equiv) .The resulting mixture was under N_2 stirred at 100°C for 6h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) to afford ethyl 4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylate (300 mg, 73.45%) MS (ESI): mass calcd. for $C_9H_{13}N_3O_2$: 195.22 m/z found: 196.05[$M+H^+$]



4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylic acid

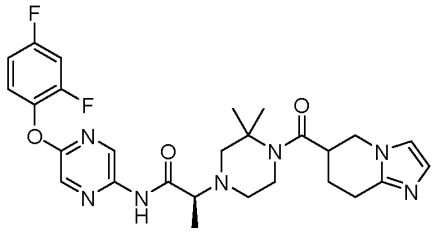
To a stirring solution ethyl 4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylate (300 mg, 1.537 mmol, 1 equiv) in methanol (0.4 mL) and water (0.4 mL) and tetrahydrofuran (0.8 mL) was added a solution of LiOH (36.80 mg, 1.537 mmol, 1 equiv) .The resulting mixture was stirred at room temperature for 6h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) to afford 4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylic acid (150 mg, 58.39%) MS (ESI): mass calcd. for $C_7H_9N_3O_2$: 167.16 m/z found: 166.05[$M-H]^-$



(2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carbonyl)piperazin-1-yl)propanamide

To a stirred solution of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (100 mg, 0.255 mmol, 1 equiv) in dimethylformamide (1 mL) was added HATU (145.71 mg, 0.383 mmol, 1.5 equiv) and 4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylic acid (64.06 mg, 0.383 mmol, 1.5 equiv) and at room temperature . The reaction mixture was stirred at room temperature for 3 h. The resulting mixture was stirred for additional overnight at room temperature. After completion of reaction, the reaction mixture was quenched by addition of water (5 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and the residue was purified by preparative HPLC using a Xselect CSH Prep Fluoro-Phenyl Column, 30 x150mm x 5µm (eluent: 12% to 42% (v/v) CH_3CN and H_2O with 0.1%FA) to afford (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carbonyl)piperazin-1-yl)propanamide (6.7 mg, 4.73%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{30}F_2N_8O_3$: 540.24 m/z, found: 541.30 $[M+H]^+$.^{1}H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.84 (d, J = 1.5 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.39 – 7.56 (m, 3H), 7.17 (t, J = 8.3 Hz, 1H), 4.20 – 4.42 (m, 2H), 3.55 (s, 4H), 2.89 (d, J = 5.2 Hz, 1H), 2.74 – 2.85 (m, 2H), 2.64 (s, 1H), 2.36 (s, 2H), 2.11 (d, J = 13.5 Hz, 1H), 1.98 (s, 1H), 1.38 (d, J = 2.2 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -113.41 (d, J = 5.2 Hz), -124.22 (d, J = 5.3 Hz)

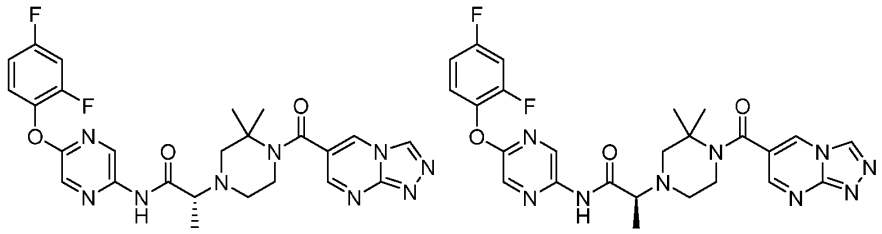
Example 236: (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carbonyl)piperazin-1-yl)propanamide



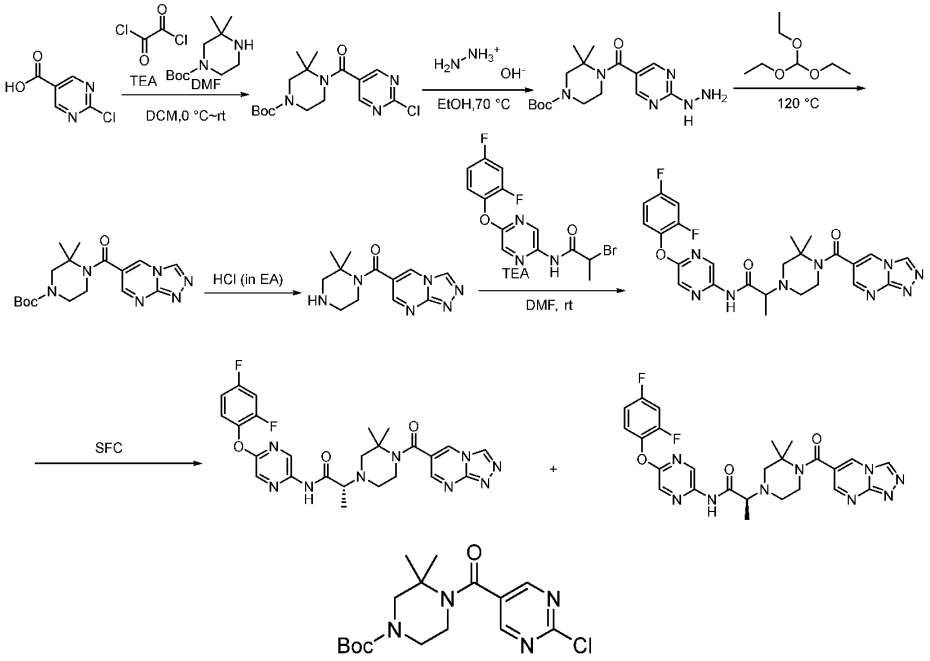
(2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carbonyl)piperazin-1-yl)propanamide

To a stirring solution (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (100 mg, 0.255 mmol, 1 equiv) in dimethylformamide (10 mL) the mixture was added 5H,6H,7H,8H-imidazo[1,2-a]pyridine-6-carboxylic acid hydrochloride (51.77 mg, 0.255 mmol, 1 equiv), HATU (145.71 mg, 0.383 mmol, 1.5 equiv) and N,N-diisopropylethylamine (132.08 mg, 1.020 mmol, 4 equiv) at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% EA/PE) and Prep-HPLC using a XBridge Prep OBD C18 Column (eluent: 35% to 56% (v/v) CH_3CN and Water(10mmol/L NH_4HCO_3+0.05%NH_3H_2O)) to afford (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carbonyl)piperazin-1-yl)propanamide (27.2 mg, 19.40%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{31}F_2N_7O_3$: 539.25, found: 540.30 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.82 (s, 1H), 8.43 (s, 1H), 7.47 (s, 2H), 7.16 (s, 1H), 6.96 (s, 1H), 6.76 (s, 1H), 4.01 (d, J = 10.7 Hz, 1H), 3.88 (t, J = 10.9 Hz, 1H), 3.53 (s, 3H), 3.14 – 3.28 (m, 1H), 2.73 (s, 4H), 2.34 (s, 2H), 1.98 (s, 1H), 1.78 (s, 1H), 1.36 (s, 6H), 1.19 (d, J = 6.8 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -113.42 (d, J = 5.4 Hz), -124.21 (d, J = 5.4 Hz).

Example 237: (R)-2-(4-([1,2,4]triazolo[4,3-a]pyrimidine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide and Example 238: (S)-2-(4-([1,2,4]triazolo[4,3-a]pyrimidine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

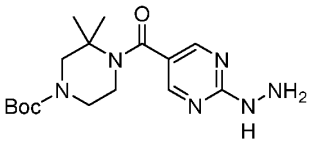


Synthetic Route:



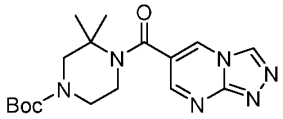
Tert-butyl 4-(2-chloropyrimidine-5-carbonyl)-3,3-dimethylpiperazine-1-carboxylate

To a solution of 2-chloropyrimidine-5-carboxylic acid (2 g, 12.615 mmol, 1 equiv) in DCM (20 mL) dimethylformamide (0.18 g, 2.523 mmol, 0.2 equiv) the mixture was cooled to 0 °C, then oxalyl chloride (3.20 g, 25.230 mmol, 2 equiv). The mixture was warmed to room temperature stirred at room temperature for 1 h. After completion of reaction the mixture was concentrated under reduced pressure. The product was dissolved in DCM (20 mL) then added tert-butyl 3,3-dimethylpiperazine-1-carboxylate (2.70 g, 12.615 mmol, 1 equiv) and TEA (3.83 g, 37.845 mmol, 3 equiv). The mixture was stirred at room temperature for 1 h. After completion of reaction, the reaction mixture was quenched by water (20 mL) extracted with ethyl acetate (3 x 100 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated to afford tert-butyl 4-(2-chloropyrimidine-5-carbonyl)-3,3-dimethylpiperazine-1-carboxylate (2.2 g, 49.15%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{23}ClN_4O_3$: 354.15 m/z, found: 355.20 $[M+H]^+$.



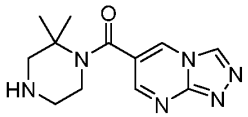
Tert-butyl 4-(2-hydrazineylpyrimidine-5-carbonyl)-3,3-dimethylpiperazine-1-carboxylate

To a solution of tert-butyl 4-(2-chloropyrimidine-5-carbonyl)-3,3-dimethylpiperazine-1-carboxylate (1.7 g, 4.791 mmol, 1 equiv) in ethyl alcohol (30 mL) the mixture was added hydrazine hydrate (85%) (1.20 g, 23.955 mmol, 5.0 equiv). The mixture was stirred at 70 °C for 3 h. After completion reaction the reaction was quenched by water (50 mL) then extracted with EA (3 x 100 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% EA/PE) to afford tert-butyl 4-(2-hydrazinylpyrimidine-5-carbonyl)-3,3-dimethylpiperazine-1-carboxylate (1.0 g, 59.56%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{26}N_6O_3$: 350.21 m/z, found: 351.10 $[M+H]^+$.



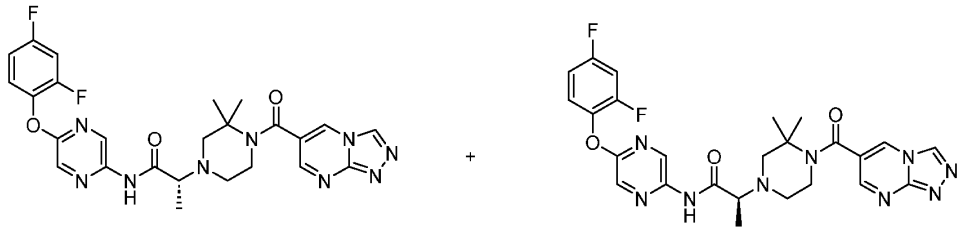
Tert-butyl 4-([1,2,4]triazolo[4,3-a]pyrimidine-6-carbonyl)-3,3-dimethylpiperazine-1-carboxylate

To a solution of tert-butyl 4-(2-hydrazinylpyrimidine-5-carbonyl)-3,3-dimethylpiperazine-1-carboxylate (900 mg, 2.568 mmol, 1 equiv) in triethyl orthoformate (10 mL). The mixture was stirred at 120 °C for 2 h. After completion reaction the reaction was cooled to room temperature. The resulting mixture was concentrated under reduced pressure then purified by silica gel chromatography (0-50% EA/PE) to afford tert-butyl 4-([1,2,4]triazolo[4,3-a]pyrimidine-6-carbonyl)-3,3-dimethylpiperazine-1-carboxylate (500 mg, 54.01%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{24}N_6O_3$: 360.19 m/z, found: 361.15 $[M+H]^+$.



[1,2,4]triazolo[4,3-a]pyrimidin-6-yl(2,2-dimethylpiperazin-1-yl)methanone

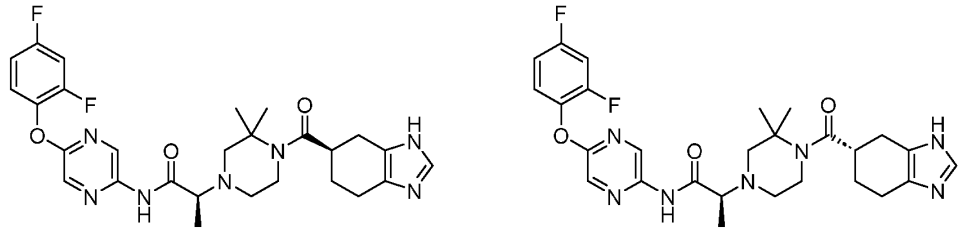
To a solution of tert-butyl 4-([1,2,4]triazolo[4,3-a]pyrimidine-6-carbonyl)-3,3-dimethylpiperazine-1-carboxylate (400 mg, 1.11 mmol, 1 equiv) in EA (5 mL) was added HCl (2N in EA, 5 mL) at rt .The resulting mixture was stirred for 3h at rt. The product was precipitated by the addition of diethyl ether. The precipitated solids were collected by filtration and washed with diethyl ether. The resulting mixture was concentrated under reduced pressure. MS (ESI): mass calcd. for $C_{12}H_{16}N_6O$ 260.14 m/z, found 261.20 $[M+H]^+$.



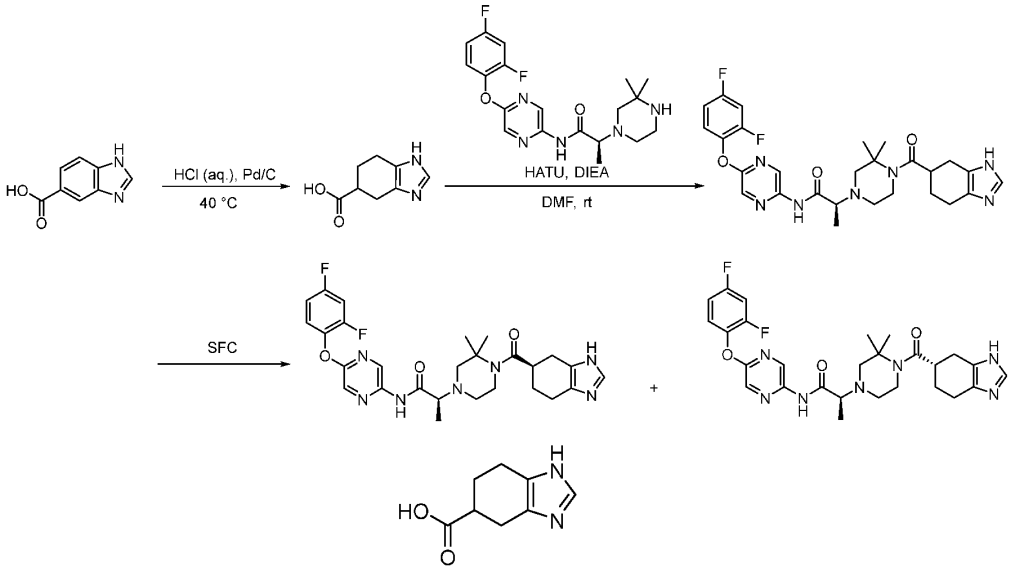
(R)-2-(4-([1,2,4]triazolo[4,3-a]pyrimidine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide and (S)-2-(4-([1,2,4]triazolo[4,3-a]pyrimidine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

To a solution of [1,2,4]triazolo[4,3-a]pyrimidin-6-yl(2,2-dimethylpiperazin-1-yl)methanone in DMF (3 mL) the mixture was added 2-bromo-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (110.07 mg, 0.307 mmol, 1.0 equiv) then added TEA (93.30 mg, 0.921 mmol, 3.0 equiv). The mixture was stirred at room temperature for 16 h. After completion reaction the reaction was cooled to room temperature quenched by water (10 mL) then extracted with EA (3 x 20 mL). The resulting mixture was concentrated under reduced pressure purified by silica gel column (0-10% DCM/MeOH) to afford product, the product was purified by Chiral-HPLC using a CHIRALPAK IF 2*25 cm, 5 μm column (eluent: 50% (v/v) EtOH and Hex: DCM=3: 1 0.5% 2M NH_3-MeOH) to afford (R)-2-(4-([1,2,4]triazolo[4,3-a]pyrimidine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (12.2 mg, 7.24%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{25}F_2N_9O_3$: 537.20, found: 538.25 $[M+H]^+$, ^1H NMR (300 MHz, DMSO-d_6) δ 10.44 (s, 1H), 9.56 (d, J = 2.3 Hz, 1H), 8.88 (dd, J = 15.4, 1.8 Hz, 2H), 8.76 (s, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.39 – 7.56 (m, 2H), 7.11 – 7.24 (m, 1H), 3.51 – 3.61 (m, 1H), 3.40 – 3.50 (m, 2H), 2.60 – 2.80 (m, 2H), 2.38 – 2.47 (m, 1H), 1.96 – 2.07 (m, 1H), 1.50 (d, J = 3.5 Hz, 6H), 1.21 (s, 3H).and (S)-2-(4-([1,2,4]triazolo[4,3-a]pyrimidine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy) pyrazin-2-yl)propanamide (31.4 mg, 18.71%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{25}F_2N_9O_3$: 537.20, found: 538.25 $[M+H]^+$, ^1H NMR (300 MHz, DMSO-d_6) δ 10.44 (s, 1H), 9.56 (d, J = 2.3 Hz, 1H), 8.88 (dd, J = 15.3, 1.9 Hz, 2H), 8.76 (s, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.40 – 7.56 (m, 2H), 7.11 – 7.24 (m, 1H), 3.56 (q, J = 7.0 Hz, 1H), 3.42 – 3.50 (m, 2H), 2.72 – 2.82 (m, 1H), 2.61 – 2.71 (m, 1H), 2.52 – 2.57 (m, 1H), 2.41 – 2.49 (m, 1H), 1.50 (d, J = 3.5 Hz, 6H), 1.22 (d, J = 7.0 Hz, 3H).

Example 239: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-6-carbonyl)piperazin-1-yl)propanamide and Example 240: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-6-carbonyl)piperazin-1-yl)propanamide

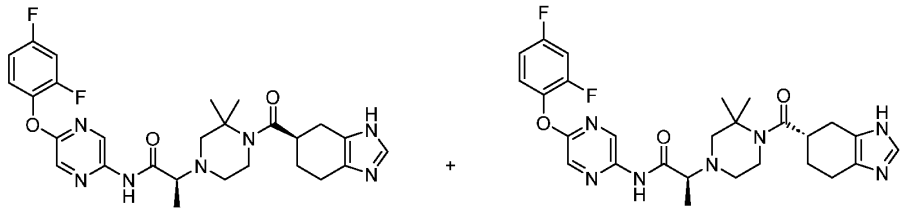


Synthetic Route:



Synthesis of 4,5,6,7-tetrahydro-1H-benzo[d]imidazole-5-carboxylic acid

To a stirring solution 1H-1,3-benzodiazole-5-carboxylic acid (1 g, 6.167 mmol, 1 equiv) in water (20 mL) and 1N HCl (2 mL) was added a solution of 10% Pd/C (0.3 g). The resulting mixture was under H_2 stirred at 40 °C for 16 h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) to 4,5,6,7-tetrahydro-1H-benzo[d]imidazole-5-carboxylic acid (1 g, 97.57%). MS (ESI): mass calcd. for $C_8H_{10}N_2O_2$: 166.18 m/z found: 167.00 [M+H$^+$]

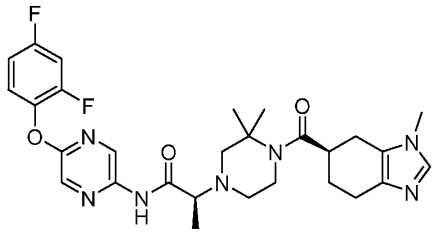


Synthesis of ((S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-6-carbonyl)piperazin-1-yl)propanamide and (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-6-carbonyl)piperazin-1-yl)propanamide

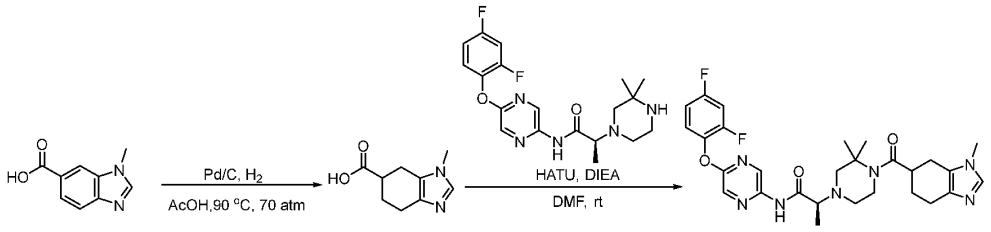
To a stirred solution of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (100 mg, 0.255 mmol, 1 equiv) in dimethylformamide (1 mL) was added 4,5,6,7-tetrahydro-1H-benzo[d]imidazole-5-carboxylic acid (63.68 mg, 0.383 mmol, 1.5 equiv) and HATU (194.28 mg, 0.510 mmol, 2 equiv) and DIEA (132.08 mg, 1.020 mmol, 4 equiv) at room temperature. The reaction mixture was stirred at room temperature for 3 h. The resulting mixture was stirred for additional overnight at room temperature. After completion of reaction, the reaction mixture was quenched by addition of water (5 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and the residue was purified by preparative HPLC using a YMC-Actus Triart C18 ExRS30 x150mm x 5μm (eluent: 35% to 56% (v/v) CH_3CN and H_2O with NH_4HCO_3+0.05%NH_3H_2O) to (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-methyl-1H-benzo[d][1,2,3]triazole-6-carbonyl)piperazin-1-yl)propanamide (20 mg,15%) as a white solid. The product purified by Chiral-HPLC using a CHIRALPAK IF 2*25 cm, 5 μm column (eluent:50% (v/v) MTBE(0.1%DEA) and EtOH) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-6-carbonyl)piperazin-1-yl)propanamide (3.4 mg, 2.44%). MS (ESI): mass calcd. for $C_{27}H_{31}F_2N_7O_3$: 539.25 m/z, found: 540.30 $[M+H]^+$, ^1H NMR (300 MHz, DMSO-d_6) δ 8.82 (s, 1H), 8.44 (s, 1H), 7.37 – 7.53 (m, 3H), 7.16 (t, J = 8.5 Hz, 1H),3.50 – 3.65 (m, 3H) 2.96 (d, J = 15.0 Hz, 1H), 2.61 – 2.75 (m, 2H), 2.50 (s, 4H),2.34 (s, 2H), 1.88 (d, J = 13.0 Hz, 1H), 1.63 (t, J = 11.3 Hz, 1H), 1.38 (s, 6H), 1.19 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.43 (d, J = 5.3 Hz), -124.22 (d, J = 5.1 Hz). And (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-4,5,6,7-tetrahydro-1H-

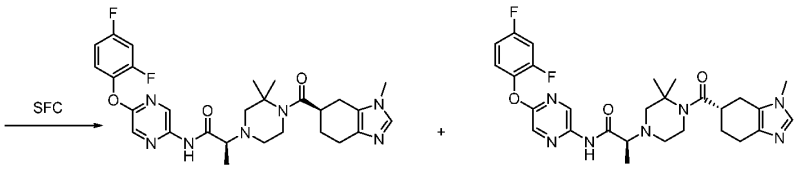
benzo[d]imidazole-6-carbonyl)piperazin-1-yl)propanamide (4.3 mg, 3.08%) ,MS (ESI): mass calcd. for $C_{27}H_{31}F_2N_7O_3$: 539.25 m/z, found: 540.30$[M+H]^+$.^{1}H NMR (300 MHz, DMSO-d_6) δ 8.82 (s, 1H), 8.43 (d, J = 1.5 Hz, 1H), 7.43 – 7.53 (m, 2H),7.37 – 7.43 (m, 1H), 7.16 (td, J = 9.5, 9.0, 2.8 Hz, 1H),3.55 – 3.62 (m, 3H), 2.94 (s, 1H), 2.65 – 2.77 (m, 1H), 2.52 – 2.64 (m, 2H),2.51 (s, 3H), 2.34 (d, J = 2.8 Hz, 2H), 1.88 (d, J = 12.8 Hz, 1H), 1.63 (t, J = 10.6 Hz, 1H), 1.38 (s, 6H), 1.19 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.42 (d, J = 5.2 Hz), -124.22 (d, J = 5.3 Hz).

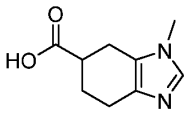
Example 241: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-1-methyl-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-6-carbonyl)piperazin-1-yl)propanamide and Example 242: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-1-methyl-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-6-carbonyl)piperazin-1-yl)propanamide



Synthetic Route:

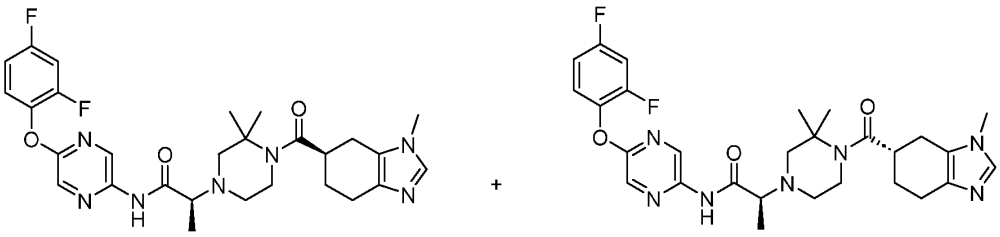






1-methyl-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-6-carboxylic acid

To a stirring solution of3-methyl-1,3-benzodiazole-5-carboxylic acid (300 mg, 1.703 mmol, 1 equiv) in Acetic acid (30 mL) was added a solution of Pd/C (18.12 mg, 0.170 mmol, 0.1 equiv). The mixture was stirred at 90 °C for 15 h under H_2 (70 atm). The reaction mixture was filtered through a pad of celite and concentrated under reduced pressure to afford 1-methyl-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-6-carboxylic acid (300 mg, 97.76%) as a white solid. MS (ESI): mass calcd. for $C_9H_{12}N_2O_2$: 180.207 m/z, found 181.00 $[M+H]^+$.

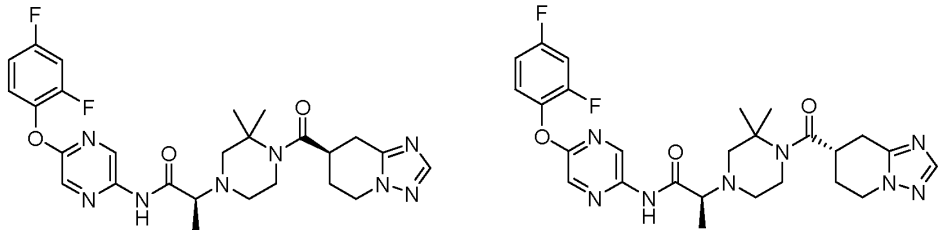


Synthesis of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-1-methyl-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-6-carbonyl)piperazin-1-yl)propanamide and (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-1-methyl-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-6-carbonyl)piperazin-1-yl)propanamide

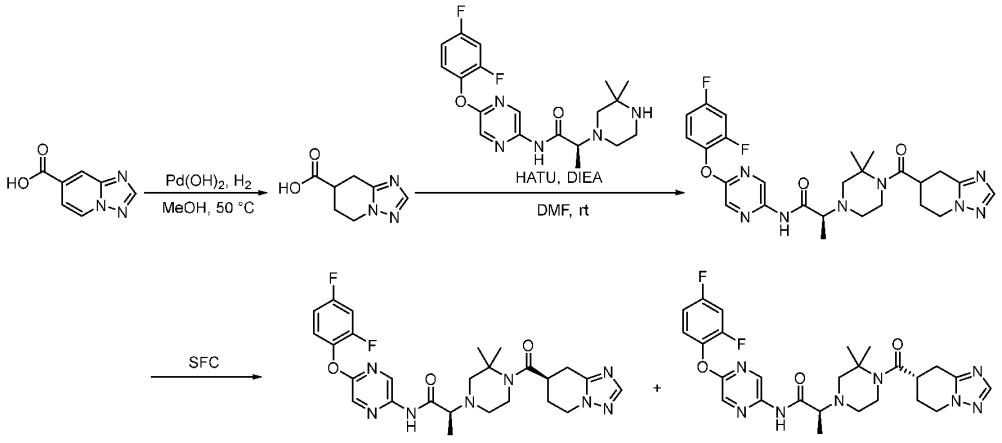
To a solution of 1-methyl-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-6-carboxylic acid (100 mg, 0.555 mmol, 1 equiv) in N,N-dimethylformamide((5 mL) the mixture was added (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (217.21 mg, 0.555 mmol, 1.0 equiv) then added HATU (316.49 mg, 0.833 mmol, 1.5 equiv) and DIEA (215.16 mg, 1.665 mmol, 3.0 equiv). The mixture was stirred at room temperature for 3 h. After completion reaction the reaction was cooled to room temperature quenched by water (30 mL) then extracted with EA (3 x 100 mL). The resulting mixture was concentrated under reduced pressure purified by silica gel column (0-10% MeOH/DCM) to afford product, the product was purified by Chiral-HPLC using a CHIRALPAK IF 2*25 cm, 5 μm column (eluent: 60% (v/v) EtOH and Hex: DCM=3: 1(0.5% 2M NH_3-MeOH) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-1-methyl-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-6-carbonyl)piperazin-1-yl)propanamide (44.6 mg, 14.00%) as a white solid. MS (ESI): mass calcd. for $C_{28}H_{33}F_2N_7O_3$: 553.26, found: 554.30 $[M+H]^+$. ^{1}HNMR (300

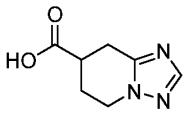
MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.40 – 7.55 (m, 2H), 7.37 (s, 1H), 7.11 – 7.24 (m, 1H), 3.50 – 3.59 (m, 3H), 3.47 (s, 3H), 2.88 – 3.01 (m, 1H), 2.60 – 2.77 (m, 2H), 2.57 (d, J = 7.5 Hz, 2H), 2.42 – 2.47 (m, 2H), 2.36 (s, 2H), 1.82 – 1.94 (m, 1H), 1.53 – 1.69 (m, 1H), 1.39 (d, J = 4.3 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H). And (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-1-methyl-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-6-carbonyl)piperazin-1-yl)propanamide (43.5 mg, 14.00%) as a white solid. MS (ESI): mass calcd. for $C_{28}H_{33}F_2N_7O_3$: 553.26, found: 554.35 $[M+H]^+$. ^{1}HNMR (300 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.40 – 7.55 (m, 2H), 7.37 (s, 1H), 7.10-7.24 (m, 1H), 3.49 – 3.59 (m, 3H), 3.47 (s, 3H), 2.88-3.02 (m, 1H), 2.68 – 2.78 (m, 1H), 2.53 – 2.66 (m, 3H), 2.43 – 2.48 (m, 2H), 2.36 (s, 2H), 1.82 – 1.93 (m, 1H), 1.53 – 1.67 (m, 1H), 1.40 (s, 6H), 1.20 (d, J = 6.9 Hz, 3H).

Example 243: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)piperazin-1-yl)propanamide and Example 244: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)piperazin-1-yl)propanamide



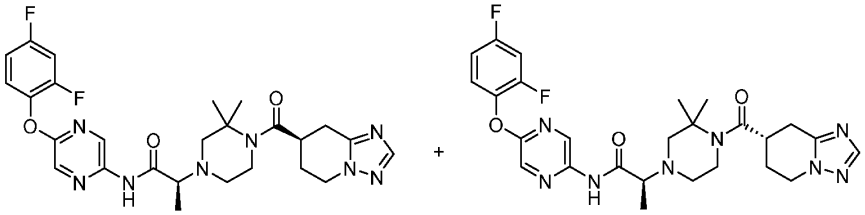
Synthetic Route:





5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylic acid

To a solution of [1,2,4]triazolo[1,5-a]pyridine-7-carboxylic acid (200 mg, 1.226 mmol, 1 equiv) in MeOH (15 mL) was added $Pd(OH)_2$ (172.16 mg, 1.226 mmol, 1 equiv) in a pressure tank. The mixture was hydrogenated at 50 °C under 50 atm of hydrogen pressure for 24 h, filtered through a Celite pad and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, water (0.01%FA) in ACN, 5% to 100% gradient in 30 min to afford 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylic acid (100 mg, 48.79%) as a yellow oil. MS (ESI): mass calcd. for $C_7H_9N_3O_2$: 167.07m/z, found:168.05 $[M+H]^+$.

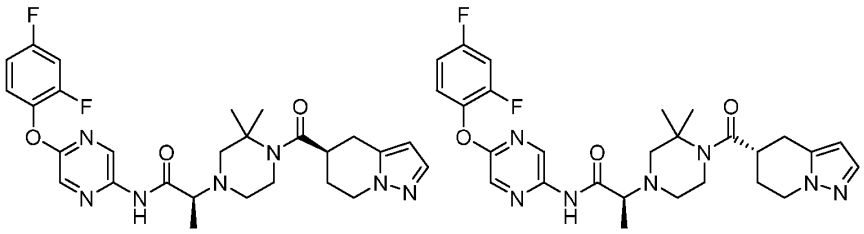


Synthesis of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)piperazin-1-yl)propenamide and (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)piperazin-1-yl)propanamide

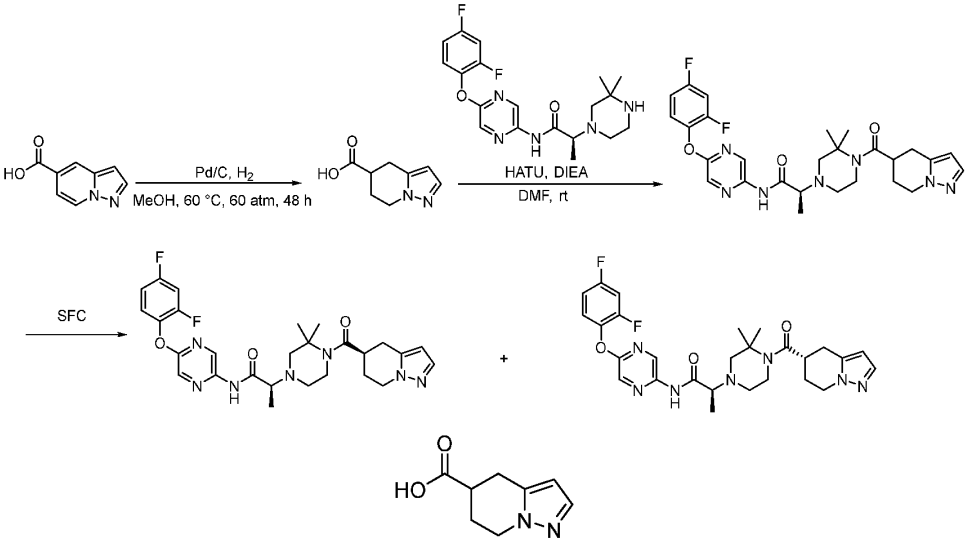
To a solution of 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylic acid (80 mg, 0.479 mmol, 1 equiv) in DMF (3 mL). (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (100 mg, 0.255 mmol, 0.53 equiv), HATU (272.95 mg, 0.718 mmol, 1.5 equiv) and DIEA (247.41 mg, 1.916 mmol, 4 equiv) added at rt. The resulting mixture was stirred for 2h at rt. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-15%DCM/MeOH) and Prep-HPLC using a Xselect CSH C_{18} OBD 30*150 mm, 5μm Column (eluent: 19% to 49% ACN and Water(0.1% FA) to afford (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)piperazin-1-yl)propanamide (70 mg, 75%) as a white solid. The product was separated by Chiral-HPLC using a CHIRALPAK

ID, 2*25 cm, 5 μm Column (eluent:40% (v/v) MTBE(0.5% 2M NH_3-MeOH) and MEOH: DCM=1: 1) to offer (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)piperazin-1-yl)propanamide (26.9 mg, 10.26%) as a white solid. MS (ESI): mass calcd. For $C_{26}H_{30}F_2N_8O_3$: 540.24m/z, found: 541.30$[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.84 (d, J = 1.5 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.83 (s, 1H), 7.41 – 7.55 (m, 2H), 7.13 – 7.23 (m, 1H), 4.00 – 4.16 (m, 2H), 3.48 – 3.63 (m, 3H), 2.77 – 2.93 (m, 2H), 2.65 – 2.77 (m, 2H), 2.60 – 2.65 (m, 1H), 2.36 (s, 2H), 2.06 – 2.17 (m, 1H), 1.91 – 2.05 (m, 1H), 1.38 (d, J = 4.2 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -113.4200, -124.2058. and (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)piperazin-1-yl)propanamide (26.3 mg, 10.01%) as a white solid, MS (ESI): mass calcd. For $C_{26}H_{30}F_2N_8O_3$: 540.24 m/z, found: 541.30 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.84 (d, J = 1.5 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.83 (s, 1H), 7.41 – 7.55 (m, 2H), 7.13 – 7.23 (m, 1H), 4.00 – 4.16 (m, 2H), 3.48 – 3.63 (m, 3H), 2.77 – 2.93 (m, 2H), 2.65 – 2.77 (m, 2H), 2.60 – 2.65 (m, 1H), 2.36 (s, 2H), 2.06 – 2.17 (m, 1H), 1.91 – 2.05 (m, 1H), 1.38 (d, J = 4.2 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -113.4200, -124.2058.

Example 245: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)piperazin-1-yl)propanamide and Example 246: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)piperazin-1-yl)propanamide

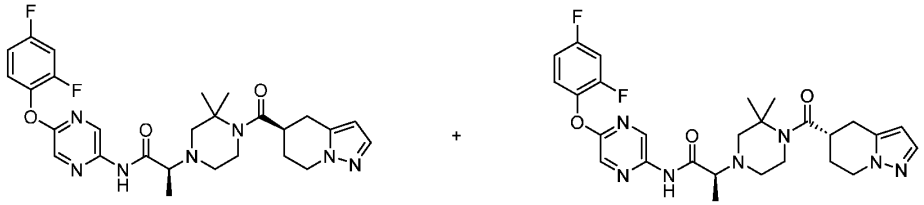


Synthetic Route:



4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carboxylic acid

To a stirring solution of pyrazolo[1,5-a]pyridine-5-carboxylic acid (300 mg, 1.850 mmol, 1 equiv) in methanol (20 mL) was added a solution of 10% Pd/C (50 mg). The mixture was stirred at 60 °C for 14 h under hydrogen (60 atm). The mixture was concentrated to dryness under reduced pressure to provide the crude product, which was purified by C18 (0-30% H_2O/ACN) to afford 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carboxylic acid (200 mg, 65.05%) as a white solid. MS (ESI): mass calcd. for $C_8H_{10}N_2O_2$: 166.18 m/z, found: 167.00 $[M+H]^+$.

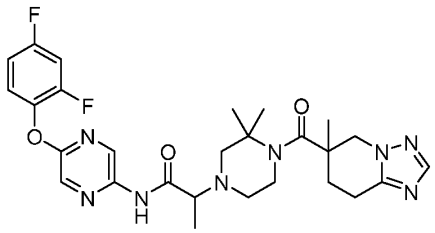


(*S*)-*N*-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((*R*)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)piperazin-1-yl)propanamide and (*S*)-*N*-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((*S*)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)piperazin-1-yl)propanamide

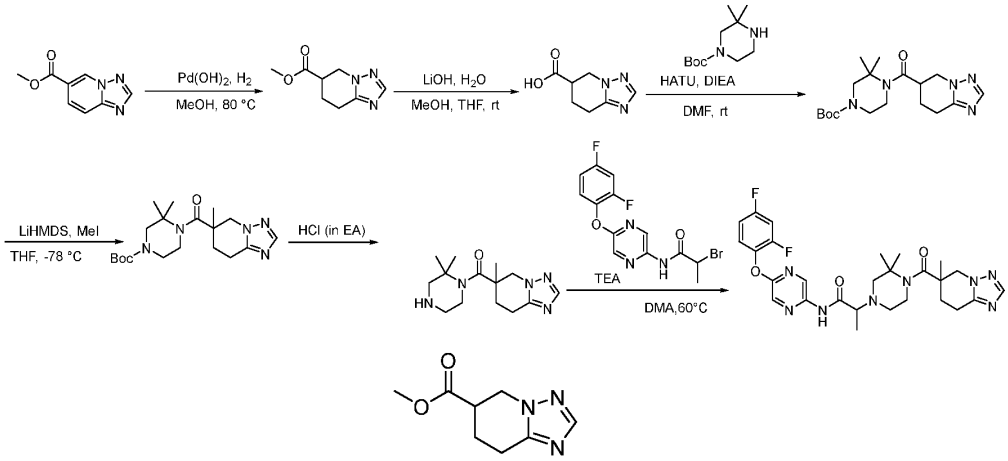
To a solution of 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carboxylic acid (80 mg, 0.481 mmol, 1 equiv) in dimethylformamide (5 mL) was added (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (226.12 mg, 0.577 mmol, 1.2 equiv) and HATU (366.09 mg, 0.962 mmol, 2 equiv) and DIEA (124.44

mg, 0.962 mmol, 2 equiv). The mixture was stirred at room temperature for 2 h. The mixture was concentrated to dryness under reduced pressure to provide the crude product, which was purified by Prep-HPLC using for a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 40% to 70% (v/v) Water(10mmol/L NH_4HCO_3+0.05%NH_3H_2O) and ACN) to afford (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)piperazin-1-yl)propanamide was purified by chiral-HPLC using a CHIRALPAK IK 25 cm x 2 cm x 5 μm column (eluent: 50% (v/v) Hex: DCM=3: 1(0.5% 2M NH3-MeOH) and EtOH) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)piperazin-1-yl)propanamide (23.7 mg, first peak) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{31}F_2N_7O_3$: 539.25 m/z, found: 540.35 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.39 – 7.56 (m, 2H), 7.33 (d, J = 1.8 Hz, 1H), 7.11 – 7.24 (m, 1H), 5.98 (d, J = 1.8 Hz, 1H), 3.95 – 4.17 (m, 2H), 3.47 – 3.58 (m, 3H), 3.16 (s, 1H), 2.86 (dd, J = 16.6, 4.8 Hz, 1H), 2.66 – 2.80 (m, 2H), 2.56 – 2.66 (m, 1H), 2.28 – 2.43 (m, 2H), 2.06 (d, J = 13.3 Hz, 1H), 1.91 (s, 1H), 1.38 (d, J = 3.1 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -113.40 (d, J = 5.4 Hz), -124.20 (d, J = 5.2 Hz). And (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)piperazin-1-yl)propanamide (20.9 mg, second peak) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{31}F_2N_7O_3$: 539.25 m/z, found: 540.30 $[M+H]^+$.^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.83 (d, J = 1.8 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.39 – 7.55 (m, 2H), 7.33 (d, J = 1.7 Hz, 1H), 7.17 (t, J = 8.3 Hz, 1H), 5.98 (s, 1H), 3.99 – 4.18 (m, 2H), 2.75 – 2.87 (m, 1H), 2.58 – 2.74 (m, 2H), 2.35 (s, 2H), 2.06 (d, J = 13.0 Hz, 1H), 1.91 (s, 1H), 1.38 (s, 6H), 1.20 (d, J = 6.9 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -113.39 (d, J = 5.1 Hz), -124.20 (d, J = 5.2 Hz), -218.49.

Example 247: N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)piperazin-1-yl)propanamide

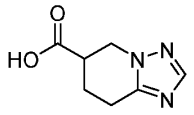


Synthetic Route:



Methyl 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate

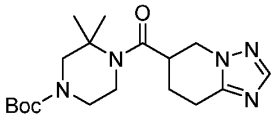
To a solution of methyl [1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (2 g, 11.289 mmol, 1 equiv) in MeOH (100 mL) was added $Pd(OH)_2$ (2.59 g, 11.289 mmol, 1 equiv) in a pressure tank. The mixture was hydrogenated at 80 °C under 50 psi of hydrogen pressure for 24 h, filtered through a Celite pad and concentrated under reduced pressure to afford methyl 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (1.5 g, 73.33%) as a yellow oil. MS (ESI): mass calcd. for$C_8H_{11}N_3O_2$:181.09 m/z, found:182.15 $[M+H]^+$.



Synthesis of 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid

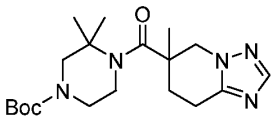
To a solution of methyl 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (1.8 g, 9.934 mmol, 1 equiv) in THF (20 mL), MeOH (15 mL) and water (5 mL). LiOH (0.48 g, 1.561 mmol, 2 equiv) added at rt. The resulting mixture was stirred for 2 h at rt. The resulting mixture was concentrated under vacuum. The residue was acidified to pH 2~3 with 3N HCl. The precipitated solids were collected by filtration and washed with H_2O (5 mL) to afford

5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid (1 g, 60.2%) as a yellow oil. MS (ESI): mass calcd. for $C_7H_9N_3O_2$ 167.07 m/z, found:168.05 $[M+H]^+$.



Synthesis of tert-butyl 3,3-dimethyl-4-(5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)piperazine-1-carboxylate

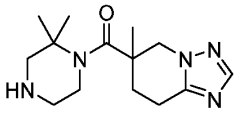
To a solution of 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid (2 g, 11.964 mmol, 1 equiv) in DMF (20 mL) tert-butyl 3,3-dimethylpiperazine-1-carboxylate (2.56 g, 11.964 mmol, 1 equiv), HATU (4.33 g, 17.946 mmol, 1.5 equiv) and DIEA (4.64 g, 35.892 mmol, 3 equiv) were added at rt. The mixture was allowed to warm to rt and stirred for 2 h. The reaction mixture was quenched by water (50 mL). The resulting mixture was extracted with EA (3*100 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20% DCM/MeOH) to afford tert-butyl 3,3-dimethyl-4-(5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)piperazine-1-carboxylate (700 mg, 16.10%) as a yellow oil. MS (ESI): mass calcd. for $C_{18}H_{29}N_5O_3$: 363.23 m/z, found: 364.25 $[M+H]^+$.



Synthesis of tert-butyl 3,3-dimethyl-4-(6-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)piperazine-1-carboxylate

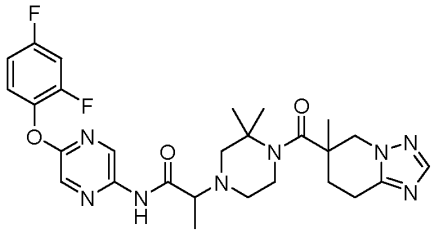
To a solution of tert-butyl 3,3-dimethyl-4-(5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)piperazine-1-carboxylate (700 mg, 1.926 mmol, 1 equiv) in THF (5 mL). LiHMDS (2N in THF, 1.6 mL, 3.274 mmol, 1.7 equiv) added at -78 °C under N_2. The resulting mixture was stirred for 1h at -78 °C. Methyl iodide (683.41 mg, 4.815 mmol, 2.5 equiv) was added at -78 °C. The resulting mixture was stirred for 2 h at -78 °C. The reaction was quenched with NH_4Cl (25 mL) at rt. The resulting mixture was extracted with EA (3*50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20%DCM/MeOH) to afford tert-butyl 3,3-dimethyl-4-(6-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)piperazine-1-carboxylate (160

mg, 22.01%) as a yellow oil, MS (ESI): mass calcd. for $C_{19}H_{31}N_5O_5$: 377.24 m/z, found: 378.15 $[M+H]^+$.



Synthesis of (2,2-dimethylpiperazin-1-yl)(6-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridin-6-yl)methanone

To a solution of tert-butyl 3,3-dimethyl-4-(6-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)piperazine-1-carboxylate (160 mg, 0.424 mmol, 1 equiv) in EA (1 mL). HCl in EA (2 mL) was added at 0 degrees. The mixture was allowed to warm to RT and stirred for 2 h. The resulting mixture was concentrated under vacuum. The precipitated solids were collected by filtration and washed with diethyl ether (20 mL) to afford (2,2-dimethylpiperazin-1-yl)(6-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridin-6-yl)methanone (100 mg, 85.06%) as a yellow oil, MS (ESI): mass calcd. for $C_{14}H_{23}N_5O$: 277.19 m/z, found: 278.00 $[M+H]^+$.

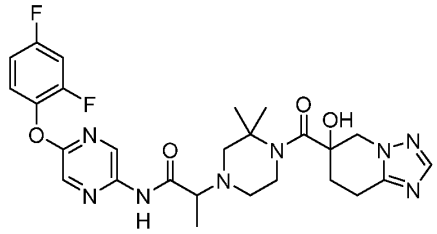


Synthesis of tert-butyl 3,3-dimethyl-4-(6-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)piperazine-1-carboxylate

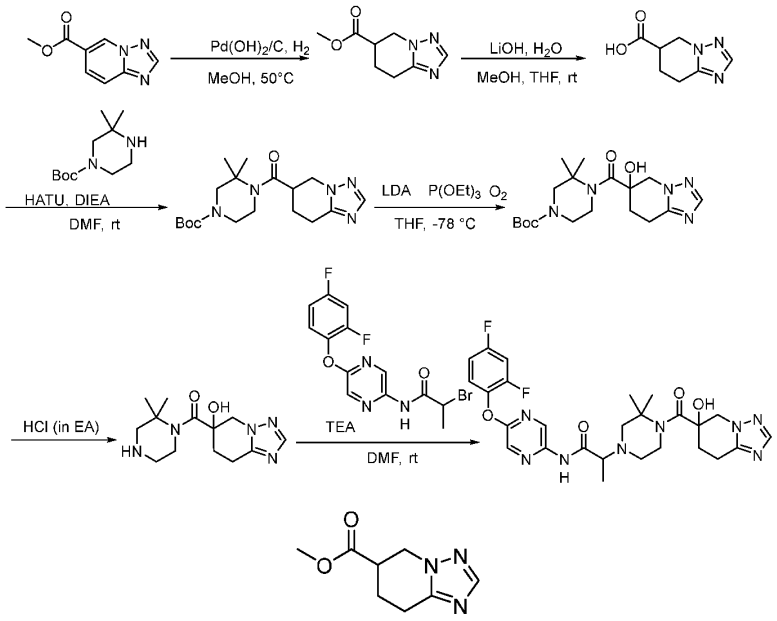
To a solution of (2,2-dimethylpiperazin-1-yl)(6-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridin-6-yl)methanone (200 mg, 0.721 mmol, 1 equiv) in DMA (5 mL).2-bromo-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (258.24 mg, 0.721 mmol, 1 equiv) and TEA (218.90 mg, 2.163 mmol, 3 equiv) added at rt. The resulting mixture was stirred for 12h at 60 degrees. After cooled to room temperature, the resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-15%DCM/MeOH) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 20% to 50% ACN and Water (0.1% FA) to afford N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)piperazin-1-

yl)propanamide (9.8 mg, 2.44%) as a white solid, MS (ESI): mass calcd. for$C_{27}H_{32}F_2N_8O_3$: 554.26 m/z, found: 555.30 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.39 (d, J = 2.9 Hz, 2H), 8.83 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.78 (d, J = 0.9 Hz, 1H), 7.40 – 7.56 (m, 2H), 7.11 – 7.24 (m, 1H), 4.54 (d, J = 12.6 Hz, 1H), 3.86 – 3.75 (m, 1H), 3.44 – 3.69 (m, 3H), 2.55 – 2.94 (m, 4H), 2.34 – 2.44 (m, 1H), 2.19 – 2.34 (m, 2H), 1.90 – 2.05 (m, 1H), 1.32 (d, J = 6.6, 3.0 Hz, 3H), 1.11 – 1.27 (m, 9H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.437, -124.231.

Example 248: N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(6-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

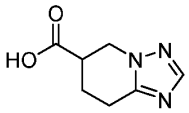


Synthetic Route:



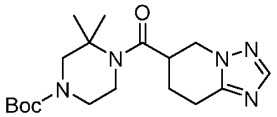
Methyl 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate

To a solution of methyl [1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (2 g, 11.289 mmol, 1 equiv) in 50 mL MeOH was added $Pd(OH)_2/C$ (10%, 2 g) in a pressure tank. The mixture was hydrogenated at 50 °C under 20 atm of hydrogen pressure for 12 h, filtered through a Celite pad and concentrated under reduced pressure. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford methyl 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (1.8 g, 88.00%) as a white solid. MS (ESI): mass calcd. for $C_8H_{11}N_3O_2$: 181.19 m/z, found: 182.20 $[M+H]^+$.



5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid

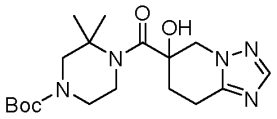
To a solution of methyl methyl 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (150 mg, 0.828 mmol, 1 equiv) in methanol (1 mL), tetrahydrofuran (2 mL) and water (1 mL) was added LiOH (29.74 mg, 1.242 mmol, 1.5 equiv) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The mixture was acidified pH = 5 with HCl (1N). The aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-30% DCM/MeOH) to afford 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid (110 mg, 79.49%) as a white solid. MS (ESI): mass calcd. for $C_7H_9N_3O_2$: 167.20 m/z, found 168.15 $[M+H]^+$.



tert-butyl 3,3-dimethyl-4-(5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)piperazine-1-carboxylate

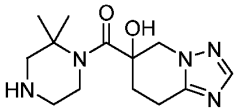
To a stirring solution 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid (110 mg, 0.658 mmol, 1 equiv) in dimethylformamide (5 mL) the mixture was added tert-butyl 3,3-dimethylpiperazine-1-carboxylate (169.22 mg, 0.790 mmol, 1.2 equiv), HATU (375.30 mg, 0.987 mmol, 1.5 equiv) and N,N-diisopropylethylamine (340.19 mg, 2.632 mmol, 4 equiv) at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and

concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford tert-butyl3,3-dimethyl-4-(5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)piperazine-1-carboxylate (180 mg, 75.26%) as a white solid. MS (ESI): mass calcd. for $C_{18}H_{29}N_5O_3$: 363.45 m/z, found: 364.25 $[M+H]^+$.



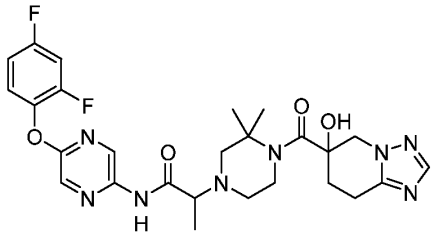
tert-butyl 4-(6-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazine-1-carboxylate

To a solution of tert-butyl 3,3-dimethyl-4-{5H,6H,7H,8H-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl}piperazine-1-carboxylate (500 mg, 1.376 mmol, 1 equiv) in tetrahydrofuran (10 mL) the mixture was cooled to -78 °C then added LDA (1N in THF, 1.38 mL, 2.752 mmol, 2 equiv). The mixture was stirred at -78 °C for 0.5 h under O_2. The was passed through this solution for 5 min, the mixture was added triethyl phosphite (45.72 mg, 0.276 mmol, 2 equiv). The reaction was stirred at -78°C for 10 min. After completion reaction the reaction was quenched with NH_4Cl solution (5 mL) then extracted with EA (3x 50 mL) .The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford tert-butyl 4-(6-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazine-1-carboxylate (170 mg, 32.57%) as a yellow solid. MS (ESI): mass calcd. for $C_{18}H_{29}N_5O_4$: 379.22 m/z, found: 380.10 $[M+H]^+$.



(2,2-dimethylpiperazin-1-yl)(6-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridin-6-yl)methanone

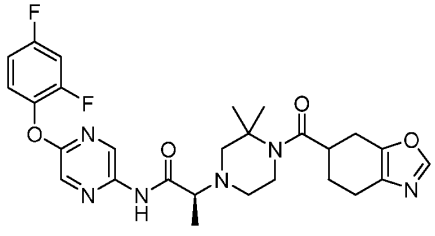
To a solution of tert-butyl 4-{6-hydroxy-5,7,8-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl}-3,3-dimethylpiperazine-1-carboxylate (150 mg, 0.395 mmol, 1 equiv) in EA (2 mL) and 4N HCl in EA (2 mL). The mixture was stirred at room temperature for 1 h. After completion reaction the reaction was diluted with diethyl ether (50 mL). The mixture was filtered and washed with diethyl ether (10 mL) to afford (2,2-dimethylpiperazin-1-yl)(6-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridin-6-yl)methanone (82 mg, 74.26%) as a yellow solid. MS (ESI): mass calcd. for $C_{13}H_{21}N_5O_2$: 279.17m/z, found: 280.15 $[M+H]^+$.



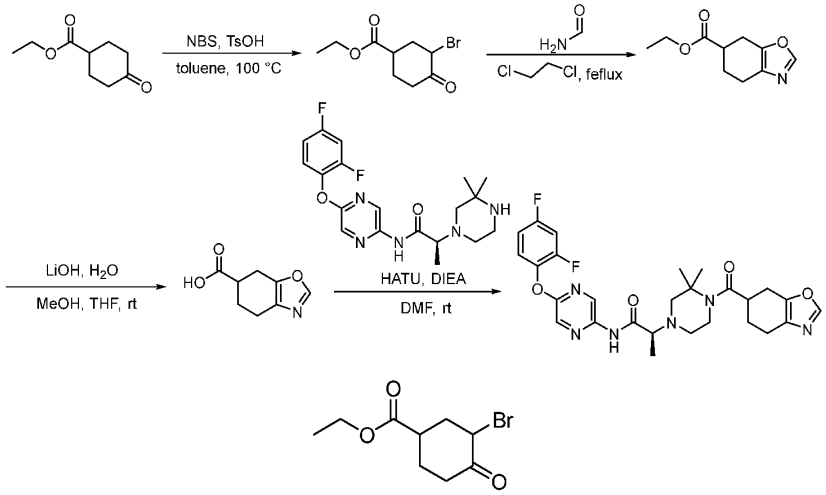
N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(6-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

To a solution of 6-(2,2-dimethylpiperazine-1-carbonyl)-5,7,8-[1,2,4]triazolo[1,5-a]pyridin-6-ol (30 mg, 0.107 mmol, 1 equiv) in dimethylformamide (1 mL) the mixture was added 2-bromo-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (38.46 mg, 0.107 mmol, 1.0 equiv) then added TEA (32.60 mg, 0.321 mmol, 3.0 equiv). The mixture was stirred at room temperature for 5 h. After completion reaction the reaction was quenched with water (30 mL) then extracted with EA (3x10 mL). The resulting mixture was concentrated under reduced pressure purified by silica gel column (0-10% DCM/MeOH) to afford product, the product was purified by Prep-HPLC YMC-Actus Triart C18 ExRS Column, 19*250 mm*5 μm; (eluent: 27% to 40% (v/v)Water(10mmol/L NH_4HCO_3) to ACN to afford N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(6-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (14.7 mg, 24.37%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{30}F_2N_8O_4$: 556.24, found: 557.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.91 (s, 1H), 7.39 – 7.56 (m, 2H), 7.11 – 7.24 (m, 1H), 5.79 (dd, J = 6.7, 1.5 Hz, 1H), 4.76 – 4.90 (m, 1H), 4.00 – 4.22 (m, 2H), 3.44 – 3.63 (m, 4H), 2.58 – 2.76 (m, 2H), 2.33 – 2.45 (m, 2H), 2.18 – 2.33 (m, 1H), 1.77 (q, J = 12.0 Hz, 1H), 1.35 – 1.51 (m, 6H), 1.16 – 1.27 (m, 3H).

Example 249: (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(4,5,6,7-tetrahydrobenzo[d]oxazole-6-carbonyl)piperazin-1-yl)propanamide

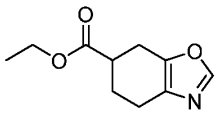


Synthetic Route:



ethyl 3-bromo-4-oxocyclohexane-1-carboxylate

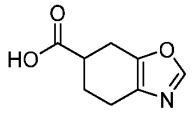
To a stirring solution ethyl 4-oxocyclohexane-1-carboxylate (1.5 g, 8.813 mmol, 1 equiv) in toluene (20 mL) was added a solution of para-toluene sulfonate (0.15 g, 0.881 mmol, 0.1 equiv) and NBS (1.73 g, 9.694 mmol, 1.1 equiv) .The resulting mixture was stirred at 100°C for 6h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% PE/EA) to afford ethyl 3-bromo-4-oxocyclohexane-1-carboxylate (1.4 g, 63.77%) MS (ESI): mass calcd. for $C_9H_{13}BrO_3$: 248.10 m/zfound: 249.10[M+H^+]



ethyl 4,5,6,7-tetrahydrobenzo[d]oxazole-6-carboxylate

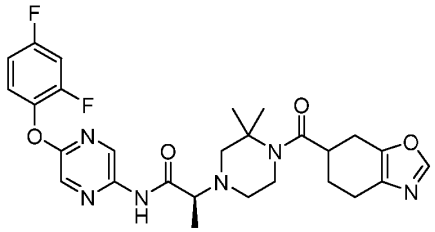
To a stirring solution ethyl 3-bromo-4-oxocyclohexane-1-carboxylate (200 mg x7, 0.803 mmol, 1 equiv) in ethylene dichloride (2 mL) was added a solution of formamide (180.81 mg, 4.015 mmol, 5 equiv), The resulting mixture was stirred at room temperature for 6h. The reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-

100% PE/EA) to afford ethyl 4,5,6,7-tetrahydrobenzo[d]oxazole-6-carboxylate (10 mg x7, 6.38%) MS (ESI): mass calcd. for $C_8H_9NO_3$: 195.05 m/zfound: 196.10[M^+H^+].



4,5,6,7-tetrahydrobenzo[d]oxazole-6-carboxylic acid

To a stirring solution ethyl 4,5,6,7-tetrahydrobenzo[d]oxazole-6-carboxylate (40 mg, 0.205 mmol, 1 equiv) in methanol (0.2 mL) and water (0.2 mL) and tetrahydrofuran (0.4 mL) was added a solution of lithiumol (4.91 mg, 0.205 mmol, 1 equiv).The resulting mixture was stirred at room temperature for 6h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% ACN/H_2O) to afford 4,5,6,7-tetrahydrobenzo[d]oxazole-6-carboxylic acid (20 mg, 58.39%) MS (ESI): mass calcd. for $C_8H_9NO_3$: 167.16 m/zfound: 168.10[M^+H^+]

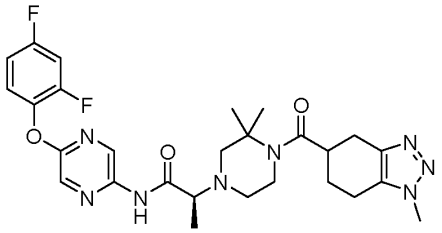


(2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(4,5,6,7-tetrahydrobenzo[d]oxazole-6-carbonyl)piperazin-1-yl)propanamide

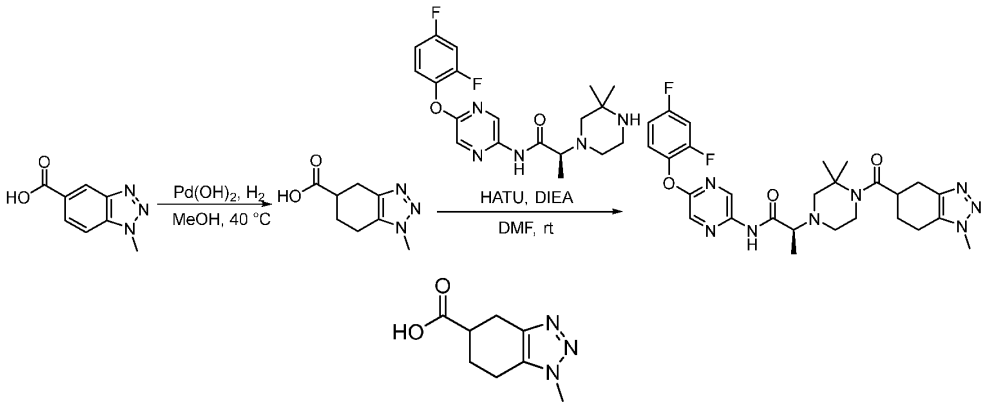
To a stirred solution of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (60 mg, 0.153 mmol, 1 equiv) in dimethylformamide (1 mL) was added [(dimethylamino)({3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy})methylidene]dimethylazanium (87.43 mg, 0.229 mmol, 1.5 equiv) and 4,5,6,7-tetrahydrobenzo[d]oxazole-6-carboxylic acid (38.44 mg, 0.229 mmol, 1.5 equiv) and DIEA (59.44 mg, 0.459 mmol, 3 equiv) at room temperature. The reaction mixture was stirred at room temperature for 3 h. The resulting mixture was stirred for additional overnight at room temperature. After completion of reaction, the reaction mixture was quenched by addition of water (5 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20%

DCM/MeOH) and the residue was purified by preparative HPLC using a XBridge Prep Shield RO18 OBD Column, 30x150mm x 5μm (eluent: 24% to 42% (v/v) CH_3CN and H_2O with NH_4HCO_3+0.05%NH_3H_2O) to afford (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(4,5,6,7-tetrahydrobenzo[d]oxazole-6-carbonyl)piperazin-1-yl)propanamide (3.4 mg, 4.05%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{30}F_2N_6O_4$: 540.23m/z, found: 541.30$[M^+H]^+$ ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.42 (d, J = 5.4 Hz), -124.22 (d, J = 5.2 Hz). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.38 (s, 1H), 8.82 (d, J = 1.4 Hz, 1H), 8.43 (d, J = 1.4 Hz, 1H), 8.12 (s, 1H), 7.46 (qd, J = 8.9, 8.0, 4.3 Hz, 2H), 7.15 (t, J = 8.3 Hz, 1H), 3.51 (s, 4H), 3.08 (s, 1H), 2.56 – 2.77 (m, 5H), 2.33 (s, 2H), 1.89 (d, J = 13.5 Hz, 1H), 1.64 (s, 1H), 1.36 (d, J = 2.7 Hz, 6H), 1.18 (d, J = 6.8 Hz, 3H).

Example 250: (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-methyl-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carbonyl)piperazin-1-yl)propanamide



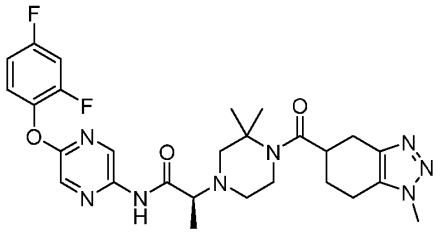
Synthetic Route:



1-methyl-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carboxylic acid

To a solution of 1-methyl-1,2,3-benzotriazole-5-carboxylic acid (200 mg, 1.129 mmol, 1 equiv) in 100 mL MeOH was added 10% $Pd(OH)_2$ (0.2 g) in a pressure tank. The mixture was

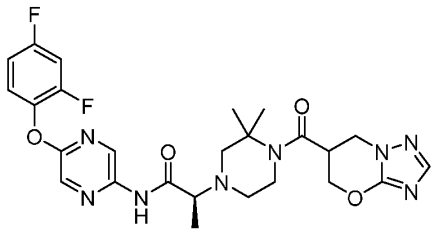
hydrogenated at 40 °C under 20 atm of hydrogen pressure for 24 h, filtered through a Celite pad and concentrated under reduced pressure to afford 1-methyl-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carboxylic acid (0.2 g, crude) as a white solid. MS (ESI): mass calcd. for $C_8H_{11}N_3O_2$: 181.15, found:182.25 $[M+H]^+$.



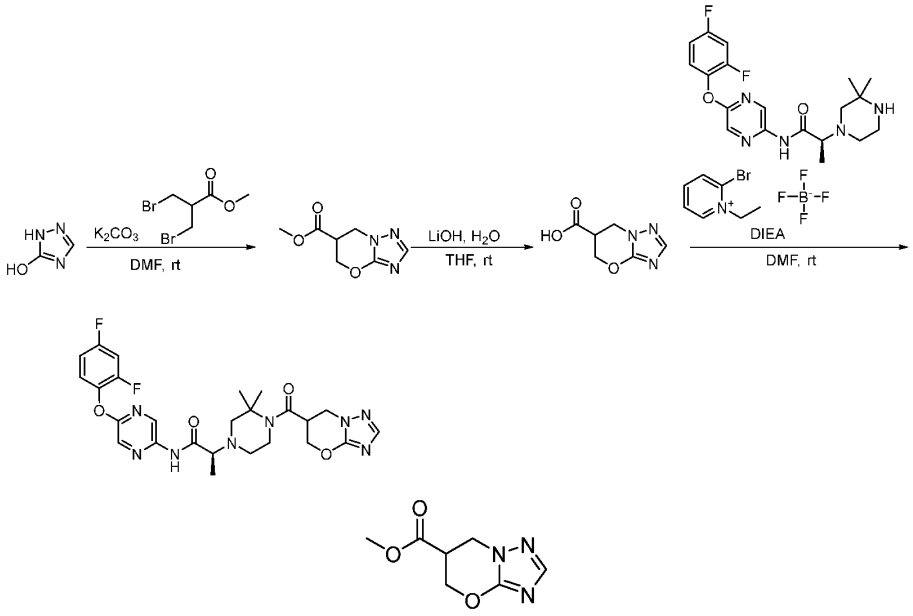
(2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-methyl-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carbonyl)piperazin-1-yl)propanamide

To a stirring solution (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (100 mg, 0.255 mmol, 1 equiv) in dimethylformamide (10 mL) the mixture was added 1-methyl-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carboxylic acid (46.29 mg, 0.255 mmol, 1 equiv) , HATU (145.71 mg, 0.383 mmol, 1.5 equiv) and N,N-diisopropylethylamine (132.08 mg, 1.020 mmol, 4 equiv) at rt. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% EA/PE) and Prep-HPLC using a XBridge Prep Phenyl Hexy OBD C18 19*250 mm, 5μm Column (eluent: 40% to 70% (v/v) CH_3CN and Water (10mmol/L NH_4HCO_3)) to afford (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-methyl-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carbonyl)piperazin-1-yl)propanamide (38.4 mg, 24.70%) as a white solid. MS (ESI): mass calcd. for $C_{28}H_{34}F_2N_8O_5$: 554.26, found: 555.25 $[M+H]^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 8.47 (s, 2H), 7.71 (d, J = 7.3 Hz, 1H), 4.19 (q, J = 6.9 Hz, 1H), 3.90 – 4.09 (m, 1H), 3.39 – 3.70 (m, 3H), 3.25 (d, J = 12.6 Hz, 1H), 1.83 – 2.07 (m, 3H),1.45 – 1.87 (m, 11H), 1.20 – 1.44 (m, 7H).^{19}F NMR (376 MHz, DMSO-d_6) δ -113.45 (d, J = 5.3 Hz), -124.24 (d, J = 5.4 Hz).

Example 251: (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(6,7-dihydro-5H-[1,2,4]triazolo[5,1-b][1,3]oxazine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

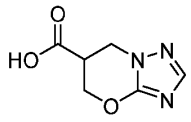


Synthetic Route:



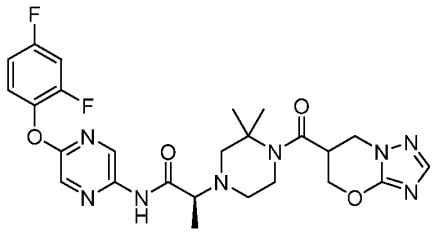
methyl 6,7-dihydro-5H-[1,2,4]triazolo[5,1-b][1,3]oxazine-6-carboxylate

To a solution of 2H-1,2,4-triazol-3-ol (500 mg, 5.878 mmol, 1 equiv) in DMF (10 mL) the mixture was added methyl 3-bromo-2-(bromomethyl)propanoate (1527.78 mg, 5.878 mmol, 1 equiv) and K_2CO_3 (2437.02 mg, 17.634 mmol, 3 equiv). The mixture was stirred at room temperature for 2 h. After completion reaction the reaction was filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford methyl methyl 6,7-dihydro-5H-[1,2,4]triazolo[5,1-b][1,3]oxazine-6-carboxylate (512 mg, 47.56%) as a white solid. MS (ESI): mass calcd. for $C_7H_9N_3O_3$: 183.06 m/z, found: 184.10 $[M+H]^+$.



6,7-dihydro-5H-[1,2,4]triazolo[5,1-b][1,3]oxazine-6-carboxylic acid

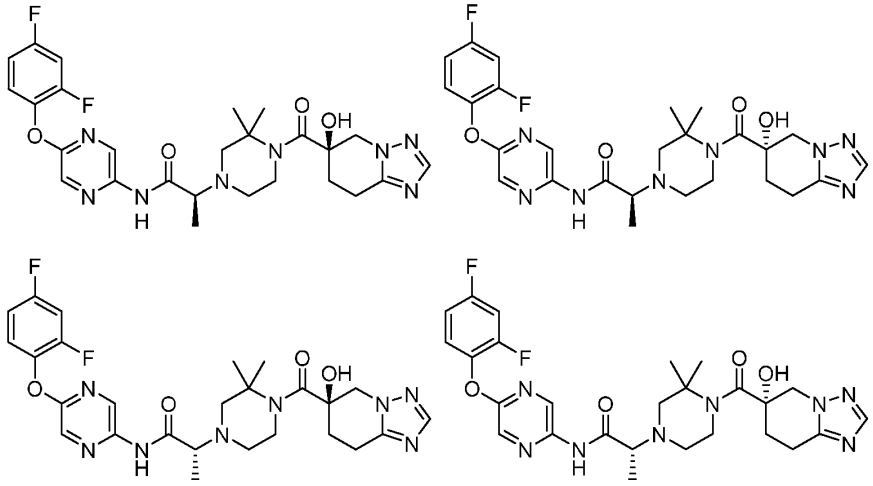
To a solution of methyl methyl 6,7-dihydro-5H-[1,2,4]triazolo[5,1-b][1,3]oxazine-6-carboxylate (400 mg, 2.184 mmol, 1 equiv) in THF (10 mL) and H_2O (5 mL) the mixture was added LiOH (78.45 mg, 3.276 mmol, 1.5 equiv). The mixture was stirred at room temperature for 2 h. After completion of reaction the mixture was precipitated by acidified neutralized to (pH =3) with (4N HCl). The precipitated solids were collected by filtration to afford 6,7-dihydro-5H-[1,2,4]triazolo[5,1-b][1,3]oxazine-6-carboxylic acid (265 mg, 71.74%) as a yellow solid. MS (ESI): mass calcd. for $C_6H_7N_3O_3$: 169.05 m/z, found: 170.10 $[M+H]^+$.



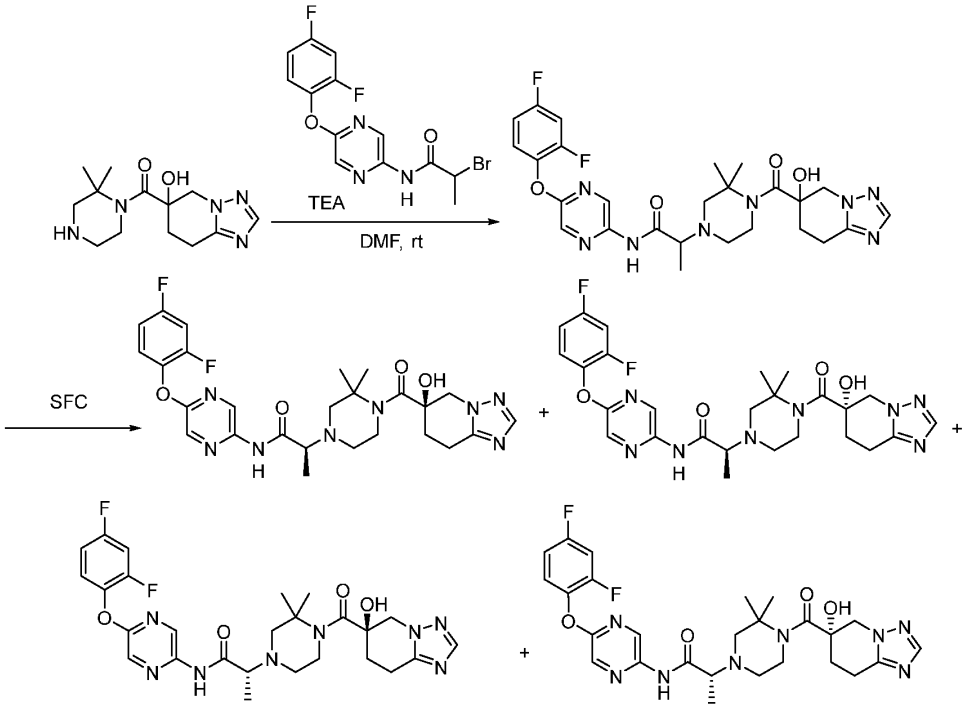
Synthesis of (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(6,7-dihydro-5H-[1,2,4]triazolo[5,1-b][1,3]oxazine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

To a solution of 6,7-dihydro-5H-[1,2,4]triazolo[5,1-b][1,3]oxazine-6-carboxylic acid (30 mg, 0.177 mmol, 1 equiv) in N,N-dimethylformamide (2 mL) the mixture was added (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (69.43 mg, 0.177 mmol, 1.0 equiv) then added 2-bromo-1-ethylpyridin-1-ium tetrafluoroborate (97.15 mg, 0.354 mmol, 2.0 equiv) and DIEA (45.85 mg, 0.354 mmol, 2.0 equiv). The mixture was stirred at room temperature for 1 h. After completion reaction the reaction was quenched by water (10 mL) then extracted with EA (3 x 30 mL). The resulting mixture was concentrated under reduced pressure purified by silica gel column (0-10% MeOH/DCM) to afford product, the product was purified by Perp-HPLC Column: XBridge Prep OBD C18 Column, 30*150 cm*5 μm; (eluent: 37% to 50% (v/v) and ACN water (10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(6,7-dihydro-5H-[1,2,4]triazolo[5,1-b][1,3]oxazine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (7.9 mg, 7.94%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{28}F_2N_8O_4$: 542.22m/z, found: 543.30 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 11.68 (s, 1H), 10.38 (s, 1H), 8.83 (d, J = 1.5 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.81 (d, J = 10.1, 1H), 7.36 – 7.55 (m, 2H), 7.10 – 7.24 (m, 1H), 5.24 (s, 1H), 5.17 (s, 1H), 4.32 (s, 2H), 3.50 (q, J = 6.8 Hz, 1H), 3.35 – 3.43 (m, 2H), 2.60 – 2.70 (m, 2H), 2.50 – 2.60 (m, 2H), 1.36 (s, 6H), 1.11 – 1.22 (m, 3H).

