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(71) Applicant *(for all designated States except US)*: **IRM LLC** [US/—]; Hurst Holme, 12 Trott Road, Hamilton, HM 11 (BM).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **ALPER, Phillip** [US/US]; 5460 Caminito Exquisito, San Diego, California 92130 (US). **AZIMIOARA, Mihai** [US/US]; 3770 La Jolla Village Drive, La Jolla, California 92037 (US). **COW, Christopher** [CA/US]; 10878 Creekbridge Place, San Diego, California 92128 (US). **EPPLE, Robert** [AT/US]; 8045 Via San Saba, San Diego, California 92122 (US). **JIANG, Songchun** [CN/US]; 10512 Rancho Carmel Drive, San Diego, California 92128 (US). **LELAIS, Gerald** [CH/US]; 13335 Tiverton Road, San Diego, California 92130 (US). **MICHELLYS, Pierre-yves** [FR/US]; 1416 Corte Bravo, San Marcos, California 92069 (US). **MUTNICK, Daniel** [US/US]; 4526 Florida Street, Apartment 5, San Diego, California 92116 (US). **NIKULIN, Victor** [RU/US]; 1957 Cassia Road, Apartment 103, Carlsbad, California 92011 (US). **WESTCOTT-BAKER, Lucas** [US/US]; 7948 Avenida Navidad #99, San Diego, California 92122 (US).

(74) Agents: REID, Scott et al.; Genomics Institute of the NovartisResearch Foundation, 10675 John Jay Hopkins Drive, San Diego, California 92121 (US).

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(54) Title: COMPOUNDS AND COMPOSITIONS AS MODULATORS OF GPR119 ACTIVITY

(57) Abstract: The invention provides compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with the activity of GPR119.

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COMPOUNDS AND COMPOSITIONS AS MODULATORS OF GPR119 ACTIVITY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Patent Application Number 60/974,064, filed 20 September 2007 and U.S. Provisional Patent Application Number 61/045,263, filed 15 April 2008. The full disclosures of these applications are incorporated herein by reference in their entirety and for all purposes.

BACKGROUND OF THE INVENTION

Field of the Invention

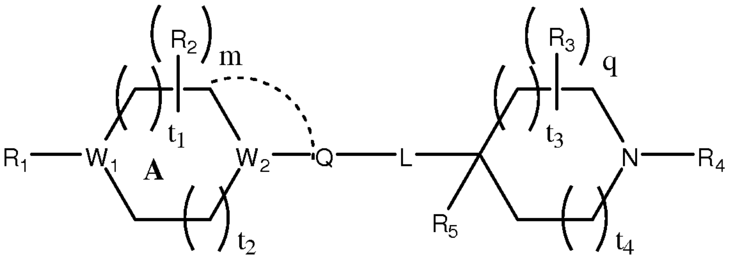
[0002] The invention provides compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with the activity of GPR119.

Background

[0003] GPR119 is a G-protein coupled receptor (GPCR) that is mainly expressed in the pancreas, small intestine, colon and adipose tissue. The expression profile of the human GPR119 receptor indicates its potential utility as a target for the treatment of obesity and diabetes. The novel compounds of this invention modulate the activity of GPR119 and are, therefore, expected to be useful in the treatment of GPR119-associated diseases or disorders such as, but not limited to, diabetes, obesity and associated metabolic disorders.

SUMMARY OF THE INVENTION

[0004] In one aspect, the present invention provides a compound of Formula I:



[0005] in which:

[0006] Q is a divalent or trivalent radical selected from C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-8}cycloalkyl and C_{3-8}heterocycloalkyl; wherein said aryl, heteroaryl, cycloalkyl or heterocycloalkyl of Q is optionally substituted with up to 3 radicals independently selected from halo, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, $-C(O)R_{20}$ and $-C(O)OR_{20}$; wherein R_{20} is selected from hydrogen and C_{1-6}alkyl; and optionally connecting a carbon adjacent to W_2 through a CR_{31}, O, S or NR_{31} with a carbon of Q (indicated by the dotted line) to form a 5-membered ring fused to rings A and Q (such as the fused rings in examples V1-V5, *infra*); wherein R_{31} is selected from hydrogen and C_{1-6}alkyl;

[0007] W_1 and W_2 are independently selected from CR_{21} and N; wherein R_{21} is selected from hydrogen, cyano, C_{1-6}alkyl and $-C(O)OR_{25}$; wherein R_{25} is selected from hydrogen and C_{1-6}alkyl; ring A can have up to 2 ring carbons substituted with a group selected from $-C(O)-$, $-C(S)-$ and $-C(=NOR_{30})-$ and can be partially unsaturated with up to 2 double bonds; wherein R_{30} is selected from hydrogen and C_{1-6}alkyl;

[0008] L is selected from C_{1-6}alkylene, C_{2-6}alkenylene, $-(CH_2)_nO-$, $-OC(O)(CH_2)_n-$, $-C(O)O(CH_2)_n-$, $-NR_{26}(CH_2)_n-$ and $-O(CH_2)_n-$; wherein R_{26} is selected from hydrogen and C_{1-6}alkyl; and n is selected from 0, 1, 2, 3, 4 and 5; wherein any alkyl of L can be optionally substituted with 1 to 3 radicals independently selected from halo, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, $-C(O)R_{22}$ and $-C(O)OR_{22}$; wherein R_{22} is selected from hydrogen and C_{1-6}alkyl;

[0009] m is selected from 0, 1, 2, 3 and 4;

[0010] q is selected from 0, 1, 2, 3 and 4;

[0011] t_1, t_2, t_3 and t_4 are each independently selected from 0, 1 and 2;

[0012] R_1 is selected from $-X_1S(O)_{0-2}X_2R_{6a}$, $-X_1S(O)_{0-2}X_2OR_{6a}$, $-X_1S(O)_{0-2}X_2C(O)R_{6a}$, $-X_1S(O)_{0-2}X_2C(O)OR_{6a}$, $-X_1S(O)_{0-2}X_2OC(O)R_{6a}$ and $-X_1S(O)_{0-2}NR_{6a}R_{6b}$; wherein X_1 is selected from a bond, O, $NR_{7a}R_{7b}$ and C_{1-4}alkylene; X_2 is selected from a bond and C_{1-4}alkylene; R_{6a} is selected from hydrogen, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-8}heterocycloalkyl and C_{3-8}cycloalkyl; wherein said aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R_{6a} is optionally substituted with 1 to 3 radicals independently selected from hydroxy, halo, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, cyano-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy and C_{6-10}aryl-C_{1-4}alkoxy; R_{6b} is selected from hydrogen and C_{1-6}alkyl; and R_{7a} and R_{7b} are independently selected from hydrogen and C_{1-6}alkyl;

[0013] R_2 and R_3 are independently selected from hydrogen, halo, hydroxy, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, $-C(O)R_{23}$, and $-C(O)OR_{23}$; wherein R_{23} is selected from hydrogen and C_{1-6}alkyl;

[0014] R_4 is selected from R_8 and $-C(O)OR_8$; wherein R_8 is selected from C_{1-6}alkyl, C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-8}cycloalkyl and C_{3-8}heterocycloalkyl; wherein said aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_8 is optionally substituted with 1 to 3 radicals independently selected from halo, C_{1-6}alkyl, C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy and halo-substituted-C_{1-6}alkoxy;

[0015] R_5 is selected from hydrogen, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy and halo-substituted-C_{1-6}alkoxy.

[0016] In a second aspect, the present invention provides a pharmaceutical composition which contains a compound of Formula I or a N-oxide derivative, individual isomers and mixture of isomers thereof; or a pharmaceutically acceptable salt thereof, in admixture with one or more suitable excipients.

[0017] In a third aspect, the present invention provides a method of treating a disease in an animal in which modulation of GPR119 activity can prevent, inhibit or ameliorate the pathology and/or symptomology of the diseases, which method comprises administering to the animal a therapeutically effective amount of a compound of Formula

I or a N-oxide derivative, individual isomers and mixture of isomers thereof, or a pharmaceutically acceptable salt thereof.

[0018] In a fourth aspect, the present invention provides the use of a compound of Formula I in the manufacture of a medicament for treating a disease in an animal in which GPR119 activity contributes to the pathology and/or symptomology of the disease.

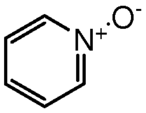
[0019] In a fifth aspect, the present invention provides a process for preparing compounds of Formula I and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, and the pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0020] "Alkyl" as a group and as a structural element of other groups, for example halo-substituted-alkyl and alkoxy, can be straight-chained, branched, cyclic or spiro. C_{1-6}alkoxy includes methoxy, ethoxy, and the like. Halo-substituted alkyl includes trifluoromethyl, pentafluoroethyl, and the like.

[0021] "Aryl" means a monocyclic or fused bicyclic aromatic ring assembly containing six to ten ring carbon atoms. For example, aryl can be phenyl or naphthyl, preferably phenyl. "Arylene" means a divalent radical derived from an aryl group. "Heteroaryl" is as defined for aryl where one or more of the ring members are a heteroatom. For example, C_{1-10}heteroaryl includes pyridyl, indolyl, indazolyl, quinoxalinyl, quinolinyl, benzofuranyl, benzopyranyl, benzothiopyranyl, benzo[1,3]dioxole, imidazolyl, benzo-imidazolyl, pyrimidinyl, furanyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, thienyl, 1H-pyridin-2-onyl, 6-oxo-1,6-dihydro-pyridin-3-yl, etc. "C_{6-10}arylC_{0-4}alkyl" means an aryl as described above connected via a alkylene grouping. For example, C_{6-10}arylC_{0-4}alkyl includes phenethyl, benzyl, etc. Heteroaryl also includes the N-oxide derivatives, for example, pyridine N-oxide derivatives with the following structure:



[0022] “Cycloalkyl” means a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing the number of ring atoms indicated. For example, C_{3-10}cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc. “Heterocycloalkyl” means cycloalkyl, as defined in this application, provided that one or more of the ring carbons indicated, are replaced by a moiety selected from -O-, -N=, -NR-, -C(O) -, -S-, -S(O) - or $-S(O)_2-$, wherein R is hydrogen, C_{1-4}alkyl or a nitrogen protecting group. For example, C_{3-8}heterocycloalkyl as used in this application to describe compounds of the invention includes morpholino, pyrrolidinyl, piperazinyl, piperidinyl, piperidinylone, 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl, 2-oxo-pyrrolidin-1-yl, 2-oxo-piperidin-1-yl, etc.

[0023] GPR119 means G protein-coupled receptor 119 (GenBank® Accession No. AAP72125) is also referred to in the literature as RUP3 and GPR116. The term GPR119 as used herein includes the human sequences found in GeneBank accession number AY288416, naturally-occurring allelic variants, mammalian orthologs, and recombinant mutants thereof.

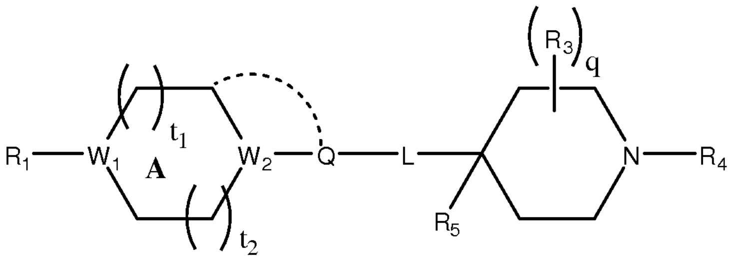
[0024] “Halogen” (or halo) preferably represents chloro or fluoro, but can also be bromo or iodo.

[0025] “Treat”, “treating” and “treatment” refer to a method of alleviating or abating a disease and/or its attendant symptoms.

Description of the Preferred Embodiments

[0026] The present invention provides compounds, compositions and methods for the treatment of diseases in which modulation of GPR119 activity can prevent, inhibit or ameliorate the pathology and/or symptomology of the diseases, which method comprises administering to the animal a therapeutically effective amount of a compound of Formula I.

[0027] In one embodiment, with reference to compounds of Formula I, are compounds of of Formula Ia:



[0028] in which:

[0029] Q is a divalent or trivalent radical selected from C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-8}cycloalkyl and C_{3-8}heterocycloalkyl; wherein said aryl, heteroaryl, cycloalkyl or heterocycloalkyl of Q is optionally substituted with up to 3 radicals independently selected from halo, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, $-C(O)R_{20}$ and $-C(O)OR_{20}$; wherein R_{20} is selected from hydrogen and C_{1-6}alkyl; and optionally connecting a carbon adjacent to W_2 through a CR_{31} or O with a carbon of Q (indicated by the dotted line in Formula Ia) to form a 5-membered ring fused to rings A and Q (such as the fused rings in examples V1-V5, *infra*); wherein R_{31} is selected from hydrogen and C_{1-6}alkyl;

[0030] W_1 and W_2 are independently selected from CR_{21} and N; wherein R_{21} is selected from hydrogen, cyano, C_{1-6}alkyl and $-C(O)OR_{25}$; wherein R_{25} is selected from hydrogen and C_{1-6}alkyl; ring A can have up to 2 ring carbons substituted with a group selected from $-C(O)-$, $-C(S)-$ and $-C(=NOR_{30})-$ and can be partially unsaturated with up to 2 double bonds; wherein R_{30} is selected from hydrogen and C_{1-6}alkyl;

[0031] L is selected from C_{1-6}alkylene, C_{2-6}alkenylene, $-(CH_2)_nO-$, $-NR_{26}CH_2)_n-$, $-OC(O)(CH_2)_n-$, $-C(O)O(CH_2)_n-$ and $-O(CH_2)_n-$; wherein R_{26} is selected from hydrogen and C_{1-6}alkyl; wherein n is selected from 0, 1, 2, 3, 4 and 5; wherein any alkyl of L can be optionally substituted with 1 to 3 radicals independently selected from halo, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, $-C(O)R_{22}$ and $-C(O)OR_{22}$; wherein R_{22} is selected from hydrogen and C_{1-6}alkyl;

[0032] t_1 and t_2 are each independently selected from 0, 1 and 2;

[0033] q is selected from 0, 1, 2, 3 and 4;

[0034] R_1 is selected from$-X_1S(O)_{0-2}X_2R_{6a}$, $-X_1S(O)_{0-2}X_2OR_{6a}$, $-X_1S(O)_{0-2}X_2C(O)R_{6a}$, $-X_1S(O)_{0-2}X_2C(O)OR_{6a}$, $-X_1S(O)_{0-2}X_2OC(O)R_{6a}$ and $-X_1S(O)_{0-2}NR_{6a}R_{6b}$;

wherein X_1 is selected from a bond, O, $NR_{7a}R_{7b}$ and C_{1-4}alkylene; X_2 is selected from a bond and C_{1-4}alkylene; R_{6a} is selected from hydrogen, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-8}heterocycloalkyl and C_{3-8}cycloalkyl; wherein said aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R_{6a} is optionally substituted with 1 to 3 radicals independently selected from hydroxy, halo, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, cyano-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy and C_{6-10}aryl-C_{1-4}alkoxy; R_{6b} is selected from hydrogen and C_{1-6}alkyl; and R_{7a} and R_{7b} are independently selected from hydrogen and C_{1-6}alkyl;

[0035] R_3 is selected from hydrogen, halo, hydroxy, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, –C(O)R_{23}, and –C(O)OR_{23}; wherein R_{23} is selected from hydrogen and C_{1-6}alkyl;

[0036] R_4 is selected from R_8 and –C(O)OR_8; wherein R_8 is selected from C_{1-6}alkyl, C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-8}cycloalkyl and C_{3-8}heterocycloalkyl; wherein said aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_8 is optionally substituted with 1 to 3 radicals independently selected from halo, C_{1-6}alkyl, C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy and halo-substituted-C_{1-6}alkoxy;

[0037] R_5 is selected from hydrogen, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy and halo-substituted-C_{1-6}alkoxy.

[0038] In a further embodiment, Q is a divalent or trivalent radical selected from phenyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, 1,2,4-oxadiazolyl, and thiazolyl; wherein said phenyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl and thiazolyl of Q is optionally substituted with up to 3 radicals independently selected from halo, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, –C(O)OR_{20} and –C(O)R_{20}; wherein R_{20} is selected from hydrogen and C_{1-6}alkyl; and optionally connecting a carbon adjacent to W_2 through a CR_{31} or O with a carbon of Q to form a 5-membered ring fused to rings A and Q; wherein R_{31} is selected from hydrogen and C_{1-6}alkyl.

[0039] In a further embodiment, W_1 and W_2 are independently selected from CR_{21} and N; wherein R_{21} is selected from hydrogen, cyano, C_{1-6}alkyl and –C(O)OR_{25}; wherein R_{25} is selected from hydrogen and C_{1-6}alkyl; ring A can have a ring carbon substituted with a group selected from –C(O)–, –C(S)– and –C(=NOR_{30})– and can be partially unsaturated with a double bond; wherein R_{30} is selected from hydrogen and C_{1-6}alkyl; and L is selected from $-O(CH_2)_{0-4}-$, $-(CH=CH)-$, $-OC(O)-$, $-NH(CH_2)_{0-4}-$, $-NCH_3(CH_2)_{0-4}-$ and $-(CH_2)_{1-4}-$.

[0040] In another embodiment, $R_1$is selected from $-X_1S(O)_{0-2}X_2R_{6a}$, $-X_1S(O)_{0-2}X_2OR_{6a}$, $-X_1S(O)_{0-2}X_2C(O)OR_{6a}$, $-X_1S(O)_{0-2}X_2OC(O)R_{6a}$ and $-X_1S(O)_{0-2}NR_{6a}R_{6b}$; wherein X_1 is selected from a bond and O; X_2 is selected from a bond and C_{1-4}alkylene; R_{6a} is selected from hydrogen, halo, cyano, methyl, ethyl, propyl, isopropyl, ethenyl, pyridinyl, pyrrolidinyl, piperidinyl, morpholino, isoxazolyl, tetrazolyl, phenyl and imidazolyl; wherein said piperidinyl, pyridinyl, pyrrolidinyl, morpholino, isoxazolyl, tetrazolyl, phenyl or imidazolyl of R_{6a} is optionally substituted with 1 to 3 radicals independently selected from hydroxy, halo, C_{1-6}alkyl and benzoxy; and R_{6b} is selected from hydrogen, methyl and ethyl.

[0041] In another embodiment, R_4 is selected from R_8 and $-C(O)OR_8$; wherein R_8 is selected from isopropyl, cyclopropyl, t-butyl, 1,2,4-oxadiazolyl, pyrimidinyl, pyridinyl, pyridazinyl, tetrahydro-2H-pyranyl, tetrahydrofuranyl, oxetanyl, 2H-tetrazolyl and thiazolyl; wherein said cyclopropyl, 1,2,4-oxadiazolyl, pyrimidinyl, pyridinyl, pyridazinyl, tetrahydro-2H-pyranyl, tetrahydrofuranyl, oxetanyl, 2H-tetrazolyl or thiazolyl of R_8 is optionally substituted with 1 to 3 radicals independently selected from halo, trifluoromethyl, isopropyl, t-butyl, methyl, ethyl and cyclopropyl optionally substituted with methyl; and R_5 is selected from hydrogen and methoxy.

[0042] In another embodiment are compounds selected from: isopropyl 4-((4-((4-methanesulfonylpiperazin)-1-yl)phenoxy)methyl)piperidine-1-carboxylate, isopropyl 4-(2-(4-(4-(methylsulfonyl)piperazin-1-yl)phenoxy)ethyl)piperidine-1-carboxylate, isopropyl 4-(3-(4-(4-(methylsulfonyl)piperazin-1-yl)phenoxy)propyl)piperidine-1-carboxylate, isopropyl 4-(4-(4-(4-(methylsulfonyl)piperazin-1-yl)phenoxy)butyl)piperidine-1-carboxylate, Isopropyl 4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate, *tert*-Butyl 4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate, Isopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, *tert*-Butyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, 3-Cyclopropyl-5-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, 5-

Cyclopropyl-3-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, 2-(4-(Methylsulfonyl)piperazin-1-yl)-5-((1-(5-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)methoxy)pyrazine, 5-Isopropyl-3-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, Tetrahydro-2H-pyran-4-yl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, (S)-Tetrahydrofuran-3-yl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, (R)-Tetrahydrofuran-3-yl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, 2-Isopropyl-5-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)thiazole, 2-((1-(2-methyl-2H-tetrazol-5-yl)piperidin-4-yl)methoxy)-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazine, Oxetan-3-yl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, Isopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate, Isopropyl 4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridazin-3-yloxy)methyl)piperidine-1-carboxylate, Isopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrimidin-2-yloxy)methyl)piperidine-1-carboxylate, (E)-isopropyl 4-(2-(6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yl)vinyl)piperidine-1-carboxylate, Isopropyl 4-(2-(6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yl)ethyl)piperidine-1-carboxylate, (E)-Isopropyl 4-(2-(2-(4-(methylsulfonyl)piperazin-1-yl)pyrimidin-5-yl)vinyl)piperidine-1-carboxylate, 5-Ethyl-2-(4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)pyrimidine, 1-(Methylsulfonyl)-4-(5-((1-(5-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)methoxy)pyridin-2-yl)piperazine, 1-Methylcyclopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, 5-Ethyl-2-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)pyrimidine, 2-((1-(5-Methylpyridin-2-yl)piperidin-4-yl)methoxy)-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazine, 1-Methylcyclopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate, 5-Ethyl-2-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyridin-2-yloxy)methyl)piperidin-1-yl)pyrimidine, 3-Isopropyl-5-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, 3-Isopropyl-5-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyridin-2-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, 1-Methylcyclopropyl 4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate, 5-

Isopropyl-3-(4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, 2-((1-(5-Fluoropyridin-2-yl)piperidin-4-yl)methoxy)-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazine, 3-Isopropyl-5-(4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, *tert*-Butyl 4-((5-(4-(methylsulfonyl)-1,4-diazepan-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, *tert*-Butyl 4-((5-(4-(methylsulfonyl)-1,4-diazepan-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, *tert*-butyl 4-((5-(4-(methylsulfonyl)piperidin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, 1-Methylcyclopropyl 4-((5-(4-(methylsulfonyl)piperidin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, *tert*-Butyl 4-(2-(3-(4-(methylsulfonyl)piperazin-1-yl)-1,2,4-oxadiazol-5-yl)ethyl)piperidine-1-carboxylate, *tert*-Butyl 4-(3-(3-(4-(methylsulfonyl)piperazin-1-yl)-1,2,4-oxadiazol-5-yl)propyl)piperidine-1-carboxylate, 5-(3-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)propyl)-3-(4-(methylsulfonyl)piperazin-1-yl)-1,2,4-oxadiazole, Isopropyl 4-(3-(3-(4-(methylsulfonyl)piperazin-1-yl)-1,2,4-oxadiazol-5-yl)propyl)piperidine-1-carboxylate, 3-Isopropyl-5-(4-(2-(5-(4-(methylsulfonyl)piperazin-1-yl)thiazol-2-yl)ethyl)piperidin-1-yl)-1,2,4-oxadiazole, Isopropyl 4-((4-(1-methanesulfonyl-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)methyl)piperidine-1-carboxylate, isopropyl 4-(4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)piperidine-1-carboxylate, isopropyl 4-(2-(4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)ethyl)piperidine-1-carboxylate, isopropyl 4-(3-(4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)propyl)piperidine-1-carboxylate, isopropyl 4-(4-(4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)butyl)piperidine-1-carboxylate, 1-methylcyclopropyl 4-((4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)methyl)piperidine-1-carboxylate, 5-isopropyl-3-(4-((4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, Isopropyl 4-((4-(1-methanesulfonylpiperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate, isopropyl 4-(4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)piperidine-1-carboxylate, isopropyl 4-(2-(4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)ethyl)piperidine-1-carboxylate, isopropyl 4-(3-(4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)propyl)piperidine-1-carboxylate, isopropyl 4-(4-(4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)butyl)piperidine-1-carboxylate, 1-Methylcyclopropyl 4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-

carboxylate, 2-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)-5-(trifluoromethyl)pyridine, 5-isopropyl-3-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, 3-chloro-2-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)-5-(trifluoromethyl)pyridine, 5-chloro-2-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)pyridine, 3-chloro-6-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)pyridazine, 5-bromo-2-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)pyrimidine, 5-ethyl-2-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)pyrimidine, 5-fluoro-2-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)pyridine, 3-isopropyl-5-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, 3-tert-butyl-6-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)pyridazine, 5-fluoro-2-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)pyrimidine, Isopropyl 4-(2-(3-(1-methanesulfonyl-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)ethyl)piperidine-1-carboxylate, 1-Methylcyclopropyl 4-methoxy-4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, 1-methylcyclopropyl 4-((6-formyl-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, 1-Methylcyclopropyl 4-((6-chloro-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, 1-Methylcyclopropyl 4-((5-(4-(3-methoxy-3-oxopropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, 3-(4-(5-((1-((1-methylcyclopropoxy)carbonyl)-piperidin-4-yl)methoxy)pyrazin-2-yl)piperazin-1-ylsulfonyl)propanoic acid, 3-(4-(5-((1-((1-methylcyclopropoxy)carbonyl)piperidin-4-yl)methoxy)pyrazin-2-yl)piperazin-1-ylsulfonyl)propanoic acid, 3-(4-(5-((1-((1-methylcyclopropoxy)carbonyl)piperidin-4-yl)methoxy)pyrazin-2-yl)piperazin-1-ylsulfonyl)propanoic acid, 3-(4-(5-((1-((1-methylcyclopropoxy)carbonyl)piperidin-4-yl)methoxy)pyrazin-2-yl)piperazin-1-ylsulfonyl)propanoic acid, 3-(4-(5-((1-((1-methylcyclopropoxy)carbonyl)piperidin-4-yl)methoxy)pyrazin-2-yl)piperazin-1-ylsulfonyl)propanoic acid, 3-(4-(5-((1-((1-methylcyclopropoxy)carbonyl)piperidin-4-yl)methoxy)pyrazin-2-yl)piperazin-1-ylsulfonyl)propanoic acid; 1-methylcyclopropyl 4-((5-(4-(3-cyanopropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-(1Htetrazol-5-yl)propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(vinylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(2-(piperidin-1-yl)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(2-morpholinoethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(2-(dimethylamino)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((5-(4-(3-chloropropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((5-(4-(3-acetoxypropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-aminopropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(2-ethoxyethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-(pyrrolidin-1-yl)propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-(2-methyl-1H-imidazol-1-yl)propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-(dimethylamino)propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(isopropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(isobutylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(sec-butylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-acetoxy-2,2-dimethylpropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-hydroxy-2,2-dimethylpropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(4-(2-(pyridin-3-yl)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(4-(2-(pyridin-4-yl)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-

Methylcyclopropyl 4-((5-(4-sulfamoylpiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; *tert*-Butyl 4-((5-(4-(morpholinosulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(ethylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(ethylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(ethylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(ethylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(ethylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(ethylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-fluoro-6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; tert-Butyl 4-((5-(4-(methylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(4-(methylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(2-oxo-4-(propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(4-(isopropylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(4-(isopropylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(2-oxo-4-(propylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(isopropylsulfonyl)-2-oxopiperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-(5-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)pyrazin-2-yl)-4-(methylsulfonyl)piperazin-2-one; 1-(5-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)pyridin-2-yl)-4-(methylsulfonyl)piperazin-2-one; *tert*-Butyl 4-((2,6-difluoro-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2-methyl-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((3-methoxy-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2,6-dimethyl-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2,5-dimethyl-4-(1-

(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2-(methoxycarbonyl)-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2-chloro-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((3-methyl-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2,3-dimethyl-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2-fluoro-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((4-(1-(methylsulfonyl)piperidin-4-yl)-2-(trifluoromethyl)phenoxy)methyl)piperidine-1-carboxylate; 2-(4-((2,6-Difluoro-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)-5-ethylpyrimidine; 1-Methylcyclopropyl 4-((2,6-difluoro-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; 3-(4-(4-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-3,5-difluorophenyl)piperidin-1-ylsulfonyl)propyl acetate; 1-Methylcyclopropyl 4-((4-(1-(3-acetoxypropylsulfonyl)piperidin-4-yl)-2,6-difluorophenoxy)methyl)piperidine-1-carboxylate; 3-(4-(4-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-3,5-difluorophenyl)piperidin-1-ylsulfonyl)propan-1-ol; 1-Methylcyclopropyl 4-((2,6-difluoro-4-(1-(3-hydroxypropylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; Isopropyl 4-((5-(1,2,3,6-tetrahydro-1-methanesulfonylpyridin-4-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((6-(1,2,3,6-tetrahydro-1-methanesulfonylpyridin-4-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; Isopropyl 4-(2-(6-(1,2,3,6-tetrahydro-1-methanesulfonylpyridin-4-yl)pyridin-3-yloxy)ethyl)piperidine-1-carboxylate; 2-(4-((5-(1,2,3,6-Tetrahydro-1-methanesulfonylpyridin-4-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-5-ethylpyrimidine; 2-(4-((6-(1,2,3,6-Tetrahydro-1-methanesulfonylpyridin-4-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)-5-ethylpyrimidine; 2-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-5-(1-methanesulfonylpiperidin-4-yl)pyrazine; 2-(4-((6-(1-Methanesulfonylpiperidin-4-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)-5-ethylpyrimidine; 3-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-6-(1-methanesulfonylpiperidin-4-yl)pyridazine; 2-(4-((5-(1-Methanesulfonylpiperidin-4-yl)pyridin-2-yloxy)methyl)piperidin-1-yl)-5-ethylpyrimidine; 1-*tert*-Butyl 4-(4-(1-(methylsulfonyl)piperidin-4-yl)phenyl) piperazine-1,4-dicarboxylate; *N*-((1-(5-

Ethylpyrimidin-2-yl)piperidin-4-yl)methyl)-4-(1-(methylsulfonyl)piperidin-4-yl)aniline; *N*-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methyl)-*N*-methyl-4-(1-(methylsulfonyl)piperidin-4-yl)aniline; 4-(4-((1-(5-fluoropyrimidin-2-yl)piperidin-4-yl)methoxy)phenyl)-1-(methylsulfonyl)piperidine-4-carboxylic acid; 2-[(2-{4-[5-({1-[(1-methylcyclopropoxy)carbonyl]piperidin-4-yl}methoxy)pyrazin-2-yl]-3-oxopiperazine-1-sulfonyl}ethyl)amino]acetic acid; 1-methylcyclopropyl 4-{[(5-{4-[(2-carbamimidamidoethane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3-methyl-3-nitrobutane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(1-benzylpyrrolidine-3-sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(carbamoylmethane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(1-carbamoyl-1-methylethane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(2-oxo-4-{[2-(pyrrolidin-1-yl)ethane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(morpholin-4-yl)ethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(dimethylamino)propane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)ethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(dimethylcarbamoyl)methane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[1-(2-methylpropyl)pyrrolidine-3-sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(2-oxo-4-{[3-(1H-pyrazol-1-yl)propane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[2-oxo-4-(pyrrolidine-3-sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(2-amino-2-methylpropane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(1-

methylpyrrolidin-3-yl)methane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(azetidin-1-yl)ethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(2-oxo-4-{[2-(1H-pyrazol-1-yl)ethane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(1-methylpyrrolidine-3-sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[1-(dimethylcarbamoyl)-1-methylethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(3,3-difluoroazetidin-1-yl)ethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(dimethylamino)-3-methylbutane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(2-{[2-(tert-butoxy)-2-oxoethyl]amino}ethane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(azetidine-3-sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(3,3-difluoroazetidin-1-yl)propane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(azetidin-1-yl)propane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{2-oxo-4-[(3S)-pyrrolidine-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3S)-1-methylpyrrolidine-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3R)-1-methylpyrrolidine-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3S)-pyrrolidine-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3R)-pyrrolidine-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(azetidine-3-sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{2-oxo-4-[(pyrrolidin-3-ylmethane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(1-

hydroxy-2-methylpropane-2-sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(2-hydroxyethane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(azetidin-3-ylmethane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(1-methylpyrrolidin-2-yl)methane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{2-oxo-4-[(3R)-pyrrolidine-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(1-methylazetidine-3-sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(1-methylazetidine-3-sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(1-methylazetidin-3-yl)methane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(1-methylazetidin-3-yl)methane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({3-[(3S,4S)-3,4-dihydroxypyrrolidin-1-yl]propane}sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({2-[(3S,4S)-3,4-dihydroxypyrrolidin-1-yl]ethane}sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(azetidin-3-ylmethane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{2-oxo-4-[(pyrrolidin-2-ylmethane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3-aminopropane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(2-aminoethane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(3-methanesulfonamidoazetidin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(dimethylamino)ethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(2-oxo-4-{[3-(pyrrolidin-1-yl)propane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(morpholin-4-yl)propane]sulfonyl}-2-

oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(3-methyloxetan-3-yl)methane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(acetyloxy)propane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3,3,3-trifluoropropane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[(2E)-2-(hydroxyimino)-4-methanesulfonylpiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3-chloropropane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3-hydroxypropane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({[1-(dimethylamino)cyclopropyl]methane}sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({[1-(dimethylamino)cyclopropyl]methane}sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3-hydroxy-3-methylbutane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{2-oxo-4-[(3R)-oxolane-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{2-oxo-4-[(3S)-oxolane-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(acetyloxy)-3-methylbutane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({6-[4-({[1-(azetidin-1-yl)cyclopropyl]methane}sulfonyl)piperazin-1-yl]pyridin-3-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({[1-(benzylamino)cyclopropyl]methane}sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({[1-(azetidin-1-yl)cyclopropyl]methane}sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(1-hydroxycyclopropyl)methane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(1-

hydroxycyclopropyl)ethane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({2-[1-(acetyloxy)cyclopropyl]ethane}sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({[1-(benzyloxy)cyclopropyl]methane}sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(1-aminocyclopropyl)methane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(1-hydroxycyclopropyl)ethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{2,6-difluoro-4-[3-(N-methylmethanesulfonamido)azetidin-1-yl]phenoxymethyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[2,6-difluoro-4-(3-methanesulfonamidoazetidin-1-yl)phenoxymethyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{2,6-difluoro-4-[3-(2-methylpropane-1-sulfonamido)azetidin-1-yl]phenoxymethyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{4-[3-(N,2-dimethylpropane-1-sulfonamido)azetidin-1-yl]-2,6-difluorophenoxymethyl}piperidine-1-carboxylate; 5-ethyl-2-{4-[({2-methanesulfonyl-1H,2H,3H,4H-pyrazino[1,2-a]indol-8-yl}oxy)methyl]piperidin-1-yl}pyrimidine; 11-{[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]oxy}-5-methanesulfonyl-8-oxa-5-azatricyclo[7.4.0.0{2,7}]trideca-1(13),2(7),9,11-tetraene; 11-{[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]methoxy}-5-methanesulfonyl-8-oxa-5-azatricyclo[7.4.0.0{2,7}]trideca-1(13),2(7),9,11-tetraene; tert-butyl 4-[({2-methanesulfonyl-1H,2H,3H,4H-pyrazino[1,2-a]indol-8-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({2-methanesulfonyl-1H,2H,3H,4H-pyrazino[1,2-a]indol-8-yl}oxy)methyl]piperidine-1-carboxylate; propan-2-yl 4-{3-[3-(1-methanesulfonylpiperidin-4-yl)phenoxy]propyl}piperidine-1-carboxylate; propan-2-yl 4-{2-[3-(1-methanesulfonylpiperidin-4-yl)phenoxy]ethyl}piperidine-1-carboxylate; propan-2-yl 4-[3-(1-methanesulfonylpiperidin-4-yl)phenoxymethyl]piperidine-1-carboxylate; propan-2-yl 4-{3-[3-(1-methanesulfonyl-1,2,3,6-tetrahydropyridin-4-yl)phenoxy]propyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-methanesulfonyl-2-sulfanylidenepiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl (3S,4S)-3-hydroxy-4-{[(6-{4-[(2-

methylpropane)sulfonyl]piperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl (3R,4S)-3-hydroxy-4-{[(6-{4-[(2-methylpropane)sulfonyl]piperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-hydroxy-4-{[(6-{4-[(2-methylpropane)sulfonyl]piperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(6-{4-[(2-hydroxy-2-methylpropane)sulfonyl]piperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl (3S,4R)-3-methoxy-4-{[(6-{4-[(2-methylpropane)sulfonyl]piperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(3,3-difluoroazetidin-1-yl)propane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(azetidin-1-yl)propane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3-methoxypropane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(6-{4-[(3-chloropropane)sulfonyl]-2-oxopiperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(azetidin-1-yl)ethane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[6-(4-{[3-(azetidin-1-yl)propane]sulfonyl}piperazin-1-yl)pyridin-3-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(pyrrolidine-3-sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(3,3-difluoroazetidin-1-yl)ethane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(6-{4-[(3-hydroxypropane)sulfonyl]-2-oxopiperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[6-(4-{[3-(azetidin-1-yl)propane]sulfonyl}-2-oxopiperazin-1-yl)pyridin-3-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[2,6-difluoro-4-(4-methanesulfonyl-2-oxopiperazin-1-yl)phenoxymethyl]piperidine-1-carboxylate; and 1-methylcyclopropyl 4-[({5-[4-(oxetane-3-sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate.

[0043] Further compounds of the invention are detailed in the Examples and Tables, *infra*.

[0044] The present invention includes all pharmaceutically acceptable isotopically-labeled compounds of the invention, i.e. compounds of formula (I), wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the invention comprises isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

[0045] Certain isotopically-labelled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may 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.

[0046] Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

[0047] Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

Pharmacology and Utility

[0048] Compounds of the invention modulate the activity of GPR119 and, as such, are useful for treating diseases or disorders in which the activity of GPR119 contributes to the pathology and/or symptomology of the disease. This invention further provides compounds of this invention for use in the preparation of medicaments for the treatment of diseases or disorders in which GPR119 activity contributes to the pathology and/or symptomology of the disease.

[0049] The resultant pathologies of Type II diabetes are impaired insulin signaling at its target tissues and failure of the insulin-producing cells of the pancreas to secrete an appropriate degree of insulin in response to a hyperglycemic signal. Current therapies to treat the latter include inhibitors of the β-cell ATP-sensitive potassium channel to trigger the release of endogenous insulin stores, or administration of exogenous insulin. Neither of these achieves accurate normalization of blood glucose levels and both carry the risk of inducing hypoglycemia. For these reasons, there has been intense interest in the development of pharmaceuticals that function in a glucose-dependent action, i.e. potentiators of glucose signaling. Physiological signaling systems which function in this manner are well-characterized and include the gut peptides GLP-l, GIP and PACAP. These hormones act via their cognate G-protein coupled receptor to stimulate the production of cAMP in pancreatic β-cells. The increased cAMP does not appear to result in stimulation of insulin release during the fasting or pre-prandial state. However, a series of biochemical targets of cAMP signaling, including the ATP-sensitive potassium channel, voltage-sensitive potassium channels and the exocytotic machinery, are modified in such a way that the insulin secretory response to a postprandial glucose stimulus is markedly enhanced. Accordingly, agonists of novel, similarly functioning, β-cell GPCRs, including GPR119, would also stimulate the release of endogenous insulin and consequently promote normoglycemia in Type II diabetes. It is also established that increased cAMP, for example as a result of GLP-l stimulation, promotes β-cell proliferation, inhibits β-cell death and thus improves islet mass. This positive effect on β-cell mass is expected to be beneficial in both Type II diabetes, where insufficient insulin is produced, and Type I diabetes, where β-cells are destroyed by an inappropriate autoimmune response.

[0050] Some β-cell GPCRs, including GPR119, are also present in the hypothalamus where they modulate hunger, satiety, decrease food intake, controlling or decreasing weight and energy expenditure. Hence, given their function within the hypothalamic circuitry, agonists or inverse agonists of these receptors mitigate hunger, promote satiety and therefore modulate weight.

[0051] It is also well-established that metabolic diseases exert a negative influence on other physiological systems. Thus, there is often the codevelopment of multiple disease states (e.g. type I diabetes, type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia, obesity or cardiovascular disease in "Syndrome X") or secondary diseases which clearly occur secondary to diabetes (e.g. kidney disease, peripheral neuropathy). Thus, it is expected that effective treatment of the diabetic condition will in turn be of benefit to such interconnected disease states.

[0052] In an embodiment of the invention is a method for treatment of a metabolic disease and/or a metabolic-related disorder in an individual comprising administering to the individual in need of such treatment a therapeutically effective amount of a compound of the invention or a pharmaceutical composition thereof. The metabolic diseases and metabolic-related disorders are selected from, but not limited to, hyperlipidemia, type 1 diabetes, type 2 diabetes mellitus, idiopathic type 1 diabetes (Type Ib), latent autoimmune diabetes in adults (LADA), early-onset type 2 diabetes (EOD), youth-onset atypical diabetes (YOAD), maturity onset diabetes of the young (MODY), malnutrition-related diabetes, gestational diabetes, coronary heart disease, ischemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, myocardial infarction (e.g. necrosis and apoptosis), dyslipidemia, post-prandial lipemia, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity, osteoporosis, hypertension, congestive heart failure, left ventricular hypertrophy, peripheral arterial disease, diabetic retinopathy, macular degeneration, cataract, diabetic nephropathy, glomerulosclerosis, chronic renal failure, diabetic neuropathy, metabolic syndrome, syndrome X, premenstrual syndrome, coronary heart disease, angina pectoris, thrombosis, atherosclerosis, myocardial infarction, transient ischemic attacks, stroke, vascular restenosis, hyperglycemia, hyperinsulinemia, hyperlipidemia, hypertrygliceridemia, insulin resistance, impaired glucose metabolism, conditions of impaired glucose tolerance, conditions of impaired fasting plasma glucose, obesity, erectile dysfunction, skin and connective tissue disorders, foot ulcerations and ulcerative colitis, endothelial dysfunction and impaired vascular compliance.

[0053] In an embodiment of the invention are therapeutic benefits of GPR119 activity modulators derived from increasing levels of GIP and PPY. For example, neuroprotection, learning and memory, seizures and peripheral neuropathy.

[0054] GLP-1 and GLP-1 receptor agonists have been shown to be effective for treatment of neurodegenerative diseases and other neurological disorders. GLP-1 and exendin-4 have been shown to stimulate neurite outgrowth and enhance cell survival after growth factor withdrawal in PC12 cells. In a rodent model of neurodegeneration, GLP-1 and exendin-4 restore cholinergic marker activity in the basal forebrain. Central infusion of GLP-1 and exendin-4 also reduce the levels of amyloid-β peptide in mice and decrease amyloid precursor protein amount in cultured PC12 cells. GLP-1 receptor agonists have been shown to enhance learning in rats and the GLP-1 receptor knockout mice show deficiencies in learning behavior. The knockout mice also exhibit increased susceptibility to kainate-induced seizures which can be prevented by administration of GLP-1 receptor agonists. GLP-1 and exendin-4 has also been shown to be effective in treating pyridoxine-induced peripheral nerve degeneration, an experimental model of peripheral sensory neuropathy.

[0055] Glucose-dependent insulinotropic polypeptide (GIP) has also been shown to have effects on proliferation of hippocampal progenitor cells and in enhancing sensorimotor coordination and memory recognition.

[0056] In an embodiment of the invention are therapeutic benefits of GPR119 activity modulators. For example, GLP-2 and short bowel syndrome (SBS). Several studies in animals and from clinical trials have shown that GLP-2 is a trophic hormone that plays an important role in intestinal adaptation. Its role in regulation of cell proliferation, apoptosis, and nutrient absorption has been well documented. Short bowel syndrome is characterized by malabsorption of nutrients, water and vitamins as a result of disease or surgical removal of parts of the small intestine (eg. Crohn’s disease). Therapies that improve intestinal adaptation are thought to be beneficial in treatment of this disease. In fact, phase II studies in SBS patients have shown that teduglutide, a GLP-2 analog, modestly increased fluid and nutrient absorption.

[0057] In an embodiment of the invention are therapeutic benefits of GPR119 activity modulators derived from increasing levels of GIP and PPY. For example, GLP-1, GIP and osteoporosis. GLP-1 has been shown to increase calcitonin and calcitonin related gene peptide (CGRP) secretion and expression in a murine C-cell line (CA-77). Calcitonin inhibits bone resorption by osteoclasts and promotes mineralization of skeletal bone. Osteoporosis is a disease that is caharacterized by reduced bone mineral density and thus GLP-1 induced increase in calcitonin might be therapeutically beneficial.

[0058] GIP has been reported to be involved in upregulation of markers of new bone formation in osetoblasts including collagen type I mRNA and in increasing bone mineral density. Like GLP-1, GIP has also been shown to inhibit bone resorption.

[0059] In an embodiment of the invention are therapeutic benefits of GPR119 activity modulators derived from increasing levels of GIP and PPY. For example, PPY and gastric emptying. GPR119 located on the pancreatic polypeptide (PP) cells of the islets has been implicated in the secretion of PPY. PPY has been reported to have profound effects on various physiological processes including modulation of gastric emptying and gastrointestinal motility. These effects slow down the digestive process and nutrient uptake and thereby prevent the postprandial elevation of blood glucose. PPY can suppress food intake by changing the expression of hypothalamic feeding-regulatory peptides. PP-overexpressing mice exhibited the thin phenotype with decreased food intake and gastric emptying rate.

[0060] In accordance with the foregoing, the present invention further provides a method for preventing or ameliorating the symptamology of any of the diseases or disorders described above in a subject in need thereof, which method comprises administering to said subject a therapeutically effective amount (*See, "Administration and Pharmaceutical Compositions", infra*) of a compound of Formula I or a pharmaceutically acceptable salt thereof. For any of the above uses, the required dosage will vary depending on the mode of administration, the particular condition to be treated and the effect desired.

Administration and Pharmaceutical Compositions

[0061] In general, compounds of the invention will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with one or more therapeutic agents. A therapeutically effective amount can vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to 2.5mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5mg to about 100mg, conveniently administered, e.g. in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from ca. 1 to 50mg active ingredient.

[0062] Compounds of the invention can be administered as pharmaceutical compositions by any conventional route, in particular enterally, e.g., orally, e.g., in the form of tablets or capsules, or parenterally, e.g., in the form of injectable solutions or suspensions, topically, e.g., in the form of lotions, gels, ointments or creams, or in a nasal or suppository form. Pharmaceutical compositions comprising a compound of the present invention in free form or in a pharmaceutically acceptable salt form in association with at least one pharmaceutically acceptable carrier or diluent can be manufactured in a conventional manner by mixing, granulating or coating methods. For example, oral compositions can be tablets or gelatin capsules comprising the active ingredient together with a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrollidone; if desired d) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbents, colorants, flavors and sweeteners. Injectable compositions can be aqueous isotonic solutions or suspensions, and suppositories can be prepared from fatty emulsions or suspensions. The compositions can be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they can also contain other therapeutically valuable substances. Suitable formulations for transdermal applications include an effective amount of a compound of the present invention with a carrier. A carrier can include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin. Matrix transdermal formulations can also be used. Suitable formulations for topical application, e.g., to the skin and eyes, are preferably aqueous solutions, ointments, creams or gels well-known in the art. Such can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[0063] Compounds of the invention can be administered in therapeutically effective amounts in combination with one or more therapeutic agents (pharmaceutical combinations).

[0064] For example, synergistic effects can occur with other anti-obesity agents, anorectic agents, appetite suppressant and related agents. Diet and/or exercise can also have synergistic effects. Anti-obesity agents include, but are not limited to, apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, MCR-4 agonists, cholescystokinin-A (CCK-A) agonists, serotonin and norepinephrine reuptake inhibitors (for example, sibutramine), sympathomimetic agents, β3 adrenergic receptor agonists, dopamine agonists (for example, bromocriptine), melanocyte-stimulating hormone receptor analogs, cannabinoid 1 receptor antagonists [for example, compounds described in WO2006/047516), melanin concentrating hormone antagonists, leptons (the OB protein), leptin analogues, leptin receptor agonists, galanin antagonists, lipase inhibitors (such as tetrahydrolipstatin, i.e., Orlistat), anorectic agents (such as a bombesin agonist), Neuropeptide-Y antagonists, thyromimetic agents, dehydroepiandrosterone or an analogue thereof, glucocorticoid receptor agonists or antagonists, orexin receptor antagonists, urocortin binding protein antagonists, glucagon-like peptide- 1 receptor agonists, ciliary neutrotrophic factors (such as Axokine^{TM}), human agouti-related proteins (AGRP), ghrelin receptor antagonists, histamine 3 receptor antagonists or reverse agonists, neuromedin U receptor agonists, noradrenergic anorectic agents (for example, phentermine, mazindol and the like) and appetite suppressants (for example, bupropion).

[0065] Where compounds of the invention are administered in conjunction with other therapies, dosages of the co-administered compounds will of course vary depending on the type of co-drug employed, on the specific drug employed, on the condition being treated and so forthours.

[0066] A combined preparation or pharmaceutical composition can comprise a compound of the invention as defined above or a pharmaceutical acceptable salt thereof and at least one active ingredient selected from:

[0067] a) anti-diabetic agents such as insulin, insulin derivatives and mimetics; insulin secretagogues such as the sulfonylureas, e.g., Glipizide, glyburide and Amaryl; insulinotropic sulfonylurea receptor ligands such as meglitinides, e.g., nateglinide and repaglinide; insulin sensitizer such as protein tyrosine phosphatase-1B (PTP-1B) inhibitors such as PTP-112; GSK3 (glycogen synthase kinase-3) inhibitors such as SB-517955, SB-4195052, SB-216763, NN-57-05441 and NN-57-05445; RXR ligands such as GW-0791 and AGN-194204; sodium-dependent glucose co-transporter inhibitors such as T-1095; glycogen phosphorylase A inhibitors such as BAY R3401; biguanides such as metformin; alpha-glucosidase inhibitors such as acarbose; GLP-1 (glucagon like peptide-1), GLP-1 analogs such as Exendin-4 and GLP-1 mimetics; DPPIV (dipeptidyl peptidase IV) inhibitors such as DPP728, LAF237 (vildagliptin - Example 1 of WO 00/34241), MK-0431, saxagliptin, GSK23A ; an AGE breaker; a thiazolidone derivative (glitazone) such as pioglitazone, rosiglitazone, or *(R)*-1-{4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzenesulfonyl}-2,3-dihydro-1*H*-indole-2-carboxylic acid described in the patent application WO 03/043985, as compound 19 of Example 4, a non-glitazone type PPAR gamma agonist e.g. GI-262570; Diacylglycerol acetyltransferase (DGAT) inhibitors such as those disclosed in WO 2005044250, WO 2005013907, WO 2004094618 and WO 2004047755;

[0068] b) hypolipidemic agents such as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, e.g., lovastatin and related compounds such as those disclosed in U.S. Pat. No. 4,231,938, pitavastatin, simvastatin and related compounds such as those disclosed in U.S. Pat. Nos. 4,448,784 and 4,450,171, pravastatin and related compounds such as those disclosed in U.S. Pat. No.4,346,227, cerivastatin, mevastatin and related compounds such as those disclosed in U.S. Pat. No. 3,983,140, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin and related statin compounds disclosed in U.S. Pat. No. 5,753,675, rivastatin, pyrazole analogs of mevalonolactone derivatives as disclosed in U.S. Pat. No. 4,613,610, indene analogs of mevalonolactone derivatives as disclosed in PCT application WO 86/03488, 6-[2- (substituted-pyrrol-1-yl)-alkyl)pyran-2-ones and derivatives thereof as disclosed in U.S. Pat. No. 4,647,576, Searle's SC-45355 (a 3- substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone as disclosed in PCT application WO 86/07054, 3- carboxy-2- hydroxy-propane-phosphonic acid derivatives as disclosed in French Patent No. 2,596,393, 2,3-disubstituted pyrrole, furan and thiophene derivatives as disclosed in European Patent Application No. 0221025, naphthyl analogs of mevalonolactone as disclosed in U.S. Pat. No. 4,686,237, octahydronaphthalenes such as disclosed in U.S. Pat. No. 4, 499,289, keto analogs of mevinolin (lovastatin) as disclosed in European Patent Application No.0,142,146 A2, and quinoline and pyridine derivatives disclosed in U.S. Pat. Nos. 5,506,219 and 5,691,322. In addition, phosphinic acid compounds useful in inhibiting HMG CoA reductase suitable for use herein are disclosed in GB 2205837; squalene synthase inhibitors; FXR (farnesoid X receptor) and LXR (liver X receptor) ligands; cholestyramine; fibrates; nicotinic acid and aspirin;

[0069] c) an anti-obesity agent or appetite regulating agent such as a CB1 activity modulator, melanocortin receptor (MC4R) agonists, melanin-concentrating hormone receptor (MCHR) antagonists, growth hormone secretagogue receptor (GHSR) antagonists, galanin receptor modulators, orexin antagonists, CCK agonists, GLP-1 agonists, and other Pre-proglucagon-derived peptides; NPY1 or NPY5 antagonsist, NPY2 and NPY4 modulators, corticotropin releasing factor agonists, histamine receptor-3 (H3) modulators, aP2 inhibitors, PPAR gamma modulators, PPAR delta modulators, acetyl-CoA carboxylase (ACC) inihibitors, 11-β-HSD-1 inhibitors, adinopectin receptor modulators; beta 3 adrenergic agonists, such as AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer) or other known beta 3 agonists as disclosed in U.S. Pat. Nos. 5,541,204, 5,770,615, 5, 491,134, 5,776,983 and 5,488,064, a thyroid receptor beta modulator, such as a thyroid receptor ligand as disclosed in WO 97/21993 (U. Cal SF), WO 99/00353 (KaroBio) and GB98/284425 (KaroBio), a SCD-1 inhibitor as disclosed in WO2005011655, a lipase inhibitor, such as orlistat or ATL-962 (Alizyme), serotonin receptor agonists, (e.g., BVT- 933 (Biovitrum)), monoamine reuptake inhibitors or releasing agents, such as fenfluramine, dexfenfluramine, fluvoxamine, fluoxetine, paroxetine, sertraline, chlorphentermine, cloforex, clortermine, picilorex, sibutramine, dexamphetamine, phentermine, phenylpropanolamine or mazindol, anorectic agents such as topiramate (Johnson & Johnson), CNTF (ciliary neurotrophic factor)/Axokine® (Regeneron), BDNF (brain-derived neurotrophic factor), leptin and leptin receptor modulators, phentermine, leptin, bromocriptine, dexamphetamine, amphetamine, fenfluramine, dexfenfluramine, sibutramine, orlistat, dexfenfluramine, mazindol, phentermine, phendimetrazine, diethylpropion, fluoxetine, bupropion, topiramate, diethylpropion, benzphetamine, phenylpropanolamine or ecopipam, ephedrine, pseudoephedrine;

[0070] d) anti-hypertensive agents such as loop diuretics such as ethacrynic acid, furosemide and torsemide; diuretics such as thiazide derivatives, chlorithiazide, hydrochlorothiazide, amiloride; angiotensin converting enzyme (ACE) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perinodopril, quinapril, ramipril and trandolapril; inhibitors of the Na-K-ATPase membrane pump such as digoxin; neutralendopeptidase (NEP) inhibitors e.g. thiorphan, terteo-thiorphan, SQ29072; ECE inhibitors e.g. SLV306; ACE/NEP inhibitors such as omapatrilat, sampatrilat and fasidotril; angiotensin II antagonists such as candesartan, eprosartan, irbesartan, losartan, telmisartan and valsartan, in particular valsartan; renin inhibitors such as aliskiren, terlakiren, ditekiren, RO 66-1132, RO-66-1168; beta-adrenergic receptor blockers such as acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol, sotalol and timolol; inotropic agents such as digoxin, dobutamine and milrinone; calcium channel blockers such as amlodipine, bepridil, diltiazem, felodipine, nicardipine, nimodipine, nifedipine, nisoldipine and verapamil; aldosterone receptor antagonists; aldosterone synthase inhibitors; and dual ET/AII antagonist such as those disclosed in WO 00/01389.

[0071] e) a HDL increasing compound;

[0072] f) Cholesterol absorption modulator such as Zetia® and KT6-971;

[0073] g) Apo-A1 analogues and mimetics;

[0074] h) thrombin inhibitors such as Ximelagatran;

[0075] i) aldosterone inhibitors such as anastrazole, fadrazole, eplerenone;

[0076] j) Inhibitors of platelet aggregation such as aspirin, clopidogrel bisulfate;

[0077] k) estrogen, testosterone, a selective estrogen receptor modulator, a selective androgen receptor modulator;

[0078] l) a chemotherapeutic agent such as aromatase inhibitors e.g. femara, anti-estrogens, topoisomerase I inhibitors, topoisomerase II inhibitors, microtubule active agents, alkylating agents, antineoplastic antimetabolites, platin compounds, compounds decreasing the protein kinase activity such as a PDGF receptor tyrosine kinase inhibitor preferably Imatinib ({ N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidine-amine }) described in the European patent application EP-A-0 564 409 as example 21 or 4-Methyl-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-benzamide described in the patent application WO 04/005281 as example 92; and

[0079] m) an agent interacting with a 5-HT$_3$ receptor and/or an agent interacting with 5-HT$_4$ receptor such as tegaserod described in the US patent No. 5510353 as example 13, tegaserod hydrogen maleate, cisapride, cilansetron;

[0080] n) an agent for treating tobacco abuse, e.g., nicotine receptor partial agonists, bupropion hypochloride (also known under the tradename Zyban$^{®}$) and nicotine replacement therapies;

[0081] o) an agent for treating erectile dysfunction, e.g., dopaminergic agents, such as apomorphine), ADD/ADHD agents (e.g., Ritalin$^{®}$, Strattera$^{®}$, Concerta$^{®}$ and Adderall$^{®}$);

[0082] p) an agent for treating alcoholism, such as opioid antagonists (e.g., naltrexone (also known under the tradename ReVia$^{®}$) and nalmefene), disulfiram (also known under the tradename Antabuse$^{®}$), and acamprosate (also known under the tradename Campral$^{®}$)). In addition, agents for reducing alcohol withdrawal symptoms may also be co-administered, such as benzodiazepines, beta- blockers, clonidine, carbamazepine, pregabalin, and gabapentin (Neurontin$^{®}$);

[0083] q) other agents that are useful including anti-inflammatory agents (e.g., COX-2 inhibitors) ; antidepressants (e.g., fluoxetine hydrochloride (Prozac$^{®}$)); cognitive improvement agents (e.g., donepezil hydrochloride (Aircept$^{®}$) and other acetylcholinesterase inhibitors); neuroprotective agents (e.g., memantine) ; antipsychotic medications (e.g., ziprasidone (Geodon®), risperidone (Risperdal®), and olanzapine (Zyprexa®));

[0084] or, in each case a pharmaceutically acceptable salt thereof; and optionally a pharmaceutically acceptable carrier.

[0085] The invention also provides for a pharmaceutical combinations, e.g. a kit, comprising a) a first agent which is a compound of the invention as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent. The kit can comprise instructions for its administration.

[0086] The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

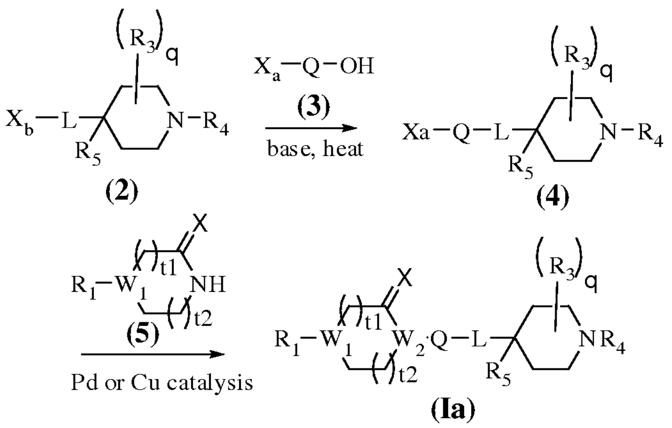
[0087] The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of Formula I and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of Formula I and a co-agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.

Processes for Making Compounds of the Invention

[0088] The present invention also includes processes for the preparation of compounds of the invention. In the reactions described, it can be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups can be used in accordance with standard practice, for example, see T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry", John Wiley and Sons, 1991.

[0089] In the following schemes, several methods of preparing the compounds of the present invention are illustrative. One of skill in the art will appreciate that these methods are representative, and in no way inclusive of all methods for preparing the compounds of the present invention. The radicals in the schemes are as described in Formula I.

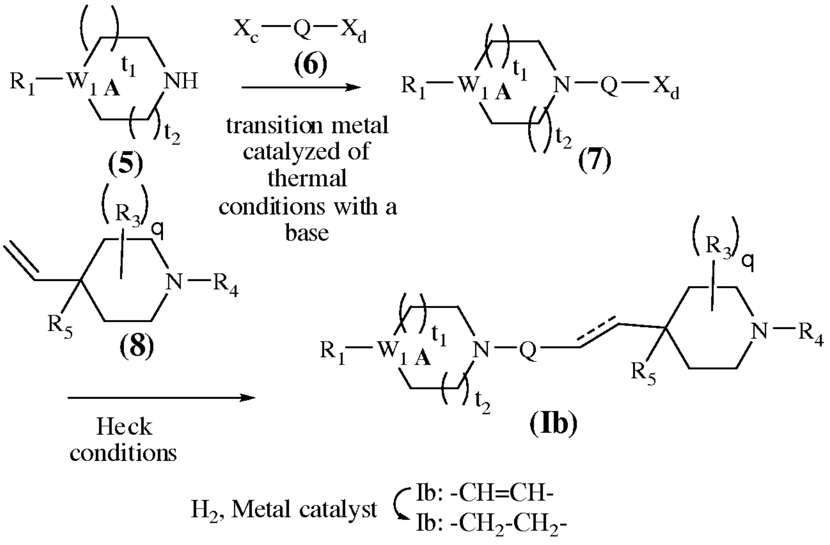
Reaction Scheme I



[0090] A compound of Formula Ia, where W_2 is nitrogen, can be prepared as in reaction scheme I by reacting a compound of formula 3 (where X_a refers to a chloride, bromide, iodide, triflate, nonaflate, or the like) with a compound of the formula 2 (where X_b refers to a leaving group such as an aryl- or alkylsulfonate ester, halide, epoxide where R_5 is the oxygen of the epoxide, or other appropriate group familiar to one skilled in the art) in a suitable solvent such as N,N-dimethylformamide, tetrahydrofuran and the like in the presence of a suitable base such as Cs_2CO_3, NaH or the like at an elevated temperature of up to about 80°C to generate an intermediate of the formula 4. A compound of the formula 5 (where C=X can be a C=O or CH_2) can be coupled with a compound of the formula 4 using the Pd or Cu methodology known in the art (for example, Shafir, A, Buchwald, S. F.; *J. Am Chem. Soc.* **2006**, 128, 8742 and references cited therein and Hartwig, J. F. *Handbook of Organopalladium Chemistry for Organic*

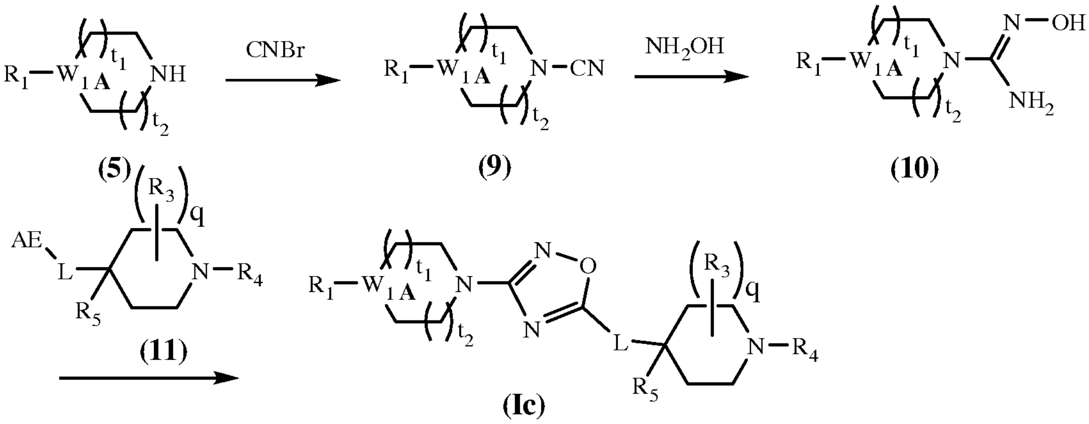
Synthesis, Negishi, E., Ed., Wiley-Interscience: Weinheim, 2002). In this scheme, it is understood that the groups may be protected versions of the radicals defined in the Summary of the Invention which may be deprotected and manipulated to a final compound of the invention after completion of this scheme or in the middle of the scheme.

Reaction Scheme II



[0091] A compound of the Formula Ib, wherein W_2 is N and L can be –CH=CH- or -CH_2-CH_2-, can be prepared as in reaction scheme II. A compound of the formula 5 can be reacted with a compound of the formula 6 (where X_c and X_d both independently represent leaving groups such as F, Cl, Br, OTf, etc. with X_c being the more reactive group) using either the transition metal catalysis mentioned in scheme 1 or using a stoichiometric base such as K_2CO_3, triethylamine and the like in a suitable solvent such as N,N-dimethylformamide and the like at an elevated temperature to generate an intermediate of the formula 7. Intermediate 7 can then be reacted with an olefin of the formula 8 using heck reaction conditions (for example, Littke, A. F.; Fu, G. C, *J. Am. Chem. Soc.* **2001**, 123, 6989) to generate compounds where L is –(CH=CH)- which can subsequently be reduced using hydrogen and a catalytic amount of a transition metal such as Pd/C and the like to compounds where L is $-(CH_2)_2-$. In this scheme, it is understood that the groups can be protected versions of the radicals defined in the Summary of the Invention which can be deprotected and manipulated to the final compound after completion of this scheme or in the middle of the scheme.

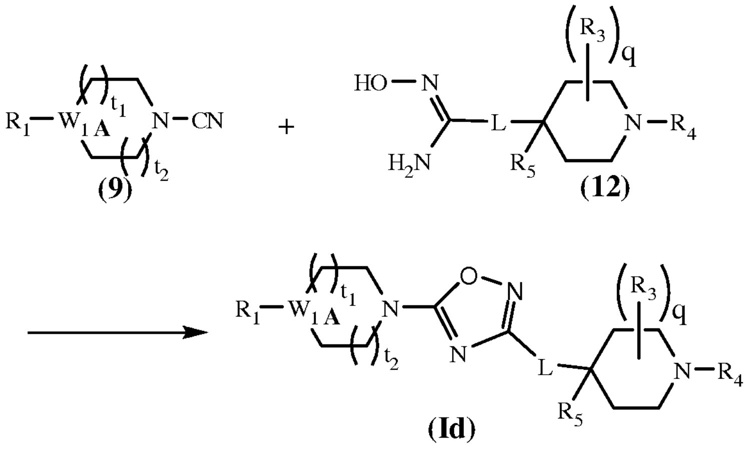
Reaction Scheme III



[0092] A compound of the Formula Ic, in which Q is a heteroaryl group such as 1,2,4-oxadiazolyl (as shown) and W_2 is N, can be prepared as in reaction scheme III by reacting a compound of the formula 5 with cyanogen bromide in a suitable solvent system such as aqueous Na_2CO_3 and dichloromethane and the to generate a compound of the formula 9. This intermediate can then be reacted with hydroxylamine in an appropriate solvent such as ethanol and the like at an elevated temperature such as 60 °C to furnish a compound of the formula 10. Intermediate 10 can then be reacted with a compound of the formula 11 (where AE stands for an acid equivalent such as a carboxylic acid, alkyl ester or activated ester such as an NHS ester and the like) using any of the protocols known in the literature (such as *Science of Synthesis* **2004**, *13*, 127, *Tetrahedron Lett.* **2006**, *47*, 3629 and *J. Med. Chem.* **2004**, *47*, 5821) to afford the desired compounds of the formula Ic. In this scheme, it is understood that the groups designated can be protected versions of the radicals defined in the Summary of the

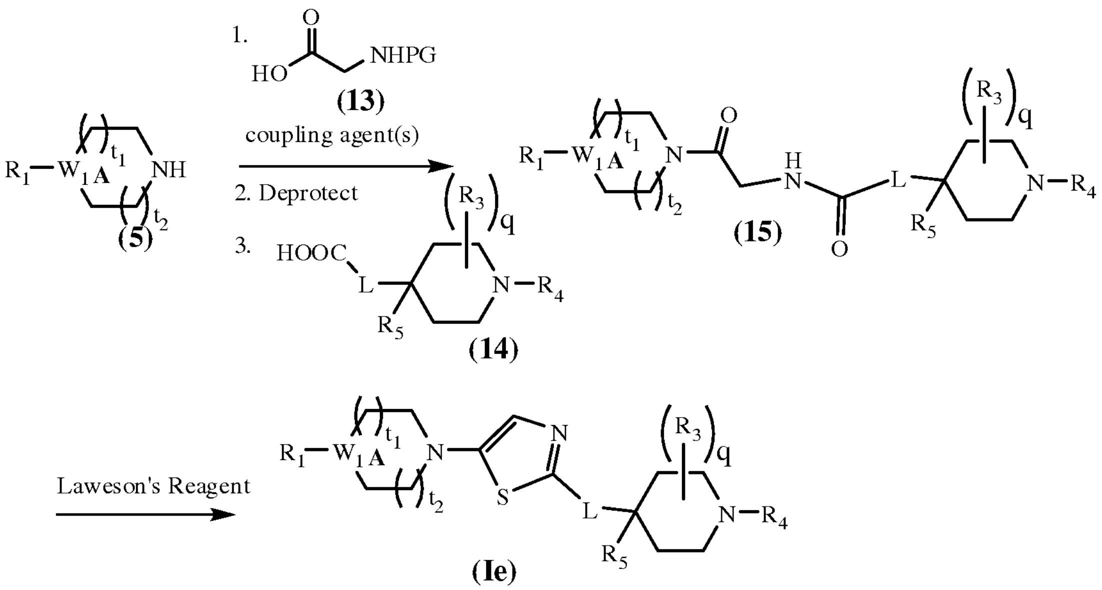
Invention which can be deprotected and manipulated to the final compound after completion of this scheme or in the middle of the scheme.

Reaction Scheme IV



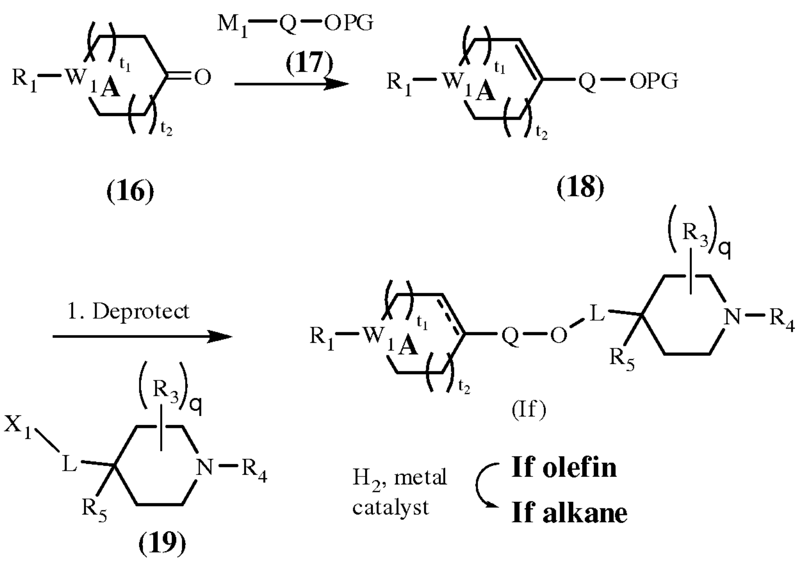
[0093] A compound of the Formula Id can be prepared as in reaction scheme IV by reacting a compound of the formula 9 with a compound of the formula 12 in a solvent such as tetrahydrofuran or the like in the presence of a Lewis acid such as $ZnCl_2$ and the like at an elevated temperature. In this scheme, it is understood that the groups designated can be protected versions of the radicals defined in the Summary of the Invention which can be deprotected and manipulated to the final compound after completion of this scheme or in the middle of the scheme.

Reaction Scheme V



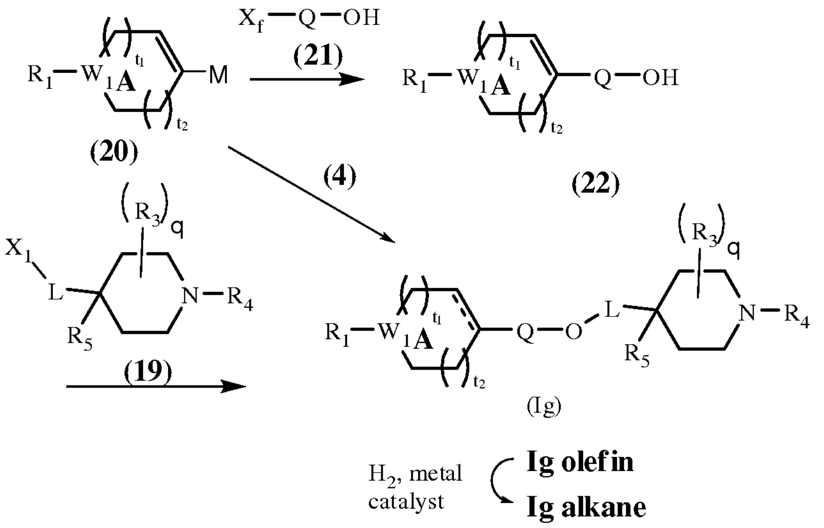
[0094] A compound of the Formula Ie, in which Q is thiazolyl (as sown above) and W_2 is N, can be prepared as in reaction scheme V by reacting a compound of the formula 5 with a protected glycine derivative of the formula 13 using appropriate coupling reagents followed by deprotection and coupling with a carboxylate of the formula 14 to generate an intermediate of the formula 15. This intermediate can then be cyclized using Lawesson's reagent or other thiotransfer/dehydrating agent in an appropriate solvent such as xylene at an elevated temperature such as 130 °C to generate the desired compound of the formula Ie. In this scheme, it is understood that the groups designated can be protected versions of the radicals defined in the Summary of the Invention which can be deprotected and manipulated to the final compound after completion of this scheme or in the middle of the scheme.

Reaction Scheme VI



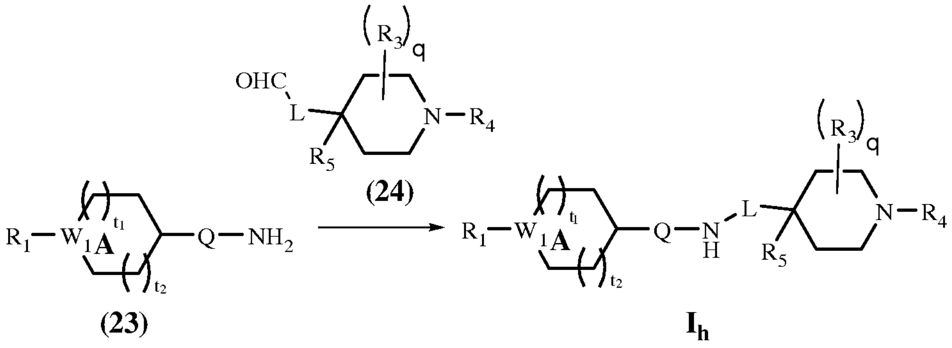
[0095] A compound of the Formula If, can be prepared as in reaction scheme VI. A ketone derivative of formula 16 can be reacted with an organometal reagent of formula 17 such as a Grignard reagent or the like to furnish after dehydration with an acid such as TFA and the like, an olefin of the formula 18. This material can be deprotected with the appropriate reagents followed by reaction with an electophile of the formula 19 where X_1 can be a leaving group such as mesylate, halide or the like in an appropriate solvent such as N,N-dimethylformamide or the like using a base such as Cs_2CO_3 or the like to afford If as the olefin. The olefin can then be reduced with a metal catalyst such as Pd/C or the like with hydrogen gas or the appropriate hydrogen transfer reagent to afford If as an alkane. In this scheme, it is understood that the groups designated can be protected versions of the radicals defined in the Summary of the Invention which can be deprotected and manipulated to the final compound after completion of this scheme or in the middle of the scheme.

Reaction Scheme VII



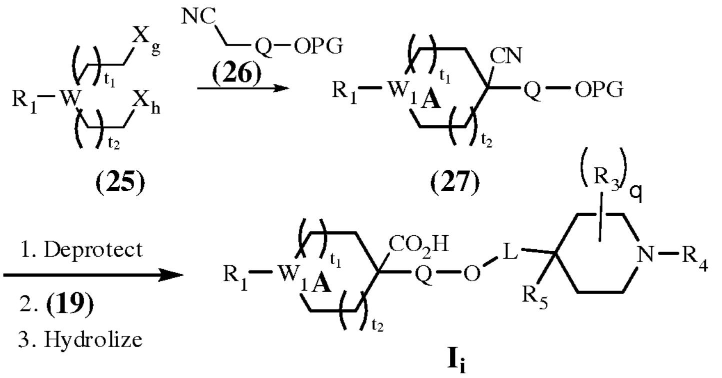
[0096] A compound of the Formula Ig, can be prepared as in reaction scheme VII. A vinyl metal derivative of formula 19 (where M is B, Sn, Si, Mg, Zn or other metals known to participate in metal catalyzed coupling reactions) can be reacted with a halide of formula 21 (where X_f refers to a chloride, bromide, iodide, triflate, nonaflate, or the like) using an appropriate metal catalyst such as Pd with an appropriate liand system such as familiar to those skilled in the art to generate an intermediate of formula 22. This intermediate can then be alkylated with an intermediate of formula 18 as outlined in scheme VI to afford Ig as an olefin. The olefin can then be reduced with a metal catalyst such as Pd/C or the like with hydrogen gas or the appropriate hydrogen transfer reagent to afford Ig as an alkane. Alternatively, Ig can be prepared by carrying out a metal mediated coupling on a compound of formula 20 with a compound of formula 4 and manipulating as before to get to the alkane. In this scheme, it is understood that the groups designated can be protected versions of the radicals defined in the Summary of the Invention which can be deprotected and manipulated to the final compound after completion of this scheme or in the middle of the scheme.

