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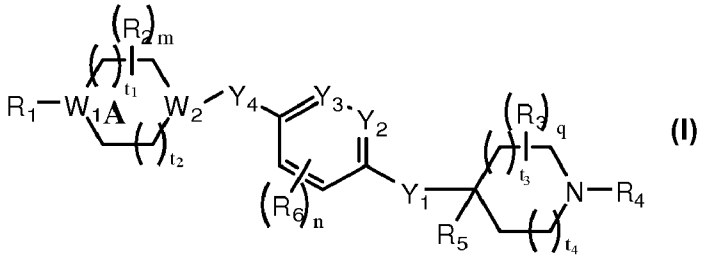

(I)

(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; such as, but not limited to, diabetes, obesity and associated metabolic disorders. Formula (I) is a compound, in which A can have up to 2 ring -CH2- group substituted with -C(O)- and can be partially unsaturated with up to 2 double bonds; Wi and W2 are independently selected from CR10 and N; wherein R10 is selected from hydrogen and C1_6alkyl; Yi is selected from NRn, O and S; wherein Rn is selected from hydrogen and C1_ 6alkyl; Y2 and Y3 are independently selected from CH and N; Y4 is selected from CH2, OCH2 and NR15; wherein R15 is selected from hydrogen and C1_6alkyl; or the pharmaceutically acceptable salts thereof.

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COMPOUNDS AND COMPOSITIONS AS MODULATORS OF GPR119 ACTIVITY

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of priority to U.S. Provisional Patent Application Number 61/043,100, filed 07 April 2008. The full disclosure of this application is incorporated herein by reference in its entirety and for all purposes.

BACKGROUND OF THE INVENTION

Field of the Invention

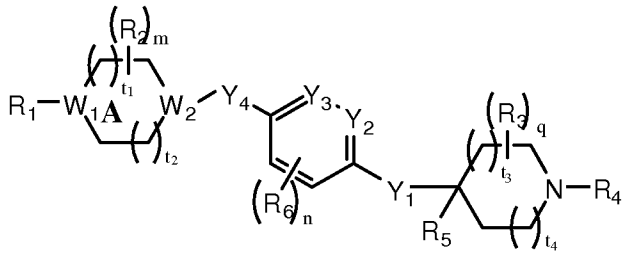
[0002] The invention provides compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with the activity of GPR119.

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] A can have up to 2 ring $-CH_2-$ group substituted with $-C(O)-$ and can be partially unsaturated with up to 2 double bonds;

[0007] m and n are independently selected from 0, 1, 2, 3 and 4;

[0008] q is selected from 0, 1, 2, 3 and 4;

[0009] t_1, t_2, t_3 and t_4 are each independently selected from 0, 1 and 2;

[0010] R_1 is selected from hydrogen, cyano, $-X_1S(O)_{0-2}X_2R_{6a}$, $-X_1N(S(O)_{0-2}X_2R_{6a})R_{6a}$, $-X_1S(O)_{0-2}X_2OR_{6a}$, $-X_1S(O)_{0-2}X_2C(O)R_{6a}$, $-X_1C(O)OR_{6a}$, $-X_1R_{6a}$, $-X_1S(O)_{0-2}X_2C(O)OR_{6a}$ 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, C_{1-6}alkyl, C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-8}heterocycloalkyl and C_{1-8}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, 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;

[0011] R_2 and R_3 are independently selected from 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, $-C(O)R_8$, and $-C(O)OR_8$; wherein R_8 is selected from hydrogen and C_{1-6}alkyl;

[0012] R_4 is selected from R_9 and $-C(O)OR_9$; wherein R_9 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_9 is optionally substituted with 1 to 3 radicals independently selected from halo, cyano, 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, halo-substituted-C_{1-6}alkoxy and $-C(O)OR_{17}$, $-C(O)R_{19}$ and $-C(O)NR_{17}R_{18}$; wherein R_{17} and R_{18} are independently selected from hydrogen and C_{1-6}alkyl; or R_{17} and R_{18} together with the nitrogen

atom to which R_{17} and R_{18} are attached form C_{3-8}heterocycloalkyl; R_{19} is selected from C_{1-6}alkyl and C_{3-8}heterocycloalkyl; wherein said cycloalkyl or heterocycloalkyl substituents of R_9 are optionally further substituted with 1 to 3 C_{1-6}alkyl radicals;