Example 252: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-6-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide, Example 253: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-6-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide, Example 254: (R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-6-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide, and Example 255: (R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-6-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide



Synthetic Route:



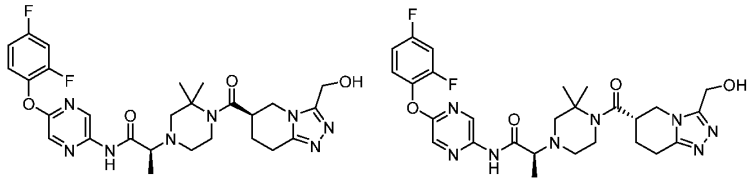
(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-6-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide, (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-6-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide, (R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-6-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide and (R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-6-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

To a solution of 6-(2,2-dimethylpiperazine-1-carbonyl)-5H,7H,8H-[1,2,4]triazolo[1,5-a]pyridin-6-ol (50 mg, 0.179 mmol, 1 equiv) in N,N-dimethylformamide (5 mL) the mixture was added 2-bromo-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (64.10 mg, 0.179 mmol, 1.0 equiv) then added TEA (54.34 mg, 0.537 mmol, 3.0 equiv). The mixture was stirred at room temperature for 5 h. After completion reaction the reaction was quenched by water (10 mL) then extracted with EA (3 x 20 mL). The residue was washed with water (3 x 10 mL). The resulting mixture was concentrated under reduced pressure purified by silica gel column (0-10% MeOH/DCM) to afford product, the product was purified by Chiral-HPLC

using a CHIRALPAK IF 2*25 cm, 5 μm column (eluent: 40% (v/v) EtOH and Hex: DCM=3: 1(0.5% 2M NH3-MeOH) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-6-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (assumed, 2.2 mg, 2.19%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{30}F_2N_8O_4$: 556.24m/z, found: 557.30 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.80 – 8.87 (m, 1H), 8.41 – 8.49 (m, 1H), 7.85 – 7.94 (m, 1H), 7.39 – 7.54 (m, 2H), 7.17 (t, J = 8.6 Hz, 1H), 5.75 – 5.84 (m, 1H), 4.75 – 4.90 (m, 1H), 4.00 – 4.22 (m, 2H), 3.45 – 3.63 (m, 4H), 2.71 – 2.79 (m, 1H), 2.58 – 2.66 (m, 1H), 2.29 – 2.45 (m, 2H), 2.18 – 2.29 (m, 1H), 1.77 (q, J = 12.0 Hz, 1H), 1.39 (s, 6H), 1.17 – 1.27 (m, 3H). And (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-6-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (assumed, 6.4 mg, 6.37%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{30}F_2N_8O_4$: 556.24m/z, found: 557.30 $[M+H]^+$, ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.90 (s, 1H), 7.39 – 7.55 (m, 2H), 7.10 – 7.24 (m, 1H), 5.80 (d, J = 6.7 Hz, 1H), 4.77 – 4.90 (m, 1H), 4.01-4.22 (m, 2H), 3.47 – 3.63 (m, 4H), 2.61 – 2.76 (m, 2H), 2.36 (s, 2H), 2.18 – 2.31 (m, 1H), 1.78 (q, J = 11.9 Hz, 1H), 1.39 (d, J = 3.7 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H). And (R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-6-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo [1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (assumed, 2.1 mg, 2.10%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{30}F_2N_8O_4$: 556.24m/z, found: 557.30 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.83 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.5 Hz, 1H), 7.90 (s, 1H), 7.39 – 7.55 (m, 2H), 7.10 – 7.24 (m, 1H), 5.81 (d, J = 6.6 Hz, 1H), 4.76 – 4.90 (m, 1H), 4.00 – 4.22 (m, 2H), 3.48 – 3.61 (m, 4H), 2.62 – 2.78 (m, 2H), 2.36 (s, 2H), 2.24 (dd, J = 13.1, 6.1 Hz, 1H), 1.78 (q, J = 11.9 Hz, 1H), 1.39 (d, J = 3.6 Hz, 6H), 1.16 – 1.34 (m, 3H). And (R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-6-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (assumed, 4.8 mg, 4.75%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{30}F_2N_8O_4$: 556.24, found: 557.35 $[M+H]^+$, ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.90 (s, 1H), 7.39 – 7.55 (m, 2H), 7.10 – 7.24 (m, 1H), 5.79 (d, J = 6.7 Hz, 1H), 4.76 – 4.90 (m, 2H), 4.00 – 4.22 (m, 2H), 3.45 – 3.62 (m, 4H), 2.71 – 2.81 (m, 1H), 2.57 – 2.67 (m, 1H), 2.31 – 2.45 (m, 2H), 2.17 – 2.29 (m, 1H),1.78 (q, J = 11.9 Hz, 1H), 1.39 (s, 6H), 1.21 (d, J = 6.8 Hz, 3H).

Example 256: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-3-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-

yl)propanamide and Example 257: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-3-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

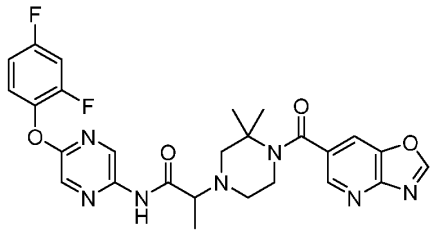


(2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-{4-[(6R)-3-(hydroxymethyl)-5H,6H,7H,8H-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl]-3,3-dimethylpiperazin-1-yl}propanamide and (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-{4-[(6S)-3-(hydroxymethyl)-5H,6H,7H,8H-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl]-3,3-dimethylpiperazin-1-yl}propanamide

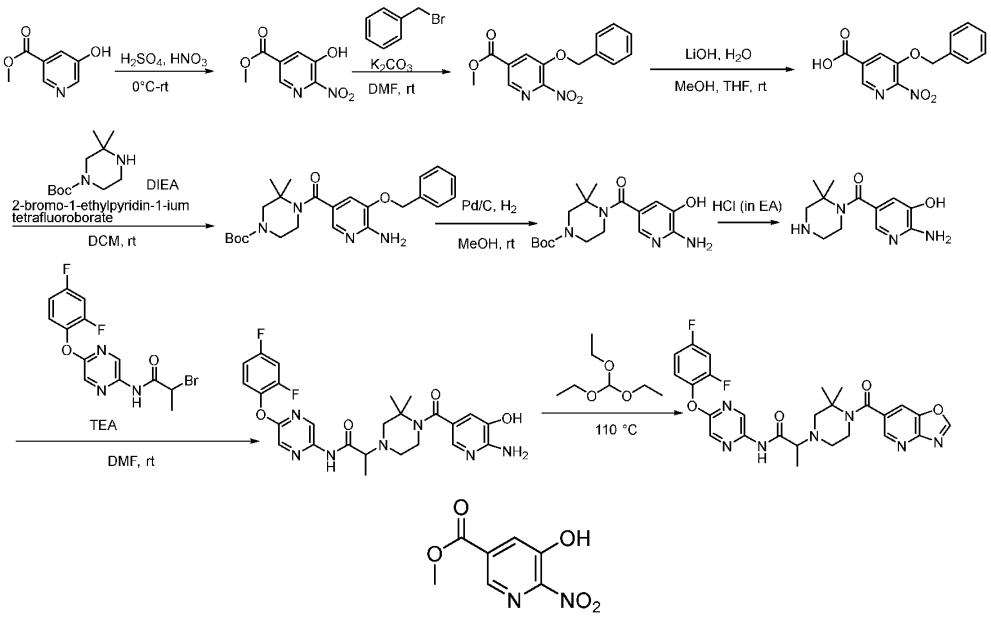
To a solution of (2S)-2-[4-(3-{[(tert-butyldimethylsilyl)oxy]methyl}-5H,6H,7H,8H-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl]-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (200 mg, 0.292 mmol, 1 equiv) in THF (3 mL) was added Triethylamine trihydrofluoride (376.62 mg, 2.336 mmol, 8 equiv) at rt .The resulting mixture was stirred for overnight at 60 °C. After cooled to room temperature the reaction mixture was quenched by water and extracted with EA (3*30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 28% to 46% (v/v) CH_3CN and H_2O, NH_4HCO_3) to afford (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(3-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (70 mg, 24%) as a white solid. The product was separated by Chiral-HPLC using a CHIRALPAK IG, 2*25 cm, 5 μm column (eluent: 20% (v/v) Hex: DCM=3: 1(0.5% 2M NH3-MeOH) and EtOH) to offer (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-3-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (17.1 mg, 39.7%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{32}F_2N_8O_4$ 570.602m/z, found 571.30 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.40 – 7.54 (m, 2H), 7.17 (t, J = 8.7 Hz, 1H), 5.42 (t, J = 5.6 Hz, 1H), 4.54 (d, J = 5.7 Hz, 2H), 4.10 (dd, J = 12.5, 5.0 Hz, 1H), 3.85 – 3.99 (m, 1H), 3.48 – 3.59(m, 3H), 2.72 – 2.90 (m, 3H), 2.59 – 2.65 (m, 1H), 2.29 – 2.46 (m, 3H), 1.96

– 2.11(m, 1H), 1.75 – 1.83 (m, 1H), 1.38 (s, 6H), 1.21 (d, *J* = 6.8 Hz, 3H). And (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-3-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (21.7 mg, 42.7%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{32}F_2N_8O_4$ 570.602m/z, found 571.30[M+H]$^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.42 (s, 1H), 8.84 (s, 1H), 8.45 (s, 1H), 7.47 (d, *J* = 10.2 Hz, 2H), 7.19 (d, *J* = 9.2 Hz, 1H), 5.42 (t, *J* = 5.6 Hz, 1H), 4.54 (d, *J* = 5.7 Hz, 2H), 4.10 (d, *J* = 10.9 Hz, 1H), 3.92 (t, *J* = 10.9 Hz, 1H), 3.55 (s, 3H), 2.85 (s, 2H), 2.70 (s, 2H), 2.24 – 2.40 (m, 3H), 1.92 – 2.12(m, 1H),1.68 – 1.87 (m, 1H), 1.38 (d, *J* = 4.0 Hz, 6H), 1.20 (d, *J* = 6.8 Hz, 3H).

Example 258: N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(oxazolo[4,5-b]pyridine-6-carbonyl)piperazin-1-yl)propanamide

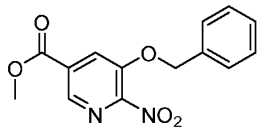


Synthetic Route:



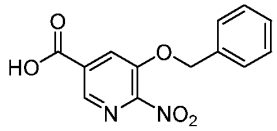
methyl 5-hydroxy-6-nitronicotinate

To a solution of methyl 5-hydroxypyridine-3-carboxylate (5 g, 32.651 mmol, 1 equiv) in H_2SO_4 (25 mL). Then HNO_3 (2.58 g, 21.596 mmol, 4 equiv) was added at 0 °C. The reaction mixture was stirred at room temperature for 0.5h. After completion of reaction, the crude product was re-crystallized from ice water to afford methyl 5-hydroxy-6-nitropyridine-3-carboxylate (5 g) as a yellow solid. The residue obtained was purified by silica gel chromatography (0-60% PE/EA) to afford methyl 5-hydroxy-6-nitronicotinate (3.5 g, 54.10%) as a white solid. MS (ESI): mass calcd. for $C_{14}H_{26}N_2O_3$: 198.03 m/z, found: 196.9 $[M-H]^-$.



methyl 5-(benzyloxy)-6-nitronicotinate

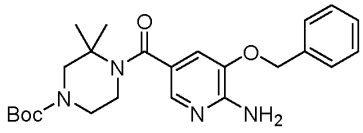
To a solution of methyl 5-hydroxy-6-nitronicotinate (3 g, 15.141 mmol, 1 equiv) in dimethylformamide (30 mL) was added K_2CO_3 (6.32 g, 45.423 mmol, 3 equiv) and benzyl bromide (4.40 g, 25.740 mmol, 1.7 equiv) at rt. The resulting mixture was stirred for 2 hours at room temperature. After completion of reaction, the reaction mixture was quenched by water (50 mL) and extracted with EA (80 mL x 3). The combined organic phase was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-40% PE/EA) to afford methyl 5-(benzyloxy)-6-nitronicotinate (2.8 g, 64.15%) as a white solid. MS (ESI): mass calcd. for $C_{14}H_{12}N_2O_5$: 288.07 m/z, found: 289.05 $[M+H]^+$.



5-(benzyloxy)-6-nitronicotinic acid

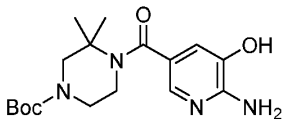
To a solution of 5-(benzyloxy)-6-nitronicotinate (2.7 g, 9.367 mmol, 1 equiv) in methanol (5 mL), tetrahydrofuran (10 mL) and water (5 mL) was added LiOH (0.45 g, 18.734 mmol, 2 equiv) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated to dryness under reduced pressure to provide the mixture. The mixture was acidified pH = 5 with HCl (1N). The precipitated solids were collected by filtration and washed with water. The product was precipitated by the addition of diethyl ether. The product is obtained (5-(benzyloxy)-6-nitronicotinic acid (2 g, 77.86%)) by

filtration and drying. MS (ESI): mass calcd. for $C_{13}H_{10}N_2O_5$: 274.06 m/z, found: 273.00 [M-H]$^-$.



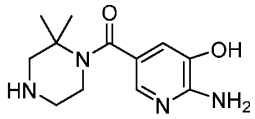
***tert*-butyl 4-(6-amino-5-(benzyloxy)nicotinoyl)-3,3-dimethylpiperazine-1-carboxylate**

To a stirred solution of (5-(benzyloxy)-6-nitronicotinic acid (1 g, 3.647 mmol, 1 equiv) in DCM (20 mL) was added tert-butyl 3,3-dimethylpiperazine-1-carboxylate (0.94 g, 4.376 mmol, 1.2 equiv) and 2-bromo-1-ethylpyridin-1-ium tetrafluoroborate (2.00 g, 7.294 mmol, 2 equiv) at room temperature. The reaction mixture was stirred at room temperature for a period of overnight. After completion of reaction, the reaction mixture was quenched by water (10 mL) and extracted with EA (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (40-100% PE/EA) to afford tert-butyl 4-(6-amino-5-(benzyloxy)nicotinoyl)-3,3-dimethylpiperazine-1-carboxylate (300 mg, 18.67%) as a white solid. MS (ESI): mass calcd. for $C_{24}H_{32}N_4O_4$: 440.24 m/z, found: 441.15 [M+H]$^+$.



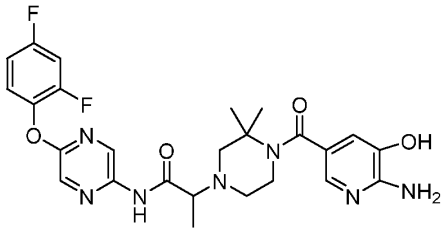
***tert*-butyl 4-(6-amino-5-hydroxynicotinoyl)-3,3-dimethylpiperazine-1-carboxylate**

To a stirred solution of tert-butyl 4-(6-amino-5-(benzyloxy)nicotinoyl)-3,3-dimethylpiperazine-1-carboxylate (300 mg, 0.681 mmol, 1 equiv) in methanol (6 mL) was added Pd/C (7.25 mg, 0.068 mmol, 0.1 equiv) under H_2. The reaction mixture was stirred at room temperature for 1 h under H_2. The resulting mixture was filtered, the filter cake was washed with MeOH. The filtrate was concentrated under reduced pressure. The product was precipitated by the addition of diethyl ether. The product is obtained (tert-butyl 4-(6-amino-5-hydroxynicotinoyl)-3,3-dimethylpiperazine-1-carboxylate (0.2 g, 83.8%) by filtration and drying. MS (ESI): mass calcd. for $C_{17}H_{26}N_4O_4$: 350.20 m/z, found: 351.15 [M+H]$^+$.



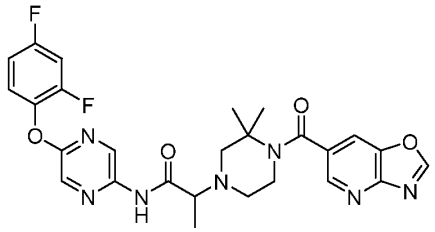
(6-amino-5-hydroxypyridin-3-yl)(2,2-dimethylpiperazin-1-yl)methanone

To a stirred solution of (tert-butyl 4-(6-amino-5-hydroxynicotinoyl)-3,3-dimethylpiperazine-1-carboxylate (300 mg, 0.856 mmol, 1 equiv) in EA (3 mL) was added HCl (4 M in EA, 3 mL). The reaction mixture was stirred at room temperature for 1 h. The product was precipitated by the addition of diethyl ether. The product is obtained ((6-amino-5-hydroxypyridin-3-yl)(2,2-dimethylpiperazin-1-yl)methanone (200 mg, 93.33%)) by filtration and drying. MS (ESI): mass calcd. for $C_{12}H_{18}N_4O_2$: 250.14 m/z, found: 251.10 $[M+H]^+$.



***N*-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(oxazolo[4,5-b]pyridine-6-carbonyl)piperazin-1-yl)propanamide**

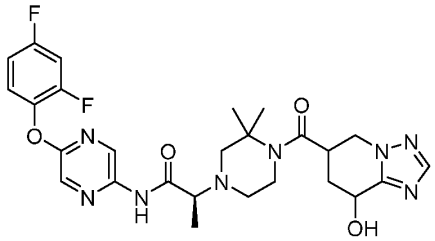
To a solution of 2-amino-5-(2,2-dimethylpiperazine-1-carbonyl)pyridin-3-ol (200 mg, 0.799 mmol, 1 equiv) in dimethylformamide (5 mL) was added TEA (242.57 mg, 2.397 mmol, 3 equiv) and 2-bromo-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (343.40 mg, 0.959 mmol, 1.2 equiv) at rt. The resulting mixture was stirred for 2 hours at room temperature. After completion of reaction, the reaction mixture was quenched by water (10 mL) and extracted with EA (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) to afford 2-[4-(6-amino-5-hydroxypyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl]-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (280 mg, 66.43%) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{27}F_2N_7O_4$: 527.21 m/z, found: 528.20 $[M+H]^+$.



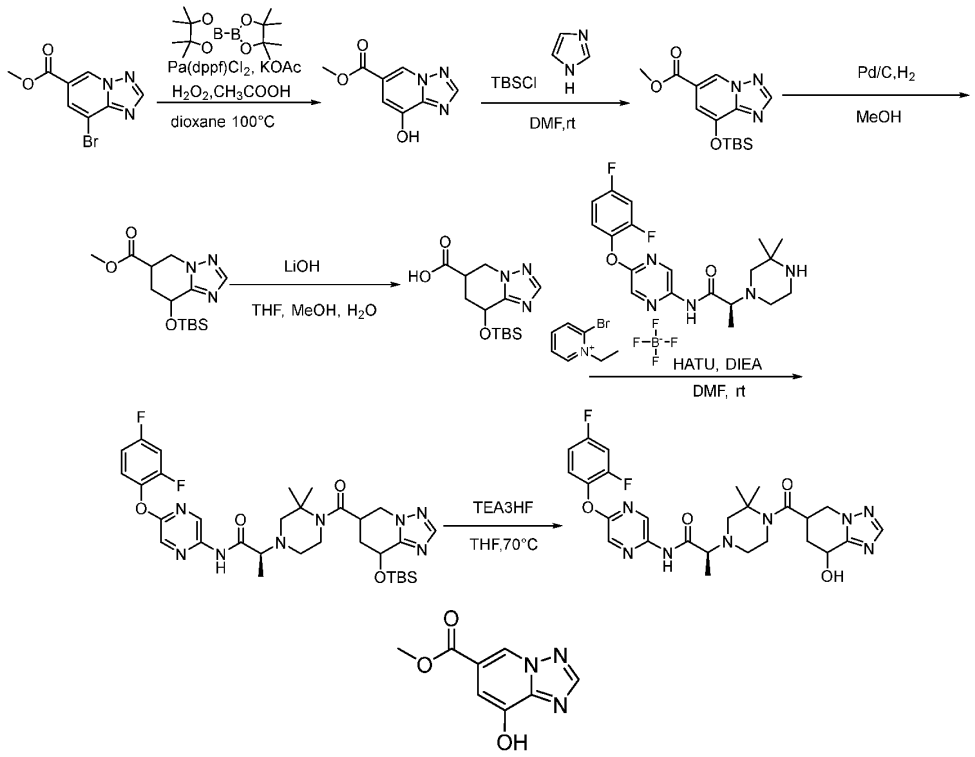
***N*-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(oxazolo[4,5-b]pyridine-6-carbonyl)piperazin-1-yl)propanamide**

To a stirring solution ((6-amino-5-hydroxypyridin-3-yl)(2,2-dimethylpiperazin-1-yl)methanone (280 mg, 0.531 mmol, 1 equiv) in triethyl orthoformate (3 mL) . The mixture was stirred at 110 °C for 3 h. After cooled to room temperature, the reaction was concentrated to dryness under reduced pressure to provide the crude product, which was purified by silica gel chromatography (0-5% DCM/MeOH) to afford N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(oxazolo[4,5-b]pyridine-6-carbonyl)piperazin-1-yl)propanamide (24.2 mg, 7.77%) as a yellow solid. MS (ESI): mass calcd. for $C_{26}H_{25}F_2N_7O_4$: 537.19 m/z, found: 538.25 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H), 9.14 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.61 (d, J = 1.8 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.33 (d, J = 1.8 Hz, 1H), 7.48 (dtd, J = 14.5, 9.3, 4.3 Hz, 2H), 7.17 (ddd, J = 10.6, 8.3, 2.3 Hz, 1H), 3.54 (q, J = 6.8 Hz, 1H), 3.28 – 3.40 (m,3H), 3.17 (d, J = 5.2 Hz, 1H), 2.57 – 2.78 (m, 2H), 1.50 (d, J = 3.9 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H).^{19}F NMR (376 MHz, DMSO-d_6) δ -113.43 (d, J = 5.3 Hz), -124.21 (d, J = 5.1 Hz).

Example 259: (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(8-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

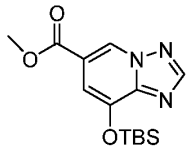


Synthetic Route:



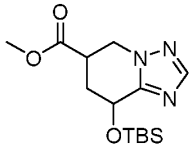
methyl 8-hydroxy-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate

To a solution of methyl 8-bromo-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (1.2 g, 4.686 mmol, 1 equiv) in dioxane (60 mL) the mixture was added bis(pinacolato)diboron (2.62 g, 10.309 mmol, 2.2 equiv), KOAc (1.38 g, 14.058 mmol, 3.0 equiv) then added Pd(dppf)Cl_2 (0.34 g, 0.469 mmol, 0.1 equiv). The mixture was stirred at 100°C for 6 h. under N_2. After completion reaction the reaction was cooled to room temperature added AcOH (0.84 g, 14.058 mmol, 3.0 equiv), H_2O (1.27 g, 70.290 mmol, 15.0 equiv), the mixture was stirred at room temperature for 20 min then added H_2O_2 (53.13 mg, 1.562 mmol, 2.0 equiv). The mixture was stirred at room temperature for 1 h. After completion reaction the reaction was quenched by water (50 mL) then extracted with EA (3x 200 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% MeOH/DCM) to afford methyl 8-hydroxy-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (512 mg, 56.56%) as a yellow solid. MS (ESI): mass calcd. for $C_8H_7N_3O_3$: 193.05 m/z, found: 194.10 $[M+H]^+$.



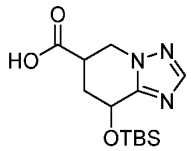
methyl 8-((tert-butyldimethylsilyl)oxy)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate

To a solution of methyl 8-hydroxy-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (400 mg, 2.071 mmol, 1 equiv) in dimethylformamide (10 mL) the mixture was added t-butyldimethylchlorosilane (468.17 mg, 3.107 mmol, 1.5 equiv) and imidazole (352.45 mg, 5.178 mmol, 2.5 equiv). The mixture was stirred at room temperature for 2 h. After completion reaction the reaction was quenched by water (20 mL) then extracted with EA (3 x 100 mL) then washed with water (3x 30 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-30% EA/PE) to afford methyl 8-((tert-butyldimethylsilyl)oxy)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (352 mg, 55.29%) as a yellow solid. MS (ESI): mass calcd. for $C_{14}H_{21}N_3O_3Si$: 307.14 m/z, found: 308.15 $[M+H]^+$.



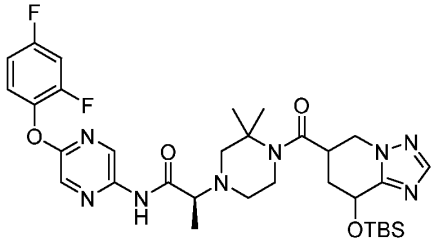
methyl 8-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate

To a solution of methyl 8-[(tert-butyldimethylsilyl)oxy]-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (300 mg, 0.976 mmol, 1 equiv) in methanol (20 mL) the mixture was added Pd/C (51.92 mg, 0.488 mmol, 0.5 equiv). The mixture was stirred at 50°C for 16 h under H_2 (3 atm). After completion reaction the reaction was cooled to room temperature filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% MeOH/DCM) to afford methyl 8-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (102 mg, 33.56%) as a yellow solid. MS (ESI): mass calcd. for $C_{14}H_{25}N_3O_3Si$: 311.17 m/z, found: 312.10 $[M+H]^+$.



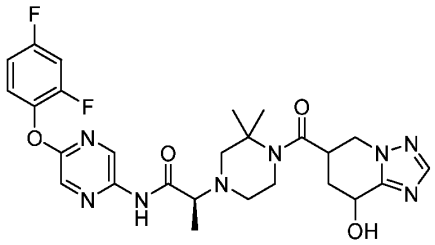
8-((tert-butyldimethylsilyl)oxy)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid

To a solution of methyl 8-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (100 mg, 0.321 mmol, 1 equiv) in THF (2 mL) MeOH (1 mL) and MeOH (1 mL), the mixture was added LiOH(11.53 mg, 0.482 mmol, 1.5 equiv). The mixture was stirred at room temperature for 2 h. After completion of reaction the mixture was precipitated by acidified neutralized to (pH =3) with (4N HCl). The precipitated solids were collected by filtration to afford 8-((tert-butyldimethylsilyl)oxy)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid (81 mg, 84.82%) as a yellow solid. MS (ESI): mass calcd. for $C_{13}H_{23}N_3O_3Si$: 297.15 m/z, found: 298.20 $[M+H]^+$.



(2S)-2-(4-(8-((tert-butyldimethylsilyl)oxy)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

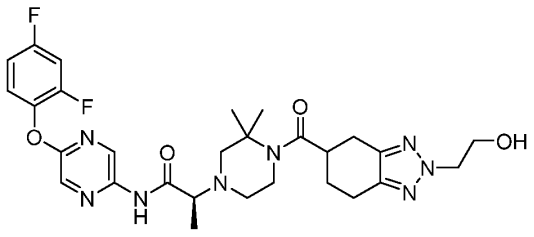
To a solution of 8-((tert-butyldimethylsilyl)oxy)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid (60 mg, 0.202 mmol, 1 equiv) in dimethylformamide (3 mL) the mixture was added 2-bromo-1-ethylpyridin-1-ium tetrafluoroborate (82.87 mg, 0.303 mmol, 1.5 equiv) (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (78.96 mg, 0.202 mmol, 1 equiv) then DIEA (78.22 mg, 0.606 mmol, 3 equiv). The mixture was stirred at room temperature for 2 h. After completion reaction the reaction was quenched by water (5 mL) then extracted with EA (3 x 30 mL). The resulting mixture was concentrated under reduced pressure then purified by by silica gel chromatography (0-10% MeOH/DCM) to afford (2S)-2-(4-(8-((tert-butyldimethylsilyl)oxy)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (53 mg, 39.16%) as a yellow solid. MS (ESI): mass calcd. for $C_{32}H_{44}F_2N_8O_4Si$: 670.32 m/z, found: 671.10 $[M+H]^+$.



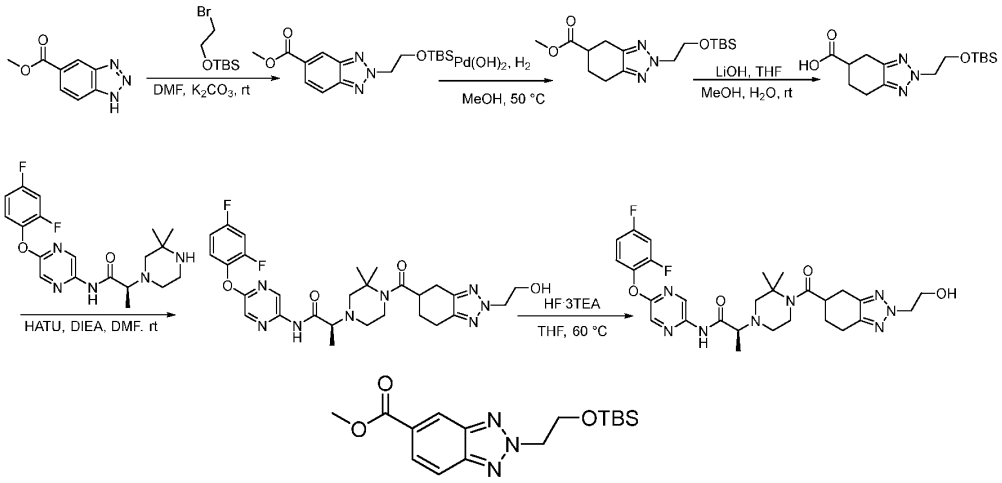
(2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(8-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

To a solution of (2S)-2-(4-(8-((tert-butyldimethylsilyl)oxy)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (20 mg, 0.030 mmol, 1 equiv) in tetrahydrofuran (1 mL) then added Triethylamine trihydrofluoride (0.2 mL). The mixture was stirred at 70°C for 2 h. After completion reaction the reaction was cooled to room temperature quenched by water (10 mL) then extracted with EA (3 x 30 mL). The resulting mixture was concentrated under reduced pressure purified by silica gel column (0-10% MeOH/DCM) to afford product, the product was purified by Prep-HPLC using a C18 column (eluent: 20% to 70% (v/v) CH_3CN and H_2O, NH_4HCO_3) to afford (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(8-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (4.7 mg, 28.00%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{30}F_2N_8O_4$: 556.24 m/z, found: 557.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.42(s, 1H), 8.84(s, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.87 – 7.95 (m, 1H), 7.39 – 7.56 (m, 2H), 7.04 – 7.24 (m, 1H), 5.91(dd, J = 5.3, 1.9 Hz, 1H), 4.72 – 4.80 (m, 1H), 4.18 – 4.29 (m, 1H), 3.99 – 4.18 (m, 1H), 3.45 – 3.66 (m, 4H), 2.65 – 2.76(m, 1H), 2.25 – 2.45 (m, 3H), 1.99 – 2.09 (m, 2H), 1.39 (s, 6H), 1.21 – 1.28(m, 3H).

Example 260: (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(2-(2-hydroxyethyl)-4,5,6,7-tetrahydro-2H-benzo[d][1,2,3]triazole-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide



Synthetic Route :



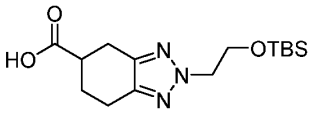
methyl 2-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2H-benzo[d][1,2,3]triazole-5-carboxylate

To a solution of methyl 1H-1,2,3-benzotriazole-5-carboxylate (500 mg, 2.822 mmol, 1 equiv) in DMF (6 mL). potassium methaneperoxoate potassium) and (2-bromoethoxy)(tert-butyl)dimethylsilane) added at rt. The resulting mixture was stirred for 12 h at 50 °C. After cooled to room temperature, the resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100%PE/EA) to afford methyl 2-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2H-benzo[d][1,2,3]triazole-5-carboxylate (assumed, 300 mg, 31.69%) as a yellow oil, MS (ESI): mass calcd. for$C_{16}H_{25}N_3O_3Si$:335.17, found:336.10$[M+H]^+$.

methyl 2-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4,5,6,7-tetrahydro-2H-benzo[d][1,2,3]triazole-5-carboxylate

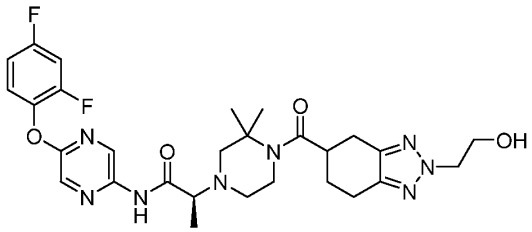
To a solution of methyl 2-{2-[(tert-butyldimethylsilyl)oxy]ethyl}-1,2,3-benzotriazole-5-carboxylate (1 g, 2.981 mmol, 1 equiv) in MeOH (15 mL) was added $Pd(OH)_2$ (0.42 g, 2.981 mmol, 1 equiv) in a pressure tank. The mixture was hydrogenated at 50 °C under 50 psi of hydrogen pressure for 24 h, filtered through a Celite pad and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the

following conditions: column, C18 silica gel; mobile phase, water (0.01%FA) in ACN, 5% to 100% gradient in 30 min to afford methyl methyl 2-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4,5,6,7-tetrahydro-2H-benzo[d][1,2,3]triazole-5-carboxylate (700 mg, 69.17%) as a yellow oil. , MS (ESI): mass calcd. for$C_{16}H_{29}N_3O_3Si$:339.20, found:340.10[M+H]$^+$.



2-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4,5,6,7-tetrahydro-2H-benzo[d][1,2,3]triazole-5-carboxylic acid

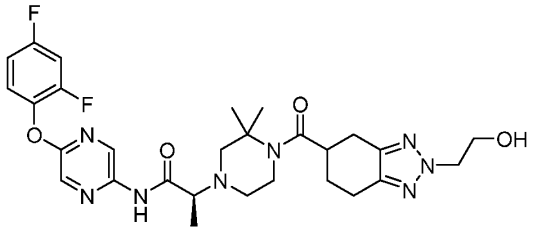
To a solution of 2-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4,5,6,7-tetrahydro-2H-benzo[d][1,2,3]triazole-5-carboxylate (900 mg, 2.651 mmol, 1 equiv) in THF (5 mL), methanol (3 mL, 0.008 mmol, 0.24 equiv), LiOH (126.98 mg, 1.561 mmol, 2 equiv) and water (1 mL, 0.014 mmol, 0.43 equiv) added at rt. The resulting mixture was stirred for 2h at rt. The resulting mixture was concentrated under vacuum. The residue was acidified to pH 2~3 with 3N HCl. The precipitated solids were collected by filtration and washed with H_2O (5 mL) to afford 2-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4,5,6,7-tetrahydro-2H-benzo[d][1,2,3]triazole-5-carboxylic acid (700 mg, 81.13%) as a yellow oil. MS (ESI): mass calcd. for $C_{15}H_{27}N_3O_3Si$:325.18, found:326.10[M+H]$^+$.



(2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(2-(2-hydroxyethyl)-4,5,6,7-tetrahydro-2H-benzo[d][1,2,3]triazole-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

To a solution of 2-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4,5,6,7-tetrahydro-2H-benzo[d][1,2,3]triazole-5-carboxylic acid (700 mg, 2.151 mmol, 1 equiv) in DMF (3 mL). (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (841.81 mg, 2.151 mmol, 1 equiv), HATU (1.64 g, 4.302 mmol, 2 equiv) and DIEA (2.22 g, 17.208 mmol, 8 equiv) added at rt. The resulting mixture was stirred for 2h at rt. The resulting mixture was extracted with EA (3*100mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to

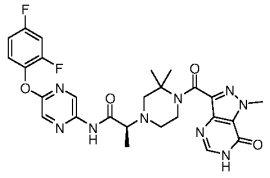
yield a crude product which was directly purified by flash chromatography (0-100%PE/EA) to afford (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(2-(2-hydroxyethyl)-4,5,6,7-tetrahydro-2H-benzo[d][1,2,3]triazole-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (300 mg, 31.69%) as a yellow oil, MS (ESI): mass calcd. for$C_{34}H_{48}F_2N_8O_4Si$:698.35, found:699.25$[M+H]^+$.



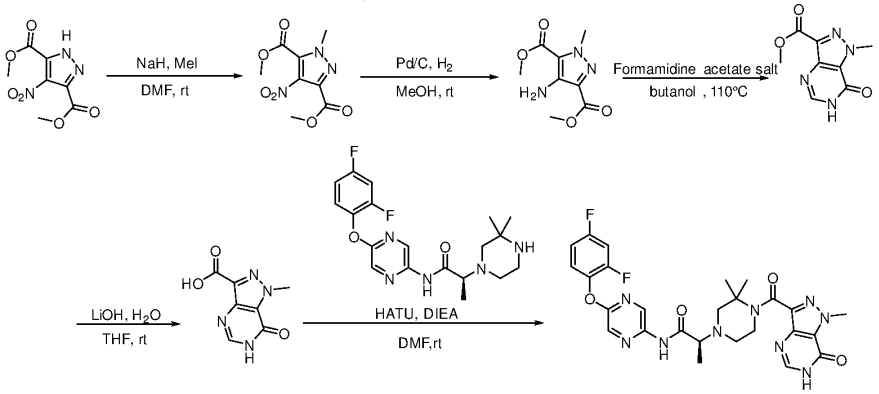
(2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(2-(2-hydroxyethyl)-4,5,6,7-tetrahydro-2H-benzo[d][1,2,3]triazole-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

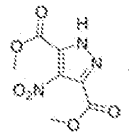
To a solution of (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(2-(2-hydroxyethyl)-4,5,6,7-tetrahydro-2H-benzo[d][1,2,3]triazole-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (70 mg, 0.120 mmol, 1 equiv) in THF (4 mL).triethylamine trihydrofluoride (4 mL, 0.025 mmol, 0.21 equiv) added at rt. The resulting mixture was stirred for 20 min at 60 degrees. After cooled to room temperature, The resulting mixture was concentrated under reduced pressure and Prep-HPLC using a XBridge Prep OBD C18 30*150 mm, 5μm Column (eluent: 14% to 44% ACN and H_2O (10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(2-(2-hydroxyethyl)-4,5,6,7-tetrahydro-2H-benzo[d][1,2,3]triazole-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (18.7 mg, 26.49%) as a white solid, MS (ESI): mass calcd. For $C_{28}H_{34}F_2N_8O_4$: 584.27.19, found: 585.35$[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.39 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.39 – 7.55 (m, 2H), 7.10 – 7.24 (m, 1H), 4.86 (t, J = 5.5 Hz, 1H), 4.30 (t, J = 5.8 Hz, 2H), 3.80 (dd, J = 5.7 Hz, 2H), 3.53 (s, 3H), 2.96 – 3.08 (m, 1H), 2.63 – 2.75 (m, 6H), 2.28 – 2.44 (m, 2H), 1.89 – 2.00 (m, 1H), 1.62 – 1.68 (m, 1H), 1.38 (t, J = 1.9 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.447, -124.237.

Example 261: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidine-3-carbonyl)piperazin-1-yl)propenamide



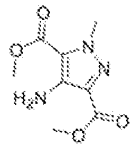
Synthetic Scheme





Synthesis of dimethyl 1-methyl-4-nitro-1H-pyrazole-3,5-dicarboxylate

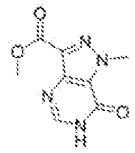
To a solution of 3,5-dimethyl 4-nitro-1H-pyrazole-3,5-dicarboxylate (2 g, 8.728 mmol, 1 equiv) in DMF (20 mL) was added sodium hydride (60% in oil, 0.35 g, 8.728 mmol, 1 equiv) at 0°C. The mixture was stirred for 15 min. Methyl iodide (1.5 g, 10.474 mmol, 1.2 equiv) was added and the mixture was allowed to warm to room temperature and stirred for 1h. The reaction mixture was quenched by water (30 mL) and extracted with DCM (3 x 30 mL). The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford dimethyl 1-methyl-4-nitro-1H-pyrazole-3,5-dicarboxylate (1 g, 47.12%) as a white solid. MS (ESI): mass calcd. for $C_8H_9N_3O_6$: 243.04, found: 244.20 $[M+H]^+$.



Synthesis of dimethyl 4-amino-1-methyl-1H-pyrazole-3,5-dicarboxylate

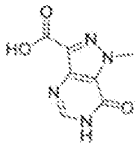
To a solution of dimethyl 1-methyl-4-nitro-1H-pyrazole-3,5-dicarboxylate (1 g, 4.112 mmol, 1 equiv) in MeOH (20 mL) was added Pd/C (10%, 0.3 g) under nitrogen atmosphere. The

mixture was hydrogenated at room temperature for 1h using a hydrogen balloon. The mixture was filtered through a Celite pad and concentrated under reduced pressure to afford dimethyl 4-amino-1-methyl-1H-pyrazole-3,5-dicarboxylate (600 mg, 63.65%) as a white solid. MS (ESI): mass calcd. for $C_8H_{11}N_3O_4$: 213.07, found: 214.20 $[M+H]^+$.



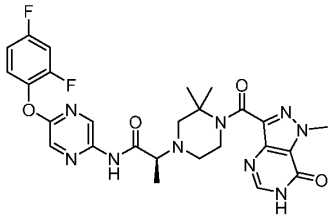
Synthesis of methyl 1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidine-3-carboxylate

To a stirred solution of dimethyl 4-amino-1-methyl-1H-pyrazole-3,5-dicarboxylate (200 mg, 0.938 mmol, 1 equiv) in butanol (5 mL) was added formamidine acetate salt (117.20 mg, 1.126 mmol, 1.2 equiv). The reaction mixture was stirred at 110 °C temperature for 6h. After cooled to room temperature, the mixture was concentrated to dryness under reduced pressure to provide the crude product, which was purified by silica gel chromatography (0-10% MeOH/DCM) to afford methyl 1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidine-3-carboxylate (120 mg, 61.45%) as a colorless oil. MS (ESI): mass calcd. for $C_8H_8N_4O_3$: 208.17 m/z, found 209.15 $[M+H]^+$.



Synthesis of 1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidine-3-carboxylic acid

To a solution of methyl 1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidine-3-carboxylate (100 mg, 0.480 mmol, 1 equiv) in tetrahydrofuran (2 mL) and water (2 mL) was added LiOH (23.01 mg, 0.960 mmol, 2 equiv) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The mixture was acidified pH = 5 with HCl (1N). The aqueous layer was extracted with ethyl acetate (30 mL x 3). The organic layer was concentrated. The residue obtained was purified by C18 column (0-40% H_2O/CH_3CN) to afford 1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidine-3-carboxylic acid (60 mg, 64.33%) as a white solid. MS (ESI): mass calcd. for $C_7H_6N_4O_3$: 194.15 m/z, found 195.20 $[M+H]^+$.

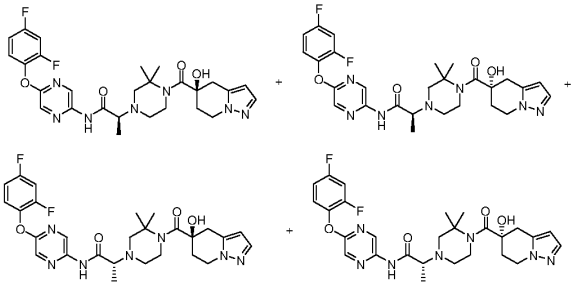


Synthesis of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidine-3-carbonyl)piperazin-1-yl)propanamide

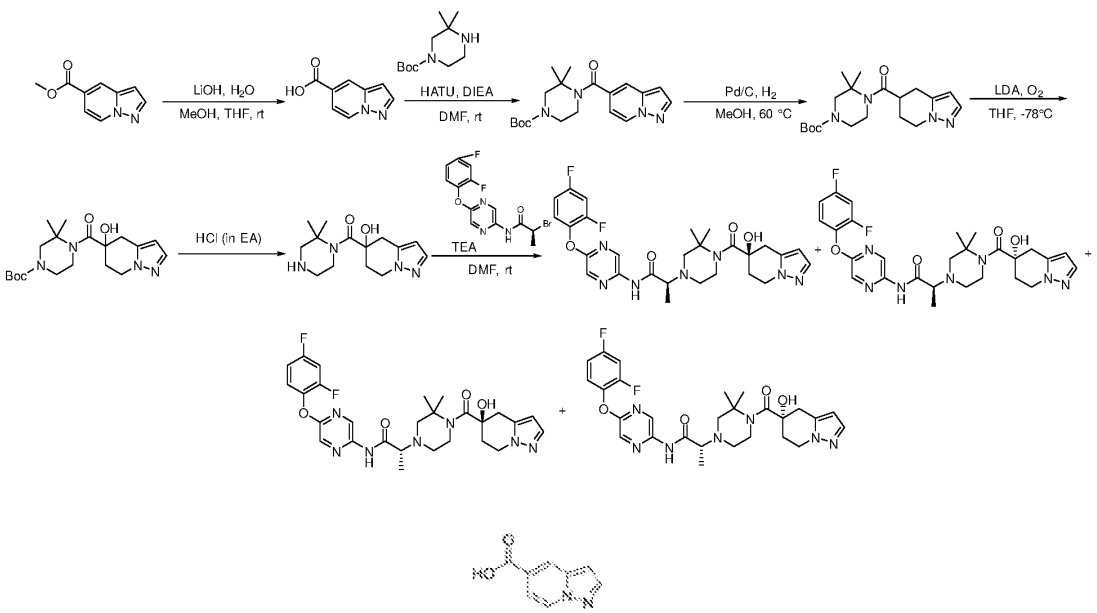
To a stirring solution (2S)-N-[5-(2,4-difluorophenoxy) pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl) propanamide (60 mg, 0.153 mmol, 1 equiv) in dimethylformamide (3 mL) the mixture was added 1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidine-3-carboxylic acid (29.76 mg, 0.153 mmol, 1 equiv), HATU (87.43 mg, 0.229 mmol, 1.5 equiv) and N, N -diisopropylethylamine (79.25 mg, 0.612 mmol, 4 equiv) at room temperature. The resulting mixture was stirred for additional 1h at room temperature. After completion of reaction, the reaction mixture was quenched by addition of water (5 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidine-3-carbonyl)piperazin-1-yl)propanamide (73 mg, 82.79%). MS (ESI): mass calcd. for $C_{26}H_{27}F_2N_9O_4$: 567.21 m/z, found: 568.25 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.43 (s, 1H), 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.91 (s, 1H), 7.41 – 7.53 (m, 2H), 7.10 – 7.22 (m, 1H), 4.19 (s, 3H), 3.51 (q, J = 6.9 Hz, 1H), 3.35 – 3.45 (m, 2H), 2.67 – 2.73 (m, 1H), 2.56 – 2.61 (m, 1H), 2.45 (s, 2H), 1.49 (d, J = 1.9 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H).

Example 265: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-5-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propenamide, Example 264: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-5-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propenamide, Example 263: (R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-5-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide and Example 262: (R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-5-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-

yl)propanamide

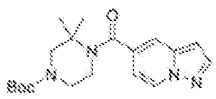


Synthetic Scheme



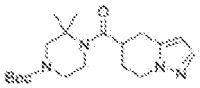
Synthesis of pyrazolo[1,5-a]pyridine-5-carboxylic acid

To a solution of methyl pyrazolo[1,5-a]pyridine-5-carboxylate (3 g, 17.029 mmol, 1 equiv) in methanol (10 mL), tetrahydrofuran (20 mL) and water (10 mL) was added LiOH (0.82 g, 34.058 mmol, 2 equiv) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure. The mixture was acidified pH = 5 with HCl (4N). The precipitated solids were collected by filtration and washed with water to afford pyrazolo[1,5-a]pyridine-5-carboxylic acid (2.5 g, 90.54%). MS (ESI): mass calcd. for $C_8H_6N_2O_2$: 162.04 m/z, found: 163.00 $[M+H]^-$.



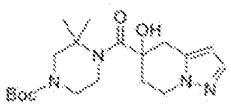
Synthesis of tert-butyl 3,3-dimethyl-4-(pyrazolo[1,5-a]pyridine-5-carbonyl)piperazine-1-carboxylate

To a stirred solution of pyrazolo[1,5-a]pyridine-5-carboxylic acid (2.6 g, 16.035 mmol, 1 equiv) in DMF (40 mL) was added DIEA (6.22 g, 48.105 mmol, 3 equiv) and HATU (9.15 g, 24.053 mmol, 1.5 equiv) and tert-butyl 3,3-dimethylpiperazine-1-carboxylate (4.12 g, 19.242 mmol, 1.2 equiv) at room temperature. The reaction mixture was stirred at room temperature for a period of overnight. After completion of reaction, the reaction mixture was quenched by water (50 mL) and extracted with EA (50 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) to afford tert-butyl 3,3-dimethyl-4-(pyrazolo[1,5-a]pyridine-5-carbonyl)piperazine-1-carboxylate (4 g, 69.60%) as a white solid. MS (ESI): mass calcd. for $C_{19}H_{26}N_4O_3$: 358.20 m/z, found: 359.10 $[M+H]^+$.



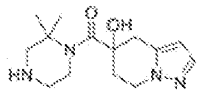
Synthesis of tert-butyl 3,3-dimethyl-4-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)piperazine-1-carboxylate

To a stirring solution of tert-butyl 3,3-dimethyl-4-{pyrazolo[1,5-a]pyridine-5-carbonyl}piperazine-1-carboxylate (4 g, 11.159 mmol, 1 equiv) in ethyl alcohol (50 mL) was added a solution of Pd/C (0.12 g, 1.116 mmol, 0.1 equiv). The mixture was stirred at 60 °C for 15 h under H_2 (40 atm). After cooled to room temperature the reaction was filtered through a celite pad and concentrated under reduced pressure to afford the crude product, which was purified by silica gel chromatography (0-10% DCM/MeOH) to afford tert-butyl 3,3-dimethyl-4-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)piperazine-1-carboxylate (4 g, 98.89%) as a white solid. MS (ESI): mass calcd. for $C_{19}H_{30}N_4O_3$: 362.23 m/z, found 363.05 $[M+H]^+$.



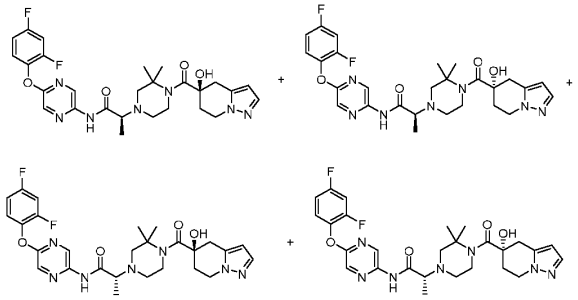
Synthesis of tert-butyl 4-(5-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazine-1-carboxylate

To a solution of tert-butyl 3,3-dimethyl-4-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)piperazine-1-carboxylate (2.5 g, 6.897 mmol, 1 equiv) in THF (100 mL) the mixture was cooled to -78°C then added 2M LDA (in THF, 4.83 mL, 9.656 mmol, 1.4 equiv) under N_2 at -78°C. The resulting mixture was stirred at -78°C for 0.5h. The resulting mixture was added $P(OEt)_3$ (2.29 g, 13.794 mmol, 2 equiv) and introduced O_2 stirred at -78°C for 0.5h. The reaction was quenched by water (30 mL) and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-30% PE/EA) to afford 4-(5-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazine-1-carboxylate (712 mg, 27.28%) as a yellow solid. MS (ESI): mass calcd. for $C_{19}H_{30}N_4O_4$: 378.23, found: 379.10 $[M+H]^+$.



Synthesis of (2,2-dimethylpiperazin-1-yl)(5-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-5-yl)methanone

To a stirred solution of 4-(5-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazine-1-carboxylate (700 mg, 1.850 mmol, 1 equiv) in EA (8 mL) was added HCl (4 M in EA, 8 mL). The reaction mixture was stirred at room temperature for 1 h. The product was precipitated by the addition of diethyl ether. The product is obtained ((2,2-dimethylpiperazin-1-yl)(5-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-5-yl)methanone (450 mg, 87.41%)) by filtration and drying. MS (ESI): mass calcd. for $C_{14}H_{22}N_4O_2$: 278.17 m/z, found: 279.10 $[M+H]^+$.



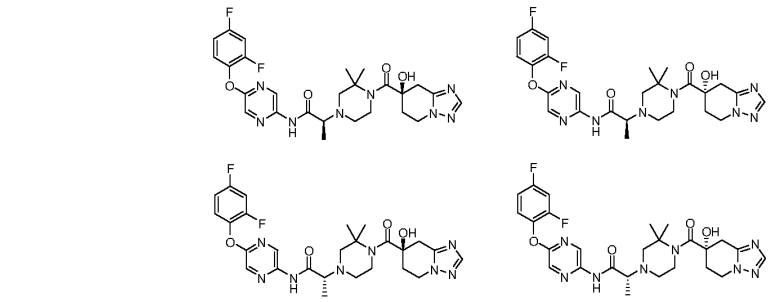
Synthesis of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-5-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide & (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-5-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide & (R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-5-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide & (R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-5-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

To a stirring solution of (2,2-dimethylpiperazin-1-yl)(5-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-5-yl)methanone (300 mg, 1.078 mmol, 1 equiv) in DMF (15 mL) was added a solution of TEA (327.18 mg, 3.234 mmol, 3 equiv) and 2-bromo-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (463.19 mg, 1.294 mmol, 1.2 equiv). The mixture was stirred at room temperature for 2 h. The reaction was quenched by water (20 mL) and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-30% MeOH/DCM) to afford 0.3 g product as a white solid. The compound was separated by chiral-HPLC using a CHIRALPAK IF, 2*25 cm, 5 μm column (eluent: 10% (v/v) MtBE (0.5% 2M NH_3-MeOH) and MEOH: DCM=1: 1 to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-5-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (assumed, 61 mg, 10.15%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{31}F_2N_7O_4$: 555.24 m/z, found 556.30 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.56 – 7.40 (m, 2H), 7.32 (d, J = 1.8 Hz, 1H), 7.11 – 7.24 (m, 1H), 5.95 (d, J = 2.2 Hz, 2H), 3.99 – 4.10 (m, 2H), 3.88 – 3.97 (m, 2H), 3.45 – 3.58 (m, 1H), 3.13 (d, J = 16.6 Hz, 1H), 2.92 (d, J = 16.6 Hz, 1H), 2.71 – 2.79 (m, 1H), 2.56 – 2.67 (m, 1H), 2.29 – 2.47 (m, 2H), 2.19 – 2.33 (m, 1H), 2.13 (d, J = 14.0 Hz, 1H), 1.37 (d, J = 3.8 Hz, 6H), 1.21 (d, J = 3.6 Hz, 3H). And (R)-N-(5-(2,4-

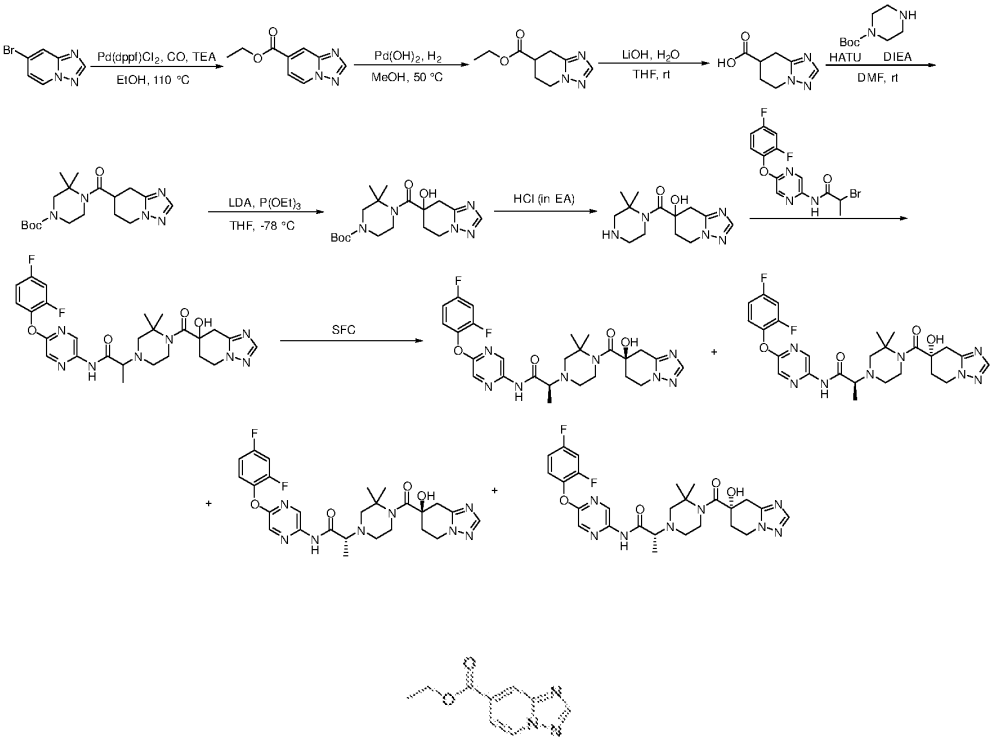
difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-5-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (assumed, 45.2 mg, 7.52%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{31}F_2N_7O_4$:555.24 m/z, found 556.30 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.46 (d, *J* = 1.4 Hz, 1H), 7.56 – 7.40 (m, 2H), 7.32 (d, *J* = 1.8 Hz, 1H), 7.11 – 7.24 (m, 1H), 5.95 (d, *J* = 2.2 Hz, 2H), 3.99 – 4.10 (m, 2H), 3.88 – 3.97 (m, 2H), 3.45 – 3.58 (m, 1H), 3.13 (d, *J* = 16.6 Hz, 1H), 2.92 (d, *J* = 16.6 Hz, 1H), 2.71 – 2.79 (m, 1H), 2.56 – 2.67 (m, 1H), 2.29 – 2.47 (m, 2H), 2.19 – 2.33 (m, 1H), 2.13 (d, *J* = 14.0 Hz, 1H), 1.37 (d, *J* = 3.8 Hz, 6H), 1.21 (d, *J* = 3.6 Hz, 3H). And other isomers 120 mg. The mixture was separated by chiral-HPLC using a CHIRALPAK IF, 2*25 cm, 5 μm column (eluent: 20% (v/v) Hex: DCM=3: 1 (0.5% 2M NH_3-MeOH) and EtOH to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-5-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (assumed, 30.5 mg, 5.07%) as a yellow solid. MS (ESI): mass calcd. for $C_{27}H_{31}F_2N_7O_4$: 555.24 m/z, found 556.30 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.84 (d, *J* = 1.4 Hz, 1H), 8.46 (d, *J* = 1.4 Hz, 1H), 7.40 – 7.56(m, 2H), 7.32 (d, *J* = 1.8 Hz, 1H), 7.11 – 7.24 (m, 1H), 5.95 (d, *J* = 1.7 Hz, 2H), 3.91 – 4.10 (m, 4H), 3.50 (q, *J* = 6.8 Hz, 1H), 3.13 (d, *J* = 16.6 Hz, 1H), 2.92 (d, *J* = 16.6 Hz, 1H), 2.69 – 2.79 (m, 1H), 2.57 – 2.67 (m, 1H), 2.39 (d, *J* = 2.7 Hz, 2H), 2.08 – 2.30 (m, 1H), 1.37 (d, *J* = 2.2 Hz, 6H), 1.20 (d, *J* = 6.9 Hz, 3H). And (R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-5-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (assumed, 45.2 mg, 7.6%) as a yellow solid. MS (ESI): mass calcd. for $C_{27}H_{31}F_2N_7O_4$: 555.24 m/z, found 556.30 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.84 (d, *J* = 1.4 Hz, 1H), 8.46 (d, *J* = 1.4 Hz, 1H), 7.40 – 7.56 (m, 2H), 7.32 (d, *J* = 1.8 Hz, 1H), 7.11 – 7.24 (m, 1H), 5.96 (d, *J* = 1.6 Hz, 2H), 3.99 – 4.11(m, 2H), 3.87 – 3.96 (m, 2H), 3.50 (q, *J* = 6.8 Hz, 1H), 3.14 (d, *J* = 16.6 Hz, 1H), 2.92 (d, *J* = 16.6 Hz, 1H), 2.69 – 2.79 (m, 1H), 2.55 – 2.68 (m, 1H), 2.29 – 2.46 (m, 2H), 2.13 (m, 1H), 1.37 (d, *J* = 2.3 Hz, 6H), 1.20 (d, *J* = 6.8 Hz, 3H).

Example 269: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-7-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)propenamide, Example 268: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-7-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)propenamide, Example 267: (R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-7-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-

a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide and Example 266: (R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-7-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide



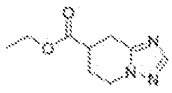
Synthetic Scheme



Synthesis of ethyl [1,2,4]triazolo[1,5-a]pyridine-7-carboxylate

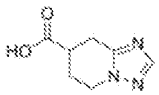
To a solution of 7-bromo-[1,2,4]triazolo[1,5-a]pyridine (5 g, 25.25 mmol, 1 equiv) in 30 mL EtOH was added Pd(dppf)Cl_2 (1.85g, 2.525 mmol, 0.1 equiv) and TEA (7.67 g, 75.75mmol, 3 equiv) in a pressure tank. The mixture was purged with nitrogen for 5 min and then was

pressurized to 20 atm with carbon monoxide at 110 °C for 24 h. The reaction mixture was cooled to room temperature and filtered to remove insoluble solids. The residue obtained was purified by silica gel chromatography (0-40% EA/PE) to afford ethyl [1,2,4]triazolo[1,5-a]pyridine-7-carboxylate (4g, 82.86%) as a white solid. MS (ESI): mass calcd. for $C_9H_9N_3O_2$: 191.07, found: 192.25 $[M+H]^+$.



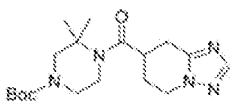
Synthesis of ethyl 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylate

To a solution of ethyl [1,2,4]triazolo[1,5-a]pyridine-7-carboxylate (3.5g, 18.306mmol, 1 equiv) in methanol (10 mL) was added 10% $Pd(OH)_2$ (0.5 g) in a pressure tank. The mixture was hydrogenated at 50 °C under 30 atm of hydrogen pressure for 24 h, filtered through a Celite pad and concentrated under reduced pressure. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford ethyl 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylate (3g, 83.94%) as a white solid. MS (ESI): mass calcd. for $C_9H_{13}N_3O_2$: 195.10, found:196.25 $[M+H]^+$.



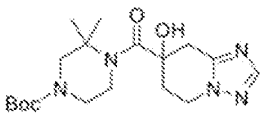
Synthesis of 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylic acid

To a solution of ethyl 5H,6H,7H,8H-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylate (2.2 g, 11.269 mmol, 1 equiv) in THF (20 mL),MeOH (10 mL) and H_2O (10 mL) was added LiOH (0.40 g, 16.904 mmol, 1.5 equiv). The mixture was stirred at room temperature for 2 h. After completion of reaction the mixture was precipitated by acidified neutralized to (pH =3) with (4N HCl). The precipitated solids were collected by filtration to afford 5H,6H,7H,8H-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylic acid (1.6 g, 84.93%) as a yellow solid. MS (ESI): mass calcd. for $C_7H_9N_3O_2$: 167.07, found: 168.15 $[M+H]^+$.



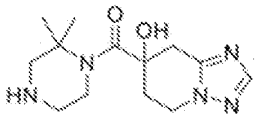
Synthesis of tert-butyl 3,3-dimethyl-4-(5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)piperazine-1-carboxylate

To a solution of 5H,6H,7H,8H-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylic acid (1.45 g, 8.674 mmol, 1 equiv) in DMF (50 mL) was added tert-butyl 3,3-dimethylpiperazine-1-carboxylate (1.86 g, 8.674 mmol, 1 equiv), HATU (4.95 g, 13.011 mmol, 1.5 equiv) then added DIEA (3.36 g, 26.022 mmol, 3 equiv). The mixture was stirred at room temperature for 2 h. After completion reaction the reaction was quenched by water (30 mL) then extracted with EA (3x 30 mL) then washed with water (30 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% MeOH/DCM) to afford tert-butyl 3,3-dimethyl-4-(5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)piperazine-1-carboxylate (2.4 g, 76.13%) as a yellow solid. MS (ESI): mass calcd. for $C_{18}H_{29}N_5O_3$: 363.23, found: 364.25 $[M+H]^+$.



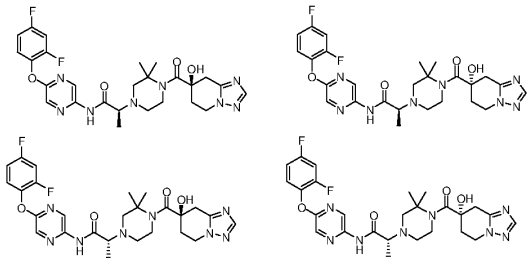
Synthesis of tert-butyl 4-(7-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazine-1-carboxylate

To a solution of tert-butyl tert-butyl 3,3-dimethyl-4-(5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)piperazine-1-carboxylate (2.4 g, 6.603 mmol, 1 equiv) in THF (80 mL) was cooled to -78°C then added 2N LDA (in THF, 8.25 mL, 16.508 mmol, 2.5 equiv). The mixture was stirred at -78°C for 0.5 h under N_2. O_2 was passed through this solution for 10 min, the mixture was added $P(OEt)_3$ (2.19 g, 13.206 mmol, 2 equiv). The reaction was stirred at -78°C for 10 min. After completion reaction the reaction was quenched by NH_4Cl solution (30 mL) then extracted with EA (3 x 30 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% MeOH/DCM) to afford tert-butyl 4-(7-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazine-1-carboxylate (1.2 g, 47.89%) as a yellow solid. MS (ESI): mass calcd. for $C_{18}H_{29}N_5O_4$: 379.22, found: 380.25 $[M+H]^+$.



Synthesis of (2,2-dimethylpiperazin-1-yl)(7-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridin-7-yl)methanone hydrochloride

To a solution of tert-butyl 4-(7-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazine-1-carboxylate (1.1 g, 2.899 mmol, 1 equiv) in EA (15 mL), 4N HCl (in EA, 10 mL) was added at rt. The mixture was stirred at room temperature for 1 h. After completion reaction the reaction was diluted with diethyl ether (50 mL). The mixture was filtered and washed with diethyl ether to afford (2,2-dimethylpiperazin-1-yl)(7-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridin-7-yl)methanone hydrochloride (682 mg, 74.63%) as a yellow solid. MS (ESI): mass calcd. for $C_{13}H_{21}N_5O_2$: 279.17, found: 280.20 $[M+H]^+$.



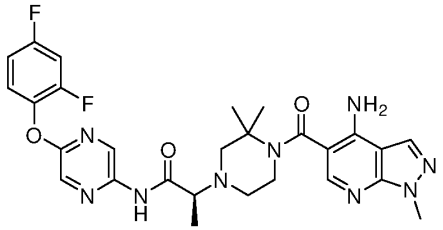
Synthesis of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-7-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide & (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-7-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)propenamide & (R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-7-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide & (R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-7-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

To a solution of (2,2-dimethylpiperazin-1-yl)(7-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridin-7-yl)methanone hydrochloride (339 mg, 1.074 mmol, 1 equiv) in N,N-dimethylformamide (10 mL) was added 2-bromo-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (384.63 mg, 1.074 mmol, 1 equiv) then added TEA (326.03 mg, 3.222 mmol, 3 equiv). The mixture was stirred at room temperature for 5 h. After completion reaction the reaction was quenched by water (20 mL) then extracted with EA (3 x 50 mL). The residue was

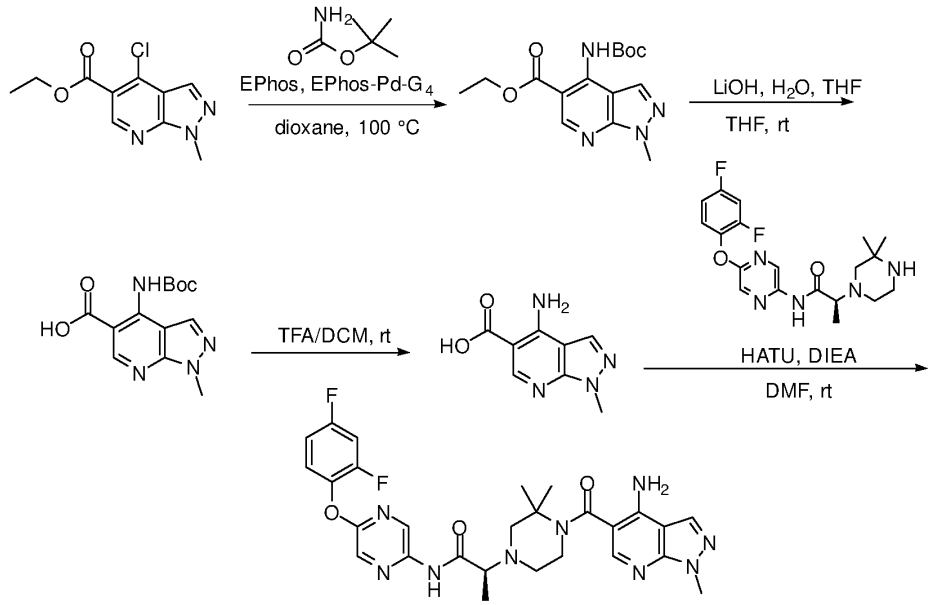
washed with water (3 x 10 mL). The resulting mixture was concentrated under reduced pressure purified by silica gel column (0-10% MeOH/DCM) to afford product. The crude product was purified by chiral-HPLC using a CHIRALPAK IF 25 cm x 2 cm x 5 μm column (eluent: 50% (v/v) EtOH and (HEX: DCM=3: 1) (0.05% 2M NH_3-MeOH)) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-7-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (assumed, 24.1 mg, 4.00%) as a white solid. (MS (ESI): mass calcd. for $C_{26}H_{30}F_2N_8O_4$: 556.24, found: 557.35 $[M+H]^+$),^{1}H NMR (400 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.83 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.88 (s, 1H), 7.41 – 7.53 (m, 2H), 7.12 – 7.22 (m, 1H), 5.92 (d, J = 6.3 Hz, 1H), 4.83 (t, J = 6.6 Hz, 1H), 4.11 – 4.23 (m, 1H), 3.92 – 4.04 (m, 1H), 3.46 – 3.63 (m, 3H), 3.22 – 3.31 (m, 1H), 2.58 – 2.77 (m, 2H), 2.28 – 2.41 (s, 2H), 2.10 – 2.22 (m, 1H), 1.93 – 2.10 (m, 1H), 1.37 (d, J = 10.9 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H). (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-7-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (assumed, 30.8 mg, 5.13%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{30}F_2N_8O_4$: 556.24, found: 557.30 $[M+H]^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.88 (s, 1H), 7.41-7.54 (m, 2H), 7.12 – 7.22 (m, 1H), 5.91 (d, J = 6.3 Hz, 1H), 4.83 (t, J = 6.6 Hz, 1H), 4.11 – 4.22 (m, 1H), 3.93 – 4.02 (m, 1H), 3.47 – 3.64 (m, 3H), 3.21 – 3.31 (m, 1H), 2.68 – 2.78 (m, 1H), 2.57 – 2.66 (m, 1H), 2.30 – 2.42 (m, 2H), 2.11 – 2.20 (m, 1H), 1.92 – 2.10 (m, 1H), 1.37 (d, J = 5.5 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H). (R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-7-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (assumed, 27.1 mg, 4.51%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{30}F_2N_8O_4$: 556.24, found: 557.35 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.84 (d, J = 1.5 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.88 (s, 1H), 7.41 – 7.53 (m, 2H), 7.12 – 7.22 (m, 1H), 5.92 (d, J = 6.3 Hz, 1H), 4.83 (t, J = 6.6 Hz, 1H), 4.11 – 4.22 (m, 1H), 3.92 – 4.03 (m, 1H), 3.46 – 3.65 (m, 3H), 3.21 – 3.31 (m, 1H), 2.69 – 2.78 (m, 1H), 2.57 – 2.65 (m, 1H), 2.30 – 2.42 (m, 2H), 2.10 – 2.20 (m, 1H), 1.92 – 2.07 (m, 1H), 1.37 (d, J = 5.5 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H). (R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-7-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (assumed, 26.2 mg, 4.36%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{30}F_2N_8O_4$: 556.24, found: 557.30 $[M+H]^+$,^{1}H NMR (400 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.83 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.88 (s, 1H), 7.41 – 7.53 (m, 2H), 7.12 – 7.22 (m, 1H), 5.92 (d, J = 6.4 Hz, 1H), 4.83 (t, J = 6.6 Hz, 1H), 4.11 – 4.22 (m, 1H), 3.92 – 4.03 (m, 1H), 3.47 – 3.62 (m, 3H), 3.22 – 3.31 (m, 1H), 2.68 – 2.77 (m, 1H), 2.59 – 2.68 (m, 1H), 2.35 (s, 2H), 2.10 – 2.21 (m, 1H),

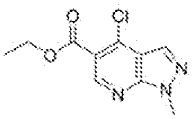
1.93 – 2.07 (m, 1H), 1.37 (d, *J* = 10.9 Hz, 6H), 1.20 (d, *J* = 6.9 Hz, 3H).

Example 270: ((S)-2-(4-(4-amino-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide



Synthetic Scheme

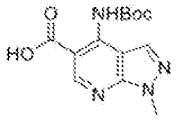




Synthesis of ethyl 4-((tert-butoxycarbonyl)amino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

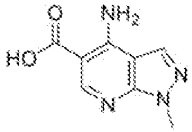
To a solution of ethyl 4-chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (500

mg, 2.086 mmol, 1 equiv) in dioxane (5 mL) was added tert-butyl carbamate (1.22 g, 10.430 mmol, 5 equiv), Ephos (111.58 mg, 0.209 mmol, 0.1 equiv), EPhos Pd G4 (191.64 mg, 0.209 mmol, 0.1 equiv) and Cs_2CO_3 (2.04 g, 6.258 mmol, 3 equiv). The reaction was stirred at 100 °C for 2 h under N_2. After cooled to room temperature the reaction mixture was quenched by water (30 mL) and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford ethyl 4-((tert-butoxycarbonyl)amino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate as a white solid. MS (ESI): mass calcd. for $C_{15}H_{20}N_4O_4$: 320.17 m/z, found: 321.10 $[M+H]^+$.



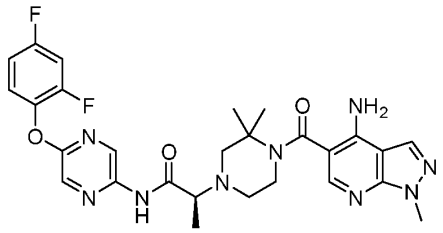
Synthesis of 4-((tert-butoxycarbonyl)amino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid

To a solution of ethyl ethyl 4-((tert-butoxycarbonyl)amino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (210 mg, 0.656 mmol, 1 equiv) in H_2O (1 mL), MeOH (3 mL) and THF (3 mL). The reaction was stirred at 25 °C for 2 h. After completion of reaction the mixture was acidified neutralized to (pH =3) with (4N HCl). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by C18 column (0-60% H_2O/CH_3CN) 4-((tert-butoxycarbonyl)amino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid (170 mg, 88.72%) as a white solid. MS (ESI): mass calcd. for $C_{13}H_{16}N_4O_4$: 292.17 m/z, found: 293.15 $[M+H]^+$.



Synthesis of 4-amino-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid

To a solution of 4-((tert-butoxycarbonyl)amino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid (100 mg, 0.34 mmol, 1 equiv) in DCM (3 mL) added TFA (1.5 mL). The reaction was stirred at 25 °C for 2 h. The reaction mixture was concentrated to afford 4-amino-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid (80 mg, crude) as a yellow oil. MS (ESI): mass calcd. for $C_8H_8N_4O_2$: 192.06 m/z, found: 193.10 [M+H]+.

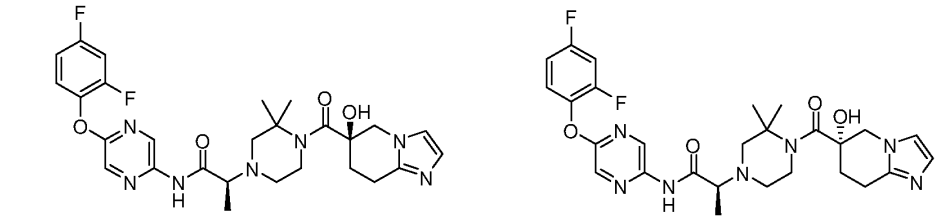


Synthesis of (S)-2-(4-(4-amino-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

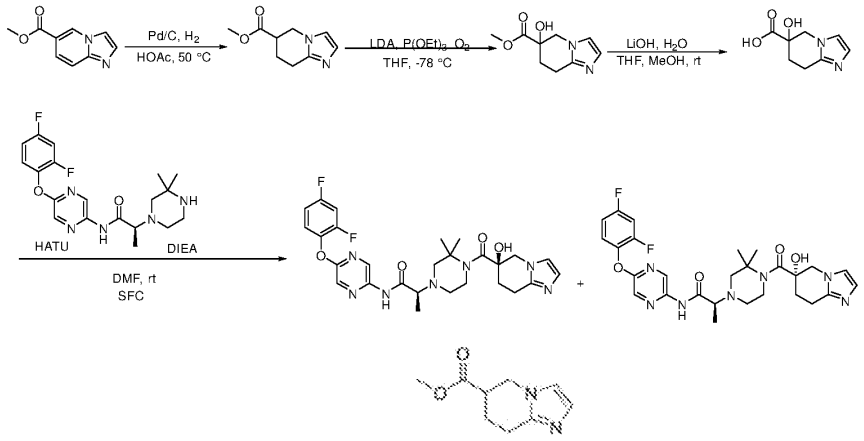
To a solution of 4-amino-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid (50 mg, 0.260 mmol, 1 equiv) in DMF (1 mL) was added (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (81.47 mg, 0.208 mmol, 0.8 equiv), HATU (148.39 mg, 0.390 mmol, 1.5 equiv) and DIEA (100.88 mg, 0.780 mmol, 3 equiv). The reaction was stirred at 25 °C for 2 h. The reaction mixture was quenched by water (5 mL) and extracted with EA (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford (S)-2-(4-(4-amino-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (2.5 mg, 1.65%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{29}F_2N_9O_3$: 565.24 m/z, found: 566.15 $[M+H]^+$.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.5 Hz, 1H), 8.22 (s, 1H), 8.09 (s, 1H), 7.40 – 7.52 (m, 2H), 7.10 – 7.21 (m, 3H), 3.91 (s, 3H), 3.52 – 3.61 (m, 1H), 3.41 – 3.49 (m, 2H), 2.73 – 2.82 (m, 2H), 2.45 – 2.52 (m, 2H), 1.48 (d, J = 1.9 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H).

