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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 August 2013 (22.08.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/123444 A1

(51) International Patent Classification:
C07D 403/12 (2006.01) *C07D 405/12* (2006.01)
C07D 401/14 (2006.01) *C07D 409/12* (2006.01)
A61K 31/44 (2006.01) *C07D 417/12* (2006.01)
A61K 31/496 (2006.01) *C07D 403/14* (2006.01)
A61K 31/505 (2006.01) *C07D 213/52* (2006.01)
C07D 401/04 (2006.01) *A61P 3/08* (2006.01)
C07D 401/12 (2006.01)

(21) International Application Number:
PCT/US2013/026508

(22) International Filing Date:
15 February 2013 (15.02.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/600,058 17 February 2012 (17.02.2012) US

(71) Applicant: **AMGEN INC.** [US/US]; One Amgen Center Drive, Thousand Oaks, CA 91320-1799 (US).

(72) Inventors: **ASHTON, Kate**; 30948 Minute Man Way, Westlake Village, CA 91361 (US). **BOURBEAU, Matthew, Paul**; 23510 Aetna Street, Woodland Hills, CA 91367 (US). **HONG, Fang-Tsao**; 822 Lynnmere Drive, Thousand Oaks, CA 91360 (US). **LIU, Longbin**; 753 Rushing Creek Place, Thousand Oaks, CA 91360 (US). **NISHIMURA, Nobuko**; 24050 Arminta Street, West Hills, CA 91304 (US). **NORMAN, Mark, H.**; 130 Venus Street, Thousand Oaks, CA 91360 (US). **POON, Steve, F.**; 5147 Comercio Avenue, Woodland Hills, CA 91364 (US). **STEC, Markian, M.**; One Amgen Center Drive, Thousand Oaks, CA 91320-1799 (US). **ST. JEAN, David, J., JR**; 4690 Marrisa Way, Camarillo, CA 93012 (US). **TAMAYO, Nuria, A.**; 4394 Camino De La Rosa, Newbury Park, CA 91320 (US). **YANG, Kevin, C.**; 8871 Camino Real Avenue, San Gabriel, CA 91775 (US).

(74) Agent: **CRISSEY, Todd, M.**; Amgen Inc., One Amgen Center Drive, M.S. 28-2-C, Thousand Oaks, CA 91320-1799 (US).

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

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

Declarations under Rule 4.17:

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

Published:

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

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: SULFONYL COMPOUNDS THAT INTERACT WITH GLUCOKINASE REGULATORY PROTEIN

(57) Abstract: The present invention relates to sulfonyl compounds that interact with glucokinase regulatory protein. In addition, the present invention relates to methods of treating type 2 diabetes, and other diseases and/or conditions where glucokinase regulatory protein is involved using the compounds, or pharmaceutically acceptable salts thereof, and pharmaceutical compositions that contain the compounds, or pharmaceutically acceptable salts thereof.

WO 2013/123444 A1

SULFONYL COMPOUNDS THAT INTERACT WITH GLUCOKINASE REGULATORY PROTEIN

FIELD OF THE INVENTION

The present invention relates to sulfonyl compounds, or pharmaceutically acceptable salts thereof, as defined herein, that interact with glucokinase regulatory protein. In addition, the present invention relates to methods of treating type 2 diabetes, and other diseases and/or conditions where glucokinase regulatory protein is involved using the compounds, or the pharmaceutically acceptable salts thereof, and pharmaceutical compositions that contain the compounds, or pharmaceutically acceptable salts thereof.

BACKGROUND OF THE INVENTION

Glucokinase (GK) is a member of a family of four hexokinases that are critical in the cellular metabolism of glucose. Specifically GK, also known as hexokinase IV or hexokinase D, facilitates glucose induced insulin secretion from pancreatic β-cells as well as glucose conversion into glycogen in the liver. GK has a unique catalytic activity that enables the enzyme to be active within the physiological range of glucose (from 5mM glucose to 10mM glucose).

Genetically modified mouse models support the role of GK playing an important role in glucose homeostasis. Mice lacking both copies of the GK gene die soon after birth from severe hyperglycemia, whereas mice lacking only one copy of the GK gene present with only mild diabetes. Mice that are made to overexpress the GK gene in their livers are hypoglycemic.

Numerous human mutations in the GK gene have been identified, with the vast majority of them resulting in proteins with impaired or absent enzymatic activity. These loss-of-function mutations are thought to contribute to the hyperglycemia seen with maturity-onset diabetes of the young type II (MODY-2). A small fraction of these mutations result in a GK with increased catalytic function. These individuals present with moderate to severe hypoglycemia.

GK activity in the liver is transiently regulated by glucokinase regulatory protein (GKRP). GK catalytic activity is inhibited when GK is bound to GKRP. This interaction is antagonized by increasing concentrations of both glucose and fructose -1-phosphate (F1P). The complex of the two proteins is localized primarily to the nuclear compartment of a cell. Post prandially as both glucose and fructose levels rise, GK released from GKRP translocates to the cytoplasm. Cytoplasmic GK is now free of the inhibitory effects of GKRP and able to kinetically respond to glucose. Evidence from the Zucker diabetic fatty rat (ZDF) indicates that their glucose intolerance may be a result of this mechanism failing to function properly.

A compound that acts directly on GKRP to disrupt its interaction with GK and hence elevate levels of cytoplasmic GK is a viable approach to modulate GK activity. Such an approach would avoid the unwanted hypoglycemic effects of over stimulation of GK catalytic activity, which has been seen in the development of GK activators. A compound having such an effect would be useful in the treatment of diabetes and other diseases and/or conditions in which GKRP and/or GK plays a role. The present invention provides compounds that bind GKRP and disrupts its interaction with GK.

SUMMARY OF THE INVENTION

In embodiment 1, the present invention provides compounds, or pharmaceutically acceptable salts thereof, selected from:

2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol;

2-(6-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(2-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-5-pyrimidinyl)-3,3,3-trifluoro-1,2-propanediol;

2-(4-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-((4-(hydroxymethyl)tetrahydro-2h-pyran-4-yl)methyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

1,1,1-trifluoro-2-(4-((2S)-2-(((1-methylethyl)amino)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol;

1,1,1-trifluoro-2-(4-((2S)-2-((((3-methyl-3-oxetanyl)methyl)amino)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol;

2-(4-((2S)-2-((cyclobutylamino)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-1,1,1-trifluoro-2-propanol;

1,1,1-trifluoro-2-(4-((2R)-2-(((1-methylethyl)sulfonyl)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol;

2-(4-(4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-3,3,3-trifluoro-1,2-propanediol;

2-(2-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-((1Z)-2-chloro-1-propen-1-yl)-1-piperazinyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol;

(2S)-2-(2-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-((1Z)-2-chloro-1-propen-1-yl)-1-piperazinyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol;

2-(6-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-3,3,3-trifluoro-1,2-propanediol;

2-(4-((2*S*)-4-((6-amino-3-pyridazinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-((2S)-4-((6-amino-3-pyridazinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-3,3,3-trifluoro-1,2-propanediol;

2-(4-(4-((5-amino-1,3-thiazol-2-yl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-((2S)-4-((6-amino-5-methyl-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-((2S)-4-((6-amino-5-bromo-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

3-bromo-5-(((3S)-3-(1-propyn-1-yl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinyl)sulfonyl)-2-pyridinol;

2-amino-5-(((3S)-3-(1-propyn-1-yl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinyl)sulfonyl)-3-pyridinecarbonitrile;

(2R)-2-(4-(4-((6-amino-3-pyridinyl)sulfonyl)-2-($^{2}H_3$)-1-propyn-1-yl-1-piperazinyl)phenyl)-1,1,1-trifluoro-2-propanol;

2-(4-(4-((6-amino-2-(methylamino)-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-(4-((6-amino-2-methoxy-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-(4-((6-amino-2-(benzyloxy)-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-(4-((6-amino-2-(1-propyn-1-yl)-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-(4-((6-amino-2-(1-propyn-1-yl)-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-(4-((6-amino-3-pyridinyl)sulfonyl)-2-(2-methyl-1-propen-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-(4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-butyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-(4-((6-amino-3-pyridinyl)sulfonyl)-2-(3,3-dimethyl-1-butyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-((1z)-1-propen-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-(4-((6-amino-3-pyridinyl)sulfonyl)-2-propyl-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

3-(4-((6-amino-3-pyridinyl)sulfonyl)-1-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-2-piperazinyl)-2-propyn-1-ol;

2-(4-(4-((6-amino-3-pyridinyl)sulfonyl)-2-(3-fluoro-1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-((2S)-4-((2-amino-5-pyrimidinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

(2R)-2-(4-((2S)-4-((2-amino-5-pyrimidinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1-trifluoro-2-propanol;

2-(6-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-5-chloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

3-(4-((6-amino-3-pyridinyl)sulfonyl)-1-(5-(2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-2-piperazinyl)-2-propyn-1-ol;

2-(2-((2S)-4-((6-amino-3-pyridazinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol;

1,1,1-trifluoro-2-(6-(4-(phenylsulfonyl)phenyl)-5-(1-propyn-1-yl)-3-pyridinyl)-2-propanol;

2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-chloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(1-propyn-1-yl)-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-cyclopropyl-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(3-methoxy-1-propyn-1-yl)-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

(2R)-4-(2-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)-3-pyridinyl)-3-butyn-2-ol;

3-(2-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)-3-pyridinyl)-2-propyn-1-ol;

1,1,1,3,3,3-hexafluoro-2-(5'-(phenylsulfonyl)-2,2'-bipyridin-5-yl)-2-propanol;
2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(3-methoxy-1-propyn-1-yl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol;

2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(cyclopropylethynyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol;

(2R)-4-(2-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(2,2,2-trifluoro-1-hydroxy-1-methylethyl)-3-pyridinyl)-3-butyn-2-ol;

(2S)-4-(2-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(2,2,2-trifluoro-1-hydroxy-1-methylethyl)-3-pyridinyl)-3-butyn-2-ol;

2-(2-(4-((6-amino-5-fluoro-3-pyridinyl)sulfonyl)phenyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol;

2-(2-(4-((6-amino-5-methyl-3-pyridinyl)sulfonyl)phenyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol;

2-(2-(4-((6-amino-3-pyridazinyl)sulfonyl)phenyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol; or

2-(5'-((6-amino-3-pyridinyl)sulfonyl)-2,2'-bipyridin-5-yl)-1,1,1-trifluoro-2-propanol.

In embodiment 2, the present invention provides methods of treating type 2 diabetes, hyperglycemia, impaired glucose tolerance, insulin resistance, retinopathy, nephropathy, neuropathy, cataracts, glaucoma, Syndrome X, or polycystic ovarian syndrome, the methods comprising administering to a patient in need thereof a therapeutically effective amount of a compound in accordance with embodiment 1, or a pharmaceutically acceptable salt thereof.

In embodiment 3, the present invention provides methods of treating in accordance with embodiment 2 wherein the treatment is for type 2 diabetes.

In embodiment 4, the present invention provides pharmaceutical compositions comprising a compound in accordance with embodiment 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

DETAILED DESCRIPTION

The present invention provides sulfonyl compounds, as defined above, or pharmaceutically acceptable salts thereof. The present invention also provides pharmaceutical compositions comprising a compound of the present invention, or pharmaceutically acceptable salts thereof, and methods of treating diseases and/or conditions, such as diabetes, using compounds of the present invention, or pharmaceutically acceptable salts thereof.

The term "alkyl" means a straight or branched chain hydrocarbon. Representative examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, sec-butyl, pentyl and hexyl. Typical alkyl groups are alkyl groups having from 1 to 8 carbon atoms, which groups are commonly represented as C_{1-8}alkyl.

The term "alkoxy" means an alkyl group bonded to an oxygen atom. Representative examples of alkoxy groups include methoxy, ethoxy, tert-butoxy, propoxy and isobutoxy. Common alkoxy groups are C_{1-8}alkoxy.

The term "halogen" or "halo" means chlorine, fluorine, bromine or iodine.

The term "alkenyl" means a branched or straight chain hydrocarbon having one or more carbon-carbon double bonds. Representative examples alkenyl groups include ethenyl, propenyl, allyl, butenyl and 4-methylbutenyl. Common alkenyl groups are C_{2-8}alkenyl.

The term "alkynyl" means a branched or straight chain hydrocarbon having one or more carbon-carbon triple bonds. Representative examples of alkynyl groups include ethynyl, propynyl (propargyl) and butynyl. Common alkynyl groups are C_{2-8} alkynyl.

The term "cycloalkyl" means a cyclic, nonaromatic hydrocarbon. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A cycloalkyl group can contain one or more double bond. Examples of cycloalkyl groups that contain double bonds include cyclopentenyl, cyclohexenyl, cyclohexadienyl and cyclobutadienyl. Common cycloalkyl groups are C_{3-8} cycloalkyl groups.

The term "perfluoroalkyl" means an alkyl group in which all of the hydrogen atoms have been replaced with fluorine atoms. Common perfluoroalkyl groups are C_{1-8}perfluoroalkyl. An example of a common perfluoroalkyl group is $-CF_3$.

The term "acyl" means a group derived from an organic acid by removal of the hydroxy group (-OH). For example, the acyl group $CH_3C(=O)-$ is formed by the removal of the hydroxy group from $CH_3C(=O)OH$.

The term "aryl" means a cyclic, aromatic hydrocarbon. Examples of aryl groups include phenyl and naphthyl. Common aryl groups are six to thirteen membered rings.

The term "heteroatom" as used herein means an oxygen, nitrogen or sulfur atom.

The term "heteroaryl" means a cyclic, aromatic hydrocarbon in which one or more carbon atoms of an aryl group have been replaced with a heteroatom. If the heteroaryl group contains more than one heteroatom, the heteroatoms may be the same or different. Examples of heteroaryl groups include pyridyl, pyrimidinyl, imidazolyl, thienyl, furyl, pyrazinyl, pyrrolyl, indolyl, triazolyl, pyridazinyl, indazolyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, naphthyridinyl, quinoxalinyl, isothiazolyl and benzo[b]thienyl. Common heteroaryl groups are five to thirteen membered rings that contain from 1 to 4 heteroatoms. Heteroaryl groups that are five and six membered rings that contain 1 to 3 heterotaoms are particularly common.

The term "heterocycloalkyl" means a cycloalkyl group in which one or more of the carbon atoms has been replaced with a heteroatom. If the heterocycloalkyl group contains more than one heteroatom, the heteroatoms may be the same or different. Examples of heterocycloalkyl groups include tetrahydrofuryl, morpholinyl, piperazinyl, piperidinyl and pyrrolidinyl. It is also possible for the heterocycloalkyl group to have one or more double bonds, but is not aromatic. Examples of heterocycloalkyl groups containing double bonds include dihydrofuran. Common heterocycloalkyl groups are three to ten membered rings containing from 1 to 4 heteroatoms. Heterocycloalkyl groups that are five and six membered rings that contain 1 to 2 heterotaoms are particularly common.

It is also noted that the cyclic ring groups, i.e., aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, can comprise more than one ring. For example, the naphthyl group is a fused bicyclic ring system. It is also intended that the present invention include ring groups that have bridging atoms, or ring groups that have a spiro orientation.

Representative examples of five to six membered aromatic rings, optionally having one or two heteroatoms, are phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyridiazinyl, pyrimidinyl, and pyrazinyl.

Representative examples of partially saturated, fully saturated or fully unsaturated five to eight membered rings, optionally having one to three heteroatoms, are cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and phenyl. Further exemplary five membered rings are furyl, thienyl, pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 1,3-dioxolanyl, oxazolyl, thiazolyl, imidazolyl, 2H-imidazolyl, 2-imidazolinyl, imidazolidinyl, pyrazolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2-dithiolyl, 1,3-dithiolyl, 3H-1,2-oxathiolyl, 1,2,3-oxadizaolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4oxadiazolyl, 1,2,3-triazolyl, 1,2,4-trizaolyl, 1,3,4-thiadiazolyl, 3H-1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-dioxazolyl, 5H-1,2,5-oxathiazolyl, and 1,3-oxathiolyl.

Further exemplary six membered rings are 2H-pyranyl, 4H-pyranyl, pyridinyl, piperidinyl, 1,2-dioxinyl, 1,3-dioxinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyndazinyl, pyrimidinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-trithianyl, 4H-1,2-oxazinyl, 2H-1,3-oxazinyl, 6H-1,3-oxazinyl, 6H-1,2-oxazinyl, 1,4-oxazinyl, 2H-1,2-oxazinyl, 4H-1,4-oxazinyl, 1,2,5-oxathiazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,2,6-(3 oxathiazinyl, and 1,4,2-oxadiazinyl.

Further exemplary seven membered rings are azepinyl, oxepinyl, thiepinyl and 1,2,4-triazepinyl.

Further exemplary eight membered rings are cyclooctyl, cyclooctenyl and cyclooctadienyl.

Exemplary bicyclic rings consisting of two fused partially saturated, fully saturated or fully unsaturated five and/or six membered rings, optionally having one to four heteroatoms, are indolizinyl, indolyl, isoindolyl, indolinyl, cyclopenta(b)pyridinyl, pyrano(3,4-b)pyrrolyl, benzofuryl, isobenzofuryl, benzo(b)thienyl, benzo(c)thienyl, 1H-indazolyl, indoxazinyl, benzoxazolyl, anthranilyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, indenyl, isoindenyl, naphthyl, tetralinyl, decalinyl, 2H-1-benzopyranyl, pyrido(3,4-b)pyridinyl, pyrido(3,2-b)pyridinyl, pyrido(4,3-b)-

pyridinyl, 2H-1,3-benzoxazinyl, 2H-1,4-benzoxazinyl, 1H-2,3-benzoxazinyl, 4H-3,1-benzoxazinyl, 2H-1,2-benzoxazinyl and 4H-1,4-benzoxazinyl.

A cyclic ring group may be bonded to another group in more than one way. If no particular bonding arrangement is specified, then all possible arrangements are intended. For example, the term "pyridyl" includes 2-, 3-, or 4-pyridyl, and the term "thienyl" includes 2-, or 3-thienyl.

The term “substituted” means that a hydrogen atom on a molecule or group is replaced with a group or atom. Typical substitutents include: halogen, $C_{1\text{-}8}$alkyl, hydroxyl, $C_{1\text{-}8}$alkoxy, $-NR^xR^x$, nitro, cyano, halo or perhalo$C_{1\text{-}8}$alkyl, $C_{2\text{-}8}$alkenyl, $C_{2\text{-}8}$alkynyl, $-SR^x$, $-S(=O)_2R^x$, $-C(=O)OR^x$, $-C(=O)R^x$, wherein each R^x is independently hydrogen or C_1-C_8 alkyl. It is noted that when the substituent is $-NR^xR^x$, the R^x groups may be joined together with the nitrogen atom to form a ring.

The term “oxo”, when used as a substituent, means the =O group, which is typically attached to a carbon atom.

A group or atom that replaces a hydrogen atom is also called a substituent.

Any particular molecule or group can have one or more substituent depending on the number of hydrogen atoms that can be replaced.

The symbol "–" represents a covalent bond and can also be used in a radical group to indicate the point of attachment to another group. In chemical structures, the symbol is commonly used to represent a methyl group in a molecule.

The term "therapeutically effective amount" means an amount of a compound that ameliorates, attenuates or eliminates one or more symptom of a particular disease or condition, or prevents or delays the onset of one of more symptom of a particular disease or condition.

The term "patient" means animals, such as dogs, cats, cows, horses, sheep and humans. Particular patients are mammals. The term patient includes males and females.

The term "pharmaceutically acceptable" means that the referenced substance, such as a compound of the present invention or a formulation containing a compound of the present invention, or a particular excipent, are suitable for administration to a patient.

The terms "treating", "treat" or "treatment" and the like include preventative (e.g., prophylactic) and palliative treatment.

The term “patient in need thereof” means a patient who has or is at risk of having a GKRP/GK mediated disease or condition, such as type 2 diabetes.

The term “excipient” means any pharmaceutically acceptable additive, carrier, diluent, adjuvant, or other ingredient, other than the active pharmaceutical ingredient (API), which is typically included for formulation and/or administration to a patient.

The compounds of the present invention are administered to a patient in a therapeutically effective amount. The compounds can be administered alone or as part of a pharmaceutically acceptable composition or formulation. In addition, the compounds or compositions can be administered all at once, as for example, by a bolus injection, multiple times, such as by a series of tablets, or delivered substantially uniformly over a period of time, as for example, using transdermal delivery. It is also noted that the dose of the compound can be varied over time.

In addition, the compounds of the present invention can be administered alone, in combination with other compounds of the present invention, or with other pharmaceutically active compounds. The other pharmaceutically active compounds can be intended to treat the same disease or condition as the compounds of the present invention or a different disease or condition. If the patient is to receive or is receiving multiple pharmaceutically active compounds, the compounds can be administered simultaneously, or sequentially. For example, in the case of tablets, the active compounds may be found in one tablet or in separate tablets, which can be administered at once or sequentially in any order. In addition, it should be recognized that the compositions may be different forms. For example, one or more compound may be delivered via a tablet, while

another is administered via injection or orally as a syrup. All combinations, delivery methods and administration sequences are contemplated.

The compounds of the present invention may be used in the manufacture of a medicament for the treatment of a disease and/or condition mediated by GKRP/GK, such as type 2 diabetes.

The compounds of the present invention may be used in combination with other pharmaceutically active compounds. It is noted that the term "pharmaceutically active compounds" can include biologics, such as proteins, antibodies and peptibodies. Examples of other pharmaceutically active compounds include, but are not limited to: (a) dipeptidyl peptidase IV (DPP-IV) inhibitors such as Vildagliptin (Novartis), Sitagliptin (Merck&Co.), Saxagliptin (BMS) Alogliptin (Takeda); (b) insulin sensitizers including (i) PPARγ agonists such as the glitazones (e.g., troglitazone, pioglitazone, edaglitazone, rosiglitazone, and the like) and other PPAR ligands, including PPARα/γ dual agonists such as muraglitazar (BMS) and tesaglitazar (AstraZeneca), and PPARα agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and bezafibrate), (ii) biguanides such as metformin and phenformin, and (iii) protein tyrosine phosphatase-lB (PTP-1B) inhibitors; (c) insulin or insulin mimetics; (d) incretin and incretin mimetics such as (i) Exenatide available from Amylin Pharmaceuticals, (i) amylin and amylin mimetics such as pramlintide acetate, available as Symlin®, (iii) GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists, (iv) GIP, GIP mimetics and GIP receptor agonists; (e) sulfonylureas and other insulin secretagogues, such as tolbutamide, glyburide, gliclazide, glipizide, glimepiride, meglitinides, and repaglinide; (f) α-glucosidase inhibitors (such as acarbose and miglitol); (g) glucagon receptor antagonists; (h) PACAP, PACAP mimetics, and PACAP receptor agonists; (i) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, cerivastatin, fluvastatin, atorvastatin, itavastatin, and rosuvastatin, and other statins), (ii) sequestrants such as cholestyramine, colestipol and dialkylaminoalkyl derivatives of a cross-linked dextran, (iii) nicotinyl alcohol, nicotinic acid or a salt thereof, (iv) PPARα agonists such as fenofibric acid

derivatives (gemfibrozil, clofibrate, fenofibrate and bezafibrate), (v) PPARα/γ dual agonists such as muraglitazar (BMS) and tesaglitazar (AstraZeneca), (vi) inhibitors of cholesterol absorption, such as beta-sitosterol and ezetimibe, (vii) acyl CoA:cholesterol acyltransferase inhibitors such as avasimibe, and (viii) anti-oxidants such as probucol; (j) PPARδ agonists such as GW-501516 from GSK; (k) anti-obesity compounds such as fenfluramine, dexfenfluramine, phentemine, sibutramine, orlistat, neuropeptide Y1 or Y5 antagonists, MTP inhibitors, squalene synthase inhibitor, lipoxygenase inhibitor, ACAT inhibitor, Neuropeptide Cannabinoid CB-1 receptor antagonists, CB-1 receptor inverse agonists and antagonists, fatty acid oxidation inhibitors, appetite suppressants (l) adrenergic receptor agonists, melanocortin receptor agonists, in particular - melanocortin-4 receptor agonists, ghrelin antagonists, and melanin- concentrating hormone (MCH) receptor antagonists; (m) ileal bile acid transporter inhibitors; (n) agents intended for use in inflammatory conditions such as aspirin, non steroidal anti-inflammatory drugs, glucocorticoids, azalfidine, and selective cyclooxygenase-2 inhibitors; (o) antihypertensive agents such as ACE inhibitors (enalapril, lisinopril, captopril, quinapril, fosinoprol, ramipril, spirapril, tandolapril), angiotensin-II (AT-1) receptor blockers (losartan, candesartan, irbesartan, valsartan, telmisartan, eprosartan), beta blockers and calcium channel blockers; and (p) glucokinase activators (GKAs); (q) agents which can be used for the prevention, delay of progression or treatment of neurodegenerative disorders, cognitive disorders or a drug for improving memory such as anti-inflammatory drugs, antioxidants, neuroprotective agents, glutamate receptor antagonists, acetylcholine esterase inhibitors, butyrylcholinesterase inhibitors, MAO inhibitors, dopamine agonists or antagonists, inhibitors of gamma and beta secretases, inhibitors of amyloid aggregation, amyloid beta peptide, antibodies to amyloid beta peptide, inhibitors of acetylcholinesterase, glucokinase activators, agents directed at modulating GABA, NMDA, cannabinoid, AMPA, kainate, phosphodiesterase (PDE), PKA, PKC, CREB or nootropic systems; (r) leukocyte growth promotors intended for the treatment and prevention of reduced bone marrow production, infectious diseases, hormone dependent disorders,

inflammatory diseases, HIV, allergies, leukocytopenia, and rheumatism; (s) SGLT2 inhibitor; (t) glycogen phosphorylase inhibitor; (u) aP2 inhibitors; (v) aminopeptidase N inhibitor (w) vasopeptidase inhibitors like neprilysin inhibitors and/or ACE inhibitors or dual NEP/ACE inhibitor; (x) growth hormone secretagogue for enhancing growth hormone levels and for treating growth retardation / dwarfism or metabolic disorders or where the disorder is an injury, or a wound in need of healing, or a mammalian patient recovering from surgery; (y) 5-HT 3 or 5-HT 4 receptor modulators (tegaserod, cisapride, nor-cisapride, renzapride, zacopride, mosapride, prucalopride, buspirone, norcisapride, cilansetron, ramosetron, azasetron, ondansetron, etc.); (Za) aldose reductase inhibitors; (Zb) sorbitol dehydrogenase inhibitors; (Zc) AGE inhibitors; (Zd) erythropoietin agonist such as EPO, EPO mimetics, and EPO receptor agonists. The compounds of the present invention may also be used in combination with GPR40 agonists.

Examples of glucokinase activators that can be used in combination with the compounds of the present invention include those set forth in published PCT patent application no. WO 2009/042435, published April 2, 2009. Examples of specific compounds, or pharmaceutically acceptable salts thereof, disclosed in the published application that may be used in combination with the compounds of the present invention, or pharmaceutically acceptable salts thereof, include compounds selected from:

(S)-1-(5-(5-bromo-3-(2-methylpyridin-3-yloxy)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)ethane-1,2-diol;

(S)-1-(5-(5-trifluoromethyl-3-(2-methylpyridin-3-yloxy)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)ethane-1,2-diol;

(S)-1-(5-(5-phenylthio-3-(2-methylpyridin-3-yloxy)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl) ethane-1,2-diol;

(S)-1-(5-(5-phenylthio-3-(pyridin-3-yloxy)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)piperidin-1-yl)ethane-1,2-diol;

(S)-1-(5-(3-(2-methylpyridin-3-yloxy)-5-(pyridin-2-ylthio)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)ethane-1,2-diol;

(S)-1-(5-(5(2hydroxyethylthio)-3-(2-methylpyridin-3-yloxy)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)ethane-1,2-diol;

(S)-1-(5-(4-fluorophenoxy)-5-pyridin-2-ylthio)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl) ethane-1,2-diol;

(R)-1-(2-(5-bromo-3-(4-fluorophenoxy)pyridin-2-ylamino)thiazol-4-yl)ethane-1,2-diol;

(S)-1-(2-(5-bromo-3-(4-fluorophenoxy)pyridin-2-ylamino)thiazol-4-yl)ethane-1,2-diol;

(R)-1-(2-(3-(4-fluorophenoxy)-5-(pyridin-2-ylthio)pyridin-2-ylamino)thiazol-4-yl)-ethane-1,2-diol;

(1S)-1-(5-(5-bromo-3-(5,6,7,8-tetrahydroquinolin-5-yloxy)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)ethane-1,2-diol;

(S)-1-(5-(5-bromo-3-(1-(2-hydroxyethyl)-1H-pyrazol-4-yloxy)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)ethane-1,2-diol;

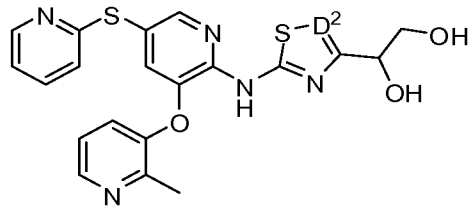
(R)-1-(2-(5-bromo-3-(2-methylpyridin-3-yloxy)pyridin-2-ylamino)thiazol-4-yl)-ethane-1,2-diol;

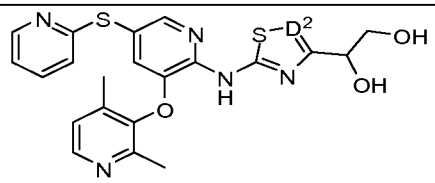
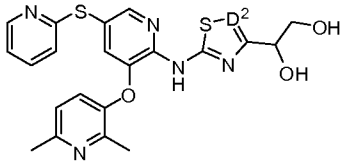
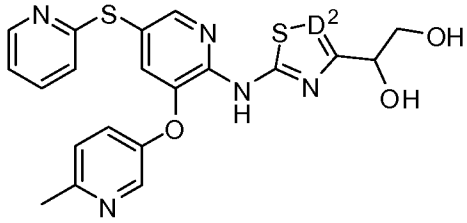
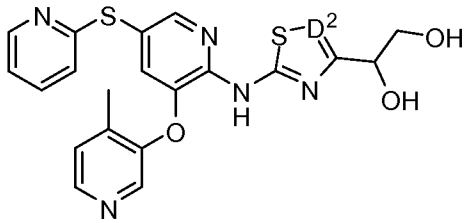
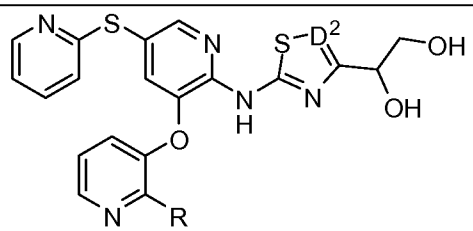
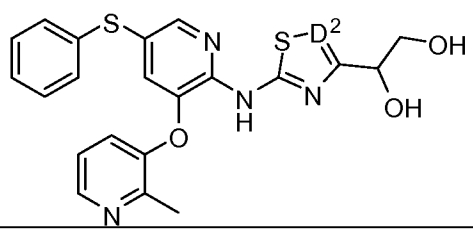
(S)-1-(5-(5-(2-hydroxyethylthio)-3-(pyridin-3-yloxy)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)ethane-1,2-diol;

(S)-1-(5-(5-bromo-3-(1-methyl-1H-pyrazol-4-yloxy)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)ethane-1,2-diol;

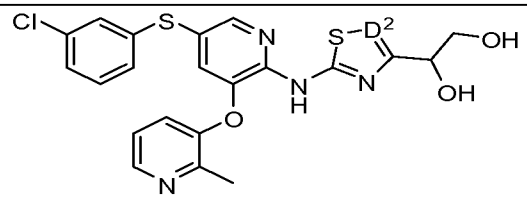
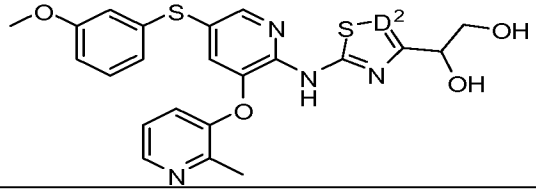
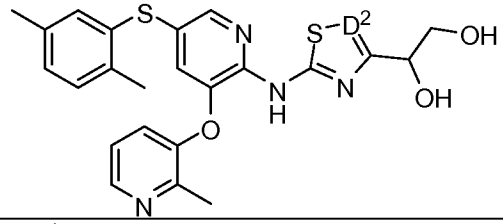
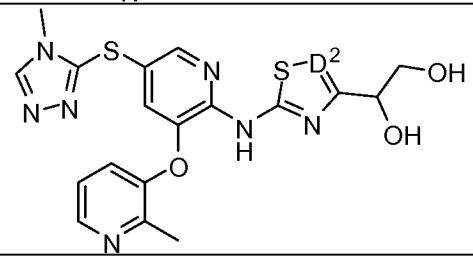
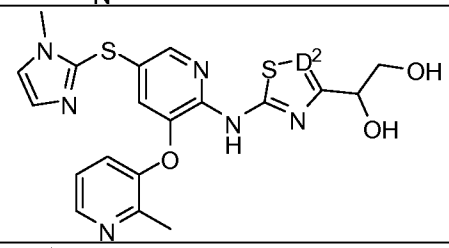
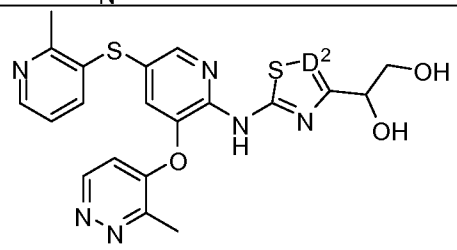
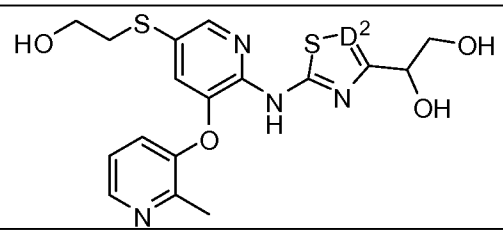
(S)-1-(5-(3-(1-methyl-1H-pyrazol-4-yloxy)-5-(2-methylpyridin-3-ylthio)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)ethane-1,2-diol;

(S)-1-(5-(5-(2-methylpyridin-3-ylthio)-3-(1,3,5-trimethyl-1H-pyrazol-4-yloxy)-pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)ethane-1,2-diol;

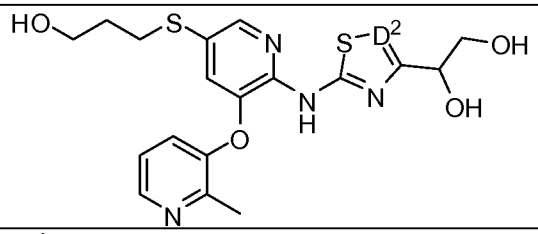
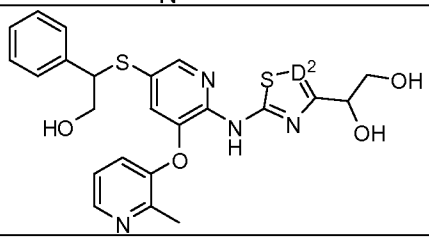
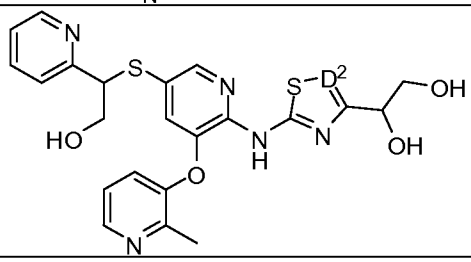
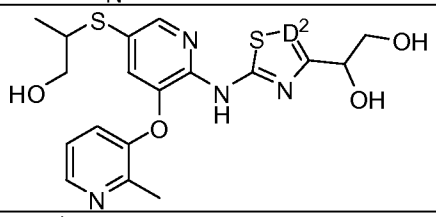
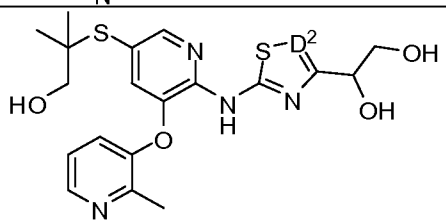
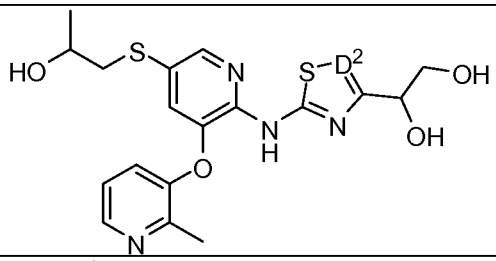
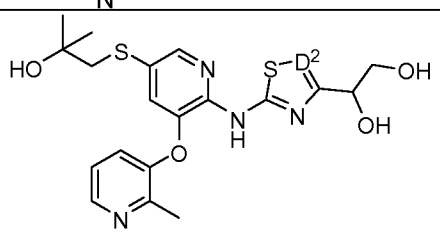
	D^2 = CH
	D^2 = N

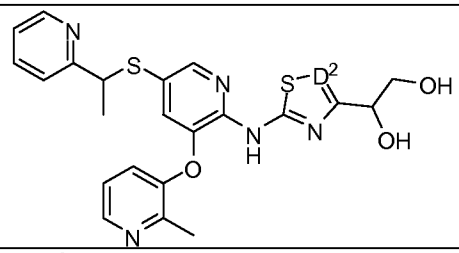
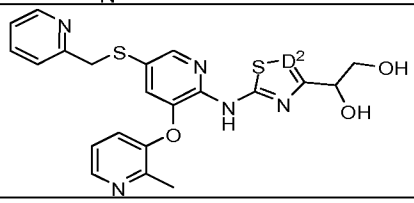
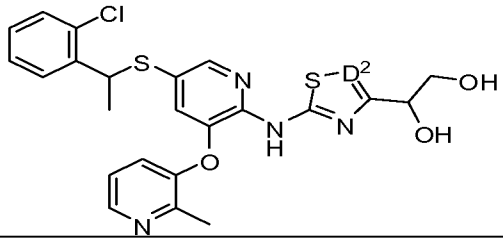
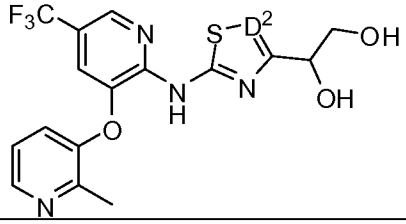
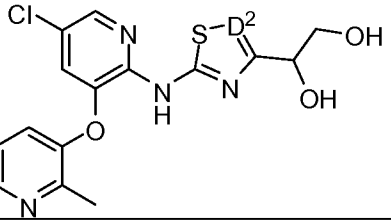
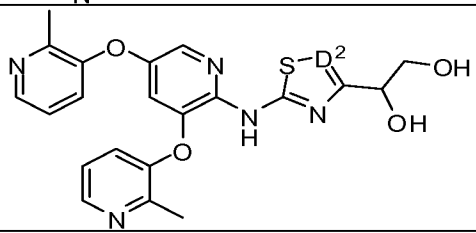
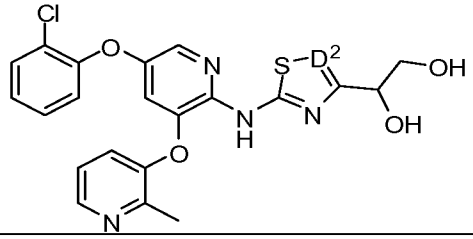
	D^2 = CH
	D^2 = N
	D^2 = CH
	D^2 = N
	D^2 = CH
	D^2 = N
	D^2 = CH
	D^2 = N
	D^2 = CH R = Et, iPr, CH_2OH, CH_2CH_2OH, or CF_3
	D^2 = N R = Et, iPr, CH_2OH, CH_2CH_2OH, or CF_3
	D^2 = CH
	D^2 = N

5

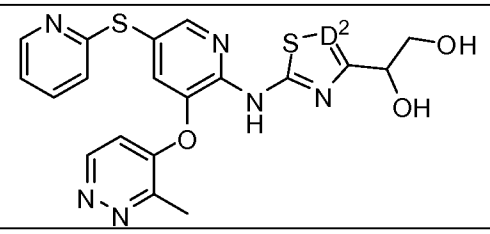
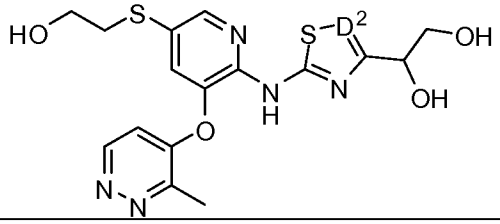
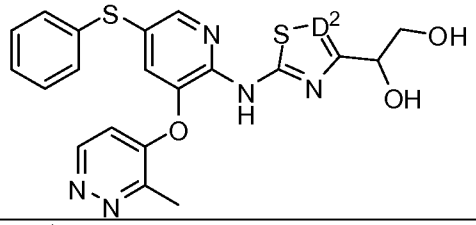
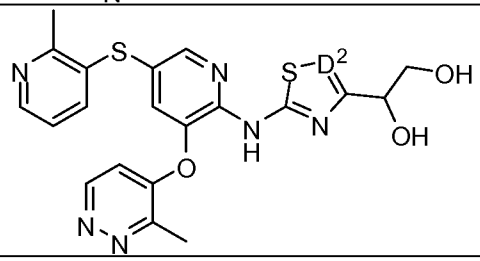
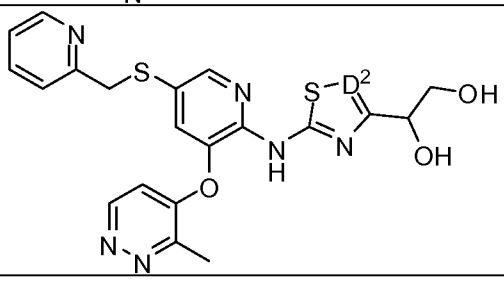
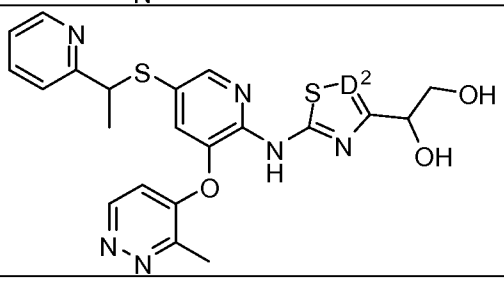
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N

5

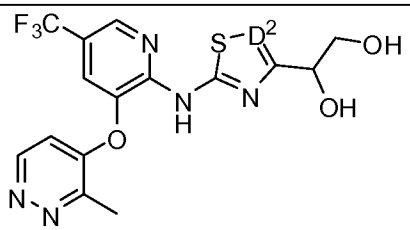
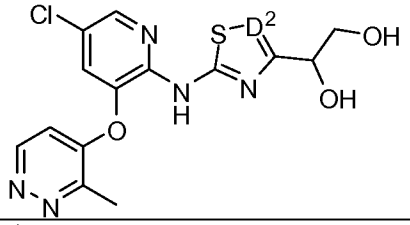
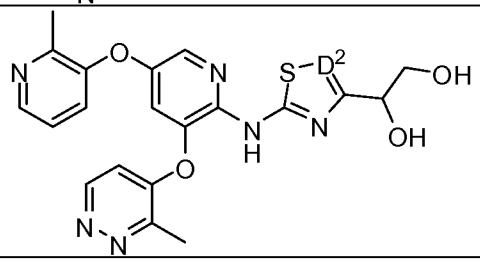
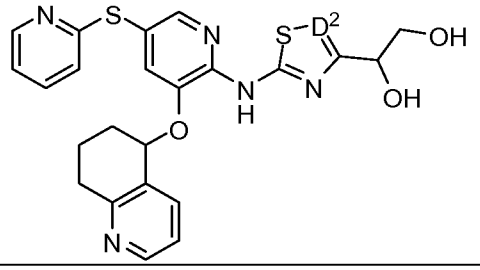
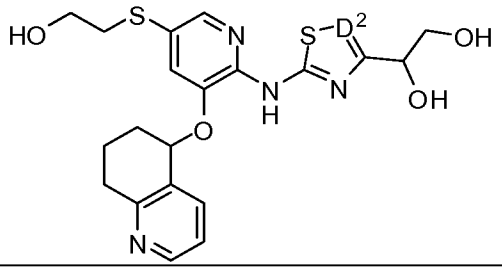
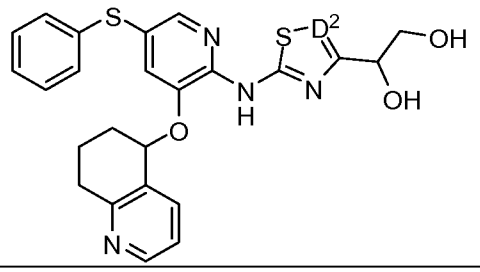
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N

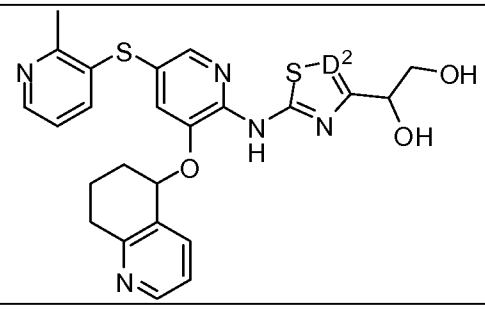
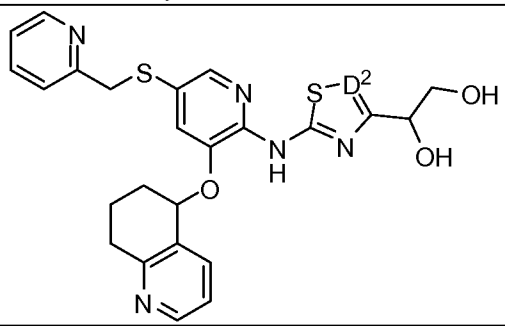
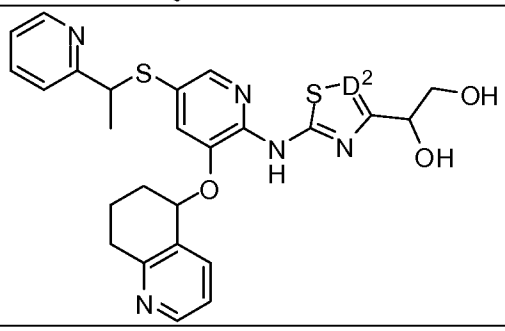
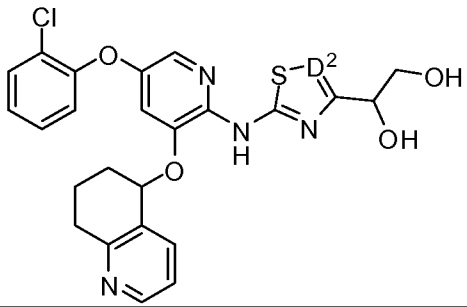
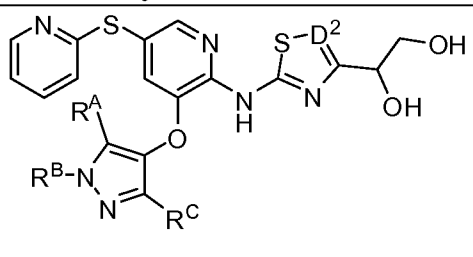
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N

5

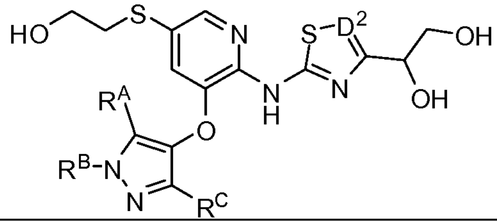
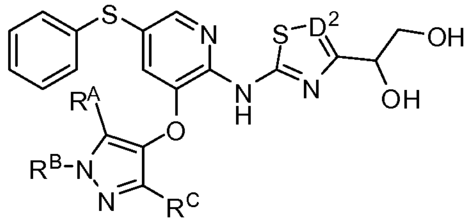
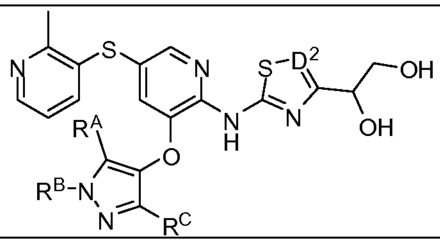
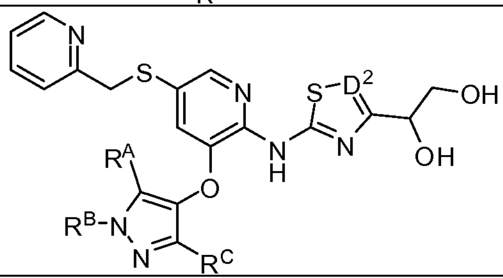
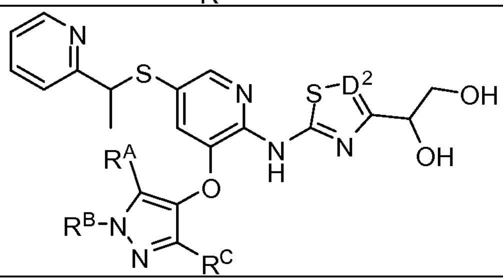
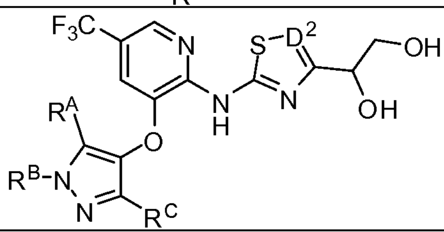
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N

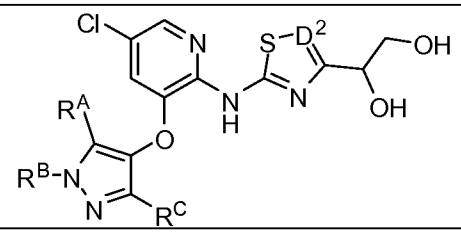
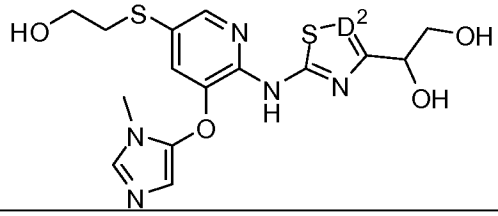
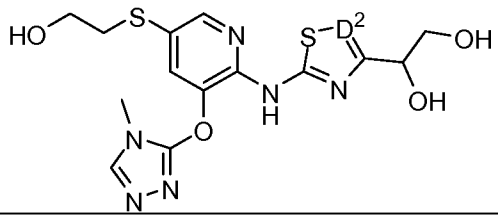
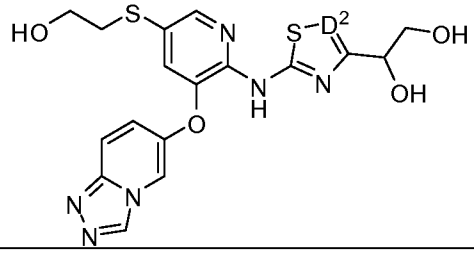
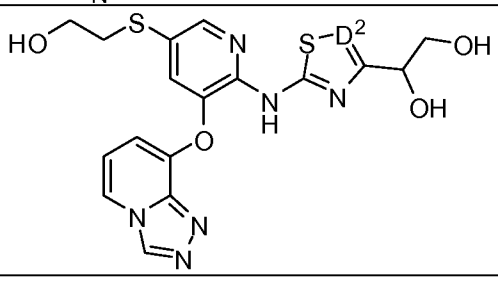
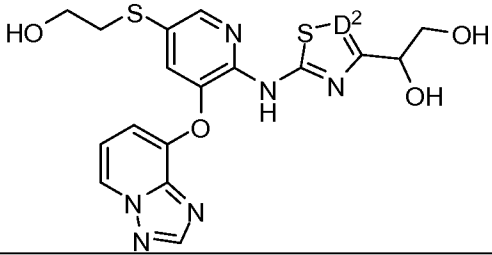
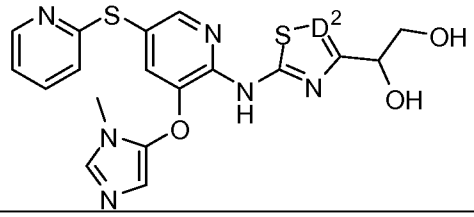
5

	D^2 = CH
	D^2 = N
	D^2 = CH
	D^2 = N
	D^2 = CH
	D^2 = N
	D^2 = CH
	D^2 = N
	D^2 = CH
	D^2 = N
	D^2 = CH
	D^2 = N

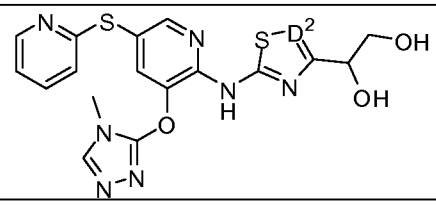
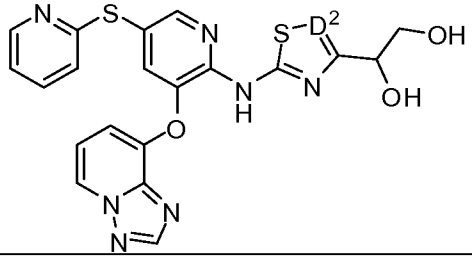
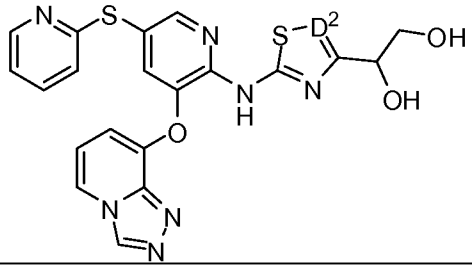
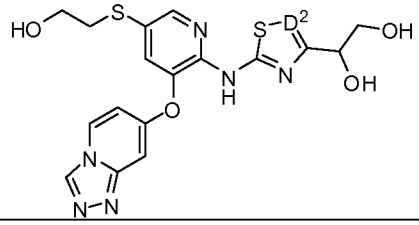
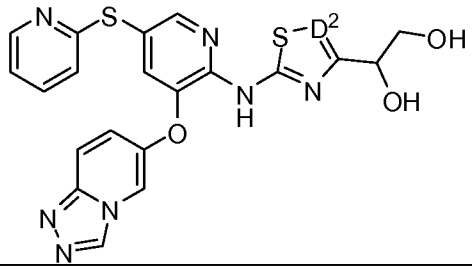
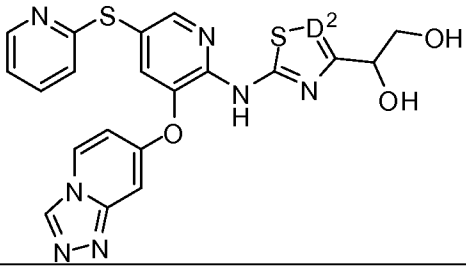
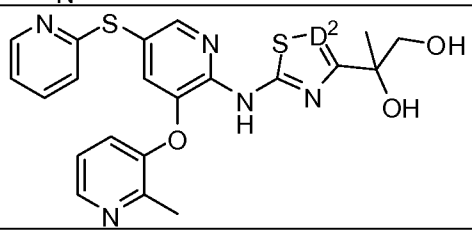
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH R^A, R^B, R^C are independently H or Me D^2 = N R^A, R^B, R^C are independently H or Me

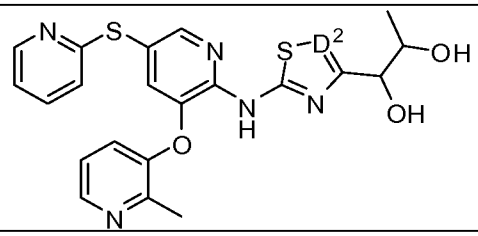
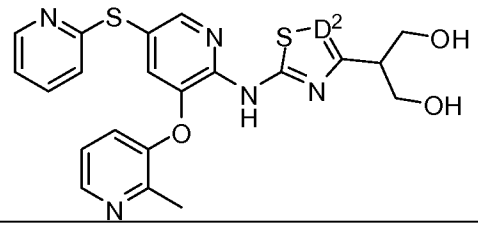
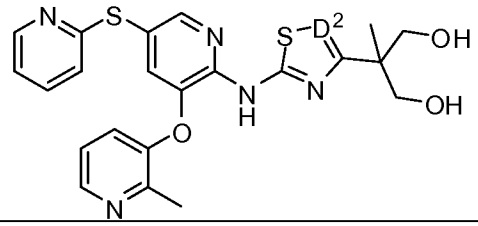
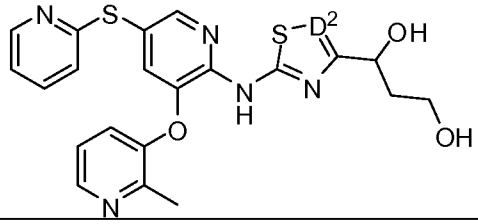
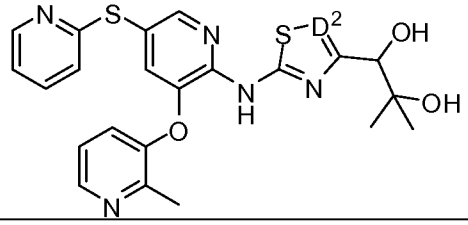
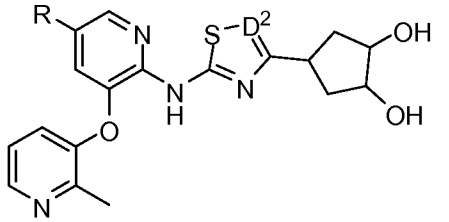
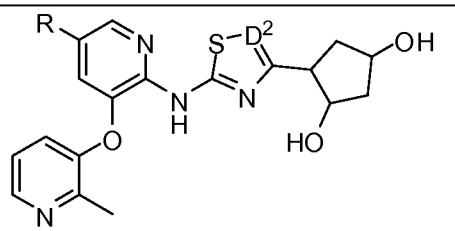
5

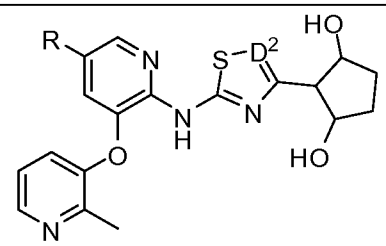
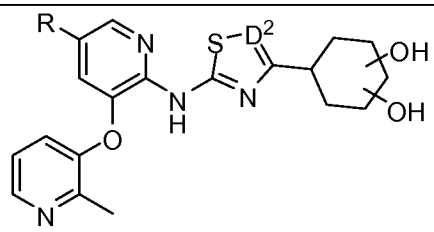
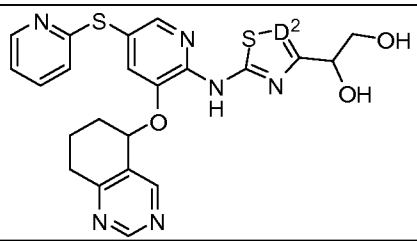
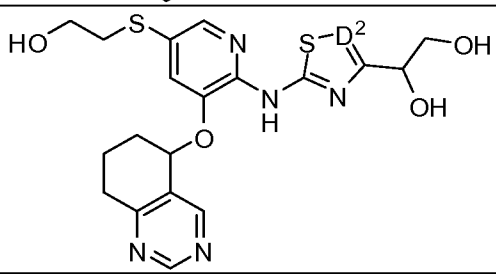
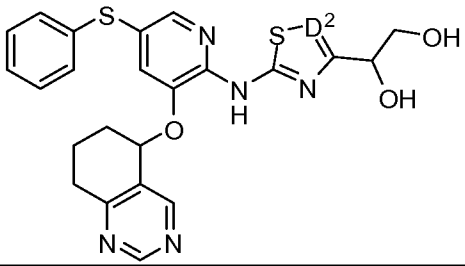
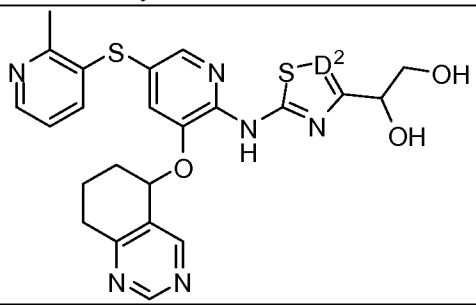
	D^2 = CH R^A, R^B, R^C are independently H or Me
	D^2 = N R^A, R^B, R^C are independently H or Me
	D^2 = CH R^A, R^B, R^C are independently H or Me
	D^2 = N R^A, R^B, R^C are independently H or Me
	D^2 = CH R^A, R^B, R^C are independently H or Me
	D^2 = N R^A, R^B, R^C are independently H or Me
	D^2 = CH R^A, R^B, R^C are independently H or Me
	D^2 = N R^A, R^B, R^C are independently H or Me
	D^2 = CH R^A, R^B, R^C are independently H or Me
	D^2 = N R^A, R^B, R^C are independently H or Me
	D^2 = CH R^A, R^B, R^C are independently H or Me
	D^2 = N R^A, R^B, R^C are independently H or Me

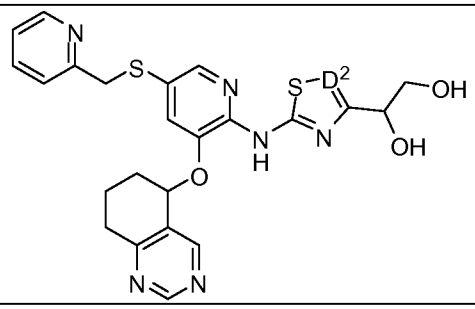
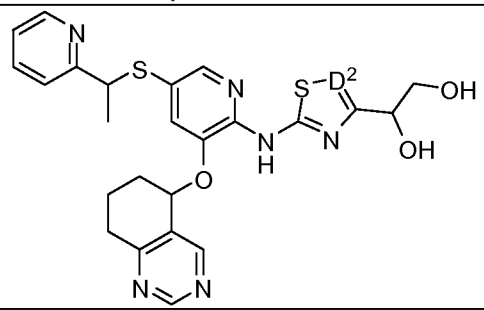
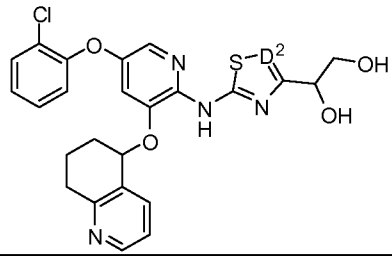
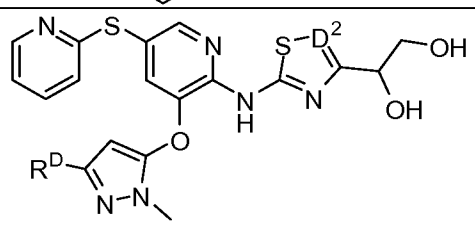
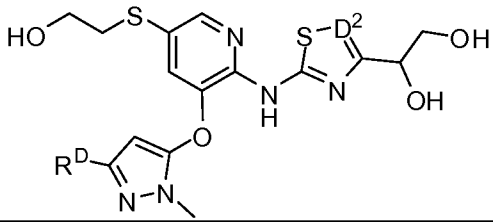
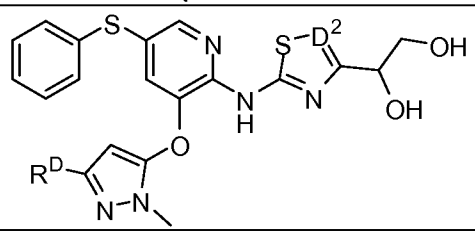
	D^2 = CH R^A, R^B, R^C are independently H or Me
	D^2 = N R^A, R^B, R^C are independently H or Me
	D^2 = CH
	D^2 = N
	D^2 = CH
	D^2 = N
	D^2 = CH
	D^2 = N
	D^2 = CH
	D^2 = N
	D^2 = CH
	D^2 = N
	D^2 = CH
	D^2 = N