Reaction Scheme VIII



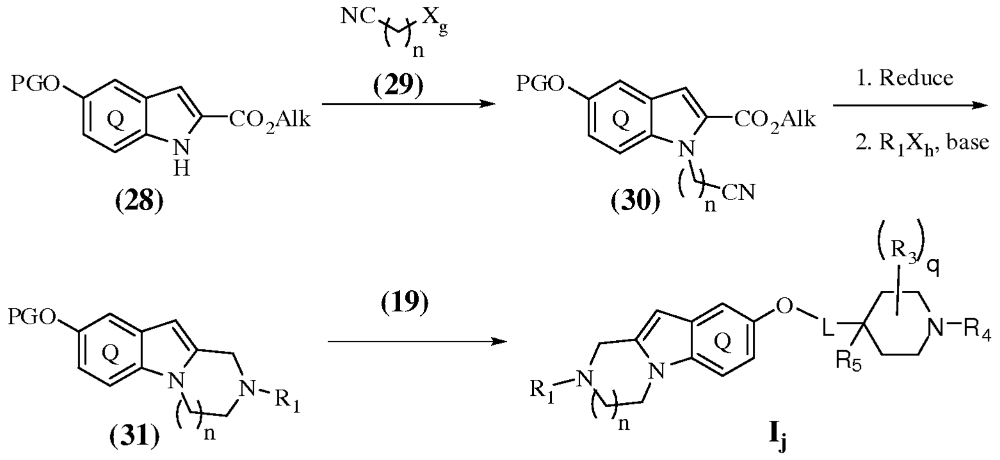
[0097] A compound of the Formula Ih, can be prepared as in reaction scheme VIII. A compound of formula 23 can be reductively aminated with a compound of formula 24 using the appropriate reductant such as $NaHB(OAc)_3$, $NaCNBH_3$ and the like in an appropriate solvent such as dichloromethane, methanol, ethanol and the like to afford I_h. The amine in I_h can then be further manipulated. In this scheme, it is understood that the groups designated can be protected versions of the radicals defined in the Summary of the Invention which can be deprotected and manipulated to the final compound after completion of this scheme or in the middle of the scheme.

Reaction Scheme IX



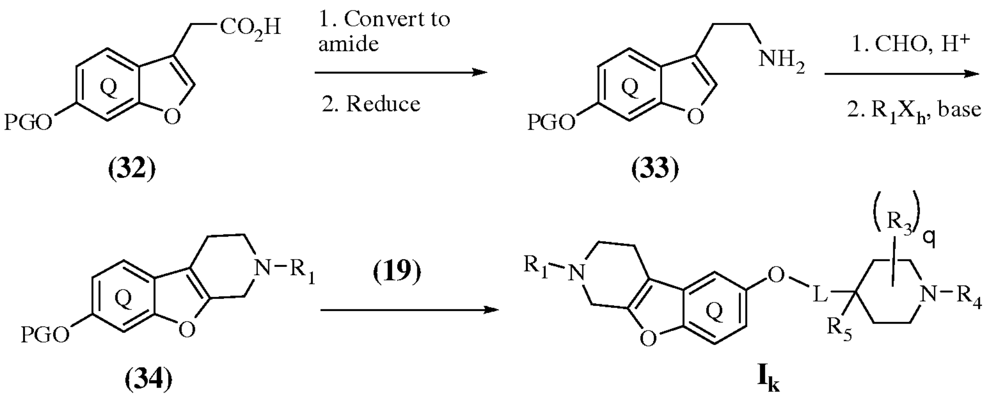
[0098] A compound of the Formula Ii, can be prepared as in reaction scheme IX. A compound of formula 25 (Where X_g and X_h can be chosen from chloro, bromo, iodo, mesylate, tosylate and the like) can be reacted with a compound of formula 26 using an appropriate base such as sodium hydride, LDA and the like in an appropriate solvent such as N,N-dimethylformamide, N-methylpyrrolidinone, DMSO, tetrahydrofuran and the like at an elevated temperature such as 75 °C or similar to afford an intermediate of formula 27. This material can then be manipulated in a similar fashion to intermediate 18 in scheme VI to arrive at I_i. In this scheme, it is understood that the groups designated can be protected versions of the radicals defined in the Summary of the Invention which can be deprotected and manipulated to the final compound after completion of this scheme or in the middle of the scheme.

Reaction Scheme X



[0099] A compound of the Formula Ij, can be prepared as in reaction scheme X. A compound of formula 28 can be reacted with a compound of formula 29 (where X_g can be chosen from chloro, bromo, iodo, mesylate, tosylate and the like) using an appropriate base such as cesium carbonate, sodium hydride, LDA and the like in an appropriate solvent such as N,N-dimethylformamide, N-methylpyrrolidinone, DMSO, tetrahydrofuran and the like to afford an intermediate of formula 30. This material can then be reduced using an appropriate metal hydride such as LAH or BH_3 and then functionalized with the appropriate electrophile R_1X_h (where X_h can be chosen from chloro, bromo, succinate, p-nitrophenyl and the like) to afford an intermediate of the formula 31. This material can then be manipulated in a similar fashion to intermediate 18 in scheme VI to arrive at I_j. In this scheme, it is understood that the groups designated can be protected versions of the radicals defined in the Summary of the Invention which can be deprotected and manipulated to the final compound after completion of this scheme or in the middle of the scheme.

Reaction Scheme XI



[00100] A compound of the Formula Ik, can be prepared as in reaction scheme XI. A compound of formula 32 can be converted to an amide by reacting with an activating agent such as oxlyl chloride or the like in an appropriate solvent such as dichloromethane or the like followed by reaction with ammonia or an equivalent followed by reduction with an appropriate reagent such as LAH or BH_3 to afford an intermediate of the formula 33. This material can then be cyclized with formaldehyde and acid such as acetic acid or the like followed by functionalization with an appropriate R_1X_h (where X_h can be chosen from chloro, bromo, succinate, p-nitrophenyl and the like) to afford an intermediate of the formula 34. This material can then be manipulated in a similar fashion to intermediate 18 in scheme VI to arrive at I_k. In this scheme, it is understood that the groups designated can be protected versions of the radicals defined in the Summary of the Invention which can be deprotected and manipulated to the final compound after completion of this scheme or in the middle of the scheme.

[00101] Detailed descriptions of the synthesis of compounds of the Invention are given in the Examples, *infra*.

Additional Processes for Making Compounds of the Invention

[00102] A compound of the invention can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of the invention can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Alternatively, the salt forms of the compounds of the invention can be prepared using salts of the starting materials or intermediates.

[00103] The free acid or free base forms of the compounds of the invention can be prepared from the corresponding base addition salt or acid addition salt from, respectively. For example a compound of the invention in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound of the invention in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc.).

[00104] Compounds of the invention in unoxidized form can be prepared from N-oxides of compounds of the invention by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, or the like) in a suitable inert organic solvent (e.g. acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80 °C.

[00105] Prodrug derivatives of the compounds of the invention can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier et al., (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of the invention with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbanochloridate, para-nitrophenyl carbonate, or the like).

[00106] Protected derivatives of the compounds of the invention can be made by means known to those of ordinary skill in the art. A detailed description of techniques applicable to the creation of protecting groups and their removal can be found in T. W. Greene, "Protecting Groups in Organic Chemistry", 3rd edition, John Wiley and Sons, Inc., 1999.

[00107] Compounds of the present invention can be conveniently prepared, or formed during the process of the invention, as solvates (e.g., hydrates). Hydrates of compounds of the present invention can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

[00108] Compounds of the invention can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of the compounds of the invention, dissociable complexes are preferred (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, “Enantiomers, Racemates and Resolutions”, John Wiley And Sons, Inc., 1981.

[00109] In summary, the compounds of Formula I can be made by a process, which involves:

(a) that of reaction schemes I to XI; and

(b) optionally converting a compound of the invention into a pharmaceutically acceptable salt;

(c) optionally converting a salt form of a compound of the invention to a non-salt form;

(d) optionally converting an unoxidized form of a compound of the invention into a pharmaceutically acceptable N-oxide;

(e) optionally converting an N-oxide form of a compound of the invention to its unoxidized form;

(f) optionally resolving an individual isomer of a compound of the invention from a mixture of isomers;

(g) optionally converting a non-derivatized compound of the invention into a pharmaceutically acceptable prodrug derivative; and

(h) optionally converting a prodrug derivative of a compound of the invention to its non-derivatized form.

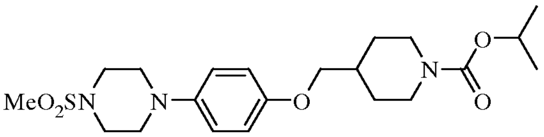
[00110] Insofar as the production of the starting materials is not particularly described, the compounds are known or can be prepared analogously to methods known in the art or as disclosed in the Examples hereinafter.

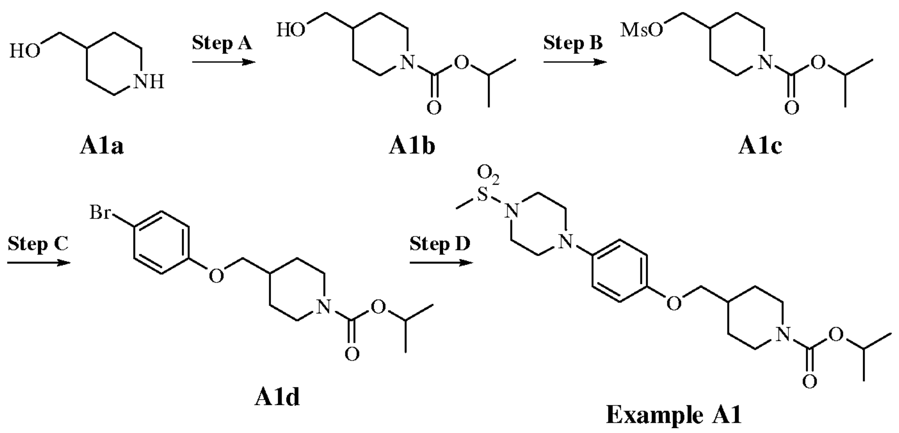
[00111] One of skill in the art will appreciate that the above transformations are only representative of methods for preparation of the compounds of the present invention, and that other well known methods can similarly be used.

Examples

[00112] The present invention is further exemplified, but not limited, by the following Examples that illustrate the preparation of compounds of the invention.

Example A1: Isopropyl 4-((4-((4-methanesulfonylpiperazin)-1-yl)phenoxy)methyl)piperidine-1-carboxylate.





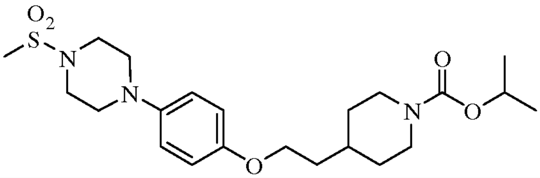
[00113] **Step A**: To a solution of **A1a** (5.26 g, 45.7 mmol) in dry dimethoxyethane (30 mL) is added triethylamine (8.0 g, 56.9 mmol). To the resulting mixture, a 1.0-M solution of isopropyl chloroformate in toluene (50 mL) is added dropwise, with vigorous stirring, over 10 min. A white precipitate forms. The suspension is stirred at room temperature for 4 hours; the white precipitate is filtered off, washed with more dimethoxyethane, and discarded. The resulting solution is concentrated to dryness to yield **A1b**; ^{1}H NMR (DMSO-d_6, 400.13 MHz): δ 4.75 (septet, J = 6.2 Hz, 1H), 4.49 (t, J = 5.3 Hz, 1H), 3.95 (dd, J = 5.6, 5.6 Hz, 2H), 3.24 (br, 2H), 1.63 (dd, J = 2.0, 12.9 Hz, 2H), 1.51 (m, 1H), 1.17 (d, J = 6.2 Hz, 6H), 0.98 (m, 2H); no mass spectrum could be obtained.

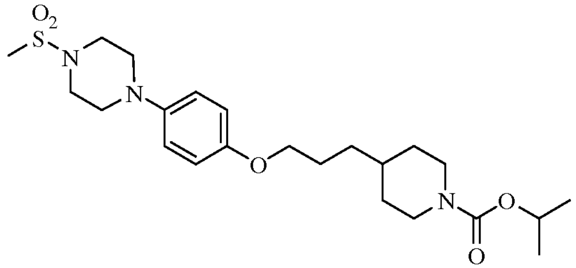
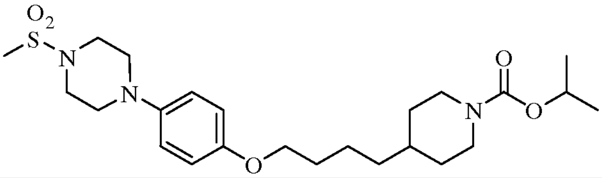
[00114] **Step B**: To a solution of **A1b** (4.25 g, 21.1 mmol) in dichloromethane (30mL) is added triethylamine (4.5 g, 32.0 mmol) in one portion. The resulting mixture is cooled in an ice/water bath and methanesulfonyl chloride (1.8 mL, 23.2 mmol) is added dropwise, with stirring, over 5 min. The bath is removed and the resulting solution is stirred at room temperature for 30 min. The reaction mixture is added to water (40 mL) and extracted with dichloromethane (2 x 40 mL). The combined organic extracts are washed with saturated ammonium chloride aqueous solution, dried over $MgSO_4$, and concentrated to yield **A1c**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 4.74 (septet, J = 6.2 Hz, 1H), 4.07 (d, J = 6.4 Hz, 2H), 3.99 (d, J = 11.0 Hz, 2H), 3.17 (s, 3H), 2.51 (br, 2H), 1.88 (dd, J = 1.6, 14.6 Hz, 2H), 1.68 (m, 1H), 1.18 (d, J = 6.2 Hz, 6H), 1.17 (m, 2H); ESIMS calcd. for $C_{11}H_{22}NO_5S$ ($M+H^+$) 280.11, found 280.2.

[00115] **Step C**: A solution of **A1c** (0.42 g, 1.50 mmol) and 4-bromophenol (0.26 g, 1.50 mmol) in acetonitrile (5.0 mL) is treated with powdered cesium carbonate (0.60 g, 1.84 mmol) and the mixture is stirred at 65 °C for 16 hours. Cooling to room temperature, filtration and concentration yields **A1d**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.36 (d, J = 9.0 Hz, 2H), 6.76 (d, J = 9.0 Hz, 2H), 4.91 (septet, J = 6.2 Hz, 1H), 4.19 (br, 2H), 3.76 (d, J = 6.4 Hz, 2H), 3.26 (br, 2H), 2.78 (m, 2H), 1.96 (m, 1H), 1.82 (dd, J = 1.6, 14.6 Hz, 2H), 1.30 (m, 2H), 1.28 (d, J = 6.2 Hz, 6H); ESIMS calcd. for $C_{16}H_{23}BrNO_3$ ($M+H^+$) 356.1, found 356.0.

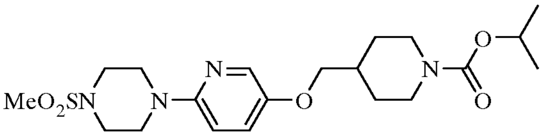
[00116] **Step D**: A solution of **A1d** (0.55 g, 1.50 mmol), 4-methanesulfonyl-piperazine (0.25 g, 1.52 mmol), and tri-*t*-butylphosphonium tetrafluoroborate (92.2 mg, 0.32 mmol) in dry dioxane (6mL) is treated with powdered cesium carbonate (1.03 g, 3.16 mmol) and the mixture is degassed using argon. Tris(dibenzylidene acetone)dipalladium(0) (0.15 g, 0.16 mmol) is added and the mixture is degassed again with argon. The suspension is stirred vigorously under argon at 110 °C for 18hours. Cooling, filtration and purification using mass-triggered reverse phase HPLC yields **A1**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 6.90 (d, J = 8.9 Hz, 2H), 6.84 (d, J = 8.9 Hz, 2H), 4.92 (septet, J = 6.2 Hz, 1H), 4.19 (br, 2H), 3.76 (d, J = 6.4 Hz, 2H), 3.39 (t, J = 3.9 Hz, 4H), 3.17 (t, J = 3.9 Hz, 4H), 2.83 (s, 1H), 2.77 (t, J = 11.2 Hz, 2H), 1.96 (m, 1H), 1.83 (dd, J = 1.4, 14.2 Hz, 2H), 1.27 (m, 2H), 1.24 (d, J = 6.2 Hz, 6H); ESIMS calcd. for $C_{21}H_{34}N_3O_5S$ ($M+H^+$) 440.2, found 440.2.

[00117] By following a similar procedure as the one used for preparing **A1** from **A1a** except substituting the appropriate alcohol for **A1a**, the following examples are obtained:

Example	Structure	Analytical data
A2		ESIMS calcd. for $C_{22}H_{36}N_3O_5S$ ($M+H^+$) 454.2, found 454.2.

A3		ESIMS calcd. for $C_{23}H_{38}N_3O_5S$ (M+H$^+$) 468.2, found 468.2.
A4		ESIMS calcd. for $C_{24}H_{40}N_3O_5S$ (M+H$^+$) 482.2, found 482.2.

Example B1: Isopropyl 4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate.

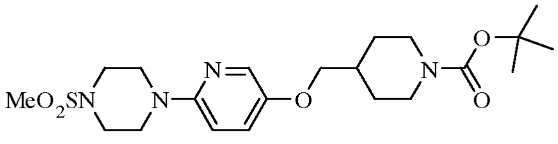


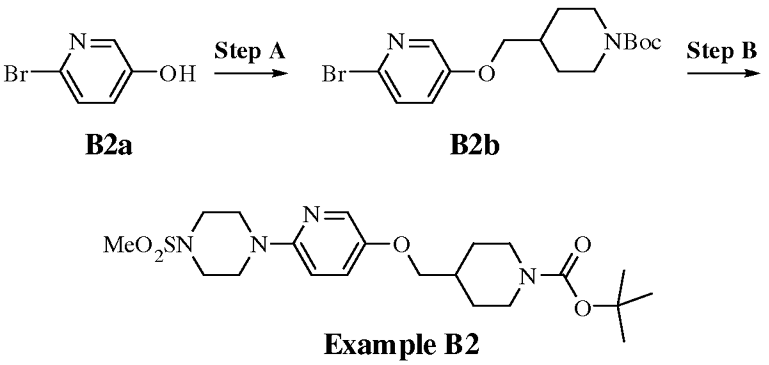
[00118] By following a similar procedure as the one used for preparing **A1** from **A1a** except substituting 2-chloro-5-hydroxypyridine for 4-bromophenol and performing step D as follows, **B1** is prepared;

[00119] A flask is charged with Pd_2dba_3 (6 mg, 0.006 mmol), xantphos (11 mg, 0.019 mmol), 1-(methylsulfonyl)piperazine (63 mg, 384 mmol), sodium *tert*-butoxide (46 mg, 0.48 mmol), and a solution of isopropyl 4-((6-chloropyridin-3-yloxy)methyl)piperidine-1-carboxylate (100 mg, 0.32 mmol) in toluene (1mL). The reaction is purged by bubbling nitrogen through the solution for 5 minutes and then sealed. The reaction is then dipped into a pre-heated 100 °C bath and stirred at this temperature for 3 hours. After cooling to room temperature, the reaction is treated with ethyl acetate and water and the aqueous phase is isolated, washed with ethyl acetate once more and discarded. The combined organics are dried over $MgSO_4$ and the solvent is removed. The residue is purified on a silica gel column using a linear gradient of 0-100% ethyl acetate in hexane as eluent to afford **B1**; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.92 (d, J = 3.0, 1H), 7.18 (dd, J = 3.0, 9.1, 1H), 6.67 (d, J = 9.1, 1H), 4.91 (m, 1H), 4.20

(m, 2H), 3.78 (d, *J* = 6.4, 2H), 3.56 (m, 4H), 3.34 (m, 4H), 2.81 (s, 3H), 2.76 (m, 2H), 1.94 (m, 1H), 1.81 (m, 2H), 1.29 (m, 2H), 1.24, d, *J* = 6.2, 6H); ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{33}N_4O_5S$ calcd.: 441.2, found: 441.3.

Example B2. *tert*-Butyl 4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate.



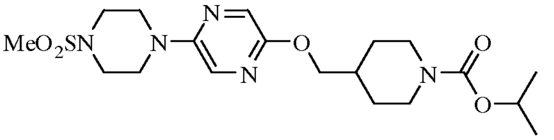


[00120] **Step A:** A solution of **B2a** (4.00 g, 23 mmol) and tert-butyl 4-((methylsulfonyloxy)methyl)piperidine-1-carboxylate (7.08 g, 24 mmol) in N-methylpyrrolidinone (50 mL) is treated with Cs_2CO_3 (9.74 g, 30 mmol) and heated to 100 °C overnight. The reaction is then diluted with ethyl acetate, extracted with water 3 times, dried over $MgSO_4$, filtered, evaoparted and crystallized from toluene/hexane to afford **B2b**; ESIMS *m/z* for $(M\text{-}t\mathrm{Bu}+H)^+$ $C_{12}H_{16}BrN_2O_3$ calcd.: 315.0, found: 315.0.

[00121] **Step B:** Following the procedure for the palladium coupling outlined for **B1** above, substituting **B2b** for isopropyl 4-((6-chloropyridin-3-yloxy)methyl)piperidine-1-carboxylate, **B2** is prepared; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.91 (d, *J* = 2.9, 1H), 7.15 (dd, *J* = 9.1, 3.1, 1H), 6.65 (d, *J* = 9.0, 1H), 4.15 (m, 2H), 3.78 (d, *J* = 6.4, 2H), 3.54 (m,

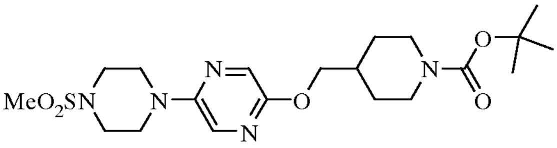
4H), 3.33 (m, 4H), 2.81 (s, 3H), 2.72 (m, 2H), 1.93 (m, 1H), 1.80 (m, 2H), 1.46 (s, 9H), 1.25 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{35}N_4O_5S$ calcd.: 455.2, found: 455.2.

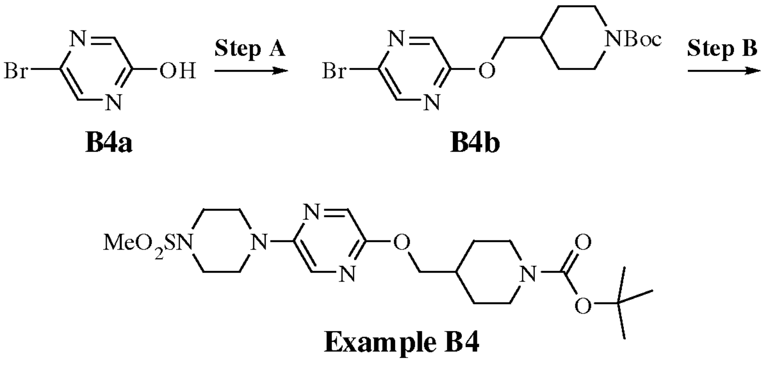
Example B3: Isopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00122] By following a similar procedure as the one used for preparing **B1** except using 2-bromo-5-hydroxypyrazine as the heterocycle, **B3** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, *J* = 1.4, 1H), 7.62 (d, *J* = 1.5, 1H), 4.92 (m, 1H), 4.18 (m, 2H), 4.08 (d, *J* = 6.5, 2H), 3.52 (m, 4H), 3.37 (m, 4H), 2.82 (s, 3H), 2.76 (m, 2H), 1.96 (m, 1H), 1.79 (m, 2H), 1.29 (m, 2H), 1.24, (d, *J* = 6.2, 6H); ESIMS *m/z* for $(M+H)^+$ $C_{19}H_{32}N_5O_5S$ calcd.: 442.2, found: 442.3.

Example B4: *tert*-Butyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.

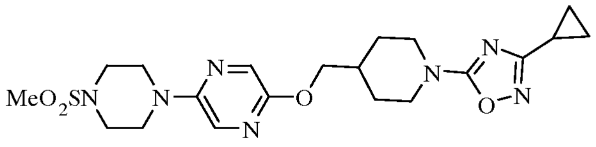




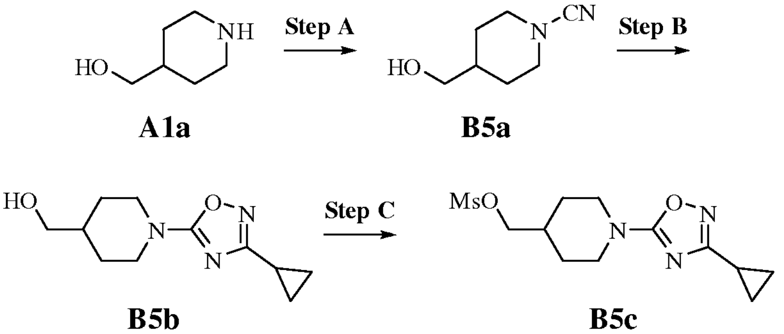
[00123] **Step A:** By following a similar procedure as the one used for preparing **B2b** from **B2a** except substituting **B4a** for **B2a, B4b** is prepared; ESIMS *m/z* for (M-*t*Bu+H$^+$) $C_{11}H_{15}BrN_3O_3$ calcd.: 316.0, found: 316.0.

[00124] **Step B:** By following the procedure for the palladium coupling outlined for the preparation of **B1** except substituting **B4b** for isopropyl 4-((6-chloropyridin-3-yloxy)methyl)piperidine-1-carboxylate, **B4** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, *J* = 1.2, 1H), 7.62 (d, *J* = 1.2, 1H), 4.13 (m, 2H), 4.08 (d, *J* = 6.8, 2H), 3.52 (m, 4H), 3.37 (m, 4H), 2.82 (s, 3H), 2.72 (m, 2H), 1.93 (m, 1H), 1.46 (s, 9H), 1.26 (m, 2H); ESIMS *m/z* for (M+H)$^+$ $C_{20}H_{34}N_5O_5S$ calcd.: 456.2, found: 456.2.

Example B5: 3-Cyclopropyl-5-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole.



[00125] By following a similar procedure as the one used for preparing **B3** from **B2a** except substituting **B5c** (see scheme below) for **B2a, B5** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88 (d, *J* = 1.3, 1H), 7.62 (d, *J* = 1.4, 1H), 4.16 (m, 2H), 4.10 (d, *J* = 6.8, 2H), 3.53 (m, 4H), 3.37 (m, 4H), 3.05 (ddd, *J* = 12.9, 12.9, 2.8, 2H), 2.82 (s, 3H), 2.02 (m, 1H), 1.88 (m, 4H), 1.41 (m, 2H), 0.94 (m, 4H); ESIMS *m/z* for (M+H)$^+$ $C_{20}H_{30}N_7O_4S$ calcd.: 464.2, found: 464.3.

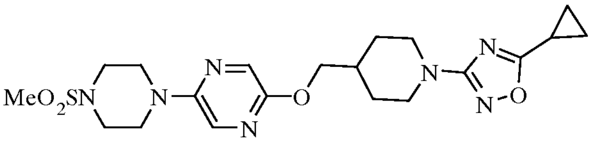


[00126] **Step A:** A sample of **A1a** (10.19 g, 84.9 mmol) is treated with a solution of K_2CO_3 (24.5 g, 177 mmol) in water (100 mL). The reaction is cooled in an ice/water bath and treated with a solution of cyanogen bromide (10.31 g, 97.3 mmol) in dichloromethane (100 mL) dropwise. After stirring for an hour, the organic layer is isolated and the aqueous layer is extracted once more with dichloromethane. The combined organic extracts are dried over $MgSO_4$, filtered and evaporated to afford **B5a**; ESIMS *m/z* for $(M+H)^+$ $C_7H_{13}N_2O$ calcd.: 141.1, found: 141.1.

[00127] **Step B:** A solution of **B5a** (993 mg, 7.1 mmol), N'-hydroxycyclopropane carboximidamide (1.064 g, 10.6 mmol) and $ZnCl_2$ (1.448 g, 10.6 mmol) in dioxane (25 mL) is heated to 100 °C overnight. The reaction is then evaporated to dryness and partitioned between ethyl acetate and 1 M HCl. The organics are isolated, extracted with 1 M HCl once more, dried over $MgSO_4$, filtered, evaporated and purified by silica gel to afford **B5b**; ESIMS *m/z* for $(M+H)^+$ $C_{11}H_{18}N_3O_2$ calcd.: 224.1, found: 224.1.

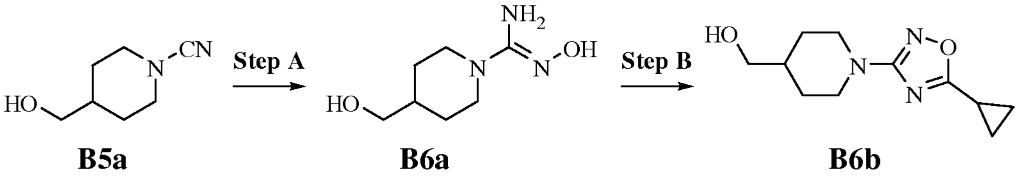
[00128] **Step C:** A solution of **B5b** (278.4 mg, 1.25 mmol) and triethylamine (131 mg, 130 mmol) in dichloromethane (1 mL) is cooled in an ice/water bath, treated with methanesulfonyl chloride (149 mg, 1.3 mmol) and stirred overnight. The reaction is diluted with water and extracted with dichloromethane. The organics are dried over $MgSO_4$, filtered, evaporated and purified on silica gel using a linear gradient of 0 to 100% ethyl acetate in hexane to afford **E5c**; ESIMS *m/z* for $(M+H)^+$ $C_{12}H_{20}N_3O_4S$ calcd.: 302.1, found: 302.1.

Example B6: 5-Cyclopropyl-3-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole.



[00129] By following a similar procedure as the one used for **B5** except substituting **B6b** (see scheme below) for **B5b**, **B6** is obtained; ^1H NMR ($CDCl_3$, 400

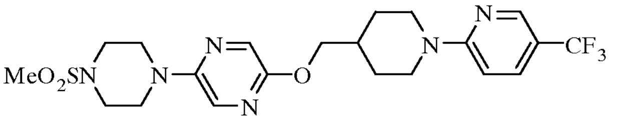
MHz): δ 7.87 (d, *J* = 1.5, 1H), 7.63 (d, *J* = 1.5, 1H), 4.10 (d, *J* = 6.8, 2H), 4.00 (m, 2H), 3.53 (m, 4H), 3.37 (m, 4H), 2.89 (ddd, *J* = 12.7, 12.7, 2.7, 2H), 2.82 (s, 3H), 2.00 (m, 1H), 1.86 (m, 4H), 1.40 (ddd, *J* = 25.0, 12.4, 4.3, 2H), 1.14 (m, 4H); ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{29}N_7O_4S$ calcd.: 464.2, found: 464.3.



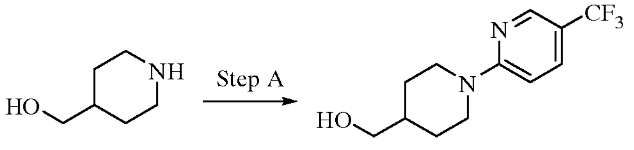
[00130] **Step A:** A solution of **B5a** (4.01 g, 28.6 mmol) and hydroxylamine (3.51 mL of a 50% by weight aqueous solution, 57.2 mmol) in ethanol (50 mL) is sealed and heated to 60 °C overnight. The solvent is then removed to **B6a**; ESIMS *m/z* for $(M+H)^+$ $C_7H_{16}N_3O_2$ calcd.: 174.1, found: 174.1.

[00131] **Step B:** A solution of **B6a** (905 mg, 5.2 mmol) and 2,5-dioxopyrrolidin-1-yl cyclopropanecarboxylate (957 mg, 5.2 mmol) in dioxane (50 mL) is heated to 80 °C for 3 hours and then 70 °C overnight. The reaction is then cooled to room temperature, concentrated and purified on silica gel using a linear gradient of 0-80% ethyl acetate in hexane to afford **B6b**; ESIMS *m/z* for $(M+H)^+$ $C_{11}H_{18}N_3O_2$ calcd.: 224.1, found: 224.1.

Example B7: 2-(4-(Methylsulfonyl)piperazin-1-yl)-5-((1-(5-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)methoxy)pyrazine.



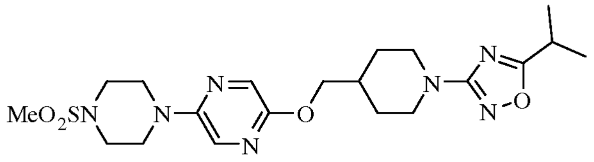
[00132] By following a similar procedure as the one used for preparing **B3** from **B2a** except substituting **B7a** (see scheme below) for **A1b, B7** is prepared; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.37 (m, 1H), 7.88 (d, *J* = 1.4, 1H), 7.63 (d, *J* = 1.4, 1H), 7.60 (dd, *J* = 9.1, 2.5, 1H), 6.65 (d, *J* = 9.1, 1H), 4.45 (m, 2H), 4.11 (d, *J* = 6.5, 1H), 3.53 (m, 4H), 3.37 (m, 4H), 2.95 (m, 2H), 2.82 (s, 3H), 2.11 (m, 1H), 1.93 (m, 2H), 1.37 (ddd, *J* = 24.9, 12.5, 4.1, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{28}F_3N_6O_3S$ calcd.: 501.2, found: 501.3.



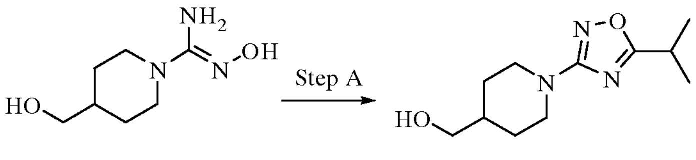
A1a **B7a**

[00133] **Step A:** A mixture of **A1a** (522.5 mg, 4.5 mmol), 2-chloro-5-trifluoromethylpyridine (1.19 g, 6.5 mmol) and K_2CO_3 (941 mg, 6.8 mmol) in N,N-dimethylformamide (8 mL) is heated to 160 °C for 10 minutes, cooled to room temperature and diluted with ethyl acetate and water. The organics are extracted with water, dried over MgSO4, filtered, evaporated and purified on silica gel using a linear gradient of 0 to 100% ethyl acetate in hexane to afford **B1a**; ESIMS *m/z* for $(M+H)^+$ $C_{12}H_{16}F_3N_2O$ calcd.: 261.1, found: 261.1.

Example B8: 5-Isopropyl-3-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole.



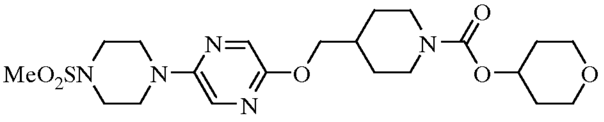
[00134] By following a similar procedure as the one used for preparing **B6** from **B6b** except substituting **B8a** (see scheme below) for **B6b, B8** is prepared; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.88 (d, *J* = 1.5, 1H), 7.63 (d, *J* = 1.5, 1H), 7.60 (dd, *J* = 9.1, 2.5, 1H), 4.11 (d, *J* = 6.6, 1H), 3.53 (m, 4H), 3.37 (m, 4H), 3.07 (m, 1H), 2.92 (ddd, *J* = 12.7, 12.7, 2.7, 2H), 2.82 (s, 3H), 2.01 (m, 1H), 1.88 (m, 2H), 1.42 (m, 2H), 1.35 (d, *J* = 7.0, 6H); ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{32}N_7O_4S$ calcd.: 466.2, found: 466.2.



B6a **B8a**

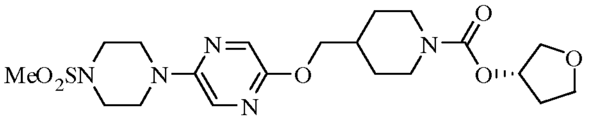
[00135] **Step A:** A solution of **B6a** (460.3 mg, 2.7 mmol) and isobutyric anhydride (420 mg, 2.7 mmol) in dioxane (3 mL) is heated to 150 °C for 5 minutes. The reaction is cooled to room temperature and diluted with ethyl acetate and water. The organics are isolated and washed once with water, dried over $MgSO_4$, filtered, evaporated and purified on silica using a linear gradient of ethyl acetate in hexane to afford **B8a**. A satisfactory mass spectal analysis could not be obtained.

Example B9: Tetrahydro-2H-pyran-4-yl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



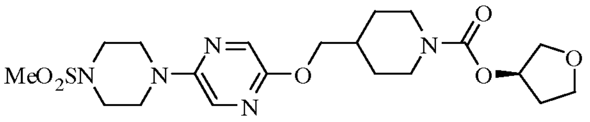
[00136] By following a similar procedure as the one used for preparing **B3** from **A1a** except substituting 4-nitrophenyl tetrahydro-2H-pyran-4-yl carbonate for isopropyl chloroformate in the first step, **B9** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, *J* = 1.5, 1H), 7.62 (d, *J* = 1.5, 1H), 4.87 (m, 1H), 4.20 (m, 2H), 4.09 (d, *J* = 6.5, 1H), 3.89 (m, 2H), 3.57 (m, 2H), 3.54 (m, 4H), 3.46 (m, 4H), 2.82 (s, 3H), 2.80 (m, 2H), 1.95 (m, 3H), 1.82 (m, 2H), 1.67 (m, 3H), 1.28 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{34}N_5O_6S$ calcd.: 484.2, found: 484.2.

Example B10: (S)-Tetrahydrofuran-3-yl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



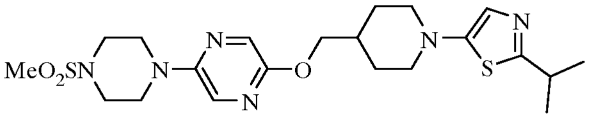
[00137] By following a similar procedure as the one used for preparing **B3** from **A1a** except substituting (S)-4-nitrophenyl tetrahydrofuran-3-yl carbonate for isopropyl chloroformate in the first step, **B10** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, *J* = 1.5, 1H), 7.62 (d, *J* = 1.5, 1H), 5.26 (m, 1H), 4.18 (m, 2H), 4.08 (d, *J* = 6.5, 1H), 3.89 (m, 4H), 3.53 (m, 4H), 3.47 (m, 4H), 2.82 (s, 3H), 2.80 (m, 2H), 2.17 (m, 1H), 2.00 (m, 2H), 1.82 (m, 2H), 1.27 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{31}N_5O_6S$ calcd.: 470.2, found: 470.2.

Example B11: (R)-Tetrahydrofuran-3-yl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



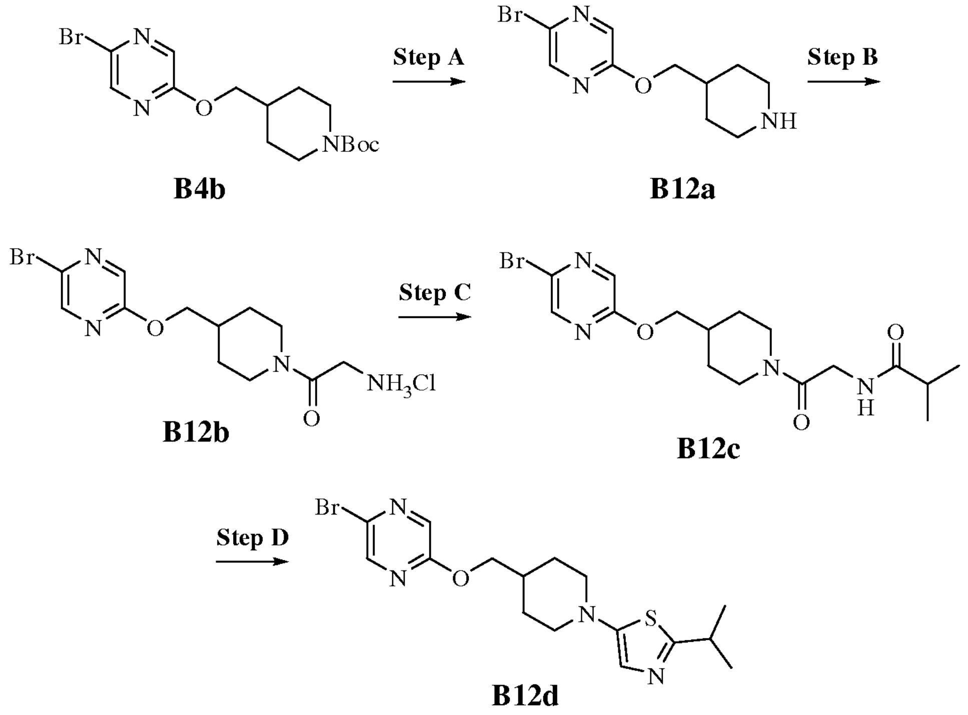
[00138] By following a similar procedure as the one used for preparing **B3** from **A1a** except substituting (R)-4-nitrophenyl tetrahydrofuran-3-yl carbonate for isopropyl chloroformate in the first step, **B11** is prepared with data identical to **B10**.

Example B12: 2-Isopropyl-5-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)thiazole.



[00139] By following a similar procedure as the one used for preparing **B3** from **A1d** except substituting **B12d** (see scheme below) for **A1d**, **B12** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88 (d, *J* = 1.5, 1H), 7.63 (d, *J* = 1.5, 1H), 7.60 (dd, *J* = 9.1, 2.5, 1H), 6.79 (s, 1H), 4.13 (d, *J* = 6.2, 1H), 3.53 (m, 4H), 3.46 (m, 2H), 3.37 (m, 4H), 3.14

(m, 1H), 2.82 (s, 3H), 2.79 (m, 2H), 1.91 (m, 3H), 1.53 (m, 2H), 1.34 (d, *J* = 6.9, 6H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{33}N_6O_3S_2$ calcd.: 481.2, found: 481.2.



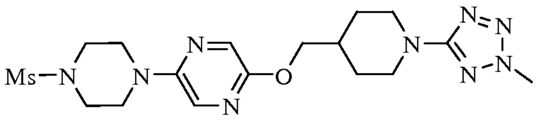
[00140] **Step A:** A sample of **B4b** (5.55 g, 14.9 mmol) is treated with 4 M HCl in dioxane (20 ml) and aged for 1 hour. The reaction is treated with water and the solvent is removed *in vacuo*. The residue is partitioned between ethyl acetate and 1 M NaOHOURS. The aqueous phase is isolated, extracted once more with ethyl acetate and discarded. The combined organics are dried over $MgSO_4$, filtered and evaporated to afford **B12a** which is used without further purification; ESIMS *m/z* for $(M+H)^+$ $C_{10}H_{15}BrN_3O$ calcd.: 272.0, found: 272.0.

[00141] **Step B:** A solution of **B12a** (1 g, 3.7 mmol), Boc-gly (966 mg, 5.5 mmol) and HOBt (596 mg, 4.4 mmol) in N-methylpyrrolidinone (5 mL) is treated with EDC (845 mg, 845 mg, 4.4 mmol) and stirred for 1 hour. The reaction is then diluted with ethyl acetate and extracted with water and saturated aqueous sodium hydrogencarbonate twice. The organics are dried over $MgSO_4$, filtered and evaporated. The residue is treated with excess 4 M HCl in dioxane and aged for 1 hour. The mixture is slurried with ether and the solid is collected to afford **B12b**; ESIMS *m/z* for $(M+H)^+$ $C_{12}H_{18}BrN_4O_2$ calcd.: 329.1, found: 329.1.

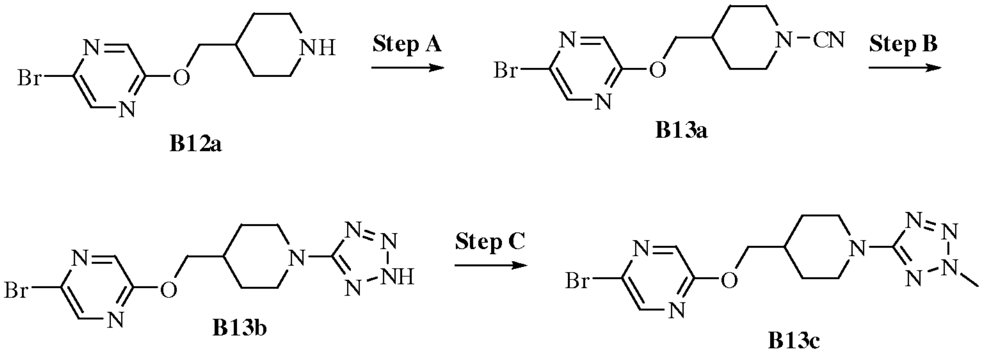
[00142] **Step C:** A suspension of **B12b** (400 mg, 1.1 mmol) in acetonitrile (8 mL) is treated with isobutyric anhydride (208 mg, 1.3 mmol) followed by triethylamine (360 mg, 3.6 mmol) and stirred for 1 hour. The solvent is removed and the residue is partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate. The aqueous phase is isolated, extracted once more with ethyl acetate and discarded. The combined organics are dried over $MgSO_4$, filtered and evaporated to afford **B12c** which is used without further purification; ESIMS *m/z* for $(M+H)^+$ $C_{16}H_{24}BrN_4O_3$ calcd.: 399.1, found: 399.1.

[00143] **Step D:** A solution of **B12c** (440 mg, 1.1 mmol) in *m*-xylene (2 mL) is treated with Laewesson's reagent (446 mmol, 1.1 mmol) and heated to 140 °C for 5 minutes and then purified on silica gel using a linear gradient of 0-100 % ethlyl acetate in hexane. The resulting material is further purified on preperative HPLC to afford **B12d**; ESIMS *m/z* for $(M+H)^+$ $C_{16}H_{22}BrN_4OS$ calcd.: 397.1, found: 397.1.

Example B13: 2-((1-(2-methyl-2H-tetrazol-5-yl)piperidin-4-yl)methoxy)-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazine.



[00144] By following a similar procedure as the one used for preparing **B3** from **A1d** except substituting **B13c** (see scheme below) for **A1d**, **B13** is prepared; ^1H NMR (400 MHz, CD_3CN) δ 7.84 (d, *J* = 0.9 Hz, 1H), 7.72 (d, *J* = 1.2 Hz, 1H), 4.10 (s, 3H), 4.10 (d, *J* = 4.8 Hz, 2H), 4.02 (m, 2H), 3.51 (t, *J* = 3.9 Hz, 4H), 3.27 (t, *J* = 3.9 Hz, 4H), 2.91 (dt, *J* = 2.1, 9.6 Hz, 2H), 2.79 (s, 3H), 1.39 (ddd, *J* = 3.3, 9.3, 16.8 Hz, 4H), 2.20 (t, *J* = 5.4 Hz, 2H), 0.88 (m, 2H); ESIMS $(M+H)^+$ $C_{17}H_{28}N_9O_3S$ cacld.: 438.2, found 438.2 (M+1).

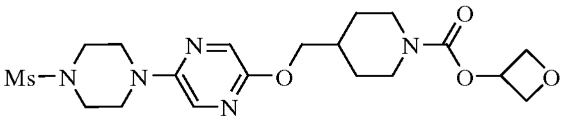


[00145] **Step A:** To a stirred suspension of **B12a** (200 mg, 0.74 mmol) and sodiumhydrogencarbonate (0.15 g, 1.78 mmol) in a mixed solvent of water (0.1 mL) and dichloromethane (1 mL) at 0 °C is added cyanogen bromide (93 mg, 0.89 mmol) in one portion. The reaction is then stirred at room temperature for 4 h and additional cyanogen bromide (93 mg, 0.89 mmol) is added. After stirring overnight, the reaction is diluted with dichloromethane (30 mL), dried over $MgSO_4$, and evaporated to give **B13a**; ESIMS $(M+H)^+$ $C_{11}H_{14}BrN_4O$ calcd.: 297.0, found 297.0.

[00146] **Step B:** The above crude **B13a** is stirred with sodium azide (143 mg, 2.2 mmol) and ammonium chloride (117 mg, 0.22 mmol) in anhydrous N,N-dimethylformamide (2 mL) at 110 °C for 2 hours. Additional sodium azide (143 mg, 2.2 mmol) and ammonium chloride (117 mg, 0.22) are added. After stirring overnight, water is added slowly to precipitate the product. The off white solid is collected by filtration, washed with water (10 mL) and dried *in vacuo* to afford **B13b**; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (d, J = 1.2 Hz, 1H), 8.20 (d, J = 0.9 Hz, 1H), 4.18 (d, J = 5.1 Hz, 2H), 3.86 (m, 2H), 3.02 (dt, J = 2.1, 9.6 Hz, 2H), 2.03 (m, 1H), 1.81 (m, 2H), 1.34 (ddd, J = 3.3, 9.6, 18.9 Hz, 2H); ESIMS $(M+H)^+$ $C_{11}H_{15}BrN_7O$ calcd.: 340.0, found: 340.0.

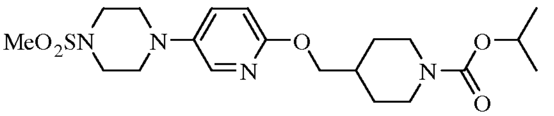
[00147] **Step C:** A mixture of **B13b** (50 mg, 0.15 mmol), iodomethane (14 uL, 0.22 mmol) and K_2CO_3 (28 mg, 0.25 mmol) in anhydrous N,N-dimethylformamide (1 mL) is stirred at room temperature for 3 hours. The solvent is evaporated *in vacuo* and the crude **B13c** is used without purification: ESIMS $(M+H)^+$ $C_{12}H_{17}BrN_7O$ calcd.: 354.1, found 354.0 (M+1).

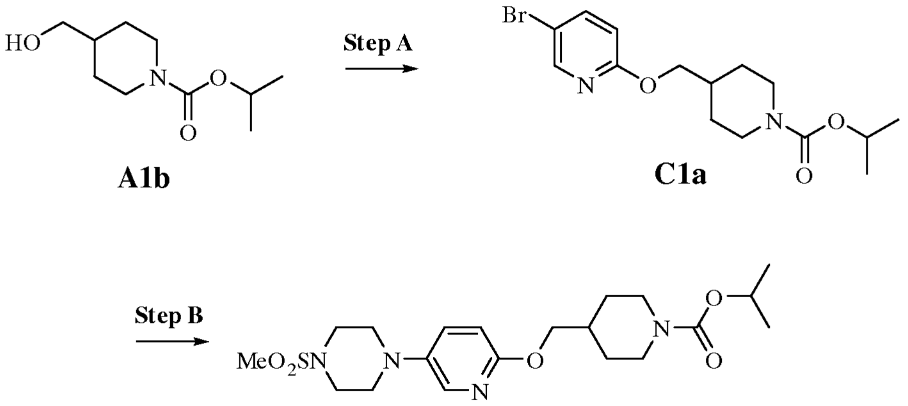
Example B14. Oxetan-3-yl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate



[00148] By following a similar procedure as the one used for preparing **B3** from **A1a** except substituting 4-nitrophenyl oxetan-3-yl carbonate for isopropyl chloroformate in the first step, **B14** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{19}H_{30}N_5O_6S$ calcd: 456.2, found: 456.0.

Example C1: Isopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate.





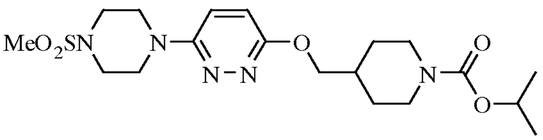
A1b **C1a**

Example C1

[00149] **Step A:** A solution of 2-chloro-5-bromopyridine (344 mg, 1.8 mmol) and **A1b** (300 mg, 1.5 mmol) in dimethylformamide (3 mL) is treated with NaH (43 mg, 1.8 mmol) and the reaction is allowed to stir overnight. After quenching by addition of water, the reaction is diluted with ethyl acetate. The organics are isolated and extracted with water once more, dried over $MgSO_4$, filtered and evaporated. The residue is purified on a silica gel column using a linear gradient of 0-50% ethyl acetate in hexane to afford **C1b**; ESIMS *m/z* for $(M+H)^+$ $C_{15}H_{22}ClN_2O_3$ calcd.: 313.1, found: 313.1.

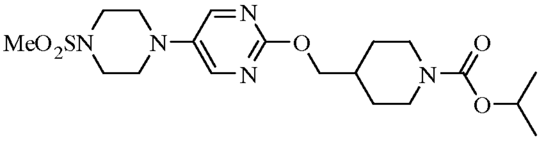
[00150] **Step B:** By following a similar Pd coupling procedure described for preparing **B1** except substituting **C1a** as the bromide coupling partner, **B14** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, *J* = 2.9, 1H), 7.18 (dd, *J* = 3.0, 8.9, 1H), 6.69 (d, *J* = 8.9, 1H), 4.91 (m, 1H), 4.18 (m, 2H), 4.09 (d, *J* = 6.4, 2H), 3.38 (m, 4H), 3.17 (m, 4H), 2.84 (s, 3H), 2.77 (m, 2H), 1.96 (m, 1H), 1.81 (m, 2H), 1.29 (m, 2H), 1.24, d, *J* = 6.3, 6H); ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{33}N_4O_5S$ calcd.: 441.2, found: 441.2.

Example C2: Isopropyl 4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridazin-3-yloxy)methyl)piperidine-1-carboxylate.



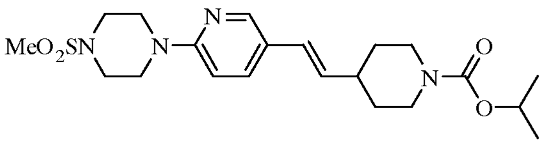
[00151] By following a similar procedure as the one used for preparing **C1** from **A1b** except substituting 2,5-dichloropyridazine for 2-chloro-5-bromopyridine in the first step, **C2** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.04 (d, *J* = 9.6, 1H), 6.88 (d, *J* = 9.6, 1H), 4.91 (m, 1H), 4.29 (m, 2H), 4.18 (m, 2H), 3.64 (m, 4H), 3.35 (m, 4H), 2.81 (s, 3H), 2.77 (m, 2H), 2.03 (m, 1H), 1.80 (m, 2H), 1.29 (m, 2H), 1.24, d, *J* = 6.4, 6H); ESIMS *m/z* for $(M+H)^+$ $C_{19}H_{32}N_5O_5S$ calcd.: 442.2, found: 442.3.

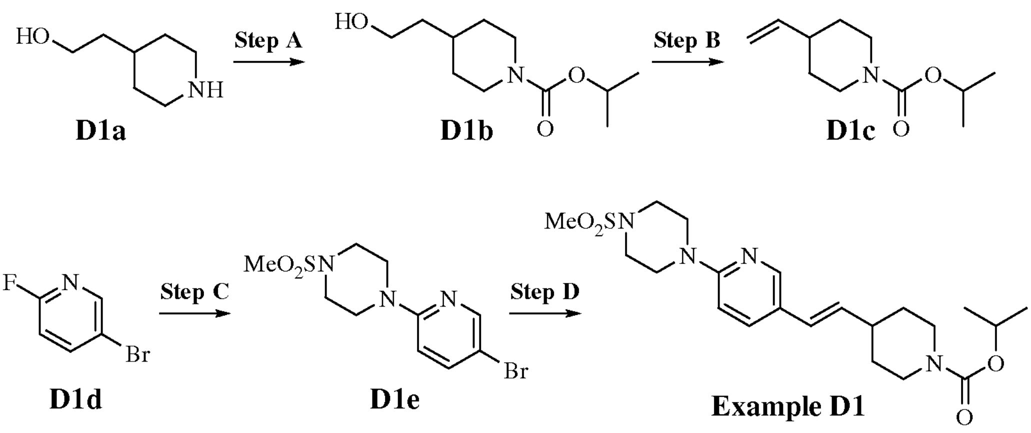
Example C3: Isopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrimidin-2-yloxy)methyl)piperidine-1-carboxylate.



[00152] By following a similar procedure as the one used for preparing **C1** from **A1b** except substituting 2-chloro-5-bromopyrimidine for 2-chloro-5-bromopyridine in the first step, **C3** is prepared; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.38 (s, 2H), 4.91 (sept., J = 6.3 Hz, 1H), 4.23 (m, 5H), 3.50 (m, 4H), 3.29 (m, 4H), 2.87 (s, 3H), 2.76 (m, 2H), 2.04 (m, 1H), 1.84 (m, 2H), 1.27 (m, 1H), 1.24 (d, J = 6.3 Hz, 6H).; ESIMS *m/z* for $(M+H)^+$ $C_{19}H_{32}N_5O_5S$ calcd.: 442.2, found: 442.3.

Example D1: (E)-isopropyl 4-(2-(6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yl)vinyl)piperidine-1-carboxylate.





[00153] **Step A:** A solution of **D1a** (10 g, 0.077 mol) in dichloromethane (100 mL) is treated with a solution of isopropyl chloroformate in toluene (93 mL of a 1M solution) dropwise. The reaction is then stirred at room temperature for 2.5 hours and quenched with saturated aqueous ammonium chloride solution. The phases are separated and the aqueous phase is extracted once more with dichloromethane and discarded. The combined organics are extracted once with 1M HCl, once with saturated aqueous sodiumhydrogencarbonate, dried over MgSO$_4$, filtered and evaporated to afford **D1b**; ESIMS *m/z* for $(M+H)^+$ $C_7H_{16}NO$ calcd.: 130.1, found: 130.1.

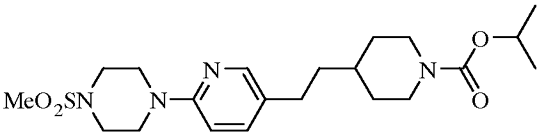
[00154] **Step B:** A cold (ice/water bath) solution of **D1b** (9.9 g, 0.046 mol) and triethylamine (6.7 mL, 0.048 mol) in dichloromethane is treated with the dropwise addition of methanesulfonyl chloride (3.7 mL, 0.048 mol) and stirred for 2 hours. The mixture is treated with water and extracted with dichloromethane. The organics are pooled, dried over $MgSO_4$, filtered and concentrated. The crude material is diluted in acetone (10 mL) and added dropwise to a slurry of lithium bromide (12 g, 0.138 mol) in acetone (50 mL). The reaction is heated to 35°C and maintained overnight. After cooling to room temperature, the reaction is concentrated, diluted with ethyl acetate and washed with water. The organic phase is collected, dried over $MgSO_4$, and concentrated. This residue is diluted in tetrahydrofuran (150 mL) and treated with the portionwise addition of potassium tert-butoxide (23.05 g, 0.2054 mol) every 30 min for 3 hours. Reaction is then heated to 40 °C and maintained overnight. Once the reaction had cooled to room temperature, saturated aqueous ammonium chloride is introduced and the reaction extracted with Et_2O. Organics are collected, dried over $MgSO_4$, concentrated, and purified *via* distillation (68°-70 °C, 180 mTorr) to afford **D1c**. ESIMS *m/z* for $(M+H)^+$ $C_{11}H_{20}NO_2$ calcd.: 198.3 found: 198.1.

[00155] **Step C:** A solution of **D1d** (321 mg, 1.8 mmol) and methanesulfonylpiperazine (300 mg, 1.8 mmol) in N-methylpyrrolidinone (2mL) is treated with K_2CO_3 (380 mg, 2.7 mmol) and heated to 160 °C for 5 minutes. The reaction is then partitioned between ethyl acetate and water and the organics are extracted with water again, dried over $MgSO_4$, filtered, evaporated and purified on silica gel using 0-100% ethyl acetate in hexane to afford **D1e**; ESIMS *m/z* for $(M+H)^+$ $C_{10}H_{15}BrN_3O_2S$ calcd.: 320.0, found: 320.1.

[00156] **Step D:** A solution of **D1e** (50 mg, 0.18 mmol), **D1c** (44 mg, 0.22 mmol) Pd_2dba_3 (5 mg, 0.006 mmol) and tri-*tert*-butylphosphonium tetrafluoroborate (3.2 mg, 0.011 mmol) and dicyclohexylmethylamine (72 mg, 0.37 mmol) in dioxane (1mL) is heated to 120 °C for 1 hour. The reaction is then partitioned between ethyl acetate and water and the organics are extracted with water once more, dried over $MgSO_4$, filtered, evaporated and purified on silica gel using a gradient of 0-100 % ethyl acetate in hexane to afford **D1**; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.11 (d, $J = 2.3$, 1H), 7.57 (dd, $J = 8.8, 2.4$, 1H), 6.63 (d, $J = 8.8$, 1H), 6.27 (d, $J = 15.9$, 1H), 5.99 (dd, $J = 16.0, 6.9$, 1H), 4.91 (m,

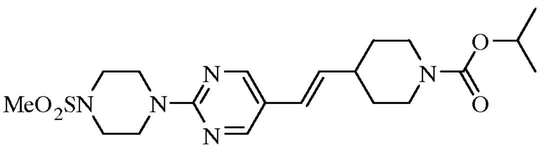
1H), 4.17 (m, 2H), 3.67 (m, 4H), 3.32 (m, 4H), 2.80 (m, 2H), 2.80 (s, 3H), 2.23 (m, 1H), 1.77 (m, 2H), 1.38 (m, 2H), 1.24, d, *J* = 6.2, 6H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{33}N_4O_4S$ calcd.: 437.2, found: 437.2.

Example D2. Isopropyl 4-(2-(6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yl)ethyl)piperidine-1-carboxylate.



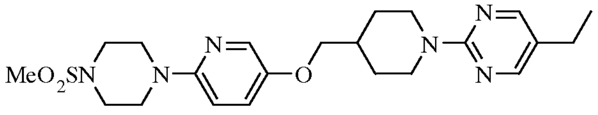
[00157] A solution of **D2** (25 mg, 0.057 mmol) in methanol (2 mL) is treated with 10% Pd/C (5 mg) and hydrogenated for 1 hour. The atmosphere is exchanged back for nitrogen and the reaction is filtered though a plug of Celite® and the solvent is removed to afford **D2**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (d, *J* = 2.2, 1H), 7.35 (dd, *J* = 8.6, 2.4, 1H), 6.63 (d, *J* = 8.6, 1H), 4.90 (m, 1H), 4.12 (m, 2H), 3.62 (m, 4H), 3.32 (m, 4H), 2.80 (s, 3H), 2.68 (m, 2H), 2.52 (m, 2H), 1.70 (m, 2H), 1.52 (m, 2H), 1.42 (m, 1H), 1.23 (d, *J* = 6.2, 6H), 1.12 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{35}N_4O_4S$ calcd.: 439.2, found: 439.3.

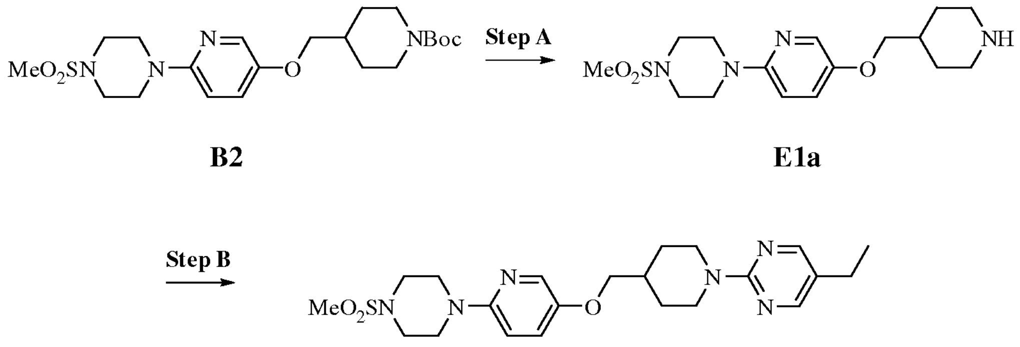
Example D3. (E)-Isopropyl 4-(2-(2-(4-(methylsulfonyl)piperazin-1-yl)pyrimidin-5-yl)vinyl)piperidine-1-carboxylate.



[00158] By following a similar procedure as the one used for preparing **D1** from **D1a** except substituting 2-chloro-5-bromopyrimidine for **D1d**, **D3** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.38 (s, 2H), 6.18 (d, J = 16.2 Hz, 1H), 6.05 (dd, J = 16.1, 6.6 Hz, 1H), 4.92 (m, 1H), 4.18 (m, 2H), 3.98 (m, 4H), 3.30 (m, 4H), 2.80 (s, 3H), 2.80 (m, 2H), 2.29 (m, 1H), 1.76 (m, 2H), 1.38 (m, 2H), 1.24 (d, J = 6.2 Hz, 6H); ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{32}N_5O_4S$ calcd.: 438.2, found: 438.3.

Example E1. 5-Ethyl-2-(4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)pyrimidine.





B2

E1a

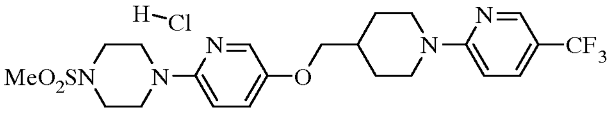
Example E1

[00159] **Step A:** A sample of **B2** (202 mg, 0.445 mmol) is treated with 4 M HCl in dioxane (3 mL) and aged for 1 hour. The solvent is then removed and the residue is partitioned between ethyl acetate and 1 M NaOH. The aqueous phase is isolated, extracted once more with ethyl acetate and discarded. The combined organics are dried over $MgSO_4$, filtered and evaporated to afford **E1a**; ESIMS *m/z* for $(M+H)^+$ $C_{16}H_{27}N_4O_3S$ calcd.: 355.2, found: 355.2.

[00160] **Step B:** The resulting material is treated with 2-chloro-5-ethylpyrimidine (121 mg, 0.85 mmol), CuI (12 mg, 0.063 mmol), diisopropylethylamine (176 mg, 1.4 mmol) and N-methylpyrrolidinone (2 mL). The resulting solution is sealed in a reaction vial and heated to 160 °C for 10 minutes using a microwave reactor. The reaction is then diluted with ethyl acetate and extracted with water once, 1 M HCl once and saturated aqueous sodiumhydrogencarbonate once, dried over $MgSO_4$, filtered, evaporated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane followed

by lyophilization from 1 M HCl to afford **E1** as the HCl salt; ^{1}H NMR (DMSO-d6, 400 MHz): δ 8.27 (s, 2H), 7.82 (d, *J* = 2.9, 1H), 7.50 (m, 1H), 7.05 (m, 1H), 4.63 (m, 2H), 3.86 (d, *J* = 6.4, 2H), 3.57 (m, 4H), 3.22 (m, 4H), 2.91 (s, 3H), 2.91 (m, 2H), 2.43 (dd, *J* = 15.1, 7.6, 2H), 2.03 (s, 1H), 1.82 (m, 2H), 1.22 (m, 2H), 1.13 (dd, *J* = 7.6, 7.6, 36H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{33}N_6O_3S$ calcd.: 461.2, found: 461.2.

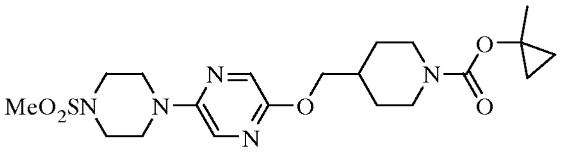
Example E2. 1-(Methylsulfonyl)-4-(5-((1-(5-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)methoxy)pyridin-2-yl)piperazine.

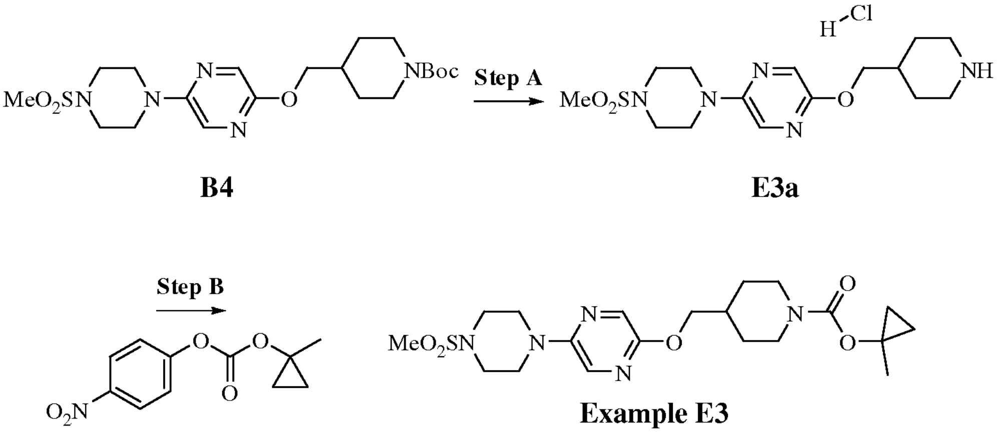


[00161] By following a similar procedure as the one used for preparing **E1** from **B2** except substituting the following procedure for **Step B**, **E2** is prepared;

[00162] A sample of **E1a** hydrochloride (900 mg, 2.3 mmol) is treated with 2-chloro-3-trifluoromethylpyridine (501 mg, 2.76 mmol), K_2CO_3 (795 mg, 5.8 mmol), N-methylpyrrolidinone (10 mL) and water (8 mL) and heated in a sealed vessel in a microwave reactor at 160 °C for 10 minutes. The resulting suspension is treated with ethyl acetate and water and filtered. The resulting solid is washed with water and ethyl acetate, dissolved in 1 M HCl and lyophilized to afford **E2** ; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22 (m, 1H), 8.10 (dd, *J* = 9.8, 2.3, 1H), 7.86 (dd, *J* = 9.9, 2.9, 1H), 7.60 (d, *J* = 2.9, 1H), 7.53 (d, *J* = 9.8, 1H), 7.42 (d, *J* = 9.1, 1H), 4.30 (m, 2H), 3.94 (d, *J* = 6.2, 1H), 3.71 (m, 4H), 3.37 (m, 4H), 2.86 (s, 3H), 2.28 (m, 1H), 2.06 (m, 2H), 1.57 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{29}F_3N_5O_3S$ calcd.: 500.2, found: 500.2.

Example E3. 1-Methylcyclopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





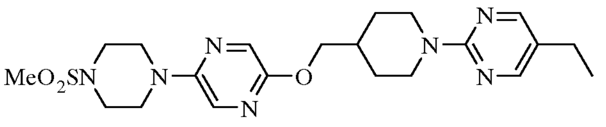
B4 E3a

E3b Example E3

[00163] **Step A:** A sample of **B4** (745 mg, 0.16 mmol) is treated with 4 M HCl in dioxane and stirred for 3 hours. The solvent is decanted and the residue is lyophilized from water to afford **E3a**; ESIMS *m/z* for $(M+H)^+$ $C_{15}H_{26}N_5O_3S$ calcd.: 356.2, found: 356.2.

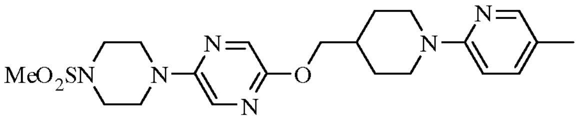
[00164] **Step B:** A sample of **E3a** (181.8 mg, 0.46 mmol) is treated with N, N-dimethylformamide (1.5 mL), **E3b** (110 mg, 0.46 mmol) and diisopropylethylamine (242 μL, 1.4 mmol) and stirred overnight. The reaction is then partitioned between ethyl acetate and water and the organics are isolated, extracted with 1 M NaOH three times, dried over $MgSO_4$, filtered, evaporated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **E3**; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, *J* = 1.5, 1H), 7.62 (d, *J* = 1.4, 1H), 4.18 (m, 2H), 4.08 (d, *J* = 6.5, 2H), 3.52 (m, 4H), 3.36 (m, 4H), 2.82 (s, 3H), 2.72 (m, 2H), 1.93 (m, 1H), 1.80 (m, 2H), 1.56 (d, *J* = 9.9, 3H), 1.23 (m, 2H), 0.87 (m, 2H), 0.62 (m,2H); ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{32}N_5O_5S$ calcd.: 454.2, found: 454.2.

Example E4. 5-Ethyl-2-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)pyrimidine.



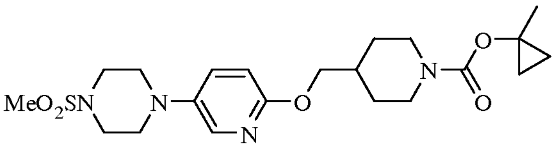
[00165] By following a similar procedure as the one used for preparing **E1** from **E1a** except substituting **E3a** for **E1a**, **E4** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (s, 2H), 7.88 (d, *J* = 1.4, 1H), 7.63 (d, *J* = 1.5, 1H), 4.76 (m, 2H), 4.11 (d, *J* = 6.6, 2H), 3.52 (m, 4H), 3.37 (m, 4H), 2.90 (m, 2H), 2.82 (s, 3H), 2.45 (dd, *J* = 15.2, 7.6, 2H), 2.08 (m, 2H), 1.90 (m, 2H), 1.33 (ddd, *J* = 24.9, 12.4, 4.2, 2H), 1.18 (dd, *J* = 7.6, 7.6, 3H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{32}N_7O_3S$ calcd.: 462.2, found: 462.3.

Example E5. 2-((1-(5-Methylpyridin-2-yl)piperidin-4-yl)methoxy)-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazine.



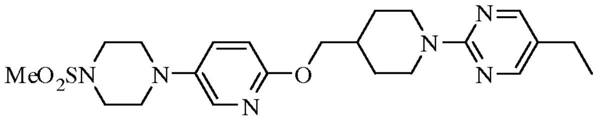
[00166] A mixture of **E3a** (103 mg, 0.26 mmol), 2-bromo-5-methylpyridine (45.3 mg, 0.26 mmol), Pd_2dba_3 (4.8 mg, 0.005 mmol), xantphos (9.1 mg, 0.016 mmol), sodium *tert*-butoxide (78 mg, 0.815 mmol) and toluene (1.5 mL) is purged with nitrogen for 5 minutes and heated in an oil bath at 100 °C overnight. The reaction is cooled to room temperature and diluted with water and ethyl acetate. The organics are dried over $MgSO_4$, filtered, evaporated and purified by silica gel column chromatography using a linear gradient of 0-100 % ethyl acetate in hexane to afford **E5**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 (m, 1H), 7.88 (d, *J* = 1.4, 1H), 7.30 (m, 1H), 6.62 (d, *J* = 8.6, 1H), 4.27 (m, 2H), 4.11 (d, *J* = 6.6, 1H), 3.53 (m, 4H), 3.37 (m, 4H), 2.82 (m, 2H), 2.82 (s, 3H), 2.19 (s, 3H), 2.02 (m, 1H), 1.91 (m, 2H), 1.42 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{31}N_6O_3S$ calcd.: 447.2, found: 447.3.

Example E6. 1-Methylcyclopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate.



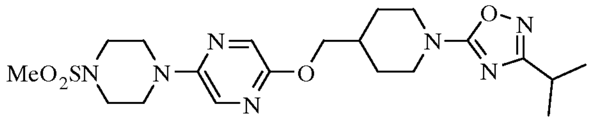
[00167] By following a similar procedure as the one used for preparing **E3** from **B4** except substituting *tert*-butyl 4-((5-(4-(methylsulfonyl) piperazin-1-yl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate for **B4**, **E6** is prepared; *tert*-Butyl 4-((5-(4-(methylsulfonyl) piperazin-1-yl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate is prepared in an analogous fashion to **B4** except using 2-fluoro-5-bromopyridine instead of **A1d**; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.78 (d, *J* = 2.9, 1H), 7.28 (dd, *J* = 8.9, 3.0, 1H), 6.68 (d, *J* = 8.9, 1H), 4.18 (m, 2H), 4.08 (d, *J* = 6.5, 2H), 3.38 (m, 4H), 3.14 (m, 4H), 2.83 (s, 3H), 2.73 (m, 2H), 1.93 (m, 1H), 1.79 (m, 2H), 1.54 (s, 3H), 1.23 (m, 2H), 0.86 (m, 2H), 0.61 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{33}N_4O_5S$ calcd: 453.2, found: 453.3.

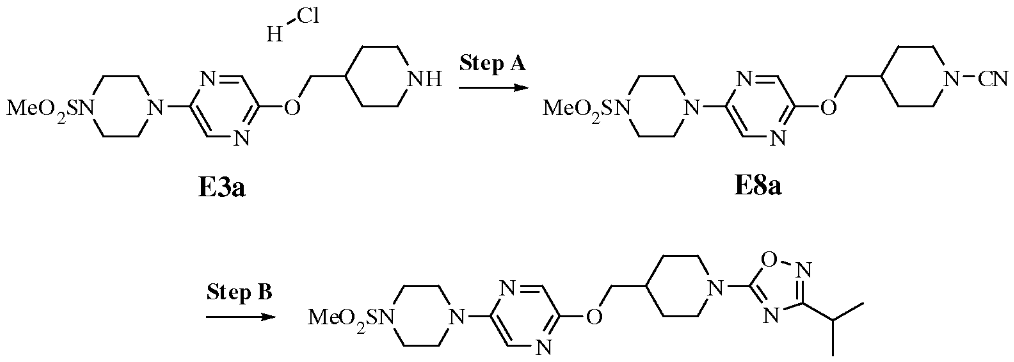
Example E7. 5-Ethyl-2-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyridin-2-yloxy)methyl)piperidin-1-yl)pyrimidine.