[0013] 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;

[0014] R_6 is selected from hydroxy, nitro, cyano, halo, C_{1-6}alkyl, C_{2-6}alkenyl, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{2-6}alkenyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-8}heterocycloalkyl, C_{3-8}cycloalkyl and $-X_3OR_{20}$, $-NR_{20}X_3OR_{21}$, $-C(O)OR_{20}$; wherein X_3 is selected from a bond, C_{1-4}alkylene and C_{2-4}alkenylene; R_{20} and R_{21} are independently selected from hydrogen and C_{1-6}alkyl;

[0015] W_1 and W_2 are independently selected from CR_{10} and N; wherein R_{10} is selected from hydrogen and C_{1-6}alkyl;

[0016] Y_1 is selected from NR_{11}, O and S; wherein R_{11} is selected from hydrogen and C_{1-6}alkyl;

[0017] Y_2 and Y_3 are independently selected from CH and N; and

[0018] Y_4 is selected from CH_2, OCH_2 and NR_{15}; wherein R_{15} is selected from hydrogen and C_{1-6}alkyl.

[0019] 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.

[0020] 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.

[0021] 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.

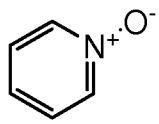
[0022] In a fifth aspect, the present invention provides a process for preparing compounds of Formula I and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, and the pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0023] "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.

[0024] "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:



[0025] "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.

[0026] 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.

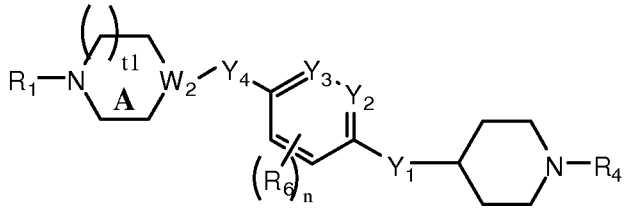
[0027] "Halogen" (or halo) preferably represents chloro or fluoro, but can also be bromo or iodo.

[0028] "Treat", "treating" and "treatment" refer to a method of alleviating or abating a disease and/or its attendant symptoms.

Description of the Preferred Embodiments

[0029] 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.

[0030] In one embodiment, with reference to compounds of Formula I, are compounds of Formula Ia:



Ia

[0031] in which:

[0032] A can have a ring $-CH_2-$ group substituted with $-C(O)-$;

[0033] t1 is selected from 0 and 1;

[0034] R_1 is selected from hydrogen, cyano, $-X_1S(O)_{0-2}X_2R_{6a}$, $-X_1S(O)_{0-2}X_2OR_{6a}$, $-X_1C(O)OR_{6a}$, $-X_1S(O)_{0-2}X_2C(O)R_{6a}$, $-X_1N(S(O)_{0-2}X_2R_{6a})R_{6a}$, $-X_1R_{6a}$, $-X_1S(O)_{0-2}X_2C(O)OR_{6a}$ 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, C_{1-6}alkyl, C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-8}heterocycloalkyl and C_{1-8}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, 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_4 is selected from R_9 and $-C(O)OR_9$; wherein R_9 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_9 is optionally substituted with 1 to 3 radicals independently selected from halo, cyano, 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, halo-substituted-C_{1-6}alkoxy and $-C(O)OR_{17}$, $-C(O)R_{19}$ and $-C(O)NR_{17}R_{18}$; wherein R_{17} and R_{18} are independently selected from hydrogen and C_{1-6}alkyl; or R_{17} and R_{18} together with the nitrogen atom to which R_{17} and R_{18} are attached form C_{3-8}heterocycloalkyl; R_{19} is selected from C_{1-6}alkyl and C_{3-8}heterocycloalkyl; wherein said cycloalkyl or heterocycloalkyl substituents of R_9 are optionally further substituted with 1 to 3 C_{1-6}alkyl radicals;