5

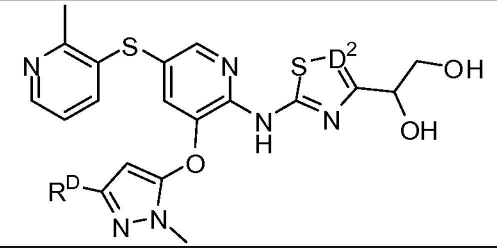
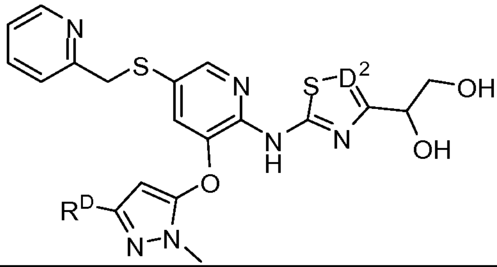
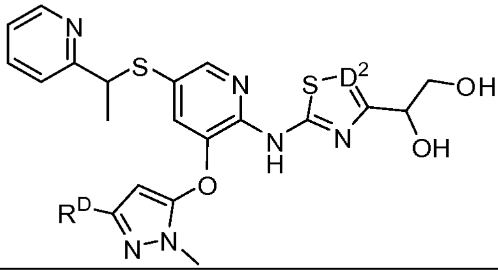
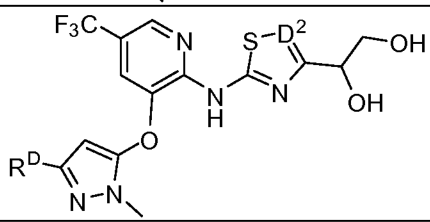
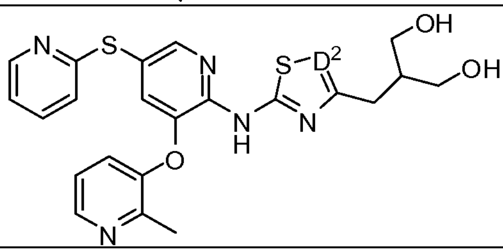
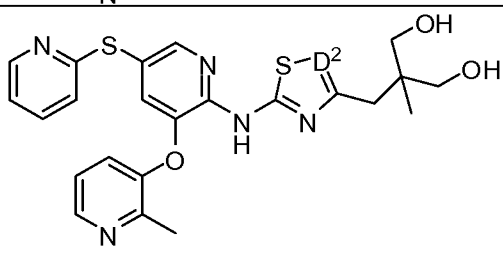
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N

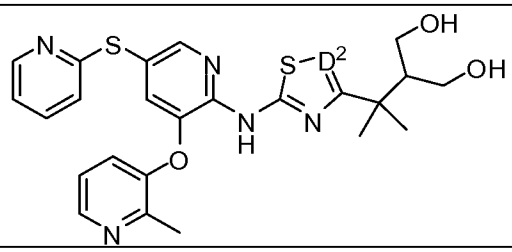
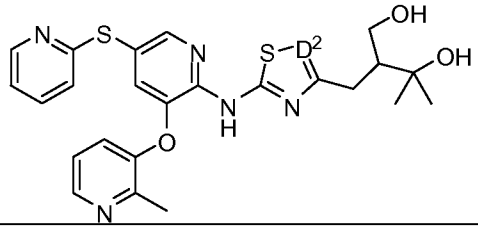
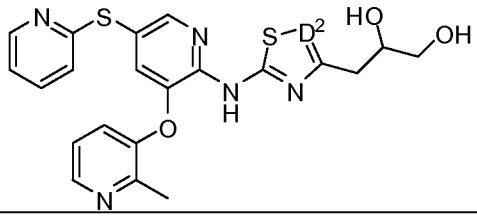
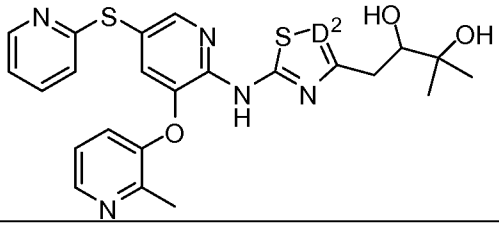
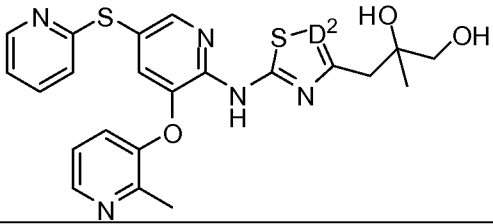
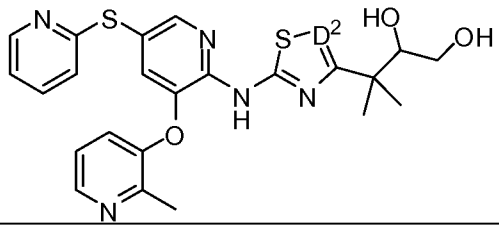
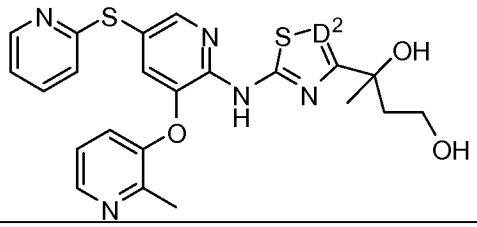
	D^2 = CH
	D^2 = N
	D^2 = CH
	D^2 = N
	D^2 = CH
	D^2 = N
	D^2 = CH
	D^2 = N
	D^2 = CH
	D^2 = N
	D^2 = CH R = S-pyrid-2-yl, CF_3, S-2-methylpyrid-3-yl
	D^2 = N R = S-pyrid-2-yl, CF_3, S-2-methylpyrid-3-yl
	D^2 = CH R = S-pyrid-2-yl, CF_3, S-2-methylpyrid-3-yl
	D^2 = N R = S-pyrid-2-yl, CF_3, S-2-methylpyrid-3-yl

	D^2 = CH R = S-pyrid-2-yl, CF_3, S-2-methylpyrid-3-yl
	D^2 = N R = S-pyrid-2-yl, CF_3, S-2-methylpyrid-3-yl
	D^2 = CH R = S-pyrid-2-yl, CF_3, S-2-methylpyrid-3-yl
	D^2 = N R = S-pyrid-2-yl, CF_3, S-2-methylpyrid-3-yl
	D^2 = CH
	D^2 = N
	D^2 = CH
	D^2 = N
	D^2 = CH
	D^2 = N
	D^2 = CH
	D^2 = N

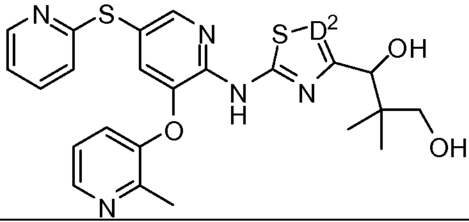
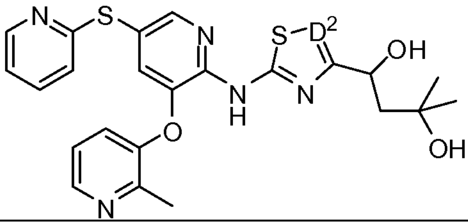
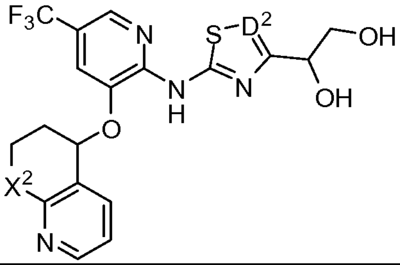
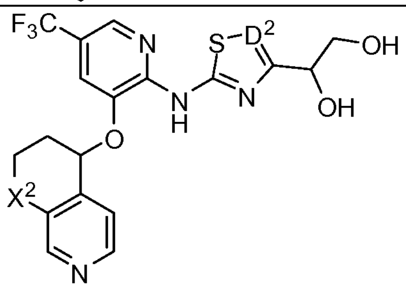
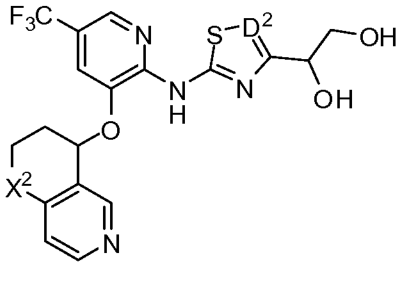
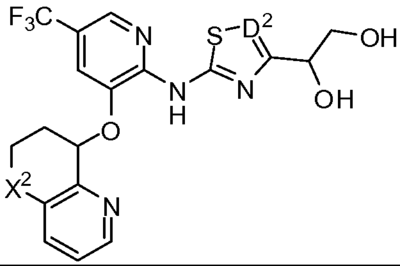
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH R^D = H, Me, or CF_3 D^2 = N R^D = H, Me, or CF_3
	D^2 = CH R^D is H, CF_3 or (1-6C alkyl) D^2 = N R^D is H, CF_3 or (1-6C alkyl)
	D^2 = CH R^D is H, CF_3 or (1-6C alkyl) D^2 = N R^D is H, CF_3 or (1-6C alkyl)

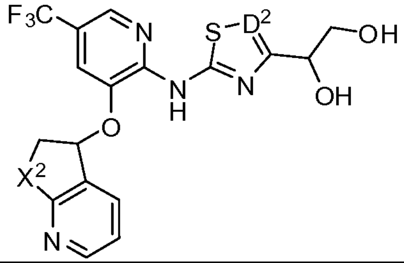
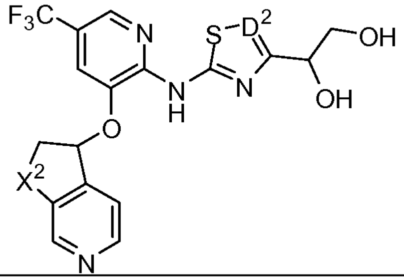
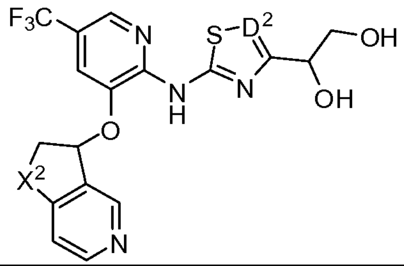
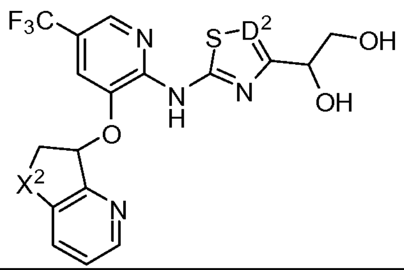
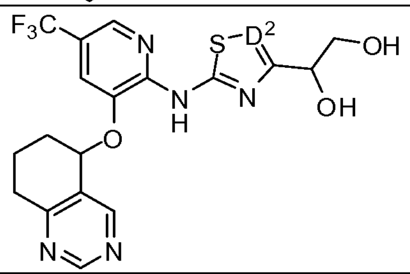
5

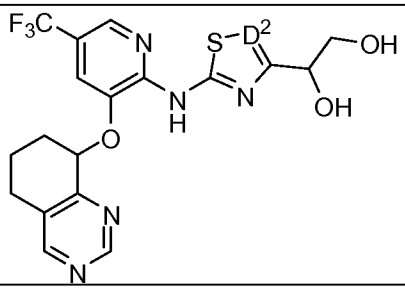
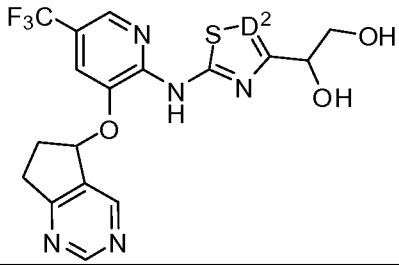
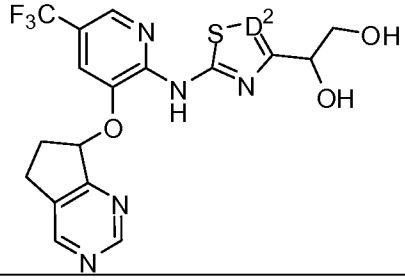
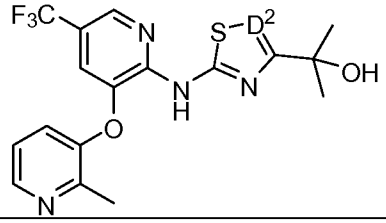
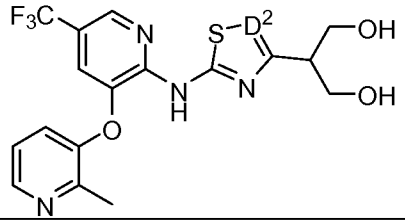
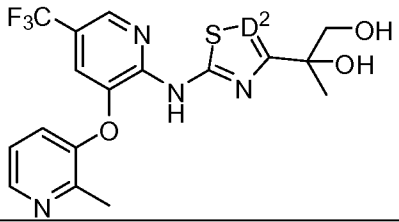
	D^2 = CH R^D is H, CF_3 or (1-6C alkyl) D^2 = N R^D is H, CF_3 or (1-6C alkyl)
	D^2 = CH R^D is H, CF_3 or (1-6C alkyl) D^2 = N R^D is H, CF_3 or (1-6C alkyl)
	D^2 = CH R^D is H, CF_3 or (1-6C alkyl) D^2 = N R^D is H, CF_3 or (1-6C alkyl)
	D^2 = CH R^D is H, CF_3 or (1-6C alkyl) D^2 = N R^D is H, CF_3 or (1-6C alkyl)
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N

	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N

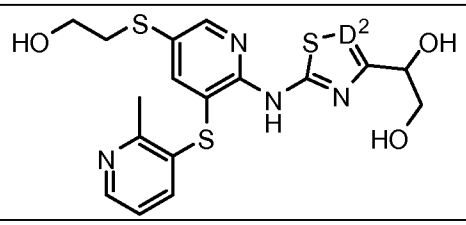
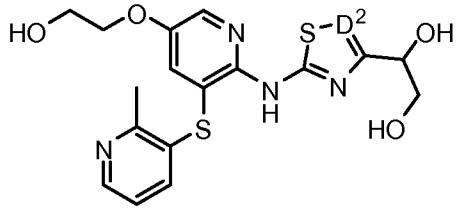
5

	$D^2 = CH$
	$D^2 = N$
	$D^2 = CH$
	$D^2 = N$
	$D^2 = CH$ $X = CH_2$
	$D^2 = CH_2$ $X = O$
	$D^2 = N$ $X = CH_2$
	$D^2 = N$ $X = O$
	$D^2 = CH$ $X = CH_2$
	$D^2 = CH_2$ $X = O$
	$D^2 = N$ $X = CH_2$
	$D^2 = N$ $X = O$
	$D^2 = CH$ $X = CH_2$
	$D^2 = CH_2$ $X = O$
	$D^2 = N$ $X = CH_2$
	$D^2 = N$ $X = O$
	$D^2 = CH$ $X = CH_2$
	$D^2 = CH_2$ $X = O$
	$D^2 = N$ $X = CH_2$
	$D^2 = N$ $X = O$

	D^2 = CH X = CH_2
	D^2 = CH_2 X = O
	D^2 = N X = CH_2
	D^2 = N X = O
	D^2 = CH X = CH_2
	D^2 = CH_2 X = O
	D^2 = N X = CH_2
	D^2 = N X = O
	D^2 = CH X = CH_2
	D^2 = CH_2 X = O
	D^2 = N X = CH_2
	D^2 = N X = O
	D^2 = CH X = CH_2
	D^2 = CH_2 X = O
	D^2 = N X = CH_2
	D^2 = N X = O
	D^2 = CH
	D^2 = N

	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N
	D^2 = CH D^2 = N

5

	D^2 = CH
	D^2 = N
	D^2 = CH
	D^2 = N

(S)-1-(5-(3-(2-methylpyridin-3-yloxy)-5-(pyridin-2-ylthio)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)ethane-1,2-diol;

(S)-1-(5-(3-(2,6-dimethylpyridin-3-yloxy)-5-(pyridin-2-ylthio)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)ethane-1,2-diol;

(S)-1-(5-(5-(cyclopropylmethylthio)-3-(2-methylpyridin-3-yloxy)pyridin-2-yl-amino)-1,2,4-thiadiazol-3-yl)ethane-1,2-diol;

(S)-1-(5-(3-(2-ethylpyridin-3-yloxy)-5-(pyridin-2-ylthio)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)ethane-1,2-diol;

(S)-1-(5-(5-(3-methoxypropylthio)-3-(2-methylpyridin-3-yloxy)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)ethane-1,2-diol;

(S)-1-(5-(3-(1-Ethyl-1H-pyrazol-5-yloxy)-5-(pyridin-2-ylthio)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)ethane-1,2-diol;

(S)-1-(5-(3-(1-ethyl-1H-pyrazol-5-yloxy)-5-(pyridin-2-ylthio)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)-2-methylpropane-1,2-diol;

(S)-1-(5-(5-(3-methylpyridin-2-ylthio)-3-(2-methylpyridin-3-yloxy)pyridin-2-yl-amino)-1,2,4-thiadiazol-3-yl)ethane-1,2-diol;

(S)-1-(5-(3-(2,4-dimethylpyridin-3-yloxy)-5-(pyridin-2-ylthio)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)ethane-1,2-diol;

(S)-2-methyl-1-(5-(3-(2-methylpyridin-3-yloxy)-5-(pyridin-2-ylthio)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)propane-1,2-diol;

(S)-1-(5-(5-(2-methoxyethylthio)-3-(2-methylpyridin-3-yloxy)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)ethane-1,2-diol;

(1S,2S)-1-(5-(3-(2-ethylpyridin-3-yloxy)-5-(pyridin-2-ylthio)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)-3-methoxypropane-1,2-diol;

(S)-2-methyl-1-(5-(5-(pyridin-2-ylthio)-3-(1,3,5-trimethyl-1H-pyrazol-4-yloxy)-pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)propane-1,2-diol;

(S)-1-(5-(5-(pyridin-2-ylthio)-3-(1,3,5-trimethyl-1H-pyrazol-4-yloxy)pyridin-2-yl-amino)-1,2,4-thiadiazol-3-yl)ethane-1,2-diol;

(S)-1-(5-(5-(2-methoxyethylthio)-3-(1,3,5-trimethyl-1H-pyrazol-4-yloxy)pyridin-2-yl-amino)-1,2,4-thiadiazol-3-yl)ethane-1,2-diol;

(R)-1-(5-(3-(2-methylpyridin-3-yloxy)-5-(pyridin-2-ylthio)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)ethane-1,2-diol;

(S)-2-(5-(3-(2-methylpyridin-3-yloxy)-5-(pyridin-2-ylthio)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)propane-1,2-diol; or

(R)-2-(5-(3-(2-methylpyridin-3-yloxy)-5-(pyridin-2-ylthio)pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)propane-1,2-diol, or the pharmaceutically acceptable salts thereof.

Other compounds that may be used in combination with the compounds of the present invention inclue the IL1-R1 compounds set forth in U.S. patent no. 7,438,910. A particular disease that can be treated with the combination is type 2 diabetes.

The compounds of the present invention can also be used in combination with FGF-21 compounds, and particularly for the treatment of type 2 diabetes. Examples of FGF-21 compounds are disclosed in U.S. patent no. 7,671,180; U.S. patent no. 7,667,008; U.S. patent no. 7,459,540; U.S. patent no. 7,696,172; PCT application publication no. WO 2010/042747; and PCT application publication no. WO 2009/149171.

The compounds of the present invention can be also be used in combination with anakinra, particularly for the treatment of type 2 diabetes.

In one particular aspect, the compounds of the present invention may be used in combination with metformin.

The compounds of the present invention are used in the treatment diseases or symptoms mediated by GKRP and/or GK (GKRP/GK). Examples of diseases or symptoms mediated by GKRP/GK include, but are not limited to, Type II (type 2) diabetes and related disorders, such as hyperglycemia, low or impaired glucose tolerance, insulin resistance, obesity, lipid disorders such as dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolernia, low HDL levels, high LDL levels, atherosclerosis, and vascular restenosis, irritable bowel syndrome, inflammatory bowel disease, including Crohn's disease and ulcerative colitis, other inflammatory conditions, pancreatitis, abdominal obesity, neurodegenerative disease, retinopathy, nephropathy, neuropathy, cataracts, glaucoma, glomerulosclerosis, foot ulcerations and unlcerative colitis, altered gastrointestinal motility, Syndrome X, ovarian hyperandrogenism, polycystic ovarian syndrome, premenstrual syndrome, other disorders where insulin resistance is a component. In Syndrome X, also known as Metabolic Syndrome, obesity is thought to promote insulin resistance, diabetes, dyslipidemia, hypertension, and increased cardiovascular risk, growth hormone deficiency, neutropenia, neuronal disorders, tumor invasion and metastasis, benign prostatic hypertrophy, gingivitis, osteoporosis, frailty of aging, intestinal injury, benign prostatic hypertrophy (BPH), and sperm motility/male contraception.

The compounds of the present invention are also useful for the prevention, delay of progression or the treatment of an early cardiac or early cardiovascular diseases or damages, renal diseases or damages, heart Failure, or heart Failure associated diseases like (i) cardiovascular diseases or damages e.g. cardiac hypertrophy, cardiac remodelling after myocardial infarction, pulmonary congestion and cardiac fibrosis in dilated or in hypertrophic cardiomyopathy, cardiomyopathy such as dilated cardiomyopathy or hypertrophic cardiomyopathy, mesanglial hypertrophy, or diabetic cardiomyopathy, left or right ventricular hypertrophy, arrhythmia, cardiac dysrhythmia, syncopy, angina pectoris, cardiac bypass reocclusion, intermittent claudication, diastolic and/or systolic dysfunction, diabetic myopathy, stroke prevention in congestive heart failure, hypertrophic medial thickening in arteries and/or large vessels,

mesenteric vasculature hypertrophy or artherosclerosis, preferably artherosclerosis in mammalian patients with hypertension of diabetes; (ii) renal diseases or damages like renal hyperfiltration such as after portal renal ablation, proteinuria in chronic renal disease, renal arteriopathy as a consequence of hypertension, nephrosclerosis, hypertensive nephrosclerosis or mesanglial hypertrophy; (iii) Heart Failure to be treated is secondary to idiopathic dilated cardiomyopathy and/or coronary ischemic disease.

The compounds of the present invention can also be used for the prevention, the delay of the onset, the delay of progression or the treatment of neurodegenerative disorders, cognitive disorders and for improving memory (both short term and long term) and learning ability wherin the (i) neurodegenerative disorder is dementia, senile dementia, schizophrenia, mild cognitive impairment, Alzheimer related dementia, Huntington's chores, tardive dyskinesia, hyperkinesias, mania, Morbus Parkinson, Steel-Richard syndrome, Down's syndrome, myasthenia gravis, nerve and brain trauma, vascular amyloidosis, cerebral haemorrhage I with amyloidosis, brain inflammation, Friedrich ataxia, acute confusion disorders, acute confusion disorders with apoptotic necrocytosis, amyotrophic lateral sclerosis, glaucoma, and Alzheimer's disease; (ii) cognitive disorders like cognitive deficits associated with schizophrenia, age-induced memory impairment, cognitive deficits associated with psychosis, cognitive impairment associated with diabetes, cognitive deficits associated with post-stroke, memory defects associated hypoxia, cognitive and attention deficits associated with senile dementia, attention deficits disorders, memory problems associated with mild cognitive impairment, impaired cognitice function associated with vascular dementia, cognitive problems associated with brain tumors, Pick's disease, cognitive deficits due to autism, cognitive deficits post electroconvulsive therapy, cognitive deficits associated with traumatic brain injury, amnesic disorders, deliriums, vitamin deficiency, dementias, impaired cognitive function associated with Parkinson's disease, attention-deficit disorders; (iii) prevention of memory impairment as a result of Alzheimer disease, Creutzfeld-Jakob disease, Pick disease, Huntington disease, AIDS, brain

injury, brain aneurysm, epilepsy, stroke, toxicant exposure, mental retardation in children, Huntington's disease; (iv) to improve learning speed and potential in educational and rehabilitation contexts.

The compounds of the present invention can also be used for stimulating an immune response in a subject having or at risk of having cancer wherein the cancer is selected from the group consisting of basal cell carcinomas including cancers of the binary tract, bladder, urinary system, bone, brain, breast, cervical, endometrial, ovarian, uterine, choriocarcinoma, central nervous system, colon and rectal cancers, connective tissue cancer, cancer of the digestive system, esophageal, gastric, stomach, larynx, liver, pancreatic, colorectal, renal cancers; cancers of the urinary system; cancers of eye, head and neck, oral cavity, skin, prostate; cancers of biliary tract, testicular, thyroid; intra- epithelial neoplasm, leukemia, acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, chronic lymphoid leukemia; and other cancers of the respiratory system, lung, small cell lung, non-small cell lung; lymphoma, Hodgkin's lymphoma, Non-Hodgkin's lymphoma; melanoma, myeloma, neuroblastoma, retinoblastoma, fibrosarcoma (bone or connective tissue sarcoma), rhabdomyosarcoma; and other cancers including neoplastic conditions, adipose cell tumors, adipose cell carcinomas, such as liposarcoma.

The compounds of the present invention can also be used for the treatment or prophylaxis of chronic inflammatory diseases such as autoimmune disorders like rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, psoriasis, allergies or asthma.

The compounds of the present invention can also be used in the treatment of pain, neuropathic pain, rheumatoid pain, osteoarthritis pain, anesthesia adjunct in mammalian patients undergoing surgery, chronic pain in advanced cancer, treatment of refractory diarrhea, biliary pain caused by gallstones.

The compounds of the present invention can also be used for the treatment of mammalian patients undergoing islet/pancreas transplantation, for the prevention or the delay of transplant rejection, or allograft rejection in transplantation, for improving pancreatic function by increasing the number and

size of pancreatic beta-cells in the treatment of Type 1 diabetes patients, and for improving pancreatic function by increasing the number and size of pancreatic beta-cells in general.

Furthermore, the compounds of the present invention can be used for the treatment of mammalian patients with acne, skin disorders (e.g. pigmentation disorders or psoriasis), scleroderma, mycoses; anxiety, anxiety neurosis, major depression disorder, drug abuse, alcohol addiction, insomnia, chronic fatigue, sleep apnea; anorexia nervosa; epilepsy; migrane; encephalomyelitis; osteoarthritis, osteoporosis, calcitonin-induced osteoporosis; male and female sexual dysfunction, infertility; Type 1 diabetes; immunosuppression, HIV infection; hematopoiesis, anemia; and for weight reduction.

Additionally, the compounds of the present invention are useful for the prevention, delay of progression or treatment of (i) bacterial infections from Escherichia coli, Staphylococcus, Streptoococcus, Pseudomonas, Clostridium difficile infection, Legionella, Pneumococcus, Haemophilus, Klebsiella, Enterobacter, Citrobacter, Neisseria, Shigella, Salmonella, Listeria, Pasteurella, Streptobacillus, Spirillum, Treponema, Actinomyces, Borrelia, Corynebacterium, Nocardia, Gardnerella, Campylobacter, Spirochaeta, Proteus, Bacteriodes, Helicobacter pylori, and anthrax infection; (ii) mycobacterial infection from tuberculosis and leprosy; (iii) viral infection from HIV, Herpes simplex virus 1, Herpes simplex virus 2, Cytomegalovirus, hepatitis A virus, hepatitis B virus, hepatitis C virus, human papilloma virus, Epstein Barr virus, rotavirus, adenovirus, influenza A virus, respiratory syncytial virus, varicella-zoster virus, small pox, monkey pox and SARS; (iv) fungal infection from candidiasis, ringworm, histoplasmosis, blastomycosis, paracoccidioidomycosis, cryptococcosis, aspergillosis, chromomycosis, mycetoma infections, pseudallescheriasis, Tinea versicolor infection; (v) parasite infection from amebiasis, Trypanosoma cruzi, Fascioliasis, Leishmaniasis, Plasmodium, Onchocerciasis, Paragonimiasis, Trypanosoma brucei, Pneumocystis, Trichomonas vaginalis, Taenia, Hymenolepsis, Echinococcus, Schistosomiasis, neurocysticerosis, Necator americanus, and Trichuris trichuria.

Since one aspect of the present invention contemplates the treatment of the disease/conditions with a combination of pharmaceutically active compounds that may be administered separately, the invention further relates to combining separate pharmaceutical compositions in kit form. The kit comprises two separate pharmaceutical compositions: a compound of the present invention, and a second pharmaceutical compound. The kit comprises a container for containing the separate compositions such as a divided bottle or a divided foil packet. Additional examples of containers include syringes, boxes and bags. Typically, the kit comprises directions for the use of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician or veterinarian.

An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

It may be desirable to provide a memory aid on the kit, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested.

Another example of such a memory aid is a calendar printed on the card, e.g., as follows "First Week, Monday, Tuesday, . . . etc . . . Second Week, Monday, Tuesday, . . . " etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also, a daily dose of a compound of the present invention can consist of one tablet or capsule, while a daily dose of the second compound can consist of several tablets or capsules and vice versa. The memory aid should reflect this and aid in correct administration of the active agents.

In another specific embodiment of the invention, a dispenser designed to dispense the daily doses one at a time in the order of their intended use is provided. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter which indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

The compounds of the present invention and other pharmaceutically active compounds, if desired, can be administered to a patient either orally, rectally, parenterally, (for example, intravenously, intramuscularly, or subcutaneously) intracisternally, intravaginally, intraperitoneally, intravesically, locally (for example, powders, ointments or drops), or as a buccal or nasal spray. All methods that are used by those skilled in the art to administer a pharmaceutically active agent are contemplated.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions, or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl

oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. Microorganism contamination can be prevented by adding various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example, sugars, sodium chloride, and the like. Prolonged absorption of injectable pharmaceutical compositions can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration include capsules, tablets, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, mannitol, and silicic acid; (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (c) humectants, as for example, glycerol; (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (a) solution retarders, as for example, paraffin; (f) absorption accelerators, as for example, quatemary ammonium compounds; (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate; (h) adsorbents, as for example, kaolin and bentonite; and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, and tablets, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be used as fillers in soft and hard filled gelatin capsules using such excipients as lactose or milk sugar, as well as high molecular weight polyethylene glycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well

known in the art. They may also contain opacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions that can be used are polymeric substances and waxes. The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage form may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame seed oil, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. Suspensions, in addition to the active compound, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administration are preferable suppositories, which can be prepared by mixing the compounds of the present invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax, which are solid at ordinary room temperature, but liquid at body temperature, and therefore, melt in the rectum or vaginal cavity and release the active component.

Dosage forms for topical administration of a compound of the present invention include ointments, powders, sprays and inhalants. The active

compound or fit compounds are admixed under sterile condition with a physiologically acceptable carrier, and any preservatives, buffers, or propellants that may be required. Opthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 3,000 mg per day. For a normal adult human having a body weight of about 70 kg, a dosage in the range of about 0.01 to about 100 mg per kilogram body weight is typically sufficient. The specific dosage and dosage range that can be used depends on a number of factors, including the requirements of the patient, the severity of the condition or disease being treated, and the pharmacological activity of the compound being administered. The determination of dosage ranges and optimal dosages for a particular patient is within the ordinary skill in the art.

The compounds of the present invention can be administered as pharmaceutically acceptable salts, esters, amides or prodrugs. The term "salts" refers to inorganic and organic salts of compounds of the present invention. The salts can be prepared in situ during the final isolation and purification of a compound, or by separately reacting a purified compound in its free base or acid form with a suitable organic or inorganic base or acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, palmitiate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts, and the like. The salts may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. See, for example, S. M. Berge, et al., "Pharmaceutical Salts," J Pharm Sci, 66: 1-19 (1977).

Examples of pharmaceutically acceptable esters of the compounds of the present invention include C_1-C_8 alkyl esters. Acceptable esters also include C_5-C_7 cycloalkyl esters, as well as arylalkyl esters such as benzyl. C_1-C_4 alkyl esters are commonly used. Esters of compounds of the present invention may be prepared according to methods that are well known in the art.

Examples of pharmaceutically acceptable amides of the compounds of the present invention include amides derived from ammonia, primary C_1-C_8 alkyl amines, and secondary C_1-C_8 dialkyl amines. In the case of secondary amines, the amine may also be in the form of a 5 or 6 membered heterocycloalkyl group containing at least one nitrogen atom. Amides derived from ammonia, C_1-C_3 primary alkyl amines and C_1-C_2 dialkyl secondary amines are commonly used. Amides of the compounds of the present invention may be prepared according to methods well known to those skilled in the art.

The term "prodrug" means compounds that are transformed in vivo to yield a compound of the present invention. The transformation may occur by various mechanisms, such as through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

To illustrate, if the compound of the invention contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as (C_1-C_8 alkyl, (C_2-$C12_2$)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)aminomethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-

C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di(C_1-C_2)alkylcarbamoyl-(C_1-C_2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-$_3$)alkyl.

Similarly, if a compound of the present invention comprises an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanoyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, –P(O)(OH)$_2$, –P(O)(O(C_1-C_6)alkyl)$_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

The compounds of the present invention may contain asymmetric or chiral centers, and therefore, exist in different stereoisomeric forms. It is contemplated that all stereoisomeric forms of the compounds as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention contemplates all geometric and positional isomers. For example, if the compound contains a double bond, both the cis and trans forms (designated as S and E, respectively), as well as mixtures, are contemplated.

Mixture of stereoisomers, such as diastereomeric mixtures, can be separated into their individual stereochemical components on the basis of their physical chemical differences by known methods such as chromatography and/or fractional crystallization. Enantiomers can can also be separated by converting the enantiomeric mixture into a diasteromeric mixture by reaction with an appropriate optically active compound (e.g., an alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some compounds may be atropisomers (e.g., substituted biaryls).

The compounds of the present invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water (hydrate), ethanol, and the like. The present invention contemplates and encompasses both the solvated and unsolvated forms.

It is also possible that compounds of the present invention may exist in different tautomeric forms. All tautomers of compounds of the present invention are contemplated. For example, all of the tautomeric forms of the tetrazole moiety are included in this invention. Also, for example, all keto-enol or imine-enamine forms of the compounds are included in this invention.

Those skilled in the art will recognize that the compound names and structures contained herein may be based on a particular tautomer of a compound. While the name or structure for only a particular tautomer may be used, it is intended that all tautomers are encompassed by the present invention, unless stated otherwise.

It is also intended that the present invention encompass compounds that are synthesized in vitro using laboratory techniques, such as those well known to synthetic chemists; or synthesized using in vivo techniques, such as through metabolism, fermentation, digestion, and the like. It is also contemplated that the compounds of the present invention may be synthesized using a combination of in vitro and in vivo techniques.

The present invention also includes isotopically-labelled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{16}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl. In another aspect, the compounds of the present invention contain one or more deuterium atoms (2H) in place of one or more hydrogen atoms.

Compounds of the present invention that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this

invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detection. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of this invention can generally be prepared by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

The compounds of the present invention may exist in various solid states including crystalline states and as an amorphous state. The different crystalline states, also called polymorphs, and the amorphous states of the present compounds are contemplated as part of this invention.

In synthesizing compounds of the present invention, it may be desirable to use certain leaving groups. The term "leaving groups" ("LG") generally refer to groups that are displaceable by a nucleophile. Such leaving groups are known in the art. Examples of leaving groups include, but are not limited to, halides (e.g., I, Br, F, Cl), sulfonates (e.g., mesylate, tosylate), sulfides (e.g., SCH_3), N-hydroxsuccinimide, N-hydroxybenzotriazole, and the like. Examples of nucleophiles include, but are not limited to, amines, thiols, alcohols, Grignard reagents, anionic species (e.g., alkoxides, amides, carbanions) and the like.

All patents and other publications recited herein are hereby incorporated by reference in their entirety.

The examples presented below illustrate specific embodiments of the present invention. These examples are meant to be representative and are not intended to limit the scope of the claims in any manner.

EXAMPLES

BIOLOGICAL ASSAYS

GKRP LC MS/MS Biochemical Assay

This assay is used to directly measure the formation of ^{13}C-glucose-6-phosphate from ^{13}C-glucose by liquid chromatography-mass spectrometry (LC MS/MS). Begin by preparing the following solutions: Compound Buffer (CB): 50mM Tris, pH 7.5 / 4mM $MgCl_2$ / 6% DMSO / fresh 10mM DTT from 1M frozen stock. Enzyme Buffer (EB): 50mM Tris, pH 7.5 / 4mM $MgCl_2$ / 6% DMSO / fresh 0.1% BSA / fresh 0.01% Brij-35 (10% BSA and 1% Brij-35 stock). GK (Glucokinase) Working Stock (5X): Dilute human His-hepatic GK to 30nM in EB buffer. Substrate Working Stock (1.47X): Dilute 13C-D-glucose (Sigma-Aldrich, St. Louis, MO) to 7.35mM from 1M stock (1M ^{13}C-D-glucose = 186.11 mg/ml in 50mM Tris pH 7.5, 4mM $MgCl_2$) and dilute ATP (EMD Chemical Inc., Gibbstown, NJ) to 0.3528mM from frozen 100mM stock and dilute 20mM fructose-6-phosphate (F6P) (Sigma-Aldrich, St. Louis, MO) to 441μM in CB buffer. GKRP (Glucokinase Regulatory Protein) (10X): Dilute GKRP to 1μM from 33.366mM stock in EB buffer. Combine the following reagents in a 96-well polypropylene plate: 34μl of Substrate Working Stock (1.47X), 5μl of 1μM GKRP (10X), and 1μl of compound or DMSO. Seal the plate and incubate for 30 minutes at room temperature while mixing. After 30 minutes add 10μl of GK Working Stock (5X). Re-seal the plate and incubate for another 30 minutes at room temperature while mixing. After the second 30 minutes, stop the reaction by the addition of 50μl of 100% acetonitrile, seal, and mix for 5-10 minutes. Run 10μl of this sample through the LC MS/MS (API 3200, Applied Biosystems Inc., Carlsbad, CA). Detection settings are for 265.2/78.8 atomic mass units.

GKRP NADPH Coupled Assay

This assay is used as an indirect measure of glucose-6-phosphate (G6P) formed from glucose due to the enzymatic activity of glucokinase. Assay format is the same as for GKRP LC MS/MS Biochemical Assay with the following exceptions. GK Working Stock (5X): Dilute human His-hepatic GK to 20nM in EB buffer. Stop & Detection Reagent (2X): Dilute β-nicotinamide adenine dinucleotide phosphate sodium salt (β-NADP) (Aldrich-Sigma, St. Louis, MO) to 2mM from 100mM stock (stock in 10mM Tris, pH 9.2) and dilute glucose-6-phosphate dehydrogenase (Aldrich-Sigma, St. Louis, MO) to 0.04Unit/µl from 10Unit/µl (stock in 10mM Tris pH 7.5 / 0.05% Brij-35) in 0.2 M Tris, pH 9.2 / 8% DMSO. After the initial 30 minute incubation add 10µl of 20nM GK diluted in EB (5X). Re-seal the plate and incubate for another 1 hour at room temperature while mixing. After 1 hour remove the seal and add 50µl of Stop & Detection Reagent and incubate for 5 minutes at room temperature while mixing. After 5 minutes read the plate using an Infinite M1000 (Tecan Systems Inc., San Jose CA) with the following detection settings: Mode: Fluorescence Top Reading, Excitation Wavelength: 340nm, Emission Wavelength: 450nm, Excitation Bandwidth: 20nm, Emission Bandwidth: 20nm, Gain: 95, Number of Flashes: 10, Flash Frequency: 400Hz, Integration Time: 20µs.

GK-GKRP Binding Assay Protocol

This assay is used to directly measure the interaction between glucokinase (GK) and glucokinase regulatory protein (GKRP). Begin by preparing the following solutions. Assay Buffer: 20mM Tris, pH 7.5 / 0.05% BSA / 1mM DTT / 1µM sorbitol–6–phosphate. Assay Procedure: Dilute avi-tagged GKRP to 10.7 nM in assay buffer. Combine the following reagents in a white 96–well half area plate. Pipette 14µl of the diluted avi-tagged GKRP into each well. Add 1µl of compound to be tested and incubate at room temperature for 20 minutes. After 20 minutes, add 5µl of assay buffer containing 6nM GK-fluorescein. Add 10µl

of AlphaScreen® beads (Perkin Elmer, Waltham MA) that have been diluted 1:333 in assay buffer. Incubate in a dark room for 2 hours at room temperature. After 2 hours read the plate using an Envision plate reader (Perkin Elmer, Waltham MA).

GKRP LC MS/MS-2 Biochemical Assay

This assay is used to directly measure the formation of ^{13}C-glucose-6-phosphate from ^{13}C-glucose by LC MS/MS. Begin by preparing the following solutions: Compound Buffer (CB): 50mM Tris, pH 7.5 / 4mM $MgCl_2$ / 6% DMSO / fresh 10mM DTT from 1M frozen stock. Enzyme Buffer (EB): 50mM Tris, pH 7.5 / 4mM $MgCl_2$ / 6% DMSO / fresh 0.1% BSA / fresh 0.01% Brij-35 (10% BSA and 1% Brij-35 stock). GK (Glucokinase) Working Stock (5X): Dilute human His-hepatic GK to 30nM in EB buffer. Substrate Working Stock (1.47X): Dilute ^{13}C-D-glucose (Sigma-Aldrich,St. Louis, MO) to 7.35mM from 1M stock and dilute ATP (EMD Chemical, Gibbstown, NJ) to 0.3528mM from frozen 100mM stock in CB buffer (1M ^{13}C-D-glucose = 186.11 mg/ml in water). Dilute 20mM fructose-6-phosphate (F6P) (Sigma-Aldrich, St. Louis, MO) to 441μM in the substrate working stock. GKRP (Glucokinase Regulatory Protein) (10X): Dilute GKRP to 280nM from 33.366mM stock in EB buffer. Combine the following reagents in a 96-well polypropylene plate: 34μL of Substrate Working Stock (1.47X), 5μl of 280nM GKRP (10X), and 1μl of compound or DMSO. Seal the plate and incubate for 30 minutes at room temperature while mixing. After 30 minutes add 10μl of GK Working Stock (5X). Re-seal the plate and incubate for another 30 minutes at room temperature while mixing. After the second 30 minutes, stop the reaction by the addition of 50μl of 100% acetonitrile, seal, and mix for 5-10 minutes. Run 10μl of this sample through the LC MS/MS (API 3200, Applied Biosystems, Carlsbad, CA). Detection settings are for 265.2/78.8 atomic mass units.

Results for compounds tested in these biological assays are set forth in the numbered examples below.

The following abbreviations may be used herein:

HATU	[dimethylamino(triazolo[4,5-b]pyridin-3-yloxy)methylidene]-dimethylazanium
Hünig's base or DIPEA	diisopropylethylamine
dppf	1,1'- bis(diphenylphosphanyl) ferrocene
dba	1,5-diphenylpenta-1,4-dien-3-one
LAH	lithium aluminum hydride
TMS	trimethylsilyl
EDC	3-(ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine
HOBt	1-hydroxybenzotriazole
TLC	thin layer chromatography
MHz	megahertz
br.	broad
s	singlet
d	doublet
t	triplet
dt	doublet of triplet
dd	doublet of doublet
quin	quintuplet
q	quartet
~	about
+ve or pos. ion	positive ion
Δ	heat
Ac	acetyl
AcOH	acetic acid
Ac_2O	acetic anhydride

ACN	acetonitrile
A-phos, Am-Phos	(bis[4-di-tert-butylphosphino)-N,N-dimethylaniline] palladium dichloride)
aq	aqueous
ATP	adenosine 5'-triphosphate
BOC or Boc	tert-butyloxycarbonyl
Bu	butyl
Bn	benzyl
Calcd or Calc'd	calculated
Conc.	concentrated
DCE	1,2-dichloroethane
DCM	dichloromethane
DEA	diethylamine
DIEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	dimethoxyl ethyl ether
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
DTT	dithiothreitol
ESI or ES	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethyl alcohol
FBS	fetal bovine serum
g	grams
h	hour
HCO_2H	formic acid
Hex	hexanes
HOAc	acetic acid

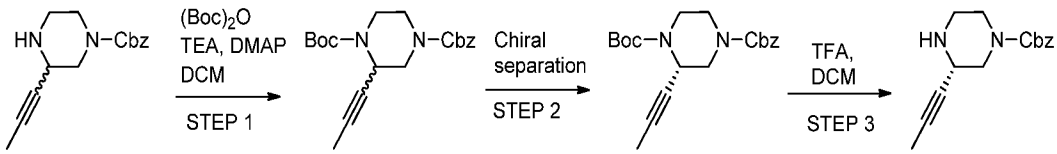
HPLC	high pressure liquid chromatography
IPA or iPrOH	isopropyl alcohol
^{i}PrMgCl	Isopropyl magnesium chloride
iPr_2NEt	N-ethyl diisopropylamine
KOAc	potassium acetate
LC MS, LC-MS or LC/MS	liquid chromatography mass spectroscopy
LDA	lithium diisopropylamide
LHMDS or LiHMDS	lithium hexamethyldisilazide
LiTMP	lithium tetramethylpiperidide
m/z	mass divided by charge
mCPBA or MCPBA	m-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeI	iodomethane
MeOD	deuterated methyl alcohol
MeOH	methyl alcohol
mg	milligrams
min	minutes
mL	milliliters
MS	mass spectra
MsCl	mesylchloride
$NaBH_4$	sodium borohydride
NaHMDS	sodium hexamethyldisilazide
NaOtBu	sodium tert-butoxide
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide
n-BuLi	n-butyllithium
NMO	N-methylmorpholine-N-oxide
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
Pd_2dba_3	tris(dibenzylideneacetone)dipalladium(0)

PMB	paramethoxybenzyl
RT or rt	room temperature
RuPhos	2-dicyclohexyl(2',6'-diisopropoxybiphenyl-2-yl)phosphine
RuPhos Palladacycle	chloro(2-dicyclohexylphosphino-2',6'-di-i-propoxy-1,1'-biphenyl)[2-(2-aminoethylphenyl)]palladium(II), methyl-t-butylether adduct
Sat. or sat'd or satd	saturated
SFC	supercritical fluid chromatography
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
$Ti(O\text{-}iPr)_4$	titanium isopropoxide
TPAP	tetrapropylammonium perruthenate
Tris	tris(hydroxymethyl)aminomethane
xantphos	(9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine)
X-Phos	2-Dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl
X-Phos palladacycle	chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2-aminoethyl)phenyl)]palladium(II)

Johnphos	2-biphenylyl(di-tert-butyl)phosphane
BINAP	1,1'-binaphthalene-2,2'-diylbis(diphenylphosphane)
NCS	1-chloro-2,5-pyrrolidinedione
Rochelle's salt	potassium sodium tartrate
XtalFluor-E	(diethylamino)difluorosulfonium tetrafluoroborate
NIS	1-iodo-2,5-pyrrolidinedione

It is noted that when a percent (%) is used with regard to a liquid, it is a percent by volume with respect to the solution. When used with a solid, it is the percent with regard to the solid composition. Throughout the Examples, chromatography columns are used for separations and purifications. Below are some representative suppliers of columns: Phenomenex, Torrance,CA (e.g., Gemini); Diacel Inc., Fort Lee, NJ (e.g.,Chiralcel®, Chiralpak®); Krackeler Scientific, Albany, NY (e.g., AccuBOND).

INTERMEDIATE A: Benzyl (3S)-3-(1-propyn-1-yl)-1-piperazinecarboxylate



STEP 1: 4-Benzyl 1-tert-butyl 2-(1-propyn-1-yl)-1,4-piperazinedicarboxylate

A 20 mL vial was charged with benzyl 3-(1-propyn-1-yl)-1-piperazinecarboxylate (0.616 g, 2.38 mmol, Intermediate L), di-tert-butyl dicarbonate (0.979 g, 4.49 mmol, Sigma-Aldrich, St. Louis, MO), DMAP(0.0287 g, 0.235 mmol, Sigma-Aldrich, St. Louis, MO), TEA (0.90 mL, 6.5 mmol) and DCM (8 mL). The mixture was stirred at rt for 30 min. The reaction mixture was partitioned between water (20 mL) and EtOAc (20 mL). The aqueous phase was extracted with EtOAc (20 mL). The organic phase was washed with saturated aqueous sodium chloride (40 mL). The organic phase was dried over sodium sulfate, filtered and concentrated under a vacuum. The resulting product was purified by column chromatography (25 g of silica, 0 to 50% EtOAc in hexanes) to afford 4-benzyl 1-tert-butyl 2-(1-propyn-1-yl)-1,4-piperazinedicarboxylate (0.488 g) as a clear oil.

STEP 2: 4-Benzyl 1-tert-butyl (2S)-2-(1-propyn-1-yl)-1,4-piperazinedicarboxylate

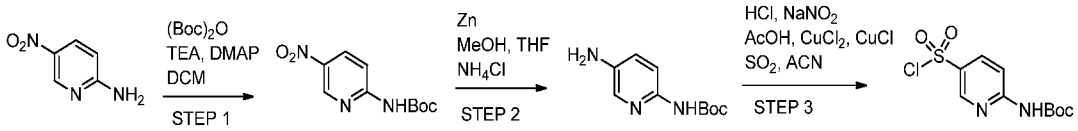
The individual enantiomers of 4-benzyl 1-tert-butyl 2-(1-propyn-1-yl)-1,4-piperazinedicarboxylate were isolated using chiral SFC. The method used was as follows: Chiralpak® ADH column (30 x 250 mm, 5 μm) using 12% ethanol in supercritical CO_2 (total flow was 170 mL/min). This produced the two enantiomers with enantiomeric excesses greater than 98%. The first eluting peak was subsequently identified as 4-benzyl 1-tert-butyl (2S)-2-(1-propyn-1-yl)-1,4-piperazinedicarboxylate and used in the next step.

STEP 3: Benzyl (3S)-3-(1-propyn-1-yl)-1-piperazinecarboxylate

A 100-mL round-bottomed flask was charged with 4-benzyl 1-tert-butyl (2S)-2-(1-propyn-1-yl)-1,4-piperazinedicarboxylate (0.145 g, 0.405 mmol), TFA (1.0 mL, 13 mmol) and DCM (2 mL). The mixture was stirred at rt for 40 min and then concentrated. Solid $NaHCO_3$ was added followed by saturated aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with 1N NaOH (40 mL), saturated aqueous $NaHCO_3$ (40 mL), water (40 mL) and saturated aqueous sodium chloride (40 mL). The organic phase was dried over sodium sulfate, filtered and concentrated under a vacuum to afford benzyl (3S)-3-(1-propyn-1-yl)-1-piperazinecarboxylate (0.100 g) as a clear oil which solidified upon standing.

^{1}H NMR (400 MHz, MeOD) δ ppm 7.43 - 7.26 (m, 5 H), 5.13 (d, J = 5.1 Hz, 2 H), 3.85 - 3.46 (m, 3 H), 3.42 - 3.33 (m, 1 H), 3.29 - 3.12 (m, 1 H), 3.00 (br. s., 1 H), 2.70 - 2.57 (m, 1 H), 1.84 - 1.73 (m, 3 H).

INTERMEDIATE B: tert-Butyl (5-(chlorosulfonyl)-2-pyridinyl)carbamate



STEP 1: tert-Butyl (5-nitro-2-pyridinyl)carbamate

A 3-L round-bottomed flask was charged with 5-nitro-2-pyridinamine (75.0 g, 539 mmol, Alfa Aesar, Ward Hill, MA) and 500 mL of DCM. To this was added triethylamine (82 g, 809 mmol), di-tert-butyl dicarbonate (129 g, 593 mmol, Sigma-Aldrich, St. Louis, MO), and DMAP (32.9 g, 270 mmol, Sigma-Aldrich, St. Louis, MO). After stirring at rt for 18 h, the mixture was diluted with water and the solid was collected by filtration. The yellow solid was washed with MeOH to give tert-butyl (5-nitro-2-pyridinyl)carbamate (94.6 g) as a slightly-yellow solid.

STEP 2: tert-Butyl (5-amino-2-pyridinyl)carbamate

A 3-L round-bottomed flask was charged with tert-butyl (5-nitro-2-pyridinyl)carbamate (96.4 g, 403 mmol), 500 mL of MeOH, 500 mL of THF, and 100 mL of sat aq NH_4Cl. To this was slowly added (over 10 min) zinc dust (105 g, 1612 mmol, Strem Chemical Inc, Newburyport, MA). The mixture was stirred at room temperature for 12 h, then filtered. The filtrate was concentrated and then diluted with EtOAc and washed with water. The organic extracts were dried with $MgSO_4$, filtered, and concentrated to give a solid which was recrystallized from MeOH to give tert-butyl (5-amino-2-pyridinyl)carbamate (38.6 g) as a light yellow solid.

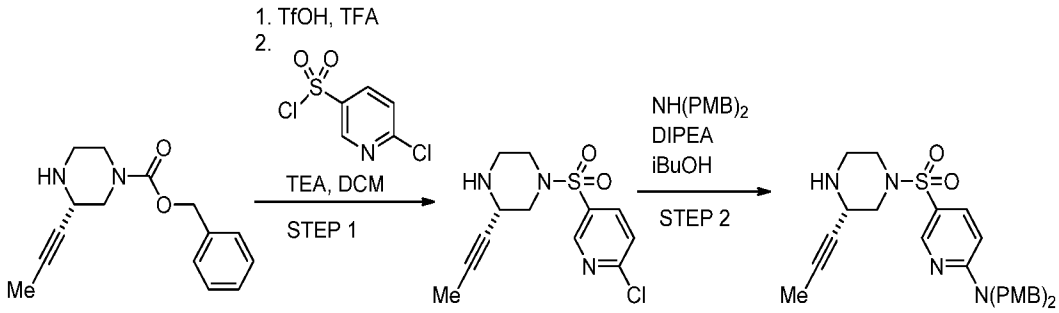
STEP 3: tert-Butyl (5-(chlorosulfonyl)-2-pyridinyl)carbamate

A 3-L round-bottomed flask was charged with sodium nitrite (15.3 g, 221 mmol, J. T. Baker, Philipsburg, NJ), 100 mL of water and 500 mL of MeCN.

After cooling to 0 °C, concentrated hydrochloric acid (231 mL, 2767 mmol) was slowly added keeping the internal temperature below 10 °C. After stirring at 0 °C for 10 min, tert-butyl (5-amino-2-pyridinyl)carbamate (38.6 g, 184 mmol) was added as a suspension in MeCN (200 mL). The mxiture was stirred for 30 min, then 150 mL of AcOH, copper(II) chloride (12.4 g, 92 mmol, Sigma-Aldrich, St. Louis, MO), and copper(I) chloride (0.183 g, 1.85 mmol, Strem Chemical Inc, Newburyport, MA) were added. SO_2 gas (Sigma-Aldrich, St. Louis, MO) was then bubbled through the solution for 15 min. The mixture was stirred at 0 °C for 30 min, then about 500 mL of ice-cold water was added. The resulting precipitate was collected by filtration and dried to give tert-butyl (5-(chlorosulfonyl)pyridin-2-yl)carbamate (15.5 g) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.92 (br. s., 1 H), 8.53 (br. s., 1 H), 8.22 (m, 2 H), 1.57 (s, 9 H).

INTERMEDIATE C: N,N-bis(4-methoxybenzyl)-5-(((3S)-3-(1-propyn-1-yl)-1-piperazinyl)sulfonyl)-2-pyridinamine



STEP 1: (3S)-1-((6-Chloro-3-pyridinyl)sulfonyl)-3-(1-propyn-1-yl)piperazine

To a stirred solution of benzyl (3S)-3-(1-propyn-1-yl)-1-piperazinecarboxylate (2.51 g, 9.71 mmol, Intermediate A) in TFA (20 mL) in a 250-mL round-bottomed flask, trifluoromethanesulfonic acid (2.59 mL, 29.1 mmol, Alfa Aesar, Ward Hill, MA) was added slowly at rt. After stirring at room

temperature for 3 min, the reaction mixture was concentrated to dryness under a vacuum. DCM (20 mL) was added to the residue followed by triethylamine (13.5 mL, 97 mmol). After the material went into solution, the mixture was cooled to 0 °C and 6-chloro-3-pyridinesulfonyl chloride (2.06 g, 9.73 mmol, *Organic Process Research & Development* **2009**, *13*, 875) was added portionwise. After 5 min stirring at 0 °C, cold water (40 mL) was added and the layers were separated. The aqueous phase was extracted with DCM (2 x 50 mL). The combined organic phases were washed with saturated aqueous sodium chloride (60 mL), dried over sodium sulfate, filtered and concentrated under a vacuum. The resulting product was purified by column chromatography (100 g of silica gel, 30 to 90% EtOAc in hexanes) to afford (3S)-1-((6-chloro-3-pyridinyl)sulfonyl)-3-(1-propyn-1-yl)piperazine (2.61 g) as an off-white solid.

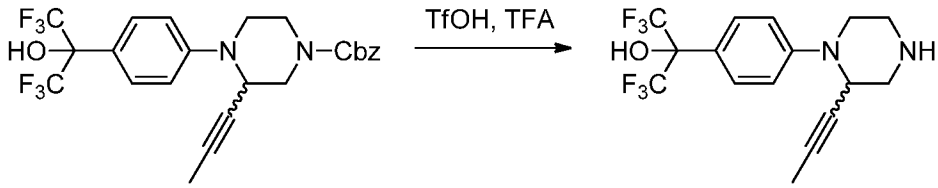
STEP 2: N,N-Bis(4-methoxybenzyl)-5-(((3S)-3-(1-propyn-1-yl)-1-piperazinyl)sulfonyl)-2-pyridinamine

Three microwave vials, each containing a mixture of (3S)-1-((6-chloro-3-pyridinyl)sulfonyl)-3-(1-propyn-1-yl)piperazine (2.6 g, 8.7 mmol), N-(4-methoxybenzyl)-1-(4-methoxyphenyl)methanamine (2.40 g, 9.33 mmol, WO2007/109810A2), and DIPEA (2.4 mL, 14 mmol) in *i*-BuOH (8.0 mL) were heated at 132 °C in a microwave reactor (Biotage AB, Inc., Uppsala, Sweden) for 3 h. The mixture from the three runs were combined and partitioned between EtOAc (200 mL) and aqueous $NaHCO_3$ (half saturated, 50 mL). The organic layer was washed with aqueous $NaHCO_3$ (3 x 50 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified (5-times total) by chromatography on silica gel using MeOH:DCM:EtOAc:hexane (4:20:20:60) as eluent to give N,N-bis(4-methoxybenzyl)-5-(((3S)-3-(1-propyn-1-yl)-1-piperazinyl)sulfonyl)-2-pyridinamine (6.6 g) as a white foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.55 (d, J = 2.54 Hz, 1 H), 7.64 (dd, J = 9.00, 2.54 Hz, 1 H), 7.13 (d, J = 8.61 Hz, 4 H), 6.87 (d, J = 8.80 Hz, 4 H), 6.47 (d, J =

9.00 Hz, 1 H), 4.75 (s, 4 H), 3.73 - 3.87 (m, 7 H), 3.51 - 3.70 (m, 2 H), 3.41 (d, *J* = 10.95 Hz, 1 H), 3.07 (dt, *J* = 12.08, 3.35 Hz, 1 H), 2.80 - 2.95 (m, 1 H), 2.45 - 2.64 (m, 2 H), 1.80 (d, *J* = 1.96 Hz, 3 H).

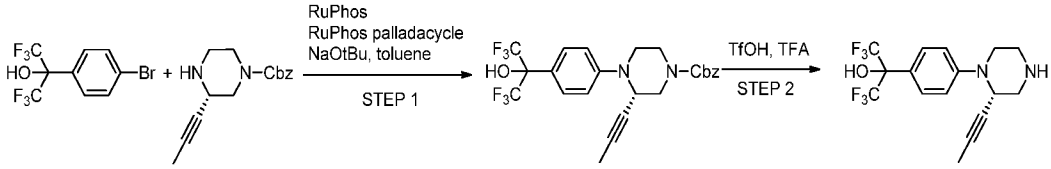
INTERMEDIATE D: 1,1,1,3,3,3-Hexafluoro-2-(4-(2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-2-propanol



To a stirred solution of benzyl 3-(1-propyn-1-yl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinecarboxylate (3.00 g, 5.99 mmol, Intermediate M) in TFA (38.4 mL) at 23 °C was added carefully dropwise trifluoromethane sulfonic acid (1.20 mL, 13.5 mmol, TCI America, Portland, OR). The reaction mixture went cloudy orange upon complete addition of TfOH. Solid $NaHCO_3$ was carefully added in portions until an orange slurry formed to which was added saturated aqueous $NaHCO_3$, followed by additional solid $NaHCO_3$ until pH 7. The mixture was diluted with EtOAc and the layers were separated. The aq. layer was extracted with EtOAc (2 x), the combined organic layers were washed with water followed by brine, dried over Na_2SO_4, filtered and concentrated to a dark brown tacky solid. This reaction was repeated on a 4.67 g scale, 60 mL TFA, 1.87 mL TfOH, and the two batches were combined for purification. The resulting product was purified by column chromatography (330 g of silica gel, 1.5 to 10% MeOH/DCM gradient followed by 10% MeOH/EtOAc flush) to give 1,1,1,3,3,3-hexafluoro-2-(4-(2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-2-propanol (3.92 g) as a light brown solid.

^{1}H NMR (400 MHz, MeOD) δ ppm 7.57 (d, *J* = 8.6 Hz, 2 H), 7.04 (d, *J* = 9.2 Hz, 2 H), 4.50 (br. s., 1 H), 3.39 (d, *J* = 11.9 Hz, 1 H), 3.18 - 3.02 (m, 4 H), 2.92 - 2.80 (m, 1 H), 1.78 (d, *J* = 2.0 Hz, 3 H).

INTERMEDIATE E: 1,1,1,3,3,3-Hexafluoro-2-(4-((2S)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-2-propanol



STEP 1: Benzyl (3S)-3-(1-propyn-1-yl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinecarboxylate

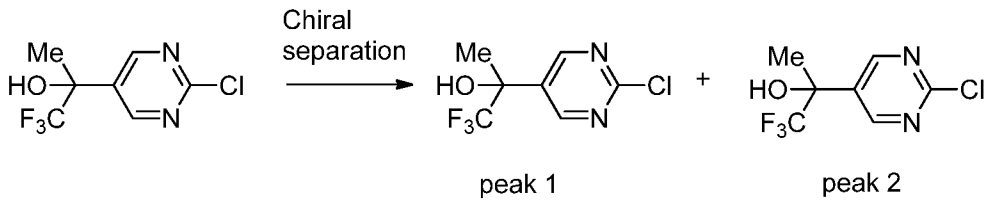
A 1-L pressure tube was charged with benzyl (3S)-3-(1-propyn-1-yl)-1-piperazinecarboxylate (9.89 g, 38.3 mmol, Intermediate A), 2-(4-bromophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (16.11 g, 49.9 mmol, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3009), RuPhos Palladacycle (1.57 g, 1.93 mmol, Strem Chemical Inc, Newburyport, MA), RuPhos (1.83 g, 3.92 mmol, Strem Chemical Inc, Newburyport, MA) and sodium 2-methylpropan-2-olate (9.20 g, 96 mmol, Strem Chemical Inc, Newburyport, MA) and toluene (200 mL). The mixture was degassed by bubbling Ar gas through the mixture for 5 min. The tube was capped and heated in an oil bath at 100 °C for 2 h and 20 min. The reaction mixture was cooled to rt and partitioned between water (300 mL) and EtOAc (200 mL). The aqueous phase was extracted with EtOAc (2 x 200 mL). The combined organic phases were washed with water (500 mL) and saturated aqueous sodium chloride (500 mL). The organic phase was dried over sodium sulfate, filtered and concentrated under a vacuum. The resulting product was purified by column chromatography (twice, 340 g of silica, 0 to 50% EtOAc in hexanes then 100 g of silica, 0 to 10% EtOAc in DCM) to afford benzyl (3S)-3-(1-propyn-1-yl)-4-(4-

(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinecarboxylate (14.12 g) as a light yellow foam.

STEP 2: 1,1,1,3,3,3-Hexafluoro-2-(4-((2S)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-2-propanol

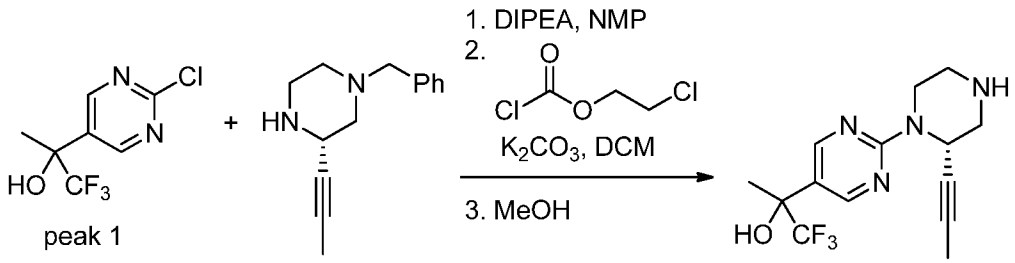
To a solution of benzyl (3S)-3-(1-propyn-1-yl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinecarboxylate (0.79 g, 1.6 mmol) in TFA (10 mL) was added trifluoromethanesulfonic acid (0.421 mL, 4.74 mmol, Alfa Aesar, Ward Hill, MA) slowly. Upon addition of the triflic acid a precipitate formed. The mixture was allowed to stir for 10 minutes and then concentrated and treated with saturated aqueous $NaHCO_3$. The solution was extracted with EtOAc (2x) and the combined extracts were washed with water and brine and then dried and concentrated to afford 1,1,1,3,3,3-hexafluoro-2-(4-((2S)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-2-propanol (0.568 g) as a brown solid.