Example 272: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-6-hydroxy-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide and Example 271: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-6-hydroxy-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

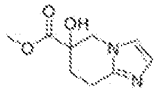


Synthetic Scheme



Synthesis of methyl 5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carboxylate

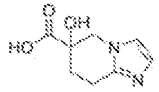
To a solution of methyl imidazo[1,2-a]pyridine-6-carboxylate (3 g, 17.029 mmol, 1 equiv) in acetic acid (100 mL) was added 10% Pd/C (0.9 g). The mixture was stirred at 50°C for 16 h under H_2 (0.5 Mpa). After completion reaction the reaction was cooled to room temperature filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% MeOH/DCM) to afford methyl 5H,6H,7H,8H-imidazo[1,2-a]pyridine-6-carboxylate (2.5 g, 81.47%) as a yellow oil. MS (ESI): mass calcd. for $C_9H_{12}N_2O_2$: 180.09, found: 181.10 $[M+H]^+$.



Synthesis of methyl 6-hydroxy-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carboxylate

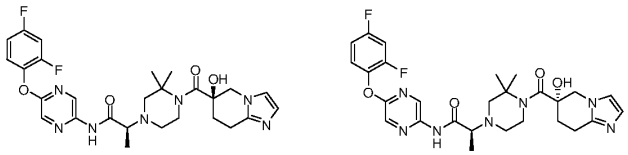
To a solution of methyl 5H,6H,7H,8H-imidazo[1,2-a]pyridine-6-carboxylate (500 mg, 2.775 mmol, 1 equiv) in THF (20 mL) was cooled to -78°C then added 2N LDA (4.0 mL, 8.047 mmol, 2.9 equiv) under N_2. The mixture was stirred at -78°C for 0.5 h under N_2. O_2 was passed

through this solution for 5min, the mixture was added $P(OEt)_3$ (922.03 mg, 5.550 mmol, 2 equiv). The reaction was stirred at -78°C for 30 min. After completion reaction the reaction was quenched by NH_4Cl solution (10 mL) then extracted with EA (3 x 50 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% MeOH/DCM) to afford methyl 6-hydroxy-5H,7H,8H-imidazo[1,2-a]pyridine-6-carboxylate (141 mg, 25.90%) as a yellow solid. MS (ESI): mass calcd. for $C_9H_{12}N_2O_3$: 196.08, found: 197.10 $[M+H]^+$.



Synthesis of 6-hydroxy-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carboxylic acid

To a solution of methyl 6-hydroxy-5H,7H,8H-imidazo[1,2-a]pyridine-6-carboxylate (90 mg, 0.459 mmol, 1 equiv) in tetrahydrofuran (2 mL) methanol (1 mL) and water (1 mL) was added LiOH (16.48 mg, 0.689 mmol, 1.5 equiv). The mixture was stirred at room temperature for 2 h. After completion of reaction the mixture was acidified neutralized to (pH =3) with (4N HCl). The residue was purified by C18 column (0-60% H_2O/CH_3CN) to afford 6-hydroxy-5H,7H,8H-imidazo[1,2-a]pyridine-6-carboxylic acid (289 mg, 88.93%) as a yellow solid. MS (ESI): mass calcd. for $C_8H_{10}N_2O_3$: 182.07, found: 183.15 $[M+H]^+$.

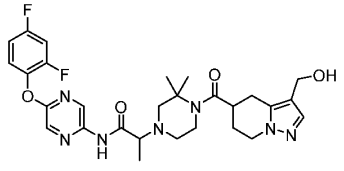


Synthesis of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-6-hydroxy-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide and (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-6-hydroxy-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

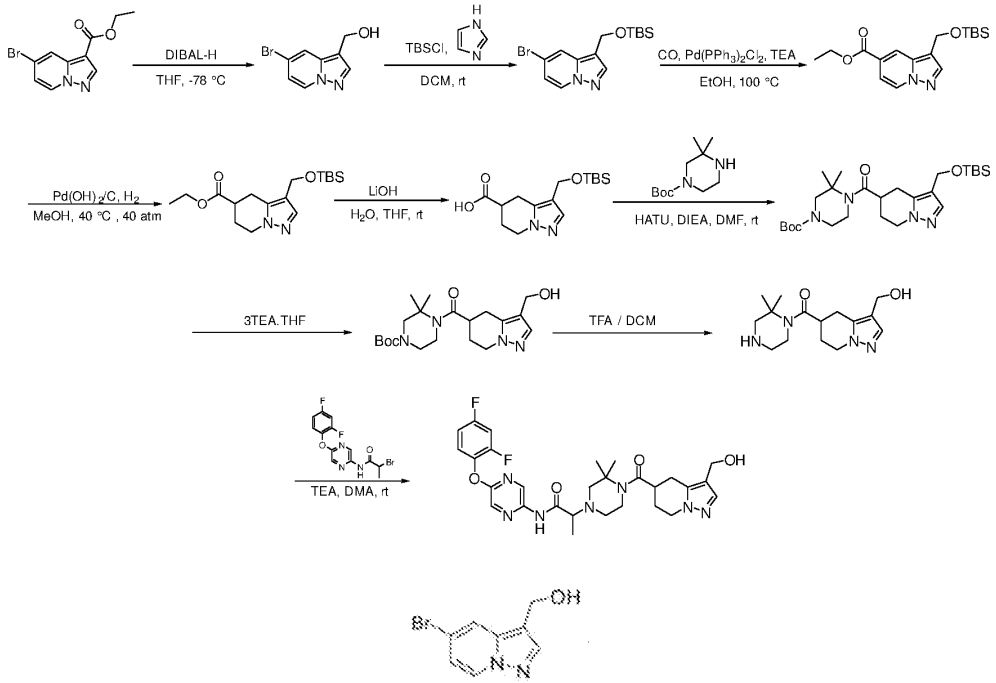
To a solution of 6-hydroxy-5H,7H,8H-imidazo[1,2-a]pyridine-6-carboxylic acid (50 mg, 0.274 mmol, 1 equiv) in N,N-dimethylformamide (5 mL) was added (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (75.20 mg, 0.192 mmol, 0.7 equiv), HATU (156.54 mg, 0.411 mmol, 1.5 equiv) then added DIEA (106.42 mg, 0.822 mmol, 3 equiv). The mixture was stirred at room temperature for 2 h. After completion reaction the reaction was quenched by water (10 mL) then extracted with EA (3 x 50 mL). The

residue was washed with water (3 x 10 mL). The resulting mixture was concentrated under reduced pressure purified by silica gel column (0-10% MeOH/DCM) to afford product. The compound was separated by chiral-HPLC using a CHIRALPAK IF 25 cm x 2 cm x 5 μm column (eluent: 50% (v/v) EtOH and (HEX: DCM=3: 1) (0.05% 2M NH_3-MeOH)) to afford to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-6-hydroxy-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (assumed, 29.8 mg, 19.47%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{31}F_2N_7O_4$: 555.24, found: 556.35 $[M+H]^+$),^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, 1H), 8.84 (s, 1H), 8.46 (d, *J* = 1.5 Hz, 1H), 7.41 – 7.54 (m, 2H), 7.12 – 7.22 (m, 1H), 6.94 (d, *J* = 1.4 Hz, 1H), 6.77 (d, *J* = 1.3 Hz, 1H), 6.09 (d, *J* = 2.0 Hz, 1H), 4.24 (d, *J* = 12.9 Hz, 1H), 3.82 – 4.07 (m, 3H), 3.42 – 3.69 (m, 1H), 2.61 – 2.86 (m, 4H), 2.39 (s, 2H), 2.04 – 2.13 (m, 2H), 1.36 (d, *J* = 2.8 Hz, 6H), 1.20 (d, *J* = 6.9 Hz, 3H). And (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-6-hydroxy-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (assumed, 31.7 mg, 20.71%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{31}F_2N_7O_4$: 555.24, found: 556.35 $[M+H]^+$,^{1}H NMR (400 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.84 (d, *J* = 1.4 Hz, 1H), 8.46 (d, *J* = 1.5 Hz, 1H), 7.41 – 7.54 (m, 2H), 7.12 – 7.22 (m, 1H), 6.94 (d, *J* = 1.3 Hz, 1H), 6.77 (d, *J* = 1.2 Hz, 1H), 6.08 (s, 1H), 4.25 (d, *J* = 13.0 Hz, 1H), 4.01 – 4.11 (m, 1H), 3.92 (d, *J* = 13.0 Hz, 1H), 3.78 – 3.87 (m, 1H), 3.42 – 3.69 (m, 1H), 2.71 – 2.86 (m, 2H), 2.56 – 2.72 (m, 2H), 2.33 – 2.46 (m, 2H), 2.03 – 2.15 (s, 2H), 1.36 (d, *J* = 11.0 Hz, 6H), 1.20 (d, *J* = 6.9 Hz, 3H).

Example 273: N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(3-(hydroxymethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide



Synthetic Scheme



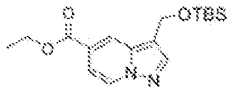
Synthesis of (5-bromopyrazolo[1,5-a]pyridin-3-yl)methanol

To a stirred solution of ethyl 5-bromopyrazolo[1,5-a]pyridine-3-carboxylate (2 g, 7.432 mmol, 1 equiv) in tetrahydrofuran (40 mL) was added 1M DIBAL-H (in DCM, 14.8 mL, 14.86 mmol, 2.0 equiv) at -78 °C under N_2. The reaction mixture was stirred at room temperature for a period of 3h at -78°C. The reaction was quenched by Na_2SO_4 (*aq.*). The resulting mixture was filtered, the filter cake was washed with MeOH. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column (PE/EA=3:1) to afford (5-bromopyrazolo[1,5-a]pyridin-3-yl)methanol (1 g, 59.26%) as a yellow oil. MS (ESI): mass calcd. for $C_8H_7BrN_2O$: 225.97 m/z, found: 226.90 $[M+H]^+$.

Synthesis of 5-bromo-3-(((tert-butyldimethylsilyl)oxy)methyl)pyrazolo[1,5-a]pyridine

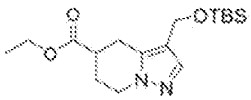
To a stirred solution of (5-bromopyrazolo[1,5-a]pyridin-3-yl)methanol (1 g, 4.404 mmol, 1 equiv) in DCM (20 mL) was added imidazole (0.90 g, 13.212 mmol, 3 equiv) and t-butyldimethylchlorosilane (1.33 g, 8.808 mmol, 2 equiv) at room temperature. The reaction mixture was stirred at room temperature for a period of 2 h. The mixture was concentrated to

dryness under reduced pressure to provide the crude product, which was purified by silica gel chromatography (0-20% PE/EA) to afford 5-bromo-3-(((tert-butyldimethylsilyl)oxy)methyl)pyrazolo[1,5-a]pyridine (1.3 g, 86.48%) as a white solid. MS (ESI): mass calcd. for $C_{14}H_{21}BrN_2OSi$: 340.06 m/z, found 341.00 $[M+H]^+$.



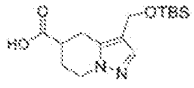
Synthesis of ethyl 3-(((tert-butyldimethylsilyl)oxy)methyl)pyrazolo[1,5-a]pyridine-5-carboxylate

To a stirring solution 5-bromo-3-(((tert-butyldimethylsilyl)oxy)methyl)pyrazolo[1,5-a]pyridine (1.3 g, 3.809 mmol, 1 equiv) in ethyl alcohol (30 mL) was added a solution of $Pd(PPh_3)_2Cl_2$ (0.266 g, 0.38 mmol, 0.1 equiv) and TEA (1.16 g, 11.427 mmol, 3 equiv). The mixture was stirred at 100 °C for 16 h under CO. The mixture was concentrated to dryness under reduced pressure to provide the crude product, which was purified by silica gel chromatography (0-20% PE/EA) to afford ethyl 3-(((tert-butyldimethylsilyl)oxy)methyl)pyrazolo[1,5-a]pyridine-5-carboxylate (800 mg, 62.80%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{26}N_2O_3Si$: 334.17 m/z, found 335.00 $[M+H]^+$.



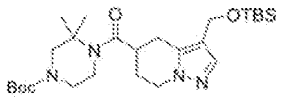
Synthesis of ethyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carboxylate

To a stirring solution of ethyl 3-(((tert-butyldimethylsilyl)oxy)methyl)pyrazolo[1,5-a]pyridine-5-carboxylate (1.5 g, 4.484 mmol, 1 equiv) in ethyl alcohol (30 mL) was added a solution of 10%Pd/C (0.5 g) . The mixture was stirred at 40 °C for 15 h under H_2 (40 atm). After cooled to room temperature, filtered through a celite pad and concentrated under reduced pressure to afford ethyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carboxylate (1.3 g, 85.63%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{30}N_2O_3Si$: 338.20 m/z, found 339.10 $[M+H]^+$.



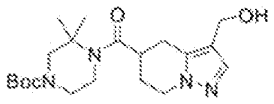
Synthesis of 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carboxylic acid

To a solution of ethyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carboxylate (1 g, 2.954 mmol, 1 equiv) in MeOH (3 mL) , tetrahydrofuran (6 mL) and water (3 mL) was added LiOH (0.14 g, 5.908 mmol, 2 equiv) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The mixture was acidified pH = 5 with HCl (1N). The precipitated solids were collected by filtration and washed with water to afford 3-(((tert-butyldimethylsilyl)oxy)methyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carboxylic acid (900 mg, 98.13%)) by filtration and drying. MS (ESI): mass calcd. for $C_{15}H_{26}N_2O_3Si$: 310.17 m/z, found: 311.20 $[M+H]^-$.



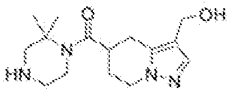
Synthesis of tert-butyl 4-(3-(((tert-butyldimethylsilyl)oxy)methyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazine-1-carboxylate

To a stirred solution of 3-(((tert-butyldimethylsilyl)oxy)methyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carboxylic acid (900 mg, 2.899 mmol, 1 equiv) in dimethylformamide (15 mL) was added DIEA (1 mL, 5.798 mmol, 2 equiv) and HATU (2.2 g, 5.798 mmol, 2 equiv) and tert-butyl 3,3-dimethylpiperazine-1-carboxylate (0.7 g, 3.479 mmol, 1.2 equiv) at room temperature. The reaction mixture was stirred at room temperature for a period of overnight. After completion of reaction, the reaction mixture was quenched by water (20 mL) and extracted with EA (30 mL x 3). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) to afford tert-butyl 4-(3-(((tert-butyldimethylsilyl)oxy)methyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazine-1-carboxylate (560 mg, 38.12%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{46}N_4O_4Si$: 506.33 m/z, found: 507.40 $[M+H]^+$.



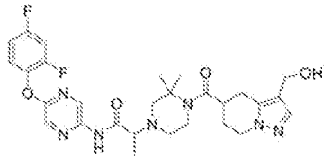
Synthesis of tert-butyl 4-(3-(hydroxymethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazine-1-carboxylate

To a solution of tert-butyl 4-(3-(((tert-butyldimethylsilyl)oxy)methyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazine-1-carboxylate (450 mg, 0.888 mmol, 1 equiv) in tetrahydrofuran (4 mL) and triethylamine trihydrofluoride (1 mL) at rt. The resulting mixture was stirred for 0.5 hours at 60 °C. After cooled to room temperature, the reaction was quenched by water (10 mL) and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford tert-butyl 4-(3-(hydroxymethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazine-1-carboxylate (220 mg, 63.12%) as a white solid. MS (ESI): mass calcd. for $C_{20}H_{32}N_4O_4$: 392.24 m/z, found 393.15 $[M+H]^+$.



Synthesis of (2,2-dimethylpiperazin-1-yl)(3-(hydroxymethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-5-yl)methanone

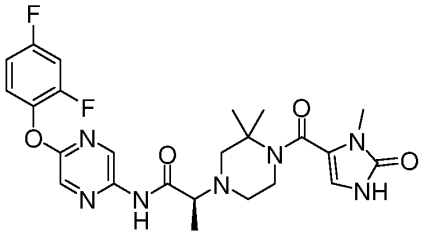
To a stirred solution of tert-butyl 4-(3-(hydroxymethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazine-1-carboxylate (220 mg, 0.561 mmol, 1 equiv) in DCM (3 mL) was added TFA (1 mL). The reaction mixture was stirred at room temperature for 0.5 h. The mixture was concentrated to dryness under reduced pressure to provide the crude product, which was purified by C18 (0-40% H_2O/ACN) to afford (2,2-dimethylpiperazin-1-yl)(3-(hydroxymethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-5-yl)methanone (130 mg, 79.32%) as a white solid. MS (ESI): mass calcd. for $C_{15}H_{24}N_4O_2$: 292.19 m/z, found: 292.95 $[M+H]^+$.



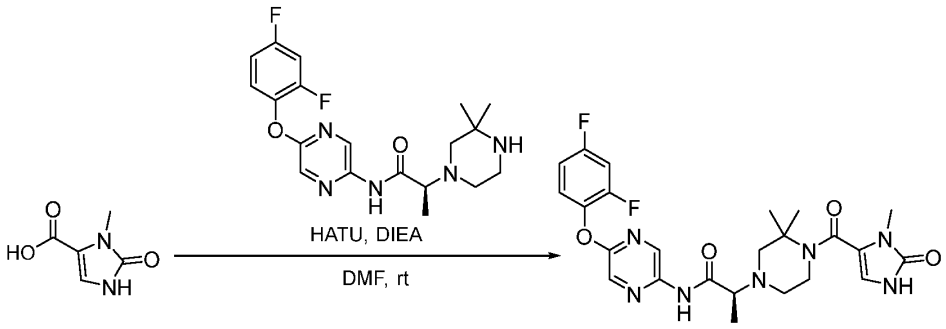
Synthesis of N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(3-(hydroxymethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

To a stirring solution (2,2-dimethylpiperazin-1-yl)(3-(hydroxymethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-5-yl)methanone (100 mg, 0.342 mmol, 1 equiv) in DMA (8 mL) was added a solution of TEA (103.83 mg, 1.026 mmol, 3 equiv) and (2S)-2-bromo-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]propanamide (146.99 mg, 0.410 mmol, 1.2 equiv). The mixture was stirred at room temperature for 2 h. The mixture was concentrated to dryness under reduced pressure to provide the crude product, which was purified by C18 column (CH_3CN & H_2O) & Prep-HPLC (Column DAICELDC pakP4VP4.6*50 mm, 3m; (eluent: MeOH 1%2MNH_3MeOH)) to afford N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(3-(hydroxymethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (25.9 mg, 13.22%) as a white solid. MS (ESI): mass calcd. for $C_{28}H_{33}F_2N_7O_4$: 569.26 m/z, found 592.30 $[M+Na]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.39 – 7.56 (m, 2H), 7.28 (s, 1H), 7.11 – 7.24 (m, 1H), 4.61 (t, J = 5.3 Hz, 1H), 4.27 (d, J = 5.4 Hz, 2H), 3.93 – 4.16 (m, 2H), 3.46 – 3.59 (m, 3H), 3.05 – 3.21 (m, 1H), 2.80 – 2.96 (m, 1H), 2.50 – 2.71 (m, 3H), 2.37 (s, 2H), 2.00 – 2.11 (m, 1H), 1.86 – 2.00 (m, 1H), 1.40 (d, J = 1.7 Hz, 6H), 1.26 (d, J = 7.0 Hz, 3H).

Example 274: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(3-methyl-2-oxo-2,3-dihydro-1H-imidazole-4-carbonyl)piperazin-1-yl)propanamide



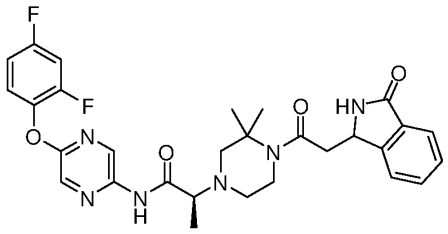
Synthetic Scheme



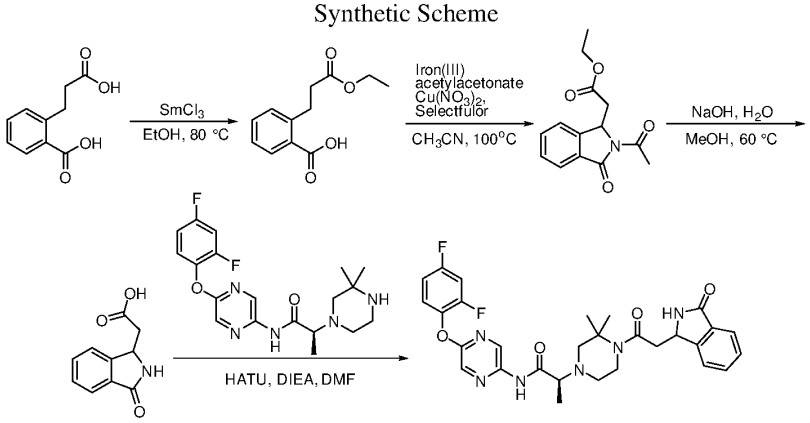
Synthesis of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(3-methyl-2-oxo-2,3-dihydro-1H-imidazole-4-carbonyl)piperazin-1-yl)propanamide

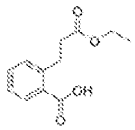
To a solution of 3-methyl-2-oxo-1H-imidazole-4-carboxylic acid (50 mg, 0.352 mmol, 1 equiv) in DMF (3 mL), (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (137.71 mg, 0.352 mmol, 1 equiv), HATU (267.56 mg, 0.704 mmol, 2 equiv) and DIEA (136.42 mg, 1.056 mmol, 3 equiv) was added at rt. The mixture was allowed to warm to rt and stirred for 2h. The reaction was quenched with H_2O (10 mL). The resulting mixture was extracted with EA (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20%DCM/MeOH) and Prep-HPLC using a Column: YMC-Actus Triart C18 ExRS30*150 mm; (eluent: 37% to 59% ACN and H_2O (10mmol/L NH_4CO_3+0.05% NH_3H_2O) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(3-methyl-2-oxo-2,3-dihydro-1H-imidazole-4-carbonyl)piperazin-1-yl)propanamide (9.3 mg, 5.11%) as a white solid. MS (ESI): mass calcd. for $C_{24}H_{27}F_2N_7O_4$: 515.21 m/z, found: 516.30 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.50 (br, 1H), 10.39 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.40 – 7.56 (m, 2H), 7.11 – 7.24 (m, 1H), 6.82 (s, 1H), 3.46 – 3.46 (m, 3H), 3.12 (s, 3H), 2.70 – 2.80 (m, 1H), 2.59 – 2.69 (m, 1H), 2.39 (s, 2H), 1.40 (d, J = 2.3 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H).

Example 275: (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(2-(3-oxoisoindolin-1-yl)acetyl)piperazin-1-yl)propanamide



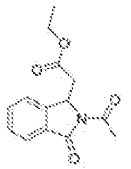
Synthetic Scheme





Synthesis of 2-(3-ethoxy-3-oxopropyl)benzoic acid

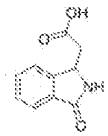
To a solution of 2-(2-carboxyethyl)benzoic acid (200 mg, 1.030 mmol, 1 equiv) in EtOH (10 mL) added $SmCl_3$ (5 mg). The reaction was stirred at 80 °C for 2 h. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-30%) to afford 2-(3-ethoxy-3-oxopropyl)benzoic acid (0.2 g, 87.7%) as a white solid. MS (ESI): mass calcd. for $C_{12}H_{14}O_4$: 222.17 m/z, found: 223.15 $[M+H]^+$.



Synthesis of ethyl 2-(2-acetyl-3-oxo-1H-isoindol-1-yl)acetate)

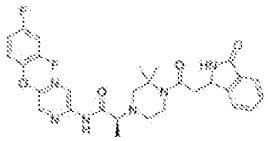
To a solution of 2-(3-ethoxy-3-oxopropyl)benzoic acid (200 mg, 0.900 mmol, 1

equiv) in CH_3CN (10 mL) added Selectfulor (637.62 mg, 1.800 mmol, 2 equiv) and Iron (III) acetylacetonate (63.57 mg, 0.180 mmol, 0.2 equiv) and $Cu(NO_3)_2$ (3 mg). The reaction was stirred at 100 °C under for 12 h under N_2. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-30%) to afford ethyl 2-(2-acetyl-3-oxo-1H-isoindol-1-yl)acetate) (140 mg, 60.5%) as a white solid. MS (ESI): mass calcd. for $C_{20}H_{24}ClN_5O_2$: 261.17 m/z, found: 262.15 $[M+H]^+$.



Synthesis of 2-(3-oxoisoindolin-1-yl)acetic acid

To a solution of ethyl 2-(2-acetyl-3-oxo-1H-isoindol-1-yl)acetate) (140 mg, 0.536 mmol, 1 equiv) in THF (1 mL), H_2O (1 mL) and MeOH (1 mL) added NaOH (42.8 mg, 1.07 mmol, 2 equiv). The reaction was stirred at 100 °C under for 12 h. After completion reaction the reaction was cooled to room temperature. The mixture was acidified pH = 4 with HCl (1N). The residue obtained was purified by C18 column (0-50% H_2O/CH_3CN) to afford 2-(3-oxoisoindolin-1-yl)acetic acid (0.1 g, 95.6%) as a white solid.



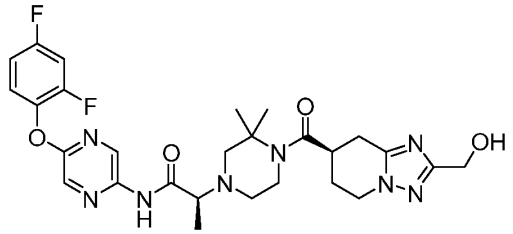
Synthesis of (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(2-(3-oxoisoindolin-1-yl)acetyl)piperazin-1-yl)propanamide

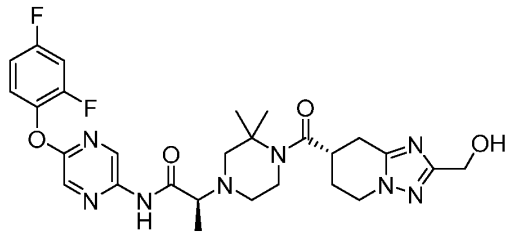
To a solution of 2-(3-oxoisoindolin-1-yl)acetic acid (100 mg, 0.523 mmol, 1 equiv) in DMF (3 mL) was added (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (163.79 mg, 0.418 mmol, 0.8 equiv), HATU (258.55 mg, 0.680 mmol, 1.3 equiv) and DIEA (202.81 mg, 1.569 mmol, 3 equiv). The reaction was stirred at 25 °C for 2 h. Quenched with water (10 mL) and extracted with EA (3 x 10 ml). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by C18 column H_2O/CH_3CN (0-50%) to afford (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(2-(3-oxoisoindolin-1-yl)acetyl)piperazin-1-yl)propanamide (46.9 mg, 15.82%) as a white solid. MS (ESI): mass calcd. for $C_{29}H_{30}F_2N_6O_4$:

564.17 m/z, found: 565.15 $[M+H]^+$.

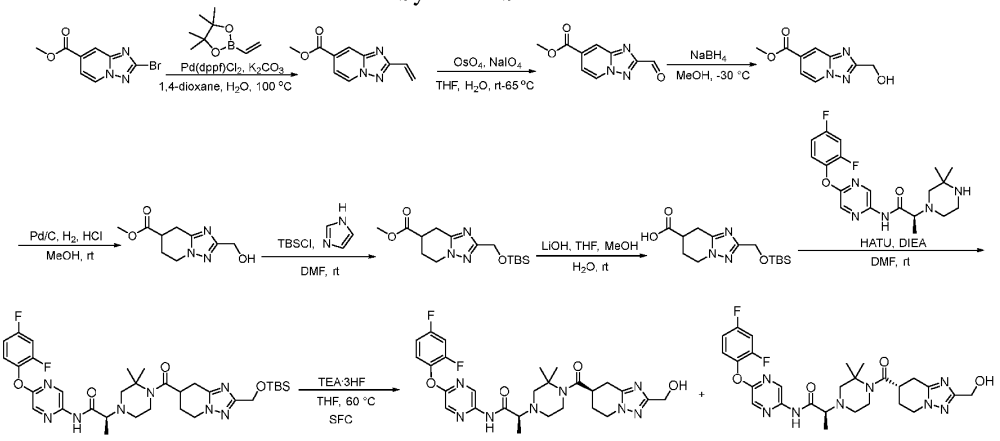
^{1}H NMR (300 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.83 (d, J = 1.5 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 8.31 (s, 1H), 7.59 – 7.69 (m, 3H), 7.38 – 7.51 (m, 3H), 7.12 – 7.23 (m, 1H), 4.91 (t, J = 6.5 Hz, 1H), 3.49 – 3.55 (m, 1H), 3.39 – 3.46 (m, 2H), 2.82 – 2.94 (m, 1H), 2.59 – 2.69 (m, 3H), 2.25 – 2.40 (m, 2H), 1.46 (d, J = 1.8 Hz, 6H), 1.18 (d, J = 6.8 Hz, 3H).

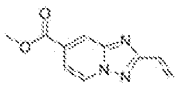
Example 277: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-2-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide and Example 276: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-2-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide





Synthetic Scheme





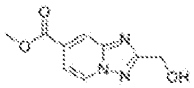
Synthesis of methyl 2-vinyl-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylate

To a solution of methyl 2-bromo-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylate (2.5 g, 9.763 mmol, 1 equiv) in 1,4-dioxane (30 ml) & water (3 mL, 0.056 mmol, 0.71 equiv) K_2CO_3 (2.72 g, 19.526 mmol, 2 equiv), $Pd(dppf)Cl_2$ (0.71 g, 0.976 mmol, 0.1 equiv) was added at rt under N_2 atmosphere. The mixture was allowed to warm to 100 °C and stirred for 12h under N_2. After cooled room temperature, the resulting mixture was filtered. The filter cake was washed with 1,4-dioxane. The filtrate was concentrated under reduced pressure. The resulting was purified by flash chromatography (0-30% PE/EA) to afford methyl 2-vinyl-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylate (1 g, 50.41%) as a yellow oil. MS (ESI): mass calcd. For $C_{10}H_9NO_2$: 203.07 m/z, found: 204.05 $[M+H]^+$.



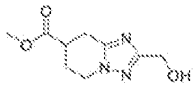
Synthesis of methyl 2-formyl-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylate

To a solution of methyl 2-vinyl-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylate (1 g, 4.921 mmol, 1 equiv) in THF (15 mL) and water (15 mL). Sodium periodate (4.21 g, 19.684 mmol, 4 equiv) was added at rt. After 10 min, osmium tetroxide (in ^{t}BuOH, 1 mL) was added at rt. The mixture was allowed to warm to 65°C and stirred for 4 h. After cooled room temperature, the reaction mixture was quenched by addition of water (30 mL). The resulting mixture was extracted with EA (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100%PE/EA) to afford methyl 2-formyl-[1,2,4] triazol [1,5-a]pyridine-7-carboxylate (600 mg, 59.42%) as a yellow oil. MS (ESI): mass calcd. for $C_9H_7N_3O_3$: 205.05 m/z, found: 206.10 $[M+H]^+$.



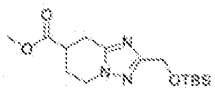
Synthesis of methyl 2-(hydroxymethyl)-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylate

To a solution of methyl 2-formyl-[1,2,4] triazol [1,5-a]pyridine-7-carboxylate (200 mg, 0.975 mmol, 1 equiv) in MeOH (5 mL). $NaBH_4$ (35.89 mg, 0.975 mmol, 1 equiv) was added at -30 °C. The reaction was stirred for 2h at -30 °C. The reaction mixture was quenched by addition of water (5 mL). The resulting mixture was extracted with DCM/MeOH (4:1, 3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-30%PE/EA) to afford methyl 2-(hydroxymethyl)-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylate (200 mg, 99.03%) as a yellow oil. MS (ESI): mass calcd. for $C_9H_6N_3O_3$: 207.06 m/z, found: 208.05 $[M+H]^+$.



Synthesis of methyl 2-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylate

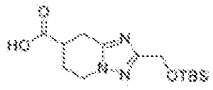
To a solution of methyl 2-(hydroxymethyl)-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylate (200 mg, 0.965 mmol, 1 equiv) in MeOH (5 mL) was added Pd/C (10%, 50 mg) under nitrogen atmosphere and 4N HCl (0.1 mL). The mixture was hydrogenated at room temperature for 12 h under hydrogen atmosphere using a hydrogen balloon. The mixture was filtered through a Celite pad and concentrated under reduced pressure to afford methyl 2-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylate (200 mg, 98.09%) as a yellow solid. MS (ESI): mass calcd. For $C_9H_{13}N_3O_3$: 211.20, found: 212.15 $[M+H]^+$.



Synthesis of methyl 2-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylate

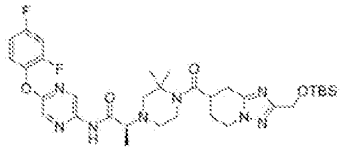
To a solution of methyl 2-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylate (200 mg, 0.947 mmol, 1 equiv) in DMF (5 mL). Imidazole (193.39 mg, 2.841 mmol, 3 equiv) and TBSCl (285.43 mg, 1.894 mmol, 2 equiv) was added at rt. The resulting mixture was stirred for 2h at rt. The reaction mixture was quenched by addition of water (5 mL). The resulting mixture was extracted with EA (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under

vacuum to yield a crude product which was directly purified by flash chromatography (0-30%PE/EA) to afford methyl 2-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylate (100 mg, 32.45%) as a yellow solid. MS (ESI): mass calcd. For $C_{15}H_{27}N_3O_3Si$: 325.18 m/z, found: 326.10 $[M+H]^+$.



Synthesis of 2-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylic acid

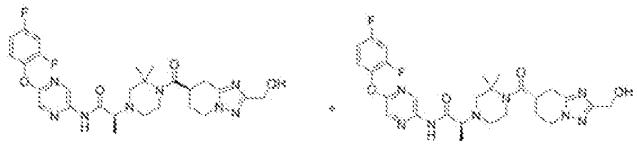
To a solution of methyl 2-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylate (200 mg, 0.614 mmol, 1 equiv) in THF (5 mL), MeOH (3 mL) and water (1 mL) LiOH (29.43 mg, 1.561 mmol, 2 equiv) was added at rt. The resulting mixture was stirred for 2h at rt. The resulting mixture was concentrated under vacuum. The residue was acidified to pH 2~3 with 4N HCl (*aq.*). The precipitated solids were collected by filtration and washed with H_2O to afford 2-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylic acid (150 mg, 78.38%) as a white solid. MS (ESI): mass calcd. for $C_{14}H_{25}N_3O_3Si$: 311.17 m/z, found: 312.20 $[M+H]^+$.



Synthesis of (2S)-2-(4-(2-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

To a solution of 2-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carboxylic acid (100 mg, 0.321 mmol, 1 equiv) in DMF (4 mL) (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (125.67 mg, 0.321 mmol, 1 equiv), HATU (244.17 mg, 0.642 mmol, 2 equiv) and DIEA (331.98 mg, 2.568 mmol, 8 equiv) was added at rt. The mixture was allowed to warm to rt and stirred for 2h. The reaction mixture was quenched by addition of water (10 mL). The resulting mixture was extracted with EA (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20% DCM/MeOH) to afford (2S)-2-(4-

(2-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (30 mg, 13.64%) as a white solid. MS (ESI): mass calcd. For $C_{33}H_{46}F_2N_8O_4Si$: 684.34 m/z, found: 685.20 $[M+H]^+$.

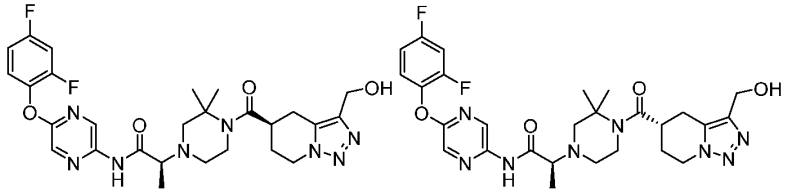


Synthesis of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-2-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

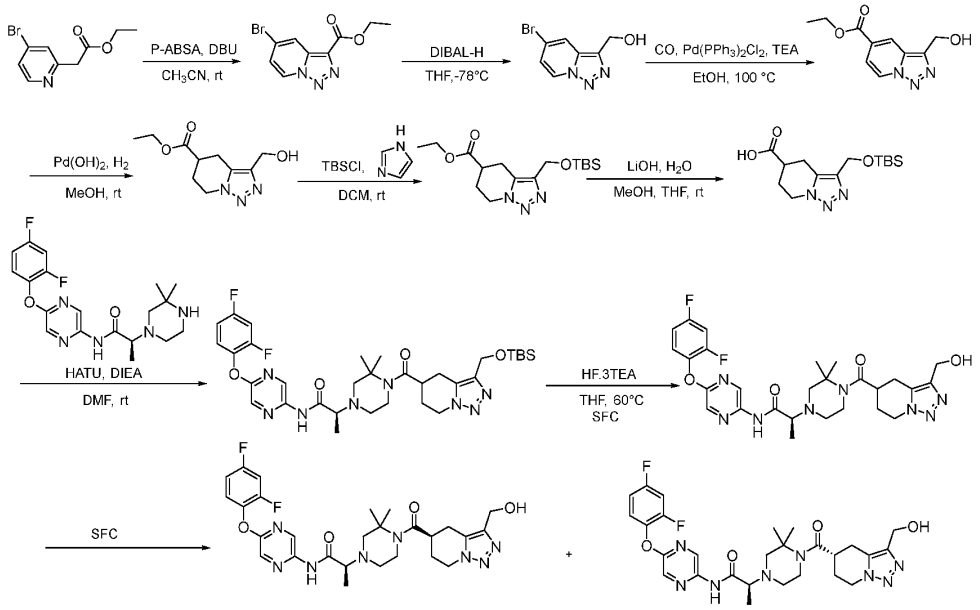
To a solution of (2S)-2-(4-(2-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (50 mg, 0.073 mmol, 1 equiv) in THF (1 mL), TEA·3HF (0.5 mL, 0.003 mmol, 0.04 equiv) was added at rt. The resulting mixture was stirred for 20 min at 60 °C. After cooled to room temperature, the resulting mixture was concentrated under reduced pressure and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 27% to 57% ACN and H_2O (10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(2-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide as a crude. The crude was separated by Chiral-HPLC using a CHIRALPAK IF, 2*25 cm, 5 μm column (eluent: 40% (v/v) MTBE(0.5% 2M NH_3-MeOH) and MEOH: DCM=1: 1) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-2-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (assumed, 3.9 mg, 60.56%) as a white solid. MS (ESI): mass calcd. for$C_{27}H_{32}F_2N_8O_4$: 570.25 m/z, found:571.30 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.41 – 7.54 (m, 2H), 7.12 – 7.22 (m, 1H), 5.13 (t, J = 6.0 Hz, 1H), 4.34 (d, J = 5.9 Hz, 2H), 3.95 – 4.13 (m, 2H), 3.48 – 3.62 (m, 3H), 2.83 (d, J = 6.9 Hz, 2H), 2.62 – 2.74 (m, 2H), 2.53 – 2.60 (m, 1H), 2.35 (s, 2H), 2.06 – 2.15 (m, 1H), 1.86 – 2.03 (m, 1H), 1.38 (d, J = 4.6 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H). And (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-2-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (assumed, 3.6 mg, 60.56%) as a white solid, MS (ESI): mass calcd. for$C_{27}H_{32}F_2N_8O_4$: 570.25 m/z, found: 571.30 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.41 – 7.55 (m, 2H), 7.13

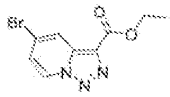
– 7.23 (m, 1H), 5.14 (t, *J* = 6.0 Hz, 1H), 4.35 (d, *J* = 5.9 Hz, 2H), 3.95 – 4.12 (m, 2H), 3.47 – 3.57 (m, 3H), 2.83 (d, *J* = 6.9 Hz, 2H), 2.72 – 2.80 (m, 1H), 2.59 – 2.64 (m, 1H), 2.54 – 2.57 (m, 1H), 2.30 – 2.43 (m, 2H), 2.06 – 2.15 (m, 1H), 1.89 – 2.03 (m, 1H), 1.38 (d, *J* = 4.6 Hz, 6H), 1.20 (d, *J* = 6.9 Hz, 3H).

Example 279: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-3-(hydroxymethyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide and Example 278: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-3-(hydroxymethyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide



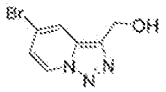
Synthetic Scheme





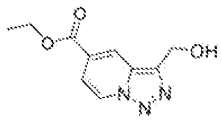
Synthesis of ethyl 5-bromo-[1,2,3]triazolo[1,5-a]pyridine-3-carboxylate

To a stirring solution ethyl 2-(4-bromopyridin-2-yl)acetate (500 mg, 2.048 mmol, 1 equiv) in acetonitrile (5 mL) was added a solution of 4-acetamidobenzene-1-sulfonyl azide (492.12 mg, 2.048 mmol, 1 equiv) and DBU (467.79 mg, 3.072 mmol, 1.5 equiv). The resulting mixture was stirred at room temperature for 6h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-30% PE/EA) to afford ethyl 5-bromo-[1,2,3]triazolo[1,5-a]pyridine-3-carboxylate (100 mg, 18.07%) MS (ESI): mass calcd. for $C_9H_8BrN_3O_2$: 268.98 found: 269.90 $[M+H]^+$.



Synthesis of (5-bromo-[1,2,3]triazolo[1,5-a]pyridin-3-yl)methanol

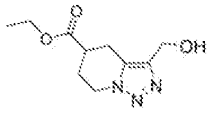
To a stirring solution ethyl 5-bromo-[1,2,3]triazolo[1,5-a]pyridine-3-carboxylate (400 mg, 1.481 mmol, 1 equiv) in tetrahydrofuran (2 mL) was added a solution of 1 M DIBAL-H (in DCM, 2.9 mL, 2.962 mmol, 2 equiv) under N_2. The resulting mixture was stirred at -78°C for 6h. The reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-30% PE/EA) to afford 5-bromo-[1,2,3]triazolo[1,5-a]pyridin-3-yl)methanol (0.3 g, 88.5%). MS (ESI): mass calcd. for $C_7H_6BrN_3O$: 226.98 found: 227.95 $[M+H]^+$.



Synthesis of ethyl 3-(hydroxymethyl)-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylate

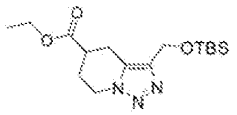
To a stirring solution 5-bromo-[1,2,3]triazolo[1,5-a]pyridin-3-yl)methanol (350 mg, 1.535 mmol, 1 equiv) in ethyl alcohol (15 mL) was added $Pd(PPh_3)_2Cl_2$ (107.72 mg, 0.153 mmol, 0.1

equiv) and TEA (465.92 mg, 4.605 mmol, 3 equiv). The resulting mixture was under CO stirred at 100°C for 16h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford ethyl 3-(hydroxymethyl)-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylate (300 mg, 88.36%). MS (ESI): mass calcd. for $C_{10}H_{11}N_3O_3$: 221.21 found: 222.05 $[M+H]^+$.



Synthesis of ethyl 3-(hydroxymethyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylate

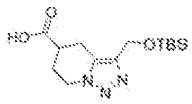
To a stirring solution ethyl 3-(hydroxymethyl)-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylate (300 mg, 1.356 mmol, 1 equiv) in methanol (100 mL) was added a solution of 10% $Pd(OH)_2$ (0.1 g). The resulting mixture was under H_2 stirred at 60°C for 16h. After cooled to room temperature the reaction was filtered through a Celite pad and concentrated under reduced pressure to afford ethyl 3-(hydroxymethyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylate (300 mg, 98.21%). MS (ESI): mass calcd. for $C_{10}H_{15}N_3O_3$: 225.24 found: 226.10 $[M+H]^+$.



Synthesis of ethyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylate

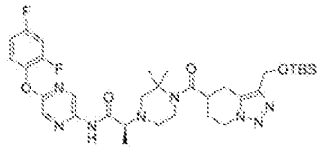
To a stirring solution ethyl 3-(hydroxymethyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylate (300 mg, 1.332 mmol, 1 equiv) in DCM (3 mL) was added a solution of t-butyldimethylchlorosilane (301.11 mg, 1.998 mmol, 1.5 equiv) and imidazole (272.02 mg, 3.996 mmol, 3 equiv). The resulting mixture was stirred at rt for 6h. The reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The

residue obtained was purified by silica gel chromatography (0-30% PE/EA) to afford ethyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylate (400 mg, 88.46%). MS (ESI): mass calcd. for $C_{16}H_{29}N_3O_3Si$: 339.19 found: 340.10 $[M+H]^+$.



Synthesis of 3-(((tert-butyldimethylsilyl)oxy)methyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylic acid

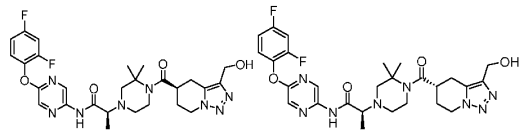
To a stirring solution ethyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylate (400 mg, 1.178 mmol, 1 equiv) in methanol (1 mL) and tetrahydrofuran (2 mL) and water (1 mL) was added a solution of LiOH (85 mg, 3.53 mmol, 3 equiv). The resulting mixture was stirred at room temperature for 6h. The mixture was acidified to pH 4 with 2 N HCl (*aq.*). The mixture was extracted with DCM/MeOH (5:1, 20 mL x 3). The combined organic extracts and concentrated. The residue obtained was purified by C18 column (CH_3CN/H_2O) to afford 3-(((tert-butyldimethylsilyl)oxy)methyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylic acid (168 mg, 45.78%). MS (ESI): mass calcd. for $C_{14}H_{25}N_3O_3Si$: 311.16 found: 312.10 $[M+H]^+$.



Synthesis of (2S)-2-(4-(3-(((tert-butyldimethylsilyl)oxy)methyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

To a stirring solution 3-(((tert-butyldimethylsilyl)oxy)methyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylic acid (150 mg, 0.482 mmol, 1 equiv) in DMF (2 mL) was added a solution of (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (188.51 mg, 0.482 mmol, 1 equiv), HATU (274.68 mg, 0.723 mmol, 1.5 equiv) and DIEA (248.99 mg, 1.928 mmol, 4 equiv). The resulting mixture was stirred at room temperature for 6h. The reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by

silica gel chromatography (0-10% DCM/MeOH) to afford (2S)-2-(4-(3-(((tert-butyldimethylsilyl)oxy)methyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (80 mg, 24.25%).MS (ESI): mass calcd. for $C_{33}H_{46}F_2N_8O_4Si$: 684.33 found: 685.20 $[M+H]^+$.

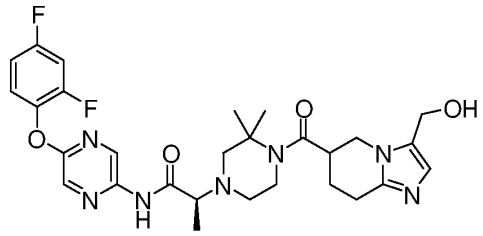


Synthesis of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-3-(hydroxymethyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide and (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-3-(hydroxymethyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

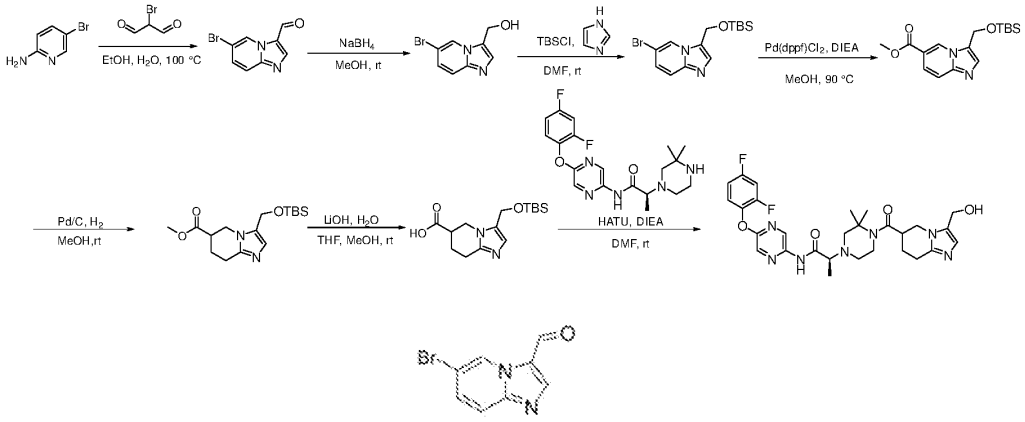
To a stirred solution of (2S)-2-(4-(3-(((tert-butyldimethylsilyl)oxy)methyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (80 mg, 0.117 mmol, 1 equiv) in tetrahydrofuran (3 mL) was added TEA·3HF (0.6 mL) at room temperature. The reaction mixture was stirred at 60°C for 3 h. After completion of reaction, the reaction mixture was quenched by addition of water (5 mL) under rt.. The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(3-(hydroxymethyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (58 mg) as a white solid. The product was separated by Chiral-Prep-HPLC (Lux 5um Cellulose-4, 2.12*25 cm x 5 μm column (eluent: 50% (v/v) EtOH and (HEX: DCM=3: 1) (0.05% 2M NH3-MeOH)) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-3-(hydroxymethyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (assumed, 15 mg, 22.45%). MS (ESI): mass calcd. for $C_{27}H_{32}F_2N_8O_4$: 570.25 m/z, found: 571.30 $[M+H]^+$, ^1H NMR (500 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.84 (s, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.42 –7.53 (m,2H), 7.14 – 7.22 (m,1H), 4.99 (t, J = 5.6 Hz, 1H), 4.47 (d, J = 5.5 Hz, 2H), 4.32 – 4.42 (m,1H), 4.19 – 4.29 (m,1H), 3.49 – 3.59 (m,3H), 3.17 – 3.27 (m,1H), 2.86 – 2.98 (m, 1H), 2.71 – 2.81 (m, 2H), 2.59 – 2.67 (m, 1H), 2.32 – 2.42 (m, 2H), 2.06 – 2.12 (m, 1H), 1.87 – 1.98 (m, 1H), 1.39 (d, J = 4.3 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H). and (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-3-(hydroxymethyl)-

4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (assumed, 14.7 mg, 21.95%). MS (ESI): mass calcd. for $C_{27}H_{32}F_2N_8O_4$: 570.25 m/z, found: 571.30 $[M+H]^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.84 (s, 1H), 8.46 (s, 1H), 7.42 – 7.53 (m, 2H), 7.14 – 7.22 (m,1H), 4.98 (t, J = 5.7 Hz, 1H), 4.47 (d, J = 5.2 Hz, 2H), 4.32 – 4.42 (m,1H), 4.19 – 4.29 (m,1H), 3.49 – 3.59 (m, 3H), 3.19 – 3.27 (m, 1H), 2.85 – 2.98 (m, 1H), 2.68 – 2.80 (m, 2H), 2.59 – 2.67 (m,1H), 2.35 (s, 2H), 2.06 – 2.12 (m, 1H), 1.87 – 1.98 (m, 1H), 1.39 (d, J = 2.5 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H).

Example 280: (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(3-(hydroxymethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide



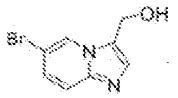
Synthetic Scheme



Synthesis of 6-bromoimidazo[1,2-a]pyridine-3-carbaldehyde

5-bromopyridin-2-amine (1 g, 5.780 mmol, 1.00 equiv) and 2-bromopropanedial (1.31 g, 8.670 mmol, 1.50 equiv) were dissolved in the mixture of ethanol and water (1:1, total 5 ml) and placed in the pressure vial, equipped with a magnetic bar. The mixture was stirred for 1 min and purge with N_2 via syringe. Then microwave (MW) irradiation (with initial 150 W power) was

applied. The reaction mixture was stirred at 100 °C for 10 min. The mixture was allowed to cool down to room temperature. The precipitated solids were collected by filtration and washed with water (3 x 5 mL). The resulting mixture was concentrated under reduced pressure to product 6-bromoimidazo[1,2-a]pyridine-3-carbaldehyde (670 mg, 51.51%). MS (ESI): mass calcd. for $C_8H_5BrN_2O$: 223.96 m/z, found 224.90 $[M+H]^+$.



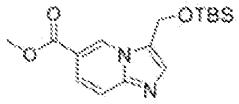
Synthesis of (6-bromoimidazo[1,2-a]pyridin-3-yl)methanol

To a solution of 6-bromoimidazo[1,2-a]pyridine-3-carbaldehyde (1.9 g, 8.443 mmol, 1 equiv) in MeOH (10 mL) was added $NaBH_4$ (1.55 g, 42.215 mmol, 5 equiv) at rt. The resulting mixture was stirred for 3h at rt. The reaction was quenched with H_2O (30 mL) at rt. The resulting mixture was extracted with EA (3 x 60 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-10% DCM/MeOH) to afford (6-bromoimidazo[1,2-a]pyridin-3-yl)methanol (1.5 g, 78.25%). MS (ESI): mass calcd. for $C_8H_7BrN_2O$: 225.97 m/z, found 226.95 $[M+H]^+$.



Synthesis of 6-bromo-3-(((tert-butyldimethylsilyl)oxy)methyl)imidazo[1,2-a]pyridine

To a stirred solution of (6-bromoimidazo[1,2-a]pyridin-3-yl)methanol (1.4 g, 6.166 mmol, 1 equiv) in anhydrous DMF (15 mL) was imidazole (1.26 g, 18.498 mmol, 3 equiv) and TBSCl (3.72 g, 24.664 mmol, 4 equiv) at room temperature. The reaction mixture was stirred at room temperature for a period of 2h. After completion of reaction, the reaction mixture was quenched by addition of water 30 mL. The aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude product which was further purified by column chromatography (0-30%PE/EA) to afford desired compound 6-bromo-3-(((tert-butyldimethylsilyl)oxy)methyl)imidazo[1,2-a]pyridine (1.6 g, 76.03%). MS (ESI): mass calcd. for $C_{14}H_{21}BrN_2Osi$: 340.06 m/z, found 341.15 $[M+H]^+$.



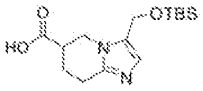
Synthesis of methyl 3-(((tert-butyldimethylsilyl)oxy)methyl)imidazo[1,2-a]pyridine-6-carboxylate

To a solution of 6-bromo-3-(((tert-butyldimethylsilyl)oxy)methyl)imidazo[1,2-a]pyridine (1.3 g, 3.809 mmol, 1 equiv) in 25 m MeOH was added $Pd(dppf)Cl_2$ (0.28 g, 0.381 mmol, 0.1 equiv), DIEA (4.92 g, 38.090 mmol, 10 equiv) in a pressure tank. The mixture was pressurized to 30 atm with carbon monoxide at 90 °C for overnight. The reaction mixture was cooled to room temperature and filtered to remove insoluble solids. The resulting mixture was concentrated under reduced pressure. The residue/crude product was purified by reverse phase flash to afford methyl 3-(((tert-butyldimethylsilyl)oxy)methyl)imidazo[1,2-a]pyridine-6-carboxylate (1.1 g, 86%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{24}N_2O_3Si$: 320.16 m/z, found 321.10 $[M+H]^+$.



Synthesis of methyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carboxylate

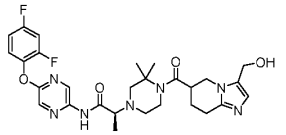
To a solution of methyl 3-(((tert-butyldimethylsilyl)oxy)methyl)imidazo[1,2-a]pyridine-6-carboxylate (1.4 g, 4.369 mmol, 1 equiv) in 20 mL MeOH was added Pd/C (10%, 0.5 g) in a pressure tank. The mixture was hydrogenated at room temperature under 30 atm of hydrogen pressure for overnight, filtered through a Celite pad and concentrated under reduced pressure methyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carboxylate (1.1 g, 80%). MS (ESI): mass calcd. for $C_{16}H_{28}N_2O_3Si$: 324.19 m/z, found 325.10 $[M+H]^+$.



Synthesis of 3-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carboxylic acid

To a solution of methyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-

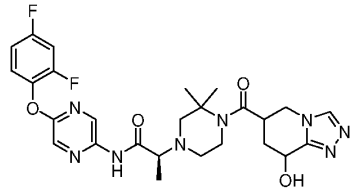
tetrahydroimidazo[1,2-a]pyridine-6-carboxylate (1.1 g, 3.390 mmol, 1 equiv) in THF (8 mL), MeOH (4 mL) and H_2O (4 mL) was added LiOH (162.37 mg, 6.780 mmol, 2 equiv) at rt .The resulting mixture was stirred for 3 h at rt. The mixture was acidified to pH 4 with 4 N HCl (*aq.*). The resulting mixture was filtered, the filter cake was washed with H_2O to afford 3-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carboxylic acid (0.6 g, 57.01%). MS (ESI): mass calcd. for $C_{15}H_{26}N_2O_3Si$: 310.17 m/z, found 311.10 $[M+H]^+$.



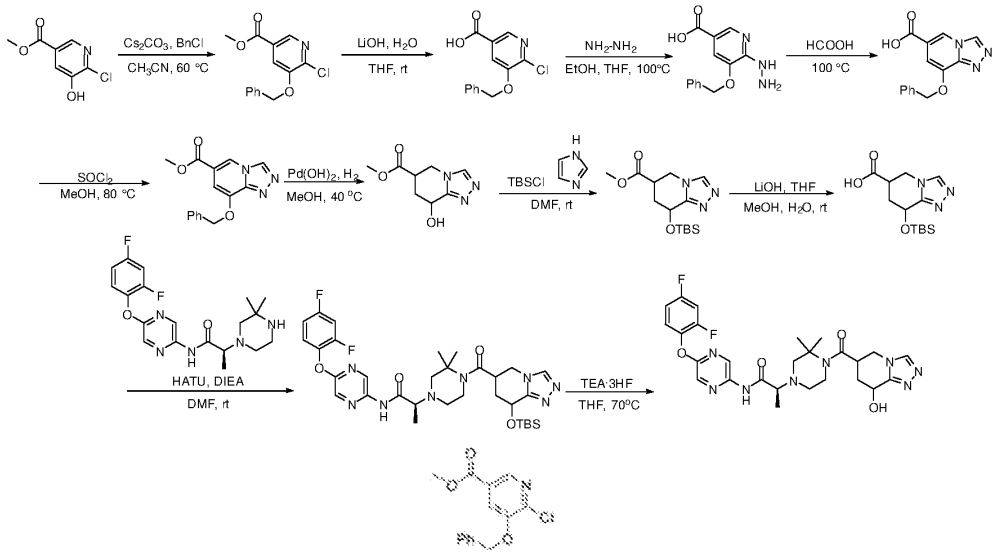
Synthesis of (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(3-(hydroxymethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

To a solution of 3-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carboxylic acid (100 mg, 0.322 mmol, 1 equiv) in DMF (3 mL) was added (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (126.07 mg, 0.322 mmol, 1 equiv), HATU (183.71 mg, 0.483 mmol, 1.5 equiv) and DIEA (249.78 mg, 1.932 mmol, 6 equiv) at rt. The resulting mixture was stirred for 2h at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford product (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(3-(hydroxymethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide as a white solid. MS (ESI): mass calcd. for $C_{28}H_{33}F_2N_7O_4$: 569.26 m/z, found 570.25 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d4) δ 8.89 (s, 1H), 8.30 (s, 1H), 7.29 – 7.39 (m, 1H), 7.12 – 7.20 (m, 2H), 6.86 (s, J = 4.5 Hz, 1H), 4.55 – 4.63 (m, 3H), 4.18 – 4.23 (m, 1H), 4.04 – 4.11 (m, 1H), 3.64 – 3.81 (m, 3H), 2.85 – 3.03 (m, 5H), 2.43 – 2.50 (m, 2H), 2.14 – 2.24 (m, 1H), 1.93 – 2.14 (m, 1H), 1.53 (d, J = 3.0 Hz, 6H), 1.34 (d, J = 6.9 Hz, 3H).

Example 281: (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(8-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

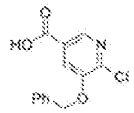


Synthetic Scheme



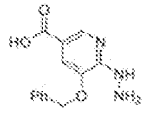
Synthesis of methyl 5-(benzyloxy)-6-chloronicotinate

To a stirred solution of methyl 6-chloro-5-hydroxypyridine-3-carboxylate (1 g, 5.331 mmol, 1 equiv) in anhydrous CH_3CN was added Cs_2CO_3 (8.68 g, 26.655 mmol, 5 equiv) stirred for 1h at room temperature. To the above mixture was added benzyl chloride (1.35 g, 10.662 mmol, 2 equiv) dropwise over 5 min at room temperature. The resulting mixture was stirred for additional 3h at 60°C. The mixture was allowed to cool down to room temperature. The reaction was quenched with H_2O (30 mL). The resulting mixture was extracted with EA (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (5-25% PE/EA) to afford methyl 5-(benzyloxy)-6-chloropyridine-3-carboxylate (0.9 g, 57.85%) as a white solid. MS (ESI): mass calcd. for $C_{14}H_{12}ClNO_3$: 277.05 m/z, found 278.10 $[M+H]^+$.



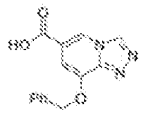
Synthesis of 5-(benzyloxy)-6-chloronicotinic acid

To a stirred solution of methyl 5-(benzyloxy)-6-chloropyridine-3-carboxylate (0.9 g, 3.241 mmol, 1 equiv) in anhydrous THF (12 mL) and MeOH (4 mL) and H_2O (4 mL) was added LiOH (0.12 g, 4.862 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for a period of 2h. The mixture/residue was acidified to pH 6 with 4 N HCl (*aq.*). The resulting mixture was extracted with EA (3 x 20 mL). The organic layer was concentrated under vacuum to afford 5-(benzyloxy)-6-chloropyridine-3-carboxylic acid (0.8 g, 91.07%) as a white solid. MS (ESI): mass calcd. for $C_{13}H_{10}ClNO_3$: 263.03 m/z, found 264.00 $[M+H]^+$.



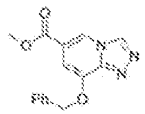
Synthesis of 5-(benzyloxy)-6-hydrazineylnicotinic acid

To a stirred solution of 5-(benzyloxy)-6-chloropyridine-3-carboxylic acid (800 mg, 3.034 mmol, 1 equiv) in anhydrous EtOH (8 mL) was added 99% hydrazine (1.9 g, 60.680 mmol, 20 equiv) and THF (2 mL) at 0°C. The reaction mixture was stirred at 100°C for a period of 2h. The resulting mixture was concentrated under reduced pressure. This resulted in 5-(benzyloxy)-6-hydrazinylpyridine-3-carboxylic acid (650 mg, 74.12%) as a yellow solid. MS (ESI): mass calcd. for $C_{13}H_{13}N_3O_3$: 259.09 m/z, found 260.05 $[M+H]^+$.



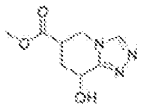
Synthesis of 8-(benzyloxy)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid

To a stirred solution of 5-(benzyloxy)-6-hydrazinylpyridine-3-carboxylic acid (650 mg, 2.507 mmol, 1 equiv) in anhydrous formic acid (10 mL). The reaction mixture was stirred at 100°C for a period of 2h. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. This resulted in 8-(benzyloxy)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid (600 mg, 81.09%) as a white solid. MS (ESI): mass calcd. for: $C_{14}H_{11}N_3O_3$: 269.08 m/z, found: 270.00 $[M+H]^+$.



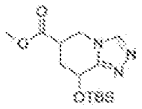
Synthesis of methyl 8-(benzyloxy)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylate

To a stirred solution of 8-(benzyloxy)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid (600 mg, 2.228 mmol, 1 equiv) in anhydrous MeOH (20 mL) was added thionyl chloride (1.6 mL, 22.280 mmol, 10 equiv) at 0°C. The reaction mixture was stirred at 80°C for a period of 2h. After cooled to room temperature the reaction was quenched by water (30 mL) and extracted with DCM/MeOH (50 mL x 3). The combined organic extracts were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-10% DCM/MeOH) to afford methyl 8-(benzyloxy)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylate (0.5 g, 67.88%) as a yellow solid. MS (ESI): mass calcd. for $C_{15}H_{13}N_3O_3$: 283.09 m/z, found 284.00 $[M+H]^+$.



Synthesis of methyl 8-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylate

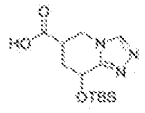
To a solution of 8-(benzyloxy)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid (1.4 g, 5.199 mmol, 1 equiv) in MeOH (30 mL) was added $Pd(OH)_2$ (10%, 0.5 g) in a pressure tank. The mixture was hydrogenated for overnight at 40 °C in 20 atm. The mixture was filtered through a celite pad and concentrated under reduced pressure. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) to afford methyl 8-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylate (800 mg, 78.03%) as a white solid. MS (ESI): mass calcd. for $C_8H_{11}N_3O_3$: 197.08 m/z, found 198.10 $[M+H]^+$.



Synthesis of methyl 8-((tert-butyldimethylsilyl)oxy)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylate

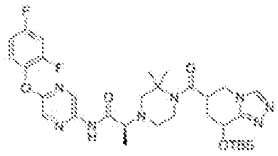
To a stirred solution of methyl 8-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylate (100 mg, 0.507 mmol, 1 equiv) in anhydrous DMF (2 mL) was added t-butyldimethylchlorosilane (114.65 mg, 0.760 mmol, 1.5 equiv) and imidazole (103.57 mg,

1.521 mmol, 3 equiv) at room temperature. The reaction mixture was stirred at room temperature for a period of overnight. After completion of reaction, the reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) to afford methyl 8-((tert-butyldimethylsilyl)oxy)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylate (85 mg, 53.82%) as a white solid. MS (ESI): mass calcd. for $C_{14}H_{25}N_3O_3Si$: 311.17 m/z, found 312.10 $[M+H]^+$.



Synthesis of 8-((tert-butyldimethylsilyl)oxy)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid

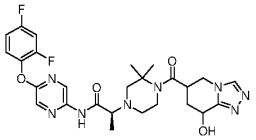
To a stirred solution of methyl 8-[(tert-butyldimethylsilyl)oxy]-5H,6H,7H,8H-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylate (500 mg, 1.605 mmol, 1 equiv) in anhydrous H_2O (1 mL) and THF (3 mL) and MeOH (1 mL) was added LiOH (57.67 mg, 2.407 mmol, 1.5 equiv) at room temperature. The reaction mixture was stirred at room temperature for a period of 3h. The mixture was acidified to pH 5 with conc. HCl. The precipitated solids were collected by filtration and washed with H_2O to afford 8-((tert-butyldimethylsilyl)oxy)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid (280 mg, 58.64%) as a white solid. MS (ESI): mass calcd. for $C_{13}H_{23}N_3O_3Si$: 297.15 m/z, found 298.05 $[M+H]^+$.



Synthesis of (2S)-2-(4-(8-((tert-butyldimethylsilyl)oxy)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

To a stirred solution of 8-((tert-butyldimethylsilyl)oxy)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid (300 mg, 1.009 mmol, 1 equiv) in anhydrous DMF (5 mL) was added (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (592.21 mg, 1.513 mmol, 1.5 equiv) and HATU (767.04 mg, 2.018 mmol, 2 equiv) and DIEA (391.09 mg, 3.027 mmol, 3 equiv) at room temperature.

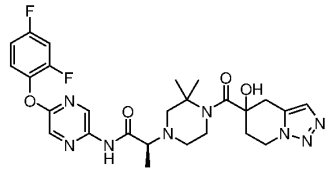
The reaction mixture was stirred at room temperature for a period of 2h. After completion of reaction, the reaction was quenched by water (10 mL) and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (5-20% DCM/MeOH) to afford (2S)-2-(4-(8-((tert-butyldimethylsilyl)oxy)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (200 mg, 21.93%) as a white solid. MS (ESI): mass calcd. for $C_{32}H_{44}F_2N_8O_4Si$: 670.32 m/z, found 671.20 $[M+H]^+$.



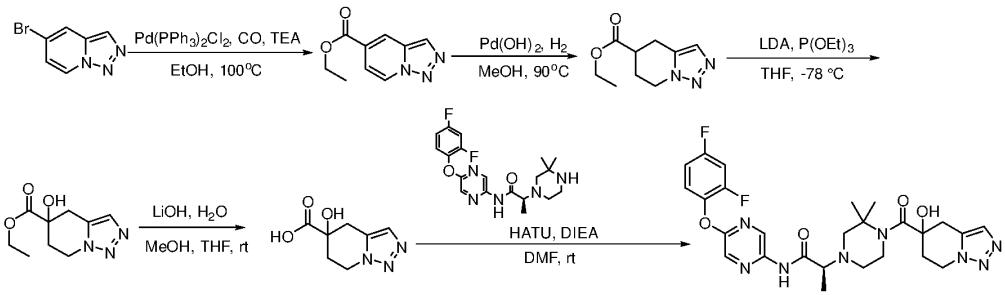
Synthesis of (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(8-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

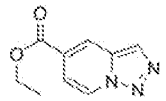
To a stirred solution of (2S)-2-(4-(8-((tert-butyldimethylsilyl)oxy)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (195 mg, 0.291 mmol, 1 equiv) in THF (5 mL), was added (2 mL) TEA·3HF at room temperature. The reaction mixture was stirred at 70°C for a period of 2h. After cooled to room temperature the reaction was quenched by water (10 mL) and extracted with EA (30 mL x 3). The combined organic extracts were washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (5-25% DCM/MeOH) and Prep-HPLC using a Column: XBridge Prep OBD C18 Column, 150 mm x 30 mm x 5 μm (eluent: 26% to 48% CH_3CN and H_2O, 10mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(8-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propenamide (6.3 mg, 3.88%) as a white solid. MS (ESI): mass calcd. for: $C_{26}H_{30}F_2N_8O_4$: 556.23 m/z, found: 557.30 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.42 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.5 Hz, 1H), 8.39 (s, 1H), 7.42 – 7.52 (m, 2H), 7.18 (t, J = 8.7 Hz, 1H), 5.90 (s, 1H), 4.88 (s, 1H), 4.21 (dd, J = 12.6, 4.9 Hz, 1H), 3.90 (t, J = 12.0 Hz, 1H), 3.50 – 3.56 (m, 4H), 2.69 – 2.83 (m, 2H), 2.29 – 2.47 (m, 2H), 1.92 – 2.12 (m, 2H), 1.39 (d, J = 2.5 Hz, 6H), 1.21 (d, J = 7.0 Hz, 3H).

Example 282: (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-hydroxy-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide



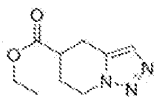
Synthetic Scheme





Synthesis of ethyl [1,2,3]triazolo[1,5-a]pyridine-5-carboxylate

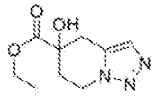
To a stirring solution 5-bromo-[1,2,3]triazolo[1,5-a]pyridine (3 g, 3.334 mmol, 1 equiv) in ethyl alcohol (100 mL) was added a solution of TEA (1.3 mL, 10.002 mmol, 3 equiv) and $Pd(PPh_3)_2Cl_2$ (233.98 mg, 0.333 mmol, 0.1 equiv). The resulting mixture under CO was stirred at 100°C for 16h. After cooled to room temperature the reaction was quenched by water (50 mL) and extracted with EA (50 mL x 3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-30% PE/EA) to afford ethyl [1,2,3]triazolo[1,5-a]pyridine-5-carboxylate (1.8 g, 62.06%). MS (ESI): mass calcd. for $C_9H_9N_3O_2$: 191.07 found: 192.05 $[M+H]^+$.



Synthesis of ethyl 4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylate

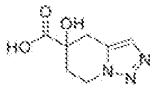
To a stirring solution ethyl [1,2,3]triazolo[1,5-a]pyridine-5-carboxylate (1 g, 5.230 mmol, 1 equiv) in methanol (200 mL) was added a solution of palladiumdiol (1.47 g, 10.460 mmol,

2 equiv). The resulting mixture under H_2 was stirred at 90°C for 16h. After cooled to room temperature the reaction was filtered through a Celite pad and concentrated under reduced pressure to afford ethyl 4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylat (700 mg, 68.55%). MS (ESI): mass calcd. for $C_9H_{13}N_3O_2$: 195.10 found: 196.15 $[M+H]^+$.



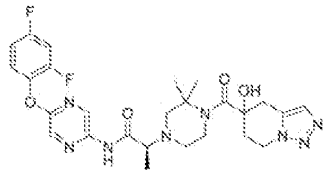
Synthesis of ethyl 5-hydroxy-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylate

To a stirring solution ethyl 4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylat (300 mg, 1.537 mmol, 1 equiv) in tetrahydrofuran (3 mL) was added a solution of 2 M LDA (in THF, 1.5 mL, 3.074 mmol, 2 equiv) under N_2 at -78°C. The resulting mixture was stirred at -78°C for 0.5h. The resulting mixture was added $P(OEt)_3$ (766.01 mg, 4.611 mmol, 3 equiv) and introduced O_2 stirred at -78°C for 0.5h. The reaction was quenched by water (10 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-30% PE/EA) to afford ethyl 5-hydroxy-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylate (150 mg, 46.21%). MS (ESI): mass calcd. for $C_9H_{13}N_3O_3$: 211.10 found: 212.10 $[M+H]^+$.



Synthesis of 5-hydroxy-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylic acid

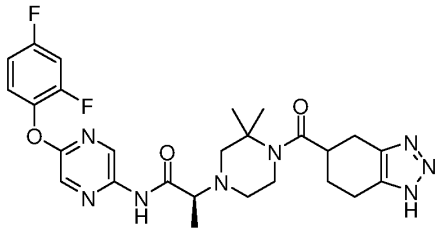
To a stirring solution ethyl 5-hydroxy-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylate (70 mg, 0.331 mmol, 1 equiv) in MeOH (0.2 mL) and water (0.2 mL) and THF (0.4 mL) was added a solution of LiOH (24 mg, 0.993 mmol, 3 equiv). The resulting mixture stirred at room temperature for 5h. The mixture was acidified to pH 4 with 2 N HCl (*aq.*). The residue obtained was purified by C18 column (CH_3CN/H_2O) to afford 5-hydroxy-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylic acid (40 mg, 65.89%). MS (ESI): mass calcd. for $C_7H_9N_3O_3$: 183.06 found: 184.20 $[M+H]^+$.



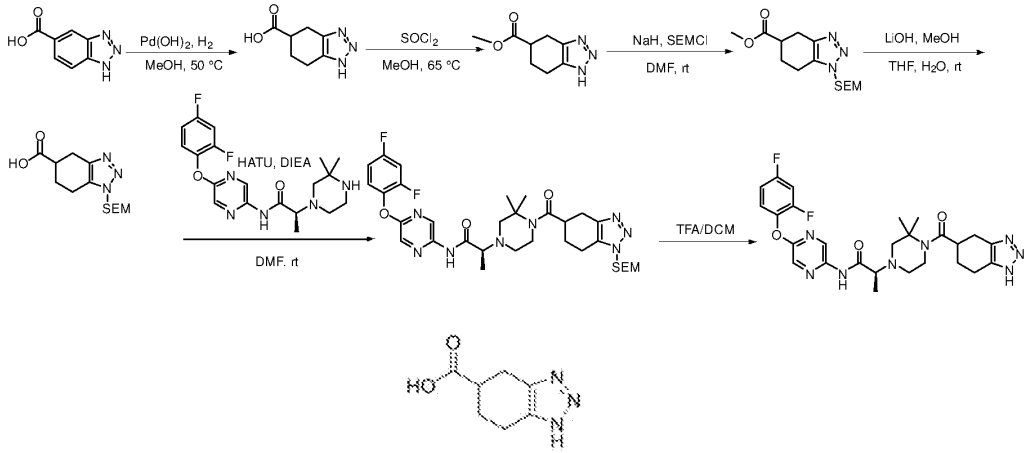
Synthesis of (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-hydroxy-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

To a stirred solution of 5-hydroxy-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carboxylic acid (50 mg, 0.273 mmol, 1 equiv) in DMF (1 mL) was added (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (106.85 mg, 0.273 mmol, 1 equiv), HATU (155.69 mg, 0.410 mmol, 1.5 equiv) and DIEA (141.12 mg, 1.092 mmol, 4 equiv) at room temperature. The reaction mixture was stirred at room temperature for 3 h. The resulting mixture was stirred for additional overnight at room temperature. After completion of reaction, the reaction mixture was quenched by addition of water (5 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% DCM/MeOH) and Prep-HPLC using a Column: Xselect CSH C18 OBD Column, 30*150mm, 5μm (eluent: 19% to 49% (v/v) CH_3CN and H_2O, 0.1% FA) to afford (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-hydroxy-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (6.7 mg, 4.39%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{30}F_2N_8O_4$: 556.24 m/z, found: 557.30 $[M+H]^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 10.42 (d, J = 2.3 Hz, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.42 – 7.53 (m, 3H), 7.15 – 7.20 (m, 1H), 6.11 (s, 1H), 4.34 – 4.43 (m, 1H), 4.20 – 4.29 (m, 1H), 3.81 – 4.05 (m, 2H), 3.45 – 3.54 (m, 1H), 3.18 (d, J = 16.8 Hz, 1H), 2.75 (d, J = 16.8 Hz, 1H), 2.57 – 2.67 (m, 1H), 2.35 – 2.45 (m, 2H), 2.16 – 2.32 (m, 2H), 1.37 (d, J = 5.2 Hz, 6H), 1.21 (d, J = 5.2 Hz, 3H).

Example 283: (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carbonyl)piperazin-1-yl)propanamide

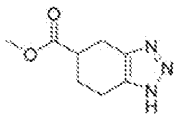


Synthetic Scheme



Synthesis of 4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carboxylic acid

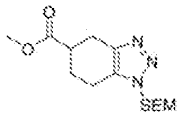
To a solution of 1H-1,2,3-benzotriazole-5-carboxylic acid (1 g, 6.130 mmol, 1 equiv) in MeOH (300 mL) was added 10% $Pd(OH)_2$ (0.4 g) in a pressure tank. The mixture was hydrogenated at 50 °C under 30 atm of hydrogen pressure for 24 h. After cooled room temperature, filtered through a celite pad and concentrated under reduced pressure to afford 4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carboxylic acid (1 g, 81.13%) as a yellow oil. MS (ESI): mass calcd. for $C_7H_9N_3O_2$: 167.70 m/z, found:168.05 $[M+H]^+$.