[0036] R_6 is selected from hydroxy, nitro, cyano, halo, C_{1-6}alkyl, C_{2-6}alkenyl, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{2-6}alkenyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-8}heterocycloalkyl, C_{3-8}cycloalkyl and $-X_3OR_{20}$, $-NR_{20}X_3OR_{21}$, $-C(O)OR_{20}$; wherein X_3 is selected from a bond, C_{1-4}alkylene and C_{2-4}alkenylene; R_{20} and R_{21} are independently selected from hydrogen and C_{1-6}alkyl;

[0037] W_2 is selected from CR_{10} and N; wherein R_{10} is selected from hydrogen and C_{1-6}alkyl;

[0038] Y_1 is selected from NH, O and S; and

[0039] Y_2 and Y_3 are independently selected from CH and N;

[0040] Y_4 is selected from CH_2, OCH_2 and NR_{15}; wherein R_{15} is selected from hydrogen and C_{1-6}alkyl.

[0041] In another embodiment, A can have a ring $-CH_2-$ group substituted with –C(O)–; t1 is selected from 0 and 1; and R_1 is selected from hydrogen, cyano, $-S(O)_{0-2}X_2R_{6a}$, $-X_1N(S(O)_{0-2}X_2R_{6a})R_{6a}$, $-X_1R_{6a}$, $-X_1C(O)OR_{6a}$ and $-S(O)_{0-2}X_2OR_{6a}$; wherein X_1 is selected from a bond and C_{1-4}alkylene; X_2 is selected from a bond and C_{1-4}alkylene; R_{6a} is selected from hydrogen, C_{1-6}alkyl and C_{1-10}heteroaryl optionally substituted with C_{1-6}alkyl.

[0042] In another embodiment, R_4 is selected from R_9 and $-C(O)OR_9$; wherein R_9 is selected from *tert*-butyl, pyridinyl, pyrimidinyl, 1,2,4-oxadiazol-5-yl, tetrazolyl and cyclopropyl; wherein said pyridinyl, pyrimidinyl, 1,2,4-oxadiazol-5-yl, tetrazolyl or cyclopropyl of R_9 is optionally substituted with a radical selected from halo, cyano, trifluoromethyl, isopropyl, methyl, ethyl, methoxy-carbonyl, dimethyl-amino-carbonyl, amino-carbonyl and morpholino-carbonyl.

[0043] In another embodiment, R_6 is selected from fluoro, chloro, bromo, trifluoromethoxy, methyl, methoxy, methoxy-carbonyl, 3-methoxyprop-1-enyl, methoxy-propyl, vinyl, phenyl, pyrazolyl, 5-chloropent-1-enyl, hydroxy-propyl, methoxy-ethyl-amino and morpholino; W_2 is selected from CH and N; Y_1 is selected from NH, O and S; and Y_2 and Y_3 are independently selected from CH and N; Y_4 is selected from CH_2, OCH_2 and NCH_3.

[0044] In another embodiment are compounds selected from: 5-Ethyl-2-(4-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine; 5-ethyl-2-(4-(3-methyl-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine; 5-ethyl-2-(4-(3-methoxy-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine; 5-ethyl-2-(4-(3-fluoro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine; 2-(4-(3-chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; 5-ethyl-2-(4-(2-methyl-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine; 5-ethyl-2-(4-(2-fluoro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine; 2-(4-(2-chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; 2-(4-(2-

bromo-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; 5-ethyl-2-(4-(2-methoxy-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine; 5-ethyl-2-(4-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)-2-(trifluoromethoxy)phenoxy)piperidin-1-yl)pyrimidine; 2-(4-(2,3-difluoro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; 2-(4-(2-chloro-6-fluoro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; 5-ethyl-2-(4-(6-((4-(methylsulfonyl)piperazin-1-yl)methyl)pyridin-3-yloxy)piperidin-1-yl)pyrimidine; 5-ethyl-2-(4-(5-((4-(methylsulfonyl)piperazin-1-yl)methyl)pyridin-2-yloxy)piperidin-1-yl)pyrimidine; *tert*-Butyl 4-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidine-1-carboxylate; 1-methylcyclopropyl 4-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidine-1-carboxylate; 5-Fluoro-2-(4-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine; 1-(4-(1-(5-fluoropyridin-2-yl)piperidin-4-yloxy)benzyl)-4-(methylsulfonyl)piperazine; 1-(methylsulfonyl)-4-(4-(1-(5-(trifluoromethyl)pyridin-2-yl)piperidin-4-yloxy)benzyl)piperazine; 5-(4-(2-chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole; 3-(4-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)piperazin-1-ylsulfonyl)propan-1-ol; 5-Ethyl-2-(4-(4-((1-(methylsulfonyl)piperidin-4-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine; *tert*-Butyl 4-(2-fluoro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenylamino) piperidine-1-carboxylate; 1-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)-4-(methylsulfonyl)piperazin-2-one, methyl 2-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)benzoate; 1-methylcyclopropyl 4-(2-chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidine-1-carboxylate; methyl 2-(4-(2-chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine-5-carboxylate; 2-(4-(2-chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine; 5-bromo-2-(4-(2-chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)-phenoxy)piperidin-1-yl)pyrimidine; 5-chloro-2-(4-(2-chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine; 2-(4-(2-Chloro-4-((4-(methylsulfonyl)-piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine-5-carboxamide; 2-(4-(2-chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-N,N-dimethylpyrimidine-5-carboxamide; (2-(4-(2-chloro-