INTERMEDIATE F: (2R)-2-(2-Chloro-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol or (2S)-2-(2-chloro-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol



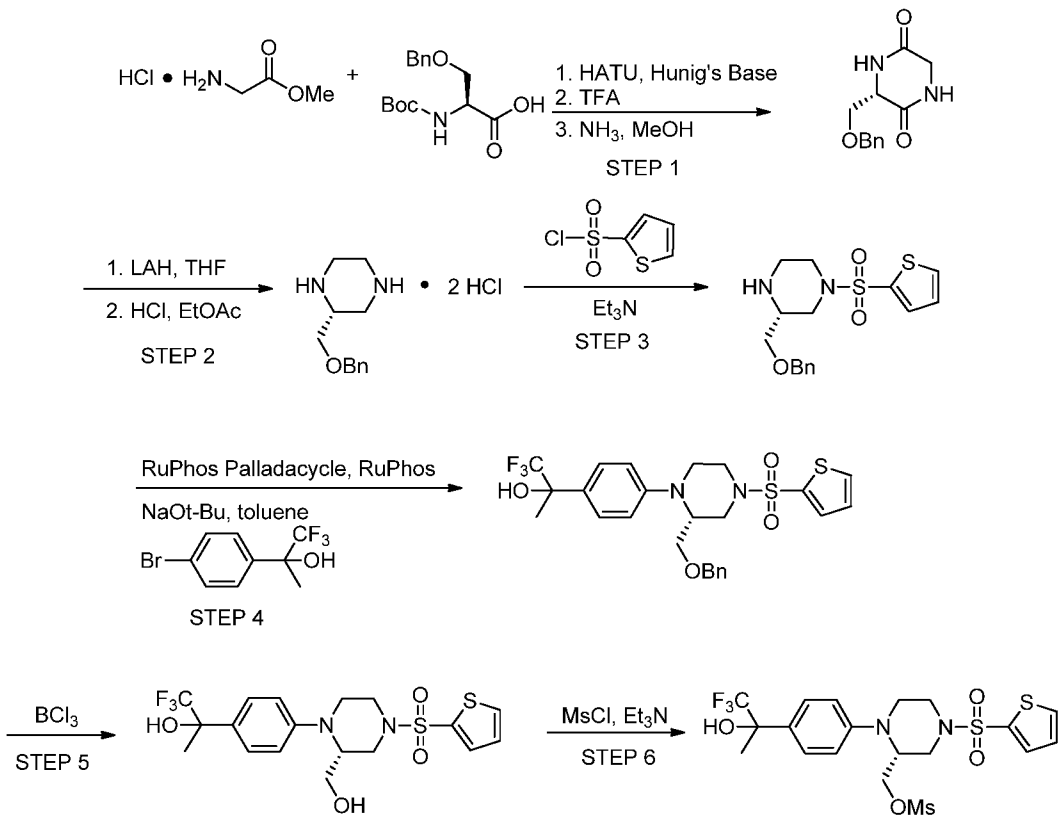
The individual enantiomers of 2-(2-chloro-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol were isolated using chiral chromatography. The method used was as follows: Chiralcel® AS column (100 x 500 mm, 20 μm) using 10% IPA in heptane (total flow was 400 mL/min). The first eluting peak was collected with enantiomeric excesses greater than 98%.

INTERMEDIATE G: (2R)-1,1,1-Trifluoro-2-(2-((2S)-2-(1-propyn-1-yl)-1-piperazinyl)-5-pyrimidinyl)-2-propanol or (2S)-1,1,1-trifluoro-2-(2-((2S)-2-(1-propyn-1-yl)-1-piperazinyl)-5-pyrimidinyl)-2-propanol



A 20-mL vial was charged with (3S)-1-benzyl-3-(1-propyn-1-yl)piperazine (0.700 g, 3.27 mmol, Example 35, Step 4), (2R)-2-(2-chloro-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol or (2S)-2-(2-chloro-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol (0.814 g, 3.59 mmol, Intermediate F (PEAK #1)), 3 mL of NMP, and Hunig's base (1.71 mL, 9.80 mmol). The vial was sealed and heated at 140 °C for 12 h. The mixture was cooled to rt and purified by column chromatography (0 to 50% EtOAc in hexanes) to give the intermediate amine. To this was added 20 mL of DCM, potassium carbonate (0.903 g, 6.53 mmol, Sigma-Aldrich, St. Louis, MO), and 2-chloroethyl chlorocarbonate (1.06 mL, 9.80 mmol, Sigma-Aldrich, St. Louis, MO). After stirring for 30 min at rt, the mixture was filtered and concentrated to give an oil. To this oil was added 15 mL of MeOH. The mixture was heated at reflux for 1 h then cooled to rt and concentrated. The oil was slurried with EtOAc to give (2R)-1,1,1-trifluoro-2-(2-((2S)-2-(1-propyn-1-yl)-1-piperazinyl)-5-pyrimidinyl)-2-propanol or (2S)-1,1,1-trifluoro-2-(2-((2S)-2-(1-propyn-1-yl)-1-piperazinyl)-5-pyrimidinyl)-2-propanol (0.590 g) as an off-white solid.

INTERMEDIATE H: ((2R)-4-(2-thiophenylsulfonyl)-1-(4-(2,2,2-trifluoro-1-hydroxy-1-methylethyl)phenyl)-2-piperazinyl)methyl methanesulfonate



STEP 1: (3S)-3-((Benzyloxy)methyl)-2,5-piperazinedione

A 1-L round-bottomed flask was charged with O-benzyl-N-(tert-butoxycarbonyl)-L-serine (150 g, 508 mmol, Sigma-Aldrich, St. Louis, MO), glycine methyl ester hydrochloride (65.0 g, 518 mmol, Sigma-Aldrich, St. Louis, MO), HATU (203 g, 533 mmol, Sigma-Aldrich, St. Louis, MO) and DMF (400 mL). At room temperature, Hünig's base (177 mL, 1016 mmol) was added over a period of 1 h. The mixture was then diluted with EtOAc (1000 mL) and washed with water (4 x 450 mL). The organic extract was then dried ($MgSO_4$), filtered, and concentrated. The crude material was dissolved in CH_2Cl_2 (500 mL) and the precipitate that formed was filtered off and discarded. TFA (157 mL) was then added to the solution over a period of 1h. The mixture was concentrated to give the TFA salt as an oil. To this was added 800 mL of 2 M NH_3 in MeOH (Sigma-Aldrich, St. Louis, MO). The resulting solution was stirred at room temperature

for 12 h. After that time, another 500 mL 2M NH_3 in MeOH was added and stirring was continued for 4 h. After removing approximately half of the volatiles under a vacuum, a white solid precipitated. The solid was collected by filtration and rinsed with 1L of diethyl ether. The solid was dried overnight under reduced pressure (< 1 Torr;133 Pa) to give (S)-3-(benzyloxymethyl)piperazine-2,5-dione (72.8 g).

STEP 2: (2R)-2-((Benzyloxy)methyl)piperazine dihydrochloride

A solution of LAH (1.87 g, 49.3 mmol) in THF (50 mL) was chilled to 0 °C. To this mixture was added (3S)-3-((benzyloxy)methyl)-2,5-piperazinedione (3.85 g, 16.44 mmol) slowly portion wise. The mixture was allowed to warm to room temperature and then heated at reflux for 1 h. Afterwards, the mixture was chilled to 0 °C and the reaction was quenched with an excess of solid sodium sulfate decahydrate (approximately 50 g). After stirring at room temperature for 1 h, the mixture was filtered. The filtrate was concentrated to give (R)-2-(benzyloxymethyl)piperazine (2.60 g) as a yellow oil. To this was added excess HCl (4M in dioxane) to deliver (2R)-2-((benzyloxy)methyl)piperazine dihydrochloride.

STEP 3: (3R)-3-((Benzyloxy)methyl)-1-(2-thiophenylsulfonyl)piperazine

A 1-L round-bottomed flask was charged with (R)-2-(benzyloxymethyl)piperazine dihydrochloride (55.5 g, 199 mmol) and 300 mL of CH_2Cl_2. After cooling to 0 °C, triethylamine (111 mL, 795 mmol) and 2-thiophenesulfonyl chloride (36.3 g, 199 mmol, Sigma-Aldrich, St. Louis, MO) were added. This mixture was stirred at 0 °C for 30 min and then diluted with water. The organics were separated, dried ($MgSO_4$), filtered and concentrated to give a brown oil. Purification via column chromatography on silica gel (25 to 100% EtOAc in hexanes) gave (3R)-3-((benzyloxy)methyl)-1-(2-thiophenylsulfonyl)piperazine (47.8 g) as a light-brown solid.

STEP 4: 2-(4-((2R)-2-((Benzyloxy)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-1,1,1-trifluoro-2-propanol

A 1-L pressure vessel was charged with 2-(4-bromophenyl)-1,1,1-trifluoropropan-2-ol (43.8 g, 163 mmol, Intermediate O), (3R)-3-((benzyloxy)methyl)-1-(2-thiophenylsulfonyl)piperazine (47.8 g, 136 mmol), 200 mL of toluene, and sodium tert-butoxide (32.6 g, 339 mmol). After bubbling nitrogen gas through the solution for 5 min, chloro(2-dicyclohexylphosphino-2',6'-di-i-propoxy-1,1'-biphenyl)[2-(2-aminoethylphenyl)]palladium(II), methyl-t-butylether adduct (RuPhos Palladacycle) (0.99 g, 1.36 mmol, Strem Chemicals, Newburyport, MA) and 2-dicyclohexyl(2',6'-diisopropoxybiphenyl-2-yl)phosphine (RuPhos) (0.63 g, 1.36 mmol, Strem Chemicals, Newburyport, MA) were added. The vessel was sealed and heated at 65 °C for 12 h. After that time, the mixture was diluted with water and extracted with EtOAc, dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel (0 to 60% EtOAc in hexanes) gave 2-(4-((2R)-2-((benzyloxy)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-1,1,1-trifluoro-2-propanol (54.4 g) as a yellow foam.

STEP 5: 1,1,1-Trifluoro-2-(4-((2R)-2-(hydroxymethyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol

A 2-L round-bottomed flask was charged with 2-(4-((2R)-2-((benzyloxy)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-1,1,1-trifluoro-2-propanol (54.4 g, 101 mmol) and 200 mL of CH_2Cl_2. After cooling to 0 °C, BCl_3 (1M in CH_2Cl_2, 302 mL, 302 mmol, Sigma-Aldrich, St. Louis, MO) was added over 10 min. After 30 min at 0 °C, the mixture was carefully diluted with MeOH and then concentrated and purified via column chromatography on silica gel (0 to 3% MeOH in CH_2Cl_2) to give 1,1,1-trifluoro-2-(4-((2R)-2-

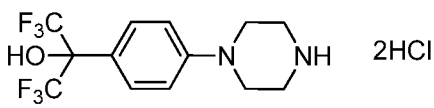
(hydroxymethyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol (42.7 g) as a tan foam.

STEP 6: ((2R)-4-(2-Thiophenylsulfonyl)-1-(4-(2,2,2-trifluoro-1-hydroxy-1-methylethyl)phenyl)-2-piperazinyl)methyl methanesulfonate

A 1-L round-bottomed flask was charged with 1,1,1-trifluoro-2-(4-((2R)-2-(hydroxymethyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol (42.7 g, 95 mmol), 200 mL of CH_2Cl_2, and triethylamine (15.18 mL, 109 mmol). After cooling to 0°C, methanesulfonyl chloride (7.75 g, 99 mmol) was added. After 5 min, another 1 equiv of triethylamine and methanesulfonyl chloride were added. The mixture was then diluted with water and extracted with CH_2Cl_2. The combined organics were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel (0 to 50% EtOAc in hexanes) gave ((2R)-4-(2-thiophenylsulfonyl)-1-(4-(2,2,2-trifluoro-1-hydroxy-1-methylethyl)phenyl)-2-piperazinyl)methyl methanesulfonate (35.0 g) as a light-yellow brittle foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.68 (dd, J = 4.99, 1.08 Hz, 1 H), 7.60 (dd, J = 3.81, 1.08 Hz, 1 H), 7.47 (d, J = 8.61 Hz, 2 H), 7.19 (dd, J = 4.99, 3.81 Hz, 1 H), 6.89 (d, J = 8.80 Hz, 2 H), 4.38 - 4.48 (m, 1 H), 4.22 - 4.31 (m, 2 H), 3.92 (d, J = 11.93 Hz, 1 H), 3.84 (d, J = 11.15 Hz, 1 H), 3.45 - 3.54 (m, 1 H), 3.31 (td, J = 11.93, 3.52 Hz, 1 H), 2.97 (s, 3 H), 2.77 (d, J = 11.74 Hz, 1 H), 2.65 (td, J = 11.15, 3.33 Hz, 1 H), 1.74 (s, 3 H). m/z (ESI, +ve ion) 529.1 (M+H

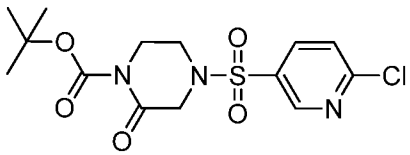
INTERMEDIATE I: 1,1,1,3,3,3-Hexafluoro-2-(4-(1-piperazinyl)phenyl)-2-propanol dihydrochloride



A 1-L pressure vessel was charged with 2-(4-bromophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (70.8 g, 219 mmol, *Bioorg. Med. Chem. Lett.* 2002, *12*,

3009), tert-butyl piperazine-1-carboxylate (40.0 g, 215 mmol, Sigma-Aldrich, St. Louis, MO), 200 mL of toluene, and sodium tert-butoxide (43.3 g, 451 mmol). nitrogen gas was bubbled through the solution for 5 min then chloro(2-dicyclohexylphosphino-2',6'-di-i-propoxy-1,1'-biphenyl)[2-(2-aminoethylphenyl)]palladium(II), methyl-t-butylether adduct (RuPhos Palladacycle) (1.57 g, 2.15 mmol, Strem Chemicals Inc, Newburyport, MA) and 2-dicyclohexyl(2',6'-diisopropoxybiphenyl-2-yl)phosphine (RuPhos) (2.00 g, 4.30 mmol, Strem Chemicals Inc, Newburyport, MA) were added. The vessel was sealed and heated at 65 °C for 2 h. The mixture was then diluted with water and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give an oil. To this material was added 200 mL of EtOAc and 200 mL of 4N HCl in dioxane. The solution was heated at 80 °C for 12 h and the resulting suspension was then allowed to cool to room temperature. The solid precipitate was collected by filtration to give 1,1,1,3,3,3-hexafluoro-2-(4-(1-piperazinyl)phenyl)-2-propanol dihydrochloride (76.2 g) as a white solid.

INTERMEDIATE J: tert-Butyl 4-((6-chloro-3-pyridinyl)sulfonyl)-2-oxo-1-piperazinecarboxylate



STEP 1: 4-((6-chloro-3-pyridinyl)sulfonyl)-2-piperazinone

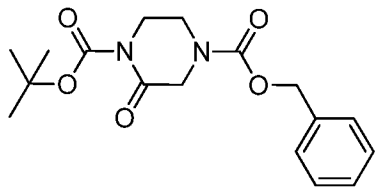
To a mixture of 2-piperazinone (0.46 g, 4.59 mmol, Sigma-Aldrich, St. Louis, MO) and triethylamine (1.5 mL, 10.76 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added 6-chloropyridine-3-sulfonyl chloride (0.974 g, 4.59 mmol, *Organic Process Research & Development* 2009, *13*, 875). The resulting slurry was stirred at room temperature for 30 min and then was concentrated. The residue was mixed with saturated aqueous $NaHCO_3$ (10 mL) and was stirred at room temperature for 1 d. The slurry was filtered, washed with water (3 x 5 mL), and

dried under reduced pressure to give 4-((6-chloro-3-pyridinyl)sulfonyl)-2-piperazinone as a white solid (1.12 g).

STEP 2: tert-Butyl 4-((6-chloro-3-pyridinyl)sulfonyl)-2-oxo-1-piperazinecarboxylate

To a mixture of 4-((6-chloro-3-pyridinyl)sulfonyl)-2-piperazinone (1.12 g, 4.06 mmol), DMAP (0.50 g, 4.09 mmol), and triethylamine (0.60 mL, 4.30 mmol) in CH_2Cl_2 (10 mL) was added Boc_2O (1.81 mL, 7.79 mmol, Sigma-Aldrich, St. Louis, MO). After 19 h, the mixture was concentrated and the residue was suspended in EtOAc (40 mL). The mixture was washed with aqueous 0.1 M HCl (1.0 mmol, 10 mL), water (10 mL), and then saturated aqueous NH_4Cl (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The resulting solid was agitated in hot CH_2Cl_2-hexane (1:1, 20 mL) and then collected by filtration to give tert-butyl 4-((6-chloro-3-pyridinyl)sulfonyl)-2-oxo-1-piperazinecarboxylate (1.17 g).

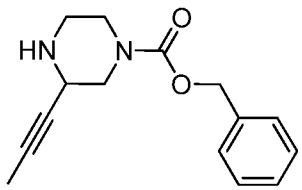
INTERMEDIATE K: 4-Benzyl 1-tert-butyl 2-oxo-1,4-piperazinedicarboxylate



A 2-L Erlenmeyer flask was charged with 2-piperazinone (36.5 g, 364 mmol, Sigma-Aldrich, St. Louis, MO), sodium carbonate (116 g, 1093 mmol), 600 mL of dioxane, and 150 mL of water. To this was slowly added benzyl chloroformate (62.1 g, 364 mmol, Sigma-Aldrich, St. Louis, MO) at room temperature over 20 min. After the addition was complete, the mixture was stirred for 2 h and then diluted with water and extracted with EtOAc (2 L). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give a white solid. To this solid was added 500 mL of DCM, triethylamine (128 mL, 911 mmol), DMAP (4.45 g, 36.4 mmol), and di-tert-butyl dicarbonate (119 g,

546 mmol, Sigma-Aldrich, St. Louis, MO). After 1 h at room temperature, the mixture was diluted with water and the organics were separated. The organics were dried ($MgSO_4$), filtered, and concentrated to give a brown oil. To this oil was added 100 mL of DCM followed by 1 L of hexane. The resulting white solid was collected by filtration to give 4-benzyl 1-tert-butyl 2-oxo-1,4-piperazinedicarboxylate (101 g).

INTERMEDIATE L: Benzyl 3-(1-propyn-1-yl)-1-piperazinecarboxylate



STEP 1: Benzyl (2-((tert-butoxycarbonyl)amino)ethyl)(2-oxo-3-pentyn-1-yl)carbamate

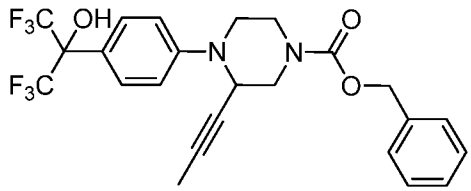
A 150-mL round-bottomed flask was charged with 4-benzyl 1-tert-butyl 2-oxo-1,4-piperazinedicarboxylate (1.41 g, 4.22 mmol, Intermeidate K)) and THF (5 mL). 1-propynylmagnesium bromide (0.5 M in THF, 20.0 mL, 10.0 mmol, Sigma-Aldrich, St. Louis, MO) was added at 0 °C slowly. The mixture was stirred at 0 °C for 2 h. Saturated aqueous NH_4Cl (40 mL) was added and the aqueous phase was extracted with EtOAc (200 mL, then 2 x 100 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under a vacuum. The crude product was purified by column chromatography (50 g of silica, 0 to 50% EtOAc in hexanes) to afford benzyl (2-((tert-butoxycarbonyl)amino)ethyl)(2-oxo-3-pentyn-1-yl)carbamate (1.55 g) as a clear oil.

STEP 2: Benzyl 3-(1-propyn-1-yl)-1-piperazinecarboxylate

A 3-L round-bottomed flask was charged with 2-((tert-butoxycarbonyl)amino)ethyl)(2-oxo-3-pentyn-1-yl)carbamate (82.2 g, 219 mmol)

and 300 mL of DCM. After cooling to -10 °C, TFA (169 mL, 2195 mmol) was added and the resulting dark solution was stirred at room temperature for 15 min. Sodium triacetoxyborohydride (186 g, 878 mmol, Sigma-Aldrich, St. Louis, MO) was then added portion-wise over 10 min. After 2 h, the mixture was concentrated, diluted with EtOAc (1 L), and neutralized with 5 N NaOH. The layers were separated and the organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated. The resulting orange oil was purified via column chromatography (750 g of silica gel, 0 to 4.5 % MeOH/DCM) to give benzyl 3-(1-propyn-1-yl)-1-piperazinecarboxylate (43.7 g) as a brown foam.

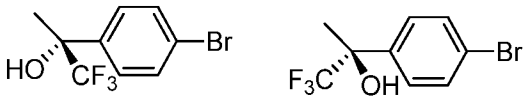
INTERMEDIATE M: Benzyl 3-(1-propyn-1-yl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinecarboxylate



A 150-mL reaction vessel was charged with benzyl 3-(1-propyn-1-yl)-1-piperazinecarboxylate (Intermediate L) (2.88 g, 11.2 mmol), 2-(4-bromophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (4.36 g, 13.5 mmol, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3009), dicyclohexyl(2',6'-diisopropoxy-[1,1'-biphenyl]-2-yl)phosphine, RuPhos (0.530 g, 1.14 mmol, Sigma-Aldrich, St. Louis, MO), RuPhos Palladacycle (0.417 g, 0.572 mmol, Strem Chemical Inc, Newburyport, MA), sodium tert-butoxide (2.73 g, 28.4 mmol, Strem Chemical Inc, Newburyport, MA) and toluene (35 mL). The mixture was degassed by bubbling Ar through the solution for 10 min. The vessel was sealed and heated at 100 °C for 1.5 h. The reaction mixture was cooled to room temerature and water (100 mL) was added. The aqueous phase was extracted with EtOAc (3 x 100 mL) and the combined organic phases were washed with saturated aqueous sodium chloride (150 mL). The organic extracts were dried over sodium sulfate, filtered and concentrated under a vacuum. The crude product was purified by column chromatography (100 g of silica, 0 to 50% EtOAc in hexanes) to afford benzyl 3-(1-propyn-1-yl)-

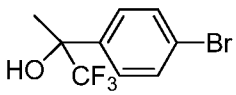
4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinecarboxylate as a yellow solid.

Intermediate N: (2R)-2-(4-bromophenyl)-1,1,1-trifluoro-2-propanol and (2S)-2-(4-bromophenyl)-1,1,1-trifluoro-2-propanol



A 500 mL round-bottomed flask was charged with 1,4-dibromobenzene (30.27 g, 128 mmol, Sigma-Aldrich, St. Louis, MO) and 200 mL of ether. After cooling to -78 °C, n-BuLi (59.0 mL, 2.5 M in hexanes, 148 mmol) was added. This mixture was stirred for 15 min at -78 °C, then 1,1,1-trifluoro-2-propanone (24.2 mL, 257 mmol, Sigma-Aldrich, St. Louis, MO) was added. Stirring was continued at -78 °C for 30 min then the mixture was quenched with 100 mL of saturated aqueous NH_4Cl. The mixture was extracted with EtOAc (250 mL), dried ($MgSO_4$) and concentrated to give an oil. Purification via column chromatography (330 g of silica, 0 to 30% EtOAc in hexanes) gave 2-(4-bromophenyl)-1,1,1-trifluoro-2-propanol (21.50 g) as a colorless oil. The isomeric mixture obtained above was separated using the following chiral SFC method: Chiralcel® OJH column (250 x 30 mm) using 5% isopropanol in supercritical CO_2 (total flow was 120 mL/min). This produced two products with enantiomeric excesses over 95%. The absolute stereochemistry was assigned based on vibrational circular dichroism (VCD) methodology (*Chirality* **2008**, 20, 643) which furnished an assignment consistent with that assumed in a literature example (*Org. Lett.* **2007**, 9(18), 3707).

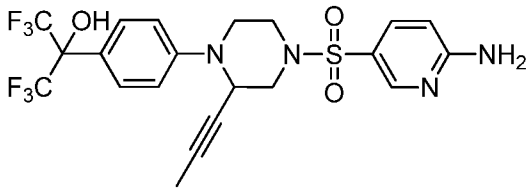
INTERMEDIATE O: 2-(4-Bromophenyl)-1,1,1-trifluoro-2-propanol



A 500 mL round-bottomed flask was charged with 1,4-dibromobenzene (30.27 g, 128 mmol, Sigma-Aldrich, St. Louis, MO) and 200 mL of ether. After cooling to -78 °C, n-BuLi (59.0 mL, 2.5 M in hexanes, 148 mmol) was added.

This mixture was stirred for 15 min at -78 °C, then 1,1,1-trifluoro-2-propanone (24.2 mL, 257 mmol, Sigma-Aldrich, St. Louis, MO) was added. Stirring was continued at -78 °C for 30 min then the mixture was quenched with 100 mL of saturated aqueous NH_4Cl. The mixture was extracted with EtOAc (250 mL), dried ($MgSO_4$) and concentrated to give an oil. Purification via column chromatography (330 g of silica, 0 to 30% EtOAc in hexanes) gave 2-(4-bromophenyl)-1,1,1-trifluoro-2-propanol (21.50 g) as a colorless oil.

INTERMEDIATE P: 2-(4-(4-((6-Amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol



STEP 1: 4-Benzyl 1-tert-butyl 2-oxo-1,4-piperazinedicarboxylate

A 2-L Erlenmeyer flask was charged with 2-piperazinone (36.5 g, 364 mmol, Sigma-Aldrich, St. Louis, MO), sodium carbonate (116 g, 1093 mmol), 600 mL of dioxane, and 150 mL of water. To this was slowly added benzyl chloroformate (62.1 g, 364 mmol, Sigma-Aldrich, St. Louis, MO) at room temperature over 20 min. After the addition was complete, the mixture was stirred for 2 h and then diluted with water and extracted with EtOAc (2 L). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give a white solid. To this solid was added 500 mL of DCM, triethylamine (128 mL, 911 mmol), DMAP (4.45 g, 36.4 mmol), and di-tert-butyl dicarbonate (119 g, 546 mmol, Sigma-Aldrich, St. Louis, MO). After 1 h at room temperature, the mixture was diluted with water and the organics were separated. The organics were dried ($MgSO_4$), filtered, and concentrated to give a brown oil. To this oil was added 100 mL of DCM followed by 1 L of hexane. The resulting white solid was collected by filtration to give 4-benzyl 1-tert-butyl 2-oxo-1,4-piperazinedicarboxylate (101 g).

STEP 2: Benzyl (2-((tert-butoxycarbonyl)amino)ethyl)(2-oxo-3-pentyn-1-yl)carbamate

A 150-mL round-bottomed flask was charged with 4-benzyl 1-tert-butyl 2-oxo-1,4-piperazinedicarboxylate (1.41 g, 4.22 mmol) and THF (5 mL). 1-Propynylmagnesium bromide (0.5 M in THF, 20.0 mL, 10.0 mmol, Sigma-Aldrich, St. Louis, MO) was added at 0 °C slowly. The mixture was stirred at 0 °C for 2 h. Saturated aqueous NH_4Cl (40 mL) was added and the aqueous phase was extracted with EtOAc (200 mL, then 2 x 100 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under a vacuum. The crude product was purified by column chromatography (50 g of silica, 0 to 50% EtOAc in hexanes) to afford benzyl (2-((tert-butoxycarbonyl)amino)ethyl)(2-oxo-3-pentyn-1-yl)carbamate (1.55 g) as a clear oil.

STEP 3: Benzyl 3-(1-propyn-1-yl)-1-piperazinecarboxylate

A 3-L round-bottomed flask was charged with 2-((tert-butoxycarbonyl)amino)ethyl)(2-oxo-3-pentyn-1-yl)carbamate (82.2 g, 219 mmol) and 300 mL of DCM. After cooling to -10 °C, TFA (169 mL, 2195 mmol) was added and the resulting dark solution was stirred at room temperature for 15 min. Sodium triacetoxyborohydride (186 g, 878 mmol, Sigma-Aldrich, St. Louis, MO) was then added portion-wise over 10 min. After 2 h, the mixture was concentrated, diluted with EtOAc (1 L), and neutralized with 5 N NaOH. The layers were separated and the organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated. The resulting orange oil was purified via column chromatography (750 g of silica gel, 0 to 4.5 % MeOH/DCM) to give benzyl 3-(1-propyn-1-yl)-1-piperazinecarboxylate (43.7 g) as a brown foam.

STEP 4: Benzyl 3-(1-propyn-1-yl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinecarboxylate

A 150-mL reaction vessel was charged with benzyl 3-(prop-1-yn-1-yl)piperazine-1-carboxylate (2.88 g, 11.2 mmol), 2-(4-bromophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (4.36 g, 13.5 mmol, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3009), dicyclohexyl(2',6'-diisopropoxy-[1,1'-biphenyl]-2-yl)phosphine, RuPhos (0.530 g, 1.14 mmol, Sigma-Aldrich, St. Louis, MO), RuPhos Palladacycle (0.417 g, 0.572 mmol, Strem Chemical Inc, Newburyport, MA), sodium tert-butoxide (2.73 g, 28.4 mmol, Strem Chemical Inc, Newburyport, MA) and toluene (35 mL). The mixture was degassed by bubbling Ar through the solution for 10 min. The vessel was sealed and heated at 100 °C for 1.5 h. The reaction mixture was cooled to room temerature and water (100 mL) was added. The aqueous phase was extracted with EtOAc (3 x 100 mL) and the combined organic phases were washed with saturated aqueous sodium chloride (150 mL). The organic extracts were dried over sodium sulfate, filtered and concentrated under a vacuum. The crude product was purified by column chromatography (100 g of silica, 0 to 50% EtOAc in hexanes) to afford benzyl 3-(1-propyn-1-yl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinecarboxylate as a yellow solid.

STEP 5: 2-(4-(4-((6-Chloro-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol

A 500-mL round-bottomed flask was charged with benzyl 3-(1-propyn-1-yl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinecarboxylate (3.13 g, 6.25 mmol) and TFA (40 mL). Trifluoromethanesulfonic acid (1.25 mL, 14.1 mmol, Acros/Fisher Scientific, Waltham, MA) was added dropwise at room temperature. After 5 min, additional TfOH (0.45 mL, 5.1 mmol) was added. After an additional 10 min, solid $NaHCO_3$ was carefully added in portions. Saturated aqueous $NaHCO_3$ (250 mL)

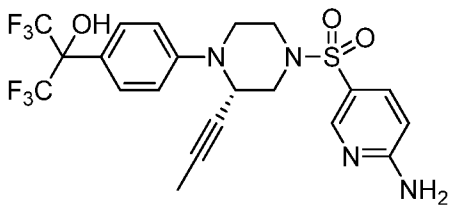
was added slowly to bring pH to approximately 7. The aqueous phase was extracted with EtOAc (100 mL). At this time, more solid $NaHCO_3$ was added to the aqueous phase and extracted again with EtOAc (100 mL). The combined organic phases were washed with water (200 mL) and saturated aqueous sodium chloride (200 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under a vacuum to afford 3.10 g of tan solid. A 500-mL round-bottomed flask was charged with this material, triethylamine (5.00 mL, 35.9 mmol) and CH_2Cl_2 (30 mL). 6-Chloropyridine-3-sulfonyl chloride (1.58 g, 7.43 mmol, *Organic Process Research & Development* **2009**, *13*, 875) was added in portions at 0 °C. The brown mixture was stirred at 0 °C for 10 min. The volume of the reaction mixture was reduced to approximately 10 mL under a vacuum then the mixture was purified twice by column chromatography (100 g of silica, 0 to 50% EtOAc in hexanes) to afford 2-(4-(4-((6-chloro-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (3.46 g) as an off-white solid.

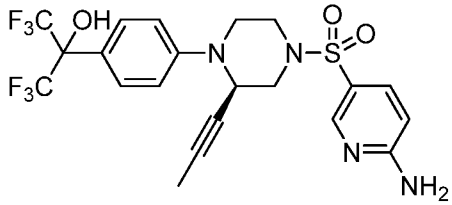
Step 6: 2-(4-(4-((6-Amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol

A 20-mL sealed tube was charged with 2-(4-(4-((6-chloro-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (0.340 g, 0.627 mmol), concentrated ammonium hydroxide (5.00 mL, 38.5 mmol) and EtOH (5 mL). The reaction mixture was heated in an Initiator (Biotage, AB, Uppsala, Sweden) at 120 °C for 1 h. The reaction mixture was further heated in a heating block at 110 °C for 5 h. The reaction mixture was concentrated and purified by column chromatography (25 g of silica, 30 to 80% EtOAc in hexanes) to afford 2-(4-(4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (0.289 g) as a mixture of two enantiomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.49 (br. s., 1 H), 7.80 (dd, *J* = 2.3, 8.8 Hz, 1 H), 7.59 (d, *J* = 8.8 Hz, 2 H), 6.97 (d, *J* = 9.0 Hz, 2 H), 6.55 (d, *J* = 8.8 Hz, 1 H), 5.05 (s, 2 H), 4.46 (br. s., 1 H), 3.85 - 3.72 (m, 2 H), 3.54 (br. s., 1 H), 3.50 - 3.34 (m, 2 H), 2.83 (dd, *J* = 3.3, 11.0 Hz, 1 H), 2.69 (dt, *J* = 3.4, 11.0 Hz, 1 H), 1.80 (s, 3 H). m/z (ESI, +ve ion) 523.1 $(M+H)^+$.

The individual enantiomers were isolated using chiral SFC. The method used was as follows: Chiralpak® ADH column (21 x 250 mm, 5 μm) using 35% methanol in supercritical CO_2 (total flow was 70 mL/min). This produced the two enantiomers with enantiomeric excesses greater than 98%.





2-(4-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol and 2-(4-((2R)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol.

FIRST ELUTING PEAK (PEAK #1)

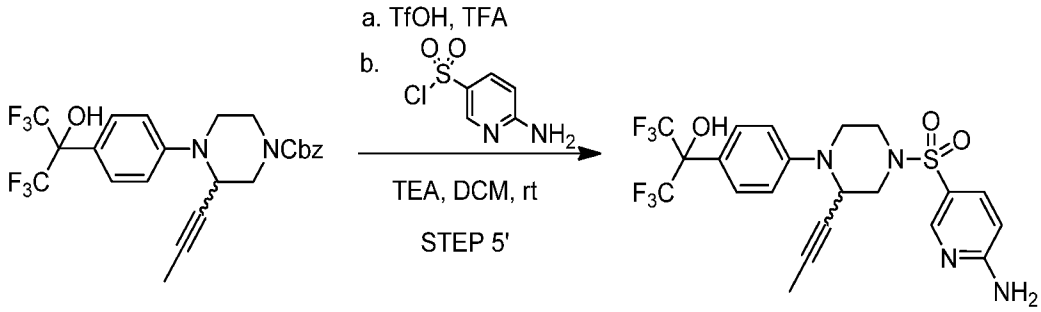
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.48 (d, *J* = 2.3 Hz, 1 H), 7.77 (dd, *J* = 2.5, 8.8 Hz, 1 H), 7.57 (d, *J* = 8.8 Hz, 2 H), 6.95 (d, *J* = 9.2 Hz, 2 H), 6.52 (d, *J* = 8.8 Hz, 1 H), 4.94 (s, 2 H), 4.44 (br. s., 1 H), 3.82 - 3.71 (m, 2 H), 3.58 - 3.33 (m, 3 H), 2.81 (dd, *J* = 3.2, 11.1 Hz, 1 H), 2.67 (dt, *J* = 3.9, 11.0 Hz, 1 H), 1.78 (d, *J* = 2.2 Hz, 3 H). m/z (ESI, +ve ion) 523.2 $(M+H)^+$.

SECOND ELUTING PEAK (PEAK #2)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.49 (d, *J* = 1.8 Hz, 1 H), 7.78 (dd, *J* = 2.3, 8.8 Hz, 1 H), 7.59 (d, *J* = 8.6 Hz, 2 H), 6.97 (d, *J* = 9.0 Hz, 2 H), 6.54 (d, *J*

= 8.8 Hz, 1 H), 4.97 (s, 2 H), 4.46 (br. s., 1 H), 3.77 (t, *J* = 11.7 Hz, 2 H), 3.67 (br. s., 1 H), 3.51 - 3.33 (m, 2 H), 2.82 (dd, *J* = 3.3, 11.0 Hz, 1 H), 2.68 (dt, *J* = 3.9, 11.1 Hz, 1 H), 1.79 (d, *J* = 2.0 Hz, 3 H). m/z (ESI, +ve ion) 523.2 $(M+H)^+$.

Alternative procedure starting after Step 4.



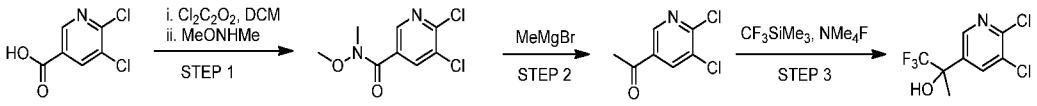
STEP 5′: 2-(4-(4-((6-Amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol

Alternatively, 2-(4-(4-((6-Amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol was synthesized from benzyl 3-(1-propyn-1-yl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinecarboxylate as follows.

A 2-L round-bottomed flask was charged with benzyl 3-(1-propyn-1-yl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinecarboxylate (21.8 g, 43.5 mmol, step 5) and TFA (130 mL). Trifluoromethanesulfonic acid (11.6 mL, 131 mmol, Acros/Fisher Scientific, Waltham, MA) was added slowly at rt resulting orange cloudy mixture. After stirring at rt for 10 min, the volume of the reaction mixture was reduced to half under a vacuum. Solid $NaHCO_3$ was added in portions until the mixture became sludge. Saturated aqueous $NaHCO_3$ (800 mL) was added slowly until the pH was about 8. The aqueous phase was extracted with EtOAc (3 x 250 mL). The combined organic phases were washed with water (500 mL) and saturated

aqueous NaCl (500 mL). The organic phase was dried over sodium sulfate, filtered and concentrated under a vacuum. This material was dissolved into DCM (200 mL) and triethylamine (31.0 mL, 222 mmol) was added. Then 6-aminopyridine-3-sulfonyl chloride (9.40 g, 48.8 mmol, published PCT patent application no. WO 2009/140309) was added in portions over 10 min period. The brown mixture was stirred at room temperature for 10 min. The reaction mixture was washed with water (300 mL) and saturated aqueous NaCl (300 mL). The organic phase was dried over sodium sulfate, filtered and concentrated under a vacuum. The crude product was purified by column chromatography (780 g of total silica, 30 to 90% EtOAc in hexanes) to afford 2-(4-(4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (19.4 g) as a mixture of two enantiomers.

INTERMEDIATE Q: 2-(5,6-Dichloro-3-pyridinyl)-1,1,1-trifluoro-2-propanol



STEP 1: 5,6-Dichloro-N-methoxy-N-methyl-3-pyridinecarboxamide

To a stirred solution of 5,6-dichloro-3-pyridinecarboxylic acid (4.13 g, 21.5 mmol, Acros/Fisher Scientific, Waltham, MA) in DCM (20 mL) at room temperature, was added oxalyl chloride (3.82 mL, 43.0 mmol, Sigma-Aldrich, St. Louis, MO), followed by a couple of drops of DMF. The reaction mixture was stirred at room temperature for 30 min and the solvent was removed under vacuum. The residue was suspended in DCM (20 mL) and cooled to 0 °C. To the reaction mixture N,O-dimethylhydroxylamine hydrochloride (2.10 g, 21.5 mmol, Sigma-Aldrich, St. Louis, MO) and Hünig's base (11.2 mL, 64.5 mmol, Sigma-Aldrich, St. Louis, MO) were added sequentially. The reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was diluted with saturated aqueous sodium bicarbonate (about 10 mL) and extracted with EtOAc (2 x 30

mL). The organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuum to afford 5,6-dichloro-N-methoxy-N-methyl-3-pyridinecarboxamide (4.85 g) as an orange solid that was used without further purification.

STEP 2: 1-(5,6-Dichloro-3-pyridinyl)ethanone

To a stirred solution of 5,6-dichloro-N-methoxy-N-methyl-3-pyridinecarboxamide (2.88 g, 12.3 mmol) in THF (15 mL) at 0 °C and under a nitrogen atmosphere, methylmagnesium bromide (12.3 mL, 36.8 mmol, 3M in ether, Sigma-Aldrich, St. Louis, MO) was added. The reaction mixture was stirred at 0 °C for 30 min and quenched by the addition of saturated aqueous ammonium chloride. The mixture was extracted with EtOAc (2 x 30 mL); the organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated under vacuum to afford the crude material as an orange solid. The crude product was triturated with hexanes, filtered, and dried under vacuum to give 1-(5,6-dichloro-3-pyridinyl)ethanone (1.61 g) as a light tan solid.

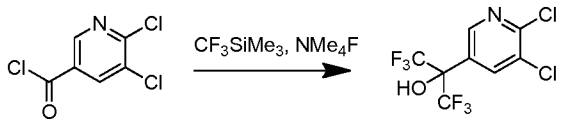
STEP 3: 2-(5,6-Dichloro-3-pyridinyl)-1,1,1-trifluoro-2-propanol

To a 50-mL round-bottomed flask was added 1-(5,6-dichloro-3-pyridinyl)ethanone (700 mg, 3.68 mmol), cesium fluoride (28 mg, 0.18 mmol, Sigma-Aldrich, St. Louis, MO), and DME (8 mL). The reaction mixture was cooled to 0 °C and under a nitrogen atmosphere (trifluoromethyl)trimethylsilane (0.65 mL, 4.42 mmol, Sigma-Aldrich, St. Louis, MO) was added. The reaction mixture was stirred at 0 °C for 1.5 h and then carefully quenched by adding aqueous 5N HCl (5 mL). The reaction mixture was stirred at room temperature for 18h. The reaction mixture was carefully diluted with saturated aqueous sodium bicarbonate (about 10 mL) and extracted with EtOAc (2 x 30 mL). The organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuum. The crude material was absorbed onto a plug of silica gel and purified

by chromatography through a silica gel column (40 g), eluting with a gradient of 0 % to 10% EtOAc in hexanes, to provide 2-(5,6-dichloro-3-pyridinyl)-1,1,1-trifluoro-2-propanol (812 mg) as a colorless oil.

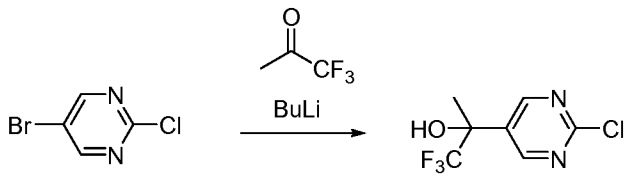
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.60 (d, J = 2.15 Hz, 1H), 8.27 (d, J = 2.15 Hz, 1H), 7.12 (s, 1H), 1.75 (s, 3H). (m/z (ESI, +ve ion) 260.0 $(M)^+$.

INTERMEDIATE R: 2-(5,6-Dichloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol



To a cooled suspension of 5,6-dichloro-3-pyridinecarbonyl chloride (2.08 g, 9.88 mmol, *Bioorg. Med. Chem. Lett.*, **2011**, *21(10)*, 2958) and tetramethylammonium fluoride (2.025 g, 21.74 mmol, Sigma-Aldrich, St. Louis, MO) in DME (50 ml) at -78 °C was added (trifluoromethyl)trimethylsilane (3.21 ml, 21.74 mmol, Oakwood Products, West Columbia, SC) and the reaction was warmed to room temperature overnight. The reaction mixture was diluted with 1N HCl (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under a vacuum to give a solid that was purified by silica gel column chromatography (0 to 50% EtOAc in hexanes) to afford 2-(5,6-dichloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (2.3 g).

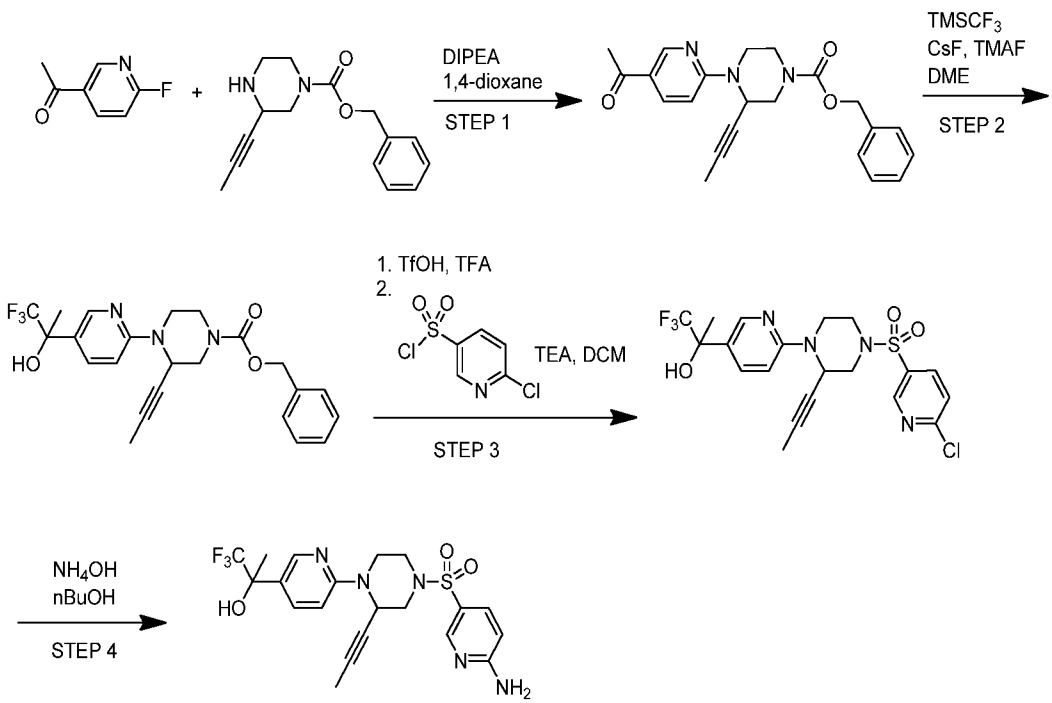
INTERMEDIATE S: 2-(2-Chloro-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol



A 500-mL round-bottomed flask was charged with 5-bromo-2-chloropyrimidine (8.53 g, 44.1 mmol, Combi-Blocks, San Diego, CA) and 100 mL of ether. After cooling to -78 °C, n-BuLi (2.5 M in hexanes, 27.6 mL, 44.1

mmol) was added. This mixture was stirred at -78 °C for 10 min, then 1,1,1,trifluoro-2-propanone (14.8 g, 132 mmol, Sigma-Aldrich, St. Louis, MO) was added. After stirring for an additional 10 min at -78 °C, the reaction was quenched with saturated aqueous NH_4Cl. The solution was extracted with EtOAc, dried ($MgSO_4$), filtered, and concentrated. Purification via column chromatography on silica gel (0 to 85% EtOAc in hexanes) gave 2-(2-chloro-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol (1.70 g) as a white solid.

Example 1: 2-(6-(4-((6-Amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol



STEP 1: Benzyl 4-(5-acetyl-2-pyridinyl)-3-(1-propyn-1-yl)-1-piperazinecarboxylate

A 20-mL vial was charged with benzyl 3-(1-propyn-1-yl)-1-piperazinecarboxylate (0.827 g, 3.20 mmol, Intermediate L), 1-(6-fluoropyridin-3-yl)ethanone (1.43 g, 9.23 mmol, Aces Pharma Inc., Princeton, NJ), DIPEA

(2.80 mL, 16.0 mmol) and 1,4-dioxane (13 mL). The vial was sealed and the mixture was stirred at 140 °C for 3 d. The reaction mixture was partitioned between water (80 mL) and EtOAc (50 mL). The aqueous phase was extracted with EtOAc (50 mL). The combined organic phases were washed with saturated aqueous sodium chloride (100 mL). The organic phase was dried over sodium sulfate, filtered and concentrated under a vacuum. The resulting product was purified by column chromatography (50 g of silica gel, 0 to 60% EtOAc in hexanes) to afford benzyl 4-(5-acetyl-2-pyridinyl)-3-(1-propyn-1-yl)-1-piperazinecarboxylate (0.495 g) as a pale yellow foam.

STEP 2: Benzyl 3-(1-propyn-1-yl)-4-(5-(2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyridinyl)-1-piperazinecarboxylate

A 150-mL round-bottomed flask was charged with benzyl 4-(5-acetyl-2-pyridinyl)-3-(1-propyn-1-yl)-1-piperazinecarboxylate (0.472 g, 1.25 mmol), trimethyl(trifluoromethyl)silane (0.240 mL, 1.63 mmol, Apollo Scientific Ltd., UK) and DME (5 mL). The mixture was cooled to 0 °C and stirred for 5 min before adding cesium fluoride (0.0164 g, 0.108 mmol, Strem Chemical Inc., Newburyport, MA). After the addition, the mixture was allowed to warm to rt. After stirring for 15 min. the reaction was cooled to 0 °C and tetramethylammonium fluoride (0.363 g, 3.90 mmol, Sigma-Aldrich, St. Louis, MO) was added portionwise. The mixture was allowed to warm to rt and was stirred for 15 h. Aqueous saturated $NaHCO_3$ (20 mL) was added and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under a vacuum. The resulting product was purified by column chromatography (50 g of silica gel, 10 to 60% EtOAc in hexanes) to afford benzyl 3-(1-propyn-1-yl)-4-(5-(2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyridinyl)-1-piperazinecarboxylate (0.299 g) as off-white foam.

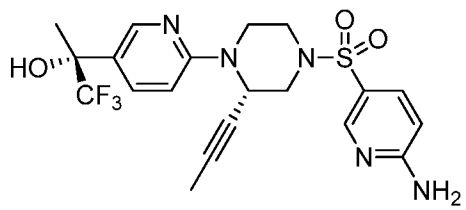
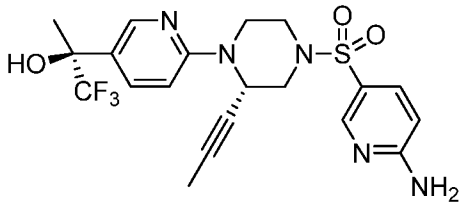
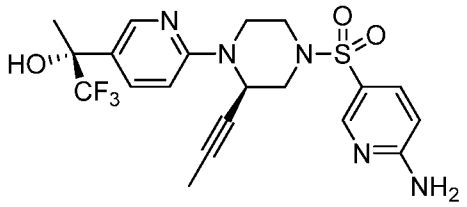
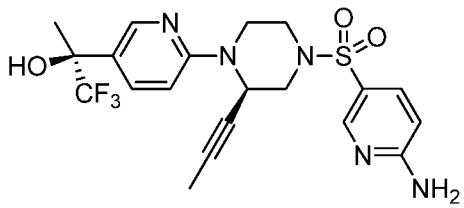
STEP 3: 2-(6-(4-((6-Chloro-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol

A 20-mL vial was charged with benzyl 3-(1-propyn-1-yl)-4-(5-(2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyridinyl)-1-piperazinecarboxylate (0.299 g, 0.668 mmol) and TFA (3 mL). Trifluoromethanesulfonic acid (0.180 mL, 2.03 mmol, Acros/Thermo Fisher Scientific, Hampton, NH) was added dropwise at room temperature. The mixture was stirred at room temperature for 2 min. Solid $NaHCO_3$ was added followed by saturated aqueous $NaHCO_3$ until a pH of about 7. The aqueous phase was extracted with EtOAc (2 x 30 mL). The combined organic phases were washed with water (50 mL) and saturated aqueous sodium chloride (50 mL). The organic phase was dried over sodium sulfate, filtered and concentrated under a vacuum. To this product, DCM (5 mL) and TEA (0.500 mL, 3.59 mmol) were added followed by portionwise addition of 6-chloro-3-pyridinesulfonyl chloride (0.174 g, 0.822 mmol, *Organic Process Research & Development* **2009**, *13*, 875). The mixture was stirred at room temperature for 5 min and then purified by column chromatography (25 g of silica gel, 0 to 60% EtOAc in hexanes) to afford 2-(6-(4-((6-chloro-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol (0.270 g) as a light yellow foam.

STEP 4: 2-(6-(4-((6-Amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol

A 20-mL vial was charged with 2-(6-(4-((6-chloro-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol (0.270 g, 0.552 mmol) and concentrated ammonium hydroxide (2.5 mL, 18 mmol, Sigma-Aldrich, St. Louis, MO) and tBuOH (2.5 mL). The vial was sealed and the reaction mixture was stirred at 120 °C for 4.5 h. The reaction mixture was concentrated and the resulting product was purified by column chromatography twice (25 g and 10 g of silica, 30 to 90% EtOAc in hexanes) to afford 2-(6-(4-((6-

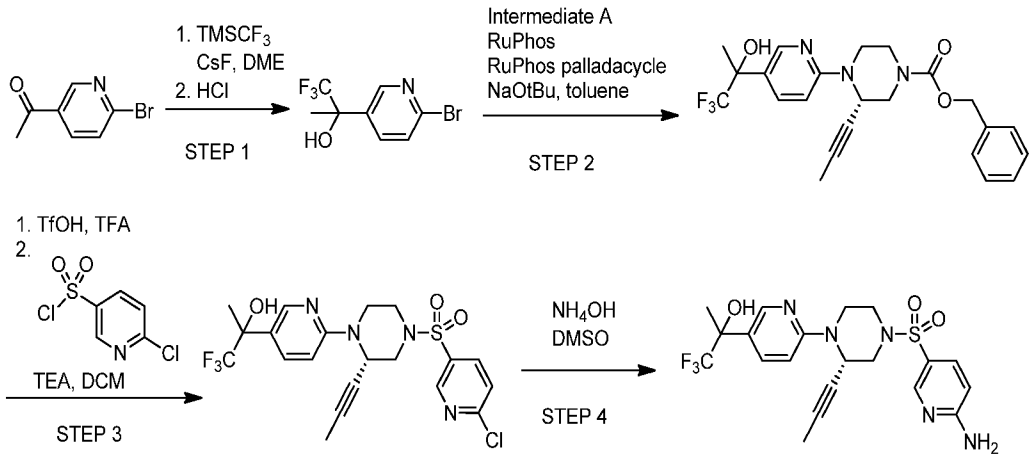
amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol (0.0320 g) as a mixture of 4 stereoisomers.

(2R)-2-(6-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol; (2S)-2-(6-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol; (2R)-2-(6-((2R)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol; and (2S)-2-(6-((2R)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.47 (d, J = 2.3 Hz, 1 H), 8.37 (s, 1 H), 7.80 - 7.68 (m, 2 H), 6.65 (d, J = 9.0 Hz, 1 H), 6.51 (d, J = 8.8 Hz, 1 H), 5.20 (br. s., 1 H), 4.98 (s, 2 H), 4.08 (d, J = 6.3 Hz, 1 H), 3.89 - 3.76 (m, 2 H), 3.39 (t, J = 11.8 Hz, 1 H), 2.69 (dd, J = 3.5, 11.2 Hz, 1 H), 2.55 (dt, J = 3.3, 11.5 Hz, 1 H), 2.35 (s, 1 H), 1.78 (d, J = 1.6 Hz, 3 H), 1.75 (s, 3 H). m/z (ESI, +ve ion) 492.1 $(M+Na)^+$. GK-GKRP IC_{50} (Binding) = 0.038 μM.

Two of the isomers from Example 1 can also be synthesized by the route described below.



STEP 1: 2-(6-Bromo-3-pyridinyl)-1,1,1-trifluoro-2-propanol

A 500-mL round-bottomed flask was charged with 1-(6-bromo-3-pyridinyl)ethanone (9.67 g, 48.3 mmol, Sigma-Aldrich, St. Louis, MO) and DME (100 mL). Trimethyl(trifluoromethyl)silane (8.60 mL, 58.2 mmol, Oakwood Products, Inc., West Columbia, SC) was added followed by cesium fluoride (0.388 g, 2.55 mmol, Strem Chemical Inc., Newburyport, MA) at 0 °C. The mixture was stirred at 0 °C for 15 min. Then 5 N hydrochloric acid (20 mL, 100 mmol) was added and the cold bath was removed. The mixture was stirred at rt for overnight. Saturated aquaous $NaHCO_3$ (150 mL) was added slowly while stirring. EtOAc (50 mL) was added and the layers were separated. The aqueous phase was extracted with EtOAc (100 mL). The combined organic phases were washed with water (200 mL) and saturated aqueous sodium chloride (200 mL). The organic phase was dried over sodium sulfate, filtered and concentrated under a vacuum to afford 2-(6-bromo-3-pyridinyl)-1,1,1-trifluoro-2-propanol (12.8 g) as a light brown oil.

STEP 2: Benzyl (3S)-3-(1-propyn-1-yl)-4-(5-(2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyridinyl)-1-piperazinecarboxylate

A 20-mL vial was charged with benzyl (3S)-3-(1-propyn-1-yl)-1-piperazinecarboxylate (1.01 g, 3.92 mmol, intermediate A), 2-(6-bromo-3-pyridinyl)-1,1,1-trifluoro-2-propanol (1.22 g, 4.52 mmol), RuPhos/RuPhos palladacycle (1:1) (0.117 g, 0.098 mmol, Strem Chemical Inc., Newburyport, MA), sodium t-butoxide (0.945 g, 9.83 mmol, Strem Chemical Inc., Newburyport, MA) and toluene (10 mL). The mixture was degassed by bubbling Ar gas through the mixture for 10 min. The vial was sealed and heated at 100 °C for 1.5 h. The reaction mixture was allowed to cool to room temperature and partitioned between water (50 mL) and EtOAc (50 mL). The aqueous phase was extracted with EtOAc (30 mL). The combined organic phases were washed with saturated aqueous sodium chloride (100 mL). The organic phase was dried over sodium sulfate, filtered and concentrated under a vacuum. The resulting product was purified by column chromatography (50 g of silica gel, 0 to 60% EtOAc in hexanes) to afford benzyl (3S)-3-(1-propyn-1-yl)-4-(5-(2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyridinyl)-1-piperazinecarboxylate (1.20 g) as a light yellow foam.

STEP 3: 2-(6-((2S)-4-((6-Chloro-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol

A 500-mL round-bottomed flask was charged with benzyl (3S)-3-(1-propyn-1-yl)-4-(5-(2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyridinyl)-1-piperazinecarboxylate (1.19 g, 2.66 mmol) and TFA (8 mL). Trifluoromethanesulfonic acid (0.71 mL, 8.00 mmol, Alfa Aesar, Ward Hill, MA) was added dropwise at room temperature. The mixture was stirred at room temperature for 2 min. Solid $NaHCO_3$ was added followed by saturated aqueous $NaHCO_3$ until a pH of about 7. The aqueous phase was extracted with EtOAc (2 x 30 mL). The combined organic phases were washed with water (50 mL) and saturated aqueous sodium chloride (50 mL). The organic phase was dried over sodium sulfate, filtered and concentrated under a vacuum. The material was dissolved DCM (8 mL) and triethylamine (2.00 mL, 14.4 mmol) followed by

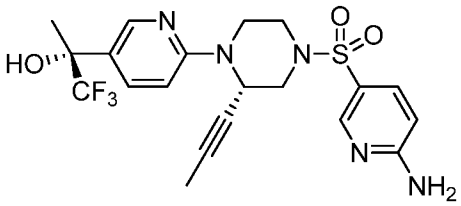
portionwise addition of 6-chloro-3-pyridinesulfonyl chloride (0.693 g, 3.27 mmol, *Organic Process Research & Development* **2009**, *13*, 875). The mixture was stirred at rt for 15 min and then concentrated. The residue was partitioned between water (60 mL) and EtOAc (60 mL). The aqueous phase was extracted with EtOAc (60mL). The combined organic phases were washed with water (100 mL) and saturated aqueous sodium chloride (100 mL). The organic phase was dried over sodium sulfate, filtered and concentrated under a vacuum. The resulting product was purified by column chromatography (50 g of silica gel, 0 to 70% EtOAc in hexanes) to afford 2-(6-((2S)-4-((6-chloro-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol (1.06 g) as a off-white foam.

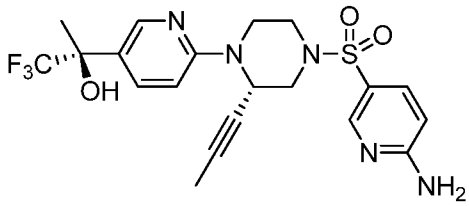
STEP 4: 2-(6-((2S)-4-((6-Amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol

Two 20-mL vials were charged with 2-(6-((2S)-4-((6-chloro-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol (1.00 g, 2.05 mmol) and DMSO (10 mL). While stirring, concentrated ammonium hydroxide (10 ml, 72 mmol, Sigma-Aldrich, St. Louis, MO) was added slowly and vials were sealed. The mixture was stirred at 100 °C for 5 h. The reaction mixture was allowed to cool to room temperature and then partitioned between water (120 mL) and EtOAc (80 mL). The aqueous phase was extracted with EtOAc (60 mL). The combined organic phases were washed with water (80 mL) and saturated aqueous sodium chloride (80 mL). The organic phase was dried over sodium sulfate, filtered and concentrated under a vacuum to afford. The resulting product was purified by column chromatography (50 g of silica gel, 30 to 90% EtOAc in hexanes) to afford 2-(6-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol (0.85 g) as a mixture of two diastereomers.

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 8.48 (d, J = 2.2 Hz, 1 H), 8.37 (s, 1 H), 7.76 (dd, J = 2.3, 8.8 Hz, 1 H), 7.72 (d, J = 8.8 Hz, 1 H), 6.64 (d, J = 9.0 Hz, 1 H), 6.51 (d, J = 8.8 Hz, 1 H), 5.21 (br. s., 1 H), 4.95 (s, 2 H), 4.06 (br. s., 1 H), 3.89 - 3.76 (m, 2 H), 3.45 - 3.34 (m, 1 H), 2.69 (dd, J = 3.5, 11.2 Hz, 1 H), 2.55 (dt, J = 3.3, 11.6 Hz, 1 H), 2.50 (s, 1 H), 1.78 (d, J = 1.4 Hz, 3 H), 1.75 (s, 3 H). m/z (ESI, +ve ion) 470.1 $(M+H)^+$.

The individual diastereomers were isolated using chiral SFC. The method used was as follows: Chiralpak® AS-H column (21 x 250 mm, 5 μm) using 25% (40 mM NH_3 in methanol) in supercritical CO_2 (total flow was 75 mL/min). This produced the two diastereomers with diastereomeric and enanteomeric excesses greater than 98%.





(2R)-2-(6-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol and (2S)-2-(6-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol.