[00168] By following a similar procedure as the one used for preparing **E1** from **E1a** except substituting *tert*-butyl 4-((5-(4-(methylsulfonyl) piperazin-1-yl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate for **E1a**, **E7** is prepared; *tert*-Butyl 4-((5-(4-(methylsulfonyl) piperazin-1-yl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate is prepared in an analogous fashion to **B4** except using 2-fluoro-5-bromopyridine instead of **A1d**; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.16 (s, 2H), 7.78 (d, *J* = 2.9, 1H), 7.28 (dd, *J* = 8.9, 3.0, 1H), 6.69 (d, *J* = 9.0, 1H), 4.73 (m, 2H), 4.11 (d, *J* = 6.6, 1H), 3.38 (m, 4H), 3.14 (m, 4H), 2.89 (m, 2H), 2.83 (s, 3H), 2.44 (dd, *J* = 15.2, 7.6, 2H), 2.08 (m, 1H), 1.90 (m, 2H), 1.34 (ddd, *J* = 24.8, 12.4, 4.1, 2H), 1.73 (dd, *J* = 7.6, 7.6, 3H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{33}N_6O_3S$ calcd.: 461.2, found: 461.3.

Example E8. 3-Isopropyl-5-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole.





E3a

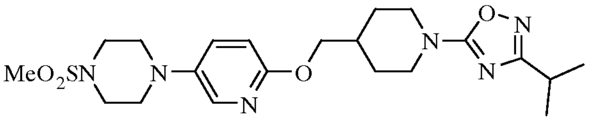
E8a

Example E8

[00169] **Step A:** A cold (ice/water bath) solution of **E3a** (256 mg, 0.65 mmol) in dichloromethane (5 mL) is treated with a solution of K_2CO_3 (298 mg, 2.2 mmol) in water (5 mL). The vigorously stirred solution is treated with a solution of cyanogen bromide (76.1 mg, 0.72 mmol) in dichloromethane (2 mL) and the reaction is allowed to stir cold for 3 hours. The phases are then separated and the organic phase is dried over $MgSO_4$, filtered and evaporated to afford **E8a** which is used without further purification; ESIMS *m/z* for $(M+H)^+$ $C_{16}H_{25}N_6O_3S$ calcd.: 381.2, found: 381.1.

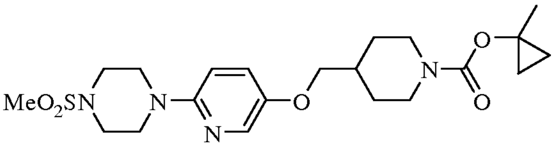
[00170] **Step B:** A solution of **E3a** (215.5 mg, 0.57 mmol) in dioxane (2 mL) is treated with N'-hydroxyisobutyrimidamide (86.8 mg, 0.85 mmol) and $ZnCl_2$ (115.8 mgL, 0.85 mmol) and stirred at 100 °C overnight. The reaction is then partitioned between ethyl acetate and 1 M NaOH and the organics are isolated, dried over $MgSO_4$, filtered, evaporated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **E8**; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.88 (d, *J* = 1.4, 1H), 7.62 (d, *J* = 1.4, 1H), 4.19 (m, 2H), 4.11 (d, *J* = 6.5, 2H), 3.53 (m, 4H), 3.37 (m, 4H), 3.08 (ddd, *J* = 12.9, 12.9, 2.8, 2H), 2.87 (m, 1H), 2.82 (s, 3H), 2.03 (m, 1H), 1.91 (m, 2H), 1.43 (ddd, *J* = 25.2, 12.5, 4.4, 2H), 1.28 (d, *J* = 7.0, 3H); ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{32}N_7O_4S$ calcd.: 466.2, found: 466.3.

Example E9. 3-Isopropyl-5-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyridin-2-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole.



[00171] By following a similar procedure as the one used for preparing **E8** from **B4** except substituting *tert*-butyl 4-((5-(4-(methylsulfonyl) piperazin-1-yl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate for **B4**, **E9** is prepared; *tert*-Butyl 4-((5-(4-(methylsulfonyl) piperazin-1-yl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate is prepared in an analogous fashion to **B4** except using 2-fluoro-5-bromopyridine instead of **A1d**; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.78 (d, *J* = 2.9, 1H), 7.29 (dd, *J* = 8.9, 3.0, 1H), 6.69 (d, *J* = 8.9, 1H), 4.17 (m, 2H), 4.13 (d, *J* = 6.5, 1H), 3.40 (m, 4H), 3.17 (m, 4H), 3.08 (ddd, *J* = 12.9, 12.9, 2.8, 2H), 2.88 (m, 1H), 2.84 (s, 3H), 2.03 (m, 1H), 1.91 (m, 2H), 1.34 (ddd, *J* = 25.1, 12.5, 4.4, 2H), 1.28 (d, *J* = 7.0, 3H); ESIMS *m/z* for (M+H)$^+$ $C_{21}H_{33}N_6O_4S$ calcd.: 465.2, found: 465.3.

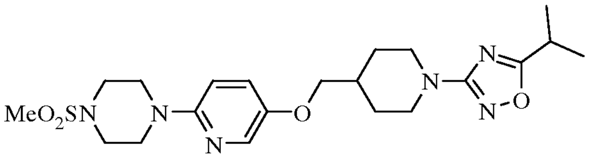
Example E10. 1-Methylcyclopropyl 4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate.

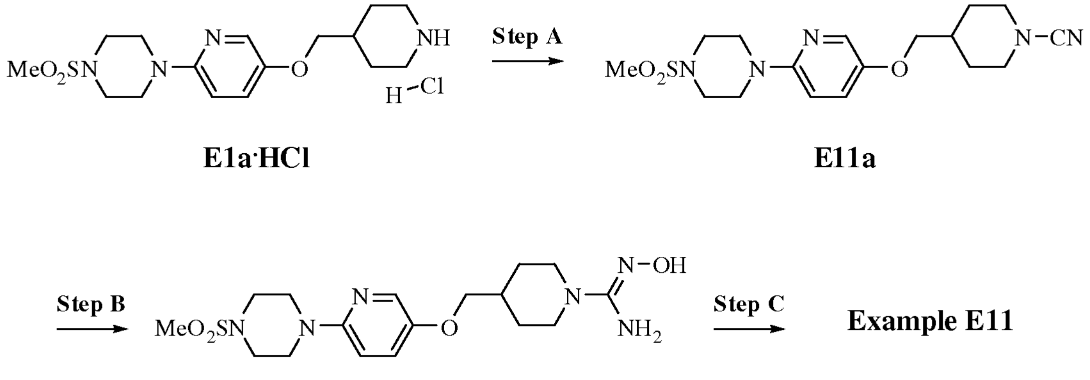


[00172] By following a similar procedure as the one used for preparing **E3** from **B4** except substituting **B2** for **B4**, **E10** is prepared; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.90 (d, *J* = 2.9, 1H), 7.14 (dd, *J* = 9.1, 3.0, 1H), 6.65 (d, *J* = 9.0, 1H), 4.12 (m, 2H), 3.77 (d, *J* = 6.3, 1H), 3.54 (m, 4H), 3.33 (m, 4H), 2.80 (s, 3H), 2.73 (m, 2H), 1.92 (m, 1H), 1.89 (m, 2H), 1.54 (s, 3H), 1.23 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for (M+H)$^+$ $C_{21}H_{33}N_4O_5S$ calcd.: 453.2, found: 453.2.

[00173]

Example E11. 5-Isopropyl-3-(4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole.





E1a·HCl

E11a

E11b

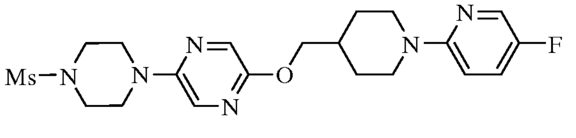
[00174] **Step A:** A mixture of **E1a·HCl** (202.3 mg, 0.52 mmol) and K_2CO_3 (143 mg, 1.0 mmol) in water (3 mL) is cooled to ice/water bath temperature and treated dropwise with a solution of cyanogen bromide (60.3 mg, 0.57 mmol) in dichlormethane (3 mL) and stirred for 2 hours while cooled. The reaction is then diluted with dichloromethane, extracted with water, dried over $MgSO_4$, filtered and evaporated to afford **E11a** which is used without further purification; ESIMS *m/z* for $(M+H)^+$ $C_{17}H_{26}N_5O_3S$ calcd.: 380.2, found: 380.2.

[00175] **Step B:** A solution of **E11a** (152.4 mg, 0.40 mmol) and hydroxylamine (492 μL of a 50% aqueous solution, 0.80 mmol) in ethanol (2 mL) is heated to 60 °C in a sealed vessel overnight. The reaction is cooled to room temperature and the resulting sample of **E11b**; ESIMS *m/z* for $(M+H)^+$ $C_{17}H_{29}N_6O_4S$ calcd.: 413.2, found: 413.2.

[00176] **Step C:** A solution of **E11b** (134.2 mg, 0.32 mmol) and isobutyric anhydride (50 mg, 0.32 mmol) in dioxane is heated at 400 W in a microwave reactor for 10 minutes (~120 °C). The reaction is cooled to room temperature, evaporated and

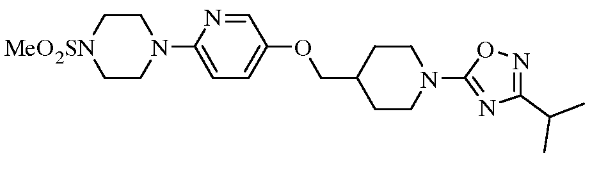
partititioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate. The organics are isolated, dried over $MgSO_4$, filtered, evaporated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane and lyophilized from 1 M HCl to afford **E11** as an HCl salt; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.92 (d, J = 3.0, 1H), 7.16 (dd, J = 9.1, 3.0, 1H), 6.65 (d, J = 9.1, 1H), 4.06 (m, 2H), 3.80 (d, J = 6.4, 1H), 3.54 (m, 4H), 3.33 (m, 4H), 3.07 (m, 1H), 2.92 (ddd, J = 12.7, 12.7, 2.7, 1H), 2.80 (s, 3H), 2.73 (m, 2H), 1.99 (m, 1H), 1.88 (m, 2H), 1.42 (m, 2H), 1.34 (d, J = 7.0, 6H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{33}N_6O_4S$ calcd.: 465.2, found: 453.3.

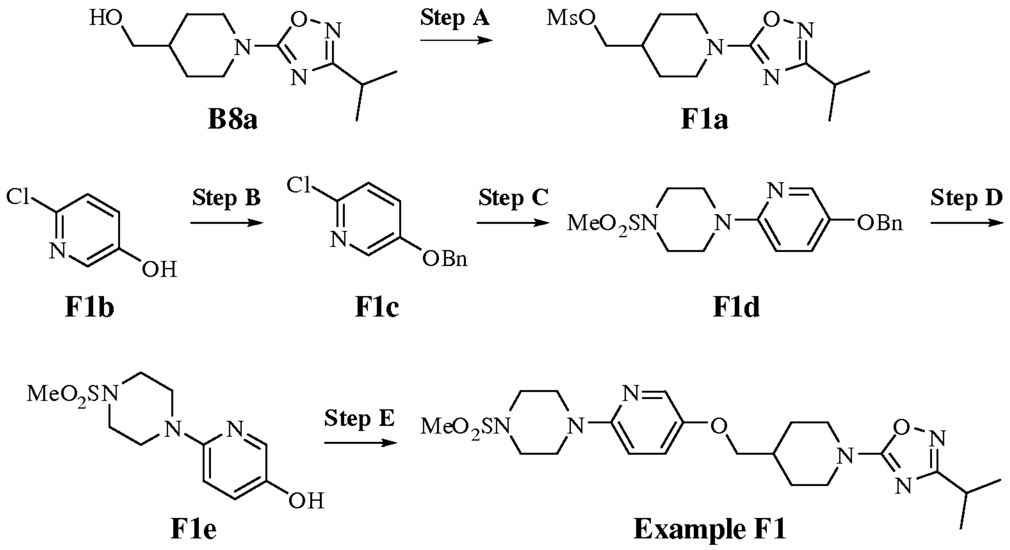
Example E12. 2-((1-(5-Fluoropyridin-2-yl)piperidin-4-yl)methoxy)-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazine.



[00177] By following a similar procedure as the one used for preparing **E5** from **E3a** except substituting 2-bromo-5-fluoropyridine for 2-bromo-5-methylpyridine and dicyclohexyl(2',6'-dimethoxybiphenyl-4-yl)phosphine for xantphos, **E12** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{28}FN_6O_3S$ calcd: 451.2, found: 451.2.

Example F1. 3-Isopropyl-5-(4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole





[00178] **Step A:** By following a similar procedure as the one used for preparing **B5c** from **B5b** except substituting **B8a** for **B5b**, **F1a** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{12}H_{22}N_3O_4S$ calcd: 304.1, found: 304.1.

[00179] **Step B:** A solution of **F1b** (3.00 g, 23.0 mmol) and benzyl chloride (2.93 mL, 25.5 mmol) in acetonitrile (50 mL) is treated with Cs_2CO_3 (15.0 g, 46.0 mmol) and the reaction mixture is heated at 90 °C for 2hours, cooled and filtered. The solvents are evaporated and the crude compound purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **F1c**; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, J = 0.8, 2.8 Hz, 1H), 7.42 (m, 4H), 7.39 (m, 1H), 7.25 (m, 2H), 5.12 (s, 2H); ESIMS calcd. for $[M+H]^+$ $C_{12}H_{11}ClNO$: 220.1 found: 220.1.

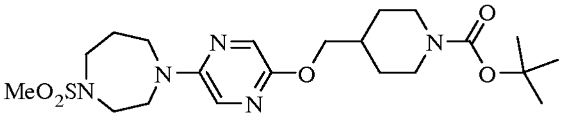
[00180] **Step C: F1c** (2.67 g, 12.2 mmol), 1-methanesulfonyl piperazine (3 g, 18.3 mmol), $Pd(OAc)_2$ (548 mg, 2.4 mmol), ((2-dicyclohexyl)phosphino)biphenyl (1.7 g, 4.8 mmol), NaO*t*Bu (3.5 g, 36.6 mmol) and toluene (20 mL) are charged to a sealed flask and degassed with bubbling Ar for 30 minutes. The mixture is heated at 120 °C for 18h, then is hot filtered to remove particulates. The filter cake is washed with ethyl acetate (10 mL) and water (20 mL) and the filtrates are combined and extracted with ethyl acetate (20 mL). The organic layer is extracted with 1N HCl (3 x 20 mL) and discarded. The acidic layer is then basified with NaOH and extracted with ethyl acetate (3 x 20 mL). The remaining organic layers are combined, dried ($MgSO_4$), filtered and

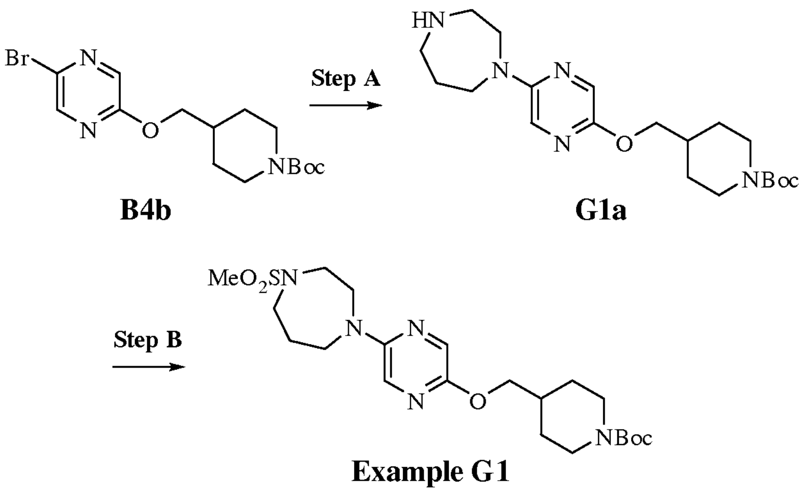
concentrated. The residue is recrystallized from ethyl acetate /Hexane to provide **F1d**; ESIMS calcd. for $[M+H]^+$ $C_{17}H_{22}N_3O_3S$: 348.1 found: 348.1.

[00181] **Step D:** A solution of **F1d** (1.3 g, 3.88 mmol) in EtOH is treated with Pd/C (0.2 g of 10%, wet). The reaction is stirred under H_2 (1 atmosphere) for 12 hours. The mixture is filtered and concentrated to provide **F1e** which is used without further purification: ESIMS calcd. for $[M+H]^+$ $C_{10}H_{16}N_3O_3S$: 258.1 found: 258.1.

[00182] **Step E:** A solution of **F1e** (97.7 mg, 0.38 mmol) and **F1a** (115.2 mg, 0.38 mmol) in N, N-dimethylformamide (1.5 mL) is treated with Cs_2CO_3 (185.6 mg, 0.57 mmol) and heated to 60 °C overnight. The reaction is cooled to room temperature, diluted with ethyl acetate, extracted with water, dried over $MgSO_4$, filtered, evaporated and purified by silica gel column chromatography using a linear gradient of 0 to 100% ethyl acetate in hexane and then lyophilized from HCl to afford **F1** as an HCl salt; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.01 (m, 0.5H), 7.92 (d, J = 2.8, 1H), 7.16 (dd, J = 9.1, 3.1, 1H), 6.66 (d, J = 9.1, 1H), 4.20 (m, 2H), 3.81 (d, J = 6.3, 1H), 3.54 (m, 4H), 3.33 (m, 4H), 3.09 (m, 2H), 2.88 (m, 1H), 2.81 (s, 3H), 2.00 (m, 1H), 1.92 (m, 2H), 1.44 (m, 2H), 1.28 (d, J = 7.0, 3H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{33}N_6O_4S$ calcd.: 465.2, found: 465.3.

Example G1. *tert*-Butyl 4-((5-(4-(methylsulfonyl)-1,4-diazepan-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.

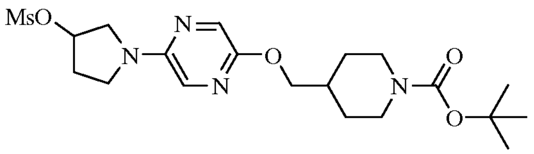




[00183] **Step A:** A mixture of **B4b** (307.5 mg, 0.83 mmol), homopiperazine (248.2 mg, 2.5 mmol), xantphos (28.7 mg, 0.050 mmol), sodium *tert*-butoxide 119 mg, 1.2 mmol) and toluene (5 mL) is sparged with nitrogen for 5 minutes and treated with Pd_2dba_3 (15.1 mg, 0.017 mmol). The reaction is then sealed and dipped into a pre-heated oil bath at 100 °C. The reaction is stirred at this temperature for 4 hours, cooled to room temperature, diluted with ethyl acetate and extracted with water twice. The organics are dried over $MgSO_4$, filtered, evaporated and purified on a silica gel column using 0-10% methanol in dichloromethane to afford **G1a**; ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{35}N_4O_3$ calcd.: 391.3, found: 391.3.

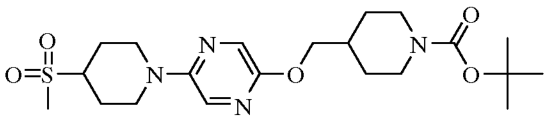
[00184] **Step B:** A solution of **G1a** (139 mg, 3.6 mmol) in dichloromethane (0.25 m L) is cooled to ice/water bath temperature and treated with triethylamine (37.4 mg, 0.37 mmol) followed by methanesulfonyl chloride (42.3 mg, 0.37 mmol) and stirred overnight. The reaction is then poured into water and extracted with dichloromethane twice. The combined organics are dried over $MgSO_4$, filtered, evaporated and purified on a silica gel column using 0-100% ethyl acetate in hexane to afford **G1**; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.79 (d, J = 2.9, 1H), 7.49 (d, J = 1.5, 1H), 4.13 (m, 2H), 4.14 (d, J = 6.5, 1H), 3.82 (m, 2H), 3.74 (dd, J = 6.3,6.3, 2H), 3.49 (m, 2H), 3.26 (m, 2H), 2.78 (s, 3H), 2.73 (m, 2H), 2.07 (m, 2H), 1.94 (m, 1H), 1.79 (m, 1H), 1.46 (s, 9H), 1.25 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{36}N_5O_5S$ calcd.: 470.2, found: 370.2 $(M\text{-}Boc+H^+)$.

Example G2 *tert*-Butyl 4-((5-(3-(methylsulfonyloxy)pyrrolidin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



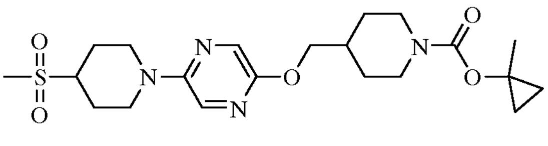
[00185] By following a similar procedure as the one used for preparing **G1** from **B4b** except substituting pyrrolidin-3-ol for homopiperazine, **G2** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 (d, J = 1.5, 1H), 7.38 (d, J = 1.5, 1H), 5.43 (m, 1H), 4.03 (m, 2H), 4.06 (d, J = 6.6, 1H), 3.82 (m, 21H), 3.74 (dd, J = 12.4, 4.4, 1H), 3.58 (m, 2H), 3.05 (s, 3H), 2.72 (m, 2H), 2.47 (m, 1H), 2.33 (m, 1H), 1.93 (m, 1H), 1.79 (m, 2H), 1.46 (s, 9H), 1.26 (m, 2H); ESIMS m/z for $(M\text{-}Boc+H)^+$ $C_{15}H_{25}N_4O_4S$ calcd.: 357.2, found: 357.2.

Example G3. *Tert*-butyl 4-((5-(4-(methylsulfonyl)piperidin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



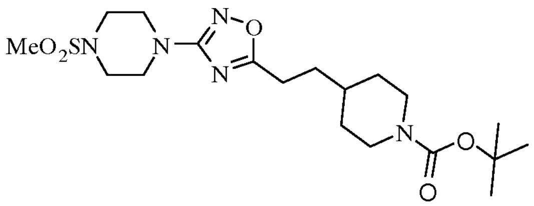
[00186] By following a similar procedure as the one used for preparing **G1a** from **B4b** except substituting 4-(methylsulfonyl)piperidine for homopiperazine, **G3** is prepared; ESIMS m/z for $(M\text{-}^tBu+H)^+$ $C_{16}H_{27}N_4O_3S$ calcd: 355.2, found: 355.2

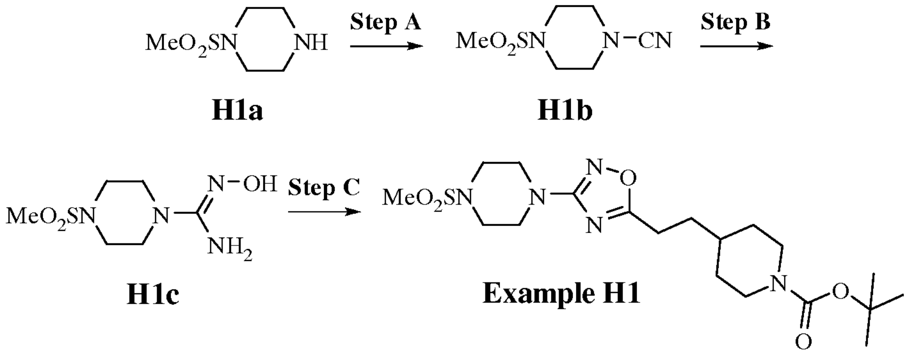
Example G4. 1-Methylcyclopropyl 4-((5-(4-(methylsulfonyl)piperidin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00187] By following a similar procedure as the one used for preparing **E3** from **B4** except substituting **G3** for **B4**, **G4** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{34}N_4O_5S$ calcd: 454.2, found: 454.2.

Example H1. ***tert*-Butyl 4-(2-(3-(4-(methylsulfonyl)piperazin-1-yl)-1,2,4-oxadiazol-5-yl)ethyl)piperidine-1-carboxylate.**



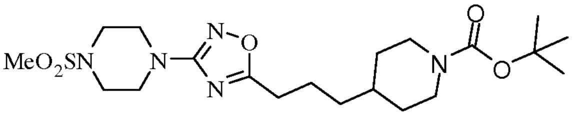


[00188] **Step A:** To a stirred a solution of potassium carbonate (2.78 g, 20.0 mmol) in water (20 mL) is added **H1a** (3.0 g, 18.3 mmol). The solution is cooled to 10 °C, then a solution of cyanogen bromide (2.12 g, 20.0 mmol) in dichloromethane (20 mL) is added dropwise over 30 min. The reaction is warmed to room temperature and stirred for 2 hours, then extracted into dichloromethane. The organic layer is washed with 1N HCl (30 mL), dried over $MgSO_4$, filtered and concentrated. The product is used without further purification.

[00189] **Step B:** A solution of **H1b** (2.6 g, 13.7 mmol) and hydroxylamine (1 mL, 15.1 mmol) in EtOH (10 mL) is heated in a sealed vial at 90 °C for 12 hours. The mixture is concentrated *in vacuo* to provide **H1c**, which is used without further purification.

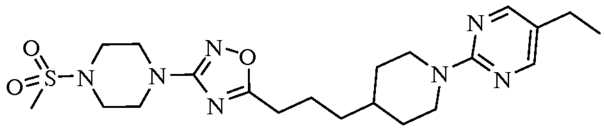
[00190] **Step C:** A solution of 1-Boc-piperidin-4-yl propionic acid acid (112 mg, 0.44 mmol) and N,N-carbonyl dimidazole (71 mg, 0.44 mmol) in N,N-dimethylformamide (0.5 mL) is stirred at room temperature for 30 min. **H1c** (107 mg, 0.48 mmol) is added, the tube is sealed and heated at 115 °C for 18 hours. The reaction mixture is cooled, extracted into ethyl acetate (10 mL), washed with water (2 x 10 mL), then brine (10 mL). The organic layer is dried over $MgSO_4$, filtered, concentrated, and purified by mass triggered reverse phase HPLC to provide **H1**; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.10 (br.s, 2H), 3.59 (m, 4H), 3.32 (m, 4H), 2.82 (s, 3H), 2.79 (t, J = 8.0 Hz, 2H), 2.68 (m, 2H), 1.71 (m, 4H), 1.46 (s, 9H), 1.15 (m, 2H) ; ESIMS *m/z* for $(M+H+Na)^+$ $C_{19}H_{33}N_5O_5SNa$ calcd.: 466.2, found: 466.2.

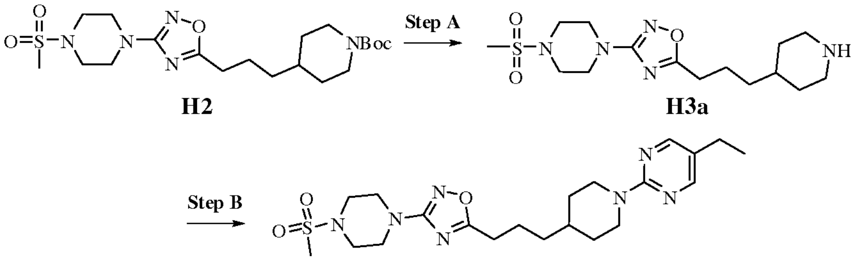
Example H2. *tert*-Butyl 4-(3-(3-(4-(methylsulfonyl)piperazin-1-yl)-1,2,4-oxadiazol-5-yl)propyl)piperidine-1-carboxylate.



[00191] By following a similar procedure as the one used for preparing **H1** from **H1a** except substituting 4-(1-Boc-piperidin-4-yl) butanoic acid for 1-Boc-piperidin-4-yl propionic acid acid, **H2** is prepared; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.08 (d, J = 13.2 Hz, 2H), 3.59 (m, 4H), 3.32 (m, 4H), 2.82 (s, 3H), 2.75 (t, J = 7.6 Hz, 2H), 2.68 (dt, J = 2.4, 13.2 Hz, 2H), 1.80 (m, 2H), 1.68 (s, 1H), 1.65 (s, 1H), 1.46 (s, 9H), 1.42 (m, 1H), 1.34 (s, 2H), 1.11 (m, 2H) ; ESIMS *m/z* for $(M+H+Na)^+$ $C_{20}H_{35}N_5O_5SNa$ calcd.: 480.2, found: 480.3.

Example H3. 5-(3-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)propyl)-3-(4-(methylsulfonyl)piperazin-1-yl)-1,2,4-oxadiazole.



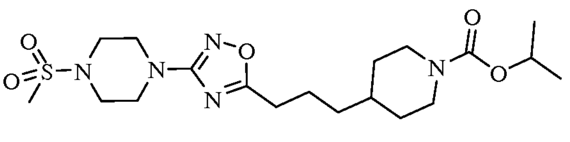


Example H3

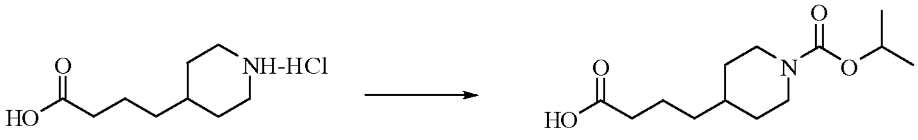
[00192] **Step A: A** solution of **H2** (261 mg, 0.57 mmol) in tetrahydrofuran (5 mL) is treated with HCl (5 mL of 4N in dioxane) and stirred at room temperature for 1 hour. The reaction is concentrated, dissolved in dichloromethane (5 mL) and concentrated *in vacuo* to remove traces of acid and provide **H3a**, which is used without further purification; ESIMS *m/z* for $(M+H)^+$ $C_{15}H_{28}N_5O_3S$ calcd.: 358.2, found: 358.2.

[00193] **Step B: H3a** (53 mg, 0.15 mmol) and 2-chloro-5-ethyl-pyrimidine (22 μL, 0.18 mmol) are dissolved in 1, 4-dioxane (1 mL). Cesium carbonate (120 mg, 0.37 mmol) is added and the tube is sealed and heated at 150 °C for 2 hours. The reaction mixture is cooled, filtered, and purified by mass triggered reverse phase HPLC to provide **H3**; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.27 (s, 2H), 4.70 (d, J = 13.2 Hz, 2H), 3.60 (m, 4H), 3.33 (m, 4H), 2.93 (dt, J = 2.0, 13.2 Hz, 2H), 2.83 (s, 3H), 2.77 (t, J = 7.6 Hz, 2H), 2.51 (q, J = 7.6 Hz, 2H), 1.84 (m, 4H), 1.58 (m, 1H), 1.37 (m, 3H), 1.22 (t, J = 7.6 Hz, 3H; ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{34}N_7O_3S$ calcd.: 464.2, found: 464.2.

Example H4. Isopropyl 4-(3-(3-(4-(methylsulfonyl)piperazin-1-yl)-1,2,4-oxadiazol-5-yl)propyl)piperidine-1-carboxylate.

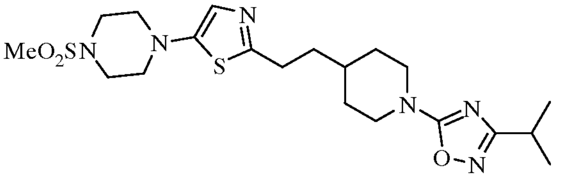


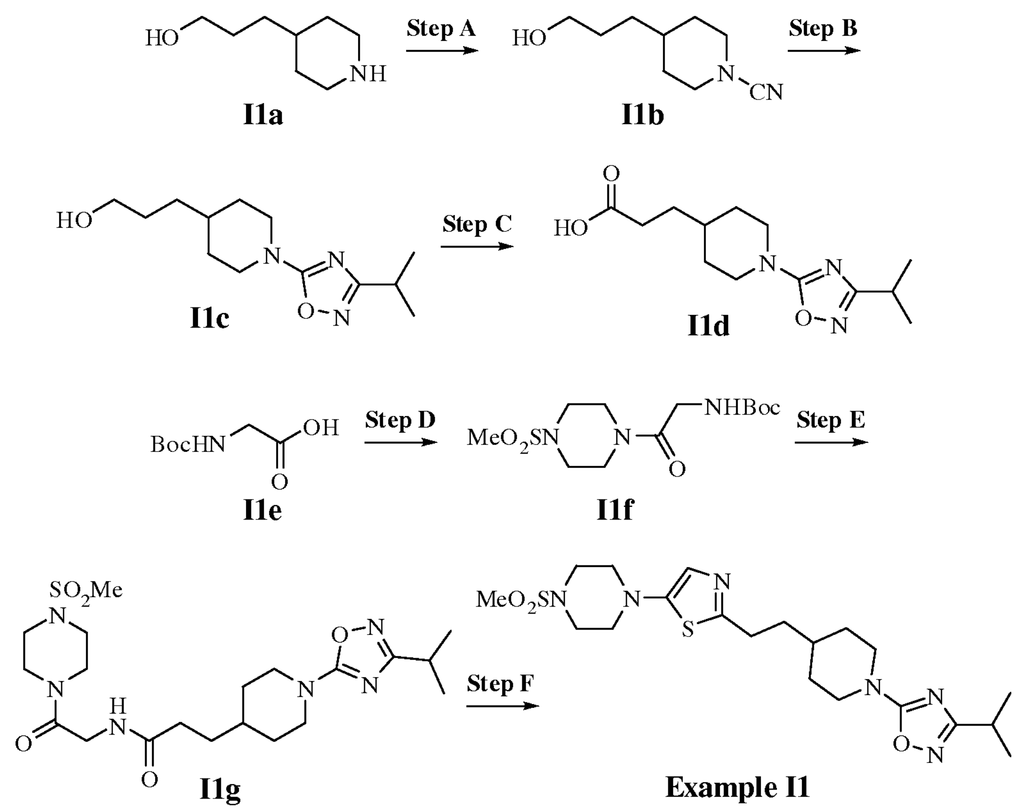
[00194] By following a similar procedure as the one used for preparing **H1** from **H1a** except substituting **H4b** (see scheme below) for 1-Boc-piperidin-4-yl propionic acid acid, **H4** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{19}H_{34}N_5O_5S$ calcd.: 444.2, found: 480.3.


H4a **H4b**

[00195] Commercially available **H4a** (20 g, 96 mmol) is suspended in dry dimethylacetamide (100 mL). Triethylamine (34 mL, 240 mmol) is added and the resulting mixture is cooled in an ice/water bath. A solution of isopropyl chloroformate in toluene (1.0M, 150 mL) is added dropwise, forming a white precipitate. The suspension is stirred at room temperature for 18 hours, then the white precipitate is filtered, washed with ethyl acetate, and discarded. The filtrate is concentrated *in vacuo* to yield **H4b**.

Example I1. 3-Isopropyl-5-(4-(2-(5-(4-(methylsulfonyl)piperazin-1-yl)thiazol-2-yl)ethyl)piperidin-1-yl)-1,2,4-oxadiazole.





[00196] **Step A:** To a stirred a suspension of sodiumhydrogencarbonate (2.80 g, 33.3 mmol) in water (1.5 mL) is added **I1a** hydrochloride salt (2.00 g, 11.1 mmol) and dichloromethane (2 mL). The mixture is cooled in ice/water bath and stirred. A solution of cyanogen bromide (1.42 g, 13.4 mmol) in dichloromethane (3 mL) is added over a period of 1 hour. The cold bath is removed and the reaction is stirred overnight. 0.33 g of Na_2CO_3 is added to ensure the reaction is basic. The reaction is diluted with dichloromethane (20 mL), dried with $MgSO_4$. The mixture is filtered, washed with dichloromethane, and evaporated to give **I1b**; ESIMS *m/z* for $(M+H)^+$ $C_9H_{17}N_2O$ calcd.: 169.1, found: 169.1.

[00197] **Step B:** A solution of **I1b** (1.87 g, 11.1 mmol) and N'-hydroxy isobutyrimidamide (1.70 g, 16.7 mmol) in ethyl acetate (40 mL) is treated with a solution of $ZnCl_2$ (16.7mL, 1N in ether) dropwise. A white precipitate is formed. After stirring at room temperature for 15 minutes, the precipitate stuck on the flask and made stirring difficult. The solid is triturated with ether (40 mL) and stirred for 4 hours until a yellow suspension is obtained. The solid is collected by filtration, washed with ether (30 mL) and dried to give a yellow solid which is used without purification for the next step;

ESIMS *m/z* for $(M+H)^+$ $C_{13}H_{27}N_4O_2$ calcd.: 271.2, found: 271.2. The intermediate material (422 mg) is treated with dioxane (10 mL) and 4M HCl in dioxane (0.5 mL) and heated to 100 °C for 1 hour. The reaction is then cooled to room temperature and the solvent is removed. The residue is diluted with ethyl acetate and extracted with 1 M HCl twice, dried over $MgSO_4$, filtered and evaporated to afford **I1c**; ESIMS *m/z* for $(M+H)^+$ $C_{13}H_{24}N_3O_2$ calcd.: 254.2, found: 254.2.

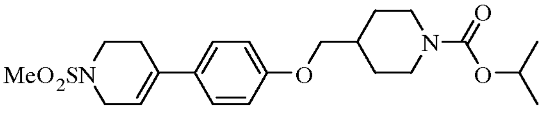
[00198] **Step C:** A solution of **I1c** (368 mg, 1.45 mmol) in acetonitrile (8 mL) is treated with NaH_2PO_4 (218 mg, 1.8 mmol), Na_2HPO_4 (258 mg, 1.8 mmol), TEMPO free radical (16 mg, 0.1 mmol), $NaClO_2$ (328 mg of an 80% pure sample, 2.91 mmol) and water (8mL). After all the reagents went into solution, 10% bleach (22 μL, 0.03 mmol) is added and the reaction is stirred overnight. The acetonitrile is removed *in vacuo* and the resulting solution is extracted with ethyl acetate once and the organics are discarded. The aqueous phase is made acidic (pH<1) with concentrated HCl and extracted twice with ethyl acetate and discarded. The combined organics are dried over $MgSO_4$ and the solvent is removed to afford **I1d**; ESIMS *m/z* for $(M+H)^+$ $C_{13}H_{22}N_3O_3$ calcd.: 268.2, found: 268.1.

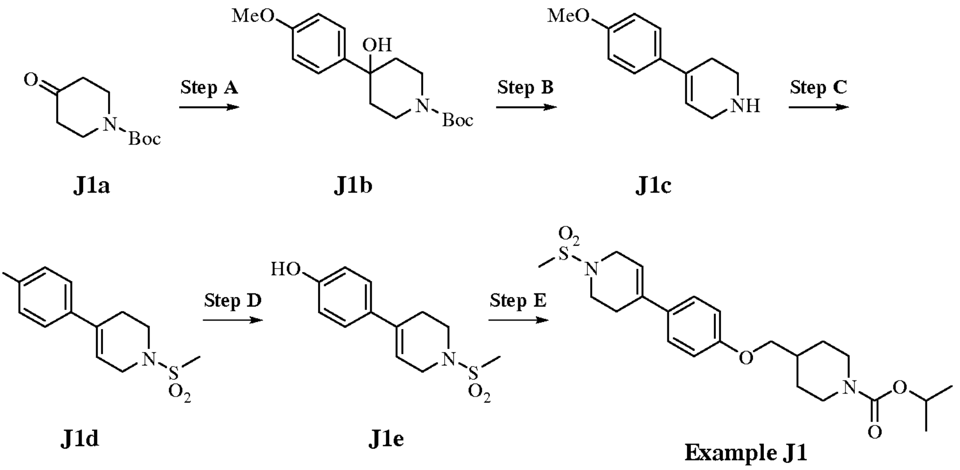
[00199] **Step D.** A solution of **I1e** (250 mg, 1.4 mol) and methanesulfonyl piperazine (258 mg, 1.6 mmol) in dichloromethane (4 mL) is treated with HOBt hydrate (328 mg, 2.1 mmol) followed by EDC (356 mg, 1.9 mmol). After stirring for 3 hours, the reaction is diluted with ethyl acetate and extracted with water, 1M HCl and 1 M NaOH, dried over $MgSO_4$, filtered and evaporated to afford **I2f** ; ESIMS *m/z* for $(M+H)^+$ $C_{12}H_{24}N_3O_5S$ calcd.: 322.1, found: 322.2.

[00200] **Step E.** A sample of **I1f** (388 mg, 1.2 mmol) is treated with 4 M HCl in dioxane (4 mL) and aged for 1 hour. The solvent is removed and the residue is treated with **I1d** (298 mg, 1.1 mmol), HATU (502 mg, 1.3 mmol) and N-methylpyrrolidinone (4 mL). The solution is then treated with triethylamine (0.39 mL, 2.8 mmol) and stirred for 2 hours. The reaction is then diluted with 1M NaOH and saturated with NaCl. The resulting solution is extracted 4 times with ethyl acetate and discarded. The combined organics are dried over MgSO4, filtered, evaporated and further purified on a UV triggered HPLC to afford **I1g**; ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{35}N_6O_5S$ calcd.: 471.2, found: 471.1.

[00201] **Step F.** A suspension of **I1g** (354 mg, 0.75 mmol) and Lawesson's reagent (304 mg, 0.75 mmol) in *m*-xylene (3 mL) is dipped into an oil bath which is preheated to 140 °C and stirred for 5 minutes. The reaction is then cooled to room temperature and loaded onto silica gel and purified using a linear gradient of 0-100% ethyl acetate to afford **F1**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.86 (s, 1H), 4.12, (2, 2H), 3.38 (m, 4H), 3.19 (m, 4H), 3.02 (m, 2H), 2.99 (m, 3H), 2.83 (s, 3H), 1.80 (m, 2H), 1.73 (dd, *J* = 15.3, 7.1, 21H), 1.40 (m, 1H), 1.24 (m, 2H), 1.28 (d, *J* = 7.0, 6H); ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{33}N_6O_3S_2$ calcd.: 469.2, found: 469.1.

Example J1: Isopropyl 4-((4-(1-methanesulfonyl-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)methyl)piperidine-1-carboxylate.





[00202] **Step A**: 4-Bromoanisole (4.5 mL, 36.0 mmol) is dissolved in dry tetrahydrofuran (50 mL) and cooled to –78 °C under nitrogen. A solution of *n*-butyllithium (1.6 M in hexane (22.0 mL, 35.2 mmol) is slowly added with stirring. The mixture is stirred at –78 °C for 2 hours. A solution of **J1a** (7.28 g, 36.5 mmol) in dry tetrahydrofuran (80 mL) under nitrogen is cooled to –78 °C. The suspension of organolithium prepared above is slowly cannulated with stirring into the solution of **J1a**,

using a 20-mL tetrahydrofuran rinse. The resulting mixture is stirred at –78 °C for 30 minutes, then at 0 °C for 15 min. Addition of saturated ammonium chloride solution (60 mL) and extraction with ethyl acetate, washing with brine and concentration in vacuo yield an oil. The residue is purified using a linear gradient of 10-80% ethyl acetate in hexane to afford **J1b**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.39 (d, J = 8.9 Hz, 2H), 6.89 (d, J = 8.9 Hz, 2H), 3.99 (br., 2H), 3.81 (s, 3H), 1.96 (br, 2H), 1.71 (m, 4H), 1.49 (s, 9H); no mass spectrum could be obtained.

[00203] **Step B**: To a solution of **J1b** (6.29 g, 20 mmol) in dichloromethane (120mL) is added trifluoroacetic acid (20 mL), slowly, with stirring. The resulting solution is stirred at room temperature for 3 hours. Concentration, dilution with dichloromethane (50 mL), washing with saturated aqueous sodiumhydrogencarbonate solution, drying over $MgSO_4$ and concentration yields **J1c**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.30 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.93 (m, 1H), 3.82 (s, 5H), 3.40 (t, J = 6.0 Hz, 2H), 2.77 (m, 2H); ESIMS calcd. for $C_{12}H_{16}NO$ (M+H$^+$) 190.1, found 190.0.

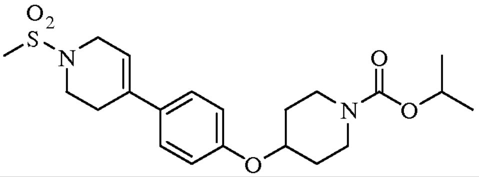
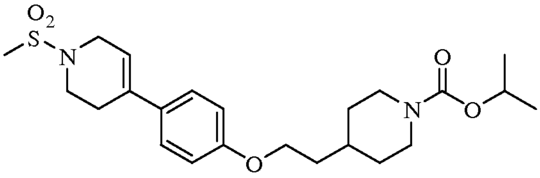
[00204] **Step C**: To a solution of **J1c** (3.41 g, 18 mmol) in dichloromethane (80 mL) is added triethylamine (4.5 mL, 32.0 mmol) in one portion. The resulting mixture is cooled in an ice/water bath and methanesulfonyl chloride (1.75 mL, 22.5 mmol) is added dropwise, with stirring, over 5 minutes. The resulting solution is stirred at room temperature for 30 min. The reaction mixture is added to water (40 mL) and extracted with dichloromethane (2 x 40 mL). The combined organic extracts are washed with saturated ammonium chloride aqueous solution, dried over $MgSO_4$, and concentrated to yield **J1d**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.31 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.98 (m, 1H), 3.96 (q, J = 3.2 Hz, 2H), 3.82 (s, 3H), 3.52 (t, J = 5.7 Hz, 2H), 2.86 (s, 3H), 2.64 (m, 2H); ESIMS calcd. for $C_{13}H_{18}NO_3S$ (M+H$^+$) 268.1, found 268.1.

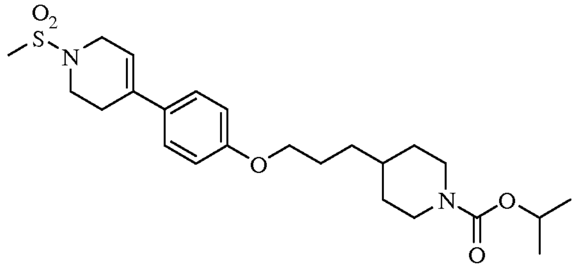
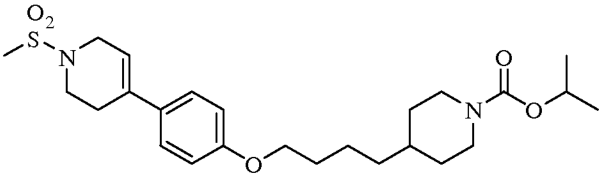
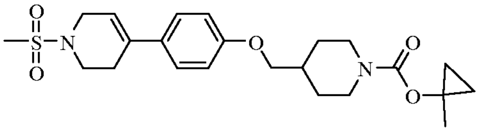
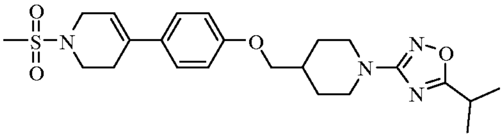
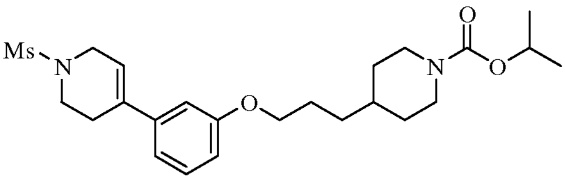
[00205] **Step D**: A solution of **J1d** (3.71 g, 13.9 mmol) in dichloromethane (100 mL) is treated with boron tribromide (5.0 mL, 51.9 mmol) slowly and stirred at room temperature for 3 hours. The mixture is poured over crushed ice and, after the ice melts, it is extracted with dichloromethane. Washing with saturated aqueous sodiumhydrogencarbonate solution, water, and saturated ammonium chloride, drying over $MgSO_4$ and concentration yield **J1e**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.27 (d, J

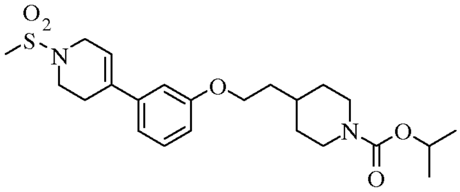
= 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.97 (m, 1H), 4.85 (s, 1H), 3.95 (q, *J* = 3.2 Hz, 2H), 3.52 (t, *J* = 5.7 Hz, 2H), 2.86 (s, 3H), 2.63 (m, 2H); ESIMS calcd. for $C_{12}H_{16}NO_3S$ (M+H$^+$) 254.1, found 254.1.

[00206] **Step E**: A solution of **J1e** (0.12 g, 0.47 mmol) in acetonitrile (3 mL) is treated with **A1c** (0.16 g, 0.57 mmol) followed by powdered cesium carbonate (0.20 g, 0.6 mmol) and stirred at 60 °C for 5 hours. Cooling, filtration and purification using mass-triggered reverse phase HPLC affords **J1**; ^{1}H NMR (CDCl$_3$, 400.13 MHz): δ 7.30 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.97 (m, 1H), 4.92 (septet, *J* = 6.2 Hz, 1H), 4.19 (br, 2H), 3.95 (dd, *J* = 2.6, 5.9 Hz, 2H), 3.81 (d, *J* = 6.3 Hz, 2H), 3.52 (t, *J* = 5.8 Hz, 2H), 2.85 (s, 3H), 2.78 (m, 2H), 2.63 (m, 2H), 1.97 (m, 1H), 1.83 (dd, *J* = 1.0, 13.4 Hz, 2H), 1.25 (m, 2H), 1.24 (d, *J* = 6.2 Hz, 6H); ESIMS calcd. for $C_{22}H_{33}N_2O_5S$ (M+H$^+$) 437.2, found 437.1.

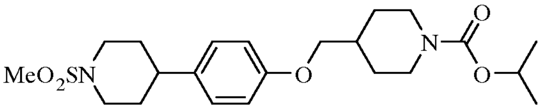
[00207] By following a similar procedure as the one used for preparing **J1** from **HJ1a** except substituting the appropriate methanesulfonate for intermediate **A1c** in **Step E** and/or 3-bromoanisole for 4-bromoanisole, the following examples are prepared;

Example	Structure	Analytical data
J2		ESIMS calcd. for $C_{21}H_{31}N_2O_5S$ (M+H$^+$) 423.2, found 423.1.
J3		^{1}H NMR (CDCl$_3$, 400.13 MHz): δ 7.30 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.97 (m, 1H), 4.92 (septet, *J* = 6.2 Hz, 1H), 4.12 (br, 2H), 4.02 (t, *J* = 5.8, 2H), 3.95 (dd, *J* = 2.6, 5.9 Hz, 2H), 3.52 (t, *J* = 5.8 Hz, 2H), 2.85 (s, 3H), 2.74 (m, 2H), 2.64 (m, 2H), 1.85 (m, 1H), 1.73 (dd, *J* = 1.0, 13.4 Hz, 2H), 1.24 (d, *J* = 6.2 Hz, 6H), 1.18 (m, 2H); ESIMS calcd. for $C_{23}H_{35}N_2O_5S$ (M+H$^+$) 451.2, found 451.2.

J4		^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.29 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.97 (m, 1H), 4.91 (septet, *J* = 6.2 Hz, 1H), 4.13 (br, 2H), 3.52 (t, *J* = 5.8 Hz, 2H), 2.85 (s, 3H), 2.71 (m, 2H), 2.63 (m, 2H), 1.81 (m, 2H), 1.70 (m, 5H), 1.42 (m, 4H), 1.24 (d, *J* = 6.2 Hz, 6H), 1.12 (m, 2H); ESIMS calcd. for $C_{24}H_{37}N_2O_5S$ (M+H$^+$) 465.2, found 465.1.
J5		ESIMS calcd. for $C_{25}H_{39}N_2O_5S$ (M+H$^+$) 479.3, found 479.1.
J6		^{1}H-NMR (400MHz, DMSO-d6) δ 7.37 (m, 2H), 6.90 (m, 2H), 6.08 (m, 1H), 3.70-4.05 (m, 6H), 2.92 (s, 3H), 2.75 (m, 2H), 2.56 (m, 2H), 1.91 (m, 1H), 1.73 (m, 2H), 1.46 (s, 3H), 1.13 (m, 2H), 0.76 (m, 2H), 0.59 (m, 2H); ESIMS calcd. for $C_{23}H_{33}N_2O_5S$ (M+H$^+$) 449.2, found 448.8.
J7		^{1}H-NMR (400MHz, DMSO-d6) δ 7.38 (m, 2H), 6.92 (m, 2H), 6.08 (m, 1H), 3.86 (m, 6H), 3.10 (h, 1H, J = 7.0 Hz), 2.92 (s, 3H), 2.91 (m, 2H), 2.56 (m, 2H), 1.97 (m, 1H), 1.82 (m, 2H), 1.30 (m, 2H), 1.26 (d, 6H, J = 7.0 Hz); ESIMS calcd. for $C_{23}H_{33}N_4O_4S$ (M+H$^+$) 461.2, found 460.8.
J8		^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.25 (dd, *J* = 7.8, 8.2 Hz, 1H), 6.95 (dd, *J* = 2.2, 7.8 Hz, 1H), 6.89 (dd, *J* = 1.9, 2.2 Hz, 1H), 6.81 (dd, *J* = 1.9, 8.2 Hz, 1H), 6.07 (tt, *J* = 1.5, 3.5 Hz, 1H), 4.91 (septet, *J* = 6.2 Hz, 1H), 4.13 (br. s, 2H), 3.96 (m, 4H), 3.52 (t, *J* = 5.7 Hz, 2H), 2.86 (s, 3H), 2.73 (t, *J* = 12.4 Hz, 2H), 2.65 (m, 2H), 1.81 (m, 2H), 1.71 (d, *J* = 12.7 Hz, 2H), 1.46 (m, 1H), 1.41 (m, 2H), 1.24 (d, J = 6.3

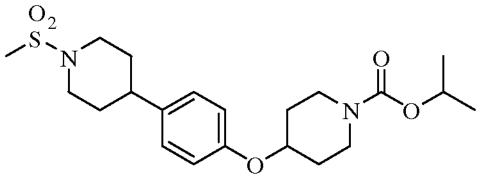
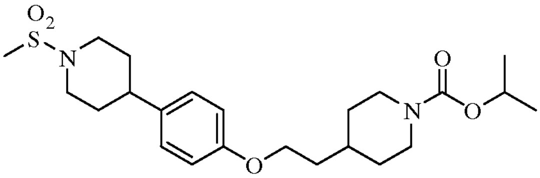
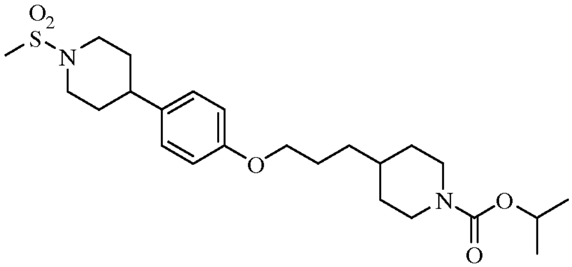
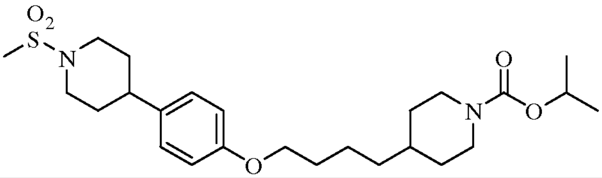
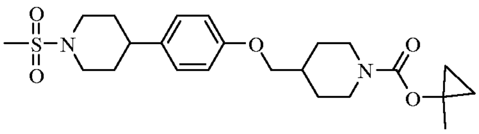
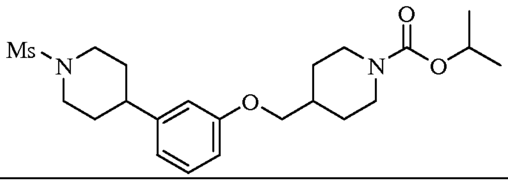
		Hz, 6H), 1.12 (ddd, *J* = 4.2, 12.7, 13.0 Hz, 2H); ESIMS calcd. for $C_{24}H_{37}N_2O_5S$ (M+H$^+$) 465.2, found 465.2.
J9		^{1}H NMR (CDCl$_3$, 400.13 MHz): δ 7.26 (dd, *J* = 7.9, 8.1 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 6.89 (dd, *J* = 1.8, 2.2 Hz, 1H), 6.82 (dd, *J* = 2.0, 7.8 Hz, 1H), 6.07 (m, 1H), 4.91 (septet, *J* = 6.2 Hz, 1H), 4.13 (br, 2H), 4.02 (t, *J* = 5.8 Hz, 2H), 3.97 (dd, *J* = 2.7, 6.0 Hz, 2H), 3.52 (t, J = 5.7 Hz, 2H), 2.86 (s, 3H), 2.74 (t, *J* = 12.4 Hz, 2H), 2.66 (m, 2H), 1.80 (m, 2H), 1.74 (m, 3H), 1.24 (d, *J* = 6.2 Hz, 6H), 1.20 (m, 2H); ESIMS calcd. for $C_{23}H_{35}N_2O_5S$ (M+H$^+$) 451.2, found 451.2.

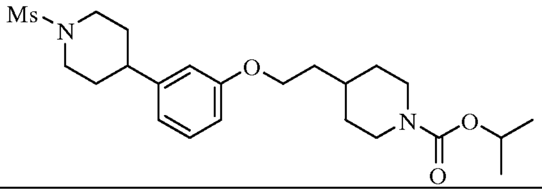
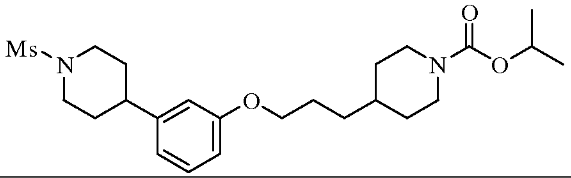
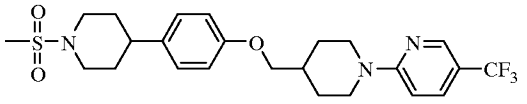
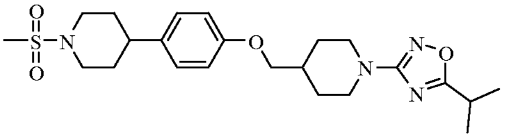
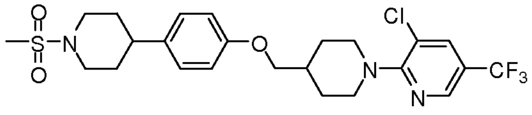
Example J10: Isopropyl 4-((4-(1-methanesulfonylpiperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate.

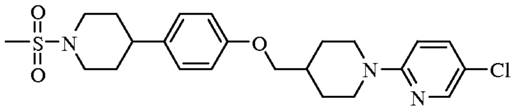
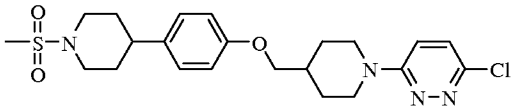
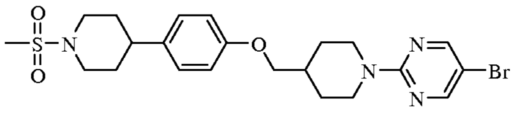
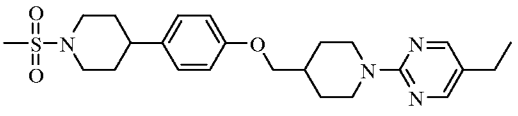
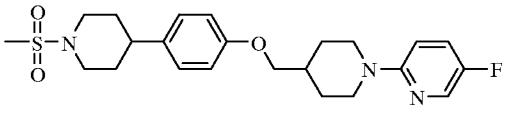


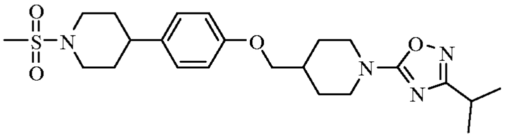
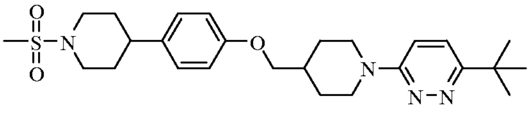
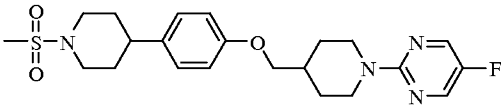
[00208] A solution of **J1** (0.18 g, 0.4 mmol) in ethanol (10 mL) and ethyl acetate (2 mL) is treated with palladium(0) on charcoal (5%, 0.12 g). The mixture is stirred under 1 atm hydrogen for 18 hours. Filtration, concentration, and purification using mass-triggered reverse phase HPLC yields **J9**; ^{1}H NMR (CD$_3$CN, 400.13 MHz): δ 7.19 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.95 (septet, *J* = 6.2 Hz, 1H), 4.16 (br, 2H), 3.83 (d, *J* = 6.4 Hz, 2H), 3.78 (m, 2H), 2.81 (s, 3H), 2.78 (m, 4H), 2.61 (tt, *J* = 3.6, 12.1 Hz, 1H), 2.01 (m, 1H), 1.90 (m, 2H), 1.81 (m, 2H), 1.71 (m, 2H), 1.23 (d, *J* = 6.2 Hz, 6H), 1.22 (m, 2H); ESIMS calcd. for $C_{22}H_{35}N_2O_5S$ (M+H$^+$) 439.2, found 439.2.

[00209] By following a similar procedure as the one used for preparing **J10** from **J1** except substituting the olefin for intermediate **J1** or by following a similar procedure as the one used for preparing **J1** from **J1a** except substituting 4-(4-methoxyphenyl)piperidine or 4-(3-methoxyphenyl)piperidine for **J1c**, the following examples are prepared;

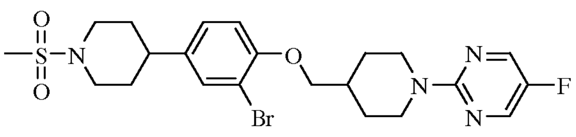
Example	Structure	Analytical data
J11		ESIMS calcd. for $C_{21}H_{33}N_2O_5S$ (M+H$^+$) 425.2, found 425.0.
J12		ESIMS calcd. for $C_{23}H_{37}N_2O_5S$ (M+H$^+$) 453.2, found 453.2.
J13		ESIMS calcd. for $C_{24}H_{39}N_2O_5S$ (M+H$^+$) 467.3, found 467.2.
J14		ESIMS calcd. for $C_{25}H_{41}N_2O_5S$ (M+H$^+$) 481.3, found 481.1.
J15		^{1}H-NMR (400MHz, $CDCl_3$) δ 7.11 (m, 2H), 6.83 (m, 2H), 4.12 (m, 2H), 3.93 (m, 2H), 3.77 (d, 2H, J = 6.3 Hz), 2.81 (s, 3H), 2.75 (m, 2H), 2.55 (tt, 1H, J = 3.5, 12.1 Hz), 1.93 (m, 2H), 1.81 (m, 4H), 1.55 (s, 3H), 1.26 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H). ESIMS calcd. for $C_{23}H_{35}N_2O_5S$ (M+H$^+$) 451.2, found 451.2.
J16		ESIMS calcd. for $C_{22}H_{35}N_2O_5S$ (M+H$^+$) 439.2, found 439.1.

J17		ESIMS calcd. for $C_{23}H_{37}N_2O_5S$ (M+H$^+$) 453.2, found 453.1.
J18		ESIMS calcd. for $C_{24}H_{39}N_2O_5S$ (M+H$^+$) 467.3, found 467.1.
J19		^{1}H-NMR (400MHz, DMSO-d6) δ 8.38 (m, 1H), 7.75 (dd, 1H, J = 2.5, 9.2 Hz), 7.16 (m, 2H), 6.96 (d, 1H, J = 9.2 Hz), 6.86 (m, 2H), 4.46 (m, 2H), 3.82 (d, 2H, J = 6.4 Hz), 3.65 (m, 2H), 2.95 (m, 2H), 2.88 (s, 3H), 2.78 (m, 2H), 2.56 (tt, 1H, J = 3.5, 12.3 Hz), 2.07 (m, 1H), 1.83 (m, 4H), 1.62 (m, 2H), 1.24 (m, 2H). ESIMS calcd. for $C_{24}H_{31}F_3N_3O_3S$ (M+H$^+$) 498.2, found 497.8.
J20		^{1}H-NMR (400MHz, DMSO-d6) δ 7.16 (m, 2H), 6.86 (m, 2H), 3.87 (m, 2H), 3.82 (d, 2H, J = 6.5 Hz), 3.65 (m, 2H), 3.10(h, 1H, J = 7.0Hz), 2.90 (m, 2H), 2.89 (s, 3H), 2.78 (m, 3H), 2.56 (tt, 1H, J = 3.4, 12.2 Hz), 1.95 (m, 1H), 1.82 (m, 4H), 1.62 (m, 2H), 1.29 (m, 2H), 1.26 (d, 6H, J = 7.0 Hz). ESIMS calcd. for $C_{23}H_{35}N_4O_4S$ (M+H$^+$) 463.2, found 463.2.
J21		^{1}H-NMR (400MHz, DMSO-d6) δ 8.54 (m, 1H), 8.16 (d, 1H, J = 2.0 Hz), 7.17 (m, 2H), 6.88 (m, 2H), 4.04 (m, 2H), 3.86 (d, 2H, J = 6.4 Hz), 3.65 (m, 2H), 2.93 (m, 2H), 2.89 (s, 3H), 2.78 (m, 2H), 2.56 (tt, 1H, J = 3.5, 12.2 Hz), 2.01 (m, 1H), 1.86 (m, 4H), 1.62 (m, 2H), 1.43 (m, 2H). ESIMS calcd. for $C_{24}H_{30}ClF_3N_3O_3S$ (M+H$^+$) 532.2, found 531.9.

J22		^{1}H-NMR (400MHz, DMSO-d6) δ 8.08 (d, 1H, J =2.5 Hz), 7.56 (dd, 1H, J = 2.7, 9.1 Hz), 7.16 (m, 2H), 6.87 (m, 3H), 4.29 (m, 2H), 3.81 (d, 2H, J = 6.4 Hz), 3.65 (m, 2H), 2.88 (s, 3H), 2.81 (m, 4H), 2.56 (tt, 1H, J = 3.4, 11.9 Hz), 2.00 (m, 1H), 1.82 (m, 4H), 1.62 (m, 2H), 1.25 (m, 2H). ESIMS calcd. for $C_{23}H_{31}ClN_3O_3S$ (M+H$^+$) 464.2, found 464.2.
J23		^{1}H-NMR (400MHz, DMSO-d6) δ 7.50 (d, 1H, J =9.6 Hz), 7.41 (d, 1H, J = 9.7 Hz), 7.16 (m, 2H), 6.87 (m, 2H), 4.37 (m, 2H), 3.82 (d, 2H, J = 6.4 Hz), 3.64 (m, 2H), 2.96 (m, 2H), 2.88 (s, 3H), 2.78 (m, 2H), 2.56 (tt, 1H, J = 3.4, 11.9 Hz), 2.06 (m, 1H), 1.84 (m, 4H), 1.62 (m, 2H), 1.29 (m, 2H). ESIMS calcd. for $C_{22}H_{30}ClN_4O_3S$ (M+H$^+$) 465.2, found 465.2.
J24		^{1}H-NMR (400MHz, DMSO-d6) δ 8.43 (s, 2H), 7.16 (m, 2H), 6.86 (m, 2H), 4.61 (m, 2H), 3.81 (d, 2H, J = 6.6 Hz), 3.65 (m, 2H), 2.93 (m, 2H), 2.88 (s, 3H), 2.78 (m, 2H), 2.55 (m, 1H), 2.05 (m, 1H), 1.82 (m, 4H), 1.62 (m, 2H), 1.22 (m, 2H). ESIMS calcd. for $C_{22}H_{30}BrN_4O_3S$ (M+H$^+$) 509.1, found 508.9.
J25		^{1}H-NMR (400MHz, DMSO-d6) δ 8.24 (s, 2H), 7.16 (m, 2H), 6.86 (m, 2H), 4.65 (m, 2H), 3.81 (d, 2H, J = 6.4 Hz), 3.65 (m, 2H), 2.87 (m, 2H), 2.89 (s, 3H), 2.78 (m, 2H), 2.56 (tt, 1H, J = 3.5, 11.9 Hz), 2.42 (q, 2H, J = 7.6 Hz), 2.03 (m, 1H), 1.82 (m, 4H), 1.62 (m, 2H), 1.20 (m, 2H), 1.12 (t, 3H, J = 7.6). ESIMS calcd. for $C_{24}H_{35}N_4O_3S$ (M+H$^+$) 459.2, found 459.2.
J26		^{1}H-NMR (400MHz, DMSO-d6) δ 8.07 (d, 1H, J = 3.1 Hz), 7.49 (ddd, 1H, J = 3.1, 8.4,9.2 Hz), 7.16 (m, 2H), 6.88 (m, 3H), 4.23 (m, 2H), 3.82 (d,

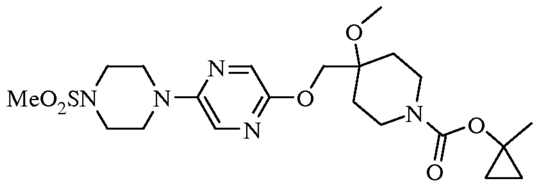
		2H, J = 6.4 Hz), 3.65 (m, 2H), 2.89 (s, 3H), 2.79 (m, 4H), 2.57 (tt, 1H, J = 3.5, 12.0 Hz), 1.98 (m, 1H), 1.82 (m, 4H), 1.62 (m, 2H), 1.27 (m, 2H). ESIMS calcd. for $C_{23}H_{31}FN_3O_3S$ (M+H$^+$) 448.2, found 448.2.
J27		^{1}H-NMR (400MHz, DMSO-d6) δ 7.16 (m, 2H), 6.87 (m, 2H), 3.99 (m, 2H), 3.83 (d, 2H, J = 6.4 Hz), 3.65 (m, 2H), 3.12(m, 2H), 2.89 (s, 3H), 2.79 (m, 3H), 2.56 (tt, 1H, J = 3.5, 11.9 Hz), 1.99 (m, 1H), 1.84 (m, 4H), 1.62 (m, 2H), 1.31 (m, 2H), 1.18 (d, 6H, J = 6.9 Hz). ESIMS calcd. for $C_{23}H_{35}N_4O_4S$ (M+H$^+$) 463.2, found 463.2.
J28		^{1}H-NMR (400MHz, DMSO-d6) δ 8.10 (d, 1H, J = 10.0 Hz), 8.01 (d, 1H, J = 10.0 Hz), 7.17 (m, 2H), 6.87 (m, 2H), 4.31 (m, 2H), 3.84 (d, 2H, J = 6.4 Hz), 3.66 (m, 2H), 3.25 (m, 2H), 2.89 (s, 3H), 2.78 (m, 2H), 2.56 (tt, 1H, J = 3.4, 12.3 Hz), 2.16 (m, 1H), 1.92 (m, 2H), 1.82 (m, 2H), 1.62 (m, 2H), 1.41 (m, 2H), 1.32 (s, 9H). ESIMS calcd. for $C_{26}H_{39}N_4O_3S$ (M+H$^+$) 486.3, found 486.3.
J29		^{1}H-NMR (400MHz, DMSO-d6) δ 8.42 (d, 2H, J = 0.8 Hz), 7.16 (m, 2H), 6.86 (m, 2H), 4.60 (m, 2H), 3.82 (d, 2H, J = 6.4 Hz), 3.65 (m, 2H), 2.91 (m, 2H), 2.88 (s, 3H), 2.78 (m, 2H), 2.56 (tt, 1H, J = 3.5, 11.9 Hz), 2.03 (m, 1H), 1.82 (m, 4H), 1.62 (m, 2H), 1.21 (m, 2H). ESIMS calcd. for $C_{22}H_{30}FN_4O_3S$ (M+H$^+$) 449.2, found 448.8.

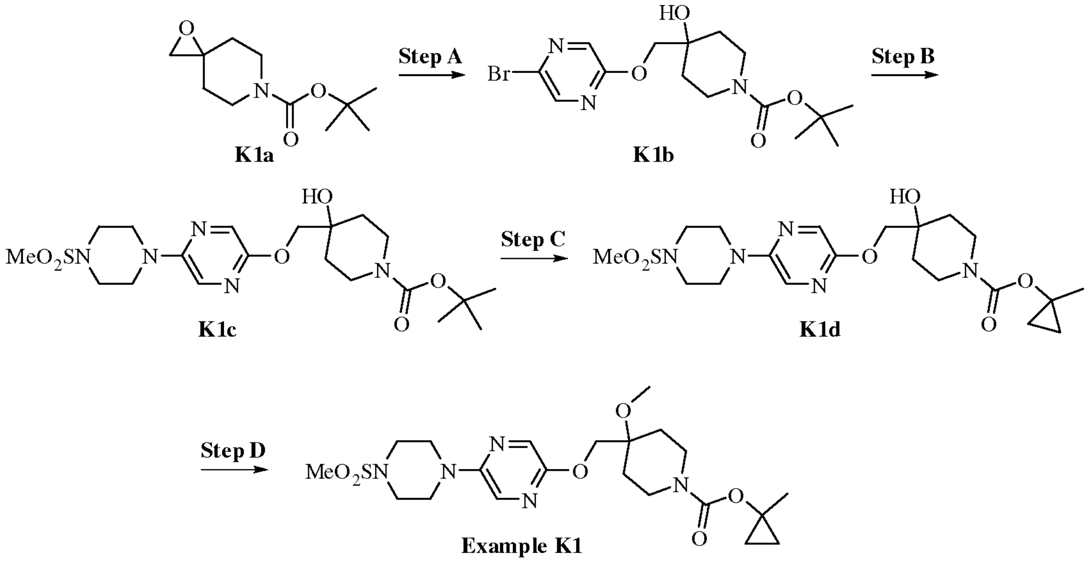
Example J30: 2-(4-((2-Bromo-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)-5-fluoropyrimidine



[00210] This material is prepared when a large scale preparation of **J28** from 4-(4-methoxyphenyl)piperidine in place of **J1c** following the scheme outlined for **J1** yielded a brominated byproduct in **step D:** ^{1}H-NMR (400MHz, DMSO-d6) δ 8.43 (d, 2H, J = 0.8 Hz), 7.45 (d, 1H, J = 2.1 Hz), 7.21 (dd, 1H, J = 2.1, 8.6 Hz), 7.04 (d, 1H, J = 8.6 Hz), 4.61 (m, 2H), 3.91 (d, 2H, J = 6.3 Hz), 3.65 (m, 2H), 2.93 (m, 2H), 2.89 (s, 3H), 2.77 (m, 2H), 2.59 (tt, 1H, J = 3.5, 12.0 Hz), 2.07 (m, 1H), 1.84 (m, 4H), 1.62 (m, 2H), 1.27 (m, 2H). ESIMS calcd. for $C_{22}H_{29}BrFN_4O_3S$ (M+H$^+$) 527.1, found 527.1.

Example K1: 1-Methylcyclopropyl 4-methoxy-4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





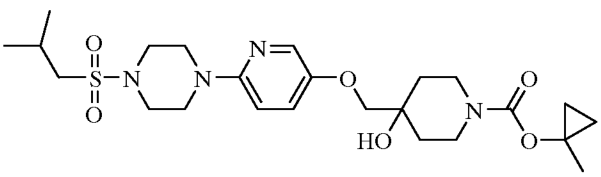
[00211] **Step A:** A solution of **K1a** (2.22 g, 10.4 mmol) and 2-bromo-5-hydroxypyrazine (2 g, 11.4 mmol) in N-methylpyrrolidinone (10 mL) is treated with K_2CO_3 (2.37 g, 17.1 mmol) and heated to 80 °C overnight. After cooling to room temperature, the reaction is diluted with ethyl acetate and extracted with water twice. The organics are dried over $MgSO_4$, filtered evaporated and purified by silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **K1b**; ESIMS *m/z* for $(M+H^+)$ $C_{15}H_{23}BrN_3O_4$ calcd.: 388.1, found: 388.2.

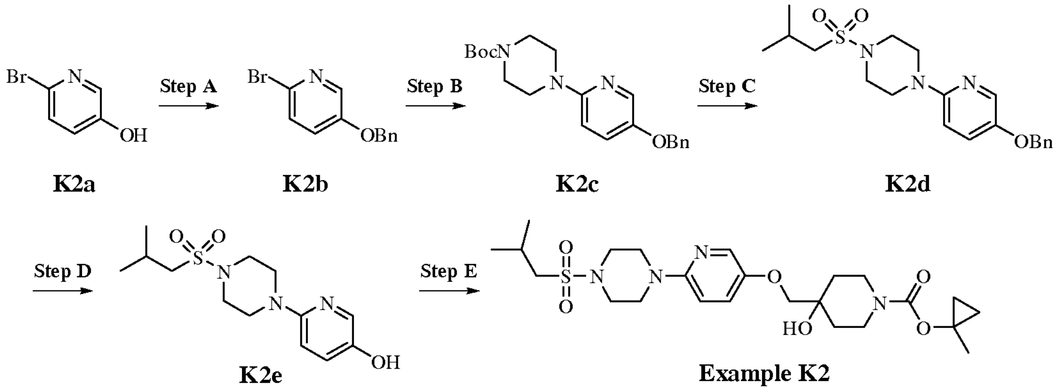
[00212] **Step B:** By following a similar procedure as the one used for preparing **B1** from isopropyl 4-((6-chloropyridin-3-yloxy)methyl)piperidine-1-carboxylate except substituting **K1b** for isopropyl 4-((6-chloropyridin-3-yloxy)methyl)piperidine-1-carboxylate, **K1c** is prepared; ESIMS *m/z* for $(M+H^+)$ $C_{20}H_{34}N_5O_6S$ calcd.: 472.2, found: 472.2.