4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidin-5-yl)(morpholino)methanone; 2-(4-(2-Chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine-5-carbonitrile; 2-(4-(2-Chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-(2H-tetrazol-5-yl)pyrimidine; 2-(4-(2-Chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-(2-methyl-2H-tetrazol-5-yl)pyrimidine; (E)-5-Ethyl-2-(4-(2-(3-methoxyprop-1-enyl)-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine; 3-(2-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yloxy)-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenyl)propan-1-ol; 5-ethyl-2-(4-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)-2-vinylphenoxy)piperidin-1-yl)pyrimidine; 5-ethyl-2-(4-(5-((4-(methylsulfonyl)piperazin-1-yl)methyl)biphenyl-2-yloxy)piperidin-1-yl)pyrimidine; 5-ethyl-2-(4-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)-2-(1H-pyrazol-5-yl)phenoxy)piperidin-1-yl)pyrimidine; (E)-2-(4-(2-(5-chloropent-1-enyl)-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; (E)-4-(2-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yloxy)-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenyl)but-3-en-1-ol; 3-(2-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yloxy)-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenyl)propan-1-ol; 2-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yloxy)-N-(2-methoxyethyl)-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)aniline; 4-(2-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yloxy)-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenyl)morpholino; 2-(4-(2-Chloro-4-((1-(methylsulfonyl)piperidin-4-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; 3-(4-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)piperidin-1-ylsulfonyl)propan-1-ol; 2-(4-(2-chloro-4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; 2-(4-(2-Chloro-4-((2-methyl-4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; 2-(4-(2-Chloro-4-((2-methyl-4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; N-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)phenyl)-N-methyl-1-(methylsulfonyl)piperidin-4-amine; 4-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)piperazine-1-carbonitrile; 2-(4-(2-Chloro-4-((4-(2-methyl-2H-tetrazol-5-yl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; 1-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)piperidine-4-carbonitrile; 2-(4-(2-chloro-4-((4-

(2-methyl-2H-tetrazol-5-yl)piperidin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; 2-(4-(2-Chloro-4-((1-(methylsulfonyl)azetidin-3-yloxy)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; 2-(4-(2-Chloro-4-((1-(methylsulfonyl)azetidin-3-yloxy)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; and N-(1-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)azetidin-3-yl)-N-methylmethanesulfonamide.

[0045] Further compounds of the invention are detailed in the Examples and Table I, *infra*.

Pharmacology and Utility

[0046] 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.

[0047] 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-1 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.

[0048] 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.

[0049] 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.

[0050] 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.

[0051] 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.

[0052] 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.

[0053] 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.

[0054] 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.

[0055] 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.

[0056] 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.

[0057] 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.

[0058] 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

[0059] 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.

[0060] 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.

[0061] Compounds of the invention can be administered in therapeutically effective amounts in combination with one or more therapeutic agents (pharmaceutical combinations).

[0062] 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).

[0063] 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 forth.

[0064] 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:

[0065] 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;

[0066] 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;

[0067] 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;

[0068] 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.