FIRST ELUTING PEAK (PEAK #1)

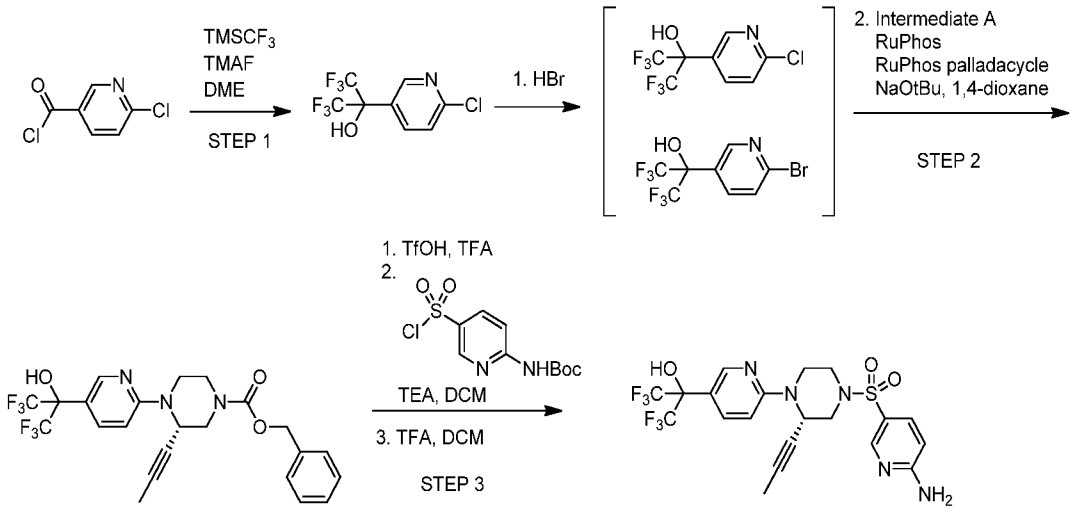
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.46 (d, J = 2.2 Hz, 1 H), 8.37 (d, J = 2.2 Hz, 1 H), 7.75 (dd, J = 2.4, 8.7 Hz, 1 H), 7.71 (dd, J = 2.2, 9.0 Hz, 1 H), 6.64 (d, J = 9.0 Hz, 1 H), 6.50 (d, J = 8.6 Hz, 1 H), 5.19 (br. s., 1 H), 4.99 (s, 2 H), 4.07 (d, J = 12.9 Hz, 1 H), 3.88 - 3.75 (m, 2 H), 3.38 (dt, J = 3.0, 12.4 Hz, 1 H), 2.72 - 2.59 (m, 2 H), 2.54 (dt, J = 3.2, 11.6 Hz, 1 H), 1.77 (d, J = 2.2 Hz, 3 H),

1.74 (s, 3 H). m/z (ESI, +ve ion) 470.1 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.009 μM.

SECOND ELUTING PEAK (PEAK #2)

^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.49 (d, J = 2.2 Hz, 1 H), 8.38 (s, 1 H), 7.77 (dd, J = 2.1, 8.7 Hz, 1 H), 7.73 (dd, J = 1.8, 8.8 Hz, 1 H), 6.65 (d, J = 8.8 Hz, 1 H), 6.52 (d, J = 8.8 Hz, 1 H), 5.22 (br. s., 1 H), 4.94 (s, 2 H), 4.08 (d, J = 12.7 Hz, 1 H), 3.90 - 3.77 (m, 2 H), 3.41 (dt, J = 2.9, 12.3 Hz, 1 H), 2.70 (dd, J = 3.5, 11.2 Hz, 1 H), 2.61 - 2.51 (m, 1 H), 2.36 (s, 1 H), 1.80 (d, J = 1.8 Hz, 3 H), 1.76 (s, 3 H). m/z (ESI, +ve ion) 470.1 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.006 μM.

EXAMPLE 2: 2-(6-((2S)-4-((6-Amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol



STEP 1: 2-(6-Chloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol

A 100-mL round-bottomed flask was charged with of 6-chloro-3-pyridinecarbonyl chloride (0.604 g, 3.43 mmol, Alfa Aesar, Ward Hill, MA), tetramethylammonium fluoride (0.978 g, 10.5 mmol, Sigma-Aldrich, St. Louis,

MO) and DME (10 mL). Trimethyl(trifluoromethyl)silane (1.60 mL, 10.82 mmol, Oakwood Products, Inc., West Columbia, SC) was added at -78 °C. The mixture was stirred and allowed to warm up to room temperature slowly. The stirring was continued for 15 h. The reaction mixture was partitioned between saturated aqueous sodium bicarbonate (50 mL) and EtOAc (30 mL). The aqueous phase was extracted with EtOAc (40 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under a vacuum. The resulting product was purified by column chromatography (25 g of silica gel, 0 to 40% EtOAc in hexanes) to afford 2-(6-chloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (0.556 g) as a flaky glassy solid.

STEP 2: Benzyl (3S)-3-(1-propyn-1-yl)-4-(5-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)-2-pyridinyl)-1-piperazinecarboxylate

A 20 mL vial was charged with 2-(6-chloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (0.162 g, 0.580 mmol) and DCM (2 mL). Hydrobromic acid in acetic acid (0.50 mL, 3.04 mmol, Sigma-Aldrich, St. Louis, MO) was added dropwise at room temperature. The mixture was stirred at rt for 5 h. The cap was removed and the mixture was warmed up to 50 °C to remove the DCM. More HBr (1 mL) was added and the mixture was stirred at 50 °C for an additional 10 h. Solid $NaHCO_3$ was then added followed by saturated aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under a vacuum to afford 0.167 g of tan solid. A 5 mL vial was charged with this solid (0.160 g), benzyl (3S)-3-(1-propyn-1-yl)-1-piperazinecarboxylate (0.129 g, 0.500 mmol, Intermediate A), RuPhos palladacycle/RuPhos (1:1) (0.041 g, 0.034 mmol, Strem Chemical Inc., Newburyport, MA), sodium t-butoxide (0.1199 g, 1.248 mmol, Strem Chemical Inc., Newburyport, MA) and 1,4-dioxane (2 mL). The mixture was degassed by bubbling Ar gas through the mixture for 5 min. The vial was sealed and the reaction mixture was stirred at 100 °C for 75 min. The reaction mixture was

partitioned between a mixture of water (20 mL) and saturated aqueous NH_4Cl (20 mL) and EtOAc (20 mL). The aqueous phase was further extracted with EtOAc (20 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under a vacuum. The resulting product was purified by column chromatography (25 g of silica gel, 0 to 60% EtOAc in hexanes) to afford benzyl (3S)-3-(1-propyn-1-yl)-4-(5-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)-2-pyridinyl)-1-piperazinecarboxylate (0.135 g) as a pale yellow foam.

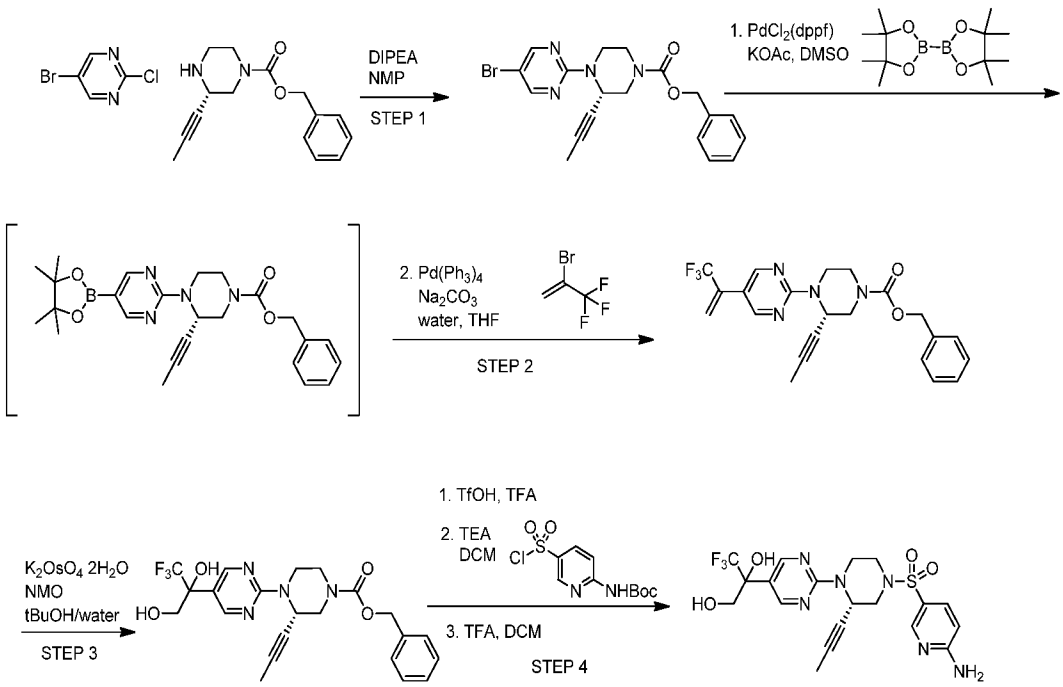
STEP 3: 2-(6-((2S)-4-((6-Amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol

A 100-mL round-bottomed flask was charged with (3S)-3-(1-propyn-1-yl)-4-(5-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)-2-pyridinyl)-1-piperazinecarboxylate (0.135 g, 0.269 mmol,) and TFA (2 mL). Trifluoromethanesulfonic acid (0.080 mL, 0.90 mmol, Alfa Aesar, Ward Hill, MA) was added dropwise at room temperature. The mixture was stirred for 3 min. The reaction mixture was concentrated under a vacuum to dryness and DCM (2.5 mL) was added followed by triethylamine (0.400 mL, 2.87 mmol). The mixture was stirred for 3 min then tert-butyl (5-(chlorosulfonyl)-2-pyridinyl)carbamate (0.0856 g, 0.292 mmol, Intermediate B) was added. The mixture was stirred for 5 min. The reaction mixture was concentrated under a vacuum and taken into DCM (2 mL). TFA (1 mL) was added and the brown mixture was stirred at room temperature for 80 min. 0.5 mL of TFA was added and the mixture was stirred at room temperature for additional 25 min. The solvent was removed and the residue was partitioned between saturated aqueous $NaHCO_3$ (20 mL) and EtOAc (20 mL). The aqueous phase was extracted with EtOAc (20 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (40 mL), water (40 mL) and saturated aqueous NaCl (40 mL). The organic phase was dried over sodium sulfate, filtered and concentrated. The resulting product was purified by column chromatography (25 g of silica gel, 30 to 100% EtOAc in hexanes) to afford 2-(6-((2S)-4-((6-amino-3-

pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (0.072 g) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.49 (dd, J = 2.0, 9.6 Hz, 2 H), 7.79 (dd, J = 2.3, 8.8 Hz, 2 H), 6.68 (d, J = 9.1 Hz, 1 H), 6.54 (d, J = 8.8 Hz, 1 H), 5.25 (br. s., 1 H), 5.09 (s, 2 H), 4.21 - 4.10 (m, 1 H), 3.92 - 3.77 (m, 2 H), 3.71 - 3.36 (m, 2 H), 2.71 (dd, J = 3.7, 11.3 Hz, 1 H), 2.58 (dt, J = 3.2, 11.8 Hz, 1 H), 1.81 (d, J = 2.0 Hz, 3 H). m/z (ESI, +ve ion) 524.1 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.008 μM.

EXAMPLE 3: 2-(2-((2S)-4-((6-Amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-5-pyrimidinyl)-3,3,3-trifluoro-1,2-propanediol



STEP 1: Benzyl (3S)-4-(5-bromo-2-pyrimidinyl)-3-(1-propyn-1-yl)-1-piperazinecarboxylate

A 20-mL vial was charged with benzyl (3S)-3-(1-propyn-1-yl)-1-piperazinecarboxylate (1.52 g, 5.89 mmol, Intermediate A), 5-bromo-2-

chloropyrimidine (1.26 g, 6.52 mmol, Combi-Blocks, inc. San Diego, CA), DIPEA (3.08 mL, 17.7 mmol) and NMP (8 mL). The vial was sealed and the reaction mixture was stirred at 140 °C for 2.5 h and then 14 h at 100 °C. At that time, additional 5-bromo-2-chloropyrimidine (0.209 g, 1.08 mmol) was added and the heating was resumed at 140 °C for 5.5 h. The reaction mixture was partitioned between water (50 mL) and EtOAc (50 mL). The aqueous phase was extracted with EtOAc (50 mL). The combined organic phases were washed with water (100 mL) and saturated aqueous sodium chloride (100 mL). The organic phase was dried over sodium sulfate, filtered and concentrated under a vacuum. The resulting product was purified by column chromatography (50 g of silica gel, 0 to 30% EtOAc in hexanes) to afford benzyl (3S)-4-(5-bromo-2-pyrimidinyl)-3-(1-propyn-1-yl)-1-piperazinecarboxylate (2.25 g) as a white foam.

STEP 2: Benzyl (3S)-3-(1-propyn-1-yl)-4-(5-(1-(trifluoromethyl)ethenyl)-2-pyrimidinyl)-1-piperazinecarboxylate

A 150-mL round-bottomed flask was charged with (S)-benzyl 4-(5-bromopyrimidin-2-yl)-3-(prop-1-yn-1-yl)piperazine-1-carboxylate (2.08 g, 5.01 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (1.33 g, 5.25 mmol, Oakwood Products, Inc., West Columbia, SC), $PdCl_2$dppf dichloromethane adduct (0.209 g, 0.256 mmol, Strem Chemical Inc., Newburyport, MA), and potassium acetate (1.49 g, 15.2 mmol, Sigma-Aldrich, St. Louis, MO). The flask was flushed with nitrogen. DMSO (15 mL) was added and the reaction mixture was stirred at 100 °C for 24 h. The mixture was cooled to room temperature then diluted with EtOAc (80 mL). Aqueous saturated $NaHCO_3$ (80 mL) was added and the layers were separated. The combined organic phases were washed with saturated aqueous $NaHCO_3$ (2 x 50 mL). The organic phase was dried over sodium sulfate, filtered and concentrated under a vacuum. This material was dissolved into DCM and filtered through a pad of silca gel using 50% EtOAc in hexanes as eluent. The filtrate was concentrated to afford boronic ester (0.675 g). A 5-mL vial was charged with this material (0.600

g), $Pd(PPh_3)_4$ (0.076 g, 0.066 mmol, Strem Chemical Inc., Newburyport, MA), sodium carbonate (0.413 g, 3.89 mmol, JT Baker, Phillipsburg, NJ), THF (3 mL) and water (1 mL). The vial was flushed with nitrogen and sealed. 2-Bromo-3,3,3-trifluoro-1-propene (0.404 mL, 3.89 mmol, Sigma-Aldrich, St. Louis, MO) was cooled in an ice bath then added to the reaction mixture via syringe. The mixture was stirred at 60 °C for 15 h. After allowing to cool to room temperature, the reaction mixture was diluted with EtOAc (30 mL) and the organic phase was washed with saturated aqueous $NaHCO_3$ (3 x 30 mL). The organic phase was dried over sodium sulfate, filtered and concentrated under a vacuum. The resulting product was purified by column chromatography (50 g of silica gel, 0 to 30% EtOAc in hexanes) to afford benzyl (3S)-3-(1-propyn-1-yl)-4-(5-(1-(trifluoromethyl)ethenyl)-2-pyrimidinyl)-1-piperazinecarboxylate (0.257 g) as a yellow oil.

STEP 3: Benzyl (3S)-3-(1-propyn-1-yl)-4-(5-(2,2,2-trifluoro-1-hydroxy-1-(hydroxymethyl)ethyl)-2-pyrimidinyl)-1-piperazinecarboxylate

A 5-mL vial was charged with benzyl (3S)-3-(1-propyn-1-yl)-4-(5-(1-(trifluoromethyl)ethenyl)-2-pyrimidinyl)-1-piperazinecarboxylate (0.250 g, 0.581 mmol), potassium osmate dihydrate (14 mg, 0.038 mmol, Sigma-Aldrich, St. Louis, MO), NMO hydrate (152 mg, 1.13 mmol, Acros/Thermo Fisher Scientific, Hampton, NH), *t*-BuOH (1 mL) and water (1 mL). The mixture was sonicated for 5 min before stirred at room temperature for 2 days. At that time additional potassium osmate dihydrate (23.4 mg, 0.064 mmol) and NMO hydrate (165 mg, 1.22 mmol) were added. The reaction mixture was stirred at room temperature for additional 24 h. 10% $Na_2S_2O_3$ was added and the mixture was stirred for 30 min. The mixture was then extracted with DCM (3 x 10 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under a vacuum. The resulting product was purified by column chromatography (25 g of silica gel, 10 to 80% EtOAc in hexanes) to afford benzyl (3S)-3-(1-propyn-1-yl)-4-(5-

(2,2,2-trifluoro-1-hydroxy-1-(hydroxymethyl)ethyl)-2-pyrimidinyl)-1-piperazinecarboxylate (0.029) g as a white solid.

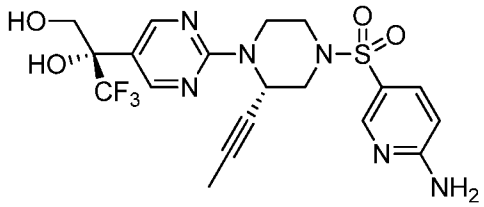
STEP 4: 2-(2-((2S)-4-((6-Amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-5-pyrimidinyl)-3,3,3-trifluoro-1,2-propanediol

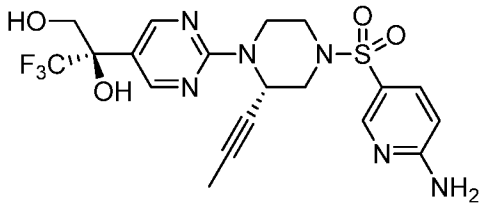
A 20-mL vial was charged with (3S)-3-(1-propyn-1-yl)-4-(5-(2,2,2-trifluoro-1-hydroxy-1-(hydroxymethyl)ethyl)-2-pyrimidinyl)-1-piperazinecarboxylate (0.029 g, 0.062 mmol) and TFA (0.5 mL). Trifluoromethanesulfonic acid (0.020 mL, 0.23 mmol, Alfa Aesar, Ward Hill, MA) was added dropwise at room temperature. The mixture was stirred at room temperature for 3 min and then concentrated under a vacuum. To the residue DCM (1 mL) was added followed by triethylamine (0.087 mL, 0.62 mmol). The mixture was stirred at room temperature for 5 min then tert-butyl (5-(chlorosulfonyl)pyridin-2-yl)carbamate (0.0267 g, 0.091 mmol, Intermediate B) was added. After 2 h of stirring, additional TEA (0.30 mL) was added. After stirring for 10 min the reaction mixture was concentrated. The residue was dissolved in DCM (1 mL) and TFA (0.5 mL). The mixture was stirred at rt for 30 min and then partitioned between saturated aqueous sodium bicarbonate (10 mL) and EtOAc (10 mL). The aqueous phase was extracted with EtOAc (10 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under a vacuum. The resulting product was purified by column chromatography (10 g of silica gel, 40 to 100% EtOAc in hexanes) to afford 2-(2-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-5-pyrimidinyl)-3,3,3-trifluoro-1,2-propanediol (0.0210 g) as a mixture of two diastereomers.

^{1}H NMR (300 MHz, MeOD) δ ppm 8.56 (s, 2 H), 8.31 (d, J = 2.0 Hz, 1 H), 7.74 (dd, J = 2.5, 8.9 Hz, 1 H), 6.61 (d, J = 8.3 Hz, 1 H), 5.69 (br. s., 1 H), 4.60 (d, J = 12.9 Hz, 1 H), 4.08 - 3.88 (m, 2 H), 3.79 (d, J = 11.5 Hz, 2 H), 3.40 (d, J = 3.2

Hz, 1 H), 2.62 (dd, J = 3.5, 11.5 Hz, 1 H), 2.46 (dt, J = 3.2, 11.8 Hz, 1 H), 1.79 (d, J = 2.2 Hz, 3 H). m/z (ESI, +ve ion) 487.1 $(M+H)^+$.

The individual diastereomers were isolated using chiral SFC. The method used was as follows: Chiralpak® AS-H column (21 x 250 mm, 5 μm) using 25% (20 mM NH_3 in methanol) in supercritical CO_2 (total flow was 70 mL/min). This produced the two diastereomers with diastereomeric excesses greater than 98%.





(2S)-2-(2-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-5-pyrimidinyl)-3,3,3-trifluoro-1,2-propanediol and (2R)-2-(2-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-5-pyrimidinyl)-3,3,3-trifluoro-1,2-propanediol.

FIRST ELUTING PEAK (PEAK #1)

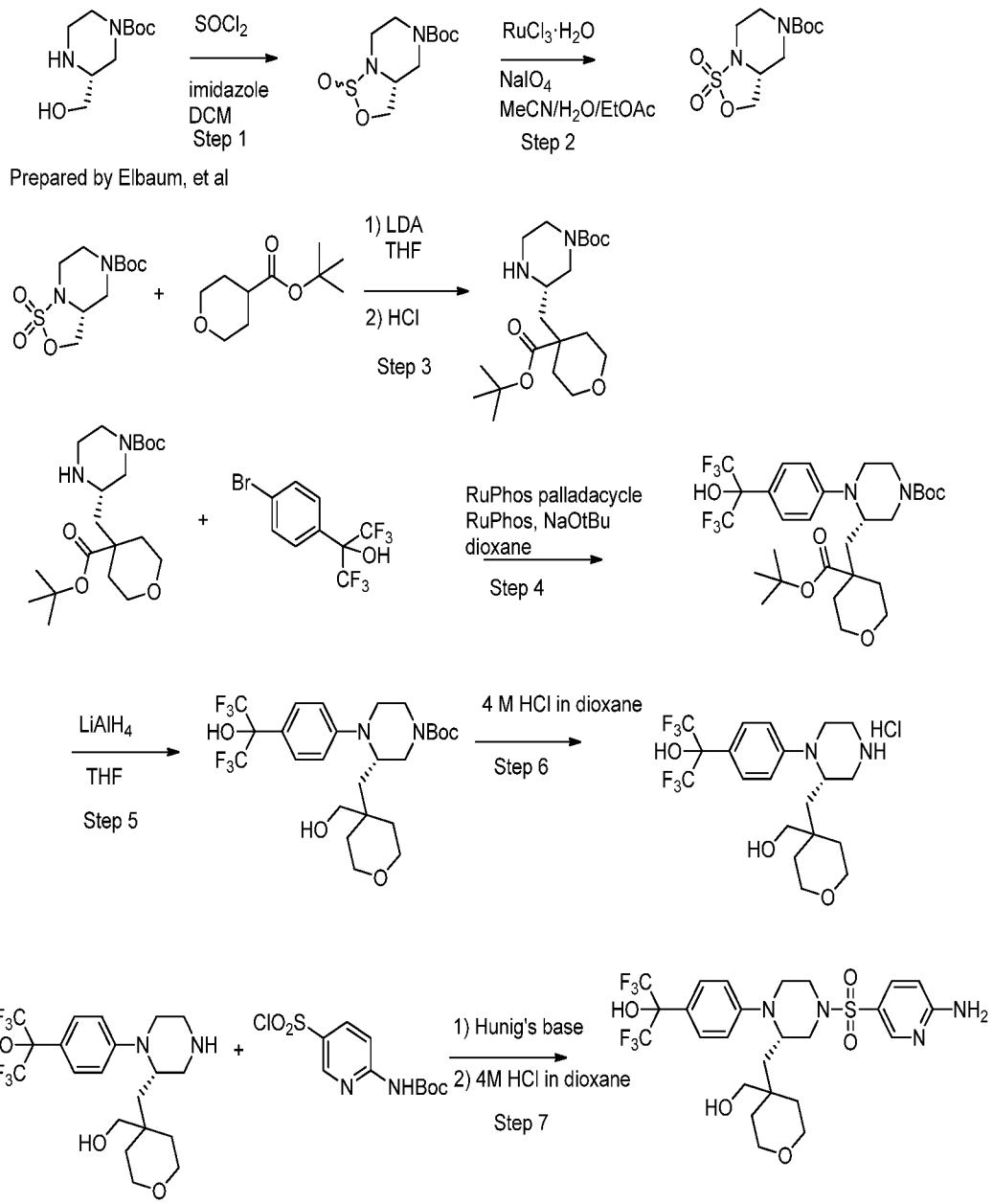
^{1}H NMR (300 MHz, MeOD) δ ppm 8.55 (s, 2 H), 8.29 (d, J = 2.2 Hz, 1 H), 7.72 (dd, J = 2.5, 8.9 Hz, 1 H), 6.60 (d, J = 8.9 Hz, 1 H), 5.68 (br. s., 1 H), 4.59 (d, J = 13.4 Hz, 1 H), 4.06 - 3.87 (m, 2 H), 3.77 (d, J = 11.4 Hz, 2 H), 3.41 - 3.33 (m, 1 H), 2.60 (dd, J = 3.7, 11.7 Hz, 1 H), 2.44 (dt, J = 3.1, 11.9 Hz, 1 H), 1.78 (d, J = 2.2 Hz, 3 H). m/z (ESI, +ve ion) 487.1 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.049 μM.

SECOND ELUTING PEAK (PEAK #2)

^{1}H NMR (300 MHz, MeOD) δ ppm 8.55 (s, 2 H), 8.29 (d, J = 2.3 Hz, 1 H), 7.72 (dd, J = 2.5, 8.9 Hz, 1 H), 6.60 (d, J = 8.9 Hz, 1 H), 5.67 (br. s., 1 H),

4.59 (d, J = 13.3 Hz, 1 H), 4.08 - 3.86 (m, 2 H), 3.82 - 3.70 (m, 2 H), 3.40 - 3.33 (m, 1 H), 2.60 (dd, J = 3.5, 11.7 Hz, 1 H), 2.44 (dt, J = 3.3, 11.9 Hz, 1 H), 1.78 (d, J = 2.0 Hz, 3 H). m/z (ESI, +ve ion) 487.1 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.006 μM.

EXAMPLE 4: 2-(4-((2S)-4-((6-Amino-3-pyridinyl)sulfonyl)-2-((4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)methyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol



STEP 1: tert-Butyl (3a*R*)tetrahydro[1,2,3]oxathiazolo[3,4-a]pyrazine-5(3H)-carboxylate 1-oxide

Imidazole (30.2 g, 444 mmol) was taken up in 240 mL of DCM and chilled to 0 °C. Thionyl chloride (9.76 mL, 134 mmol) was added slowly to the

mixture. After 5 min, the mixture was warmed to room temperature and stirred for 1 h. The mixture was then cooled to -78 °C. *t*-Butyl (3R)-3-(hydroxymethyl)-1-piperazinecarboxylate (10.33 g, 47.8 mmol, *Tetrahedron*, **2007**, *63*, 3057-3065) was added dropwise in 240 mL of DCM via addition funnel. The mixture was then warmed to room temperature and stirred for 18 h. The mixture was quenched with 200 mL of aq. NH_4Cl and diluted with 200 mL of water. The mixture was partitioned and the aqueous portion was extracted with 200 mL of DCM. The combined organic extracts were dried over $MgSO_4$. Filtration and concentration under reduced pressure afforded tert-butyl (3a*R*)tetrahydro[1,2,3]oxathiazolo[3,4-a]pyrazine-5(3H)-carboxylate 1-oxide (12.23 g) as a white solid.

STEP 2: tert-Butyl (3a*R*)tetrahydro[1,2,3]oxathiazolo[3,4-a]pyrazine-5(3H)-carboxylate 1,1-dioxide

Tert-butyl (3a*R*)tetrahydro[1,2,3]oxathiazolo[3,4-a]pyrazine-5(3H)-carboxylate 1-oxide (12.23 g, 46.6 mmol) was taken up in 300 mL of MeCN and 50 mL of EtOAc and chilled to 0 °C. Sodium periodate (12.96 g, 60.6 mmol, Riedel de Haen AG, Switzerland) was added in 100 mL of water, followed by ruthenium chloride hydrate (0.021 g, 0.093 mmol, Oakwood Products, Inc., West Columbia, SC). The mixture was allowed to warm to room temperature and stirred for 12 h. The reaction was quenched with 200 mL of aq. NH_4Cl and 200 mL of water and extracted twice with 300 mL of DCM. The combined organic extracts were dried over $MgSO_4$. Filtration and concentration under reduced pressure afforded tert-butyl (3a*R*)tetrahydro[1,2,3]oxathiazolo[3,4-a]pyrazine-5(3H)-carboxylate 1,1-dioxide (11.6 g) as a tan solid.

STEP 3: tert-Butyl (3S)-3-((4-(tert-butoxycarbonyl)tetrahydro-2H-pyran-4-yl)methyl)-1-piperazinecarboxylate

Diisopropylamine (1.02 mL, 7.25 mmol) was taken up in 40 mL of THF and chilled to 0 °C. Butyllithium (2.5 M solution in hexanes, 2.90 mL, 7.25 mmol, Sigma-Aldrich, St. Louis, MO) was added to the mixture, and the mixture was stirred for 15 minutes and then chilled to -78 °C. Tert-butyl tetrahydro-2H-pyran-4-carboxylate (1.44 g, 7.73 mmol, published PCT patent application no. WO 2008112217) was added slowly to the mixture in 5 mL of THF. After 30 minutes, tert-butyl (3a*R*)tetrahydro[1,2,3]oxathiazolo[3,4-a]pyrazine-5(3H)-carboxylate 1,1-dioxide (1.35 g, 4.83 mmol) was added to the mixture dropwise in 5 mL of THF. The mixture was warmed to room emperature and stirred for 15 minutes. The reaction was quenched with 40 mL of 0.5 M aq HCl and stirred for 5 hours. The mixture was then basified with 10.0 M aq NaOH and extracted twice with 100 mL of DCM. The combined organic extracts were dried over $MgSO_4$. Filtration and concentration under reduced pressure, followed by flash chromatography on silica gel (40 g, 1% to 10% MeOH/DCM) afforded tert-butyl (3S)-3-((4-(tert-butoxycarbonyl)tetrahydro-2H-pyran-4-yl)methyl)-1-piperazinecarboxylate (0.95 g) as an orange solid.

STEP 4: tert-Butyl (3S)-3-((4-(tert-butoxycarbonyl)tetrahydro-2H-pyran-4-yl)methyl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinecarboxylate

Tert-butyl (3S)-3-((4-(tert-butoxycarbonyl)tetrahydro-2H-pyran-4-yl)methyl)-1-piperazinecarboxylate (0.72 g, 1.873 mmol), 2-(4-bromophenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (0.907 g, 2.81 mmol, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3009), sodium t-butoxide (0.540 g, 5.62 mmol, Sigma-Aldrich, St. Louis, MO), RuPhos Palladacycle methyl-t-butyl ether adduct (0.076 g, 0.094 mmol, Sigma-Aldrich, St. Louis, MO), and RuPhos (0.044 g, 0.094 mmol, Strem Chemicals, Inc., Newburyport, MA) were taken up in 5 mL of dioxane and heated to 80 °C. After 1 hour, the reaction was cooled to room temperature. The mixture was diluted with 40 mL of EtOAc and washed with 10 mL of aq NH_4Cl and 10 mL of brine, then dried over $MgSO_4$. Filtration and concentration under

reduced pressure, followed by flash chromatography on silica gel (5% to 60% EtOAc/hexanes) afforded tert-butyl (3S)-3-((4-(tert-butoxycarbonyl)tetrahydro-2H-pyran-4-yl)methyl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinecarboxylate (0.10 g) as a yellow solid.

STEP 5: tert-Butyl (3S)-3-((4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)methyl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinecarboxylate

Tert-butyl (3S)-3-((4-(tert-butoxycarbonyl)tetrahydro-2H-pyran-4-yl)methyl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinecarboxylate (0.10 g, 0.160 mmol) was taken up in 3 mL of THF. Lithium aluminum hydride (1.0 M solution in diethyl ether, 0.48 mL, 0.48 mmol, Sigma-Aldrich, St. Louis, MO) was added to the mixture. After 18 h, the reaction was carefully quenched with 2 mL of aq. Rochelle's salt. The mixture was then diluted with 2 mL of water and 6 mL of EtOAc and stirred for 15 min. The mixture was extracted with 10 mL of EtOAc and the combined organic extracts were washed with 10 mL of brine and dried over $MgSO_4$. Filtration and concentration under reduced pressure, followed by flash chromatography on silica gel (4 g, eluted with 5% to 50% EtOAc/hexanes) afforded tert-butyl (3S)-3-((4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)methyl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinecarboxylate (0.038 g) as a white solid.

STEP 6: 1,1,1,3,3,3-Hexafluoro-2-(4-((2S)-2-((4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)methyl)-1-piperazinyl)phenyl)-2-propanol hydrochloride

Tert-butyl (3S)-3-((4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)methyl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinecarboxylate (0.038 g, 0.068 mmol) was taken up in hydrogen chloride (4.0 M solution in dioxane, 2.0 mL, 8.00 mmol, Sigma-Aldrich, St. Louis, MO).

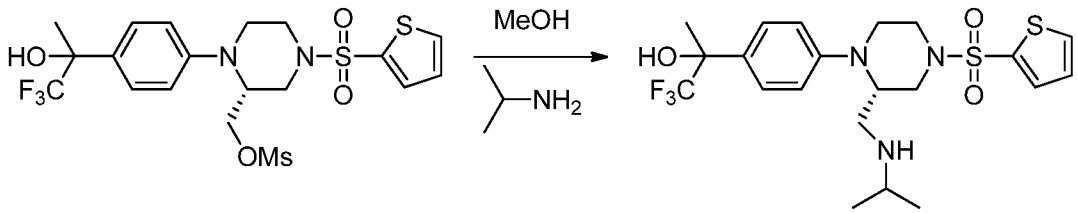
After 5 h, the solvent was removed under reduced pressure, affording 1,1,1,3,3,3-hexafluoro-2-(4-((2S)-2-((4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)methyl)-1-piperazinyl)phenyl)-2-propanol hydrochloride (0.034 g). The product was carried on without additional purification.

STEP 7: 2-(4-((2S)-4-((6-Amino-3-pyridinyl)sulfonyl)-2-((4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)methyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol

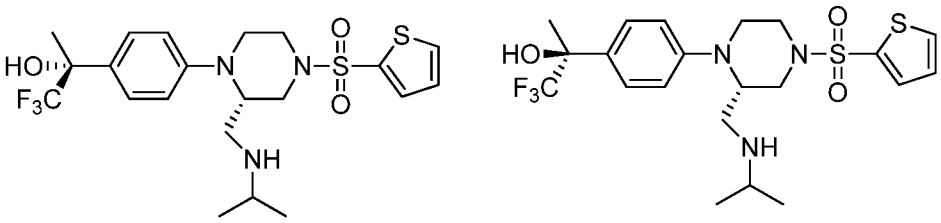
Tert-butyl (3S)-3-((4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)methyl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinecarboxylate (0.034 g, 0.069 mmol) was taken up in 1 mL of DCM. Hunig's base (0.048 mL, 0.276 mmol, Sigma-Aldrich, St. Louis, MO) and tert-butyl (5-(chlorosulfonyl)pyridin-2-yl)carbamate (0.020 g, 0.069 mmol, Intermediate B) were added. After 18 h, the reaction was diluted with 15 mL of DCM and washed with 5 mL of $NaHCO_3$. The organic portion was dried over $MgSO_4$. Filtration and concentration under reduced pressure, followed by flash chromatography on silica gel (4g, elute with 25% to 95% EtOAc/hexanes) afforded tert-butyl (5-(((3S)-3-((4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)methyl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinyl)sulfonyl)-2-pyridinyl)carbamate (0.032 g) as a white solid. Tert-butyl (5-(((3S)-3-((4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)methyl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinyl)sulfonyl)-2-pyridinyl)carbamate (0.032 g, 0.045 mmol) was taken up in 1 mL of 4.0 M HCl in dioxane. The mixture was stirred for 15 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (1% to 8% 2.0 M NH_3 in MeOH/DCM) afforded 2-(4-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-((4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)methyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (0.018 g) as a white solid.

^{1}H NMR (400 MHz, MeOD) δ ppm 8.30 (d, *J* = 2.3 Hz, 1 H), 7.74 (dd, *J* = 2.4, 8.9 Hz, 1 H), 7.56 (d, *J* = 8.8 Hz, 2 H), 7.01 (d, *J* = 9.0 Hz, 2 H), 6.64 (d, *J* = 8.8 Hz, 1 H), 4.25 (br. s., 1 H), 3.74 (br. s., 2 H), 3.68 - 3.53 (m, 2 H), 3.49 - 3.35 (m, 5 H), 3.10 (ddd, *J* = 3.1, 8.6, 11.8 Hz, 1 H), 2.77 - 2.62 (m, 1 H), 2.49 (dt, *J* = 3.8, 11.1 Hz, 1 H), 2.02 - 1.94 (m, 1 H), 1.77 - 1.35 (m, 5 H). m/z (ESI, +ve ion) 613.1 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.406 μM.

EXAMPLE 5: 1,1,1-Trifluoro-2-(4-((2S)-2-(((1-methylethyl)amino)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol



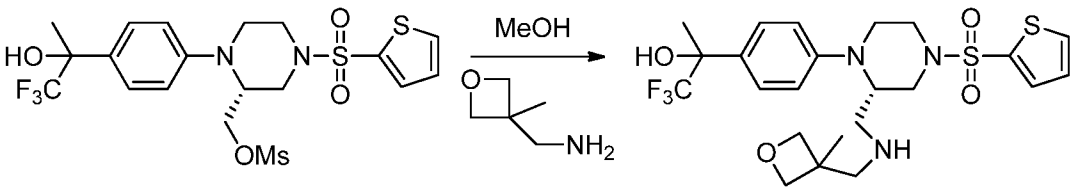
To a 20-mL microwave vial was added ((2R)-4-(thiophen-2-ylsulfonyl)-1-(4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)phenyl)piperazin-2-yl)methyl methanesulfonate (1.0 g, 1.9 mmol, Intermediate H), 2-propanamine (2.5 mL, 28 mmol, Sigma-Aldrich, St. Louis, MO), and MeOH (10.0 mL). The vial was sealed and heated in a microwave reactor (Biotage AB, Inc., Uppsala, Sweden) at 140 °C for 30 min. After cooling to room temperature, the reaction mixture was concentrated and the resulting product was purified by column chromatography (80 g of silica gel, 100% CH_2Cl_2 first then 2 to 5% 2M NH_3 in MeOH/CH_2Cl_2) to afford 1,1,1-trifluoro-2-(4-((2S)-2-(((1-methylethyl)amino)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol (0.720 g) as a mixture of two isomers.



(2R)-1,1,1-trifluoro-2-(4-((2S)-2-(((1-methylethyl)amino)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol and (2S)-1,1,1-trifluoro-2-(4-((2S)-2-(((1-methylethyl)amino)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol

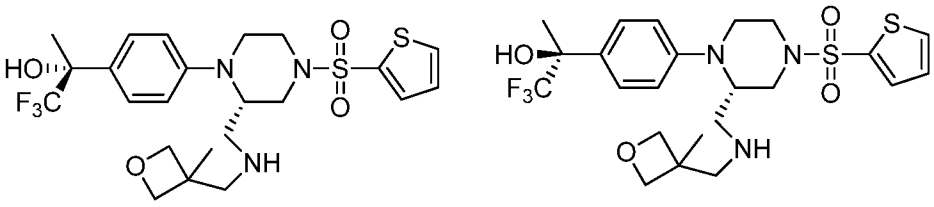
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.64 (dd, *J* = 1.2, 5.0 Hz, 1 H), 7.57 (dd, *J* = 1.2, 3.7 Hz, 1 H), 7.43 (d, *J* = 8.6 Hz, 2 H), 7.17 (dd, *J* = 3.7, 5.0 Hz, 1 H), 6.86 (d, *J* = 8.9 Hz, 2 H), 4.00 - 3.84 (m, 2 H), 3.77 (d, *J* = 11.7 Hz, 1 H), 3.55 - 3.42 (m, 1 H), 3.32 (dt, *J* = 3.4, 12.0 Hz, 1 H), 2.99 (dd, *J* = 8.7, 12.2 Hz, 1 H), 2.84 - 2.54 (m, 4 H), 1.75 (s, 3 H), 1.02 (dd, *J* = 2.4, 6.2 Hz, 6 H) (2 exchangable protons were not observed). m/z (ESI, +ve ion) 492.0 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 2.55 μM.

EXAMPLE 6: 1,1,1-Trifluoro-2-(4-((2S)-2-((((3-methyl-3-oxetanyl)methyl)amino)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol



A 20-mL vial was charged with 3-aminomethyl-3-methyloxetane (0.156 g, 1.135 mmol, Advanced Chemblocks, Burlingame, CA), DIPEA (0.823 mL, 4.73 mmol), and MeOH (3 mL). The vial was capped and stirred for 5 min. ((2R)-4-(thiophen-2-ylsulfonyl)-1-(4-(1,1,1-trifluoro-2-hydroxypropan-2-

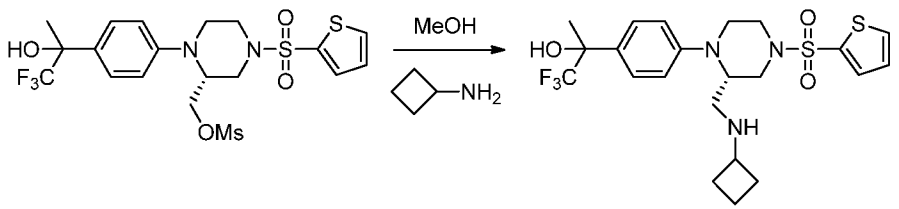
yl)phenyl)piperazin-2-yl)methyl methanesulfonate (0.500 g, 0.946 mmol, Intermediate H) in MeOH (10 mL) was added. The vial was sealed and heated at 140 °C for 30 min. The reaction mixture was concentrated and the resulting product was purified by column chromatography on silica gel (80 g, 10% to 40% acetone in hexanes) to afford 1,1,1-trifluoro-2-(4-((2S)-2-((((3-methyl-3-oxetanyl)methyl)amino)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol (0.265 g) as a mixture of two isomers.



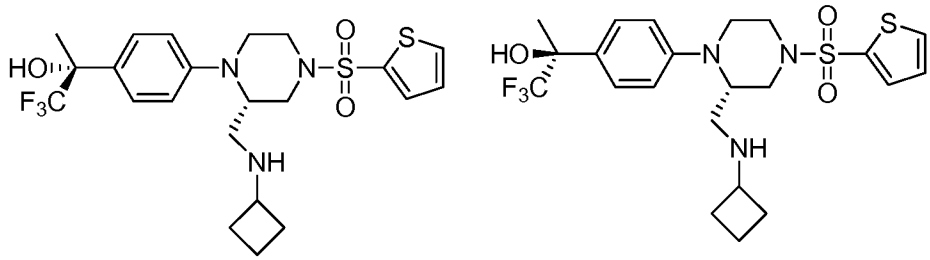
(2R)-1,1,1-trifluoro-2-(4-((2S)-2-((((3-methyl-3-oxetanyl)methyl)amino)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol and (2S)-1,1,1-trifluoro-2-(4-((2S)-2-((((3-methyl-3-oxetanyl)methyl)amino)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.65 (dd, J = 1.3, 5.0 Hz, 1 H), 7.58 (dd, J = 1.2, 3.7 Hz, 1 H), 7.45 (d, J = 8.8 Hz, 2 H), 7.18 (dd, J = 3.8, 5.0 Hz, 1 H), 6.86 (d, J = 8.9 Hz, 2 H), 4.40 (d, J = 5.7 Hz, 1 H), 4.34 - 4.25 (m, 3 H), 3.92 (dd, J = 10.8, 12.6 Hz, 2 H), 3.79 (d, J = 11.4 Hz, 1 H), 3.49 - 3.39 (m, 1 H), 3.39 - 3.23 (m, 1 H), 3.03 - 2.91 (m, 1 H), 2.88 - 2.77 (m, 1 H), 2.77 - 2.67 (m, 3 H), 2.67 - 2.50 (m, 2 H), 1.74 (s, 3 H), 1.27 (s, 1 H), 1.23 (s, 3 H). m/z (ESI, +ve ion) 534.2 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 1.54 μM.

EXAMPLE 7: 2-(4-((2S)-2-((Cyclobutylamino)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-1,1,1-trifluoro-2-propanol



A 20-mL vial was charged with ((2R)-4-(thiophen-2-ylsulfonyl)-1-(4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)phenyl)piperazin-2-yl)methyl methanesulfonate (0.500 g, 0.946 mmol, Intermediate H), cyclobutylamine (0.202 mL, 2.84 mmol, Sigma-Aldrich, St. Louis, MO), and MeOH (10.0 mL). The vial was sealed and heated at 140 °C for 30 min. The reaction mixture was concentrated. The resulting product was purified by column chromatography (80 g of silica gel, 2 to 10% 2M NH_3 in DCM) to afford 2-(4-((2S)-2-((cyclobutylamino)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-1,1,1-trifluoro-2-propanol (0.300 g) as a mixture of two isomers.

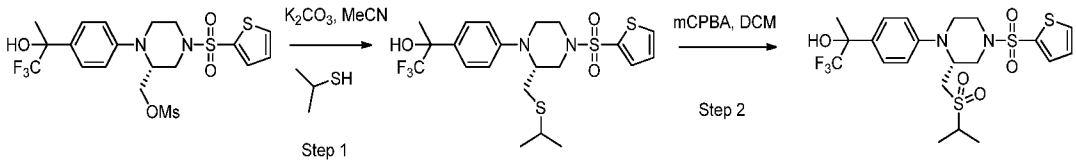


(2R)-2-(4-((2S)-2-((cyclobutylamino)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-1,1,1-trifluoro-2-propanol and (2S)-2-(4-((2S)-2-((cyclobutylamino)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-1,1,1-trifluoro-2-propanol.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.64 (dd, J = 1.3, 5.0 Hz, 1 H), 7.58 (dd, J = 1.3, 3.8 Hz, 1 H), 7.44 (d, J = 8.8 Hz, 2 H), 7.17 (dd, J = 3.8, 5.0 Hz, 1 H), 6.85 (d, J = 9.1 Hz, 2 H), 3.97 - 3.83 (m, 2 H), 3.81 - 3.69 (m, 1 H), 3.54 - 3.43 (m, 1 H), 3.31 (dd, J = 3.4, 11.6 Hz, 1 H), 3.27 - 3.13 (m, 1 H), 2.94 (dd, J = 9.1, 12.2 Hz, 1 H), 2.73 - 2.53 (m, 3 H), 2.40 (d, J = 3.9 Hz, 1 H), 2.27 - 2.07 (m, 2 H),

1.75 (s, 3 H), 1.71 - 1.56 (m, 5 H). m/z (ESI, +ve ion) 504.0 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 3.7 μM.

EXAMPLE 8: 1,1,1-Trifluoro-2-(4-((2R)-2-(((1-methylethyl)sulfonyl)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol



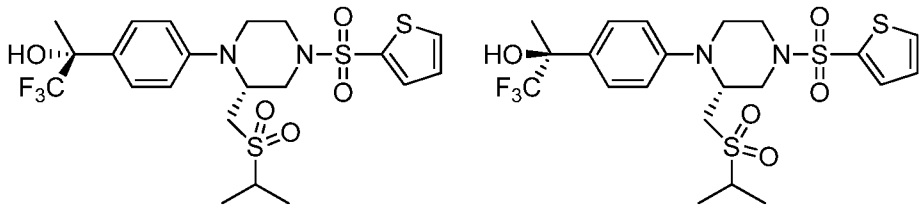
STEP 1: 1,1,1-Trifluoro-2-(4-((2R)-2-(((1-methylethyl)sulfanyl)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol

A 5-mL vial was charged with ((2R)-4-(thiophen-2-ylsulfonyl)-1-(4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)phenyl)piperazin-2-yl)methyl methanesulfonate (0.200 g, 0.378 mmol, Intermediate H), potassium carbonate (0.110 g, 0.757 mmol, J.T.Baker, Phillipsburg, NJ), 2-propanethiol (0.071 mL, 0.757 mmol, Sigma-Aldrich, St. Louis, MO), and MeCN (3.0 mL). The vial was sealed and heated at 140 °C for 40 min. The reaction mixture was filtered and the filtrate was concentrated. The resulting product was purified by silica gel column chromatography (24 g, 10% to 30% acetone in hexanes) to afford 1,1,1-trifluoro-2-(4-((2R)-2-(((1-methylethyl)sulfanyl)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol (0.075 g) as a white solid.

STEP 2: 1,1,1-Trifluoro-2-(4-((2R)-2-(((1-methylethyl)sulfonyl)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol

A 20-mL vial was charged with 1,1,1-trifluoro-2-(4-((2R)-2-(((1-methylethyl)sulfanyl)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol (0.075 g, 0.147 mmol), DCM (2.0 mL), and MCPBA (0.070 g, 0.295 mmol, Aldrich, St. Louis, MO). The vial was capped and the mixture was stirred

at rt for 2 h. The reaction mixture was partitioned between EtOAc (20 mL) and water (10 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The resulting product was purified by silica gel column chromatography (24 g, 10% to 20% acetone in hexanes) to afford 1,1,1-trifluoro-2-(4-((2R)-2-(((1-methylethyl)sulfonyl)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol (0.040 g) as a mixture of two isomers.



(2R)-1,1,1-trifluoro-2-(4-((2R)-2-(((1-methylethyl)sulfonyl)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol and (2S)-1,1,1-trifluoro-2-(4-((2R)-2-(((1-methylethyl)sulfonyl)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol.

This mixture was resolved using preparative SFC (Chiralpak® AD-H column (4.6 x 150 mm, 5 μm) eluting with 60% liquid CO_2 in 40% methanol with 40 mM ammonia at a flow rate of 60 mL/min) to give two products in greater than 99% diastereomeric excess.

FIRST ELUENT PEAK (PEAK# 1)

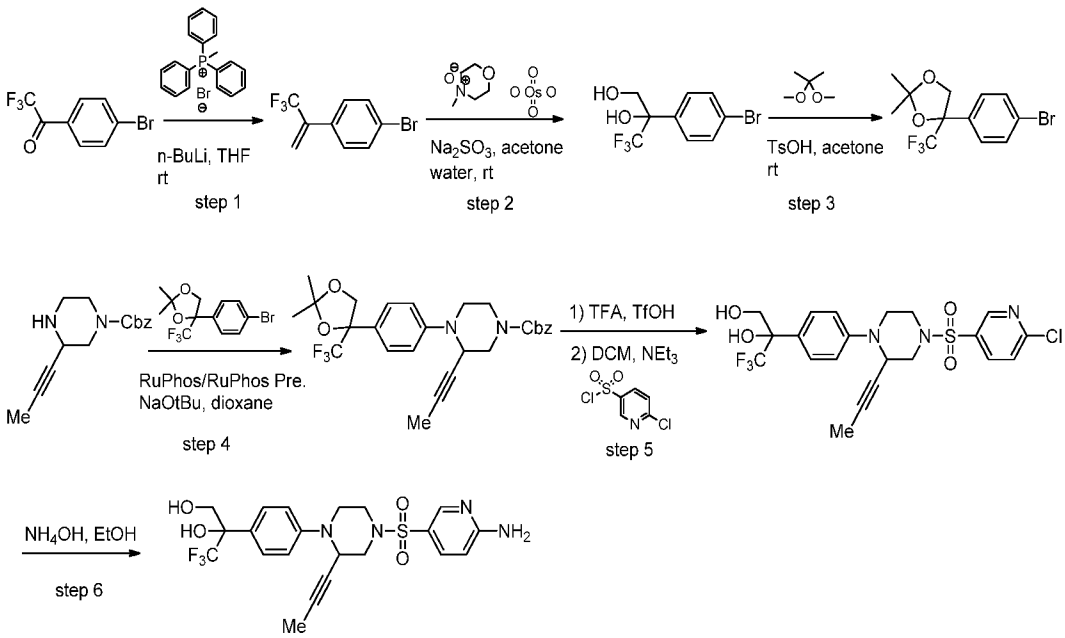
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.68 (dd, J = 1.3, 5.0 Hz, 1 H), 7.61 (dd, J = 1.3, 3.8 Hz, 1 H), 7.50 (d, J = 8.8 Hz, 2 H), 7.19 (dd, J = 3.8, 5.0 Hz, 1 H), 6.96 (d, J = 8.9 Hz, 2 H), 4.63 (d, J = 8.2 Hz, 1 H), 4.13 (d, J = 11.8 Hz, 1 H), 3.89 (dd, J = 1.9, 10.1 Hz, 1 H), 3.68 (dd, J = 9.5, 13.6 Hz, 1 H), 3.56 (d, J = 12.4 Hz, 1 H), 3.21 - 3.02 (m, 2 H), 2.89 - 2.73 (m, 2 H), 2.65 (dt, J = 3.4, 11.5 Hz, 1

H), 2.36 (s, 1 H), 1.75 (s, 3 H), 1.43 - 1.27 (m, 6 H). m/z (ESI, +ve ion) 541.0 $(M+H)^+$.GK-GKRP IC_{50} (Binding) = 2.72 μM.

SECOND ELUENT PEAK (PEAK# 2)

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.68 (dd, *J* = 1.3, 5.0 Hz, 1 H), 7.61 (dd, *J* = 1.3, 3.8 Hz, 1 H), 7.50 (d, *J* = 8.8 Hz, 2 H), 7.19 (dd, *J* = 3.8, 5.0 Hz, 1 H), 6.96 (d, *J* = 9.1 Hz, 2 H), 4.63 (d, *J* = 8.2 Hz, 1 H), 4.21 - 4.07 (m, 1 H), 3.95 - 3.84 (m, 1 H), 3.68 (dd, *J* = 9.5, 13.3 Hz, 1 H), 3.57 (d, *J* = 12.4 Hz, 1 H), 3.23 - 3.01 (m, 2 H), 2.90 - 2.73 (m, 2 H), 2.65 (dt, *J* = 3.5, 11.5 Hz, 1 H), 2.34 (s, 1 H), 1.75 (s, 3 H), 1.36 (dd, *J* = 6.9, 11.5 Hz, 6 H). m/z (ESI, +ve ion) 541.2 $(M+H)^+$.GK-GKRP IC_{50} (Binding) = 1.23 μM.

EXAMPLE 9: 2-(4-(4-((6-Amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-3,3,3-trifluoro-1,2-propanediol



STEP 1: 1-Bromo-4-(1-(trifluoromethyl)ethenyl)benzene

To a 1-L round-bottomed flask was added methyl phenylphosphonium bromide (25.4 g, 71.1 mmol, Sigma-Aldrich, St. Louis, MO) and toluene (75 mL). The resulting mixture was stirred for 5 min then concentrated and dried under a high vacuum for 30 min. To this residue was added THF (300 mL) followed by adding butyllithium (2.5 M in hexanes, 29.0 mL, 71.1 mmol, Aldrich, St. Louis, MO) dropwise via an addition funnel at room temperature. After being stirred for 1 h, a solution of 1-(4-bromophenyl)-2,2,2-trifluoroethanone (15.0 g, 59.3 mmol, Matrix Scientific, Columbia, SC) in THF (20 mL) was added to the reaction mixture dropwise via an addition funnel. The reaction was stirred at rt for 2 h. The reaction was quenched with saturated aqueous NH_4Cl and the mixture was concentrated. The residue was partitioned between ether (150 mL) and saturated aqueous NH_4Cl (80 mL). The organic layer was washed with water, brine, dried over $MgSO_4$, filtered, and concentrated. The resulting product was purified by column chromatography (330 g of silica gel, 2 to 5% EtOAc in hexanes) to afford 1-bromo-4-(1-(trifluoromethyl)ethenyl)benzene (14.0 g) as a brown liquid.

STEP 2: 2-(4-Bromophenyl)-3,3,3-trifluoro-1,2-propanediol

To a solution of 1-bromo-4-(1-(trifluoromethyl)ethenyl)benzene (13.5 g, 53.8 mmol) in acetone (100 mL) and water (100 mL) was added NMO (6.90 g, 59.2 mmol, Sigma-Aldrich, St. Louis, MO) and osmium tetroxide (0.140 mL, 2.70 mmol, Sigma-Aldrich, St. Louis, MO). The resulting mixture was stirred at rt for 6 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was partitioned between EtOAc (100 mL) and water (30 mL). The aqueous layer was extracted with EtOAc (2 x 75 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting product was purified by column chromatography (330 g of silica gel, 0 to 8% MeOH in

DCM) to afford 2-(4-bromophenyl)-3,3,3-trifluoro-1,2-propanediol (14.5 g) as an off-white solid.

STEP 3: 4-(4-Bromophenyl)-2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolane

To a solution of 2-(4-bromophenyl)-3,3,3-trifluoro-1,2-propanediol (14.5 g, 51.0 mmol) in acetone (200 mL) was added 2,2-dimethoxypropane (19.0 mL, 153 mmol, Sigma-Aldrich, St. Louis, MO) and p-toluenesulfonic acid (0.485 g, 2.54 mmol, Sigma-Aldrich, St. Louis, MO). The resulting mixture was stirred at rt for 20 h. Additional 2,2-dimethoxypropane (19.0 mL, 153 mmol, Sigma-Aldrich, St. Louis, MO) and p-toluenesulfonic acid (0.485 g, 2.54 mmol, Sigma-Aldrich, St. Louis, MO) were added and the reaction was continued to stir for 20 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL). The reaction mixture was concentrated and the residue was partitioned between EtOAc (100 mL) and saturated aqueous $NaHCO_3$ (60 mL). The aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting product was purified by column chromatography (330 g of silica gel, 0 to 8% EtOAc in hexanes) to afford 4-(4-bromophenyl)-2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolane (15.7 g) as a colorless liquid.

STEP 4: 4-(4-(2,2-Dimethyl-4-(trifluoromethyl)-1,3-dioxolan-4-yl)phenyl)-3-(1-propyn-1-yl)-1-piperazinecarboxylate

A 5 mL vial was charged with benzyl 3-(1-propyn-1-yl)-1-piperazinecarboxylate (0.120 g, 0.465 mmol, Intermediate L), 4-(4-bromophenyl)-2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolane (0.170 g, 0.511 mmol), RuPhos (0.011 g, 0.023 mmol, Strem, Newburyport, MA), RuPhos Palladacycle (0.020 g, 0.024 mmol, Strem, Newburyport, MA), sodium tert-butoxide (0.112 g, 1.16 mmol, Sigma-Aldrich, St. Louis, MO), and dioxane (2.0 mL). The resulting mixture was degassed by bubbling N_2 gas for 5 min. The vial

was sealed and heated at 100 °C for 1 h. The reaction mixture was allowed to cool to room temperature and partitioned between EtOAc (70 mL) and water (30 mL). The aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The resulting product was purified by column chromatography (40 g of silica gel, 10% to 30% EtOAc in hexanes) to afford 4-(4-(2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolan-4-yl)phenyl)-3-(1-propyn-1-yl)-1-piperazinecarboxylates (0.160 g) as a light brown solid.

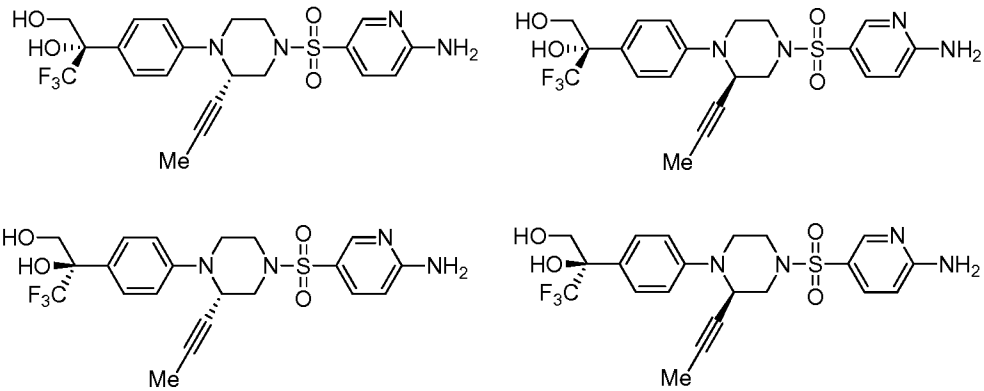
STEP 5: 2-(4-(4-((6-Chloro-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-3,3,3-trifluoro-1,2-propanediol

To a 50 mL round-bottomed flask was added 4-(4-(2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolan-4-yl)phenyl)-3-(1-propyn-1-yl)-1-piperazinecarboxylates (0.160 g, 0.318 mmol) and TFA (2.0 mL, Sigma-Aldrich, St. Louis, MO). After the substrate was completely dissolved in TFA, trifluoromethanesulfonic acid (0.090 mL, 0.955 mmol, Alfa Aesar, Ward Hill, MA) was added and the resulting mixture was stirred for 1 h. The reaction mixture was concentrated to dryness and the residue was neutralized by adding saturated aqueous $NaHCO_3$ (40 mL) then extracted with EtOAc (3 x 70 mL) and 10% IPA in $CHCl_3$ (3 x 70 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting intermediate was redissolved in DCM (15 mL). Triethylamine (0.230 mL, 1.60 mmol, Sigma-Aldrich, St. Louis, MO) and 6-chloropyridine-3-sulfonyl chloride (0.080 g, 0.360 mmol, *Organic Process Research & Development* **2009**, *13*, 875) were added. The reaction mixture was stirred at rt for 1 h. The reaction mixture was partitioned between DCM (60 mL) and water (30 mL). The aqueous layer was extracted with DCM (2 x 40 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting product was purified by column chromatography (40 g of silica gel, 10% to 40% acetone in hexanes) to afford 2-(4-(4-((6-chloro-3-

pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-3,3,3-trifluoro-1,2-propanediol (0.090 g) as a white solid.

STEP 6: 2-(4-(4-((6-Amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-3,3,3-trifluoro-1,2-propanediol

A 20-mL vial was charged with 2-(4-(4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-3,3,3-trifluoro-1,2-propanediol (0.090 g, 0.180 mmol), EtOH (3.0 mL), and concentrated ammonium hydroxide (, 3.0 mL, 77.0 mmol, Sigma-Aldrich, St. Louis, MO). The vial was sealed and heated at 120 °C for 7 h. The reaction mixture was concentrated and the resulting product was partitioned between water (30 mL) and DCM (70 mL). The aqueous layer was extracted with DCM (2 x 30 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting product was purified by column chromatography (40 g of silica gel, 0 to 10% MeOH in DCM) to afford 2-(4-(4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-3,3,3-trifluoro-1,2-propanediol (0.060 g) as a mixture of four isomers.



(2S)-2-(4-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-3,3,3-trifluoro-1,2-propanediol; (2S)-2-(4-((2R)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-3,3,3-

trifluoro-1,2-propanediol; (2R)-2-(4-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-3,3,3-trifluoro-1,2-propanediol; and (2R)-2-(4-((2R)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-3,3,3-trifluoro-1,2-propanediol.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.50 (d, *J* = 2.2 Hz, 1 H), 7.78 (dd, *J* = 2.3, 8.8 Hz, 1 H), 7.45 (d, *J* = 8.6 Hz, 2 H), 6.96 (d, *J* = 8.9 Hz, 2 H), 6.53 (d, *J* = 8.6 Hz, 1 H), 4.98 (s, 2 H), 4.42 (br. s., 1 H), 4.26 (d, *J* = 12.0 Hz, 1 H), 3.90 (d, *J* = 12.0 Hz, 1 H), 3.75 (t, *J* = 10.2 Hz, 2 H), 3.64 (br. s., 1 H), 3.47 - 3.34 (m, 2 H), 2.85 (dd, *J* = 3.2, 11.1 Hz, 1 H), 2.70 (td, *J* = 7.5, 11.2 Hz, 1 H), 1.79 (d, *J* = 1.8 Hz, 3 H). m/z (ESI, +ve ion) 485.1 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.017 μM

This mixture of isomers were resolved using preparative SFC (Chiralpak® ASH column (21 x 250 mm, 5μm, Chiral Technologies, Inc., West Chester, PA) eluting with 75% liquid CO_2 in 25% methanol with 20mM NH_3 at a flow rate of 55 ml/min) to give four products in greater than 98% diastereomeric excess.

FIRST ELUENT PEAK (PEAK# 1)

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.49 (d, *J* = 1.9 Hz, 1 H), 7.80 (dd, *J* = 2.4, 8.8 Hz, 1 H), 7.45 (d, *J* = 8.8 Hz, 2 H), 6.96 (d, *J* = 8.9 Hz, 2 H), 6.55 (d, *J* = 8.6 Hz, 1 H), 5.17 (br. s., 2 H), 4.42 (d, *J* = 2.0 Hz, 1 H), 4.26 (d, *J* = 12.0 Hz, 1 H), 3.95 - 3.85 (m, 1 H), 3.81 - 3.66 (m, 2 H), 3.44 - 3.33 (m, 2 H), 2.86 (dd, *J* = 3.4, 11.3 Hz, 1 H), 2.79 - 2.63 (m, 1 H), 1.78 - 1.79 (d, *J* = 2.0 Hz, 3 H). (2 exchangable protons were not observed). m/z (ESI, +ve ion) 485.1 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.028 μM.