[00213] **Step C**: **:** By following a similar procedure as the one used for preparing **E3** from **B4** except substituting **K1c B4**, **K1d** is prepared; ESIMS *m/z* for $(M+H^+)$ $C_{20}H_{32}N_5O_6S$ calcd.: 470.2, found: 470.2.

[00214] **Step D:** A solution of **K1d** (75 mg, 0.16 mmol) in N, N-dimethylformamide is treated with dimethylsulfate (80 mg, 0.63 mmol) followed by NaH (30 mg, 1.25 mmol). After stirring at room temperature for 1 hour, the reaction is treated with water and ethyl acetate. The organics are isolated, washed with water, dried over $MgSO_4$, filtered evaporated and purified by silica gel using a linear gradient of 50-100% ethyl acetate in hexane to afford **K1**; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 7.94 (d, J = 1.5 Hz, 1H), 7.61 (d, J = 1.4 Hz, 1H), 4.20 (m, 2H), 3.91 (m, 2H), 3.54 (m, 4H), 3.37 (m, 4H), 3.29 (s, 3H), 3.13 (m, 2H), 2.82 (s, 3H), 1.89 (m, 2H), 1.55 (m, 2H), 1.55 s, 3H), 0.87 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{21}H_{34}N_5O_6S$ $(M+H^+)$ 484.2, found 484.1.

Example K2: 1-methylcyclopropyl 4-hydroxy-4-((6-(4-(isobutylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate.





[00215] **Step A**: A solution of **K2a** (2.0 g, 11.5 mmol) and benzyl bromide (2.36 g, 13.8 mmol) in N-methylpyrrolidinone (15 mL) is treated with K_2CO_3 (2.38 g, 17.2 mmol) and stirred at 60 °C overnight. The reaction is cooled to room temperature, diluted with ethyl acetate and extracted with water twice. The organics are then dried over $MgSO_4$, filtered evaporated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **K2b**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 8.13 (d, *J* = 3.1 Hz, 1H), 7.38 (m, 6H), 7.15 (dd, *J* = 3.2, 8.7 Hz, 1H), 5.09 (s, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{12}H_{11}BrNO$ calcd: 264.0, found: 264.0.

[00216] **Step B**: A roundbottom flask is charged with **K2b** (2.55 g, 9.65 mmol), Pd_2dba_3 (177 mg, 0.19 mmol), xantphos (335 mg, 0.58 mmol) and tert-butyl piperazine-1-carboxylate (2.16 g, 11.6 mmol) followed by dry toluene (30 mL). The flask is sparged with dry nitrogen, treated with NaO*t*Bu (1.39 g, 14.5 mmol), sealed, dipped into a pre heated 100 °C oil bath and stirred for 2 hours. The reaction is then cooled to room temperature, diluted with ethyl acetate and extracted with water twice. The organics are then dried over $MgSO_4$, filtered evaporated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **K2c**; ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{28}N_3O_3$ calcd: 370.2, found: 370.1.

[00217] **Step C**: A solution of **K2c** (970 mg, 2.2 mmol) in 1:1 TFA/ dichloromethane (10 mL) is aged for 1 hour and the solvent is removed. The resulting residue is partitioned between ethyl acetate and 1 M HCl. The aqueous phase is collected and the organics are extracted once more with 1 M HCl and discarded. The combined

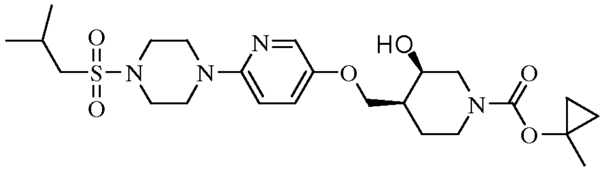
aqueous extracts are made basic with solid Na_2CO_3 and extracted three times with dichloromethane. The combined organics are dried over $MgSO_4$, filtered, evaporated, dissolved in dichloromethane (10 mL) and treated with triethylamine (337 mg, 3.33 mmol) followed by isobutanesulfonyl chloride (452 mg, 2.89 mmol). After stirring for 30 minutes, the reaction is diluted with ethyl acetate, extracted with saturated aqueous sodiumhydrogencarbonate twice, dried over $MgSO_4$, filtered and evaporated to afford **K2d**; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 7.99 (d, J = 2.8 Hz, 1H), 7.38 (m, 5H), 7.22 (dd, J = 3.2, 9.1 Hz, 1H), 6.64 (d, J = 9.0 Hz, 1H), 5.04 (s, 2H), 3.52 (m, 4H), 3.37 (m, 4H), 2.76 (d, J = 6.6 Hz, 2H), 1.12 (d, J = 6.7 Hz, 6H); ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{28}N_3O_3S$ calcd: 390.2, found: 390.2.

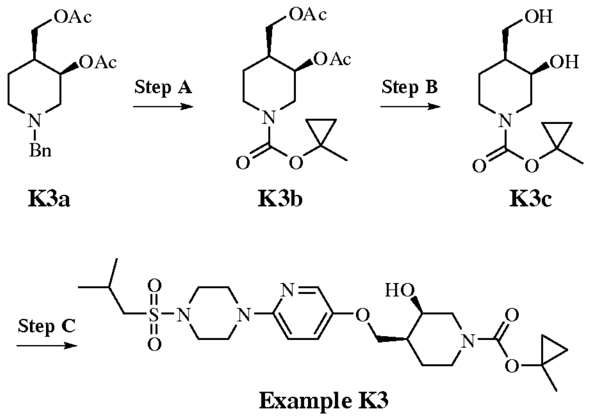
[00218] **Step D**: A solution of **K2d** (0.80 g, 2.0 mmol) in ethanol (10 mL) is treated with $Pd(OH)_2$ (50 mg) and hydrogenated overnight. The catalyst is removed by filtration through Celite® and resubjected to hydrogenation with 100 mg of 10% Pd/C overnight. The catalyst is removed by filtration through Celite® and the solvent is removed. The resulting material is slurried in hexane, collected and dried to afford **K2e**; ESIMS *m/z* for $(M+H)^+$ $C_{13}H_{22}N_3O_3S$ calcd: 300.1, found: 300.1.

[00219] **Step E**: A solution of **K2e** (75 mg, 0.25 mmol) and **K1a** (64 mg, 0.30 mmol) in N-methylpyrrolidinone (2 mL) is treated with K_2CO_3 (52 mg, 0.38 mmol) and stirred at 80 °C overnight. The reaction is then cooled to room temperature, partitioned between ethyl acetate and water and extracted with water once more. The organics are dried over $MgSO_4$, filtered, evaporated, dissolved in dichloromethane (2 mL) and treated with TFA (2 mL). After stirring for 1 hour, the solvent is removed and the residue is dissolved in dichloromethane, treated with **E3b** (59 mg, 0.25 mmol) and excess triethylamine and stirred overnight. The reaction is then partitioned between ethyl acetate and water and extracted with water once more. The organics are dried over $MgSO_4$, filtered, evaporated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **K2;** ^1H NMR ($CDCl_3$, 400.13 MHz): δ 7.93 (d, J = 3.0 Hz, 1H), 7.18 (dd, J = 3.1, 9.1 Hz, 1H), 6.65 (d, J = 9.2 Hz, 1H), 3.99 (m, 2H), 3.77 (s, 2H), 3.52 (m, 4H), 3.37 (m, 4H), 3.20 (m, 2H), 2.77 (d, J = 6.6 Hz, 2H), 2.32 (m, 1 H), 2.12 (s, 1H), 1.72 (m, 2H), 1.55 (m, 3H), 1.12 (d, J = 6.7 Hz, 6H), 0.87 (m, 2H), 0.63 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{38}N_4O_6S$ calcd: 510.3, found: 511.5.

[00220]

Example K3: (+/-)-(cis)-1-methylcyclopropyl 3-hydroxy-4-((6-(4-(isobutylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate





[00221] **Step A**: A solution of **K3a** (420 mg, 1.4 mmol) (Helv. Chim. Acta **2004**, 87, 2629) in EtOH containing 1% by volume TFA (150 mL) is hydrogenated in an H-Cube apparatus at 50 atmospheres of H_2 and 70 °C. The solvent is then removed and the residue is co-evaporated twice with toluene, dissolved in dichloromethane (10 mL) and treated with **E3b** (342 mg, 1.4 mmol), excess triethylamine and a few crystals of DMAP. The reaction is stirred overnight, partitioned between ethyl acetate and saturated aqueous sodiumhydrogencarbonate and extracted with satutated aqueous sodium carbonate twice. The organics are then dried over $MgSO_4$, filtered evaporated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **K3b**; ESIMS *m/z* for $(M+H)^+$ $C_{15}H_{24}NO_6$ calcd: 314.2, found: 314.1.

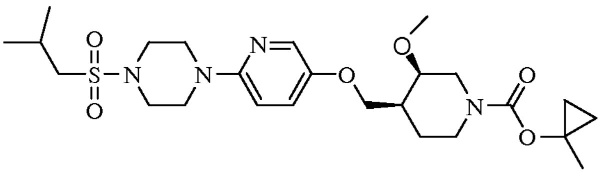
[00222] **Step B**: A solution of **K3b** (333 mg, 1.1 mmol) in MeOH is treated with a solution of $Mg(OMe)_2$ (5.6 mL of a 0.57 M solution, 3.2 mmol) and stirred for 1 hour. The reaction is then quenched with excess prewashed Amberlite IR-120 H^+ resin and

filtered. The solvent is removed to afford **K3c**; ESIMS *m/z* for $(M+H)^+$ $C_{11}H_{20}NO_4$ calcd: 230.1, found: 230.1.

[00223] **Step C**: A solution of DIAD (88 mg, 0.22 mmol) in dichloromethane (0.5 mL) is cooled in an ice bath and treated with a solution of PPh_3 (114 mg, 0.44 mmol) in dichloromethane (1 mL). The solution is stirred for 15 minutes and treated with a solution of **K3c** (50 mg, 0.22 mmol) and **K2d** (65 mg, 0.22 mmol) in dichloromethane (1.5 mL). The reaction is sealed and heated to 50 °C overnight. The reaction is cooled to room temperature and loaded onto a silica gel column and purified using a linear gradient of 0-100% ethyl acetate in hexane. The product fractions are partitioned between ethyl acetate and 1 M HCl. The aqueous phase is collected and the organics are extracted once more with 1 M HCl and discarded. The combined aqueous extracts are made basic with solid Na_2CO_3 and extracted three times with ethyl acetate. The combined organics are dried over $MgSO_4$, filtered and evaporated to afford **K3**; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 7.93 (d, *J* = 2.9 Hz, 1H), 7.17 (dd, *J* = 3.1, 9.1 Hz, 1H), 6.64 (d, *J* = 9.1 Hz, 1H), 4.19 (m, 2H), 4.09 (m, 1H), 4.03 (dd, *J* = 7.6, 9.1 Hz, 1H), 3.84 (dd, *J* = 6.0, 9.1 Hz, 1H), 3.51 (m, 4H), 3.37 (m, 4H), 2.91 (m, 1H), 2.78 (m, 1H), 2.76 (d, *J* = 6.6 Hz, 2H), 2.32 (m, 1H), 2.00 (m, 1H), 1.86 (m, 1H), 1.68 (m, 1H), 1.55 (s, 3H), 1.12 (d, *J* = 6.7 Hz, 6H), 0.88 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{39}N_4O_6S$ calcd: 511.3, found: 511.4.

[00224]

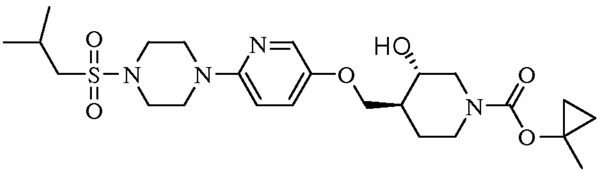
Example K4: (+/-)-(cis)-1-Methylcyclopropyl 4-((6-(4-(isobutylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)-3-methoxypiperidine-1-carboxylate



[00225] A solution of **K3** (25 mg, 0.22 mmol) in N, N-dimethylformamide (2 mL) is treated with excess (~100 uL) dimethylsulfate and excess (~40 mg) of NaH. The reaction is stirred for 1 hour and then diluted with ethyl acetate and water. The organics are isolated and washed once more with water, dried over MgSO4, filtered, evaporated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **K4**; ^{1}H NMR (CDCl$_3$, 400.13 MHz): δ 7.93 (d, *J* = 2.9 Hz, 1H), 7.16 (dd, *J* = 3.0, 9.1 Hz, 1H), 6.64 (d, *J* = 9.1 Hz, 1H), 4.53 (m, 0.5H), 4.28 (m, 1H), 4.00 (m, 1.5 H), 3.78 (m, 1H), 3.52 (m, 4H), 3.75 (m, 7H), 2.76 (d, *J* = 6.6 Hz, 2H), 2.72 (m, 2H), 2.32 (m, 1H), 2.03 (m, 1H), 1.59 (m, 1H), 1.55 (s, 3H), 1.48 (m, 1H), 1.12 (d, *J* = 6.7 Hz, 6H), 0.87 (m, 2H), 0.61 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{25}H_{41}N_4O_6S$ calcd: 525.3, found: 525.2.

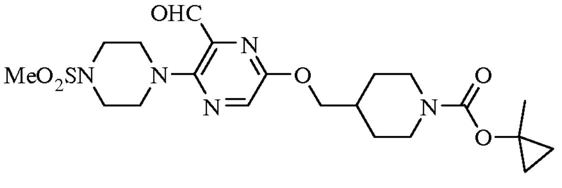
[00226]

Example K5: (+/-)-(Trans)-1-methylcyclopropyl 3-hydroxy-4-((6-(4-(isobutylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate



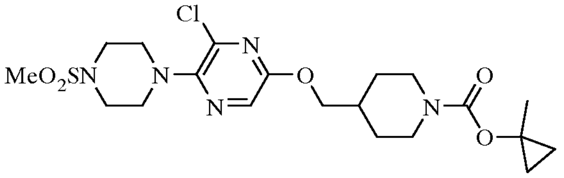
[00227] By following a similar procedure as the one used for preparing **K3** from **K3a** except substituting the trans- isomer of **K3a** (Helv. Chim. Acta **2004**, 87, 2629) for **K3a**, **K5** is prepared; ^{1}H NMR (CDCl$_3$, 400.13 MHz): δ 7.93 (d, *J* = 3.0 Hz, 1H), 7.24 (dd, *J* = 3.0, 9.1 Hz, 1H), 6.69 (d, *J* = 9.2 Hz, 1H), 4.17 (m, 3H), 4.05 (m, 2H), 3.56 (m, 5 H), 3.37 (m, 4H), 2.77 (d, *J* = 6.6 Hz, 2H), 2.72 (m, 1H), 2.58 (m, 1H), 2.31 (m, 1H), 1.90 (m, 1H), 1.78 (m, 1H), 1.55 (s, 3H), 1.40 (m, 1H), 1.12 (d, *J* = 6.7 Hz, 6H), 0.87 (m, 2H), 0.61 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{39}N_4O_6S$ calcd: 511.3, found: 511.4.

Example L1: 1-methylcyclopropyl 4-((6-formyl-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



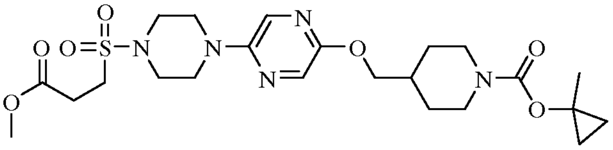
[00228] A solution of **E3** (109 mg, 0.24 mmol) in N,N-dimethylformamide (2.2 mL) is treated with $POCl_3$ (165 mg, 1.1 mmol) and heated to 70 °C for 2 hours. The reaction is then cooled to room temperature, quenched with water and diluted with ethyl acetate. The organics are exracted with water twice more, dried over $MgSO_4$, filtered evaporated and purified by silica gel using a linear gradient of 50-100% ethyl acetate in hexane to afford **L1**; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 9.93 (s, 1H), 8.04 (s, 1H), 4.19 (d, J = 6.4 Hz, 1H), 4.15 (m, 2H), 3.50 (m, 4H), 3.43 (m, 4H), 2.83 (s, 3H), 2.74 (m, 2H), 1.97 (m, 1H), 1.81 (m, 2H), 1.55 (s, 3H), 1.27 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{21}H_{32}N_5O_6S$ ($M+H^+$) 482.2, found 482.1.

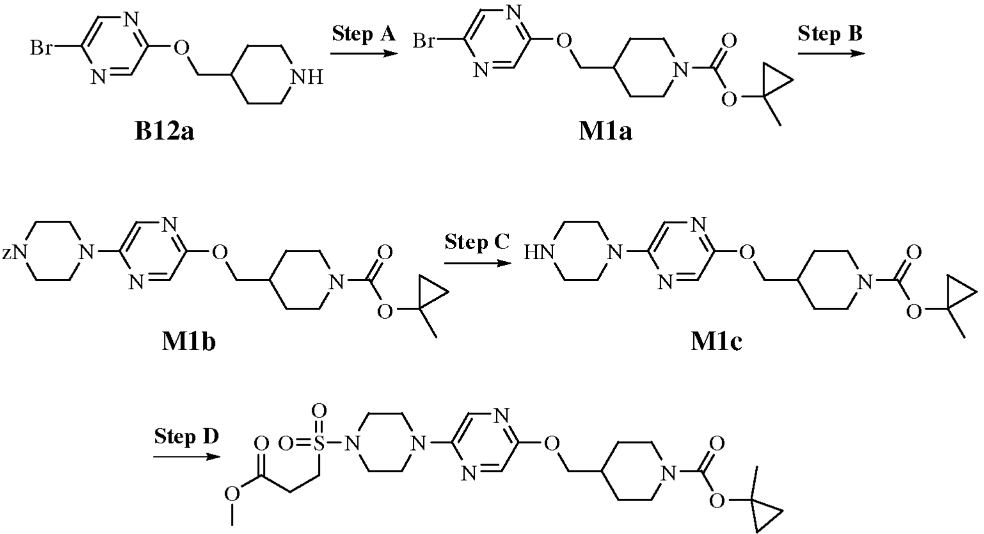
Example L2: 1-Methylcyclopropyl 4-((6-chloro-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00229] By following a similar procedure as the one used for preparing **L1** from **E3** except using NCS at 50 °C in dichloroethane overnight as the reaction conditions, **K5** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{31}ClN_5O_5S$ calcd: 488.2, found: 487.7.

Example M1: 1-Methylcyclopropyl 4-((5-(4-(3-methoxy-3-oxopropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





[00230] **Step A:** By following a similar procedure as the one used for preparing **E3** from **E3a** except substituting **B12a** for **E3a**, **M1a** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{15}H_{22}BrN_3O_3$ calcd: 371.2, found: 371.1.

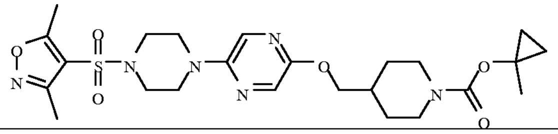
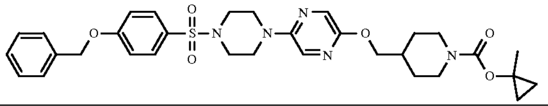
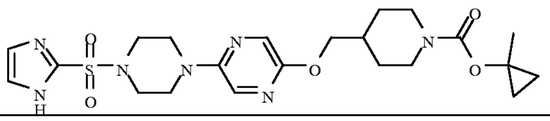
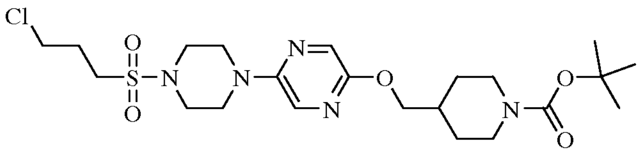
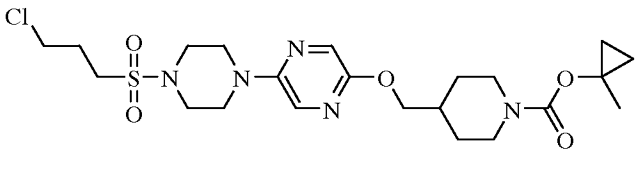
[00231] **Step B:** : By following a similar procedure as the one used for preparing **B1** from isopropyl 4-((6-chloropyridin-3-yloxy)methyl)piperidine-1-carboxylate except substituting **M1a** for isopropyl 4-((6-chloropyridin-3-yloxy)methyl)piperidine-1-carboxylate and benzyl piperazine-1-carboxylate for 1-(methylsulfonyl)piperazine, **M1b** is prepared; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 1.5 Hz, 1H), 7.59 (d, *J* = 1.4 Hz, 1H), 7.35 (m, 5H), 5.16 (s, 2H), 4.18 (m, 2H), 4.06 (d, *J* = 6.6 Hz, 2H), 3.65 (m, 4H), 3.38 (m, 4H), 2.74 (m, 2H), 1.94 (m, 1H), 1.79 (m, 2H), 1.54 (s, 3H), 1.24 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{27}H_{36}N_5O_5$ calcd: 510.3, found: 510.0.

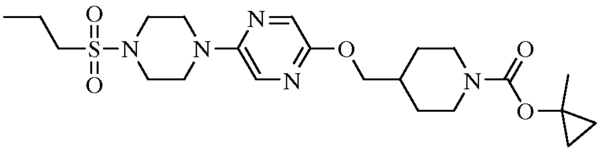
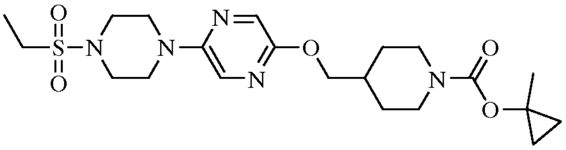
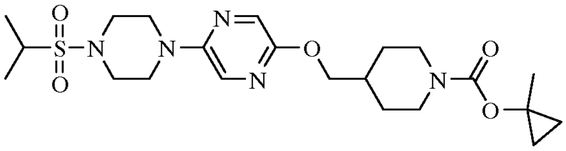
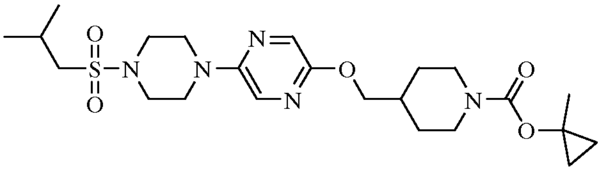
[00232] **Step C:** A mixture of **M1b** (494mg, 0.969 mmol) and 10% Pd/C (45 mg) in ethanol (5 mL) is purged with H_2 (g) for 30 minutes and then left to stir at room temperature under an atmosphere of H_2 overnight. The crude reaction is then filtered through a pad of Celite® and **M1c** is obtained with 95%+ purity. ESIMS *m/z* for $(M+H)^+$ $C_{19}H_{30}N_5O_3$ calcd: 376.2, found: 376.0.

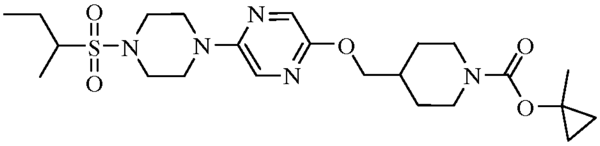
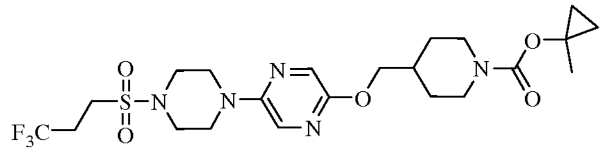
[00233] **Step D:** A solution of **M1c** (100 mg, 0.266 mmol) in dichloromethane (1 mL) is treated with triethylamine (74.2 mL, 0.533 mmol) followed by methyl 3-(chlorosulfonyl)propanoate (50 mg, 0.27 mmol) and stirred at room temperature for 4 hours. The crude reaction is then concentrated and purified directly via a mass-directed

HPLC to afford **M1**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 1.5 Hz, 1H), 7.61 (d, *J* = 1.5 Hz, 1H), 4.18 (m, 2H), 4.07 (d, *J* = 6.5 Hz, 2H), 3.73 (s, 3H), 3.49 (m, 4H), 3.42 (m, 4H), 3.28 (t, *J* = 7.3 H, 2H), 2.85 (t, *J* = 7.7 Hz, 2H), 2.74 (m, 2H), 1.93 (m, 1H), 1.81 (m, 2H), 1.54 (s, 3H), 1.24 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{36}N_5O_7S$ calcd: 526.2, found: 526.2.

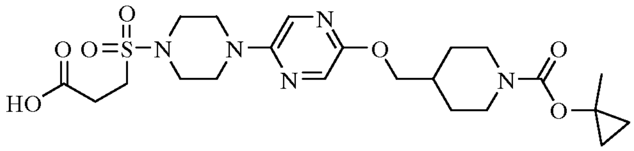
[00234] By following a similar procedure as the one used for preparing **M1** from **E12a** except substituting commercially available sulfonyl chlorides for methyl 3-(chlorosulfonyl)propanoate (in the case of **M5**, also substituting **B4bB** for **M1a**), the following examples are prepared;

Example	Structure	Analytical data
M2		ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{35}N_6O_6S$ calcd: 535.2, found: 535.2.
M3		ESIMS *m/z* for $(M)^+$ $C_{32}H_{39}N_5O_6S$ calcd: 621.3, found: 621.7.
M4		ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{32}N_7O_5S$ calcd: 506.2, found: 506.2.
M5		^{1}H NMR (400 MHz, CD_3CN) δ 7.87 (d, J = 1.4 hz, 1H), 7.62 (d, J - 1.5 Hz, 1H), 4.15 (m, 2H), 4.08 (d, J = 6.6 Hz, 2H), 3.70 (t, J = 6.1 Hz, 2H), 3.51 (m, 4H), 3.43 (m, 4H), 3.11 (t, J = 7.4 Hz, 2H), 2.73 (m, 2H), 2.32 (m, 2H), 1.94 (m, 1H), 1.79 (m, 2H), 1.46 (s, 9H), 1.26 (m, 2H); ESIMS *m/z* for $(M\text{-}Boc+H)^+$ $C_{17}H_{29}ClN_5O_3S$ calcd: 418.2, found: 418.2.
M6		^{1}H-NMR (400MHz, $CDCl_3$) δ 7.87 (d, *J* = 1.4 Hz, 1H), 7.63 (d, *J* = 1.4 Hz, 1H), 4.21 (m, 2H), 4.08 (d, *J* = 6.5Hz, 2H), 3.70 (t, *J* = 6.1 Hz, 2H), 3.51 (m, 4H), 3.44 (m, 4H), 3.12 (m, 2H), 2.74 (dd, *J* = 12.3, 12.2 Hz, 2H), 2.32 (m, 2H), 1.95 (m, 1H),

		1.79 (m, 2H), 1.55 (s, 3H), 1.25 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{22}H_{35}ClN_5O_5S$ $[M]^+$ 516.2, found 516.0.
M7		^{1}H NMR (400 MHz, CD_3CN) δ 7.89 (d, J = 1.4 Hz, 1H), 7.82 (d, J = 1.2 Hz, 1H), 4.19 (m, 2H), 4.10 (d, J = 6.5 Hz, 2H), 3.51 (m, 8H), 2.93 (m, 2H), 2.74 (dd, J= 12.7, 12.0 Hz, 1H), 1.91 (m, 3H), 1.79 (m, 2H), 1.55 (s, 3H), 1.25 (m, 2H), 1.07 (t, J = 7.4 Hz, 3H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{36}N_5O_5S$ calcd: 482.3 , found: 482.2.
M8		^{1}H NMR (400 MHz, CD_3CN) δ 7.96 (s, 1H), 7.91 (d, J = 1.4 Hz, 1H), 4.17 (m, 2H), 4.11 (d, J = 6.5 Hz, 2H), 3.58 (m, 4H), 3.54 (m, 4H), 3.01 (m, 2H), 2.74 (dd, J = 12.2, 11.9 Hz, 2H), 1.95 (m, 1H), 1.79 (m, 2H), 1.55 (s, 3H), 1.40 (t, J = 7.4 Hz, 3H), 1.25 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{34}N_5O_5S$ calcd: 468.2 , found: 468.2.
M9		^{1}H NMR (400 MHz, CD_3CN) δ 7.91 (m, 2H), 4.18 (m, 2H), 4.11 (d, J = 6.5 Hz, 2H), 3.63 (m, 4H), 3.50 (m, 4H), 3.25 (sept., J = 6.8 Hz, 1H), 2.74 (dd, J = 12.2, 12.1 Hz, 2H), 1.94 (m, 1H), 1.78 (m, 2H), 1.55 (s, 3H), 1.37 (d, J = 6.9 Jz, 6H), 1.25 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{36}N_5O_5S$ calcd: 482.2 , found: 482.2.
M10		^{1}H NMR (400 MHz, CD_3CN) δ 7.89 (d, J = 1.4 Hz, 1H), 7.81 (d, J = 1.1 Hz, 1H), 4.18 (m, 2H), 4.10 (d, J = 6.5 Hz, 2H), 3.53 (m, 4H), 3.47 (m, 4H), 2.79 (d, J = 6.6 Hz, 2H), 2.74 (m, 2H), 2.32 (m, 1H), 1.95 (m, 1H), 1.78 (m, 2H), 1.55 (s, 3H), 1.24 (m, 2H), 1.12 (d, J =

		6.7 Hz, 6H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{38}N_5O_5S$ calcd: 496.3 , found: 496.3.
M11		^{1}H NMR (400 MHz, CD_3CN) δ 7.87 (d, J = 1.5 Hz, 1H), 7.62 (d, J = 1.5 Hz, 1H), 4.19 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 3.50 (m, 4H), 3.46 (m, 4H), 2.98 (m, 1H), 2.75 (dd, J = 12.2, 12.1 Hz, 2H), 2.03 (m, 1H), 1.80 (m, 1H), 1.79 (m, 2H), 1.56 (m, 1H), 1.55 (s, 3H), 1.35 (d, J = 6.9 Hz, 3H), 1.26 (m, 2H), 1.03 (t, J = 7.5 hz, 3H), 0.87 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{38}N_5O_5S$ calcd: 496.3 , found: 496.2.
M12		^{1}H-NMR (400MHz, $CDCl_3$) δ 7.87 (d, *J* = 1.4Hz, 1H), 7.62 (d, *J* = 1.4Hz, 1H), 4.20 (m, 2H), 4.08 (d, *J* = 6.5Hz, 2H), 3.52 (m, 4H), 3.45 (m, 2H), 3.13 (m, 2H), 2.74 (dd, *J* = 12.2, 12.2 Hz, 2H), 2.66 (m, 2H), 1.94 (m, 1H), 1.79 (m, 2H), 1.56 (s, 3H), 1.25 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. $C_{22}H_{33}F_3N_5O_5S$ $[M+H]^+$ 536.2, found 536.3.

Example M13: 3-(4-(5-((1-((1-Methylcyclopropoxy)carbonyl)piperidin-4-yl)methoxy)pyrazin-2-yl)piperazin-1-ylsulfonyl)propanoic acid.

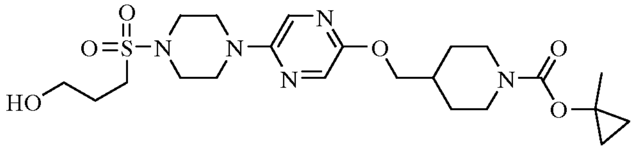


[00235] A solution of **M1** (18.8 mg, 0.035 mmol) in TETRAHYDROFURAN (1 mL) and water (0.25 mL) is treated with LiOH (3 mg) and stirred overnight. The crude

reaction is then concentrated and purified directly via a mass-directed HPLC to afford **M13**. ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{34}N_5O_7S$ calcd: 512.2, found: 512.3.

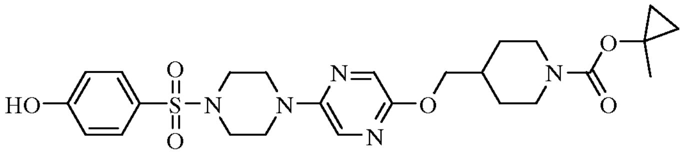
[00236]

Example M14: 1-Methylcyclopropyl 4-((5-(4-(3-hydroxypropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



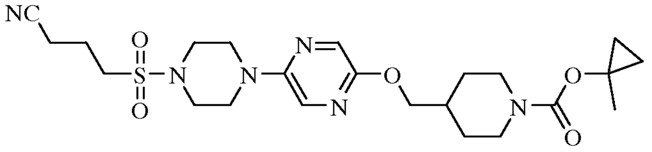
[00237] A solution of **M1** (18.8 mg, 0.035 mmol) in 2 M $LiBH_4$ in tetrahydrofuran (1 mL) is heated to 50 °C and stirred overnight. The crude reaction is then concentrated and purified directly via a mass-directed HPLC to afford **M14**. ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{36}N_5O_6S$ calcd: 498.2, found: 498.3.

Example M15: 1-Methylcyclopropyl 4-((5-(4-(4-hydroxyphenylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



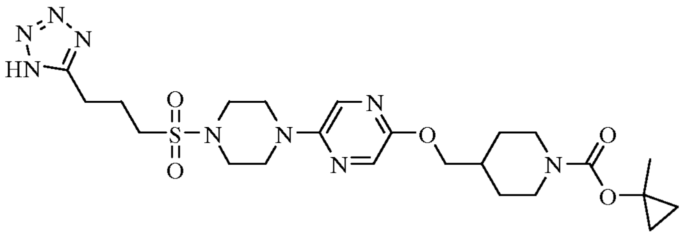
[00238] A solution of **M3** (44.5 mg, 0.071 mmol) in ethanol (2 mL) is treated with 5% Pd/C (10 mg) and hydrogenated under atmospheric pressure overnight. The catalyst is removed by filtration through Celite® and the reaction is concentrated and purified directly via a mass-directed HPLC to afford **M15**. ESIMS *m/z* for $(M+H)^+$ $C_{25}H_{33}N_5O_6S$ calcd: 531.2, found: 531.7.

Example M16: 1-Methylcyclopropyl 4-((5-(4-(3-cyanopropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



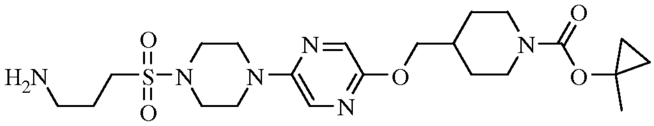
[00239] A solution of **M6** (19 mg, 0.037 mmol) in N,N-dimethylformamide (0.5 mL) is treated with KCN (3.6 mg, 0.055 mmol) and cesium carbonate (24 mg, 0.077 mmol) and heated to 80 °C for 1.5 hours. The reaction is then diluted with water and extracted with ethyl acetate three times and diethyl ether twice. The combined organics are dried over $MgSO_4$, filtered evaporated and purified by silica gel using a linear gradient of 50-100% ethyl acetate in hexane to afford **M16**. ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 1.6 Hz, 1H), 7.62 (d, J = 1.6 Hz, 1H), 4.28-3.95 (m, 2H), 4.08 (d, J = 6.4 Hz, 2H), 3.53-3.50 (m, 4H), 3.44-3.42 (m, 4H), 3.07 (t, J = 6.8 Hz, 2H), 2.74 (br t, J = 12.0 Hz, 2H), 2.64 (t, J = 7.2 Hz, 2H), 2.24 (quintet, J = 7.2 Hz, 2H), 2.01-1.89 (m, 1H), 1.81-1.77 (m, 2H), 1.54 (s, 3H), 1.30-1.17 (m, 2H), 0.88-0.84 (m, 2H), 0.64-0.60 (m, 2H); ESIMS m/z for $(M+H)^+$ $C_{23}H_{35}N_6O_5S$ calcd: 507.2, found: 507.2.

Example M17: 1-Methylcyclopropyl 4-((5-(4-(3-(1H-tetrazol-5-yl)propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



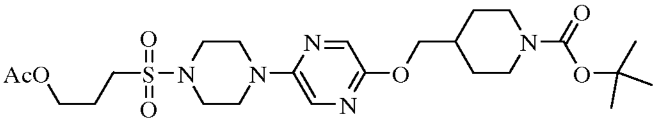
[00240] A solution of **M16** (12 mg, 0.024 mmol) in isopropanol (0.1 mL) and water (0.3 mL) is treated with $ZnBr_2$ (27 mg, 0.12 mmol) and NaN_3 (7.7 mg, 0.12 mmol) and heated to 150 °C overnight. The reaction is filtered through a syringe filter and purified directly via a mass-directed HPLC to afford **M17**; ^{1}H NMR (400 MHz, CD_3CN) δ 7.83 (d, *J* = 1.6 Hz, 1H), 7.71 (d, *J* = 1.6 Hz, 1H), 4.16-3.89 (m, 2H), 4.06 (d, *J* = 6.4 Hz, 2H), 3.49-3.46 (m, 4H), 3.35-3.32 (m, 4H), 3.12-3.04 (m, 4H), 2.81-2.70 (m, 2H), 2.28-2.20 (m, 2H), 1.78-1.71 (m, 3H), 1.48 (s, 3H), 1.22-1.12 (m, 2H), 0.81-0.78 (m, 2H), 0.60-0.57 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{36}N_9O_5S$ calcd: 550.3, found: 550.3.

Example M18: 1-Methylcyclopropyl 4-((5-(4-(3-aminopropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



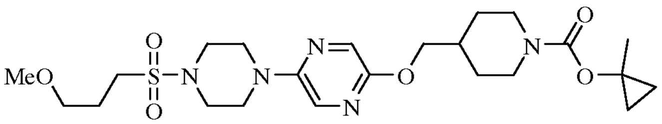
[00241] A solution of **M6** (113 mg, 0.22 mmol) in N,N-dimethylformamide (1 mL) is treated with NaN_3 (42.7 mg, 0.67 mmol) and heated to 90 °C overnight. The reaction is cooled to room temperature, partitioned between water and ethyl acetate. The organics are exracted with water twice more, dried over $MgSO_4$, filtered evaporated and purified by silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford the intermediate azide which is dissolved in ethanol (1 mL) and treated with 10% Pd/C (20 mg) and hydrogenated at room temperature overnight. The catalyst is removed by filtration through Celite® and the reaction is concentrated and purified directly via a mass-directed HPLC to afford **M18.** ^{1}H NMR (400 MHz, CD_3CN) δ 7.86 (d, J = 1.4 Hz, 1H), 7.61 (d, J = 1.5 Hz, 1H), 4.19 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 3.50 (m, 4H), 3.42 (m, 4H), 3.05 (m, 2H), 2.88 (t, J = 6.7 Hz, 2H), 2.74 (dd, J = 13.0, 12.0 Hz, 2H), 1.98 (m, 3H), 1.79 (m, 2H), 1.54 (s, 3H), 1.24 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{37}N_6O_5S$ calcd: 497.3 , found: 497.6.

Example M19: ***Tert*-butyl 4-((5-(4-(3-acetoxypropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.**



[00242] A solution of **M5** (154 mg, 0.30 mmol) in N,N-dimethylformamide (2 mL) is treated with sodium acetate (73 mg, 0.89 mmol) and sodium iodide (45 mg, 0.30 mmol) and heated to 120 °C overnight . The reaction is cooled to room temperature, partitioned between water and ethyl acetate. The organics are exracted with water twice more, dried over $MgSO_4$, filtered evaporated and purified by silica gel using a linear gradient of 0-100% ethyl acetate in dichloromethane to afford **M19;** ^1H NMR (400 MHz, CD_3CN) δ 7.87 (d, J = 1.4 Hz, 1H), 7.83 (d, J = 1.5 Hz, 1H), 4.20 (t, J = 6.1 Hz, 2H), 1.14 (m, 2H), 4.08 (d, J = 6.6 Hz, 1H), 3.51 (m, 4H), 3.44 (m, 4H), 3.02 (m, 2H), 2.74 (m, 2H), 2.19 (m, 2H), 2.07 (s, 3H), 1.95 (m, 1H), 1.80 (m, 2H), 1.46 (s, 9H), 1.26 (m, 2H); ESIMS *m/z* for $(M\text{-}Boc+H)^+$ $C_{19}H_{32}N_5O_5S$ calcd: 442.2 , found: 442.3.

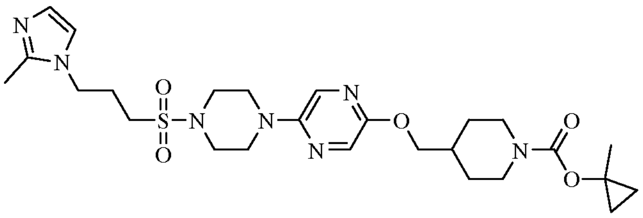
Example M20: 1-Methylcyclopropyl 4-((5-(4-(3-methoxypropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00243] A solution of **M6** (26 mg, 0.049 mmol) in methanol (1 mL) is treated with a 0.5 M solution of sodium methoxide in methanol (0.2 mL, 0.1 mmol) and heated to 65 °C overnight and at 95 °C for 10 hours. The reaction is cooled to room temperature, the

solvent is removed *in vacuo* and the crude residue is purified by silica gel using a linear gradient of 0-80% ethyl acetate in hexane to afford **M20.** ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.86 (d, J = 1.2 Hz, 1H), 7.61 (d, J = 1.6 Hz, 1H), 4.15 (m, 2H), 4.07 (d, J = 6.4 Hz, 2H), 3.49 (m, 6H), 3.42 (m, 4H), 3.33 (s, 3H), 3.04 (m, 2H), 2.74 (t, J = 12.4 Hz, 2H), 2.09 (m, 2H), 1.94 (m, 1H), 1.79 (d, J = 12.4 Hz, 2H), 1.54 (s, 3H), 1.24 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{37}N_5O_6S$ calcd: 511.3, found: 512.2.

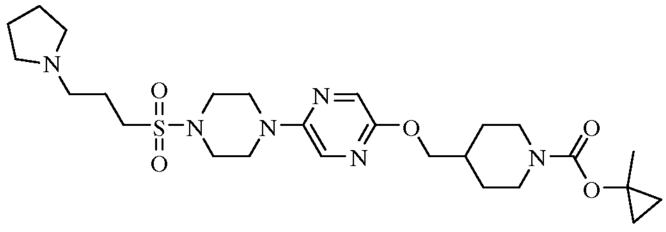
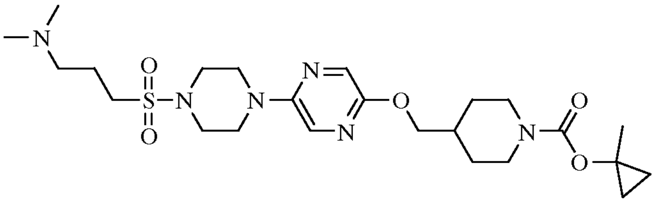
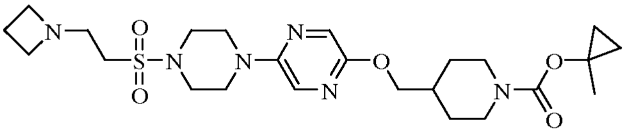
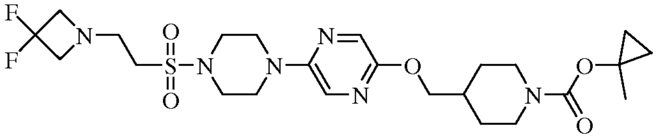
Example M21: 1-Methylcyclopropyl 4-((5-(4-(3-(2-methyl-1H-imidazol-1-yl)propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00244] A solution of **M6** (53 mg, 0.10 mmol) in tetrahydorfuran (1 mL) is treated with 2-methylimidazole (8.5 mg, 0.10 mmol) and heated to 65 °C overnight. The reaction is cooled to room temperature, the solvent is removed *in vacuo* and the crude residue is purified directly *via* a mass-directed HPLC to afford **M21**. ^{1}H NMR (400 MHz, CD$_3$CN) δ 7.86 (d, J = 1.4 Hz, 1H), 7.62 (d, J = 1.4 Hz, 1H), 7.29 (d, J = 2.0 Hz, 1H), 7.18 (d, J = 1.8 Hz, 1H), 4.34 (t, J = 7.0 Hz, 2H), 4.18 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 3.51 (m, 4H), 3.41 (m, 4H), 2.93 (m, 2H), 2.83 (s, 3H), 2.74 (m, 2H), 2.42 (m, 2H), 1.94 (m, 1H), 1.79 (m, 2H), 1.54 (s, 3H), 1.25 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{40}N_7O_5S$ calcd: 562.3 , found: 562.5.

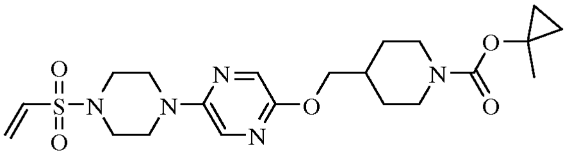
[00245] By following the procedure for **M21** using the appropriate amine nucleophiles, the following examples are obtained:

Example	Structure	Analytical data

M22		^{1}H NMR (400 MHz, CD_3CN) δ 7.85 (d, J = 1.4 Hz, 1H), 7.61 (d, J = 1.5 Hz, 1H), 4.18 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 3.51 (m, 4H), 3.43 (m, 4H), 3.19 (m, 6H), 2.74 (dd, J = 12.4, 12.3 Hz, 2H), 2.36 (m, 2H), 2.08 (m, 5H), 1.94 (m, 2H), 1.79 (m, 2H), 1.54 (s, 3H), 1.25 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{43}N_6O_5S$ calcd: 551.3 , found: 551.5.
M23		^{1}H NMR (400 MHz, CD_3CN) δ 7.85 (d, J = 1.5 Hz, 1H), 7.61 (d, J = 1.5 Hz, 1H), 4.18 (m, 2H), 4.07 (d, J = 6.6 Hz, 2H), 3.51 (m, 4H), 3.44 (m, 4H), 3.18 (m, 2H), 2.98 (m, 2H), 2.74 (dd, J = 12.4, 12.3, Hz, 2H), 2.63 (s, 6H), 2.30 (m, 2H), 1.94 (m, 1H), 1.79 (m, 2H), 1.54 (s, 3H), 1.25 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{41}N_6O_5S$ calcd: 525.3 , found: 525.3.
M-24		^{1}H NMR (400 MHz, CD_3CN) δ 7.86 (d, J = 1.2 Hz, 1H), 7.82 (d, J = 1.6 Hz, 1H), 4.10 (d, J = 6.4 Hz, 2H), 4.07 (m, 2H), 3.55 (m, 2H), 3.41 (m, 2H), 3.15 (t, J = 7.2 Hz, 4H), 3.01 (m, 2H), 2.83 (m, 2H), 2.74 (m, 2H), 1.95 (m, 3H), 1.78 (m, 2H), 1.50 (s, 3H), 1.22 (m, 2H), 0.79 (m, 2H), 0.58 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{38}N_6O_5S$ calcd: 522.3, found: 523.2.
M-25		^{1}H NMR (400 MHz, CD_3CN) δ 7.83 (d, J = 1.2 Hz, 1H), 7.71 (d, J = 1.6 Hz, 1H), 4.06 (d, J = 6.8 Hz, 2H), 4.00 (m, 2H), 3.59 (t, J = 12.4 Hz, 4H), 3.48 (m, 4H), 3.32 (m, 4H), 3.06 (m, 2H), 2.95 (m, 2H), 2.74 (m, 2H), 2.10 (m, 1H), 1.76 (m, 2H), 1.49 (s, 3H), 1.17 (m, 2H), 0.79 (m, 2H), 0.59 (m, 2H);

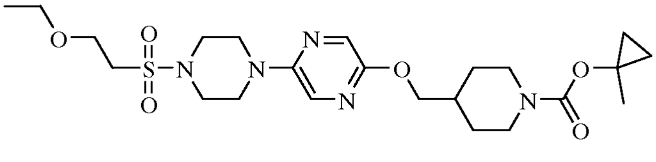
		ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{36}F_2N_6O_5S$ calcd: 558.2, found: 559.2.

Example M26: 1-Methylcyclopropyl 4-((5-(4-(vinylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



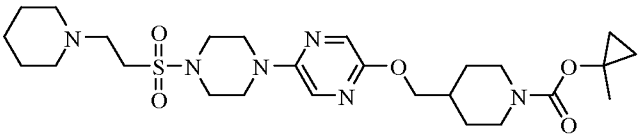
[00246] A solution of **M1c** (308 mg, 0.82 mmol) in tetrahydorfuran (4 mL) is cooled in an ice/water bath and treated with triethylamine (299 mg, 3.0 mmol) followed by 2-chloroethanesulfonyl chloride (401 mg, 2.5 mmol) added over 10 minutes. The reaction is stirred for an hour and then evaporated and partitioned between water and ethyl acetate. The organics are exracted with water twice more, dried over $MgSO_4$, filtered evaporated and purified by silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **M26**; ^{1}H NMR (400 MHz, CD_3CN) δ 7.91 (d, J = 2.9Hz, 1H), 7.15 (dd, J = 9.1, 3.1 Hz, 1H), 6.65 (d, J = 9.1 Hz, 1H), 4.19 (m, 2H), 3.81 (d, J = 6.3 Hz, 2H), 3.54 (m, 4H), 3.34 (m, 4H), 3.08 (ddd, J = 13.1, 2.8, 2.8 Hz, 2H), 2.80 (s, 3H), 2.04 (m, 1H), 1.92 (m, 2H), 1.44 (m, 2H), 1.28 (m, 6H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{32}N_5O_5S$ calcd: 466.2, found: 466.2.

Example M27: 1-Methylcyclopropyl 4-((5-(4-(2-ethoxyethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00247] By following a similar procedure as the one used for preparing **M20** from **M6** except substituting **M26** for **M6**, **M27** is prepared; ^{1}H NMR (400 MHz, CD_3CN) δ 7.86 (d, J = 1.5 Hz, 1H), 7.61 (d, J = 1.5 Hz, 1H), 4.18 (m, 2H), 4.07 (d, J = 6.6 Hz, 2H), 3.80 (t, J = 6.0 Hz, 2H), 3.51 (m, 6H), 3.43 (m, 4H), 3.24 (t, J = 5.9 Hz, 2H), 2.74 (dd, J = 12.3, 12.0 Hz, 2H), 1.94 (m, 1H), 1.79 (m, 2H), 1.54 (s, 3H), 1.23 (m, 2H), 1.17 (t, J = 7.0 Hz, 3H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{38}N_5O_6S$ calcd: 512.3 , found: 512.6.

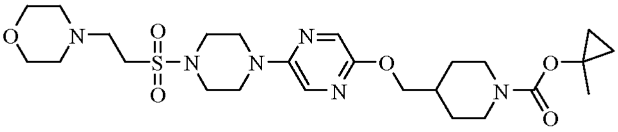
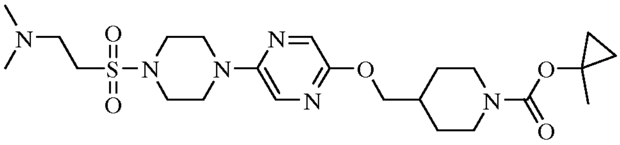
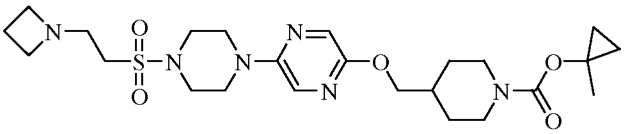
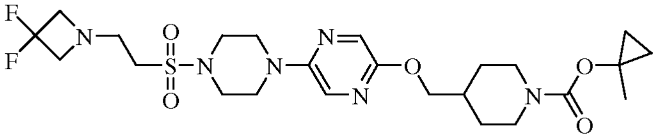
Example M28: 1-Methylcyclopropyl 4-((5-(4-(2-(piperidin-1-yl)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



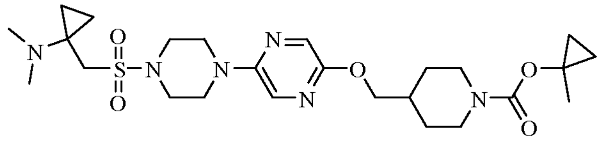
[00248] A solution of **M26** (27 mg, 0.058 mmol) in ethanol (0.5 mL) is treated with piperidine (13.3 mg, 0.12 mmol) and stirred at room temperture overnight. The reaction is diluted with N,N-dimethylformamide and purified directly *via* a mass-directed HPLC to afford **M27**; ^{1}H NMR (400 MHz, CD_3CN) δ 7.87 (d, J = 1.4 Hz, 1H), 7.64 (d, J = 1.4 Hz, 1H), 4.19 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 3.70 (m, 2H), 3.49 (m, 8H), 3.42 (m, 4H), 2.75 (m, 4H), 1.93 (m, 6H), 1.80 (m, 2H), 1.54 (s, 3H), 1.45 (m, 1H), 1.24 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{43}N_6O_5S$ calcd: 551.3, found: 551.3.

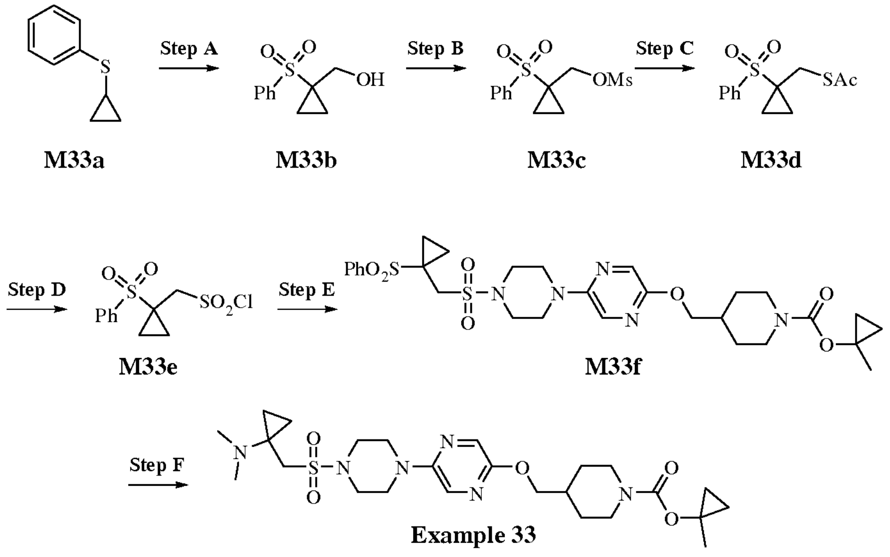
[00249] By following a similar procedure as the one used for preparing **M28** from **M26** except substituting a commercially available amine for piperidine, the following examples are prepared;

Example	Structure	Analytical data

M29		^{1}H NMR (400 MHz, CD_3CN) δ 7.86 (s, 1H), 7.62 (s, 1H), 4.19 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 3.97 (m, 5H), 3.49 (m, 5H), 3.42 (m, 5H), 2.74 (m, 2H), 1.94 (m, 1H), 1.79 (m, 2H), 1.54 (s, 3H), 1.24 (m, 2H), 0.86 (m, 2H), 0.61 (m, 2); ESIMS *m/z* for $(M+H)^+$ $C_{25}H_{41}N_6O_6S$ calcd: 553.3, found: 553.2.
M30		^{1}H NMR (400 MHz, CD_3CN) δ 7.88 (s, 1H), 7.64 (s, 1H), 4.18 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 3.51 (m, 8H), 3.44 (m, 4H), 2.94 (s, 6H), 2.76 (m, 2H), 1.96 (m, 1H), 1.80 (m, 2H), 1.54 (s, 3H), 1.24 (m, 2H), 0.87 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{39}N_6O_5S$ calcd: 511.3, found: 511.2.
M31		^{1}H NMR (400 MHz, CD_3CN) δ 7.86 (d, J = 1.2 Hz, 1H), 7.82 (d, J = 1.6 Hz, 1H), 4.10 (d, J = 6.4 Hz, 2H), 4.07 (m, 2H), 3.55 (m, 2H), 3.41 (m, 2H), 3.15 (t, J = 7.2 Hz, 4H), 3.01 (m, 2H), 2.83 (m, 2H), 2.74 (m, 2H), 1.95 (m, 3H), 1.78 (m, 2H), 1.50 (s, 3H), 1.22 (m, 2H), 0.79 (m, 2H), 0.58 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{38}N_6O_5S$ calcd: 522.3, found: 523.2.
M32		^{1}H NMR (400 MHz, CD_3CN) δ 7.83 (d, J = 1.2 Hz, 1H), 7.71 (d, J = 1.6 Hz, 1H), 4.06 (d, J = 6.8 Hz, 2H), 4.00 (m, 2H), 3.59 (t, J = 12.4 Hz, 4H), 3.48 (m, 4H), 3.32 (m, 4H), 3.06 (m, 2H), 2.95 (m, 2H), 2.74 (m, 2H), 2.10 (m, 1H), 1.76 (m, 2H), 1.49 (s, 3H), 1.17 (m, 2H), 0.79 (m, 2H), 0.59 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{36}F_2N_6O_5S$ calcd: 558.2, found: 559.2.

Example M33: 1-Methylcyclopropyl 4-((5-(4-((1-(dimethylamino)cyclopropyl)methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





[00250] **Step A**: A solution of **M33a** (5.0 g, 33 mmol) in acetic acid (50 mL) is treated with 30% aqueous hydrogen peroxide (7.92 g of solution, 70 mmol) and stirred at 100 °C for 1 hour. The solvent was then removed and the reaction was coevaporated with toluene 3 times.

[00251] A sample of **M33a** (4 g, 22 mmol) in tetrahydrofuran (40 mL) is cooled in an ice/water bath and treated with BuLi in hexane (13.2 mL of a 2 M solution, 26 mmol) and stirred for 20 minutes. The resulting yellow solution is treated with paraformaldehyde (1.65 g, 55 mmol) and allowed to stir for 1 hour. The reaction is then quenched with saturated aqueous ammonium chloride and filtered through a pad of Celite® using ethyl acetate. The organics are isolated, dried over $MgSO_4$, filtered, evaporated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **M33b**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (m, 2H), 7.68 (m, 1H), 7.59 (m, 2H), 3.64 (d, J = 6.4 Hz, 2H), 2.72 (dd, J = 6.4, 6.4 Hz, 1H), 1.64 (m, 2H), 1.07 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{10}H_{13}O_3S$ calcd: 213.1, found: 213.0.

[00252] **Step B**: A solution of **M33b** (4.2 g, 20 mmol) in dichloromethane (40 mL) is treated with triethylamine (3.0 g of solution, 30 mmol), cooled in an ice/water bath and treated methanesulfonyl chloride (2.95 g, 26 mmol). The solution is stirred overnight an allowed to come to room temperature. The reaction is then quenched with aqueous 1 M HCl and extracted with dichloromethane twice. The organics are dried over $MgSO_4$, filtered, evaporated and triturated with diethyl ether to afford **M33c**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (m, 2H), 7.68 (m, 1H), 7.59 (m, 2H), 4.41 (s, 2H), 2.82 (s, 3H), 1.80 (m, 2H), 1.21 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{11}H_{15}O_5S_2$ calcd: 291.0, found: 291.0.

[00253] **Step C**: A solution of **M33c** (3 g, 10 mmol) in N, N-dimethylformide (30 mL) is treated with potassium thioacetate (1.3 g, 11 mmol) and water (20 mL) and stirred at 60 °C overnight. The reaction is diluted with ethyl acetate and extracted with water twice. The organics are isolated, dried over $MgSO_4$, filtered, evaporated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **M33d**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (m, 2H), 7.69 (m, 1H), 7.59 (m, 2H), 3.26 (s, 2H), 2.26 (m, 3H), 1.68 (m, 2H), 1.02 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{12}H_{15}O_3S_2$ calcd: 271.1, found: 271.0.

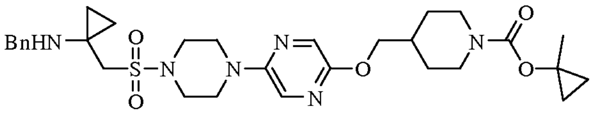
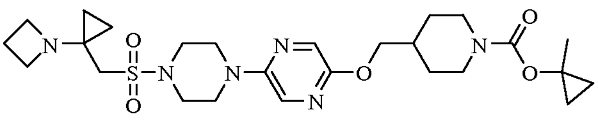
[00254] **Step D**: A cold (ice/water bath) solution of acetonitrile (2.1 mL) and 2 M HCl (419 μL, 0.84 mmol) is treated with NCS (838 mg, 6.27 mmol), allowed to stir for 5 minutes and treated dropwise with a solution of **M33d** (358 mg, 1.6 mmol) in acetonitrile (419 μL). After 30 minutes of stirring, the reaction is diluted with diethyl ether and extracted with brine, water and saturated sodium thiosulfate. The organics are isolated, dried over $MgSO_4$, filtered and to afford **M33e**; ESIMS *m/z* for $(M+H)^+$ $C_{10}H_{12}ClO_4S_2$ calcd: 295.0, found: 294.9.

[00255] **Step E**: A cold (ice/water bath) solution of **M1c** (524 mg, 1.4 mmol) and triethylamine (282 mg, 2.8 mmol) in dichloromethane (5 mL) is treated with a solution of **M33e** (solution of the crude from the last step) in dichlormethane (3 mL). After 2 hours of stirring, the reaction is evaporated and purified silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **M33f**; ESIMS *m/z* for $(M+H)^+$ $C_{29}H_{40}N_5O_7S_2$ calcd: 634.2, found: 634.2.

[00256] **Step F**: A solution of **M33f** (157 mg, 0.25 mmol) in 2 M dimethylamine in tetrahydrofuran (2 mL, 4 mmol) is treated with potassium *tert*-butoxide (28 mg, 0.25 mmol) and stirred for 1 hour. The reaction is evaporated, diluted with methanol and purified directly *via* a mass-directed HPLC to afford **M33;** ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.86 (d, *J* = 1.4 Hz, 1H), 7.61 (d, *J* = 1.4 Hz, 1H), 4.20 (m, 2H), 4.07 (d, *J* = 6.5 Hz, 2H), 3.50 (m, 4H), 3.39 (m, 4H), 3.07 (s, 2H), 2.74 (dd, *J* = 12.4, 12.3 Hz, 2H), 2.37 (s, 6H), 1.94 (m, 1H), 1.79 (m, 2H), 1.55 (s, 3H), 1.25 (m, 2H), 0.93 (m, 2H), 0.86 (m, 4H); ESIMS calcd. for $C_{25}H_{41}N_6O_5S$ $[M+H]^+$ 537.3, found 537.4.

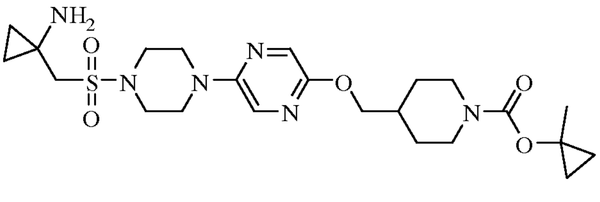
[00257]

[00258] By following the procedure for **M33** using the appropriate amine nucleophiles in step F, the following examples are obtained:

Example	Structure	Analytical data
M34		^{1}H-NMR (400MHz, $CDCl_3$) δ 7.86 (d, *J* = 1.5 Hz, 1H), 7.61 (d, *J* = 1.5 Hz, 1H), 7.31 (m, 5H), 4.14 (m, 2H), 4.09 (d, *J* = 6.5 Hz, 2H), 3.83 (s, 2H), 3.49 (m, 4H), 3.38 (m, 4H), 3.06 (s, 2H), 2.75 (m, 2H), 1.94 (m, 1H), 1.79 (m, 2H), 1.55 (s, 3H), 1.26 (m, 2H), 0.92 (m, 2H), 0.87 (m, 2H), 0.71 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{30}H_{43}N_6O_5S$ $[M+H]^+$ 599.3, found 599.5.
M35		^{1}H-NMR (400MHz, $CDCl_3$) δ 7.86 (d, *J* = 1.4 Hz, 1H), 7.61 (d, *J* = 1.4 Hz, 1H), 3.82-4.21 (m, 6H), 4.07 (d, *J* = 6.5 Hz, 2H), 3.49 (m, 7H), 3.41 (m, 5H), 2.74 (dd, *J* = 12.5, 12.3 Hz, 2H), 1.94 (m, 1H), 1.79 (m, 2H), 1.55 (s, 3H), 1.24 (m, 6H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{26}H_{41}N_6O_5S$ $[M+H]^+$

		549.3, found 549.4.

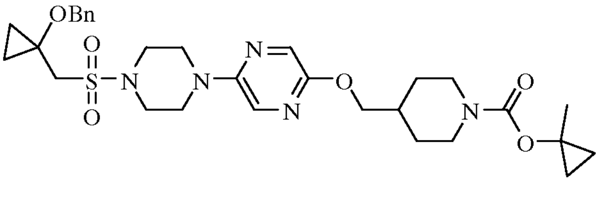
Example M36: 1-Methylcyclopropyl 4-((5-(4-((1-aminocyclopropyl)methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00259] A solution of **M34** (29 mg, 0.048 mmol) in ethanol (1 mL) and acetic acid (0.1 mL) is treated with 10% Pd/C (Degussa type) and hydrogenated at room pressure for 2 hours. The atmosphere is exchanged for nitrogen and the catalyst is removed by filtration through Celite®. The crude material is diluted with methanol and purified directly *via* a mass-directed HPLC to afford **M36;** ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.86 (d, *J* = 1.4 Hz, 1H), 7.61 (d, *J* = 1.4 Hz, 1H), 4.20 (m, 2H), 4.07 (d, *J* = 6.5 Hz, 2H), 3.50 (m, 4H), 3.39 (m, 4H), 3.07 (s, 2H), 2.74 (dd, *J* = 12.4, 12.3 Hz, 2H), 2.37 (s, 6H), 1.94 (m, 1H), 1.79 (m, 2H), 1.55 (s, 3H), 1.25 (m, 2H), 0.93 (m, 2H), 0.86 (m, 4H); ESIMS calcd. for $C_{23}H_{37}N_6O_5S$ $[M+H]^+$ 509.3, found 509.5.

[00260]

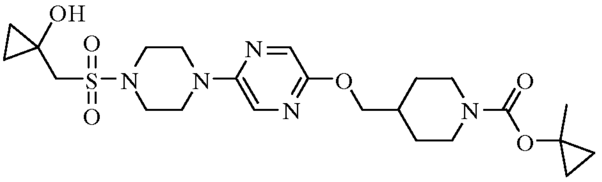
Example M37: 1-methylcyclopropyl 4-((5-(4-((1-(benzyloxy)cyclopropyl)methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00261] A solution of **M33f** (147 mg, 0.23 mmol) in benzyl alcohol (1 mL) is treated with sodium hydride (12 mg, 0.5 mmol) and stirred for 24 hours. The reaction is purified directly *via* a mass-directed HPLC to afford **M37**; ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.84 (d, *J* = 1.4 Hz, 1H), 7.56 (d, *J* = 1.4 Hz, 1H), 7.25 (m, 5H), 4.55 (s, 2H), 4.20 (m, 2H), 4.07 (d, *J* = 6.5 Hz, 2H), 3.46 (m, 8H), 3.31 (s, 2H), 2.75 (dd, *J* = 12.3, 12.3 Hz, 2H), 1.94 (m, 1H), 1.80 (m, 2H), 1.54 (s, 3H), 1.25 (m, 2H), 1.08 (m, 2H), 0.87 (m, 4H), 0.62 (m, 2H); ESIMS calcd. for $C_{30}H_{42}N_5O_6S$ $[M+H]^+$ 600.3, found 600.5.

[00262]

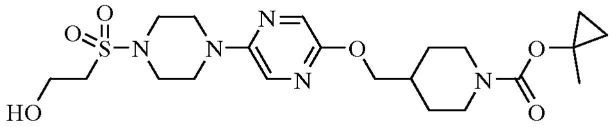
Example M38: 1-Methylcyclopropyl 4-((5-(4-((1-hydroxycyclopropyl)methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.

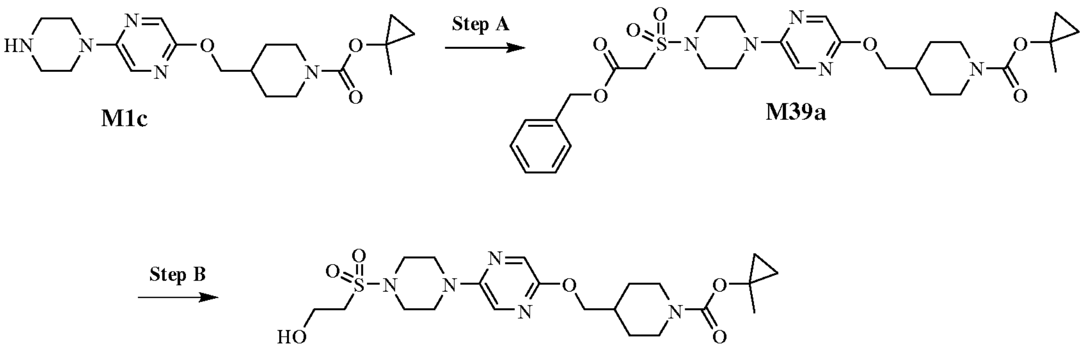


[00263] A solution of **M33f** (11.6 mg, 0.018 mmol) in tetrahydrofuran (0.5 mL) is treated with potassium *tert*-butoxide (2 mg, 0.02 mmol) and stirred for 5 minutes. The reaction is then treated with water (50 μL) and trimethylphosphine (9 μL of a 1 M solution in tetrahydrofuran, 0.009 mmol) and stirred at 45 °C overnight. The reaction is diluted with ethyl acetate and washed with water. The organics are dried over $MgSO_4$, filtered evaporated and purified *via* a mass-directed HPLC to afford **M38**; ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.62 (s, 1H), 4.18 (m, 2H), 4.07 (d, *J* = 6.5 Hz, 2H), 3.51 (m, 8H), 3.21 (s, 2H), 2.75 (dd, *J* = 12.4, 12.4 Hz, 2H), 2.34 (bs, 1H), 1.94 (m, 1H), 1.79 (m, 2H), 1.54 (s, 3H), 1.28 (m, 2H), 1.10 (m, 2H), 0.86 (m, 4H), 0.62 (m, 2H); ESIMS calcd. for $C_{23}H_{36}N_5O_6S$ $[M+H]^+$ 510.2, found 510.4.

[00264]

Example M39: 1-Methylcyclopropyl 4-((5-(4-(2-hydroxyethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate



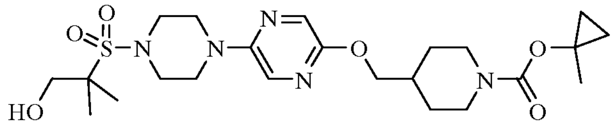


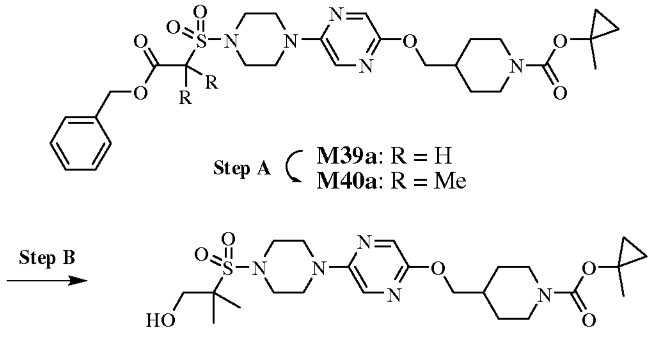
Example M39

Step A: By following a similar procedure as the one used for preparing **M1** from **M1c** except substituting benzyl 2-(chlorosulfonyl)acetate for methyl 3-(chlorosulfonyl)propanoate, **M39a** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{28}H_{38}N_5O_7S$ calcd: 588.3, found: 588.2.

Step B: A solution of **M39a** (20 mg, 0.034 mmol) in methanol (3 mL) is treated with sodium borohydride (13 mg, 0.34 mmol) and heated at 80 °C for 2 hours. The mixture is cooled, diluted with water and extracted with ethyl acetate. The organic layer is washed with brine, dried ($MgSO_4$), filtered, concentrated and purified using mass-triggered reverse phase HPLC to afford **M39**; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 1.6 Hz, 1H), 7.64 (d, J = 1.6 Hz, 1H), 4.11 (s, 4H), 3.54 (m, 4H), 3.47 (m, 4H), 3.21 (m, 2H), 2.77 (m, 2H), 1.96 (m, 1H), 1.82 (m, 2H), 1.57 (s, 3H), 1.28 (m, 2H), 0.89 (m, 2H), 0.65 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{34}N_5O_6S$ calcd: 484.2, found: 484.2.

Example M40: 1-Methylcyclopropyl 4-((5-(4-(1-hydroxy-2-methylpropan-2-ylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



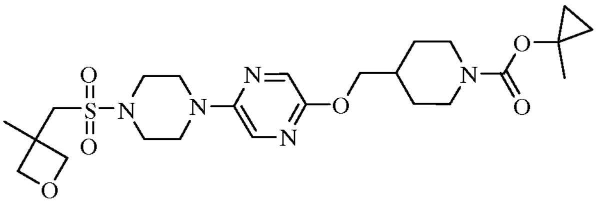


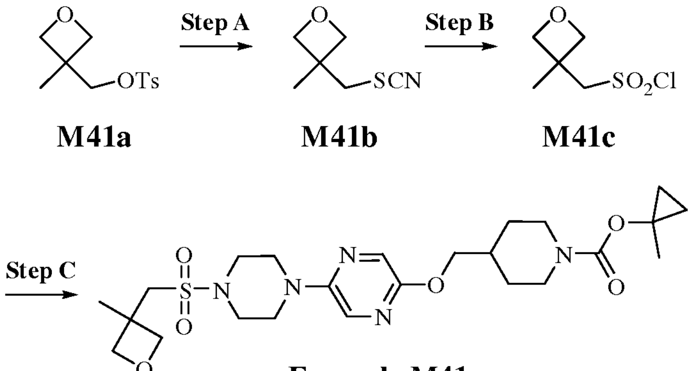
Example M40

Step A: A solution of **M39a** (40 mg, 0.068 mmol) in dimethylformamide (2 mL) is treated with potassium carbonate (50 mg, 0.36 mmol) and methyl iodide (46 mg, 0.32 mmol) and heated to 60 °C for 2 hours. The reaction is then partitioned between ethyl acetate and water. The organics are washed with water and brine, dried over $MgSO_4$, filtered evaporated and used crude for the next step; ESIMS *m/z* for $(M+H)^+$ $C_{30}H_{42}N_5O_7S$ calcd: 616.3, found: 616.3.

By following a similar procedure as the one used for preparing **M39** from **M39a** except substituting **M40a** for **M39a**, **M40** is prepared; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 1.6 Hz, 1H), 7.62 (d, J = 1.6 Hz, 1H), 4.10 (d, J = 6.4 Hz, 2H), 3.75 (s, 2H), 3.59 (m, 4H), 3.48 (m, 4H), 2.76 (m, 2H), 1.97 (m, 1H), 1.81 (m, 2H), 1.57 (s, 3H), 1.40 (m, 6H), 1.27 (m, 2H), 0.89 (m, 2H), 0.64 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{38}N_5O_6S$ calcd: 512.3, found: 512.2.

Example M41: 1-Methylcyclopropyl 4-((5-(4-((3-methyloxetan-3-yl)methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





M41a **M41b** **M41c**

Example M41

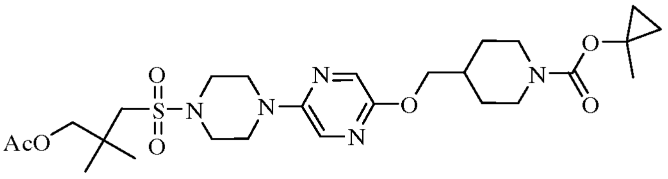
[00265] **Step A**: A solution of **M41a** (1.01 g, 3.9 mmol) in ethanol (25 mL) is treated with potassium thiocyanate (767 mg, 7.9 mmol) and stirred at reflux overnight. The solvent is then removed to afford **M41b** which is used crude. ESIMS *m/z* for $(M+H)^+$ $C_6H_{10}NOS$ calcd: 144.1, found: 144.0.