Synthesis of methyl 4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carboxylate

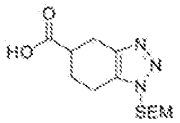
To a solution of 4,5,6,7-tetrahydro-1H-1,2,3-benzotriazole-5-carboxylic acid (1 g, 5.982 mmol, 1 equiv) in MeOH (30 mL), thionyl chloride (1.42 g, 11.964 mmol, 2 equiv) was added at rt. The resulting mixture was stirred for 2 h at 65 °C. After cooled to room temperature, the resulting mixture was concentrated, quenched by ice-water (30 mL) and extracted with EA (3 x

50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-30% PE/EA) to afford methyl 4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carboxylate (500 mg, 46.13%) as a yellow oil. MS (ESI): mass calcd. fo $rC_8H_{11}N_3O_2$: 181.09, found: 182.05 $[M+H]^+$.



Synthesis of methyl 1-((2-(trimethylsilyl)ethoxy)methyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carboxylate

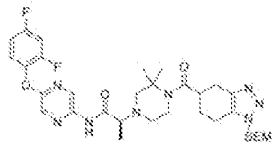
To a solution of methyl 4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carboxylate (1 g, 5.519 mmol, 1 equiv) in DMF (20 mL), 60% sodium hydride (0.44 g, 11.038 mmol, 2 equiv) was added at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred for 30 min at rt. SEMCl (1.84 g, 11.038 mmol, 2 equiv) was added at 0 °C. The resulting mixture was stirred for 2h at rt. The reaction was quenched by water (30 mL). The resulting mixture was extracted with EA (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-30%PE/EA) to afford methyl 1-((2-(trimethylsilyl)ethoxy)methyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carboxylate (500 mg, 82.223%) as a yellow oil. MS (ESI): mass calcd. for $C_{14}H_{25}N_3O_3Si$: 311.17, found: 312.00 $[M+H]^+$.



Synthesis of 1-((2-(trimethylsilyl)ethoxy)methyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carboxylic acid

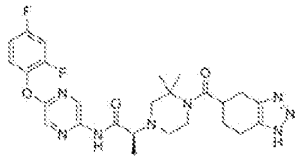
To a solution of methyl 1-((2-(trimethylsilyl)ethoxy)methyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carboxylate (500 mg, 1.605 mmol, 1 equiv) in THF (2 mL), methanol (2 mL) and water (2 mL), LiOH (77 mg, 3.21 mmol, 2 equiv) was added at rt. The resulting mixture was stirred for 2h at rt. The resulting mixture was concentrated under vacuum. The residue was acidified to pH 2~3 with 4N HCl (*aq.*). The precipitated solids were collected by filtration and washed with H_2O to afford 1-((2-(trimethylsilyl)ethoxy)methyl)-4,5,6,7-

tetrahydro-1H-benzo[d][1,2,3]triazole-5-carboxylic acid (100 mg, 52.15%) as a yellow solid. MS (ESI): mass calcd. for $C_{13}H_{23}N_3O_3Si$: 297.15, found: 298.15 $[M+H]^+$.



Synthesis of (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-((2-(trimethylsilyl)ethoxy)methyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carbonyl)piperazin-1-yl)propanamide

To a solution of 1-((2-(trimethylsilyl)ethoxy)methyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carboxylic acid (200 mg, 0.67 mmol, 1 equiv) in DMF (3 mL), (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (263.20 mg, 0.67 mmol, 1 equiv), HATU (511.36 mg, 0.134 mmol, 2 equiv) and DIEA (695.27 mg, 5.36 mmol, 8 equiv) was added at rt. The mixture was allowed to warm to rt and stirred for 2h. The reaction was quenched by water (10 mL). The resulting mixture was extracted with EA (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20%DCM/MeOH) to afford (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-((2-(trimethylsilyl)ethoxy)methyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carbonyl)piperazin-1-yl)propanamide (200 mg, 17.73%) as a white solid. MS (ESI): mass calcd. for $C_{32}H_{44}F_2N_8O_4Si$: 670.32, found: 671.45 $[M+H]^+$.

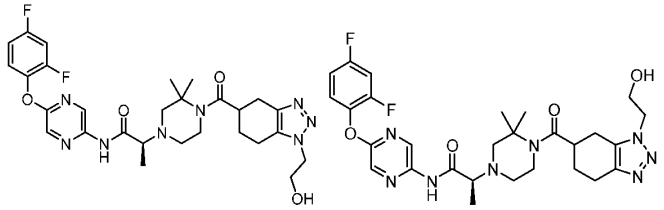


Synthesis of (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carbonyl)piperazin-1-yl)propanamide

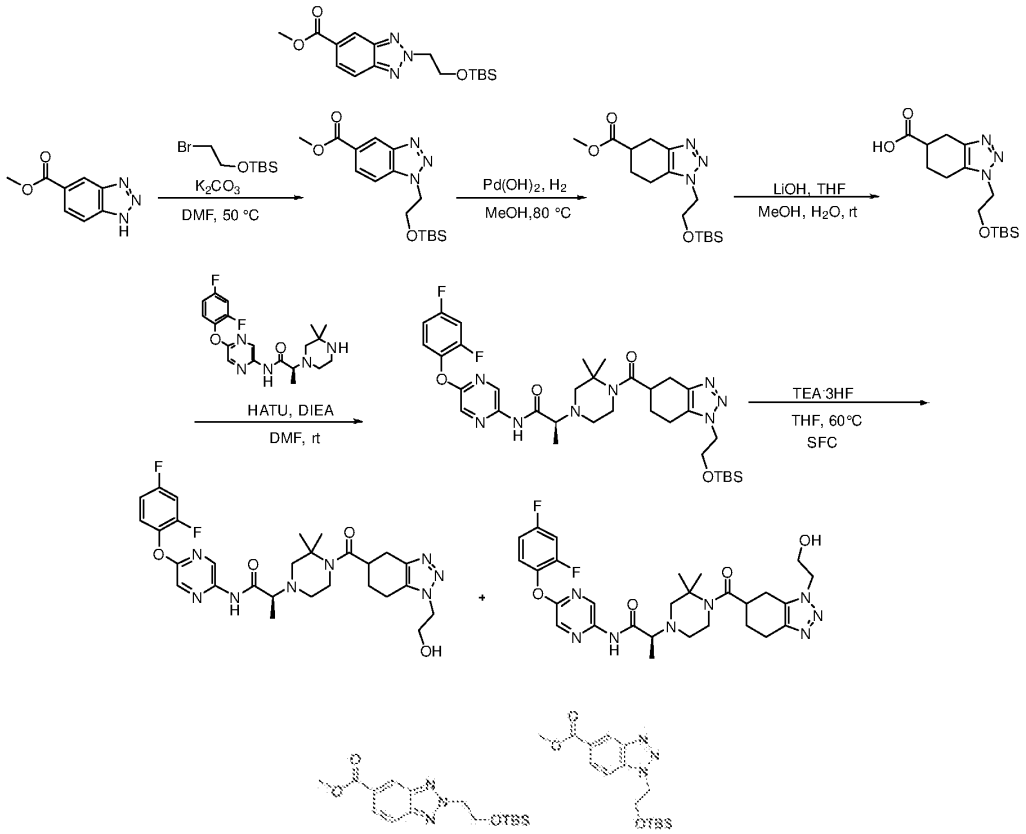
To a solution of (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-((2-(trimethylsilyl)ethoxy)methyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carbonyl)piperazin-1-yl)propanamide (100 mg, 0.149 mmol, 1 equiv) in DCM (4 mL), TFA (1 mL) was added at 0 °C. The resulting mixture was stirred for 2h at rt. The resulting mixture was concentrated under reduced pressure and Prep-HPLC using a Column: XBridge Prep OBD C18

Column, 30*150 mm, 5μm; (eluent: 34% to 57% Water (10mmol/L NH_4HCO_3+0.05%NH_3H_2O) and ACN) to afford (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carbonyl)piperazin-1-yl)propanamide (31.7 mg, 38.95%) as a white solid. MS (ESI): mass calcd. for $C_{26}H_{30}F_2N_8O_3$: 540.24, found: 541.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 14.38 (br, 1H), 10.40 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.39 – 7.56 (m, 2H), 7.10 – 7.24 (m, 1H), 3.45 – 3.59 (m, 3H), 2.99 – 3.09 (m, 1H), 2.57 – 2.79 (m, 6H), 2.35 (s, 2H), 1.95 (d, J = 13.5 Hz, 1H), 1.60 – 1.73 (m, 1H), 1.39 (t, J = 1.8 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H).

Example 285: (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(1-(2-hydroxyethyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide and Example 284: (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(1-(2-hydroxyethyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

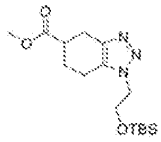


Synthetic Scheme



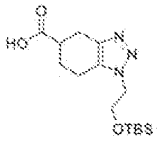
Synthesis of methyl 1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1H-benzo[d][1,2,3]triazole-5-carboxylate

To a solution of methyl 1H-1,2,3-benzotriazole-5-carboxylate (1 g, 5.645 mmol, 1 equiv) in DMF (15 mL) K_2CO_3 (2.36 g, 16.935 mmol, 3 equiv) and (2-bromoethoxy)(tert-butyl)dimethylsilane (2.70 g, 11.290 mmol, 2 equiv) was added at rt. The resulting mixture was stirred for 12 h at 50 °C. After cooled to room temperature, the reaction mixture was quenched by addition of water (20 mL). The resulting mixture was extracted with EA (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-30%PE/EA) to afford methyl 1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1H-benzo[d][1,2,3]triazole-5-carboxylate (large polarity, 700 mg, 36.97%) as a yellow oil. MS (ESI): mass calcd. For $C_{16}H_{25}N_3O_3Si$: 335.17 m/z, found: 336.10 $[M+H]^+$. And methyl 2-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2H-benzo[d][1,2,3]triazole-5-carboxylate (small polarity, 600 mg, 31.62%) as a yellow solid.



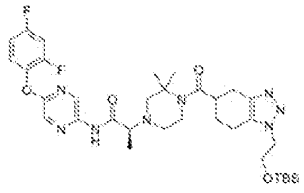
Synthesis of methyl 1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carboxylate

To a solution of methyl 1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1H-benzo[d][1,2,3]triazole-5-carboxylate (1 g, 2.981 mmol, 1 equiv) in MeOH (30 mL) was added $Pd(OH)_2$ (0.42 g, 2.981 mmol, 1 equiv) in a pressure tank. The mixture was hydrogenated at 80 °C under 50 atm of hydrogen pressure for 24 h. After cooled to room temperature, filtered through a celite pad and concentrated under reduced pressure to afford methyl 1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carboxylate (800 mg, 79.05%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{29}N_3O_3Si$: 339.20, found: 340.10 $[M+H]^+$.



Synthesis of 1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carboxylic acid

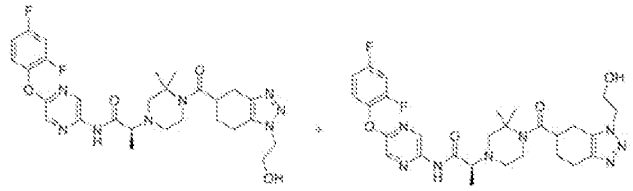
To a solution of methyl 1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carboxylate (200 mg, 0.589 mmol, 1 equiv) in THF (2 mL), methanol (2 mL) and water (1 mL), LiOH (42 mg, 1.767 mmol, 3 equiv) was added at rt. The resulting mixture was stirred for 2h at rt. The resulting mixture was concentrated under vacuum. The residue was acidified to pH 2~3 with 4 NHCl (*aq.*). The precipitated solids were collected by filtration and washed with H_2O to afford 1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carboxylic acid (100 mg, 52.15%) as a white solid. MS (ESI): mass calcd. for $C_{15}H_{27}N_3O_3Si$: 325.18, found: 326.10 $[M+H]^+$.



Synthesis of (2S)-2-(4-(1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-

difluorophenoxy)pyrazin-2-yl)propanamide

To a solution of 1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carboxylic acid (300 mg, 0.922 mmol, 1 equiv) in DMF (3 mL), (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethylpiperazin-1-yl)propanamide (360.78 mg, 0.922 mmol, 1 equiv), HATU (700.93 mg, 1.844 mmol, 2 equiv) and DIEA (357.38 mg, 2.766 mmol, 3 equiv) was added at rt. The mixture was allowed to warm to rt and stirred for 2 h. the reaction mixture was quenched by addition of water (20 mL). The resulting mixture was extracted with EA (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-20%DCM/MeOH) to afford (2S)-2-(4-(1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (100 mg, 15.52%) as a white solid. MS (ESI): mass calcd. For $C_{34}H_{48}F_2N_8O_4Si$: 698.35, found: 699.25 $[M+H]^+$.

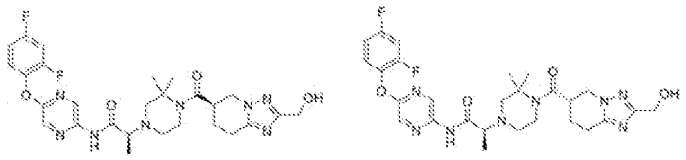


Synthesis of (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(1-(2-hydroxyethyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

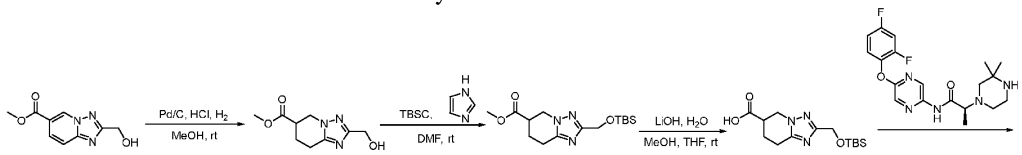
To a solution of (2S)-2-(4-(1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (100 mg, 0.143 mmol, 1 equiv) in THF (2 mL), triethylamine trihydrofluoride (0.4 mL) added at rt. The resulting mixture was stirred for 20 min at 60 °C. After cooled to room temperature, the resulting mixture was concentrated under reduced pressure and purified by C18 column & chiral-HPLC using a CHIRALPAK IF, 2*25 cm, 5 μm column (eluent: 20% (v/v) Hex: DCM=3: 1 (0.5% 2M NH_3-MeOH) and EtOH) to afford (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(1-(2-hydroxyethyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (assumed, 7.0 mg, 8.33%) as a white solid. MS (ESI): mass calcd. for $C_{28}H_{34}F_2N_8O_4$: 584.27, found: 585.35 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.5 Hz, 1H), 7.41 – 7.54 (m, 2H), 7.12 – 7.22 (m, 1H), 4.95 (t, J = 5.4 Hz, 1H),

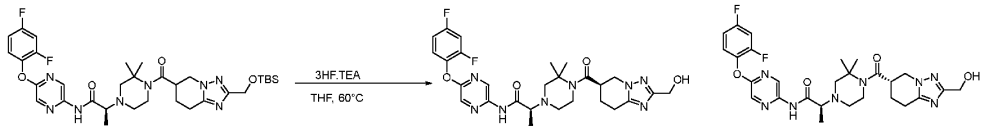
4.26 (t, *J* = 5.4, 2.3 Hz, 2H), 3.70 – 3.74 (m, 2H), 3.47 – 3.67 (m, 3H), 2.99 – 3.03 (m, 1H), 2.57 – 2.84 (m, 6H), 2.37 (s, 2H), 1.93 (d, *J* = 13.5 Hz, 1H), 1.53 – 1.67 (m, 1H), 1.39 (d, *J* = 2.5 Hz, 6H), 1.22 (d, *J* = 6.8 Hz, 3H). And (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(1-(2-hydroxyethyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (assumed, 6.5 mg, 7.75%) as a white solid. MS (ESI): mass calcd. for $C_{28}H_{34}F_2N_8O_4$: 584.27, found: 585.35 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.84 (d, *J* = 1.4 Hz, 1H), 8.45 (d, *J* = 1.4 Hz, 1H), 7.41 – 7.54 (m, 2H), 7.12 – 7.22 (m, 1H), 4.96 (t, *J* = 5.4 Hz, 1H), 4.22 – 4.22 (m, 2H), 3.70 – 3.74 (m, 2H), 3.47 – 3.56 (m, 3H), 2.94 – 3.00 (m, 1H), 2.60 – 2.77 (m, 6H), 2.35 (s, 2H), 1.96 (d, *J* = 13.4 Hz, 1H), 1.58 – 1.70 (m, 1H), 1.39 (d, *J* = 4.4 Hz, 6H), 1.22 (d, *J* = 6.8 Hz, 3H).

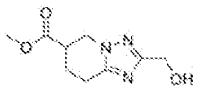
Example 287: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-2-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide and Example 286: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-2-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propenamide



Synthetic Scheme

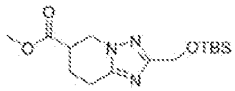






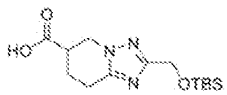
Synthesis of methyl 2-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate

To a solution of methyl 2-(hydroxymethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (180 mg, 0.869 mmol, 1 equiv) in methanol (10 mL), HCl (0.2 mL) was added Pd/C (10%, 60 mg) in a pressure tank. The mixture was hydrogenated at room temperature under 30 psi of hydrogen pressure for 2 h, filtered through a celite pad and concentrated under reduced pressure to offer methyl 2-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (150 mg, 81.74%) as a yellow solid.MS (ESI): mass calcd. for $C_9H_{13}N_3O_3$: 211.10 m/z, found 212.15 $[M+H]^+$.



Synthesis of methyl 2-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate

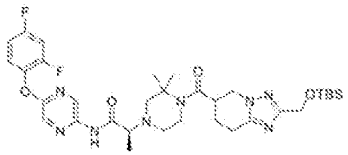
To a solution of methyl 2-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (150 mg, 0.710 mmol, 1 equiv) in dimethylformamide (5 mL) was added imidazole (145.04 mg, 2.130 mmol, 3 equiv), TBSCl (160.55 mg, 1.065 mmol, 1.5 equiv), the mixture was stirred for 2 h at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-10% MeOH/DCM) to afford methyl 2-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (180 mg, 77.87%) as a yellow solid. MS (ESI): mass calcd. for $C_{15}H_{27}N_3O_3Si$: 325.18 m/z, found 326.10 $[M+H]^+$.



Synthesis of 2-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid

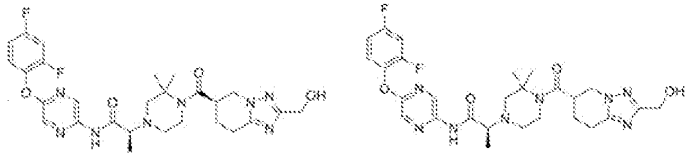
To a solution of methyl 2-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydro-

[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (180 mg, 0.553 mmol, 1 equiv) in H_2O (0.5 mL), MeOH (3 mL) and THF (3 mL) was added LiOH (26.49 mg, 1.106 mmol, 2 equiv). The mixture was stirred for 2 h at rt. The mixture was acidified to pH =5 with 4 N HCl. The precipitated solids were collected by filtration to afford 2-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid (120 mg, 69.67%) as a yellow solid. MS (ESI): mass calcd. for $C_{14}H_{25}N_3O_3Si$: 311.17 m/z, found 312.05 $[M+H]^+$.



Synthesis of (2S)-2-(4-(2-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

To a solution of 2-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid (100 mg, 0.321 mmol, 1 equiv) in dimethylformamide (5 mL) was added (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (125.67 mg, 0.321 mmol, 1 equiv), HATU (183.12 mg, 0.482 mmol, 1.5 equiv), DIEA (165.99 mg, 1.284 mmol, 4 equiv), the mixture was stirred for 2 h at rt. The reaction was quenched with NaCl (*aq.*, 10 mL), and then the mixture was extracted with EtOAc (2 x 20 mL), The combined organic layers were dried over Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography to afford (2S)-2-(4-(2-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (100 mg, 45.48%) as a yellow solid. MS (ESI): $C_{33}H_{46}F_2N_8O_4Si$: 684.34, found: 684.80 $[M+H]^+$.

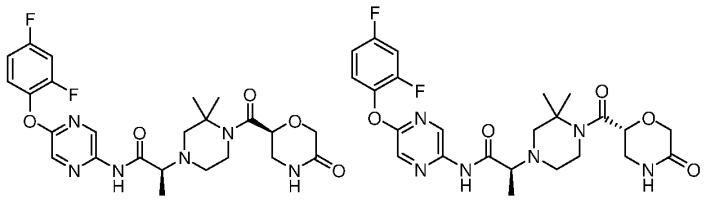


Synthesis of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-2-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)pro

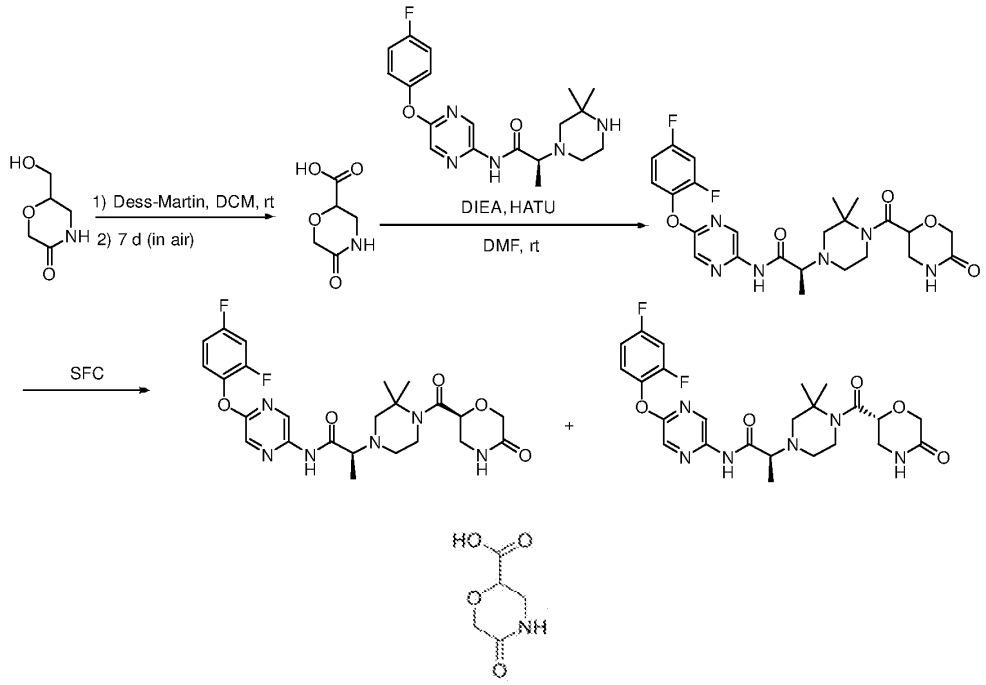
panamide & (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-2-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

To a solution of (2S)-2-(4-(2-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide (200 mg, 0.292 mmol, 1 equiv) in tetrahydrofuran (5 mL), TEA·3HF (0.5 mL). The resulting mixture was stirred for 1 h at 60 °C. After cooled to room temperature the reaction mixture was quenched by water and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-15% DCM/MeOH) to afford 70 mg crude product as a white solid. The product was separated by chiral-HPLC using a CHIRALPAK IE, 2*25 cm, 5 μmcolumn (eluent: 40% (v/v) MtBE (0.5% 2M NH3-MeOH) and EtOH) to afford (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-2-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (assumed, 21.9 mg, 13.10%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{32}F_2N_8O_4$ 570.25 m/z, found 571.25 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4) δ 8.87 (d, J = 1.4 Hz, 1H), 8.26 (d, J = 1.4 Hz, 1H), 7.23 – 7.41 (m, 1H), 7.09 – 7.20 (m, 1H), 7.02 (t, J = 3.0 Hz, 1H), 4.56 (s, 2H), 4.15 – 4.28 (m, 2H), 3.63 – 3.73 (m, 2H), 3.45 – 3.56 (m, 1H), 3.32 – 3.41 (m, 1H), 2.86 – 3.00 (m, 2H), 2.70 – 2.89 (m, 2H), 2.43 (s, 2H), 2.14 – 2.25 (m, 1H), 1.99 – 2.01 (m, 1H), 1.49 (d, J = 3.9 Hz, 6H), 1.31 (d, J = 7.0 Hz, 3H). And (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-2-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide (assumed, 23.6 mg, 14.10%) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{32}F_2N_8O_4$ 570.25 m/z, found 571.25 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4) δ 8.87 (d, J = 1.4 Hz, 1H), 8.26 (d, J = 1.4 Hz, 1H), 7.23 – 7.41 (m, 1H), 7.09 – 7.20 (m, 1H), 7.02 (t, J = 3.0 Hz, 1H), 4.56 (s, 2H), 4.15 – 4.28 (m, 2H), 3.63 – 3.73 (m, 2H), 3.45 – 3.56 (m, 1H), 3.32 – 3.41 (m, 1H), 2.86 – 3.00 (m, 2H), 2.70 – 2.89 (m, 2H), 2.43 (s, 2H), 2.14 – 2.25 (m, 1H), 1.99 – 2.01 (m, 1H), 1.49 (d, J = 3.9 Hz, 6H), 1.31 (d, J = 7.0 Hz, 3H).

Example 289: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-5-oxomorpholine-2-carbonyl)piperazin-1-yl)propanamide and Example 288: (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-5-oxomorpholine-2-carbonyl)piperazin-1-yl)propanamide

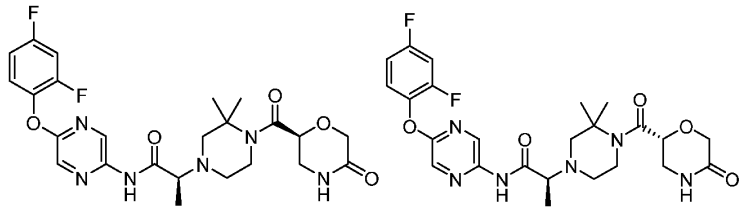


Synthetic Scheme



Synthesis of 5-oxomorpholine-2-carboxylic acid

To a solution of 6-(hydroxymethyl)morpholin-3-one (200 mg, 1.525 mmol, 1 equiv) in DCM (5 mL) was added Dess-Martin (970.35 mg, 2.287 mmol, 1.5 equiv) at 0 °C, the mixture was stirred for 1 h at rt. The reaction mixture was concentrated under vacuum to yield a crude product which was directly purified by C18 to afford 5-oxomorpholine-2-carbaldehyde 200 mg as a white solid. 5-oxomorpholine-2-carbaldehyde was placed in air for 7 days to afford 5-oxomorpholine-2-carboxylic acid (200 mg, 90.36%) as a white solid. MS (ESI): $C_5H_7NO_4$: 145.04 m/z, found: 146.05 $[M+H]^+$.



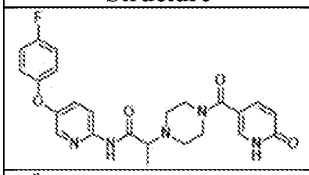
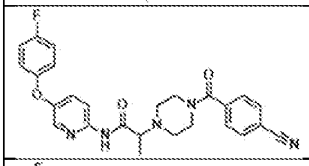
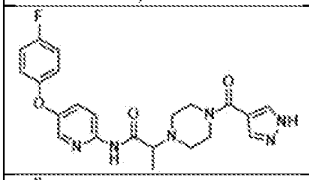
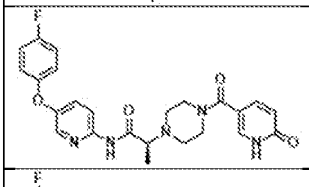
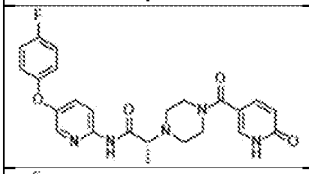
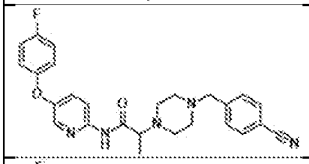
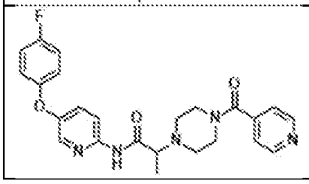
Synthesis of (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-5-oxomorpholine-2-carbonyl)piperazin-1-yl)propenamide & (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-5-oxomorpholine-2-carbonyl)piperazin-1-yl)propanamide

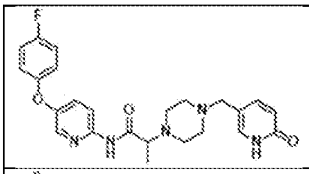
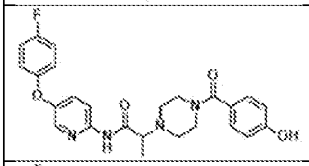
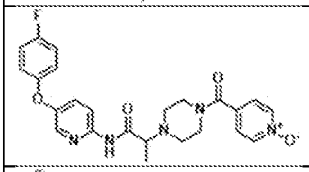
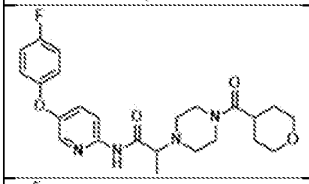
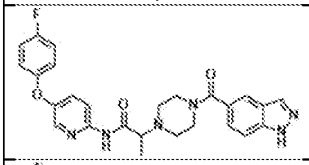
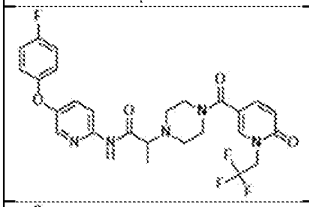
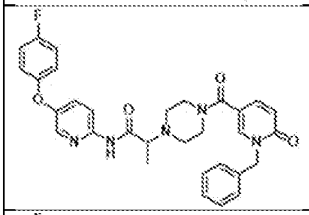
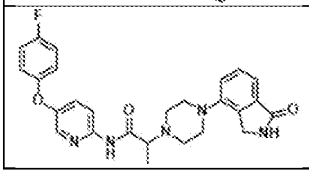
To a solution of 5-oxomorpholine-2-carboxylic acid (100 mg, 0.689 mmol, 1 equiv) in DMF (3 mL) was added (2S)-N-[5-(2,4-difluorophenoxy)pyrazin-2-yl]-2-(3,3-dimethylpiperazin-1-yl)propanamide (269.73 mg, 0.689 mmol, 1 equiv), HATU (393.04 mg, 1.033 mmol, 1.5 equiv), DIEA (445.33 mg, 3.445 mmol, 5 equiv). The resulting mixture was stirred for 3 h at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 20 mL). The mixture was combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 60 mg (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxomorpholine-2-carbonyl)piperazin-1-yl)propanamide as a white solid. The product was separated by chiral-HPLC using a CHIRALPAK IF, 2*25 cm, 5 μm column (eluent: 50% (v/v) MTBE (0.5% 2M NH_3-MeOH) and MeOH: DCM=1: 1) to afford to (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-5-oxomorpholine-2-carbonyl)piperazin-1-yl)propenamide (assumed, 24.5 mg, 6.83%) as a white solid. MS (ESI): mass calcd. for $C_{24}H_{28}F_2N_6O_5$ 518.21 m/z, found 519.25 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4) δ 8.86 (d, J = 1.4 Hz, 1H), 8.26 (d, J = 1.4 Hz, 1H), 7.21-7.43 (m, 1H), 7.07-7.21 (m, 1H), 6.89-7.07 (m, 1H), 4.58 (dd, J = 8.7, 3.6 Hz, 1H), 4.15 – 4.29 (m, 2H), 3.70-3.91 (m, 1H), 3.49 – 3.65 (m, 2H), 3.32 – 3.42 (m, 2H), 2.72-2.98 (m, 1H), 2.53-2.72 (m, 1H), 2.42-2.52 (m, 1H), 2.28-2.52 (m, 1H), 1.49 (s, 6H), 1.31 (d, J = 7.0 Hz, 3H). And (S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-5-oxomorpholine-2-carbonyl)piperazin-1-yl)propanamide (assumed, 15.9 mg, 4.44%) as a white solid. MS (ESI): mass calcd. for $C_{24}H_{28}F_2N_6O_5$ 518.21 m/z, found 519.25 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4) δ 8.86 (d, J = 1.4 Hz, 1H), 8.26 (d, J = 1.4 Hz, 1H), 7.21 – 7.43 (m, 1H), 7.07 – 7.21 (m, 1H), 6.89 – 7.07 (m, 1H), 4.45 – 4.70 (m, 1H), 4.15 – 4.29 (m, 2H), 3.65 – 3.89 (m, 1H), 3.49 – 3.65 (m, 2H), 3.32 – 3.42 (m, 2H), 2.65 – 2.91 (m, 2H), 2.28 – 2.58 (m,

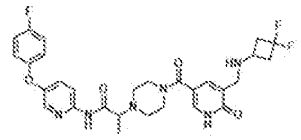
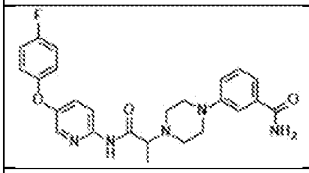
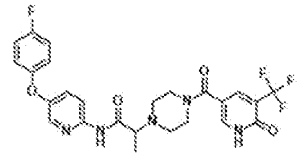
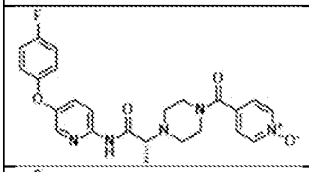
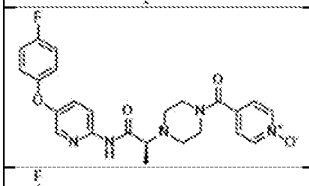
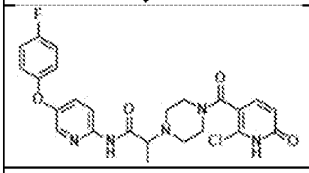
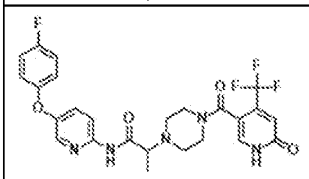
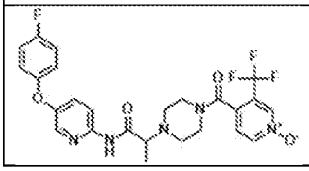
2H), 1.49 (s, 6H), 1.31 (d, J = 7.0 Hz, 3H).

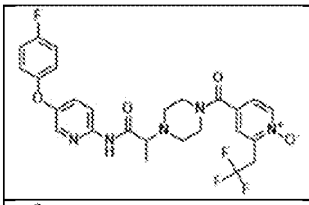
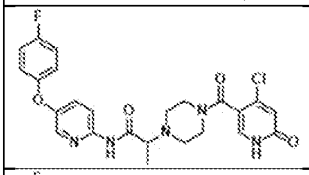
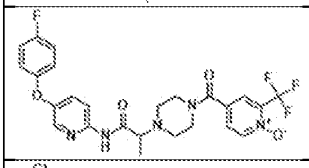
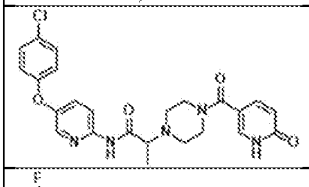
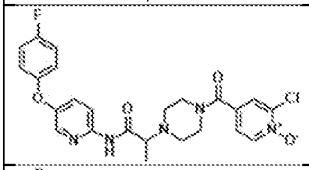
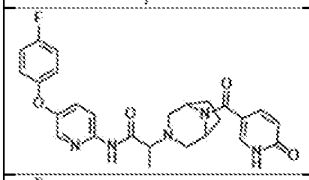
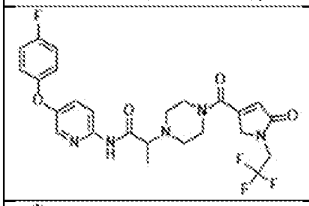
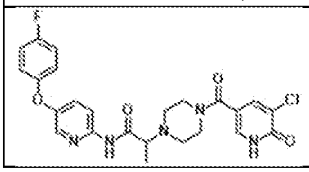
Exemplary compounds are shown in Table 1 below.

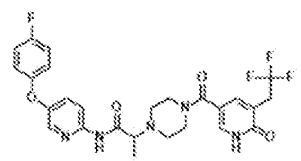
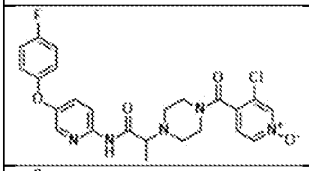
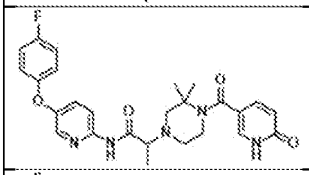
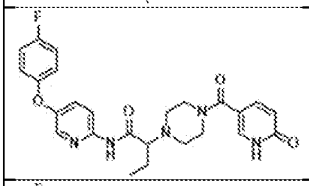
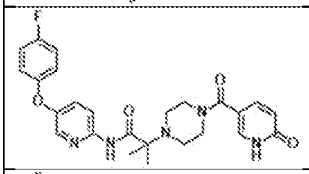
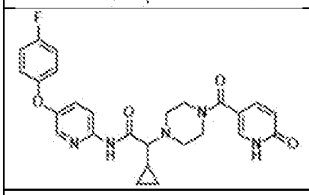
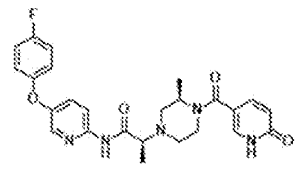
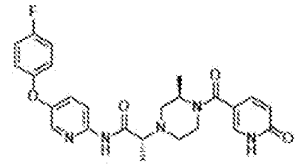
Table 1: Exemplary Compounds.

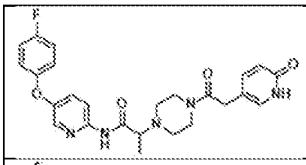
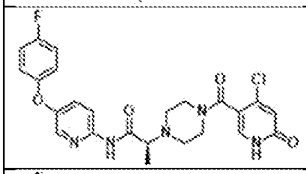
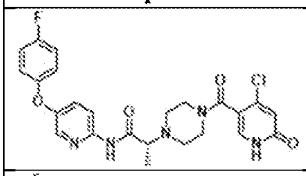
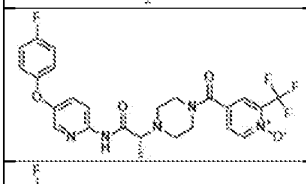
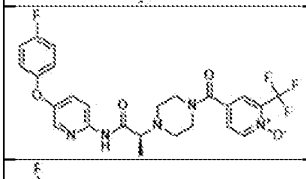
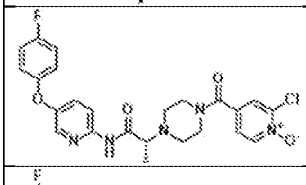
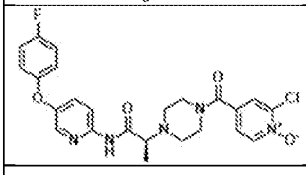
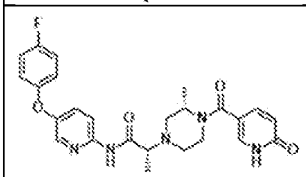
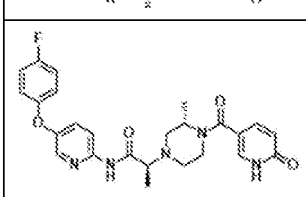
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	2	ME	2-(4-(4-cyanobenzoyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	3	ME	2-(4-(1H-pyrazole-4-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	4	SUS	(S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide
	5	SUS	(R)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide
	6	ME	2-(4-(4-cyanobenzyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	7	ME	N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-isonicotinoylpiperazin-1-yl)propanamide

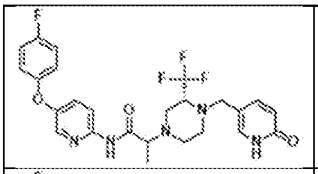
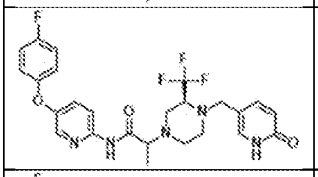
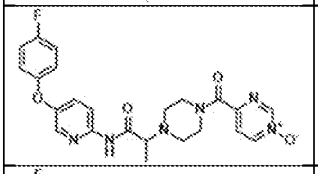
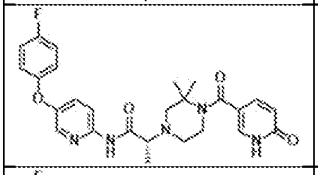
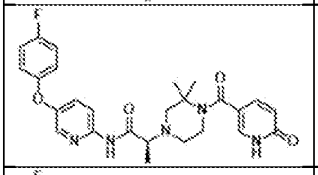
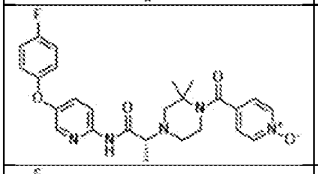
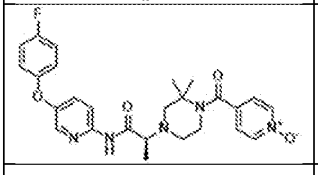
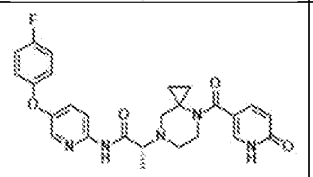
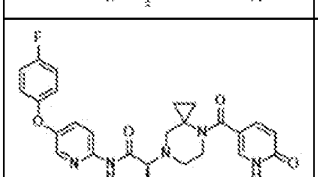
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	9	ME	N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(4-hydroxybenzoyl)piperazin-1-yl)propanamide
	10	ME	4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide
	11	ME	N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(tetrahydro-2H-pyran-4-carbonyl)piperazin-1-yl)propanamide
	12	ME	2-(4-(1H-indazole-5-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	13	ME	N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide
	14	ME	2-(4-(1-benzyl-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	15	ME	N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(1-oxoisoindolin-4-yl)piperazin-1-yl)propanamide

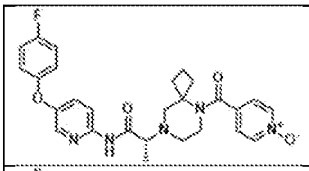
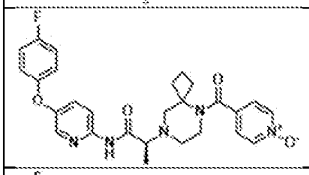
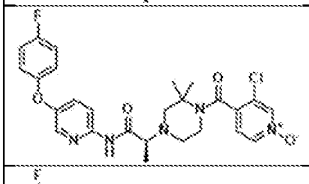
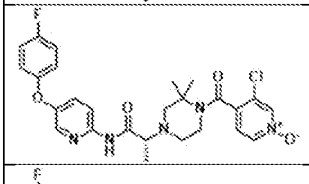
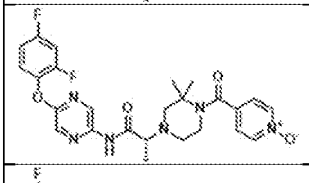
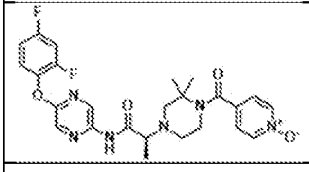
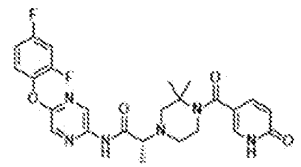
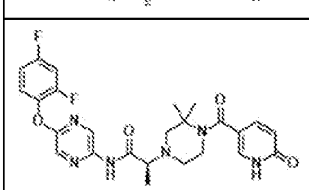
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	17	ME	3-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazin-1-yl)benzamide
	18	ME	N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-5-(trifluoromethyl)-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide
	19	SUS	(R)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide
	20	SUS	(S)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide
	21	ME	2-(4-(2-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	22	ME	N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-4-(trifluoromethyl)-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide
	23	ME	4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)-3-(trifluoromethyl)pyridine 1-oxide

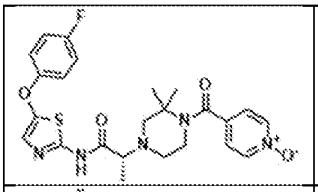
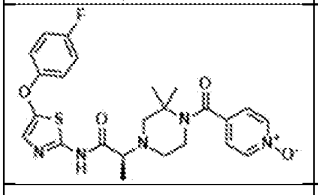
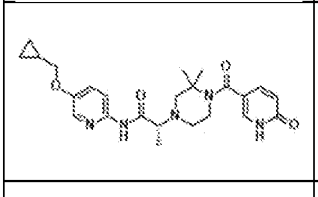
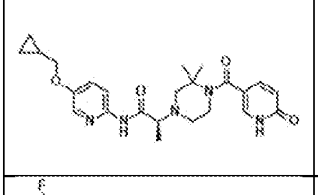
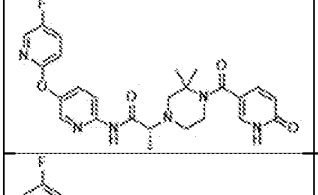
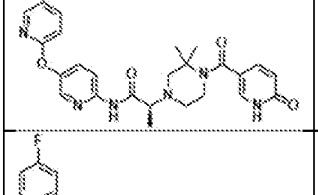
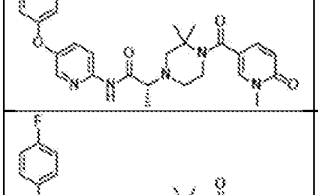
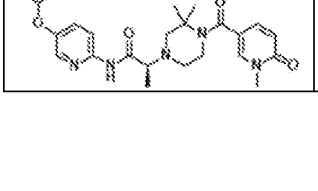
	24	ME	4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)-2-(2,2,2-trifluoroethyl)pyridine 1-oxide
	25	ME	2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	26	ME	4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)-2-(trifluoromethyl)pyridine 1-oxide
	27	ME	N-(5-(4-chlorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide
	28	ME	2-chloro-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide
	29	ME	N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(8-(6-oxo-1,6-dihydropyridine-3-carbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)propanamide
	30	ME	N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(5-oxo-1-(2,2,2-trifluoroethyl)-2,5-dihydro-1H-pyrrole-3-carbonyl)piperazin-1-yl)propanamide
	31	ME	2-(4-(5-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

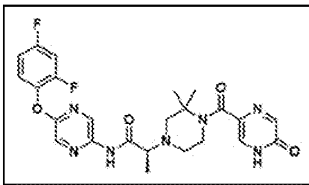
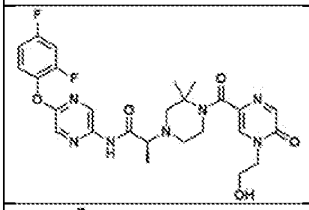
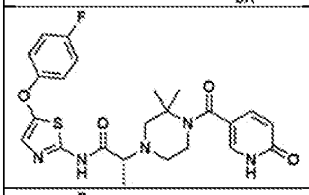
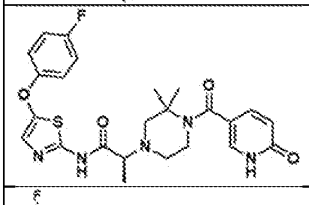
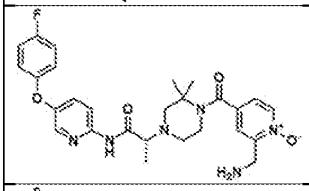
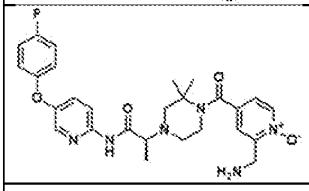
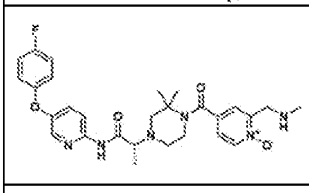
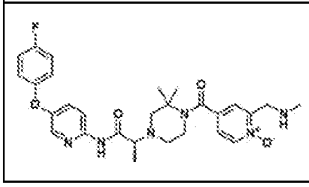
	32	ME	N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-5-(2,2,2-trifluoroethyl)-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide
	33	ME	3-chloro-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide
	34	ME	2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	35	ME	N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)butanamide
	36	No Stereo	N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-methyl-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide
	37	ME	2-cyclopropyl-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)acetamide
	38	SUS	(S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((R)-3-methyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide
	39	SUS	(R)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((R)-3-methyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

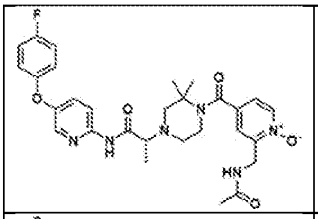
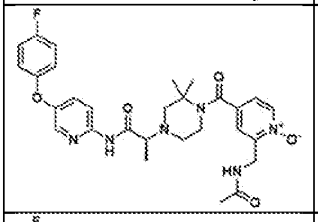
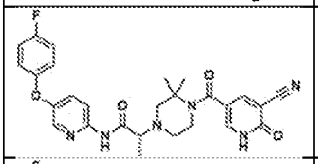
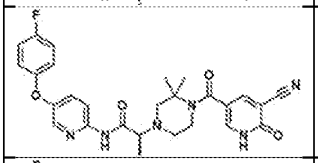
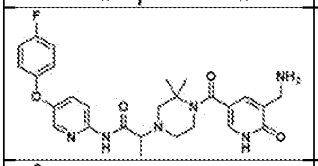
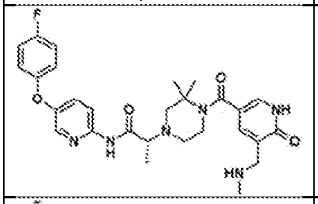
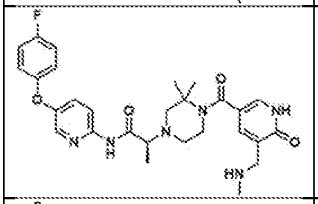
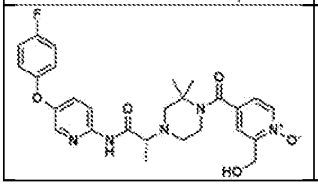
	40	ME	N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(2-(6-oxo-1,6-dihydropyridin-3-yl)acetyl)piperazin-1-yl)propanamide
	41	SUS	(S)-2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	42	SUS	(R)-2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	43	SUS	(R)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)-2-(trifluoromethyl)pyridine 1-oxide
	44	SUS	(S)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)-2-(trifluoromethyl)pyridine 1-oxide
	45	SUS	(R)-2-chloro-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide
	46	SUS	(S)-2-chloro-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide
	47	SUS	(R)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((S)-3-methyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide
	48	SUS	(S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((S)-3-methyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

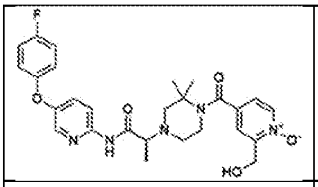
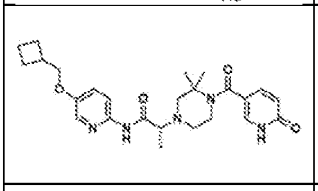
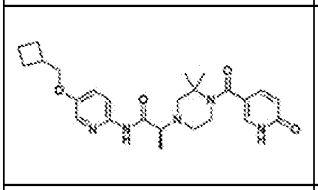
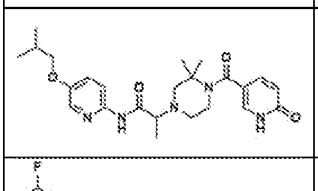
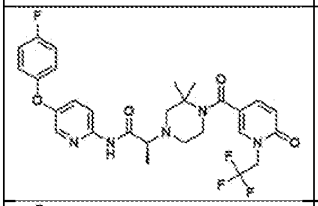
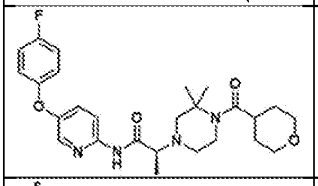
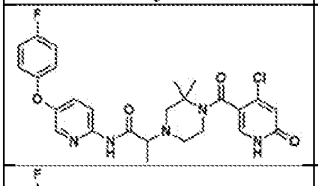
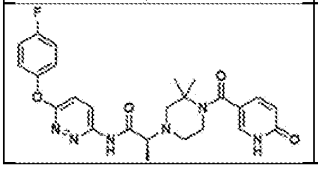
	49	MD	N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((R)-4-((6-oxo-1,6-dihydropyridin-3-yl)methyl)-3-(trifluoromethyl)piperazin-1-yl)propanamide
	50	MD	N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-((S)-4-((6-oxo-1,6-dihydropyridin-3-yl)methyl)-3-(trifluoromethyl)piperazin-1-yl)propanamide
	51	ME	4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)piperazine-1-carbonyl)pyrimidine 1-oxide
	52	SUS	(R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	53	SUS	(S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	54	SUS	(R)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	55	SUS	(S)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	56	SUS	(R)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)-4,7-diazaspiro[2.5]octan-7-yl)propanamide
	57	SUS	(S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(6-oxo-1,6-dihydropyridine-3-carbonyl)-4,7-diazaspiro[2.5]octan-7-yl)propanamide

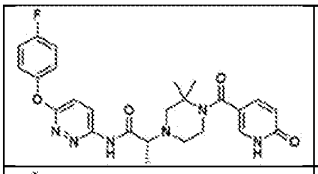
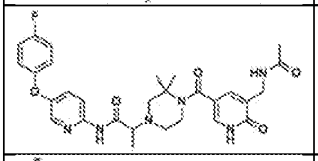
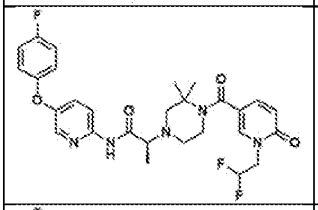
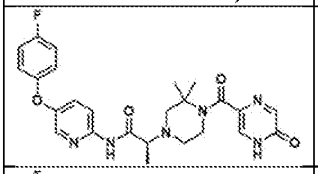
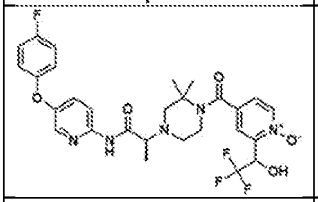
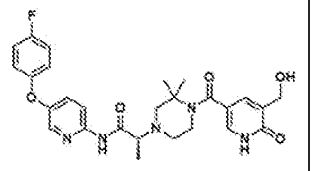
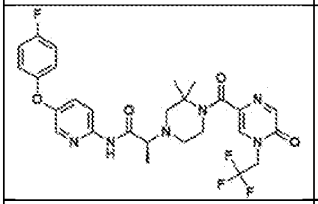
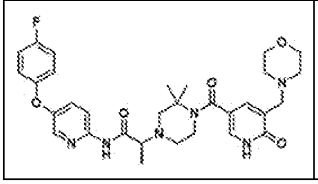
	58	SUS	(R)-4-(8-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-5,8-diazaspiro[3.5]nonane-5-carbonyl)pyridine 1-oxide
	59	SUS	(S)-4-(8-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-5,8-diazaspiro[3.5]nonane-5-carbonyl)pyridine 1-oxide
	60	SUS	(S)-3-chloro-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	61	SUS	(R)-3-chloro-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	62	SUS	(R)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	63	SUS	(S)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	64	SUS	(R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide
	65	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

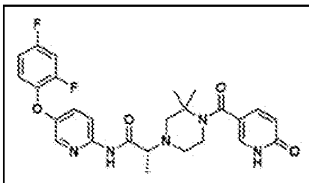
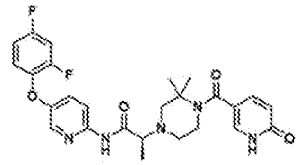
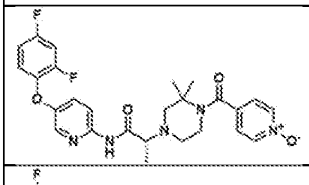
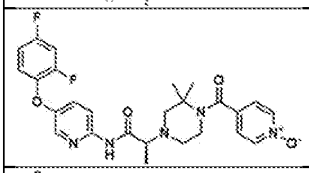
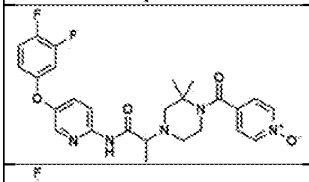
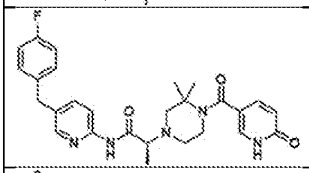
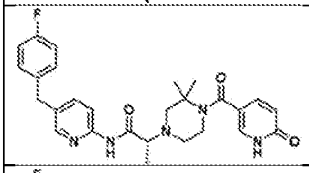
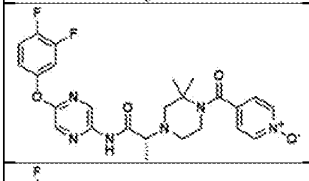
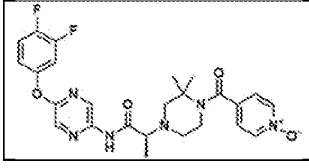
	66	SUS	(R)-4-(4-(1-((5-(4-fluorophenoxy)thiazol-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	67	SUS	(S)-4-(4-(1-((5-(4-fluorophenoxy)thiazol-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	68	SUS	(R)-N-(5-(cyclopropylmethoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide
	69	SUS	(S)-N-(5-(cyclopropylmethoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide
	70	SUS	(R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-((5-fluoropyridin-2-yl)oxy)pyridin-2-yl)propanamide
	71	SUS	(S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-((5-fluoropyridin-2-yl)oxy)pyridin-2-yl)propanamide
	72	SUS	(R)-2-(3,3-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	73	SUS	(S)-2-(3,3-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

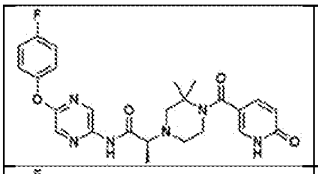
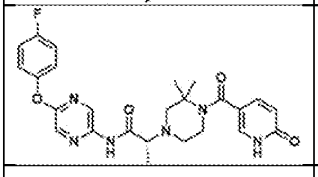
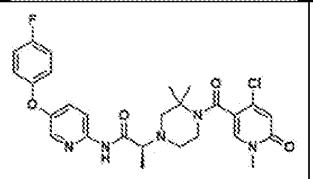
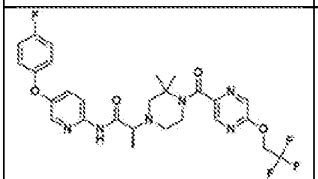
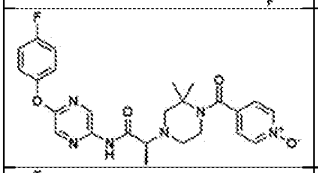
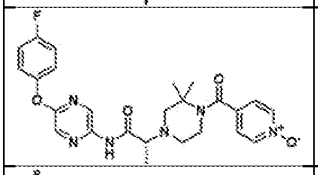
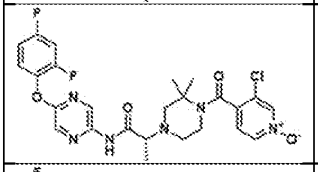
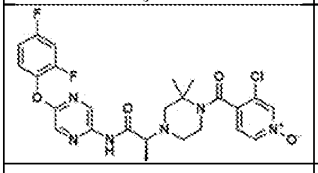
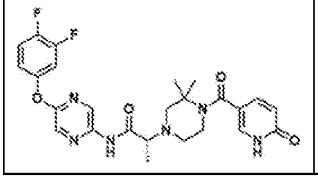
	74	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide
	75	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(4-(2-hydroxyethyl)-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	76	SKS	(R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)thiazol-2-yl)propanamide
	77	SKS	(S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)thiazol-2-yl)propanamide
	78	SKS	(R)-2-(aminomethyl)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	79	SKS	(S)-2-(aminomethyl)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	80	SKS	(R)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-((methylamino)methyl)pyridine 1-oxide
	81	SKS	(S)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-((methylamino)methyl)pyridine 1-oxide

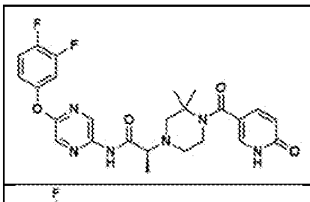
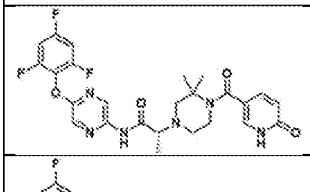
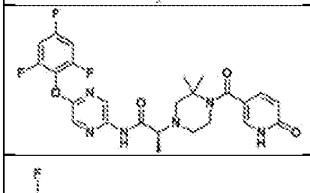
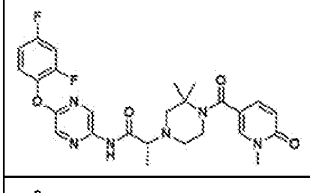
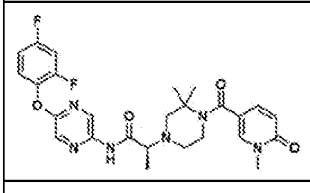
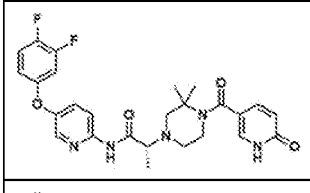
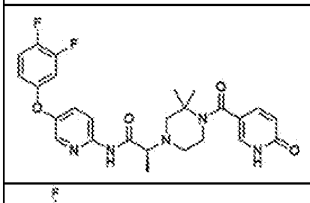
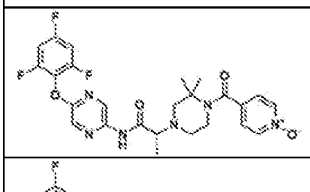
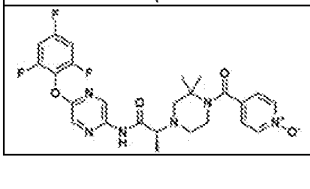
	82	SKS	(R)-2-(acetamidomethyl)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	83	SKS	(S)-2-(acetamidomethyl)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	84	SKS	(R)-2-(4-(5-cyano-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	85	SKS	(S)-2-(4-(5-cyano-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	86	ME	2-(4-(5-(aminomethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	87	SKS	(R)-2-(3,3-dimethyl-4-(5-((methylamino)methyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	88	SKS	(S)-2-(3,3-dimethyl-4-(5-((methylamino)methyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	89	SKS	(R)-4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide

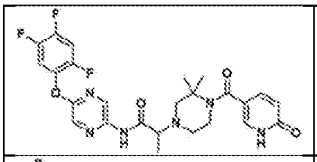
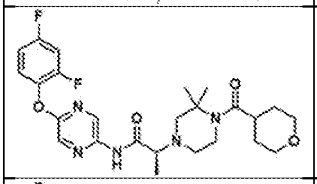
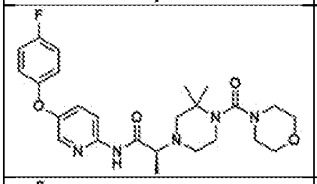
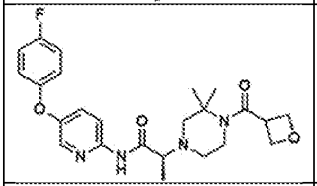
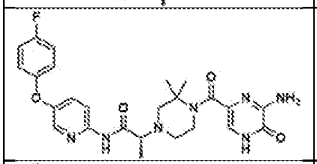
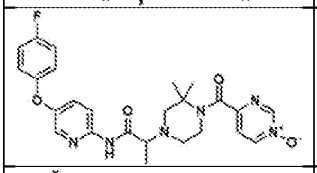
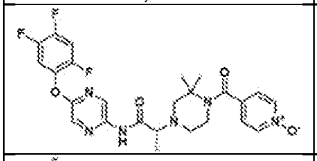
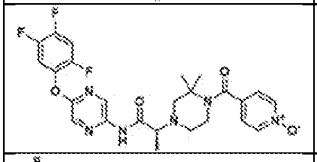
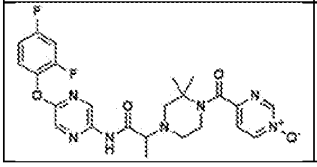
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	91	SUS	(R)-N-(5-(cyclobutylmethoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide
	92	SUS	(S)-N-(5-(cyclobutylmethoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide
	93	ME	2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-isobutoxypyridin-2-yl)propanamide
	94	SKS	(S)-2-(3,3-dimethyl-4-(6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	95	SKS	(S)-2-(3,3-dimethyl-4-(tetrahydro-2H-pyran-4-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	96	ME	2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	97	SUS	(S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(6-(4-fluorophenoxy)pyridazin-3-yl)propanamide

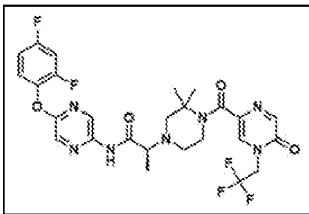
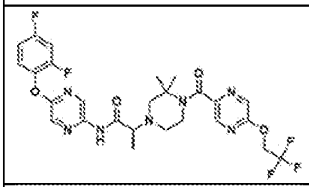
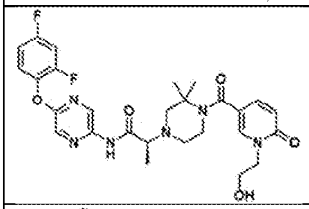
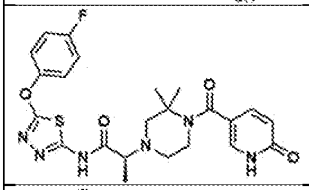
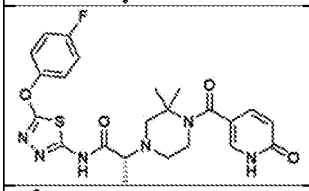
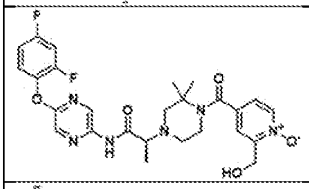
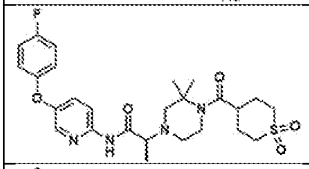
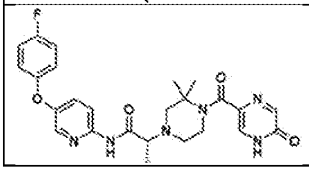
	98	SUS	(R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(6-(4-fluorophenoxy)pyridazin-3-yl)propanamide
	99	ME	2-(4-(5-(acetamidomethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	100	SKS	(S)-2-(4-(1-(2,2-difluoroethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	101	SKS	(S)-2-(3,3-dimethyl-4-(5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	102	MD	4-(4-((S)-1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(2,2,2-trifluoro-1-hydroxyethyl)pyridine 1-oxide
	103	SKS	(S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-(5-(hydroxymethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	104	SKS	(S)-2-(3,3-dimethyl-4-(5-oxo-4-(2,2,2-trifluoroethyl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	105	SKS	(S)-2-(3,3-dimethyl-4-(5-(morpholinomethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

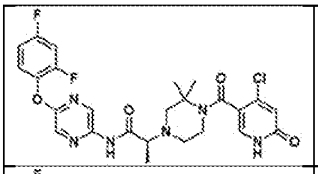
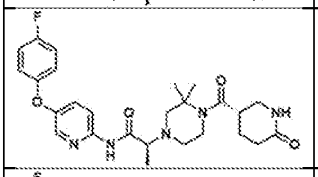
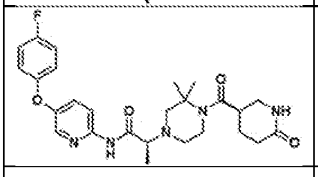
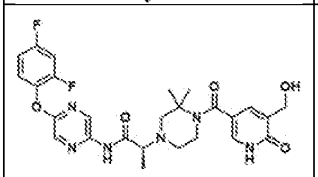
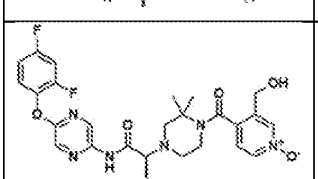
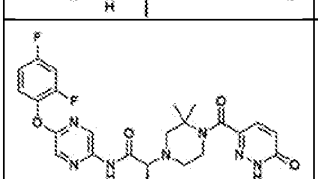
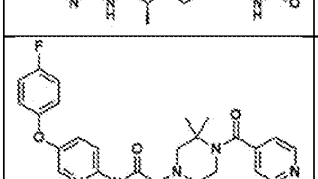
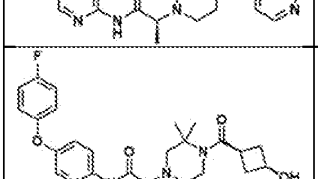
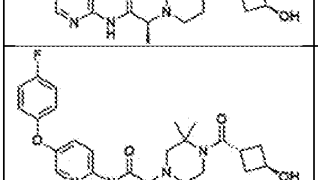
	106	SKS	(R)-N-(5-(2,4-difluorophenoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide
	107	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide
	108	SKS	(R)-4-(4-(1-((5-(2,4-difluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	109	SKS	(S)-4-(4-(1-((5-(2,4-difluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	110	ME	4-(4-(1-((5-(3,4-difluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	111	SKS	(S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorobenzyl)pyridin-2-yl)propanamide
	112	SKS	(R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorobenzyl)pyridin-2-yl)propanamide
	113	SKS	(R)-4-(4-(1-((5-(3,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	114	SKS	(S)-4-(4-(1-((5-(3,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide

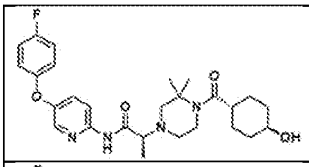
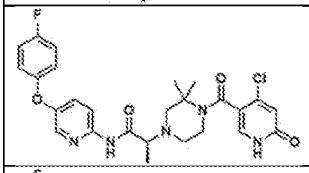
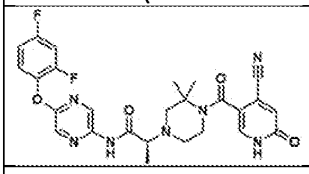
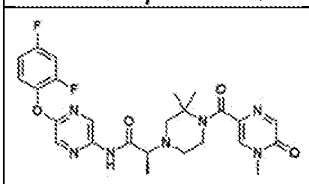
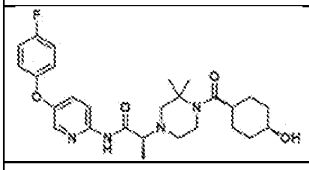
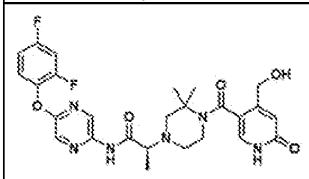
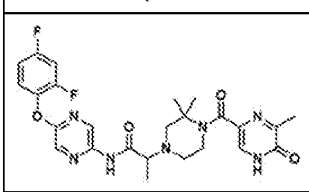
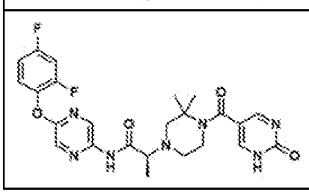
	115	SKS	(S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)propanamide
	116	SKS	(R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)propanamide
	117	SKS	(S)-2-(4-(4-chloro-1-methyl-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	118	SKS	(S)-2-(3,3-dimethyl-4-(5-(2,2,2-trifluoroethoxy)pyrazine-2-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	119	SKS	(S)-4-(4-(1-((5-(4-fluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	120	SKS	(R)-4-(4-(1-((5-(4-fluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	121	SKS	(R)-3-chloro-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	122	SKS	(S)-3-chloro-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	123	SKS	(R)-N-(5-(3,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide

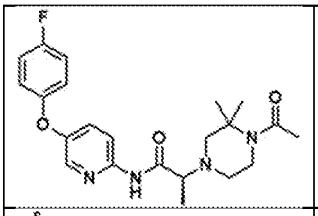
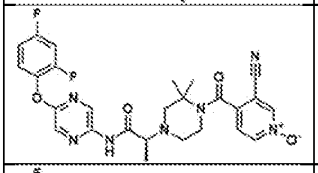
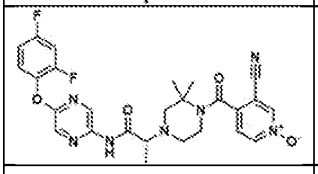
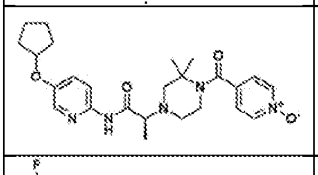
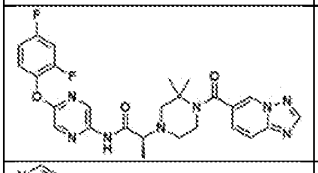
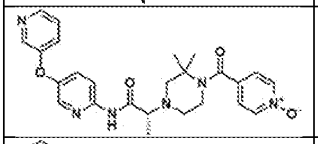
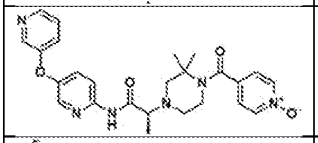
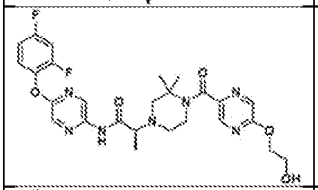
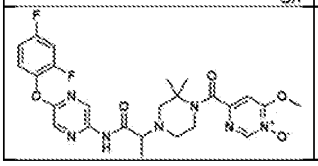
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	125	SKS	(R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(2,4,6-trifluorophenoxy)pyrazin-2-yl)propanamide
	126	SKS	(S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(2,4,6-trifluorophenoxy)pyrazin-2-yl)propanamide
	127	SKS	(R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide
	128	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide
	129	SKS	(R)-N-(5-(3,4-difluorophenoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide
	130	SKS	(S)-N-(5-(3,4-difluorophenoxy)pyridin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)propanamide
	131	SKS	(R)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(2,4,6-trifluorophenoxy)pyrazin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide
	132	SKS	(S)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(2,4,6-trifluorophenoxy)pyrazin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide

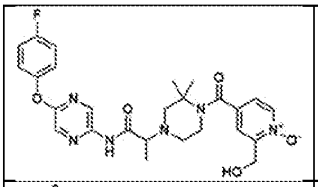
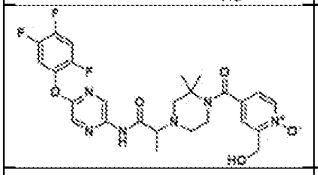
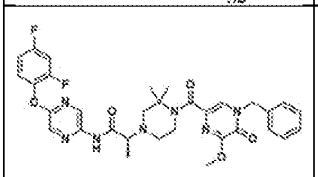
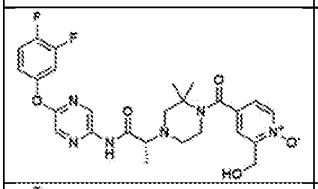
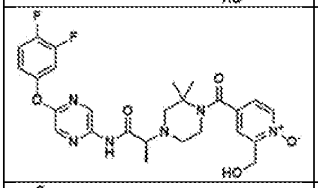
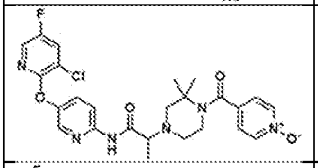
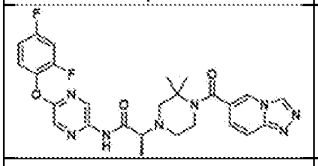
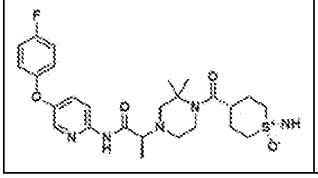
	133	ME	2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(2,4,5-trifluorophenoxy)pyrazin-2-yl)propanamide
	134	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(tetrahydro-2H-pyran-4-carbonyl)piperazin-1-yl)propanamide
	135	SKS	(S)-2-(3,3-dimethyl-4-(morpholine-4-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	136	SKS	(S)-2-(3,3-dimethyl-4-(oxetane-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	137	SKS	(S)-2-(4-(6-amino-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	138	ME	4-(4-(1-((5-(4-fluorophenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyrimidine 1-oxide
	139	SKS	(R)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(2,4,5-trifluorophenoxy)pyrazin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide
	140	SKS	(S)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(2,4,5-trifluorophenoxy)pyrazin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide
	141	ME	4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyrimidine 1-oxide

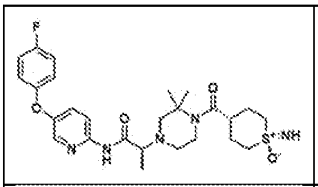
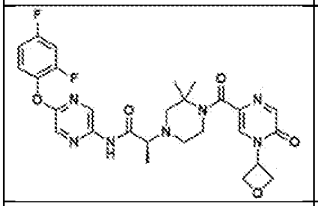
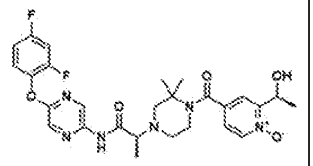
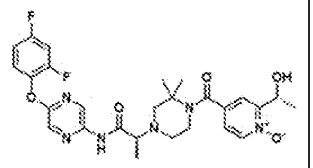
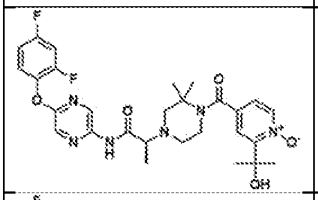
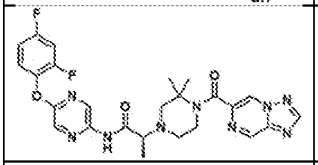
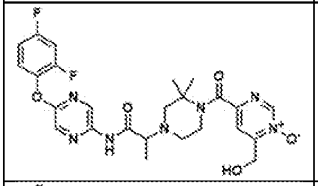
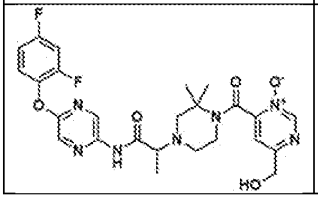
	142	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-4-(2,2,2-trifluoroethyl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide
	143	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-(2,2,2-trifluoroethoxy)pyrazine-2-carbonyl)piperazin-1-yl)propanamide
	144	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(1-(2-hydroxyethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	145	SUS	(S)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)-1,3,4-thiadiazol-2-yl)propanamide
	146	ME	(R)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)-1,3,4-thiadiazol-2-yl)propanamide
	147	SKS	(S)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide
	148	SKS	(S)-2-(4-(1,1-dioxidotetrahydro-2H-thiopyran-4-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	149	SKS	(R)-2-(3,3-dimethyl-4-(5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide

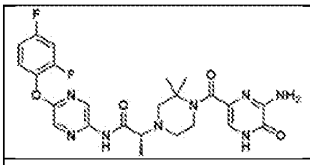
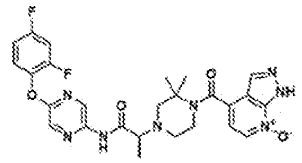
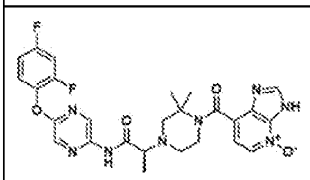
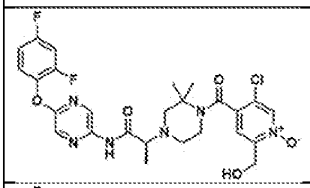
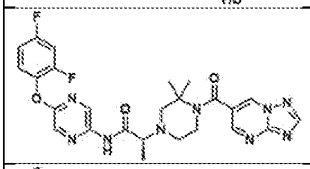
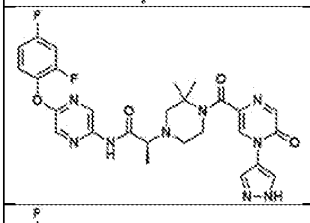
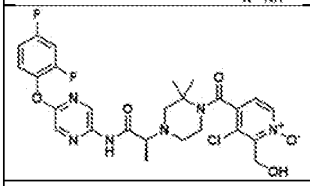
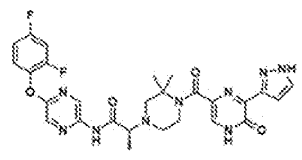
	150	SKS	(S)-2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide
	151	SUS	(S)-2-(3,3-dimethyl-4-((S)-6-oxopiperidine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	152	SUS	(S)-2-(3,3-dimethyl-4-((R)-6-oxopiperidine-3-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	153	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-(hydroxymethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	154	SKS	(S)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-3-(hydroxymethyl)pyridine 1-oxide
	155	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-oxo-1,6-dihydropyridazine-3-carbonyl)piperazin-1-yl)propanamide
	156	SKS	(S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-isonicotinoyl-3,3-dimethylpiperazin-1-yl)propanamide
	157	SKS	(S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-((1s,3R)-3-hydroxycyclobutane-1-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	158	SKS	(S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-((1r,3S)-3-hydroxycyclobutane-1-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

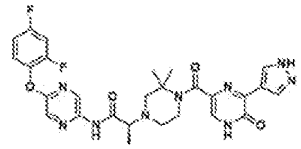
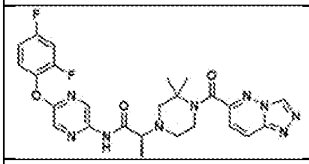
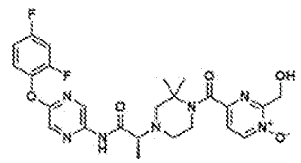
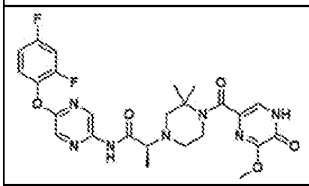
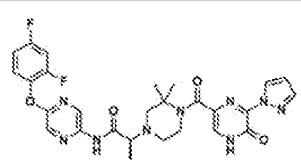
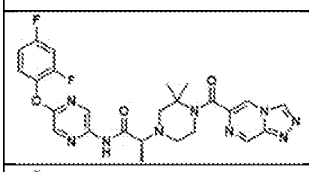
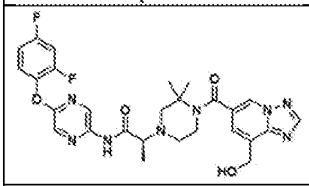
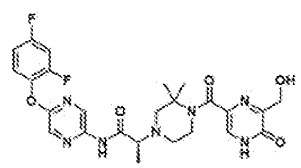
	159	SKS	(S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-((1r,4S)-4-hydroxycyclohexane-1-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	160	SKS	(S)-2-(4-(4-chloro-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	161	SKS	(S)-2-(4-(4-cyano-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide
	162	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(4-methyl-5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide
	163	SKS	(S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-((1s,4R)-4-hydroxycyclohexane-1-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	164	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(4-(hydroxymethyl)-6-oxo-1,6-dihydropyridine-3-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	165	ME	N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-methyl-5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide
	166	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(2-oxo-1,2-dihydropyrimidine-5-carbonyl)piperazin-1-yl)propanamide

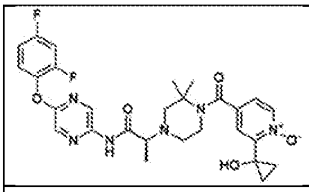
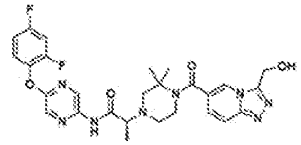
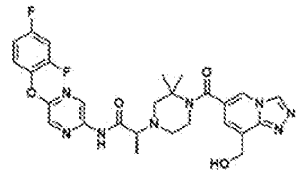
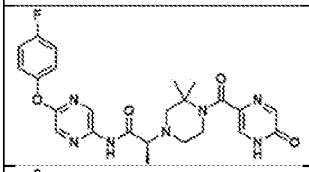
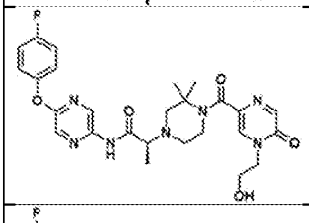
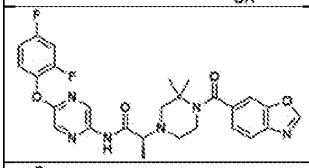
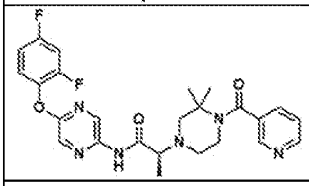
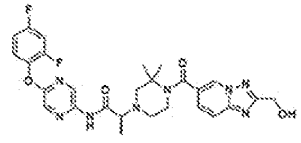
	167	SKS	(S)-2-(4-acetyl-3,3-dimethylpiperazin-1-yl)-N-(5-(4-fluorophenoxy)pyridin-2-yl)propanamide
	168	SKS	(S)-3-cyano-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	169	SKS	(R)-3-cyano-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	170	SKS	(S)-4-(4-(1-((5-(cyclopentyloxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	171	SKS	(S)-2-(4-([1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide
	172	SKS	(R)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(pyridin-3-yloxy)pyridin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide
	173	SKS	(S)-4-(2,2-dimethyl-4-(1-oxo-1-((5-(pyridin-3-yloxy)pyridin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)pyridine 1-oxide
	174	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-(2-hydroxyethoxy)pyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	175	ME	4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-6-methoxypyrimidine 1-oxide

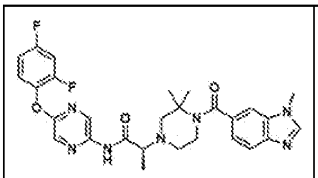
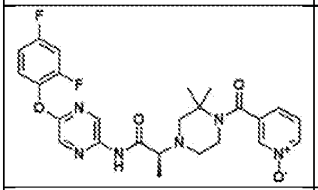
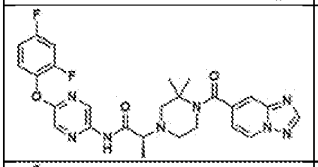
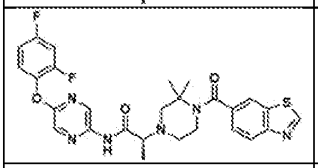
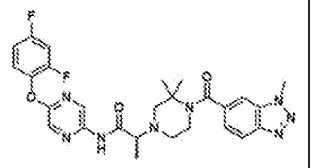
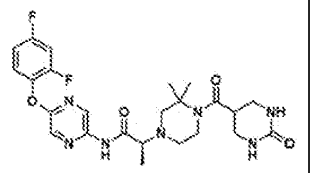
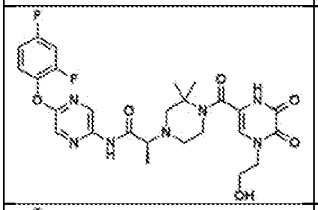
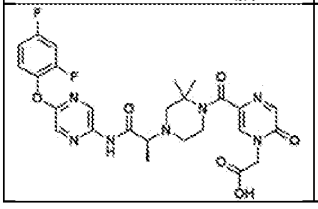
	176	ME	4-(4-(1-((5-(4-fluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide
	177	ME	4-(2,2-dimethyl-4-(1-oxo-1-((5-(2,4,5-trifluorophenoxy)pyrazin-2-yl)amino)propan-2-yl)piperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide
	178	SKS	(S)-2-(4-(4-benzyl-6-methoxy-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide
	179	SKS	(R)-4-(4-(1-((5-(3,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide
	180	SKS	(S)-4-(4-(1-((5-(3,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide
	181	ME	4-(4-(1-((5-((3-chloro-5-fluoropyridin-2-yl)oxy)pyridin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	182	SKS	(S)-2-(4-([1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide
	183	SUS	(S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-((1R,4s)-1-imino-1-oxidohexahydro-1l6-thiopyran-4-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

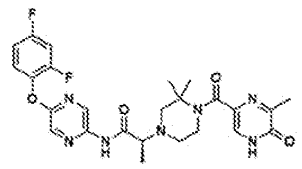
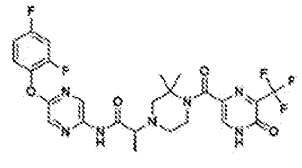
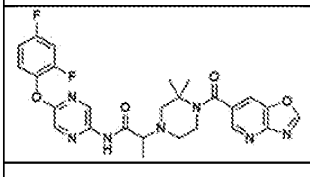
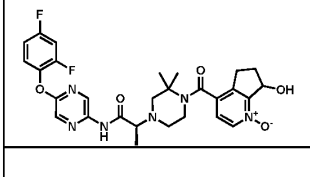
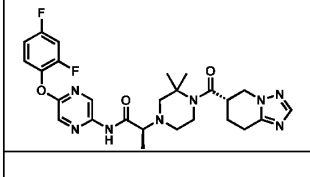
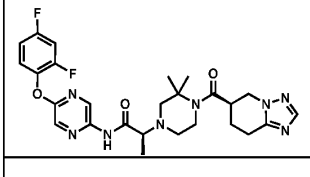
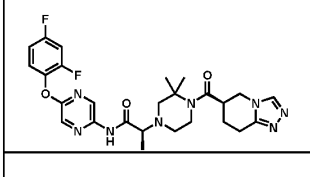
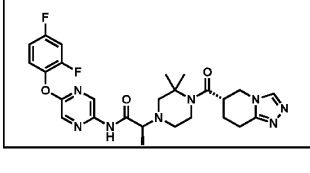
	184	SUS	(S)-N-(5-(4-fluorophenoxy)pyridin-2-yl)-2-(4-((1S,4r)-1-imino-1-oxidohexahydro-1l6-thiopyran-4-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	185	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(4-(oxetan-3-yl)-5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide
	186	SUS	4-(4-((S)-1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-((S)-1-hydroxyethyl)pyridine 1-oxide
	187	SUS	4-(4-((S)-1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-((R)-1-hydroxyethyl)pyridine 1-oxide
	188	SKS	(S)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(2-hydroxypropan-2-yl)pyridine 1-oxide
	189	SKS	(S)-2-(4-([1,2,4]triazolo[1,5-a]pyrazine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide
	190	ME	4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-6-(hydroxymethyl)pyrimidine 1-oxide
	191	ME	6-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-4-(hydroxymethyl)pyrimidine 1-oxide

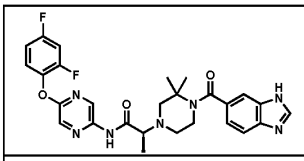
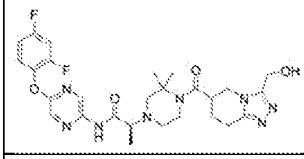
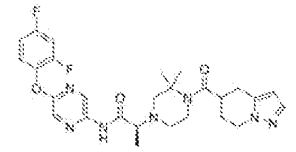
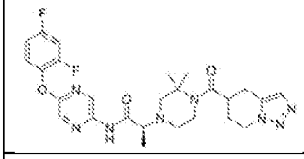
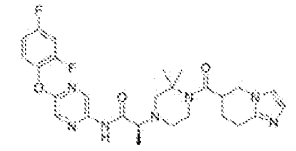
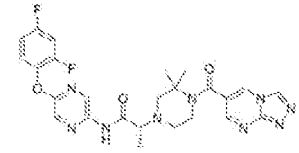
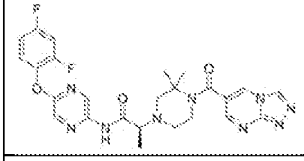
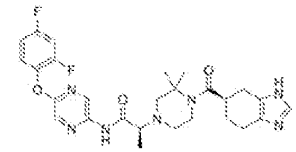
	192	SKS	(S)-2-(4-(6-amino-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide
	193	SKS	(S)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-1H-pyrazolo[3,4-b]pyridine 7-oxide
	194	SKS	(S)-7-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-3H-imidazo[4,5-b]pyridine 4-oxide
	195	SKS	(S)-5-chloro-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide
	196	SKS	(S)-2-(4-([1,2,4]triazolo[1,5-a]pyrimidine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide
	197	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-4-(1H-pyrazol-4-yl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide
	198	SKS	(S)-3-chloro-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyridine 1-oxide
	199	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-6-(1H-pyrazol-3-yl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide

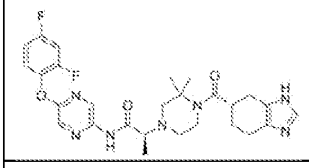
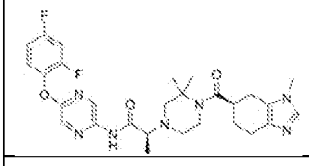
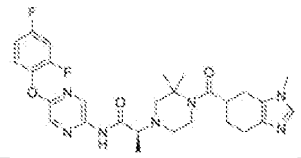
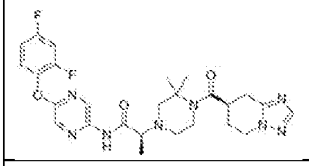
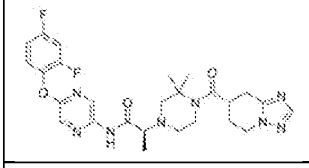
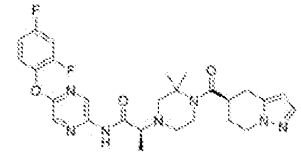
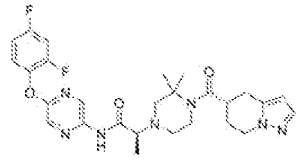
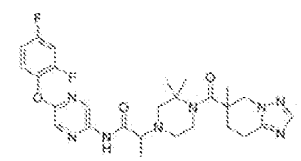
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	201	SKS	(S)-2-(4-([1,2,4]triazolo[4,3-b]pyridazine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide
	202	SKS	(S)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(hydroxymethyl)pyrimidine 1-oxide
	203	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(6-methoxy-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	204	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-6-(1H-pyrazol-1-yl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide
	205	SKS	(S)-2-(4-([1,2,4]triazolo[4,3-a]pyrazine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide
	206	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(8-(hydroxymethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	207	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(6-(hydroxymethyl)-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

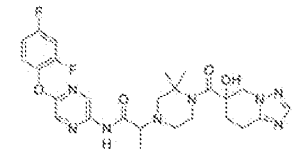
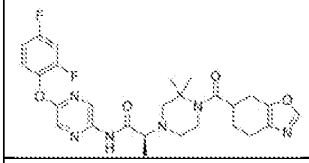
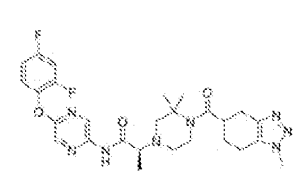
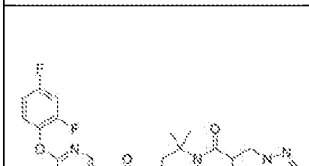
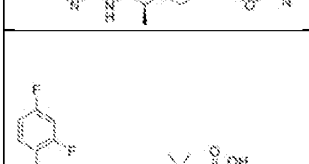
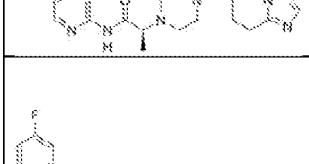
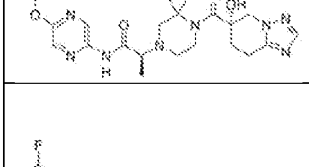
	208	SKS	(S)-4-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-(1-hydroxycyclopropyl)pyridine 1-oxide
	209	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(3-(hydroxymethyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	210	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(8-(hydroxymethyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	211	SKS	(S)-2-(3,3-dimethyl-4-(5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)propanamide
	212	SKS	(S)-N-(5-(4-fluorophenoxy)pyrazin-2-yl)-2-(4-(4-(2-hydroxyethyl)-5-oxo-4,5-dihydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	213	SKS	(S)-2-(4-(benzo[d]oxazole-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide
	214	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-nicotinoylpiperazin-1-yl)propanamide
	215	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(2-(hydroxymethyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

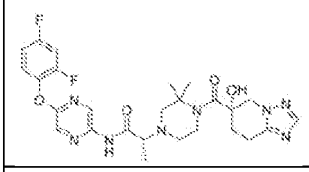
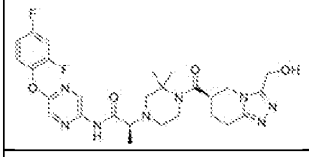
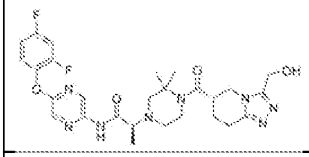
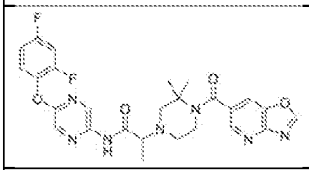
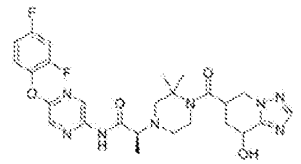
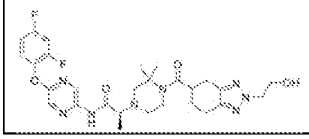
	216	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-methyl-1H-benzo[d]imidazole-6-carbonyl)piperazin-1-yl)propanamide
	217	SKS	(S)-3-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)pyridine 1-oxide
	218	SKS	(S)-2-(4-([1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide
	219	SKS	(S)-2-(4-(benzo[d]thiazole-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide
	220	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-methyl-1H-benzo[d][1,2,3]triazole-6-carbonyl)piperazin-1-yl)propanamide
	221	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(2-oxohexahydropyrimidine-5-carbonyl)piperazin-1-yl)propanamide
	222	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(4-(2-hydroxyethyl)-5,6-dioxo-1,4,5,6-tetrahydropyrazine-2-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	223	SKS	(S)-2-(5-(4-(1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-2-oxopyrazin-1(2H)-yl)acetic acid

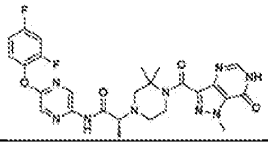
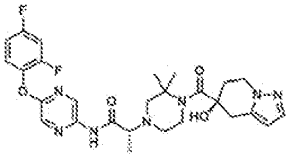
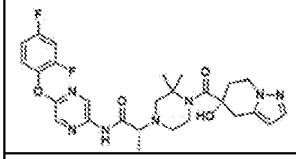
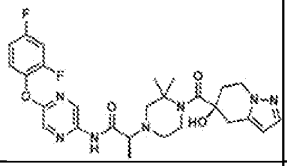
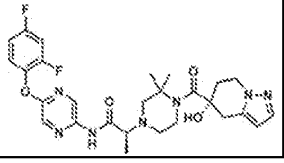
	224	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-methyl-5-oxo-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide
	225	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5-oxo-6-(trifluoromethyl)-4,5-dihydropyrazine-2-carbonyl)piperazin-1-yl)propanamide
	226	ME	N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(oxazolo[4,5-b]pyridine-6-carbonyl)piperazin-1-yl)propanamide
	227	MD	4-(4-((S)-1-((5-(2,4-difluorophenoxy)pyrazin-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethylpiperazine-1-carbonyl)-7-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridine 1-oxide
	228	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)piperazin-1-yl)propanamide
	229	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)piperazin-1-yl)propanamide
	230	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)piperazin-1-yl)propanamide
	231	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)piperazin-1-yl)propanamide

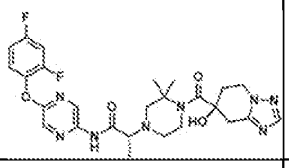
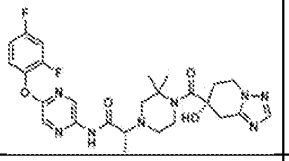
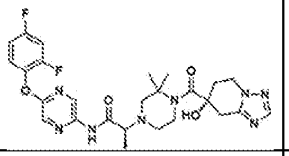
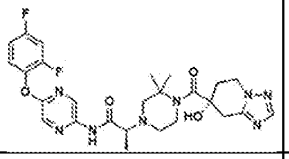
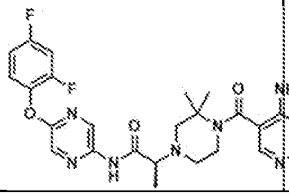
	232	SKS	(S)-2-(4-(1H-benzo[d]imidazole-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide
	233	MD	(2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(3-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	234	MD	(2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)piperazin-1-yl)propanamide
	235	MD	(2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carbonyl)piperazin-1-yl)propanamide
	236	MD	(2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carbonyl)piperazin-1-yl)propanamide
	237	SKS	(R)-2-(4-([1,2,4]triazolo[4,3-a]pyrimidine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide
	238	SKS	(S)-2-(4-([1,2,4]triazolo[4,3-a]pyrimidine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide
	239	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-6-carbonyl)piperazin-1-yl)propanamide

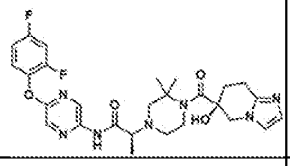
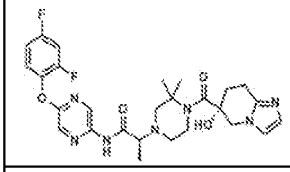
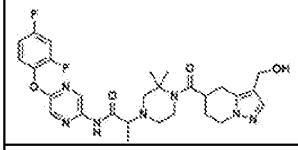
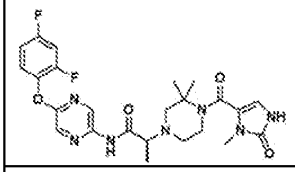
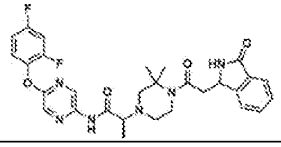
	240	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-6-carbonyl)piperazin-1-yl)propanamide
	241	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-1-methyl-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-6-carbonyl)piperazin-1-yl)propanamide
	242	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-1-methyl-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-6-carbonyl)piperazin-1-yl)propanamide
	243	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)piperazin-1-yl)propanamide
	244	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)piperazin-1-yl)propanamide
	245	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)piperazin-1-yl)propanamide
	246	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)piperazin-1-yl)propanamide
	247	MD	N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(6-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)piperazin-1-yl)propanamide

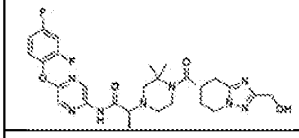
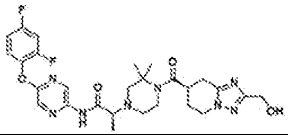
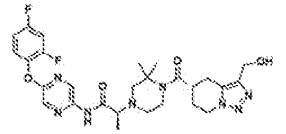
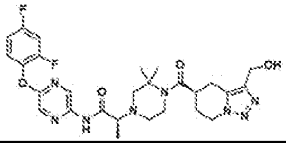
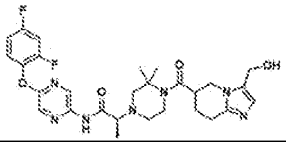
	248	MD	N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(6-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	249	MD	(2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(4,5,6,7-tetrahydrobenzo[d]oxazole-6-carbonyl)piperazin-1-yl)propanamide
	250	MD	(2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-methyl-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carbonyl)piperazin-1-yl)propanamide
	251	MD	(2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(6,7-dihydro-5H-[1,2,4]triazolo[5,1-b][1,3]oxazine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	252	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-6-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	253	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-6-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	254	SUS	(R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-6-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

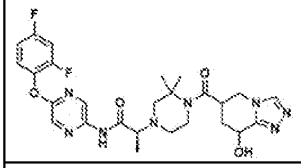
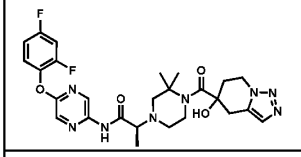
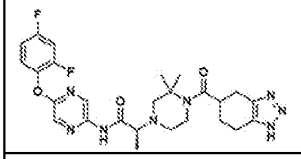
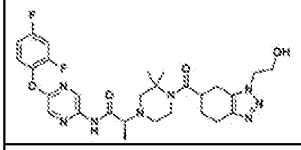
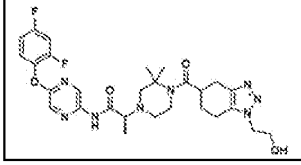
	255	SUS	(R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-6-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	256	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-3-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	257	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-3-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	258	ME	N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(oxazolo[4,5-b]pyridine-6-carbonyl)piperazin-1-yl)propanamide
	259	MD	(2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(8-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	260	MD	(2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(2-(2-hydroxyethyl)-4,5,6,7-tetrahydro-2H-benzo[d][1,2,3]triazole-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

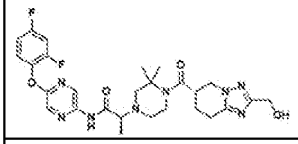
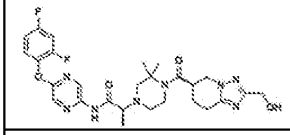
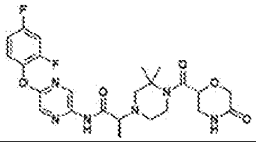
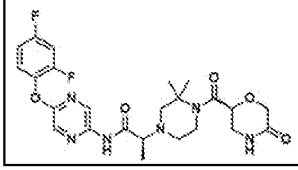
	**261**	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidine-3-carbonyl)piperazin-1-yl)propanamide
	**262**	SUS	(R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-5-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	**263**	SUS	(R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-5-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	**264**	SUS	S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-5-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propenamide
	**265**	SUS	((S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-5-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propenamide

	**266**	SUS	(R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-7-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	**267**	SUS	(R)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-7-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	**268**	SUS	((S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-7-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)propenamide
	**269**	SUS	((S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-7-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)propenamide
	**270**	SKS	((S)-2-(4-(4-amino-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)propanamide

	**271**	SUS	((S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-6-hydroxy-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	**272**	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-6-hydroxy-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	**273**	MD	N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(3-(hydroxymethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	**274**	SKS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(3-methyl-2-oxo-2,3-dihydro-1H-imidazole-4-carbonyl)piperazin-1-yl)propanamide
	**275**	MD	(2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(2-(3-oxoisoindolin-1-yl)acetyl)piperazin-1-yl)propanamide

	**276**	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-2-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	**277**	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-2-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-7-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	**278**	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-3-(hydroxymethyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	**279**	SUS	((S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-3-(hydroxymethyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	**280**	MD	(2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(3-(hydroxymethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

	**281**	MD	(2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(8-hydroxy-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	**282**	MD	(2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(5-hydroxy-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	**283**	MD	(2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-(4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carbonyl)piperazin-1-yl)propanamide
	**284**	MD	Example 250: (2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(1-(2-hydroxyethyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	**285**	MD	(2S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-(1-(2-hydroxyethyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide

	**286**	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((S)-2-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propenamide
	**287**	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(4-((R)-2-(hydroxymethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6-carbonyl)-3,3-dimethylpiperazin-1-yl)propanamide
	**288**	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((R)-5-oxomorpholine-2-carbonyl)piperazin-1-yl)propanamide
	**289**	SUS	(S)-N-(5-(2,4-difluorophenoxy)pyrazin-2-yl)-2-(3,3-dimethyl-4-((S)-5-oxomorpholine-2-carbonyl)piperazin-1-yl)propanamide

hMRGPRX2 TR-FRET IP1 Assay

Assays were performed using Expi293F Inducible cells (Invitrogen) stably expressing hMRGPRX2 via a pcZeo TetO DNA plasmid. Cell lines were maintained in suspension in Expi293 Expression Medium (ThermoFisher Scientific) supplemented with 10 µg/mL Blasticidin and 10 µg/mL Zeocin and incubated at 37°C, 8% CO_2, with shaking. For assay-ready aliquots, hMRGPRX2-expressing cells were incubated at 32°C, 5% CO_2, with shaking for 30 minutes prior to a 5-hour induction with Doxycycline under the same condition. Cells were pelleted at 4°C, resuspended in Expi293 Expression media + 10% DMSO, aliquoted, and kept frozen at -80°C until ready for use.

For the assay, concentration-response curves of test and reference compounds were added to 384-well plates using an Echo 650 liquid handler (Beckman Coulter) and backfilled with DMSO to a final concentration of 0.5%. Aliquots of frozen hMRGPRX2-expressing cells were quickly thawed and washed with phosphate-buffered saline (Sigma-Aldrich) to remove media and DMSO. The cells were resuspended in kit-supplied Stimulation Buffer at 0.952 x 106 cells/mL (10000 cells/well). 10.5 µL of the hMRGPRX2-expressing cell dilution was added to each well of the assay plate and incubated with the compounds for 15 minutes in a 37°C, 0% CO_2 incubator. 3.5 µL of Vehicle control or an EC_{80}¬ concentration of an endogenous neuropeptide (Cortistatin-14, Tocris) was added to stimulate IP1 production and was incubated for 60 minutes at 37°C, 0% CO_2. Following this incubation, the cells were lysed and accumulated IP1 was measured using the cisbio IP1 Gq dynamic HTRF kit (PerkinElmer) according to manufacturer instructions. The HTRF signal was quantified using a BMG Clariostar plate reader optimized for HTRF assays. The HTRF ratio was determined by dividing the signal output at 655 nm by that at 620 nm. Data were normalized to the signal produced by the EC_{80} concentration of Cortistatin-14 (0% inhibition) and vehicle (no agonist, 100% inhibition). Normalized data was plotted as a function of the concentration of test compound and the 50% inhibition (IC_{50}) values were determined using a fit of the data to a four-parameter equation.

LAD2 Beta-Hexosaminidase Degranulation Assay

LAD2 cells were maintained in suspension in StemProTM-34 serum free media (ThermoFisher Scientific) supplemented with provided Nutrient Supplement, L-Glutamine, Penicillin-Streptomycin, and human SCF and incubated at 37°C, 5% CO2. Cells were passaged into a new flask once density exceeds 0.8 x 106 cells/mL. Prior to performing the degranulation assay, cells were incubated at 37°C, 5% CO2 in Tyrode's buffer overnight. The next day, concentration-response curves of test and reference compounds were added to 384-well plates using an Echo 650 liquid handler (Beckman Coulter) and backfilled with DMSO to a final concentration of 0.3%. LAD2 cells incubated in Tyrode's buffer overnight were spun down, aspirated, and resuspended in pre-warmed, fresh Tyrode's buffer at 0.4 x 106 cells/mL. 20,000 cells were seeded to each well of the assay plate and incubated with the compounds for 15 minutes in a 37°C, 5% CO2 incubator. 20nL of Vehicle control or an EC90¬ concentration of Cortistatin-14 (Tocris) was added via Echo 650 liquid handler and incubated for 30 minutes at 37°C, 5% CO2. Following this incubation, the cells were pelleted via centrifugation. In wells designated for maximal degranulation controls, the supernatant

was fully aspirated and cells were lysed with 50 µL 0.1% Triton-X for 5 minutes. 25 µL of supernatant was then transferred into a new plate with 25 µL of 2nM p-nitrophenyl-acetyl-D-glucosamine (pNAG) (pH 4.5) and incubated for 60 minutes at 37°C, 5% CO2. The reaction was stopped with 50 µL of 0.4M glycine at pH 10.7. Absorbance at 405 nm was detected using a BMG Clariostar plate reader.

Percent degranulation was determined by (405m absorbance of sample/405m absorbance of Triton X average) *100. Data were normalized to the signal produced by the EC_{90} concentration of Cortistatin-14 (0% inhibition) and vehicle (no agonist, 100% inhibition). Normalized data was plotted as a function of the concentration of test compound, and the 50% inhibition (IC_{50}) values were determined using a fit of the data to a four-parameter equation. Activity ranges are given as follows: "+++" denotes an IC_{50} value < 100 nM, "++" denotes IC_{50} value between 100 nM and 1000 nM, and "+" denotes an IC_{50} value between 1001 nM and 10000 nM.

Compound characterization data and activity data for exemplary MRGPRX2 antagonists in the hMRGPRX2 TR-FRET IP1 and LAD2 Beta-Hexosaminidase Degranulation Assay are shown in Table 2 below.

Table 2. Data and Characterization for Compound 1 to 260.

Ex.	MRGPRX2 IP1 Activity Bin	LAD2 Activity Bin	^{1}H NMR	LCMS
1	++	++	1H NMR (300 MHz, DMSO-d6) δ 11.84 (s, 1H), 10.25 (s, 1H), 8.13 (dd, J = 6.0, 2.9 Hz, 2H), 7.43 – 7.60 (m, 3H), 7.16 – 7.29 (m, 2H), 7.02 – 7.15 (m, 2H), 6.33 (d, J = 9.4 Hz, 1H), 3.44 – 3.58 (m, 5H), 2.58 (tt, J = 9.3, 4.9 Hz, 4H), 1.19 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C24H24FN5O4: 465.18, m/z, found: 466.05 [M+H]+

2	+		1H NMR (300 MHz, DMSO-d6) δ 10.23 (s, 1H), 8.13 (dd, J = 6.0, 2.9 Hz, 2H), 7.92 (d, J = 7.9 Hz, 2H), 7.58 (d, J = 7.9 Hz, 2H), 7.52 (dd, J = 9.1, 2.9 Hz, 1H), 7.23 (t, J = 8.8 Hz, 2H), 7.08 (dd, J = 9.1, 4.4 Hz, 2H), 3.67 (s, 2H), 3.52 (d, J = 6.9 Hz, 3H), 2.51 – 2.79 (m, 4H), 1.19 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C26H24FN5O3: 473.19 m/z, found: 474.05 [M+H]+
3	+		1H NMR (300 MHz, DMSO-d6) δ 13.17 (s, 1H), 10.24 (s, 1H), 8.14 (dd, J = 5.9, 2.9 Hz, 2H), 8.06 (s, 1H), 7.72 (s, 1H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.16 – 7.31 (m, 2H), 7.04 – 7.16 (m, 2H), 3.64 (t, J = 4.9 Hz, 4H), 3.51 (q, J = 6.8 Hz, 1H), 2.51 – 2.66 (m, 4H), 1.20 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C22H23FN6O3: 438.18 m/z, found: 439.10 [M+H]+
4	+		1H NMR (300 MHz, DMSO-d6) δ 11.84 (s, 1H), 10.25 (s, 1H), 8.13 (dd, J = 6.0, 2.9 Hz, 2H), 7.42 – 7.60 (m, 3H), 7.17 – 7.29 (m, 2H), 7.02 – 7.16 (m, 2H), 6.33 (d, J = 9.4 Hz, 1H), 3.45 – 3.59 (m, 5H), 2.50 – 2.67 (m, 4H), 1.19 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C24H24FN5O4: 465.18 m/z, found: 466.10 [M+H]+,

5	+		1H NMR (300 MHz, DMSO-d6) δ 11.84 (s, 1H), 10.25 (s, 1H), 8.13 (dd, J = 6.0, 2.9 Hz, 2H), 7.42 – 7.60 (m, 3H), 7.17 – 7.29 (m, 2H), 7.02 – 7.17 (m, 2H), 6.33 (d, J = 9.4 Hz, 1H), 3.44 – 3.59 (m, 5H), 2.50 – 2.67 (m, 4H), 1.21 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C24H24FN5O4: 465.18 m/z, found: 466.15 [M+H]+,
6	+		1H NMR (300 MHz, DMSO-d6) δ 10.12 (s, 1H), 8.09 – 8.18 (m, 2H), 7.84 – 7.75 (m, 2H), 7.58 – 7.47 (m, 3H), 7.30 – 7.16 (m, 2H), 7.15 – 7.02 (m, 2H), 3.58 (s, 2H), 3.42 (q, J = 6.8 Hz, 1H), 2.53 – 2.61 (m, 4H), 2.40 – 2.46 (m, 4H), 1.18 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C26H26FN5O2: 459.525 m/z, found 460.10 [M+H]+
7	+	++	1H NMR (300 MHz, DMSO-d6) δ 10.25 (s, 1H), 8.62 – 8.70 (m, 2H), 8.09 – 8.18 (m, 2H), 7.52 (dd, J = 9.1, 2.9 Hz, 1H), 7.34 – 7.42 (m, 2H), 7.16 – 7.31 (m, 2H), 7.03 – 7.15 (m, 2H), 3.64 – 3.69 (m, 2H), 3.52 (d, J = 7.0 Hz, 1H), 3.26 – 3.36 (m, 2H), 3.53 – 3.68 (m, 4H), 1.19 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C24H24FN5O3: 449.19 m/z, found 450.15 [M+H]+.

8	+		1H NMR (400 MHz, DMSO-d6) δ 11.46 (s, 1H), 10.11 (s, 1H), 8.10 – 8.17 (m, 2H), 7.49 – 7.57 (m, 1H), 7.33 – 7.40 (m, 1H), 7.18 – 7.29 (m, 3H), 7.04 – 7.14 (m, 2H), 6.29 (d, J = 9.4 Hz, 1H), 3.36 – 3.45 (m, 1H), 3.17 – 3.22 (m, 2H), 2.52 – 2.57 (m, 4H), 2.37 – 2.41 (m, 4H), 1.17 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd: For C24H26FN5O3: 451.20 m/z, found: 452.15 [M+H]+
9	+		1H NMR (400 MHz, DMSO-d6) δ 10.23 (s, 1H), 9.83 (s, 1H), 8.10 – 8.17 (m, 2H), 7.49 – 7.55 (m, 1H), 7.18 – 7.28 (m, 4H), 7.05 – 7.17 (m, 2H), 6.74 – 6.81 (m, 2H), 3.43 – 3.60(m, 5H), 2.50 – 2.64 (m, 4H), 1.19 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C25H25FN4O4: 464.19 m/z, found 465.15 [M+H]+
10	+		1H NMR (400 MHz, DMSO-d6) δ 10.25 (s, 1H), 8.24 (d, J = 6.6 Hz, 2H), 8.11 – 8.16 (m, 2H), 7.49 – 7.55 (m, 1H), 7.45 (d, J = 6.5 Hz, 2H), 7.19 – 7.22 (m, 2H), 7.05 – 7.14 (m, 2H), 3.40 – 3.65 (m, 5H), 2.45 – 2.65 (m, 4H), 1.19 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C24H24FN5O4: 465.18 m/z, found 466.10 [M+H]+.

11	++	++	1H NMR (400 MHz, DMSO-d6) δ 10.26 (s, 1H), 8.10 – 8.17 (m, 2H), 7.53 (dd, J = 8.9, 3.0 Hz, 1H), 7.19 – 7.31 (m, 2H), 7.04 – 7.14 (m, 2H), 3.79 – 3.87 (m, 2H), 3.44 – 3.58 (m, 5H), 3.31 – 3.41 (m, 2H), 2.80 – 2.90 (m, 1H), 2.66 – 2.69 (m, 2H), 2.32 – 2.35 (m, 2H) 1.46 – 1.51 (m, 4H), 1.18 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C24H29FN4O4: 456.22 m/z, found 457.15 [M+H]+.
12	+	++	1H NMR (400 MHz, DMSO-d6) δ 13.26 (s, 1H), 10.27 (s, 1H), 8.12 – 8.18 (m, 3H), 7.85 (s, 1H), 7.49 – 7.62 (m, 2H), 7.38 (dd, J = 8.6, 1.5 Hz, 1H), 7.24 (t, J = 8.8 Hz, 2H), 7.04 – 7.14 (m, 2H), 3.43 – 3.58 (m, 4H), 2.62 (s, 1H), 2.41 – 2.61 (m, 4H), 1.20 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C26H25FN6O3: 488.20 m/z, found: 489.10 [M+H]+
13	++	++	1H NMR (300 MHz, DMSO-d6) δ 10.25 (s, 1H), 8.13 (dd, J = 6.0, 2.9 Hz, 2H), 7.97 (d, J = 2.5 Hz, 1H), 7.47 – 7.61 (m, 2H), 7.16 – 7.31 (m, 2H), 7.02 – 7.15 (m, 2H), 6.51 (d, J = 9.5 Hz, 1H), 4.89 (q, J = 9.1 Hz, 2H), 3.46 – 3.58 (m, 5H), 2.52 – 2.68 (m, 4H), 1.19 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C26H25F4N5O4: 547.18 m/z, found 548.10 [M+H]+

14	++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.27 (s, 1H), 8.15 (dd, J = 6.1, 2.9 Hz, 2H), 8.10 (d, J = 2.6 Hz, 1H), 7.46 – 7.56 (m, 2H), 7.26 – 7.39 (m, 4H), 7.24 (t, J = 8.7 Hz, 2H), 7.09 (dd, J = 9.0, 4.5 Hz, 2H), 6.45 (d, J = 9.3 Hz, 1H), 5.14 (s, 2H), 3.53 (t, J = 6.1 Hz, 5H), 2.43 – 2.67 (m, 4H), 1.19 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C31H30FN5O4: 555.23 m/z, found 556.15 [M+H]+
15	+		1H NMR (400 MHz, DMSO-d6) δ 10.26 (s, 1H), 8.57 (s, 1H), 8.12 – 8.20 (m, 2H), 7.50 – 7.58 (m, 1H), 7.40 (t, J = 7.7 Hz, 1H), 7.19 – 7.30 (m, 3H), 7.05 – 7.17 (m, 3H), 4.36 (s, 2H), 3.09 – 3.13 (m, 4H), 2.66 – 2.80 (m, 4H), 1.24 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C26H26FN5O3: 475.20 m/z, found 476.10 [M+H]+
16	+		1H NMR (400 MHz, DMSO-d6) δ 11.84 (s, 1H), 10.28 (s, 1H), 8.14 (dd, J = 6.1, 2.9 Hz, 2H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.47 (q, J = 2.5 Hz, 2H), 7.24 (t, J = 8.8 Hz, 2H), 7.04 – 7.17 (m, 2H), 3.54 (t, J = 5.2 Hz, 5H),3.38 – 3.51(m,2H) 3.08 – 3.18 (m, 1H), 2.67 – 2.79 (m, 2H), 2.52 – 2.64 (m, 5H), 2.22 – 2.40 (m, 2H), 1.16 – 1.26 (m, 3H).	MS (ESI): mass calcd. for C29H31F3N6O4: 584.24 m/z, found: 585.20 [M+H]+

17	+		1H NMR (400 MHz, DMSO-d6) δ 10.25 (s, 1H), 8.11 – 8.20 (m, 2H), 7.92 (s, 1H), 7.54 (dd, J = 9.0, 3.0 Hz, 1H), 7.16 – 7.32 (m, 5H), 7.04 – 7.16 (m, 3H), 3.52 (q, J = 6.8 Hz, 1H), 3.22 (d, J =5.1Hz, 4H), 2.61 – 2.79 (m, 4H), 1.24 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C25H26FN5O3: 463.20 m/z, found: 464.15 [M+H]+
18	+		1H NMR (400 MHz, DMSO-d6) δ 12.25 (br, 1H), 10.27 (s, 1H), 8.11 – 8.18 (m, 2H), 7.88 – 7.92 (m, 2H), 7.52 (dd, J = 9.0, 3.0 Hz, 1H), 7.19-7.23 (m , 2H), 7.08 (dd, J = 9.0, 4.5 Hz, 2H), 3.39-3.57 (m , 5H), 2.58 (tq, J = 11.7, 5.9, 5.2 Hz, 4H), 1.19 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C25H23F4N5O4: 533.17, found: 534.10 [M+H]+
19	+		1H NMR (400 MHz, DMSO-d6) δ 10.26 (s, 1H), 8.21 – 8.28 (m, 2H), 8.10 – 8.17 (m, 2H), 7.53 (dd, J = 9.2, 2.9 Hz, 1H), 7.42 – 7.48 (m, 2H), 7.24 (t, J = 8.8 Hz, 2H), 7.05 – 7.14 (m, 2H), 3.42 – 3.63 (m, 5H), 2.53 – 2.68 (m, 4H), 1.20 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C24H24FN5O4: 465.18 m/z, found: 466.10 [M+H]+
20	++		1H NMR (400 MHz, DMSO-d6) δ 10.26 (s, 1H), 8.21 – 8.28 (m, 2H), 8.10 – 8.17 (m, 2H), 7.53 (dd, J = 9.2, 2.9 Hz, 1H), 7.42 – 7.48 (m, 2H), 7.24 (t, J = 8.8 Hz, 2H), 7.05 – 7.14 (m, 2H), 3.42 – 3.63 (m, 5H), 2.53 – 2.68 (m, 4H), 1.20 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C24H24FN5O4: 465.18 m/z, found: 466.10 [M+H]+

21	+		1H NMR (400 MHz, DMSO-d6) δ 10.28 (s, 1H), 8.10 – 8.17 (m, 2H), 7.61 (d, J = 8.2 Hz, 1H), 7.53 (dd, J = 9.0, 3.0 Hz, 1H), 7.19 – 7.29 (m, 2H), 7.04 – 7.14 (m, 2H), 6.62 (d, J = 8.3 Hz, 1H), 3.58 – 3.64 (m, 2H), 3.46 – 356 (m, 1H), 3.17 – 3.42 (m,2H), 2.52 – 2.71 (m, 4H), 1.18 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C24H23ClFN5O4: 499.14 m/z, found: 500.05 [M+H]+
22	+		1H NMR (400 MHz, DMSO-d6) δ 12.34 (s, 1H), 10.27 (s, 1H), 8.10 – 8.17 (m, 2H), 7.70 (s, 1H), 7.53 (dd, J = 8.9, 3.0 Hz, 1H), 7.19 – 7.30 (m, 2H), 7.04 – 7.14 (m, 2H), 6.79 (s, 1H), 3.66 – 3.70 (m, 1H), 3.51 (q, J = 6.8 Hz, 1H), 3.32 – 3.43 (m, 3H), 2.54 – 2.76 (m, 4H), 1.18 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C25H23F4N5O4: 533.17 m/z, found: 534.10 [M+H]+
23	++	++	1H NMR (400 MHz, DMSO-d6) δ 10.29 (s, 1H), 8.75 (d, J = 1.7 Hz, 1H), 8.48 – 8.55 (m, 1H), 8.09 – 8.17 (m, 2H), 7.50 – 7.62 (m, 2H), 7.19 – 7.30 (m, 2H), 7.04 – 7.14 (m, 2H), 3.71 (s, 1H), 3.48 - 3.59 (m, 2H), 3.25 – 3.27 (m, 2H), 2.65 – 2.75 (m, 2H), 2.30 - 2.39 (m, 2H), 1.15 – 1.21 (m, 3H).	MS (ESI): mass calcd. for C25H23F4N5O4: 533.484 m/z, found 534.15 [M+H]+

24	++	++	1H NMR (400 MHz, DMSO-d6) δ 10.26 (s, 1H), 8.39 (d, J = 6.7 Hz, 1H), 8.10 – 8.17 (m, 2H), 7.67 (d, J = 2.4 Hz, 1H), 7.45 – 7.56 (m, 2H), 7.18 – 7.28 (m, 2H), 7.05 – 7.12 (m, 2H), 4.02 - 4.05 (m, 2H), 3.32 - 3.68 (m, 5H), 2.52 – 2.68 (s, 4H), 1.19 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C26H25F4N5O4: 547.511 m/z, found: 548.15 [M+H]+
25	++	+++	1H NMR (300 MHz, DMSO-d6) δ 12.08 (s, 1H), 10.27 (s, 1H), 8.09 – 8.18 (m, 2H), 7.60 (s, 1H), 7.49 – 7.56 (m, 1H), 7.17 – 7.31 (m, 2H), 7.03 – 7.16 (m, 2H), 6.56 (s, 1H), 3.62 (s, 2H), 3.48 – 3.56 (m, 1H), 3.48 – 3.40 (m, 2H), 2.53 – 2.56 (m, 4H), 1.19 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C24H23ClFN5O4: 499.93 m/z, found: 500.05 [M+H]+
26	++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.26 (s, 1H), 8.48 (d, J = 6.7 Hz, 1H), 8.13 (dd, J = 6.0, 2.9 Hz, 2H), 7.97 (d, J = 2.4 Hz, 1H), 7.73 (dd, J = 6.7, 2.5 Hz, 1H), 7.52 (dd, J = 9.1, 2.9 Hz, 1H), 7.18 – 7.29 (m, 2H), 7.04 – 7.13 (m, 2H), 3.30 – 3.67 (m, 5H), 2.59 – 2.64 (m, 4H), 1.19 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for: C25H23F4N5O4: 533.14 m/z, found: 534.10 [M+H]+

27	+		1H NMR (300 MHz, DMSO-d6) δ 11.85 (s, 1H), 10.30 (s, 1H), 8.12 – 8.22 (m, 2H), 7.54 – 7.64 (m, 2H), 7.38 – 7.52 (m, 3H), 7.00 – 7.11 (m, 2H), 6.34 (d, J = 9.4 Hz, 1H), 3.50 – 3.55 (m, 5H), 2.55 – 2.59 (m, 4H), 1.19 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for:C24H24ClN5O4: 482.15 m/z, found: 482.15 [M+H]+
28	++		1H NMR (300 MHz, DMSO-d6) δ 10.28 (s, 1H), 8.47 (d, J = 6.7 Hz, 1H), 8.14 (dd, J = 6.0, 2.9 Hz, 2H), 7.89 (d, J = 2.4 Hz, 1H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.45 (dd, J = 6.7, 2.4 Hz, 1H), 7.17 – 7.30 (m, 2H), 7.02 – 7.16 (m, 2H), 3.34 – 3.68 (m, 5H), 2.54 – 2.65 (4H), 1.19 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C24H23ClFN5O4: 499.14 m/z, found: 500.10 [M+H]+
29	+		1H NMR (400 MHz, DMSO-d6) δ 11.86 (s, 1H), 10.16 (s, 1H), 8.19 – 8.10 (m, 2H), 7.63 (d, J = 2.5 Hz, 1H), 7.54 (ddd, J = 9.0, 7.9, 2.8 Hz, 2H), 7.28 – 7.19 (m, 2H), 7.13 – 7.05 (m, 2H), 6.35 (d, J = 9.5 Hz, 1H), 4.34 – 4.38 (m, 2H), 3.44 (d, J = 7.1 Hz, 1H), 2.68 – 2.76 (m, 2H), 2.51 – 2.58 (m, 2H), 1.89 – 1.98 (m, 2H), 1.78 – 1.85 (m, 2H), 1.17 (d, J = 6.9 Hz, 3H).	MS: mass calcd. for C26H26FN5O4: 491.20, found: 492.10 [M+H]+

30	+		1H NMR (300 MHz, DMSO-d6) δ 10.28 (d, J = 3.3 Hz, 1H), 8.14 (dd, J = 5.9, 2.9 Hz, 2H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.32 – 7.17 (m, 2H), 7.09 – 7.15 (m, 2H), 6.34 – 6.41 (m, 1H), 4.27 – 4.44(m,2H), 4.21 (t, J = 9.7 Hz, 1H), 3.39 – 3.63 (m, 6H) , 2.59 (dt, J = 9.4, 5.2 Hz, 4H), 1.19 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C25H25F4N5O4: 535.18 m/z, found: 536.15 [M+H]+
31	+		1H NMR (300 MHz, DMSO-d6) δ 12.40 (s, 1H), 10.27 (s, 1H), 8.10 - 8.18 (m, 2H), 7.79 (d, J = 2.3 Hz, 1H), 7.58 – 7.63 (m, 1H), 7.49 – 7.56 (m, 1H), 7.17 – 7.31 (m, 2H), 7.02 – 7.16 (m, 2H), 3.45 – 3.60(m, 5H), 2.50 – 2.65 (m, 4H), 1.19 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C24H23ClFN5O4: 499.93 m/z, found: 500.05 [M+H]+
32	+		1H NMR (400 MHz, Acetonitrile-d3) δ 8.18 (d, J = 9.1 Hz, 1H), 8.09 (d, J = 2.6 Hz, 1H), 7.62 (s, 1H), 7.55 (d, J = 2.4 Hz, 1H), 7.44 (dd, J = 9.0, 2.7 Hz, 1H), 7.03 – 7.15 (m,4H), 3.64 – 3.71 (m, 4H), 3.33 – 3.67 (m, 3H), 3.26 (s, 2H), 2.54 – 2.76 (m, 3H), 2.61 (s, 2H),1.27 (d, J = 7.3 Hz, 3H).	MS (ESI): mass calcd. for C26H25F4N5O4: 547.51 m/z found: 548.10 [M+H]+

33	++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.26 (s, 1H), 8.60 (d, J = 1.7 Hz, 1H), 8.23 – 8.28 (m, 1H), 8.09 – 8.16 (m, 2H), 7.45 – 7.56 (m, 2H), 7.18 – 7.28 (m, 2H), 7.05 – 7.14 (m, 2H), 3.54 (q, J = 6.8 Hz, 1H), 3.49 – 3.58 (m, 2H), 3.24 – 3.31 (m, 2H), 2.53 – 2.60 (m, 4H), 1.19 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for: C24H23ClFN5O4: 499.14 m/z, found: 500.05 [M+H]+
34	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 11.84 (s, 1H), 10.19 (s, 1H), 8.16 (d, J = 8.6 Hz, 2H), 7.44 – 7.59 (m, 3H), 7.14 – 7.20 (m, 4H), 6.32 (d, J = 9.6 Hz, 1H), 3.46 – 3.52 (m, 1H), 2.73 (s, 2H), 2.41 (s, 4H), 1.41 (s, 6H), 1.18 – 1.24 (m, 3H).	MS (ESI): mass calcd. for C26H28FN5O4: 493.21 m/z, found: 494.15 [M+H]+
35	+	+++	1H NMR (300 MHz, DMSO-d6) δ 10.51 (s, 1H), 8.10 – 8.21 (m, 2H), 7.45 – 7.57 (m, 3H), 7.24 (t, J = 8.8 Hz, 2H), 7.04 – 7.16 (m, 2H), 6.33 (d, J = 9.5 Hz, 1H), 3.44 – 3.57 (m, 5H), 2.61 (dd, J = 11.2, 5.3 Hz, 4H), 1.69 – 1.79 (m, 1H), 1.54 – 1.64 (m, 1H), 0.87 (t, J = 7.3 Hz, 3H).	MS (ESI): mass calcd. for C25H26FN5O4: 479.20 m/z, found: 480.15[M+H]+

36	+	++	1H NMR (400 MHz, DMSO-d6) δ 11.87 (s, 1H), 9.85 (s, 1H), 8.07 – 8.18 (m, 2H), 7.47 – 7.62 (m, 3H), 7.24 (t, J = 8.8 Hz, 2H), 7.04 – 7.14 (m, 2H), 6.34 (d, J = 9.5 Hz, 1H), 3.46 – 3.80 (s, 4H), 2.49 (d, J = 4.1 Hz, 4H), 1.22 (s, 6H).	MS (ESI): mass calcd. for C25H26FN5O4: 479.20, found: 480.10 [M+H]+
37	+		1H NMR (300 MHz, DMSO-d6) δ 11.71 (s, 1H), 10.20 (s, 1H), 8.10 – 8.20 (m, 2H), 7.40 – 7.66 (m, 3H), 7.17 – 7.30 (m, 2H), 7.04 – 7.16 (m, 2H), 6.34 (d, J = 9.5 Hz, 1H), 3.43 – 3.54 (m, 5H), 2.71 – 2.82 (m, 2H), 2.28 – 2.32 (m, 1H), 2.19 – 2.23 (m, 1H), 1.10 (d, J = 8.1 Hz, 1H), 0.66 (d, J = 8.8 Hz, 1H), 0.46 (d, J = 8.8 Hz, 1H), 0.33 (d, J = 4.0 Hz, 2H).	MS (ESI): mass calcd. for: C26H26FN5O4: 491.20 m/z, found: 492.15 [M+H]+
38	+	+	1H NMR (400 MHz, DMSO-d6) δ 11.83 (s, 1H), 10.19 (s, 1H), 8.11 – 8.18 (m, 2H), 7.50 – 7.57 (m, 2H), 7.46 (dd, J = 9.4, 2.6 Hz, 1H), 7.24 (t, J = 8.8 Hz, 2H), 7.04 – 7.17 (m, 2H), 6.34 (d, J = 9.4 Hz, 1H), 4.34 (s, 1H), 3.83 (d, J = 12.9 Hz, 1H), 3.38 – 3.47 (m,1H), 3.35 (s,1H), 3.24 (t, J = 12.6 Hz, 1H), 2.84 (d, J = 11.1 Hz, 1H), 2.72 (d, J = 11.5 Hz, 1H), 2.22 (td, J = 11.6, 3.3 Hz, 1H), 1.31 (d, J = 6.7 Hz, 3H), 1.19 (d, J = 7.0 Hz, 3H).	MS (ESI): mass calcd. for C25H26FN5O4: 479.20 m/z, found: 480.15 [M+H]+

39	+		1H NMR (400 MHz, DMSO-d6) δ 11.83 (s, 1H), 10.16 (s, 1H), 8.14 (dd, J = 6.0, 2.9 Hz, 2H), 7.43 – 7.58 (m, 3H), 7.18 – 7.29 (m, 2H), 7.04 – 7.14 (m, 2H), 6.34 (d, J = 9.5 Hz, 1H), 4.33 (s, 1H), 3.85 (d, J = 13.0 Hz, 1H), 3.54 (q, J = 6.8 Hz, 1H), 3.21 – 3.32 (m, 1H), 2.85 (d, J = 11.4 Hz, 1H), 2.58 (d, J = 11.4 Hz, 1H), 2.36 – 2.48 (m, 2H), 1.31 (d, J = 6.7 Hz, 3H), 1.16 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C25H26FN5O4: 479.20 m/z, found: 480.15 [M+H]+
40	+		1H NMR (300 MHz, DMSO-d6) δ 11.38 (s, 1H), 10.25 (s, 1H), 8.09 – 8.17 (m, 2H), 7.53 (dd, J = 9.0, 3.0 Hz, 1H), 7.15 – 7.32 (m, 4H), 7.04 – 7.15 (m, 2H), 6.26 (d, J = 9.3 Hz, 1H), 3.41 – 3.57 (m, 7H), 2.56 – 2.58 (m, 3H), 2.46 – 2.49 (m, 1H), 1.14 – 1.27 (m, 3H).	MS (ESI): mass calcd. for: C25H26FN5O4: 479.20 m/z, found: 480.10 [M+H]+
41	++	+++	1H NMR (300 MHz, DMSO-d6) δ 12.08 (s, 1H), 10.27 (s, 1H), 8.09 – 8.18 (m, 2H), 7.60 (s, 1H), 7.49 – 7.56 (m, 1H), 7.17 – 7.31 (m, 2H), 7.03 – 7.16 (m, 2H), 6.56 (s, 1H), 3.62 (s, 2H), 3.48 – 3.56 (m, 1H), 3.48 – 3.40 (m, 2H), 2.53 – 2.56 (m, 4H), 1.19 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C24H23ClFN5O4: 499.93 m/z, found: 500.05 [M+H]+

42	+		1H NMR (300 MHz, DMSO-d6) δ 12.08 (s, 1H), 10.27 (s, 1H), 8.09 – 8.18 (m, 2H), 7.60 (s, 1H), 7.49 – 7.56 (m, 1H), 7.17 – 7.31 (m, 2H), 7.03 – 7.16 (m, 2H), 6.56 (s, 1H), 3.62 (s, 2H), 3.48 – 3.56 (m, 1H), 3.48 – 3.40 (m, 2H), 2.53 – 2.56 (m, 4H), 1.19 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C24H23ClFN5O4: 499.93 m/z, found: 500.05 [M+H]+
43	+		1H NMR (300 MHz, DMSO-d6) δ 10.27 (s, 1H), 8.49 (d, J = 6.7 Hz, 1H), 8.09 – 8.18 (m, 2H), 7.97 (d, J = 2.4 Hz, 1H), 7.74 (dd, J = 6.7, 2.5 Hz, 1H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.02 – 7.16 (m, 2H), 3.61 – 3.64 (m, 2H), (s, 2H), 3.47 – 3.60 (m, 2H), 3.37 – 3.46 (m, 2H), 2.62 (s, 3H), 1.20 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C25H23F4N5O4: 533.11 m/z, found 534.05 [M+H]+
44	++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.27 (s, 1H), 8.49 (d, J = 6.7 Hz, 1H), 8.09 – 8.18 (m, 2H), 7.97 (d, J = 2.4 Hz, 1H), 7.74 (dd, J = 6.7, 2.5 Hz, 1H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.02 – 7.16 (m, 2H), 3.61 – 3.64 (m, 2H), 3.47 – 3.60 (m, 2H), 3.37 – 3.46 (m, 2H), 2.62 (s, 3H), 1.20 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C25H23F4N5O4: 533.11 m/z, found 534.10 [M+H]+

45	+		1H NMR (300 MHz, DMSO-d6) δ 10.27 (s, 1H), 8.47 (d, J = 6.7 Hz, 1H), 8.14 (dd, J = 6.0, 2.9 Hz, 2H), 7.89 (d, J = 2.3 Hz, 1H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.44 (dd, J = 6.7, 2.4 Hz, 1H), 7.31 – 7.17 (m, 2H), 7.16 – 7.02 (m, 2H), 3.39 – 3.67 (m, 5H), 2.51 – 2.64 (m, 4H), 1.19 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C24H23ClFN5O4: 499.14 m/z, found: 500.10 [M+H]+
46	++		1H NMR (300 MHz, DMSO-d6) δ 10.27 (s, 1H), 8.47 (d, J = 6.7 Hz, 1H), 8.14 (dd, J = 6.0, 2.9 Hz, 2H), 7.89 (d, J = 2.3 Hz, 1H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.44 (dd, J = 6.7, 2.4 Hz, 1H), 7.31 – 7.17 (m, 2H), 7.16 – 7.02 (m, 2H), 3.39 – 3.67 (m, 5H), 2.51 – 2.64 (m, 4H), 1.19 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C24H23ClFN5O4: 499.14 m/z, found: 500.10 [M+H]+
47	+		1H NMR (300 MHz, DMSO-d6) δ 11.80 (s, 1H), 10.18 (s, 1H), 8.10 – 8.19 (m, 2H), 7.48 – 7.58 (m, 2H), 7.46 (dd, J = 9.4, 2.6 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.03 – 7.16 (m, 2H), 6.34 (d, J = 9.4 Hz, 1H), 4.34 (s, 1H), 3.84 (d, J = 13.2 Hz, 1H), 3.42 (q, J = 6.9 Hz, 1H), 3.24 (t, J = 12.4 Hz, 1H), 2.84 (d, J = 11.1 Hz, 1H), 2.72 (d, J = 11.3 Hz, 1H), 2.53 (s, 1H), 2.22 (t, J = 11.1 Hz, 1H), 1.31 (d, J = 6.7 Hz, 3H), 1.15 – 1.27 (m, 3H).	MS (ESI): mass calcd. for C25H26FN5O4 479.11 m/z, found 480.10 [M+H]+

48	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 11.81 (s, 1H), 10.15 (s, 1H), 8.14 (dd, J = 6.0, 2.9 Hz, 2H), 7.48 – 7.58 (m, 2H), 7.47 (dd, J = 9.4, 2.6 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.03 – 7.16 (m, 2H), 6.34 (d, J = 9.4 Hz, 1H), 4.29 – 4.37 (m, 1H), 3.85 (d, J = 13.0 Hz, 1H), 3.54 (q, J = 6.7 Hz, 1H), 2.85 (d, J = 11.1 Hz, 1H), 2.58 (d, J = 11.4 Hz, 1H), 2.35 – 2.50 (m, 2H), 1.32 (d, J = 6.7 Hz, 3H), 1.16 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C25H26FN5O4 479.11m/z, found 480.10 [M+H]+
49	+	++	1H NMR (300 MHz, DMSO-d6) δ 11.33 (s, 1H), 10.07 (d, J = 18.4 Hz, 1H), 8.10 – 8.18 (m, 2H), 7.43 – 7.57 (m, 1H), 7.39 (dd, J = 9.5, 2.3 Hz, 1H), 7.17 – 7.31 (m, 3H), 7.03 – 7.16 (m, 2H), 6.32 (d, J = 9.4 Hz, 1H), 3.36 – 3.68 (m, 5H), 2.78 – 3.02 (m, 2H), 2.53 – 2.73 (m, 2H), 2.32 (d, J = 18.5 Hz, 1H), 1.17 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C25H25F4N5O3: 519.19 m/z, found 520.10 [M+H]+
50	++	++	1H NMR (300 MHz, DMSO-d6) δ 11.43 (s, 1H), 10.07 (d, J = 18.4 Hz, 1H), 8.11 – 8.18 (m, 2H), 7.43 – 7.57 (m, 1H), 7.39 (dd, J = 9.5, 2.3 Hz, 1H), 7.18 – 7.29 (m, 3H), 7.03 – 7.14 (m, 2H), 6.32 (d, J = 9.4 Hz, 1H), 3.36 – 3.68 (m, 4H), 2.77 – 3.01 (m, 2H), 2.52 – 2.71 (m, 2H), 2.32 (d, J = 18.5 Hz, 1H), 1.17 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C25H25F4N5O3: 519.19 m/z, found 520.10 [M+H]+

51	++	+	1H NMR (300 MHz, DMSO-d6) δ 12.62 (s, 1H), 10.28 (s, 1H), 8.22 (d, J = 1.1 Hz, 1H), 8.09 – 8.18 (m, 2H), 7.48 – 7.55 (m, 1H), 7.17 – 7.31 (m, 2H), 7.03 – 7.13 (m, 2H), 6.36 (d, J = 1.1 Hz, 1H), 3.49 – 3.63 (m, 3H), 3.27 – 3.41 (m, 2H), 2.52 – 2.64 (m, 4H), 1.19 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C23H23FN6O4: 466.473 m/z, found: 467.05 [M+H]+
52	+	++	1H NMR (300 MHz, DMSO-d6) δ 11.84 (s, 1H), 10.18 (s, 1H), 8.11 – 8.20 (m, 2H), 7.40 – 7.60 (m, 3H), 7.17 – 7.31 (m, 2H), 7.03 – 7.16 (m, 2H), 6.32 (d, J = 9.5 Hz, 1H), 3.49 (q, J = 6.8 Hz, 1H), 3.34 – 3.40（m,2H), 2.68 – 2.79 (m, 1H), 2.57 – 2.67 (m, 1H), 2.41 (s, 2H), 1.41 (d, J = 2.0 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C26H28FN5O4: 493.21 found: 494.10 [M+H]+.
53	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 11.84 (s, 1H), 10.18 (s, 1H), 8.11 – 8.20 (m, 2H), 7.40 – 7.60 (m, 3H), 7.17 – 7.31 (m, 2H), 7.03 – 7.16 (m, 2H), 6.32 (d, J = 9.5 Hz, 1H), 3.49 (q, J = 6.8 Hz, 1H), 3.34 – 3.40（m, 2H), 2.68 – 2.79 (m, 1H), 2.57 – 2.67 (m, 1H), 2.41 (s, 2H), 1.41 (d, J = 2.0 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C26H28FN5O4: 493.21 found: 494.05 [M+H]+

54	++	++	1H NMR (400 MHz, DMSO-d6) δ 10.21 (s, 1H), 8.19 – 8.26 (m, 2H), 8.12 – 8.19 (m, 2H), 7.53 (dd, J = 9.0, 3.1 Hz, 1H), 7.40 – 7.47 (m, 2H), 7.19 – 7.30 (m, 2H), 7.05 – 7.14 (m, 2H), 3.51 (q, J = 6.9 Hz, 1H), 2.67 – 2.76 (m, 1H), 2.57 – 2.65 (m, 1H), 2.41 – 2.49 (m, 4H), 1.46 (d, J = 3.8 Hz, 6H), 1.18 – 1.26 (m, 3H).	MS (ESI): mass calcd. for C26H28FN5O4: 493.53 m/z, found: 494.05 [M+H]+
55	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.21 (s, 1H), 8.19 – 8.26 (m, 2H), 8.12 – 8.19 (m, 2H), 7.53 (dd, J = 9.0, 3.1 Hz, 1H), 7.40 – 7.47 (m, 2H), 7.19 – 7.30 (m, 2H), 7.05 – 7.14 (m, 2H), 3.51 (q, J = 6.9 Hz, 1H), 2.67 – 2.76 (m, 1H), 2.57 – 2.65 (m, 1H), 2.41 – 2.49 (m, 4H), 1.46 (d, J = 3.8 Hz, 6H), 1.18 – 1.26 (m, 3H).	MS (ESI): mass calcd. for C26H28FN5O4: 493.53 m/z, found: 494.05 [M+H]+
56	+		1H NMR (400 MHz, DMSO-d6) δ 11.78 (s, 1H), 10.21 (s, 1H), 8.10 – 8.18 (m, 2H), 7.60 (d, J = 2.6 Hz, 1H), 7.52 (ddd, J = 9.6, 6.5, 2.8 Hz, 2H), 7.18 – 7.29 (m, 2H), 7.04 – 7.14 (m, 2H), 6.33 (d, J = 9.5 Hz, 1H), 3.50 – 3.92 (m, 2H), 3.45 (d, J = 6.8 Hz, 1H), 2.56 – 2.69 (m, 4H), 1.18 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 17.9 Hz, 4H).	MS (ESI): mass calcd. for C26H26FN5O4: 491.20 m/z, found: 492.05 [M+H]+

57	++	++	1H NMR (400 MHz, DMSO-d6) δ 11.78 (s, 1H), 10.21 (s, 1H), 8.10 – 8.18 (m, 2H), 7.60 (d, J = 2.6 Hz, 1H), 7.52 (ddd, J = 9.6, 6.5, 2.8 Hz, 2H), 7.18 – 7.29 (m, 2H), 7.04 – 7.14 (m, 2H), 6.33 (d, J = 9.5 Hz, 1H), 3.50 – 3.92 (m, 2H), 3.45 (d, J = 6.8 Hz, 1H), 2.56 – 2.69 (m, 4H), 1.18 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 17.9 Hz, 4H).	MS (ESI): mass calcd. for C26H26FN5O4: 491.20 m/z, found: 492.05 [M+H]+.
58	+		1H NMR (400 MHz, DMSO-d6) δ 10.25 (s, 1H), 8.20 – 8.27 (m, 2H), 8.10 – 8.17 (m, 2H), , 7.18 – 7.29 (m, 2H), 7.09 (ddd, J = 6.7, 5.4, 3.0 Hz, 2H), 3.51 (q, J = 6.9 Hz, 1H), 2.75 (s, 2H), 2.35 – 2.47 (m, 4H), 2.14 – 2.28 (m, 4H), 1.59 – 1.69 (m, 2H), 1.18 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C27H28FN5O4: 505.11 m/z, found 506.05 [M+H]+
59	++	++	1H NMR (400 MHz, DMSO-d6) δ 10.25 (s, 1H), 8.20 – 8.27 (m, 2H), 8.10 – 8.17 (m, 2H), 7.44 – 7.52 (m, 3H), 7.18 – 7.29 (m, 2H), 7.04 – 7.14 (m, 2H), 3.51 (q, J = 6.9 Hz, 1H), 2.75 (s, 2H), 2.35 – 2.47 (m, 4H), 2.14 – 2.28 (m, 4H), 1.59 – 1.69 (m, 2H), 1.18 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C25H23F4N5O4: 505.11 m/z, found 506.05 [M+H]+

60	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.20 (s, 1H), 8.57 (d, J = 1.7 Hz, 1H), 8.23 (dd, J = 6.7, 1.7 Hz, 1H), 8.09 – 8.18 (m, 2H), 7.52 (dd, J = 9.1, 3.0 Hz, 1H), 7.42 (d, J = 6.7 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.03 – 7.16 (m, 2H), 3.50 (q, J = 6.8 Hz, 1H), 3.22 – 3.31 (m, 2H), 2.60 – 2.70 (m, 2H), 2.42 – 2.48 (m, 2H), 1.43 – 1.55 (m, 6H), 1.14 – 1.27 (m, 3H).	MS (ESI): mass calcd. for: C26H27ClFN5O4: 527.98 m/z, found: 528.15 [M+H]+
61	++		1H NMR (300 MHz, DMSO-d6) δ 10.20 (s, 1H), 8.57 (d, J = 1.7 Hz, 1H), 8.23 (dd, J = 6.7, 1.7 Hz, 1H), 8.09 – 8.18 (m, 2H), 7.52 (dd, J = 9.1, 3.0 Hz, 1H), 7.42 (d, J = 6.7 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.03 – 7.16 (m, 2H), 3.50 (q, J = 6.8 Hz, 1H), 3.22 – 3.31 (m, 2H), 2.60 – 2.70 (m, 2H), 2.42 – 2.48 (m, 2H), 1.43 – 1.55 (m, 6H), 1.14 – 1.27 (m, 3H).	MS (ESI): mass calcd. for: C26H27ClFN5O4: 527.98 m/z, found: 528.15 [M+H]+
62	++	++	1H NMR (300 MHz, DMSO-d6) δ 10.44 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.17 – 8.27 (m, 2H), 7.38 – 7.56 (m, 4H), 7.11 – 7.24 (m, 1H), 3.54 (q, J = 6.8 Hz, 1H), 3.27 – 3.34 (m, 2H), 2.67 – 2.75 (m, 1H), 2.57 – 2.66 (m, 1H), 2.37 – 3.48 (m, 2H), 1.45 (d, J = 3.0 Hz, 6H), 1.16 – 1.26 (m, 3H).	MS (ESI): mass calcd. for C25H26F2N6O4: 512.518 m/z, found: 513.10 [M+H]+

63	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.44 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.17 – 8.27 (m, 2H), 7.38 – 7.56 (m, 4H), 7.11 – 7.24 (m, 1H), 3.54 (q, J = 6.8 Hz, 1H), 3.27 – 3.34 (m, 2H), 2.67 – 2.75 (m, 1H), 2.57 – 2.66 (m, 1H), 2.37 – 3.48 (m, 2H), 1.45 (d, J = 3.0 Hz, 6H), 1.16 – 1.26 (m, 3H).	MS (ESI): mass calcd. for C25H26F2N6O4: 512.518 m/z, found: 513.10 [M+H]+
64	++		1H NMR (300 MHz, DMSO-d6) δ 11.81 (s, 1H), 10.40 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.56 (d, J = 2.5 Hz, 1H), 7.39 – 7.54 (m, 3H), 7.17 (tdd, J = 9.1, 3.0, 1.6 Hz, 1H), 6.32 (d, J = 9.4 Hz, 1H), 3.52 (t, J = 6.9 Hz, 1H),3.33 – 3.40 (m,2H), 2.67 – 2.78(m,1H), 2.58 – 2.67 (m, 1H), 2.40 (d, J = 2.1 Hz, 2H), 1.40 (d, J = 2.8 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C25H26F2N6O: 512.20 m/z, found: 513.20 [M+H]+

65	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 11.82 (s, 1H), 10.40 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.56 (d, J = 2.6 Hz, 1H), 7.39 – 7.54(m, 3H), 7.11 – 7.24 (m, 1H), 6.32 (d, J = 9.4 Hz, 1H), 3.52 (t, J = 6.9 Hz, 1H), 3.34 – 3.38 (m, 2H), 2.68 – 2.78 (m, 1H), 2.58 – 2.68 (m, 1H), 2.33 – 2.48 (m, 2H), 1.40 (d, J = 2.7 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C25H26F2N6O: 512.20 m/z, found: 513.20 [M+H]+
66	++	++	1H NMR (400 MHz, DMSO-d6) δ 11.95 (s, 1H), 8.17 – 8.25 (m, 2H), 7.38 – 7.46 (m, 2H), 7.15 – 7.30 (m, 5H), 3.54 (q, J = 6.9 Hz, 1H), 3.29 (d, J = 5.3 Hz, 2H), 2.69 (dt, J = 10.3, 4.8 Hz, 1H), 2.59 (dt, J = 10.8, 5.2 Hz, 1H), 2.37 – 2.49 (m, 2H), 1.43 (d, J = 4.8 Hz, 6H), 1.26 – 1.18 (m, 3H).	MS (ESI): mass calcd. for C24H26FN5O4S: 499.17 m/z, found: 500.20 [M+H]+
67	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 11.95 (s, 1H), 8.17 – 8.25 (m, 2H), 7.38 – 7.46 (m, 2H), 7.15 – 7.30 (m, 5H), 3.54 (q, J = 6.9 Hz, 1H), 3.29 (d, J = 5.3 Hz, 2H), 2.69 (dt, J = 10.3, 4.8 Hz, 1H), 2.59 (dt, J = 10.8, 5.2 Hz, 1H), 2.37 – 2.49 (m, 2H), 1.43 (d, J = 4.8 Hz, 6H), 1.26 – 1.18 (m, 3H).	MS (ESI): mass calcd. for C24H26FN5O4S: 499.17 m/z, found: 500.25 [M+H]+