SECOND ELUENT PEAK (PEAK# 2)

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.49 (d, *J* = 2.2 Hz, 1 H), 7.78 (dd, *J* = 2.3, 8.8 Hz, 1 H), 7.45 (d, *J* = 8.8 Hz, 2 H), 6.96 (d, *J* = 9.1 Hz, 2 H), 6.53 (d, *J* = 8.8 Hz, 1 H), 5.00 (s, 2 H), 4.42 (d, *J* = 2.2 Hz, 1 H), 4.26 (d, *J* = 11.8 Hz, 1 H), 3.90 (d, *J* = 12.0 Hz, 1 H), 3.83 - 3.67 (m, 2 H), 3.43 - 3.33 (m, 2 H), 2.85 (dd, *J* = 3.4, 11.1 Hz, 1 H), 2.70 (td, *J* = 7.2, 11.3 Hz, 1 H), 1.79 (d, *J* = 2.2 Hz, 3 H). (2 exchangable protons were not observed). m/z (ESI, +ve ion) 485.1 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.721 μM.

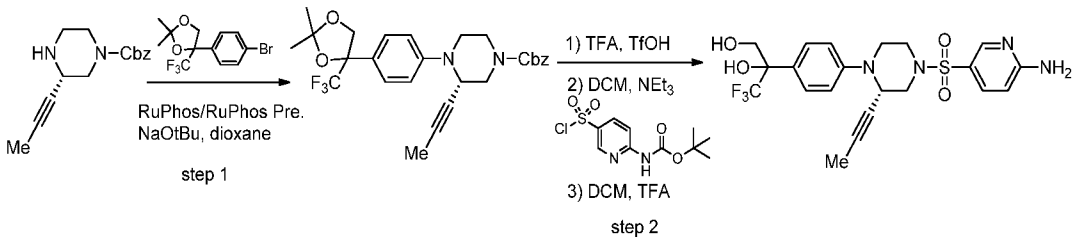
THIRD ELUENT PEAK (PEAK# 3)

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.49 (d, *J* = 2.2 Hz, 1 H), 7.78 (dd, *J* = 2.4, 8.7 Hz, 1 H), 7.45 (d, *J* = 8.6 Hz, 2 H), 6.96 (d, *J* = 9.1 Hz, 2 H), 6.53 (d, *J* = 8.8 Hz, 1 H), 4.99 (s, 2 H), 4.42 (d, *J* = 2.3 Hz, 1 H), 4.26 (d, *J* = 12.0 Hz, 1 H), 3.90 (d, *J* = 12.0 Hz, 1 H), 3.81 - 3.68 (m, 2 H), 3.43 - 3.33 (m, 2 H), 2.85 (dd, *J* = 3.4, 11.2 Hz, 1 H), 2.70 (td, *J* = 7.2, 11.1 Hz, 1 H), 1.79 (d, *J* = 2.0 Hz, 3 H). (2 exchangable protons were not observed). m/z (ESI, +ve ion) 485.1 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.003 μM.

FOURTH ELUENT PEAK (PEAK# 4)

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.49 (d, *J* = 2.3 Hz, 1 H), 7.78 (dd, *J* = 2.4, 8.7 Hz, 1 H), 7.45 (d, *J* = 8.6 Hz, 2 H), 6.96 (d, *J* = 8.9 Hz, 2 H), 6.54 (d, *J* = 8.8 Hz, 1 H), 5.02 (s, 2 H), 4.42 (d, *J* = 2.2 Hz, 1 H), 4.26 (d, *J* = 12.0 Hz, 1 H), 3.90 (d, *J* = 12.0 Hz, 1 H), 3.81 - 3.64 (m, 2 H), 3.43 - 3.31 (m, 2 H), 2.85 (dd, *J* = 3.4, 11.3 Hz, 1 H), 2.70 (td, *J* = 7.3, 11.2 Hz, 1 H), 1.78 (d, *J* = 2.0 Hz, 3 H). (2 exchangable protons were not observed). m/z (ESI, +ve ion) 485.2 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.385 μM.

AN ALTERNATE ROUTE FOR EXAMPLE 9 (PEAK #1 AND PEAK #3)



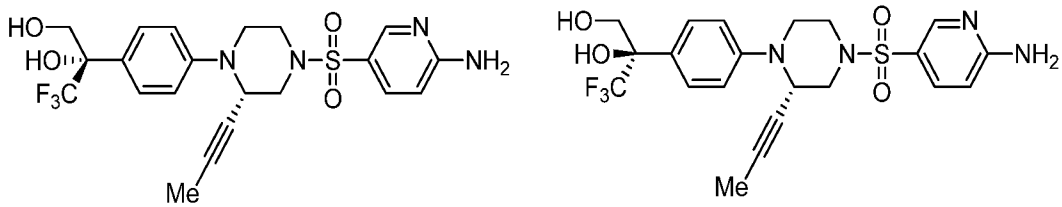
STEP 1: (3S)-4-(4-(2,2-Dimethyl-4-(trifluoromethyl)-1,3-dioxolan-4-yl)phenyl)-3-(1-propyn-1-yl)-1-piperazinecarboxylate

A 20-mL vial was charged with benzyl (3S)-3-(1-propyn-1-yl)-1-piperazinecarboxylate (2.50 g, 9.70 mmol, Intermediate A), 4-(4-bromophenyl)-2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolane (3.30 g, 10.2 mmol, STEP 3 above), RuPhos (0.230 g, 0.484 mmol, Strem, Newburyport, MA), RuPhos Palladacycle (0.400 g, 0.484 mmol, Strem, Newburyport, MA), sodium tert-butoxide (2.30 g, 24.2 mmol, Sigma-Aldrich, St. Louis, MO), and dioxane (15 mL). The resulting mixture was degassed by bubbling nitrogen gas for 5 min. The vial was sealed and heated at 100 °C for 1 h. The reaction mixture was allowed to cool to rt and partitioned between EtOAc (150 mL) and water (50 mL). The aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting product was purified by column chromatography (330 g of silica gel, 10% to 30% EtOAc in hexanes) to afford (3S)-4-(4-(2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolan-4-yl)phenyl)-3-(1-propyn-1-yl)-1-piperazinecarboxylate (3.3 g) as a light brown solid.

STEP 2: 2-(4-((2S)-4-((6-Amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-3,3,3-trifluoro-1,2-propanediol

To a 250-mL round-bottomed flask was added (3S)-4-(4-(2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolan-4-yl)phenyl)-3-(1-propyn-1-yl)-1-piperazinecarboxylate (5.0 g, 10.6 mmol), and TFA (60.0 mL, Sigma-Aldrich, St.

Louis, MO). After the compound was completely dissolved in TFA, trifluoromethane sulfonic acid (3.0 mL, 64.0 mmol, Alfa Aesar, Lawrence, KS) was added and the resulting mixture was stirred for 1 h. The reaction mixture was concentrated to dryness and the residue was neutralized with saturated aqueous $NaHCO_3$ (100 mL) and then extracted with EtOAc (3 x 200 mL) and 10% IPA in $CHCl_3$ (3 x 200 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting intermediate was dissolved in DCM (100 mL). Triethylamine (7.50 mL, 53.4 mmol, Sigma-Aldrich, St. Louis, MO) and tert-butyl (5-(chlorosulfonyl)pyridin-2-yl)carbamate (3.50 g, 12.0 mmol, Intermediate B) were added. The reaction mixture was stirred at rt for 1 h. The reaction mixture was concentrated to dryness. The residue was redissolved in DCM (100 mL) and TFA (21.0 mL, 277 mmol, Aldrich, St. Louis, MO) was added. The resulting mixture was stirred at rt for 3 h, then concentrated to dryness. The residue was neutralized with saturated aqueous $NaHCO_3$ (100 mL) then extracted with EtOAc (3 x 200 mL) and 10% IPA in $CHCl_3$ (2 x 200 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting product was purified by column chromatography (330 g of silica gel, 0 to 10% MeOH in DCM) to afford 2-(4-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-3,3,3-trifluoro-1,2-propanediol (4.7 g) as a mixture of two isomers.



(2S)-2-(4-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-3,3,3-trifluoro-1,2-propanediol; (2R)-2-(4-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-3,3,3-trifluoro-1,2-propanediol.

This mixture of isomers were resolved using preparative SFC (Chiralpak® ASH column (21 x 250 mm, 5μm, Chiral Technologies, Inc., West Chester, PA) eluting with 70% liquid CO_2 in 30% methanol with 20mM NH_3 at a flow rate of 75 ml/min) to give two products in greater than 98% diastereomeric excess.

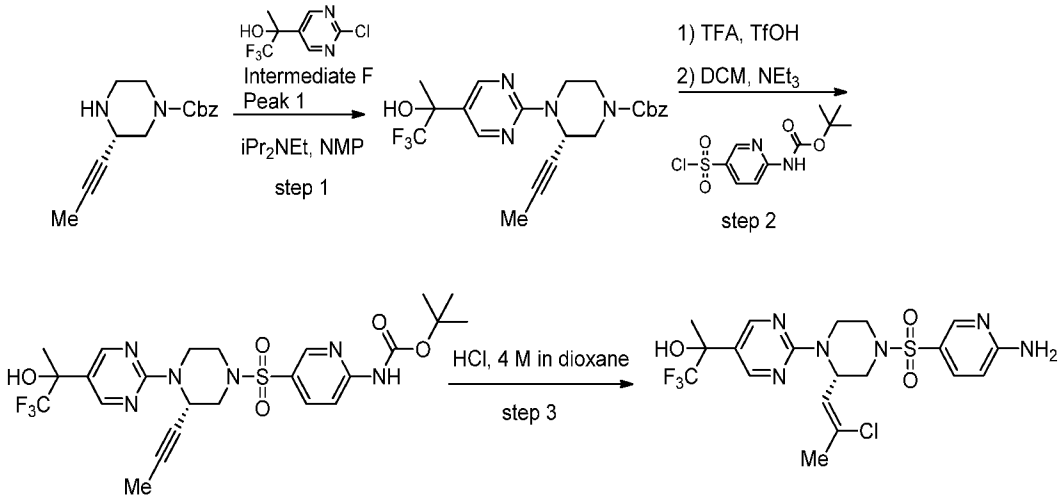
FIRST ELUENT PEAK (PEAK# 1)

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.49 (d, *J* = 1.9 Hz, 1 H), 7.80 (dd, *J* = 2.4, 8.8 Hz, 1 H), 7.45 (d, *J* = 8.8 Hz, 2 H), 6.96 (d, *J* = 8.9 Hz, 2 H), 6.55 (d, *J* = 8.6 Hz, 1 H), 5.17 (br. s., 2 H), 4.42 (d, *J* = 2.0 Hz, 1 H), 4.26 (d, *J* = 12.0 Hz, 1 H), 3.95 - 3.85 (m, 1 H), 3.81 - 3.66 (m, 2 H), 3.44 - 3.33 (m, 2 H), 2.86 (dd, *J* = 3.4, 11.3 Hz, 1 H), 2.79 - 2.63 (m, 1 H), 1.78 - 1.79 (d, *J* = 2.0 Hz, 3 H). (2 exchangable protons were not observed). m/z (ESI, +ve ion) 485.1 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.028 μM.

SECOND ELUENT PEAK (PEAK# 2)

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.49 (d, *J* = 2.2 Hz, 1 H), 7.78 (dd, *J* = 2.4, 8.7 Hz, 1 H), 7.45 (d, *J* = 8.6 Hz, 2 H), 6.96 (d, *J* = 9.1 Hz, 2 H), 6.53 (d, *J* = 8.8 Hz, 1 H), 4.99 (s, 2 H), 4.42 (d, *J* = 2.3 Hz, 1 H), 4.26 (d, *J* = 12.0 Hz, 1 H), 3.90 (d, *J* = 12.0 Hz, 1 H), 3.81 - 3.68 (m, 2 H), 3.43 - 3.33 (m, 2 H), 2.85 (dd, *J* = 3.4, 11.2 Hz, 1 H), 2.70 (td, *J* = 7.2, 11.1 Hz, 1 H), 1.79 (d, *J* = 2.0 Hz, 3 H). (2 exchangable protons were not observed). m/z (ESI, +ve ion) 485.1 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.003 μM.

EXAMPLE 10: (2R)-2-(2-((2S)-4-((6-Amino-3-pyridinyl)sulfonyl)-2-((1Z)-2-chloro-1-propen-1-yl)-1-piperazinyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol; or (2S)-2-(2-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-((1Z)-2-chloro-1-propen-1-yl)-1-piperazinyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol



STEP 1: (3S)-3-(1-Propyn-1-yl)-4-(5-((1R)-2,2,2-Trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-1-piperazinecarboxylate; or (3S)-3-(1-propyn-1-yl)-4-(5-((1S)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-1-piperazinecarboxylate

A 1-L pressure vessel was charged with benzyl (3S)-3-(1-propyn-1-yl)-1-piperazinecarboxylate (11.0 g, 43.0 mmol, Intermediate A), (2R)-1,1,1-trifluoro-2-(2-((2S)-2-(1-propyn-1-yl)-1-piperazinyl)-5-pyrimidinyl)-2-propanol or (2S)-1,1,1-trifluoro-2-(2-((2S)-2-(1-propyn-1-yl)-1-piperazinyl)-5-pyrimidinyl)-2-propanol (12.0 g, 51.6 mmol, Intermediate F, peak 1), NMP (200 mL), and DIEA (27.0 mL, 155 mmol, Sigma-Aldrich, St. Louis, MO). The vessel was sealed and heated at 140 °C for 20 h. The reaction mixture was cooled to rt and concentrated and the residue was partitioned between EtOAc (200 mL) and water (80 mL). The aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting product was purified by column chromatography (330 g of silica gel, 10 to 30% EtOAc in hexanes) to afford (3S)-3-(1-propyn-1-yl)-4-(5-((1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-1-piperazinecarboxylate or (3S)-3-(1-propyn-1-yl)-4-(5-((1S)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-1-piperazinecarboxylate (13.0 g) as a yellow foam.

STEP 2: (5-(((3S)-3-(1-Propyn-1-yl)-4-(5-((1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-1-piperazinyl)sulfonyl)-2-pyridinyl)carbamate; or (5-(((3S)-3-(1-propyn-1-yl)-4-(5-((1S)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-1-piperazinyl)sulfonyl)-2-pyridinyl)carbamate

A 100-mL round-bottomed flask was charged with (3S)-3-(1-propyn-1-yl)-4-(5-((1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-1-piperazinecarboxylate or (3S)-3-(1-propyn-1-yl)-4-(5-((1S)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-1-piperazinecarboxylate ((0.300 g, 0.669 mmol) and TFA (4.0 mL, Sigma-Aldrich, St. Louis, MO). After the substrate was completely dissolved in TFA, trifluoromethane sulfonic acid (0.180 mL, 2.01 mmol, Alfa Aesar, Lawrence, KS) was added and the resulting mixture was stirred for 1 h. The reaction mixture was concentrated to dryness and the residue was neutralized with saturated aqueous $NaHCO_3$ (50 mL) and then extracted with EtOAc (2 x 100 mL) and 10% IPA in $CHCl_3$ (2 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting intermediate was redissolved in DCM (15 mL). Triethylamine (0.500 mL, 3.50 mmol, Aldrich, St. Louis, MO) and tert-butyl (5-(chlorosulfonyl)pyridin-2-yl)carbamate (0.220 g, 0.752 mmol, Intermediate B) were added. The reaction was stirred at rt for 1 h. The reaction mixture was partitioned between DCM (70 mL) and water (40 mL). The aqueous layer was extracted with DCM (2 x 40 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The resulting product was purified by column chromatography (40 g of silica gel, 10% to 30% acetone in hexanes) to afford (5-(((3S)-3-(1-propyn-1-yl)-4-(5-((1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-1-piperazinyl)sulfonyl)-2-pyridinyl)carbamate or (5-(((3S)-3-(1-propyn-1-yl)-4-(5-((1S)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-1-piperazinyl)sulfonyl)-2-pyridinyl)carbamate (0.350 g) as a white solid.

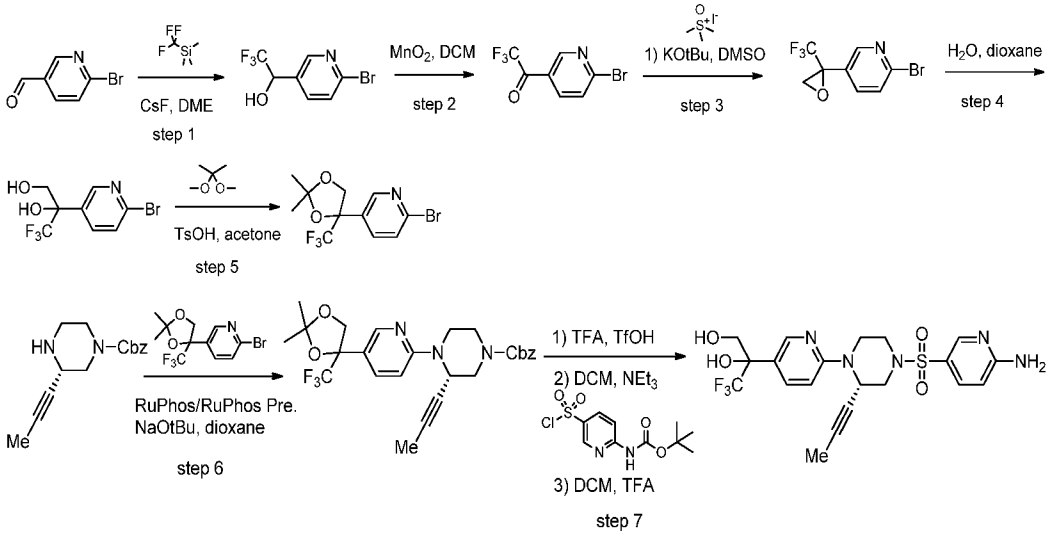
STEP 3: (2R)-2-(2-((2S)-4-((6-Amino-3-pyridinyl)sulfonyl)-2-((1Z)-2-chloro-1-propen-1-yl)-1-piperazinyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol or (2S)-2-

(2-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-((1Z)-2-chloro-1-propen-1-yl)-1-piperazinyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol

A 5-mL vial was charged with tert-butyl (5-(((3S)-3-(1-propyn-1-yl)-4-(5-((1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-1-piperazinyl)sulfonyl)-2-pyridinyl)carbamate or (5-(((3S)-3-(1-propyn-1-yl)-4-(5-((1S)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-1-piperazinyl)sulfonyl)-2-pyridinyl)carbamate (0.050 g, 0.088 mmol) and hydrogen chloride (4M in dioxane, 3.0 mL, 12.0 mmol, Aldrich, St. Louis, MO). The vial was sealed and heated at 70 °C for 20 h. The reaction mixture was cooled to rt and concentrated. The residue was neutralized with saturated aqueous $NaHCO_3$ (10 mL). The resulting mixture was extracted with DCM (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The resulting product was purified by column chromatography (12 g of silica gel, 10 to 30% acetone in hexanes) to afford (2R)-2-(2-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-((1Z)-2-chloro-1-propen-1-yl)-1-piperazinyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol or (2S)-2-(2-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-((1Z)-2-chloro-1-propen-1-yl)-1-piperazinyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol (0.025 g) as a white foam.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.47 (s, 2 H), 8.43 (d, J = 1.9 Hz, 1 H), 7.72 (dd, J = 2.3, 8.8 Hz, 1 H), 6.52 (d, J = 8.8 Hz, 1 H), 5.91 (s, 2 H), 5.01 (s, 2 H), 4.77 (d, J = 12.6 Hz, 1 H), 3.85 - 3.70 (m, 2 H), 3.43 - 3.23 (m, 1 H), 2.57 (d, J = 11.7 Hz, 1 H), 2.50 - 2.31 (m, 2 H), 2.15 (s, 3 H), 1.74 (s, 3 H). m/z (ESI, +ve ion) 507.1 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.080 μM.

EXAMPLE 11: 2-(6-((2S)-4-((6-Amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-3,3,3-trifluoro-1,2-propanediol



STEP 1: 1-(6-Bromo-3-pyridinyl)-2,2,2-trifluoroethanol

To a solution of 6-bromo-3-pyridinecarbaldehyde (4.0 g, 21.50 mmol, Frontier Scientific, Newark, DE) in DME (60 mL) was added trimethyl(trifluoromethyl)silane (4.80 mL, 32.3 mmol, Oakwood Products, West Columbia, SC) and cesium fluoride (0.660 g, 4.30 mmol, Alfa Aesar, Lawrence, KS). The reaction mixture was stirred at rt for 20 h. The reaction mixture was quenched with 1N HCl (10 mL) and stirred for 30 min then concentrated. The residue was partitioned between EtOAc (200 mL) and saturated aqueous $NaHCO_3$ (100 mL). The aqueous layer was extracted with EtOAc (2 x 75 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting product was purified by column chromatography (120 g of silica gel, 10 to 30% acetone in hexanes) to afford 1-(6-bromo-3-pyridinyl)-2,2,2-trifluoroethanol (4.4 g) as a colorless oil.

STEP 2: 1-(6-Bromo-3-pyridinyl)-2,2,2-trifluoroethanone

To a solution of 1-(6-bromo-3-pyridinyl)-2,2,2-trifluoroethanol (2.2 g, 8.60 mmol) in THF (60 mL) was added manganese dioxide (14.2 g, 164 mmol, Sigma-Aldrich, St. Louis, MO). The reaction mixture was capped and stirred at

rt for 36 h. The reaction mixture was filtered through a pad of diatomaceous earth and the filtrate was concentrated. The resulting product was purified by column chromatography (80 g of silica gel, 10 to 30% acetone in hexanes) to afford 1-(6-bromo-3-pyridinyl)-2,2,2-trifluoroethanone (1.1 g) as a light yellow paste.

STEP 3: 2-Bromo-5-(2-(trifluoromethyl)-2-oxiranyl)pyridine

To a suspension of potassium t-butoxide (0.180 g, 1.58 mmol, Sigma-Aldrich, St. Louis, MO) in DMSO (5.0 mL) at rt was added trimethylsulfoxonium iodide (0.385 g, 1.73 mmol, Sigma-Aldrich, St. Louis, MO). The resulting mixture was stirred at rt for 30 min. A solution of 1-(6-bromo-3-pyridinyl)-2,2,2-trifluoroethanone (0.400 g, 1.56 mmol) in DMSO (5 mL) was added and the reaction mixture was continued to stir at rt for 4 h. The reaction mixture was partitioned between EtOAc (80 mL) and water (30 mL). The organic layer was washed with water (3 x 40 mL), dried over $MgSO_4$, filtered and concentrated. The resulting product was purified by column chromatography (80 g of silica gel, 10 to 20% acetone in hexanes) to afford 2-bromo-5-(2-(trifluoromethyl)-2-oxiranyl)pyridine (0.230 g) as a yellow oil.

STEP 4: 2-(6-Bromo-3-pyridinyl)-3,3,3-trifluoro-1,2-propanediol

To a solution of 2-bromo-5-(2-(trifluoromethyl)-2-oxiranyl)pyridine (0.210 g, 0.783 mmol) in dioxane (1.0 mL) was added water (2.0 mL). The resulting mixture was heated at 65 °C for 20 h. The reaction mixture was cooled to rt and extracted with EtOAc (3 x 40 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting product was purified by column chromatography (40 g of silica gel, 10 to 30% acetone in hexanes) to afford 2-(6-bromo-3-pyridinyl)-3,3,3-trifluoro-1,2-propanediol (0.185 g) as a pale yellow solid.

STEP 5: 2-Bromo-5-(2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolan-4-yl)pyridine

To a solution of 2-(6-bromo-3-pyridinyl)-3,3,3-trifluoro-1,2-propanediol (0.310 g, 1.08 mmol) in acetone (5 mL) was added 2,2-dimethoxypropane (0.8 mL, 6.6 mmol, Sigma-Aldrich, St. Louis, MO) and p-toluenesulfonic acid monohydrate (0.022 mg, 0.110 mmol, Sigma-Aldrich, St. Louis, MO). The resulting mixture was stirred at rt for 20 h. The reaction mixture was quenched with saturated aqueous NaHCO3 (2 mL) and the solvent was removed. The residue was partitioned between EtOAc (100 mL) and saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The resulting product was purified by column chromatography (40 g of silica gel, 5 to 30% acetone in hexanes) to afford 2-bromo-5-(2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolan-4-yl)pyridine (0.290 g) as a yellow oil.

STEP 6: (3S)-4-(5-(2,2-Dimethyl-4-(trifluoromethyl)-1,3-dioxolan-4-yl)-2-pyridinyl)-3-(1-propyn-1-yl)-1-piperazinecarboxylate

A 5-mL vial was charged with benzyl (3S)-3-(1-propyn-1-yl)-1-piperazinecarboxylate (0.100 g, 0.387 mmol, Intermediate A), 2-bromo-5-(2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolan-4-yl)pyridine (0.140 g, 0.429 mmol), RuPhos (0.010 g, 0.020 mmol, Strem, Newburyport, MA), RuPhos Palladacycle (0.020 g, 0.020 mmol, Strem, Newburyport, MA), sodium t-butoxide (0.095 g, 0.968 mmol, Sigma-Aldrich, St. Louis, MO), and dioxane (3.0 mL). The resulting mixture was degassed by bubbling N_2 gas for 5 min. The vial was sealed and heated at 100 °C for 1 h. The reaction mixture was cooled to rt and partitioned between EtOAc (60 mL) and water (30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting product was purified by column chromatography (24 g of silica gel, 10% to 30% EtOAc in hexanes) to

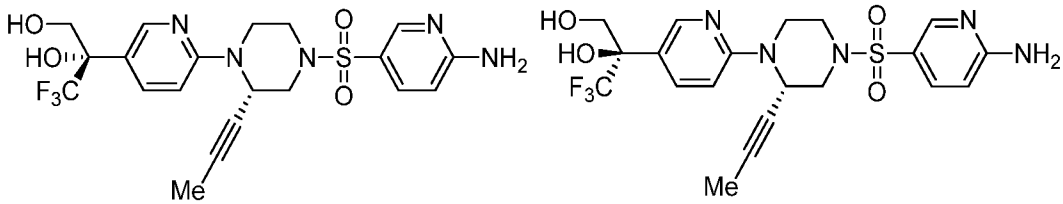
afford (3S)-4-(5-(2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolan-4-yl)-2-pyridinyl)-3-(1-propyn-1-yl)-1-piperazinecarboxylate (45 mg) as a yellow paste.

STEP 7: 2-(6-((2S)-4-((6-Amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-3,3,3-trifluoro-1,2-propanediol

To a 20-mL vial which contained (3S)-4-(5-(2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolan-4-yl)-2-pyridinyl)-3-(1-propyn-1-yl)-1-piperazinecarboxylate (0.100 g, 0.199 mmol) was added TFA (2.0 mL, Sigma-Aldrich, St. Louis, MO). After the substrate was completely dissolved in TFA, trifluoromethane sulfonic acid (0.060 mL, 0.60 mmol, Alfa Aesar, Lawrence, KS) was added and the resulting mixture was stirred for 1 h. The reaction mixture was concentrated to dryness and the residue was neutralized with saturated aqueous $NaHCO_3$ (15 mL) then extracted with EtOAc (3 x 20 mL) and 10% IPA in $CHCl_3$ (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting intermediate was dissolved in DCM (10 mL). Triethylamine (0.140 mL, 0.993 mmol, Sigma-Aldrich, St. Louis, MO) and tert-butyl (5-(chlorosulfonyl)pyridin-2-yl)carbamate (0.065 g, 0.222 mmol, Intermediate B) were added. The reaction mixture was stirred at rt for 1 h. The reaction mixture was concentrated to dryness. The residue was dissolved in DCM (10 mL) and TFA (0.50 mL, 5.96 mmol, Sigma-Aldrich, St. Louis, MO) was added. After 2 h, the reaction mixture was concentrated to dryness. The residue was neutralized with saturated aqueous $NaHCO_3$ (10 mL) then extracted with EtOAc (3 x 30 mL) and 10% IPA in CHCl3 (2 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting product was purified by column chromatography (24 g of silica gel, 0 to 10% 2M NH_3 in MeOH in DCM) to afford 2-(6-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-3,3,3-trifluoro-1,2-propanediol (0.060 g) as a mixture of two isomers.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.48 (d, *J* = 2.2 Hz, 1 H), 8.34 (br. s., 1 H), 7.88 - 7.59 (m, 2 H), 6.67 (d, *J* = 8.9 Hz, 1 H), 6.52 (d, *J* = 8.8 Hz, 1 H), 5.20 (br. s., 1 H), 4.96 (s, 2 H), 4.28 (d, *J* = 11.8 Hz, 1 H), 4.10 (d, *J* = 12.4 Hz, 1 H), 3.96 - 3.68 (m, 3 H), 3.54 - 3.30 (m, 1 H), 2.72 (d, *J* = 8.2 Hz, 1 H), 2.66 - 2.46 (m, 1 H), 1.80 (d, *J* = 1.8 Hz, 3 H). (2 exchangable protons were not observed). m/z (ESI, +ve ion) 486.1 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.024 μM.

This mixture was resolved using preparative SFC (Chiralcel® ODH column (21 x 250mm, 5μm, Chiral Technologies, Inc., West Chester, PA) eluting with 80% liquid CO_2 in 20% methanol with 0.2% diethylamine at a flow rate of 70 ml/min) to give 2 products in greater than 99% diastereomeric excess.



(2S)-2-(6-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-3,3,3-trifluoro-1,2-propanediol; and (2R)-2-(6-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-3,3,3-trifluoro-1,2-propanediol.

FIRST ELUENT PEAK (PEAK# 1)

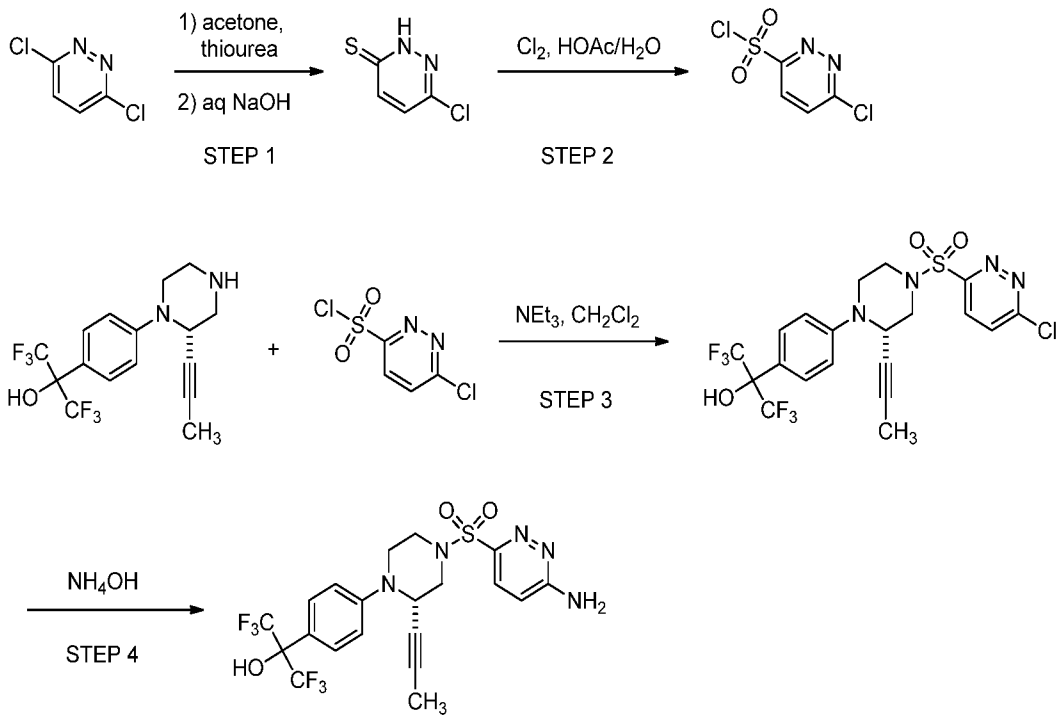
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.48 (d, *J* = 1.9 Hz, 1 H), 8.34 (s, 1 H), 7.83 - 7.66 (m, 2 H), 6.67 (d, *J* = 9.1 Hz, 1 H), 6.52 (d, *J* = 8.9 Hz, 1 H), 5.20 (br. s., 1 H), 4.97 (s, 2 H), 4.28 (d, *J* = 12.0 Hz, 1 H), 4.10 (d, *J* = 13.6 Hz, 1 H), 3.94 - 3.76 (m, 3 H), 3.67 (br. s., 1 H), 3.53 - 3.34 (m, 1 H), 2.73 (dd, *J* = 3.7, 11.4 Hz, 1 H), 2.66 - 2.50 (m, 1 H), 1.80 (d, *J* = 2.0 Hz, 3 H). (1 exchangable proton was

not observed). m/z (ESI, +ve ion) 486.1 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.008 μM.

SECOND ELUENT PEAK (PEAK# 2)

^1H NMR (300 MHz, DMSO-d_6) δ ppm 8.33 - 8.28 (m, 1 H), 8.23 (d, *J* = 2.2 Hz, 1 H), 7.73 (dd, *J* = 2.2, 8.9 Hz, 1 H), 7.63 (dd, *J* = 2.5, 8.9 Hz, 1 H), 6.99 (s, 2 H), 6.84 (d, *J* = 9.1 Hz, 1 H), 6.52 (d, *J* = 8.9 Hz, 1 H), 6.43 (s, 1 H), 5.34 (br. s., 1 H), 5.16 (t, *J* = 5.8 Hz, 1 H), 4.15 (d, *J* = 12.6 Hz, 1 H), 3.97 - 3.76 (m, 2 H), 3.64 (d, *J* = 10.1 Hz, 2 H), 3.14 - 3.05 (m, 1 H), 2.45 (d, *J* = 3.1 Hz, 1 H), 2.37 - 2.21 (m, 1 H), 1.75 (d, *J* = 2.0 Hz, 3 H). m/z (ESI, +ve ion) 486.1 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.036 μM.

EXAMPLE 12: 2-(4-((2*S*)-4-((6-Amino-3-pyridazinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol



STEP 1: 6-Chloro-3(2*H*)-pyridazinethione

To a 250-mL round-bottomed flask was added thiourea (3.8 g, 50 mmol, Sigma-Aldrich, St. Louis, MO) and acetone (150 ml). To this suspension was added 3,6-dichloropyridazine (7.5 g, 50 mmol, Sigma-Aldrich, St. Louis, MO). The solution was stirred at reflux for 2 h and then allowed to cool to rt. The mixture was filtered and the filtercake was washed with acetone and dried by passing air through the filtercake. The isolated solid was treated with aq sodium hydroxide (a solution made from 4 g NaOH in 80 mL H_2O) until the solution was homogeneous (about 40 mL). The solution was stirred for 5 min at rt and then was acidified with conc HCl until a pH of about 5. A precipitate had formed and this was filtered, washed with H_2O and then dried under a vacuum to afford 6-chloro-3(2*H*)-pyridazinethione (4.2 g) as a yellow solid.

STEP 2: 6-Chloro-3-pyridazinesulfonyl chloride

To the 250-mL round-bottomed flask was added 6-chloro-3(2*H*)-pyridazinethione (2.6 g, 17.6 mmol), water (110 ml) and acetic acid (11 ml). The solution was cooled to 0 °C and chlorine gas (Sigma-Aldrich, St. Louis, MO) was bubbled into the reaction mixture at a minimal rate with the internal temperature being kept below 5 °C. Cl_2 was added for 75 min and then N_2 was bubbled through the reaction mixture. The mixture was filtered and the filtercake was washed with ice cold water and then dried under vacuum to afford 6-chloro-3-pyridazinesulfonyl chloride (1.2 g,) as a yellow sticky solid that was used immediately.

STEP 3: 2-(4-((2S)-4-((6-Chloro-3-pyridazinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol

To a resealable vial was added 1,1,1,3,3,3-hexafluoro-2-(4-((2*S*)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-2-propanol (1.2 g, 3.3 mmol, Intermediate E), CH_2Cl_2 (13 mL), triethylamine (2.3 mL, 16 mmol) and 6-chloro-3-pyridazinesulfonyl chloride (0.70 g, 3.3 mmol). The solution was stirred at rt for

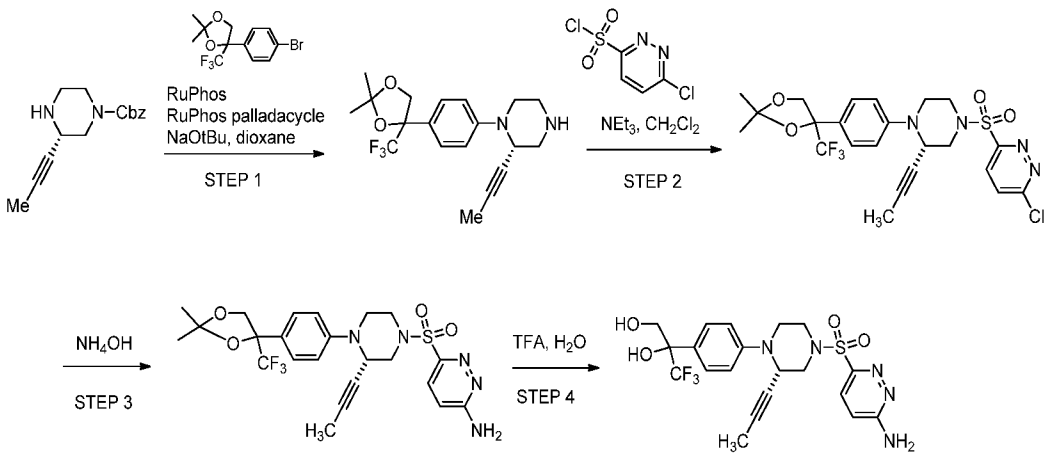
5 hours. To the reaction mixture was added saturated aqueous $NaHCO_3$. This was stirred for 5 min and then the solution was pippetted onto a phase separation cartridge (Radleys Discovery Technologies, Essex, UK) with the organic phase being collected and passed through a plug of Na_2SO_4. The collected solution was concentrated and purified by silica gel chromatography (0 to 60% EtOAc/hexane) which afforded 2-(4-((2S)-4-((6-chloro-3-pyridazinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (0.52 g)

STEP 4: 2-(4-((2*S*)-4-((6-Amino-3-pyridazinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol

To a 20-mL microwave vial was added 2-(4-((2*S*)-4-((6-chloro-3-pyridazinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (0.52 g, 0.96 mmol), ethanol (6 mL) and ammonium hydroxide (12 mL). The mixture was stirred and heated at 100 °C for 60 min in the microwave. The solution was partially concentrated and then diluted with aq $NaHCO_3$ (75 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined extracts were washed with water (1 x 50 mL), brine (50 mL) and then dried (Na_2SO_4) and concentrated. The resulting product was purified by preparative SFC (Chiralpak® IC column (250 x 20mm, 5μm) eluting with 80% liquid CO_2 in 20% methanol at a flow rate of 70 ml/min) twice to afford 2-(4-((2*S*)-4-((6-amino-3-pyridazinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.44 (s, 1H), 7.67 (d, *J* = 9.4 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.28 (s, 2H), 7.01 - 7.09 (m, *J* = 9.2 Hz, 2H), 6.90 (d, *J* = 9.4 Hz, 1H), 4.85 (br s, 1H), 3.69 - 3.81 (m, 2H), 3.63 (d, *J* = 12.1 Hz, 1H), 3.11 (dt, *J* = 2.7, 11.9 Hz, 1H), 3.00 (dd, *J* = 3.2, 11.8 Hz, 1H), 2.77 (dt, *J* = 2.8, 11.8 Hz, 1H), 1.74 (d, *J* = 2.0 Hz, 3H). m/z (ESI, +ve ion) 523.7 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.0065 μM.

EXAMPLE 13: 2-(4-((2S)-4-((6-Amino-3-pyridazinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-3,3,3-trifluoro-1,2-propanediol



STEP 1: (2S)-1-(4-(2,2-Dimethyl-4-(trifluoromethyl)-1,3-dioxolan-4-yl)phenyl)-2-(1-propyn-1-yl)piperazine

Two 20 mL vials were charged with benzyl (3S)-3-(1-propyn-1-yl)-1-piperazinecarboxylate (5.00 g, 19.4 mmol, Intermediate A), 4-(4-bromophenyl)-2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolane (3.30 g, 10.16 mmol, Example 9, Step 3), RuPhos (0.452 g, 0.968 mmol, Strem, Newburyport, MA), RuPhos Palladacycle (0.791 g, 0.968 mmol, Strem, Newburyport, MA), sodium tert-butoxide (4.65 g, 48.4 mmol, Sigma-Aldrich, St. Louis, MO) and dioxane (30.0 mL). The resulting mixture was degassed by bubbling N_2 gas through the mixture for 5 min. The vials were sealed and heated at 100 °C for 1 h. The reaction mixture was allowed to cool to room temperature and partitioned between EtOAc (300 mL) and water (150 mL). The aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting product was purified by column chromatography (330 g of silica, 10% to 30% EtOAc in hexanes first then 3 to 5% MeOH in DCM) to afford (2S)-1-(4-(2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolan-4-yl)phenyl)-2-(1-propyn-1-yl)piperazine (0.620 g).

STEP 2: 3-Chloro-6-(((3*S*)-4-(4-(2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolan-4-yl)phenyl)-3-(1-propyn-1-yl)-1-piperazinyl)sulfonyl)pyridazine

Following the procedure for Example 12, Step 3, the reaction of (2*S*)-1-(4-(2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolan-4-yl)phenyl)-2-(1-propyn-1-yl)piperazine and 6-chloro-3-pyridazinesulfonyl chloride (Example 12, Step 2) delivered 3-chloro-6-(((3*S*)-4-(4-(2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolan-4-yl)phenyl)-3-(1-propyn-1-yl)-1-piperazinyl)sulfonyl)pyridazine.

STEP 3: 6-(((3S)-4-(4-(2,2-Dimethyl-4-(trifluoromethyl)-1,3-dioxolan-4-yl)phenyl)-3-(1-propyn-1-yl)-1-piperazinyl)sulfonyl)-3-pyridazinamine

Following the procedure for Example 12, Step 4, the reaction of 3-chloro-6-(((3*S*)-4-(4-(2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolan-4-yl)phenyl)-3-(1-propyn-1-yl)-1-piperazinyl)sulfonyl)pyridazine and ammonium hydroxide in ethanol at 85 °C for 60 min in a microwave reactor delivered 6-(((3S)-4-(4-(2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolan-4-yl)phenyl)-3-(1-propyn-1-yl)-1-piperazinyl)sulfonyl)-3-pyridazinamine.

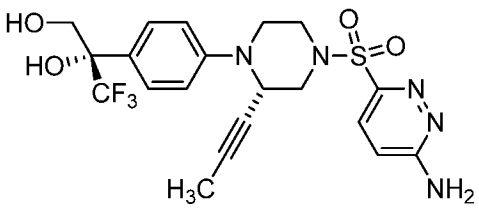
Step 4: 2-(4-((2S)-4-((6-Amino-3-pyridazinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-3,3,3-trifluoro-1,2-propanediol

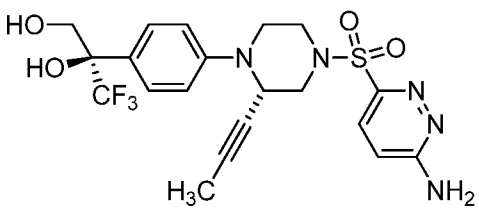
To a resealable vial was added 6-(((3S)-4-(4-(2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolan-4-yl)phenyl)-3-(1-propyn-1-yl)-1-piperazinyl)sulfonyl)-3-pyridazinamine (0.12 g, 0.23 mmol), TFA (3 mL) and water (0.0041 mL, 0.23 mmol). The reaction mixture was stirred for 3 h at rt. The TFA was removed by flushing the vial with N_2 gas. To the residue was added saturated aqueous $NaHCO_3$ and CH_2Cl_2. This was stirred for 5 min and then the solution was transferred onto a phase separation cartridge (Radleys Discovery Technologies, Essex, UK) with the organic phase being collected and passed through a plug of Na_2SO_4. The collected solution was concentrated and

purified by silica gel chromatography (0.0 to 9.0% MeOH/CH_2Cl_2) to afford 2-(4-((2*S*)-4-((6-amino-3-pyridazinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-3,3,3-trifluoro-1,2-propanediol (0.040 g) as a mixture of two isomers.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.67 (d, *J* = 9.4 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.27 (s, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 9.4 Hz, 1H), 6.22 (s, 1H), 5.04 - 5.11 (m, 1H), 4.77 (br s, 1H), 3.78 - 3.89 (m, 2H), 3.68 - 3.77 (m, 2H), 3.53 (d, *J* = 9.8 Hz, 1H), 3.10 (t, *J* = 11.4 Hz, 1H), 3.00 (dd, *J* = 3.1, 11.7 Hz, 1H), 2.71 - 2.82 (m, 1H), 1.73 (d, *J* = 1.6 Hz, 3H). m/z (ESI, +ve ion) 485.9 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.017 μM.

This mixture of isomers was resolved using preparative SFC (Chiralpak® AD-H (21 x 250 mm, 5 μm) eluting with 50% liquid CO_2 in 50% i-PrOH at a flow rate of 50 mL/min) to give two products in greater than 95% diastereomeric excess.





(2S)-2-(4-((2S)-4-((6-amino-3-pyridazinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-3,3,3-trifluoro-1,2-propanediol and (2R)-2-(4-((2S)-4-((6-amino-3-pyridazinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-3,3,3-trifluoro-1,2-propanediol.

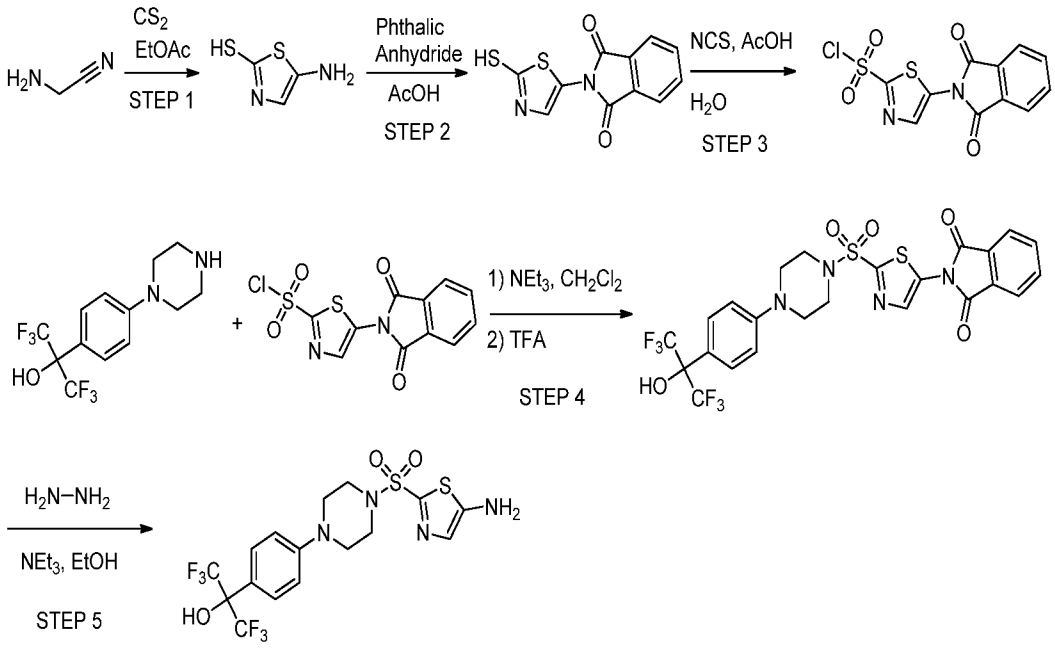
FIRST ELUTING PEAK (PEAK #1)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.67 (d, J = 9.0 Hz, 1H), 7.42 (d, J = 7.4 Hz, 2H), 7.28 (br s, 2H), 6.95 (d, J = 7.6 Hz, 2H), 6.90 (d, J = 9.2 Hz, 1H), 6.22 (br s, 1H), 5.07 (br s, 1H), 4.77 (br s, 1H), 3.84 (br s, 2H), 3.67 - 3.78 (m, 2H), 3.53 (d, J = 12.1 Hz, 1H), 3.10 (t, J = 11.5 Hz, 1H), 3.00 (d, J = 11.7 Hz, 1H), 2.77 (t, J = 11.4 Hz, 1H), 1.74 (br s, 3H). m/z (ESI, +ve ion) 485.9 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.074 μM.

SECOND ELUTING PEAK (PEAK #2)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.67 (d, J = 9.2 Hz, 1H), 7.42 (d, J = 7.6 Hz, 2H), 7.27 (br s, 2H), 6.95 (d, J = 7.6 Hz, 2H), 6.90 (d, J = 9.2 Hz, 1H), 6.21 (br s, 1H), 5.01 - 5.13 (m, 1H), 4.77 (br s, 1H), 3.78 - 3.92 (m, 2H), 3.66 - 3.77 (m, 2H), 3.52 (d, J = 11.5 Hz, 1H), 3.10 (t, J = 11.4 Hz, 1H), 3.00 (d, J = 11.9 Hz, 1H), 2.77 (t, J = 11.4 Hz, 1H), 1.73 (br s, 3H). m/z (ESI, +ve ion) 485.9 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.005 μM.

EXAMPLE 14: 2-(4-(4-((5-amino-1,3-thiazol-2-yl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol



STEP 1: 5-Amino-1,3-thiazole-2-thiol

To a solution of carbon disulfide (4.8 mL, 80 mmol, Sigma-Aldrich) in ethyl acetate (100 mL) at 0 °C was added aminoacetonitrile (3.0 mL, 54 mmol, Sigma-Aldrich, St. Louis, MO). The solution was stirred for 1 h at 0 °C and then filtered. The isolated solid was used without further purification (4.2 g).

STEP 2: 2-(2-Sulfanyl-1,3-thiazol-5-yl)-1H-isoindole-1,3(2H)-dione

To a resealable vial was added 5-amino-1,3-thiazole-2-thiol (0.26 g, 2.0 mmol), phthalic anhydride (0.31 g, 2.07 mmol, J.T. Baker, Philipsburg, NJ) and acetic acid (10 mL). The mixture was stirred and heated at 100 °C for 1 day and then was allowed to cool to rt. The solution was poured into water and extracted with EtOAc (3 x 75 mL). The combined extracts were washed with water (2 x 75 mL), dried (Na_2SO_4) and concentrated onto silica. Purification by silica gel chromatography (0 to 60% EtOAc/hexane) afforded 2-(2-sulfanyl-1,3-thiazol-5-yl)-1*H*-isoindole-1,3(2H)-dione (0.40 g) as a brown solid.

STEP 3: 5-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-1,3-thiazole-2-sulfonyl chloride

To a 25-mL round-bottomed flask was added 2-(2-sulfanyl-1,3-thiazol-5-yl)-1*H*-isoindole-1,3(2*H*)-dione (0.20 g, 0.76 mmol), acetic acid (4.5 mL), and water (0.5 mL). The solution was cooled to 0 °C and NCS (0.31 g, 2.3 mmol, Sigma-Aldrich, St. Louis, MO) was added in one portion. The solution was stirred at 0 °C for 10 min and then allowed to warm to rt and stir for 1 h. The solution was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. The material was used without further purification.

STEP 4: 2-(2-((4-(4-(2,2,2-Trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinyl)sulfonyl)-1,3-thiazol-5-yl)-1*H*-isoindole-1,3(2*H*)-dione

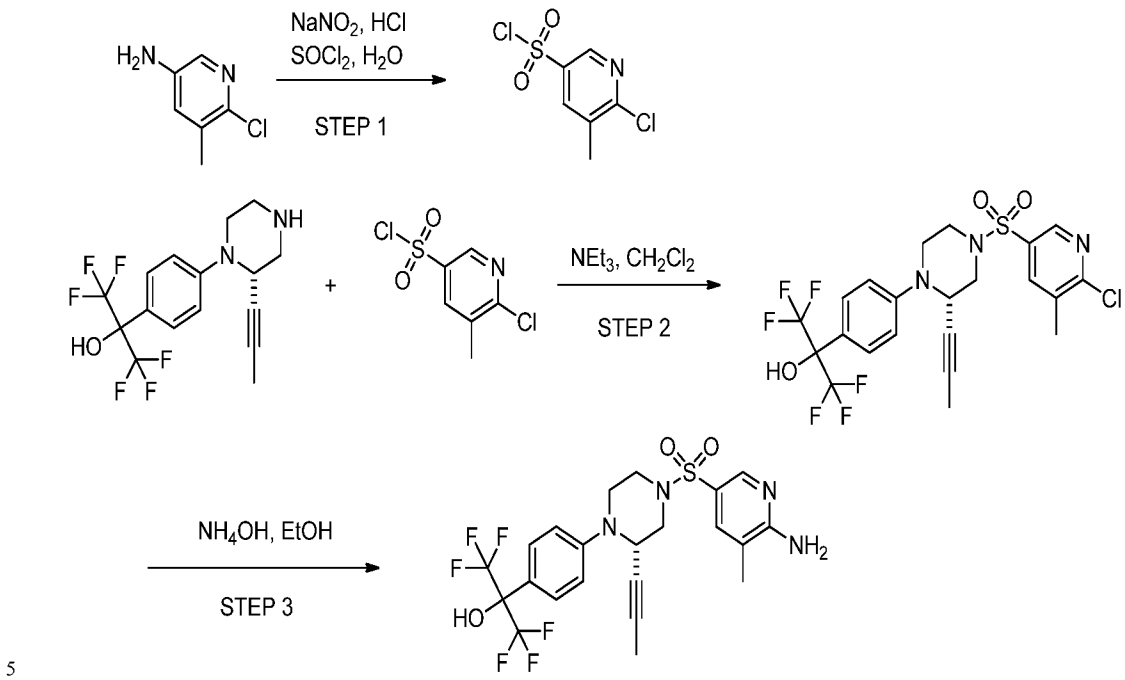
To a resealable vial was added 1,1,1,3,3,3-hexafluoro-2-(4-(1-piperazinyl)phenyl)-2-propanol dihydrochloride (0.28 g, 0.69 mmol, Intermediate I), dichloromethane (6 mL), triethylamine (0.48 mL, 3.4 mmol) and finally 5-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1,3-thiazole-2-sulfonyl chloride (0.25 g, 0.75 mmol). The mixture was stirred at rt for 15 h. The reaction mixture was concentrated and then purified by HPLC (Gemini®-NX (Phenomenex, Torrance, CA) 10 μm C_{18} 110 Å LC Column, 2 to 100% CH_3CN (0.1% TFA)/H_2O (0.1% TFA) over 15 min then 100% CH_3CN (0.1% TFA) for 5 minutes at 20 mL/min) to obtain a mixture of the phthalimide (minor) and its open form carboxylic acid (major). To a resealable vial was added a portion of the phthalimide/carboxylic acid mixture (0.052 g) and TFA (1.5 mL). The solution was stirred and heated at 70 °C for 16 h. The solution was allowed to cool to rt and then concentrated to afford 2-(2-((4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinyl)sulfonyl)-1,3-thiazol-5-yl)-1*H*-isoindole-1,3(2*H*)-dione.

STEP 5: 2-(4-(4-((5-Amino-1,3-thiazol-2-yl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol

To a solution of 2-(2-((4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinyl)sulfonyl)-1,3-thiazol-5-yl)-1*H*-isoindole-1,3(2*H*)-dione (0.051 g, 0.081 mmol) in ethanol (1.5 mL) was added triethylamine (0.045 mL, 0.33 mmol) and finally hydrazine monohydrate (0.0040 mL, 0.081 mmol, Fluka Chemie GmbH, Switzerland). The solution was stirred at rt for 16 h and then poured into saturatued aqueous $NaHCO_3$ (50 mL) and extracted with EtOAc (3 x 50 mL). The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated onto silica. Purification by silica gel chromatography (0 to 5.0% MeOH/CH_2Cl_2) followed by repurification with 0 to 70% EtOAc/hexanes afforded 2-(4-(4-((5-aminothiazol-2-yl)sulfonyl)piperazin-1-yl)phenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (0.021 g) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.42 (s, 1H), 7.47 (d, J = 8.6 Hz, 2H), 6.96 - 7.06 (m, 3H), 6.74 (s, 2H), 3.26 - 3.31 (m, 4H), 3.16 - 3.25 (m, 4H). m/z (ESI, +ve ion) 490.7 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.589 μM.

EXAMPLE 15: 2-(4-((2S)-4-((6-Amino-5-methyl-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol



STEP 1: 6-Chloro-5-methyl-3-pyridinesulfonyl chloride

In a 250-mL three neck round bottom flask, thionyl chloride (7.5 mL, Spectrochem, India) was added dropwise to water (45 mL) maintained at 0 to 5 °C, over a period of 15 minutes. The resulting solution was stirred at 20 °C for 17 h. In another 100-mL three neck round bottom flask, the solution of 6-chloro-5-methylpyridin-3-amine (3.0 g, 21.12 mmol, S2Sbiochemsys, India) in acetonitrile (60 mL) was cooled to 0 °C and concentrated HCl (24 mL, SD Fine-Chem India) was added drop wise. The resulting solution was stirred at the same temperature for 5 min. An aqueous solution of $NaNO_2$ (1.73 g, 25.1 mmol, Spectrochem, India, dissolved in 5 mL of water) was added drop wise over a period of 15 minutes. The resulting mixture was stirred for 30 min at 0 °C and added to the solution in the first flask at 0 °C. The resulting mixture was stirred at 0 °C for 45 min. The reaction mixture was diluted with water (100 mL) and extracted with EtOAc (200 mL). The organic layer was separated and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure and the residue obtained was purified by silica gel (60 to 120 mesh) column chromatography

(eluent 5% EtOAc-hexanes) to give 6-chloro-5-methyl-3-pyridinesulfonyl chloride (1.6 g) as a white solid.

STEP 2: 2-(4-((2S)-4-((6-Chloro-5-methyl-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol

Following the procedure for Example 12, Step 3, the reaction of 1,1,1,3,3,3-hexafluoro-2-(4-((2S)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-2-propanol (Intermediate E) and 6-chloro-5-methyl-3-pyridinesulfonyl chloride delivered 2-(4-((2S)-4-((6-chloro-5-methyl-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol.

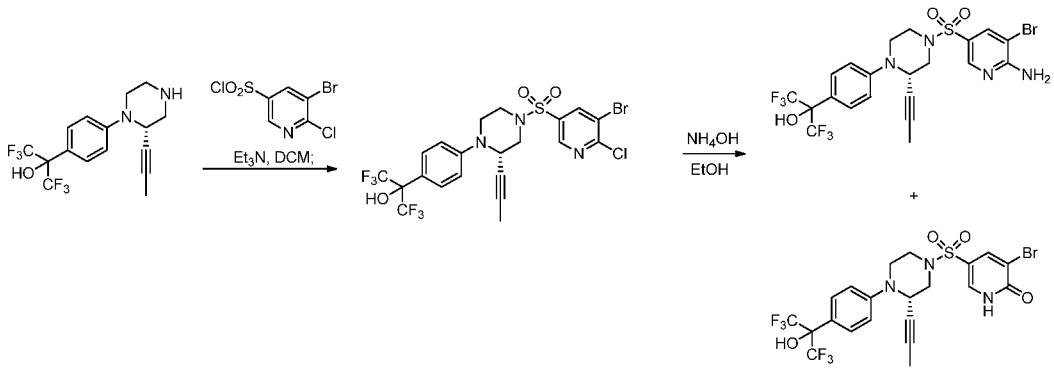
STEP 3: 2-(4-((2S)-4-((6-Amino-5-methyl-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol

Following the procedure for Example 12, Step 4, the reaction of 2-(4-((2*S*)-4-((6-chloro-5-methyl-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol with ammonium hydroxide in ethanol at 110 °C for 12 h delivered 2-(4-((2S)-4-((6-amino-5-methyl-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.43 (s, 1H), 8.14 (d, J = 2.4 Hz, 1H), 7.44 - 7.54 (m, 3H), 7.03 (d, J = 9.0 Hz, 2H), 6.80 (br s, 2H), 4.82 (br s, 1H), 3.55 - 3.67 (m, 3H), 3.05 - 3.16 (m, 1H), 2.52 - 2.57 (m, 1H), 2.30 - 2.41 (m, 1H), 2.09 (s, 3H), 1.75 (d, J = 1.8 Hz, 3H). m/z (ESI, +ve ion) 536.7 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.006 μM.

EXAMPLE 16: 2-(4-((2S)-4-((6-Amino-5-bromo-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol and 3-bromo-5-(((3S)-3-(1-propyn-1-yl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-

(trifluoromethyl)ethyl)phenyl)-1-piperazinyl)sulfonyl)-2-pyridinol (tautomeric form's name (S)-3-bromo-5-((4-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-3-(prop-1-yn-1-yl)piperazin-1-yl)sulfonyl)pyridin-2(1H)-one)



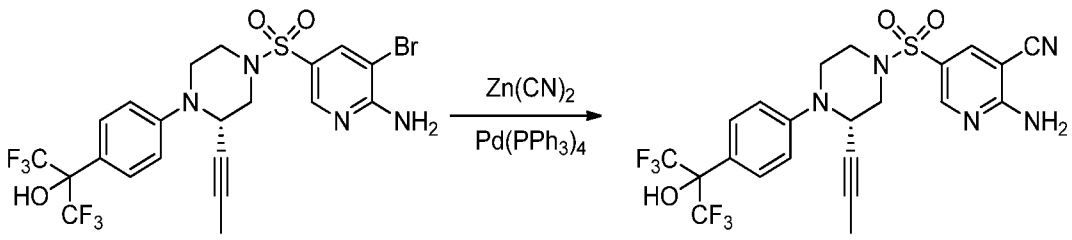
To a stirred solution of 1,1,1,3,3,3-hexafluoro-2-(4-((2S)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-2-propanol (300 mg, 0.819 mmol, Intermediate E) in CH_2Cl_2 (3.00 mL) and Et_3N (0.342 mL, 2.457 mmol) was added 5-bromo-6-chloro-3-pyridinesulfonyl chloride (286 mg, 0.983 mmol, Lancaster Synthesis, Ward Hill, MA) in portion over 3 min at 0 °C and the mixture was stirred at the same temperature for 10 min prior to the addition of water (10 min) resulting in two layers. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the organic extracts were washed with saturated aqueous NaCl (20 mL) and dried over Na_2SO_4. The solution was filtered and concentrated under a vacuum to give the resulting material as a yellow foam. The residue was taken up to a solution in ethanol (4.00 mL) and concentrated ammonium hydroxide aqueous solution (0.032 mL, 0.819 mmol) was added and the overall mixture was heated at 115 °C overnight. After cooled to rt, the mixture was diluted with cold water and the white precipitate was collected and dried to give 2-(4-((2S)-4-((6-amino-5-bromo-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (344 mg) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.43 (br. s., 1H), 8.28 (br. s., 1H), 7.96 (br. s., 1H), 7.46 - 7.56 (m, J = 7.82 Hz, 2H), 7.32 (br. s., 2H), 6.98 - 7.10 (m, J = 7.43 Hz, 2H), 4.83 (br. s., 1H), 3.54 - 3.74 (m, 3H), 3.10 (t, J = 11.93 Hz, 1H), 2.65 (d, J = 12.52 Hz, 1H), 2.44 (d, J = 2.35 Hz, 1H), 1.75 (br. s., 3H). m/z (ESI, +ve ion) 601.0 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.028 μM.

The separated aqueous layer was extracted with EtOAc (3 x 15mL) and the combined organic extracts were washed with saturated aqueous NaCl (30 mL) and dried over Na_2SO_4. The solution was filtered and concentrated under a vacuum to give the resulting material as a light-yellow oil. The resulting material was absorbed onto a plug of silica gel and purified by chromatography through a silica gel column (12 g), eluting with a gradient of 0% to 7% 2M NH_3·MeOH in CH_2Cl_2, to provide 3-bromo-5-(((3S)-3-(1-propyn-1-yl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinyl)sulfonyl)-2-pyridinol (7 mg) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.90 (br. s., 1H), 8.45 (s, 1H), 8.05 (s, 1H), 7.98 (s, 1H), 7.51 (d, J = 8.80 Hz, 2H), 7.07 (d, J = 9.00 Hz, 2H), 4.85 (br. s., 1H), 3.55 - 3.77 (m, 3H), 3.10 (t, J = 10.76 Hz, 1H), 2.83 (d, J = 8.80 Hz, 1H), 2.64 - 2.71 (m, 1H), 1.71 - 1.80 (m, 3H). m/z (ESI, +ve ion) 602.0 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.157 μM.