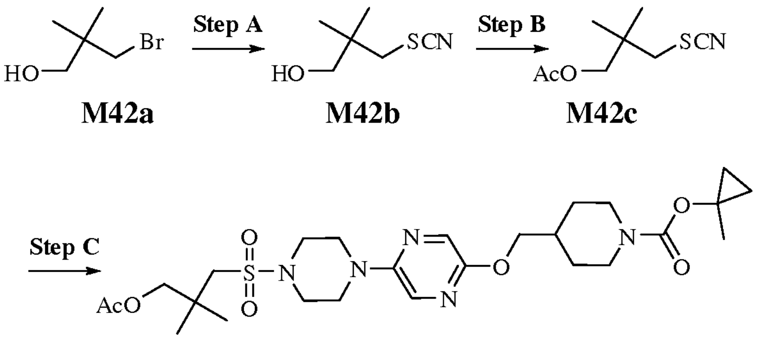
[00266] **Step B:** A suspension of **M41b** (crude from step A) in water (5 mL) is cooled in an ice/water bath and treated with a slow stream of chlorine gas for 30 minutes. The reaction is then extracted with diethyl ether and the organics are washed with saturted aqueous sodium bisulfate solution followed by saturated aqueous sodiumhydrogencarbonate solution. The organics are then dried over Na_2SO_4, filtered and evaporated to afford **M41b** which was used crude in the next reaction; ESIMS *m/z* for $(M+H)^+$ $C_5H_{10}ClO_3S$ calcd: 185.0, found: 185.0.

[00267] **Step C**: By following a similar procedure as the one used for preparing **M1** from **M1c** except substituting **M41c** for methyl 3-(chlorosulfonyl)propanoate, **M41** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.87 (d, *J* = 1.4 Hz, 1H), 7.62 (d, *J* = 1.5 Hz, 1H), 4.64 (d, *J* = 6.3 Hz, 2H), 4.46 (d, *J* = 6.4 Hz, 2H), 4.22 (m, 2H), 4.08 (d, *J* = 6.6 Hz, 2H), 3.53 (m, 4H), 3.40 (m, 4H), 3.25 (s, 2H), 2.74 (dd, *J* = 12.4, 12.4 Hz, 2H), 1.94 (m,

1H), 1.79 (m, 2H), 1.65 (s, 3H), 1.55 (s, 3H), 1.25 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{24}H_{38}N_5O_6S$ $[M+H]^+$ 524.3, found 524.2.

Example M42: 1-Methylcyclopropyl 4-((5-(4-(3-acetoxy-2,2-dimethylpropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





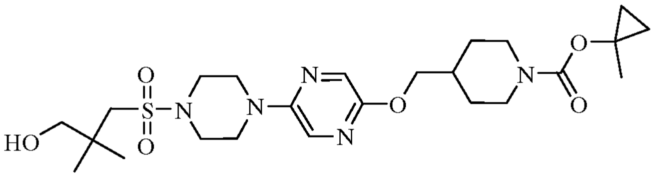
Example M42

[00268] **Step A**: A solution of **M42a** (2 g, 12 mmol) in N,N-dimethylformamide (7.2 mL) is treated with potassium thiocyanate (1.75 g, 18 mmol) and stirred at 140 °C for 4 hours. The reaction is cooled to room temperature and partitioned between diethyl ether and water. The aqueous phase is extracted with diethyl ether once more and discarded. The combined organics are dried over $MgSO_4$, filtered, evaporated and distilled on a Kugelrohr apparatus to afford **M42b**; ESIMS *m/z* for $(M+H)^+$ $C_6H_{12}NOS$ calcd: 146.1, found: 146.1.

[00269] **Step B:** A solution of **M42b** (1.54 g, 10.6 mmol) in pyridine (10 mL) is cooled in an ice/water bath and treated with aetic anhydride (10 mL). The reaction is allowed to stir overnight as the ice bath melts. The solvent is removed and the residue is partitioned between ethyl acetate and water. The organics are washed with 1 M HCl twice and then saturated aqueous sodiumhydrogencarbonate solution. The organics are then dried over $MgSO_4$, filtered and evaporated to afford **M42c** which was used crude in the next reaction; ESIMS *m/z* for $(M+H)^+$ $C_8H_{14}NO_2S$ calcd: 188.1, found: 188.1.

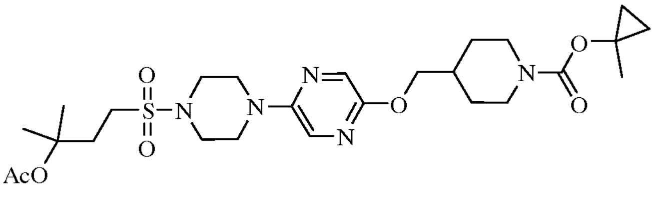
[00270] **Step C**: By following a similar procedure as the one used for preparing **M41** from **M41b** except substituting **M42c** for **M41b**, **M42** is obtained; ^1H NMR (400 MHz, CD_3CN) δ 7.86 (d, J = 1.4 Hz, 1H), 7.61 (d, J = 1.4 Hz, 1H), 4.19 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 4.00 (s, 2H), 3.50 (m, 5H), 3.37 (m, 4H), 2.86 (s, 2H), 2.73 (dd, J = 12.4, 12.3 Hz, 2H), 2.08 (s, 3H), 1.94 (m, 1H), 1.79 (m, 2H), 1.54 (s, 3H), 1.27 (m, 2H), 1.22 (s, 6H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{42}N_5O_7S$ calcd: 568.3 , found: 568.4.

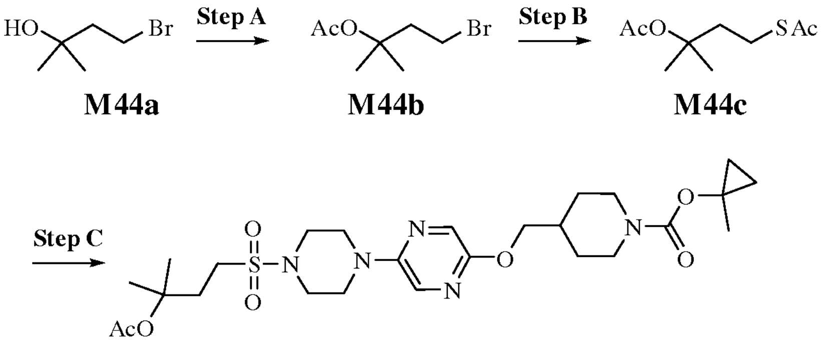
Example M43: 1-Methylcyclopropyl 4-((5-(4-(3-hydroxy-2,2-dimethylpropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00271] **Step A**: A solution of **M42** (48 mg, 0.085 mmol) in tetrahydrofuran (1.5 mL) is treated with lithium hydroxide (7 mg, 0.17 mmol) and stirred for 1 day. The solvent is removed and the residue is purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **M43;** ^1H NMR (400 MHz, CD_3CN) δ 7.89 (d, J = 1.4 Hz, 1H), 7.67 (s, 1H), 4.36 (s, 2H), 4.17 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 3.51 (m, 4H), 3.37 (m, 4H), 2.87 (s, 2H), 2.76 (dd, J = 12.2, 11.6 Hz, 2H), 1.94 (m, 2H), 1.80 (m, 2H), 1.53 (s, 3H), 1.26 (m, 2H), 1.24 (s, 6H), 1.14 (s, 1H), 0.87 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{40}N_5O_6S$ calcd: 526.3 , found: 526.2.

Example M44: 1-Methylcyclopropyl 4-((5-(4-(3-acetoxy-3-methylbutylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





M44a **M44b** **M44c**

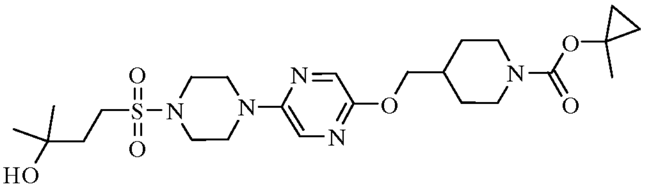
Example M44

[00272] **Step A**: A solution of **M44a** (1.48 g, 8.9 mmol) in dichloromethane (49 mL) is cooled in an ice/water bath and treated with pyridine (913 mg, 12mmol) and acetyl chloride (868 mg, 11 mmol) and the reaction is allowed to stir overnight as the ice bath melts. The reaction is then quenched with water. The organic phase is isolated, dried over $MgSO_4$, filtered, evaporated and the residue is purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **M44b**; A satisfactory ESIMS could not be obtained.

[00273] **Step B:** A solution of **M44b** (750 mg, 3.6 mmol) in N,N-dimethylfromamide (10 mL) is cooled in an ice/water bath and treated with potassium thioacetate (410 mg, 3.6 mmol). The reaction is stirred overnight and partitioned between ethyl acetate and water. The organics are extracted with water once more, dried over $MgSO_4$, filtered and evaporated to afford **M44c** which is used in the next step crude; ESIMS *m/z* for $(M+Na)^+$ $C_9H_{16}NaO_3S$ calcd: 227.1, found: 227.0.

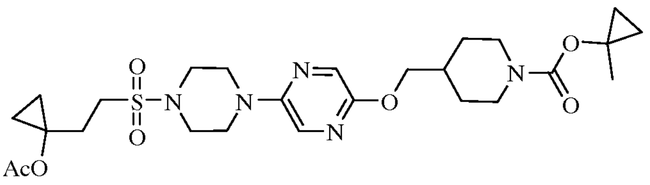
[00274] **Step C**: By following a similar procedure as the one used for preparing **M32** from **M32d** except substituting **M44c** for **M32d**, **M44** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.86 (d, *J* = 1.4 Hz, 1H), 7.61 (d, *J* = 1.5 Hz, 1H), 4.20 (m, 2H), 4.07 (d, *J* = 6.5 Hz, 2H), 3.50 (m, 4H), 3.44 (m, 4H), 3.02 (m, 2H), 2.74 (dd, *J* = 13.2, 12.6 Hz, 2H), 2.22 (m, 2H), 1.98 (s, 3H), 1.96 (m, 1H), 1.80 (m, 2H), 1.55 (s, 3H), 1.48 (s, 6H), 1.25 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{24}H_{38}N_5O_5S$ $[M-OAc]^+$ 508.3, found 508.4.

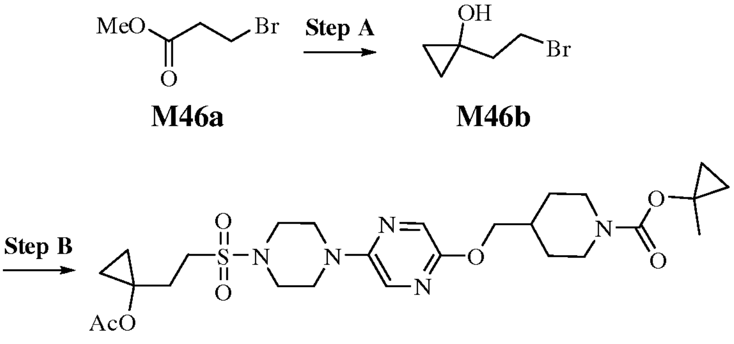
Example M45: 1-Methylcyclopropyl 4-((5-(4-(3-hydroxy-3-methylbutylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



A solution of **M44** (199 mg, 0.35 mmol) in methanol (3.9 mL) is treated with NaOMe (1.1 mL of a 6.4M solution, 7 mmol) and stirred for 2.5 hours. The reaction is quenched with saturated aqueous ammonium chloride and the solvent is removed. The residue is dissolved in dichloromethane and washed with water, dried over $MgSO_4$, filtered, evaporated and the residue is purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **M45**; ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.86 (d, *J* = 1.5 Hz, 1H), 7.62 (d, *J* = 1.5Hz, 1H), 4.20 (m, 2H), 4.07 (d, *J* = 6.5 Hz, 2H), 3.50 (m, 4H), 3.44 (m, 4H), 3.09 (m, 2H), 2.74 (dd, *J* = 12.9, 12.7 Hz, 2H), 1.92-2.01 (m, 3H), 1.79 (m, 2H), 1.55 (s, 3H), 1.27 (m, 8H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{24}H_{40}N_5O_6S$ $[M+H]^+$ 526.3, found 526.2.

Example M46: 1-Methylcyclopropyl 4-((5-(4-(2-(1-acetoxycyclopropyl)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





M46a **M46b**

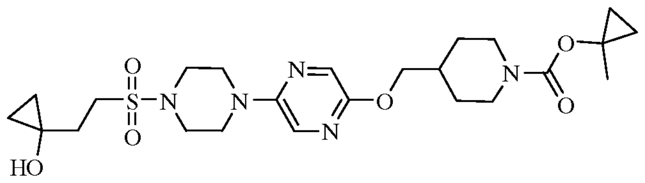
Example M46

[00275] **Step A**: A solution of **M46a** (1.99 g, 12 mmol) in diethyl ether (40 mL) is treated with titanium(IV)isopropoxide (369 mg, 1.2 mmol) followed by dropwise addition of ethylmagnesium bromide (8.8 mL of a 3 M solution in diethyl ether, 26 mmol). The reaction is quenched into ice cold 10% sulfuric acid and the aqueous phase is extracted with ether once more. The combined organics are dried over $MgSO_4$, filtered, evaporated and the residue is purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **M46b**; ^{1}H-NMR (400MHz, $CDCl_3$) δ 3.60 (dd, *J* = 7.3, 7.3 Hz, 2H), 2.41 (s, 1H), 2.10 (dd, *J* = 7.3, 7.3 Hz, 2H), 0.78 (m, 2H), 0.52 (m, 2H); A satisfactory ESIMS spectrum could not be obtained.

[00276] **Step B**: By following a similar procedure as the one used for preparing **M33** from **M33c** except substituting **M46b** for **M33c**, **M46** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.86 (d, *J* = 1.4 Hz, 1H), 7.61 (d, *J* = 1.4 Hz, 1H), 4.20 (m, 2H), 4.07 (d, *J* = 6.5 Hz, 2H), 3.49 (m, 4H), 3.41 (m, 4H), 3.11 (ddd, *J* = 8.2, 5.2, 5.2 Hz, 2H), 2.74 (dd, *J* = 12.2, 12.0 Hz, 2H), 2.25 (ddd, J = 8.2, 4.7, 4.7 Hz, 2H), 2.00 (s, 3H), 1.94 (m, 1H), 1.79 (m, 2H), 1.54 (s, 3H), 1.25 (m, 2H), 0.93 (m, 2H), 0.86 (m, 2H), 0.76 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{26}H_{40}N_5O_7S$ $[M+H]^+$ 566.3, found 566.4.

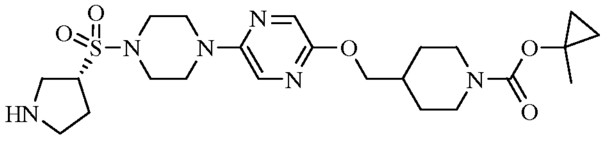
[00277]

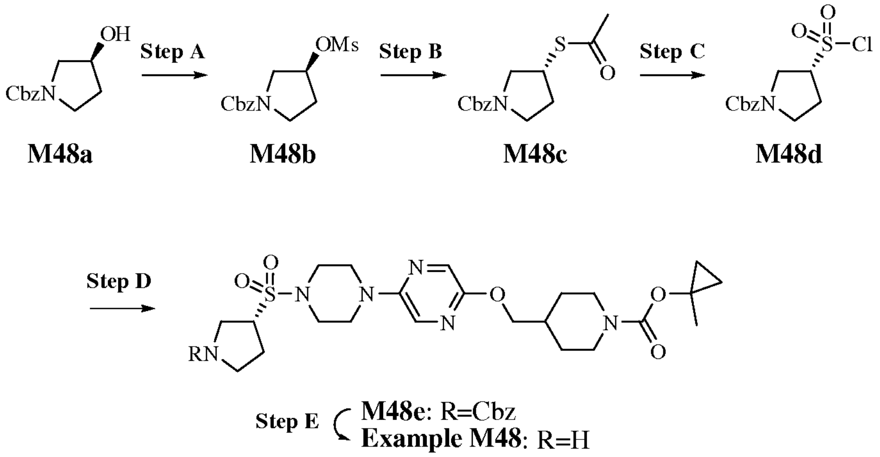
Example M47: 1-Methylcyclopropyl 4-((5-(4-(2-(1-hydroxycyclopropyl)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



By following a similar procedure as the one used for preparing **M43** from **M42** except substituting **M46** for **M42**, **M47** is prepared; ^{1}H-NMR (400MHz, CDCl$_3$) δ 7.87 (d, *J* = 1.5 Hz, 1H), 7.62 (d, *J* = 1.4 Hz, 1H), 4.19 (m, 2H), 4.08 (d, *J* = 6.5 Hz, 2H), 3.51 (m, 4H), 3.43 (m, 4H), 3.21 (m, 2H), 2.74 (dd, *J* = 12.3, 12.3 Hz, 2H), 2.27 (bs, 1H), 2.08 (m, 2H), 1.94 (m, 1H), 1.79 (m, 2H), 1.55 (s, 3H), 1.25 (m, 2H), 0.86 (m, 4H), 0.62 (m, 2H), 0.56 (m, 2H); ESIMS calcd. for $C_{24}H_{38}N_5O_6S$ [M+H]$^+$ 524.3, found 524.5.

Example M48: (R)-1-methylcyclopropyl 4-((5-(4-(pyrrolidin-3-ylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate





M48a **M48b** **M48c** **M48d**

M48e: R=Cbz
Example M48: R=H

Step A: A solution of **M48a** (10 g, 45.2 mmol) in dichloromethane (200 mL) is cooled in an ice/water bath and treated with diisopropylethylamine (9.4 mL, 54.3 mmol) followed by dropwise addition of methanesulfonyl chloride (3.8 mL, 50 mmol). The resulting solution is stirred at 0 °C for 1 hour, concentrated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **M48b**; ESIMS *m/z* for $(M+H)^+$ $C_{13}H_{18}NO_5S$ calcd: 300.1, found: 300.0.

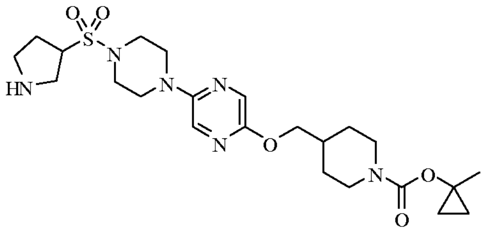
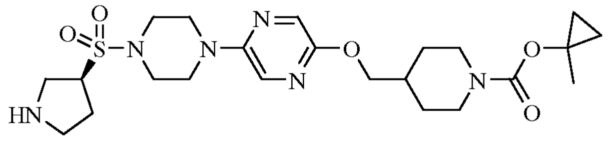
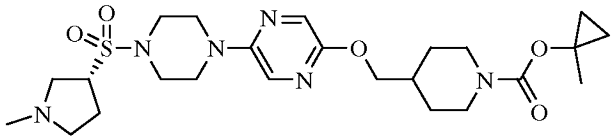
Step B: A solution of **M48b** (14.1 g, 45 mmol) and thiolacetic acid (6.4 mL, 90 mmol) in dimethylformamide (200 mL) is treated with Cs_2CO_3 (30 g, 90 mmol) and heated at 60 °C for 14 hours. The mixture is diluted with water and extracted with ethyl acetate (3x). The organic layers are combined, washed with water (2x) and brine, dried over $MgSO_4$, filtered, concentrated, and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **M48c**; ESIMS *m/z* for $(M+H)^+$ $C_{14}H_{18}NO_3S$ calcd: 280.1, found: 280.0.

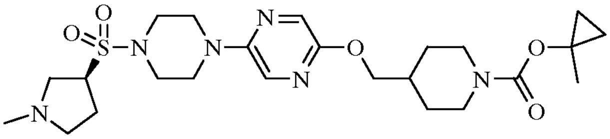
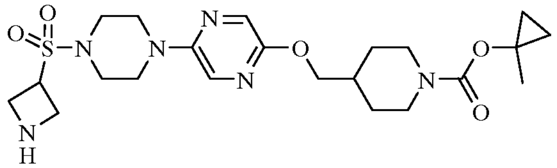
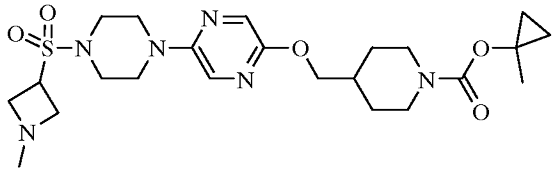
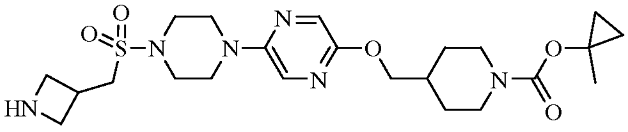
Step C: A solution of N-chlorosuccinimide (16.7 g, 125 mmol) in 2N HCl (24 mL) and acetonitrile (120 mL) is cooled in an ice/water bath and treated dropwise with a solution of **M48c** (9.2 g, 31 mmol) in acetonitrile (20 mL) over 1 hour. The solution is concentrated and partitioned between ethyl acetate and a saturated aqueous sodiumhydrogencarbonate solution. The organic layer iss washed with aqueous sodium thiosulfate and brine, dried ($MgSO_4$), filtered and concentrated to provide **M48d** as a golden oil; ESIMS *m/z* for $(M+H)^+$ $C_{12}H_{15}ClNO_4S$ calcd: 304.0, found: 304.0.

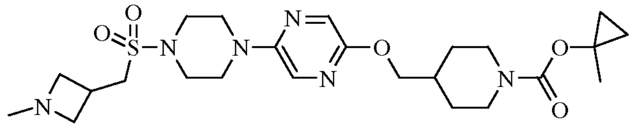
Step D: A solution of **M1c** (74 mg, 0.2 mmol) and **M48d** (67 mg, 0.22 mmol) in dichloromethane (5 mL) is treated with diisopropylethylamine (69 μL, 0.4 mmol) and stirred at room temperature for 3 hours. The mixture is concentrated and purified on silica gel using 0-100% ethyl acetate in hexane to afford **M48e**; ESIMS *m/z* for $(M+H)^+$ $C_{31}H_{43}N_6O_7S$ calcd: 643.3, found: 643.2.

Step E: A solution of **M48e** (104 mg, .16 mmol) in methanol (10 mL) is treated with Pd/C (10%, wet) and stirred under 1 atm H_2 for 14 hours. The mixture is filtered through Celite®, concentrated, and purified on silica gel using 0-10% MeOH in dichloromethane to afford **M48**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 1.2 Hz, 1H), 7.54 (d, J = 1.2 Hz, 1H), 4.01 (d, J = 4.8 Hz, 2H), 3.52 (m, 1H), 3.40 (m, 9H), 3.14 (m, 1H), 3.07 (dd, J = 5.2, 8.4 Hz, 1H), 2.80 (m, 1H), 2.67 (m, 2H), 2.08 (m, 2H), 1.98 (s, 2H), 1.87 (m, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.18 (m, 2H), 0.79 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{37}N_6O_5S$ calcd: 509.3, found: 509.2.

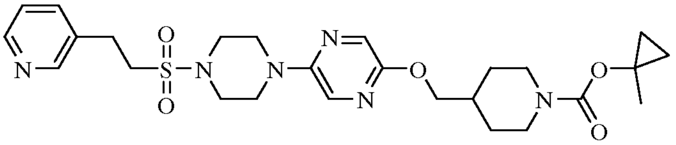
[00278] By following the procedure for making **M48** from **M48a** using the appropriate commercially available starting alcohols in place of **M48a** and in some cases performing reductive methylations, the following examples are prepared;

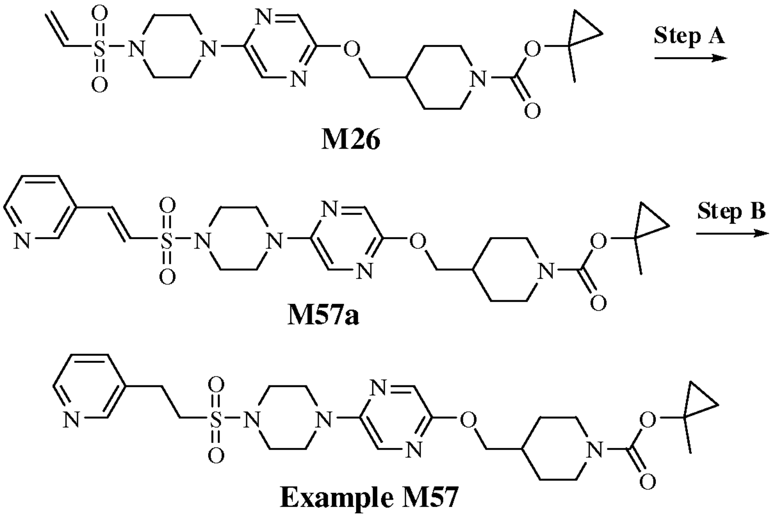
Example	Structure	Analytical data
M49		^{1}H NMR (400 MHz, CD_3CN) δ 7.82 (d, J = 1.6 Hz, 1H), 7.70 (d, J = 1.6 Hz, 1H), 4.06 (d, J = 6.8 Hz, 2H), 4.00 (m, 2H), 3.63 (m, 1H), 3.46 (m, 4H), 3.36 (m, 4H), 3.12 (m, 2H), 2.95 (m, 1H), 2.77 (m, 3H), 2.10 (m, 5H), 1.76 (m, 2H), 1.73 (s, 3H), 1.18 (m, 2H), 0.79 (m, 2H), 0.59 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{37}N_6O_5S$ calcd: 509.3, found: 509.2.
M50		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 0.8 Hz, 1H), 7.54 (d, J = 0.8 Hz, 1H), 4.01 (d, J = 4.8 Hz, 2H), 3.53 (m, 1H), 3.40 (m, 9H), 3.14 (m, 1H), 3.08 (dd, J = 5.2, 8.4 Hz, 1H), 2.81 (m, 1H), 2.68 (m, 2H), 2.08 (m, 2H), 2.00 (s, 2H), 1.87 (m, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.18 (m, 2H), 0.79 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{37}N_6O_5S$ calcd: 509.3, found: 509.2.
M51		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 1.2 Hz, 1H), 7.54 (d, J = 1.2 Hz, 1H), 4.01 (d, J = 4.8 Hz, 2H), 3.64 (m, 1H), 3.40 (m, 8H), 2.87 (m, 1H), 2.73 (m, 1H), 2.67 (m, 2H), 2.61 (m, 1H), 2.31 (s, 3H), 2.00 (m, 2H), 1.98 (s, 2H), 1.72 (m, 2H), 1.48 (s, 3H), 1.18 (m, 2H), 0.79 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for

		$(M+H)^+$ $C_{24}H_{39}N_6O_5S$ calcd: 523.3, found: 523.2.
M52		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 1.2 Hz, 1H), 7.54 (d, J = 1.2 Hz, 1H), 4.01 (d, J = 4.8 Hz, 2H), 3.64 (m, 1H), 3.40 (m, 8H), 2.87 (m, 1H), 2.73 (m, 1H), 2.67 (m, 2H), 2.61 (m, 1H), 2.31 (s, 3H), 2.00 (m, 2H), 1.98 (s, 2H), 1.72 (m, 2H), 1.48 (s, 3H), 1.18 (m, 2H), 0.79 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{39}N_6O_5S$ calcd: 523.3, found: 523.2.
M53		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 1.0 Hz, 1H), 7.53 (d, J = 1.0 Hz, 1H), 4.09 (m, 1H), 4.05 (m, 2H), 4.01 (d, J = 4.4 Hz, 2H), 3.40 (m, 4H), 3.38 (m, 4H), 2.67 (m, 2H), 1.94 (br s, 1H), 1.87 (m, 1H), 1.71 (m, 2H), 1.48 (s, 3H), 1.18 (m, 2H), 0.79 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{35}N_6O_5S$ calcd: 495.2, found: 495.2.
M54		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 0.8 Hz, 1H), 7.53 (d, J = 0.8 Hz, 1H), 4.00 (d, J = 4.4 Hz, 2H), 3.85 (m, 1H), 3.57 (m, 2H), 3.41 (m, 4H), 3.34 (m, 4H), 2.67 (m, 2H), 2.29 (s, 3H), 1.87 (m, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.18 (m, 2H), 0.79 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{37}N_6O_5S$ calcd: 509.3, found: 509.2.
M55		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 1.4 Hz, 1H), 7.53 (d, J = 1.4 Hz, 1H), 4.01 (d, J = 6.8 Hz, 2H), 3.75 (m, 2H), 3.43 (m, 6H), 3.33 (m, 4H), 3.16 (m, 2H), 2.67 (m, 2H), 1.87 (m, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.18 (m, 3H), 0.79 (m, 2H), 0.54 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{37}N_6O_5S$ calcd: 509.3, found: 509.2

M56		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 1.6 Hz, 1H), 7.53 (d, J = 1.6 Hz, 1H), 4.01 (d, J = 6.8 Hz, 2H), 3.42 (m, 6H), 3.33 (m, 4H), 3.14 (d, J = 7.2 Hz, 2H), 2.98 (m, 2H), 2.69 (m, 2H), 2.25 (s, 3H), 1.87 (m, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.18 (m, 3H), 0.80 (m, 2H), 0.54 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{39}N_6O_5S$ calcd: 523.3, found: 523.2

Example M57: 1-Methylcyclopropyl 4-((5-(4-(2-(pyridin-3-yl)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate





M26

M57a

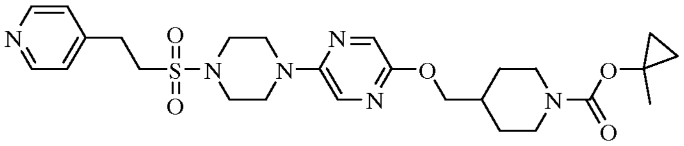
Example M57

[00279] **Step A:** A sealed vessel containing **M26** (50 mg, 0.11 mmol), 3-bromopyridine (10 μL, 0.11 mmol), Pd_2dba_3 (3.0 mg, 0.0032 mmol), tri-t-butylphosphonium tetrafluoroborate (2.0 mg, 0.0064 mmol), dicyclohexylmethylamine (45 mL, 0.21 mmol), and dioxane (1 mL) is heated at 120 °C overnight. The reaction is

cooled to room temperature and is diluted with water and extracted with ethyl acetate. The organic phase is dried over $MgSO_4$, filtered, evaporated, and purified on silica gel using a linear gradient of 0 to 100% ethyl acetate in dichloromethane to afford **M57a**; ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{34}N_6O_5S$ calcd: 543.2 , found: 543.2.

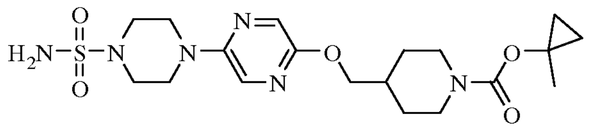
[00280] **Step B:** A solution of **M57a** from the previous step in ethanol (1mL) is sparged with H_2 (g) for 30 minutes and then left under an atmosphere of H_2 (g) overnight. The reaction is filtered over Celite®, concentrated, and purified by mass directed HPLC using a linear gradient of 10 to 90% acetonitrile in water to afford **M57**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.79 (s, 1H), 8.65 (m, 1H), 8.09 (m, 1H), 7.86 (d, J = 1.4 Hz, 1H), 7.68 (m, 1H), 7.61 (d, J = 1.4 Hz, 1H), 4.20 (m, 2H), 4.08 (d, J = 6.5 Hz, 2H), 3.50 (m, 4H), 3.42 (m, 2H), 3.33 (m, 2H), 3.24 (m, 2H), 2.74 (m, 2H), 1.79 (m, 2H), 1.55 (s, 3H), 1.25 (m, 3H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{37}N_6O_5S$ calcd.: 545.3, found: 545.3.

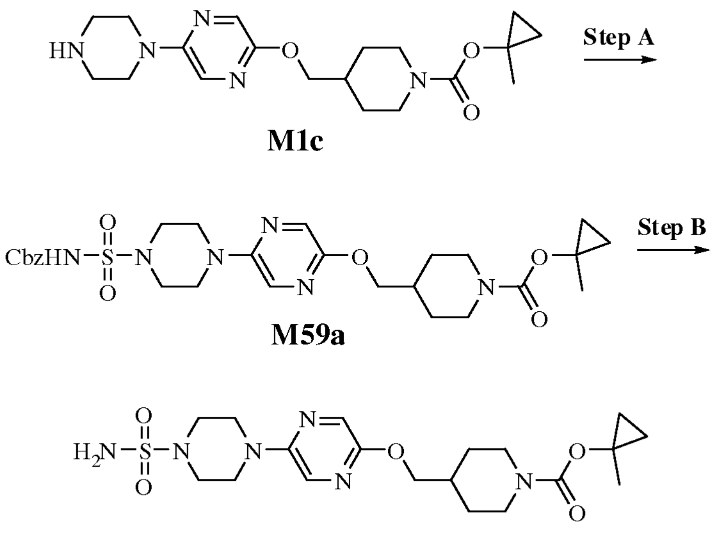
Example M58: 1-Methylcyclopropyl 4-((5-(4-(2-(pyridin-4-yl)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate



[00281] By following a similar procedure as for the preparation of **M57** from **M26** except substituting 4-bromopyridine for 3-bromopyridine, **M58** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.80 (s, 2H), 7.87 (s, 1H), 7.74 (s, 2H), 7.63 (s, 1H), 4.20 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 3.50 (m, 4H), 3.43 (m, 4H), 3.40 (m, 2H), 3.26 (m, 2H), 2.74 (m, 2H), 1.94 (m, 1H), 1.78 (m, 2H), 1.54 (s, 3H), 1.24 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{37}N_6O_5S$ calcd.: 545.3, found: 545.4.

Example M59: 1-Methylcyclopropyl 4-((5-(4-sulfamoylpiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate



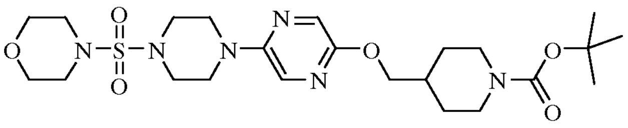


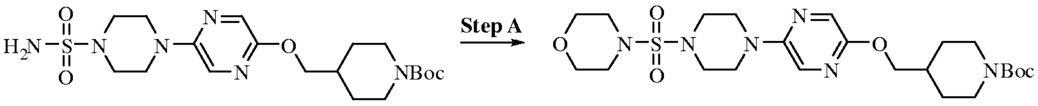
Example M59

[00282] **Step A:** A solution of chlorosulfonyl isocyanate (230 μL, 2.65 mmol) in *n*-hexanes (2.4 mL) is added dropwise to a solution **M1c** (1.0g, 2.7 mmol) in *n*-hexanes (5 mL) and stirred at room temperature for 45 minutes. A solution of benzyl alcohol (274μL, 2.65 mmol) and triethylamine (554 μL, 3.97 mmol) in tetrahydrofuran (10 mL) is then introduced dropwise. After 2 hr., the reaction is treated with water and extracted with dichloromethane. The organic phase is dried ($MgSO_4$), filtered, evaporated and chromatographed on silica gel using a linear gradient of 0 to 100% ethyl acetate in dichloromethane to afford **M59a**. ESIMS *m/z* for $(M+H)^+$ $C_{27}H_{37}N_6O_7S$ calcd.: 589.2, found: 589.3.

[00283] **Step B:** A solution of **M59a** (300 mg, 0.509mmol) in ethanol (5 mL) is treated with 5% Pd/C (30 mg) and subjected to a H_2 (g) flush for 30 minutes. The reaction is left under an atmosphere of H_2 (g) overnight and is then filtered over Celite® and concentrated to afford **M59**; ESIMS *m/z* for $(M+H)^+$ $C_{19}H_{31}N_6O_5S$ calcd.: 455.2, found: 455.3.

Example M60: *tert*-Butyl 4-((5-(4-(morpholinosulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate

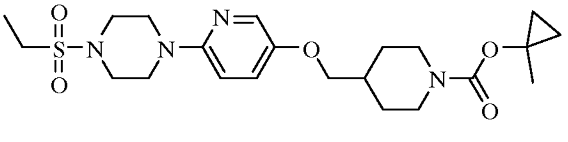


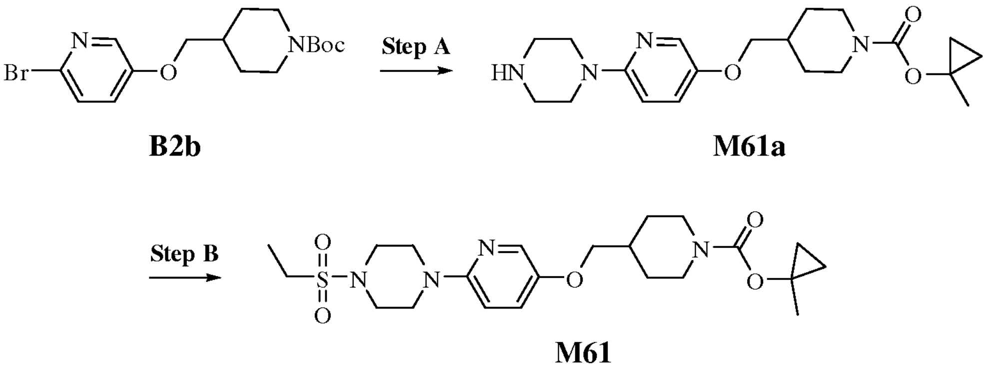


M60a **Example 60**

[00284] A sample of **M60a** is prepared in an analogous manner to **M30**. A microwave reaction vial is charged **M60a** (64 mg, 0.14 mmol), 2-bromoethyl ether (18 µL, 0.14 mmol), potassium carbonate (40 mg, 0.28 mmol) and N,N-dimethylformamide (2 mL), sealed and heated to 150 °C for 5 minutes *via* microwave. The reaction is cooled to room temperature and poured over water and extracted with ethyl acetate. The organic phase is dried ($MgSO_4$), filtered, evaporated, and purified on silica gel using a linear gradient of 0 to 100% ethyl acetate in hexane to afford **M60**; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.95 (s, 1H), 7.91 (s, 1H), 4.16 (m, 2H), 4.11 (d, $J = 6.5$ Hz, 2H), 3.74 (m, 4H), 3.53 (m, 6H), 3.44 (m, 1H), 3.27 (m, 5H), 2.73 (m, 2H), 1.96 (m, 1H), 1.78 (m, 2H), 1.46 (s, 9H), 1.26 (m, 2H). ESIMS *m/z* for $(M+H-CO_2{}^tBu)^+$ $C_{18}H_{31}N_6O_4S$ calcd.: 427.2, found: 427.2.

Example M61: 1-Methylcyclopropyl 4-((6-(4-(ethylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate





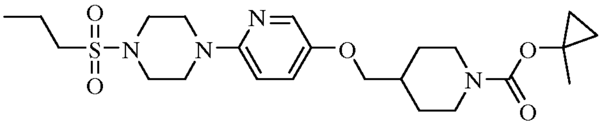
B2b **M61a**

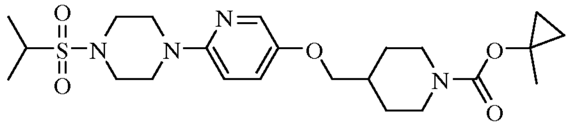
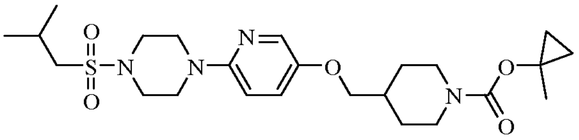
M61

[00285] **Step A:** By following a similar procedure as for the one used for the preparation of **M1c** from **B12a** except substituting **B2b** for **B12a**, **M61a** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{31}N_4O_3$ calcd.: 375.2, found: 375.2.

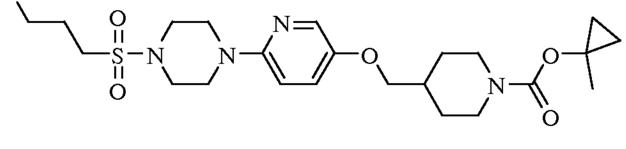
Step A: By following a similar procedure as the one used for preparing **M1** from **M1c** except substituting **M61a** for **M1c** and ethanesulfonyl chloride for methyl 3-(chlorosulfonyl)propanoate, **M61** is prepared; ^{1}H NMR (400 MHz, CD_3CN) δ 7.80 (m, 1H), 7.26 (m, 1H), 6.65 (m, 1H), 4.05 (m, 2H), 3.70 (d, J = 6.3 Hz, 2H), 3.52 (m, 3H), 3.37 (m, 4H), 3.21 (m, 1H), 2.92 (m, 2H), 2.67 (dd, J = 12.4, 12.4 Hz, 2H), 1.86 (m, 1H), 1.72 (m, 2H), 1.47 (s, 3H), 1.31 (t, J = 7.3 Hz, 3H), 1.17 (m, 2H), 0.79 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{35}N_4O_5S$ calcd: 467.2 , found: 467.2.

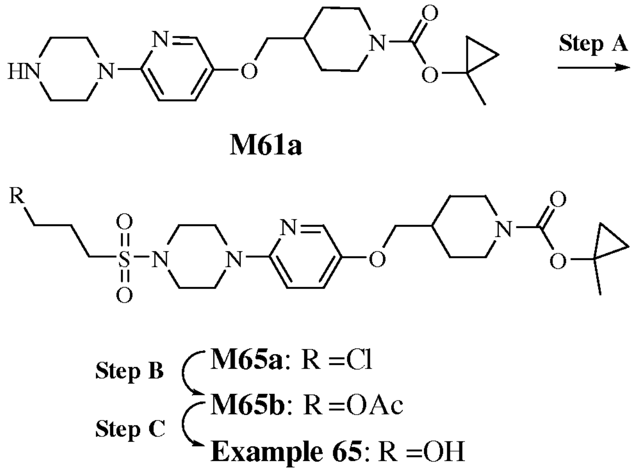
[00286] By following a similar procedure as for the one used for the preparation of **M61** from **M61a** except substituting commercially available sulfonyl chlorides for **M61a**, the following examples are obtained:

Example	Structure	Analytical data
M62		^{1}H NMR (400 MHz, CD_3CN) δ 7.88 (m, 1H), 7.24 (m, 1H), 6.71 (m, 1H), 4.13 (m, 2H), 3.78 (d, J = 6.3 Hz, 2H), 3.59 (m, 3H), 3.43 (m, 4H), 3.28 (m, 1H), 2.91 (m, 2H), 2.74 (dd, J = 12.2, 12.1 Hz, 2H), 1.89 (m, 3H), 1.80 (m, 2H), 1.55 (s, 3H), 1.24 (m, 2H), 1.07 (t, J = 7.4 Hz, 3H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for

		$(M+H)^+$ $C_{23}H_{37}N_4O_5S$ calcd: 481.2 , found: 481.2.
M63		^{1}H NMR (400 MHz, CD_3CN) δ 7.89 (d, J = 2.8 Hz, 1H), 7.24 (m, 1H), 6.67 (d, J = 8.9 Hz, 1H), 4.12 (m, 2H), 3.77 (d, J = 6.3 Hz, 2H), 3.50 (m, 8H), 3.22 (sept., J = 6.8 Hz, 1H), 2.74 (dd, J = 12.4, 12.3 Hz, 2H), 1.93 (m, 1H), 1.80 (m, 2H), 1.55 (s, 3H), 1.36 (d, J = 6.9 Hz, 6H), 1.23 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{37}N_4O_5S$ calcd: 481.2 , found: 481.2.
M64		^{1}H NMR (400 MHz, CD_3CN) δ 7.88 (m, 1H), 7.24 (m, 1H), 6.71 (m, 1H), 4.13 (m, 2H), 3.78 (d, J = 6.3 Hz, 2H), 3.59 (m, 3H), 3.40 (m, 4H), 3.29 (m, 1H), 2.77 (d, J = 6.6 Hz, 2H), 2.74 (dd, J = 12.6, 12.6 Hz, 2H), 2.31 (m, 1H), 1.94 (m, 1H), 1.80 (m, 2H), 1.55 (s, 3H), 1.24 (m, 2H), 1.12 (d, J = 6.7 Hz, 6H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{39}N_4O_5S$ calcd: 495.3 , found: 495.3.

Example M65: 1-Methylcyclopropyl 4-((6-(4-(3-hydroxypropylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate





M61a

M65a: R =Cl

M65b: R =OAc

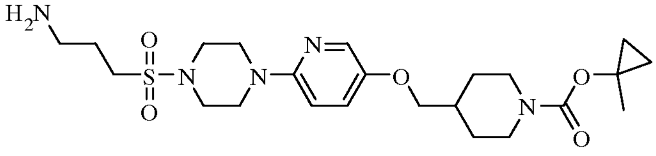
Example 65: R =OH

[00287] **Step A:** By following a similar procedure as for the one used for the preparation of **M6** from **M1c** except substituting **M61a** for **M1c**, **M65a** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{36}ClN_4O_5S$ calcd.: 515.2, found: 515.2.

Step B: By following a similar procedure as the one used for preparing **M19** from **M5** except substituting **M65a** for **M5**, **M65b** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{25}H_{39}N_4O_7S$ calcd: 539.3 , found: 539.2.

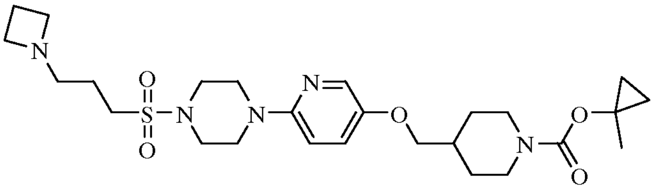
Step C: By following a similar procedure as the one used for preparing **M43** from **M42** except substituting **M65b** for **M42**, **Example 65** is prepared; ^1H NMR (400 MHz, CD_3CN) δ 7.88 (d, J = 3.0 Hz, 1H), 7.19 (dd, J = 9.2, 2.8 Hz, 1H), 6.68 (d, J = 9.1 Hz, 1H), 4.11 (m, 2H), 3.77 (m, 4H), 3.55 (m, 4H), 3.41 (m, 4H), 3.08 (m, 2H), 2.74 (dd, J = 12.3, 12.3 Hz, 2H), 2.08 (m, 2H), 1.92 (m, 2H), 1.80 (m, 2H), 1.54 (s, 3H), 1.24 (m, 2H), 0.85 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{37}N_4O_6S$ calcd: 497.2 , found: 497.3.

Example M66: 1-Methylcyclopropyl 4-((6-(4-(3-aminopropylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate



[00288] By following a similar procedure as for the one used for the preparation of **M18** from **M16** except substituting **M65a** for **M16**, **M66** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{38}N_5O_5S$ calcd: 496.3 , found: 496.3.

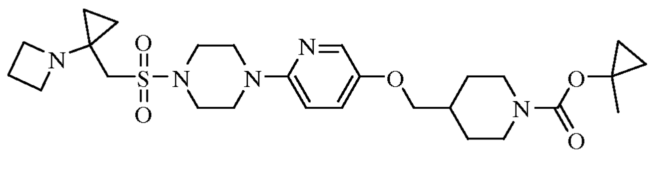
Example M67: 1-Methylcyclopropyl 4-((6-(4-(3-(azetidin-1-yl)propylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate.



[00289] By following a similar procedure as for the one used for the preparation of **M21** from **M6** except substituting **M65a** for **M21** and azetidine for 2-methylimidazole, **M67** is prepared; ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.91 (d, J = 3.2 Hz, 1H), 7.27 (dd, J = 3.2, 9.2 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 4.06 (m, 2H), 3.85 (d, J = 6.4 Hz, 2H), 3.52 (m, 4H), 3.34 (m, 4H), 3.09 (t, J = 6.8 Hz, 4H), 3.05 (m, 2H), 2.80 (m, 2H), 2.44 (d, J = 6.8 Hz, 2H), 1.96 (m, 3H), 1.78 (m, 4H), 1.50 (s, 3H), 1.23 (m, 2H), 0.79 (m, 2H), 0.58 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{41}N_5O_5S$ calcd: 535.3, found: 536.3.

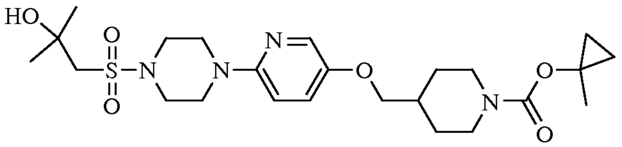
[00290]

Example M68: 1-Methylcyclopropyl 4-((6-(4-((1-(azetidin-1-yl)cyclopropyl)methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate.



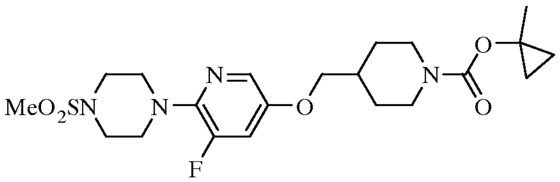
[00291] By following a similar procedure as for the one used for the preparation of **M35** from **M1c** except substituting **M61a** for **M1c**, **M68** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.92 (d, *J* = 2.9 Hz, 1H), 7.14 (dd, *J* = 9.1, 3.0 Hz, 1H), 6.64 (d, *J* = 9.1 Hz, 1H), 4.13 (m, 2H), 3.77 (d, *J* = 6.3 Hz, 2H), 3.54 (m, 4H), 3.49 (m, 4H), 3.06 (m, 4H), 3.01 (s, 2H), 2.74 (m, 2H), 1.91 (m, 2H), 1.85 (m, 2H), 1.80 (m, 2H), 1.55 (s, 3H), 1.25 (m, 2H), 0.86 (m, 4H), 0.70 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{27}H_{42}N_5O_5S$ $[M+H]^+$ 548.3, found 548.4.

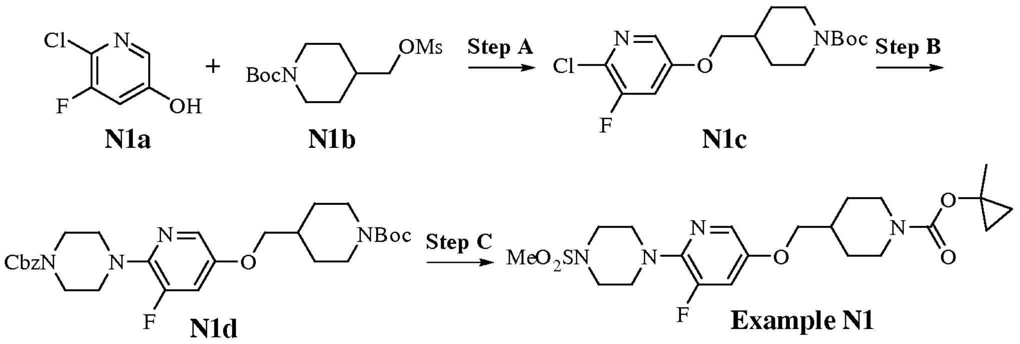
Example M69: 1-Methylcyclopropyl 4-((6-(4-(2-hydroxy-2-methylpropylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate



[00292] A solution of **E10** (50 mg, 0.11 mmol) in tetrahydrofuran (3 mL) is cooled to –78 °C and treated excess butyllithium in hexane (2M, 250 μL). After stirring for 15 minutes, excess dry acetone is added and the reaction is stirred for an additional 30 minutes. The reaction is quenched with saturated aqueous ammonium chloride solution, warmed to room temperature and partitioned between ethyl acetate and water. The organics are isolated, dried over $MgSO_4$, filtered, evaporated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **M69**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 2.8 Hz, 1H), 7.15 (dd, J = 3.0, 9.1 Hz, 1H), 6.64 (d, J = 9.1 Hz, 1H), 4.13 (m, 2H), 3.77 (d, J = 6.3 Hz, 2H), 3.52 (m, 5H), 3.36 (m, 4H), 3.04 (s, 2H), 2.73 (m, 2H), 1.93 (m, 1H), 1.80 (m, 2H), 1.54 (s, 3H), 1.44 (s, 6H), 1.25 (m, 2H), 0.87 (m, 2H), 0.61 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{39}N_4O_6S$ calcd: 511.3, found: 511.5.

Example N1: 1-Methylcyclopropyl 4-((5-fluoro-6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate



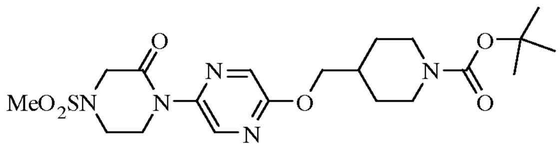


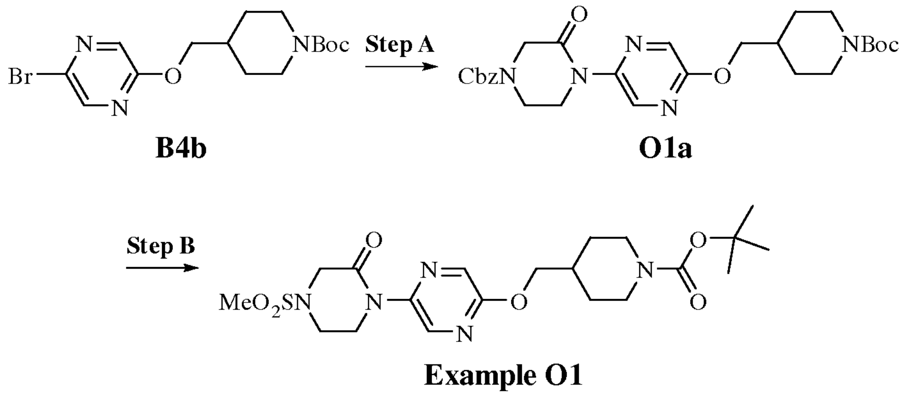
[00293] **Step A:** A solution of **N1a** (100 mg, 0.678 mmol) and **N1b** (219 mg, 0.746 mmol) in N-methylpyrrolidinone (2 mL) is treated with Cs_2CO_3 (331 mg, 1.01 mmol) and heated to 80 °C for 2 hours. The reaction is cooled to room temperature, diluted with ethyl acetate and extracted with water twice. The organics are dried over $MgSO_4$, filtered, evaporated and purified on silica using a linear gradient of 0 to 50% ethyl acetate in hexanes to afford **N1c**. ESIMS *m/z* for $(M+H)^+$ $C_{16}H_{23}Cl\ FN_2O_3$ calcd: 345.1, found: 289.0 (M-*t*Bu+H^+).

[00294] **Step B:** By following a similar procedure as the one used for preparing **B1** from isopropyl 4-((6-chloropyridin-3-yloxy)methyl)piperidine-1-carboxylate except substituting **N1c** for isopropyl 4-((6-chloropyridin-3-yloxy)methyl)piperidine-1-carboxylate and benzyl piperazine-1-carboxylate for 1-(methylsulfonyl)piperazine, **N1d** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{28}H_{38}FN_4O_5$ calcd: 529.3, found: 529.2.

[00295] **Step C:** A solution of **N1d** (132 mg, 0.25 mmol) in a mixture of methanol and dioxane (2 mL, 1:1) is treated with 10 mg of 5% Pd/C and hydrogenated overnight at balloon pressure. The atmosphere in the reaction is then exchanged back to N_2 and the reaction is filtered through Celite® and the the solvent is removed. The resulting oil is coevaporated with toluene twice, dissolved in dichloromethane (2 mL) containing triethylamine (51 mg, 0.50 mmol) and treated with methanesulfonyl chloride (43 mg, 0.38 mmol) as a solution in dichloromethane (1 mL) and stirred for 1 hour. The solvent is removed and the reaction is treated with neat trifluoroacetic acid (3 mL). After 20 minutes of stirring, the solvent is removed and the reaction is coevaporated with toluene twice and treated with dichlormethane (2 mL), **E3b** (71 mg, 0.30 mmol) and excess triethylamine. After 2 h of stirring, the reaction is diluted with ethyl acetate, extracted with 1 M NaOH twice, saturated sodiumhydrogencarbonate once, dried over $MgSO_4$, filtered, evaporated and purified on silica gel using a linear gradient of 0 to 100% ethyl acetate in hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 2.5 Hz, 1H), 7.07 (dd, J = 2.5, 13.0 Hz, 1H), 4.14 (m, 2H), 3.80 (d, J = 6.3 Hz, 2H), 3.53 (m, 4H), 3.40 (m, 4H), 2.82 (s, 3H), 2.74 (m, 2H), 1.95 (m, 1H), 1.80 (m, 2H), 1.55 (s, 3H), 1.26 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS m/z for $(M+H)^+$ $C_{21}H_{32}FN_4O_5S$ calcd: 471.2, found: 471.2.

Example O1: tert-Butyl 4-((5-(4-(methylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.

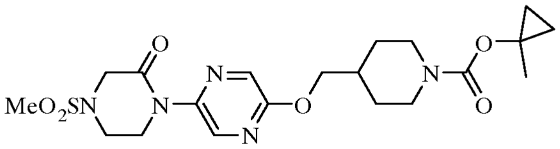




[00296] **Step A:** A sealable flask is charged with **B4b** (4.00 g, 11 mmol) and benzyl 3-oxopiperazine-1-carboxylate (3.02 g, 13 mmol), Pd_2dba_3 (295 mg, 0.32 mmol), Xantphos (560 mg, 0.97 mmol) and Cs_2CO_3 (10.5 g, 32 mmol). The flask is evacuated and back filled with nitrogen, sealed, treated with dioxane (60 mL) and dipped into a pre-heated 120 °C bathours. After 2 hours, the reaction is cooled to room temperature, diluted with ethyl acetate and extracted with water twice. The organics are dried over $MgSO_4$, filtered, evaporated and purified on silica using a step gradient of 25, 50 and 75% ethyl acetate in hexanes to afford **O1a**; ESIMS *m/z* for $(M\text{-}Boc+H)^+$ $C_{22}H_{28}N_5O_4$ calcd: 426.2, found: 426.1.

[00297] **Step B:** A solution of **O1a** (80 mg, 0.15 mmol) in MeOH (2 mL) is treated with 10 mg of 5% Pd/C and hydrogenated at balloon pressure overnight. The catalyst is removed by filtration through Celite® and the solvent is removed. The residue is coevaporated with toluene twice, dissolved in dichloromethane (2 mL) and treated with excess triethylamine followed by methanesulfonyl chloride (21 mg, 0.18 mmol) dissolved in dichloromethane (1 mL). After 1 hour of stirring, the reaction is diluted with ethyl acetate and extracted with water twice. The organics are dried over $MgSO_4$, filtered, evaporated and purified on silica using a linear gradient of 30 to 100% ethyl acetate in hexanes to afford **O1**; ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 1.4 Hz, 1H), 8.02 (d, J = 1.4 Hz, 1H), 4.19 (d, J = 6.5 Hz, 2H), 4.15 (m, 2H), 4.13 (s, 2H), 4.08 (m, 2H), 3.68 (m, 2H), 2.92 (s, 3H), 2.74 (m, 2H), 1.98 (m, 1H), 1.79 (m, 2H), 1.46 (s, 9H), 1.27 (m, 2H); ESIMS *m/z* for $(M+Na)^+$ $C_{20}H_{31}N_5NaO_6S$ calcd: 492.2, found: 492.2.

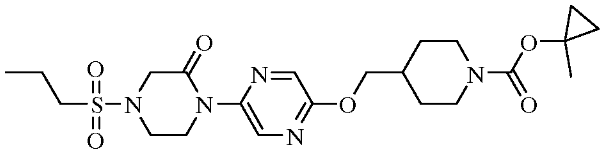
Example O2: 1-Methylcyclopropyl 4-((5-(4-(methylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.

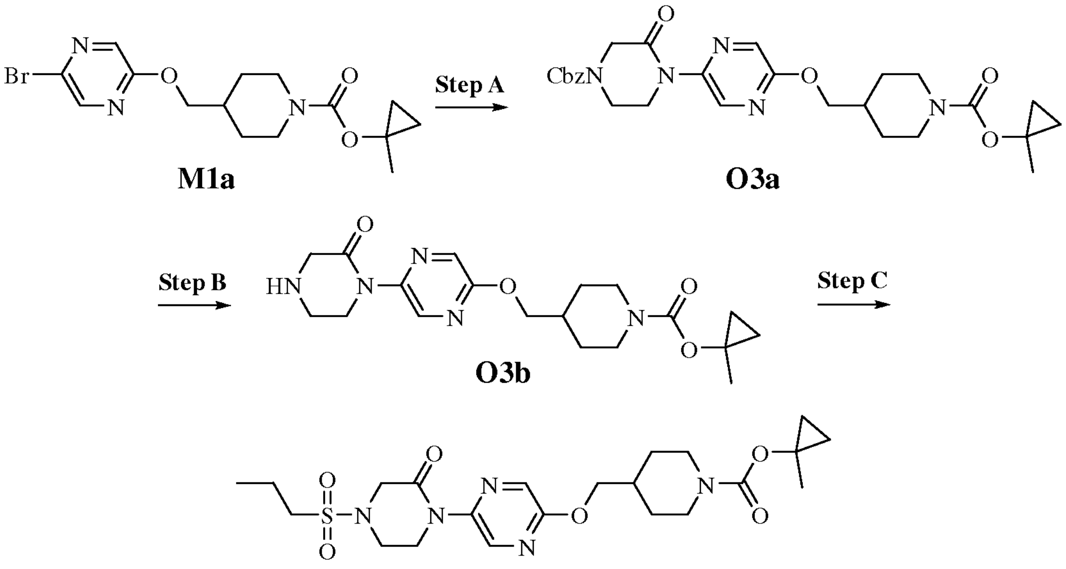


[00298] A sample of **O1** (50 mg, 0.11 mmol) is treated with trifluoroacetic acid (1 mL) and aged for 20 minutes. The solvent is removed and the residue is treated with dichloromethane (2 mL), excess triethylamine and **E3b** (30.3 mg, 0.13 mmol). After stirring for 3 hours, the reaction is diluted with ethyl acetate, extracted with 1 M NaOH twice, saturated sodiumhydrogencarbonate once, dried over $MgSO_4$, filtered, evaporated

and purified on silica gel using a linear gradient of 0 to 100% ethyl acetate in hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 1.4 Hz, 1H), 8.02 (d, *J* = 1.4 Hz, 1H), 4.18 (d, *J* = 6.5 Hz, 2H), 4.12 (s, 2H), 4.12 (m, 2H), 4.07 (m, 2H), 3.67 (m, 2H), 2.93 (s, 3H), 2.72 (m, 2H), 1.98 (m, 1H), 1.79 (m, 2H), 1.54 (s, 3H), 1.25 (m, 2H), 0.87 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{30}N_5O_6S$ calcd: 468.2, found: 468.1.

Example O3: 1-Methylcyclopropyl 4-((5-(2-oxo-4-(propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





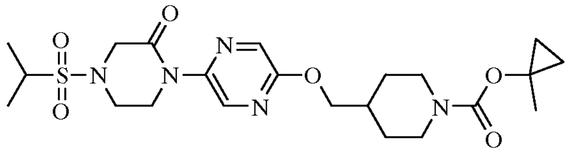
Example O3

[00299] **Step A:** By following a similar procedure as the one used for preparing **O1a** from **B4b** except substituting **M1a** for **B4b**, **O3a** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{27}H_{34}N_5O_6$ calcd: 524.2, found: 524.2.

[00300] **Step B:** A solution of **O3a** (3.01 g, 0.15 mmol) in MeOH (30 mL) is treated with 101 mg of 20% $Pd(OH)_2/C$ and hydrogenated at balloon pressure for 5 hours. The catalyst is removed by filtration through Celite® and the solvent is removed to afford **O3b**; ESIMS *m/z* for $(M+H)^+$ $C_{19}H_{28}N_5O_4$ calcd: 390.2, found: 390.1.

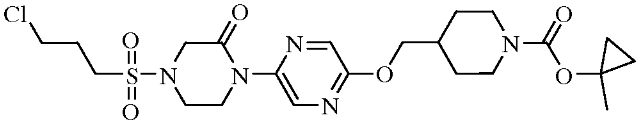
[00301] **Step C:** A solution of **O3b** (203 mg, 0.52 mmol) in dichloromethane (1.5 mL) is treated with triethylamine (55 mg, 0.54 mmol) and *n*-propanesulfonyl chloride (77 mg, 0.54 mmol) and stirred for 4 hours. Then, another identical portion of triethylamine and *n*-propylsulfonyl chloride is added and the reaction is stirred overnight. The reaction mixture is then loaded directly onto a silica gel column and eluted with a linear gradient of 0 to 100% ethyl acetate in hexane to afford **O3**; ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 1.4 Hz, 1H), 8.02 (d, J = 1.4 Hz, 1H), 4.18 (d, J = 6.5 Hz, 1H), 4.17 (m, 2H), 4.15 (s, 2H), 4.05 (m, 2H), 3.70 (m, 2H), 3.01 (m, 2H), 2.75 (dd, J = 12.3, 12.2 Hz, 2H), 1.98 (m, 1H), 1.89 (m, 2H), 1.79 (m, 2H), 1.55 (s, 3H), 1.26 (m, 2H), 1.09 (t, J = 7.4 Hz, 3H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{34}N_5O_6S$ calcd: 496.2, found: 496.2.

Example O4: 1-Methylcyclopropyl 4-((5-(4-(isopropylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate



[00302] By following a similar procedure as the one used for preparing **O3** from **O3b** except substituting 3-chloropropanesulfonyl chloride for *n*-propanesulfonyl chloride, **O4** is prepared; ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 1.4 Hz, 1H), 8.02 (d, J = 1.4 Hz, 1H), 4.21 (s, 2H), 4.19 (m, 2H), 4.19 (d, J = 6.5 Hz, 2H), 4.04 (m, 2H), 3.75 (m, 2H), 3.28 (sept., J = 6.8 Hz, 1H), 2.75 (dd, J = 12.3, 12.3 Hz, 2H), 1.98 (m, 1H), 1.78 (m, 2H), 1.55 (s, 3H), 1.40 (d, J = 6.8 Hz, 6H), 1.26 (m, 2H), 0.87 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{34}N_5O_6S$ calcd: 496.2, found: 496.2.

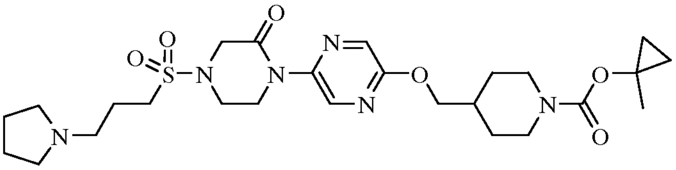
Example O5: 1-Methylcyclopropyl 4-((5-(4-(3-chloropropylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate



[00303] By following a similar procedure as the one used for preparing **O3** from **O3b** except substituting *iso*-propylsulfonyl chloride for *n*-propylsulfonyl chloride, **O5** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 8.65 (d, *J* = 1.4 Hz, 1H), 8.02 (d, *J* = 1.4Hz, 1H), 4.21 (m, 2H), 4.18 (d, *J* = 6.6 Hz, 2 H), 4.17 (s, 2H), 4.07 (m, 2H), 3.71 (m, 4H), 3.21 (m, 2H), 2.75 (dd, *J* = 12.4, 12.3 Hz, 2H), 2.33 (m, 2H), 1.97 (m, 1H), 1.79 (m, 2H), 1.55 (s, 3H), 1.26 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{22}H_{33}ClN_5O_6S$ $[M+H]^+$ 530.2, found 530.3.

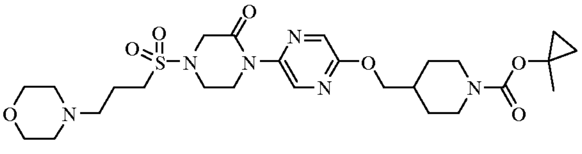
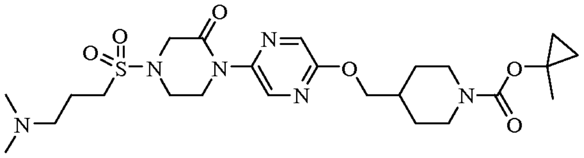
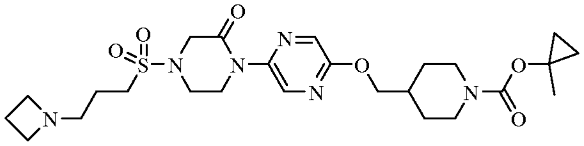
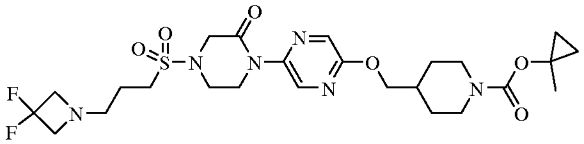
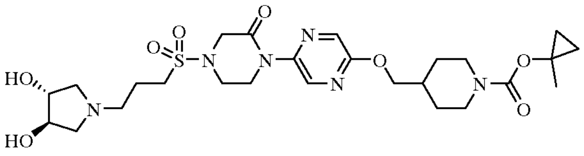
[00304]

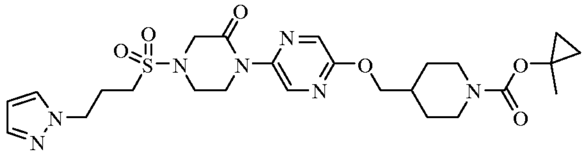
Example O6: 1-Methylcyclopropyl 4-((5-(2-oxo-4-(3-(pyrrolidin-1-yl)propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate



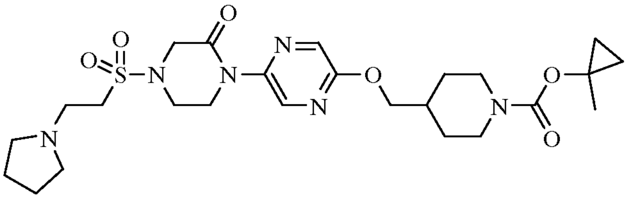
A solution of **O5** (15 mg, 0.03 mmol) in N,N-dimethylformamide (700 μL) is treated with pyrrolidine (23 μL, 0.28 mmol) and subjected to microwave irradiation (200 °C, 5 min). The solution is purified using mass directed reverse phase HPLC to afford **O6**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 1.2 Hz, 1H), 8.04 (d, J = 1.2 Hz, 1H), 4.20 (d, J = 6.8 Hz, 2H), 4.18 (s, 2H), 4.07 (m, 2H), 3.72 (m, 2H), 3.18 (m, 2H), 2.77 (m, 2H), 2.66 (m, 2H), 2.59 (br s, 3H), 2.07 (m, 3H),1.83 (m, 5H), 1.57 (s, 3H), 1.28 (m, 2H), 0.89 (m, 2H), 0.65 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{41}N_6O_6S$ calcd: 565.3, found: 565.2.

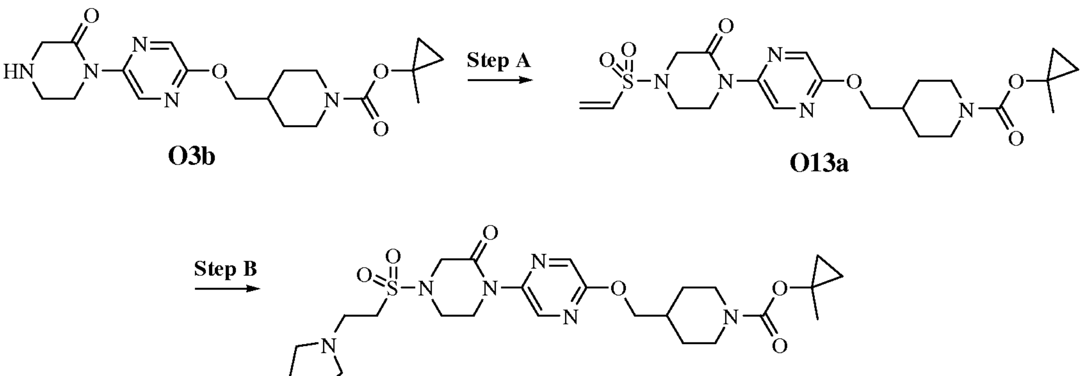
[00305] By following a similar procedure as for the one used for the preparation of **O6** from **O5** except substituting the appropriate amines for pyrrolidine, the following examples are obtained:

O7		^{1}H NMR (400 MHz, CDCl$_3$) δ 8.64 d, J = 1.6 Hz, 1H), 8.04 (d, J = 1.6 Hz, 1H), 4.20 (d, J = 6.4 Hz, 2H), 4.18 (s, 2H), 4.07 (m, 2H), 3.72 (m, 4H), 3.32 (m, 8H), 3.15 (m, 2H), 2.77 (m, 2H), 2.46 (m, 4H), 2.02 (m, 4H), 1.80 (m, 2H), 1.56 (s, 3H), 1.29 (m, 2H), 0.87 (m, 2H), 0.64 (m, 2H); ESIMS *m/z* for (M+H)$^+$ $C_{26}H_{41}N_6O_7S$ calcd: 581.3, found: 581.2.
O8		^{1}H NMR (400 MHz, CDCl$_3$) δ 8.49 d, J = 1.4 Hz, 1H), 7.86 (d, J = 1.4 Hz, 1H), 4.03 (d, J = 6.4 Hz, 2H), 4.00 (s, 2H), 3.89 (m, 2H), 3.54 (m, 2H), 2.97 (m, 2H), 2.59 (m, 2H), 2.33 (m, 2H), 2.12 (s, 6H), 1.87 (m, 4H), 1.64 (m, 2H), 1.39 (s, 3H), 1.10 (m, 2H), 0.71 (m, 2H), 0.46 (m, 2H); ESIMS *m/z* for (M+H)$^+$ $C_{24}H_{39}N_6O_6S$ calcd: 539.3, found: 539.2.
O9		^{1}H NMR (400 MHz, CDCl$_3$) δ 8.44 (d, J = 1.6 Hz, 1H), 7.81 (d, J = 1.6 Hz, 1H), 3.98 (d, J = 6.8 Hz, 2H), 3.94 (s, 2H), 3.84 (m, 2H), 3.48 (m, 2H), 2.98 (m, 3H), 2.89 (m, 2H), 2.54 (m, 2H), 2.31 (m, 2H), 1.86 (m, 2H), 1.78 (m, 1H), 1.65 (m, 4H), 1.34 (s, 3H), 1.05 (m, 2H), 0.66 (m, 2H), 0.41 (m, 2H); ESIMS *m/z* for (M+H)$^+$ $C_{25}H_{39}N_6O_6S$ calcd: 551.3, found: 551.3.
O10		^{1}H NMR (400 MHz, CDCl$_3$) δ 8.51 (d, J = 1.2 Hz, 1H), 7.88 (d, J = 1.2 Hz, 1H), 4.04 (d, J = 6.4 Hz, 2H), 4.01 (s, 2H), 3.91 (m, 3H), 3.56 (m, 2H), 3.43 (t, J = 12.0 Hz, 4H), 2.97 (m, 2H), 2.56 (m, 4H), 1.84 (m, 1H), 1.78 (m, 2H), 1.66 (m, 2H), 1.41 (s, 3H), 1.13 (m, 2H), 0.73 (m, 2H), 0.48 (m, 2H); ESIMS *m/z* for (M+H)$^+$ $C_{25}H_{37}F_2N_6O_6S$ calcd: 587.3, found: 587.2.
O11		^{1}H NMR (400 MHz, CDCl$_3$) δ 8.57 (d, J = 1.4 Hz, 1H), 7.95 (d, J = 1.4 Hz, 1H), 4.12 (d, J = 6.4 Hz, 2H), 4.10 (s, 2H), 4.06 (m, 2H), 3.98 (m, 3H), 3.64 (m, 2H), 3.07 (m, 2H), 2.94 (m, 2H), 2.68 (m, 2H), 2.58 (m, 2H), 2.43 (dd, J = 3.6,

		10.4 Hz, 2H), 1.95 (m, 4H), 1.72 (m, 2H), 1.48 (s, 3H), 1.18 (m, 2H), 0.80 (m, 2H), 0.56 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{41}N_6O_8S$ calcd: 597.3, found: 597.3.
O12		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 1.2 Hz, 1H), 8.04 (d, J = 1.2 Hz, 1H), 7.54 (d, J = 1.6 Hz, 1H), 7.46 (d, J = 1.6 Hz, 1H), 6.29 (m, 1H), 4.35 (m, 2H), 4.20 (d, J = 6.4 Hz, 2H), 4.12 (s, 2H), 4.05 (m, 3H), 3.68 (m, 2H), 2.99 (m, 2H), 2.77 (m, 2H), 2.45 (m, 2H), 2.00 (m, 1H), 1.82 (m, 2H), 1.57 (s, 3H), 1.28 (m, 2H), 0.89 (m, 2H), 0.64 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{25}H_{36}N_7O_6S$ calcd: 562.2, found: 562.3.