68	+		1H NMR (300 MHz, DMSO-d6) δ 11.83 (s, 1H), 9.96 (s, 1H), 7.99 – 8.09 (m, 2H), 7.56 (d, J = 2.6 Hz, 1H), 7.38 – 7.50 (m, 2H), 6.32 (d, J = 9.5 Hz, 1H), 3.87 (d, J = 7.0 Hz, 2H), 3.40 – 3.52 (m, 1H), 3.32 – 3.39 (m, 2H), 2.68 – 2.77 (m, 1H), 2.56 – 2.65 (m, 1H), 2.40 (s, 2H), 1.41 (d, J = 1.9 Hz, 6H), 1.23 – 1.28 (m, 1H), 1.14 – 1.22 (m, 3H), 0.52 – 0.64 (m, 2H), 0.27 – 0.38 (m, 2H)	MS (ESI): mass calcd. for C24H31N5O4 453.543 m/z, found 454.25 [M+H]+
69	++	++	1H NMR (300 MHz, DMSO-d6) δ 11.83 (s, 1H), 9.96 (s, 1H), 7.99 – 8.09 (m, 2H), 7.56 (d, J = 2.6 Hz, 1H), 7.38 – 7.50 (m, 2H), 6.32 (d, J = 9.5 Hz, 1H), 3.87 (d, J = 7.0 Hz, 2H), 3.40 – 3.52 (m, 1H), 3.32 – 3.39 (m, 2H), 2.68 – 2.77 (m, 1H), 2.56 – 2.65 (m, 1H), 2.40 (s, 2H), 1.41 (d, J = 1.9 Hz, 6H), 1.23 – 1.28 (m, 1H), 1.14 – 1.22 (m, 3H), 0.52 – 0.64 (m, 2H), 0.27 – 0.38 (m, 2H).	MS (ESI): mass calcd. for C24H31N5O4 453.543 m/z, found 454.25 [M+H]+

70	+		1H NMR (400 MHz, DMSO-d6) δ 11.84 (s, 1H), 10.18 (s, 1H), 8.15 – 8.24 (m, 3H), 7.86 (td, J = 8.5, 3.1 Hz, 1H), 7.62 – 7.71 (m, 1H), 7.57 (d, J = 2.6 Hz, 1H), 7.47 (dd, J = 9.4, 2.6 Hz, 1H), 7.20 (dd, J = 9.0, 3.6 Hz, 1H), 6.32 (d, J = 9.4 Hz, 1H), 3.50 (q, J = 6.9, 6.3 Hz, 1H), 2.70 – 2.77 (m, 1H), 2.63 (d, J = 5.7 Hz, 1H), 2.48 – 2.53 (m, 2H), 2.33 – 2.46 (m, 2H), 1.41 (d, J = 2.9 Hz, 6H), 1.23 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C25H27FN6O4: 494.21 m/z, found: 495.15 [M+H]+
71	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 11.84 (s, 1H), 10.18 (s, 1H), 8.15 – 8.24 (m, 3H), 7.86 (td, J = 8.5, 3.1 Hz, 1H), 7.62 – 7.71 (m, 1H), 7.57 (d, J = 2.6 Hz, 1H), 7.47 (dd, J = 9.4, 2.6 Hz, 1H), 7.20 (dd, J = 9.0, 3.6 Hz, 1H), 6.32 (d, J = 9.4 Hz, 1H), 3.50 (q, J = 6.9, 6.3 Hz, 1H), 2.70 – 2.77 (m, 1H), 2.63 (d, J = 5.7 Hz, 1H), 2.48 – 2.53 (m, 2H), 2.33 – 2.46 (m, 2H), 1.41 (d, J = 2.9 Hz, 6H), 1.23 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C25H27FN6O4: 494.21 m/z, found: 495.15 [M+H]+

72	+	++	1H NMR (300 MHz, DMSO-d6) δ 10.17 (s, 1H), 8.11 – 8.20 (m, 2H), 7.99 (d, J = 2.5 Hz, 1H), 7.53 (dd, J = 9.0, 3.0 Hz, 1H), 7.46 (dd, J = 9.4, 2.5 Hz, 1H), 7.17 – 7.32 (m, 2H), 7.04 – 7.16 (m, 2H), 6.38 (d, J = 9.3 Hz, 1H), 3.46 – 3.56 (m, 1H), 3.46 (s, 3H), 3.32 (s, 2H), 2.70 – 2.82 (m, 1H), 2.59 – 2.70 (m, 1H), 2.43 (s, 2H), 1.43 (s, 6H), 1.22 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C27H30FN5O4: 507.23 m/z, found: 508.20 [M+H]+
73	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.17 (s, 1H), 8.11 – 8.21 (m, 2H), 7.99 (d, J = 2.5 Hz, 1H), 7.53 (dd, J = 8.9, 3.1 Hz, 1H), 7.46 (dd, J = 9.3, 2.6 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.03 – 7.16 (m, 2H), 6.38 (d, J = 9.3 Hz, 1H), 3.46 – 3.55 (m, 1H), 3.46 (s, 3H), 3.34 – 3.42 (m, 2H), 2.71 – 2.81 (m, 1H), 2.59 – 2.71 (m, 1H), 2.43 (s, 2H), 1.43 (s, 6H), 1.22 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C27H30FN5O4: 507.23, found: 508.20 [M+H]+

74	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 12.60 (s, 1H), 10.39 (s, 1H), 8.85 (s, 1H), 8.46 (d, J = 1.5 Hz, 1H), 7.89 (d, J = 1.2 Hz, 1H), 7.75 (s, 1H), 7.41 – 7.54 (m, 2H), 7.12 – 7.22 (m, 1H), 3.45 – 3.56 (m, 3H), 2.68 – 2.77 (m, 1H), 2.56 – 2.65 (m, 1H), 2.35 – 2.47 (m, 2H), 1.43 (d, J = 2.8 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C24H25F2N7O4: 513.19, found: 514.10 [M+H]+.
75	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.85 (d, J = 1.5 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.97 (d, J = 1.1 Hz, 1H), 7.93 (d, J = 1.0 Hz, 1H), 7.39 – 7.55 (m, 2H), 7.11 – 7.24 (m, 1H), 4.96 (t, J = 5.6 Hz, 1H), 3.98 (t, J = 5.2 Hz, 2H), 3.64 (d, J = 5.4 Hz, 2H), 3.52 (d, J = 6.5 Hz, 3H), 2.69 – 2.79 (m, 1H), 2.57 – 2.67 (m, 1H), 2.35 – 2.49 (m, 2H), 1.44 (d, J = 2.1 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C26H29F2N7O5: 557.22 m/z, found 558.10 [M+H]+
76	++		1H NMR (400 MHz, Acetonitrile-d3) 7.57 – 7.68 (m, 1H), 7.47 – 7.57 (m, 1H), 7.22 – 7.38 (m, 4H), 7.06 – 7.14 (m, 1H), 6.39 (d, J = 9.4, 0.7 Hz, 1H), 3.40 – 3.55 (m, 3H), 2.70 – 2.85 (m, 1H), 2.60 – 2.70 (m, 1H), 2.33 – 2.48 (m, 2H), 1.50 (d, J = 4.3 Hz, 6H), 1.24 – 1.32 (m, 3H).	MS (ESI): mass calcd. for C24H26FN5O4S: 499.2 m/z, found: 500.25 [M+H] +
77	+++	+++	1H NMR (400 MHz, Acetonitrile-d3) δ 7.55 – 7.65 (m, 1H), 7.47 – 7.55 (m, 1H), 7.13 – 7.21 (m, 4H), 7.06 – 7.13 (m, 1H), 6.37 (d, J = 9.5 Hz, 1H),3.40 – 3.57 (m, 3H), 2.74 – 2.88 (m, 1H), 2.60 – 2.73 (m, 1H), 2.36 – 2.48 (m, 2H), 1.50 (d, J = 4.2 Hz, 6H), 1.31 – 1.32 (m, 3H).	MS (ESI): mass calcd. for C24H26FN5O4S: 499.2 m/z, found: 500.20 [M+H] +

78	+		1H NMR (300 MHz, DMSO-d6) δ 10.20 (s, 1H), 8.24 (d, J = 6.5 Hz, 1H), 8.11 – 8.19 (m, 2H), 7.61 (d, J = 2.5 Hz, 1H), 7.49 – 7.57 (m, 1H), 7.29 – 7.37 (m, 1H), 7.19 – 7.28 (m, 2H), 7.09 – 7.14 (m, 2H), 3.79 (s, 2H), 3.43 – 3.55 (m, 1H), 2.67 – 2.77 (m, 2H), 2.59 – 2.64 (m, 2H), 2.45 – 2.50 (m, 2H),1.48 (d, J = 2.4 Hz, 6H), 1.17 – 1.27 (m, 3H)	MS (ESI): mass calcd. for C27H31FN6O4 522.24 m/z, found: 523.35[M+H]+
79	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.20 (s, 1H), 8.24 (d, J = 6.6 Hz, 1H), 8.11 – 8.19 (m, 2H), 7.61 (d, J = 2.5 Hz, 1H), 7.49 – 7.57 (m, 1H), 7.29 – 7.37 (m, 1H), 7.19 – 7.28 (m, 2H), 7.03 – 7.16 (m, 2H), 3.78 (s, 2H), 3.45 – 3.58 (m, 1H), 2.67 – 2.78 (m, 2H), 2.57 – 2.66 (m, 2H), 2.43– 2.52 (m, 2H), 1.48 (d, J = 2.4 Hz, 6H), 1.17 – 1.28 (m, 3H)	MS (ESI): mass calcd. for C27H31FN6O4 522.24 m/z, found: 523.35 [M+H]+
80	++		1H NMR (300 MHz, DMSO-d6) δ 10.20 (s, 1H), 8.27 (d, J = 6.6 Hz, 1H), 8.11 – 8.20 (m, 2H), 7.48 – 7.58 (m, 2H), 7.30 – 7.38 (m, 1H), 7.17 – 7.30 (m, 2H), 7.04 – 7.16 (m, 2H), 3.75 (s, 2H), 2.68 – 2.78 (m, 1H), 2.58 – 2.65 (m, 1H), 2.42 – 2.50 (m, 4H), 2.26 – 2.33 (m, 3H),1.47 (d, J = 2.4 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H)	MS (ESI): mass calcd. for C28H33FN6O4, 536.25 found: 537.25 [M+H]+
81	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.20 (s, 1H), 8.27 (d, J = 6.6 Hz, 1H), 8.11 – 8.22 (m, 2H), 7.48 – 7.57 (m, 2H), 7.30 – 7.39 (m, 1H), 7.17 – 7.31 (m, 2H), 7.04 – 7.16 (m, 2H), 3.76 (s, 2H), 3.51 (q, J = 6.8 Hz, 1H), 2.67– 2.77 (m, 1H), 2.55 – 2.63 (m, 1H), 2.45 – 2.48(m, 4H), 2.26 – 2.33 (m, 3H),	MS (ESI): mass calcd. for C28H33FN6O4, 536.25 found: 537.25 [M+H]+

			1.47 (d, J = 2.4 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H)	
82	+		1H NMR (300 MHz, DMSO-d6) δ 10.23 (s, 1H), 8.47 (t, J = 6.0 Hz, 1H), 8.30 (d, J = 6.6 Hz, 1H), 8.11 – 8.20 (m, 2H), 7.53 (dd, J = 9.0, 3.1 Hz, 1H), 7.38 (dd, J = 6.6, 2.5 Hz, 1H), 7.17 – 7.32 (m, 3H), 7.03 – 7.16 (m, 2H), 4.32 (d, J = 5.9 Hz, 2H), 3.53 (q, J = 6.6 Hz, 1H), 2.56– 2.77 (m, 2H), 2.50 – 2.54 (m, 2H), 2.45 – 2.48(m, 2H), 1.91 (s, 3H), 1.46 (d, J = 3.7 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C29H33FN6O5, 564.25 found: 565.30 [M+H]+
83	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.23 (s, 1H), 8.47 (t, J = 5.9 Hz, 1H), 8.30 (d, J = 6.6 Hz, 1H), 8.11 – 8.20 (m, 2H), 7.53 (dd, J = 8.9, 3.1 Hz, 1H), 7.38 (dd, J = 6.6, 2.5 Hz, 1H), 7.17 – 7.32 (m, 3H), 7.04 – 7.16 (m, 2H), 4.32 (d, J = 5.9 Hz, 2H), 3.53 (q, J = 6.7 Hz, 1H), 2.56 – 2.76 (m, 2H), 2.50 – 2.54 (m, 2H), 2.45 – 2.48(m, 2H), 1.91 (s, 3H), 1.46 (d, J = 3.7 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C29H33FN6O5, 564.25 m/z found: 565.30 [M+H]+
84	+		1H NMR (300 MHz, DMSO-d6) δ 11.98 – 12.70 (br, 1H), 10.18 (s, 1H), 8.11 – 8.20 (m, 3H), 7.93 (d, J = 2.6 Hz, 1H), 7.53 (dd, J = 9.0, 3.1 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.02 – 7.16 (m, 2H), 3.50 (q, J = 6.8 Hz, 1H), 3.32 – 3.42 (m, 2H), 2.69 – 2.81 (m, 1H), 2.57 – 2.69 (m, 1H), 2.35 – 2.50 (m, 2H), 1.42 (d, J = 2.3 Hz, 6H), 1.14 – 1.27 (m, 3H)	MS (ESI): mass calcd. for C27H27FN6O4: 518.21, found: 519.25 [M+H]+
85	++	+++	1H NMR (300 MHz, DMSO-d6) δ 11.79 – 12.52 (br, 1H), 10.18 (s, 1H), 8.11 – 8.20 (m, 3H), 7.93 (d, J = 2.6 Hz, 1H), 7.53 (dd, J =	. MS (ESI): mass calcd. for C27H27FN6O4: 518.21, found: 519.25 [M+H]+

			9.0, 3.1 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.02 – 7.16 (m, 2H), 3.50 (q, J = 6.8 Hz, 1H), 3.32 – 3.42 (m, 2H), 2.69 – 2.81 (m, 1H), 2.59 – 2.69 (m, 1H), 2.35 – 2.49 (m, 2H), 1.42 (d, J = 2.3 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H)	
86	++		1H NMR (400 MHz, DMSO-d6) δ 10.17 (s, 1H), 8.12 – 8.19 (m, 2H), 7.44 – 7.57 (m, 3H), 7.19 – 7.32 (m, 2H), 7.05 – 7.15 (m, 2H), 3.44 – 3.54 (m, 3H), 3.34 – 3.42 (m, 1H), 2.56 – 2.78 (m, 3H), 2.42 (s, 2H), 1.42 (d, J = 2.2 Hz, 6H), 1.18 – 1.27 (m, 3H)	MS (ESI): mass calcd. for C27H31FN6O4: 522.24, found: 523.15 [M+H]+
87	+		1H NMR (400 MHz, DMSO-d6) δ 10.18 (s, 1H), 8.12 – 8.18 (m, 2H), 7.41 – 7.57 (m, 3H), 7.19 – 7.29 (m, 2H), 7.06 – 7.15 (m, 2H), 3.49 (d, J = 6.9 Hz, 1H), 3.43 (s, 2H), 3.35 – 3.41 (m, 2H), 2.73 (d, J = 5.5 Hz, 1H), 2.63 (d, J = 5.4 Hz, 1H), 2.42 (s, 2H), 2.27 (s, 3H), 1.42 (d, J = 2.4 Hz, 6H), 1.18 – 1.27 (m, 3H)	MS(ESI): mass calcd. for C28H33FN6O4: 536.25, found: 537.30 [M+H]+
88	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.18 (s, 1H), 8.12 – 8.19 (m, 2H), 7.41 – 7.57 (m, 3H), 7.19 – 7.29 (m, 2H), 7.05 – 7.15 (m, 2H), 3.44 – 3.54 (m, 1H), 3.43 (s, 2H),3.36 – 3.40 (m, 2H), 2.70 – 2.78 (m, 1H), 2.58 – 2.66 (m, 1H), 2.42 (s, 2H), 2.27 (s, 3H), 1.42 (d, J = 2.4 Hz, 6H), 1.18 – 1.26 (m, 3H).	MS (ESI): mass calcd. for C28H33FN6O4: 536.25, found: 537.30 [M+H]+
89	++		1H NMR (300 MHz, DMSO-d6) δ 10.20 (s, 1H), 8.26 (d, J = 6.6 Hz, 1H), 8.11 – 8.20 (m, 2H), 7.48 – 7.58 (m, 2H), 7.35 – 7.38 (m, J = 6.6, 2.5 Hz, 1H), 7.18 – 7.30 (m, 2H), 7.07 – 7.13 (m, 2H), 5.66 (t, J = 5.8 Hz, 1H),	MS (ESI): mass calcd. for C27H30FN5O5 523.22 m/z, found 524.25 [M+H]+

			4.58 (d, J = 5.7 Hz, 2H), 3.51 (q, J = 7.0 Hz, 1H), 3.30 – 3.37 (m, 2H), 2.49 – 2.54 (m, 2H), 2.48 (s, 2H), 1.48 (d, J = 2.0 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H)	
90	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.20 (s, 1H), 8.26 (d, J = 6.6 Hz, 1H), 8.11 – 8.20 (m, 2H), 7.48 – 7.58 (m, 2H), 7.36 (dd, J = 6.6, 2.6 Hz, 1H), 7.17 – 7.30 (m, 2H), 7.10 (ddd, J = 6.7, 5.4, 3.1 Hz, 2H), 5.66 (t, J = 5.8 Hz, 1H), 4.58 (d, J = 5.7 Hz, 2H), 3.51 (q, J = 6.7 Hz, 1H), 3.30 – 3.37 (m, 2H), 2.49 – 2.54 (m, 2H), 2.48 (s, 2H), 1.48 (d, J = 2.0 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C27H30FN5O5 523.11m/z, found 524.30 [M+H]+
91	+		1H NMR (400 MHz, DMSO-d6) δ 11.83 (s, 1H), 9.97 (s, 1H), 8.01 – 8.01 (m, 2H), 7.56 (d, J = 2.6 Hz, 1H), 7.41 – 7.51 (m, 2H), 6.32 (d, J = 9.5 Hz, 1H), 4.00 (d, J = 6.7 Hz, 2H), 3.41 – 3.50 (m, 1H), 3.32 – 3.41 (m, 2H), 2.67 – 2.77 (m, 2H), 2.56 – 2.66 (m, 1H), 2.40 (d, J = 2.4 Hz, 2H), 2.01 – 2.13 (m, 4H), 1.76 – 2.00 (m, 4H), 1.41 (d, J = 2.5 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C25H33N5O4: 467.25, found: 468.20 [M+H]+
92	+		1H NMR (400 MHz, DMSO-d6) δ 11.83 (s, 1H), 9.97 (s, 1H), 8.01 – 8.01 (m, 2H), 7.56 (d, J = 2.6 Hz, 1H), 7.41 – 7.51 (m, 2H), 6.32 (d, J = 9.5 Hz, 1H), 4.00 (d, J = 6.7 Hz, 2H), 3.41 – 3.50 (m, 1H), 3.32 – 3.41 (m, 2H), 2.67 – 2.77 (m, 2H), 2.56 – 2.66 (m, 1H), 2.40 (d, J = 2.4 Hz, 2H), 2.01 – 2.13 (m, 4H), 1.76 – 2.00 (m, 4H), 1.41 (d, J = 2.5 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C25H33N5O4: 467.25, found: 468.20[M+H]+

93	++		1H NMR (300 MHz, DMSO-d6) δ 11.82 (s, 1H), 9.97 (s, 1H), 8.00 – 8.10 (m, 2H), 7.56 (d, J = 2.6 Hz, 1H), 7.36 – 7.45 (m, 2H), 6.32 (d, J = 9.5 Hz, 1H), 3.79 (d, J = 6.5 Hz, 2H), 3.45 (q, J = 6.8 Hz, 1H), 3.34 – 3.39 (m, 2H), 2.73 (s, 1H), 2.61 (d, J = 11.6 Hz, 1H), 2.40 (s, 2H), 1.92 – 2.11 (m, 1H), 1.41 (d, J = 1.9 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.7 Hz, 6H)	MS (ESI): mass calcd. for C24H33N5O4 : 455.25 m/z, found: 456.25 [M+H]+
94	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.18 (s, 1H), 8.11 – 8.20 (m, 2H), 8.00 (s, 1H), 7.48 – 7.58 (m, 2H), 7.18 – 7.30 (m, 2H), 7.04 – 7.15 (m, 2H), 6.50 (d, J = 9.4 Hz, 1H), 4.92 (q, J = 9.1 Hz, 2H), 3.49 – 3.56 (m, 1H), 3.35 – 3.40 (m,1H), 2.63 – 2.69 (m, 1H), 2.44 (s, 2H), 1.43 (d, J = 2.5 Hz, 6H), 1.18 – 1.28(m, 5H)	MS (ESI): mass calcd. for C28H29F4N5O4: 575.22, found: 576.20 [M+H]+
95	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.14 (s, 1H), 8.14 (dd, J = 6.0, 2.9 Hz, 2H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.03 – 7.16 (m, 2H), 3.82 (dt, J = 11.1, 3.3 Hz, 2H), 3.49 (s, 2H), 3.43 – 3.51 (m, 1H), 3.31 – 3.46 (m, 1H), 3.37 (s, 1H), 2.50 – 2.52 (m, 4H), 2.33 (s, 1H), 1.53 (td, J = 9.2, 8.2, 3.7 Hz, 4H), 1.37 (d, J = 2.4 Hz, 6H), 1.15 – 1.27 (m, 4H)	MS (ESI): mass calcd. for C18H18ClN5O: 484.24, found: 485.20 [M+H]+
96	+		1H NMR (300 MHz, DMSO-d6) δ 10.16 (s, 1H), 8.10-8.19 (m, 2H), 7.90 (s, 1H), 7.52 (dd, J = 9.1, 2.9 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.04 – 7.16 (m, 2H), 6.66 (s, 1H), 3.40 – 3.55 (m, 2H), 3.27 (s, 2H), 2.61-2.67 (m, 2H), 2.42 (s, 2H), 1.48	MS (ESI): mass calcd. for C26H26FN5O2: 527.17 m/z, found 528.25 [M+H] +

			(d, J = 2.8 Hz, 6H), 1.14 – 1.27 (m, 3H)	
97	+		1H NMR (400 MHz, DMSO-d6) δ 11.84 (s, 1H), 10.66 (s, 1H), 8.43 (d, J = 9.5 Hz, 1H), 7.50 – 7.59 (m, 3H), 7.21 – 7.33 (m, 4H), 6.32 (d, J = 9.5 Hz, 1H), 3.56 (q, J = 6.8 Hz, 1H), 3.35 – 3.40 (m, 2H), 2.70 – 2.80 (m, 1H), 2.60 – 2.70 (m, 1H), 2.36 – 2.47 (m, 2H), 1.40 (d, J = 3.4 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C25H27FN6O4: 494.2 m/z, found: 495.20 [M+H] +
98	+		1H NMR (400 MHz, DMSO-d6) δ 11.84 (s, 1H), 10.66 (s, 1H), 8.43 (d, J = 9.5 Hz, 1H), 7.50 – 7.59 (m, 3H), 7.21 – 7.33 (m, 4H), 6.32 (d, J = 9.5 Hz, 1H), 3.56 (q, J = 6.8 Hz, 1H), 3.35 – 3.42 (m, 2H), 2.70 – 2.80 (m, 1H), 2.60 – 2.70 (m, 1H), 2.36 – 2.47 (m, 2H), 1.40 (d, J = 3.4 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C25H27FN6O4: 494.2 m/z, found: 495.20 [M+H] +
99	++	+++	1H NMR (400 MHz, DMSO-d6) δ 11.90 (s, 1H), 10.21 (s, 1H), 8.12 – 8.26 (m, 3H), 7.49 – 7.57 (m, 2H), 7.19 – 7.30 (m, 3H), 7.04 – 7.14 (m, 2H), 3.99 (d, J = 5.8 Hz, 2H), 3.52 (q, J = 6.9 Hz, 1H), 2.56 – 2.76 (m, 2H), 2.47 – 2.50 (m, 2H), 2.36 – 2.47 (m, 2H), 1.86 (s, 3H), 1.41 (d, J = 4.5 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C29H33FN6O5: 564.24, found: 565.15 [M+H]+
100	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.19 (s, 1H), 8.12 – 8.19 (m, 2H), 7.99 (d, J = 2.7 Hz, 1H), 7.48 – 7.57 (m, 2H), 7.19 – 7.30 (m, 2H), 7.05 – 7.14 (m, 2H), 6.46 (d, J = 9.4 Hz, 2H), 4.39 – 4.52 (m, 2H), 3.46 – 3.56 (m, 1H), 3.34 – 3.41 (m, 2H), 2.60 – 2.81 (m, 2H), 2.38 – 2.48 (m, 2H), 1.43 (d,	MS (ESI): mass calcd. for C28H30F3N5O4: 557.22, found: 558.15 [M+H]+

			J = 3.6 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H)	
101	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 12.55 (s, 1H), 10.18 (s, 1H), 8.11 – 8.20 (m, 2H), 7.89 (d, J = 1.3 Hz, 1H), 7.75 (s, 1H), 7.53 (dd, J = 9.0, 3.0 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.03 – 7.16 (m, 2H), 3.41 – 3.52 (m, 3H), 2.68 – 2.78 (m, 1H), 2.60 (d, J = 4.9 Hz, 1H), 2.42 (d, J = 2.9 Hz, 2H), 1.44 (d, J = 1.9 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H)	MS (ESI): mass calcd. for C25H27FN6O4 494.11m/z, found 495.25 [M+H]+
102	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 11.82 (s, 1H), 10.19 (s, 1H), 8.12 – 8.19 (m, 2H), 7.44 – 7.49 (m, 3H), 7.19 – 7.30 (m, 2H), 7.05 – 7.15 (m, 2H), 5.14 (t, J = 5.6 Hz, 1H), 4.29 (d, J = 5.5 Hz, 2H), 3.50 (q, J = 6.8 Hz, 1H), 3.34 – 3.42 (m, 2H), 2.68 – 2.78 (m, 1H), 2.57 – 2.67 (m, 1H), 2.42 (s, 2H), 1.42 (d, J = 1.9 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd for C28H29F4N5O5 591.21 m/z, found 592.30 [M+H]+
103	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 11.82 (s, 1H), 10.19 (s, 1H), 8.12 – 8.19(m, 2H), 7.44 – 7.49(m, 3H), 7.19 – 7.30 (m, 2H), 7.05 – 7.15 (m, 2H), 5.14 (t, J = 5.6 Hz, 1H), 4.29 (d, J = 5.5 Hz, 2H), 3.50 (q, J = 6.8 Hz, 1H), 3.34 – 3.42 (m, 2H), 2.68 – 2.78 (m, 1H), 2.57 – 2.67 (m, 1H), 2.42 (s, 2H), 1.42 (d, J = 1.9 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd for C27H30FN5O5 523.56 m/z, found 524.25 [M+H]+
104	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.20 (s, 1H), 8.05 – 8.19 (m, 4H), 7.53 (dd, J = 8.9, 3.1 Hz, 1H), 7.19 – 7.30 (m, 2H), 7.05 – 7.15 (m, 2H), 4.86 – 4.97 (m, 2H), 3.42 – 3.57 (m, 3H), 2.56 – 2.79 (m, 2H), 2.38 – 2.49 (m, 2H), 1.45 (d, J = 3.1	MS (ESI): mass calcd. for C27H28F4N6O4: 576.21,found:577.25 [M+H]+

			Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H)	
105	++		1H NMR (300 MHz, DMSO-d6) δ 11.86 (s, 1H), 10.22 (s, 1H), 8.11 – 8.21 (m, 2H), 7.47 – 7.58 (m, 2H), 7.45 (d, J = 2.5 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.04 – 7.16 (m, 2H), 3.46 – 3.60 (m, 5H), 3.34 – 3.40 (m, 2H), 3.25 – 3.29(m, 2H), 2.69 – 2.78 (m, 1H), 2.57 – 2.64 (m, 1H),2.40 (dt, J = 9.4, 4.4 Hz, 6H), 1.42 (d, J = 3.2 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H)	MS (ESI): mass calcd. for C31H37FN6O5 592.11m/z, found 593.25 [M+H]+
106	+++		1H NMR (300 MHz, DMSO-d6) δ 11.78 (s, 1H), 10.18 (s, 1H), 8.09 – 8.19 (m, 2H), 7.42 – 7.59 (m, 4H), 7.30 (td, J = 9.2, 5.6 Hz, 1H), 7.13 (tdd, J = 9.1, 3.0, 1.6 Hz, 1H), 6.32 (d, J = 9.5 Hz, 1H), 3.49 (q, J = 6.8 Hz, 1H), 3.36 (d, J = 6.1 Hz, 2H), 2.73 (t, J = 5.9 Hz, 1H), 2.5 – 2.66 (m, 1H), 2.40 (s, 2H), 1.40 (d, J = 2.2 Hz, 6H), 1.21 (t, J = 7.3 Hz, 3H)	MS (ESI): mass calcd. for C26H27F2N5O4: 511.20 m/z, found: 512.20 [M+H]+
107	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 11.72 (s, 1H), 10.18 (s, 1H), 8.09 – 8.19 (m, 2H), 7.41 – 7.60 (m, 4H),7.30 (td, J = 9.2, 5.6 Hz, 1H), 7.13 (tdd, J = 9.1, 3.0, 1.6 Hz, 1H), 6.32 (d, J = 9.5 Hz, 1H), 3.49 (q, J = 6.9 Hz, 1H), 3.36 – 3.39(s, 2H), 2.72 (q, J = 5.6, 5.0 Hz, 1H), 2.53 – 2.64(m, 1H) 2.40 (s, 2H), 1.40 (d, J = 2.2 Hz, 6H), 1.21 (t, J = 7.3 Hz, 3H)	MS (ESI): mass calcd. for C26H27F2N5O4: 511.20 m/z, found: 512.25 [M+H]+
108	+++	++	1H NMR (300 MHz, DMSO-d6) δ 10.21 (s, 1H), 8.17 – 8.27 (m, 2H), 8.09 – 8.23 (m, 2H), 7.38 – 7.58 (m, 4H), 7.30 (td, J = 9.3, 5.6 Hz, 1H), 7.13 (ddd, J = 9.3, 8.1, 3.0 Hz, 1H), 3.50 (q, J = 6.8 Hz, 1H), 3.32 (s, 2H), 2.71 (d, J = 5.3 Hz, 1H), 2.61 (q, J	MS (ESI): mass calcd. for C26H27F2N5O4: 511.20 m/z, found: 512.25 [M+H]+

			= 5.5 Hz, 1H), 2.38 – 2.48 (m, 2H), 1.45 (d, J = 3.0 Hz, 6H), 1.21 (t, J = 7.6 Hz, 3H)	
109	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.21 (s, 1H), 8.09 – 8.27 (m, 4H), 7.38 – 7.58 (m, 4H), 7.30 (td, J = 9.2, 5.6 Hz, 1H), 7.13 (ddd, J = 9.3, 8.1, 3.0 Hz, 1H), 3.50 (q, J = 6.8 Hz, 1H),3.32 (s, 2H), 2.71 (d, J = 5.4 Hz, 1H), 2.61 (q, J = 5.6 Hz, 1H), 2.38 – 2.48 (m, 2H), 1.45 (d, J = 3.0 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C26H27F2N5O4: 511.20 m/z, found: 512.25 [M+H]+
110	+++		1H NMR (300 MHz, DMSO-d6) δ 10.22 (s, 1H), 8.11 – 8.24 (m, 4H), 7.57 (dd, J = 9.0, 3.0 Hz, 1H), 7.37 – 7.52 (m, 3H), 7.17 – 7.30 (m, 1H), 6.80 – 6.92 (m, 1H), 3.49 (dd, J = 7.7, 5.9 Hz, 1H), 3.34 – 3.40 (m, 2H),2.70 (q, J = 5.6, 5.1 Hz, 1H), 2.60 (q, J = 5.7 Hz, 1H), 2.35 – 2.45 (m, 2H), 1.44 (d, J = 2.8 Hz, 6H), 1.13 – 1.22 (m, 3H)	MS (ESI): mass calcd. for C26H27F2N5O4 511.20 m/z, found 512.20 [M+H]+
111	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 11.75 (s, 1H), 10.07 (s, 1H), 8.24 (d, J = 2.3 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.65 (dd, J = 8.5, 2.4 Hz, 1H), 7.56 (d, J = 2.6 Hz, 1H), 7.47 (dd, J = 9.5, 2.7 Hz, 1H), 7.24 – 7.33 (m, 2H), 7.07 – 7.18 (m, 2H), 6.32 (d, J = 9.4 Hz, 1H), 3.92 (s, 2H), 3.48 (dt, J = 13.8, 6.7 Hz, 1H), 2.72 (dt, J = 10.5, 4.6 Hz, 1H), 2.60 (dt, J = 10.5, 4.6 Hz, 1H), 2.51 – 2.53 (m, 2H), 2.33 – 2.44 (m, 2H), 1.40 (d, J = 3.0 Hz, 6H), 1.19 (d, J = 7.0 Hz, 3H)	MS (ESI): mass calcd. for C27H30FN5O3: 491.23, found: 492.25 [M+H]+
112	+	++	1H NMR (400 MHz, DMSO-d6) δ 11.83 (s, 1H), 10.07 (s, 1H), 8.24 (d, J = 2.4 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.65 (dd, J = 8.5, 2.4	MS (ESI): mass calcd. for C27H30FN5O3: 491.23, found: 492.30[M+H]+

			Hz, 1H), 7.56 (d, J = 2.6 Hz, 1H), 7.47 (dd, J = 9.5, 2.6 Hz, 1H), 7.24 – 7.33 (m, 2H), 7.07 – 7.18 (m, 2H), 6.32 (d, J = 9.4 Hz, 1H), 3.92 (s, 2H), 3.48 (dt, J = 13.9, 6.6 Hz, 1H),2.73 (dd, J = 11.1, 4.8 Hz, 1H), 2.56 – 2.65 (m, 1H), 2.51 – 2.53 (m, 2H), 2.33 – 2.44 (m, 2H), 1.40 (d, J = 3.0 Hz, 6H), 1.19 (d, J = 6.9 Hz, 3H)	
113	+		1H NMR (300 MHz, DMSO-d6) δ 10.43 (s, 1H), 8.92 (d, J = 1.4 Hz, 1H), 8.35 (d, J = 1.5 Hz, 1H), 8.21 (d, J = 6.9 Hz, 2H), 7.46 (dd, J = 24.0, 8.3 Hz, 4H), 7.03 – 7.13 (m, 1H), 3.54 (t, J = 7.2 Hz, 1H), 2.57 – 2.67 (m, 3H), 2.45 (s, 3H), 1.45 (d, J = 2.6 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C25H26F2N6O4: 512.20 m/z, found 513.15 [M+H]+
114	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.43 (s, 1H), 8.92 (d, J = 1.4 Hz, 1H), 8.35 (d, J = 1.4 Hz, 1H), 8.21 (d, J = 6.5 Hz, 2H), 7.37 – 7.58 (m, 4H), 7.08 (dd, J = 9.0, 4.4 Hz, 1H), 3.48 – 3.58 (m, 1H), 2.57 – 2.67 (m, 3H), 2.38 – 2.49 (m, 3H), 1.45 (d, J = 2.6 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C25H26F2N6O4: 512.20 m/z, found 513.15 [M+H]+
115	+++	++	1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.89 (d, J = 1.4 Hz, 1H), 8.33 (d, J = 1.4 Hz, 1H), 8.17 – 8.28 (m, 2H), 7.38 – 7.48 (m, 2H), 7.17 – 7.34 (m, 4H), 3.54 (q, J = 6.8 Hz, 1H), 3.31 (s, 2H), 2.68 – 2.79 (m, 1H), 2.56 – 2.68 (m, 1H),2.45 (d, J = 2.5 Hz, 2H), 1.45 (d, J = 2.8 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H)	MS (ESI): mass calcd. for C25H27FN6O4: 494.21 m/z, found: 495.20 [M+H]+
116	+		1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.89 (d, J = 1.4 Hz, 1H), 8.33 (d, J = 1.4 Hz, 1H), 8.17 –	MS (ESI): mass calcd. for C25H27FN6O4: 494.21 m/z, found: 495.20 [M+H]+

			8.27 (m, 2H), 7.38 – 7.48 (m, 2H), 7.17 – 7.33 (m, 4H), 3.54 (q, J = 6.8 Hz, 1H), 3.31 (s, 2H), 2.71 (q, J = 5.6, 5.1 Hz, 1H), 2.57 – 2.67 (m, 1H), 2.45 (d, J = 2.5 Hz, 2H), 1.45 (d, J = 2.8 Hz, 6H), 1.06 – 1.27 (m, 3H)	
117	+++	+++		MS (ESI): mass calcd for C27H29ClFN5O4 541.19 m/z, found 542.25 [M+H]+
118	+		1H NMR (300 MHz, DMSO-d6) δ 10.17 (s, 1H), 8.40 – 8.48 (m, 2H), 8.08 – 8.18 (m, 2H), 7.51 (dd, J = 9.1, 2.9 Hz, 1H), 7.15 – 7.29 (m, 2H), 7.01 – 7.14 (m, 2H), 4.99 – 5.14 (m, 2H), 3.41 – 3.54 (m, 1H), 3.35 – 3.41 (m, 2H), 2.63 – 2.74 (m, 1H), 2.50 – 2.63 (m, 1H), 2.38 – 2.48 (m. 2H), 1.47 (d, J = 2.4 Hz, 6H), 1.18 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C27H28F4N6O4:576.21, found:577.30[M+H]+
119	++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.89 (d, J = 1.4 Hz, 1H), 8.33 (d, J = 1.4 Hz, 1H), 8.17 – 8.27 (m, 2H), 7.38 – 7.48 (m, 2H), 7.17 – 7.33 (m, 4H), 3.54 (q, J = 6.8 Hz, 1H), 3.31 (s, 2H), 2.71 (q, J = 5.6, 5.1 Hz, 1H), 2.57 – 2.67 (m, 1H), 2.45 (d, J = 2.5 Hz, 2H), 1.45 (d, J = 2.8 Hz, 6H), 1.06 – 1.27 (m, 3H)	MS (ESI): mass calcd. for C25H27FN6O4: 494.21 m/z, found: 495.20 [M+H]+
120	+		1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.89 (d, J = 1.4 Hz, 1H), 8.33 (d, J = 1.4 Hz, 1H), 8.17 – 8.28 (m, 2H), 7.38 – 7.48 (m, 2H), 7.17 – 7.34 (m, 4H), 3.54 (q, J = 6.8 Hz, 1H), 3.31 (s, 2H), 2.68 – 2.79 (m, 1H), 2.56 – 2.68 (m, 1H),2.45 (d, J = 2.5 Hz, 2H), 1.45 (d, J = 2.8 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H)	MS (ESI): mass calcd. for C25H27FN6O4: 494.21 m/z, found: 495.20 [M+H]+

121	++	++	1H NMR (400 MHz, DMSO-d6) δ 10.43 (s, 2H), 8.83 (d, J = 1.4 Hz, 2H), 8.57 (d, J = 1.7 Hz, 2H), 8.45 (d, J = 1.4 Hz, 2H), 8.22 (dd, J = 6.6, 1.8 Hz, 2H), 7.54 – 7.39 (m, 7H), 7.25 – 7.13 (m, 3H), 3.58 – 3.48 (m, 3H), 2.69 – 2.61 (m, 3H), 2.56 (dd, J = 10.8, 5.1 Hz, 12H), 2.45 (d, J = 3.0 Hz, 4H), 1.50 (s, 11H), 1.24 (s, 1H), 1.19 (d, J = 6.9 Hz, 6H)	MS (ESI): mass calcd. for C25H25ClF2N6O4: 546.16 m/z, found: 547.15 [M+H]+
122	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.43 (s, 2H), 8.83 (d, J = 1.4 Hz, 2H), 8.57 (d, J = 1.7 Hz, 2H), 8.45 (d, J = 1.4 Hz, 2H), 8.22 (dd, J = 6.6, 1.8 Hz, 2H), 7.54 – 7.39 (m, 7H), 7.25 – 7.13 (m, 3H), 3.58 – 3.48 (m, 3H), 2.69 – 2.61 (m, 3H), 2.56 (dd, J = 10.8, 5.1 Hz, 12H), 2.45 (d, J = 3.0 Hz, 4H), 1.50 (s, 11H), 1.24 (s, 1H), 1.19 (d, J = 6.9 Hz, 6H)	MS (ESI): mass calcd. for C25H25ClF2N6O4: 546.16 m/z, found: 547.15 [M+H]+
123	+		1H NMR (300 MHz, Acetonitrile-d3) δ 9.33 (s, 1H), 8.87 (d, J = 1.4 Hz, 1H), 8.10 – 8.22 (m, 1H), 7.83 (d, J = 2.4 Hz, 1H), 7.53 (dd, J = 9.4, 2.4 Hz, 1H), 7.26 – 7.38 (m, 1H), 7.11 – 7.24 (m, 1H), 7.00 (dd, J = 9.0, 4.3 Hz, 1H), 6.47 (d, J = 9.4 Hz, 1H), 5.59 (q, J = 7.2 Hz, 1H), 3.33 (q, J = 4.6 Hz, 2H), 2.86 (t, J = 5.2 Hz, 2H), 2.67 (s, 2H), 1.72 (d, J = 7.3 Hz, 3H), 1.44 (s, 6H)	MS (ESI): mass calcd. for C25H26F2N6O4: 512.20 m/z, found 513.15 [M+H]+
124	+++	+++	1H NMR (300 MHz, Acetonitrile-d3) δ 9.33 (s, 1H), 8.87 (d, J = 1.4 Hz, 1H), 8.10 – 8.22 (m, 1H), 7.83 (d, J = 2.4 Hz, 1H), 7.53 (dd, J = 9.4, 2.4 Hz, 1H), 7.26 – 7.38 (m, 1H), 7.11 – 7.24 (m, 1H), 7.00 (dd, J = 9.0, 4.3 Hz, 1H), 6.47 (d, J = 9.4 Hz, 1H), 5.59 (q, J = 7.2 Hz, 1H),	MS (ESI): mass calcd. for C25H26F2N6O4: 512.20 m/z, found 513.15 [M+H]+

			3.33 (q, J = 4.6 Hz, 2H), 2.86 (t, J = 5.2 Hz, 2H), 2.67 (s, 2H), 1.72 (d, J = 7.3 Hz, 3H), 1.44 (s, 6H)	
125	++	++	1H NMR (400 MHz, DMSO-d6) δ 11.82 (s, 1H), 10.46 (s, 1H), 8.86 (d, J = 1.4 Hz, 1H), 8.58 (d, J = 1.4 Hz, 1H), 7.56 (d, J = 2.6 Hz, 1H), 7.42 -7.53 (m, 3H), 6.32 (d, J = 9.5 Hz, 1H), 3.48 – 3.58 (m, 1H), 3.32 – 3.39 (m, 2H), 2.67 – 2.77 (m, 1H), 2.59 – 2.66 (m, 1H), 2.34 – 2.46 (m, 2H), 1.40 (d, J = 4.2 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C25H25F3N6O4: 530.19, found: 531.20 [M+H]+
126	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 11.78 (s, 1H), 10.46 (s, 1H), 8.86 (d, J = 1.4 Hz, 1H), 8.58 (d, J = 1.4 Hz, 1H), 7.56 (d, J = 2.5 Hz, 1H), 7.43 – 7.52 (m, 3H), 6.32 (d, J = 9.5 Hz, 1H), 3.53 (d, J = 7.1 Hz, 1H), 3.34 – 3.42(m, 2H) ,2.69 – 2.77 (m, 1H), 2.59 – 2.66 (m, 1H), 2.34 – 2.46 (m, 2H), 1.40 (d, J = 4.2 Hz, 6H), 1.17 – 1.26 (m, 3H)	MS (ESI): mass calcd. for C25H25F3N6O4: 530.19, found: 531.20 [M+H]+
127	+	++	1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.99 (d, J = 2.5 Hz, 1H), 7.39 – 7.55 (m, 3H), 7.11 – 7.24 (m, 1H), 6.37 (d, J = 9.3 Hz, 1H), 3.48 – 3.59 (m, 1H), 3.45 (s, 3H), 3.32 – 3.42 (m, 2H), 2.70 – 2.80 (m, 1H), 2.59 – 2.69 (m, 1H), 2.34 – 2.48 (m, 2H), 1.41 (d, J = 3.0 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H)	MS (ESI): mass calcd. for C26H28F2N6O4: 526.21 m/z, found: 527.25 [M+H]+
128	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.99 (d, J = 2.5 Hz, 1H), 7.39 – 7.55 (m, 3H), 7.11 – 7.24 (m, 1H), 6.37 (d, J = 9.3 Hz, 1H), 3.48 – 3.59 (m, 1H), 3.45 (s,	MS (ESI): mass calcd. for C26H28F2N6O4: 526.21 m/z, found: 527.25 [M+H]+

			3H), 3.32 – 3.42 (m, 2H), 2.70 – 2.80 (m, 1H), 2.59 – 2.69 (m, 1H), 2.34 – 2.48 (m, 2H), 1.41 (d, J = 3.0 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H)	
129	+		1H NMR (400 MHz, DMSO-d6) δ 11.71 (s, 1H), 10.22 (s, 1H), 8.14 – 8.22 (m, 2H), 7.54 – 7.64 (m, 2H), 7.41 – 7.53 (m, 2H), 7.26 (ddd, J = 11.8, 6.7, 3.0 Hz, 1H), 6.85 -6.93 (m, 1H), 6.32 (d, J = 9.5 Hz, 1H), 3.45 – 3.55 (m, 1H), 3.35 – 3.40 (m, 2H), 2.70 – 2.78 (m, 1H), 2.58 – 2.65 (m, 1H), 2.41 (s, 2H), 1.41 (d, J = 3.0 Hz, 6H), 1.18 – 1.26 (m, 3H)	MS: mass calcd. for C26H27F2N5O4: 511.20, found: 512.25 [M+H]+
130	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 11.77 (s, 1H), 10.22 (s, 1H), 8.14 – 8.22 (m, 2H), 7.54 – 7.64 (m, 2H), 7.41 – 7.53 (m, 2H), 7.26 (ddd, J = 10.9, 6.7, 2.9 Hz, 1H), 6.85 – 6.92 (m, 1H), 6.32 (d, J = 9.5 Hz, 1H), 3.47 – 3.54 (m, 1H), 3.35 – 3.40 (m, 2H), 2.58 – 2.78 (m, 2H), 2.41 (s, 2H), 1.41 (d, J = 2.9 Hz, 6H), 1.18 – 1.26 (m, 3H)	MS: mass calcd. for C26H27F2N5O4: 511.20, found: 512.25 [M+H]+
131	+		1H NMR (400 MHz, DMSO-d6) δ 10.50 (s, 1H), 8.83 – 8.88 (m, 1H), 8.58 (d, J = 1.5 Hz, 1H), 8.22 (d, J = 6.8 Hz, 2H), 7.36 – 7.53 (m, 4H), 3.49 – 3.60 (m, 1H), 3.25 – 3.34 (m, 2H), 2.68 – 2.76 (m, 1H), 2.58 – 2.67 (m, 1H), 2.39 – 2.51 (m, 2H), 1.45 (d, J = 4.6 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C25H25F3N6O4: 530.21 m/z found: 531.20 [M+H]+
132	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.50 (s, 1H), 8.86 (d, J = 1.4 Hz, 1H), 8.58 (d, J = 1.4 Hz, 1H), 8.18 – 8.27 (m, 2H), 7.39 – 7.53 (m, 4H), 3.49 – 3.59 (m, 1H), 2.39 – 2.48 (m, 2H), 2.66 – 2.76 (m, 1H), 2.58 – 2.67 (m,	MS (ESI): mass calcd. for C25H25F3N6O4: 530.21 m/z found: 531.20 [M+H]+

			1H), 2.39 – 2.51 (m, 2H), 1.45 (d, J = 4.5 Hz, 6H), 1.17 – 1.23 (m, 3H)	
133	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 11.80 (s, 1H), 10.43 (s, 1H), 8.87 (d, J = 1.5 Hz, 1H), 8.47 (d, J = 1.4 Hz, 1H), 7.67 – 7.90 (m, 2H), 7.56 (d, J = 2.6 Hz, 1H), 7.47 (dd, J = 9.5, 2.6 Hz, 1H), 6.32 (d, J = 9.5 Hz, 1H), 3.53 (d, J = 7.1 Hz, 1H), 3.35 – 3.38 (s, 2H), 2.69 – 2.78 (m, 1H), 2.64 (q, J = 5.3 Hz, 1H), 2.40 (s, 2H), 1.40 (d, J = 2.7 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H)	MS (ESI): mass calcd. for C25H25F3N6O4: 530.19 m/z, found: 531.25 [M+H]+
134	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.38 (s, 1H), 8.83 (d, J = 1.5 Hz, 1H), 8.45 (d, J = 1.3 Hz, 1H), 7.48 (qd, J = 8.8, 4.3 Hz, 2H), 7.11 – 7.24 (m, 1H), 3.81 (dt, J = 11.0, 3.3 Hz, 2H), 3.49 (dt, J = 8.1, 4.7 Hz, 3H), 3.38 (d, J = 6.1 Hz, 1H), 2.81 (q, J = 6.9, 6.2 Hz, 1H), 2.75 – 2.87 (m, 2H), 2.55 – 2.75 (m, 1H), 2.32 (s, 2H), 1.50 (dd, J = 8.0, 3.4 Hz, 4H), 1.35 (d, J = 2.0 Hz, 6H), 1.19 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C25H31F2N5O4: 503.23 m/z, found: 504.30 [M+H]+
135	++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.12 (s, 1H), 8.15 (dd, J = 6.0, 2.9 Hz, 2H), 7.52 (dd, J = 9.1, 2.9 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.04 – 7.16 (m, 2H), 3.53 (t, J = 4.5 Hz, 4H), 3.45 (d, J = 6.9 Hz, 1H), 3.21 (t, J = 4.7 Hz, 4H), 3.11 (s, 2H), 2.63 – 2.73 (m, 1H), 2.57 (d, J = 5.3 Hz, 1H), 2.27 (s, 2H), 1.30 (d, J = 2.8 Hz, 6H), 1.18 (d, J = 6.8 Hz, 3H)	MS (ESI): mass calcd. for C25H32FN5O4: 485.24 m/z, found: 486.25 [M+H] +
136	+		1H NMR (300 MHz, DMSO-d6) δ 10.16 (s, 1H), 8.18 – 8.09 (m, 2H), 7.52 (dd, J = 9.1, 2.9 Hz, 1H), 7.31 – 7.17 (m, 2H), 7.16 –	MS (ESI): mass calcd. forC24H29FN4O4:456.22, found:457.20[M+H]+

			7.02 (m, 2H), 4.69 – 4.54 (m, 4H), 4.03 (tt, J = 8.5, 6.9 Hz, 1H), 3.47 (p, J = 6.9, 6.2 Hz, 1H), 3.09 (t, J = 5.4 Hz, 2H), 2.71 – 2.51 (m, 4H), 2.34 (s, 2H), 1.42 (d, J = 2.6 Hz, 6H), 1.18 (d, J = 6.8 Hz, 3H)	
137	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.14 (s, 1H), 8.11 – 8.20 (m, 2H), 7.48 – 7.57 (m, 1H), 7.24 (t, J = 8.8 Hz, 1H), 7.04 – 7.15 (m, 3H), 7.05 (d, J = 16.1 Hz, 1H), 3.49 – 3.66 (m, 1H). 3.40 – 3.49 (m, 2H), 2.59 – 2.68 (m, 2H),2.38 (d, J = 3.3 Hz, 2H), 1.43 (s, 6H), 1.10 – 1.27(m, 3H)	MS (ESI): mass calcd. for C25H28FN7O4 509.54 m/z, found 510.25[M+H]+
138	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.19 (s, 1H), 9.03 (d, J = 2.0 Hz, 1H), 8.61 (dd, J = 6.8, 2.1 Hz, 1H), 8.15 (dd, J = 6.0, 2.9 Hz, 2H), 7.66 (d, J = 6.8 Hz, 1H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.24 (t, J = 8.8 Hz, 2H), 7.04 – 7.16 (m, 2H), 3.47 – 3.55 (m, 5H), 2.53 – 2.66 (m, 2H), 1.48 (d, J = 2.5 Hz, 6H), 1.30 (s, 1H), 1.21 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C25H27FN6O4:494.21, found:495.30 [M+H]+
139	++		1H NMR (300 MHz, DMSO-d6) δ 10.46 (s, 1H), 8.87 (d, J = 1.4 Hz, 1H), 8.47 (d, J = 1.4 Hz, 1H), 8.18 – 8.27 (m, 2H), 7.78 (ddt, J = 20.5, 11.0, 7.6 Hz, 2H), 7.39 – 7.48 (m, 2H), 3.55 (q, J = 6.8 Hz, 1H), 3.34 (s, 2H), 2.72 (q, J = 5.4, 5.0 Hz, 1H), 2.62 (dt, J = 10.8, 4.9 Hz, 1H), 2.46 (d, J = 2.8 Hz, 2H), 1.45 (d, J = 2.7 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C25H25F3N6O4: 530.19 m/z, found: 531.25 [M+H]+
140	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.46 (s, 1H), 8.87 (d, J = 1.4 Hz, 1H), 8.47 (d, J = 1.4 Hz, 1H), 8.17 – 8.26 (m, 2H), 7.78 (ddt, J = 20.4, 11.0, 7.7 Hz, 2H), 7.38	MS (ESI): mass calcd. for C25H25F3N6O4: 530.19 m/z, found: 531.25 [M+H]+

			– 7.48 (m, 2H), 3.55 (q, J = 6.8 Hz, 1H), 3.34 (s, 2H), 2.68 – 2.79 (m, 1H), 2.57 – 2.68 (m, 1H), 2.46 (d, J = 2.8 Hz, 2H), 1.45 (d, J = 2.7 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H)	
141	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 9.01 (dd, J = 2.1, 1.0 Hz, 1H), 8.82 (d, J = 1.4 Hz, 1H), 8.59 (dd, J = 6.8, 2.0 Hz, 1H), 8.43 (d, J = 1.4 Hz, 1H), 7.64 (dd, J = 6.8, 1.0 Hz, 1H), 7.37 – 7.54 (m, 2H), 7.09 – 7.22 (m, 1H), 3.48 – 3.56 (m, 1H), 3.36 – 3.45 (m, 2H), 2.63 – 2.75 (m, 1H), 2.55 – 2.63 (m, 1H), 2.40 – 2.48 (m, 2H), 1.44 (d, J = 2.2 Hz, 6H), 1.14 – 1.25 (m, 3H)	MS (ESI): mass calcd. for C24H25F2N7O4:513.19, found:514.20[M+H]+
142	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.40 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 8.05 – 8.13 (m, 2H), 7.39 – 7.55 (m, 2H), 7.10 – 7.24 (m, 1H), 4.84 – 4.99 (m, 2H), 3.45 – 3.60 (m, 3H), 2.68 – 2.79 (m, 1H), 2.60 – 2.68 (m, 1H), 2.43 (d, J = 3.0 Hz, 2H), 1.44 (d, J = 2.0 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H)	MS (ESI): mass calcd. for C26H26F5N7O4: 595.20, found: 596.30 [M+H]+
143	++		1H NMR (400 MHz, DMSO-d6) δ 10.43 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.42 – 8.49 (m, 3H), 7.41 – 7.54 (m, 2H), 7.18 (ddt, J = 11.0, 8.6, 2.2 Hz, 1H), 5.09 (q, J = 8.9 Hz, 2H), 3.53 (q, J = 6.9 Hz, 1H), 3.39 (t, J = 5.4 Hz, 2H), 2.72 (dd, J = 11.1, 5.2 Hz, 1H), 2.59 (dt, J = 10.9, 5.3 Hz, 1H), 2.46 (d, J = 5.1 Hz, 2H), 1.48 (d, J = 3.0 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C26H26F5N7O4 595.20 m/z, found 596.25[M+H]+
144	+++	+++	1H NMR (400 MHz, DMSO-d6) δ10.42 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.5 Hz, 1H), 7.86 (d, J = 2.5 Hz, 1H), 7.42 – 7.55	MS (ESI): mass calcd. for C27H30F2N6O5: 556.20, found: 557.25 [M+H]+

			(m, 3H), 7.13 – 7.23 (m, 1H), 6.38 (d, J = 9.3 Hz, 1H), 4.92 (t, J = 5.4 Hz, 1H), 3.98 (t, J = 5.2 Hz, 2H), 3.48 – 3.65 (m, 3H), 3.37 – 3.42 (m, 2H), 2.70 – 2.78 (m, 1H), 2.59 – 2.69 (m, 1H), 2.41 (s, 2H), 1.41 (d, J = 4.4 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H)	
145	+		1H NMR (300 MHz, DMSO-d6) δ 12.42 (s, 1H), 8.17 – 8.25 (m, 2H), 7.36 – 7.51 (m, 4H), 7.28 – 7.35 (m, 2H), 3.55 (d, J = 7.0 Hz, 1H), 3.27 (s, 2H), 2.58 – 2.73 (m, 2H), 2.40 (t, J = 11.0 Hz, 2H), 1.42 (d, J = 2.9 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C23H25FN6O4S: 500.16 m/z, found 501.15 [M+H]+
146	+		1H NMR (300 MHz, DMSO-d6) δ 12.42 (s, 1H), 8.17 – 8.25 (m, 2H), 7.36 – 7.51 (m, 4H), 7.28 – 7.35 (m, 2H), 3.53 (t, J = 6.9 Hz, 1H), 3.21 – 3.25 (m, 2H), 2.56 – 2.63 (m, 2H), 2.33 – 2.50 (m, 2H), 1.42 (d, J = 2.9 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H)	MS (ESI): mass calcd. for C23H25FN6O4S: 500.16 m/z, found 501.15 [M+H]+
147	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.44 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.26 (d, J = 6.6 Hz, 1H), 7.42 – 7.55 (m, 3H), 7.36 (dd, J = 6.7, 2.6 Hz, 1H), 7.18 (ddt, J = 11.2, 9.1, 2.3 Hz, 1H), 5.68 (t, J = 5.8 Hz, 1H), 4.57 (d, J = 5.7 Hz, 2H), 3.54 (q, J = 7.0 Hz, 1H), 3.35 (s, 2H), 2.56 – 2.79 (m, 2H), 2.46 (d, J = 2.5 Hz, 2H), 1.46 (d, J = 2.9 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H)	MS (ESI): mass calcd. for C26H28F2N6O5 542.54 m/z, found 543.30[M+H]+
148	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.17 (s, 1H), 8.14 (dd, J = 6.0, 2.9 Hz, 2H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.04 – 7.16 (m, 2H), 3.42 – 3.52 (m, 3H), 3.10 – 3.25 (m, 2H), 2.93 – 3.09 (m,	MS (ESI): mass calcd. for C26H33FN4O5S 532.22 m/z, found 533.30 [M+H]+

			3H), 2.67 – 2.79 (m, 1H), 2.56 – 2.66 (m, 1H), 2.26 – 2.38 (m, 2H), 1.82 – 2.03 (d, J = 5.8 Hz, 4H), 1.37 (d, J = 3.0 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H)	
149	++	+++	1H NMR (400 MHz, DMSO-d6) δ 12.62 (s, 1H), 10.19 (s, 1H), 8.12 – 8.19 (m, 2H), 7.85 (s, 1H), 7.77 (s, 1H), 7.53 (dd, J = 8.9, 3.1 Hz, 1H), 7.18 – 7.29 (m, 2H), 7.05 – 7.14 (m, 2H), 3.49 (tt, J = 8.9, 5.4 Hz, 3H), 2.57 – 2.75 (m, 2H), 2.35 – 2.47 (m, 2H), 1.44 (d, J = 2.6 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C25H27FN6O4 494.21 m/z, found 495.25 [M+H]+
150	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 12.01 (s, 1H), 10.42 (s, 1H), 8.81 – 8.85 (m, 1H), 8.45 (d, J = 1.5 Hz, 1H), 7.41 – 7.55 (m, 3H), 7.12 – 7.22 (m, 1H), 6.52 (s, 1H), 3.52 (q, J = 6.9 Hz, 1H), 2.50 – 2.71 (m, 2H), 2.56 (dt, J = 11.1, 5.2 Hz, 2H), 2.35 – 2.48 (m, 2H), 1.45 (s, 6H), 1.19 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C25H26ClF2N6O4 546.16 m/z, found 547.20 [M+H]+
151	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.16 (s, 1H), 8.14 (dd, J = 6.1, 2.9 Hz, 2H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.41 (s, 1H), 7.17 – 7.31 (m, 2H), 7.04 – 7.16 (m, 2H), 5.07 (s, 2H), 4.35 (s, 6H), 3.45 – 3.55(m, 4H), 3.16 – 3.25 (m, 2H), 2.98 (s, 1H), 2.55 – 2.63 (m, 2H), 2.34 (d, J = 3.1 Hz, 2H), 2.12 – 2.26 (m, 1H), 1.70 – 1.90 (m, 2H), 1.37 (d, J = 3.3 Hz, 6H), 1.16 – 1.27 (m, 3H)	MS (ESI): mass calcd. for C26H32FN5O4: 497.24, found: 498.20 [M+H]+
152	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.16 (s, 1H), 8.14 (dd, J = 6.0, 2.9 Hz, 2H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.41 (s, 1H), 7.18 – 7.30 (m, 2H), 7.04 – 7.16 (m, 2H), 3.51 (s, 3H), 3.48 (d, J	MS (ESI): mass calcd. for C26H32FN5O4: 497.24, found: 498.20 [M+H]+

			= 6.9 Hz, 1H), 3.16 (d, J = 10.4 Hz, 2H), 2.70-2.80 (m, 1H), 2.60 – 2.69 (m, 1H), 2.34 (s, 2H), 2.05 – 2.29 (m, 2H), 1.80-1.90 (m, 1H), 1.37 (d, J = 1.5 Hz, 6H), 1.27 – 1.15 (m, 4H)	
153	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 11.78 (s, 1H), 10.42 (s, 1H), 8.85 (s, 1H), 8.46 (s, 1H), 7.48 (qd, J = 9.9, 9.1, 4.5 Hz, 4H), 7.13 – 7.23 (m, 1H), 5.16 (s, 1H), 4.28 (s, 2H), 3.49 – 3.57 (m, 3H), 2.72 (dt, J = 10.5, 4.9 Hz, 1H), 2.63 (q, J = 5.8, 5.3 Hz, 1H), 2.41 (s, 2H), 1.41 (d, J = 2.8 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C26H28F2N6O5: 542.21 m/z, found: 543.30 [M+H]+
154	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.83 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 8.08 – 8.21 (m, 2H), 7.40 – 7.56 (m, 2H), 7.24 (d, J = 6.5 Hz, 1H), 7.12 – 7.24 (m, 1H), 5.49 (t, J = 5.5 Hz, 1H), 4.45 (d, J = 5.3 Hz, 2H), 3.53 (d, J = 6.7 Hz, 1H), 3.21 (s, 2H), 2.63 (d, J = 5.4 Hz, 2H), 2.40 – 2.47 (m, 2H), 1.48 (d, J = 2.0 Hz, 6H), 1.19 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C26H28F2N6O5: 542.22m/z, found 543.25 [M+H]+
155	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 13.12 (s, 1H), 10.43 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.5 Hz, 1H), 7.39 – 7.45 (m, 3H), 7.10 – 7.24 (m, 1H), 6.91 (d, J = 9.8 Hz, 1H), 3.42 – 3.59 (m, 3H), 2.65 – 2.78 (m, 1H), 2.53 – 2.65 (m, 1H), 2.40 – 2.47 (m, 2H), 1.43 (d, J = 2.3 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H)	MS (ESI): mass calcd. for C24H25F2N7O4:513.19, found:514.20[M+H]+
156	++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.19 (s, 1H), 8.64 (d, J = 4.9 Hz, 2H), 8.10 – 8.19 (m, 2H), 7.52 (dd, J = 9.1, 3.0 Hz, 1H), 7.36 (d, J =	MS (ESI): mass calcd. for C26H28FN5O3:477.22, found:478.25[M+H]+

			5.3 Hz, 2H), 7.24 (t, J = 8.7 Hz, 2H), 7.09 (dd, J = 9.1, 4.3 Hz, 2H), 3.43 – 3.56 (m, 1H), 3.26 (d, J = 5.4 Hz, 2H), 2.64 – 2.73 (m, 1H), 2.53 – 2.63 (m, 1H), 2.4 – 2.49 (m, 2H), 1.49 (d, J = 2.7 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H)	
157	++		1H NMR (300 MHz, DMSO-d6) δ 10.15 (s, 1H), 8.09 – 8.18 (m, 2H), 7.47 – 7.58 (m, 1H), 7.17 – 7.30 (m, 2H), 7.17 – 7.02 (m, 2H), 5.02 (dd, J = 7.0, 1.2 Hz, 1H), 3.82 – 4.01 (m, 1H), 3.39 – 3.51 (m, 1H), 3.23 – 3.32 (m, 2H), 2.60 – 2.70 (m, 3H), 2.21 – 2.34 (m, 4H), 1.81 – 1.97 (m, 2H), 1.34 – 1.41 (m, 6H), 1.18 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C25H31FN4O4:470.23, found:471.30[M+H]+
158	++		1H NMR (400 MHz, DMSO-d6) δ 10.15 (s, 1H), 8.10 – 8.17 (m, 2H), 7.52 (dd, J = 9.1, 2.9 Hz, 1H), 7.18 – 7.29 (m, 2H), 7.04 – 7.14 (m, 2H), 5.03 (d, J = 5.9 Hz, 1H), 4.05 (h, J = 6.6 Hz, 1H), 3.44 (q, J = 6.9 Hz, 1H), 13.26 (s, 2H), 3.10 (dq, J = 9.5, 4.8 Hz, 1H), 2.64 (q, J = 5.8 Hz, 1H), 2.55 (t, J = 5.6 Hz, 1H), 2.26 – 2.37 (m, 4H), 1.97 (tdd, J = 9.7, 6.4, 2.5 Hz, 2H), 1.38 (d, J = 3.0 Hz, 6H), 1.18 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C25H31FN4O4 470.23 m/z, found 471.30[M+H]+
159	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.16 (s, 1H), 8.14 (dd, J = 6.0, 2.9 Hz, 2H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.03 – 7.13 (m, 2H), 4.53 (d, J = 4.3 Hz, 1H), 3.46 (d, J = 7.1 Hz, 3H), 2.64 – 2.75 (m, 1H), 7.54 – 2.64 (m, 1H), 7.03 – 7.13 (m, 2H), 2.35 – 1.47 (m, 2H), 2.31 (s, 2H), 1.81 (dd, J = 12.4, 4.1 Hz, 2H), 1.61 (d, J = 12.8	MS (ESI): mass calcd. for C27H35FN4O4 498.29 m/z, found 499.35[M+H]+

			Hz, 2H), 1.38 – 1.22 (m, 7H), 1.07 – 1.22 (m, 6H)	
160	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 11.94 (s, 1H), 10.19 (s, 1H), 8.14 (dd, J = 6.1, 3.0 Hz, 2H), 7.49 – 7.56 (m, 2H), 7.24 (t, J = 8.8 Hz, 2H), 7.04 – 7.14 (m, 2H), 6.53 (s, 1H), 3.44 – 3.53 (m, 1H), 3.20 – 3.30 (m, 2H), 2.62 – 2.72 (m, 1H), 2.52 – 2.60 (m, 1H), 2.42 (s, 2H), 1.47 (d, J = 2.9 Hz, 6H), 1.19 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C26H27ClFN5O4: 527.17 m/z, found: 528.25 [M+H]+
161	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.42 (s, 1H), 8.83 (d, J = 1.2 Hz, 1H), 8.45 (d, J = 1.2 Hz, 1H), 7.71 (s, 1H), 7.50 – 7.45 (m, 2H), 7.21 – 7.16 (m, 1H), 6.99 (s, 1H), 3.52 (d, J = 7.1 Hz, 1H), 2.70 (s, 1H), 2.63 (s, 1H), 2.51 – 2.42 (m, 2H), 1.43 (d, J = 2.1 Hz, 6H), 1.19 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C26H25F2N7O4:537.2 m/z, found:538.25 [M+H]+
162	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.12 (s, 1H), 7.91 (d, J = 1.0 Hz, 1H), 7.41 – 7.54 (m, 2H), 7.12 – 7.22 (m, 1H), 3.45 – 3.57 (m, 6H), 2.56 – 2.78 (m, 2H), 2.36 – 2.47 (m, 2H), 1.44 (d, J = 2.8 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C25H27F2N7O4:527.21m/z, found:528.30[M+H]+
163	++		1H NMR (300 MHz, DMSO-d6) δ 10.16 (s, 1H), 8.14 (dd, J = 6.0, 2.9 Hz, 2H), 7.53 (dd, J = 9.1, 2.9 Hz, 1H), 7.17 – 7.31 (m, 2H), 7.02 – 7.16 (m, 2H), 4.27 (d, J = 3.0 Hz, 1H), 3.74 (d, J = 4.7 Hz, 1H), 3.39 – 3.54 (m, 3H), 2.63 – 2.75 (m, 1H), 2.51 – 2.63 (m, 1H), 2.44 – 2.48 (m, 1H), 2.31 (s, 2H), 1.54 – 1.79 (m, 4H), 1.26 – 1.50 (m, 10H), 1.19 (d, J = 6.8 Hz, 3H)	MS (ESI): mass calcd. for C27H35FN4O4:498.26m/z, found:499.30[M+H]+

164	+++	+++	1H NMR (300 MHz, DMSO-d-6) δ 11.46 (s, 1H), 10.39 (s, 1H), 8.83 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.39 – 7.55 (m, 2H), 7.26 (s, 1H), 7.10 – 7.23 (m, 1H), 6.39 (s, 1H), 5.29 (t, J = 5.5 Hz, 1H), 4.32 (d, J = 5.5 Hz, 2H), 3.51 (q, J = 6.8 Hz, 1H),3.33(s, 2H), 2.60 – 2.69(m, 1H), 2.55 (s, 1H), 2.39 (s, 2H), 1.42 (d, J = 1.9 Hz, 6H), 1.18 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C26H28F2N6O5: 542.544 m/z, found 543.30 [M+H]+
165	++		1H NMR (300 MHz, DMSO-d6) δ 10.39 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.58 (s, 1H), 7.39 – 7.55 (m, 2H), 7.11 – 7.24 (m, 1H), 3.50 (d, J = 4.6 Hz, 4H), 2.69 – 2.79 (m, 1H), 2.58 – 2.68 (m, 1H), 2.41 (s, 2H), 2.26 (s, 3H), 1.43 (s, 6H), 1.21 (d, J = 6.8 Hz, 3H)	MS (ESI): mass calcd. for C25H27F2N7O4:527.21 m/z, found:528.30 [M+H]+
166	+++	+++		MS (ESI): mass calcd. for C25H27F2N7O4: 513.19, found: 514.20 [M+H]+
167	+		1H NMR (400 MHz, DMSO-d6) δ 10.15 (s, 1H), 8.11 – 8.17 (m, 2H), 7.52 (dd, J = 9.1, 2.9 Hz, 1H), 7.18 – 7.29 (m, 2H), 7.04 – 7.14 (m, 2H), 3.36 – 3.48 (m, 3H), 2.64 – 2.74 (m, 1H), 2.52 – 2.61 (m, 1H), 2.31 (s, 2H), 1.96 (s, 3H), 1.37 (d, J = 3.6 Hz, 6H), 1.18 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C22H27FN4O3:414.21m/z, found:415.20[M+H]+
168	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.44 (s, 1H), 8.80 – 8.94 (m, 2H), 8.43 – 8.52 (m, 2H), 7.59 (d, J = 6.8 Hz, 1H), 7.48 (tq, J = 9.2, 6.0, 4.4 Hz, 2H), 7.18 (t, J = 8.4 Hz, 1H), 3.49 – 3.59 (m, 1H), 2.54 – 2.75 (m, 3H), 2.44 – 2.49 (m, 3H), 1.50 (d, J = 2.3 Hz, 6H), 1.18 – 1.26 (m, 3H).	MS (ESI): mass calcd. for C26H25F2N7O4 537.19 m/z, found 538.30[M+H]+

169	++		1H NMR (300 MHz, DMSO-d6) δ 10.44 (s, 1H), 8.91 (d, J = 1.8 Hz, 1H), 8.83 (d, J = 1.5 Hz, 1H), 8.42 – 8.52 (m, 2H), 7.59 (d, J = 6.8 Hz, 1H), 7.48 (qd, J = 9.0, 4.3 Hz, 2H), 7.18 (t, J = 8.8 Hz, 1H), 3.55 (q, J = 6.1, 5.3 Hz, 1H), 2.56 – 2.74 (m, 2H), 2.41 – 2.48 (m, 4H), 1.50 (d, J = 2.4 Hz, 6H), 1.18 – 1.26 (m, 3H)	MS (ESI): mass calcd. for C26H25F2N7O4 537.19 m/z, found 538.30[M+H]+
170	++	++	1H NMR (400 MHz, DMSO-d6) δ 9.97 (s, 1H), 8.19 – 8.25 (m, 2H), 7.96 – 8.07 (m, 2H), 7.38 – 7.46 (m, 3H), 4.85 (s, 1H), 3.48 (dd, J = 14.9, 8.4 Hz, 1H), 2.54 – 2.77 (m, 4H), 2.45 (d, J = 2.5 Hz, 2H), 1.88 – 1.94 (m, 2H), 1.70 (s, 4H), 1.60 (d, J = 9.2 Hz, 2H), 1.46 (d, J = 3.7 Hz, 6H), 1.16 – 1.22 (m, 3H)	MS (ESI): mass calcd. for C25H33N5O4: 467.25, found: 468.25 [M+H]+
171	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.44 (s, 1H), 9.09 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.59 (s, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.88 (d, J = 9.1 Hz, 1H), 7.67 (dd, J = 9.2, 1.7 Hz, 1H), 7.42 – 7.55 (m, 2H), 7.18 (s, 1H), 3.56 (t, J = 6.9 Hz, 1H), 2.60 – 2.79 (m, 3H), 2.46 (d, J = 11.7 Hz, 3H), 1.49 (d, J = 4.1 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C26H26F2N8O3: 536.21 m/z, found: 537.30 [M+H]+
172	+		1H NMR (400 MHz, DMSO-d6) δ 10.27 (s, 1H), 8.36 – 8.45 (m, 2H), 8.14 – 8.26 (m, 4H), 7.61 – 7.68 (m, 1H), 7.39 – 7.50 (m, 4H), 3.44 – 3.56 (m, 1H), 2.54 – 2.78 (m, 4H), 2.31 – 2.47(m, 2H), 1.48 (d, J = 4.0 Hz, 6H), 1.24 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C25H27N6O4: 476.22, found: 477.15 [M+H]+
173	+		1H NMR (400 MHz, DMSO-d6) δ 10.26 (s, 1H), 8.35 – 8.45 m, 2H), 8.15 – 8.26 (m, 4H), 7.60 – 7.67 (m,	MS (ESI): mass calcd. for C25H27N6O4: 476.22, found: 477.15 [M+H]+

			1H), 7.39 – 7.49 (m, 4H), 3.47 – 3.55 (m, 1H), 2.55 – 2.76 (m, 4H), 2.41 – 2.49 (m, 2H), 1.46 (d, J = 4.0 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H)	
174	++	++	1H NMR (300 MHz, DMSO-d6) δ 10.39 (s, 1H), 8.82 (d, J = 1.4 Hz, 1H), 8.44 (d, J = 1.4 Hz, 1H), 8.36 (d, J = 1.4 Hz, 1H), 8.24 (d, J = 1.3 Hz, 1H), 7.38 – 7.54 (m, 2H), 7.16 (t, J = 8.6 Hz, 1H), 4.90 (s, 1H), 4.34 (t, J = 5.0 Hz, 2H), 3.72 (d, J = 4.9 Hz, 2H), 3.51 (d, J = 7.1 Hz, 1H), 3.34 – 3.45 (m, 2H), 2.69 (d, J = 4.8 Hz, 1H), 2.59 (d, J = 5.6 Hz, 1H), 2.43 (s, 2H), 1.45 (d, J = 2.1 Hz, 6H), 1.19 (d, J = 6.8 Hz, 3H)	MS (ESI): mass calcd. for C26H29F2N7O5: 557.22 m/z, found 558.30 [M+H]+
175	++		1H NMR (300 MHz, DMSO-d6) δ 10.44 (s, 1H), 8.82 (d, J = 1.9 Hz, 2H), 8.45 (d, J = 1.4 Hz, 1H), 7.39 – 7.56 (m, 2H), 7.18 (d, J = 11.7 Hz, 2H), 3.91 (s, 3H), 3.50 -3.56 (m, 1H), 3.36 – 3.43 (m, 3H), 3.20 – 3.26 (m, 1H), 2.60 – 2.66 (m, 1H), 2.35 – 2.41 (m, 1H), 1.55 (d, J = 4.3 Hz, 3H), 1.46 (s, 3H), 1.15 – 1.21 (m, 3H)	MS (ESI): mass calcd. for C25H27F2N7O5:543.20 m/z, found:544.30[M+H]+
176	++		1H NMR (400 MHz, DMSO-d6) δ 10.43 (s, 1H), 8.89 (d, J = 1.5 Hz, 1H), 8.33 (d, J = 1.4 Hz, 1H), 8.26 (d, J = 6.6 Hz, 1H), 7.50 (d, J = 2.5 Hz, 1H), 7.36 (dd, J = 6.6, 2.6 Hz, 1H), 7.19 – 7.32 (m, 4H), 5.69 (t, J = 5.8 Hz, 1H), 4.57 (d, J = 5.8 Hz, 2H), 3.50 – 3.59 (m, 1H), 3.37 – 3.40 (m, 1H), 3.29 – 3.32 (m, 1H), 2.68 – 2.75 (m, 2H), 2.58 – 2.65 (m, 2H), 1.46 (d, J = 2.8 Hz, 6H), 1.18 – 1.26 (m, 3H)	MS (ESI): mass calcd. for C26H29FN6O5:524.22, found:525.25[M+H] +
177	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.49 (s, 1H), 8.87 (d, J = 1.4 Hz, 1H), 8.48	MS (ESI): mass calcd. for C26H27F3N6O5:560.20m/z, found:561.30[M+H]+