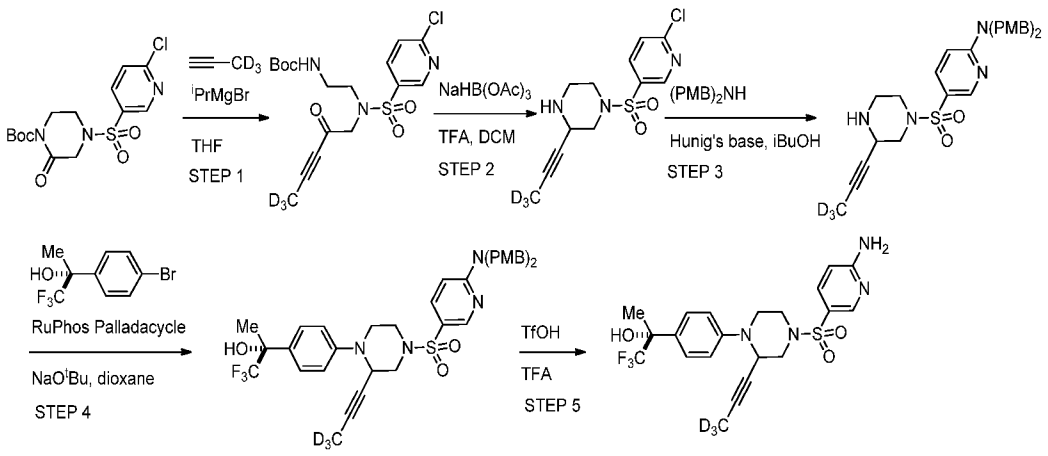
EXAMPLE 17: 2-Amino-5-(((3S)-3-(1-propyn-1-yl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinyl)sulfonyl)-3-pyridinecarbonitrile



A glass microwave reaction vessel was charged with 2-(4-((2S)-4-((6-amino-5-bromo-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (54 mg, 0.090 mmol) and zinc cyanide (21.1 mg, 0.180 mmol, Sigma-Aldrich, St. Louis, MO) and $Pd(PPh_3)_4$ (5.19 mg, 4.49 μmol, Strem Chemical Inc, Newburyport, MA) in DMF (1.5 mL). The reaction mixture was stirred and heated in a microwave reactor (Biotage AB, Inc., Upssala, Sweden) at 140 °C for 30 min. After being cooled to rt, the reaction mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 15 mL) and the combined organic extracts were washed with saturated aqueous NaCl (30 mL) and dried over Na_2SO_4. The solution was filtered and concentrated under a vacuum. The resulting material was absorbed onto a plug of silica gel and purified by chromatography through a pre-packed silica gel column (12 g), eluting with a gradient of 0% to 5% 2M NH_3·MeOH in CH_2Cl_2, to provide 2-amino-5-(((3S)-3-(1-propyn-1-yl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinyl)sulfonyl)-3-pyridinecarbonitrile (34 mg) as off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.47 - 8.56 (m, 1H), 8.45 (s, 1H), 8.17 - 8.32 (m, 1H), 7.93 (br. s., 2H), 7.41 - 7.58 (m, J = 8.41 Hz, 2H), 6.96 - 7.14 (m, J = 8.80 Hz, 2H), 4.83 (br. s., 1H), 3.55 - 3.75 (m, 3H), 3.11 (t, J = 10.56 Hz, 1H), 2.70 (d, J = 8.80 Hz, 1H), 2.55 (br. s., 1H), 1.76 (s, 3H). m/z (ESI, +ve ion) 548.2 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.059 μM.

EXAMPLE 18 : (2R)-2-(4-(4-((6-Amino-3-pyridinyl)sulfonyl)-2-($^2H_3$)-1-propyn-1-yl-1-piperazinyl)phenyl)-1,1,1-trifluoro-2-propanol



STEP 1 : tert-Butyl (2-(((6-chloro-3-pyridinyl)sulfonyl)(2-oxo(5,5,5-^{2}H)-3-pentyn-1-yl)amino)ethyl)carbamate

In a 25-mL pear-shaped flask with 1-mL markings was placed a stirring bar and THF (2 mL) under nitrogen. The flask was cooled in an dry ice-acetone bath and a stream of (3,3,3-^{2}H)-1-propyne (1 mL, 12 mmol, Sigma-Aldrich, St. Louis, MO) from a lecture bottle was introduced through a needle immersed to the THF. After about 2 mL was reached, the lecture bottle was removed and a solution of isopropylmagnesium chloride (2.0 M solution in THF, 2 mL, 4.00 mmol, Sigma-Aldrich, St. Louis, MO) was added. The cooling bath was replaced with an ice-water bath. After 20 min, more THF (5 mL) was added. Solid tert-butyl 4-((6-chloro-3-pyridinyl)sulfonyl)-2-oxo-1-piperazinecarboxylate (1.2 g, 3.19 mmol, Intermediate J) was added. After 20 min, the mixture was quenched with aqueous citric acid (1.43 N, 3 mL) and water (5 mL). The mixture was partitioned between EtOAc (50 mL) and citric acid (1.43N, 2 mL)-water (10 mL). The aqueous layer was extracted once with EtOAc (10 mL). The combined organic phase was dried over Na_2SO_4 and concentrated. The solid was washed with DCM-hexane (1:3, 10 mL) to give tert-butyl (2-(((6-chloro-3-pyridinyl)sulfonyl)(2-oxo(5,5,5-^{2}H)-3-pentyn-1-yl)amino)ethyl)carbamate (1.78 g) as a white powder.

STEP 2: 1-((6-Chloro-3-pyridinyl)sulfonyl)-3-($^2H_3$)-1-propyn-1-ylpiperazine

To a solution of tert-butyl (2-(((6-chloro-3-pyridinyl)sulfonyl)(2-oxo(5,5,5-^{2}H)-3-pentyn-1-yl)amino)ethyl)carbamate (1.78 g, 4.25 mmol) in DCM (3 mL) was added sodium triacetoxyborohydride (3 g, 14 mmol, Sigma-Aldrich, St. Louis, MO) followed by TFA (8 mL, 104 mmol, Sigma-Aldrich, St. Louis, MO). The mixture was stirred at rt for 2 h and then MeOH (5 mL) was added to the mixture. The content was concentrated and mixed with aqueous sodium carbonate to a pH of about 10. The aqueous layer was extracted with $CHCl_3$ containing ^{i}PrOH (10%) (3 x 30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to give an orange oil. The residue was purified by chromatography on silica gel using MeOH in EtOAc (1 to 5%) to give 1-((6-chloro-3-pyridinyl)sulfonyl)-3-($^2H_3$)-1-propyn-1-ylpiperazine (0.97 g) as a light yellow powder.

STEP 3: N,N-Bis(4-methoxybenzyl)-5-((3-($^2H_3$)-1-propyn-1-yl-1-piperazinyl)sulfonyl)-2-pyridinamine

A mixture of 1-((6-chloro-3-pyridinyl)sulfonyl)-3-($^2H_3$)-1-propyn-1-ylpiperazine (0.52 g, 1.717 mmol), DIPEA (0.600 mL, 3.44 mmol, Sigma-Aldrich, St. Louis, MO), and N-(4-methoxybenzyl)-1-(4-methoxyphenyl)methanamine (0.62 g, 2.409 mmol, published PCT patent application no. WO2007/109810A2) in ^{i}BuOH (1 mL) was heated at 132 °C in a microwave reactor (Biotage AB, Inc., Uppsala, Sweden) for 3 h. The mixture was partitioned between DCM (30 mL) and aqueous $NaHCO_3$ (half saturated, 30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel using MeOH:DCM:EtOAc [(0 to4):50:50] as eluent to give N,N-bis(4-methoxybenzyl)-5-((3-($^2H_3$)-1-propyn-1-yl-1-piperazinyl)sulfonyl)-2-pyridinamine (0.55 g) as a light yellow foam.

STEP 4: (2R)-2-(4-(4-((6-(Bis(4-methoxybenzyl)amino)-3-pyridinyl)sulfonyl)-2-($^2H_3$)-1-propyn-1-yl-1-piperazinyl)phenyl)-1,1,1-trifluoro-2-propanol

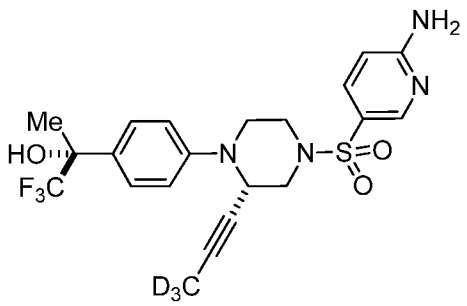
A stream of N_2 was passed through a mixture of N,N-bis(4-methoxybenzyl)-5-((3-($^2H_3$)-1-propyn-1-yl-1-piperazinyl)sulfonyl)-2-pyridinamine (0.55 g, 1.050 mmol) and (2R)-2-(4-bromophenyl)-1,1,1-trifluoro-2-propanol (0.400 g, 1.487 mmol, Intermediate N) in dioxane (5 mL) for 5 min. To this mixture was added RuPhos Palladacycle (0.1 g, 0.122 mmol, Sigma-Aldrich, St. Louis, MO) and sodium 2-methylpropan-2-olate (0.2 g, 2.081 mmol, Sigma-Aldrich, St. Louis, MO). The mixture was heated at 110 °C under N_2. After 50 min, the mixture was allowed to cool to rt and partitioned between DCM (30 mL) and HCl (0.2 N, 10 mL). The organic phase was concentrated and the residue was purified by chromatography on silica gel using EtOAc in DCM (0 to 15%) as eluent to give (2R)-2-(4-(4-((6-(bis(4-methoxybenzyl)amino)-3-pyridinyl)sulfonyl)-2-($^2H_3$)-1-propyn-1-yl-1-piperazinyl)phenyl)-1,1,1-trifluoro-2-propanol (0.55 g) as a yellow foam.

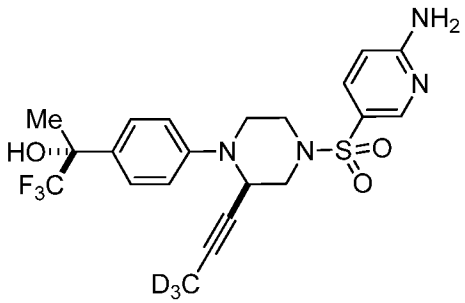
STEP 5: (2R)-2-(4-(4-((6-Amino-3-pyridinyl)sulfonyl)-2-($^2H_3$)-1-propyn-1-yl-1-piperazinyl)phenyl)-1,1,1-trifluoro-2-propanol

To a solution of (2R)-2-(4-(4-((6-(bis(4-methoxybenzyl)amino)-3-pyridinyl)sulfonyl)-2-($^2H_3$)-1-propyn-1-yl-1-piperazinyl)phenyl)-1,1,1-trifluoro-2-propanol (0.55 g, 0.773 mmol) in TFA (0.1 mL, 0.773 mmol) was added trifluoromethanesulfonic acid (3.0 mL, 0.773 mmol, Fluka Chemie GmbH, Switzerland). The dark red mixture was stirred at rt. After 20 min, the red reaction mixture was diluted with DCM (10 mL) and then added slowly to a stirred solution of Na_2CO_3 (10%, 100 mL). After 5 min, the aqueous layer was extracted with DCM (3x). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica gel using MeOH:EtOAc:DCM [(0 to 4):30:70] as eluent to give (2R)-2-(4-(4-((6-amino-3-pyridinyl)sulfonyl)-2-($^2H_3$)-1-propyn-1-yl-1-piperazinyl)phenyl)-1,1,1-trifluoro-2-propanol (0.25 g) as a mixture of two stereoisomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.75 (br. s., 3 H), 2.70 (d, *J*=8.02 Hz, 1 H), 2.85 (d, *J*=10.95 Hz, 1 H), 3.28 - 3.45 (m, 2 H), 3.73 (t, *J*=12.23 Hz, 3 H), 4.41 (br. s., 1 H), 5.04 (br. s., 2 H), 6.53 (d, *J*=8.80 Hz, 1 H), 6.93 (d, *J*=7.82 Hz, 2 H), 7.46 (d, *J*=7.63 Hz, 2 H), 7.78 (d, *J*=8.41 Hz, 1 H), 8.48 (br. s., 1 H). m/z (ESI, +ve ion) 472.2 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.028 μM.

The individual diastereomers were isolated using chiral SFC. The method used was as follows: Chiralpak® AD-H column (21 x 150 mm, 5 μm) using 40% (20 mM NH_3 in ethanol) in supercritical CO_2 (total flow was 70 mL/min). This produced the two diastereomers with diastereomeric and enanteomeric excesses greater than 99%.





(2R)-2-(4-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-($^2H_3$)-1-propyn-1-yl-1-piperazinyl)phenyl)-1,1,1-trifluoro-2-propanol and (2R)-2-(4-((2R)-4-((6-amino-3-pyridinyl)sulfonyl)-2-($^2H_3$)-1-propyn-1-yl-1-piperazinyl)phenyl)-1,1,1-trifluoro-2-propanol.

FIRST ELUTING PEAK (PEAK #1)

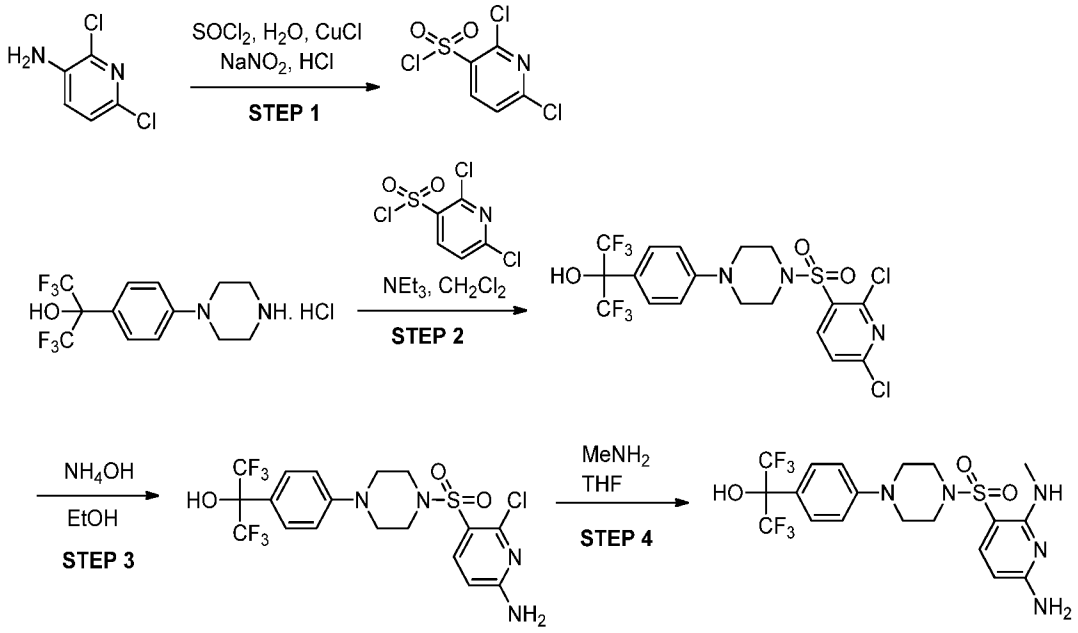
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.75 (s, 3 H), 2.69 (dt, *J* = 11.05, 7.29 Hz, 1 H), 2.84 (dd, *J* = 10.95, 3.13 Hz, 1 H), 3.27 - 3.44 (m, 2 H), 3.73 (t, *J* = 11.54 Hz, 2 H), 4.41 (br. s., 1 H), 5.04 (br. s., 2 H), 6.53 (d, *J* = 8.80 Hz, 1 H), 6.93 (d, *J* = 8.80 Hz, 2 H), 7.46 (d, *J* = 8.61 Hz, 2 H), 7.78 (dd, *J* = 8.71, 2.05 Hz, 1 H), 8.48

(d, J = 1.56 Hz, 1 H). (one exchangable proton was not observed). m/z (ESI, +ve ion) 472.2 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.009 μM.

SECOND ELUTING PEAK (PEAK #2)

^{1}H NMR (400 MHz, MeOH-d_4) δ ppm 1.68 (s, 3 H), 2.55 - 2.69 (m, 1 H), 2.80 (dd, J = 11.2, 3.3 Hz, 1 H), 3.21 - 3.31 (m, 1 H), 3.43 (d, J = 12.3 Hz, 1 H), 3.61 - 3.80 (m, 2 H), 4.57 (br. s., 1 H), 6.63 (d, J = 8.8 Hz, 1 H), 6.97 (d, J = 8.8 Hz, 2 H), 7.46 (d, J = 8.6 Hz, 2 H), 7.73 (dd, J = 8.9, 2.4 Hz, 1 H), 8.31 (d, J = 2.0 Hz, 1 H). m/z (ESI, +ve ion) 472.2 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 14.2 μM.

EXAMPLE 19: 2-(4-(4-((6-Amino-2-(methylamino)-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol



STEP 1: 2,6-Dichloro-3-pyridinesulfonyl chloride

In a 50-mL three necked round bottom flask, an aqueous solution of $NaNO_2$ (2.5 g, 36 mmol, Spectrochem, India; dissolved in 10 mL of water) was added dropwise to a solution of concentrated HCl (40 mL) in acetonitrile (100 mL) at 0 °C. The resulting solution was stirred at 0 °C for 10 min and a solution of 3-amino-2,6-dichloropyridine (5.0 g, 30.8 mmol, Matrix Scientific, Columbia, SC) in acetonitrile (50 mL) was added to the above solution at 0 °C. The resulting reaction mixture was stirred for 1 h at 0 °C. Acetic acid (50 mL), $CuCl_2 \cdot 2H_2O$ (2.62 g, 15.4 mmol) and CuCl (61 mg, 0.61 mmol) were added sequentially to the above mixture and the mixture was purged with SO_2 gas for 15 min at 0 °C. The resulting reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was diluted with cold water (100 mL) and EtOAc (200 mL). The organic layer was separated, washed with water, brine and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure and the residue obtained was purified by silica gel (60 to 120 mesh) column chromatography (eluent, 10% EtOAc-hexanes) to give 2,6-dichloro-3-pyridinesulfonyl chloride (3.5 g) as a colorless liquid.

STEP 2: 2-(4-(4-((2,6-Dichloro-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol

In 25-mL round bottom flask, 1,1,1,3,3,3-hexafluoro-2-(4-(1-piperazinyl)phenyl)-2-propanol hydrochloride (350 mg, 0.96 mmol, Intermediate I) was dissolved in DCM (10 mL) at rt under nitrogen atmosphere. Triethylamine (0.34 mL, 2.4 mmol) and 2,6-dichloro-3-pyridinesulfonyl chloride (352 mg, 1.44 mmol) were added sequentially to the above solution at rt under a nitrogen atmosphere. The resulting reaction mixture was stirred at rt under nitrogen atmosphere for 2 h. The reaction mixture was diluted with water (20 mL) and DCM (30 mL). The organic layer was separated, washed with water, brine and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced

pressure and the residue obtained was purified by silica gel (60 to120 mesh) column chromatography (eluent, 20% EtOAc-hexanes) to give 2-(4-(4-((2,6-dichloro-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (300 mg) as a yellow solid.

STEP 3: 2-(4-(4-((6-Amino-2-chloro-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol

In a 25-mL microwave vial, 2-(4-(4-((2,6-dichloro-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (0.3 g, 0.56 mmol) was dissolved in ethanol (3 mL) at rt. Concentrated aqueous ammonium hydroxide (6.0 mL) was added to the above solution at rt. The solution was capped and heated in a microwave reactor (Biotage AB, Inc., Uppsala, Sweden) at 100 °C for 2 h. The reaction vial was cooled to rt and opened carefully. The solution was concentrated under reduced pressure and the residue obtained was diluted with water (20 mL) and EtOAc (40 mL). The organic layer was separated, washed with water, brine and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure and the residue obtained was purified by silica gel (60 to 120 mesh) column chromatography (eluent, 60% EtOAc-hexanes) to give 2-(4-(4-((6-amino-2-chloro-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (0.15 g) as a white solid.

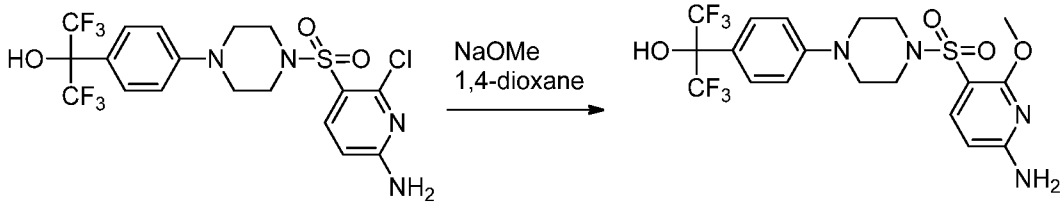
STEP 4: 2-(4-(4-((6-Amino-2-(methylamino)-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol

In a 25-mL re-sealable reaction tube, 2-(4-(4-((6-amino-2-chloro-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (0.1 g, 0.193 mmol) was dissolved in THF (2 mL) at rt. $MeNH_2$ (2M in THF, 0.48 mL, 0.96 mmol, Sigma-Aldrich, India) was added to the above solution at rt. The reaction tube was sealed and reaction mixture was heated at 80 °C for 4 h. The reaction mixture was cooled to rt and opened carefully. The solution was diluted

with cold water (10 mL) and EtOAc (20 mL) at rt. The organic layer was separated, washed with water, brine and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure and the residue obtained was purified by silica gel (60 to 120 mesh) column chromatography (eluent, 100% EtOAc) to give 2-(4-(4-((6-amino-2-(methylamino)-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (50 mg) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 8.44 (s, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 8.8 Hz, 2H), 6.66 – 6.55 (m, 3H), 5.75 (d, J = 8.8 Hz, 1H), 3.27 (m, 4H), 3.03 (m, 4H), 2.84 (d, J = 4.4 Hz, 3H). m/z (ESI, +ve ion) 514.4 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 1.32 μM.

EXAMPLE 20: 2-(4-(4-((6-Amino-2-methoxy-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol

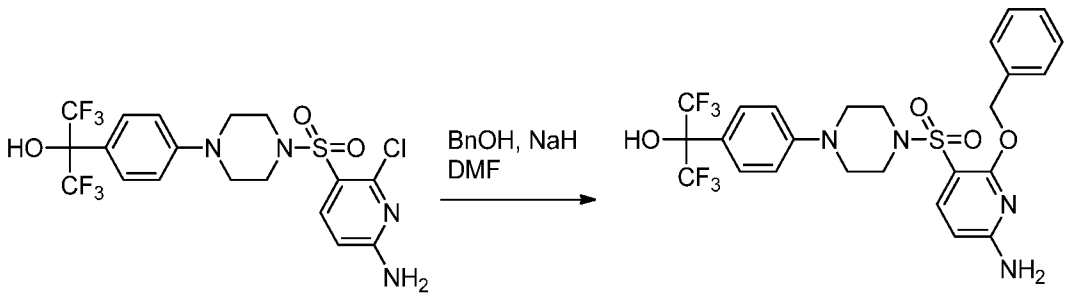


In a 25-mL re-sealable reaction tube, 2-(4-(4-((6-amino-2-chloro-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (0.1 g, 0.193 mmol, Example 19, Step 3) was dissolved in 1,4-dioxane (2 mL) at rt. NaOMe (21 mg, 0.38 mmol, Sigma-Aldrich, India) was added to the above solution at rt. The reaction tube was sealed and reaction mixture was heated at 100 °C for 12 h. The reaction mixture was cooled to rt and opened carefully. The solution was diluted with cold water (10 mL) and EtOAc (20 mL) at rt. The organic layer was separated, washed with water, brine and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure and the residue obtained was purified by silica gel (60 to 120 mesh) column chromatography

(eluent, 70% EtOAc-hexanes) to give 2-(4-(4-((6-amino-2-methoxy-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (50 mg) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 8.44 (s, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 9.2 Hz, 2H), 6.96 (s, 2H), 6.08 (d, J = 8.4 Hz, 1H), 3.83 (s, 3H), 3.26 (m, 4H), 3.13 (m, 4H). m/z (ESI, +ve ion) 514.8 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.821 μM.

EXAMPLE 21: 2-(4-(4-((6-Amino-2-(benzyloxy)-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol

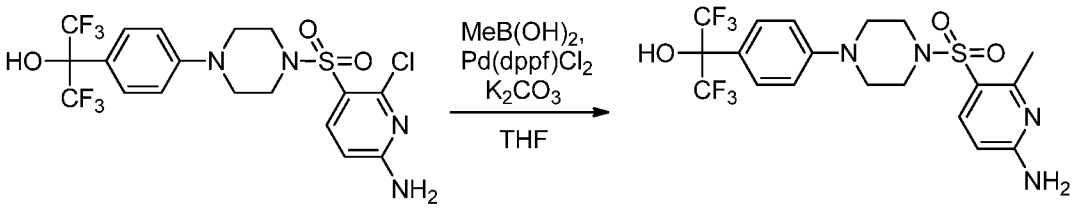


In a 25-mL re-sealable reaction tube, the solution of benzyl alcohol (31 mg, 0.289 mmol) in DMF (2 mL) was treated with NaH (60% dispersion, 15 mg, 0.38 mmol) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at same temperature for 10 min and a solution of 2-(4-(4-((6-amino-2-chloro-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (0.1 g, 0.193 mmol, Example 19, Step 3) in DMF (2 mL) was added at 0 °C under nitrogen atmosphere. The reaction tube was sealed and reaction mixture was heated at 100 °C for 6 h. The reaction mixture was cooled to rt, quenched with ice-cold water (10 mL) and diluted with EtOAc (20 mL). The organic layer was separated, washed with water, brine and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure and the residue obtained was purified by silica gel (60 to 120 mesh) column chromatography (eluent, 40%

EtOAc-hexanes) to give 2-(4-(4-((6-amino-2-(benzyloxy)-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (40 mg) as a brown solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 8.44 (s, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.51-7.45 (m, 4H), 7.42 – 7.28 (m, 3H), 7.03 – 6.93 (m, 4H), 6.10 (d, J = 8.4 Hz, 1H), 5.39 (s, 2H), 3.21-3.11 (m, 4H), 3.10-3-01 (m, 4H). m/z (ESI, +ve ion) 591.2 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 3.85 μM.

EXAMPLE 22: 2-(4-(4-((6-Amino-2-(1-propyn-1-yl)-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol

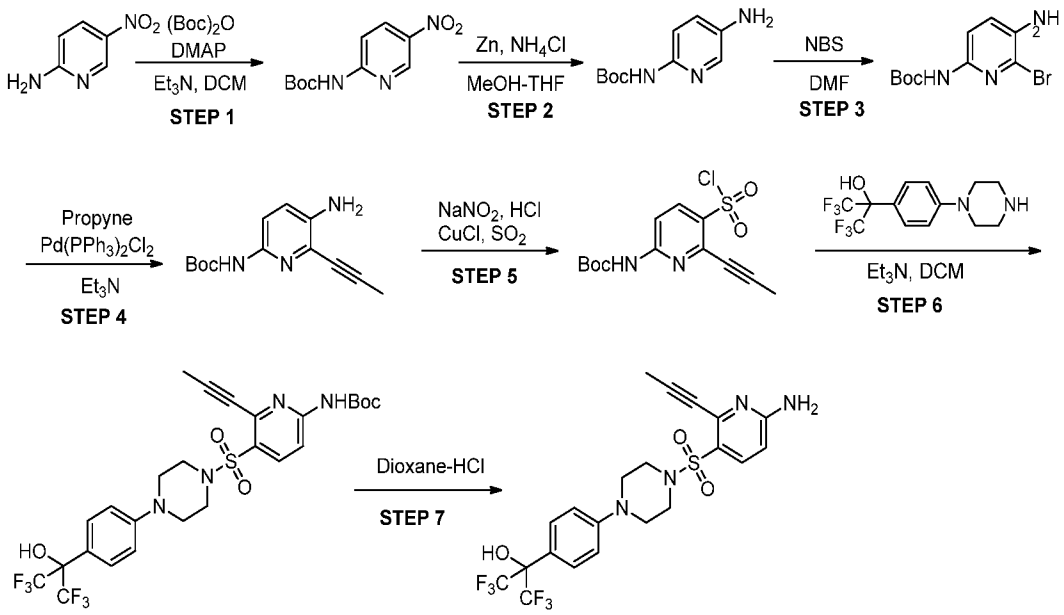


In a 25-mL re-sealable reaction tube, the suspension of 2-(4-(4-((6-amino-2-chloro-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (0.1 g, 0.193 mmol, Example 19, Step 3), methyl boronic acid (15 mg, 0.25 mmol) and K_2CO_3 (52 mg, 0.38 mmol) in THF (5 mL) was degassed by purging with argon gas at rt for 10 min. $Pd(dppf)Cl_2$ (14 mg, 0.019 mmol) was added to the above mixture at rt under argon atmosphere. The reaction tube was sealed under argon atmosphere and contents were heated at 80 °C for 4 h. The reaction mixture was cooled to rt and diluted with cold water (10 mL) and EtOAc (20 mL). The organic layer was separated, washed with water, brine and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure and the residue obtained was purified by silica gel (60 to 120 mesh) column chromatography (eluent, 30% EtOAc-hexanes) to give 2-(4-(4-((6-

amino-2-(1-propyn-1-yl)-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (50 mg) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 8.44 (s, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 6.90 (s, 2H), 6.37 (d, J = 8.8 Hz, 1H), 3.31-3.26 (m, 4H), 3.12-3.05 (m, 4H), 2.53 (s, 3H). m/z (ESI, +ve ion) 499.2 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.664 μM.

EXAMPLE 23: 2-(4-(4-((6-Amino-2-(1-propyn-1-yl)-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol



STEP 1: tert-Butyl (5-nitro-2-pyridinyl)carbamate

In a 50-mL round bottom flask, the solution of 5-nitro-2-pyridinamine (2.0 g, 14.3 mmol) in DCM (25 mL), was treated with DMAP (0.9 g, 7.2 mmol) and Et_3N (2 mL, 14.3 mmol) at rt under nitrogen atmosphere. The above solution was cooled to 0 °C and di-tert-butyl dicarbonate (3.44 g, 15.8 mmol, Sigma-Aldrich, India) was added under nitrogen atmosphere. The reaction mixture was

gradually warmed to rt and stirred for 12 h under nitrogen atmosphere. The reaction mixture was diluted with cold water (50 mL) and DCM (50 mL) at rt. The organic layer was separated, washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give tert-butyl (5-nitro-2-pyridinyl)carbamate (2.5 g) as a brown solid.

STEP 2: tert-Butyl (5-amino-2-pyridinyl)carbamate

In a 100-mL round bottom flask, the solution of tert-butyl (5-nitro-2-pyridinyl)carbamate (2.5 g, 10.46 mol) in MeOH (30 mL)-THF (20 mL) was treated sequentially with NH_4Cl (2.79 g, 52.30 mol, dissolved in 10 mL of water) and Zn powder (3.41 g, 52.30 mol) at ambient temperature. The reaction mixture was stirred at rt for 3 h. The mixture was filtered through a diatomaceous earth pad and washed with ethyl acetate. The combined filtrate was concentrated under reduced pressure and the residue obtained was diluted with ice-cold water (50 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic extracts was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give tert-butyl (5-amino-2-pyridinyl)carbamate (2 g) as a brown solid.

STEP 3: tert-Butyl (5-amino-6-bromo-2-pyridinyl)carbamate

In a 25-mL round bottom flask, the solution of tert-butyl (5-amino-2-pyridinyl)carbamate (0.5 g, 2.39 mol) in DMF (5 mL) was treated with NBS (0.43 g, 2.39 mol) in portions at rt under nitrogen atmosphere. The reaction mixture was stirred at rt for 12 h. The reaction mixture was diluted with cold water (20 mL) and EtOAc (30 mL). The organic layer was separated, washed with water, brine, dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure and the residue obtained was purified by silica gel (60 to 120 mesh) column chromatography (eluent, 8% EtOAc-hexanes) to give tert-butyl (5-amino-6-bromo-2-pyridinyl)carbamate (0.3 g) as a white solid.

STEP 4: tert-Butyl (5-amino-6-(1-propyn-1-yl)-2-pyridinyl)carbamate

In a 50-mL re-sealable reaction tube, tert-butyl (5-amino-6-bromo-2-pyridinyl)carbamate (300 mg, 1.04 mmol) and triethylamine (0.29 mL, 2.08 mmol) were dissolved in acetonitrile (10 mL) at rt. The solution was degassed by purging with argon gas at rt for 30 min. $Pd(PPh_3)_2Cl_2$ (36 mg, 0.052 mmol) and CuI (3.9 mg, 0.002 mmol) were added sequentially to the above solution at rt under argon atmosphere. The solution was homogenized by stirring at same temperature for 5 min and cooled to -10 °C before purging propyne gas through the solution for 5 minutes. The reaction tube was sealed and resulting reaction mixture was heated at 80 °C for 4 h. The reaction mixture was cooled to rt and filtered through a diatomaceous earth pad. The filtrate was diluted with cold water (30 mL) and ethyl acetate (30 mL). The organic layer was separated, washed with water, brine and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure and the residue obtained was purified by silica gel (60 to 120 mesh) column chromatography (eluent, 20% EtOAc-hexanes) to give tert-butyl (5-amino-6-(1-propyn-1-yl)-2-pyridinyl)carbamate (0.2 g) as a pale yellow oil.

STEP 5: tert-Butyl (5-(chlorosulfonyl)-6-(1-propyn-1-yl)-2-pyridinyl)carbamate

In a 50 mL three necked round bottom flask, an aqueous solution of $NaNO_2$ (67 mg, 0.97 mmol; dissolved in 2 mL of water)) was added dropwise to a solution of concentrated HCl (2 mL) in acetonitrile (5 mL) at 0 °C. The resulting solution was stirred at 0 °C for 10 min and a solution of tert-butyl (5-amino-6-(1-propyn-1-yl)-2-pyridinyl)carbamate (0.2 g, 0.81 mmol) in acetonitrile (2 mL) was added to the above solution at 0 °C. The resulting reaction mixture was stirred for 1 h at 0 °C. 2 mL of glacial acetic acid, $CuCl_2 \cdot 2H_2O$ (69 mg, 0.4 mmol) and CuCl (2 mg, 0.016 mol) were added sequentially to the above mixture and purged with SO_2 gas for 15 min at 0 °C. The resulting reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was diluted with cold water (20

mL) and ethyl acetate (50 mL). The organic layer was separated, washed with water, brine and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure to give tert-butyl (5-(chlorosulfonyl)-6-(1-propyn-1-yl)-2-pyridinyl)carbamate (0.2 g) as a brown liquid, which was carried forward to the next step without purification. .

STEP 6: tert-Butyl (6-(1-propyn-1-yl)-5-((4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinyl)sulfonyl)-2-pyridinyl)carbamate

In 25 mL round bottom flask, 1,1,1,3,3,3-hexafluoro-2-(4-(piperazin-1-yl)phenyl)propan-2-ol hydrochloride (0.25 g, 0.76 mmol, Intermediate I) was dissolved in DCM (10 mL) at rt under nitrogen atmosphere. Triethylamine (0.43 mL, 3 mmol) and tert-butyl (5-(chlorosulfonyl)-6-(1-propyn-1-yl)-2-pyridinyl)carbamate (0.3 g, 0.9 mmol) were added sequentially to the above solution at rt under a nitrogen atmosphere. The resulting reaction mixture was stirred at rt under nitrogen atmosphere for 1 h. The reaction mixture was diluted with water (20 mL) and DCM (30 mL). The organic layer was separated, washed with water, brine and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure and the residue obtained was purified by silica gel (60-120 mesh) column chromatography (eluent, 30% EtOAc-hexanes) to give tert-butyl (6-(1-propyn-1-yl)-5-((4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinyl)sulfonyl)-2-pyridinyl)carbamate (0.1 g) as a yellow solid.

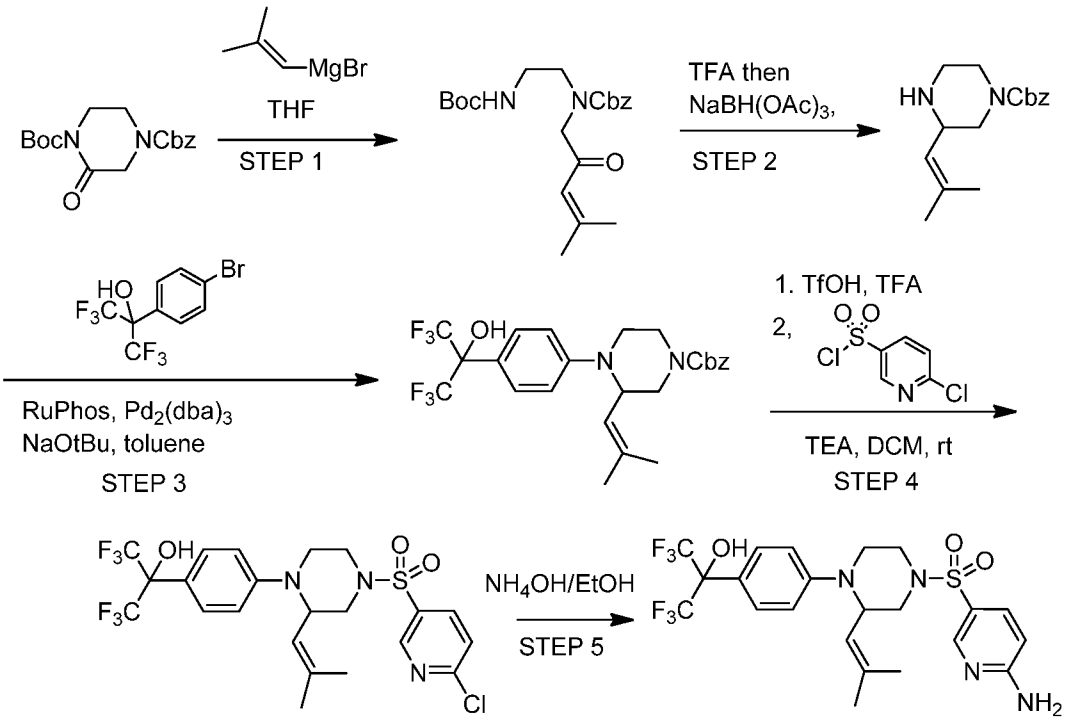
STEP 7: 2-(4-(4-((6-Amino-2-(1-propyn-1-yl)-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol

In a 25 mL round bottom flask, tert-butyl (6-(1-propyn-1-yl)-5-((4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinyl)sulfonyl)-2-pyridinyl)carbamate (100 mg, 0.16 mmol) was dissolved in DCM (5 mL) and cooled to 0 °C. A solution of HCl in 1,4-dioxane (4M, 1

mL, Sigma-Aldrich, India) was added to the above solution at 0 °C. The reaction mixture was gradually warmed to rt and stirred at rt for 2 h. The reaction mixture was basified with saturated $NaHCO_3$ solution and diluted with ethyl acetate (20 mL). The organic layer was separated, washed with water, brine and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure and the residue obtained was purified by silica gel (60 to 120 mesh) column chromatography (eluent 60% EtOAc-hexanes) to give 2-(4-(4-((6-amino-2-(1-propyn-1-yl)-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (15 mg) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.92 (d, J = 8.8 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 6.45 (d, J = 8.8 Hz, 1H), 4.98 (s, 2H), 3.40 – 3.27 (m, 8H), 2.15 (s, 3H). (one exchangable proton was not observed). m/z (ESI, +ve ion) 523.1 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 1.89 μM.

EXAMPLE 24: 2-(4-(4-((6-Amino-3-pyridinyl)sulfonyl)-2-(2-methyl-1-propen-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol



STEP 1: Benzyl (2-((tert-butoxycarbonyl)amino)ethyl)(4-methyl-2-oxo-3-penten-1-yl)carbamate

A 500-mL round-bottomed flask was charged with 4-benzyl 1-tert-butyl 2-oxo-1,4-piperazinedicarboxylate (7.0 g, 21 mmol, Intermediate K) and THF (100 mL). Bromo(2-methyl-1-propen-1-yl)magnesium (0.5 M in THF, 62.8 ml, 31.4 mmol) was added at 0 °C slowly. The mixture was stirred at 0 °C for 10 min. Saturated aqueous NH_4Cl (40 mL) was added and the aqueous phase was extracted with EtOAc (200 mL, then 2 x 100 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under a vacuum. The resulting product was purified by silica gel column chromatography (0 to 100% EtOAc in hexanes) to afford benzyl (2-((tert-butoxycarbonyl)amino)ethyl)(4-methyl-2-oxo-3-penten-1-yl)carbamate (1.3 g) as a clear oil.

STEP 2: Benzyl 3-(2-methyl-1-propen-1-yl)-1-piperazinecarboxylate

A 100-mL round-bottomed flask was charged with benzyl (2-((tert-butoxycarbonyl)amino)ethyl)(4-methyl-2-oxo-3-penten-1-yl)carbamate (0.8 g, 2.0 mmol) and 20 mL of DCM. TFA (1.5 ml, 20 mmol) was added and the resulting dark solution was stirred at room temperature for 30 min. Sodium triacetoxyborohydride (1.74 g, 8.20 mmol) was then added portionwise over 10 min. After 2h, the mixture was concentrated, diluted with EtOAc (200 mL), and neutralized with 5 N NaOH. The layers were separated and the organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. The resulting orange oil was purified via silica gel column chromatography (0 to 15 % (2M NH_3 in MeOH) in DCM) to give benzyl 3-(2-methyl-1-propen-1-yl)-1-piperazinecarboxylate (415 mg).

STEP 3: Benzyl 3-(2-methyl-1-propen-1-yl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinecarboxylate

A 20-mL reaction vessel was charged with benzyl 3-(2-methyl-1-propen-1-yl)-1-piperazinecarboxylate (415 mg, 1.513 mmol), 2-(4-bromophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (586 mg, 1.815 mmol, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3009), RuPhos (72.1 mg, 0.151 mmol, Strem Chemical Inc., Newburyport, MA), tris(dibenzylideneacetone)dipalladium (69.3 mg, 0.076 mmol, Strem Chemical Inc, Newburyport, MA), sodium tert-butoxide (363 m g, 3.78 mmol, Strem Chemical Inc, Newburyport, MA) and toluene (10 mL). The mixture was degassed by bubbling Ar gas through the solution for 10 min. Then the vials were sealed and heated at 100 °C overnight. The reaction mixtures were combined and water (100 mL) was added. The aqueous phase was extracted with EtOAc (3 x 100 mL) and the combined organic phases were washed with saturated aqueous sodium chloride (150 mL). The organic extracts were dried over sodium sulfate, filtered and concentrated under a vacuum. The resulting product was purified by silica gel column chromatography (0 to 100% EtOAc in hexanes) to afford benzyl 3-(2-methyl-1-propen-1-yl)-4-(4-(2,2,2-trifluoro-1-

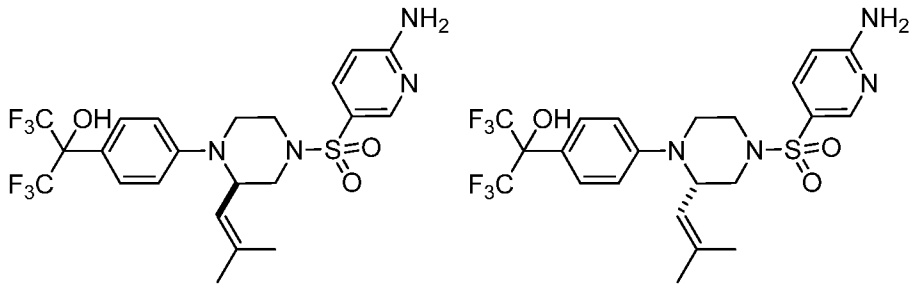
hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinecarboxylate (350 mg) as a yellow solid.

STEP 4: 2-(4-(4-((6-Chloro-3-pyridinyl)sulfonyl)-2-(2-methyl-1-propen-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol

A 50-mL round-bottomed flask was charged with benzyl 3-(2-methyl-1-propen-1-yl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinecarboxylate (350 mg, 0.678 mmol) and TFA (5 mL). Trifluoromethanesulfonic acid (0.2 ml, 2.252 mmol) was added dropwise at room temperature. After 10 min, solid $NaHCO_3$ was carefully added in portions. Saturated aqueous $NaHCO_3$ (250 mL) was added slowly to bring the pH to approximately 7. The aqueous phase was extracted with EtOAc (100 mL). At this time, more solid $NaHCO_3$ was added to the aqueous phase and extracted again with EtOAc (100 mL). The combined organic phases were washed with water (200 mL) and saturated aqueous sodium chloride (200 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under a vacuum to a solid that was used in the next reaction. A 50-mL round-bottomed flask was charged with this material, triethylamine (0.946 ml, 6.80 mmol) and CH_2Cl_2 (5 mL). 6-Chloropyridine-3-sulfonyl chloride (159 mg, 0.748 mmol, *Organic Process Research & Development* **2009**, *13*, 875) was added at room temperature. The reaction was diluted with water (100 mL) and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with water (100 mL) and saturated aqueous sodium chloride (100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under a vacuum to afford 2-(4-(4-((6-chloro-3-pyridinyl)sulfonyl)-2-(2-methyl-1-propen-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (380 mg).

Step 5: 2-(4-(4-((6-Amino-3-pyridinyl)sulfonyl)-2-(2-methyl-1-propen-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propano

A sealable tube was charged with 2-(4-(4-((6-chloro-3-pyridinyl)sulfonyl)-2-(2-methyl-1-propen-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (340 mg, 0.609 mmol), concentrated ammonium hydroxide (10 ml, 154 mmol) and EtOH (10 mL). The reaction mixture was heated at 110 °C overnight. The reaction was diluted with water (100 mL) and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with water (100 mL) and saturated aqueous sodium chloride (100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under a vacuum to a solid that was purified by silica gel column chromatography (0 to 15 % (2M NH_3 in MeOH) in DCM) and reverse-phase preparative HPLC using a Gemini 30 X 150 mm, 0.1% TFA in CH_3CN/H_2O, gradient 10% to 100% over 15 min) to afford 2-(4-(4-((6-amino-3-pyridinyl)sulfonyl)-2-(2-methyl-1-propen-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propano (10 mg) as a mixture of two enantiomers.

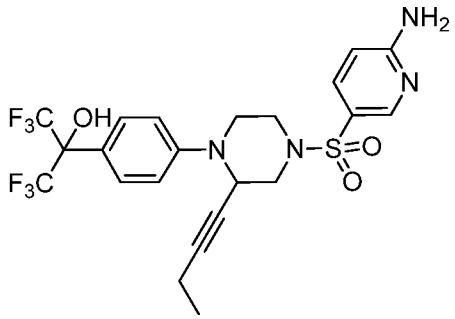


2-(4-((2R)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(2-methyl-1-propen-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol; 2-(4-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(2-methyl-1-propen-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol.

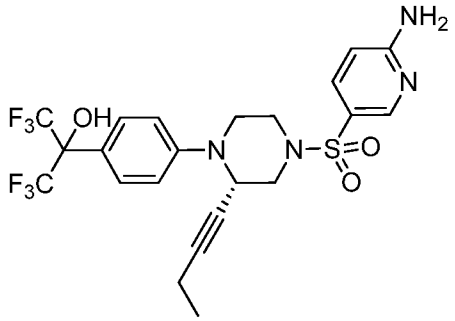
^{1}H NMR (400MHz, MeOD) δ ppm 8.42 - 8.16 (m, 1 H), 7.85 - 7.60 (m, 1 H), 7.53 (d, J = 8.6 Hz, 2 H), 6.97 (d, J = 8.8 Hz, 2 H), 6.65 (d, J = 8.8 Hz, 1 H), 5.31 (d, J = 8.8 Hz, 1 H), 4.58 - 4.41 (m, 1 H), 3.55 - 3.45 (m, 1 H), 3.42 - 3.37 (m, 2 H), 3.27 - 3.19 (m, 1 H), 3.04 - 2.95 (m, 1 H), 2.94 - 2.82 (m, 1 H), 1.66 (s, 3 H),

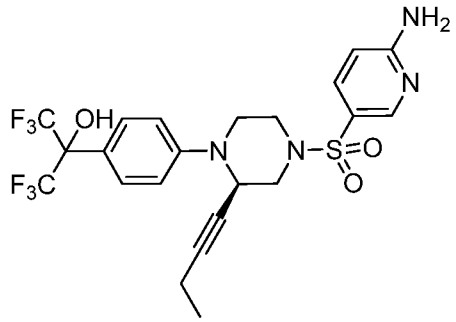
1.64 (s, 3 H). m/z (ESI, +ve ion) 539.0 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.05 μM.

EXAMPLE 25: 2-(4-(4-((6-Amino-3-pyridinyl)sulfonyl)-2-(1-butyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol



Prepared via the method described for Example 24 substituting bromo(1-butyn-1-yl)magnesium, generated from 1-butyne and ^{i}PrMgCl in place of prop-1-yn-1-ylmagnesium chloride. The compound was isolated as a mixture of two enantiomers.

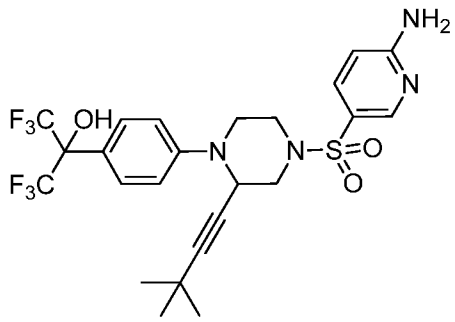




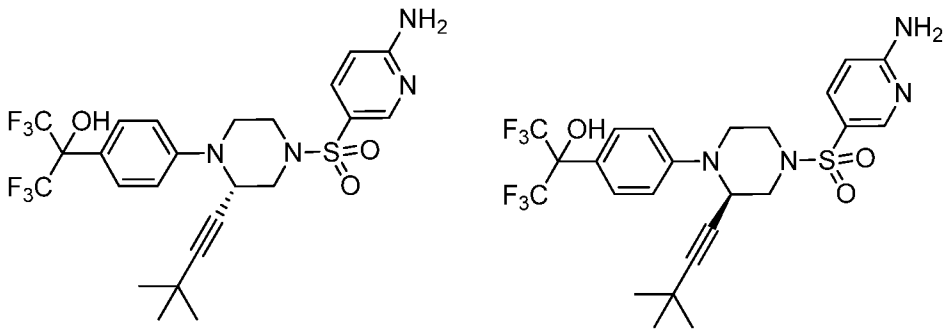
2-(4-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-butyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol and 2-(4-((2R)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-butyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol.

^{1}H NMR (400 MHz, MeOD) δ ppm 8.31 (d, J = 2.3 Hz, 1 H), 7.74 (dd, J = 2.4, 8.9 Hz, 1 H), 7.57 (d, J = 8.8 Hz, 2 H), 7.04 (d, J = 9.2 Hz, 2 H), 6.63 (d, J = 8.4 Hz, 1 H), 4.76 - 4.57 (m, 1 H), 3.82 - 3.68 (m, 2 H), 3.57 - 3.44 (m, 1 H), 3.29 - 3.20 (m, 1 H), 2.85 - 2.73 (m, 1 H), 2.68 - 2.45 (m, 1 H), 2.14 (dd, J = 1.9, 7.5 Hz, 2 H), 1.04 (t, J = 7.5 Hz, 3 H). m/z (ESI, +ve ion) 537.2 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.061 μM.

EXAMPLE 26: 2-(4-(4-((6-Amino-3-pyridinyl)sulfonyl)-2-(3,3-dimethyl-1-butyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol



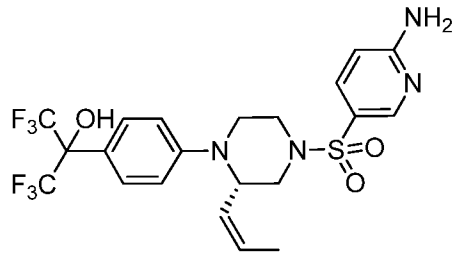
Prepared via the method described for Example 24 substituting bromo(3,3-dimethyl-1-butyn-1-yl)magnesium, generated from 3,3-dimethyl-1-butyne (Sigma-Aldrich, St. Louis, MO) and ^{i}PrMgCl (Sigma-Aldrich, St. Louis, MO), in place of prop-1-yn-1-ylmagnesium chloride. The compound was isolated as a mixtue of two enantiomers.



2-(4-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(3,3-dimethyl-1-butyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol and 2-(4-((2R)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(3,3-dimethyl-1-butyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol.

^{1}H NMR (400 MHz, MeOD) δ ppm 8.32 (d, J = 2.0 Hz, 1 H), 7.74 (dd, J = 2.4, 8.9 Hz, 1 H), 7.58 (d, J = 8.8 Hz, 2 H), 7.05 (d, J = 9.0 Hz, 2 H), 6.63 (d, J = 9.0 Hz, 1 H), 4.68 - 4.58 (m, 1 H), 3.70 (d, J = 11.2 Hz, 2 H), 3.46 (d, J = 12.1 Hz, 1 H), 3.28 - 3.22 (m, 1 H), 2.80 (dd, J = 3.3, 11.3 Hz, 1 H), 2.70 - 2.50 (m, 1 H), 1.11 (s, 9 H). m/z (ESI, +ve ion) 565.1 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 1.474 μM.

EXAMPLE 27: 2-(4-((2S)-4-((6-Amino-3-pyridinyl)sulfonyl)-2-((1Z)-1-propen-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol

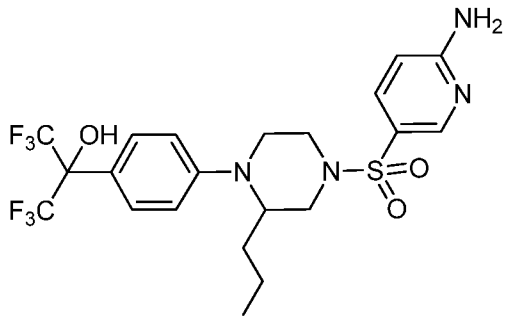


To a degassed solution of 2-(4-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (200 mg, 0.383 mmol, Intermediate P) and quinoline (0.045 mL, 0.383 mmol, Alfa-Aesar, Ward Hill, MA) in EtOH (50 ml) under argon at rt was added palladium hydroxide (53.8 mg, 0.077 mmol, Sigma-Aldrich, St. Louis, MO). The reaction was evacuated and flushed with hydrogen three times before stirring under a balloon of hydrogen for 1h. After that time, the reaction was filtered through a pad of diatomaceous earth, washing with EtOH and the filtrate was concentrated. The resulting product was purified via column chromatography on silica gel (0 to 100% EtOAc in hexanes) to give 2-(4-((2S)-4-((6-amino-3-

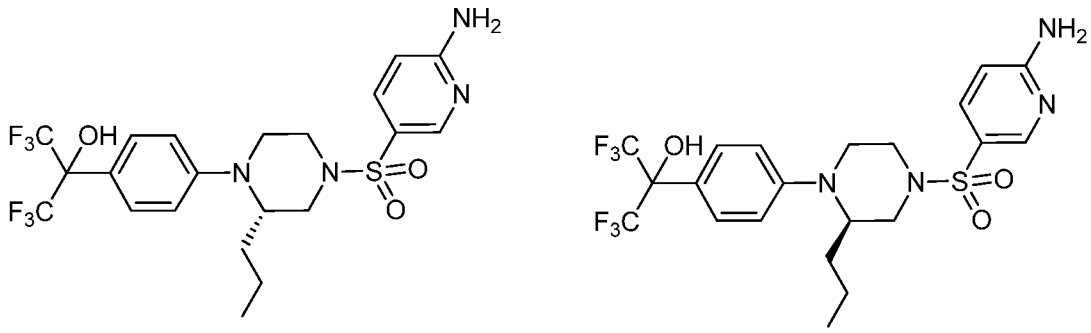
pyridinyl)sulfonyl)-2-((1Z)-1-propen-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (75 mg).

^{1}H NMR (400 MHz, MeOD) δ ppm 8.37 - 8.20 (m, 1 H), 7.74 (dd, *J* = 2.4, 8.9 Hz, 1 H), 7.54 (d, *J* = 8.8 Hz, 2 H), 7.00 (d, *J* = 9.0 Hz, 2 H), 6.65 (d, *J* = 9.0 Hz, 1 H), 5.73 - 5.46 (m, 2 H), 4.70 - 4.52 (m, 1 H), 3.57 - 3.47 (m, 1 H), 3.41 - 3.36 (m, 2 H), 3.30 - 3.24 (m, 1 H), 3.08 - 2.93 (m, 1 H), 2.93 - 2.76 (m, 1 H), 1.64 (d, *J* = 5.7 Hz, 3 H). m/z (ESI, +ve ion) 525.0 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.095 μM.

EXAMPLE 28: 2-(4-(4-((6-Amino-3-pyridinyl)sulfonyl)-2-propyl-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol



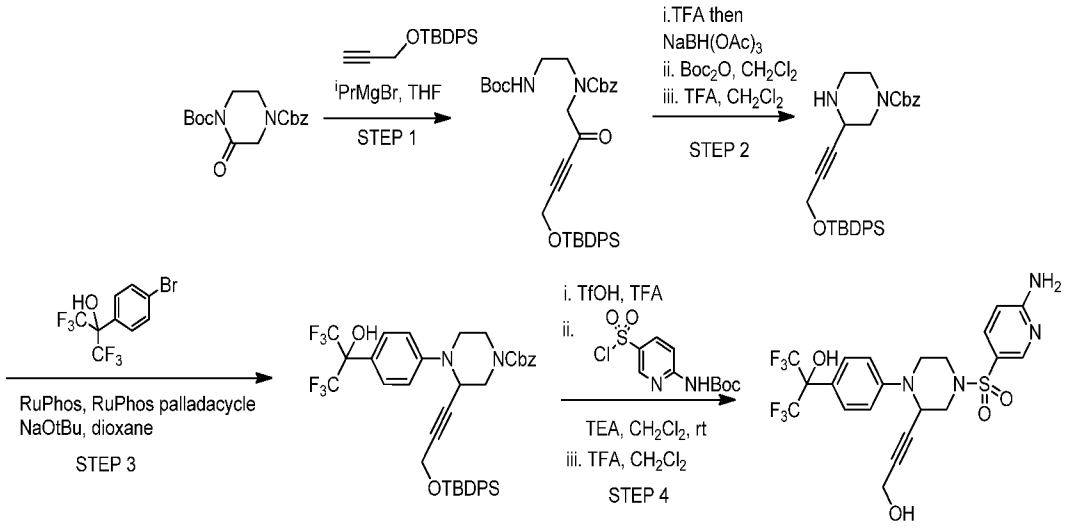
A mixture of 2-(4-(4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (65 mg, 0.124 mmol, Intermediate P) and Pd/C (26.5 mg, 0.025 mmol, Sigma-Aldrich, St. Louis, MO) in EtOH was subjected to H_2 pressure (50 atm; 5066.25 kPa) using a H_2 pressure apparatus for 6 h. Afterwards, the mixture was filtered through a pad of diatomaceous earth, and the filtrate was concentrated. The resulting material was purified by reverse-phase preparative HPLC using a Gemini 30 x 150 mm, 0.1% TFA in CH_3CN/H_2O, gradient 40% to 60% over 15 min. The dried material was then filtered through a carbonate silica plug to provide 2-(4-(4-((6-amino-3-pyridinyl)sulfonyl)-2-propyl-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (13 mg) as a mixture of two enantiomers.



2-(4-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-propyl-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol and 2-(4-((2R)-4-((6-amino-3-pyridinyl)sulfonyl)-2-propyl-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol.

^{1}H NMR (400 MHz, MeOD) δ ppm 8.32 (d, J = 2.0 Hz, 1 H), 7.96 (dd, J = 2.2, 9.3 Hz, 1 H), 7.53 (d, J = 8.6 Hz, 2 H), 6.92 (dd, J = 3.3, 9.2 Hz, 3 H), 4.04 - 3.91 (m, 1 H), 3.80 - 3.65 (m, 2 H), 3.57 - 3.52 (m, 1 H), 3.29 - 3.18 (m, 1 H), 2.76 - 2.69 (m, 1 H), 2.68 - 2.50 (m, 1 H), 1.85 - 1.72 (m, 1 H), 1.48 - 1.22 (m, 3 H), 0.91 (t, J = 7.2 Hz, 3 H). m/z (ESI, +ve ion) 527.2 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.11 μM.

EXAMPLE 29: 3-(4-((6-Amino-3-pyridinyl)sulfonyl)-1-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-2-piperazinyl)-2-propyn-1-ol



STEP 1: Benzyl (2-((tert-butoxycarbonyl)amino)ethyl)(5-((tert-butyl(diphenyl)silyl)oxy)-2-oxo-3-pentyn-1-yl)carbamate

A 150-mL round-bottomed flask was charged with THF (50 mL) and 1-propynylmagnesium bromide (2.0 M in Et_2O, 31.9 mL, 63.8 mmol, Sigma-Aldrich, St. Louis, MO) and cooled to 0 °C. Tert-butyl(diphenyl)(2-propyn-1-yloxy)silane (18.8 g, 63.8 mmol, *J. Org. Chem.*, **2003**, *68(22)* , 8471) was added as a solution in THF (50 mL) and the reaction stirred at this temp for 20 min. After this time 4-benzyl 1-tert-butyl 2-oxo-1,4-piperazinedicarboxylate (20.3 g, 60.8 mmol, Intermediate K) was added portionwise and the mixture was stirred at 0 °C for 1 h. Saturated aqueous NH_4Cl (40 mL) was added and the aqueous phase was extracted with EtOAc (200 mL, then 2 x 100 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under a vacuum. The product was used in the next step.

STEP 2: Benzyl 3-(3-((tert-butyl(diphenyl)silyl)oxy)-1-propyn-1-yl)-1-piperazinecarboxylate

A 500-mL round-bottomed flask was charged with benzyl (2-((tert-butoxycarbonyl)amino)ethyl)(5-((tert-butyl(diphenyl)silyl)oxy)-2-oxo-3-pentyn-1-yl)carbamate (38.2 g, 60.8 mmol) and 50 mL of CH_2Cl_2. After cooling to 0 °C, TFA (50 mL, 260 mmol) was added and the resulting dark solution was stirred at room temperature for 15 min. Sodium triacetoxyborohydride (51.5 g, 243 mmol, Sigma-Aldrich, St. Louis, MO) was then added portionwise over 10 min. After 1h, the mixture was diluted with EtOAc (300 mL), and neutralized with 10 N NaOH. The layers were separated and the organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. The resulting orange oil was purified via column chromatography (330 g of silica gel, 0 to 10% (2M NH_3 in MeOH) in CH_2Cl_2) to give benzyl benzyl 3-(3-((tert-butyl(diphenyl)silyl)oxy)-1-propyn-1-yl)-1-piperazinecarboxylate (12.6 g) as a brown oil. This material was taken up in CH_2Cl_2 (100 mL) and di-tert-butyl dicarbonate (6.20 mL, 27.0 mmol), triethylamine (10.25 ml, 73.7 mmol) and DMAP (0.300 g, 2.458 mmol) added. After 1h saturated aqueous NH_4Cl (40 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (200 mL, then 2 x 100 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under a vacuum. The residue was purified via column chromatography on silica gel (0 to 100% EtOAc in hexanes) to yield 4-benzyl 1-tert-butyl 2-(3-((tert-butyl(diphenyl)silyl)oxy)-1-propyn-1-yl)-1,4-piperazinedicarboxylate (2.5 g) as a clear oil. This material was dissolved in CH_2Cl_2 (20 mL) and TFA (10 mL, 135 mmol). After 20 minutes, the reaction was quenched with the addition of solid sodium bicarbonate and diluted with CH_2Cl_2 (300 mL) and water (300 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under a vacuum. The benzyl 3-(3-((tert-butyl(diphenyl)silyl)oxy)-1-propyn-1-yl)-1-piperazinecarboxylate obtained was used directly in the next step.