Example O13: 1-Methylcyclopropyl 4-((5-(2-oxo-4-(2-(pyrrolidin-1-yl)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate





O3b

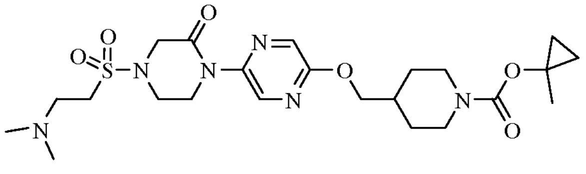
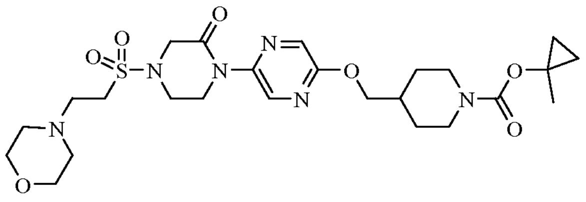
O13a

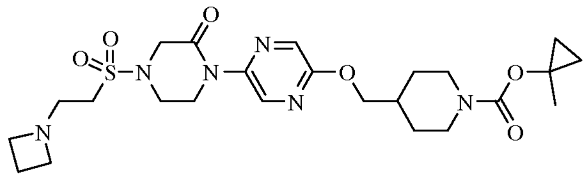
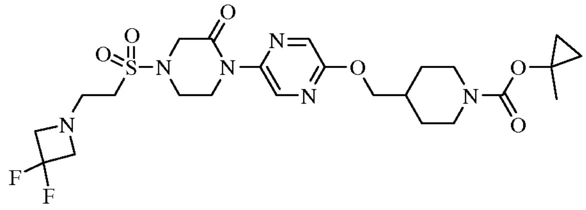
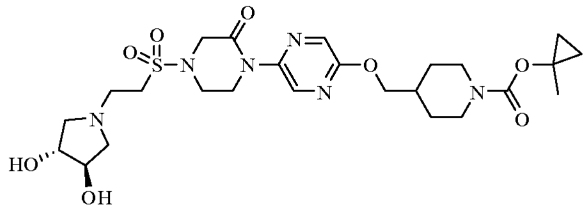
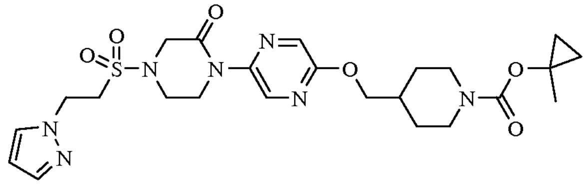
Example O13

Step A: A solution of **O3b** (600 mg, 1.51 mmol) in dichloromethane (10 mL) is treated with N,N-diisopropylethylamine (521 μL, 3.02 mmol) and 2-chloroethanesulfonyl chloride (173 μL, 1.66 mmol) and stirred for 2 hours. The reaction mixture is then loaded directly onto a silica gel column and eluted with a linear gradient of 0 to 100% ethyl acetate in hexane to afford **O13a**. ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{30}N_5O_6S$ calcd: 480.2, found: 480.2.

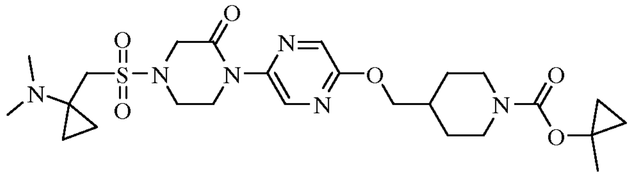
Step B: A solution of **O13a** (15 mg, 0.03 mmol) in N,N-dimethylformamide (1 mL) is treated with pyrrolidine (26 μL, 0.31 mmol) and stirred for 16 hours at room temperture. The solution is purified using mass-triggered reverse phase HPLC to afford **O13.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 1.4 Hz, 1H), 8.04 (d, J = 1.4 Hz, 1H), 4.20 (m, 4H), 4.06 (m, 3H), 3.72 (m, 2H), 3.34 (m, 2H), 3.04 (m, 2H), 2.75 (m, 6H), 2.00 (m, 1H), 1.83 (m, 6H), 1.57 (s, 3H), 1.28 (m, 2H), 0.89 (m, 2H), 0.64 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{25}H_{39}N_6O_6S$ calcd: 551.3, found: 551.2.

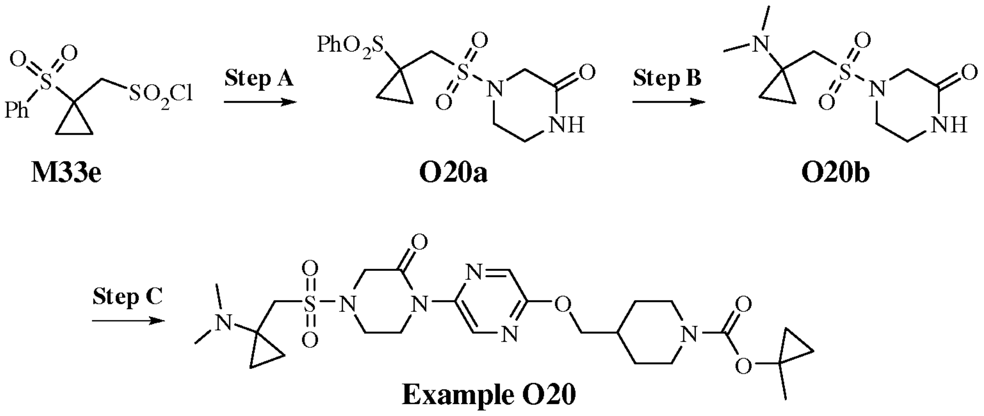
By following a similar procedure as for the one used for the preparation of **O13** from **O13a** except substituting the appropriate amines for pyrrolidine, the following examples are obtained:

Ex.	Structure	Analytical data
O14		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 1.4 Hz, 1H), 8.04 (d, J = 1.4 Hz, 1H), 4.20 (m, 4H), 4.06 (m, 3H), 3.73 (m, 2H), 3.26 (m, 2H), 2.84 (m, 2H), 2.77 (m, 2H), 2.33 (s, 6H), 2.00 (m, 1H), 1.82 (m, 2H), 1.57 (s, 3H), 1.28 (m, 2H), 0.89 (m, 2H), 0.64 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{37}N_6O_6S$ calcd: 525.3, found: 525.2.
O15		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 1.2 Hz, 1H), 8.04 (d, J = 1.2 Hz, 1H), 4.21 (m, 4H), 4.08 (m, 2H), 3.72 (m, 6H), 3.25 (m, 2H), 2.88 (m, 2H), 2.77 (m, 2H), 2.53 (m, 4H), 2.00 (m, 1H), 1.81 (m, 2H), 1.57 (s, 3H), 1.28 (m, 2H), 0.89 (m, 2H), 0.64 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{25}H_{39}N_6O_7S$ calcd: 567.3, found: 567.2.

O16		^{1}H NMR (400 MHz, CDCl$_3$) δ 8.60 (d, J = 1.2 Hz, 1H), 7.95 (d, J = 1.2 Hz, 1H), 4.15 (s, 2H), 4.12 (d, J = 6.4 Hz, 2H), 3.97 (m, 2H), 3.65 (m, 3H), 3.15 (m, 3H), 2.98 (m, 2H), 2.77 (m, 2H), 2.68 (m, 2H), 1.98 (m, 2H), 1.94 (m, 1H), 1.73 (m, 2H), 1.48 (s, 3H), 1.19 (m, 2H), 0.80 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{37}N_6O_6S$ calcd: 537.3, found: 567.3.
O17		^{1}H NMR (400 MHz, CDCl$_3$) δ 8.68 (d, J = 1.6 Hz, 1H), 8.04 (d, J = 1.6 Hz, 1H), 4.20 (m, 5H), 4.07 (m, 3H), 3.74 (m, 2H), 3.66 (t, J = 11.6 Hz, 4H), 3.09 (m, 4H), 2.77 (m, 2H), 2.00 (m, 1H), 1.81 (m, 2H), 1.57 (s, 3H), 1.29 (m, 2H), 0.89 (m, 2H), 0.64 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{35}F_2N_6O_6S$ calcd: 573.2, found: 573.2.
O18		^{1}H NMR (400 MHz, CDCl$_3$) δ 8.56 (d, J = 1.4 Hz, 1H), 7.95 (d, J = 1.4 Hz, 1H), 4.15 (s, 2H), 4.12 (d, J = 6.4 Hz, 2H), 4.03 (m, 2H), 3.98 (m, 2H), 3.66 (m, 2H), 3.26 (m, 2H), 2.95 (m, 4H), 2.68 (m, 2H), 2.48 (dd, J = 3.2, 10 Hz, 2H), 1.91 (m, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.20 (m, 2H), 0.80 (m, 2H), 0.56 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{25}H_{39}N_6O_8S$ calcd: 583.3, found: 583.3.
O19		^{1}H NMR (400 MHz, CDCl$_3$) δ 8.55 (d, J = 1.2 Hz, 1H), 7.94 (d, J = 1.2 Hz, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.41 (d, J = 2.0 Hz, 1H), 6.19 (m, 1H), 4.52 (m, 2H), 4.11 (d, J = 6.4 Hz, 2H), 3.87 (s, 2H), 3.85 (m, 2H), 3.65 (m, 2H), 3.40 (m, 2H) 2.68 (m, 2H), 1.91 (m, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.18 (m, 2H), 0.80 (m, 2H), 0.56 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{34}N_7O_6S$ calcd: 548.2, found: 548.2.

Example O20: 1-methylcyclopropyl 4-((5-(4-((1-(dimethylamino)cyclopropyl)methylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



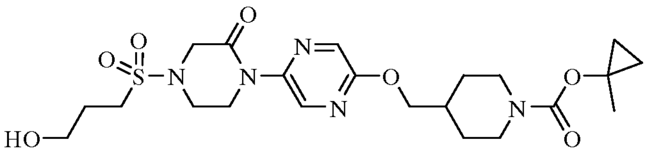


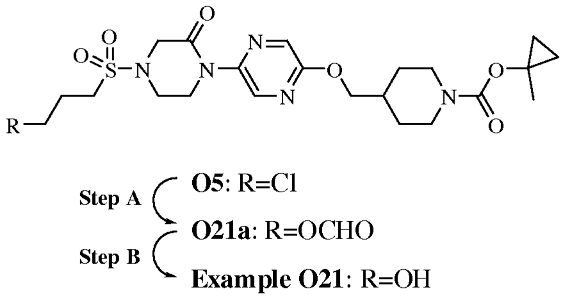
Step A: A solution of piperazin-2-one (36.5 mg, 3.7 mmol) in dichloromethane (10 mL) is treated with triethylamine (74 mg, 0.73 mmol) followed by **M33e** (108 mg, 3.7 mmol) and stirred overnight. The solvent is removed and the residue is dissolved in dimethylformamide, filtered and purified by mass triggered reverse phase HPLC to afford **O20a**; ESIMS *m/z* for $(M+H)^+$ $C_{14}H_{19}N_2O_5S_2$ calcd: 359.1, found: 359.0.

Step B: A solution of **O20a** (71.7 mg, 0.20 mmol) in 2 M dimethylamine in tetrahydrofuran solution (6 mL, 12 mmol) is treated with potassium *tert*-butoxide (34 mg, 0.30 mmol) and stirred for 1 hour at room temperture The solvent is removed and the residue is dissolved in dimethylformamide, filtered and purified by mass triggered reverse phase HPLC to afford **O20a**; ESIMS *m/z* for $(M+H)^+$ $C_{10}H_{20}N_3O_3S$ calcd: 262.1, found: 262.1.

Step C: By following a similar procedure as the one used for preparing **O3a** from **M1a** except substituting **O20b** for benzyl 3-oxopiperazine-1-carboxylate, **O20** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 8.65 (d, *J* = 1.4 Hz, 1H), 8.02 (d, *J* = 1.4Hz, 1H), 4.25 (m, 2H), 4.19 (d, *J* = 6.5 Hz, 2H), 4.17 (s, 2H), 4.04 (m, 2H), 3.70 (m, 2H), 3.16 (s, 2H), 2.75 (dd, *J* = 15.2, 13.8 Hz, 2H), 2.29 (s, 6H), 1.98 (m, 1H), 1.80 (m, 2H), 1.55 (s, 3H), 1.27 (m, 2H), 0.88 (m, 6H), 0.62 (m, 2H); ESIMS calcd. for $C_{25}H_{39}N_6O_6S$ $[M+H]^+$ 551.3, found 551.4.

Example O21: 1-Methylcyclopropyl 4-((5-(4-(3-hydroxypropylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





O5: R=Cl

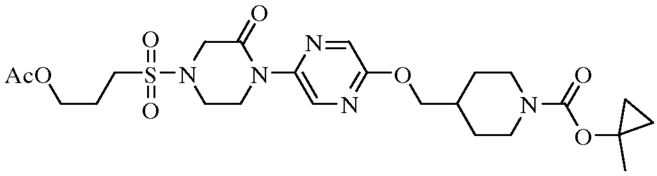
O21a: R=OCHO

Example O21: R=OH

Step A: A solution of **O5** (2.76 g, 5.2 mmol), NaI (790 mg, 5.3 mmol) and sodium formate (1.06 g, 15.6 mmol) in dimethylformamide (30 mL) is heated at 120 °C for 2 hours. The mixture is diluted with water, extracted with ethyl acetate (2x) and the organics are washed with water & brine, dried ($MgSO_4$), filtered and concentrated to provide crude **O21a**, which is used in the next step without further purification; ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{34}N_5O_8S$ calcd: 540.2, found: 540.2.

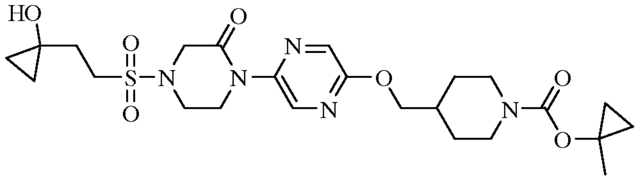
Step B: A solution of **O21a** (crude from the last step) in a 1:1 mixture of methanol and water (40 mL) is treated with sodiumhydrogencarbonate (2.2 g, 26.0 mmol) and stirred at room temperature for 1 hour. The mixture is extracted with ethyl acetate and the organics are washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue is purified on silica gel using 0-10% methanol in dichloromethane to afford **O21**; ^{1}H NMR (400 MHz, $CDCl_3$) □ 8.66 (d, J = 1.4 Hz, 1H), 8.04 (d, J = 1.4 Hz, 1H), 4.20 (m, 4H), 4.08 (m, 2H), 3.82 (m, 2H), 3.74 (m, 2H), 3.22 (m, 2H), 2.77 (m, 2H), 2.12 (m, 2H), 2.00 (m, 1H), 1.83 (m, 2H), 1.74 (t, J = 4.8 Hz, 1H), 1.60 (s, 2H), 1.57 (s, 3H), 1.28 (m, 2H), 0.89 (m, 2H), 0.65 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{34}N_5O_7S$ calcd: 512.2, found: 512.2.

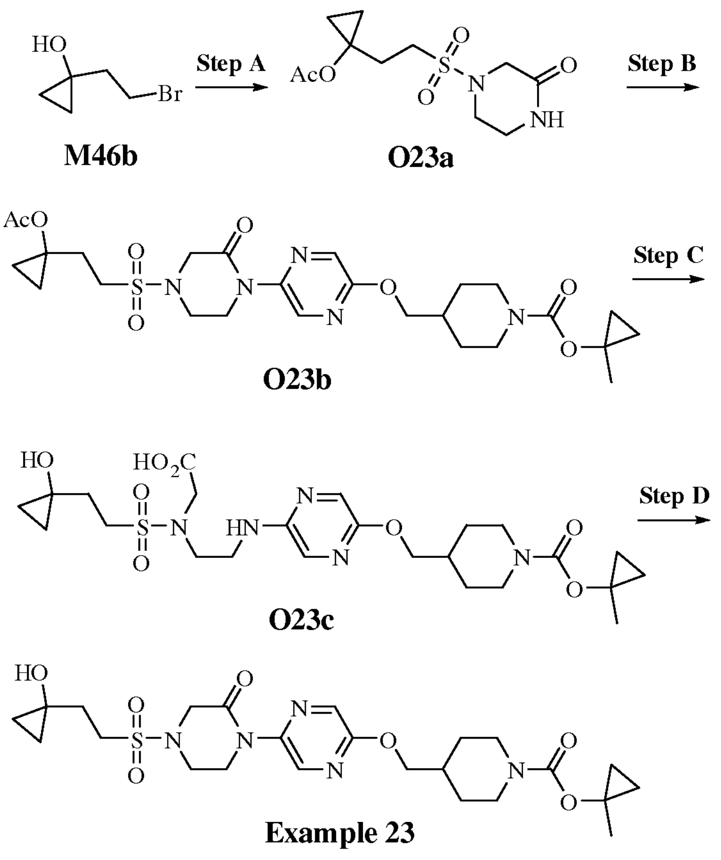
Example O22: 1-Methylcyclopropyl 4-((5-(4-(3-acetoxypropylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00306] By following a similar procedure as the one used for preparing **M19** from **M5** except substituting **O5** for **M5**, **O22** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 8.65 (d, *J* = 1.4 Hz, 1H), 8.02 (d, *J* = 1.4 Hz, 1H), 4.19 (m, 8H), 4.06 (m, 2H), 3.72 (m, 2H), 3.12 (m, 2H), 2.75 (dd, *J* = 12.4, 12.4 Hz, 2H), 2.15-2.22 (m, 2H), 2.08 (s, 3H), 1.98 (m, 1H), 1.79 (m, 2H), 1.55 (s, 3H), 1.27 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{24}H_{36}N_5O_8S$ $[M+H]^+$ 554.2, found 554.2.

Example O23: 1-Methylcyclopropyl 4-((5-(4-(2-(1-hydroxycyclopropyl)ethylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





M46b **O23a** **O23b** **O23c** **Example 23**

[00307] **Step A**: By following a similar procedure as the one used for preparing **M46** from **M46b** except substituting piperazin-2-one for **M1c** and purifying by HPLC, **O23a** is prepared; ESIMS calcd. for $C_{11}H_{19}N_2O_5S$ $[M+H]^+$ 291.1, found 291.1.

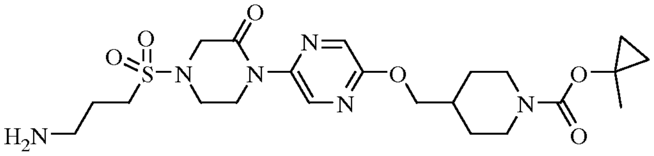
Step B: By following a similar procedure as the one used for preparing **O3a** from **M1a** except substituting **O23b** for benzyl 3-oxopiperazine-1-carboxylate, **O23b** is prepared; ESIMS calcd. for $C_{26}H_{38}N_5O_8S$ $[M+H]^+$ 580.2, found 580.3.

Step C: A solution of **O23b** (37.4 mg, 0.65 mmol) in methanol (1 mL) and water (0.1 mL) is treated with LiOH (5.7 mg, 0.1 mmol) and stirred overnight. The reaction is then purified directly by mass triggered reverse phase HPLC to afford **O23c**. ESIMS calcd. for $C_{24}H_{38}N_5O_8S$ $[M+H]^+$ 556.2, found 556.2.

Step D: A solution of **O23c** (20 mg, 0.036 mmol) in dichloromethane (1 mL) is treated with HATU (13.7 mg, 0.036 mmol) and N,N-diisopropylethylamine (4.6 mg, 0.036 mmol) and stirred overnight. The solvent is removed and the residue is dissolved in methanol and purified directly by mass triggered reverse phase HPLC. ^{1}H-NMR

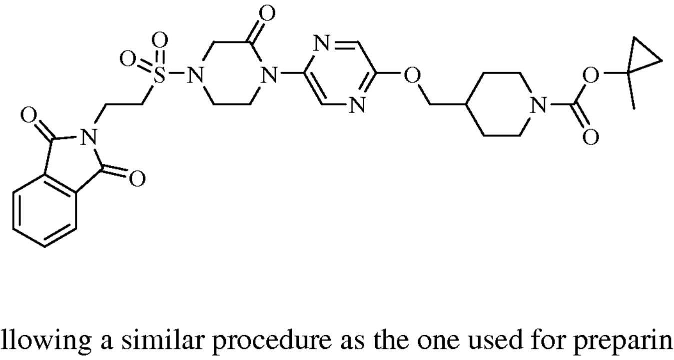
(400MHz, $CDCl_3$) δ 8.64 (d, *J* = 1.4 Hz, 1H), 8.02 (d, *J* = 1.4 Hz, 1H), 4.25 (m, 2H), 4.20 (s, 2H), 4.18 (s, 2H), 4.06 (m, 2H), 3.73 (m, 2H), 3.33 (ddd, *J* = 7.7, 5.3, 5.3 Hz, 2H), 2.74 (dd, *J* = 12.3, 12.1 Hz, 2H), 2.27 (s, 1H), 2.07 (ddd, *J* = 7.7, 5.2, 5.2 Hz, 2H), 1.98 (m, 1H), 1.80 (m, 2H), 1.55 (s, 3H), 1.26 (m, 2H), 0.86 (m, 4H), 0.62 (m, 2H), 0.57 (m, 2H); ESIMS calcd. for $C_{24}H_{36}N_5O_7S$ $[M+H]^+$ 538.2, found 538.8.

Example O24: 1-Methylcyclopropyl 4-((5-(4-(3-aminopropylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



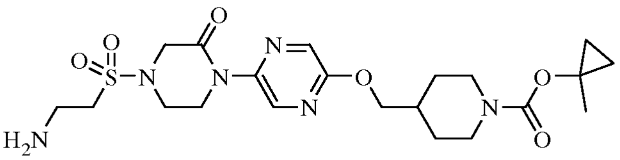
By following a similar procedure as the one used for preparing **M18** from **M6** except substituting **O5** for **M6**, **O23b** is prepared; ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 1.4 Hz, 1H), 7.82 (d, J = 1.4 Hz, 1H), 3.99 (d, J = 6.8 Hz, 2H), 3.97 (s, 2H), 3.86 (m, 2H), 3.51 (m, 2H), 2.96 (m, 2H), 2.68 (t, J = 6.8 Hz, 2H), 2.55 (m, 2H), 1.78 (m, 3H), 1.60 (m, 2H), 1.35 (s, 3H), 1.18 (br s, 2H), 1.06 (m, 2H), 0.67 (m, 2H), 0.42 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{35}N_6O_6S$ calcd: 511.2, found: 511.2.

Example O25: 1-Methylcyclopropyl 4-((5-(4-(2-(1,3-dioxoisoindolin-2-yl)ethylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



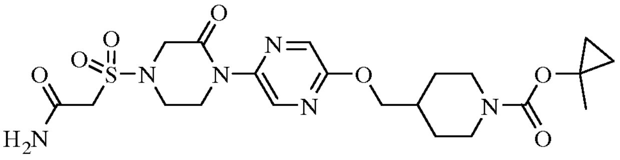
By following a similar procedure as the one used for preparing **O3** from **O3b** except substituting 2-(1,3-dioxoisoindolin-2-yl)ethanesulfonyl chloride for *n*-propanesulfonyl chloride, **O25** is prepared; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.58 (d, J = 1.4 Hz, 1H), 7.94 (d, J = 1.4 Hz, 1H), 7.80 (m, 2H), 7.67 (m, 2H), 4.10 (s, 7H), 3.99 (m, 2H), 3.67 (m, 2H), 3.40 (t, J = 6.8 Hz, 2H), 2.68 (m, 2H), 1.94 (m, 1H), 1.73 (m, 2H), 1.50 (s, 3H), 1.20 (m, 2H), 0.80 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for (M+H)$^+$ $C_{29}H_{35}N_6O_8S$ calcd: 627.2, found: 627.2.

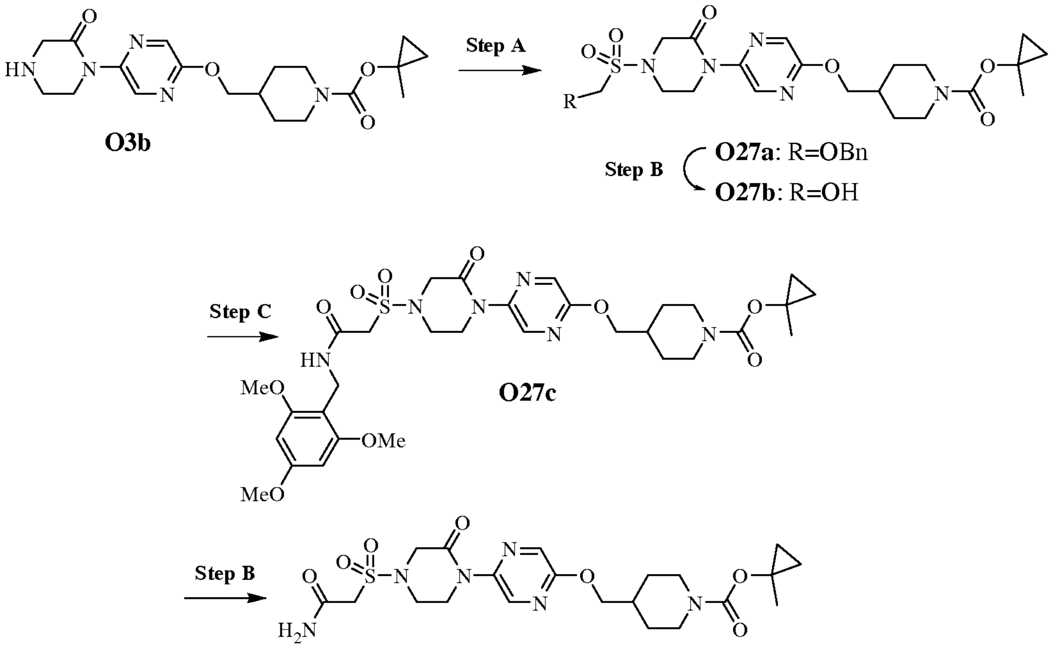
Example O26: 1-Methylcyclopropyl 4-((5-(4-(2-aminoethylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



A solution of **O25** (15 mg, 0.02 mmol) in ethanol (2 mL) is treated with hydrazine (8 μL, 0.24 mmol) and stirred for 1 hour. The solution iss concentrated and purified using mass-triggered reverse phase HPLC to afford **O26**; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.51 (d, J = 1.4 Hz, 1H), 7.88 (d, J = 1.4 Hz, 1H), 4.05 (m, 4H), 3.92 (m, 2H), 3.58 (m, 2H), 3.10 (m, 2H), 3.03 (m, 2H), 2.61 (m, 2H), 1.85 (m, 1H), 1.66 (m, 2H), 1.41 (s, 3H), 1.13 (m, 2H), 0.73 (m, 2H), 0.49 (m, 2H); ESIMS *m/z* for (M+H)$^+$ $C_{21}H_{33}N_6O_6S$ calcd: 497.2, found: 497.2.

Example O27: 1-Methylcyclopropyl 4-((5-(4-(2-amino-2-oxoethylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





Example O27

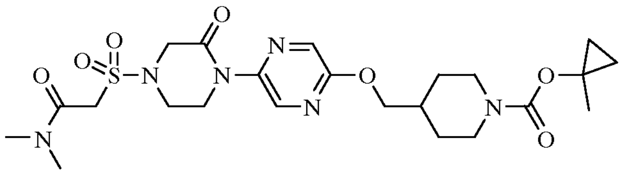
Step A: By following a similar procedure as the one used for preparing **O3** from **O3b** except substituting benzyl 2-(chlorosulfonyl)acetate for *n*-propanesulfonyl chloride, **O27a** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{28}H_{36}N_5O_8S$ calcd: 602.2, found: 602.1.

Step B: By following a similar procedure as the one used for preparing **M48** from **M48e**, **O27b** is prepared; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 1.2 Hz, 1H), 7.80 (d, J = 1.2 Hz, 1H), 4.11 (s, 2H), 3.96 (m, 3H), 3.84 (m, 5H), 3.59 (m, 2H), 2.53 (m, 2H), 1.76 (m, 1H), 1.57 (m, 2H), 1.32 (s, 3H), 1.05 (m, 2H), 0.64 (m, 2H), 0.40 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{30}N_5O_8S$ calcd: 512.2, found: 512.1.

Step C: A solution of **O27b** (60 mg, 0.12 mmol), HATU (89 mg, 0.23 mmol) and 2,4,6-trimethoxybenzylamine-HCl (33 mg, 0.14 mmol) in dichloromethane (10 mL) is treated with diisopropylethylamine (61 μL, 0.35 mmol) and the mixture is stirred at room temperature for 14 hours. The mixture is diluted with water and extracted with dichloromethane. The organics are dried, filtered, and concentrated to provide **O27c**, which was used without further purification. ESIMS *m/z* for $(M+H)^+$ $C_{31}H_{43}N_6O_{10}S$ calcd: 691.3, found: 691.2.

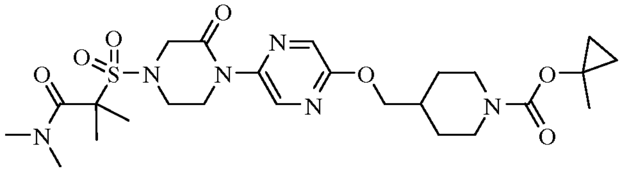
Step B: A solution of **O27c** (0.12 mmol) in dichloromethane (2 mL) is treated with TFA (1 mL) and aged for 1 hour at room temperature. The residue is concentrated and purified using mass-triggered reverse phase HPLC to afford **O27**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 1.6 Hz, 1H), 7.95 (d, J = 1.6 Hz, 1H), 4.19 (s, 2H), 4.12 (d, J = 6.4 Hz, 2H), 3.99 (m, 2H), 3.90 (s, 2H), 3.72 (m, 2H), 2.68 (m, 3H), 1.89 (m, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.13 (m, 2H), 0.80 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{31}N_6O_7S$ calcd: 511.2, found: 511.2.

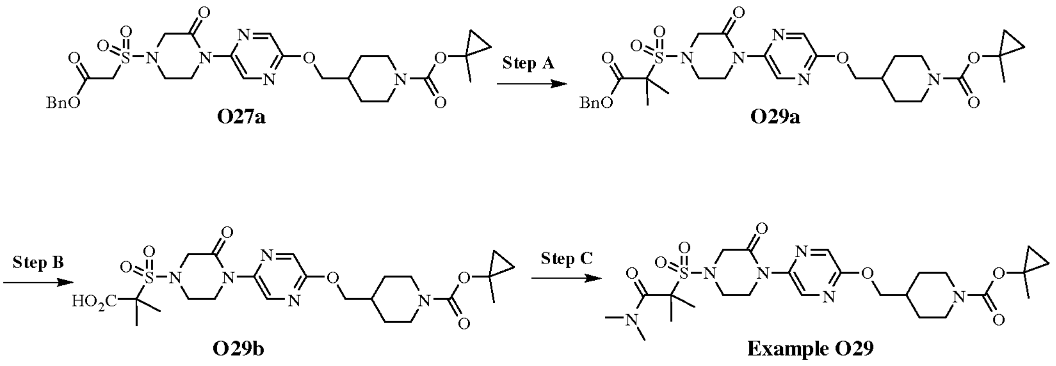
Example O28: 1-Methylcyclopropyl 4-((5-(4-(2-(dimethylamino)-2-oxoethylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



By following a similar procedure as the one used for preparing **O27c** from **O27b** except substituting dimethylamine-HCl for 2,4,6-trimethoxybenzylamine-HCl, **O28** is prepared; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 1.6 Hz, 1H), 8.03 (d, J = 1.6 Hz, 1H), 4.28 (s, 2H), 4.19 (m, 4H), 4.06 (m, 2H), 3.82 (s, 2H), 3.23 (s, 3H), 3.04 (s, 3H), 2.77 (m, 2H), 2.00 (m, 1H), 1.81 (m, 2H), 1.57 (s, 3H), 1.28 (m, 2H), 0.88 (m, 2H), 0.64 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{35}N_6O_7S$ calcd: 539.2, found: 539.2.

Example O29: 1-Methylcyclopropyl 4-((5-(4-(1-(dimethylamino)-2-methyl-1-oxopropan-2-ylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



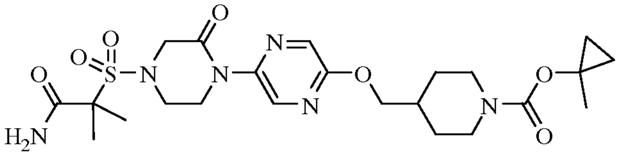


Step A: A solution of **O27a** (200 mg, 0.33 mmol) in dimethylformamide (5 mL) is treated with potassium carbonate (138 mg, 1.0 mmol) and iodomethane (63 μL, 1.0 mmol) and heated at 70 °C for 1 hour. The mixture is diluted with water and extracted with ethyl acetate. The organic layer is washed with water and brine, dried ($MgSO_4$), filtered and concentrated to provide **O29a**; ESIMS *m/z* for $(M+H)^+$ $C_{30}H_{40}N_5O_8S$ calcd: 630.3, found: 630.3.

Step B: A solution of **O29a** (crude from **Step A**) and ammonium formate (~1 mmol) in methanol (5 mL) is treated with Pd/C (wet, 10%) and heated at 80 °C for 1 hour. The mixture is cooled, filtered, and the filtrate is washed with water and ethyl acetate. The layers are separated and the organic layer is washed with 1N HCl and brine, then dried over $MgSO_4$, filtered and concentrated. The residue is purified using mass-triggered reverse phase HPLC to afford **O29b**; ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 1.6 Hz, 1H), 8.05 (d, J = 1.6 Hz, 1H), 4.43 (s, 2H), 4.21 (d, J = 6.4 Hz, 2H), 4.05 (m, 2H), 3.87 (br s, 2H), 2.78 (m, 2H), 2.03 (m, 1H), 1.82 (s, 6H), 1.57 (s, 3H), 1.28 (m, 2H), 0.89 (m, 2H), 0.65 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{34}N_5O_8S$ calcd: 540.2, found: 540.1.

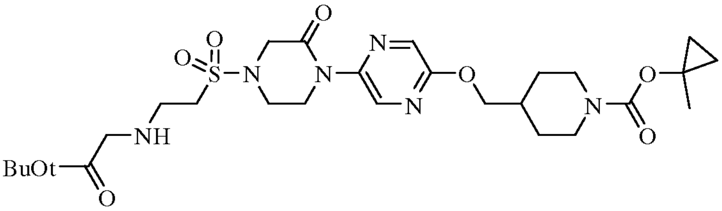
Step C: By following a similar procedure as the one used for preparing **O27c** from **O27b** except substituting dimethylamine-HCl for 2,4,6-trimethoxybenzylamine-HCl and **O29b** for **O27c**, **O29** is prepared; ^1H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 1.4 Hz, 1H), 7.87 (d, J = 1.4 Hz, 1H), 4.14 (s, 2H), 4.04 (d, J = 6.4 Hz, 2H), 3.88 (m, 2H), 3.66 (s, 2H), 2.60 (m, 2H), 1.84 (m, 1H), 1.65 (m, 2H), 1.54 (s, 6H), 1.41 (s, 6H), 1.11 (m, 2H), 0.73 (m, 2H), 0.48 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{25}H_{39}N_6O_7S$ calcd: 567.3, found: 567.2.

Example O30: 1-Methylcyclopropyl 4-((5-(4-(1-amino-2-methyl-1-oxopropan-2-ylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



By following a similar procedure as the one used for preparing **O27** from **O27b** except substituting **O29b** for **O27b**, **O30** is prepared; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.66 (d, J = 1.4 Hz, 1H), 8.03 (d, J = 1.4 Hz, 1H), 4.23 (s, 2H), 4.20 (d, J = 6.4 Hz, 2H), 4.02 (m, 2H), 3.78 (s, 2H), 2.77 (m, 2H), 2.00 (m, 1H), 1.81 (s, 6H), 1.57 (s, 3H), 1.27 (m, 2H), 0.89 (m, 2H), 0.64 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{35}N_6O_7S$ calcd: 539.2, found: 539.2.

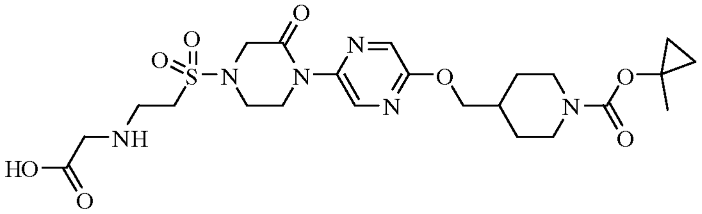
Example O31: 1-Methylcyclopropyl 4-((5-(4-(2-(2-tert-butoxy-2-oxoethylamino)ethylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



A solution of **O13a** (50 mg, 0.10 mmol), t-butylglycine-HCl (105 mg, 0.62 mmol) and diisopropylethylamine (108 μL, 0.62 mmol) in methanol (2 mL) and dimethylformamide (2 mL) and stirred at room temperture for 14 hours. The mixture is diluted with water and extracted with ethyl acetate. The organics are washed with water then brine, dried over $MgSO_4$, and filtered. The residue is concentrated and purified using mass-triggered reverse phase HPLC to afford **O31**; ^{1}H NMR (400 MHz, CDCl$_3$) δ

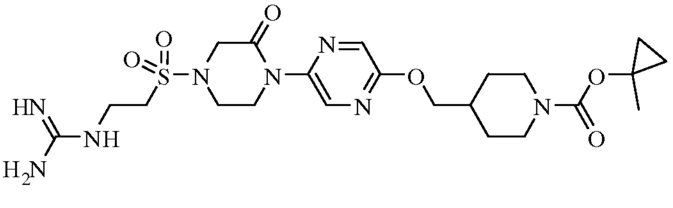
8.66 (d, J = 1.2 Hz, 1H), 8.04 (d, J = 1.2 Hz, 1H), 4.20 (s, 4H), 4.07 (m, 2H), 3.76 (m, 2H), 3.48 (s, 2H), 3.40 (m, 2H), 3.28 (m, 2H), 2.77 (m, 2H), 2.00 (m, 1H), 1.82 (m, 2H), 1.57 (s, 3H), 1.49 (s, 9H), 1.28 (m, 2H), 0.89 (m, 2H), 0.64 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{27}H_{43}N_6O_8S$ calcd: 611.3, found: 611.2.

Example O32: 2-(2-(4-(5-((1-((1-Methylcyclopropoxy)carbonyl)piperidin-4-yl)methoxy)pyrazin-2-yl)-3-oxopiperazin-1-ylsulfonyl)ethylamino)acetic acid.



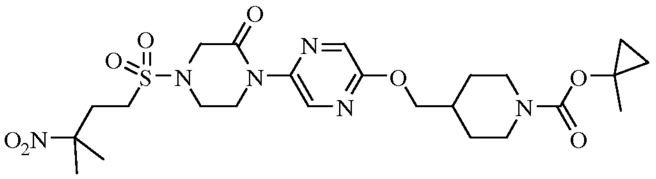
A solution of **O31** (31 mg, 0.05 mmol) in dichloromethane (1 mL) is treated with HCl (1 mL of 4N in dioxane) and aged for 2 hours at room temperature. The mixture is concentrated and purified using mass-triggered reverse phase HPLC to afford the **O32**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 1.4 Hz, 1H), 7.90 (d, J = 1.4 Hz, 1H), 4.01 (m, 4H), 3.88 (m, 2H), 3.46 (m, 8H), 2.69 (m, 2H), 1.88 (m, 1H), 1.69 (m, 2H), 1.47 (s, 3H), 1.18 (m, 2H), 0.80 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{35}N_6O_8S$ calcd: 555.2, found: 555.1.

Example O33: 1-Methylcyclopropyl 4-((5-(4-(2-guanidinoethylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



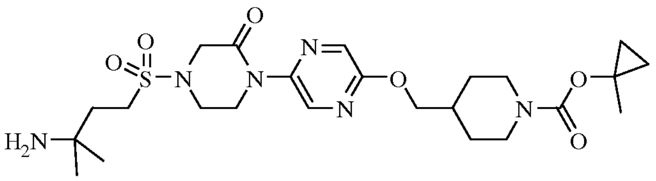
A solution of **O26** (22 mg, 0.044 mmol) and 3,5-dimethoxypyrazole-1-carboxamidine nitrate (13 mg, 0.066 mmol) in dimethylformamide (3 mL) is treated with diisopropylethylamine (23 µL, 0.13 mmol) and stirred at room temperature for 14 hours. The mixture is diluted with aqueous sodiumhydrogencarbonate and extracted with ethyl acetate. The organic layer is washed with brine, dried over $MgSO_4$, filtered, concentrated and purified using mass-triggered reverse phase HPLC to afford **O33**; ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 1.4 Hz, 1H), 7.93 (d, J = 1.4 Hz, 1H), 4.11 (m, 4H), 4.06 (m, 2H), 3.92 (m, 2H), 3.62 (m, 3H), 2.68 (m, 2H), 1.80 (m, 1H), 1.72 (m, 2H), 1.18 (m, 3H), 0.80 (m, 2H), 0.56 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{35}N_8O_6S$ calcd: 539.2, found: 539.2.

Example O34: 1-Methylcyclopropyl 4-((5-(4-(3-methyl-3-nitrobutylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



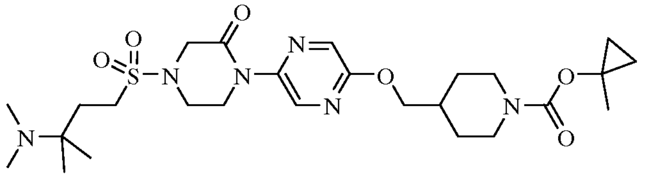
A solution of **O13a** (62 mg, 0.13 mmol) and 2-nitropropane (116 µL, 1.29 mmol) in methanol (0.5 mL) and tetrahydrofuran (1 mL) is treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (154 µL, 1.03 mmol) and stirred at room temperature for 14 hours. The mixture is diluted with water, extracted with ethyl acetate, and washed with brine. The organic layer is dried ($MgSO_4$), filtered, concentrated and purified on silica gel using 0-100% ethyl acetate in dichloromethane to afford **O34**; ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 1.4 Hz, 1H), 7.95 (d, J = 1.4 Hz, 1H), 4.11 (m, 4H), 4.00 (m, 2H), 3.65 (m, 2H), 2.99 (m, 2H), 2.68 (m, 2H), 2.35 (m, 2H), 1.92 (m, 1H), 1.72 (m, 2H), 1.59 (s, 6H), 1.48 (s, 3H), 1.18 (m, 2H), 0.80 (m, 2H), 0.56 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{37}N_6O_8S$ calcd: 569.2, found: 569.2.

Example O35: 1-Methylcyclopropyl 4-((5-(4-(3-amino-3-methylbutylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



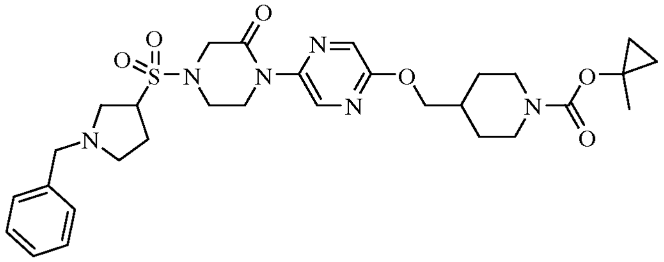
A solution of **O34** (105 mg, 0.18 mmol) in a mixture of methanol (5 mL) and tetrahydrofuran (4 mL) is treated with $NiCl_2$ (72 mg, 0.55 mmol) followed by sodium borohydride (21 mg, 0.55 mmol) and the resulting mixture is stirred at room temperature for 3 hours. The mixture is diluted with ethyl acetate and filtered, then washed with saturated aqueous sodium hydrogencarbonate and brine. The organic layer is dried ($MgSO_4$), filtered, concentrated and purified using mass-triggered reverse phase HPLC to afford **O35**; ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 1.2 Hz, 1H), 8.04 (d, J = 1.2 Hz, 1H), 4.20 (d, J = 6.4 Hz, 2H), 4.18 (s, 2H), 4.05 (m, 2H), 3.74 (m, 2H), 3.27 (m, 2H), 2.75 (m, 2H), 2.00 (m, 3H), 1.80 (m, 2H), 1.56 (s, 3H), 1.35 (m, 2H), 1.29 (s, 6H), 0.88 (m, 2H), 0.64 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{39}N_6O_6S$ calcd: 539.3, found: 539.2.

Example O36: 1-Methylcyclopropyl 4-((5-(4-(3-(dimethylamino)-3-methylbutylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



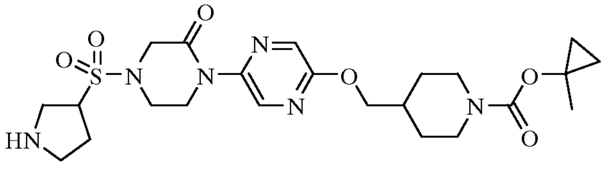
A solution of **O35** (56 mg, 0.10 mmol) in dimethylformamide (2 mL) is treated with K_2CO_3 (43 mg, 0.31 mmol) and iodomethane (13 μL, 0.21 mmol) and stirred at room temperature for 3 hours. The mixture is diluted with water, extracted with ethyl acetate, and washed with water and brine. The organic extracts are dried ($MgSO_4$), filtered, concentrated and purified using mass-triggered reverse phase HPLC to afford **O36**; ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 1.2 Hz, 1H), 8.04 (d, J = 1.2 Hz, 1H), 4.20 (d, J = 6.4 Hz, 2H), 4.18 (s, 2H), 4.07 (m, 2H), 3.72 (m, 2H), 3.21 (m, 2H), 2.77 (m, 2H), 2.35 (br s, 4H), 2.02 (m, 3H), 1.82 (m, 2H), 1.57 (s, 3H), 1.29 (m, 2H), 1.15 (br s, 6H), 0.88 (m, 2H), 0.64 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{43}N_6O_6S$ calcd: 567.3, found: 567.2.

Example O37: 1-Methylcyclopropyl 4-((5-(4-(1-benzylpyrrolidin-3-ylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



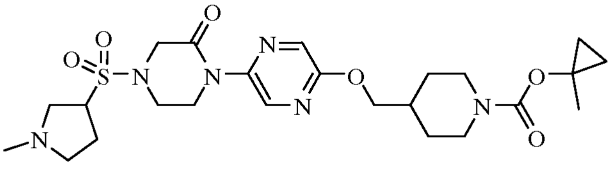
A solution of **O13a** (96 mg, 0.20 mmol) and N-trimethylsilyl-N-cyanomethylbenzylamine (104 µL, 0.42 mmol) in acetonitrile (5 mL) is treated with AgF (54 mg, 0.42 mmol) and heated at 75 °C for 4 hours. The mixture is filtered, washed with ethyl acetate, concentrated and purified on silica gel using 0-100% ethyl acetate in hexane to afford **O37**; ESIMS *m/z* for $(M+H)^+$ $C_{30}H_{41}N_6O_6S$ calcd: 613.3, found: 613.2.

Example O38: 1-Methylcyclopropyl 4-((5-(2-oxo-4-(pyrrolidin-3-ylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



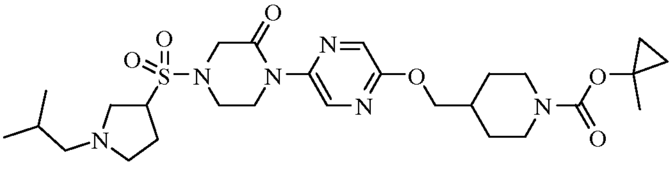
A solution of **O37** (45 mg) in EtOH (5 mL) is hydrogenated in an H-cube® (Pd/C, 50 bar H_2, 70 °C, 1 mL/min) device. The residue is concentrated to provide **O38** ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 1.4 Hz, 1H), 7.95 (d, J = 1.4 Hz, 1H), 4.11 (m, 4H), 3.98 (m, 2H), 3.68 (m, 2H), 3.50 (m, 1H), 3.40 (dd, J = 4.0, 13.2 Hz, 1H), 3.13 (m, 2H), 2.83 (m, 1H), 2.68 (m, 2H), 2.10 (m, 2H), 1.89 (m, 1H), 1.73 (m, 5H), 1.48 (s, 3H), 1.18 (m, 2H), 0.80 (m, 2H), 0.56 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{35}N_6O_6S$ calcd: 523.2, found: 523.2.

Example O39: 1-Methylcyclopropyl 4-((5-(4-(1-methylpyrrolidin-3-ylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



A solution of **O38** (24 mg, 0.05 mmol) and paraformaldehyde (~0.25 mmol) in 1,2-dichloroethane (5 mL) was treated with acetic acid (50 μL) and heated at 80 °C for 1 hour. $NaBH(OAc)_3$ (20 mg, 0.09 mmol) is added and the mixture is stirred at 80 °C for an additional 2 hours. The mixture is cooled, diluted with saturted aqueous sodiumhydrogencarbonate, and extracted with dichloromethane (2x). The organic layers are dried over $MgSO_4$, filtered, concentrated, and purified using mass-triggered reverse phase HPLC to afford **O39**; ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 1.4 Hz, 1H), 7.95 (d, J = 1.4 Hz, 1H), 4.17 (d, J = 7.2 Hz, 2H), 4.12 (d, J = 6.4 Hz, 2H), 3.71 (m, 3H), 2.86 (m, 1H), 2.66 (m, 3H), 2.33 (s, 3H), 2.18 (m, 2H), 1.91 (m, 1H), 1.73 (m, 2H), 1.48 (s, 3H), 1.20 (m, 2H), 0.80 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{37}N_6O_6S$ calcd: 537.3, found: 537.2.

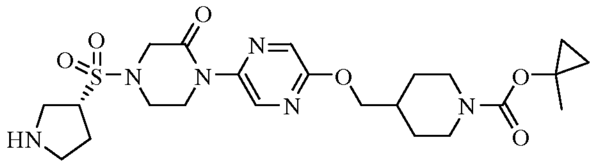
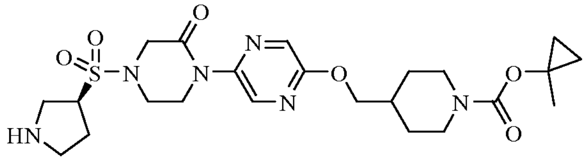
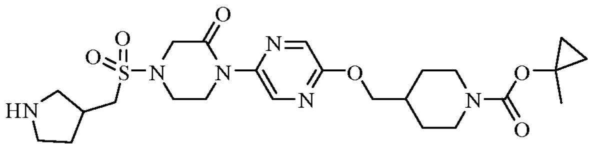
Example O40: 1-Methylcyclopropyl 4-((5-(4-(1-isobutylpyrrolidin-3-ylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.

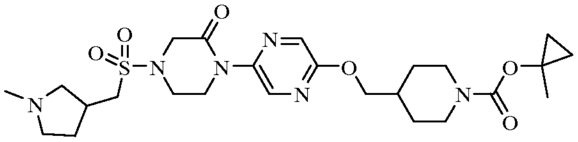
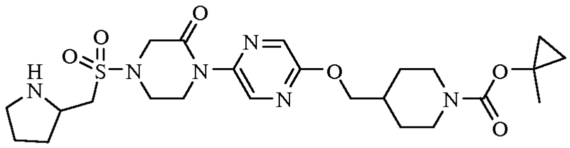
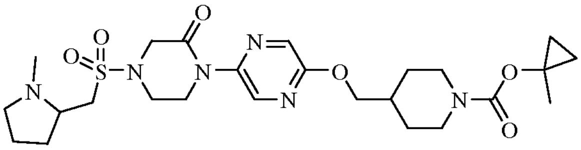
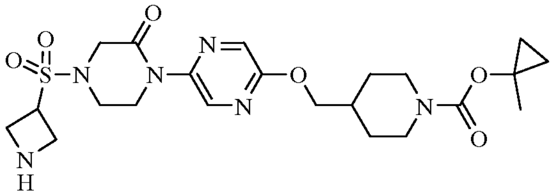
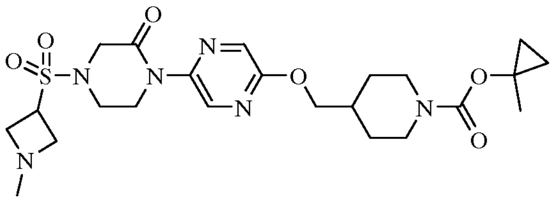


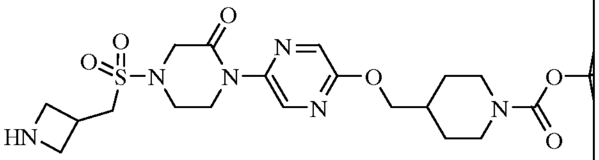
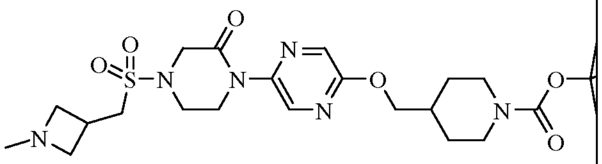
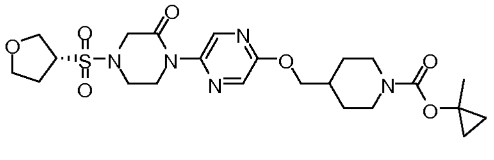
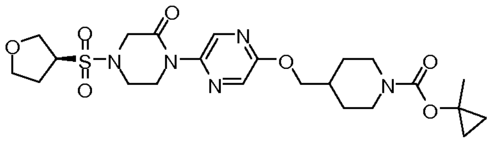
By following a similar procedure as the one used for preparing **O39** from **O38** except substituting isobutyraldehyde for paraformaldehyde, **O40** is prepared; ^1H

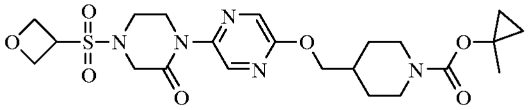
NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 1.2 Hz, 1H), 7.94 (d, J = 1.2 Hz, 1H), 4.18 (d, J = 6.0 Hz, 2H), 4.12 (d, J = 4.4 Hz, 2H), 3.96 (m, 2H), 3.69 (m, 2H), 2.80 (m, 2H), 2.68 (m, 2H), 2.58 (m, 2H), 2.17 (m, 3H), 1.91 (m, 1H), 1.73 (m, 2H), 1.65 (m, 1H), 1.48 (s, 3H), 1.20 (m, 2H), 0.84 (m, 6H), 0.79 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{27}H_{43}N_6O_6S$ calcd: 579.3, found: 579.2

By following a similar procedure as the one used for preparing **M48** from **M48a** except substituting the appropriate alcohol for **M48a** and **O3b** for **M1c**, followed in some cases by reductive aminations as in the preparation of **O39** and **O40**, the following compounds are prepared;

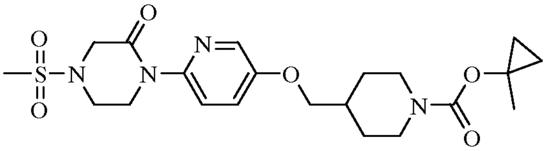
Ex.	Structure	Analytical data
O41		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 1.4 Hz, 1H), 7.95 (d, J = 1.4 Hz, 1H), 4.11 (m, 4H), 3.97 (m, 2H), 3.68 (m, 2H), 3.60 (m, 1H), 3.39 (dd, J = 4.0, 12.8 Hz, 1H), 3.10 (m, 2H), 2.82 (m, 1H), 2.68 (m, 2H), 2.08 (m, 2H), 1.91 (s, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.20 (m, 2H), 0.80 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{35}N_6O_6S$ calcd: 523.2, found: 523.2.
O42		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 1.4 Hz, 1H), 7.95 (d, J = 1.4 Hz, 1H), 4.11 (m, 4H), 3.97 (m, 2H), 3.68 (m, 2H), 3.60 (m, 1H), 3.39 (dd, J = 4.0, 12.8 Hz, 1H), 3.10 (m, 2H), 2.82 (m, 1H), 2.68 (m, 2H), 2.08 (m, 2H), 1.91 (s, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.20 (m, 2H), 0.80 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{35}N_6O_6S$ calcd: 523.2, found: 523.2.
O43		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 1.4 Hz, 1H), 7.82 (d, J = 1.4 Hz, 1H), 3.98 (d, J = 6.4 Hz, 2H), 3.95 (s, 2H), 3.85 (m, 2H), 3.50 (m, 2H), 3.13 (m, 2H), 2.89 (m, 4H), 2.61 (m, 5H), 1.97 (m, 5H), 1.78 (m, 2H), 1.59 (m, 2H), 1.44 (m, 2H), 1.35 (s, 3H), 1.05 (m, 2H), 0.67 (m, 2H), 0.43 (m, 2H); ESIMS *m/z* for $(M+H)^+$

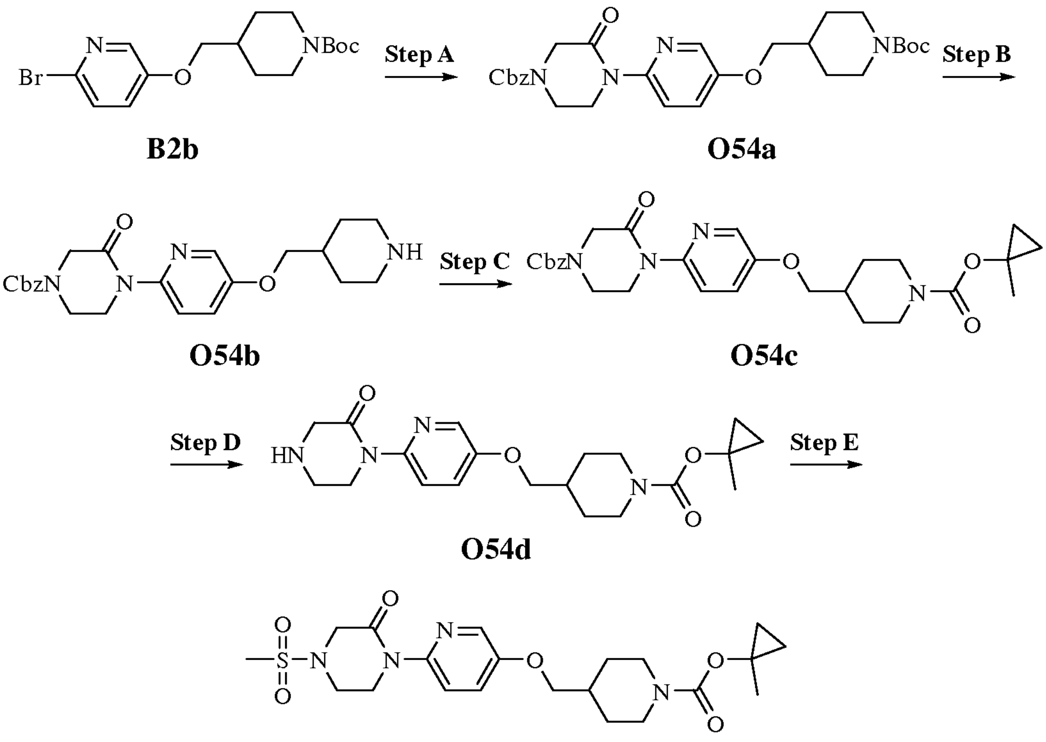
		$C_{24}H_{37}N_6O_6S$ calcd: 537.3, found: 537.3.
O44		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, J = 1.2 Hz, 1H), 7.95 (d, J = 1.2 Hz, 1H), 4.11 (d, J = 6.4 Hz, 2H), 4.08 (s, 2H), 3.98 (m, 2H), 3.62 (m, 2H), 3.04 (m, 2H), 2.68 (m, 6H), 2.50 (m, 2H), 2.33 (s, 3H), 2.17 (m, 1H), 1.91 (m, 2H), 1.72 (m, 5H), 1.62 (m, 2H), 1.48 (s, 3H), 1.18 (m, 2H), 0.79 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{25}H_{39}N_6O_6S$ calcd: 551.3, found: 551.2.
O45		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 1.2 Hz, 1H), 7.94 (d, J = 1.2 Hz, 1H), 4.15 (m, 5H), 3.99 (m, 2H), 3.65 (m, 3H), 3.24 (m, 1H), 3.12 (dd, J = 4.0, 14.0 Hz, 1H), 2.99 (m, 2H), 2.68 (m, 2H), 2.04 (m, 2H), 1.85 (m, 9H), 1.48 (s, 3H), 1.20 (m, 2H), 0.80 (m, 2H), 0.56 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{37}N_6O_6S$ calcd: 537.3, found: 537.3.
O46		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 1.2 Hz, 1H), 7.95 (d, J = 1.2 Hz, 1H), 4.11 (d, J = 6.4 Hz, 2H), 4.10 (s, 2H), 3.99 (m, 2H), 3.64 (m, 2H), 2.68 (m, 2H), 2.37 (s, 2H), 2.20 (s, 2H), 1.90 (m, 1H), 1.74 (m, 4H), 1.48 (s, 3H), 1.20 (m, 2H), 0.79 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{25}H_{39}N_6O_6S$ calcd: 551.3, found: 551.2.
O47		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.95 (s, 1H), 4.16 (m, 2H), 4.12 (m, 4H), 4.02 (m, 2H), 3.97 (m, 2H), 3.82 (m, 2H), 3.66 (m, 3H), 2.68 (m, 2H), 2.04 (m, 2H), 1.91 (m, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.18 (m, 2H), 0.80 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{33}N_6O_6S$ calcd: 509.2, found: 509.2.
O48		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 1.0 Hz, 1H), 7.95 (d, J = 1.0 Hz, 1H), 4.14 (s, 2H), 4.12 (d, J = 4.4 Hz, 2H), 3.96 (m, 2H), 3.90 (m, 1H), 3.67 (m, 2H), 3.54 (m, 2H), 3.44 (m, 2H), 2.68 (m, 2H), 2.30 (s, 3H), 1.91 (m, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.18 (m, 2H), 0.80 (m, 2H), 0.55 (m,

		2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{35}N_6O_6S$ calcd: 523.2, found: 523.2.
O49		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 1.2 Hz, 1H), 7.94 (d, J = 1.4 Hz, 1H), 4.12 (d, J = 6.8 Hz, 2H), 4.06 (s, 2H), 3.98 (m, 2H), 3.77 (m, 2H), 3.72 (m, 1H), 3.62 (m, 2H), 3.44 (m, 2H), 3.26 (m, 2H), 3.18 (m, 1H), 2.68 (m, 2H), 1.90 (m, 1H), 1.73 (m, 2H), 1.48 (s, 3H), 1.20 (m, 3H), 0.80 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{35}N_6O_6S$ calcd: 523.2, found: 523.2.
O50		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 1.6 Hz, 1H), 7.94 (d, J = 1.6 Hz, 1H), 4.12 (d, J = 6.8 Hz, 2H), 3.98 (m, 3H), 3.72 (m, 1H), 3.62 (m, 2H), 3.43 (m, 2H), 3.23 (d, J = 7.2 Hz, 2H), 2.95 (m, 2H), 2.84 (m, 1H), 2.68 (m, 2H), 2.23 (s, 3H), 1.91 (m, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.20 (m, 3H), 0.80 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{37}N_6O_6S$ calcd: 537.3, found: 537.2.
O51		^{1}H-NMR (400MHz, $CDCl_3$) δ 8.64 (d, *J* = 1.4 Hz, 1H), 8.02 (d, *J* = 1.4 Hz, 1H), 4.23 (m, 2H), 4.19 (m, 2H), 4.06-4.06 (m, 5H), 3.84 (m, 2H), 3.76 (m, 2H), 2.74 (m, 2H), 2.33 (m, 2H), 1.98 (m, 1H), 1.80 (m, 2H), 1.55 (s, 3H), 1.26 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{23}H_{34}N_5O_7S$ $[M+H]^+$ 524.2, found 524.3.
O52		^{1}H-NMR (400MHz, $CDCl_3$) δ 8.65 (d, *J* = 1.4 Hz, 1H), 8.02 (d, *J* = 1.4 Hz, 1H), 4.21 (m, 2H), 4.18 (d, *J* = 6.5 Hz, 2H), 4.11-4.16 (m, 2H), 3.98-4.06 (m, 5H), 3.84 (m, 2H), 3.76 (m, 2H), 2.75 (dd, *J* = 12.3, 12.3 Hz, 2H), 2.33 (m, 2H), 1.97 (m, 1H), 1.79 (m, 2H), 1.55 (s, 3H), 1.26 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{23}H_{34}N_5O_7S$ $[M+H]^+$ 524.2, found 524.4.

O53		^{1}H-NMR (400MHz, $CDCl_3$) δ8.65 (d, *J* = 1.4 Hz, 1H), 8.02 (d, *J* = 1.4 Hz, 1H), 4.93 (m, 4H), 4.51 (tt, *J* = 8.0, 6.4 Hz, 1H), 3.95-4.30 (m, 8H), 3.75 (m, 2H), 2.75 (m, 2H), 1.98 (m, 1H), 1.79 (m, 2H), 1.55 (s, 3H), 1.26 (m, 2H), 0.87 (m, 2H), 0.63 (m, 2H); ESIMS calcd. for $C_{22}H_{32}N_5O_7S$ $[M+H]^+$ 510.2, found 510.2.

Example O54: 1-Methylcyclopropyl 4-((5-(4-(isopropylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





Example O54

[00308] **Step A:** : By following a similar procedure as the one used for preparing **O1a** from **B4b** except substituting **B2b** for **B4b**, **O54a** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{28}H_{37}N_4O_6$ calcd: 525.3, found: 525.2.

[00309] **Step B:** A sample of **O54a** (200 mg, 0.38 mmol) is treated with trifluoroacetic acid (3 mL) and aged for 30 minutes. The solvent is removed and the reaction is treated with ethyl acetate and extracted with 1 M HCl three times. The organics are discarded and the aqueous layer is made basic with solid Na_2CO_3 and extracted with ethyl acetate three times. The combined organics are dried over $MgSO_4$, filtered and evaporated to afford **O54b**; ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{29}N_4O_4$ calcd: 425.2, found: 425.2.

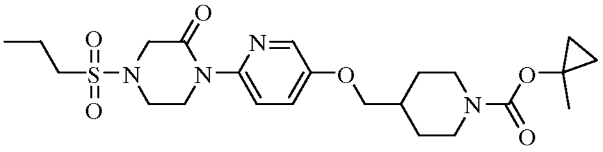
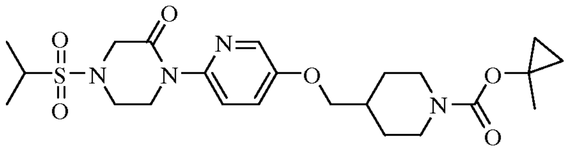
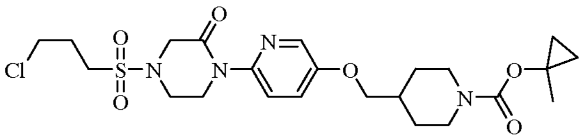
[00310] **Step C:** By following a similar procedure as the one used for preparing **O2** from **O1** except substituting **O54b** for **O1**, **O54c** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{28}H_{35}N_4O_6$ calcd: 523.3, found: 523.2.

[00311] **Step D:** By following a similar procedure as the one used for preparing **O3b** from **O3a** except substituting **O54c** for **O3a**, **O54d** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{29}N_4O_4$ calcd: 389.2, found: 389.2.

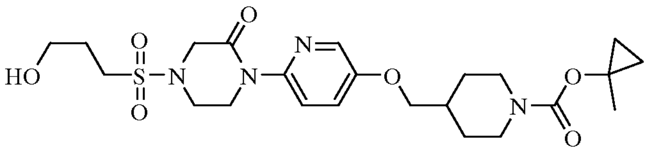
[00312] **Step E:** By following a similar procedure as the one used for preparing **O3** from **O3b** except substituting **O54d** for **O3b** and methanesulfonyl chloride for *n*-propanesulfonyl chloride, **O54** is prepared; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 2.9 Hz, 1H), 7.66 (d, J = 9.0 Hz, 1H), 7.17 (dd, J = 2.9, 9.0, 1H), 4.10 (m, 2H), 4.05 (m, 2H), 4.03 (s, 2H), 3.77 (d, J = 6.3 Hz, 2H), 3.58 (m, 2H), 2.48 (s, 3H), 2.69 (m, 2H), 1.90 (m, 1H), 1.74 (m, 2H), 1.48 (s, 3H), 1.20 (m, 2H)), 0.79 (m, 2H), 0.57 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{31}N_4O_6S$ calcd: 467.2, found: 467.2.

[00313] By following a similar procedure as the one used for preparing **O54** from **O54d** except substituting the appropriate sulfonyl chloride for methanesulfonyl chloride, the following compounds are made;

Ex.	Structure	Analytical data

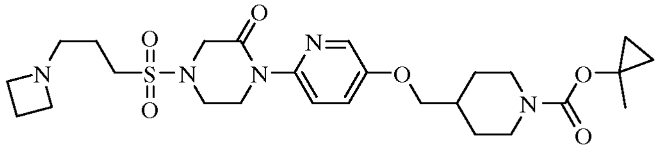
O55		^{1}H NMR (400 MHz, CDCl$_3$) δ 8.07 (d, J = 2.9 Hz, 1H), 7.73 (d, J = 9.0 hz, 1H), 7.24 (dd, J = 9.0, 3.0 Hz, 1H), 4.20 (m, 2H), 4.13 (s, 2H), 4.09 (m, 2H), 3.84 (d, J = 6.3 Hz, 2H), 3.68 (m, 2H), 3.00 (m, 2H), 2.76 (dd, J = 12.4, 12.4 Hz, 2H), 1.98 (m, 1H), 1.89 (m, 2H), 1.82 (m, 2H), 1.55 (s, 3H), 1.27 (m, 2H), 1.08 (t, J = 7.5 Hz, 3H), 0.87 (m, 2H), 0.63 (m, 2H); ESIMS *m/z* for (M+H)$^+$ C$_{23}$H$_{35}$N$_4$O$_6$S calcd.: 495.2, found: 495.6.
O56		^{1}H NMR (400 MHz, CDCl$_3$) δ 8.07 (d, J = 2.7 Hz, 1H), 7.73 (d, J = 9.0 Hz, 1H), 7.24 (dd, J = 9.0, 3.0 Hz, 1H), 4.18 (s, 2H), 4.16 (m, 2H), 4.08 (m, 2H), 3.84 (d, J = 6.3 Hz, 2H), 3.73 (m, 2H), 3.27 (sept., J = 6.8 Hz, 1H), 2.76 (dd, J = 12.3, 12.3 Hz, 2H), 1.97 (m, 1H), 1.82 (m, 2H), 1.55 (s, 3H), 1.40 (d, J = 6.8 Hz, 6H), 1.27 (m, 2H), 0.87 (m, 2H), 0.63 (m, 2H); ESIMS *m/z* for (M+H)$^+$ C$_{23}$H$_{35}$N$_4$O$_6$S calcd.: 495.2, found: 495.6.
O57		^{1}H NMR (400 MHz, CDCl$_3$) δ 8.00 (d, J = 2.8 Hz, 1H), 7.67 (d, J = 9.2 Hz, 1H), 7.17 (dd, J = 9.2, 3.2 Hz, 1H), 4.15 (m, 2H), 4.08 (m, 2H), 4.04 (m, 2H), 3.78 (d, J = 6.4 Hz, 2H), 3.63 (m, 2H), 3.15 (m, 2H), 2.69 (t, J = 12.4 Hz, 2H), 2.26 (m, 2H), 1.91 (m, 1H), 1.75 (d, J = 12.4 Hz, 2H), 1.49 (s, 3H), 1.20 (m, 2H), 0.80 (m, 2H), 0.56 (m, 2H); ESIMS *m/z* for (M+H)$^+$ C$_{23}$H$_{34}$ClN$_4$O$_6$S calcd.: 529.2, found: 529.1.

Example O58: 1-Methylcyclopropyl 4-((6-(4-(3-hydroxypropylsulfonyl)-2-oxopiperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate.



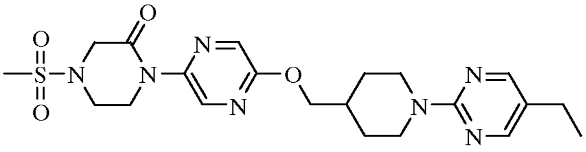
By following a similar procedure as the one used for preparing **O21** from **O5** except substituting **O57** for **O5**, **O58** is prepared; ^{1}H NMR (400 MHz, CD_3CN) δ 8.09 (d, J = 2.1 Hz, 1H), 7.65 (d, J = 6.9 Hz, 1H), 7.34 (dd, J = 3.0, 6.6 Hz, 1H), 4.02 (s, 2H), 4.01 (m, 2H), 3.96 (m, 2H), 3.90 (d, J = 4.8 Hz, 2H), 3.63 (m, 2H), 3.59 (dd, J = 4.5, 9.0 Hz, 2H), 3.16 (m, 2H), 2.79 (m, 3H), 1.92 (m, 1H), 1.77 (m, 2H), 1.49 (s, 3H), 1.19 (m, 2H), 0.80 (m, 2H), 0.59 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{54}N_4O_7S$ calcd.: 511.2, found: 511.1.

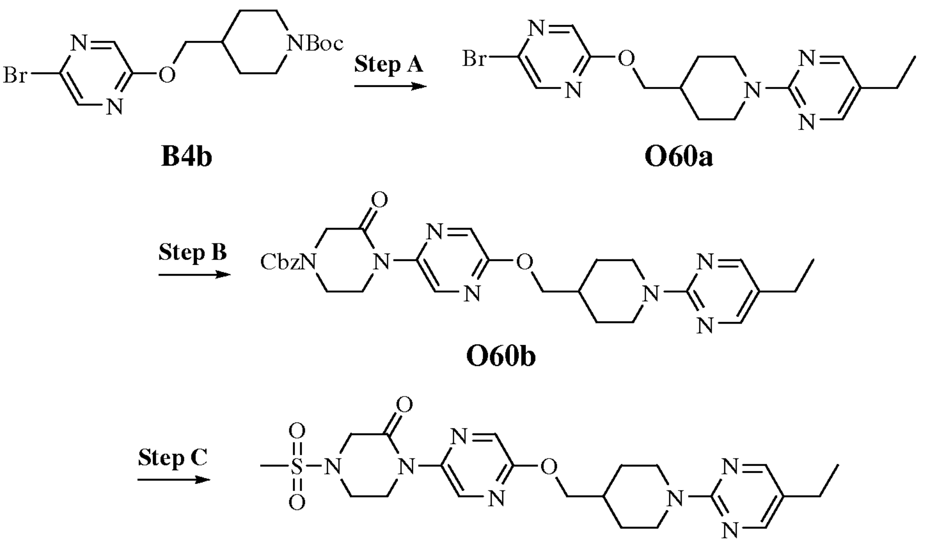
Example O59: 1-Methylcyclopropyl 4-((6-(4-(3-(azetidin-1-yl)propylsulfonyl)-2-oxopiperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate.



By following a similar procedure as the one used for preparing **O16** from **O5** except substituting **O57** for **O5**, **O59** is prepared; ^{1}H NMR (400 MHz, CD_3CN) δ 8.09 (d, J = 3.2 Hz, 1H), 7.66 (d, J = 9.2 Hz, 1H), 7.33 (dd, J = 9.2, 3.2 Hz, 1H), 4.02 (m, 2H), 4.01 (m, 2H), 3.97 (m, 2H), 3.90 (d, J = 6.4 Hz, 2H), 3.63 (m, 2H), 3.41 (m, 2H), 3.19 (m, 2H), 2.70 (m, 4H), 2.10 (m, 4H), 1.80 (m, 4H), 1.49 (s, 3H), 1.20 (m, 2H), 0.80 (m, 2H), 0.59 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{40}N_5O_6S$ calcd.: 550.3, found: 550.1.

Example O60: 1-(5-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)pyrazin-2-yl)-4-(methylsulfonyl)piperazin-2-one.





B4b **O60a** **O60b**

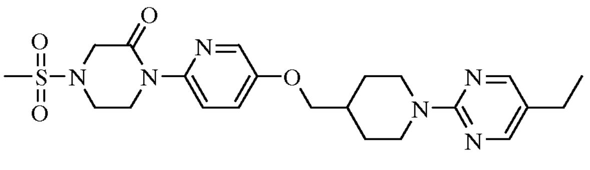
Example O60

[00314] **Step A:** By following a procedure similar to the one used for preparing **E1** from **E1a**, except substituting **B4b** for **E1a**, **O60a** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{16}H_{21}BrN_5O$ calcd: 378.1, found: 378.1.

[00315] **Step B:** By following a procedure similar to the one used for preparing **O1a** from **B4b**, except substituting **O60a** for **B4b**, **O60b** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{28}H_{34}N_7O_4$ calcd: 532.3, found: 532.2.

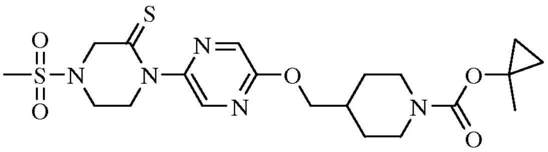
[00316] **Step C:** By following a procedure similar to the one used for preparing **O3** from **O3b**, except substituting **O60b** for **O3b**, and methanesulfonyl chloride for *n*-propanesulfonyl chloride, **O60** is prepared; ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 1.4 Hz, 1H), 8.41 (s, 2H), 8.04 (d, J = 1.4 Hz, 1H), 4.72 (m, 2H), 4.25 (d, J = 6.4, 2H), 4.14 (s, 2H), 4.09 (m, 2H), 3.68 (m, 2H), 3.21 (m, 2H), 2.94 (s, 3H), 2.60 (dd, J = 15.2, 7.6, 2H), 2.22 (m, 1H), 2.05 (m, 2H), 1.48 (m, 2H), 1.26 (dd, J = 7.6, 7.6, 3H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{29}N_7O_4S$ calcd: 476.2, found: 476.3.

Example O61: 1-(5-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)pyridin-2-yl)-4-(methylsulfonyl)piperazin-2-one.