			(d, J = 1.4 Hz, 1H), 8.26 (d, J = 6.6 Hz, 1H), 7.70 – 7.89 (m, 2H), 7.50 (d, J = 2.5 Hz, 1H), 7.36 (dd, J = 6.7, 2.6 Hz, 1H), 5.68 (t, J = 5.8 Hz, 1H), 4.57 (d, J = 5.7 Hz, 2H), 3.55 (d, J = 6.8 Hz, 1H), 2.68 – 2.75 (m, 1H), 2.58 – 2.66 (m, 2H), 2.46 (d, J = 2.7 Hz, 2H), 1.46 (d, J = 2.8 Hz, 6H), 1.21 (d, J = 6.9 Hz, 4H)	
178	++		1H NMR (400 MHz, DMSO-d6) δ 10.37 (s, 1H), 8.83 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.80 (s, 1H), 7.41 – 7.54 (m, 2H), 7.27 – 7.41 (m, 5H), 7.13 – 7.22 (m, 1H), 5.12 (s, 2H), 3.84 (s, 3H), 3.45 – 3.60 (m, 3H), 2.59 – 2.79 (m, 2H), 2.35 – 2.46 (m, 2H), 1.42 (d, J = 1.8 Hz, 6H), 1.20 (d, J = 7.0 Hz, 3H)	MS (ESI): mass calcd. for C32H33F2N7O5: 633.25, found: 634.35 [M+H]+
179	+		1H NMR (400 MHz, DMSO-d6) δ 10.47 (s, 1H), 8.92 (d, J = 1.4 Hz, 1H), 8.37 (d, J = 1.4 Hz, 1H), 8.26 (d, J = 6.6 Hz, 1H), 7.39 – 7.57 (m, 3H), 7.36 (dd, J = 6.6, 2.6 Hz, 1H), 7.04 – 7.13 (m, 1H), 5.68 (t, J = 5.8 Hz, 1H), 4.57 (d, J = 5.8 Hz, 2H), 3.55 (p, J = 6.8 Hz, 1H), 2.68 – 2.76 (m, 1H), 2.58 – 2.66 (m, 1H), 2.47 (d, J = 2.3 Hz, 4H), 1.46 (d, J = 2.8 Hz, 6H), 1.18 – 1.26 (m, 3H)	MS (ESI): mass calcd. for C26H28F2N6O5 542.21 m/z, found 543.30 [M+H]+
180	++		1H NMR (400 MHz, DMSO-d6) δ 10.47 (s, 1H), 8.92 (d, J = 1.4 Hz, 1H), 8.37 (d, J = 1.4 Hz, 1H), 8.26 (d, J = 6.6 Hz, 1H), 7.40 – 7.56 (m, 3H), 7.36 (dd, J = 6.6, 2.6 Hz, 1H), 7.08 (dtd, J = 8.9, 3.3, 1.8 Hz, 1H), 5.68 (t, J = 5.7 Hz, 1H), 4.57 (d, J = 5.8 Hz, 2H), 3.55 (p, J = 6.9 Hz, 1H), 2.58 – 2.76 (m, 2H), 2.47 (d, J = 2.3 Hz, 4H),	MS (ESI): mass calcd. for C26H28F2N6O5 542.21 m/z, found 543.30 [M+H]+

			1.46 (d, J = 2.8 Hz, 6H), 1.18 – 1.26 (m, 3H)	
181	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.25 (s, 1H), 8.31 (dd, J = 7.8, 2.7 Hz, 1H), 8.26 (d, J = 2.9 Hz, 1H), 8.26 – 8.24 (m, 3H), 8.14 (d, J = 2.7 Hz, 1H), 7.72 (dd, J = 9.0, 2.9 Hz, 1H), 7.40 – 7.47 (m, 2H), 3.53 (d, J = 7.0 Hz, 1H), 3.37 (m, 2H), 2.73 (dt, J = 10.5, 5.0 Hz, 2H), 2.47 (d, J = 4.2 Hz, 2H), 1.47 (d, J = 3.8 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C25H26ClFN6O4: 528.17 m/z, found 529.25 [M+H]+
182	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.47 (s, 1H), 9.26 (s, 1H), 8.86 (d, J = 1.5 Hz, 1H), 8.75 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.79 (d, J = 9.4 Hz, 1H), 7.42 – 7.55 (m, 2H), 7.37 (dd, J = 9.5, 1.6 Hz, 1H), 7.13 – 7.23 (m, 1H), 3.52 – 3.62 (m, 1H), 3.41 (d, J = 10.9 Hz, 2H), 2.59 – 2.80 (m, 2H), 2.44 – 2.50 (m, 2H), 1.47 (d, J = 4.4 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C26H26F2N8O3:536.21m/z, found:537.30[M+H]+
183	++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.16 (s, 1H), 8.13 (dd, J = 6.0, 2.9 Hz, 2H), 7.52 (dd, J = 9.1, 2.9 Hz, 1H), 7.30 – 7.16 (m, 2H), 7.03 – 7.15 (m, 2H), 3.42 (s, 3H), 2.86 - 3.15 (m, 5H), 2.72 (d, J = 11.9 Hz, 2H), 2.33 (s, 2H), 1.85 – 2.04 (m, 4H), 1.36 (d, J = 2.8 Hz, 6H), 1.19 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C26H34FN5O4S: 531.65 m/z, found 532.25[M+H] +
184	++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.15 (s, 1H), 8.13 (dd, J = 6.1, 2.9 Hz, 2H), 7.52 (dd, J = 9.1, 2.9 Hz, 1H), 7.16 – 7.29 (m, 2H), 7.03 – 7.14 (m, 2H), 3.80 – 3.85(m,1H), 3.00 (d, J = 6.8 Hz, 2H), 2.86 - 3.15 (m, 5H), 2.72 (d, J = 11.9	MS (ESI): mass calcd. for C26H34FN5O4S: 531.65 m/z, found 532.25[M+H] +

			Hz, 2H), 2.33 (s, 2H), 1.90 (d, J = 5.3 Hz, 4H), 1.36 (d, J = 2.6 Hz,6H), 1.15 – 1.26 (m, 3H)	
185	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.42 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.03 (d, J = 1.1 Hz, 1H), 7.94 (d, J = 1.0 Hz, 1H), 7.41 – 7.55 (m, 2H), 7.18 – 7.23 (m, 1H), 5.45 – 5.51 (m, 1H), 4.76 – 4.87 (m, 4H), 3.49 – 3.52 (m, 1H), 3.44 – 3.47 (m, 2H), 2.68 – 2.77 (m, 2H), 2.42 – 2.48 (m, 2H), 1.47 (d, J = 3.0 Hz, 6H), 1.17 – 1.26 (m, 3H)	MS (ESI): mass calcd. for C27H29F2N7O5:569.17 m/z, found:570.20 [M+H]+
186	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.45 (s, 1H), 8.85 (d, J = 1.5 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.23 (d, J = 6.6 Hz, 1H), 7.55 (d, J = 2.6 Hz, 1H), 7.41 – 7.54 (m, 2H), 7.35 (dd, J = 6.6, 2.6 Hz, 1H), 7.13 – 7.23 (m, 1H), 5.68 (d, J = 4.9 Hz, 1H), 5.00 – 5.10 (m, 1H), 3.55 (q, J = 6.8 Hz, 1H), 3.36 – 3.42 (m, 2H), 2.60 – 2.76 (m, 2H), 2.46 (s, 2H), 1.46 (s, 6H), 1.35 (d, J = 6.3 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C27H30F2N6O5: 556.22, found: 557.35 [M+H]+
187	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.45 (s, 1H), 8.85 (d, J = 1.5 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.23 (d, J = 6.6 Hz, 1H), 7.55 (d, J = 2.6 Hz, 1H), 7.41 – 7.54 (m, 2H), 7.35 (dd, J = 6.6, 2.6 Hz, 1H), 7.13 – 7.23 (m, 1H), 5.68 (d, J = 4.9 Hz, 1H), 5.00 – 5.10 (m, 1H), 3.55 (q, J = 6.8 Hz, 1H), 3.36 – 3.42 (m, 2H), 2.60 – 2.76 (m, 2H), 2.46 (s, 2H), 1.46 (s, 6H), 1.35 (d, J = 6.3 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C27H30F2N6O5: 556.22, found: 557.35 [M+H]+
188	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.45 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.43	MS (ESI): mass calcd. for C28H32F2N6O5:570.24 m/z, found:571.25 [M+H]+

			– 8.48 (m, 1H), 8.22 – 8.29 (m, 1H), 7.62 – 7.67 (m, 1H), 7.55 – 7.42 (m, 2H), 7.35 – 7.42 (m, 1H), 7.13 – 7.23 (m, 1H), 6.46 (s, 1H), 3.50 – 3.59 (m, 1H), 2.59 – 2.76 (m, 2H), 2.41 – 2.49 (m, 4H), 1.58 (s, 6H), 1.44 – 1.49 (m, 6H), 1.21 (d, J = 6.9 Hz, 3H)	
189	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.44 (s, 1H), 9.39 (d, J = 1.5 Hz, 1H), 9.31 (d, J = 1.4 Hz, 1H), 8.81 – 8.88 (m, 2H), 8.46 (d, J = 1.5 Hz, 1H), 7.41 – 7.54 (m, 2H), 7.12 – 7.22 (m, 1H), 3.49 – 3.59 (m, 1H), 3.45 (t, J = 5.3 Hz, 2H), 2.56 – 2.77 (m, 2H), 2.46 (d, J = 11.8 Hz, 2H), 1.51 (d, J = 3.2 Hz, 6H), 1.21 (d, J = 7.0 Hz, 3H)	MS (ESI): mass calcd. for C25H25F2N9O3:537.20m/z, found:538.30[M+H]+
190	+++		1H NMR (300 MHz, Methanol-d4) δ 8.99 (s, 1H), 8.88 (s, 1H), 8.28 (s, 1H), 7.94 (s, 1H), 7.25 – 7.40 (m, 1H), 7.08 – 7.20 (m, 1H), 6.96 – 7.07 (m, 1H), 4.79 (s, 2H), 4.53 (q, J = 7.0 Hz, 1H), 3.61 – 3.84 (m, 2H), 3.30 (s, 1H), 3.12 – 3.22 (m, 1H), 3.00 – 3.10 (m, 1H), 2.92 (s, 2H), 1.65 (dd, J = 6.1, 3.0 Hz, 6H), 1.50 (d, J = 7.0 Hz, 3H)	MS (ESI): mass calcd. for C25H27F2N7O5: 543.20, found: 544.30 [M+H]+
191	++		1H NMR (300 MHz, Methanol-d4) δ 9.00 (s, 1H), 8.88 (s, 1H), 8.28 (s, 1H), 7.65 (s, 1H), 7.27 – 7.41 (m, 1H), 7.09 – 7.22 (m, 1H), 6.98 – 7.09 (m, 1H), 4.70 (s, 2H), 4.61 (s, 1H), 3.44 – 3.63 (m, 2H), 2.43 – 2.90 (m, 4H), 1.69 (d, J = 4.3 Hz, 6H), 1.24-1.39 (m, 3H)	MS (ESI): mass calcd. for C25H27F2N7O5 543.20, found: 544.30 [M+H]+
192	+++	+++		MS (ESI): mass calcd. for C24H26F2N8O4:528.20 m/z, found:529.25[M+H]+

193	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.40 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 8.34 (d, J = 6.1 Hz, 1H), 8.28 (s, 1H), 7.40 – 7.56 (m, 2H), 7.17 (dd, J = 10.5, 7.3 Hz, 2H), 3.53 (d, J = 6.9 Hz, 1H), 3.35 – 3.39 (m, 2H), 2.62 – 2.72 (m, 1H), 2.53 – 2.59 (m, 2H), 2.48 – 2.52 (m, 1H), 1.53 (s, 6H), 1.21 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C26H26F2N8O4 552.20 m/z, found 553.25 [M+H]+
194	++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.84 (s, 1H), 8.45 (s, 1H), 8.35 (s, 1H), 8.15 (d, J = 6.5 Hz, 1H), 7.48 (tq, J = 9.2, 6.1, 4.5 Hz, 2H), 7.17 (td, J = 8.7, 3.0 Hz, 2H), 3.53 (d, J = 7.0 Hz, 4H), 2.61 – 2.76 (m, 3H), 1.53 (s, 6H), 1.21 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C26H26F2N8O4: 552.20 m/z, found: 553.30[M+H]+
195	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.43 (s, 1H), 8.83 (d, J = 1.4 Hz, 1H), 8.61 (s, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.41 – 7.55 (m, 2H), 7.38 (s, 1H), 7.13 – 7.23 (m, 1H), 5.68 – 5.76 (m, 1H), 4.51 – 4.59 (m, 2H), 3.48 – 3.58 (m, 1H), 3.22 – 3.32 (m, 3H), 2.62 – 2.67 (m, 1H), 2.40 – 2.47 (m, 2H), 1.52 (s, 6H), 1.19 (d, J = 7.0 Hz, 3H)	MS (ESI): mass calcd. for C26H27ClF2N6O5: 576.17 m/z, found: 577.25 [M+H]+
196	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.45 (s, 1H), 9.57 (d, J = 2.3 Hz, 1H), 8.91 (d, J = 2.3 Hz, 1H), 8.86 (d, J = 1.4 Hz, 1H), 8.76 (s, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.2 – 7.55 (m, 2H), 7.13 – 7.23 (m, 1H), 3.49 – 3.61 (m, 1H), 3.46 (t, J = 5.3 Hz, 2H), 2.62 – 2.81 (m, 2H), 2.43 – 2.50 (m, 2H), 1.50 (d, J = 5.0 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C25H25F2N9O3:537.20m/z, found: 538.30[M+H]+

197	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 11.23 – 11.87 (m, 1H), 9.70 – 10.68 (m, 1H), 8.85 (s, 1H), 8.52 (s, 1H), 8.21 – 8.31 (m, 3H), 8.06 – 8.14 (m, 1H), 7.43 – 7.56 (m, 2H), 7.00 – 7.31 (m, 1H), 3.16 – 4.67 (m, 7H), 1.43 – 1.77 (m, 9H)	MS (ESI): mass calcd. for C27H27F2N9O:579.22 m/z, found:580.25 [M+H]+
198	++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.43 (s, 1H), 8.83 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 8.31 (d, J = 6.7 Hz, 1H), 7.41 – 7.56 (m, 2H), 7.38 (d, J = 6.7 Hz, 1H), 7.11 – 7.24 (m, 1H), 5.44 (t, J = 6.2 Hz, 1H), 4.71 – 4.82 (m, 2H), 3.53 (q, J = 6.8 Hz, 1H), 3.18 – 3.30 (m, 2H), 2.63 (s, 2H), 2.45 (s, 2H), 1.51 (s, 6H), 1.19 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C26H27ClF2N6O5: 576.22 m/z, found 577.15 [M+H] +
199	+		1H NMR (400 MHz, DMSO-d6) δ 10.40 (s, 1H), 8.85 (s, 1H), 8.46 (s, 1H), 7.75 (s, 1H), 7.62 (s, 1H), 7.48 (d, J = 9.8, 9.4, 4.3 Hz, 2H), 7.17 (td, J = 8.8, 2.9 Hz, 1H), 7.05 (s, 1H), 3.47 – 3.62 (m, 3H), 2.78 – 2.86 (m, 1H), 2.67 – 2.75 (m, 1H), 2.46 (d, J = 6.7 Hz, 2H), 1.47 (d, J = 2.7 Hz, 6H), 1.23 (d, J = 6.8 Hz, 3H)	MS (ESI): mass calcd. for C27H27F2N9O4 579.22 m/z, found 580.35[M+H]+
200	++		1H NMR (300 MHz, DMSO-d6) δ 12.61 (s, 1H), 10.40 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.5 Hz, 2H), 8.11 (s, 1H), 7.60 (s, 1H), 7.40 – 7.56 (m, 2H), 7.17 (t, J = 8.8 Hz, 1H), 3.64 (s, 2H), 3.53 (d, J = 7.0 Hz, 1H), 2.84 (d, J = 6.4 Hz, 1H), 2.67 – 2.75 (m, 1H), 2.43 – 2.48 (m, 2H), 1 .46 (s, 6H), 1.28(dd, J = 20.2, 6.6 Hz, 3H)	MS (ESI): mass calcd. for C27H27F2N9O4 579.22 m/z, found 580.40[M+H]+
201	+++	+++	1H NMR (300 MHz, DMSO-d6) δ10.47 (s, 1H), 9.69 (d, J = 0.8 Hz, 1H), 8.84	MS (ESI): mass calcd. for C25H25F2N9O3: 537.20, found: 538.25 [M+H]+

			(d, J = 1.4 Hz,1H), 8.41 - 8.50 (m, 2H), 7.37 – 7.56 (m, 3H), 7.12 – 7.24 (m, 1H), 3.49 – 3.62 (m, 1H), 3.45 (s, 2H), 2.65 – 2.75 (m, 1H), 2.54 – 2.64 (m,1H), 2.43 – 2.48 (m, 2H),1.51 (s, 6H), 1.20 (d, J = 6.9 Hz, 3H).19F NMR (282 MHz, DMSO-d6) δ -113.42 (d, J = 5.3 Hz), -124.21 (d, J = 5.3 Hz).	
202	++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.42 (s, 1H), 8.80 (s, 1H), 8.43 (s, 1H), 8.33 (d, J = 4.7 Hz, 1H), 7.37 – 7.57 (m, 3H), 7.08 – 7.22 (m, 1H), 5.37 (t, J = 6.5 Hz, 1H), 4.65 – 4.74 (m, 2H), 3.43 – 3.58 (m, 2H), 3.05 – 3.19 (m, 1H), 2.56 – 2.75 (m, 2H), 2.29 – 2.42 (m, 2H), 1.40 – 1.60 (m, 6H), 1.05 – 1.21 (m, 3H)	MS (ESI): mass calcd. for C25H27F2N7O5: 543.20, found: 544.25 [M+H] +
203	++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.36 (s, 1H), 8.83 (s, 1H), 8.45 (s, 1H), 7.47 (tt, J = 8.7, 4.8 Hz, 2H), 7.34 (s, 1H), 7.17 (s, 1H), 3.81 (s, 3H), 3.59 (d, J = 5.1 Hz, 3H), 2.66 – 2.81 (m, 2H), 2.40 (s, 2H), 1.42 (s, 6H), 1.20 (d, J = 6.8 Hz, 3H).19F NMR (282 MHz, DMSO-d6) δ -113.38 (t, J = 5.2 Hz), -124.19 (t, J = 3.5 Hz)	MS (ESI): mass calcd for C25H27F2N7O5: 543.20 m/z, found: 544.25[M+H]+
204	+		1H NMR (300 MHz, DMSO-d6) δ 10.39 (s, 1H), 8.83 (s, 1H), 8.44 (s, 1H), 7.60 – 8.02 (m, 2H), 7.45 (s, 2H), 7.16 (s, 1H), 6.47 (s, 1H), 3.43 – 3.72 (m, 4H), 2.63 – 2.86 (m, 3H), 1.43 (s, 6H), 1.21 (s, 3H)	MS (ESI): mass calcd. for C27H27F2N9O4:579.22 m/z, found:580.30 [M+H]+
205	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.45 (s, 1H), 9.45 (d, J = 0.7 Hz, 1H), 9.39 (d, J = 1.6 Hz, 1H), 8.86 (dd, J = 3.9, 1.5 Hz, 2H), 8.46 (d, J = 1.4 Hz, 1H), 7.42 -7.55	MS (ESI): mass calcd. for C25H25F2N9O3: 537.20 m/z, found: 538.25 [M+H]+

			(m, 2H), 7.13-7.23 (m, 1H), 3.49-3.59 (m, 1H), 3.45 (t, J = 5.3 Hz, 2H), 2.57-2.76 (m, 2H), 2.41 - 2.50 (m, 2H), 1.49 (d, J = 3.2 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H)	
206	+		1H NMR (300 MHz, DMSO-d6) δ 10.44 (s, 1H), 8.93 – 9.00 (m, 1H), 8.86 (d, J = 1.4 Hz, 1H), 8.55 (s, 1H), 8.46 (d, J = 1.5 Hz, 1H), 7.57 – 7.65 (m, 1H), 7.40 – 7.55 (m, 2H), 7.11 – 7.24 (m, 1H), 5.65 (t, J = 5.7 Hz, 1H), 4.86 (d, J = 5.7 Hz, 2H), 3.55 (q, J = 6.8 Hz, 1H), 3.36-3.45 (m, 2H), 2.69 – 2.79 (m, 1H),2.59 – 2.69 (m, 1H), 2.42 – 2.55 (m, 2H), 1.50 (d, J = 2.2 Hz, 6H), 1.22 (d, J = 6.8 Hz, 3H)	MS (ESI): mass calcd. for C27H28F2N8O4: 566.22 m/z, found: 567.25 [M+H]+
207	++		1H NMR (300 MHz, DMSO-d6) δ 10.38 (s, 1H), 8.83 (d, J = 1.4 Hz, 1H), 8.43 (d, J = 1.4 Hz, 1H), 7.64 (s, 1H), 7.38 – 7.54 (m, 2H), 7.09 – 7.22 (m, 1H), 4.42 (s, 2H), 3.43 – 3.64 (m, 4H), 2.68 – 2.80 (m, 1H), 2.55 – 2.68 (m, 2H), 2.40 (s, 2H), 1.42 (d, J = 1.6 Hz, 6H), 1.19 (d, J = 6.8 Hz, 3H)	MS (ESI): mass calcd. for C25H27F2N7O5: 543.20, found: 544.25 [M+H]+
208	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.43 (s, 1H), 8.84 (d, J = 1.5 Hz, 1H), 8.45 (d, J = 1.5 Hz, 1H), 8.29 (d, J = 6.7 Hz, 1H), 7.47 (pd, J = 10.1, 9.0, 4.3 Hz, 3H), 7.37 (dd, J = 6.6, 2.5 Hz, 1H), 7.17 (t, J = 8.7 Hz, 1H), 6.48 (s, 1H), 3.49 – 3.56 (m, 1H), 2.57 – 2.74 (m, 3H), 2.45 (d, J = 4.1 Hz, 2H), 1.45 (d, J = 3.3 Hz, 6H), 1.34 – 1.17 (m, 6H), 1.00 (q, J = 5.1 Hz, 2H)	MS (ESI): mass calcd. for C28H30F2N6O5: 568.22m/z, found 569.20 [M+H]+
209	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.42 (s, 1H), 8.84 (s, 1H), 8.57 (s, 1H), 8.45 (s, 1H), 7.78 (d, J = 9.4 Hz, 1H), 7.34 – 7.55 (m,	MS (ESI): mass calcd. for C27H28F2N8O4: 566.22 m/z, found: 567.25[M+H]+

			13H), 7.17 (t, J = 8.2 Hz, 1H), 5.79 (d, J = 5.8 Hz, 1H), 5.01 (d, J = 5.8 Hz, 2H), 3.41 (s, 3H), 2.66 – 2.78 (m, 1H), 2.58 – 2.65 (m, 1H),2.44 – 2.55 (m, 2H), 1.49 (d, J = 2.3 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H)	
210	++		1H NMR (300 MHz, Methanol-d4) δ 9.25 (s, 1H), 8.89 (s, 1H), 8.64 (s, 1H), 8.28 (d, J = 1.5 Hz, 1H), 7.52 (d, J = 1.8 Hz, 1H), 7.34 (td, J = 8.9, 5.5 Hz, 1H), 7.15 (ddd, J = 11.0, 8.5, 2.9 Hz, 1H), 7.04 (t, J = 9.3 Hz, 1H), 5.03 (s, 2H), 3.57 (s, 2H), 3.38 - 3.51 (m, 1H), 2.78 – 2.90 (m, 1H), 2.66 – 2.76 (m, 1H), 2.58 (s, 2H), 1.63 (s, 6H), 1.28 – 1.40 (m, 3H)	MS (ESI): mass calcd. for C27H28F2N8O4: 566.57 m/z, found: 567.25 [M+H]+
211	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.39 (s, 1H), 8.90 (d, J = 1.4 Hz, 1H), 8.33 (d, J = 1.4 Hz, 1H), 7.87 (d, J = 1.2 Hz, 1H), 7.77 (d, J = 1.3 Hz, 1H), 7.25 (td, J = 5.9, 5.3, 3.2 Hz, 4H), 3.43 – 3.56 (m, 3H), 2.68 – 2.78 (m, 1H), 2.56 – 2.65 (m, 1H), 2.49 – 2.34 (m, 2H), 1.43 (d, J = 2.0 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H)	MS (ESI): mass calcd. for C24H26FN7O4 495.20 m/z, found 496.25 [M+H]+
212	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.40 (s, 1H), 8.90 (s, 1H), 8.31 – 8.36 (m, 1H), 7.96 (d, J = 15.9 Hz, 2H), 7.19 – 7.31 (m, 4H), 4.96 (t, J = 5.6 Hz, 1H), 3.98 (t, J = 5.2 Hz, 2H), 3.60 – 3.69 (m, 2H), 3.48 – 3.57 (m, 3H), 2.54 – 2.79 (m, 2H), 2.36 – 2.48 (m, 2H), 1.44 (d, J = 3.0 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C26H30FN7O5: 539.23 m/z, found: 540.10 [M+H]+
213	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.85 (d, J = 1.8 Hz, 2H), 8.45 (d, J = 1.4 Hz, 1H), 7.84 (dd, J = 4.8, 3.3 Hz, 2H), 7.39 –	MS (ESI): mass calcd. for C27H26F2N6O4: 536.20 m/z, found: 537.30[M+H]+

			7.55 (m, 3H), 7.11 – 7.24 (m, 1H), 3.53 (q, J = 6.8 Hz, 1H), 3.32 (s, 2H), 2.71 (dt, J = 10.2, 4.8 Hz, 1H), 2.61 (q, J = 5.9, 5.4 Hz, 1H), 2.47 (d, J = 2.7 Hz, 2H), 1.49 (d, J = 2.3 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H)	
214	+		1H NMR (400 MHz, DMSO-d6) δ 10.43 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.58 – 8.67 (m, 2H), 8.46 (d, J = 1.5 Hz, 1H), 7.78 – 7.85 (m, 1H), 7.41 – 7.54 (m, 3H), 7.12 – 7.22 (m, 1H), 3.48 – 3.58 (m, 1H), 3.30 (t, J = 5.3 Hz, 2H), 2.67 – 2.56 (m, 2H), 2.40 – 2.49 (m, 2H), 1.47 (d, J = 3.6 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H)	MS (ESI): mass calcd. For C25H26F2N6O3:496.20 m/z, found 497.25 [M+H]+
215	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.43 (s, 1H), 9.01 (t, J = 1.3 Hz, 1H), 8.85 (d, J = 1.5 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.78 (dd, J = 9.2, 0.9 Hz, 1H), 7.64 (dd, J = 9.2, 1.7 Hz, 1H), 7.41 – 7.54 (m, 2H), 7.12 – 7.22 (m, 1H), 5.50 (t, J = 6.2 Hz, 1H), 4.65 (d, J = 6.1 Hz, 2H), 3.54 (q, J = 6.9 Hz, 1H), 3.38 (d, J = 10.8 Hz, 2H), 3.30 – 3.31 (m, 1H), 2.74 (dd, J = 11.3, 5.1 Hz, 1H), 2.60 – 2.67 (m, 1H), 2.45 (d, J = 11.6 Hz, 1H), 1.48 (d, J = 4.0 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C27H28F2N8O4: 566.22m/z, found 567.20 [M+H]+
216	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.86 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.28 (s, 1H), 7.61 – 7.70 (m, 2H), 7.40 – 7.56 (m, 2H), 7.27 (dd, J = 8.2, 1.6 Hz, 1H), 7.11 -7.23 (m, 1H), 3.87 (s, 3H), 3.53 (q, J = 6.8 Hz, 1H), 3.36 (s, 1H), 3.33 (s, 1H), 2.77 – 2.67 (m, 1H), 2.66 – 2.56 (m, 1H), 2.47 (s, 2H),	MS (ESI): mass calcd. for C28H29F2N7O3: 549.583 m/z, found: 550.25 [M+H]+

			1.50 (d, J = 1.9 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H)	
217	+		1H NMR (300 MHz, DMSO-d6) δ 10.43 (s, 1H), 8.84 (d, J = 1.5 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.19 – 8.30 (m, 2H), 7.48 (ddd, J = 18.3, 9.4, 4.6 Hz, 3H), 7.31 (d, J = 7.8 Hz, 1H), 7.18 (t, J = 8.8 Hz, 1H), 3.54 (d, J = 7.0 Hz, 1H), 3.28 – 3.33 (m, 2H), 2.69 (d, J = 5.1 Hz, 1H), 2.55 – 2.64 (m, 1H), 2.45 (d, J = 4.1 Hz, 2H), 1.46 (d, J = 2.8 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H)	MS (ESI): mass calcd. for C25H26F2N6O4 512.20 m/z, found 513.25 [M+H]+
218	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.44 (s, 1H), 9.00 (d, J = 7.0, 0.9 Hz, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.58 (s, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.86 (t, J = 1.3 Hz, 1H), 7.41 – 7.54 (m, 2H), 7.13 – 7.23 (m, 2H), 3.49 – 3.59 (m, 1H), 2.56 – 2.76 (m, 2H), 2.42 – 2.51 (m, 4H), 1.50 (d, J = 3.7 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. forC26H26F2N8O3:536.21m/z, found:537.30[M+H]+
219	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.42 (s, 1H), 9.49 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.28 (d, J = 1.6 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.57 (dd, J = 8.4, 1.7 Hz, 1H), 7.35 – 7.41 (m, 2H), 7.11 – 7.24 (m, 1H), 3.54 (d, J = 7.0 Hz, 1H), 3.33 – 3.38 (m, 2H), 2.67 – 2.81 (m, 1H), 2.57 – 2.66 (m, 1H), 2.46 – 2.49 (m, 2H), 1.50 (d, J = 2.3 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H). 19F NMR (282 MHz, DMSO-d6) δ -113.43 (d, J = 5.2 Hz), -124.22 (d, J = 5.3 Hz)	MS (ESI): mass calcd. for C27H26F2N6O3S: 552.17, found: 553.25 [M+H]+
220	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.40 s, 1H), 8.82 – 8.88 (m, 1H), 8.44 (d, J = 1.4 Hz, 1H), 8.05 (d, J =	MS (ESI): mass calcd. for C27H28F2N8O3: 550.23m/z, found: 551.30[M+H]+

			8.6 Hz, 1H), 7.93 (s, 1H), 7.35 – 7.53 (m, 3H), 7.10 – 7.23 (m, 1H), 4.34 (s, 3H), 3.53 (d, J = 7.0 Hz, 1H), 3.30 (d, J = 5.3 Hz, 2H), 2.55 – 2.78 (m, 2H), 2.49 (s, 2H), 1.48 – 1.55 (m, 6H), 1.21 (d, J = 6.8 Hz, 3H)	
221	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.39 (s, 1H), 8.83 (d, J = 1.4 Hz, 1H), 8.44 (d, J = 1.5 Hz, 1H), 7.47 (dtd, J = 11.1, 8.9, 7.9, 4.3 Hz, 2H), 7.17 (s, 1H), 6.13 (s, 2H), 3.46 – 3.55 (m, 3H), 3.01 - 3.10 (m, 5H), 2.66 – 2.76(m, 1H), 2.57 – 2.65 (m, 1H), 2.33 (s, 2H), 1.34 (d, J = 1.6 Hz, 6H), 1.19 (d, J = 6.8 Hz, 3H)	MS (ESI): mass calcd. for C24H29F2N7O4: 517.22m/z, found 518.25 [M+H]+
222	+		1H NMR (300 MHz, DMSO-d6) δ 11.25 (s, 1H), 10.32 – 10.44 (m, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.39 – 7.55 (m, 2H), 7.12 – 7.25 (m, 1H), 6.80 (s, 1H), 4.87 (t, J = 5.8 Hz, 1H), 3.78 (d, J = 5.6 Hz, 2H), 3.48 – 3.65 (m, 5H), 2.70 – 2.81 (m, 1H), 2.59 – 2.71 (m, 1H), 2.33 – 2.49 (m, 2H), 1.39 (d, J = 4.1 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H)	MS (ESI): mass calcd. for C26H29F2N7O6:573.21m/z, found:574.25[M+H]+
223	+++		1H NMR (300 MHz, DMSO-d6) δ 10.40 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.89 (d, J = 10.3 Hz, 2H), 7.40 – 7.56 (m, 2H), 7.10 – 7.24 (m, 1H), 4.28 (s, 2H), 3.47 – 3.57 (m, 3H), 2.76 (d, J = 7.2 Hz, 1H), 2.63 (d, J = 5.8 Hz, 1H), 2.41 (d, J = 3.9 Hz, 2H), 1.44 (d, J = 2.0 Hz, 6H), 1.17-1.27 (m, 3H)	MS (ESI): mass calcd. for C26H27F2N7O6: 571.15, found: 572.20 [M+H]+
224	++	+++	1H NMR (400 MHz, DMSO-d6) δ 12.36 (s, 1H), 10.38 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz,	MS (ESI): mass calcd. for C25H27F2N7O4 527.53 m/z, found 528.25[M+H]+.

			1H), 7.56 (s, 1H), 7.41 – 7.53 (m, 2H), 7.12 – 7.22 (m, 1H), 3.51 (d, J = 6.0 Hz, 3H), 2.70 – 2.77 (m, 1H), 2.59 – 2.68 (m, 1H), 2.41 (s, 2H), 2.26 (s, 3H), 1.40 – 1.45 (m, 6H), 1.21 (d, J = 6.9 Hz, 3H).	
225	+		1H NMR (300 MHz, DMSO-d6) δ 10.39 (s, 1H), 8.84 (s, 1H), 8.45 (s, 1H), 8.15 (s, 1H), 7.48 (ddt, J = 14.9, 9.3, 4.6 Hz, 2H), 7.17 (td, J = 8.5, 2.9 Hz, 1H), 3.48 – 3.57 (m, 2H), 3.17 (s, 1H), 2.69 – 2.79 (m, 1H), 2.64 (q, J = 5.2 Hz, 1H), 2.41 (s, 2H), 1.43 (s, 6H), 1.20 (d, J = 6.7 Hz, 3H)	MS (ESI): mass calcd. for C25H24F5N7O4: 581.18m/z, found: 582.25[M+H]+
226	++		1H NMR (400 MHz, DMSO-d6) δ 10.43 (s, 1H), 9.14 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.61 (d, J = 1.8 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.33 (d, J = 1.8 Hz, 1H), 7.48 (dtd, J = 14.5, 9.3, 4.3 Hz, 2H), 7.17 (ddd, J = 10.6, 8.3, 2.3 Hz, 1H), 3.54 (q, J = 6.8 Hz, 1H), 3.28 – 3.40 (m,3H), 3.17 (d, J = 5.2 Hz, 1H), 2.57 – 2.78 (m, 2H), 1.50 (d, J = 3.9 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C26H25F2N7O4: 537.19 m/z, found: 538.25 [M+H] +
227	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.42 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.09 (d, J = 6.5 Hz, 1H), 7.41 – 7.55 (m, 2H), 7.26 (d, J = 6.5 Hz, 1H), 7.18 (s, 1H), 5.47 (d, J = 5.0 Hz, 1H), 5.21 (s, 1H), 3.49 – 3.57 (m, 1H), 3.25 (s, 2H), 3.01 (s, 1H), 2.72 – 2.82 (m, 1H), 2.55 – 2.71(m, 2H), 2.44 (d, J = 4.8 Hz, 2H), 2.26 – 2.34 (m, 1H), 1.89 (s, 1H), 1.47 (t, J = 1.8 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C27H30F2N6O5: 556.22, found: 557.35 [M+H]+
228	+	+	1H NMR (300 MHz, DMSO-d6) δ 10.40 (s, 1H), 8.84 (d, J =1.4 Hz, 1H), 8.45	MS (ESI): mass calcd. for C26H30F2N8O3: 540.24 m/z, found 541.25 [M+H]+

			(d, J = 1.4 Hz, 1H), 7.83 (s, 1H), 7.39 – 7.50 (m, 2H), 7.10 – 7.24 (m, 1H), 4.02 – 4.22 (m, 2H), 3.40 – 3.63 (m, 4H), 2.69 – 2.96 (m, 3H), 2.55 – 2.65 (m, 1H), 2.29 – 2.47 (m, 2H), 2.00 – 2.11 (m, 1H), 1.80 – 1.98 (m, 1H), 1.38 (s, 6H), 1.16 – 1.27 (m, 3H).	
229	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.40 (s, 1H), 8.81 – 8.88 (m, 1H), 8.42 – 8.49 (m, 1H), 7.83 (d, J = 2.0 Hz, 1H), 7.39 – 7.56 (m, 2H), 7.11 – 7.24 (m, 1H), 4.02 – 4.22 (m, 2H), 3.41 – 3.63 (m, 4H), 2.66 – 2.94 (m, 4H), 2.31 – 2.41 (m, 2H), 2.00 – 2.13 (m, 1H),1.82 – 1.98 (m, 1H), 1.38 (s, 6H), 1.16 – 1.27 (m, 3H).	MS (ESI): mass calcd. for C26H30F2N8O3: 540.24 m/z, found 541.25 [M+H] +.
230	++		1H NMR (300 MHz, DMSO-d6) δ 10.43 (s, 1H), 8.84 (s, 1H), 8.32 – 8.49 (m, 2H), 7.40 – 7.71 (m, 2H), 7.18 (t, J = 8.5 Hz, 1H), 3.89 – 4.18 (m, 2H), 3.50 – 3.61 (m, 4H), 2.72 – 2.89 (m, 3H), 2.58 – 2.62 (m, 1H), 2.28 – 2.44 (m, 2H), 1.99 – 2.09 (m, 1H), 1.74 – 1.93 (m, 1H), 1.37 (s, 6H), 1.21 (d, J = 6.6 Hz, 3H).	MS (ESI): mass calcd. for C26H30F2N8O3: 540.24m/z, found: 541.30[M+H]+.
231	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.43 (s, 1H), 8.84 (s, 1H), 8.32 – 8.49 (m, 2H), 7.40 – 7.71 (m, 2H), 7.18 (t, J = 8.5 Hz, 1H), 3.89 – 4.18 (m, 2H), 3.50 – 3.61 (m, 4H), 2.72 – 2.89 (m, 3H), 2.58 – 2.62 (m, 1H), 2.28 – 2.44 (m, 2H), 1.99 – 2.09 (m, 1H), 1.74 – 1.93 (m, 1H), 1.37 (s, 6H), 1.21 (d, J = 6.6 Hz, 3H).	MS (ESI): mass calcd. For C26H30F2N8O3: 540.24 m/z, found: 541.30 [M+H]+.
232	++		1H NMR (300 MHz, DMSO-d6) δ 12.60 (s, 1H), 10.40 (s, 1H), 8.85 (d, J = 1.5 Hz, 1H), 8.45 (d, J = 1.4 Hz,	MS (ESI): mass calcd. for C27H27F2N7O3: 535.21 m/z, found: 536.30 [M+H]+

			1H), 8.31 (s, 1H), 7.57 - 7.73 (m, 2H), 7.39 - 7.55 (m, 2H), 7.29 (s, 1H), 7.10 - 7.24 (m, 1H), 3.53 (d, J = 7.0 Hz, 1H), 3.32 (s, 2H),2.71 (d, J = 5.2 Hz, 1H), 2.56 – 2.66 (m, 1H), 2.46 (d, J = 2.1 Hz, 2H), 1.48 (d, J = 1.8 Hz, 6H), 1.22 (d, J = 6.9 Hz, 3H).	
233	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.43 (s, 1H), 8.84 (d, J = 1.5 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.19 – 8.30 (m, 2H), 7.48 (ddd, J = 18.3, 9.4, 4.6 Hz, 3H), 7.31 (d, J = 7.8 Hz, 1H), 7.18 (t, J = 8.8 Hz, 1H), 3.54 (d, J = 7.0 Hz, 1H), 3.28 – 3.33 (m, 2H), 2.69 (d, J = 5.1 Hz, 1H), 2.55 – 2.64 (m, 1H), 2.45 (d, J = 4.1 Hz, 2H), 1.46 (d, J = 2.8 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C27H32F2N8O4 570.25 m/z, found 571.35 [M+H]+.
234	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.40 (s, 1H), 8.84 (d, J = 1.5 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.39 - 7.55 (m, 2H), 7.33 (d, J = 1.8 Hz, 1H), 7.10 - 7.24 (m, 1H), 5.98 (d, J = 1.8 Hz, 1H), 3.95 – 4.20 (m, 2H), 3.45 - 3.60 (m, 3H), 3.10 – 3.22 (m, 1H), 2.81 – 2.94 (m, 1H), 2.59 – 2.80 (m, 3H), 2.36 (d, J = 2.3 Hz, 2H), 2.04 (s, 1H), 1.83 – 2.02 (m, 1H), 1.35 – 1.42 (m, 6H), 1.20 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C27H31F2N7O3: 539.25 m/z, found: 540.20 [M+H]+.
235	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.84 (d, J = 1.5 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.39 – 7.56 (m, 3H), 7.17 (t, J = 8.3 Hz, 1H), 4.20 – 4.42 (m, 2H), 3.55 (s, 4H), 2.89 (d, J = 5.2 Hz, 1H), 2.74 – 2.85 (m, 2H), 2.64 (s, 1H), 2.36 (s, 2H), 2.11 (d, J = 13.5 Hz, 1H), 1.98 (s, 1H), 1.38 (d, J	MS (ESI): mass calcd. for C26H30F2N8O3: 540.24 m/z, found: 541.30 [M+H]+

			= 2.2 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H).	
236	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.40 (s, 1H), 8.82 (s, 1H), 8.43 (s, 1H), 7.47 (s, 2H), 7.16 (s, 1H), 6.96 (s, 1H), 6.76 (s, 1H), 4.01 (d, J = 10.7 Hz, 1H), 3.88 (t, J = 10.9 Hz, 1H), 3.53 (s, 3H), 3.14 – 3.28 (m, 1H), 2.73 (s, 4H), 2.34 (s, 2H), 1.98 (s, 1H), 1.78 (s, 1H), 1.36 (s, 6H), 1.19 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C27H31F2N7O3: 539.25, found: 540.30 [M+H]+.
237	+		1H NMR (300 MHz, DMSO-d6) δ 10.44 (s, 1H), 9.56 (d, J = 2.3 Hz, 1H), 8.88 (dd, J = 15.4, 1.8 Hz, 2H), 8.76 (s, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.39 – 7.56 (m, 2H), 7.11 – 7.24 (m, 1H), 3.51 – 3.61 (m, 1H), 3.40 – 3.50 (m, 2H), 2.60 – 2.80 (m, 2H), 2.38 – 2.47 (m, 1H), 1.96 – 2.07 (m, 1H), 1.50 (d, J = 3.5 Hz, 6H), 1.21 (s, 3H).	MS (ESI): mass calcd. for C25H25F2N9O3: 537.20, found: 538.25 [M+H]+
238	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.44 (s, 1H), 9.56 (d, J = 2.3 Hz, 1H), 8.88 (dd, J = 15.3, 1.9 Hz, 2H), 8.76 (s, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.40 – 7.56 (m, 2H), 7.11 – 7.24 (m, 1H), 3.56 (q, J = 7.0 Hz, 1H), 3.42 – 3.50 (m, 2H), 2.72 – 2.82 (m, 1H), 2.61 – 2.71 (m, 1H), 2.52 – 2.57 (m, 1H), 2.41 – 2.49 (m, 1H), 1.50 (d, J = 3.5 Hz, 6H), 1.22 (d, J = 7.0 Hz, 3H).	MS (ESI): mass calcd. for C25H25F2N9O3: 537.20, found: 538.25 [M+H]+
239	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 8.82 (s, 1H), 8.44 (s, 1H), 7.37 – 7.53 (m, 3H), 7.16 (t, J = 8.5 Hz, 1H),3.50 – 3.65 (m, 3H) 2.96 (d, J = 15.0 Hz, 1H), 2.61 – 2.75 (m, 2H), 2.50 (s, 4H),2.34 (s, 2H), 1.88 (d, J = 13.0 Hz, 1H), 1.63 (t, J =	MS (ESI): mass calcd. for C27H31F2N7O3: 539.25 m/z, found: 540.30 [M+H]+

			11.3 Hz, 1H), 1.38 (s, 6H), 1.19 (d, J = 6.8 Hz, 3H).	
240	+		1H NMR (300 MHz, DMSO-d6) δ 8.82 (s, 1H), 8.43 (d, J = 1.5 Hz, 1H), 7.43 – 7.53 (m, 2H),7.37 – 7.43 (m, 1H), 7.16 (td, J = 9.5, 9.0, 2.8 Hz, 1H),3.55 – 3.62 (m, 3H), 2.94 (s, 1H), 2.65 – 2.77 (m, 1H), 2.52 – 2.64 (m, 2H),2.51 (s, 3H), 2.34 (d, J = 2.8 Hz, 2H), 1.88 (d, J = 12.8 Hz, 1H), 1.63 (t, J = 10.6 Hz, 1H), 1.38 (s, 6H), 1.19 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C27H31F2N7O3: 539.25 m/z, found: 540.30[M+H]+
241	+++	+++	1HNMR (300 MHz, DMSO-d6) δ 10.40 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.40 – 7.55 (m, 2H), 7.37 (s, 1H), 7.11 – 7.24 (m, 1H), 3.50 – 3.59 (m, 3H), 3.47 (s, 3H), 2.88 – 3.01 (m, 1H), 2.60 – 2.77 (m, 2H), 2.57 (d, J = 7.5 Hz, 2H), 2.42 – 2.47 (m, 2H), 2.36 (s, 2H), 1.82 – 1.94 (m, 1H), 1.53 – 1.69 (m, 1H), 1.39 (d, J = 4.3 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C28H33F2N7O3: 553.26, found: 554.30 [M+H]+.
242	+		1HNMR (300 MHz, DMSO-d6) δ 10.40 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.40 – 7.55 (m, 2H), 7.37 (s, 1H), 7.10-7.24 (m, 1H), 3.49 – 3.59 (m, 3H), 3.47 (s, 3H), 2.88-3.02 (m, 1H), 2.68 – 2.78 (m, 1H), 2.53 – 2.66 (m, 3H), 2.43 – 2.48 (m, 2H), 2.36 (s, 2H), 1.82 – 1.93 (m, 1H), 1.53 – 1.67 (m, 1H), 1.40 (s, 6H), 1.20 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C28H33F2N7O3: 553.26, found: 554.35 [M+H]+.
243	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.43 (s, 1H), 8.84 (d, J = 1.5 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.83 (s, 1H), 7.41 – 7.55 (m, 2H), 7.13 – 7.23 (m, 1H), 4.00 – 4.16 (m, 2H), 3.48 – 3.63 (m, 3H), 2.77 – 2.93 (m, 2H),	MS (ESI): mass calcd. For C26H30F2N8O3: 540.24m/z, found: 541.30[M+H]+

			2.65 – 2.77 (m, 2H), 2.60 – 2.65 (m, 1H), 2.36 (s, 2H), 2.06 – 2.17 (m, 1H), 1.91 – 2.05 (m, 1H), 1.38 (d, J = 4.2 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H).	
244	+		1H NMR (400 MHz, DMSO-d6) δ 10.43 (s, 1H), 8.84 (d, J = 1.5 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.83 (s, 1H), 7.41 – 7.55 (m, 2H), 7.13 – 7.23 (m, 1H), 4.00 – 4.16 (m, 2H), 3.48 – 3.63 (m, 3H), 2.77 – 2.93 (m, 2H), 2.65 – 2.77 (m, 2H), 2.60 – 2.65 (m, 1H), 2.36 (s, 2H), 2.06 – 2.17 (m, 1H), 1.91 – 2.05 (m, 1H), 1.38 (d, J = 4.2 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. For C26H30F2N8O3: 540.24 m/z, found: 541.30 [M+H]+.
245	+		1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.39 – 7.56 (m, 2H), 7.33 (d, J = 1.8 Hz, 1H), 7.11 – 7.24 (m, 1H), 5.98 (d, J = 1.8 Hz, 1H), 3.95 – 4.17 (m, 2H), 3.47 – 3.58 (m, 3H), 3.16 (s, 1H), 2.86 (dd, J = 16.6, 4.8 Hz, 1H), 2.66 – 2.80 (m, 2H), 2.56 – 2.66 (m, 1H), 2.28 – 2.43 (m, 2H), 2.06 (d, J = 13.3 Hz, 1H), 1.91 (s, 1H), 1.38 (d, J = 3.1 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C27H31F2N7O3: 539.25 m/z, found: 540.35 [M+H]+.
246	+++	+++	1H NMR (300 MHz, DMSO-d6-) δ 10.41 (s, 1H), 8.83 (d, J = 1.8 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.39 – 7.55 (m, 2H), 7.33 (d, J = 1.7 Hz, 1H), 7.17 (t, J = 8.3 Hz, 1H), 5.98 (s, 1H), 3.99 – 4.18 (m, 2H), 2.75 – 2.87 (m, 1H), 2.58 – 2.74 (m, 2H), 2.35 (s, 2H), 2.06 (d, J = 13.0 Hz, 1H), 1.91 (s, 1H), 1.38 (s, 6H), 1.20 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C27H31F2N7O3: 539.25 m/z, found: 540.30 [M+H]+.

247	+++	++	1H NMR (300 MHz, DMSO-d6) δ 10.39 (d, J = 2.9 Hz, 2H), 8.83 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.78 (d, J = 0.9 Hz, 1H), 7.40 – 7.56 (m, 2H), 7.11 – 7.24 (m, 1H), 4.54 (d, J = 12.6 Hz, 1H), 3.86 – 3.75 (m, 1H), 3.44 – 3.69 (m, 3H), 2.55 – 2.94 (m, 4H), 2.34 – 2.44 (m, 1H), 2.19 – 2.34 (m, 2H), 1.90 – 2.05 (m, 1H), 1.32 (d, J = 6.6, 3.0 Hz, 3H), 1.11 – 1.27 (m, 9H).	MS (ESI): mass calcd. forC27H32F2N8O3: 554.26 m/z, found: 555.30 [M+H]+.
248	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.91 (s, 1H), 7.39 – 7.56 (m, 2H), 7.11 – 7.24 (m, 1H), 5.79 (dd, J = 6.7, 1.5 Hz, 1H), 4.76 – 4.90 (m, 1H), 4.00 – 4.22 (m, 2H), 3.44 – 3.63 (m, 4H), 2.58 – 2.76 (m, 2H), 2.33 – 2.45 (m, 2H), 2.18 – 2.33 (m, 1H), 1.77 (q, J = 12.0 Hz, 1H), 1.35 – 1.51 (m, 6H), 1.16 – 1.27 (m, 3H).	MS (ESI): mass calcd. for C26H30F2N8O4: 556.24, found: 557.20 [M+H]+.
249	+++		1H NMR (300 MHz, DMSO-d6) δ 10.38 (s, 1H), 8.82 (d, J = 1.4 Hz, 1H), 8.43 (d, J = 1.4 Hz, 1H), 8.12 (s, 1H), 7.46 (qd, J = 8.9, 8.0, 4.3 Hz, 2H), 7.15 (t, J = 8.3 Hz, 1H), 3.51 (s, 4H), 3.08 (s, 1H), 2.56 – 2.77 (m, 5H), 2.33 (s, 2H), 1.89 (d, J = 13.5 Hz, 1H), 1.64 (s, 1H), 1.36 (d, J = 2.7 Hz, 6H), 1.18 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C27H30F2N6O4: 540.23m/z, found: 541.30[M+H]+
250	++	+++	1H NMR (500 MHz, DMSO-d6) δ 8.47 (s, 2H), 7.71 (d, J = 7.3 Hz, 1H), 4.19 (q, J = 6.9 Hz, 1H), 3.90 – 4.09 (m, 1H), 3.39 – 3.70 (m, 3H), 3.25 (d, J = 12.6 Hz, 1H), 1.83 – 2.07 (m, 3H),1.45 – 1.87 (m, 11H), 1.20 – 1.44 (m, 7H).	MS (ESI): mass calcd. for C28H34F2N8O5: 554.26, found: 555.25 [M+H]+.

251	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 11.68 (s, 1H), 10.38 (s, 1H), 8.83 (d, J = 1.5 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.81 (d, J = 10.1, 1H), 7.36 – 7.55 (m, 2H), 7.10 – 7.24 (m, 1H), 5.24 (s, 1H), 5.17 (s, 1H), 4.32 (s, 2H), 3.50 (q, J = 6.8 Hz, 1H), 3.35 – 3.43 (m, 2H), 2.60 – 2.70 (m, 2H), 2.50 – 2.60 (m, 2H), 1.36 (s, 6H), 1.11 – 1.22 (m, 3H).	MS (ESI): mass calcd. for C25H28F2N8O4: 542.22m/z, found: 543.30 [M+H]+.
252	+++		1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.80 – 8.87 (m, 1H), 8.41 – 8.49 (m, 1H), 7.85 – 7.94 (m, 1H), 7.39 – 7.54 (m, 2H), 7.17 (t, J = 8.6 Hz, 1H), 5.75 – 5.84 (m, 1H), 4.75 – 4.90 (m, 1H), 4.00 – 4.22 (m, 2H), 3.45 – 3.63 (m, 4H), 2.71 – 2.79 (m, 1H), 2.58 – 2.66 (m, 1H), 2.29 – 2.45 (m, 2H), 2.18 – 2.29 (m, 1H), 1.77 (q, J = 12.0 Hz, 1H), 1.39 (s, 6H), 1.17 – 1.27 (m, 3H).	MS (ESI): mass calcd. for C26H30F2N8O4: 556.24m/z, found: 557.30 [M+H]+.
253	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.90 (s, 1H), 7.39 – 7.55 (m, 2H), 7.10 – 7.24 (m, 1H), 5.80 (d, J = 6.7 Hz, 1H), 4.77 – 4.90 (m, 1H), 4.01-4.22 (m, 2H), 3.47 – 3.63 (m, 4H), 2.61 – 2.76 (m, 2H), 2.36 (s, 2H), 2.18 – 2.31 (m, 1H), 1.78 (q, J = 11.9 Hz, 1H), 1.39 (d, J = 3.7 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C26H30F2N8O4: 556.24m/z, found: 557.30 [M+H]+
254	+		1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.83 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.5 Hz, 1H), 7.90 (s, 1H), 7.39 – 7.55 (m, 2H), 7.10 – 7.24 (m, 1H), 5.81 (d, J = 6.6 Hz, 1H), 4.76 – 4.90 (m, 1H), 4.00 – 4.22 (m,	MS (ESI): mass calcd. for C26H30F2N8O4: 556.24m/z, found: 557.30 [M+H]+.

			2H), 3.48 – 3.61 (m, 4H), 2.62 – 2.78 (m, 2H), 2.36 (s, 2H), 2.24 (dd, J = 13.1, 6.1 Hz, 1H), 1.78 (q, J = 11.9 Hz, 1H), 1.39 (d, J = 3.6 Hz, 6H), 1.16 – 1.34 (m, 3H).	
255	+		1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.90 (s, 1H), 7.39 – 7.55 (m, 2H), 7.10 – 7.24 (m, 1H), 5.79 (d, J = 6.7 Hz, 1H), 4.76 – 4.90 (m, 2H), 4.00 – 4.22 (m, 2H), 3.45 – 3.62 (m, 4H), 2.71 – 2.81 (m, 1H), 2.57 – 2.67 (m, 1H), 2.31 – 2.45 (m, 2H), 2.17 – 2.29 (m, 1H),1.78 (q, J = 11.9 Hz, 1H), 1.39 (s, 6H), 1.21 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C26H30F2N8O4: 556.24, found: 557.35 [M+H]+
256	+	+	1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.40 – 7.54 (m, 2H), 7.17 (t, J = 8.7 Hz, 1H), 5.42 (t, J = 5.6 Hz, 1H), 4.54 (d, J = 5.7 Hz, 2H), 4.10 (dd, J = 12.5, 5.0 Hz, 1H), 3.85 – 3.99 (m, 1H), 3.48 – 3.59(m, 3H), 2.72 – 2.90 (m, 3H), 2.59 – 2.65 (m, 1H), 2.29 – 2.46 (m, 3H), 1.96 – 2.11(m, 1H), 1.75 – 1.83 (m, 1H), 1.38 (s, 6H), 1.21 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C27H32F2N8O4 570.602m/z, found 571.30 [M+H]+.
257	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.42 (s, 1H), 8.84 (s, 1H), 8.45 (s, 1H), 7.47 (d, J = 10.2 Hz, 2H), 7.19 (d, J = 9.2 Hz, 1H), 5.42 (t, J = 5.6 Hz, 1H), 4.54 (d, J = 5.7 Hz, 2H), 4.10 (d, J = 10.9 Hz, 1H), 3.92 (t, J = 10.9 Hz, 1H), 3.55 (s, 3H), 2.85 (s, 2H), 2.70 (s, 2H), 2.24 – 2.40 (m, 3H), 1.92 – 2.12(m, 1H),1.68 – 1.87 (m, 1H), 1.38 (d, J = 4.0 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H)	MS (ESI): mass calcd. for C27H32F2N8O4 570.602m/z, found 571.30[M+H]+.

258	++		1H NMR (400 MHz, DMSO-d6) δ 10.43 (s, 1H), 9.14 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.61 (d, J = 1.8 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 8.33 (d, J = 1.8 Hz, 1H), 7.48 (dtd, J = 14.5, 9.3, 4.3 Hz, 2H), 7.17 (ddd, J = 10.6, 8.3, 2.3 Hz, 1H), 3.54 (q, J = 6.8 Hz, 1H), 3.28 – 3.40 (m,3H), 3.17 (d, J = 5.2 Hz, 1H), 2.57 – 2.78 (m, 2H), 1.50 (d, J = 3.9 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C26H25F2N7O4: 537.19 m/z, found: 538.25 [M+H] +
259	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.42(s, 1H), 8.84(s, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.87 – 7.95 (m, 1H), 7.39 – 7.56 (m, 2H), 7.04 – 7.24 (m, 1H), 5.91(dd, J = 5.3, 1.9 Hz, 1H), 4.72 – 4.80 (m, 1H), 4.18 – 4.29 (m, 1H), 3.99 – 4.18 (m, 1H), 3.45 – 3.66 (m, 4H), 2.65 – 2.76(m, 1H), 2.25 – 2.45 (m, 3H), 1.99 – 2.09 (m, 2H), 1.39 (s, 6H), 1.21 – 1.28(m, 3H).	MS (ESI): mass calcd. for C26H30F2N8O4: 556.24 m/z, found: 557.20 [M+H]+.
260	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.39 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.39 – 7.55 (m, 2H), 7.10 – 7.24 (m, 1H), 4.86 (t, J = 5.5 Hz, 1H), 4.30 (t, J = 5.8 Hz, 2H), 3.80 (dd, J = 5.7 Hz, 2H), 3.53 (s, 3H), 2.96 – 3.08 (m, 1H), 2.63 – 2.75 (m, 6H), 2.28 – 2.44 (m, 2H), 1.89 – 2.00 (m, 1H), 1.62 – 1.68 (m, 1H), 1.38 (t, J = 1.9 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. For C28H34F2N8O4: 584.27.19, found: 585.35[M+H]+.
261	++	++	1H NMR (400 MHz, DMSO-d6) δ 12.43 (s, 1H), 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.91 (s, 1H), 7.41 – 7.53 (m, 2H), 7.10 – 7.22 (m, 1H), 4.19 (s, 3H), 3.51 (q, J = 6.9 Hz, 1H), 3.35 – 3.45	MS (ESI): mass calcd. for C26H27F2N9O4: 567.21 m/z, found: 568.25 [M+H]+

			(m, 2H), 2.67 – 2.73 (m, 1H), 2.56 – 2.61 (m, 1H), 2.45 (s, 2H), 1.49 (d, J = 1.9 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H)	
262	++		1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.56 – 7.40 (m, 2H), 7.32 (d, J = 1.8 Hz, 1H), 7.11 – 7.24 (m, 1H), 5.95 (d, J = 2.2 Hz, 2H), 3.99 – 4.10 (m, 2H), 3.88 – 3.97 (m, 2H), 3.45 – 3.58 (m, 1H), 3.13 (d, J = 16.6 Hz, 1H), 2.92 (d, J = 16.6 Hz, 1H), 2.71 – 2.79 (m, 1H), 2.56 – 2.67 (m, 1H), 2.29 – 2.47 (m, 2H), 2.19 – 2.33 (m, 1H), 2.13 (d, J = 14.0 Hz, 1H), 1.37 (d, J = 3.8 Hz, 6H), 1.21 (d, J = 3.6 Hz, 3H).	MS (ESI): mass calcd. for C27H31F2N7O4: 555.24 m/z, found 556.30 [M+H]+
263	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.40 – 7.56 (m, 2H), 7.32 (d, J = 1.8 Hz, 1H), 7.11 – 7.24 (m, 1H), 5.96 (d, J = 1.6 Hz, 2H), 3.99 – 4.11(m, 2H), 3.87 – 3.96 (m, 2H), 3.50 (q, J = 6.8 Hz, 1H), 3.14 (d, J = 16.6 Hz, 1H), 2.92 (d, J = 16.6 Hz, 1H), 2.69 – 2.79 (m, 1H), 2.55 – 2.68 (m, 1H), 2.29 – 2.46 (m, 2H), 2.13 (m, 1H), 1.37 (d, J = 2.3 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C27H31F2N7O4: 555.24 m/z, found 556.30 [M+H]+
264	++		1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.40 – 7.56(m, 2H), 7.32 (d, J = 1.8 Hz, 1H), 7.11 – 7.24 (m, 1H), 5.95 (d, J = 1.7 Hz, 2H), 3.91 – 4.10 (m, 4H), 3.50 (q, J = 6.8 Hz, 1H), 3.13 (d, J = 16.6 Hz, 1H), 2.92 (d, J = 16.6 Hz, 1H), 2.69 – 2.79 (m, 1H), 2.57 – 2.67 (m,	MS (ESI): mass calcd. for C27H31F2N7O4: 555.24 m/z, found 556.30 [M+H]+

			1H), 2.39 (d, J = 2.7 Hz, 2H), 2.08 – 2.30 (m, 1H), 1.37 (d, J = 2.2 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H).	
265	++		1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.56 – 7.40 (m, 2H), 7.32 (d, J = 1.8 Hz, 1H), 7.11 – 7.24 (m, 1H), 5.95 (d, J = 2.2 Hz, 2H), 3.99 – 4.10 (m, 2H), 3.88 – 3.97 (m, 2H), 3.45 – 3.58 (m, 1H), 3.13 (d, J = 16.6 Hz, 1H), 2.92 (d, J = 16.6 Hz, 1H), 2.71 – 2.79 (m, 1H), 2.56 – 2.67 (m, 1H), 2.29 – 2.47 (m, 2H), 2.19 – 2.33 (m, 1H), 2.13 (d, J = 14.0 Hz, 1H), 1.37 (d, J = 3.8 Hz, 6H), 1.21 (d, J = 3.6 Hz, 3H).	MS (ESI): mass calcd. for C27H31F2N7O4: 555.24 m/z, found 556.30 [M+H]+
266	+++	+++	1H NMR (400 MHz, DMSO-d6) δ 10.40 (s, 1H), 8.83 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.88 (s, 1H), 7.41 – 7.53 (m, 2H), 7.12 – 7.22 (m, 1H), 5.92 (d, J = 6.4 Hz, 1H), 4.83 (t, J = 6.6 Hz, 1H), 4.11 – 4.22 (m, 1H), 3.92 – 4.03 (m, 1H), 3.47 – 3.62 (m, 3H), 3.22 – 3.31 (m, 1H), 2.68 – 2.77 (m, 1H), 2.59 – 2.68 (m, 1H), 2.35 (s, 2H), 2.10 – 2.21 (m, 1H), 1.93 – 2.07 (m, 1H), 1.37 (d, J = 10.9 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C26H30F2N8O4: 556.24, found: 557.30 [M+H]+
267	++		1H NMR (400 MHz, DMSO-d6) δ 10.40 (s, 1H), 8.84 (d, J = 1.5 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.88 (s, 1H), 7.41 – 7.53 (m, 2H), 7.12 – 7.22 (m, 1H), 5.92 (d, J = 6.3 Hz, 1H), 4.83 (t, J = 6.6 Hz, 1H), 4.11 – 4.22 (m, 1H), 3.92 – 4.03 (m, 1H), 3.46 – 3.65 (m, 3H), 3.21 – 3.31 (m, 1H), 2.69 – 2.78 (m, 1H), 2.57 – 2.65 (m, 1H), 2.30 – 2.42 (m, 2H), 2.10 –	C26H30F2N8O4: 556.24, found: 557.35 [M+H]+

			2.20 (m, 1H), 1.92 – 2.07 (m, 1H), 1.37 (d, J = 5.5 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H).	
268	++		]+, 1H NMR (400 MHz, DMSO-d6) δ 10.40 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.88 (s, 1H), 7.41-7.54 (m, 2H), 7.12 – 7.22 (m, 1H), 5.91 (d, J = 6.3 Hz, 1H), 4.83 (t, J = 6.6 Hz, 1H), 4.11 – 4.22 (m, 1H), 3.93 – 4.02 (m, 1H), 3.47 – 3.64 (m, 3H), 3.21 – 3.31 (m, 1H), 2.68 – 2.78 (m, 1H), 2.57 – 2.66 (m, 1H), 2.30 – 2.42 (m, 2H), 2.11 – 2.20 (m, 1H), 1.92 – 2.10 (m, 1H), 1.37 (d, J = 5.5 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C26H30F2N8O4: 556.24, found: 557.30 [M+H]+
269	+		1H NMR (400 MHz, DMSO-d6) δ 10.40 (s, 1H), 8.83 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.88 (s, 1H), 7.41 – 7.53 (m, 2H), 7.12 – 7.22 (m, 1H), 5.92 (d, J = 6.3 Hz, 1H), 4.83 (t, J = 6.6 Hz, 1H), 4.11 – 4.23 (m, 1H), 3.92 – 4.04 (m, 1H), 3.46 – 3.63 (m, 3H), 3.22 – 3.31 (m, 1H), 2.58 – 2.77 (m, 2H), 2.28 – 2.41 (s, 2H), 2.10 – 2.22 (m, 1H), 1.93 – 2.10 (m, 1H), 1.37 (d, J = 10.9 Hz, 6H), 1.20 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C26H30F2N8O4: 556.24, found: 557.35 [M+H]+
270	++		1H NMR (300 MHz, DMSO-d6) δ 10.40 (s, 1H), 8.85 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.5 Hz, 1H), 8.22 (s, 1H), 8.09 (s, 1H), 7.40 – 7.52 (m, 2H), 7.10 – 7.21 (m, 3H), 3.91 (s, 3H), 3.52 – 3.61 (m, 1H), 3.41 – 3.49 (m, 2H), 2.73 – 2.82 (m, 2H), 2.45 – 2.52 (m, 2H), 1.48 (d, J = 1.9 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C27H29F2N9O3: 565.24 m/z, found: 566.15 [M+H]+
271	++		1H NMR (400 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.46	MS (ESI): mass calcd. for C27H31F2N7O4: 555.24, found: 556.35 [M+H]+

			(d, J = 1.5 Hz, 1H), 7.41 – 7.54 (m, 2H), 7.12 – 7.22 (m, 1H), 6.94 (d, J = 1.3 Hz, 1H), 6.77 (d, J = 1.2 Hz, 1H), 6.08 (s, 1H), 4.25 (d, J = 13.0 Hz, 1H), 4.01 – 4.11 (m, 1H), 3.92 (d, J = 13.0 Hz, 1H), 3.78 – 3.87 (m, 1H), 3.42 – 3.69 (m, 1H), 2.71 – 2.86 (m, 2H), 2.56 – 2.72 (m, 2H), 2.33 – 2.46 (m, 2H), 2.03 – 2.15 (s, 2H), 1.36 (d, J = 11.0 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H).	
272	+		1H NMR (400 MHz, DMSO-d6) δ 10.42 (s, 1H), 8.84 (s, 1H), 8.46 (d, J = 1.5 Hz, 1H), 7.41 – 7.54 (m, 2H), 7.12 – 7.22 (m, 1H), 6.94 (d, J = 1.4 Hz, 1H), 6.77 (d, J = 1.3 Hz, 1H), 6.09 (d, J = 2.0 Hz, 1H), 4.24 (d, J = 12.9 Hz, 1H), 3.82 – 4.07 (m, 3H), 3.42 – 3.69 (m, 1H), 2.61 – 2.86 (m, 4H), 2.39 (s, 2H), 2.04 – 2.13 (m, 2H), 1.36 (d, J = 2.8 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H)	MS (ESI): mass calcd. for C27H31F2N7O4: 555.24, found: 556.35 [M+H]+
273	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.39 – 7.56 (m, 2H), 7.28 (s, 1H), 7.11 – 7.24 (m, 1H), 4.61 (t, J = 5.3 Hz, 1H), 4.27 (d, J = 5.4 Hz, 2H), 3.93 – 4.16 (m, 2H), 3.46 – 3.59 (m, 3H), 3.05 – 3.21 (m, 1H), 2.80 – 2.96 (m, 1H), 2.50 – 2.71 (m, 3H), 2.37 (s, 2H), 2.00 – 2.11 (m, 1H), 1.86 – 2.00 (m, 1H), 1.40 (d, J = 1.7 Hz, 6H), 1.26 (d, J = 7.0 Hz, 3H).	MS (ESI): mass calcd. for C28H33F2N7O4: 569.26 m/z, found 592.30 [M+Na]+
274	+++		1H NMR (300 MHz, DMSO-d6) δ 10.50 (br, 1H), 10.39 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.40 – 7.56 (m, 2H), 7.11 – 7.24 (m, 1H), 6.82 (s, 1H), 3.46 – 3.46 (m, 3H),	MS (ESI): mass calcd. for C24H27F2N7O4: 515.21 m/z, found: 516.30 [M+H]+

			3.12 (s, 3H), 2.70 – 2.80 (m, 1H), 2.59 – 2.69 (m, 1H), 2.39 (s, 2H), 1.40 (d, J = 2.3 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H).	
275	++		1H NMR (300 MHz, DMSO-d6) δ 10.40 (s, 1H), 8.83 (d, J = 1.5 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 8.31 (s, 1H), 7.59 – 7.69 (m, 3H), 7.38 – 7.51 (m, 3H), 7.12 – 7.23 (m, 1H), 4.91 (t, J = 6.5 Hz, 1H), 3.49 – 3.55 (m, 1H), 3.39 – 3.46 (m, 2H), 2.82 – 2.94 (m, 1H), 2.59 – 2.69 (m, 3H), 2.25 – 2.40 (m, 2H), 1.46 (d, J = 1.8 Hz, 6H), 1.18 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C29H30F2N6O4: 564.17 m/z, found: 565.15 [M+H]+
276	+		1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.41 – 7.55 (m, 2H), 7.13 – 7.23 (m, 1H), 5.14 (t, J = 6.0 Hz, 1H), 4.35 (d, J = 5.9 Hz, 2H), 3.95 – 4.12 (m, 2H), 3.47 – 3.57 (m, 3H), 2.83 (d, J = 6.9 Hz, 2H), 2.72 – 2.80 (m, 1H), 2.59 – 2.64 (m, 1H), 2.54 – 2.57 (m, 1H), 2.30 – 2.43 (m, 2H), 2.06 – 2.15 (m, 1H), 1.89 – 2.03 (m, 1H), 1.38 (d, J = 4.6 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. forC27H32F2N8O4: 570.25 m/z, found:571.30 [M+H]+
277	+++		1H NMR (300 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.41 – 7.54 (m, 2H), 7.12 – 7.22 (m, 1H), 5.13 (t, J = 6.0 Hz, 1H), 4.34 (d, J = 5.9 Hz, 2H), 3.95 – 4.13 (m, 2H), 3.48 – 3.62 (m, 3H), 2.83 (d, J = 6.9 Hz, 2H), 2.62 – 2.74 (m, 2H), 2.53 – 2.60 (m, 1H), 2.35 (s, 2H), 2.06 – 2.15 (m, 1H), 1.86 – 2.03 (m, 1H), 1.38 (d, J = 4.6 Hz, 6H), 1.20 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. forC27H32F2N8O4: 570.25 m/z, found:571.30 [M+H]+

278	+++	+++	1H NMR (500 MHz, DMSO-d6) δ 10.43 (s, 1H), 8.84 (s, 1H), 8.46 (s, 1H), 7.42 – 7.53 (m, 2H), 7.14 – 7.22 (m, 1H), 4.98 (t, J = 5.7 Hz, 1H), 4.47 (d, J = 5.2 Hz, 2H), 4.32 – 4.42 (m,1H), 4.19 – 4.29 (m,1H), 3.49 – 3.59 (m, 3H), 3.19 – 3.27 (m, 1H), 2.85 – 2.98 (m, 1H), 2.68 – 2.80 (m, 2H), 2.59 – 2.67 (m,1H), 2.35 (s, 2H), 2.06 – 2.12 (m, 1H), 1.87 – 1.98 (m, 1H), 1.39 (d, J = 2.5 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C27H32F2N8O4: 570.25 m/z, found: 571.30 [M+H]+.
279	+		1H NMR (500 MHz, DMSO-d6) δ 10.43 (s, 1H), 8.84 (s, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.42 –7.53 (m, 2H), 7.14 – 7.22 (m,1H), 4.99 (t, J = 5.6 Hz, 1H), 4.47 (d, J = 5.5 Hz, 2H), 4.32 – 4.42 (m,1H), 4.19 – 4.29 (m,1H), 3.49 – 3.59 (m, 3H), 3.17 – 3.27 (m,1H), 2.86 – 2.98 (m, 1H), 2.71 – 2.81 (m, 2H), 2.59 – 2.67 (m, 1H), 2.32 – 2.42 (m, 2H), 2.06 – 2.12 (m, 1H), 1.87 – 1.98 (m, 1H), 1.39 (d, J = 4.3 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H).	C27H32F2N8O4: 570.25 m/z, found: 571.30 [M+H]+
280	+++		1H NMR (400 MHz, Methanol-d4) δ 8.89 (s, 1H), 8.30 (s, 1H), 7.29 – 7.39 (m, 1H), 7.12 – 7.20 (m, 2H), 6.86 (s, J = 4.5 Hz, 1H), 4.55 – 4.63 (m, 3H), 4.18 – 4.23 (m, 1H), 4.04 – 4.11 (m, 1H), 3.64 – 3.81 (m, 3H), 2.85 – 3.03 (m, 5H), 2.43 – 2.50 (m, 2H), 2.14 – 2.24 (m, 1H), 1.93 – 2.14 (m, 1H), 1.53 (d, J = 3.0 Hz, 6H), 1.34 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C28H33F2N7O4: 569.26 m/z, found 570.25 [M+H]+
281	++		1H NMR (300 MHz, DMSO-d6) δ 10.42 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.5 Hz, 1H), 8.39 (s, 1H), 7.42 – 7.52 (m, 2H),	MS (ESI): mass calcd. for: C26H30F2N8O4: 556.23 m/z, found: 557.30 [M+H]+

			7.18 (t, J = 8.7 Hz, 1H), 5.90 (s, 1H), 4.88 (s, 1H), 4.21 (dd, J = 12.6, 4.9 Hz, 1H), 3.90 (t, J = 12.0 Hz, 1H), 3.50 – 3.56 (m, 4H), 2.69 – 2.83 (m, 2H), 2.29 – 2.47 (m, 2H), 1.92 – 2.12 (m, 2H), 1.39 (d, J = 2.5 Hz, 6H), 1.21 (d, J = 7.0 Hz, 3H).	
282	++		1H NMR (500 MHz, DMSO-d6) δ 10.42 (d, J = 2.3 Hz, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.46 (d, J = 1.4 Hz, 1H), 7.42 – 7.53 (m, 3H), 7.15 – 7.20 (m, 1H), 6.11 (s, 1H), 4.34 – 4.43 (m, 1H), 4.20 – 4.29 (m, 1H), 3.81 – 4.05 (m, 2H), 3.45 – 3.54 (m, 1H), 3.18 (d, J = 16.8 Hz, 1H), 2.75 (d, J = 16.8 Hz, 1H), 2.57 – 2.67 (m, 1H), 2.35 – 2.45 (m, 2H), 2.16 – 2.32 (m, 2H), 1.37 (d, J = 5.2 Hz, 6H), 1.21 (d, J = 5.2 Hz, 3H).	MS (ESI): mass calcd. for C26H30F2N8O4: 556.24 m/z, found: 557.30 [M+H]+
283	+++	+++	1H NMR (300 MHz, DMSO-d6) δ 14.38 (br, 1H), 10.40 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.39 – 7.56 (m, 2H), 7.10 – 7.24 (m, 1H), 3.45 – 3.59 (m, 3H), 2.99 – 3.09 (m, 1H), 2.57 – 2.79 (m, 6H), 2.35 (s, 2H), 1.95 (d, J = 13.5 Hz, 1H), 1.60 – 1.73 (m, 1H), 1.39 (t, J = 1.8 Hz, 6H), 1.21 (d, J = 6.9 Hz, 3H).	MS (ESI): mass calcd. for C26H30F2N8O3: 540.24, found: 541.20 [M+H]+.
284	+		1H NMR (400 MHz, DMSO-d6) δ 10.40 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.4 Hz, 1H), 7.41 – 7.54 (m, 2H), 7.12 – 7.22 (m, 1H), 4.96 (t, J = 5.4 Hz, 1H), 4.22 – 4.22 (m, 2H), 3.70 – 3.74 (m, 2H), 3.47 – 3.56 (m, 3H), 2.94 – 3.00 (m, 1H), 2.60 – 2.77 (m, 6H), 2.35 (s, 2H), 1.96 (d, J = 13.4 Hz, 1H), 1.58 – 1.70 (m, 1H),	MS (ESI): mass calcd. for C28H34F2N8O4: 584.27, found: 585.35 [M+H]+

			1.39 (d, J = 4.4 Hz, 6H), 1.22 (d, J = 6.8 Hz, 3H).	
285	+++		1H NMR (400 MHz, DMSO-d6) δ 10.40 (s, 1H), 8.84 (d, J = 1.4 Hz, 1H), 8.45 (d, J = 1.5 Hz, 1H), 7.41 – 7.54 (m, 2H), 7.12 – 7.22 (m, 1H), 4.95 (t, J = 5.4 Hz, 1H), 4.26 (t, J = 5.4, 2.3 Hz, 2H), 3.70 – 3.74 (m, 2H), 3.47 – 3.67 (m, 3H), 2.99 – 3.03 (m, 1H), 2.57 – 2.84 (m, 6H), 2.37 (s, 2H), 1.93 (d, J = 13.5 Hz, 1H), 1.53 – 1.67 (m, 1H), 1.39 (d, J = 2.5 Hz, 6H), 1.22 (d, J = 6.8 Hz, 3H).	MS (ESI): mass calcd. for C28H34F2N8O4: 584.27, found: 585.35 [M+H]+
286	++		1H NMR (400 MHz, Methanol-d4) δ 8.87 (d, J = 1.4 Hz, 1H), 8.26 (d, J = 1.4 Hz, 1H), 7.23 – 7.41 (m, 1H), 7.09 – 7.20 (m, 1H), 7.02 (t, J = 3.0 Hz, 1H), 4.56 (s, 2H), 4.15 – 4.28 (m, 2H), 3.63 – 3.73 (m, 2H), 3.45 – 3.56 (m, 1H), 3.32 – 3.41 (m, 1H), 2.86 – 3.00 (m, 2H), 2.70 – 2.89 (m, 2H), 2.43 (s, 2H), 2.14 – 2.25 (m, 1H), 1.99 – 2.01 (m, 1H), 1.49 (d, J = 3.9 Hz, 6H), 1.31 (d, J = 7.0 Hz, 3H).	MS (ESI): mass calcd. for C27H32F2N8O4 570.25 m/z, found 571.25 [M+H]+
287	+++	+++	1H NMR (400 MHz, Methanol-d4) δ 8.87 (d, J = 1.4 Hz, 1H), 8.26 (d, J = 1.4 Hz, 1H), 7.23 – 7.41 (m, 1H), 7.09 – 7.20 (m, 1H), 7.02 (t, J = 3.0 Hz, 1H), 4.56 (s, 2H), 4.15 – 4.28 (m, 2H), 3.63 – 3.73 (m, 2H), 3.45 – 3.56 (m, 1H), 3.32 – 3.41 (m, 1H), 2.86 – 3.00 (m, 2H), 2.70 – 2.89 (m, 2H), 2.43 (s, 2H), 2.14 – 2.25 (m, 1H), 1.99 – 2.01 (m, 1H), 1.49 (d, J = 3.9 Hz, 6H), 1.31 (d, J = 7.0 Hz, 3H).	MS (ESI): mass calcd. for C27H32F2N8O4 570.25 m/z, found 571.25 [M+H]+
288	+++	+++	1H NMR (400 MHz, Methanol-d4) δ 8.86 (d, J = 1.4 Hz, 1H), 8.26 (d, J = 1.4 Hz, 1H), 7.21 – 7.43 (m,	MS (ESI): mass calcd. for C24H28F2N6O5 518.21 m/z, found 519.25 [M+H] +

			1H), 7.07 – 7.21 (m, 1H), 6.89 – 7.07 (m, 1H), 4.45 – 4.70 (m, 1H), 4.15 – 4.29 (m, 2H), 3.65 – 3.89 (m, 1H), 3.49 – 3.65 (m, 2H), 3.32 – 3.42 (m, 2H), 2.65 – 2.91 (m, 2H), 2.28 – 2.58 (m, 2H), 1.49 (s, 6H), 1.31 (d, J = 7.0 Hz, 3H).	
289	+++	+++	1H NMR (400 MHz, Methanol-d4) δ 8.86 (d, J = 1.4 Hz, 1H), 8.26 (d, J = 1.4 Hz, 1H), 7.21-7.43 (m, 1H), 7.07-7.21 (m, 1H), 6.89-7.07 (m, 1H), 4.58 (dd, J = 8.7, 3.6 Hz, 1H), 4.15 – 4.29 (m, 2H), 3.70-3.91 (m, 1H), 3.49 – 3.65 (m, 2H), 3.32 – 3.42 (m, 2H), 2.72-2.98 (m, 1H), 2.53-2.72 (m, 1H), 2.42-2.52 (m, 1H), 2.28-2.52 (m, 1H), 1.49 (s, 6H), 1.31 (d, J = 7.0 Hz, 3H).	MS (ESI): mass calcd. for C24H28F2N6O5 518.21 m/z, found 519.25 [M+H] +

Activity Bins: IC_{50}:
+++ <100 nM
++ Between 100 nM and 1 μM
+ >1 μM

INCORPORATION BY REFERENCE

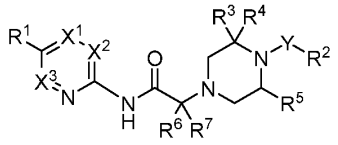
All of the U.S. patents and U.S. and PCT patent application publications cited herein are hereby incorporated by reference.