STEP 3: Benzyl 3-(3-((tert-butyl(diphenyl)silyl)oxy)-1-propyn-1-yl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinecarboxylate

A 75-mL reaction vessel was charged with benzyl 3-(3-((tert-butyl(diphenyl)silyl)oxy)-1-propyn-1-yl)-1-piperazinecarboxylate (1.7 g, 3.3 mmol), 2-(4-bromophenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (1.18 g, 3.65 mmol, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3009), RuPhos (0.08 g, 0.17 mmol, Strem Chemical Inc, Newburyport, MA), RuPhos Palladacycle (0.135 g, 0.17 mmol, Strem Chemical Inc, Newburyport, MA), sodium tert-butoxide (0.95g, 9.95 mmol, Sigma-Aldrich, St. Louis, MO) and dioxane (10 mL). The vessel was sealed and heated at 100 °C for 1.5 h. The reaction mixture was partitioned between water (200 mL) and EtOAc (200 mL). The aqueous phase was extracted with EtOAc (2 x 100 mL) and the combined organic phases were washed with saturated aqueous sodium chloride (150 mL). The organic extract was dried over sodium sulfate, filtered and concentrated under a vacuum. The resulting product was purified by silica gel column chromatography (0 to 50% EtOAc in hexanes) to afford benzyl 3-(3-((tert-butyl(diphenyl)silyl)oxy)-1-propyn-1-yl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinecarboxylate (1.07 g) as a clear oil.

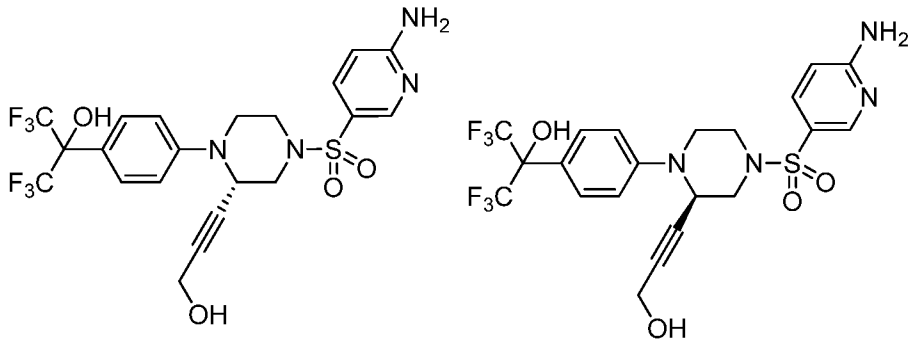
STEP 4: 3-(4-((6-Amino-3-pyridinyl)sulfonyl)-1-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-2-piperazinyl)-2-propyn-1-ol

A 100-mL round-bottomed flask was charged with benzyl 3-(3-((tert-butyl(diphenyl)silyl)oxy)-1-propyn-1-yl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinecarboxylate (1.19 g, 1.58 mmol) and TFA (5 mL, 7.4 mmol). Trifluoromethanesulfonic acid (0.15 mL, 1.6 mmol, Sigma-Aldrich, St. Louis, MO) was added dropwise at room temperature. A precipitate formed and after 10 min, solid $NaHCO_3$ was carefully added in portions. Saturated aqueous $NaHCO_3$ (250 mL) was added slowly to bring the pH to approximately 7. The aqueous phase was extracted with EtOAc (3 x 100 mL) and the combined organic phases were washed with water (200 mL) and saturated aqueous sodium chloride (200 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under a vacuum to

afford a brown solid. A 100-mL round-bottomed flask was charged with this material, triethylamine (1.1 mL, 7.9 mmol) and CH_2Cl_2 (20 mL). Tert-butyl (5-(chlorosulfonyl)-2-pyridinyl)carbamate (0.51 g, 1.73 mmol, Intermediate B) was added in portions at 0 °C. After 10 min, the volume of the reaction mixture was reduced to approximately 10 mL under a vacuum then the mixture was purified by silica gel column chromatography (0 to 100% EtOAc in hexanes) to afford tert-butyl (5-((3-(3-hydroxy-1-propyn-1-yl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinyl)sulfonyl)-2-pyridinyl)carbamate (0.58 g). This material was taken up in CH_2Cl_2 (10 mL) and TFA (5 mL, 67.3 mmol) added. After 20 minutes, the reaction was quenched with the addition of solid sodium bicarbonate and diluted with CH_2Cl_2 (300 mL) and water (300 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under a vacuum, purified by silica gel column chromatography (0 to 8% MeOH in CH_2Cl_2) to afford 3-(4-((6-amino-3-pyridinyl)sulfonyl)-1-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-2-piperazinyl)-2-propyn-1-ol (0.36 g) as a mixture of two enantiomers.

^{1}H NMR (400 MHz , MeOD) δ ppm 8.32 (d, J = 2.0 Hz, 1 H), 7.75 (dd, J = 2.5, 9.0 Hz, 1 H), 7.57 (d, J = 8.8 Hz, 2 H), 7.05 (d, J = 9.2 Hz, 2 H), 6.63 (dd, J = 0.4, 9.0 Hz, 1 H), 4.81 - 4.76 (m, 1 H), 4.16 (d, J = 1.6 Hz, 2 H), 3.84 - 3.70 (m, 2 H), 3.60 - 3.52 (m, 1 H), 3.34 - 3.26 (m, 1 H), 2.78 (dd, J = 3.3, 11.3 Hz, 1 H), 2.59 (dt, J = 3.3, 11.4 Hz, 1 H). m/z (ESI, +ve ion) 539.2 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.14 μM.

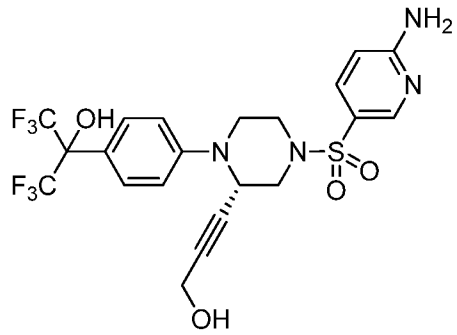
This mixture was separated using preparative SFC (Chiralpak® AD-H column (21 x 250 mm, 5 μm) eluting with 70% liquid CO_2 in 30% methanol with 20 mM ammonia at a flow rate of 60 mL/min) to give two products in greater than 99% enantiomeric excess.



3-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-1-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-2-piperazinyl)-2-propyn-1-ol and 3-((2R)-4-((6-amino-3-pyridinyl)sulfonyl)-1-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-2-piperazinyl)-2-propyn-1-ol.

FIRST ELUTING PEAK (PEAK #1)

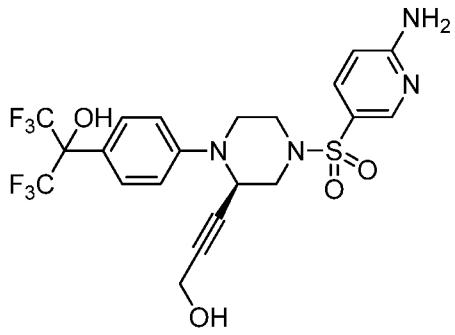
3-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-1-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-2-piperazinyl)-2-propyn-1-ol



^{1}H NMR (400 MHz , MeOD) δ ppm 8.32 (br. s., 1 H), 7.79 (d, *J* = 8.6 Hz, 1 H), 7.57 (d, *J* = 8.2 Hz, 2 H), 7.06 (d, *J* = 8.0 Hz, 2 H), 6.67 (d, *J* = 9.0 Hz, 1 H), 4.85 - 4.74 (m, 1 H), 4.16 (br. s., 2 H), 3.88 - 3.70 (m, 2 H), 3.63 - 3.52 (m, 1 H), 3.36 - 3.33 (m, 1 H), 2.88 - 2.69 (m, 1 H), 2.66 - 2.44 (m, 1 H). m/z (ESI, +ve ion) 539.0 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.006 μM.

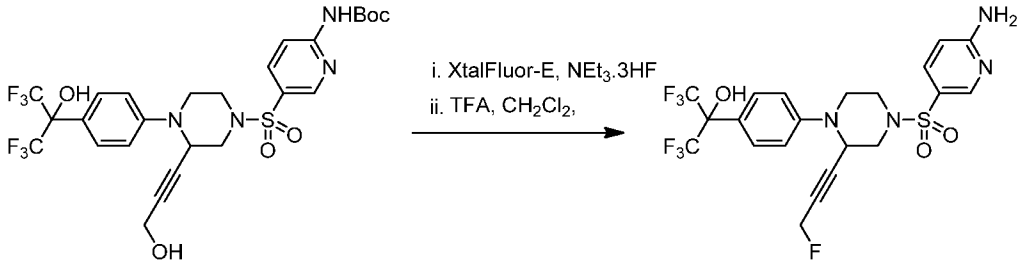
SECOND ELUTING PEAK (PEAK #2)

3-((2R)-4-((6-amino-3-pyridinyl)sulfonyl)-1-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-2-piperazinyl)-2-propyn-1-ol



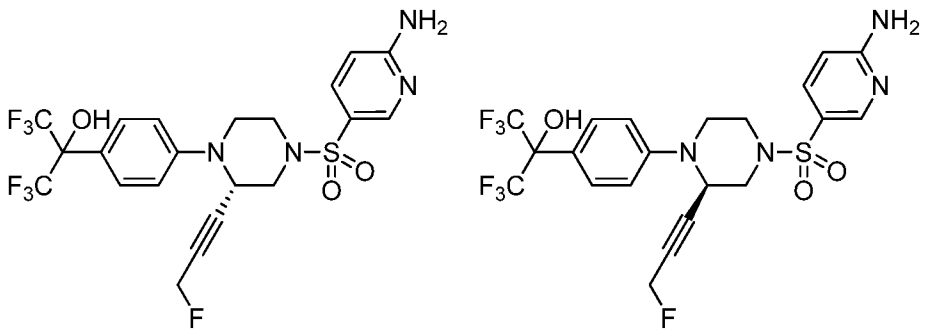
^{1}H NMR (400 MHz, MeOD) δ ppm 8.31 (d, J = 2.2 Hz, 1 H), 7.75 (dd, J = 2.4, 8.9 Hz, 1 H), 7.57 (d, J = 8.6 Hz, 2 H), 7.05 (d, J = 9.2 Hz, 2 H), 6.63 (d, J = 8.8 Hz, 1 H), 4.82 - 4.78 (m, 1 H), 4.16 (d, J = 1.4 Hz, 2 H), 3.84 - 3.70 (m, 2 H), 3.60 - 3.52 (m, 1 H), 3.34 - 3.25 (m, 1 H), 2.78 (dd, J = 3.3, 11.2 Hz, 1 H), 2.59 (dt, J = 3.2, 11.5 Hz, 1 H). m/z (ESI, +ve ion) 539.2 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 2.3 μM.

EXAMPLE 30: 2-(4-(4-((6-Amino-3-pyridinyl)sulfonyl)-2-(3-fluoro-1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol



A 50 mL round-bottomed flask was charged with XtalFluor-E (35.9 mg, 0.157 mmol, Sigma-Aldrich, St. Louis, MO), triethylamine trihydrofluoride (25.5 mg, 0.157 mmol, Sigma-Aldrich, St. Louis, MO) and CH_2Cl_2 (10 mL). A CH_2Cl_2

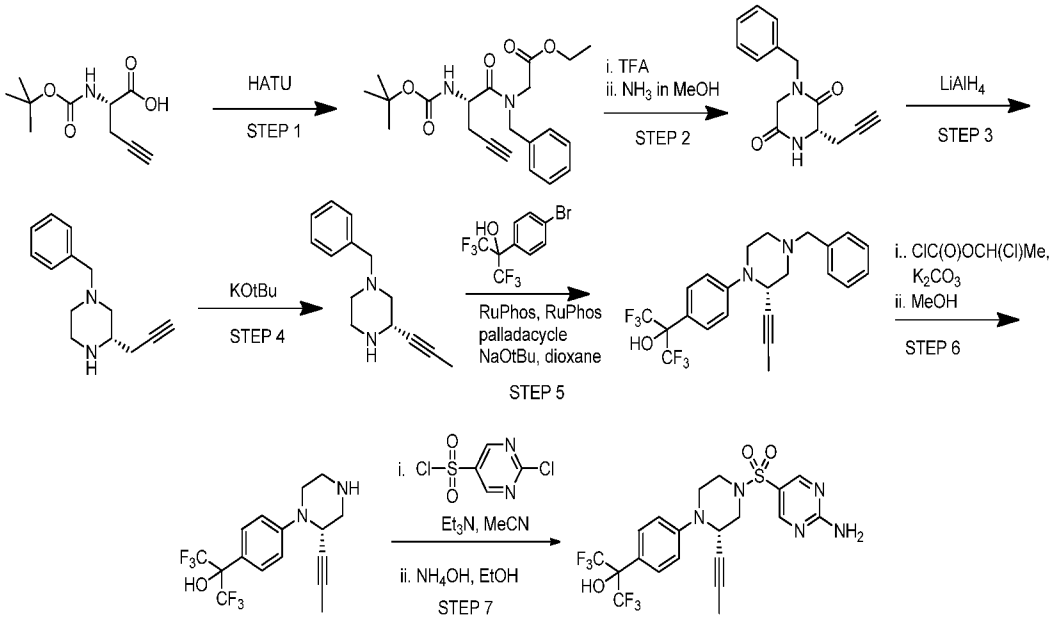
solution of tert-butyl (5-((3-(3-hydroxy-1-propyn-1-yl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinyl)sulfonyl)-2-pyridinyl)carbamate (50 mg, 0.078 mmol, Example 29, Step 4) was added to the mixture and the reaction was stirred at rt for 4 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was concentrated. The resulting protected intermediate was dissolved in 2:1 DCM-TFA solution (20 mL) and was stirrred at rt for 3 h. The mixture was concentrated and the material was purified by preparatory thin layer chromatography using 40% EtOAc-hexanes eluent. Isolation of major band provided 2-(4-(4-((6-amino-3-pyridinyl)sulfonyl)-2-(3-fluoro-1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol as a white foam that was a mixture of two enantiomers.



2-(4-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(3-fluoro-1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol and 2-(4-((2R)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(3-fluoro-1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol.

^{1}H NMR (400 MHz, MeOD) δ ppm 8.32 (d, J = 2.0 Hz, 1 H), 7.75 (dd, J = 2.4, 8.9 Hz, 1 H), 7.58 (d, J = 8.6 Hz, 2 H), 7.06 (d, J = 9.2 Hz, 2 H), 6.63 (d, J = 9.0 Hz, 1 H), 5.01 (d, J = 1.4 Hz, 1 H), 4.89 (d, J = 1.2 Hz, 1 H), 3.88 - 3.80 (m, 1 H), 3.79 - 3.71 (m, 1 H), 3.64 - 3.53 (m, 1 H), 3.30 - 3.16 (m, 2 H), 2.81 (dd, J = 3.3, 11.5 Hz, 1 H), 2.61 (dt, J = 3.2, 11.5 Hz, 1 H). m/z (ESI, +ve ion) 541.0 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.006 μM.

EXAMPLE 31: 2-(4-((2S)-4-((2-Amino-5-pyrimidinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol



STEP 1: Ethyl N-benzyl-N-((2S)-2-((tert-butoxycarbonyl)amino)-4-pentynoyl)glycinate

To a solution of (2S)-2-((tert-butoxycarbonyl)amino)-4-pentynoic acid (21.55 g, 101 mmol, Hangzhou Trylead Chemical Technology Co., Ltd., Hangzhou, China), ethyl N-benzylglycinate (19.53 mL, 101 mmol, Sigma-Aldrich, St. Louis, MO) and HATU (46.1 g, 121 mmol, Oakwood, West Columbia, SC) in DMF (75 ml) at rt was added triethylamine (28.1 mL, 202 mmol). After 10 min, 500 mL of 20% EtOAc in ether was added and the combined organic phases was washed with water (2 x 400 mL) and saturated aqueous $NaHCO_3$ (500 mL), dried over sodium sulfate, filtered and concentrated under a vacuum.

STEP 2: (3S)-1-Benzyl-3-(2-propyn-1-yl)-2,5-piperazinedione

A solution of ethyl N-benzyl-N-((2S)-2-((tert-butoxycarbonyl)amino)-4-pentynoyl)glycinate (38.4 g, 99 mmol) in CH_2Cl_2 (60 mL)/TFA (60 mL, 808 mmol) was stirred at rt for 30 min then concentrated and azeotroped with toluene (x 2). The resultant residue was dissolved in ammonia (2 M solution in methanol, 500 mL, 1000 mmol) and stirred at rt for 10 min. The reaction mixture was then concentrated and the resultant oil was dissolved in EtOAc and washed with water. The organic phase was dried over sodium sulfate, filtered and concentrated under a vacuum to give a solid that was used in the next reaction. This solid can be recrystallised from water.

STEP 3: (3S)-1-Benzyl-3-(2-propyn-1-yl)piperazine

To a solution of (3S)-1-benzyl-3-(2-propyn-1-yl)-2,5-piperazinedione (2.4 g, 7.94 mmol) in THF (10 mL) at rt was added lithium aluminum hydride (1M in THF, 31.8 mL, 31.8 mmol, Sigma-Aldrich, St. Louis, MO). After gas evolution ceased, the reaction was heated at 65 °C for 12 h. The reaction was allowed to cool to rt. Solid sodium sulfate decahydrate was carefully added until bubbling had ceased. The resulting white suspension was diluted with EtOAc and stirred at rt for 45 min and then filtered and the filtrate was concentrated. The resultant solid was used in the next reaction.

STEP 4: (3S)-1-Benzyl-3-(1-propyn-1-yl)piperazine

To a solution of (3S)-1-benzyl-3-(2-propyn-1-yl)piperazine (2.3 g, 10.7 mmol) in THF (50 mL) was added potassium t-butoxide (2.41 g, 21.5 mmol, Sigma-Aldrich, St. Louis, MO). The reaction was stirred at rt for 30 min and then quenched with water (200 mL) and EtOAc (300 mL) was added. The organic phase was dried over sodium sulfate, filtered and concentrated under a vacuum to give a solid that was purified by silica gel column chromatography (0 to 10%

MeOH in CH_2Cl_2) and then recrystallised from hexanes to afford (3S)-1-benzyl-3-(1-propyn-1-yl)piperazine (2.16 g) as an off-white solid.

STEP 5: 2-(4-((2S)-4-Benzyl-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol

A 20-mL vial was charged with (3S)-1-benzyl-3-(1-propyn-1-yl)piperazine (2.143 g, 10 mmol), 2-(4-bromophenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (3.09 g, 11.50 mmol, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3009), sodium 2-methylpropan-2-olate (1.922 g, 20.00 mmol, Sigma-Aldrich, St. Louis, MO), dioxane (5 mL), RuPhos Palladacycle (0.364 g, 0.500 mmol, Strem Chemical Inc., Newburyport, MA), and RuPhos (0.233 g, 0.500 mmol, Strem Chemical Inc., Newburyport, MA). The vial was sealed and heated at 80 °C for 12 h. The mixture was allowed to cool to rt and diluted with water and extracted with EtOAc. The combined organic phases were dried over sodium sulfate, filtered and concentrated under a vacuum to give a solid that was purified by silica gel column chromatography (0 to 40% EtOAc in hexanes) to afford 2-(4-((2S)-4-benzyl-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (1.75 g) as a slightly yellow oil.

STEP 6: 1,1,1,3,3,3-Hexafluoro-2-(4-((2S)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-2-propanol

A 250-mL round-bottomed flask was charged with 2-(4-((2S)-4-benzyl-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (1.75 g, 4.35 mmol), potassium carbonate (2.40 g, 17.4 mmol, Sigma-Aldrich, St. Louis, MO), CH_2Cl_2 (25 mL), and 1-chloroethyl chlorocarbonate (1.88 mL, 17.4 mmol, Sigma-Aldrich, St. Louis, MO). After 30 min at rt, the reaction was filtered and the filtrate was concentrated. To this oil was added MeOH (25 mL). This mixture was heated at 75 °C for 1.5 h then concentrated and slurried with ether,

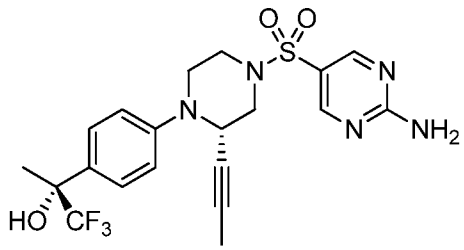
collected by filtration and dried to give 1,1,1,3,3,3-hexafluoro-2-(4-((2S)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-2-propanol (1.44 g) as a white solid.

STEP 7: 2-(4-((2S)-4-((2-Amino-5-pyrimidinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol

A 250-mL round-bottomed flask was charged with 1,1,1,3,3,3-hexafluoro-2-(4-((2S)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-2-propanol (0.70 g, 1.91 mmol), MeCN (20 mL), and TEA (0.52 mL, 3.82 mmol). To this was added 2-chloro-5-pyrimidinesulfonyl chloride (0.43 g, 2.00 mmol, Beta Pharma Scientific, Branford, CT) at room temperature. After 25 min, the reaction was concentrated under a vacuum and then dissolved in EtOH (10 mL) and conc. aqueous NH_4OH (10 mL). This mixture was stirred for 1 h at room temperature and then the EtOH was removed and the residue was partitioned between EtOAc and water. The organics were separated, dried ($MgSO_4$), filtered and concentrated. The resultant residue was then purified by silica gel column chromatography (0 to 60% EtOAc in hexanes) to afford 2-(4-((2S)-4-((2-amino-5-pyrimidinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (0.17 g).

^{1}H NMR (400 MHz, MeOD) δ ppm 8.60 (s, 2 H), 7.59 (d, J = 8.6 Hz, 2 H), 7.06 (d, J = 9.0 Hz, 2 H), 4.70 (br. s., 1 H), 3.94 - 3.70 (m, 2 H), 3.56 (d, J = 12.1 Hz, 1 H), 3.31 - 3.22 (m, 1 H), 2.89 (dd, J = 3.3, 11.5 Hz, 1 H), 2.72 (dt, J = 3.2, 11.7 Hz, 1 H), 1.77 (d, J = 2.2 Hz, 3 H); m/z (ESI, +ve ion) 524.0 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.013 μM.

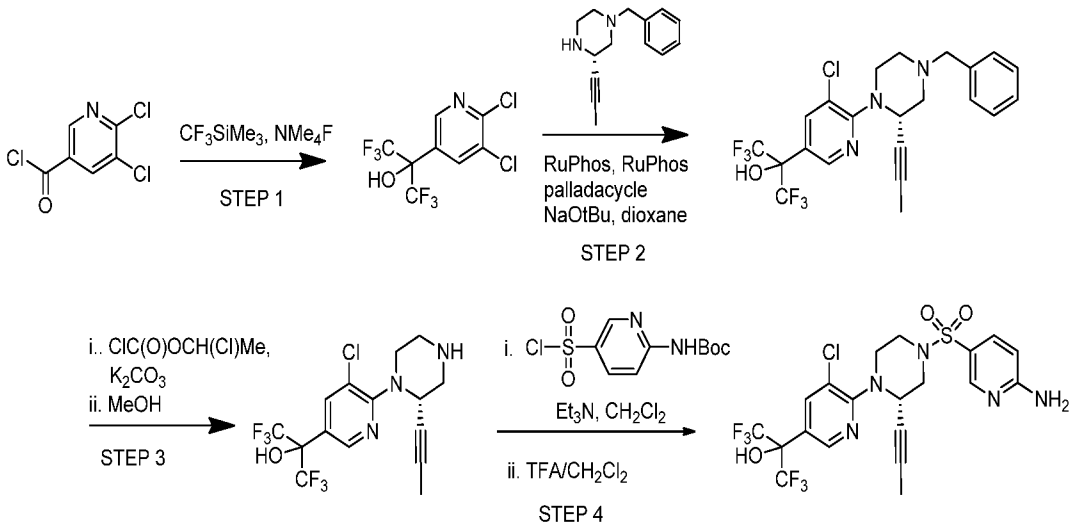
Example 32: (2R)-2-(4-((2S)-4-((2-Amino-5-pyrimidinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1-trifluoro-2-propanol



Synthesized according to the procedure reported for Example 31 substituting (2R)-2-(4-bromophenyl)-1,1,1-trifluoro-2-propanol (Intermediate N) for 2-(4-bromophenyl)-1,1,1,3,3,3-hexafluoro-2-propanol.

^{1}H NMR (400 MHz, MeOD) δ ppm 8.60 (s, 2 H), 7.48 (d, J = 8.8 Hz, 2 H), 7.00 (d, J = 9.0 Hz, 2 H), 4.64 (br. s., 1 H), 3.94 - 3.66 (m, 2 H), 3.47 (d, J = 12.1 Hz, 1 H), 3.27 (dt, J = 3.0, 11.8 Hz, 1 H), 2.90 (dd, J = 3.1, 11.5 Hz, 1 H), 2.72 (dt, J = 3.3, 11.5 Hz, 1 H), 1.76 (d, J = 2.0 Hz, 3 H), 1.70 (s, 3 H); m/z (ESI, +ve ion) 470.0 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.078 μM.

EXAMPLE 33: 2-(6-((2S)-4-((6-Amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-5-chloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol



STEP 1: 2-(5,6-Dichloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol

To a cooled suspension of 5,6-dichloro-3-pyridinecarbonyl chloride (2.08 g, 9.88 mmol, *Bioorg. Med. Chem. Lett.*, **2011**, *21(10)*, 2958) and tetramethylammonium fluoride (2.025 g, 21.74 mmol, Sigma-Aldrich, St. Louis, MO) in DME (50 ml) at -78 °C was added (trifluoromethyl)trimethylsilane (3.21 ml, 21.74 mmol, Oakwood Products, West Columbia, SC) and the reaction was warmed to rt overnight. The reaction mixture was diluted with 1N HCl (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under a vacuum to give a solid that was purified by silica gel column chromatography (0 to 50% EtOAc in hexanes) to afford 2-(5,6-dichloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (2.3 g).

STEP 2: 2-(6-((2S)-4-Benzyl-2-(1-propyn-1-yl)-1-piperazinyl)-5-chloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol

A solution of (3S)-1-benzyl-3-(1-propyn-1-yl)piperazine (1.465 g, 4.67 mmol, Example 31, Step 4), 2-(5,6-dichloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (1.465 g, 4.67 mmol), RuPhos Palladacycle (0.191 g, 0.233 mmol, Strem Chemical Inc., Newburyport, MA), RuPhos (0.109 g, 0.233 mmol, Strem Chemical Inc., Newburyport, MA) and sodium tert-butoxide (1.34 g, 14.00 mmol, Sigma-Aldrich, St. Louis, MO) in dioxane (10 mL) was heated in a sealed tube at 100 °C for 30 min. The mixture was allowed to cool to rt and the mixture was diluted with water (200 mL) and extracted with EtOAc (3 x 100 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under a vacuum to give a solid that was purified by silica gel column chromatography (0 to 100% EtOAc in hexanes) to afford 2-(6-((2S)-4-benzyl-2-(1-propyn-1-yl)-1-piperazinyl)-5-chloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (0.98 g).

STEP 3: 2-(5-Chloro-6-((2S)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol

To a suspension of 2-(6-((2S)-4-benzyl-2-(1-propyn-1-yl)-1-piperazinyl)-5-chloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (0.98 g, 1.992 mmol) and potassium carbonate (0.551 g, 3.98 mmol, Sigma-Aldrich, St. Louis, MO) in CH_2Cl_2 (20 mL) at rt was added 1-chloroethyl chloroformate (0.645 mL, 5.98 mmol, Sigma-Aldrich, St. Louis, MO). After 30 min, the reaction was filtered, the filtrate was concentrated, and the resultant oil was dissolved in MeOH (20 mL) and stirred at rt for 12 h. The reaction was then concentrated to give 2-(5-chloro-6-((2S)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (0.8 g) as an oil that was used in the next step.

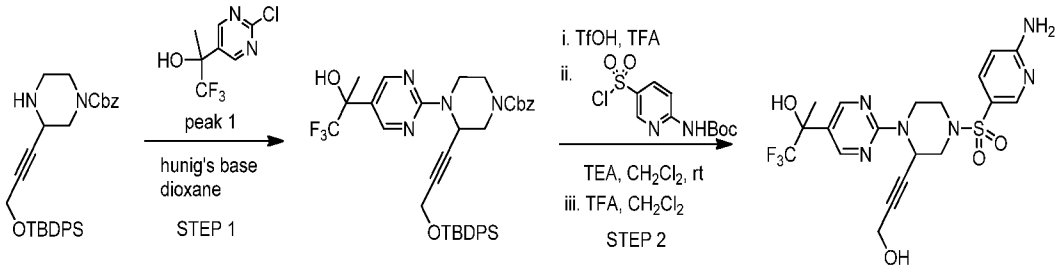
STEP 4: 2-(6-((2S)-4-((6-Amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-5-chloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol

To a solution of 2-(5-chloro-6-((2S)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (0.8 g, 1.991 mmol) and triethylamine (0.831 mL, 5.97 mmol) in CH_2Cl_2 (10 mL) at rt was added tert-butyl (5-(chlorosulfonyl)-2-pyridinyl)carbamate (0.641 g, 2.191 mmol, Intermediate B). After 10 min, the reaction was quenched with the addition of water (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under a vacuum. The resultant material was purified by silica gel column chromatography (0 to 40% EtOAc in hexanes) to afford tert-butyl (5-(((3S)-4-(3-chloro-5-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)-2-pyridinyl)-3-(1-propyn-1-yl)-1-piperazinyl)sulfonyl)-2-pyridinyl)carbamate (0.9 g). A 50-mL round bottomed flask was charged with tert-butyl (5-(((3S)-4-(3-chloro-5-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)-2-pyridinyl)-3-(1-propyn-1-yl)-1-piperazinyl)sulfonyl)-2-pyridinyl)carbamate (40 mg, 0.061 mmol), CH_2Cl_2 (3 mL), and TFA (3 mL). After stirring at rt for 30 min, the mixture was concentrated and purified by silica gel column chromatography (0 to 10% MeOH in CH_2Cl_2) to afford 2-(6-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-

yl)-1-piperazinyl)-5-chloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (10 mg).

^{1}H NMR (400 MHz, MeOD) δ ppm 8.58 - 8.39 (m, 1 H), 8.37 - 8.23 (m, 1 H), 8.05 - 7.80 (m, 2 H), 6.87 (d, J = 9.0 Hz, 1 H), 5.10 - 4.96 (m, 1 H), 3.81 - 3.68 (m, 2 H), 3.66 - 3.56 (m, 2 H), 3.03 - 2.89 (m, 1 H), 2.89 - 2.68 (m, 1 H), 1.83 - 1.63 (m, 3 H). m/z (ESI, +ve ion) 558.0 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.285 μM.

EXAMPLE 34: 3-(4-((6-Amino-3-pyridinyl)sulfonyl)-1-(5-((1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-2-piperazinyl)-2-propyn-1-ol or 3-(4-((6-amino-3-pyridinyl)sulfonyl)-1-(5-((1S)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-2-piperazinyl)-2-propyn-1-ol



STEP 1: Benzyl 3-(3-((tert-butyl(diphenyl)silyl)oxy)-1-propyn-1-yl)-4-(5-((1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-1-piperazinecarboxylate or benzyl 3-(3-((tert-butyl(diphenyl)silyl)oxy)-1-propyn-1-yl)-4-(5-((1S)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-1-piperazinecarboxylate

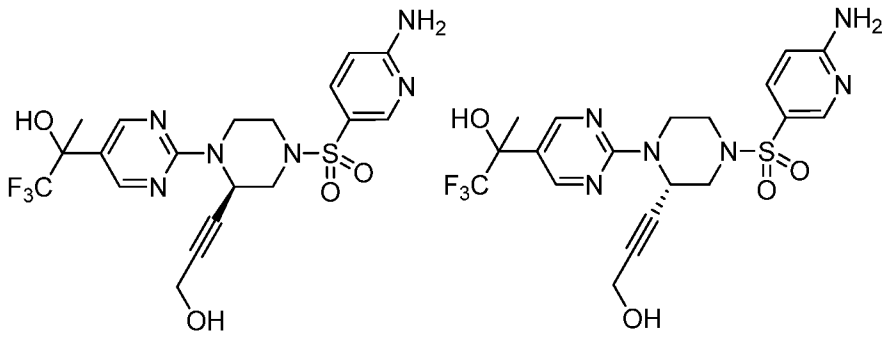
A 75-mL reaction vessel was charged with benzyl 3-(3-((tert-butyl(diphenyl)silyl)oxy)-1-propyn-1-yl)-1-piperazinecarboxylate (1.1 g, 2.145 mmol, Example 29, Step 2), (2R)-2-(2-chloro-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol or (2S)-2-(2-chloro-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol (1.120 ml, 6.44 mmol, Intermediate F, peak 1), DIPEA (1.12 mL, 6.44 mmol) and

dioxane (10 mL). The vessel was sealed and heated at 120 °C for 4 days. The reaction was diluted with water (200 mL) and EtOAc (200 mL). The aqueous phase was extracted with EtOAc (2 x 100 mL) and the combined organic phases were washed with saturated aqueous sodium chloride (150 mL). The organic extracts were dried over sodium sulfate, filtered and concentrated under a vacuum. The resulting product was purified by silica gel column chromatography (0 to 70% EtOAc in hexanes) to afford benzyl 3-(3-((tert-butyl(diphenyl)silyl)oxy)-1-propyn-1-yl)-4-(5-((1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-1-piperazinecarboxylate or 3-(3-((tert-butyl(diphenyl)silyl)oxy)-1-propyn-1-yl)-4-(5-((1S)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-1-piperazinecarboxylate (210 mg) as a clear oil.

STEP 2: 3-(4-((6-Amino-3-pyridinyl)sulfonyl)-1-(5-((1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-2-piperazinyl)-2-propyn-1-ol or 3-(4-((6-amino-3-pyridinyl)sulfonyl)-1-(5-((1S)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-2-piperazinyl)-2-propyn-1-ol

A 100-mL round-bottomed flask was charged with benzyl 3-(3-((tert-butyl(diphenyl)silyl)oxy)-1-propyn-1-yl)-4-(5-((1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-1-piperazinecarboxylate or 3-(3-((tert-butyl(diphenyl)silyl)oxy)-1-propyn-1-yl)-4-(5-((1S)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-1-piperazinecarboxylate (210 mg, 0.299 mmol) and TFA (5 mL, 7.4 mmol). Trifluoromethanesulfonic acid (0.265 mL, 2.99 mmol, Sigma-Aldrich, St. Louis, MO) was added dropwise at 0 °C. After 10 min, solid $NaHCO_3$ was carefully added in portions. Saturated aqueous $NaHCO_3$ (250 mL) was added slowly to bring the pH to approximately 7. The aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic phases were washed with water (200 mL) and saturated aqueous sodium chloride (200 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under a vacuum. A 100-mL round-bottomed flask was charged with this material, triethylamine (0.21 mL, 1.50 mmol) and CH_2Cl_2 (5 mL). Tert-butyl

(5-(chlorosulfonyl)-2-pyridinyl)carbamate (0.51 g, 1.73 mmol, Intermediate B) was added in portions at 0 °C. After 10 min, the reaction was diluted with water (100 mL) and the aqueous phase was extracted with EtOAc (3 x 100 mL) and the combined organic phases were washed with water (200 mL) and saturated aqueous sodium chloride (200 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under a vacuum. This residue was dissolved in CH_2Cl_2 (3mL) and TFA (3 mL, 38.9 mmol) was added. After 1 h, the reaction was quenched with the addition of solid sodium bicarbonate and diluted with EtOAc (3 x 100 mL) and water (300 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under a vacuum, purified by silica gel column chromatography (0 to 100% EtOAc in hexanes) to afford 3-(4-((6-amino-3-pyridinyl)sulfonyl)-1-(5-((1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-2-piperazinyl)-2-propyn-1-ol or 3-(4-((6-amino-3-pyridinyl)sulfonyl)-1-(5-((1S)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-2-piperazinyl)-2-propyn-1-ol (50 mg) as a mixture of two diastereomers.



3-((2R)-4-((6-amino-3-pyridinyl)sulfonyl)-1-(5-((1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-2-piperazinyl)-2-propyn-1-ol or 3-((2R)-4-((6-amino-3-pyridinyl)sulfonyl)-1-(5-((1S)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-2-piperazinyl)-2-propyn-1-ol; and 3-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-1-(5-((1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-2-piperazinyl)-2-propyn-1-ol or 3-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-1-(5-((1S)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-2-piperazinyl)-2-propyn-1-ol

^{1}H NMR (400 MHz, MeOD) δ ppm 8.54 (s, 2 H), 8.31 (d, *J* = 2.2 Hz, 1 H), 7.78 (dd, *J* = 2.5, 9.0 Hz, 1 H), 6.65 (d, *J* = 9.0 Hz, 1 H), 5.85 - 5.78 (m, 1 H), 4.63 (d, *J* = 13.3 Hz, 1 H), 4.20 - 4.16 (m, 2 H), 3.88 - 3.75 (m, 2 H), 3.41 - 3.34 (m, 1 H), 2.67 (dd, *J* = 3.5, 11.5 Hz, 1 H), 2.48 (dt, *J* = 3.2, 11.8 Hz, 1 H), 1.70 (s, 3 H). m/z (ESI, +ve ion) 487.1 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.097 μM.

This mixture was separated using preparative SFC (Chiralpak® AD-H column (2 x 15 cm) eluting with 60% liquid CO_2 in 40% methanol with 0.1% DEA at a flow rate of 70 mL/min) to give two products in greater than 99% diastereomeric excess.

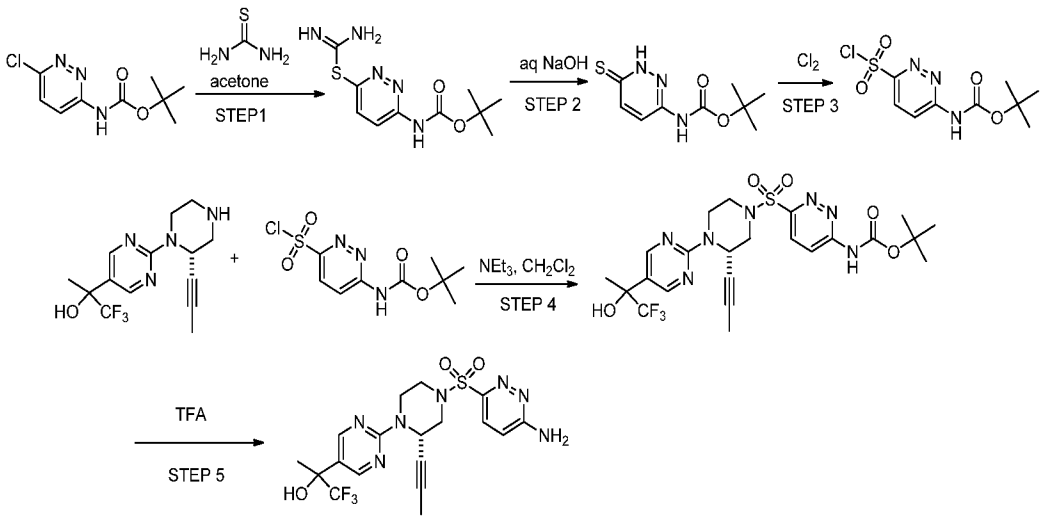
FIRST ELUTING PEAK (PEAK #1)

^{1}H NMR (400 MHz, MeOD) δ ppm 8.54 (s, 2 H), 8.32 - 8.27 (m, 1 H), 7.74 (dd, *J* = 2.5, 9.0 Hz, 1 H), 6.61 (d, *J* = 9.0 Hz, 1 H), 5.84 - 5.76 (m, 1 H), 4.63 (d, *J* = 13.3 Hz, 1 H), 4.18 (d, *J* = 1.6 Hz, 2 H), 3.87 - 3.74 (m, 2 H), 3.41 - 3.34 (m, 1 H), 2.64 (dd, *J* = 3.5, 11.5 Hz, 1 H), 2.46 (dt, *J* = 3.2, 11.8 Hz, 1 H), 1.69 (s, 3 H). m/z (ESI, +ve ion) 487.1 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.047 μM.

SECOND ELUTING PEAK (PEAK #2)

^{1}H NMR (400 MHz, MeOD) δ ppm 8.54 (s, 2 H), 8.33 - 8.24 (m, 1 H), 7.74 (dd, *J* = 2.4, 8.9 Hz, 1 H), 6.61 (d, *J* = 9.0 Hz, 1 H), 5.84 - 5.76 (m, 1 H), 4.63 (d, *J* = 13.1 Hz, 1 H), 4.18 (d, *J* = 1.8 Hz, 2 H), 3.91 - 3.72 (m, 2 H), 3.42 - 3.35 (m, 1 H), 2.64 (dd, *J* = 3.6, 11.4 Hz, 1 H), 2.46 (dt, *J* = 3.1, 11.8 Hz, 1 H), 1.69 (s, 3 H). m/z (ESI, +ve ion) 487.1 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = > 33 μM.

EXAMPLE 35: (2*R*)-2-(2-((2*S*)-4-((6-Amino-3-pyridazinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol or (2*S*)-2-(2-((2*S*)-4-((6-amino-3-pyridazinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol



STEP 1: tert-Butyl (6-(carbamimidoylsulfanyl)-3-pyridazinyl)carbamate

To a 100-mL round-bottomed flask was added thiourea (0.33 g, 4.4 mmol, Sigma-Aldrich, St. Louis, MO), acetone (20 mL) and tert-butyl (6-chloropyridazin-3-yl)carbamate (1.0 g, 4.4 mmol, Frontier Scientific Inc., Logan, UT). The solution was stirred at reflux for 2 days. After cooling to rt, the solution was filtered and the filtercake was washed with acetone and dried to afford tert-butyl (6-(carbamimidoylsulfanyl)-3-pyridazinyl)carbamate (0.37 g) as a brown solid that was used without further purification.

STEP 2: tert-Butyl (6-thioxo-1,6-dihydro-3-pyridazinyl)carbamate

To a resealable vial containing tert-butyl (6-(carbamimidoylsulfanyl)-3-pyridazinyl)carbamate (0.37 g, 1.4 mmol) was added aqueous sodium hydroxide (4 mL of a solution of 0.5 g NaOH in 10 mL H_2O). The solution was stirred at rt for 5 min and then poured into water (100 mL) and extracted with EtOAc (3 x 75 mL). The combined extracts were washed with brine (50 mL) and then dried (Na_2SO_4) and concentrated onto silica. Purification by silica gel chromatography

(10 to 70% EtOAc/hexane) afforded tert-butyl (6-thioxo-1,6-dihydro-3-pyridazinyl)carbamate (0.13 g) as a yellow solid.

STEP 3: tert-Butyl (6-(chlorosulfonyl)-3-pyridazinyl)carbamate

To a 100-mL round-bottomed flask was added tert-butyl (6-thioxo-1,6-dihydro-3-pyridazinyl)carbamate (0.13 g, 0.57 mmol), water (30 mL) and glacial acetic acid (3.0 mL). The solution was cooled to 0 °C and chlorine gas was bubbled into the stirred reaction mixture at a minimal rate with the internal temperature being kept below 5 °C. Chlorine gas was added for 1 h and then the reaction was stirred for an additional 15 min. The reaction mixture was filtered. The solid collected was washed with cold water and dried under vacuum to afford tert-butyl (6-(chlorosulfonyl)-3-pyridazinyl)carbamate (0.15 g) as a white solid.

STEP 4: tert-Butyl (6-(((3*S*)-3-(1-propyn-1-yl)-4-(5-((1*R*)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-1-piperazinyl)sulfonyl)-3-pyridazinyl)carbamate

Following the procedure for Step 3 in Example 12, the reaction of tert-butyl (6-(chlorosulfonyl)-3-pyridazinyl)carbamate and (2R)-1,1,1-trifluoro-2-(2-((2S)-2-(1-propyn-1-yl)-1-piperazinyl)-5-pyrimidinyl)-2-propanol or (2S)-1,1,1-trifluoro-2-(2-((2S)-2-(1-propyn-1-yl)-1-piperazinyl)-5-pyrimidinyl)-2-propanol (Intermediate G) delivered tert-butyl (6-(((3*S*)-3-(1-propyn-1-yl)-4-(5-((1*R*)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-1-piperazinyl)sulfonyl)-3-pyridazinyl)carbamate or tert-butyl (6-(((3*S*)-3-(1-propyn-1-yl)-4-(5-((1*S*)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-1-piperazinyl)sulfonyl)-3-pyridazinyl)carbamate.

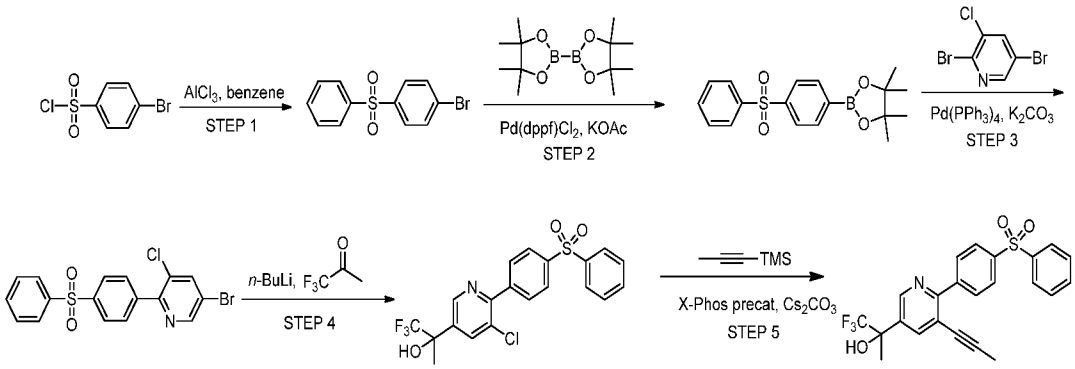
STEP 5: (2*R*)-2-(2-((2*S*)-4-((6-Amino-3-pyridazinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol or (2*S*)-2-(2-((2*S*)-4-((6-

amino-3-pyridazinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol

To a resealable vial containing tert-butyl (6-(((3*S*)-3-(1-propyn-1-yl)-4-(5-((1*R*)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-1-piperazinyl)sulfonyl)-3-pyridazinyl)carbamate or tert-butyl (6-(((3*S*)-3-(1-propyn-1-yl)-4-(5-((1*S*)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-1-piperazinyl)sulfonyl)-3-pyridazinyl)carbamate (0.095 g, 0.17 mmol) was added TFA (3 mL). The solution was stirred at rt for 30 min and then concentrated. The residue was treated with saturated aqueous $NaHCO_3$ and 25% iPrOH/$CHCl_3$. This was stirred for 5 min and then the solution was transferred onto a phase separation cartridge (Radleys Discovery Technologies, Essex, UK) with the organic phase being collected and passed through a plug of Na_2SO_4. The collected solution was concentrated. Purification by silica gel chromatography (0.0 to 6.0% MeOH/CH_2Cl_2) afforded (2*R*)-2-(2-((2*S*)-4-((6-amino-3-pyridazinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol or (2*S*)-2-(2-((2*S*)-4-((6-amino-3-pyridazinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol (0.043 g) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.57 (s, 2H), 7.65 (d, J = 8.4 Hz, 1H), 7.25 (br s, 2H), 6.88 (d, J = 8.6 Hz, 1H), 6.74 (s, 1H), 5.65 (s, 1H), 4.55 (d, J = 12.9 Hz, 1H), 3.79 (t, J = 12.1 Hz, 2H), 3.21 (t, J = 11.8 Hz, 1H), 2.91 (d, J = 12.1 Hz, 1H), 2.62 - 2.76 (m, 1H), 1.75 (s, 3H), 1.67 (s, 3H). m/z (ESI, +ve ion) 472.0 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.046 μM.

EXAMPLE 36: 1,1,1-Trifluoro-2-(6-(4-(phenylsulfonyl)phenyl)-5-(1-propyn-1-yl)-3-pyridinyl)-2-propanol



STEP1: 1-Bromo-4-(phenylsulfonyl)benzene

A 500 mL round-bottomed flask was charged with 4-bromobenzenesulfonyl chloride (10.0 g, 39.1 mmol, Sigma-Aldrich, St. Louis, MO), 100 mL of benzene and aluminum chloride (6.26 g, 47.0 mmol, Sigma-Aldrich, St. Louis, MO). After stirring at room temperature for 12 h, the mixture was diluted water (100 mL) and extracted with EtOAc (2 x 100 mL). The organic extracts were dried ($MgSO_4$) and concentrated under a vacuum to give 1-bromo-4-(phenylsulfonyl)benzene (10.50 g) as a white solid.

STEP 2: 4,4,5,5-Tetramethyl-2-(4-(phenylsulfonyl)phenyl)-1,3,2-dioxaborolane

A 250-mL round-bottomed flask was charged with 1-bromo-4-(phenylsulfonyl)benzene (2.50 g, 8.41 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (2.46 g, 9.67 mmol, Sigma-Aldrich, St. Louis, MO), [1,1′bis(diphenylphosphino)ferrocene]dichloropalladium (0.344 g, 0.421 mmol, Sigma-Aldrich, St. Louis, MO), potassium acetate (2.48 g, 25.2 mmol, Sigma-Aldrich, St. Louis, MO), and 50 mL of dioxane. This mixture was heated at 100 °C for 12 h and then cooled to room temperature. The reaction mixture was diluted with EtOAc (200 mL), filtered, and concentrated under a vacuum to give a dark solid. This solid was slurred with cold (0 °C) MeOH (50 mL) to give 4,4,5,5-tetramethyl-2-(4-(phenylsulfonyl)phenyl)-1,3,2-dioxaborolane (2.20 g) as a gray solid.

STEP 3: 5-Bromo-3-chloro-2-(4-(phenylsulfonyl)phenyl)pyridine

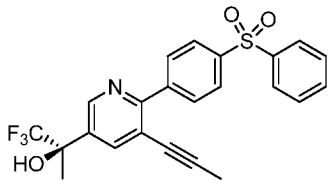
A 100-mL pressure vessel was charged with 4,4,5,5-tetramethyl-2-(4-(phenylsulfonyl)phenyl)-1,3,2-dioxaborolane (6.34 g, 18.43 mmol), 2,5-dibromo-3-chloropyridine (5.00 g, 18.43 mmol, Sigma-Aldrich, St. Louis, MO), potassium carbonate (7.64 g, 55.3 mmol), tetrakis(triphenylphosphine)palladium (1.06 g, 0.92 mmol, Strem Chemical Inc, Newburyport, MA), 20 mL of 1,2-dimethoxyethane, and 4 mL of water. The vessel was sealed and the reaction mixture was heated at 100 °C for 8 h. After cooling to room temperature, the mixture was diluted with EtOAc (30 mL) and water. The layers were separated and the organic phase was dried ($MgSO_4$), filtered, and concentrated under a vacuum to give an oil. Purification via column chromatography (40 g of silica gel, 0 to 50% EtOAc in hexanes) produced 5-bromo-3-chloro-2-(4-(phenylsulfonyl)phenyl)pyridine (2.56 g) as a tan solid.

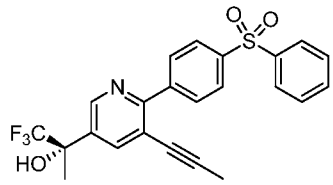
STEP 4: 2-(5-Chloro-6-(4-(phenylsulfonyl)phenyl)pyridin-3-yl)-1,1,1-trifluoropropan-2-ol

A 100-mL round-bottomed flask was charged 5-bromo-3-chloro-2-(4-(phenylsulfonyl)phenyl)pyridine (3.31 g, 8.10 mmol) and THF (25 mL). The reaction mixture was cooled to -78 °C and n-BuLi (3.56 mL, 2.5 M in hexanes, 8.91 mmol, Sigma-Aldrich, St. Louis, MO) was added drop-wise. The resulting black solution was stirred for 15 min at -78 °C and then 1,1,1-trifluoropropan-2-one (1.81 g, 16.20 mmol, Sigma-Aldrich, St. Louis, MO) was added and stirred at -78 °C for 1 h. The reaction was then quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (2 x 40 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under a vacuum, and purified via column chromatography (40 g of silica, 0 to 60% EtOAc in hexanes) to give 2-(5-chloro-6-(4-(phenylsulfonyl)phenyl)pyridin-3-yl)-1,1,1-trifluoropropan-2-ol (1.65 g).

STEP 5: 1,1,1-Trifluoro-2-(6-(4-(phenylsulfonyl)phenyl)-5-(1-propyn-1-yl)-3-pyridinyl)-2-propanol

A glass reaction vial was charged with 2-(5-chloro-6-(4-(phenylsulfonyl)phenyl)pyridin-3-yl)-1,1,1-trifluoropropan-2-ol (97 mg, 0.92 mmol), X-Phos palladacycle (8 mg, 11 μmol, Strem Chemical Inc, Newburyport, MA), cesium carbonate (0.215 g, 0.66 mmol, Sigma-Aldrich, St. Louis, MO), 1-(trimethylsilyl)-1-propyne (0.098 mL, 0.66 mmol, Sigma-Aldrich, St. Louis, MO), and ACN (1.5 mL). The vial was closed and purged with nitrogen for several minutes. The reaction mixture was heated at 80 °C for 3 h and allowed to cool to room temperature. The solvent was removed under vacuum and the crude material was absorbed onto a plug of silica gel and purified by chromatography through a silica gel column (12 g), eluting with a gradient of 0% to 20% EtOAc in hexane, to provide 1,1,1-trifluoro-2-(6-(4-(phenylsulfonyl)phenyl)-5-(1-propyn-1-yl)-3-pyridinyl)-2-propanol (38 mg) as an off-white solid and a mixture of enantiomers.

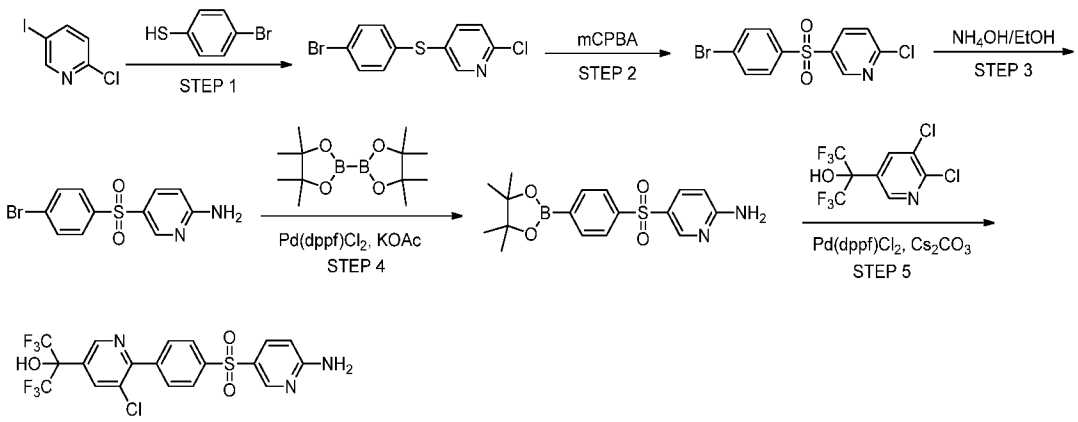




(2R)-1,1,1-trifluoro-2-(6-(4-(phenylsulfonyl)phenyl)-5-(1-propyn-1-yl)-3-pyridinyl)-2-propanol; (2S)-1,1,1-trifluoro-2-(6-(4-(phenylsulfonyl)phenyl)-5-(1-propyn-1-yl)-3-pyridinyl)-2-propanol

^{1}H NMR (400 MHz, DMSO-d_6) 8.83 (br s, 1H), 8.17 (d, J = 8.02 Hz, 2H), 8.00 - 8.12 (m, 5H), 7.62 - 7.79 (m, 3H), 7.00 (br s, 1H), 2.03 (s, 3H), 1.77 (s, 3H); m/z (ESI, +ve ion) 446.1 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.642 μM.

EXAMPLE 37: 2-(6-(4-((6-Amino-3-pyridinyl)sulfonyl)phenyl)-5-chloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol



STEP 1: 5-((4-Bromophenyl)sulfanyl)-2-chloropyridine

2-Chloro-5-iodopyridine (1.11 g, 4.64 mmol, Sigma-Aldrich, St. Louis, MO), 4-bromothiophenol (0.88 g, 4.64 mmol, Sigma-Aldrich, St. Louis, MO), copper iodide (44 mg, 0.23 mmol, Strem Chemical Inc, Newburyport, MA), potassium carbonate (1.28 g, 9.29 mmol), ethylene glycol (0.52 mL, 9.29 mmol), and iPrOH (10 mL) were added to a reaction vial. The vial was closed, purged with nitrogen for several minutes, and heated at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (20 mL) and then EtOAc (20 mL). The organic extracts were combined and the solvents were removed under reduced pressure. The residue was absorbed onto a plug of silica gel and purified by column chromatography (24 g of silica gel, 0 to 10% EtOAc in hexanes), to provide 5-((4-bromophenyl)sulfanyl)-2-chloropyridine (1.17 g) as white solid.

STEP 2: 5-((4-Bromophenyl)sulfonyl)-2-chloropyridine

5-((4-Bromophenyl)sulfanyl)-2-chloropyridine (274 mg, 0.91 mmol) and mCPBA (409 mg, 1.82 mmol, 77% by weight, Sigma-Aldrich, St. Louis, MO) in CH_2Cl_2 (5 mL) were stirred at room temperature for 2 h. The mixture was partitioned between CH_2Cl_2 (10 mL) and saturated aqueous sodium bicarbonate

(10 mL) and the layers were separated. The organic material was washed sequentially with saturated aqueous sodium bicarbonate (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered, and concentrated under a vacuum. The crude material was absorbed onto a plug of silica gel and purified by column chromatography (0 to 20% EtOAc in hexanes), to provide 5-((4-bromophenyl)sulfonyl)-2-chloropyridine (100 mg) as white solid.

STEP 3: 5-((4-Bromophenyl)sulfonyl)-2-pyridinamine

5-((4-Bromophenyl)sulfonyl)-2-chloropyridine (98 mg, 0.29 mmol), NH_4OH (3 mL, 28% in water), and EtOH (3 mL) were added to a high pressure reaction vessel. The vessel was sealed and heated at 120 °C for 18 h. After cooling to room temperature, the solvent was partially removed under vacuum. The white precipitate obtained was filtered, washed with ether, and dried under vacuum to provide 5-((4-bromophenyl)sulfonyl)-2-pyridinamine (75 mg) as a white solid.

STEP 4: 5-((4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)-2-pyridinamine

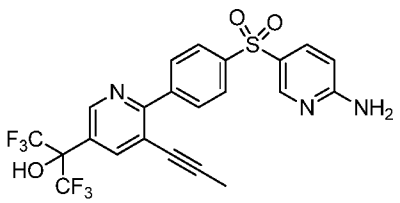
5-((4-Bromophenyl)sulfonyl)-2-pyridinamine (0.53 g, 1.69 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (0.43 g, 1.69 mmol, Sigma-Aldrich, St. Louis, MO), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (69 mg, 0.08 mmol, Strem Chemical Inc, Newburyport, MA), potassium acetate (0.50 g, 5.1 mmol, Sigma-Aldrich, St. Louis, MO), and dioxane (8 mL) were added to a reaction vial. The vial was closed, purged with nitrogen for several minutes, and heated at 100 °C for 18 h. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite® (diatomaceous earth) eluting with DCM. The filtrate was concentrated to yield 5-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)-2-pyridinamine as a brown solid that was used without further purification.

STEP 5: 2-(6-(4-((6-Amino-3-pyridinyl)sulfonyl)phenyl)-5-chloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol

A glass microwave reaction vessel was charged 5-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)-2-pyridinamine (402 mg, 1.12 mmol), 2-(5,6-dichloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (102 mg, 0.36 mmol, Intermediate R), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (38 mg, 0.05 mmol, Strem Chemical Inc, Newburyport, MA), cesium carbonate (909 mg, 2.79 mmol, Sigma-Aldrich, St. Louis, MO), DME (3 mL), and water (0.3 mL). The reaction mixture was purged with nitrogen for several minutes, and then stirred and heated in an Emrys Optimizer microwave reactor (Personal Chemistry, Biotage AB, Inc., Uppsala, Sweden) at 100 °C for 30 min. The organic layer was taken and the solvent was removed under vacuum. The crude material was absorbed onto a plug of silica gel and purified by chromatography through a silica gel column (40 g) eluting with a gradient of 100% DCM to 2% 2M NH_3/MeOH in DCM, to provide 2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-chloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (125 mg) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.46 (s, 1H), 8.90 (s, 1H), 8.49 (d, J = 2.54 Hz, 1H), 8.25 (s, 1H), 8.03 (d, J = 8.41 Hz, 2H), 7.95 (d, J = 8.41 Hz, 2H), 7.82 (dd, J = 2.54, 9.00 Hz, 1H), 7.13 (s, 2H), 6.52 (d, J = 9.00 Hz, 1H); m/z (ESI, +ve ion) 512.1 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 1.26 μM.

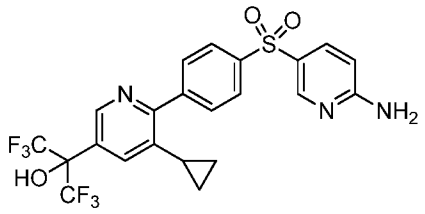
EXAMPLE 38: 2-(6-(4-((6-Amino-3-pyridinyl)sulfonyl)phenyl)-5-(1-propyn-1-yl)-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol



A glass reaction vial was charged with 2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-chloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (98 mg, 0.19 mmol, Example 37), X-Phos palladacycle (7 mg, 10 μmol, Strem Chemical Inc, Newburyport, MA), cesium carbonate (187 mg, 0.57 mmol, Sigma-Aldrich, St. Louis, MO), 1-(trimethylsilyl)-1-propyne (0.143 mL, 0.96 mmol, Sigma-Aldrich, St. Louis, MO), and ACN (2 mL). The vial was closed and purged with nitrogen for several minutes. The reaction mixture was heated at 80 °C for 18 h and allowed to cool to room temperature. The solvent was removed under vacuum and the crude material was absorbed onto a plug of silica gel and purified by chromatography through a silica gel column (12 g), eluting with a gradient of 100% DCM to 3% 2M NH_3·MeOH in DCM, to provide 2-(6-(4-((6-aminopyridin-3-yl)sulfonyl)phenyl)-5-(prop-1-yn-1-yl)pyridin-3-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (68 mg) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.30 (br s, 1H), 8.87 (br s, 1H), 8.48 (d, J = 2.35 Hz, 1H), 8.17 (d, J = 8.41 Hz, 2H), 8.12 (s, 1H), 8.02 (d, J = 8.41 Hz, 2H), 7.82 (dd, J = 2.45, 8.90 Hz, 1H), 7.13 (s, 2H), 6.52 (d, J = 9.00 Hz, 1H), 2.05 (s, 3H); m/z (ESI, +ve ion) 516.0 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.58 μM.

EXAMPLE 39: 2-(6-(4-((6-Amino-3-pyridinyl)sulfonyl)phenyl)-5-cyclopropyl-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol

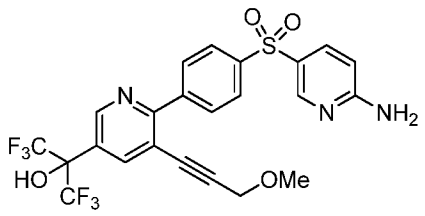


A glass reaction vial was charged with 2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-chloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (93 mg, 0.18 mmol, Example 37), X-Phos palladacycle (7 mg, 10 μmol, Strem Chemical Inc, Newburyport, MA), cesium carbonate (178 mg, 0.54 mmol, Sigma-Aldrich, St. Louis, MO), potassium cyclopropyltrifluoroborate (81

mg, 0.54 mmol, Sigma-Aldrich, St. Louis, MO), toluene (1 mL), THF (0.5 mL) and water (0.1 mL). The vial was closed and purged with nitrogen for several minutes. The reaction mixture was heated at 100 °C for 18 h and allowed to cool to room temperature. The organic layer was taken and the solvent was removed under a vacuum. The crude material was absorbed onto a plug of silica gel and purified by chromatography through a silica gel column (12 g), eluting with a gradient of 100% DCM to 2% 2M NH_3·MeOH in DCM, to provide 2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-cyclopropyl-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (29 mg) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.13 (br s, 1H), 8.72 (br s, 1H), 8.49 (s, 1H), 8.01 (d, J = 8.22 Hz, 2H), 7.92 (d, J = 8.22 Hz, 2H), 7.83 (dd, J = 1.56, 8.60 Hz, 1H), 7.65 (br s, 1H), 7.13 (br s, 2H), 6.52 (d, J = 8.80 Hz, 1H), 1.92 - 2.09 (m, 1H), 0.94 - 1.05 (m, 2H), 0.61 - 0.74 (m, 2H); m/z (ESI, +ve ion) 518.0 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 4.57 μM.