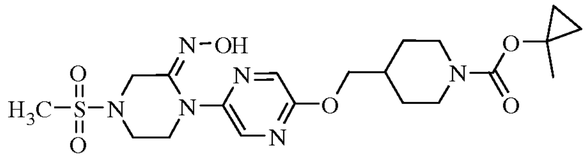
[00317] By following a procedure similar to the one used for preparing **O60** from **B4b**, except substituting **B2b** for **B4b**, **O61b** is prepared; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 2H), 8.09 (d, J = 2.9 Hz, 1H), 7.73 (d, J = 9.0 Hz, 1H), 7.25 (dd, J = 9.0, 2.9), 4.79 (m, 2H), 4.12 (m, 2H), 4.10 (s, 2H), 3.87 (d, J = 6.4, 2H), 3.64 (m, 2H), 2.92 (s, 3H), 2.91 (m, 2H), 2.46 (dd, J = 15.2, 7.6, 2H), 2.11 (m, 1H), 1.93 (m, 2H), 1.37 (m, 2H), 1.19 (dd, J = 7.6, 7.6, 3H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{31}N_6O_4S$ calcd: 475.2, found: 475.2.

Example O62: 1-Methylcyclopropyl 4-((5-(4-(methylsulfonyl)-2-thioxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



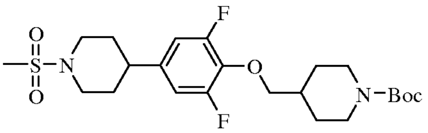
[00318] A solution of **O2** (121 mg, 0.26 mmol) in tetrahydrofuran (3 mL) is treated with Lawesson's reagent (115 mg, 0.29 mmol), sealed in a reaction vessel and stirred at 90 °C overnight. The reaction is cooled to room temperature, evaporated to dryness and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **O62**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 1.3 Hz, 1H), 8.12 (d, J = 1.4 Hz, 1H), 4.58 (s, 2H), 4.21 (m, 2H), 4.21 (d, J = 6.5 Hz, 2H), 4.03 (m, 2H), 3.78 (m, 2H), 2.98 (s, 3H), 2.77 (m, 2H), 1.99 (m, 1H), 1.81 (m, 2H), 1.55 (s, 3H), 1.29 (m, 2H), 0.87 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+Na)^+$ $C_{20}H_{29}N_5O_5S_2Na$ calcd: 506.2, found: 506.1 $(M+Na^+)$.

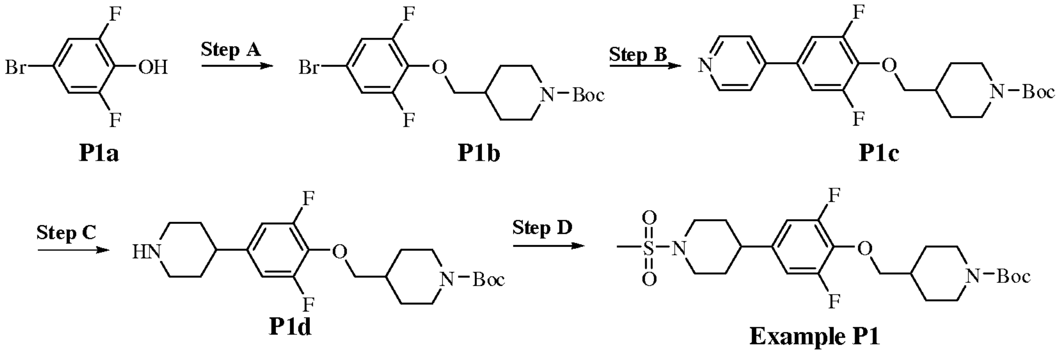
Example O63: 1-Methylcyclopropyl 4-((5-(2-(hydroxyimino)-4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00319] A solution of **O62** (30 mg, 0.062 mmol) in ethanol (1 mL) is treated with hydroxylamine (7 μL of a 50% solution, 0.12 mmol) sealed in a reaction vessel and stirred at 80 °C overnight. The reaction is cooled to room temperature and evaporated to dryness to afford **63**; ^{1}H-NMR (400MHz, $CDCl_3$) δ 8.46 (d, J = 1.4 Hz, 1H), 7.96 (d, J = 1.4Hz, 1H), 4.47 (s, 2H), 4.21 (m, 2H), 4.14 (d, J = 6.5 Hz, 2H), 3.87 (m, 2H), 3.62 (m, 2H), 3.52 (m, 1H), 2.92 (s, 3H), 2.74 (m, 2H), 1.95 (m, 1H), 1.79 (m, 2H), 1.55 (s, 3H), 1.26 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{20}H_{31}N_6O_6S$ $[M+H]^+$ 483.2, found 483.4.

Example P1: *tert*-Butyl 4-((2,6-difluoro-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate.





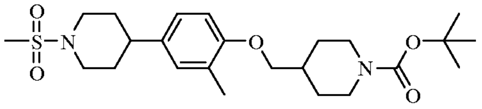
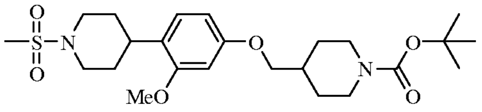
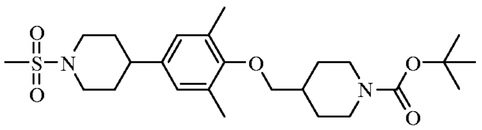
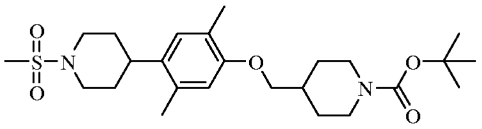
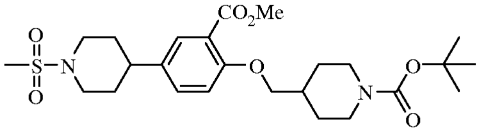
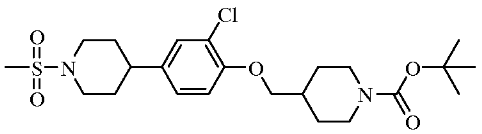
[00320] **Step A:** A mixture of **P1a** (1.67 g, 8 mmol), *tert*-butyl 4-((methylsulfonyloxy)methyl)piperidine-1-carboxylate (2.35 g, 8 mmol), and Cs_2CO_3 (3.91 g, 12 mmol) in N,N-dimethylformamide (30 mL) is heated at 90°C overnight. The reaction mixture is poured into water (200 mL), extracted with ethyl acetate (3 x 50 mL), washed with water (2 x 30 mL), dried (Na_2SO_4) and concentrated to give **P1b**; ESIMS calcd. for $C_{17}H_{22}BrF_2NNaO_3$ $(M+Na)^+$ 428.1, found 428.2. The product is used without purification.

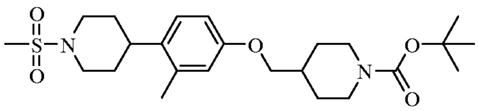
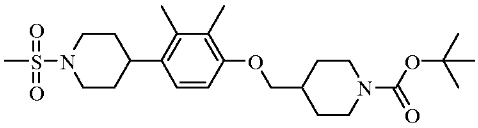
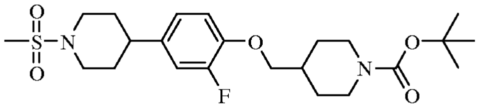
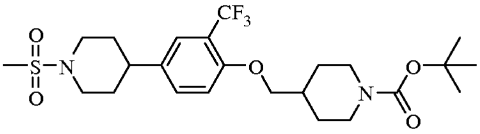
[00321] **Step B:** A mixture **P1b** (2.03 g, 5 mmol), pyridin-4-ylboronic acid (0.80 g, 6.5 mmol), Na_2CO_3 (2.65, 25 mmol), and $Pd(PPh_3)_4$ (289 mg, 0.25 mmol) in water (13 mL) and DME (52 mL)) is heated at 80°C overnight under a nitrogen atmosphere. The reaction mixture is concentrated, water (200 mL) added, extracted with ethyl acetate (3 x 100 mL), washed with water (2 x 30 mL), dried (Na_2SO_4) and concentrated. Silica gel chromatography (0% to 5% gradient of MeOH in dichloromethane) gave **P1c**; ESIMS calcd. for $C_{22}H_{27}F_2N_2O_3$ $(M+H)^+$ 405.2, found 405.2.

[00322] **Step C:** A solution **P1c** (654 mg, 1.59 mmol) and TFA (118 µL, 1.59 mmol) in EtOH (100ml) is hydrogenated using a 10% Pd/C cartridge on H-Cube (flow 1mL/min) at 70 atm and 90°C. To the resulting solution is added a saturated solution of sodiumhydrogencarbonate (1 mL) and the EtOH is evaporated. To the residue is added water (50 mL) and dichloromethane (30 mL). The aqueous phase is further extracted with dichloromethane (2 x 30 mL) and discarded. The combined organics are dried over Na_2SO_4 and concentrated to yield **P1d**; ESIMS calcd. for $C_{22}H_{33}F_2N_2O_3$ $(M+H)^+$ 411.2, found 411.2.

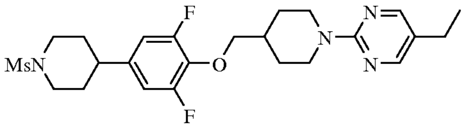
[00323] **Step D:** Methanesulfonyl chloride (117 µL, 1.5 mmol) is added dropwise to a cold (ice/water bath) solution **P1d** (411 mg, 1 mmol) and Et_3N (418 µL, 3 mmol) in dry dichloromethane (6 mL). The resulting solution is stirred at room temperature for 2 hours. The reaction mixture is added to water (40 mL) and extracted with dichloromethane (3 x 40 mL). The combined organic layers are dried (Na_2SO_4) and concentrated to yield **P1**; ^{1}H-NMR (600MHz, $CDCl_3$) δ6.74 (m, 2H), 4.14 (m, 2H), 3.94 (m, 4H), 2.82 (s, 3H), 2.75 (td, J = 12.1, 2.5 Hz, 4H), 2.53 (tt, J = 12.1, 3.6 Hz, 1H), 1.93 (m, 3H), 1.84 (m, 2H), 1.74 (m, 2H), 1.46 (s, 9H), 1.25 (qd, J = 12.4, 4.2 Hz, 2H). ESIMS calcd. for $C_{18}H_{27}F_2N_2O_3S$ $(M\text{-}Boc+H)^+$ 389.2, found 389.2.

[00324] By following a procedure similar to the one used for preparing **P1** from **P1a**, except substituting the appropriate commercially available halophenol for **P1a**, the follwing examples are prepared;

P2		^{1}H-NMR (600MHz, $CDCl_3$) δ 6.97 (m, 2H), 6.73 (d, J = 8.2 Hz, 1H), 4.15 (m, 2H), 3.92 (dt, J = 11.7, 2.1 Hz, 2H), 3.79 (d, J = 6.2 Hz, 2H), 2.81 (s, 3H), 2.75 (m, 4H), 2.52 (tt, J = 12.1, 3.6 Hz, 1H), 2.21 (s, 3H), 1.98 (m, 1H), 1.92 (m, 2H), 1.80 (m, 4H), 1.47 (s, 9H), 1.30 (qd, J = 12.4, 4.2 Hz, 2H). ESIMS calcd. for $C_{19}H_{31}N_2O_3S$ (M-Boc+H)$^+$ 367.2, found 367.2.
P3		^{1}H-NMR (600MHz, $CDCl_3$) δ 7.02 (d, J = 8.1 Hz, 1H), 6.43 (m, 2H), 4.15 (m, 2H), 3.91 (m, 2H), 3.79 (m, 5H), 2.94 (tt, J = 12.2, 3.4 Hz, 1H), 2.91 (s, 3H), 2.77 (m, 4H), 1.95 (m, 1H), 1.89 (m, 2H), 1.83 (m, 2H), 1.77 (m, 2H), 1.47 (s, 9H), 1.28 (qd, J = 12.4, 4.2 Hz, 2H). ESIMS calcd. for $C_{19}H_{31}N_2O_4S$ (M-Boc+H)$^+$ 383.2, found 383.2.
P4		^{1}H-NMR (600MHz, $CDCl_3$) δ 7.26 (s, 2H), 4.17 (m, 2H), 3.92 (m, 2H), 3.58 (d, J = 6.3 Hz, 2H), 2.81 (s, 3H), 2.75 (m, 4H), 2.48 (tt, J = 12.2, 3.6 Hz, 1H), 2.24 (s, 6H), 1.98 (m, 1H), 1.90 (m, 4H), 1.79 (m, 2H), 1.47 (s, 9H), 1.33 (qd, J = 12.4, 4.1 Hz, 2H). ESIMS calcd. for $C_{20}H_{33}N_2O_3S$ (M-Boc+H)$^+$ 381.2, found 381.2.
P5		^{1}H-NMR (600MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.58 (s, 1H), 4.15 (m, 2H), 3.94 (m, 2H), 3.77 (d, J = 6.2 Hz, 2H), 2.82 (s, 3H), 2.75 (m, 5H), 2.29 (s, 3H), 2.17 (s, 3H), 1.97 (m, 1H), 1.81 (m, 6H), 1.47 (s, 9H), 1.29 (m, 2H). ESIMS calcd. for $C_{20}H_{33}N_2O_3S$ (M-Boc+H)$^+$ 381.2, found 381.2.
P6		^{1}H-NMR (400MHz, $CDCl_3$) δ 7.63 (d, J = 2.4 Hz, 1H), 7.28 (dd, J = 8.7, 2.5 Hz, 1H), 6.89 (d, J = 8.6 Hz, 1H), 4.16 (m, 2H), 3.93 (m, 2H), 3.88 (s, 3H), 3.85 (d, J = 6.2 Hz, 2H), 2.82 (s, 3H), 2.75 (m, 4H), 2.58 (tt, J = 12.1, 3.6 Hz, 1H), 1.74-2.07 (m, 7H), 1.46 (s, 9H), 1.29 (m, 2H). ESIMS calcd. for $C_{20}H_{31}N_2O_5S$ (M-Boc+H)$^+$ 411.2, found 410.8.
P7		^{1}H-NMR (400MHz, $CDCl_3$) δ 7.20 (d, J = 2.2 Hz, 1H), 7.03 (dd, J = 8.4, 2.2 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 4.16 (m, 2H), 3.93 (m, 2H), 3.84 (d, J = 6.4 Hz, 2H), 2.82 (s, 3H), 2.75 (m, 4H), 2.53 (tt, J = 12.1, 3.6 Hz, 1H), 2.02 (m, 1H), 1.92 (m, 2H), 1.71 (m,4H), 1.46 (s, 9H), 1.29 (m, 2H). ESIMS calcd. for $C_{18}H_{28}ClN_2O_3S$ (M-Boc+H)$^+$ 387.2,

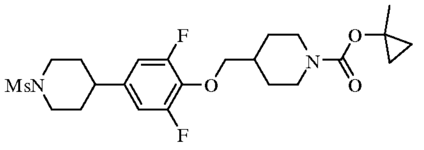
		found 386.8.
P8		^{1}H-NMR (400MHz, $CDCl_3$) δ 7.08 (d, J = 8.2 Hz, 1H), 6.71 (m, 2H), 4.14 (m, 2H), 3.94 (m, 2H), 3.77 (d, J = 6.4 Hz, 2H), 2.82 (s, 3H), 2.76 (m, 5H), 2.31 (s, 3H), 1.93 (m, 1H), 1.81 (m, 6H), 1.46 (s, 9H), 1.25 (m, 2H). ESIMS calcd. for $C_{19}H_{31}N_2O_3S$ $(M\text{-}Boc+H)^+$ 367.2, found 367.2.
P9		^{1}H-NMR (400MHz, $CDCl_3$) δ 6.99 (d, J =8.8 Hz, 1H), 6.69 (d, J = 8.7 Hz, 1H), 4.16 (m, 2H), 3.95 (m, 2H), 3.78 (d, J = 6.2 Hz, 2H), 2.72-2.84 (m, 8H), 2.24 (s, 3H), 2.18 (s, 3H), 1.83 (m, 7H), 1.47 (s, 9H), 1.30 (m, 2H). ESIMS calcd. for $C_{20}H_{33}N_2O_3S$ $(M\text{-}Boc+H)^+$ 381.2, found 381.2.
P10		^{1}H-NMR (400MHz, $CDCl_3$) δ 6.90 (m, 3H), 4.15 (m, 2H), 3.93 (m, 2H), 3.84 (d, J = 6.5 Hz, 2H), 2.82 (s, 3H), 2.75 (m, 4H), 2.54 (tt, J = 12.1, 3.6 Hz, 1H), 1.99 (m, 1H), 1.93 (m, 1H), 1.84 (m, 2H), 1.77 (m, 2H), 1.46 (s, 9H), 1.26 (m, 2H). ESIMS calcd. for $C_{18}H_{28}FN_2O_3S$ $(M\text{-}Boc+H)^+$ 371.2, found 371.2.
P11		^{1}H-NMR (400MHz, $CDCl_3$) δ 7.39 (d, J = 2.1 Hz, 1H), 7.30 (dd, J = 8.6, 2.1 Hz, 1H), 6.92 (d, J = 8.6 Hz, 1H), 4.16 (m, 2H), 3.94 (m, 2H), 3.85 (d, J = 6.1 Hz, 2H), 2.82 (s, 3H), 2.76 (m, 4H), 2.60 (tt, J = 12.1, 3.6 Hz, 1H), 2.00(m, 1H), 1.94 (m, 2H), 1.82 (m, 4H), 1.46 (s, 9H), 1.27 (m, 2H). ESIMS calcd. for $C_{19}H_{28}F_3N_2O_3S$ $(M\text{-}Boc+H)^+$ 421.2, found 421.1.

Example P12: 2-(4-((2,6-Difluoro-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)-5-ethylpyrimidine.



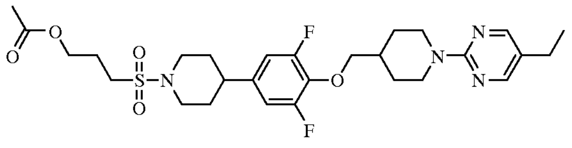
[00325] By following a procedure similar to the one used for preparing **E1** from **B2**, except substituting **P1** for **B2**, **P12** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 8.18 (s, 2H), 6.67 (d, J = 9.2 Hz, 2H), 4.70 (m, 2H), 2.91 (dt, J = 2.0, 12.4 Hz, 2H), 2.75 (s, 3H), 2.68 (dt, J = 2.4, 12.4 Hz, 2H), 2.43 (m, 3H), 2.01 (m, 3H), 1.70 (m, 2H), 1.31 (m, 2H), 1.13 (t, J = 7.6 Hz, 3H); ESIMS calcd. for $C_{24}H_{33}F_2N_4O_3S$ $[M+H]^+$ 495.2, found 495.2.

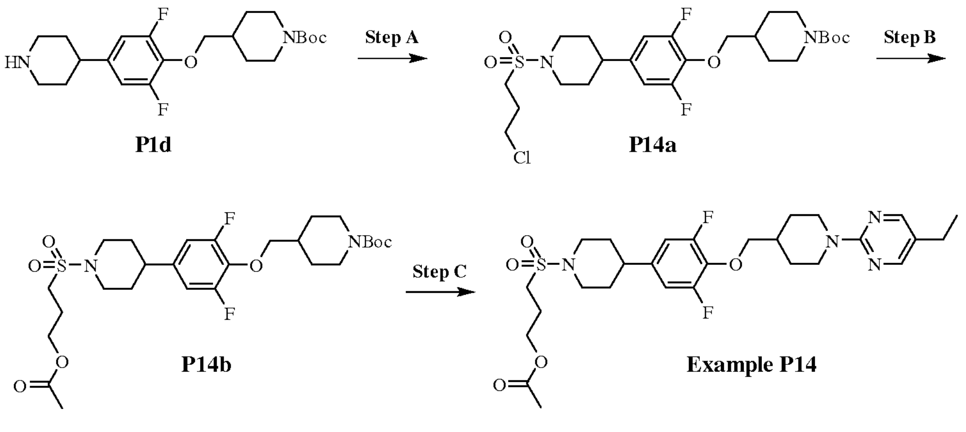
Example P13: 1-Methylcyclopropyl 4-((2,6-difluoro-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate.



[00326] By following a procedure similar to the one used for preparing **E3** from **B4**, except substituting **P1** for **B4**, **P12** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 6.74 (d, *J* = 8.8 Hz, 2H), 4.22 (m, 2H), 3.95 (m, 4H), 2.83 (s, 3H), 2.76 (dt, J = 2.4, 12.0 Hz, 4H), 2.55 (tt, *J* = 3.6, 12.4 Hz, 1H), 1.94 (m, 3H), 1.85 (m, 2H), 1.78 (m, 2H), 1.56 (s, 3H), 1.26 (m, 2H), 0.87 (m, 2H), 0.63 (m, 2H); ESIMS calcd. for $C_{23}H_{33}F_2N_2O_5S$ $[M+H]^+$ 487.2, found 487.2.

Example P14: 3-(4-(4-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-3,5-difluorophenyl)piperidin-1-ylsulfonyl)propyl acetate.



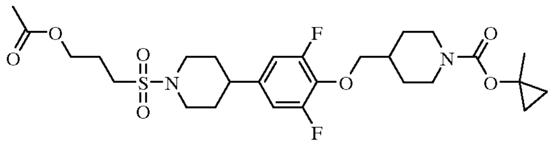


[00327] **Step A:** A solution of **P1d** (200 mg, 0.49 mmol) and 3-chloropropanesulfonyl chloride (65 µL, 0.54 mmol) in dichloromethane (10 mL) is treated with triethylamine (75 µL, 0.54 mmol) and the mixture is stirred at room temperature for 1 hour. The mixture is diluted with water (10 mL), extracted with dichloromethane, dried over $MgSO_4$, filtered and concentrated. The residue is purified on silica gel using a linear gradient of 0 to 100% ethyl acetate in hexane to afford **P14a**: ^{1}H-NMR (400MHz, $CDCl_3$) δ 6.74 (d, J = 9.2 Hz, 2H), 4.06 (m, 2H), 3.87 (m, 4H), 3.64 (t, J = 6.0 Hz, 2H), 3.04 (t, J = 6.0 Hz, 2H), 2.80 (dt, J = 2.4, 12.4 Hz, 2H), 2.65 (m, 2H), 2.49 (tt, J = 3.6, 12.4 Hz, 1H), 2.25 (m, 2H), 1.85 (m, 2H), 1.77 (m, 2H), 1.65, m, 2H), 1.39 (s, 9H), 1.18 (m, 2H); ESIMS calcd. for $C_{21}H_{30}ClF_2N_2O_5S$ $[M+H - C_4H_8]^+$ 495.2, found 495.2.

[00328] **Step B:** A solution of **P14a** (138 mg, 0.25 mmol), NaOAc (62 mg, 0.75 mmol) and NaI (38 mg, 0.25 mmol) in N,N-dimethylformamide (1 mL) is heated at 120 °C for 2 hours. The mixture is cooled, diluted with water (10 mL) and extracted with ethyl acetate (10 mL). The organic layer is washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated to provide **P14b** which is used without further purification; ESIMS calcd. for $C_{23}H_{33}F_2N_2O_7S$ $[M+H - C_4H_8]^+$ 519.2, found 519.2.

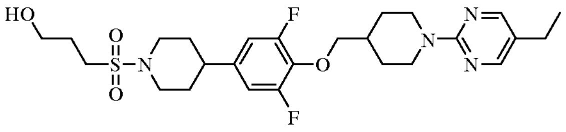
[00329] **Step C:** By following a procedure similar to the one used for preparing **E1** from **B2**, except substituting **P14b** for **B2**, **P14** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 8.36 (s, 2H), 6.76 (m, 2H), 4.76 (m, 2H), 4.22 (t, J = 6.4 Hz, 2H), 3.96 (m, 4H), 3.06 (m, 4H), 2.88 (dt, J = 2.4, 12.0 Hz, 2H), 2.56 (m, 3H), 2.17 (m, 3H), 2.11 (s, 3H), 2.04 (m, 2H), 1.97 (m, 2H), 1.71 (m, 2H), 1.42 (m, 2H), 1.24 (t, J = 7.6 Hz, 3H); ESIMS calcd. for $C_{28}H_{39}F_2N_4O_5S$ $[M+H]^+$ 581.3, found 581.2.

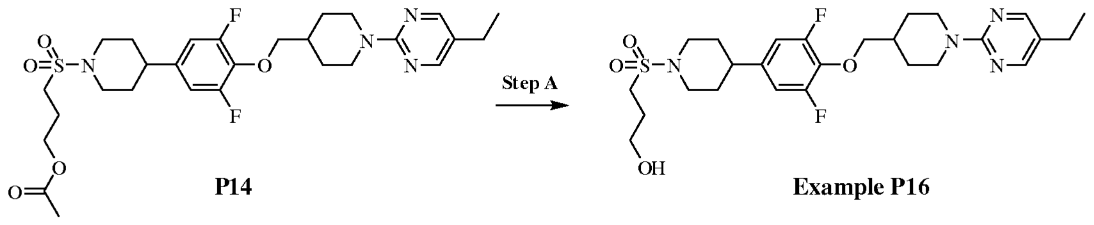
Example P15: 1-Methylcyclopropyl 4-((4-(1-(3-acetoxypropylsulfonyl)piperidin-4-yl)-2,6-difluorophenoxy)methyl)piperidine-1-carboxylate.



[00330] By following a procedure similar to the one used for preparing **P14** from **P1d**, except substituting the procedure for preparing **P13** from **P1** for **step C**, **P15** is prepared; ^{1}H-NMR (400MHz, CDCl$_3$) δ 6.75 (m, 2H), 4.22 (t, *J* = 6.0 Hz, 2H), 3.95 (m, 4H), 3.03 (m, 2H), 2.88 (dt, *J* = 2.4, 12.4 Hz, 2H), 2.76 (m, 2H), 2.57 (m, 1H), 2.17 (m, 2H), 2.09 (s, 3H), 1.92 (m, 2H), 1.88 (m, 2H), 1.72 (m, 2H), 1.56 (s, 3H), 1.25 (m, 2H), 0.87 (m, 2H), 0.63 (m, 2H); ESIMS calcd. for $C_{27}H_{39}F_2N_2O_7S$ [M+H]$^+$ 573.2, found 573.2.

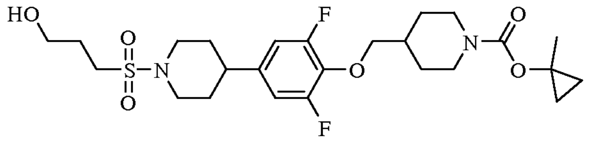
Example P16: 3-(4-(4-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-3,5-difluorophenyl)piperidin-1-ylsulfonyl)propan-1-ol.





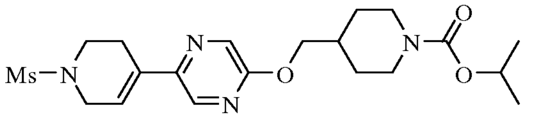
[00331] A solution of **P14** (30 mg, 0.05 mmol) in tetrahydrofuran (3 mL) is treated with LiOH hydrate (50 mg, 1.2 mmol) and the mixture is heated at 90 °C for 12 hours. The mixture is filtered, concentrated and purified by mass triggered reverse phase HPLC to afford **P16**; ^{1}H-NMR (400MHz, CDCl$_3$) δ 8.36 (s, 2H), 6.67 (m, 2H), 4.68 (m, 2H), 3.88 (m, 5H), 3.74 (t, *J* = 5.6 Hz, 2H), 3.00 (m, 4H), 2.78 (dt, *J* = 2.4, 12.0 Hz, 2H), 2.45 (m, 3H), 2.17 (m, 3H), 2.11 (s, 3H), 2.04 (m, 4H), 1.97 (m, 2H), 1.84 (m, 2H), 1.65 (m, 2H), 1.31 (m, 2H), 1.47 (t, *J* = 7.6 Hz, 3H); ESIMS calcd. for $C_{26}H_{37}F_2N_4O_4S$ [M+H]$^+$ 539.3, found 539.2.

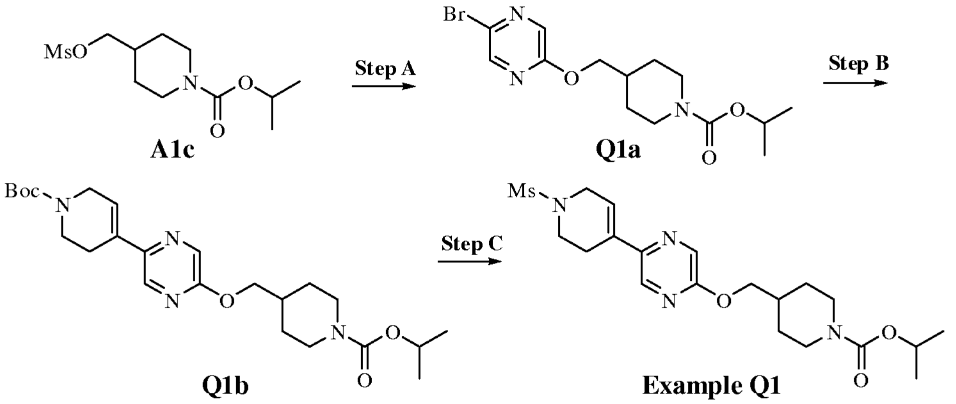
Example P17: 1-Methylcyclopropyl 4-((2,6-difluoro-4-(1-(3-hydroxypropylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate.



[00332] By following a procedure similar to the one used for preparing **P16** from **P14**, except substituting **P15** for **P14**, **P17** is prepared; ^{1}H-NMR (400MHz, CDCl$_3$) δ 6.66 (m, 2H), 3.85 (m, 4H), 3.74 (t, J = 6.0 Hz, 2H), 3.02 (m, 2H), 2.79 (dt, J = 2.4, 12.0 Hz, 2H), 2.71 (m, 2H), 2.48 (m, 2H), 2.03 (m, 2H), 1.80 (m, 5H), 1.69 (m, 2H), 1.48 (s, 3H), 1.19 (m, 2H), 0.87 (m, 2H), 0.63 (m, 2H); ESIMS calcd. for $C_{25}H_{37}F_2N_2O_6S$ $[M+H]^+$ 531.2, found 531.2.

Example Q1: Isopropyl 4-((5-(1,2,3,6-tetrahydro-1-methanesulfonylpyridin-4-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





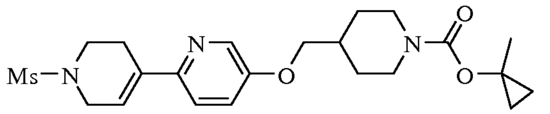
[00333] **Step A**: A solution of **A1c** (0.86 g, 3.1 mmol) and 2-bromo-5-hydroxypyrazine (0.52 g, 3.0 mmol) in dry acetonitrile (7 mL) is treated with powdered cesium carbonate (1.62 g, 5 mmol) and the mixture is stirred at 60 °C for 24 hours.

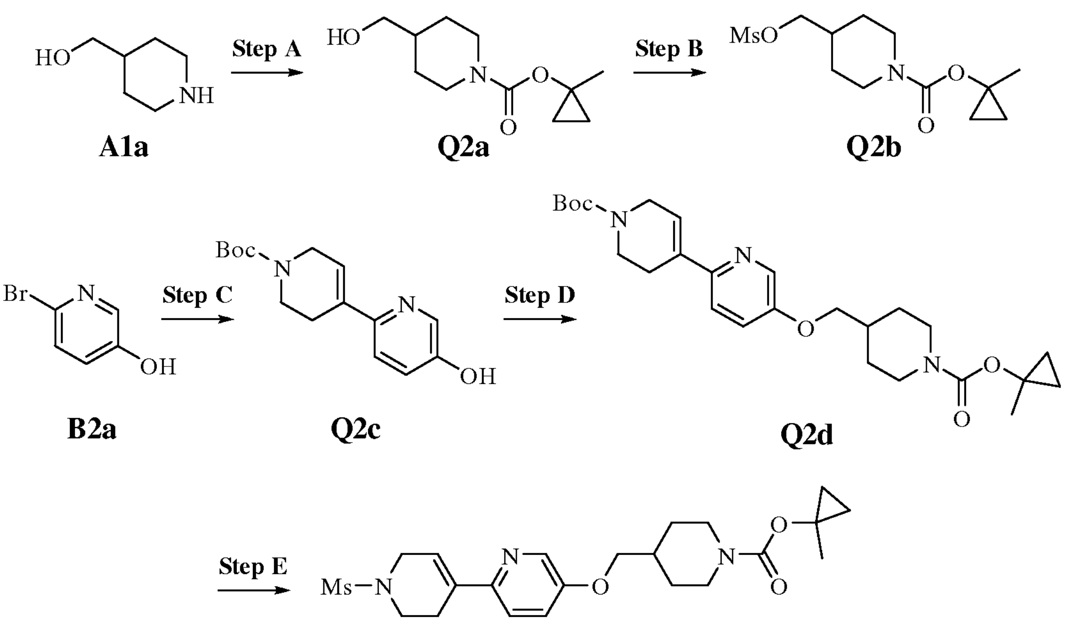
Filtration, concentration, and purification on silica gel using a linear gradient of 0 to 100% ethyl acetate in hexane affords **Q1a**; ESIMS calcd. for $C_{14}H_{21}BrN_3O_3$ (M+H$^+$) 358.1, found 358.0.

[00334] **Step B**: To a solution of **Q1a** (83.5 mg, 0.2 mmol) in 1,2-dimethoxyethane (1.5mL) are added *tert*-butyl 5,6-dihydro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-1(2*H*)-carboxylate (66.7 mg, 0.2 mmol), powdered potassium carbonate (0.10 g, 0.7 mmol), and water (0.5 g). The mixture is degassed using argon, then tetrakis-(triphenylphosphino)palladium(0) (0.08g, 0.07 mmol) is added and the mixture is heated to 180 °C for 5 min in a microwave reactor. Cooling, extraction with ethyl acetate, washing with water and brine, drying over Na_2SO_4 and concentration, followed by purification on silica gel using a linear gradient of 5 to 70% ethyl acetate in hexane affords **Q1b**; ESIMS calcd. for $C_{24}H_{37}N_4O_5$ (M+H$^+$) 461.3, found 461.1.

[00335] **Step C**: To a solution of **Q1b** (0.2 mmol) in dioxane (2 mL) is added hydrogen chloride in dioxane (4N, 1 mL), slowly, with stirring. The resulting solution is stirred at room temperature for 4 hours. After removing the solvent, the residue is dissolved in dichloromethane (3 mL) and treated with triethylamine (0.2 mL, 1.4 mmol). Then methanesulfonyl chloride (0.04 mL, 0.5 mmol) is added dropwise, with stirring, over 5 minutes. The resulting solution is stirred at room temperature for 2 hours. The solvent is removed and the resiude is purified using mass-triggered reverse phase HPLC to yield **Q1**; ESIMS calcd. for $C_{20}H_{31}N_4O_5S$ (M+H$^+$) 439.2, found 439.1.

Example Q2: 1-Methylcyclopropyl 4-((6-(1,2,3,6-tetrahydro-1-methanesulfonylpyridin-4-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate.





Example Q2

[00336] **Step A**: A solution of **A1a** (0.51 g, 4.4 mmol) in dichloromethane (7 mL) is treated with triethylamine (0.9 mL, 6.4 mmol) in one portion, followed by **E3b** (0.96 g, 4 mmol). The suspension is stirred at room temperature for 24 hours, diluted with more dichloromethane (25 mL), washed with water, saturated aqueous sodiumhydrogencarbonate (3 x 25 mL), and saturated aqueous ammonium chloride, dried over $MgSO_4$ and concentrated to yield **Q2a**; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 4.13 (br. s, 1H), 4.03 (br. s, 1H), 3.50 (m, 2H), 2.71 (t, *J* = 12 Hz, 2H), 1.67 (m, 3H), 1.38 (br. s, 1H), 1.54 (s, 3H), 1.14 (br. s, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{11}H_{20}NO_3$ ($M+H^+$) 214.1, found 214.1.

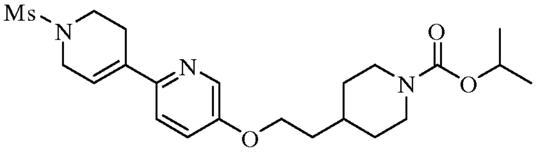
[00337] **Step B**: To a solution of **Q2a** (0.71 g, 3.4 mmol) in dichloromethane (20 mL) is added triethylamine (0.9 mL, 6.4 mmol) in one portion. The resulting mixture is cooled in an ice/water bath and methanesulfonyl chloride (0.35 mL, 4.5 mmol) is added slowly, with stirring. The bath is removed and the resulting solution is stirred at room temperature for 2 hours. The reaction mixture is diluted with more dichloromethane (20 mL), washed with water and saturated aqueous ammonium chloride, dried over $MgSO_4$ and concentrated to yield **Q2b**; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 4.22 (br. s, 2H), 4.07 (s, 2H), 3.23 (m, 1H), 3.17 (s, 3H), 2.72 (m, 2H), 1.92 (m, 1H), 1.74 (m, 2H), 1.54 (s, 3H), 1.22 (br. s, 2H), 0.86 (m, 2H), 0.63 (m, 2H); ESIMS calcd. for $C_{12}H_{22}NO_5S$ (M+H$^+$) 292.1, found 292.0.

[00338] **Step C**: To a solution of **B2a** (0.1 g, 0.6 mmol) in 1,2-dimethoxyethane (1.5mL) is added *tert*-butyl 5,6-dihydro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-1(2*H*)-carboxylate (0.13 g, 0.4 mmol), powdered potassium carbonate (0.15 g, 1.1 mmol), and water (0.5 g). The mixture is degassed using argon, then tetrakis-(triphenylphosphino)palladium(0) (0.08g, 0.07 mmol) is added and the mixture is heated to 180 °C for 5 min in a microwave reactor. Cooling, extraction with ethyl acetate, washing with water and brine, drying over Na_2SO_4 and concentration, followed by purification on silica gel using a linear gradient of 5 to 100% ethyl acetate in hexane affords **Q2c**. ESIMS calcd. for $C_{15}H_{21}N_2O_3$ (M+H$^+$) 277.2, found 277.0.

[00339] **Step D**: A solution of **Q2b** (0.05 g, 0.17 mmol) and **Q2c** (0.04 g, 0.15 mmol) in dry acetonitrile (2 mL) is treated with powdered cesium carbonate (0.1 g, 0.3 mmol) and the mixture is stirred at 60 °C for 24 hours. Filtration, concentration, and purification on silica gel using a linear gradient of 0 to 100% ethyl acetate in hexane affords **Q2d**; ESIMS calcd. for $C_{26}H_{38}N_3O_5$ (M+H$^+$) 472.3, found 472.0.

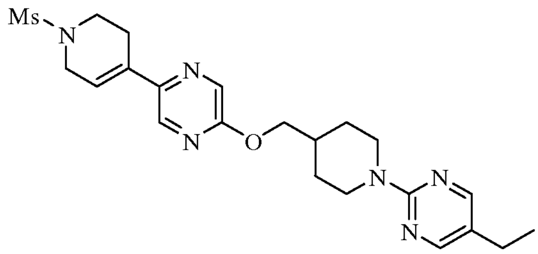
[00340] **Step E**: To a solution of **Q2d** (0.15 mmol) in dioxane (2 mL) is added hydrogen chloride in dioxane (4N, 0.5 mL), slowly, with stirring. The resulting solution is stirred at room temperature for 4 hours. The solvent is removed and the residue is dissolved in dichloromethane (3 mL) and treated with triethylamine (0.1 mL, 0.7 mmol) followed by methanesulfonyl chloride (0.025 mL, 0.3 mmol) dropwise, with stirring, over 5 minutes. The resulting solution is stirred at room temperature for 2 hours. The solvent is removed and the resulting residue is purified by mass triggered HPLC to afford **Q2**; ESIMS calcd. for $C_{22}H_{32}N_3O_5S$ (M+H$^+$) 450.2, found 450.1.

Example Q3: Isopropyl 4-(2-(6-(1,2,3,6-tetrahydro-1-methanesulfonylpyridin-4-yl)pyridin-3-yloxy)ethyl)piperidine-1-carboxylate.

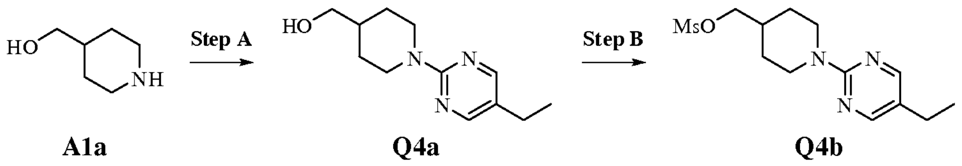


[00341] By following a procedure similar to the one used for preparing **Q1** from **A1c**, except substituting isopropyl 4-(2-(methylsulfonyloxy)ethyl)piperidine-1-carboxylate for **A1c**, **Q3** is prepared; ESIMS calcd. for $C_{22}H_{34}N_3O_5S$ ($M+H^+$) 452.2, found 452.1.

Example Q4: 2-(4-((5-(1,2,3,6-Tetrahydro-1-methanesulfonylpyridin-4-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-5-ethylpyrimidine.



[00342] By following a procedure similar to the one used for preparing **Q2** from **A1a**, except substituting **B4a** for **B2a** in **Step A** and **Q4b** (see scheme below) for **Q2b** in **Step D**, **Q4** is prepared; ESIMS calcd. for $C_{22}H_{31}N_6O_3S$ ($M+H^+$) 459.2, found 459.1.

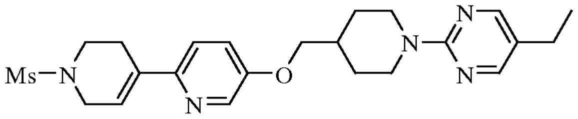


[00343] **Step A**: A solution of **A1a** (1.03 g, 9 mmol) and 2-chloro-5-ethylpyrimidine (1.1 mL, 9 mmol) in dimethylacetamide (7 mL) is treated with powdered cesium carbonate (4 g, 12.3 mmol) and the suspension is stirred at 75 °C for 48 hours. The reaction is then diluted with water (150 mL) and extracted with ethyl acetate/diethyl ether (1:1) (2 x 100 mL). The combined extracts are washed with water, saturated aqueous ammonium chloride, and brine, dried over Na_2SO_4 and concentrated to yield **Q4a**; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 8.16 (s, 2H), 4.74 (m, 2H), 3.53 (t, J = 5.9 Hz, 2H), 2.87 (td, J = 13.2, 2.4 Hz, 2H), 2.45 (q, J =7.6 Hz, 2H), 1.85 (m, 2H), 1.77 (m, 1H),

1.44 (t, *J* = 5.5 Hz, 1H), 1.23 (m, 2H), 1.18 (t, *J* = 7.6 Hz, 3H); ESIMS calcd. for $C_{12}H_{20}N_3O$ (M+H$^+$) 222.2, found 222.1.

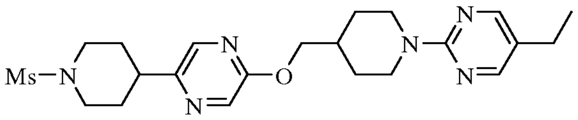
[00344] **Step B**: To a solution of **Q4a** (0.92 g, 4.2 mmol) in dichloromethane (20 mL) is added triethylamine (1.0 mL, 7.1 mmol) in one portion. The resulting mixture is cooled in an ice/water bathand methanesulfonyl chloride (0.45 mL, 5.8 mmol) is added slowly, with stirring. The bath is removed and the resulting solution is stirred at room temperature for 2 hours. The reaction mixture is diluted with more dichloromethane (20 mL), washed with water and saturated aqueous ammonium chloride, dried over $MgSO_4$ and concentrated to yield **Q4b**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 8.17 (s, 2H), 4.78 (m, 2H), 4.09 (d, *J* = 6.6 Hz, 2H), 3.02 (s, 3H), 2.88 (td, *J* = 13.2, 2.6 Hz, 2H), 2.46 (q, *J* =7.6 Hz, 2H), 2.05 (m, 2H), 1.84 (m, 1H), 1.29 (ddd, *J* = 4.4, 12.4, 12.7 Hz, 2H), 1.19 (t, *J* = 7.6 Hz, 3H); ESIMS calcd. for $C_{13}H_{22}N_3O_3S$ (M+H$^+$) 300.1, found 300.0.

Example Q5: 2-(4-((6-(1,2,3,6-Tetrahydro-1-methanesulfonylpyridin-4-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)-5-ethylpyrimidine.

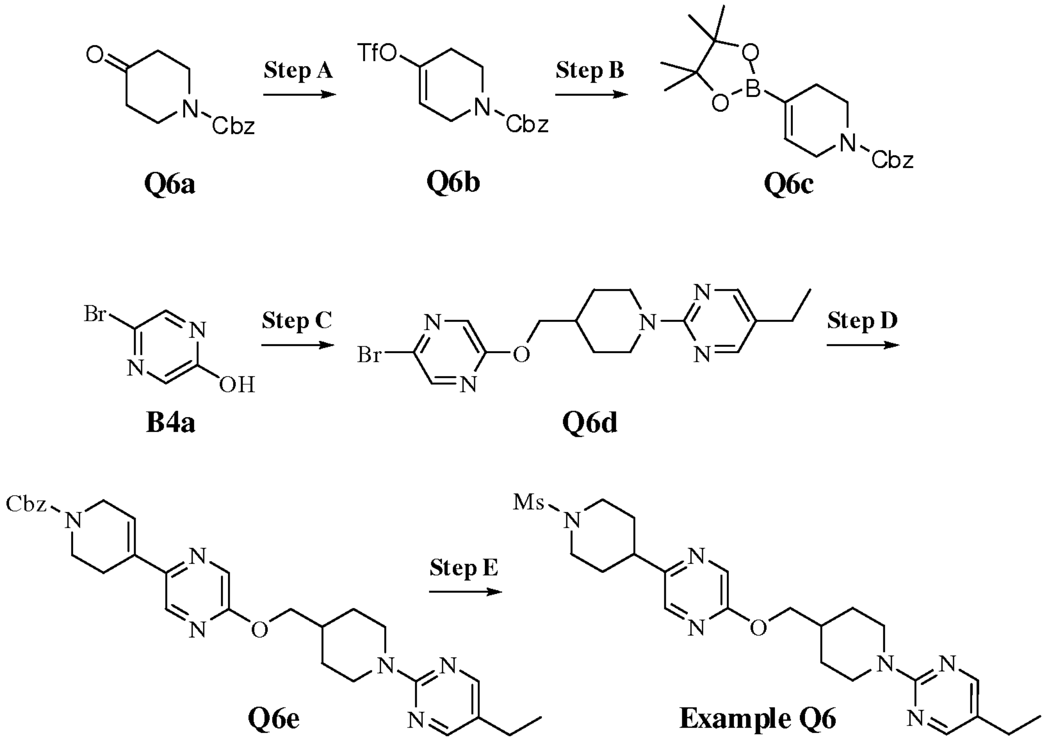


[00345] By following a procedure similar to the one used for preparing **Q2** from **Q2b**, except substituting **Q4b** for **Q2b**, **Q5** is prepared; ESIMS calcd. for $C_{23}H_{32}N_5O_3S$ (M+H$^+$) 458.2, found 458.1.

Example Q6: 2-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-5-(1-methanesulfonylpiperidin-4-yl)pyrazine.



[00346] Example **Q6** may be made from **Q5** above, by hydrogenation with palladium on carbon. However, an alternate synthesis is as follows:



[00347] **Step A**: A solution of diisopropylamine (2 mL, 14.2 mmol) in dry tetrahydrofuran (10 mL) at –78 °C under nitrogen is treated with *n*-Butyllithium (2.46 M solution in hexanes; 5 mL, 12.25 mmol) and the mixture is stirred for 15 min at –78 °C. A solution of **Q6a** (2.55 g, 10.9 mmol) in dry tetrahydrofuran (25 mL) is slowly added and stirring is continued at –78 °C for 2 hours. N-Phenyltriflimide (4.42 g, 12.4 mmol) in dry tetrahydrofuran (25 mL) is added dropwise at –78 °C. The mixture is stirred at –78 °C for 2.5 hours and at room temperature for 30 minutes. Dilution with ethyl acetate (200 mL) and saturated aqueous ammonium chloride (50 mL), washing with water and brine, drying over Na_2SO_4 and concentration followed by purification on silica gel using a linear gradient of 0 to 40% ethyl acetate in hexane affords **Q6b**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.3 - 7.4 (m, 5H), 5.78 (m, 1H), 5.16 (s, 2H), 4.13 (br. s, 2H), 3.72 (br. s, 2H), 2.47 (br. s, 2H); ^{19}F NMR ($CDCl_3$, 376 MHz): δ –75.32; ESIMS calcd. for $C_{14}H_{15}F_3NO_5S$ ($M+H^+$) 366.1, found 366.1.

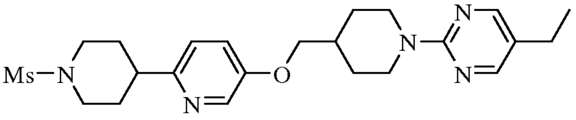
[00348] **Step B**: To a solution of **Q6a** (1.22 g, 3.3 mmol) in 1,4-dioxane (25 mL) is added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.02 g, 4 mmol), 1,1'-bis(diphenylphosphino)ferrocene (0.08 g, 0.14 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (0.11 g, 0.13 mmol) and potassium acetate powder (1.26 g, 12.8 mmol). The mixture is degassed using argon and stirred at 80 °C for 18 hours. Cooling, diluting with water (50 mL), extraction with ethyl acetate, washing with water and brine, drying over Na_2SO_4 and concentration, followed by by purification on silica gel using a linear gradient of 0 to 50% ethyl acetate in hexane affords **Q6b**; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 7.3 - 7.4 (m, 5H), 6.5 (m, 1H), 5.16 (s, 2H), 4.05 (m, 2H), 3.54 (m, 2H), 2.27 (br. s, 2H), 1.28 (s, 12H); ESIMS calcd. for $C_{19}H_{27}BNO_4$ (M+H$^+$) 344.2, found 344.1.

[00349] **Step C**: A solution of **B4a** (0.84 g, 4.8 mmol) and intermediate **Q4b** (1.28 g, 4.3 mmol) in dry dimethylacetamide (25 mL) is treated with powdered cesium carbonate (2.31 g, 7.1 mmol) and the mixture is stirred at 65 °C for 24 hours. Filtration, concentration, and by purification on silica gel using a linear gradient of 10 to 50% ethyl acetate in hexane affords **Q4d**; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 8.17 (s, 2H), 8.16 (d, J = 1.4 Hz, 1H), 8.02 (d, J = 1.4 Hz, 1H), 4.77 (m, 2H), 4.17 (d, J = 6.6 Hz, 2H), 2.88 (td, J = 13.1, 2.6 Hz, 2H), 2.46 (q, J =7.6 Hz, 2H), 2.10 (m, 2H), 1.89 (m, 1H), 1.34 (ddd, J = 4.3, 12.4, 12.6 Hz, 2H), 1.19 (t, J = 7.6 Hz, 3H); ESIMS calcd. for $C_{16}H_{21}BrN_5O$ (M+H$^+$) 378.1, found 378.1.

[00350] **Step D**: To a solution of **Q6d** (0.8 g, 2.1 mmol) in 1,2-dimethoxyethane (5 mL) is added intermediate **Q6c** (0.91 g, 2.7 mmol), powdered potassium carbonate (0.72 g, 5.2 mmol), and water (0.5 g). The mixture is degassed using argon, then tetrakis-(triphenylphosphino)palladium(0) (0.23 g, 0.2 mmol) is added and the mixture is heated to 180 °C for 20 min in a microwave reactor. Cooling, dilution with ethyl acetate, drying over Na_2SO_4 and concentration, followed by purification on silica gel using a linear gradient of 10 to 50% ethyl acetate in hexane affords **Q6e**; ESIMS calcd. for $C_{29}H_{35}N_6O_3$ (M+H$^+$) 515.3, found 515.1.

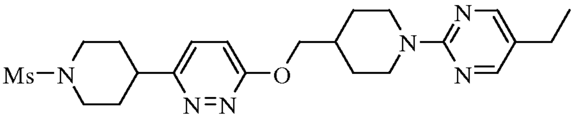
[00351] **Step E**: A solution of **Q6e** (0.6 g, 1.2 mmol) in ethyl acetate (100 mL) and ethanol (40 mL) is treated with palladium on carbon (5%; 0.85 g, 0.4 mmol) and the mixture is saturated with hydrogen gas and is then stirred at room temperature under 1 atmosphere of hydrogen for 3 hours. After filtration of the reaction through a pad of Celite® and concentration the residue is dissolved in dichloromethane (10 mL) and triethylamine (0.6 mL, 4.3 mmol). Methanesulfonyl chloride (0.15 mL, 1.9 mmol) is then slowly added, with stirring. After 2 hours, the mixture is concentrated and purified on silica gel using a linear gradient of 10 to 65% ethyl acetate in hexane to afford **Q6**. ESIMS calcd. for $C_{22}H_{33}N_6O_3S$ (M+H$^+$) 461.2, found 461.1.

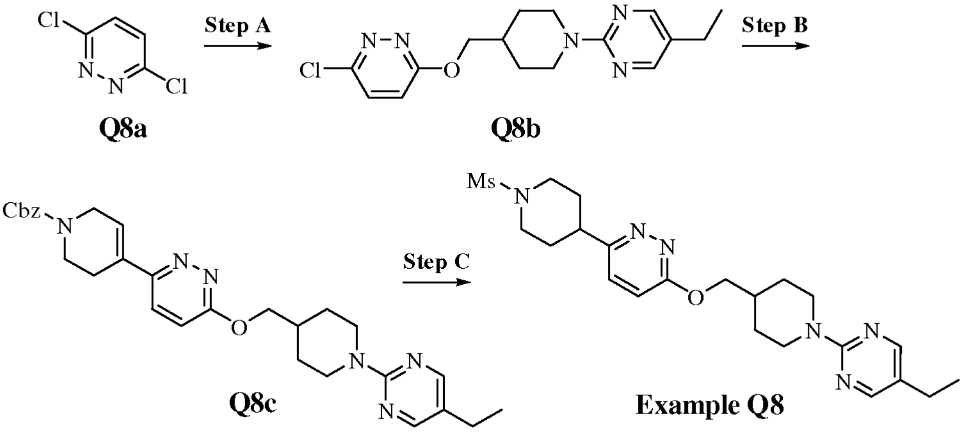
Example Q7: 2-(4-((6-(1-Methanesulfonylpiperidin-4-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)-5-ethylpyrimidine.



[00352] By following a procedure similar to the one used for preparing **Q6** from **B4a**, except substituting **B2a** for **B4a** in **Step C**, **Q7** is prepared; ESIMS calcd. for $C_{23}H_{34}N_5O_3S$ (M+H$^+$) 460.2, found 460.1.

Example Q8: 3-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-6-(1-methanesulfonylpiperidin-4-yl)pyridazine.



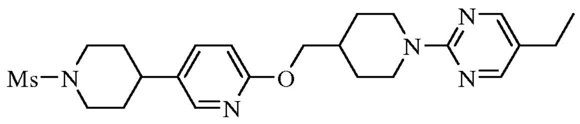


[00353] **Step A**: A solution of **Q8a** (0.64 g, 2.9 mmol) and **Q4a** (0.49 g, 3.3 mmol) in dry dimethylacetamide (6 mL) is treated with powdered potassium carbonate (0.7 g, 5.0 mmol) and the mixture is stirred at 150 °C for 2 days. Cooling, dilution with water (100 mL), extraction with ethyl acetate (2 x 100 mL), drying over Na_2SO_4, filtration, concentration, and purification on silica gel using a linear gradient of 10 to 100% ethyl acetate in hexane affords **Q8b**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 8.17 (s, 2H), 7.67 (d, J = 9.2 Hz, 1H), 6.96 (d, J = 9.2 Hz, 1H), 4.77 (m, 2H), 4.37 (d, J = 6.6 Hz, 2H), 2.90 (td, J = 13.1, 2.6 Hz, 2H), 2.46 (q, J =7.6 Hz, 2H), 2.15 (m, 2H), 1.89 (m, 1H), 1.36 (ddd, J = 4.3, 12.4, 12.6 Hz, 2H), 1.19 (t, J = 7.6 Hz, 3H); ESIMS calcd. for $C_{16}H_{21}ClN_5O$ ($M+H^+$) 334.1, found 334.1.

[00354] **Step B**: To a solution of **Q8b** (0.11 g, 0.3 mmol) in 1,2-dimethoxyethane (2 mL) is added intermediate **Q6b** (0.15 g, 0.4 mmol), powdered potassium carbonate (0.18 g, 1.3 mmol), and water (0.5 g). The mixture is degassed using argon, then tetrakis-(triphenylphosphino)palladium(0) (0.05 g, 0.04 mmol) is added and the mixture is heated to 180 °C for 20 min in a microwave reactor. Cooling, dilution with ethyl acetate, drying over Na_2SO_4 and concentration, followed by purification on silica gel using a linear gradient of 10 to 75% ethyl acetate in hexane affords **Q8c**; ESIMS calcd. for $C_{29}H_{35}N_6O_3$ ($M+H^+$) 515.3, found 515.1.

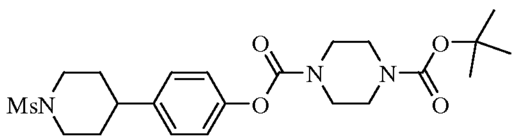
[00355] **Step C**: A solution of **Q8c** (0.15 g, 0.3 mmol) in ethyl acetate (20 mL) and ethanol (20 mL) is treated with palladium black on carbon (5%; 0.4 g, 0.2 mmol), saturated with hydrogen and then stirred at room temperature under 1 atmosphere of hydrogen for 6 hours. After exchanging the atmosphere for N_2, the reaction is filtered through a pad of Celite® and concentrated. The resulting oil is dissolved in dichloromethane (10 mL) and triethylamine (0.3 mL, 2.1 mmol). Methanesulfonyl chloride (0.05 mL, 0.6 mmol) is then slowly added, with stirring. After 2 hours, the mixture is concentrated and purified using mass-triggered reverse phase HPLC to afford **Q8**; ESIMS calcd. for $C_{22}H_{33}N_6O_3S$ ($M+H^+$) 461.2, found 461.1.

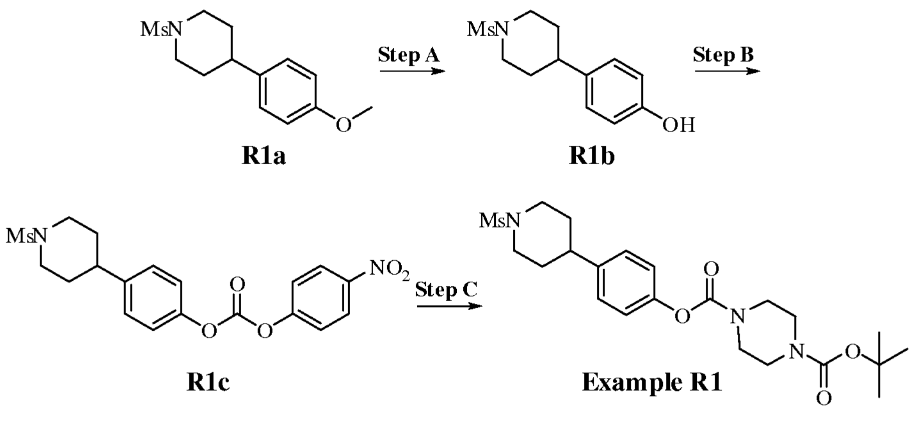
Example Q9: 2-(4-((5-(1-Methanesulfonylpiperidin-4-yl)pyridin-2-yloxy)methyl)piperidin-1-yl)-5-ethylpyrimidine.



By following a procedure similar to the one used for preparing **Q8** from **Q8a**, except substituting **C1a** for **8a**, **Q9** is prepared; ESIMS calcd. for $C_{23}H_{34}N_5O_3S$ ($M+H^+$) 460.2, found 460.2.

Example R1: 1-*tert*-Butyl 4-(4-(1-(methylsulfonyl)piperidin-4-yl)phenyl) piperazine-1,4-dicarboxylate.



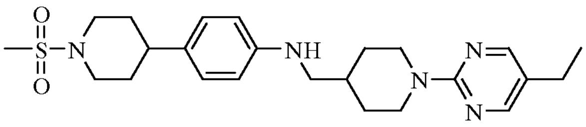


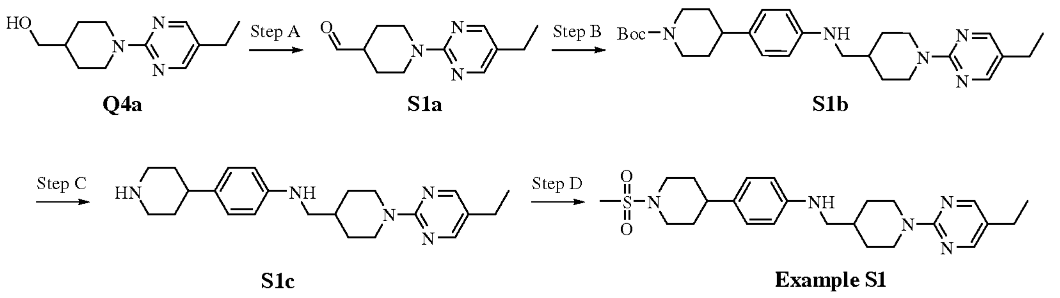
[00356] **Step A:** A solution of **R1a** (2.2 g, 8.2 mmol) in dichloromethane (10 mL) is cooled in an ice/water bath and treated with neat BBr_3 (9.21 g, 37 mmol). The reaction is stirred at ice bath temperature for 10 minutes and at room temperature for 1 hour. The reaction is then poured on to crushed ice and allowed to quenchours. The resulting solid is collected and dried to afford **R1b**; ESIMS calcd. for $C_{12}H_{17}NO_3S$ $(M+H^+)$ 256.1, found 256.1.

[00357] **Step B:** A solution of **R1b** (100 mg, 0.39 mmol) and nitrophenyl chloroformate (87 mg, 0.43 mmol) in acetonitrile (5 mL) is treated with K_2CO_3 (108 mg, 0.78 mmol) and the mixture is stirred at room temperature for 2 hours, then is filtered, concentrated, and purified on silica gel using a linear gradient of 0 to 100% ethyl acetate in hexane to afford **R1c**; ESIMS calcd. for $C_{19}H_{21}N_2O_7S$ $[M+H]^+$ 421.1, found 421.1.

[00358] **Step C:** A solution of **R1c** (41 mg, 0.10 mmol), 1-Boc-piperazine (20 mg, 0.11 mmol) and triethylamine (68 μL, 0.50 mmol) in 1,2-dichloroethane (5 mL) is heated at 50 °C for 12 hours. The mixture is concentrated *in vacuo* and purified purified using mass-triggered reverse phase HPLC to afford **R1**; ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.12 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 3.87 (m, 3H), 3.56 (m, 2H), 3.45 (m, 6H), 2.75 (s, 3H), 2.70 (m, 3H), 2.55 (m, 2H), 1.90 (m, 3H), 1.77 (m, 3H), 1.42 (s, 9H); ESIMS calcd. for $C_{22}H_{33}N_3NaO_6S$ $[M+Na]^+$ 490.2, found 490.1.

Example S1: ***N*-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methyl)-4-(1-(methylsulfonyl)piperidin-4-yl)aniline.**





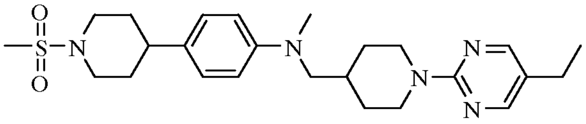
[00359] **Step A:** A solution of **Q4a** (444 mg, 2mmol) in anhydrous dichloromethane (5 mL) is added to a solution of Dess-Martin periodinane (1.018 g, 2.4 mmol) in anhydrous dichloromethane (10 mL) and stirred overnight at room temperature. Additional dichloromethane (30 mL) is added and the reaction is filtered through Celite® and concentrated. Purification on silica gel using a linear gradient of 0 to 50% ethyl acetate in hexane to affords **S1a**; ESIMS calcd. for $C_{12}H_{18}N_3O$ ($M+H^+$) 220.1, found 220.1.

[00360] **Step B:** A mixture of **S1a** (318 mg, 1.5 mmol), *tert*-butyl 4-(4-aminophenyl)piperidine-1-carboxylate (482 mg, 1.74 mmol), and $NaBH(OAc)_3$ (636 mg, 3 mmol) in dichloromethane (7 mL) is stirred at room temperature for 5 hours. The reaction is quenched with water (20 mL) and extracted with dichloromethane (3 x 20 mL), washed with water (20 mL), dried (Na_2SO_4), and concentrated. Purification on silica gel using a linear gradient of 0 to 50% ethyl acetate in hexane to affords **S1b**; ESIMS calcd. for $C_{28}H_{42}N_5O_2$ ($M+H^+$) 480.3, found 480.4.

[00361] **Step C:** A solution of **S1b** (600 mg, 1.25 mmol) in MeOH (10 mL) is treated with a 4 M solution of HCl in dioxane (25 mL, 100 mmol) and stirred at room temperature overnight. The reaction mixture is concentrated, dioxane (20 mL) added and concentrated again to form the hydrochloride salt of **S1c**; ESIMS calcd. for $C_{23}H_{34}N_5$ ($M+H^+$) 380.3, found 380.3.

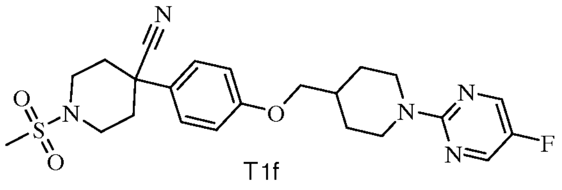
[00362] **Step D:** A cold (0°C) mixture of **S1c** (810 mg, 1.25 mmol) and triethylamine (0.892 mL, 6.4 mmol) in dichloromethane (30 mL) is treated with methanesulfonyl chloride (0.152 mL, 1.96 mmol) dropwise and stirred at room temperature for 3 hours. Additional triethylamine (0.5 mL, 3.6 mmol) and methanesulfonyl chloride (0.076 mL, 0.98 mmol) are added and the reaction is stirred at room temperature for another 30 minutes. The reaction is quenched with water (20 mL), extracted with dichloromethane (3 x 20 mL), washed with water (20 mL), dried over Na_2SO_4, and concentrated. Purification using mass-triggered reverse phase HPLC affords **S1**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (s, 2H), 7.05 (m, 2H), 6.70 (m, 2H), 4.61 (m, 2H), 3.64 (m, 2H), 2.96 (m, 2H), 2.88 (s, 3H), 2.80 (m, 4H), 2.42 (q, J = 7.6 Hz, 2H), 1.84 (m, 5H), 1.60 (m, 2H), 1.12 (m, 5H); ESIMS calcd. for $C_{24}H_{36}N_5O_2S$ $(M+H^+)$ 458.3, found 458.3.

Example S2: *N*-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methyl)-*N*-methyl-4-(1-(methylsulfonyl)piperidin-4-yl)aniline.

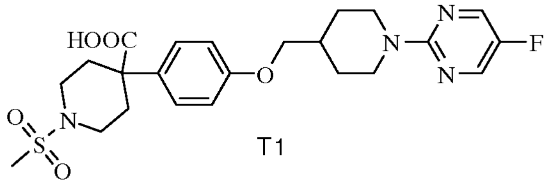


[00363] A solution of **S1** (46 mg, 0.1 mmol) in tetrahydrofuran (1 mL) is added dropwise to an ice-cold solution of 10% aqueous H_2SO_4 (0.2 mL) and 37% aqueous formaldehyde (0.1 mL, 1.2 mmol) in tetrahydrofuran (0.5 mL). $NaBH_4$ (30 mg, 0.79 mmol) is added and the reaction mixture is warmed to room temperature. After stirring for 30 minutes the reaction is quenched with 0.2 M NaOH (10 mL) and extracted with ethyl acetate (3 x 15 mL), washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The compound is purified using mass-triggered reverse phase HPLC to afford **S2**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23 (s, 2H), 7.08 (m, 2H), 6.68 (m, 2H), 4.60 (m, 2H), 3.64 (m, 2H), 3.19 (m, 2H), 2.92 (bs, 3H), 2.88 (s, 3H), 2.78 (m, 4H), 2.42 (q, J = 7.6 Hz, 2H), 1.93 (m, 1H), 1.81 (m, 2H), 1.62 (m, 4H), 1.12 (m, 5H); ESIMS calcd. for $C_{25}H_{38}N_5O_2S$ $(M+H^+)$ 472.3, found 472.3.

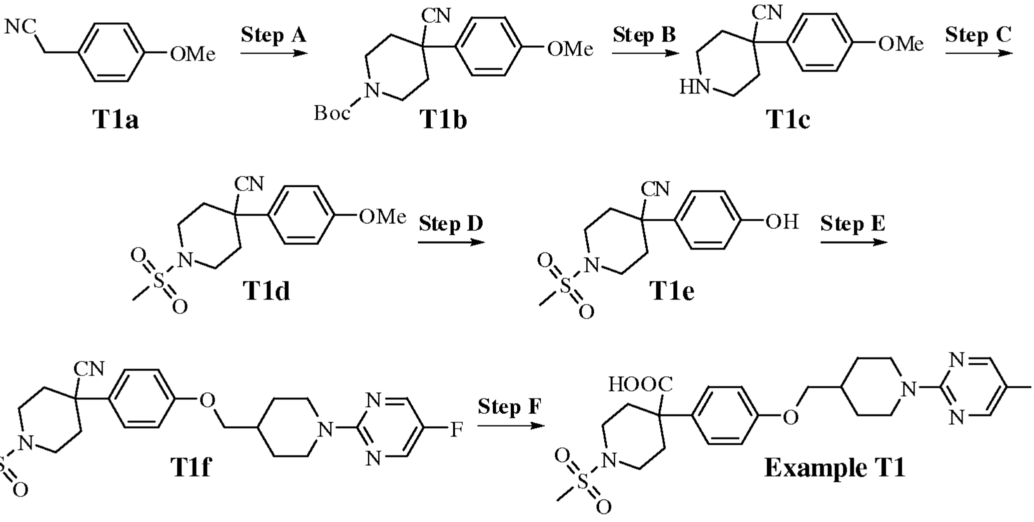
Examples T1f and T1: 4-(4-((1-(5-fluoropyrimidin-2-yl)piperidin-4-yl)methoxy)phenyl)-1-(methylsulfonyl)piperidine-4-carbonitrile and 4-(4-((1-(5-fluoropyrimidin-2-yl)piperidin-4-yl)methoxy)phenyl)-1-(methylsulfonyl)piperidine-4-carboxylic acid



T1f



T1



[00364] **Step A:** To an ice-cold suspension of NaH (60% in oil, 120 mg, 3 mmol) in anhydrous N, N-dimethylformamide (2 mL) is added **T1a** (142 µL, 1.05 mmol) and stirred for 30 minutes under a nitrogen atmosphere. To the resulting brown solution is added *tert*-butyl bis(2-chloroethyl)carbamate (242 mg, 1 mmol) in N,N-dimethylformamide (0.2 mL) and the cooling bath is removed after 15 min. The reaction mixture is heated overnight at 75 °C, cooled to room temperature and quenched with water (1 mL). More water is added (50 mL) and the reaction is extracted with dichlormethane (3 x 30 mL), dried over Na_2SO_4 and concentrated. Purification on silica gel using a linear gradient of 0 to 50% ethyl acetate in hexane to affords **T1b;** ^{1}H-NMR

(400MHz, $CDCl_3$) δ 7.38 (m, 2H), 6.93 (m, 2H), 4.26 (m, 2H), 3.82 (s, 3H), 3.19 (m, 2H), 2.08 (d, J = 12.9 Hz, 2H), 1.90 (td, J = 13.0, 4.0 Hz, 2H), 1.48 (s, 9H); ESIMS calcd. for $C_{18}H_{24}N_2NaO_3$ ($M+Na^+$) 339.2, found 388.8.

[00365] **Step B:** To a solution of **T1b** (218 mg, 0.69 mmol) in dioxane (1 mL) is added 4 M solution of HCl in dioxane (2 mL, 8 mmol) and the reaction is stirred for 2 hours at room temperature. The solvent is removed and the residue is coevaporated with dioxane (10 mL) to afford **T1c**; ESIMS calcd. for $C_{13}H_{17}N_2O$ ($M+H^+$) 217.1, found 216.9.

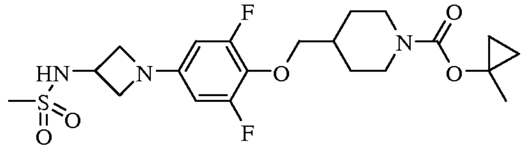
[00366] **Step C:** A cold (ice/water bath) solution of **T1c** (0.69 mmol) and triethylamine (385 µL, 2.76 mmol) in dry dichloromethane (10 mL) is treated with methanesulfonyl chloride (64 µL, 0.83 mmol) dropwise. The resulting solution is stirred at room temperature overnight. The reaction mixture is added to water (40 mL) and extracted with dichloromethane (3 x 40 mL). The combined organic layers are dried over Na_2SO_4 and concentrated to yield **T1d**; ESIMS calcd. for $C_{14}H_{19}N_2O_3S$ ($M+H^+$) 295.1, found 295.0.

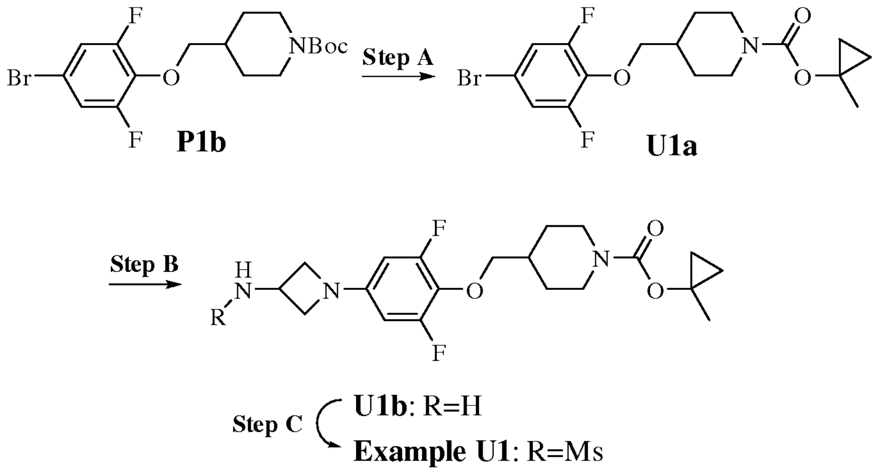
[00367] **Step D:** A solution of **T1d** (208 mg, 0.7 mmol) in anhydrous dichloromethane (3.5 mL) is cooled to -78 °C under nitrogen atmosphere and a 1M solution of BBr_3 (3.5 mL, 3.5 mmol) in dichloromethane is added dropwise. The reaction is stirred at room temperature overnight, then cooled to 0 °C and quenched with MeOH (2 mL). The reaction mixture is repeatedly concentrated with MeOH (3 x 20 mL) to afford **T1e**; ESIMS calcd. for $C_{13}H_{17}N_2O_3S$ ($M+H^+$) 281.1, found 281.0.

[00368] **Step E:** A mixture of **T1e** (196 mg, 0.7 mmol), (1-(5-fluoropyrimidin-2-yl)piperidin-4-yl)methyl methanesulfonate (202 mg, 0.7 mmol; prepared by following the procedure for **Q4a** except using 2-chloro-5-fluoropyrimidine as the electrophile), and Cs_2CO_3 (456 mg, 1.4 mmol) in acetonitrile (10 mL) is heated to 70 °C for 48 hours. The reaction mixture is concentrated and partitioned between water (20 mL) and ethyl acetate, the aqueous phase is extracted with ethyl acetate (2 x 20 mL). The combined organics are washed with water (2 x 10), dried over Na_2SO_4 and concentrated. Purification on silica gel using a linear gradient of 0 to 60% ethyl acetate in hexane to affords **T1f**; ^1H-NMR (400MHz, DMSO) δ 8.43 (d, J = 0.8 Hz, 2H), 7.46 (m, 2H), 7.00 (m, 2H), 4.61 (m, 2H), 3.87 (d, J = 6.4 Hz, 2H), 3.74 (m, 2H), 3.00 (m, 5H), 2.92 (m, 2H), 2.24 (m, 2H), 2.05 (m, 3H), 1.83 (m, 2H), 1.23 (m, 2H); ESIMS calcd. for $C_{23}H_{29}FN_5O_3S$ (M+H$^+$) 474.2, found 474.2.

[00369] **Step F:** A solution of **T1f** (30 mg, 0.063 mmol) and KOH (105 mg, 2.6 mmol) in 2-methoxyethanol (1 mL) and water (0.5 mL) is heated to 110 °C for 72 hours. The reaction mixture is acidified with 1N HCl to pH 2-3 and extracted with ethyl acetate (3 x 20 mL). The combined organics are dried over Na_2SO_4, and concentrated. The residue is purified using mass-triggered reverse phase HPLC to afford **T1**; ^{1}H-NMR (400MHz, DMSO-d6) δ 8.42 (d, J = 0.8 Hz, 2H), 7.30 (m, 2H), 6.92 (m, 2H), 4.60 (m, 2H), 3.83 (d, J = 6.4 Hz, 2H), 2.88 (m, 7H), 2.48 (m, 2H), 2.04 (m, 1H), 1.83 (m, 4H), 1.22 (m, 2H). ESIMS calcd. for $C_{23}H_{30}FN_4O_5S$ (M+H$^+$) 493.2, found 493.1

Example U1: 1-methylcyclopropyl 4-((2,6-difluoro-4-(3-(methylsulfonamido)azetidin-1-yl)phenoxy)methyl)piperidine-1-carboxylate.