EQUIVALENTS

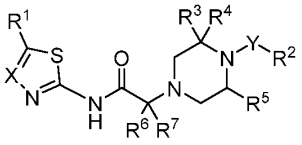
Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

We claim:

1. A compound of Formula (Ia) or (Ib):



(Ia)



(Ib)

or a pharmaceutical salt thereof; wherein:

X is N or CR^x;

X^1, X^2, and X^3 are each independently N or CR^x;

R^x is independently for each occurrence hydrogen, fluoro, or chloro;

Y is C(=O), C(=O)CH_2, CH_2, or a bond;

R^1 is -OR^{1a} or –CH_2R^{1a}; wherein R^{1a} is phenyl, (C_1-C_6)alkyl, 5- to 6-membered heteroaryl, or (C_3-C_8)cycloalkyl(C_1-C_6)alkyl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy;

R^2 is 4-, 5- or 6- membered heterocycloalkyl, 9- or 10-membered bicyclic heterocycloalkyl, 5- or 6- membered heteroaryl, 9- or 10-membered bicyclic heteroaryl, (C_3-C_8)cycloalkyl, or phenyl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, cyano, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, -C(=O)NH_2, -NH_2, (C_1-C_6)alkoxy, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)hydroxyalkoxy, (C_1-C_6)carboxyalkyl (C_1-C_6)haloalkoxy, (C_3-C_8)cycloalkyl, and 4- to 7-membered heterocycloalkyl; wherein (C_1-C_6)alkyl is optionally substituted with phenyl, 4- to 7-membered heterocycloalkyl, or –NHR^{2a}; or R^2 is (C_1-C_6)alkyl;

R^{2a} is C(=O)R^{2b}, (C_1-C_6)alkyl, or (C_3-C_8)cycloalkyl, wherein (C_1-C_6)alkyl or (C_3-C_8)cycloalkyl is optionally substituted with one or more independent instances of halo;

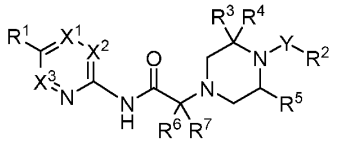
R^{2b} is (C_1-C_6)alkyl;

R^3 and R^4 are each independently hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxyalkyl, or (C_1-C_6)haloalkyl; or taken together with the carbon atom to which they are attached form a (C_3-C_6)cycloalkyl;

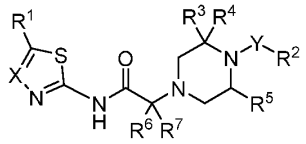
R^5 is hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxyalkyl, or (C_1-C_6)haloalkyl; or R^5 taken together with R^3 or R^4 forms $–(CH_2)_n–$; wherein n is 1, 2, or 3; and

R^6 and R^7 are independently for each occurrence hydrogen or (C_1-C_6)alkyl; or R^6 and R^7 taken together with the carbon atom to which they are attached form a (C_3-C_6)cycloalkyl.

2. A compound of Formula (Ia) or (Ib):



(Ia)



(Ib)

or a pharmaceutical salt thereof; wherein:

X is N or CR^x;

X^1, X^2, and X^3 are each independently N or CR^x;

R^x is independently for each occurrence hydrogen, fluoro, or chloro;

Y is C(=O), C(=O)CH_2, CH_2, or a bond;

R^1 is -OR^{1a} or $–CH_2R^{1a}$; wherein R^{1a} is phenyl, 5- to 6-membered heteroaryl, or (C_3-C_8)cycloalkyl(C_1-C_6)alkyl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy;

R^2 is 5- or 6- membered heterocycloalkyl, 9- or 10-membered bicyclic heterocycloalkyl 5- or 6- membered heteroaryl, 9- or 10-membered bicyclic heteroaryl, or phenyl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, cyano, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, -C(=O)NH_2, (C_1-C_6)alkoxy, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, and (C_1-C_6)haloalkoxy; wherein (C_1-C_6)alkyl is optionally substituted with phenyl or $–NHR^{2a}$;

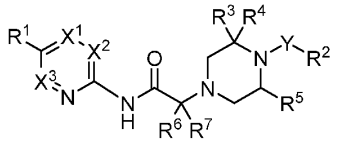
R^{2a} is (C_3-C_8)cycloalkyl, optionally substituted with one or more independent instances of halo;

R^3 and R^4 are each independently hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxyalkyl, or (C_1-C_6)haloalkyl; or taken together with the carbon atom to which they are attached form a (C_3-C_6)cycloalkyl;

R^5 is hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxyalkyl, or (C_1-C_6)haloalkyl; or R^5 taken together with R^3 or R^4 forms –$(CH_2)_n$–; wherein n is 1, 2, or 3; and

R^6 and R^7 are independently for each occurrence hydrogen or (C_1-C_6)alkyl; or R^6 and R^7 taken together with the carbon atom to which they are attached form a (C_3-C_6)cycloalkyl.

3. The compound of claim 1 or 2, wherein the compound is formula (Ia):



(Ia).

4. The compound of claim 3, wherein X^1 is N.

5. The compound of claim 3, wherein X^1 is CH.

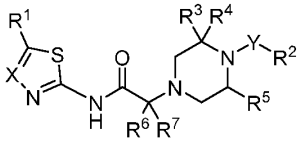
6. The compound of any one of claims 3 to 5, wherein X^2 is CH.

7. The compound of any one of claims 3 to 6, wherein X^3 is CH.

8. The compound of claim 3, wherein X^1 is N; X^2 is CH; and X^3 is CH.

9. The compound of claim 3, wherein X^1 is CH; X^2 is CH; and X^3 is CH.

10. The compound of claim 1 or 2, wherein the compound is formula (Ib):



(Ib).

11. The compound of claim 10, wherein X is CH.

12. The compound of any one of claims 1 to 11, wherein Y is C(=O).

13. The compound of any one of claims 1 to 12, wherein, R^1 is -OR^{1a}.

14. The compound of any one of claims 1 to 13, wherein R^{1a} is phenyl optionally substituted with one or two instances of fluoro or chloro.

15. The compound of claim 14, wherein R^{1a} is 4-fluorophenyl.

16. The compound of claim 14, wherein R^{1a} is 2,4-difluorophenyl.

17. The compound of claim 14, wherein R^{1a} is 4-chlorophenyl.

18. The compound of any one of claims 1 to 13, wherein R^{1a} is 6-membered heteroaryl optionally substituted with one or two instances of fluoro or chloro.

19. The compound of claim 18, wherein R^{1a} is pyridyl optionally substituted with one or two fluoro or chloro.

20. The compound of claim 17 or 19, wherein R^{1a} is 4-fluoropyridyl.

21. The compound of any one of claims 1 to 13, wherein R^{1a} is (C_3-C_8)cycloalkyl(C_1-C_6)alkyl.

22. The compound of any one of claims 1 to 13, wherein R^{1a} is cyclopropylmethyl.

23. The compound of any one of claims 1 to 22, wherein R^2 is 9- or 10-membered bicyclic heteroaryl optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, cyano, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, -C(=O)NH_2, -NH_2, (C_1-C_6)alkoxy, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)hydroxyalkoxy, (C_1-C_6)carboxyalkyl (C_1-C_6)haloalkoxy, (C_3-C_8)cycloalkyl, and 4- to 7-membered heterocycloalkyl; wherein (C_1-C_6)alkyl is optionally substituted with phenyl, 4- to 7-membered heterocycloalkyl, or –NHR^{2a}.

24. The compound of claim 23, wherein R^2 is [1,2,4]triazolo[4,3-a]pyridine, [1,2,4]triazolo[1,5-a]pyridine, [1,2,4]triazolo[1,5-a]pyrazine, [1,2,4]triazolo[1,5-a]pyrimidine, [1,2,4]triazolo[4,3-a]pyrimidine, [1,2,4]triazolo[1,5-b]pyridazine, 1H-pyrazolo[3,4-b]pyridine 7-oxide, 3H-imidazo[4,5-b]pyridine 4-oxide, benzo[d]oxazole, 1H-benzo[d]imidazole, benzo[d]thiazole, 1H-benzo[d][1,2,3]triazole, [1,2,3]oxadiazolo[4,5-b]pyridine, oxazolo[4,5-b]pyridine, 1H-indazole, 1H-pyrazolo[3,4-b]pyridine, or oxoisoindolin-1-yl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, cyano, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, -C(=O)NH_2, -NH_2, (C_1-C_6)alkoxy, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)hydroxyalkoxy, (C_1-C_6)carboxyalkyl (C_1-C_6)haloalkoxy, (C_3-C_8)cycloalkyl, and 4- to 7-membered heterocycloalkyl; wherein (C_1-C_6)alkyl is optionally substituted with phenyl, 4- to 7-membered heterocycloalkyl, or –NHR^{2a}.

25. The compound of claim 22, wherein R^2 is [1,2,4]triazolo[4,3-a]pyridine, [1,2,4]triazolo[1,5-a]pyridine, [1,2,4]triazolo[1,5-a]pyrazine, [1,2,4]triazolo[1,5-a]pyrimidine, [1,2,4]triazolo[4,3-a]pyrimidine, [1,2,4]triazolo[1,5-b]pyridazine, 1H-pyrazolo[3,4-b]pyridine 7-oxide, 3H-imidazo[4,5-b]pyridine 4-oxide, benzo[d]oxazole, 1H-

benzo[d]imidazole, benzo[d]thiazole, 1H-benzo[d][1,2,3]triazole, [1,2,3]oxadiazolo[4,5-b]pyridine, oxazolo[4,5-b]pyridine, or 1H-indazole, each of which is optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, cyano, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, -C(=O)NH_2, -NH_2, (C_1-C_6)alkoxy, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)hydroxyalkoxy, (C_1-C_6)carboxyalkyl (C_1-C_6)haloalkoxy, (C_3-C_8)cycloalkyl, and 4- to 7-membered heterocycloalkyl; wherein (C_1-C_6)alkyl is optionally substituted with phenyl, 4- to 7-membered heterocycloalkyl, or –NHR^{2a}.

26. The compound of any one of claims 1 to 22, wherein R^2 is 9- or 10-membered bicyclic heterocycloalkyl optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, cyano, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, -C(=O)NH_2, -NH_2, (C_1-C_6)alkoxy, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)hydroxyalkoxy, (C_1-C_6)carboxyalkyl (C_1-C_6)haloalkoxy, (C_3-C_8)cycloalkyl, and 4- to 7-membered heterocycloalkyl; wherein (C_1-C_6)alkyl is optionally substituted with phenyl, 4- to 7-membered heterocycloalkyl, or –NHR^{2a}.

27. The compound of claim 26, wherein R^2 is 6,7-dihydro-5H-cyclopenta[b]pyridine 1-oxide, 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine, 4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridine, 4,5,6,7-tetrahydro-1H-benzo[d]imidazole, 4,5,6,7-tetrahydrobenzo[d]oxazole, 4,5,6,7-tetrahydro-1l2-benzo[d][1,2,3]triazole, 6,7-dihydro-5H-[1,2,4]triazolo[5,1-b][1,3]oxazine, 4,5,6,7-tetrahydro-2H-benzo[d][1,2,3]triazole, isoindolin-1-one, or 7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidine; each of which is optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, cyano, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, -C(=O)NH_2, -NH_2, (C_1-C_6)alkoxy, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)hydroxyalkoxy, (C_1-C_6)carboxyalkyl (C_1-C_6)haloalkoxy, (C_3-C_8)cycloalkyl, and 4- to 7-membered heterocycloalkyl; wherein (C_1-C_6)alkyl is optionally substituted with phenyl, 4- to 7-membered heterocycloalkyl, or –NHR^{2a}.

28. The compound of claim 27, wherein R^2 is 6,7-dihydro-5H-cyclopenta[b]pyridine 1-oxide, 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine, 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine, 4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridine, 4,5,6,7-tetrahydro-1H-benzo[d]imidazole, 4,5,6,7-tetrahydrobenzo[d]oxazole, 4,5,6,7-tetrahydro-1H-

benzo[d][1,2,3]triazole, 6,7-dihydro-5H-[1,2,4]triazolo[5,1-b][1,3]oxazine, 4,5,6,7-tetrahydro-2H-benzo[d][1,2,3]triazole, or isoindolin-1-one, each of which is optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, cyano, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, -C(=O)NH_2, -NH_2, (C_1-C_6)alkoxy, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)halohydroxyalkyl, (C_1-C_6)hydroxyalkoxy, (C_1-C_6)carboxyalkyl (C_1-C_6)haloalkoxy, (C_3-C_8)cycloalkyl, and 4- to 7-membered heterocycloalkyl; wherein (C_1-C_6)alkyl is optionally substituted with phenyl, 4- to 7-membered heterocycloalkyl, or –NHR^{2a}.

29. The compound of any one of claims 1 to 22, wherein R^2 is pyridin-2(1H)-one, pyridine oxide, pyrimidine oxide, 1,5-dihydro-2H-pyrrol-2-one, phenyl, isoindolin-1-one, 1H-indazole, tetrahydro-2H-pyran, pyridine, 1H-pyrazole, 2-oxo-2,3-dihydro-1H-imidazole, 5-oxomorpholine, tetrahydropyrimidin-2(1H)-one, piperidin-2-one, pyrimidin-2(1H)-one, pyridazin-3(2H)-one, or pyrazin-2(1H)-one; each of which is optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, cyano, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, -C(=O)NH_2, (C_1-C_6)alkoxy, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, and (C_1-C_6)haloalkoxy; wherein (C_1-C_6)alkyl is optionally substituted with phenyl or –NHR^{2a}.

30. The compound of any one of claims 1 to 22, wherein R^2 is pyridin-2(1H)-one, pyridine oxide, pyrimidine oxide, 1,5-dihydro-2H-pyrrol-2-one, phenyl, isoindolin-1-one, 1H-indazole, tetrahydro-2H-pyran, pyridine, 1H-pyrazole, 2-oxo-2,3-dihydro-1H-imidazole, or 5-oxomorpholine; each of which is optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, cyano, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, -C(=O)NH_2, (C_1-C_6)alkoxy, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, and (C_1-C_6)haloalkoxy; wherein (C_1-C_6)alkyl is optionally substituted with phenyl or –NHR^{2a}.

31. The compound of any one of claims 1 to 22, wherein R^2 is pyridin-2(1H)-one, pyridine oxide, pyrimidine oxide, 1,5-dihydro-2H-pyrrol-2-one, phenyl, isoindolin-1-one, 1H-indazole, tetrahydro-2H-pyran, pyridine, or 1H-pyrazole; each of which is optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, cyano, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, -C(=O)NH_2, (C_1-C_6)alkoxy, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, and (C_1-C_6)haloalkoxy; wherein (C_1-C_6)alkyl is optionally substituted with phenyl or –NHR^{2a}.

32. The compound of claim 29, wherein R^2 is pyridin-2(1H)-one or pyridine oxide; each of which is optionally substituted with one or more substituents independently selected from the group consisting of fluoro, chloro, cyano, hydroxy, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkenyl, -$C(=O)NH_2$, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$hydroxyalkyl, and $(C_1\text{-}C_6)$haloalkoxy; wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with phenyl or $–NHR^{2a}$.

33. The compound of claim 29, wherein R^2 is unsubstituted pyridin-2(1H)-one or pyridine oxide.

34. The compound of claim 29, wherein R^2 is pyrazin-2(1H)-one optionally substituted with $(C_1\text{-}C_6)$hydroxyalkyl.

35. The compound of any one of claims 1 to 34, wherein R^{2a} is methyl.

36. The compound of any one of claims 1 to 34, wherein R^{2a} is cyclobutyl optionally substituted with at least one fluoro.

37. The compound of any one of claims 1 to 36, wherein R^{2b} is methyl.

38. The compound of any one of claims 1 to 37, wherein R^3 and R^4 are each hydrogen.

39. The compound of any one of claims 1 to 34, wherein R^3 and R^4 are each independently $(C_1\text{-}C_6)$alkyl.

40. The compound of claim 39, wherein R^3 and R^4 are each methyl.

41. The compound of any one of claims 1 to 37, wherein one of R^3 and R^4 is hydrogen.

42. The compound of claim 41, wherein one of R^3 and R^4 is $(C_1\text{-}C_6)$fluoroalkyl.

43. The compound of claim 42, wherein $(C_1\text{-}C_6)$fluoroalkyl is trifluoromethyl.

44. The compound of any one of claims 1 to 37, wherein R^3 and R^4 taken together with the carbon atom to which they are attached form a $(C_3\text{-}C_6)$cycloalkyl.

45. The compound of claim 44, wherein R^3 and R^4 taken together with the carbon atom to which they are attached form cyclopropyl.

46. The compound of claim 44, wherein R^3 and R^4 taken together with the carbon atom to which they are attached form cyclobutyl.

47. The compound of any one of claims 1 to 46, wherein R^5 is hydrogen.

48. The compound of any one of claims 1 to 43, wherein R^5 taken together with one of R^3 or R^4 forms $–(CH_2)_n–$.

49. The compound of any claim 48, wherein n is 2.

50. The compound of any one of claims 1 to 49, wherein one of R^6 or R^7 is hydrogen.

51. The compound of any one of claims 1 to 50, wherein one of R^6 or R^7 is (C_1-C_6)alkyl.

52. The compound of claim 51, wherein one of R^6 or R^7 is methyl.

53. The compound of claim 51, wherein one of R^6 or R^7 is ethyl.

54. The compound of any one of claims 1 to 49, wherein R^6 and R^7 are each hydrogen.

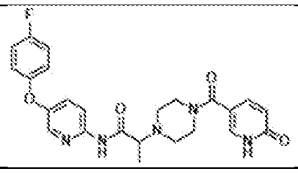
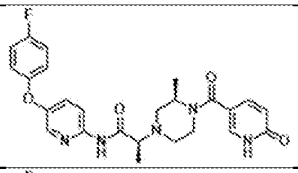
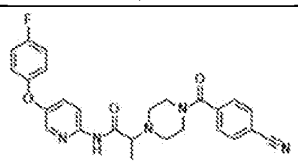
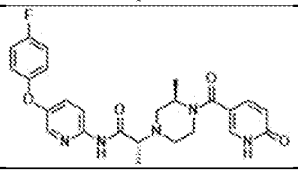
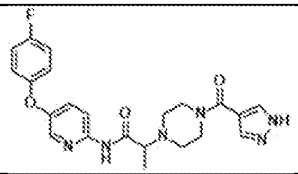
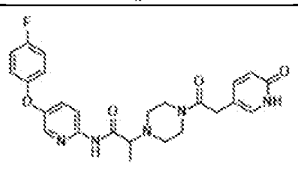
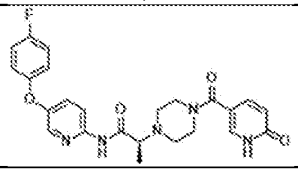
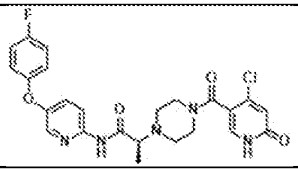
55. The compound of any one of claims 1 to 49, wherein each of R^6 and R^7 is (C_1-C_6)alkyl.

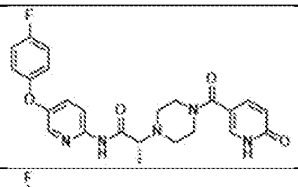
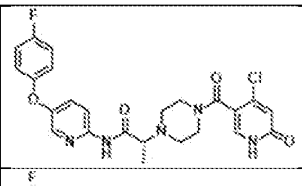
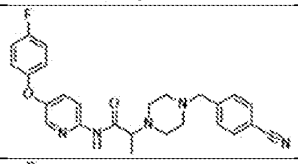
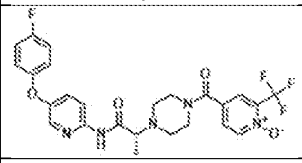
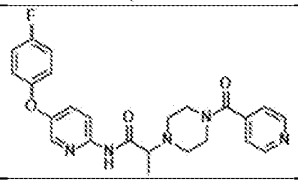
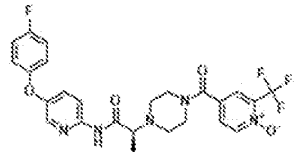
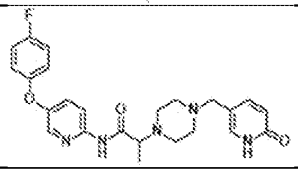
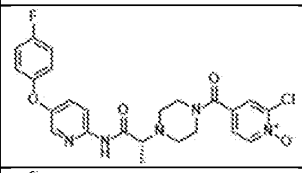
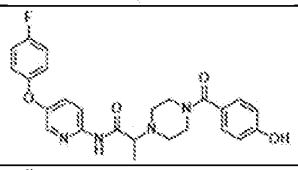
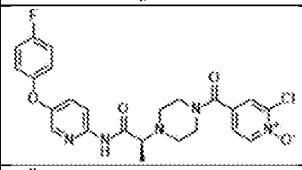
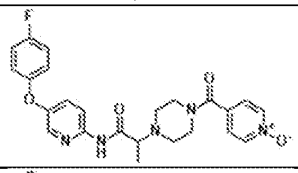
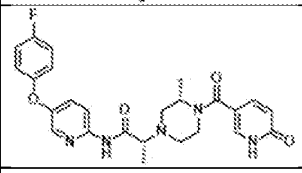
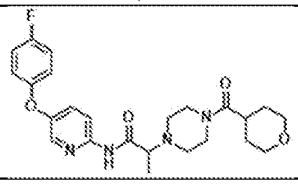
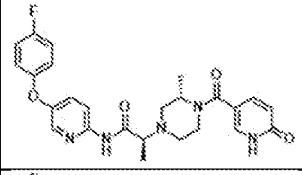
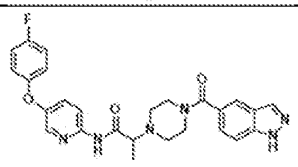
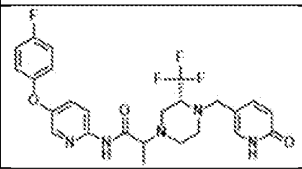
56. The compound of claim 55, wherein each of R^6 and R^7 is methyl.

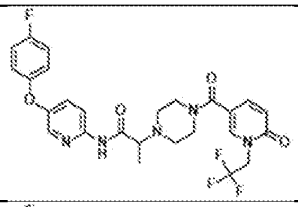
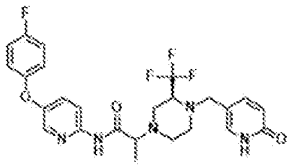
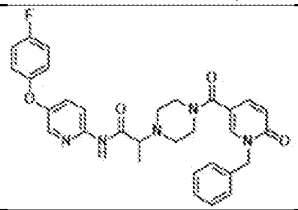
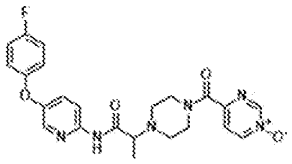
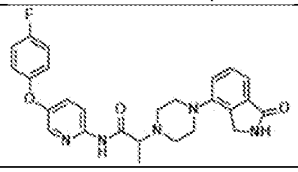
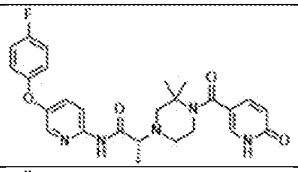
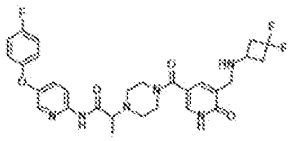
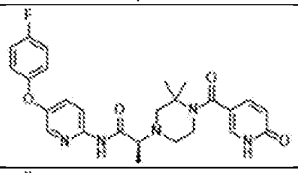
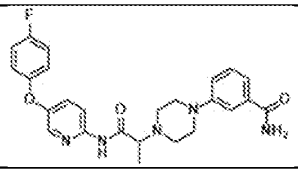
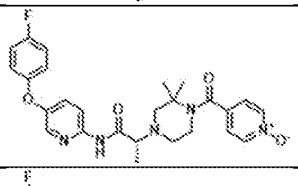
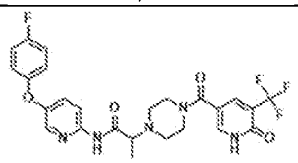
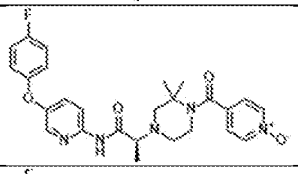
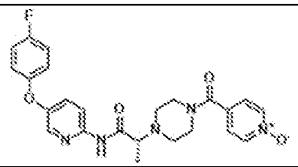
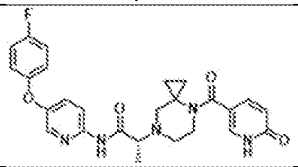
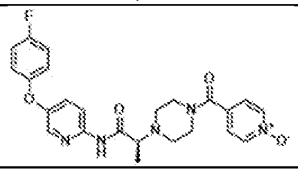
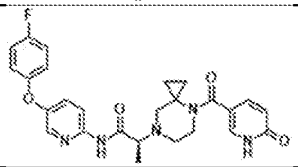
57. The compound of any one of claims 1 to 49, wherein R^6 and R^7 taken together with the carbon atom to which they are attached form a (C_3-C_6)cycloalkyl.

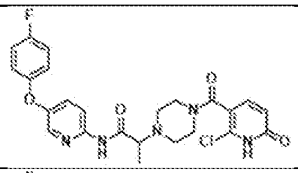
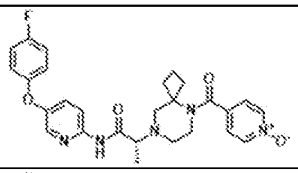
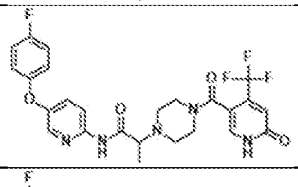
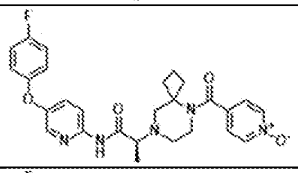
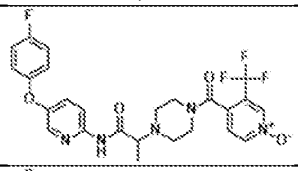
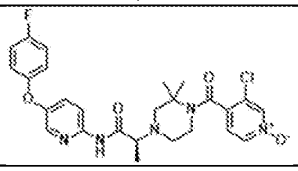
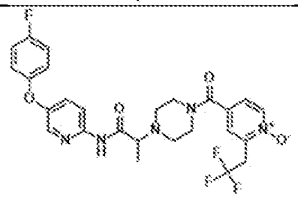
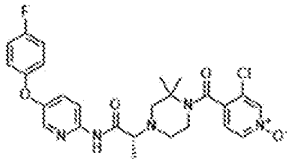
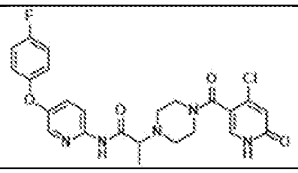
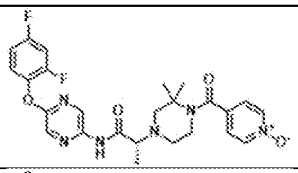
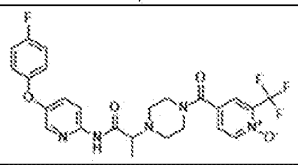
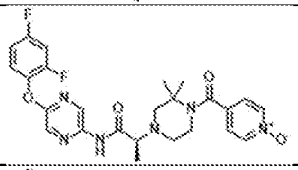
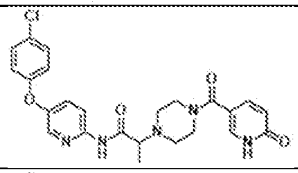
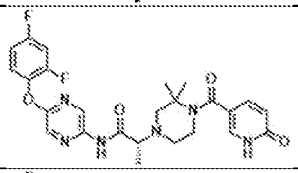
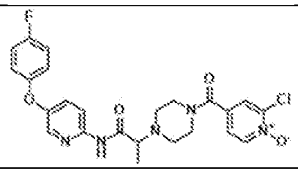
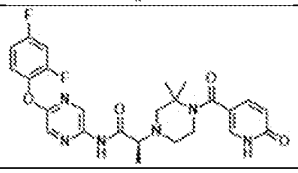
58. The compound of claim 57, wherein R^6 and R^7 taken together with the carbon atom to which they are attached form cyclopropyl.

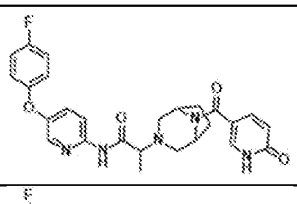
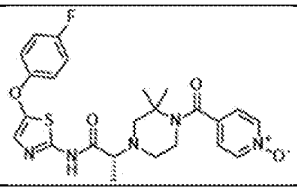
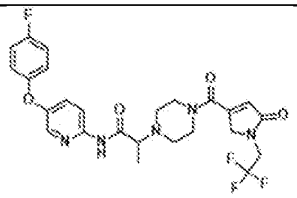
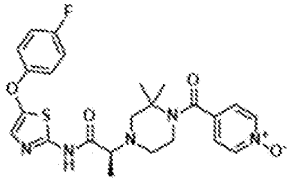
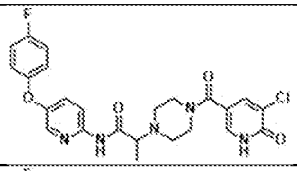
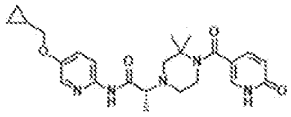
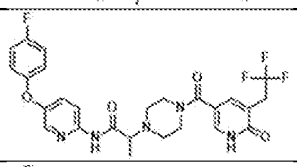
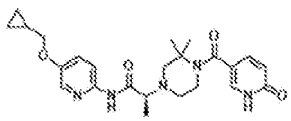
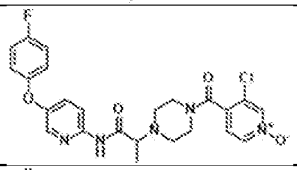
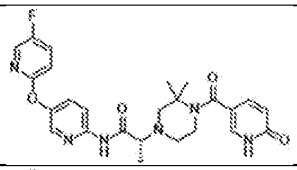
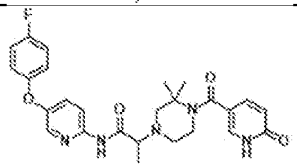
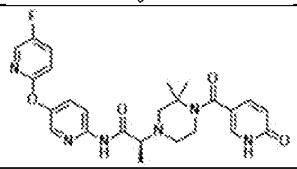
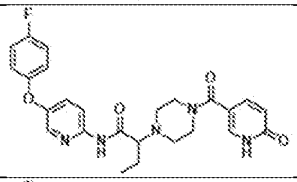
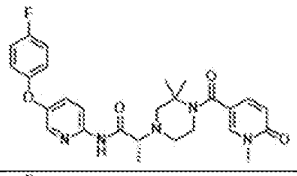
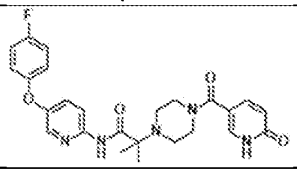
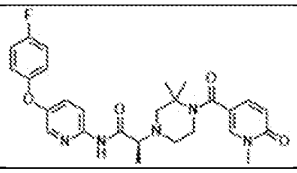
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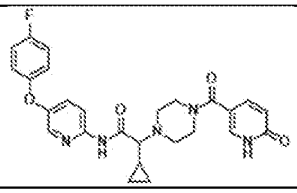
Structure	Example	Structure	Example
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	**11**		**48**
	**12**		**49**

	**13**		**50**
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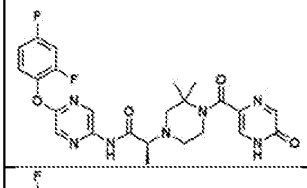
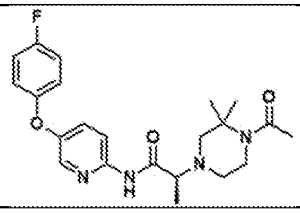
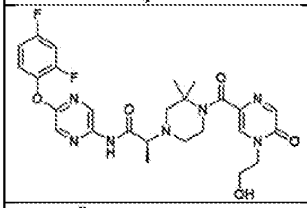
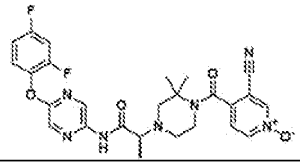
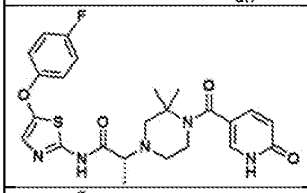
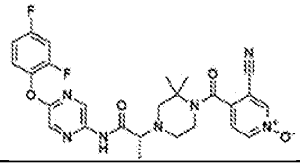
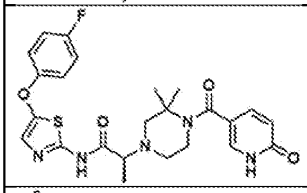
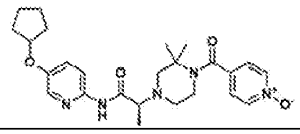
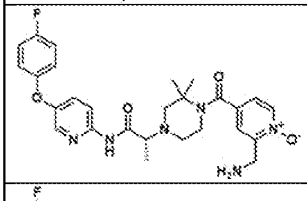
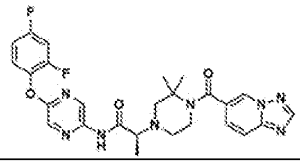
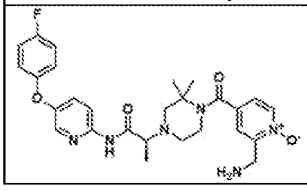
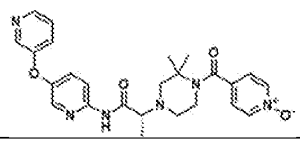
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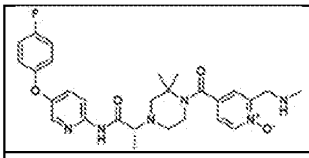
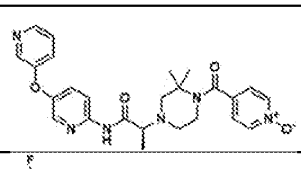
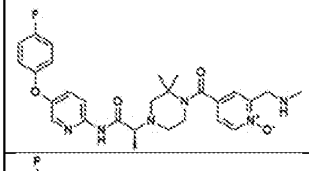
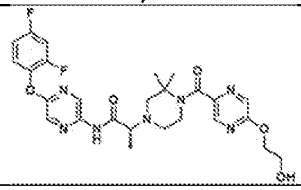
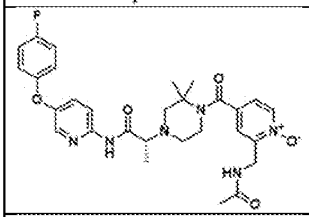
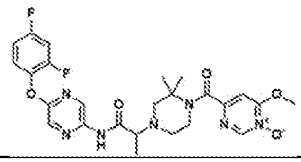
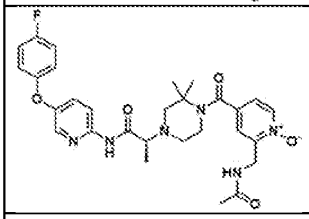
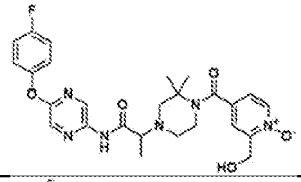
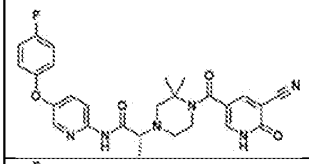
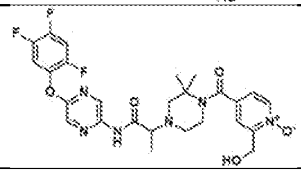
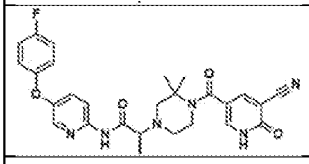
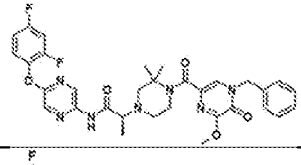
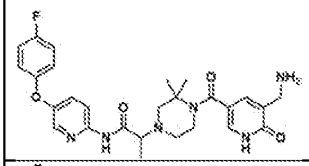
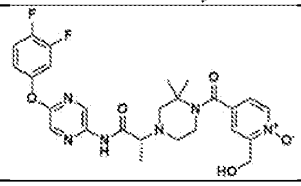
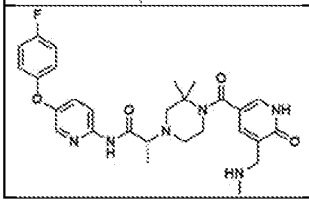
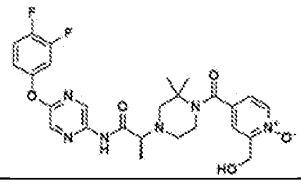
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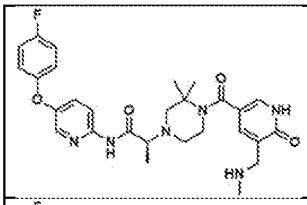
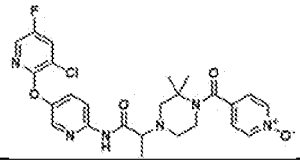
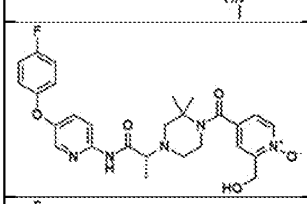
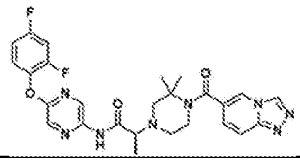
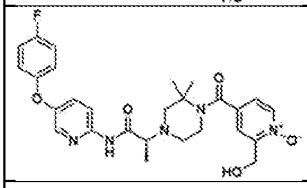
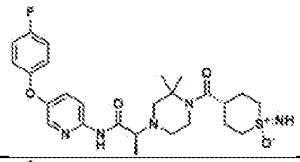
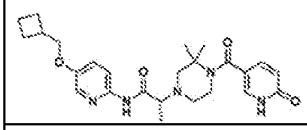
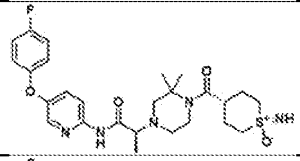
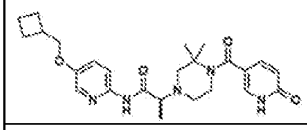
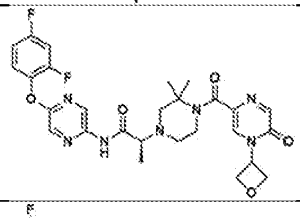
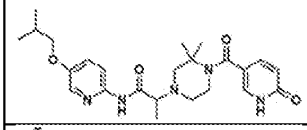
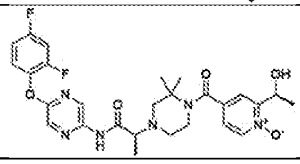
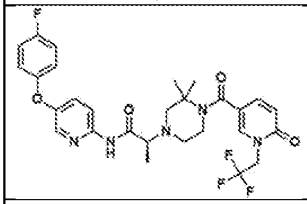
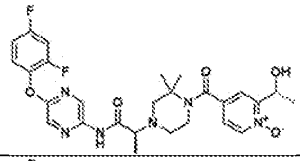
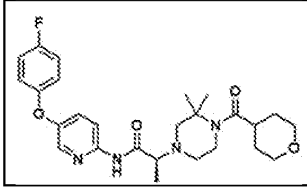
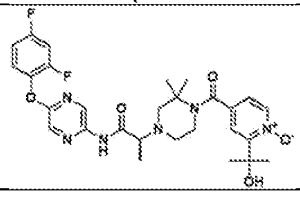
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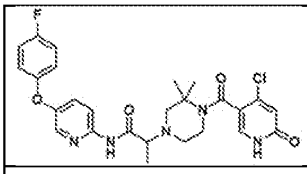
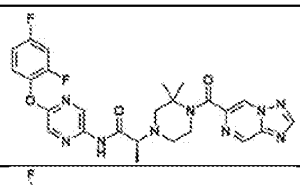
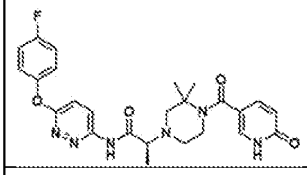
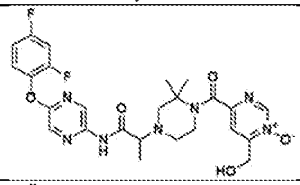
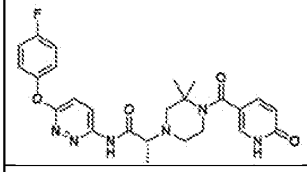
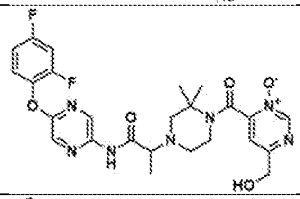
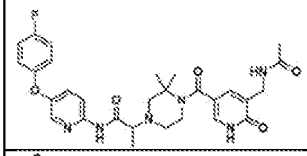
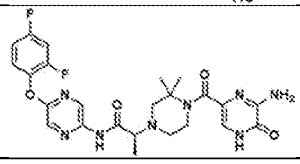
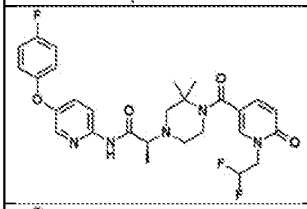
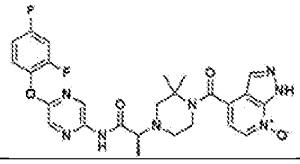
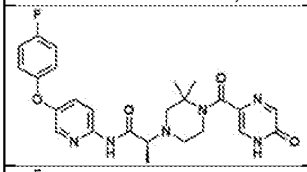
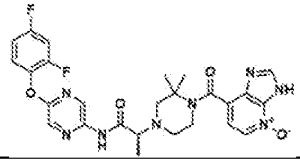
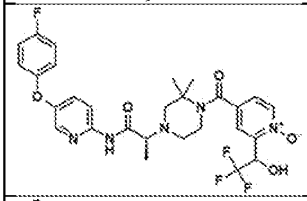
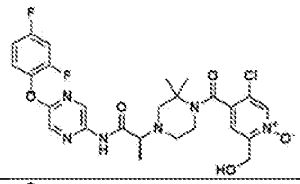
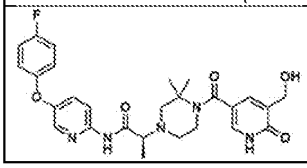
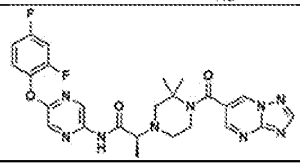
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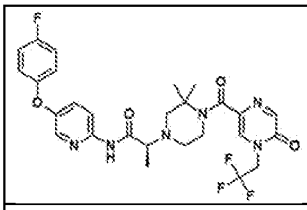
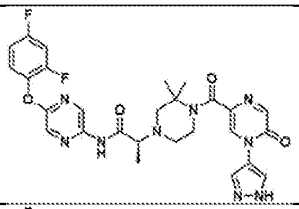
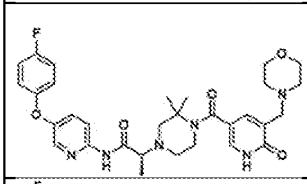
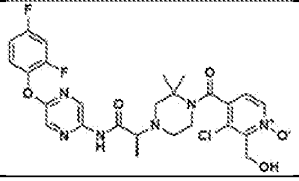
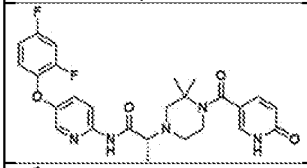
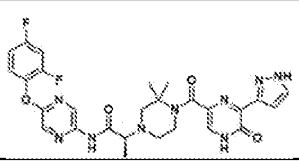
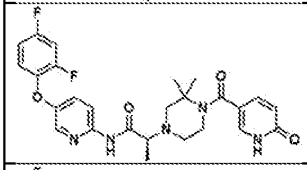
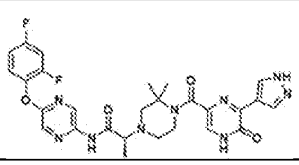
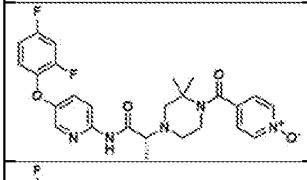
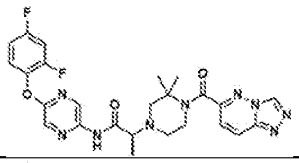
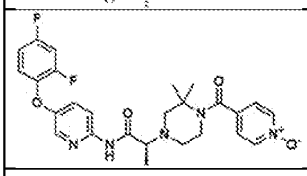
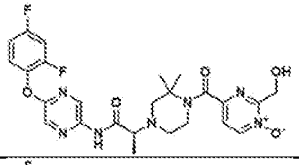
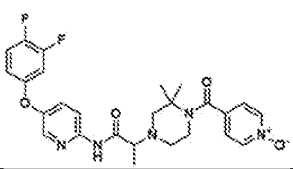
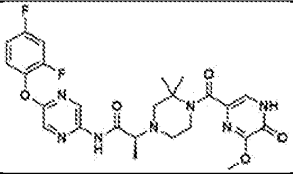
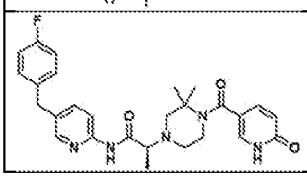
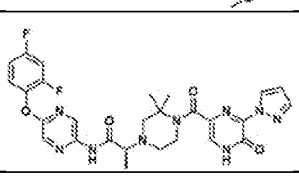
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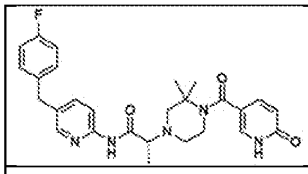
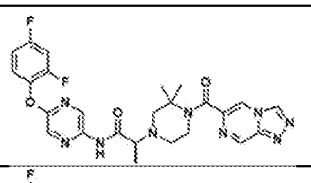
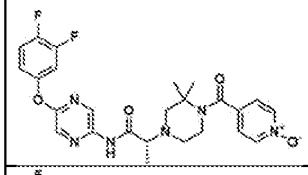
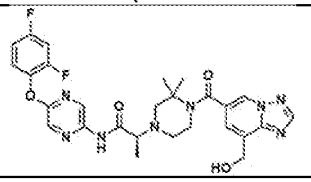
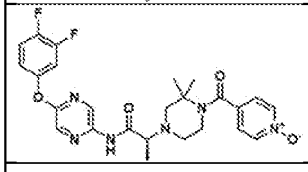
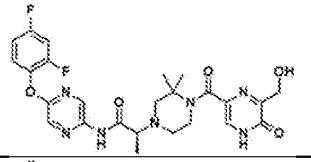
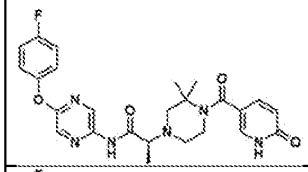
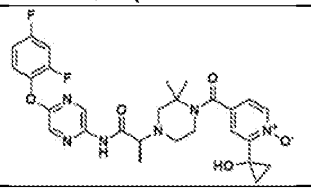
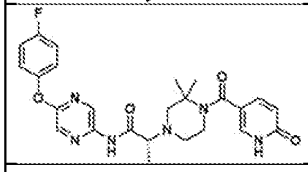
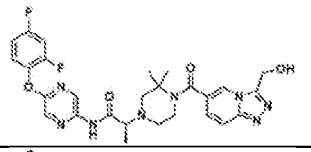
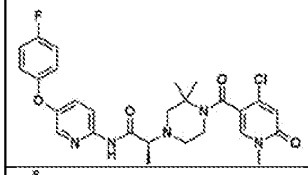
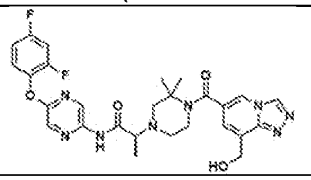
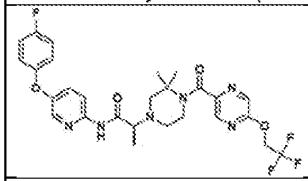
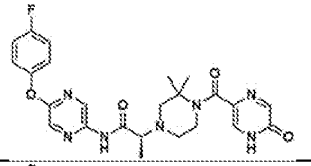
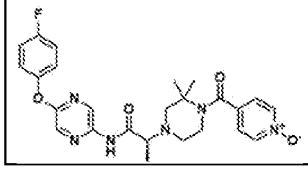
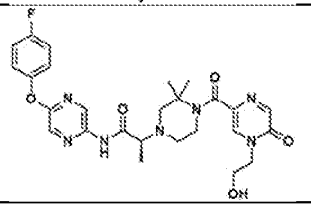
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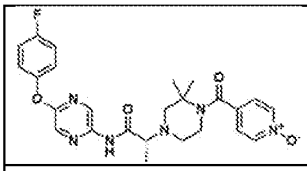
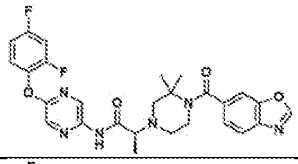
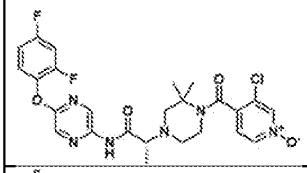
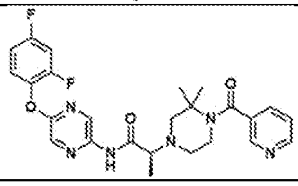
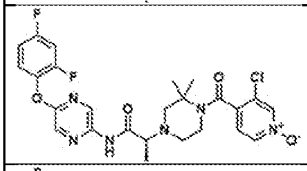
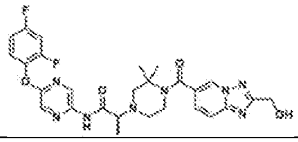
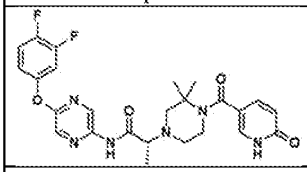
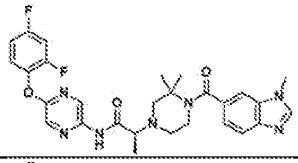
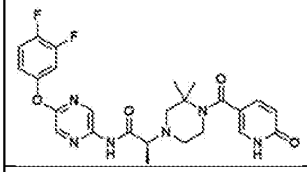
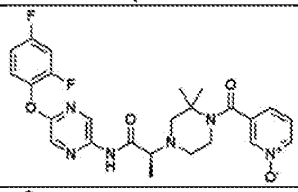
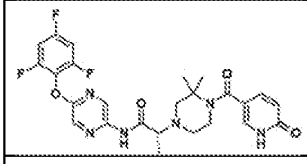
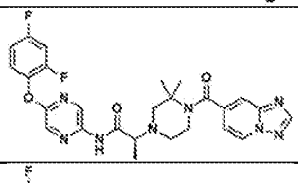
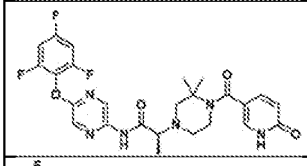
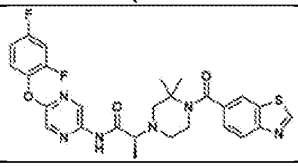
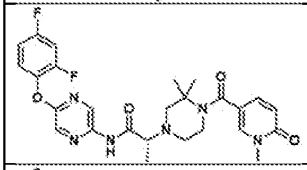
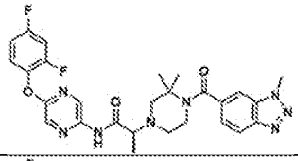
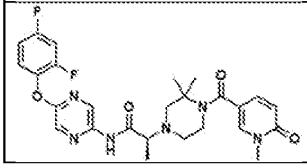
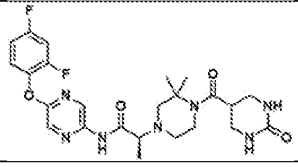
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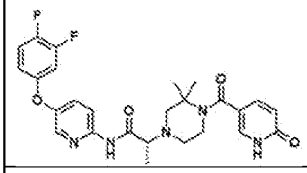
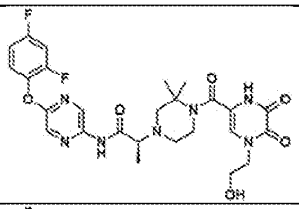
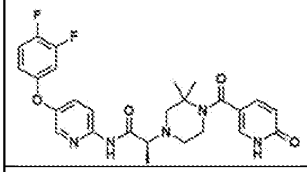
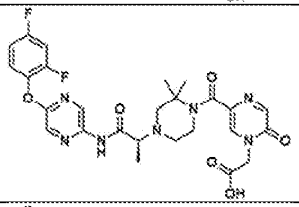
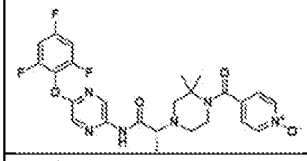
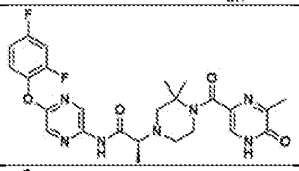
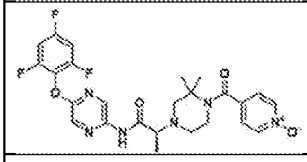
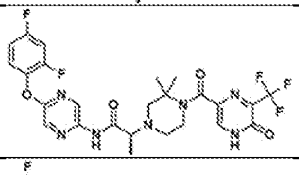
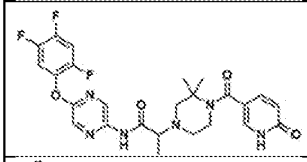
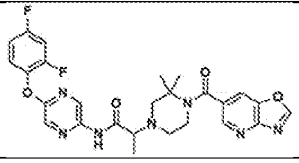
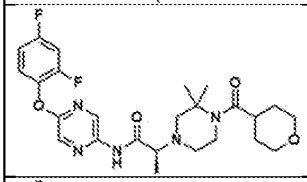
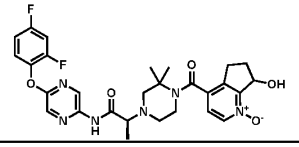
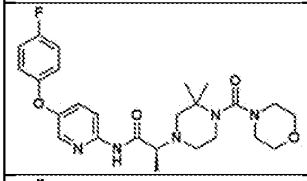
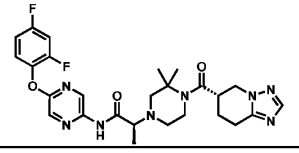
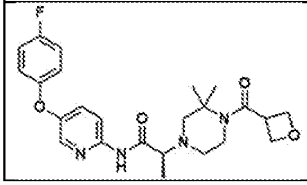
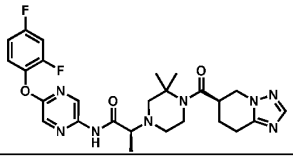
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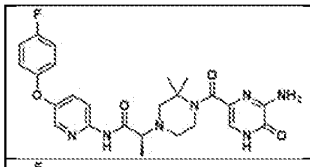
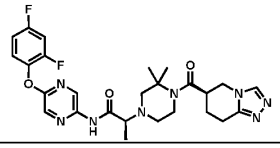
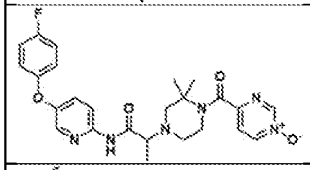
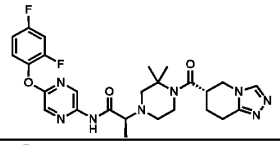
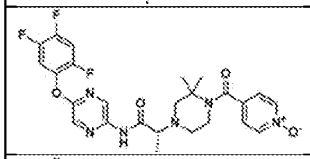
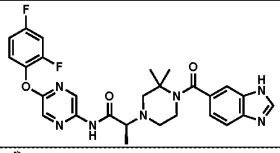
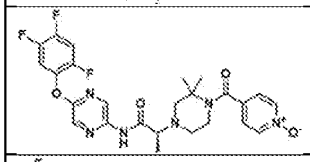
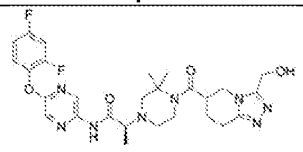
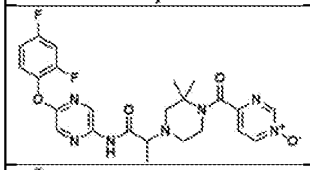
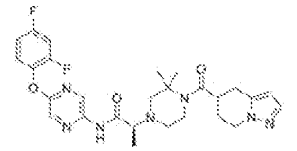
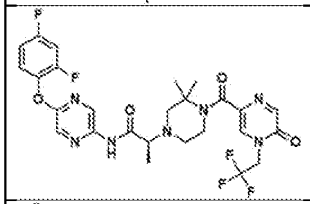
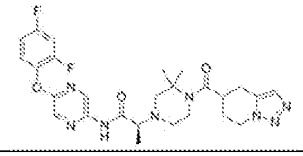
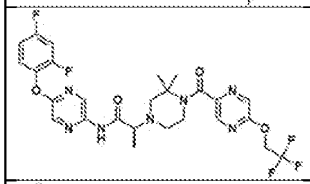
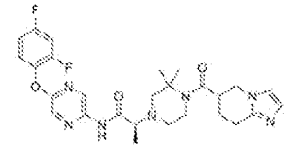
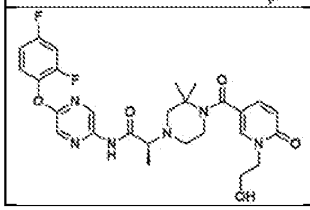
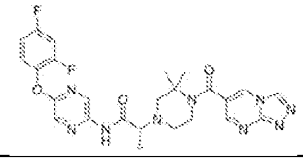
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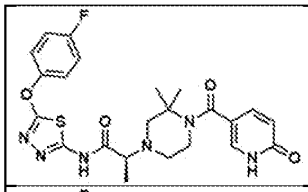
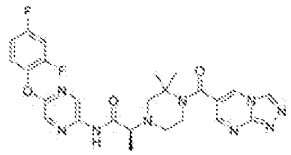
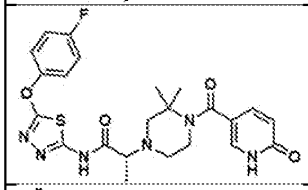
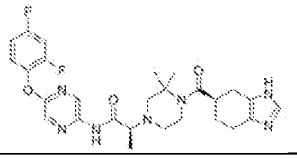
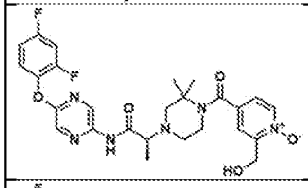
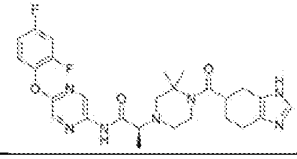
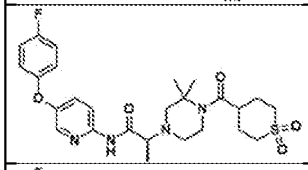
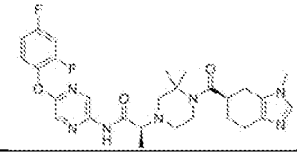
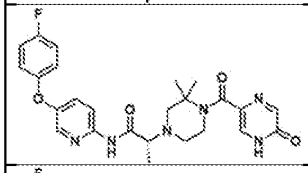
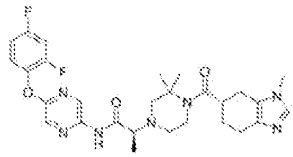
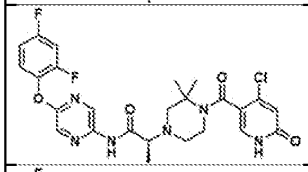
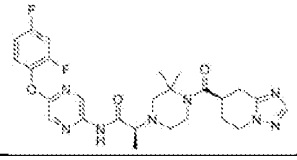
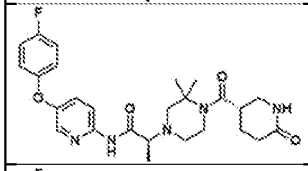
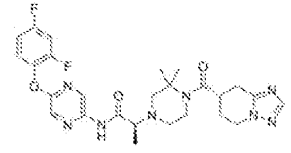
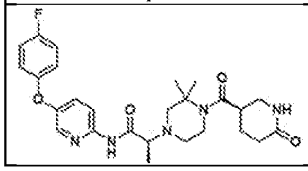
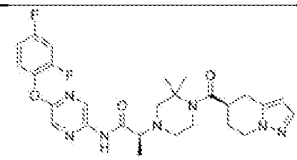
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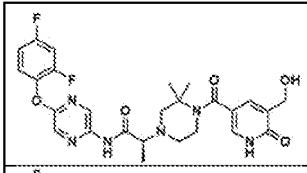
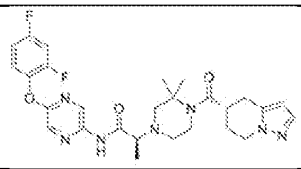
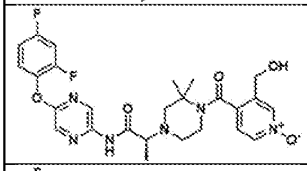
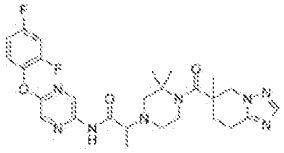
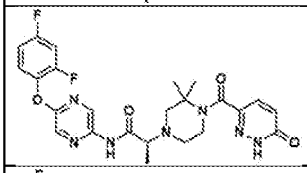
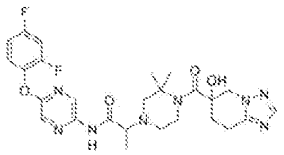
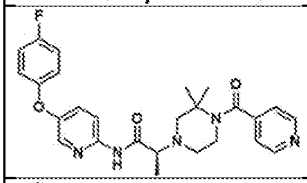
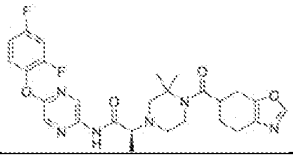
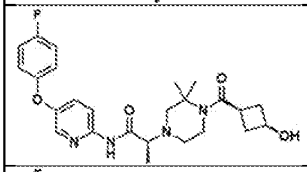
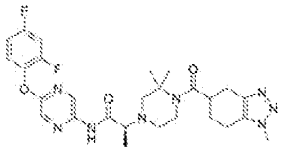
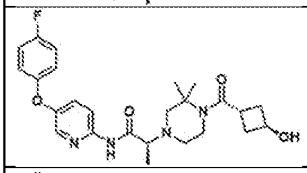
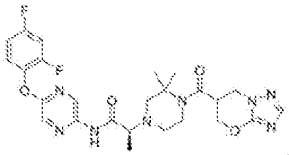
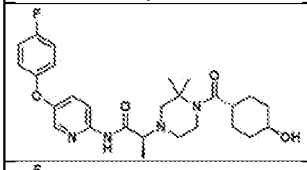
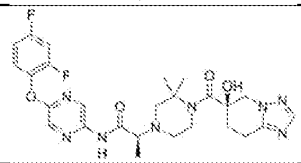
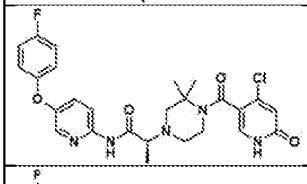
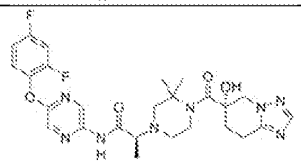
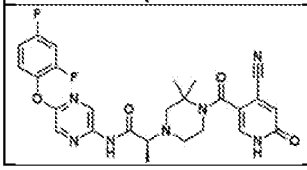
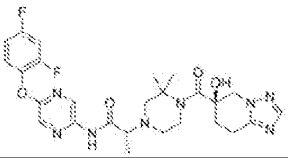
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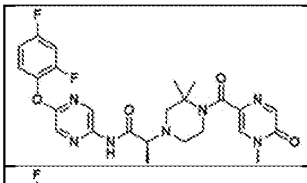
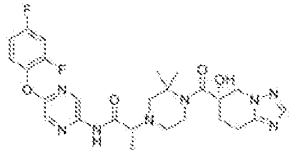
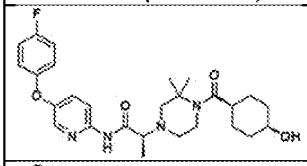
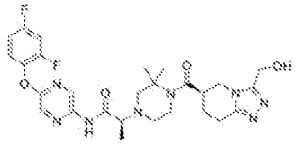
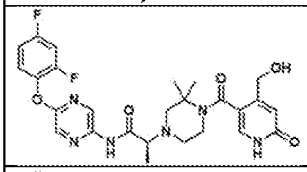
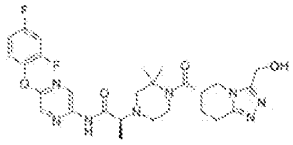
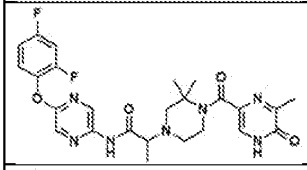
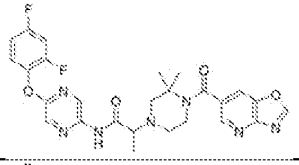
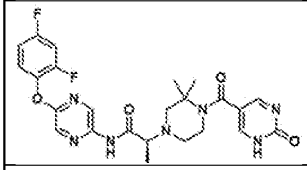
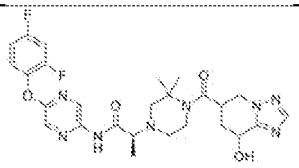
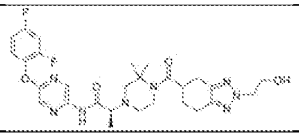
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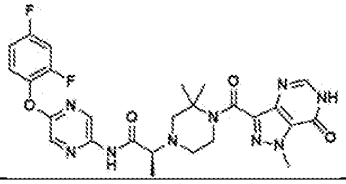
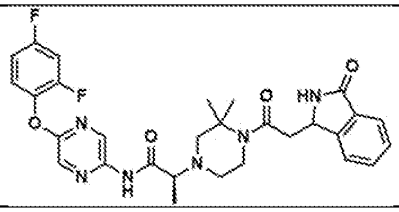
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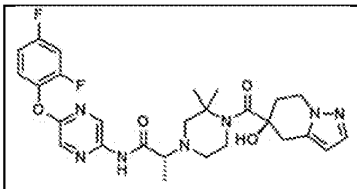
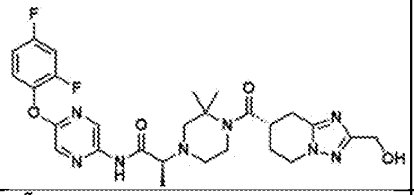
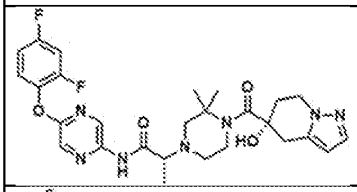
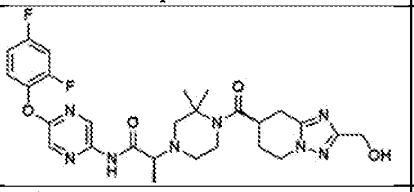
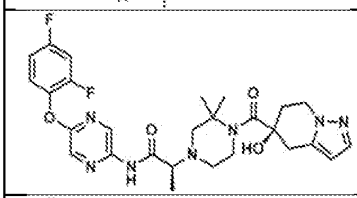
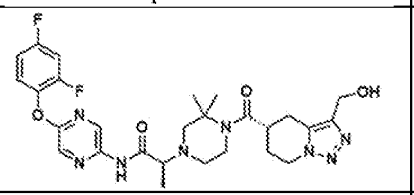
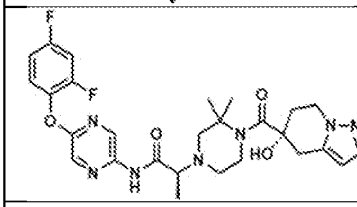
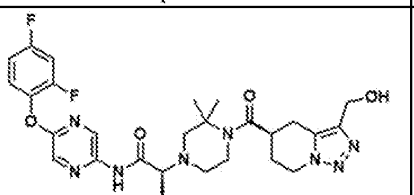
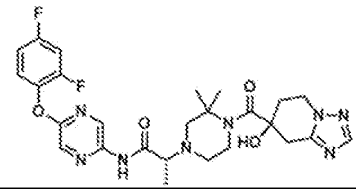
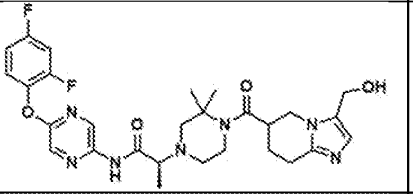
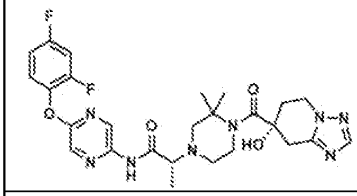
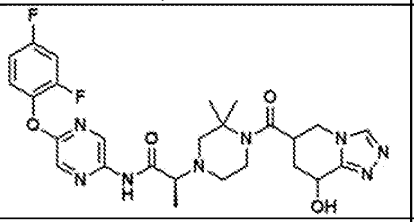
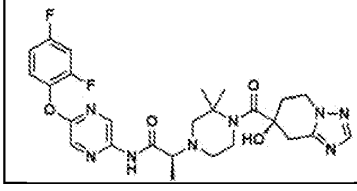
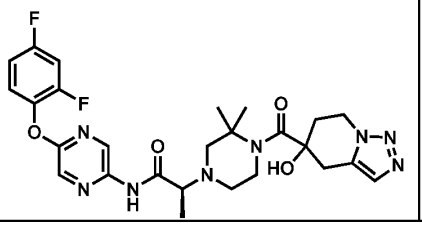
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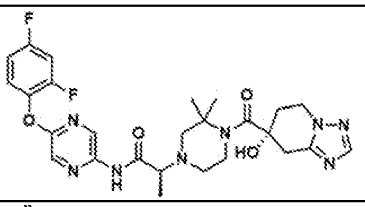
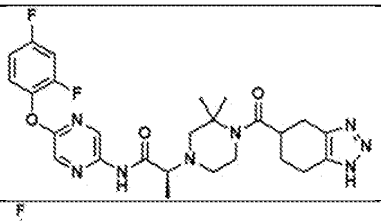
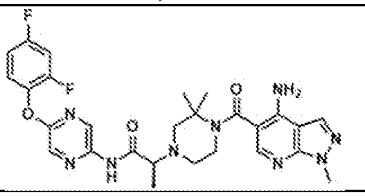
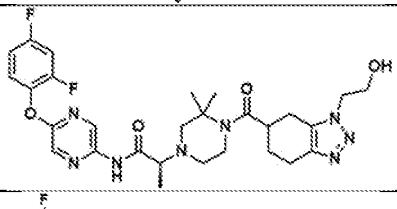
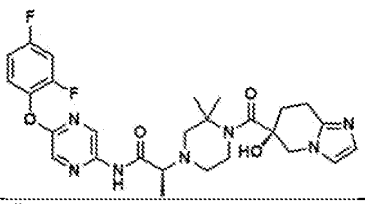
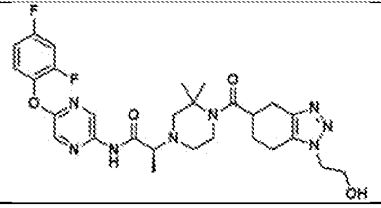
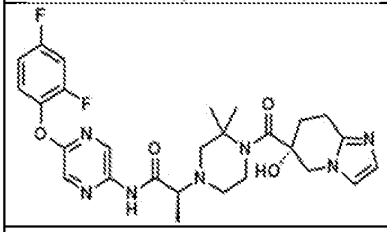
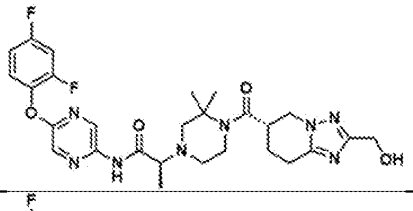
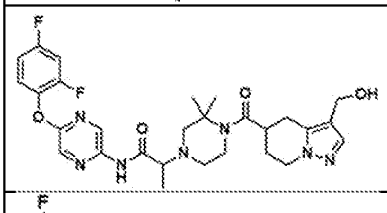
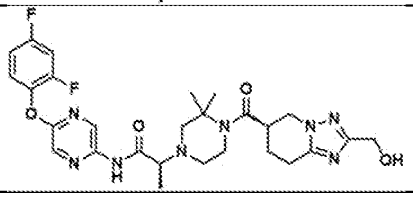
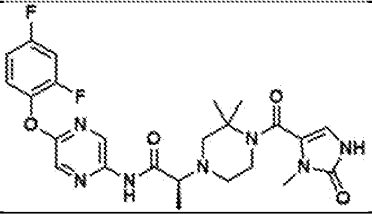
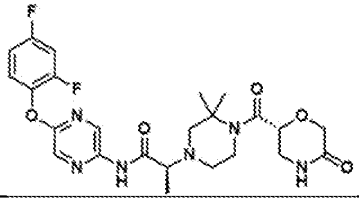
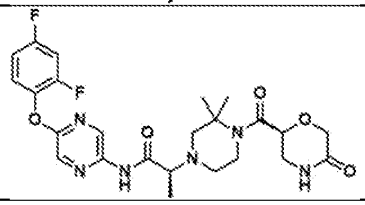
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or a pharmaceutically acceptable salt thereof.

61. A compound having the structure:

Structure	Example	Structure	Example
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or a pharmaceutically acceptable salt thereof.

62. A pharmaceutical composition, comprising a compound of any one of claims 1 to 61; and at least one pharmaceutically acceptable excipient.

63. A method of preventing or treating an MRGPRX2-mediated disease or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of the compound of any one of claims 1 to 61.

64. The method of claim 63, wherein the MRGPRX2 -mediated disease or disorder is selected from the group consisting of chronic spontaneous urticaria, prurigo nodularis, irritable bowel syndrome, chronic inducible urticaria, atopic dermatitis, osteoarthritis, rosacea, migraine, pseudo-analphylaxis, mast cell activation syndrome, mastocytosis, pruritus, neurodermatitis, contact urticaria, allergic rhinitis, asthma, acute contact dermatitis, ulcerative colitis, Crohn's disease, idiopathic chronic cough, rheumatoid arthritis, multiple sclerosis, geographic atrophy, endometriosis, seborrheic dermatitis, psoriasis, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, neuropathic itch, periodontitis, autism, abdominal aortic aneurysms, deep vein thrombosis, amyotrophic lateral sclerosis, interstitial cystitis, coronary artery disease, cancer, sickle cell disease, obesity, and ulcers.

65. The method of claim 63 or 64, wherein the MRGPRX2-mediated disease or disorder is prevented.

66. The method of claim 63 or 64, wherein the MRGPRX2-mediated disease or disorder is treated.