EXAMPLE 40: 2-(6-(4-((6-Amino-3-pyridinyl)sulfonyl)phenyl)-5-(3-methoxy-1-propyn-1-yl)-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol

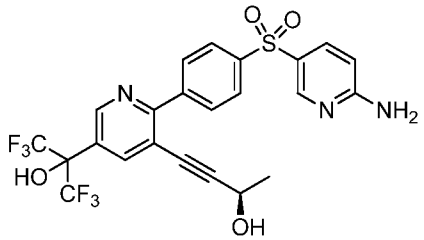


A glass reaction vial was charged with 2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-chloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (105 mg, 0.20 mmol, Example 37), X-Phos palladacycle (7 mg, 10 μmol, Strem Chemical Inc, Newburyport, MA), cesium carbonate (201 mg, 0.61 mmol, Sigma-Aldrich, St. Louis, MO), 3-methoxy-1-propyne (0.087 mL, 1.03 mmol, Sigma-Aldrich, St. Louis, MO), and ACN (3 mL). The vial was closed and purged with nitrogen for several minutes. The reaction mixture was heated at

80 °C for 18 h and allowed to cool to room temperature. The solvent was removed under a vacuum and the crude material was absorbed onto a plug of silica gel and purified by chromatography through a silica gel column (12 g), eluting with a gradient of 4 to 7% 2M NH_3·MeOH in DCM, to provide 2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(3-methoxy-1-propyn-1-yl)-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (83 mg) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.38 (br s, 1H), 8.94 (s, 1H), 8.48 (s, 1H), 8.19 (br s, 1H), 8.13 (d, J = 7.43 Hz, 2H), 8.03 (d, J = 7.63 Hz, 2H), 7.82 (d, J = 8.41 Hz, 1H), 7.15 (br s, 2H), 6.52 (d, J = 8.61 Hz, 1H), 4.30 (br s, 2H), 3.13 (s, 3H); m/z (ESI, +ve ion) 546.0 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.014 μM.

EXAMPLE 41: (2R)-4-(2-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)-3-pyridinyl)-3-butyn-2-ol

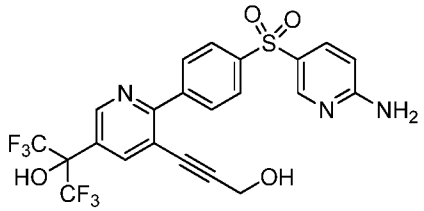


A glass reaction vial was charged with 2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-chloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (98 mg, 0.19 mmol, Example 37), X-Phos palladacycle (7 mg, 10 μmol, Strem Chemical Inc, Newburyport, MA), potassium carbonate (40 mg, 0.29 mmol, Sigma-Aldrich, St. Louis, MO), (2R)-3-butyn-2-ol (0.020 mL, 0.29 mmol, Sigma-Aldrich, St. Louis, MO), and DMA (2 mL). The vial was closed and purged with nitrogen for several minutes. The reaction mixture was heated at 110 °C for 2 h and allowed to cool to room temperature. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (2 x 10 mL). The organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuum. The crude material was absorbed onto a plug of silica gel and purified by chromatography through a silica gel column (12 g), eluting with a gradient of

2% to 5% 2M $NH_3 \cdot MeOH$ in DCM, to provide (2R)-4-(2-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(2,2,2-trifluoro-1-hydroxy-1-trifluoromethyl)ethyl)-3-pyridinyl)-3-butyn-2-ol (66 mg) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.39 (br s, 1H), 8.93 (d, J = 1.76 Hz, 1H), 8.49 (d, J = 2.15 Hz, 1H), 8.16 - 8.24 (m, 2H), 8.14 (d, J = 1.96 Hz, 1H), 7.99 - 8.09 (m, 2H), 7.83 (dd, J = 2.54, 9.00 Hz, 1H), 7.16 (s, 2H), 6.53 (d, J = 8.80 Hz, 1H), 5.54 (d, J = 5.48 Hz, 1H), 4.57 (quin, J = 6.31 Hz, 1H), 1.30 (d, J = 6.65 Hz, 3H); m/z (ESI, +ve ion) 547.0 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.045 μM.

EXAMPLE 42: 3-(2-(4-((6-Amino-3-pyridinyl)sulfonyl)phenyl)-5-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)-3-pyridinyl)-2-propyn-1-ol



STEP 1: 2-(6-(4-((6-Amino-3-pyridinyl)sulfonyl)phenyl)-5-(3-((tert-butyl(dimethyl)silyl)oxy)-1-propyn-1-yl)-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol

A glass reaction vial was charged with 2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-chloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (73 mg, 0.14 mmol, Example 37), X-Phos palladacycle (5 mg, 7 μmol, Strem Chemical Inc, Newburyport, MA), potassium carbonate (30 mg, 0.21 mmol, Sigma-Aldrich, St. Louis, MO), tert-butyl(dimethyl)(2-propyn-1-yloxy)silane (0.043 mL, 0.21 mmol, Sigma-Aldrich, St. Louis, MO), and DMA (2 mL). The vial was closed and purged with nitrogen for several minutes. The reaction mixture was heated at 110 °C for 2 h and allowed to cool to room temperature. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (2 x 10 mL). The organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuum. The crude material was absorbed

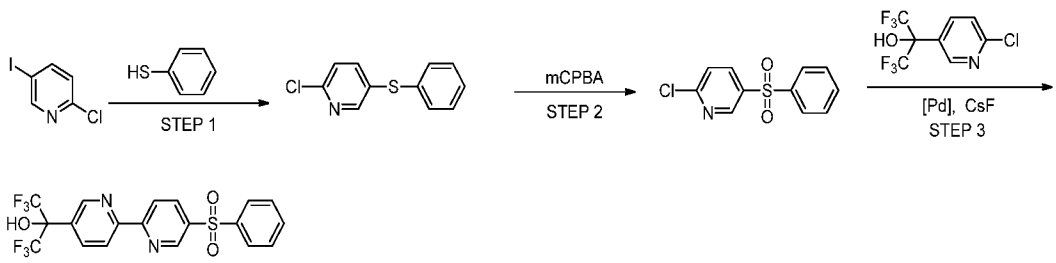
onto a plug of silica gel and purified by chromatography through a silica gel column (12 g), eluting with a gradient of 100% DCM to 4% 2M NH_3·MeOH in DCM, to provide 2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(3-((tert-butyl(dimethyl)silyl)oxy)-1-propyn-1-yl)-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (63 mg) as tan solid.

STEP 2: 3-(2-(4-((6-Amino-3-pyridinyl)sulfonyl)phenyl)-5-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)-3-pyridinyl)-2-propyn-1-ol

To a 25-mL round-bottomed flask was added 2-(6-(4-((6-aminopyridin-3-yl)sulfonyl)phenyl)-5-(3-((tert-butyldimethylsilyl)oxy)prop-1-yn-1-yl)pyridin-3-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (63 mg, 0.098 mmol), tetra-n-butylammonium fluoride (0.19 mL, 0.19 mmol, 1 M in THF, Sigma-Aldrich, St. Louis, MO), and THF (3 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with saturated aqueous ammonium chloride (5 mL) and extracted with EtOAc (5 mL). The organic extract was washed with water (3 mL) and dried over Na_2SO_4. The solution was filtered and concentrated under a vacuum. The crude material was absorbed onto a plug of silica gel and purified by chromatography through a silica gel column (12 g), eluting with a gradient of 5% to 7% 2M NH_3·MeOH in DCM, to provide 3-(2-(4-((6-aminopyridin-3-yl)sulfonyl)phenyl)-5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)prop-2-yn-1-ol (43 mg) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm9.38 (br. s., 1H), 8.94 (d, J = 1.37 Hz, 1H), 8.50 (d, J = 2.54 Hz, 1H), 8.14 - 8.28 (m, 3H), 8.03 (d, J = 8.61 Hz, 2H), 7.84 (dd, J = 2.64, 8.90 Hz, 1H), 7.17 (s, 2H), 6.53 (d, J = 9.00 Hz, 1H), 5.42 (t, J = 6.06 Hz, 1H), 4.31 (d, J = 6.06 Hz, 2H); m/z (ESI, +ve ion) 532.0 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.071 μM.

EXAMPLE 43: 1,1,1,3,3,3-Hexafluoro-2-(5'-(phenylsulfonyl)-2,2'-bipyridin-5-yl)-2-propanol



STEP 1: 2-Chloro-5-(phenylsulfanyl)pyridine

2-Chloro-5-iodopyridine (1.69 g, 7.05 mmol, Sigma-Aldrich, St. Louis, MO), benzenethiol (0.71 mL, 7.05 mmol, Sigma-Aldrich, St. Louis, MO), copper iodide (67 mg, 0.35 mmol, Strem Chemical Inc, Newburyport, MA), potassium carbonate (1.95 g, 14.1 mmol), ethylene glycol (0.79 mL, 14.1 mmol), and iPrOH (5 mL) were added to a reaction vial. The vial was closed, purged with nitrogen for several minutes, and heated at 80 °C for 5 h. After cooling to room temperature, the reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were taken and the solvent was removed under a vacuum to obtaine 2-chloro-5-(phenylsulfanyl)pyridine (1.56 g) as a tan solid This material was used without further purification.

STEP 2: 2-Chloro-5-(phenylsulfonyl)pyridine

To a solution of 2-chloro-5-(phenylsulfanyl)pyridine (1.56 g, 7.05 mmol) in DCM (15 mL) at 0 °C was added mCPBA (2.67 g, 15.5, 77% by weight, Sigma-Aldrich, St. Louis, MO). The reaction mixture was stirred at 0 °C for 1 h. The mixture was partitioned between CH_2Cl_2 (10 mL) and saturated aqueous sodium bicarbonate (10 mL) and the layers were separated. The organic material was washed sequentially with saturated aqueous sodium bicarbonate (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered, and concentrated under a vacuum. The crude material was absorbed onto a plug of silica gel and purified by silica gel

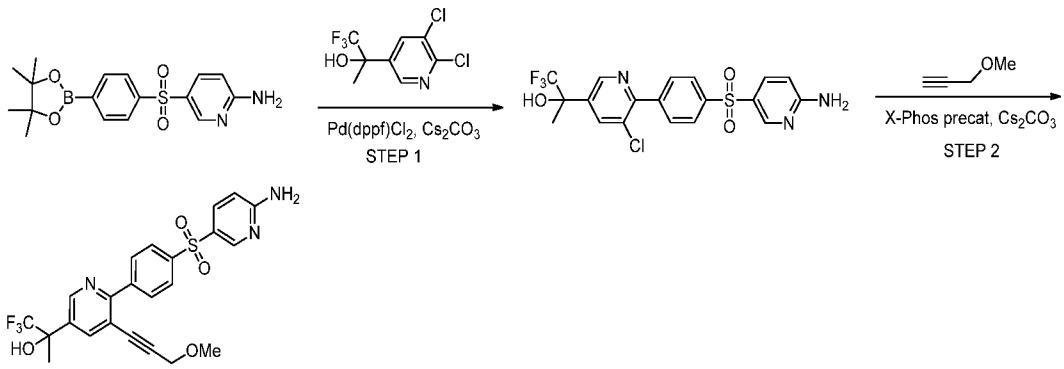
column chromatography (0 to 20% EtOAc in hexanes), to provide 2-chloro-5-(phenylsulfonyl)pyridine (764 mg) as white solid.

STEP 3: 1,1,1,3,3,3-Hexafluoro-2-(5'-(phenylsulfonyl)-2,2'-bipyridin-5-yl)-2-propanol

To a 10-mL reaction vial was added 2-(6-chloropyridin-3-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (105 mg, 0.38 mmol, Example 2, step 1), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (114 mg, 0.45 mmol, Sigma-Aldrich, St. Louis, MO), cesium fluoride (171 mg, 1.13 mmol, Sigma-Aldrich, St. Louis, MO), allylpalladium chloride dimmer (14 mg, 0.04 mmol, Strem Chemical Inc, Newburyport, MA), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (44 mg, 0.07 mmol, Strem Chemical Inc, Newburyport, MA), 2-chloro-5-(phenylsulfonyl)pyridine (114 mg, 0.45 mmol), dioxane (2 mL), and water (0.2 mL). The vial was purged with nitrogen for several minutes and then heated at 90 °C for 2 h. The reaction mixture was allowed to cool to room temperature and the organic layer was taken and filtered through a pad of Celite® (diatomaceous earth). The solvent was then removed under a vacuum. The crude material was absorbed onto a plug of silica gel and purified by chromatography through a silica gel column (12 g), eluting with a gradient of 10 to 30 % EtOAc in hexane. The product was repurified by reverse-phase preparative HPLC using a Phenomenex Gemini column, 10 micron, C18, 100 Å, 150 x 30 mm, 0.1% TFA in CH_3CN/H_2O, gradient 30% to 100% over 12 min to provide 1,1,1,3,3,3-hexafluoro-2-(5'-(phenylsulfonyl)-[2,2'-bipyridin]-5-yl)propan-2-ol (24 mg) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.28 (d, J = 1.76 Hz, 1H), 9.24 (br d, J = 10.00 Hz, 1H), 9.00 (d, J = 0.98 Hz, 1H), 8.52 - 8.63 (m, 3H), 8.30 (s, 1H), 8.06 - 8.11 (m, 2H), 7.76 (s, 1H), 7.65 - 7.71 (m, 2H); m/z (ESI, +ve ion) 463.1 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 1.73 μM.

EXAMPLE 44: 2-(6-(4-((6-Amino-3-pyridinyl)sulfonyl)phenyl)-5-(3-methoxy-1-propyn-1-yl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol

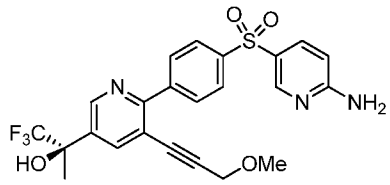


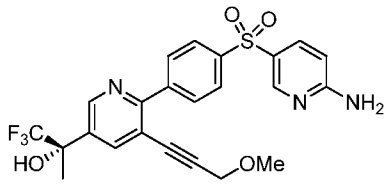
STEP 1: 2-(6-(4-((6-Amino-3-pyridinyl)sulfonyl)phenyl)-5-chloro-3-pyridinyl)-1,1,1-trifluoro-2-propanol

A glass microwave reaction vial was charged 5-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)-2-pyridinamine (304 mg, 0.84 mmol, Example 37, step 4), 2-(5,6-dichloro-3-pyridinyl)-1,1,1-trifluoro-2-propanol (183 mg, 0.70 mmol, Intermediate Q), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (29 mg, 0.04 mmol, Strem Chemical Inc, Newburyport, MA), cesium carbonate (688 mg, 2.11 mmol, Sigma-Aldrich, St. Louis, MO), DME (4 mL), and water (0.3 mL). The reaction mixture was purged with nitrogen for several minutes, and then stirred and heated in an Emrys Optimizer microwave reactor (Personal Chemistry, Biotage AB, Inc., Uppsala, Sweden) at 100 °C for 30 min. The organic layer was taken and the solvent was removed under a vacuum. The crude material was absorbed onto a plug of silica gel and purified by chromatography through a silica gel column (40 g) eluting with a gradient of 100% DCM to 1% 2M NH_3/MeOH in DCM, to provide 2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-chloro-3-pyridinyl)-1,1,1-trifluoro-2-propanol (160 mg) as an off- white solid.

STEP 2: 2-(6-(4-((6-Amino-3-pyridinyl)sulfonyl)phenyl)-5-(3-methoxy-1-propyn-1-yl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol

A glass reaction vial was charged with 2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-chloro-3-pyridinyl)-1,1,1-trifluoro-2-propanol (71 mg, 0.16 mmol), X-Phos palladacycle (6 mg, 8 μmol, Strem Chemical Inc, Newburyport, MA), cesium carbonate (152 mg, 0.46 mmol, Sigma-Aldrich, St. Louis, MO), 3-methoxy-1-propyne (0.065 mL, 0.77 mmol, Sigma-Aldrich, St. Louis, MO), and ACN (1.5 mL). The vial was closed and purged with nitrogen for several minutes. The reaction mixture was heated at 80 °C for 18 h and allowed to cool to room temperature. The solvent was removed under a vacuum and the crude material was absorbed onto a plug of silica gel and purified by chromatography through a silica gel column (12 g), eluting with a gradient of 100% DCM to 2% 2M NH_3·MeOH in DCM, to provide 2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(3-methoxy-1-propyn-1-yl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol (21 mg) as an off-white solid and a mixture of enantiomers.

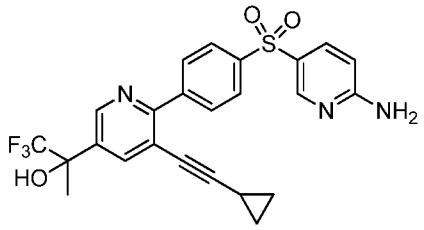




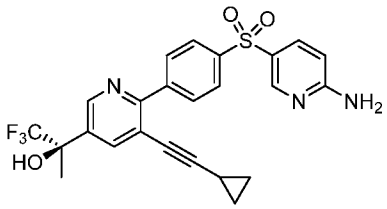
(2R)-2-(6-(4-((6-Amino-3-pyridinyl)sulfonyl)phenyl)-5-(3-methoxy-1-propyn-1-yl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol and (2S)-2-(6-(4-((6-Amino-3-pyridinyl)sulfonyl)phenyl)-5-(3-methoxy-1-propyn-1-yl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol.

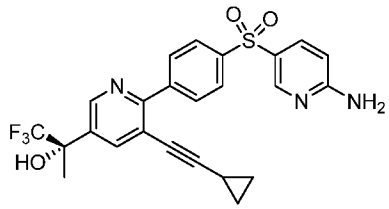
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.88 (d, J = 1.96 Hz, 1H), 8.47 (d, J = 2.35 Hz, 1H), 8.15 (d, J = 1.96 Hz, 1H), 8.06 - 8.11 (m, 2H), 7.97 - 8.02 (m, 2H), 7.80 (dd, J = 2.45, 8.90 Hz, 1H), 7.12 (br s, 2H), 7.02 (s, 1H), 6.51 (d, J = 9.19 Hz, 1H), 4.28 (s, 2H), 3.13 (s, 3H), 1.78 (s, 3H); m/z (ESI, +ve ion) 492.0 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.096 μM.

EXAMPLE 45: 2-(6-(4-((6-Amino-3-pyridinyl)sulfonyl)phenyl)-5-(cyclopropylethynyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol



A glass reaction vial was charged with 2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-chloro-3-pyridinyl)-1,1,1-trifluoro-2-propanol (80 mg, 0.17 mmol, Example 44, step 1), X-Phos palladacycle (6 mg, 8 μmol, Strem Chemical Inc, Newburyport, MA), cesium carbonate (171 mg, 0.52 mmol, Sigma-Aldrich, St. Louis, MO), ethynylcyclopropane (0.11 mL, 0.87 mmol, 70% in toluene, Sigma-Aldrich, St. Louis, MO), and ACN (1.5 mL). The vial was closed and purged with nitrogen for several minutes. The reaction mixture was heated at 80 °C for 18 h and allowed to cool to room temperature. The solvent was removed under a vacuum and the crude material was absorbed onto a plug of silica gel and purified by chromatography through a silica gel column (12 g), eluting with a gradient of 100% DCM to 2% 2M NH_3·MeOH in DCM, to provide 2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(cyclopropylethynyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol (55 mg) as a mixture of enantiomers.

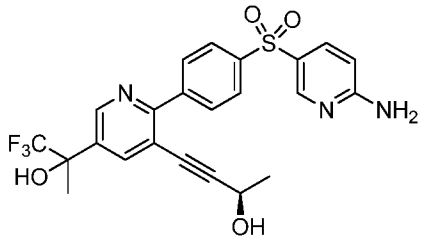




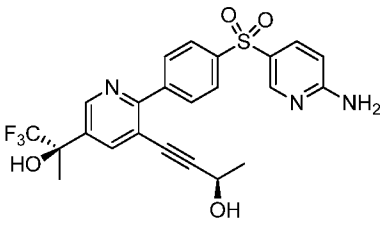
(2R)- 2-(6-(4-((6-Amino-3-pyridinyl)sulfonyl)phenyl)-5-(cyclopropylethynyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol and (2S)- 2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(cyclopropylethynyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol

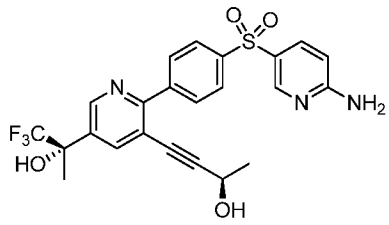
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (d, J = 1.96 Hz, 1H), 8.47 (d, J = 2.54 Hz, 1H), 8.03 - 8.11 (m, 3H), 7.95 - 8.02 (m, 2H), 7.81 (dd, J = 2.54, 9.00 Hz, 1H), 7.11 (s, 2H), 6.96 (s, 1H), 6.51 (d, J = 9.00 Hz, 1H), 1.76 (s, 3H), 1.50 (tt, J = 4.96, 8.24 Hz, 1H), 0.82 - 0.89 (m, 2H), 0.60 - 0.68 (m, 2H); m/z (ESI, +ve ion) 488.0 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.302 μM.

EXAMPLE 46: (2R)-4-(2-(4-((6-Amino-3-pyridinyl)sulfonyl)phenyl)-5-(2,2,2-trifluoro-1-hydroxy-1-methylethyl)-3-pyridinyl)-3-butyn-2-ol



A glass reaction vial was charged with 2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-chloro-3-pyridinyl)-1,1,1-trifluoro-2-propanol (425 mg, 0.93 mmol, Example 44, step 1), X-Phos palladacycle (34 mg, 0.05 mmol, Strem Chemical Inc, Newburyport, MA), cesium carbonate (907 mg, 2.78 mmol, Sigma-Aldrich, St. Louis, MO), (2R)-3-butyn-2-ol (0.361 mL, 4.64 mmol, Sigma-Aldrich, St. Louis, MO), and ACN (3 mL). The vial was closed and purged with nitrogen for several minutes. The reaction mixture was heated at 80 °C for 18 h and allowed to cool to room temperature. The solvent was removed under a vacuum and the crude material was absorbed onto a plug of silica gel and purified by chromatography through a silica gel column (40 g), eluting with a gradient of 2% to 4% 2M NH_3·MeOH in DCM, to provide (2R)-4-(2-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(2,2,2-trifluoro-1-hydroxy-1-methylethyl)-3-pyridinyl)-3-butyn-2-ol (176 mg) as a tan solid and a mixture of diastereomers.

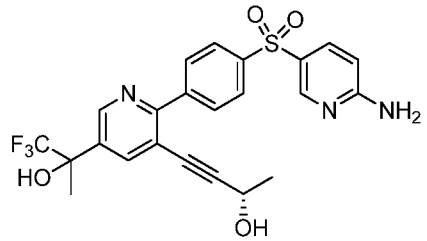




(2R)-4-(2-(4-((6-Amino-3-pyridinyl)sulfonyl)phenyl)-5-((1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-3-pyridinyl)-3-butyn-2-ol and (2R)-4-(2-(4-((6-Amino-3-pyridinyl)sulfonyl)phenyl)-5-((1S)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-3-pyridinyl)-3-butyn-2-ol

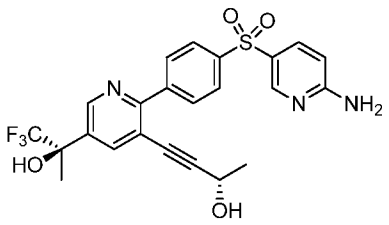
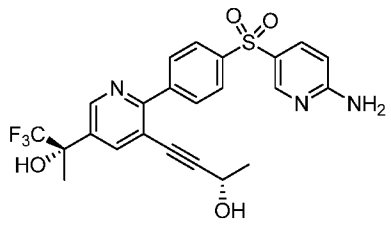
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.87 (d, J = 1.96 Hz, 1H), 8.48 (d, J = 2.35 Hz, 1H), 8.16 (d, J = 8.61 Hz, 2H), 8.11 (d, J = 2.15 Hz, 1H), 8.01 (d, J = 8.61 Hz, 2H), 7.82 (dd, J = 2.64, 8.90 Hz, 1H), 7.13 (s, 2H), 7.03 (s, 1H), 6.53 (d, J = 9.00 Hz, 1H), 5.49 (d, J = 5.67 Hz, 1H), 4.56 (quin, J = 6.26 Hz, 1H), 1.80 (s, 3H), 1.31 (d, J = 7.04 Hz, 3H); m/z (ESI, +ve ion) 492.0 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.116 μM.

EXAMPLE 47: (2S)-4-(2-(4-((6-Amino-3-pyridinyl)sulfonyl)phenyl)-5-(2,2,2-trifluoro-1-hydroxy-1-methylethyl)-3-pyridinyl)-3-butyn-2-ol



A glass reaction vial was charged with 2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-chloro-3-pyridinyl)-1,1,1-trifluoro-2-propanol (480 mg, 1.05 mmol, Example 44, step 1), X-Phos palladacycle (39 mg, 0.05 mmol, Strem Chemical Inc, Newburyport, MA), cesium carbonate (683 mg, 2.10 mmol, Sigma-Aldrich, St. Louis, MO), (2S)-3-butyn-2-ol (0.415 mL, 5.24 mmol, Sigma-Aldrich, St. Louis, MO), and ACN (5 mL). The vial was closed and purged with nitrogen for several minutes. The reaction mixture was heated at 80 °C for 18 h and allowed to cool to room temperature. The solvent was removed under a vacuum and the crude material was absorbed onto a plug of silica gel and purified by chromatography through a silica gel column (40 g), eluting with a gradient of 2% to 4% 2M NH_3·MeOH in DCM, to provide (2S)-4-(2-(4-((6-

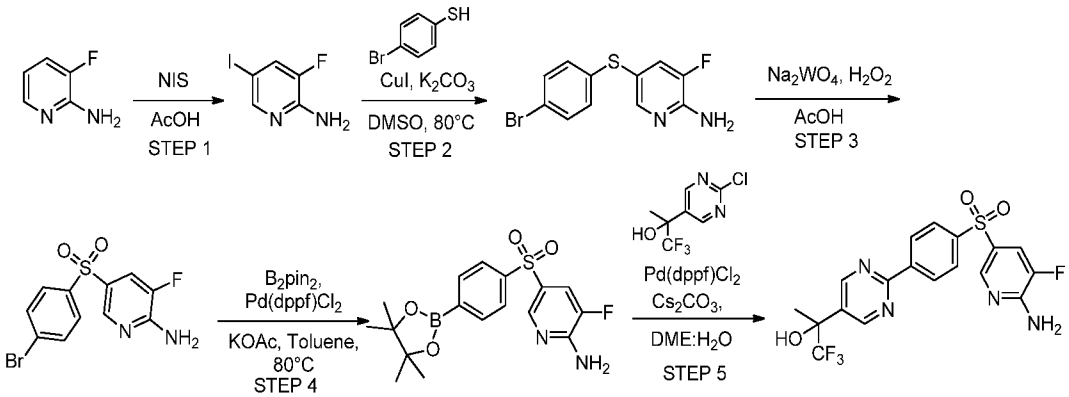
amino-3-pyridinyl)sulfonyl)phenyl)-5-(2,2,2-trifluoro-1-hydroxy-1-methylethyl)-3-pyridinyl)-3-butyn-2-ol (170 mg) as a tan solid and a mixture of diastereomers.

(2S)-4-(2-(4-((6-Amino-3-pyridinyl)sulfonyl)phenyl)-5-((1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-3-pyridinyl)-3-butyn-2-ol and (2S)-4-(2-(4-((6-Amino-3-pyridinyl)sulfonyl)phenyl)-5-((1S)-2,2,2-trifluoro-1-hydroxy-1-methylethyl)-3-pyridinyl)-3-butyn-2-ol

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.87 (d, J = 1.96 Hz, 1H), 8.48 (d, J = 2.35 Hz, 1H), 8.16 (d, J = 8.41 Hz, 2H), 8.11 (d, J = 1.96 Hz, 1H), 8.01 (d, J = 8.41 Hz, 2H), 7.82 (dd, J = 2.54, 8.80 Hz, 1H), 7.13 (s, 2H), 7.03 (s, 1H), 6.53 (d, J = 9.00 Hz, 1H), 5.49 (d, J = 5.48 Hz, 1H), 4.51 - 4.61 (m, 1H), 1.80 (s, 3H), 1.30 (d, J = 6.65 Hz, 3H) ; m/z (ESI, +ve ion) 492.0 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.274 μM.

EXAMPLE 48: 2-(2-(4-((6-Amino-5-fluoro-3-pyridinyl)sulfonyl)phenyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol



STEP 1: 3-Fluoro-5-iodo-2-pyridinamine

A 25-mL round-bottomed flask was charged with 3-fluoro-2-pyridinamine (1.0 g 8.9 mmol, Matrix Scientific, USA) and AcOH (10 mL). The reaction mixture was cooled to 0 °C and NIS (2.0 g, 8.9 mmol, Sigma-Aldrich, India) was added in portions under a nitrogen atmosphere. The reaction mixture was warmed to room temperature and stirred for 5 h. The reaction mixture was diluted with cold water (30 mL), followed by a mixture of 5% $Na_2S_2O_3$ (50 mL) and $NaHCO_3$ (100 mL) at room temperature. The solid that formed was collected via filtration, washed thoroughly with water and dried under reduced pressure at 40 °C to give 3-fluoro-5-iodo-2-pyridinamine (2.0 g) as a white solid.

STEP 2: 5-((4-Bromophenyl)sulfanyl)-3-fluoro-2-pyridinamine

In a 50-mL round-bottomed flask, the solution of 4-bromobenzenethiol (1.0 g, 5.3 mmol) and 3-fluoro-5-iodo-2-pyridinamine (0.63 g , 2.7 mmol) in DMSO (10 mL) was degassed by purging with argon gas at room temperature for 10 min. K_2CO_3 (2.18 g, 15.9 mmol) and CuI (0.05 g, 0.26 mmol) were added sequentially to the above reaction mixture at room temperature under argon atmosphere. The reaction mixture was heated overnight at 100 °C under argon atmosphere. The reaction mixture was cooled to room temperature and filtered through a pad of Celite® (diatomaceous earth). The filtrate was diluted with cold water (50 mL) and ethyl acetate (100 mL). The EtOAc layer was separated, washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue obtained was purified by silica gel (100 to 200 mesh) column chromatography (elution 30% EtOAc-hexanes) to give 5-((4-bromophenyl)sulfanyl)-3-fluoro-2-pyridinamine (400 mg) as a white solid.

STEP 3: 5-((4-Bromophenyl)sulfonyl)-3-fluoro-2-pyridinamine

In a 25-mL round-bottomed flask, the stirred solution of 5-((4-bromophenyl)sulfanyl)-3-fluoro-2-pyridinamine (700 mg, 2.34 mmol) in AcOH

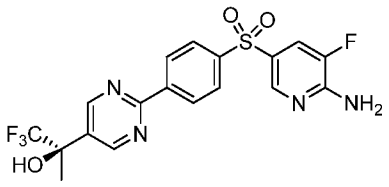
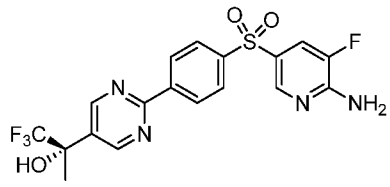
(10 mL) was cooled to 0 °C. Na_2WO_4 (404 mg, 1.17 mmol, Rankem, India) and H_2O_2 (30%, 416 mg, 11.7 mmol) were added sequentially to the above solution at the same temperature. The reaction mixture was allowed to warm to room temperature and stirred for 0.5 h. The reaction mixture was poured into a cold aqueous saturated $NaHCO_3$ solution and extracted with EtOAc. The EtOAc extract was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue obtained was purified by silica gel (100 to 200 mesh) column chromatography (elution 50% EtOAc-hexanes) to give 5-((4-bromophenyl)sulfonyl)-3-fluoro-2-pyridinamine (500 mg) as a white solid.

STEP 4: 3-Fluoro-5-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)-2-pyridinamine

In a 50-mL round-bottomed flask, the stirred solution of 5-((4-bromophenyl)sulfonyl)-3-fluoro-2-pyridinamine (500 mg, 1.50 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (769 mg, 3.03 mmol, Sigma-Aldrich, India) and KOAc (743 mg, 7.57 mmol) in toluene (5.0 mL) was degassed by purging with argon gas at room temperature for 15 min. $Pd(dppf)Cl_2$ (61 mg, 0.07 mmol, Molekula Life Sciences, India) was added to the above solution at room temperature under argon atmosphere. The resulting reaction mixture was heated at 80 °C for 2 h under argon atmosphere. The reaction mixture was cooled to room temperature and filtered through a pad of Celite® (diatomaceous earth). The filtrate was diluted with water (30 mL) and EtOAc (100 mL). The organic extract was washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue obtained was purified by silica gel (100 to 200 mesh) column chromatography (elution 30% EtOAc-hexanes) to give 3-fluoro-5-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)-2-pyridinamine (300 mg) as a white solid.

STEP 5: 2-(2-(4-((6-Amino-5-fluoro-3-pyridinyl)sulfonyl)phenyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol

In a 20-mL resealable reaction tube, the stirred solution of 2-(2-chloropyrimidin-5-yl)-1,1,1-trifluoropropan-2-ol (100 mg, 0.442 mmol, Intermediate S) and 3-fluoro-5-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)-2-pyridinamine (200 mg, 0.530 mmol) in DME (1 mL) and water (0.1 mL) was degassed by purging with argon gas at room temperature for 15 min. Cs_2CO_3 (428 mg, 1.33 mmol, Molekula Life Sciences, India) and $Pd(dppf)Cl_2$ (18 mg, 0.022 mmol, Molekula Life Sciences , India) were added sequentially to the above reaction mixture at room temperature under argon atmosphere. The reaction tube was sealed and mixture was heated at 100 °C for 30 min in a microwave reactor (Biotage AB, Inc., Uppsala, Sweden). The reaction mixture was cooled to room temperature and filtered through a pad of Celite® (diatomaceous earth). The filtrate was diluted with water (10 mL) and EtOAc (30 mL). The organic extract was washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue obtained was purified using silica gel preparative TLC (Sigma-Aldrich, India; eluent 50% EtOAc-hexanes) to give 2-(2-(4-((6-amino-5-fluoro-3-pyridinyl)sulfonyl)phenyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol (40 mg) as a white solid and a mixture of enantiomers.

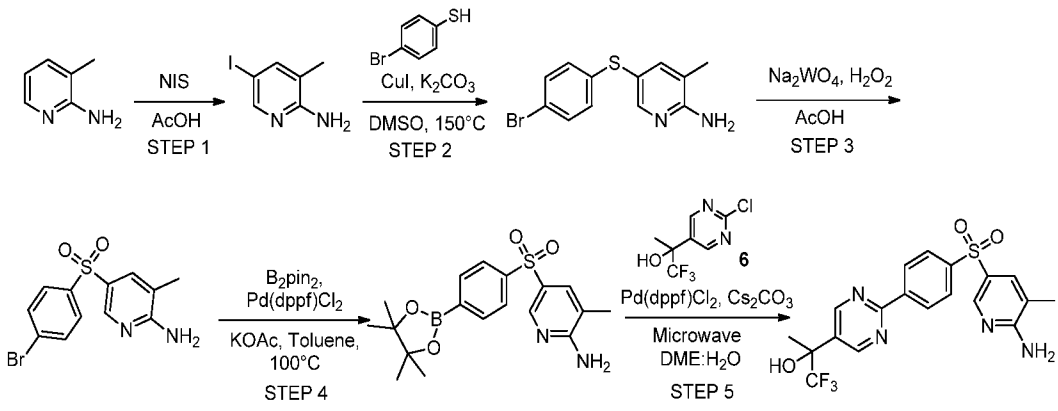



(2R)-2-(2-(4-((6-Amino-5-fluoro-3-pyridinyl)sulfonyl)phenyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol and (2S)-2-(2-(4-((6-Amino-5-fluoro-3-pyridinyl)sulfonyl)phenyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.17 (s, 2H), 8.60 (d, J = 8.4 Hz, 2H), 8.38 (s, 1H), 8.14 (d, J = 8.4 Hz, 2H), 7.90 (dd, J = 10.4, 2 Hz, 1H), 7.52 (s, 2H),

7.19 (s, 1H) 1.83 (s, 3H); m/z (ESI, +ve ion) 442.9 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.667 μM.

EXAMPLE 49: 2-(2-(4-((6-Amino-5-methyl-3-pyridinyl)sulfonyl)phenyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol



STEP 1: 5-Iodo-3-methyl-2-pyridinamine

In a 250-mL round-bottomed flask, a solution of 3-methylpyridin-2-amine (4.57 g, 42.3 mmol) in AcOH (50 mL) was cooled to 0 °C. NIS (9.5 g, 42 mmol, Sigma-Aldrich, India) was added in portions to the above solution at the same temperature under nitrogen atmosphere. The reaction mixture was warmed to room temperature and stirred at room temperature for 3 h. The reaction mixture was diluted with cold water (100 mL), followed by a mixture of 5% $Na_2S_2O_3$ (40 mL) and $NaHCO_3$ (100 mL) at room temperature. The solid that formed was filtered, washed thoroughly with water and dried rigorously under reduced pressure at 50 °C to give 5-iodo-3-methyl-2-pyridinamine (6.0 g) as a yellow solid.

STEP 2: 5-((4-Bromophenyl)sulfanyl)-3-methyl-2-pyridinamine

In a 50 mL resealable tube, a solution of 4-bromothiophenol (3.2 g, 17 mmol, Sigma-Aldrich, India) and 5-iodo-3-methyl-2-pyridinamine (2 g , 8.5

mmol) in DMSO (20 mL) was degassed by purging with argon gas at room temperature for 10 min. Potassium carbonate (3.53 g, 25.6 mmol) and cooper iodide (0.2 g ,1.1 mmol) were added sequentially to the above reaction mixture at room temperature under argon atmosphere The reaction tube was sealed under argon atmosphere and reaction mixture was heated at 150 °C for 18 h. The reaction mixture was cooled to room temperature and filtered through a Celite® (diatomaceous earth) pad. The filtrate was diluted with cold water (200 mL) and ethyl acetate (100 mL). The EtOAc layer was separated, washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue obtained was purified by silica gel (60 to120 mesh) column chromatography (eluent, 20% EtOAc-hexanes) to give 5-((4-bromophenyl)sulfanyl)-3-methyl-2-pyridinamine (2.7 g) as a white solid.

STEP 3: 5-((4-Bromophenyl)sulfonyl)-3-methyl-2-pyridinamine

In a 50-mL round-bottomed flask, the stirred solution of -((4-bromophenyl)sulfanyl)-3-methyl-2-pyridinamine (1.7 g, 5.8 mmol) in AcOH (17 mL) was cooled to 0 °C. Na_2WO_4 (0.95 g, 2.9 mmol, Sigma-Aldrich, India) and H_2O_2 (30%, 3.26 mL, 28.8 mmol) were added sequentially to the above solution at the same temperature. The reaction mixture was warmed to room temperature (30 min) and stirred for 20 minutes. The reaction mixture was poured into cold saturated $NaHCO_3$ and extracted with EtOAc. The EtOAc extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue obtained was purified by silica gel (100 to 200 mesh) column chromatography (eluent, 50% EtOAc-hexanes) to afford 5-((4-bromophenyl)sulfonyl)-3-methyl-2-pyridinamine (0.76 g) as a white solid.

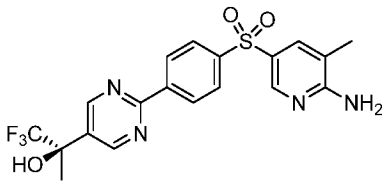
STEP 4: 3-Methyl-5-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)-2-pyridinamine

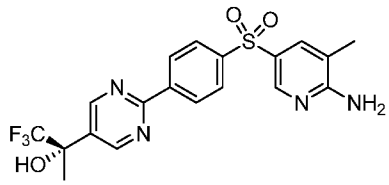
In a 20-mL resealable tube, the stirred solution of 5-((4-bromophenyl)sulfonyl)-3-methyl-2-pyridinamine (400 mg, 1.22 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (400 mg, 1.57 mmol, Sigma-Aldrich, India) and KOAc (600 mg, 6.12 mmol) in toluene (10 mL) was degassed by purging with argon gas at room temperature for 15 min. $Pd(dppf)Cl_2$ (61 mg, 0.07 mmol, Sigma-Aldrich, India) was added to the above solution at room temperature under argon atmosphere. The reaction tube was sealed under argon atmosphere and reaction mixture was heated at 100 °C for 4h. The reaction mixture was cooled to room temperature and filtered through a pad of Celite® (diatomaceous earth). The filtrate was diluted with water (50 mL) and EtOAc (50 mL). The organic extract was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue obtained was purified by silica gel (100 to 200 mesh) column chromatography (eluent, 30% EtOAc-hexanes) to give 3-methyl-5-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)-2-pyridinamine (630 mg) as a brown solid.

STEP 5: 2-(2-(4-((6-Amino-5-methyl-3-pyridinyl)sulfonyl)phenyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol

In a 20-mL resealable reaction tube, the stirred solution of 2-(2-chloropyrimidin-5-yl)-1,1,1-trifluoropropan-2-ol (250 mg, 1.10 mmol, Intermediate S), 3-methyl-5-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)-2-pyridinamine (500 mg, 1.33 mmol) in DME (10 mL) and water (1 mL) was degassed by purging with argon gas at room temperature for 15 min. Cesium carbonate (1070 mg, 3.29 mmol, Molekula Life Sciences, India) and $Pd(dppf)Cl_2$ (45 mg, 0.055 mmol, Sigma-Aldrich, India) were added sequentially to the above reaction mixture at room temperature under argon atmosphere. The reaction tube was sealed and mixture was heated at 100 °C for 30 min in a microwave reactor (Biotage AB, Inc., Uppsala, Sweden). The reaction mixture was cooled to room temperature and filtered through a pad of Celite® (diatomaceous earth). The filtrate was diluted with water (50 mL) and EtOAc (50

mL). The organic extract was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue obtained was purified by silica gel (100 to 200 mesh) column chromatography (eluent, 50% EtOAc-hexanes) to give 2-(2-(4-((6-amino-5-methyl-3-pyridinyl)sulfonyl)phenyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol (200 mg) as a white solid and a mixture of enantiomers.

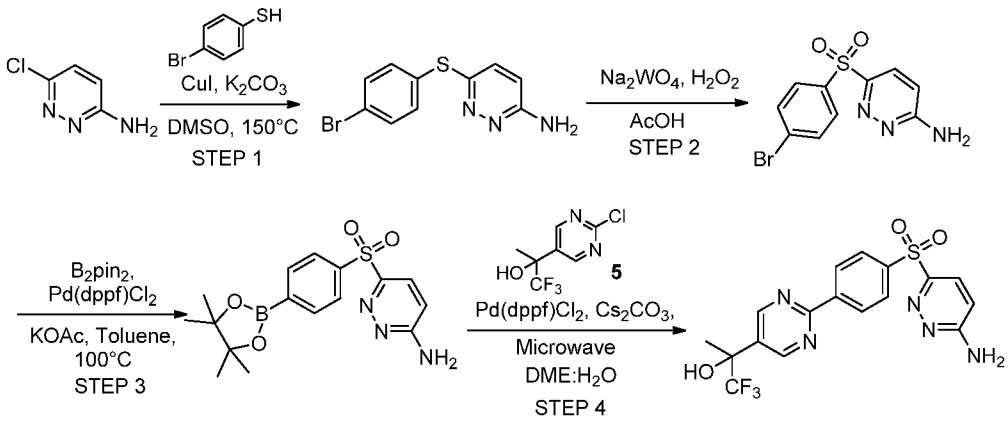




(2R)-2-(2-(4-((6-Amino-5-methyl-3-pyridinyl)sulfonyl)phenyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol and (2S)-2-(2-(4-((6-Amino-5-methyl-3-pyridinyl)sulfonyl)phenyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.16 (s, 2H), 8.60 (d, J = 8.8Hz, 2H), 8.40 (d, J = 2.4Hz, 1H), 8.10 (d, J = 8.4Hz, 2H), 7.71 (d, J = 1.2Hz, 1H), 7.18 (s, 1H), 6.89 (s, 2H), 2.07 (s, 3H), 1.83 (s, 3H); m/z (ESI, +ve ion) 439.0 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 1.48 μM.

EXAMPLE 50: 2-(2-(4-((6-Amino-3-pyridazinyl)sulfonyl)phenyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol



STEP 1: 6-((4-Bromophenyl)sulfanyl)-3-pyridazinamine

In a 50-mL resalable reaction tube, the solution of 6-chloro-3-pyridazinamine (0.5 g , 3.9 mmol, Combi-blocks, USA) and 4-bromothiophenol (1.45 g, 7.67 mmol, Sigma-Aldrich, India) in DMSO (5 mL) was degassed by purging with argon gas at room temperature for 10 min. Potassium carbonate (1.59 g, 11.5 mmol) and copper iodide (0.05 g, 0.26 mmol) were added sequentially to the above reaction mixture at room temperature under argon atmosphere The reaction tube was sealed under argon atmosphere and the reaction mixture was heated at 150 °C for 18 h under argon atmosphere. The reaction mixture was cooled to room temperature and filtered through a Celite® (diatomaceous earth) pad. The filtrate was diluted with cold water (50 mL) and ethyl acetate (50 mL). The EtOAc layer was separated, washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue obtained was purified by silica gel (60 to 120 mesh) column chromatography (eluent 50% EtOAc-hexanes) to give 6-((4-bromophenyl)sulfanyl)-3-pyridazinamine (800 mg) as a white solid.

STEP 2: 6-((4-Bromophenyl)sulfonyl)-3-pyridazinamine

In a 100-mL round-bottomed flask, the stirred solution of 6-((4-bromophenyl)sulfanyl)-3-pyridazinamine (0.8 g, 2.8 mmol) in AcOH (8 mL) was cooled to 0 °C. Na_2WO_4 (0.46 g, 1.4 mmol) and H_2O_2 (30%, 1.6 mL, 14 mmol) were added sequentially to the above solution at the same temperature. The reaction mixture was warmed to room temperature and stirred for 1h. The reaction mixture was poured into a cold saturated $NaHCO_3$ solution and extracted with EtOAc. The EtOAc extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue obtained was purified by silica gel (60 to 120 mesh) column chromatography (eluent 80% EtOAc-hexanes) to give 6-((4-bromophenyl)sulfonyl)-3-pyridazinamine (250 mg) as a white solid.

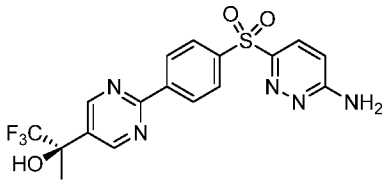
STEP 3: 6-((4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)-3-pyridazinamine

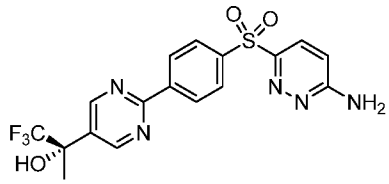
In a 10-mL resalable reaction tube, the stirred solution of 6-((4-bromophenyl)sulfonyl)-3-pyridazinamine (250 mg, 0.79 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (260 mg, 1.02 mmol, Sigma-Aldrich, India) and KOAc (400 mg, 4.08 mmol) in toluene (5 mL) was degassed by purging with argon gas at room temperature for 15 min. $Pd(dppf)Cl_2$ (32 mg, 0.039 mmol, Sigma-Aldrich, India) was added to the above solution at room temperature under argon atmosphere. The reaction tube was sealed under argon atmosphere and reaction mixture was heated at 100 °C for 4 h. The reaction mixture was cooled to room temperature and filtered through a Celite® (diatomaceous earth) pad. The filtrate was diluted with cold water (50 mL) and EtOAc (50 mL). The organic extract was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 6-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)-3-pyridazinamine (270 mg) as a brown solid.

STEP 4: 2-(2-(4-((6-Amino-3-pyridazinyl)sulfonyl)phenyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol

In a 20-mL resealable reaction tube, the stirred solution of 2-(2-chloropyrimidin-5-yl)-1,1,1-trifluoropropan-2-ol (125 mg, 0.55 mmol, Intermediate S), 6-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)-3-pyridazinamine (259 mg, 0.71 mmol) in DME (8 mL) and water (0.8 mL) was degassed by purging with argon gas at room temperature for 15 min. Cs_2CO_3 (530 mg, 1.63 mmol) and $Pd(dppf)Cl_2$ (22.6 mg, 0.027 mmol, Sigma-Aldrich, India) were added sequentially to the above reaction mixture at room temperature under argon atmosphere. The reaction tube was sealed under argon atmosphere and mixture was heated at 100 °C for 30 min in microwave (Biotage AB, Inc., Uppsala, Sweden). The reaction mixture was cooled to room

temperature and filtered through a pad of Celite® (diatomaceous earth). The filtrate was diluted with water (50 mL) and EtOAc (50 mL). The organic extract was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue obtained was purified by preparative TLC (eluent 10% MeOH-$CHCl_3$) to give 2-(2-(4-((6-amino-3-pyridazinyl)sulfonyl)phenyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol (18 mg) as a yellow solid and a mixture of enantiomers.

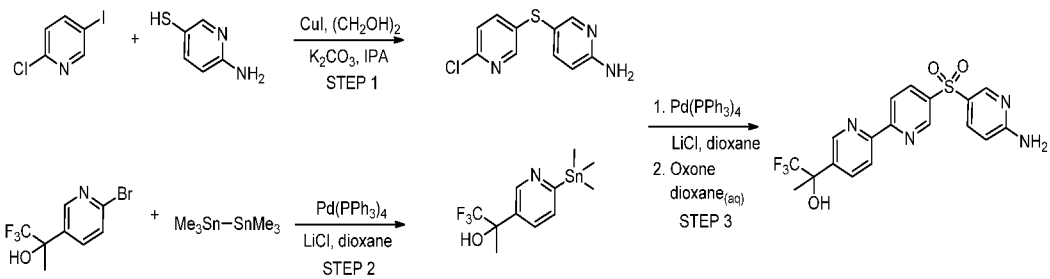




(2R)-2-(2-(4-((6-Amino-3-pyridazinyl)sulfonyl)phenyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol and (2S)-2-(2-(4-((6-Amino-3-pyridazinyl)sulfonyl)phenyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.18 (s, 2H), 8.66 (d, J = 8.4Hz, 2H), 8.15 (d, J = 8.4Hz, 2H), 7.97 (d, J = 9.2Hz, 1H), 7.48 (br s, 2H), 7.21 (s, 1H), 6.93 (d, J = 9.2Hz, 1H), 1.84(s, 3H); m/z (ESI, +ve ion) 425.9 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.32 μM.

EXAMPLE 51: 2-(5'-((6-Amino-3-pyridinyl)sulfonyl)-2,2'-bipyridin-5-yl)-1,1,1-trifluoro-2-propanol



STEP 1: 5-((6-Chloro-3-pyridinyl)sulfanyl)-2-pyridinamine

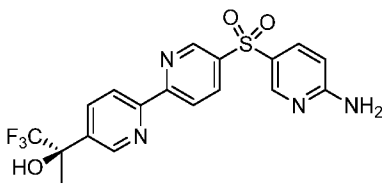
To a stirred suspension of 6-aminopyridine-3-thiol (0.518 g, 4.11 mmol, Princeton Bio, NJ), 2-chloro-5-iodopyridine (0.983 g, 4.11 mmol, Small Molecules, NJ) was added copper iodide (389 mg, 2.05 mmol, Alfa Aesar, MA), K_2CO_3 (1.418 g, 10.26 mmol), 1,2-dihydroxyethane (0.572 mL, 10.3 mmol), and 2-propanol (7 mL) and the reaction mixture was heated at 90 °C for 48 h. After being cooled to room temperature, the mixture was passed through a pad of Celite® (diatomaceous earth). The filtrate cake was washed with ethyl acetate and DCM (15 mL x 3 each). The combined organics were concentrated under a vacuum. The crude material was absorbed onto a plug of silica gel and purified by chromatography through a silica gel column (40 g), eluting with a gradient of 0 % to 70 % EtOAc in hexanes, to provide 5-((6-chloro-3-pyridinyl)sulfanyl)-2-pyridinamine (0.447 g) as an off-white solid.

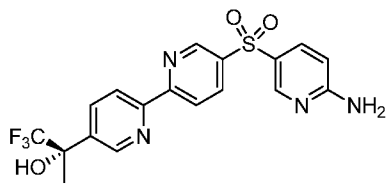
STEP 2: 1,1,1-Trifluoro-2-(6-(trimethylstannanyl)-3-pyridinyl)-2-propanol

To a stirred mixture of 2-(6-bromo-3-pyridinyl)-1,1,1-trifluoro-2-propanol (0.53 g, 1.963 mmol, Example 1, alternate route step 1), $Pd(Ph_3P)_4$ (0.113 g, 0.098 mmol, Strem Chemical Inc, Newburyport, MA), lithium chloride (0.416 g, 9.81 mmol, Sigma-Aldrich, St. Louis, MO) in dioxane (3 mL) was added hexamethylditin (0.610 mL, 2.94 mmol, Sigma-Aldrich, St. Louis, MO). The reaction mixture was stirred at 90 °C for 18 h. After cooling to room temperature, the reaction mixture was passed through a pad of Celite® (diatomaceous earth). The filter cake was washed with ethyl acetate (15 mL x 3) and the combined organic phases were concentrated under a vacuum to give the 1,1,1-trifluoro-2-(6-(trimethylstannanyl)-3-pyridinyl)-2-propanol (655 mg) as a brown semi-solid.

STEP 3: 2-(5'-((6-Amino-3-pyridinyl)sulfonyl)-2,2'-bipyridin-5-yl)-1,1,1-trifluoro-2-propanol

A stirred mixture of 5-((6-chloro-3-pyridinyl)sulfanyl)-2-pyridinamine (52 mg, 0.22 mmol), 1,1,1-trifluoro-2-(6-(trimethylstannanyl)-3-pyridinyl)-2-propanol (116 mg, 0.328 mmol), $Pd(Ph_3P)_4$ (13 mg, 11 μmol, Strem Chemical Inc, Newburyport, MA), and lithium chloride (46 mg, 1.1 mmol, Sigma-Aldrich, St. Louis, MO) in dioxane (2 mL) was heated at 90 °C for 18 h. The reaction mixture was allowed to cool to room temperature and was passed through a pad of Celite® (diatomaceous earth). The filter cake was washed with ethyl acetate (10 mL x 3) and the combined organic phases were concentrated under a vacuum. The crude material was absorbed onto a plug of silica gel and purified by chromatography through a silica gel column (12 g), eluting with a gradient of 0% to 5% 2M NH_3·MeOH in CH_2Cl_2, to provide the corresponding thioether as light-yellow solid, which was dissolved in dioxane (2 mL) and a solution of potassium peroxysulfate (269 mg, 0.438 mmol, Sigma-Aldrich, St. Louis, MO) in water (1 mL) was slowly added. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 20 mL) The organic extract was washed with brine (1 x 30 mL) and dried over Na_2SO_4. The solution was filtered and concentrated under a vacuum. The crude material was absorbed onto a plug of silica gel and purified by chromatography through a silica gel column (12 g), eluting with a gradient of 0% to 5% 2M NH_3·MeOH in CH_2Cl_2, to provide 2-(5'-((6-amino-3-pyridinyl)sulfonyl)-2,2'-bipyridin-5-yl)-1,1,1-trifluoro-2-propanol (9 mg) as an off-white solid and a mixture of enantiomers.





(2R)-2-(5'-((6-amino-3-pyridinyl)sulfonyl)-2,2'-bipyridin-5-yl)-1,1,1-trifluoro-2-propanol and (2S)-2-(5'-((6-amino-3-pyridinyl)sulfonyl)-2,2'-bipyridin-5-yl)-1,1,1-trifluoro-2-propanol

^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.15 (d, *J* = 1.76 Hz, 1H), 8.93 (s, 1H), 8.52 - 8.65 (m, 2H), 8.49 (d, *J* = 8.41 Hz, 1H), 8.41 (dd, *J* = 2.25, 8.51 Hz, 1H), 8.18 (dd, *J* = 1.76, 8.41 Hz, 1H), 7.90 (dd, *J* = 2.54, 9.00 Hz, 1H), 6.62 (d, *J* = 9.19 Hz, 1H), 1.83 (s, 3H); m/z (ESI, +ve ion) 425.2 $(M+H)^+$. GK-GKRP IC_{50} (Binding) = 0.236 μM.

CLAIMS

What is claimed is:

1. A compound, or a pharmaceutically acceptable salt thereof, selected from:

2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol;

2-(6-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(2-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-5-pyrimidinyl)-3,3,3-trifluoro-1,2-propanediol;

2-(4-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-((4-(hydroxymethyl)tetrahydro-2h-pyran-4-yl)methyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

1,1,1-trifluoro-2-(4-((2S)-2-(((1-methylethyl)amino)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol;

1,1,1-trifluoro-2-(4-((2S)-2-((((3-methyl-3-oxetanyl)methyl)amino)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol;

2-(4-((2S)-2-((cyclobutylamino)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-1,1,1-trifluoro-2-propanol;

1,1,1-trifluoro-2-(4-((2R)-2-(((1-methylethyl)sulfonyl)methyl)-4-(2-thiophenylsulfonyl)-1-piperazinyl)phenyl)-2-propanol;

2-(4-(4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-3,3,3-trifluoro-1,2-propanediol;

2-(2-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-((1Z)-2-chloro-1-propen-1-yl)-1-piperazinyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol;

(2S)-2-(2-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-((1Z)-2-chloro-1-propen-1-yl)-1-piperazinyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol;

2-(6-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-3-pyridinyl)-3,3,3-trifluoro-1,2-propanediol;

2-(4-((2*S*)-4-((6-amino-3-pyridazinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-((2S)-4-((6-amino-3-pyridazinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-3,3,3-trifluoro-1,2-propanediol;

2-(4-(4-((5-amino-1,3-thiazol-2-yl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-((2S)-4-((6-amino-5-methyl-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-((2S)-4-((6-amino-5-bromo-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

3-bromo-5-(((3S)-3-(1-propyn-1-yl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinyl)sulfonyl)-2-pyridinol;

2-amino-5-(((3S)-3-(1-propyn-1-yl)-4-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1-piperazinyl)sulfonyl)-3-pyridinecarbonitrile;

(2R)-2-(4-(4-((6-amino-3-pyridinyl)sulfonyl)-2-($^{2}H_3$)-1-propyn-1-yl-1-piperazinyl)phenyl)-1,1,1-trifluoro-2-propanol;

2-(4-(4-((6-amino-2-(methylamino)-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-(4-((6-amino-2-methoxy-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-(4-((6-amino-2-(benzyloxy)-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-(4-((6-amino-2-(1-propyn-1-yl)-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-(4-((6-amino-2-(1-propyn-1-yl)-3-pyridinyl)sulfonyl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-(4-((6-amino-3-pyridinyl)sulfonyl)-2-(2-methyl-1-propen-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-(4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-butyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-(4-((6-amino-3-pyridinyl)sulfonyl)-2-(3,3-dimethyl-1-butyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-((1z)-1-propen-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-(4-((6-amino-3-pyridinyl)sulfonyl)-2-propyl-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

3-(4-((6-amino-3-pyridinyl)sulfonyl)-1-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-2-piperazinyl)-2-propyn-1-ol;

2-(4-(4-((6-amino-3-pyridinyl)sulfonyl)-2-(3-fluoro-1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(4-((2S)-4-((2-amino-5-pyrimidinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

(2R)-2-(4-((2S)-4-((2-amino-5-pyrimidinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)phenyl)-1,1,1-trifluoro-2-propanol;

2-(6-((2S)-4-((6-amino-3-pyridinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-5-chloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

3-(4-((6-amino-3-pyridinyl)sulfonyl)-1-(5-(2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-pyrimidinyl)-2-piperazinyl)-2-propyn-1-ol;

2-(2-((2S)-4-((6-amino-3-pyridazinyl)sulfonyl)-2-(1-propyn-1-yl)-1-piperazinyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol;

1,1,1-trifluoro-2-(6-(4-(phenylsulfonyl)phenyl)-5-(1-propyn-1-yl)-3-pyridinyl)-2-propanol;

2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-chloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(1-propyn-1-yl)-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-cyclopropyl-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(3-methoxy-1-propyn-1-yl)-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol;

(2R)-4-(2-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)-3-pyridinyl)-3-butyn-2-ol;

3-(2-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)-3-pyridinyl)-2-propyn-1-ol;

1,1,1,3,3,3-hexafluoro-2-(5'-(phenylsulfonyl)-2,2'-bipyridin-5-yl)-2-propanol;
2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(3-methoxy-1-propyn-1-yl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol;

2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(cyclopropylethynyl)-3-pyridinyl)-1,1,1-trifluoro-2-propanol;

(2R)-4-(2-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(2,2,2-trifluoro-1-hydroxy-1-methylethyl)-3-pyridinyl)-3-butyn-2-ol;

(2S)-4-(2-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(2,2,2-trifluoro-1-hydroxy-1-methylethyl)-3-pyridinyl)-3-butyn-2-ol;

2-(2-(4-((6-amino-5-fluoro-3-pyridinyl)sulfonyl)phenyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol;

2-(2-(4-((6-amino-5-methyl-3-pyridinyl)sulfonyl)phenyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol;

2-(2-(4-((6-amino-3-pyridazinyl)sulfonyl)phenyl)-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol; or

2-(5'-((6-amino-3-pyridinyl)sulfonyl)-2,2'-bipyridin-5-yl)-1,1,1-trifluoro-2-propanol.

2. A method of treating type 2 diabetes, hyperglycemia, impaired glucose tolerance, insulin resistance, retinopathy, nephropathy, neuropathy, cataracts, glaucoma, Syndrome X, or polycystic ovarian syndrome, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound in accordance with claim 1, or a pharmaceutically acceptable salt thereof.

3. The method of claim 2 wherein the treatment is for type 2 diabetes.

4. A pharmaceutical composition comprising a compound in accordance with claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/026508

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/12 C07D401/14 A61K31/44 A61K31/496 A61K31/505
C07D401/04 C07D401/12 C07D405/12 C07D409/12 C07D417/12
C07C403/14 C07D213/52 A61P3/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/116107 A2 (TAKEDA SAN DIEGO INC [US]; CHERUVALLATH ZACHARIA [US]; FENG JUN [US];) 25 September 2008 (2008-09-25) examples 33,36	1-4
A	WO 2007/070506 A2 (AMGEN INC [US]; POWERS JAY P [US]; SUN DAQING [US]; TU HUA [US]; YAN X) 21 June 2007 (2007-06-21) paragraph [0140]; examples 1a-4b	1-4
X,P	WO 2012/027261 A1 (AMGEN INC [US]; ASHTON KATE [US]; BARTBERGER MICHAEL DAVID [US]; BO YU) 1 March 2012 (2012-03-01) claims 29-31	1-4

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 June 2013	13/06/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Steinreiber, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2013/026508

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008116107 A2	25-09-2008	US 2009099163 A1	16-04-2009
		WO 2008116107 A2	25-09-2008
WO 2007070506 A2	21-06-2007	AU 2006326540 A1	21-06-2007
		CA 2632027 A1	21-06-2007
		EP 1968962 A2	17-09-2008
		JP 2009519933 A	21-05-2009
		US 2007173494 A1	26-07-2007
		WO 2007070506 A2	21-06-2007
WO 2012027261 A1	01-03-2012	AR 082534 A1	12-12-2012
		AU 2011293584 A1	07-03-2013
		CA 2808590 A1	01-03-2012
		EP 2609081 A1	03-07-2013
		TW 201238941 A	01-10-2012
		US 2012225854 A1	06-09-2012
		UY 33568 A	30-03-2012
		WO 2012027261 A1	01-03-2012