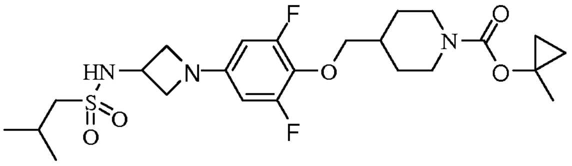
[00370] **Step A:** By following a similar procedure as that used to prepare **E3** from **E3a**, except substituting **P1b** for **E3a**, **U1a** is prepared; ESIMS calcd. for $C_{17}H_{21}BrF_2NO_3$ [M+H]$^+$: 404.1, found: 404.0.

[00371] **Step B:** By following a similar procedure as that used to prepare **B2** from **B2b**, except substituting benzyl azetidin-3-ylcarbamate for benzyl piperazine-1-

carboxylate, **U1b** is prepared; It is observed that the Cbz group is removed under reaction conditions; ESIMS calcd. for $C_{20}H_{28}F_2N_3O_3$ [M+H$^+$] 396.2, found 369.3.

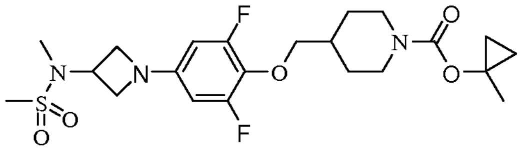
[00372] **Step C:** By following a similar procedure as that used to prepare **G1** from **G1a**, except substituting **U1b** for **G1a**, **U1** is prepared; ^{1}H-NMR (400MHz, CDCl$_3$) δ 5.95 (d, *J* = 9.7 Hz, 2H), 4.85 (d, *J* = 9.4 Hz, 1H), 4.40 (m, 1H), 4.20 (t, *J* = 7.5 Hz, 2H), 4.29-3.94 (m, 2H), 3.80 (d, *J* = 6.0 Hz, 2H), 3.65 (dd, *J* = 5.3, 8.0 Hz, 2H), 3.00 (s, 3H), 2.74 (t, *J* = 12.4 Hz, 2H), 1.9 (m, 1H), 1.82 (d, *J* = 13.1 Hz, 2H), 1.54 (s, 3H), 1.22 (m, 2H), 0.86 (t, *J* = 6.4 Hz, 2H), 0.62 (t, *J* = 6.4 Hz, 2H). ESIMS calcd. for $C_{21}H_{30}F_2N_3O_5S$ [M+H$^+$] 474.2, found 474.1.

Example U2: 1-methylcyclopropyl 4-((2,6-difluoro-4-(3-(2-methylpropylsulfonamido)azetidin-1-yl)phenoxy)methyl)piperidine-1-carboxylate.



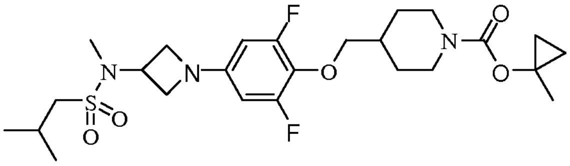
[00373] By following a similar procedure as that used to prepare **U1** from **U1c**, except substituting isobutanesulfonyl chloride for methanesulfonyl chloride, **U2** is prepared; ^{1}H-NMR (400MHz, CDCl$_3$) δ 5.96 (d, *J* = 9.6 Hz, 2H), 4.87 (d, *J* = 9.5 Hz, 1H), 4.40 (m, 1H), 4.20 (t, *J* = 7.5 Hz, 2H), 4.29-3.94 (m, 2H), 3.82 (d, *J* = 4.8 Hz, 2H), 3.65 (dd, *J* = 7.9, 5.4 Hz, 2H), 2.93 (d, *J* = 6.4 Hz, 2H), 2.75 (m, 2H), 2.28 (septet, *J* = 6.7 Hz, 1H), 1.92 (m, 1H), 1.83 (d, *J* = 12.6 Hz, 2H), 1.56 (s, 3H), 1.24 (m, 2H), 1.13 (d, *J* = 6.7 Hz, 6H), 0.87 (t, *J* = 6.3 Hz, 2H), 0.63 (t, *J* = 6.3 Hz, 2H). ESIMS calcd. for $C_{24}H_{36}F_2N_3O_5S$ [M+H$^+$] 516.2, found 516.2.

Example U3: 1-methylcyclopropyl 4-((2,6-difluoro-4-(3-(N-methylmethylsulfonamido)azetidin-1-yl)phenoxy)methyl)piperidine-1-carboxylate.



[00374] To a solution of **U1** (25 mg, 0.05 mmol) and iodomethane (4 uL, 0.06 mmol) in dry N,N-dimethylformamide (1 mL) at 0 °C is added sodium hydride (5 mg, 0.2 mmol) in one portion. The mixture is allowed to warm slowly to room temperature and stirred an additional 1 hour. The mixture is partitioned between water and dichloromethane, and the organics washed with brine, dried over $MgSO_4$, filtered, evaporated and purified on silica gel using 0-50% ethyl acetate in dichloromethane to afford **U3**; ^{1}H-NMR (400MHz, $CDCl_3$) δ 5.97 (d, *J* = 9.6 Hz, 2H), 4.71 (m, 1H), 4.06 (t, *J* = 7.8 Hz, 2H), 4.29-3.95 (m, 2H), 3.88 (dd, *J* = 8.0, 5.6 Hz, 2H), 3.81 (d, *J* = 5.8 Hz, 2H), 2.97 (s, 3H), 2.83 (s, 3H), 2.74 (m, 2H), 1.91 (m, 1H), 1.83 (d, *J* = 13.4 Hz, 2H), 1.54 (s, 3H), 1.24 (m, 2H), 0.86 (t, *J* = 6.3 Hz, 2H), 0.62 (t, *J* = 6.3 Hz, 2H). ESIMS calcd. for $C_{22}H_{32}F_2N_3O_5S$ [M+H$^+$] 488.2, found 488.2.

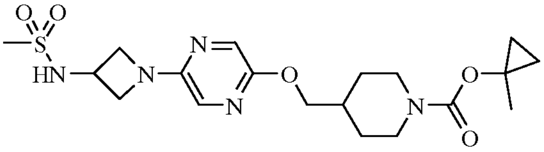
Example U4: 1-methylcyclopropyl 4-((4-(3-(N,2-dimethylpropylsulfonamido)azetidin-1-yl)-2,6-difluorophenoxy)methyl)piperidine-1-carboxylate.



[00375] By following a similar procedure as that used to prepare **U3** from **U1**, except substituting **U2** for **U1**, **U2** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 5.96 (d, *J* = 9.7 Hz, 2H), 4.77 (m, 1H), 4.04 (t, *J* = 7.9 Hz, 2H), 4.25-3.96 (m, 2H), 3.87 (dd, *J* = 5.6, 7.8 Hz, 2H), 3.81 (d, *J* = 6.3 Hz, 2H), 2.97 (s, 3H), 2.77 (d, *J* = 6.7 Hz, 2H), 2.74 (m, 2H), 2.24 (septet, *J* = 6.6 Hz, 1H), 1.91 (m, 1H), 1.83 (d, *J* = 13.3 Hz, 2H), 1.54 (s, 3H),

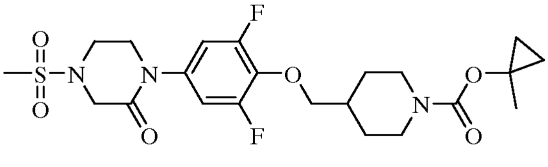
1.24 (m, 2H), 1.11 (d, *J* = 6.5 Hz, 6H), 0.86 (t, *J* = 6.3 Hz, 2H), 0.61 (t, *J* = 6.3 Hz, 2H). ESIMS calcd. for $C_{25}H_{38}F_2N_3O_5S$ [M+H$^+$] 530.3, found 530.2.

Example U5: 1-Methylcyclopropyl 4-((5-(3-(methylsulfonamido)azetidin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



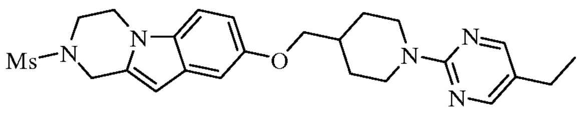
By following a similar procedure as that used to prepare **M1** from **M1a**, except substituting benzyl azetidin-3-ylcarbamate for benzyl piperazine-1-carboxylate **in step A** and methanesulfonyl chloride for methyl 3-(chlorosulfonyl)propanoate in **step d**, **U5** is prepared; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.72 (d, J = 1.4 Hz, 1H), 7.24 (d, J = 1.4 Hz, 1H), 4.73 (d, J = 9.2 Hz, 1H), 4.37 (m, 1H), 4.28 (m, 2H), 3.97 (d, J = 6.4 Hz, 2H), 3.75 (m, 2H), 3.27 (s, 3H), 2.65 (m, 2H), 1.85 (m, 1H), 1.70 (m, 2H), 1.46 (s, 3H), 1.17 (m, 3H), 0.77 (m, 2H), 0.53 (m, 2H); ESIMS *m/z* for (M+H)$^+$ $C_{19}H_{30}N_5O_5S$ calcd: 440.2, found: 440.2.

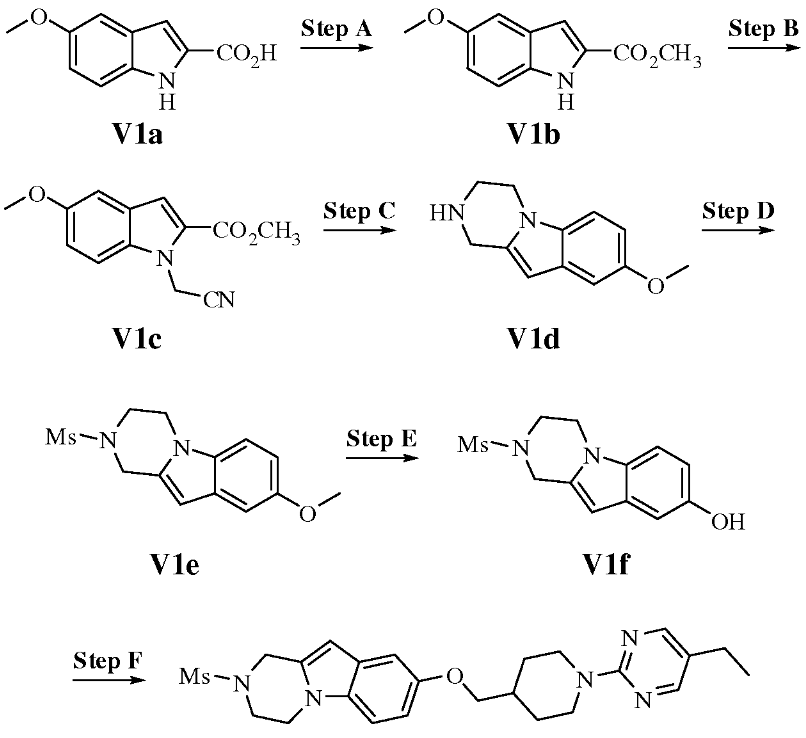
Example U6: 1-Methylcyclopropyl 4-((2,6-difluoro-4-(4-(methylsulfonyl)-2-oxopiperazin-1-yl)phenoxy)methyl)piperidine-1-carboxylate.



By following a similar procedure as that used to prepare **O2** from **B4b**, except substituting **P1b** for **B4b**, **U6** is prepared; ^{1}H-NMR (400MHz, DMSO-d6) δ 7.28 (m, 2H), 3.94 (m, 6H), 3.77 (m, 2H), 3.53 (m, 2H), 3.05 (s, 3H), 2.75 (m, 2H), 1.88 (m, 2H), 1.74 (m, 2H), 1.46 (s, 3H), 1.14 (m, 2H), 0.76 (m, 2H), 0.59 (m, 2H); ESIMS calcd. for $C_{22}H_{30}F_2N_3O_6S$ [M+H]$^+$ 502.2, found 502.2.

Example V1: 8-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-2-(methylsulfonyl)-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole.





Example V1

Step A: A suspension of **V1a** (2.26 g, 11.8 mmol) in methanol (20 mL) is treated with thionyl chloride (1.0 mL, 13.8 mmol) dropwise, with stirring. The resulting mixture is stirred at room temperature for 18h, and then concentrated to dryness. The resulting solid is triturated with 1:1 water/aqueous saturated sodiumhydrogencarbonate, filtered, washed with water and dried to afford **V1b**; ^{1}H NMR (DMSO-d$_6$, 400.13 MHz): δ 11.80 (s, 1H), 7.37 (d, J = 8.9 Hz, 1H), 7.11 (d, J = 2.2 Hz, 1H), 7.06 (d, J = 2.2 Hz, 1H), 6.92 (dd, J = 2.4, 8.9 Hz, 1H), 3.86 (s, 3H), 3.76 (s, 3H); ESIMS calcd. for $C_{11}H_{12}NO_3$ (M+H$^+$) 206.1, found 206.1.

Step B: A solution of **V1b** (1.86 g, 9.1 mmol) is in *N,N*-dimethylacetamide (25 mL) is treated with powdered cesium carbonate (5.31 g, 16.3 mmol) and chloroacetonitrile (0.90 mL, 14.3 mmol) and the mixture is stirred at 65 °C for 18 hours. Cooling to room temperature, dilution with ethyl acetate, washing with water (2x), saturated aqueous ammonium chloride and brine, drying over Na_2SO_4, filtration and concentration yields a solid. The residue is purified on silica gel using 5-30% ethyl acetate in hexanes to afford **V1c**; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 7.33 (d, $J = 8.9$ Hz, 1H), 7.30 (d, $J = 1.0$ Hz, 1H), 7.12 (m, 2H), 5.59 (s, 2H), 3.95 (s, 3H), 3.87 (s, 3H); ESIMS calcd. for $C_{13}H_{13}N_2O_3$ (M+H$^+$) 245.1, found 245.0.

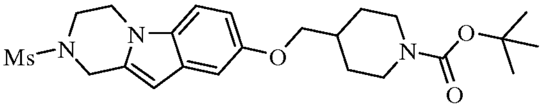
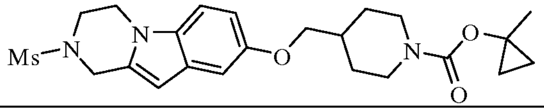
Step C: **V1d** is prepared from **V1c** according to the literature procedure described in *Bioorg. Med. Chem. Lett.* **2002**, *12*, 155-158; ESIMS calcd. for $C_{12}H_{15}N_2O$ (M+H$^+$) 203.1, found 203.1.

Step D: To a solution of **V1d** (0.58 g, 2.5 mmol) in dichloromethane (15 mL) is added triethylamine (0.7 mL, 5 mmol) in one portion. The resulting mixture is cooled in an ice/water bathand methanesulfonyl chloride (0.25 mL, 3.2 mmol) is added dropwise, with stirring, over 5 minutes. The bath is removed and the resulting solution is stirred at room temperature for 30 minutes. The reaction mixture is added to water (40 mL) and extracted with dichloromethane (2 x 40 mL). The combined organic extracts are washed with saturated aqueous ammonium chloride solution, dried over $MgSO_4$, and concentrated to yield **V1e**; ESIMS calcd. for $C_{13}H_{17}N_2O_3S$ (M+H$^+$) 281.1, found 281.2.

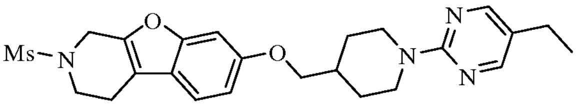
Step E: A solution of **V1e** (0.60 g, 2.1 mmol) in dichloromethane (15 mL) is treated with neat boron tribromide (0.8 mL, 8.3 mmol) at room temperature. The resulting solution is stirred at room temperature for 30 minutes. The reaction mixture is carefully added to methanol (50 mL), treated with solid Na_2CO_3 (0.4 g), filtered and concentrated to dryness. The crude **V1f** is used as such in the next step; ESIMS calcd. for $C_{12}H_{15}N_2O_3S$ (M+H$^+$) 267.1, found 267.1.

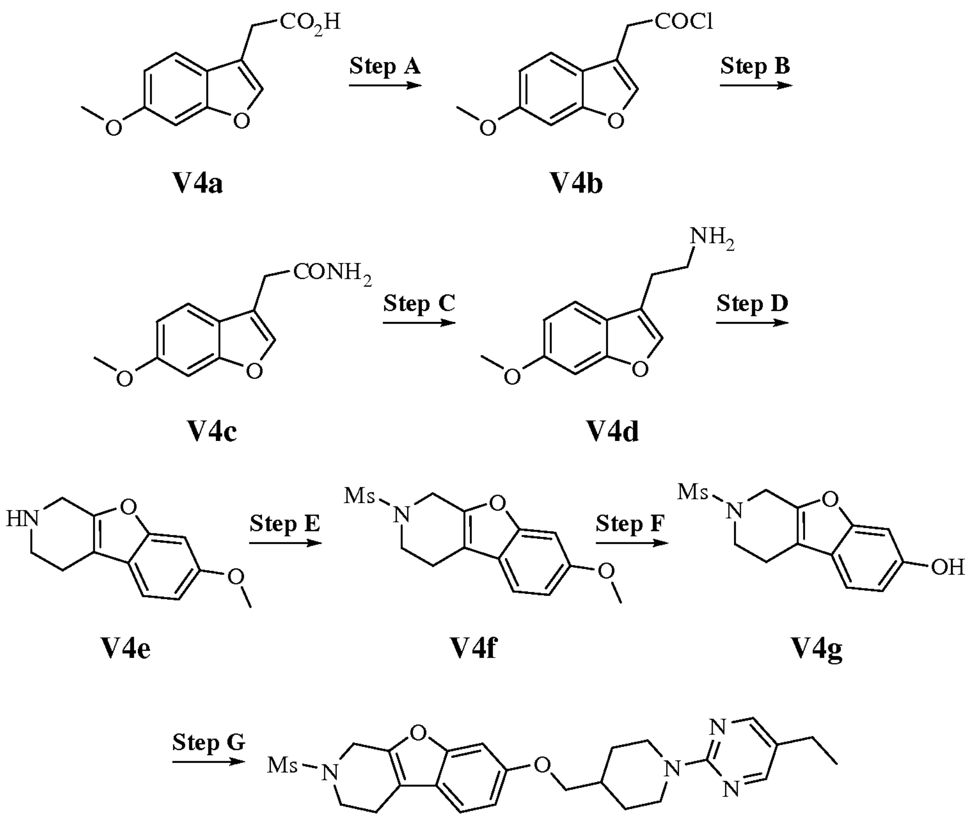
Step F: A solution of **V1f** and **Q4b** (0.03 g, 0.1 mmol) in dry acetonitrile (2 mL) is treated with powdered cesium carbonate (0.1 g, 0.3 mmol) and the mixture is stirred at 75 °C for 24 hours. Filtration and mass directed reverse phase HPLC purification yields **V1**; ESIMS calcd. for $C_{24}H_{32}N_5O_3S$ (M+H$^+$) 470.2, found 470.1.

By following a similar procedure as the one used for preparing **V1** from **V1f** except substituting the appropriate mesylate for **Q4b** the following compounds are prepared;

Example	Structure	Analytical data
V2		^{1}H NMR (CDCl$_3$, 400.13 MHz): δ 7.17 (d, J = 8.8 Hz, 1H), 7.03 (d, J = 2.3 Hz, 1H), 6.85 (dd, J = 2.3, 8.8 Hz, 1H), 6.24 (d, J = 0.7 Hz, 1H), 4.67 (s, 2H), 4.16 (br, 2H), 4.15 (t, J = 5.4 Hz, 2H), 3.84 (m, 4H), 2.87 (s, 3H), 2.76 (t, J = 12.2 Hz, 2H), 1.98 (m, 1H), 1.85 (t, J = 12.6 Hz, 2H), 1.47 (s, 9H), 1.28 (ddd, J = 4.7, 12.4, 12.4 Hz, 2H); ESIMS calcd. for $C_{23}H_{34}N_3O_5S$ (M+H$^+$) 464.2, found 464.1.
V3		ESIMS calcd. for $C_{23}H_{32}N_3O_5S$ (M+H$^+$) 462.2, found 462.2.

Example V4: 7-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-2-(methylsulfonyl)-1,2,3,4-tetrahydrobenzofuro[2,3-*c*]pyridine.





Example V4

Step A: A suspension of **V4a** (3.99 g, 19.4 mmol) is in dichloromethane (50 mL) is treated with oxalyl chloride (1.8 mL, 21.3 mmol) slowly, with stirring, followed by dimethylformamide (0.01 mL). The resulting mixture is stirred at room temperature for 1 hour, and then concentrated to dryness to yield **V4b**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.58 (t, *J* = 1.0 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 1H), 7.03 (d, *J* = 2.2 Hz, 1H), 6.92 (dd, *J* = 2.2, 8.6 Hz, 1H), 4.21 (d, *J* = 1.0 Hz, 2H), 3.84 (s, 3H).

Step B: A solution of **V4b** (19.4 mmol) in dichloromethane (100 mL) is treated with ammonia gas by slow bubbling through the stirring solution for 5 minutes. The resulting suspension is stirred in a closed flask for 2 hours. The resulting suspension is filtered, the collected solids are washed with more dichloromethane and air dried to yield **V4c**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.52 (t, *J* = 0.7 Hz, 1H), 7.43 (d, *J* = 8.6 Hz, 1H), 7.03 (d, *J* = 2.2 Hz, 1H), 6.92 (dd, *J* = 2.2, 8.6 Hz, 1H), 5.61 (s, 1H), 5.45 (s, 1H), 3.86 (s, 3H), 3.63 (d, *J* = 0.7 Hz, 2H); ESIMS calcd. for $C_{11}H_{12}NO_3$ ($M+H^+$) 206.1, found 206.1.

Step C: A solution of **V4c** (2.79 g, 13.6 mmol) in dry tetrahydrofuran (100 mL) is treated with borane solution in tetrahydrofuran (1.0 N; 50 mL, 50 mmol) and the resulting solution is stirred in a closed flask overnight. The reaction mixture is carefully treated with methanol (50 mL) and concentrated to dryness. The residue is purified by silica gel chromatography using a linear gradient of 20 to 100% ethyl acetate in hexanes to afford **V4d**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.46 (s, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 7.02 (d, *J* = 2.2 Hz, 1H), 6.90 (dd, *J* = 2.2, 8.6 Hz, 1H), 3.85 (s, 3H), 3.63 (br. s, 2H), 3.14 (tt, *J* = 6.4, 6.8 Hz, 2H), 3.02 (t, *J* = 6.4 Hz, 2H); ESIMS calcd. for $C_{11}H_{14}NO_2$ ($M+H^+$) 192.1, found 192.1.

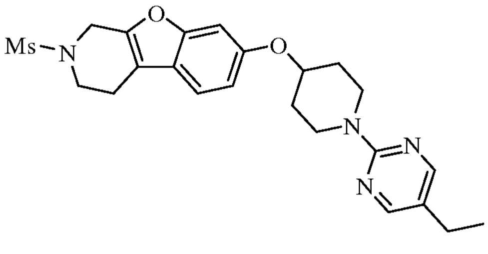
Step D: **V4e** acetic acid salt is prepared from **V4d** according to the procedure described in WO2000/020421, p. 15; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.30 (d, *J* = 8.5 Hz, 1H), 6.99 (d, *J* = 2.2 Hz, 1H), 6.86 (dd, *J* = 2.2, 8.5 Hz, 1H), 3.88 (br. s, 2H), 3.85 (s, 3H), 3.06 (t, *J* = 5.8 Hz, 2H), 2.85 (m, 2H), 2.72 (m, 1H); ESIMS calcd. for $C_{12}H_{14}NO_2$ ($M+H^+$) 204.1, found 204.1.

Step E: A solution of **V4e** acetic acid salt (0.18 g, 0.7 mmol) in dichloromethane (5 mL) is treated with triethylamine (0.2 mL, 1.4 mmol) and methanesulfonic anhydride (0.15 g, 0.86 mmol) and the mixture is stirred at room temperature for 1 hour. Washing with water, drying over $MgSO_4$ and concentration yields **V4f**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.29 (d, *J* = 8.5 Hz, 1H), 6.98 (d, *J* = 2.2 Hz, 1H), 6.84 (dd, *J* = 2.2, 8.5 Hz, 1H), 3.84 (s, 3H), 2.77 (m, 2H), 2.73 (m, 2H), 2.54 (s, 3H); ESIMS calcd. for $C_{13}H_{16}NO_4S$ ($M+H^+$) 282.1, found 282.0.

Step F: A solution of **V4f** (0.15 g, 0.5 mmol) in dichloromethane (5 mL) is treated with neat boron tribromide (0.2 mL, 2.1 mmol) at room temperature. The resulting solution is stirred at room temperature for 30 minutes. The reaction mixture is carefully added to methanol (50 mL), treated with solid Na_2CO_3 (0.4 g), filtered and concentrated to dryness to afford **V4g**; ESIMS calcd. for $C_{12}H_{14}NO_4S$ ($M+H^+$) 268.1, found 268.1.

Step G: A solution of **V4g** and **Q4b** (0.03 g, 0.1 mmol) in dry acetonitrile (2 mL) is treated with powdered cesium carbonate (0.08 g, 0.2 mmol) and the mixture is stirred at 75 °C for 24 hours. Filtration and mass directed HPLC purification yields **V4**; ESIMS calcd. for $C_{24}H_{31}N_4O_4S$ ($M+H^+$) 471.2, found 471.2.

Example V5: 7-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yloxy)-2-(methylsulfonyl)-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine.



By following a similar procedure as the one used for preparing **V4** from **V4g** except substituting 1-(5-ethylpyrimidin-2-yl)piperidin-4-yl methanesulfonate for **Q4b** the **V5** is prepared; ESIMS calcd. for $C_{23}H_{29}N_4O_4S$ ($M+H^+$) 457.2, found 457.1.

Biological Assays

Generation of Stable Cell Line

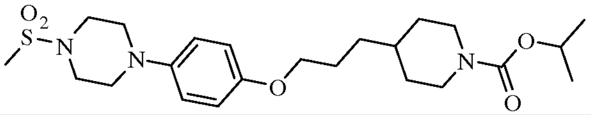
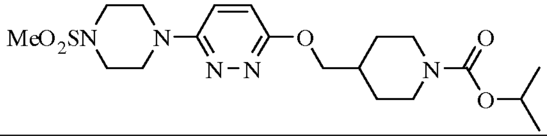
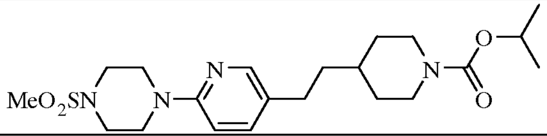
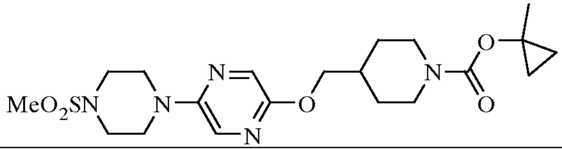
[00376] Flp-In-CHO cells (Invitrogen, Cat.# R758-07) are maintained in Ham's F12 medium supplemented with 10% fetal bovine serum, 1% antibiotic mixture and 2 mM L-glutamine. The cells are transfected with a DNA mixture containing human GPR119 (hGPR119) or mouse GPR119 (mGPR119) in the pcDNA5/FRT vector (Invitrogen) and the pOG44 vector (Invitrogen) in a 1:9 ratio using Fugene6 (Roche), according to the manufacturer's instructions. After 48 hours, the medium is changed to medium supplemented with 400 µg/mL hygromycin B to initiate the selection of stably transfected cells. The resultant cell lines are designated CHO-hGPR119 and CHO-mGPR119 respectively.

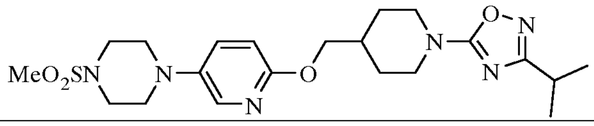
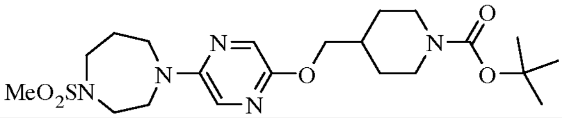
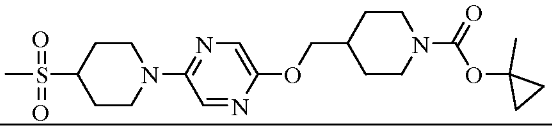
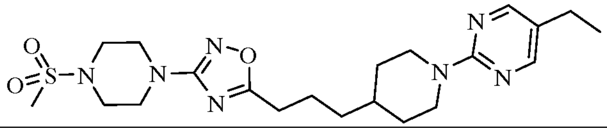
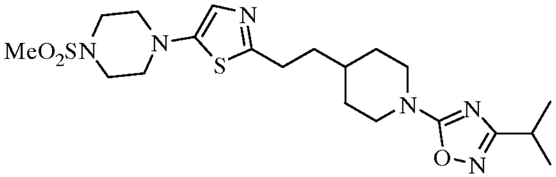
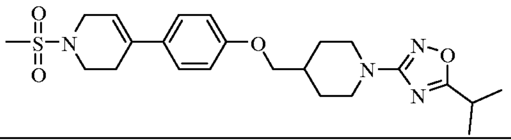
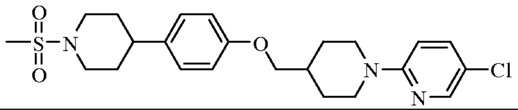
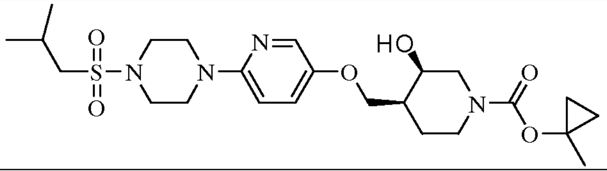
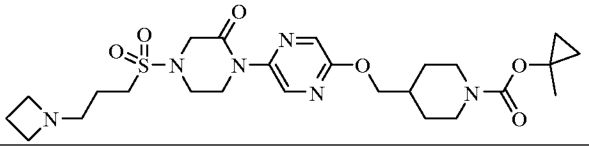
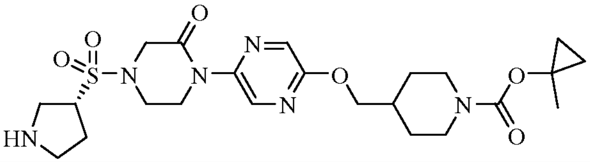
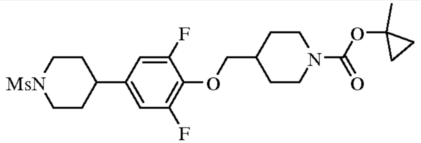
Cyclic AMP Assays

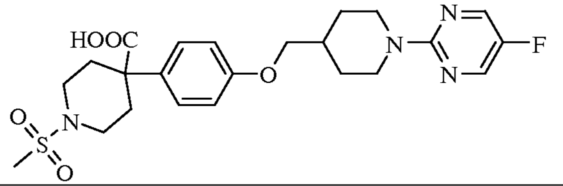
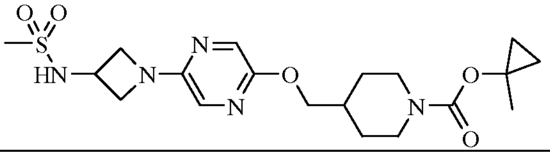
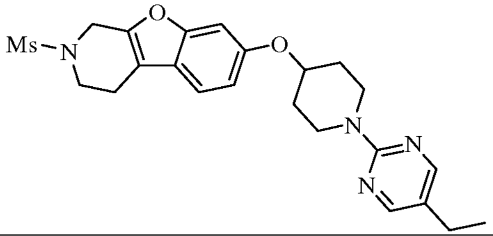
[00377] To test the activity of compounds of the invention on human GPR119, CHO-hGPR119 cells are harvested and resuspended at 300,000 cells/mL in assay media (Ham's F12 medium plus 3% lipid-depleted fetal bovine serum, 1 mM 3-isobutyl-1-methyl-xanthine (IBMX)). Cells (5 µl) are placed in each well of a white 1536-well plate. A compound of the invention (50 nL) diluted in 100% dimethyl sulfoxide (DMSO) is added to each well and the plates are incubated at 37°C for 30 minutes. cAMP concentrations are then measured using the cAMP dynamic 2 kit (Cisbio Bioassays) according to the manufacturer's instructions. 2.5 µL of diluted cAMP-XL665 is added to each well, followed by 2.5 µL diluted anti-cAMP-Cryptate. The plate is covered and incubated for one hour at room temperature, then read on an Envision plate reader (Perkin Elmer) using the HTRF method with excitation at 337 nm, and emissions measured at 620 nm and 655 nm.

[00378] Activity of compounds of the invention on mouse GPR119 is measured by a similar method in 384-well plates. CHO-mGPR119 cells are harvested and resuspended in assay media at 500,000 cells/mL. 50 µl cells are placed in each well of a white 384-well plate. A compound of the invention (500 nL) diluted in 100% DMSO is added to each well and the plates are incubated at 37°C for 30 minutes. cAMP concentrations are measured as above except that 20 µL of diluted cAMP-XL665 followed by 20 µL diluted anti-cAMP-Cryptate is added to each well.

[00379] Compounds of the invention, in free form or in pharmaceutically acceptable salt form, produced a concentration-dependent increase in intracellular cAMP level. Compounds of the invention show an EC_{50} of between $1x10^{-5}$ and $1x\ 10^{-10}M$, preferably less than 500nM, more preferably less than 100nM. The following table shows a non-limiting sample of EC_{50} measurements for compounds of the invention whereby +, ++ and +++ represent EC_{50} ranges of >800nM, 200-800nM and <200nM, respectively:

Compound	Structure	EC_{50} Activity
A3		+
C2		+
D2		++
E3		+++

E9		++
G1		+
G4		+++
H3		+++
I1		+++
J7		+++
J22		+++
K3		+++
O9		+++
O41		+++
P13		+++

T1		++
U5		+++
V5		+++

GLUTag GLP-1 assay

[00380] The effect of compounds of the invention on GLP-1 secretion can be studied in GLUTag cells (a mouse entereoendocrine cell line that secretes GLP-1). GLUTag cells are plated in poly-D-lysine-coated 96-well plates on day one in complete medium (DMEM/10% FBS). On day two, the culture medium is replaced with a low glucose medium (DMEM/5.5 mM glucose/10% FBS). One day three, cells are washed twice and pre-incubated in glucose free EBSS buffer (100 mM NaCl, 5 mM KCl, 0.8 mM $MgSO_4 \cdot 7H_2O$, 1.65 mM $NaH_2PO_4 \cdot 2H_2O$, 26 mM $NaHCO_3$, 1.6 mM $CaCl_2$, 0.1% fatty acid-free bovine serum albumin, pH 7.35) for two hours at 37 °C with 5% CO_2. After this pre-incubation period, the cells are washed again with glucose free EBSS buffer, and then stimulated with a compound of the invention at various concentrations in EBSS buffer plus 10 mM glucose and a DPP-4 inhibitor at 37 °C in the presence of 5% CO_2. At the end of the incubation, the supernatants are then collected and transferred to a HEK293 cell line that over expresses human GLP-1 receptor and a CRE-luciferase reporter construct. The CRE-luciferase construct expresses luciferase gene under the control of a cAMP response element (CRE). GLP-1-stimulated GLP-1 receptor leads to cAMP production, which in turn, up regulates luciferase expression. The HEK293-GLP-1R reporter cells are plated the night before in white 384-well plates. After incubation with the supernatants from GLUTag cells treated with a compound of the invention, the HEK293-GLP-1R reporter cells are incubated at 37 °C in the presence of 5%

CO_2 for 18 hours. Luciferase produced from the treatment is measured by the addition of Steady-Glo reagent (Promega, Cat. # E2550). The EC_{50} values are calculated with nonlinear regression using Graphpad Prism.

HIT-T15 insulin assay

[00381] The effect of GPR119 agonist on insulin secretion is studied in HIT-T15 cells (a hamster beta cell line that secrets insulin). HIT-T15 cells are obtained from ATCC and are cultured in Ham's F12 Kaighn's medium plus 10% horse serum and 2.5% fetal bovine serum. On day one, HIT-T15 cells are plated in 96-well plates and cultured for 24 hours and then the medium is replaced with a low-glucose medium (RPMI 1640 medium supplemented with 10% horse serum, 2.5% fetal bovine serum and 3.0 mM D-(+)-glucose). On day three, the cells are washed twice and then pre-incubated with glucose-free Krebs–Ringer bicarbonate buffer (KRBB) that contains 119 mM NaCl, 4.74 mM KC1, 2.54 mM $CaCl_2$, 1.19 mM KH_2PO_4, 1.19 mM $MgCl_2$, 25 mM $NaHCO_3$, 10 mM HEPES and 0.1% fatty-acid-free bovine serum albumin at pH 7.4. One hour later, the cells are washed again for three times and incubated with a compound of the invention in KRBB plus 16.5 mM glucose for 3 hours at 37 °C. After a 5 minute centrifugation at 1,000 rpm, supernatant is removed from each well and transferred into a separate plate for insulin measurement following the instructions for Cisbio insulin HTRF assay kit (Cisbio, Cat. # 62INSPEC). The EC_{50} values are calculated with nonlinear regression using Graphpad Prism.

GLP-1 Assay

[00382] Adult male wild-type C57BL/6J mice (age 9 weeks, JAX) are used as the experimental animals. In all experiments, mice are housed in a 12 hour light/dark cycle facility (light on from 5:00 a.m. to 5:00 p.m) and have access to food (Purina 5001) and water ad libitum. Mice (8 per group) are randomized into treatment groups based on their initial body weight. They are orally dosed with vehicle, DPP4 inhibitor alone, or DPP4 inhibitor and a compound of the invention, in a single dose. A glucose bolus (2 g/kg) is delivered sixty minutes post dosing. A sample is collected 2 minutes post glucose bolus.

[00383] Plasma active GLP-1 is measured in C57BL/6 mice following a single oral administration of increasing doses of a compound of the invention (3, 10 and 30 mg/kg).

Animals are fasted for 16 hours prior to compound administration. Oral doses are administered at approximately 10:00 am in a 75%PEG300:25%D5W suspension. Blood is obtained (via retro-orbital bleeding) to measure plasma levels of active GLP-1. Approximately 200 µL samples of blood are removed for analysis at 62 minutes post dosing (2 minutes post glucose bolus). All data are expressed as the mean ± SEM for each experimental group of mice. Statistical analysis of data is performed using a one-way ANOVA with a Bonferroni's Multiple Comparison Post Test (GraphPad Prism 4.02).

[00384] Treatment of mice with increasing doses of a compound of the invention (in combination with a DPP4 inhibitor) results in increasing levels of plasma active GLP-1. The magnitude of GLP-1 increase observed in the 10 mg/kg group demonstrate that some compounds of the invention can increase circulating levels of active GLP-1 by about 2.2X fold relative to the effect with a DPP4 inhibitor alone.

OGTT Assay

[00385] Adult male Zucker fa/fa rats (age 11 weeks, Charles River Labs) are used as the experimental animals. In all experiments, rats are housed in a 12 hour light/dark cycle facility (light on from 5:00 a.m. to 5:00 p.m) and have access to food (Purina 5001) and water ad libitum. Rats (6 per group) are randomized into treatment groups based on their initial body weight and are dosed (orally) with vehicle orally, a DPP4 inhibitor, or a compound of the invention. Sixty minutes after dosing, a 3 g/kg glucose bolus is administered.

[00386] A compound of the invention is dissolved in vehicle for dosing (orally using a gavage needle) at a final concentration of 0.2, 2 or 6mg/mL. Oral doses are administered at approximately 7:30 am in a 75%PEG300:25%D5W.

[00387] OGTT evaluations are performed in conscious rats that are 11 weeks of age. The rats are fasted by removing food at 6pm the day before. A baseline blood sample is taken at t = minus 60 minutes and the rats are then dosed orally with the a compound of the invention. A baseline blood sample is taken at t = zero minutes and the animals are then administered an oral glucose bolus (3 g/kg) immediately. Blood is obtained (via tail bleeding) to measure blood glucose (using a glucometer). A single drop of blood from the tail is measured for glucose using a glucometer at t = -60, 0, 10, 30, 60, 90, 120 and 180 minutes.

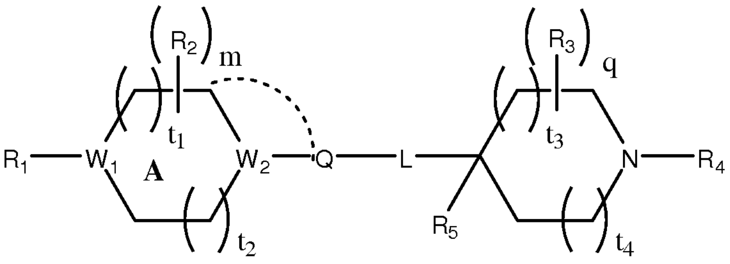
[00388] The area under the curve (AUC) is calculated using the trapezoidal rule. All data are expressed as the mean ± sem for each experimental group of rats. Statistical analysis of data is performed using a one-way ANOVA with a Bonferroni's Multiple Comparison Post Test (GraphPad Prism 4.02).

[00389] Some compounds of the invention exhibit a clear dose-dependent effect on improved glucose clearance at 3, 10, and 30 mg/kg (about 31%, about 48%, and about 56% reduction in glucose AUC, respectively) when dosed in a 75% PEG300 / 25% D5W formulation. The results demonstrate that some compounds of the invention can lower blood glucose in response to glucose challenge.

[00390] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference for all purposes.

WE CLAIM:

1. A compound of Formula I:



in which:

Q is a divalent or trivalent radical selected from $C_{6\text{-}10}$aryl, $C_{1\text{-}10}$heteroaryl, $C_{3\text{-}8}$cycloalkyl and $C_{3\text{-}8}$heterocycloalkyl; wherein said aryl, heteroaryl, cycloalkyl or heterocycloalkyl of Q is optionally substituted with up to 3 radicals independently selected from halo, $C_{1\text{-}6}$alkyl, halo-substituted-$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, halo-substituted-$C_{1\text{-}6}$alkoxy, $-C(O)R_{20}$ and $-C(O)OR_{20}$; wherein R_{20} is selected from hydrogen and $C_{1\text{-}6}$alkyl; and optionally connecting a carbon adjacent to W_2 through a CR_{31}, O, S or NR_{31} with a carbon of Q to form a 5-membered ring fused to rings A and Q; wherein R_{31} is selected from hydrogen and $C_{1\text{-}6}$alkyl;

W_1 and W_2 are independently selected from CR_{21} and N; wherein R_{21} is selected from hydrogen, cyano, $C_{1\text{-}6}$alkyl and $-C(O)OR_{25}$; wherein R_{25} is selected from hydrogen and $C_{1\text{-}6}$alkyl; ring A can have up to 2 ring carbons substituted with a group selected from $-C(O)-$, $-C(S)-$ and $-C(=NOR_{30})-$ and can be partially unsaturated with up to 2 double bonds; wherein R_{30} is selected from hydrogen and $C_{1\text{-}6}$alkyl;

L is selected from $C_{1\text{-}6}$alkylene, $C_{2\text{-}6}$alkenylene, $-(CH_2)_nO-$, $-OC(O)(CH_2)_n-$, $-C(O)O(CH_2)_n-$, $-NR_{26}(CH_2)_n-$ and $-O(CH_2)_n-$; wherein R_{26} is selected from hydrogen and $C_{1\text{-}6}$alkyl; and n is selected from 0, 1, 2, 3, 4 and 5; wherein any alkyl of L can be optionally substituted with 1 to 3 radicals independently selected from halo, $C_{1\text{-}6}$alkyl, halo-substituted-$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, halo-substituted-$C_{1\text{-}6}$alkoxy, $-C(O)R_{22}$ and $-C(O)OR_{22}$; wherein R_{22} is selected from hydrogen and $C_{1\text{-}6}$alkyl;

m is selected from 0, 1, 2, 3 and 4;

q is selected from 0, 1, 2, 3 and 4;

t_1 t_2, t_3 and t_4 are each independently selected from 0, 1 and 2;

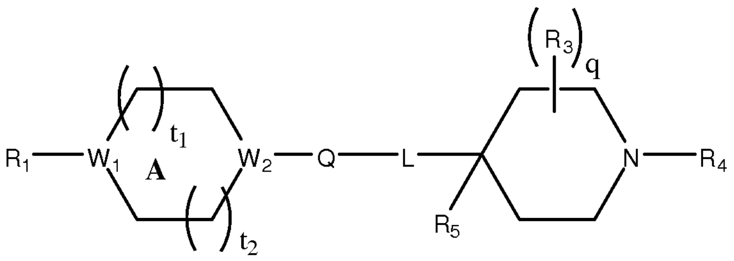
R_1 is selected from–$X_1S(O)_{0\text{-}2}X_2R_{6a}$, $-X_1S(O)_{0\text{-}2}X_2OR_{6a}$, $-X_1S(O)_{0\text{-}2}X_2C(O)R_{6a}$, $-X_1S(O)_{0\text{-}2}X_2C(O)OR_{6a}$, $-X_1S(O)_{0\text{-}2}X_2OC(O)R_{6a}$ and $-X_1S(O)_{0\text{-}2}NR_{6a}R_{6b}$; wherein X_1 is selected from a bond, O, $NR_{7a}R_{7b}$ and $C_{1\text{-}4}$alkylene; X_2 is selected from a bond and $C_{1\text{-}4}$alkylene; R_{6a} is selected from hydrogen, halo, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{6\text{-}10}$aryl, $C_{1\text{-}10}$heteroaryl, $C_{3\text{-}8}$heterocycloalkyl and $C_{3\text{-}8}$cycloalkyl; wherein said aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R_{6a} is optionally substituted with 1 to 3 radicals independently selected from hydroxy, halo, $C_{1\text{-}6}$alkyl, halo-substituted-$C_{1\text{-}6}$alkyl, hydroxy-substituted-$C_{1\text{-}6}$alkyl, cyano-substituted-$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, halo-substituted-$C_{1\text{-}6}$alkoxy and $C_{6\text{-}10}$aryl-$C_{1\text{-}4}$alkoxy; R_{6b} is selected from hydrogen and $C_{1\text{-}6}$alkyl; and R_{7a} and R_{7b} are independently selected from hydrogen and $C_{1\text{-}6}$alkyl;

R_2 and R_3 are independently selected from hydrogen, halo, hydroxy, $C_{1\text{-}6}$alkyl, halo-substituted-$C_{1\text{-}6}$alkyl, hydroxy-substituted-$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, halo-substituted-$C_{1\text{-}6}$alkoxy, $-C(O)R_{23}$, and $-C(O)OR_{23}$; wherein R_{23} is selected from hydrogen and $C_{1\text{-}6}$alkyl;

R_4 is selected from R_8 and $-C(O)OR_8$; wherein R_8 is selected from $C_{1\text{-}6}$alkyl, $C_{6\text{-}10}$aryl, $C_{1\text{-}10}$heteroaryl, $C_{3\text{-}8}$cycloalkyl and $C_{3\text{-}8}$heterocycloalkyl; wherein said aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_8 is optionally substituted with 1 to 3 radicals independently selected from halo, $C_{1\text{-}6}$alkyl, $C_{3\text{-}8}$cycloalkyl, $C_{3\text{-}8}$heterocycloalkyl, halo-substituted-$C_{1\text{-}6}$alkyl, hydroxy-substituted-$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy and halo-substituted-$C_{1\text{-}6}$alkoxy;

R_5 is selected from hydrogen, $C_{1\text{-}6}$alkyl, halo-substituted-$C_{1\text{-}6}$alkyl, hydroxy-substituted-$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy and halo-substituted-$C_{1\text{-}6}$alkoxy; or the pharmaceutically acceptable salts thereof.

2. The compound of claim 1 of Formula Ia:



in which:

Q is a divalent or trivalent radical selected from C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-8}cycloalkyl and C_{3-8}heterocycloalkyl; wherein said aryl, heteroaryl, cycloalkyl or heterocycloalkyl of Q is optionally substituted with up to 3 radicals independently selected from halo, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, $-C(O)R_{20}$ and $-C(O)OR_{20}$; wherein R_{20} is selected from hydrogen and C_{1-6}alkyl; and optionally connecting a carbon adjacent to W_2 through a CR_{31} or O with a carbon of Q to form a 5-membered ring fused to rings A and Q; wherein R_{31} is selected from hydrogen and C_{1-6}alkyl;

W_1 and W_2 are independently selected from CR_{21} and N; wherein R_{21} is selected from hydrogen, cyano, C_{1-6}alkyl and $-C(O)OR_{25}$; wherein R_{25} is selected from hydrogen and C_{1-6}alkyl; ring A can have up to 2 ring carbons substituted with a group selected from $-C(O)-$, $-C(S)-$ and $-C(=NOR_{30})-$ and can be partially unsaturated with up to 2 double bonds; wherein R_{30} is selected from hydrogen and C_{1-6}alkyl;

L is selected from C_{1-6}alkylene, C_{2-6}alkenylene, $-(CH_2)_nO-$, $-NR_{26}(CH_2)_n-$, $-OC(O)(CH_2)_n-$, $-C(O)O(CH_2)_n-$ and $-O(CH_2)_n-$; wherein R_{26} is selected from hydrogen and C_{1-6}alkyl; wherein n is selected from 0, 1, 2, 3, 4 and 5; wherein any alkyl of L can be optionally substituted with 1 to 3 radicals independently selected from halo, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, $-C(O)R_{22}$ and $-C(O)OR_{22}$; wherein R_{22} is selected from hydrogen and C_{1-6}alkyl;

t_1 and t_2 are each independently selected from 0, 1 and 2;

q is selected from 0, 1, 2, 3 and 4;

R_1 is selected from $-X_1S(O)_{0-2}X_2R_{6a}$, $-X_1S(O)_{0-2}X_2OR_{6a}$, $-X_1S(O)_{0-2}X_2C(O)OR_{6a}$, $-X_1S(O)_{0-2}X_2OC(O)R_{6a}$ and $-X_1S(O)_{0-2}NR_{6a}R_{6b}$; wherein X_1 is selected from a bond, O, $NR_{7a}R_{7b}$ and C_{1-4}alkylene; X_2 is selected from a bond and C_{1-4}alkylene; R_{6a} is selected from hydrogen, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-8}heterocycloalkyl and C_{3-8}cycloalkyl; wherein said aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R_{6a} is optionally substituted with 1 to 3 radicals independently selected from hydroxy, halo, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, cyano-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy and C_{6-10}aryl-C_{1-}

$_4$alkoxy; R_{6b} is selected from hydrogen and C_{1-6}alkyl; and R_{7a} and R_{7b} are independently selected from hydrogen and C_{1-6}alkyl;

R_3 is selected from hydrogen, halo, hydroxy, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, –C(O)R_{23}, and –C(O)OR_{23}; wherein R_{23} is selected from hydrogen and C_{1-6}alkyl;

R_4 is selected from R_8 and –C(O)OR_8; wherein R_8 is selected from C_{1-6}alkyl, C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-8}cycloalkyl and C_{3-8}heterocycloalkyl; wherein said aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_8 is optionally substituted with 1 to 3 radicals independently selected from halo, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}heterocycloalkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy and halo-substituted-C_{1-6}alkoxy;

R_5 is selected from hydrogen, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy and halo-substituted-C_{1-6}alkoxy.

3. The compound of claim 2 in which Q is a divalent or trivalent radical selected from phenyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, 1,2,4-oxadiazolyl, and thiazolyl; wherein said phenyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl and thiazolyl of Q is optionally substituted with up to 3 radicals independently selected from halo, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, –C(O)OR_{20} and –C(O)R_{20}; wherein R_{20} is selected from hydrogen and C_{1-6}alkyl; and optionally connecting a carbon adjacent to W_2 through a CR_{31} or O with a carbon of Q to form a 5-membered ring fused to rings A and Q; wherein R_{31} is selected from hydrogen and C_{1-6}alkyl.

4. The compound of claim 3 in which: W_1 and W_2 are independently selected from CR_{21} and N; wherein R_{21} is selected from hydrogen, cyano, C_{1-6}alkyl and –C(O)OR_{25}; wherein R_{25} is selected from hydrogen and C_{1-6}alkyl; with a group selected from –C(O)–, –C(S)– and –C(=NOR_{30})– and can be partially unsaturated with a double bond; wherein R_{30} is selected from hydrogen and C_{1-6}alkyl; and L is selected from –O$(CH_2)_{0-4}$–, –(CH=CH)–, –OC(O)–, –NH$(CH_2)_{0-4}$–, –$NCH_3(CH_2)_{0-4}$– and –$(CH_2)_{1-4}$–.

5. The compound of claim 4 in which: R_1 is selected from $–X_1S(O)_{0\text{-}2}X_2R_{6a}$, $–X_1S(O)_{0\text{-}2}X_2OR_{6a}$, $–X_1S(O)_{0\text{-}2}X_2C(O)OR_{6a}$, $–X_1S(O)_{0\text{-}2}X_2OC(O)R_{6a}$ and $–X_1S(O)_{0\text{-}2}NR_{6a}R_{6b}$; wherein X_1 is selected from a bond and O; X_2 is selected from a bond and $C_{1\text{-}4}$alkylene; R_{6a} is selected from hydrogen, halo, cyano, methyl, ethyl, propyl, isopropyl, ethenyl, pyridinyl, pyrrolidinyl, piperidinyl, morpholino, isoxazolyl, tetrazolyl, phenyl and imidazolyl; wherein said piperidinyl, pyridinyl, pyrrolidinyl, morpholino, isoxazolyl, tetrazolyl, phenyl or imidazolyl of R_{6a} is optionally substituted with 1 to 3 radicals independently selected from hydroxy, halo, $C_{1\text{-}6}$alkyl and benzoxy; and R_{6b} is selected from hydrogen, methyl and ethyl.

6. The compound of claim 5 in which: R_4 is selected from R_8 and $–C(O)OR_8$; wherein R_8 is selected from isopropyl, cyclopropyl, t-butyl, 1,2,4-oxadiazolyl, pyrimidinyl, pyridinyl, pyridazinyl, tetrahydro-2H-pyranyl, tetrahydrofuranyl, oxetanyl, 2H-tetrazolyl and thiazolyl; wherein said cyclopropyl, 1,2,4-oxadiazolyl, pyrimidinyl, pyridinyl, pyridazinyl, tetrahydro-2H-pyranyl, tetrahydrofuranyl, oxetanyl, 2H-tetrazolyl or thiazolyl of R_8 is optionally substituted with 1 to 3 radicals independently selected from halo, trifluoromethyl, isopropyl, t-butyl, methyl, ethyl and cyclopropyl optionally substituted with methyl; and R_5 is selected from hydrogen and methoxy.

7. The compound of claim 1 selected from: 1-Methylcyclopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, isopropyl 4-((4-((4-methanesulfonylpiperazin)-1-yl)phenoxy)methyl)piperidine-1-carboxylate, isopropyl 4-(2-(4-(4-(methylsulfonyl)piperazin-1-yl)phenoxy)ethyl)piperidine-1-carboxylate, isopropyl 4-(3-(4-(4-(methylsulfonyl)piperazin-1-yl)phenoxy)propyl)piperidine-1-carboxylate, isopropyl 4-(4-(4-(4-(methylsulfonyl)piperazin-1-yl)phenoxy)butyl)piperidine-1-carboxylate, Isopropyl 4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate, tert-Butyl 4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate, Isopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, tert-Butyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, 3-Cyclopropyl-5-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, 5-Cyclopropyl-3-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-

yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, 2-(4-(Methylsulfonyl)piperazin-1-yl)-5-((1-(5-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)methoxy)pyrazine, 5-Isopropyl-3-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, Tetrahydro-2H-pyran-4-yl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, (S)-Tetrahydrofuran-3-yl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, (R)-Tetrahydrofuran-3-yl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, 2-Isopropyl-5-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)thiazole, 2-((1-(2-methyl-2H-tetrazol-5-yl)piperidin-4-yl)methoxy)-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazine, Oxetan-3-yl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, Isopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate, Isopropyl 4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridazin-3-yloxy)methyl)piperidine-1-carboxylate, Isopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrimidin-2-yloxy)methyl)piperidine-1-carboxylate, (E)-isopropyl 4-(2-(6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yl)vinyl)piperidine-1-carboxylate, Isopropyl 4-(2-(6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yl)ethyl)piperidine-1-carboxylate, (E)-Isopropyl 4-(2-(2-(4-(methylsulfonyl)piperazin-1-yl)pyrimidin-5-yl)vinyl)piperidine-1-carboxylate, 5-Ethyl-2-(4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)pyrimidine, 1-(Methylsulfonyl)-4-(5-((1-(5-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)methoxy)pyridin-2-yl)piperazine, 5-Ethyl-2-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)pyrimidine, 2-((1-(5-Methylpyridin-2-yl)piperidin-4-yl)methoxy)-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazine, 1-Methylcyclopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate, 5-Ethyl-2-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyridin-2-yloxy)methyl)piperidin-1-yl)pyrimidine, 3-Isopropyl-5-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, 3-Isopropyl-5-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyridin-2-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, 1-Methylcyclopropyl 4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate, 5-Isopropyl-3-(4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, 2-

((1-(5-Fluoropyridin-2-yl)piperidin-4-yl)methoxy)-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazine, 3-Isopropyl-5-(4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, tert-Butyl 4-((5-(4-(methylsulfonyl)-1,4-diazepan-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, tert-Butyl 4-((5-(4-(methylsulfonyl)-1,4-diazepan-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, tert-butyl 4-((5-(4-(methylsulfonyl)piperidin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, 1-Methylcyclopropyl 4-((5-(4-(methylsulfonyl)piperidin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, tert-Butyl 4-(2-(3-(4-(methylsulfonyl)piperazin-1-yl)-1,2,4-oxadiazol-5-yl)ethyl)piperidine-1-carboxylate, tert-Butyl 4-(3-(3-(4-(methylsulfonyl)piperazin-1-yl)-1,2,4-oxadiazol-5-yl)propyl)piperidine-1-carboxylate, 5-(3-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)propyl)-3-(4-(methylsulfonyl)piperazin-1-yl)-1,2,4-oxadiazole, Isopropyl 4-(3-(3-(4-(methylsulfonyl)piperazin-1-yl)-1,2,4-oxadiazol-5-yl)propyl)piperidine-1-carboxylate, 3-Isopropyl-5-(4-(2-(5-(4-(methylsulfonyl)piperazin-1-yl)thiazol-2-yl)ethyl)piperidin-1-yl)-1,2,4-oxadiazole, Isopropyl 4-((4-(1-methanesulfonyl-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)methyl)piperidine-1-carboxylate, isopropyl 4-(4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)piperidine-1-carboxylate, isopropyl 4-(2-(4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)ethyl)piperidine-1-carboxylate, isopropyl 4-(3-(4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)propyl)piperidine-1-carboxylate, isopropyl 4-(4-(4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)butyl)piperidine-1-carboxylate, 1-methylcyclopropyl 4-((4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)methyl)piperidine-1-carboxylate, 5-isopropyl-3-(4-((4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, Isopropyl 4-((4-(1-methanesulfonylpiperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate, isopropyl 4-(4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)piperidine-1-carboxylate, isopropyl 4-(2-(4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)ethyl)piperidine-1-carboxylate, isopropyl 4-(3-(4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)propyl)piperidine-1-carboxylate, isopropyl 4-(4-(4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)butyl)piperidine-1-carboxylate, 1-Methylcyclopropyl 4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate, 2-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)-5-(trifluoromethyl)pyridine, 5-isopropyl-3-(4-((4-(1-(methylsulfonyl)piperidin-4-

yl)phenoxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, 3-chloro-2-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)-5-(trifluoromethyl)pyridine, 5-chloro-2-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)pyridine, 3-chloro-6-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)pyridazine, 5-bromo-2-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)pyrimidine, 5-ethyl-2-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)pyrimidine, 5-fluoro-2-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)pyridine, 3-isopropyl-5-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, 3-tert-butyl-6-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)pyridazine, 5-fluoro-2-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)pyrimidine, Isopropyl 4-(2-(3-(1-methanesulfonyl-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)ethyl)piperidine-1-carboxylate, 1-Methylcyclopropyl 4-methoxy-4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, 1-methylcyclopropyl 4-((6-formyl-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, 1-Methylcyclopropyl 4-((6-chloro-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, 1-Methylcyclopropyl 4-((5-(4-(3-methoxy-3-oxopropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, 3-(4-(5-((1-((1-methylcyclopropoxy)carbonyl)-piperidin-4-yl)methoxy)pyrazin-2-yl)piperazin-1-ylsulfonyl)propanoic acid, 3-(4-(5-((1-((1-methylcyclopropoxy)carbonyl)piperidin-4-yl)methoxy)pyrazin-2-yl)piperazin-1-ylsulfonyl)propanoic acid, 3-(4-(5-((1-((1-methylcyclopropoxy)carbonyl)piperidin-4-yl)methoxy)pyrazin-2-yl)piperazin-1-ylsulfonyl)propanoic acid, 3-(4-(5-((1-((1-methylcyclopropoxy)carbonyl)piperidin-4-yl)methoxy)pyrazin-2-yl)piperazin-1-ylsulfonyl)propanoic acid, 3-(4-(5-((1-((1-methylcyclopropoxy)carbonyl)piperidin-4-yl)methoxy)pyrazin-2-yl)piperazin-1-ylsulfonyl)propanoic acid, 3-(4-(5-((1-((1-methylcyclopropoxy)carbonyl)piperidin-4-yl)methoxy)pyrazin-2-yl)piperazin-1-ylsulfonyl)propanoic acid; 1-methylcyclopropyl 4-((5-(4-(3-cyanopropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-(1H-tetrazol-5-yl)propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(vinylsulfonyl)piperazin-1-yl)pyrazin-2-

yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(2-(piperidin-1-yl)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(2-morpholinoethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(2-(dimethylamino)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((5-(4-(3-chloropropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((5-(4-(3-acetoxypropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-aminopropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(2-ethoxyethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-(pyrrolidin-1-yl)propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-(2-methyl-1H-imidazol-1-yl)propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-(dimethylamino)propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(isopropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(isobutylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(sec-butylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-acetoxy-2,2-dimethylpropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-hydroxy-2,2-dimethylpropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(4-(2-(pyridin-3-yl)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(4-(2-(pyridin-4-yl)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(4-sulfamoylpiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; tert-Butyl 4-((5-(4-(morpholinosulfonyl)piperazin-1-yl)pyrazin-2-

yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(ethylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(ethylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(ethylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(ethylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(ethylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(ethylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-fluoro-6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; tert-Butyl 4-((5-(4-(methylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(4-(methylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(2-oxo-4-(propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(4-(isopropylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(4-(isopropylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(2-oxo-4-(propylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(isopropylsulfonyl)-2-oxopiperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-(5-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)pyrazin-2-yl)-4-(methylsulfonyl)piperazin-2-one; 1-(5-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)pyridin-2-yl)-4-(methylsulfonyl)piperazin-2-one; tert-Butyl 4-((2,6-difluoro-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2-methyl-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((3-methoxy-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2,6-dimethyl-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2,5-dimethyl-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2-(methoxycarbonyl)-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2-chloro-4-(1-

(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((3-methyl-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2,3-dimethyl-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2-fluoro-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((4-(1-(methylsulfonyl)piperidin-4-yl)-2-(trifluoromethyl)phenoxy)methyl)piperidine-1-carboxylate; 2-(4-((2,6-Difluoro-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)-5-ethylpyrimidine; 1-Methylcyclopropyl 4-((2,6-difluoro-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; 3-(4-(4-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-3,5-difluorophenyl)piperidin-1-ylsulfonyl)propyl acetate; 1-Methylcyclopropyl 4-((4-(1-(3-acetoxypropylsulfonyl)piperidin-4-yl)-2,6-difluorophenoxy)methyl)piperidine-1-carboxylate; 3-(4-(4-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-3,5-difluorophenyl)piperidin-1-ylsulfonyl)propan-1-ol; 1-Methylcyclopropyl 4-((2,6-difluoro-4-(1-(3-hydroxypropylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; Isopropyl 4-((5-(1,2,3,6-tetrahydro-1-methanesulfonylpyridin-4-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((6-(1,2,3,6-tetrahydro-1-methanesulfonylpyridin-4-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; Isopropyl 4-(2-(6-(1,2,3,6-tetrahydro-1-methanesulfonylpyridin-4-yl)pyridin-3-yloxy)ethyl)piperidine-1-carboxylate; 2-(4-((5-(1,2,3,6-Tetrahydro-1-methanesulfonylpyridin-4-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-5-ethylpyrimidine; 2-(4-((6-(1,2,3,6-Tetrahydro-1-methanesulfonylpyridin-4-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)-5-ethylpyrimidine; 2-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-5-(1-methanesulfonylpiperidin-4-yl)pyrazine; 2-(4-((6-(1-Methanesulfonylpiperidin-4-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)-5-ethylpyrimidine; 3-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-6-(1-methanesulfonylpiperidin-4-yl)pyridazine; 2-(4-((5-(1-Methanesulfonylpiperidin-4-yl)pyridin-2-yloxy)methyl)piperidin-1-yl)-5-ethylpyrimidine; 1-tert-Butyl 4-(4-(1-(methylsulfonyl)piperidin-4-yl)phenyl) piperazine-1,4-dicarboxylate; N-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methyl)-4-(1-(methylsulfonyl)piperidin-4-yl)aniline; N-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methyl)-N-methyl-4-(1-(methylsulfonyl)piperidin-4-yl)aniline; 4-(4-((1-(5-fluoropyrimidin-2-yl)piperidin-4-yl)methoxy)phenyl)-1-(methylsulfonyl)piperidine-4-carboxylic acid; 2-[(2-{4-

[5-({1-[(1-methylcyclopropoxy)carbonyl]piperidin-4-yl}methoxy)pyrazin-2-yl]-3-oxopiperazine-1-sulfonyl}ethyl)amino]acetic acid; 1-methylcyclopropyl 4-{[(5-{4-[(2-carbamimidamidoethane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3-methyl-3-nitrobutane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(1-benzylpyrrolidine-3-sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(carbamoylmethane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(1-carbamoyl-1-methylethane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(2-oxo-4-{[2-(pyrrolidin-1-yl)ethane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(morpholin-4-yl)ethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(dimethylamino)propane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)ethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(dimethylcarbamoyl)methane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[1-(2-methylpropyl)pyrrolidine-3-sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(2-oxo-4-{[3-(1H-pyrazol-1-yl)propane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[2-oxo-4-(pyrrolidine-3-sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(2-amino-2-methylpropane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(1-methylpyrrolidin-3-yl)methane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(azetidin-1-yl)ethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(2-oxo-4-{[2-(1H-pyrazol-1-yl)ethane]sulfonyl}piperazin-1-yl)pyrazin-2-

yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(1-methylpyrrolidine-3-sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[1-(dimethylcarbamoyl)-1-methylethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(3,3-difluoroazetidin-1-yl)ethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(dimethylamino)-3-methylbutane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(2-{[2-(tert-butoxy)-2-oxoethyl]amino}ethane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(azetidine-3-sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(3,3-difluoroazetidin-1-yl)propane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(azetidin-1-yl)propane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{2-oxo-4-[(3S)-pyrrolidine-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3S)-1-methylpyrrolidine-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3R)-1-methylpyrrolidine-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3S)-pyrrolidine-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3R)-pyrrolidine-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(azetidine-3-sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{2-oxo-4-[(pyrrolidin-3-ylmethane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(1-hydroxy-2-methylpropane-2-sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(2-hydroxyethane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(azetidin-3-ylmethane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(1-

methylpyrrolidin-2-yl)methane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{2-oxo-4-[(3R)-pyrrolidine-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(1-methylazetidine-3-sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(1-methylazetidine-3-sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(1-methylazetidin-3-yl)methane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(1-methylazetidin-3-yl)methane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({3-[(3S,4S)-3,4-dihydroxypyrrolidin-1-yl]propane}sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({2-[(3S,4S)-3,4-dihydroxypyrrolidin-1-yl]ethane}sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(azetidin-3-ylmethane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{2-oxo-4-[(pyrrolidin-2-ylmethane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3-aminopropane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(2-aminoethane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(3-methanesulfonamidoazetidin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(dimethylamino)ethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(2-oxo-4-{[3-(pyrrolidin-1-yl)propane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(morpholin-4-yl)propane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(3-methyloxetan-3-yl)methane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(acetyloxy)propane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3,3,3-trifluoropropane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[(2E)-2-

(hydroxyimino)-4-methanesulfonylpiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3-chloropropane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3-hydroxypropane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({[1-(dimethylamino)cyclopropyl]methane}sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({[1-(dimethylamino)cyclopropyl]methane}sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3-hydroxy-3-methylbutane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{2-oxo-4-[(3R)-oxolane-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{2-oxo-4-[(3S)-oxolane-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(acetyloxy)-3-methylbutane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({6-[4-({[1-(azetidin-1-yl)cyclopropyl]methane}sulfonyl)piperazin-1-yl]pyridin-3-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({[1-(benzylamino)cyclopropyl]methane}sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({[1-(azetidin-1-yl)cyclopropyl]methane}sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(1-hydroxycyclopropyl)methane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(1-hydroxycyclopropyl)ethane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({2-[1-(acetyloxy)cyclopropyl]ethane}sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({[1-(benzyloxy)cyclopropyl]methane}sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(1-aminocyclopropyl)methane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(1-hydroxycyclopropyl)ethane]sulfonyl}-2-

oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{2,6-difluoro-4-[3-(N-methylmethanesulfonamido)azetidin-1-yl]phenoxymethyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[2,6-difluoro-4-(3-methanesulfonamidoazetidin-1-yl)phenoxymethyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{2,6-difluoro-4-[3-(2-methylpropane-1-sulfonamido)azetidin-1-yl]phenoxymethyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{4-[3-(N,2-dimethylpropane-1-sulfonamido)azetidin-1-yl]-2,6-difluorophenoxymethyl}piperidine-1-carboxylate; 5-ethyl-2-{4-[({2-methanesulfonyl-1H,2H,3H,4H-pyrazino[1,2-a]indol-8-yl}oxy)methyl]piperidin-1-yl}pyrimidine; 11-{[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]oxy}-5-methanesulfonyl-8-oxa-5-azatricyclo[7.4.0.0{2,7}]trideca-1(13),2(7),9,11-tetraene; 11-{[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]methoxy}-5-methanesulfonyl-8-oxa-5-azatricyclo[7.4.0.0{2,7}]trideca-1(13),2(7),9,11-tetraene; tert-butyl 4-[({2-methanesulfonyl-1H,2H,3H,4H-pyrazino[1,2-a]indol-8-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({2-methanesulfonyl-1H,2H,3H,4H-pyrazino[1,2-a]indol-8-yl}oxy)methyl]piperidine-1-carboxylate; propan-2-yl 4-{3-[3-(1-methanesulfonylpiperidin-4-yl)phenoxy]propyl}piperidine-1-carboxylate; propan-2-yl 4-{2-[3-(1-methanesulfonylpiperidin-4-yl)phenoxy]ethyl}piperidine-1-carboxylate; propan-2-yl 4-[3-(1-methanesulfonylpiperidin-4-yl)phenoxymethyl]piperidine-1-carboxylate; propan-2-yl 4-{3-[3-(1-methanesulfonyl-1,2,3,6-tetrahydropyridin-4-yl)phenoxy]propyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-methanesulfonyl-2-sulfanylidenepiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl (3S,4S)-3-hydroxy-4-{[(6-{4-[(2-methylpropane)sulfonyl]piperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl (3R,4S)-3-hydroxy-4-{[(6-{4-[(2-methylpropane)sulfonyl]piperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-hydroxy-4-{[(6-{4-[(2-methylpropane)sulfonyl]piperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(6-{4-[(2-hydroxy-2-methylpropane)sulfonyl]piperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl (3S,4R)-3-methoxy-4-{[(6-{4-[(2-methylpropane)sulfonyl]piperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(3,3-difluoroazetidin-1-yl)propane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-

1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(azetidin-1-yl)propane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3-methoxypropane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(6-{4-[(3-chloropropane)sulfonyl]-2-oxopiperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(azetidin-1-yl)ethane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[6-(4-{[3-(azetidin-1-yl)propane]sulfonyl}piperazin-1-yl)pyridin-3-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(pyrrolidine-3-sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(3,3-difluoroazetidin-1-yl)ethane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(6-{4-[(3-hydroxypropane)sulfonyl]-2-oxopiperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[6-(4-{[3-(azetidin-1-yl)propane]sulfonyl}-2-oxopiperazin-1-yl)pyridin-3-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[2,6-difluoro-4-(4-methanesulfonyl-2-oxopiperazin-1-yl)phenoxymethyl]piperidine-1-carboxylate; and 1-methylcyclopropyl 4-[({5-[4-(oxetane-3-sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate.

8. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable excipient.

9. A method for modulating GPR119 activity, comprising administering to a system or a subject in need thereof, a therapeutically effective amount of the compound of claim 1 or pharmaceutically acceptable salts or pharmaceutical compositions thereof, thereby modulating said GPR119 activity.

10. The method of claim 9, wherein the compound of claim 1 directly contacts GPR119.

11. The method of claim 10, wherein the contacting occurs in vitro or in vivo.

12. A method for treating a disease or condition wherein modulation of GPR119 activity can prevent, inhibit or ameliorate the pathology and/or symptomology of the disease or condition, comprising administering to a subject a therapeutically effective amount of the compound of claim 1 or pharmaceutically acceptable salts or pharmaceutical compositions thereof.

13. The method of claim 12, wherein said disease or condition is selected from obesity, type 1 diabetes, type 2 diabetes mellitus, hyperlipidemia, idiopathic type 1 diabetes, latent autoimmune diabetes in adults, early-onset type 2 diabetes, youth-onset atypical diabetes, maturity onset diabetes of the young, malnutrition-related diabetes and gestational diabetes.

14. The method of claim 12, wherein said disease or condition is selected from coronary heart disease, ischemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, myocardial infarction, dyslipidemia, post-prandial lipemia, conditions of impaired glucose tolerance, conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, osteoporosis, hypertension, congestive heart failure, left ventricular hypertrophy, peripheral arterial disease, diabetic retinopathy, macular degeneration, cataract, diabetic nephropathy, glomerulosclerosis, chronic renal failure, diabetic neuropathy, metabolic syndrome, syndrome X, premenstrual syndrome, coronary heart disease, angina pectoris, thrombosis, atherosclerosis, myocardial infarction, transient ischemic attacks, stroke, vascular restenosis, hyperglycemia, hyperinsulinemia, hyperlipidemia, hypertrygliceridemia, insulin resistance, impaired glucose metabolism, conditions of impaired glucose tolerance, conditions of impaired fasting plasma glucose, obesity, erectile dysfunction, skin and connective tissue disorders, foot ulcerations and ulcerative colitis, endothelial dysfunction and impaired vascular compliance.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/075145

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/10 C07D401/14 C07D413/06 C07D413/14 C07D417/14
C07D487/04 C07D491/048 A61K31/44 A61K31/496 A61K31/4965
A61P3/10

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

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 practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/003964 A (PROSIDION LTD [GB]; BARBA OSCAR [GB]; BRADLEY STUART EDWARD [GB]; FYFE) 11 January 2007 (2007-01-11) page 1, line 1 - page 2, line 2 page 21 - page 55; examples 1-4,11,42-89 claim 1	1-14
A	WO 2007/003960 A (PROSIDION LTD [GB]; BRADLEY STUART EDWARD [GB]; DAWSON GRAHAM JOHN [GB) 11 January 2007 (2007-01-11) page 1, line 1 - page 2, line 4 page 34 - page 66; examples 1-238 claim 1	1-14

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☒ 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 document 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)

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/061489 A (PROSIDION LTD [GB]; FYFE MATTHEW [GB]; GARDNER LISA [GB]; KING-UNDERWO) 7 July 2005 (2005-07-07) page 1, line 1 - page 2, line 10 page 31 - page 149; examples 1-149 claim 1 -----	1-14
A	WO 2007/003962 A (PROSIDION LTD [GB]; BRADLEY STUART EDWARD [GB]; FYFE MATTHEW COLIN THO) 11 January 2007 (2007-01-11) page 1, line 1 - page 2, line 4 page 18 - page 76; examples 1-265 claim 1 -----	1-14

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007003964 A	11-01-2007	AU 2006264651 A1	11-01-2007
		CA 2613236 A1	11-01-2007
		EP 1909791 A1	16-04-2008
		KR 20080025190 A	19-03-2008
		NO 20080052 B	23-01-2008
WO 2007003960 A	11-01-2007	EP 1907383 A1	09-04-2008
WO 2005061489 A	07-07-2005	AU 2004303604 A1	07-07-2005
		BR PI0418149 A	17-04-2007
		CA 2549955 A1	07-07-2005
		CN 1898235 A	17-01-2007
		EP 1711491 A1	18-10-2006
		JP 2007517010 T	28-06-2007
		KR 20060127011 A	11-12-2006
WO 2007003962 A	11-01-2007	AU 2006264649 A1	11-01-2007
		CA 2613235 A1	11-01-2007
		EP 1910290 A2	16-04-2008
		KR 20080027908 A	28-03-2008
		NO 20080010 B	30-01-2008