[0069] e) a HDL increasing compound;

[0070] f) Cholesterol absorption modulator such as Zetia® and KT6-971;

[0071] g) Apo-A1 analogues and mimetics;

[0072] h) thrombin inhibitors such as Ximelagatran;

[0073] i) aldosterone inhibitors such as anastrazole, fadrazole, eplerenone;

[0074] j) Inhibitors of platelet aggregation such as aspirin, clopidogrel bisulfate;

[0075] k) estrogen, testosterone, a selective estrogen receptor modulator, a selective androgen receptor modulator;

[0076] 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

[0077] 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;

[0078] 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;

[0079] o) an agent for treating erectile dysfunction, e.g., dopaminergic agents, such as apomorphine), ADD/ADHD agents (e.g., Ritalin®, Strattera®, Concerta® and Adderall®);

[0080] 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®);

[0081] 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®));

[0082] or, in each case a pharmaceutically acceptable salt thereof; and optionally a pharmaceutically acceptable carrier.

[0083] 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.

[0084] 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.

[0085] 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,

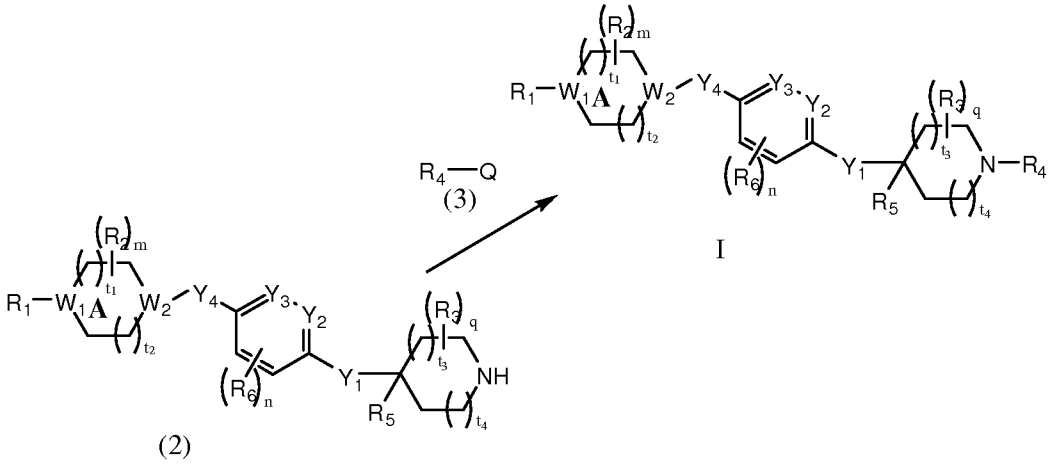
e.g. a compound of Formula I and a co-agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.

Processes for Making Compounds of the Invention

[0086] 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.

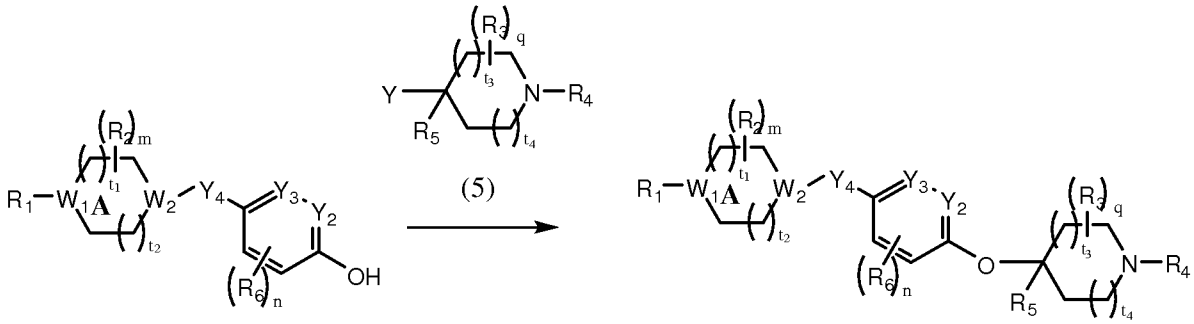
[0087] In the following schemes, several methods of preparing the compounds of the present invention are illustrative. One of skill in the art will appreciate that these methods are representative, and in no way inclusive of all methods for preparing the compounds of the present invention. The radicals in the schemes are as described in Formula I.

Reaction Scheme I



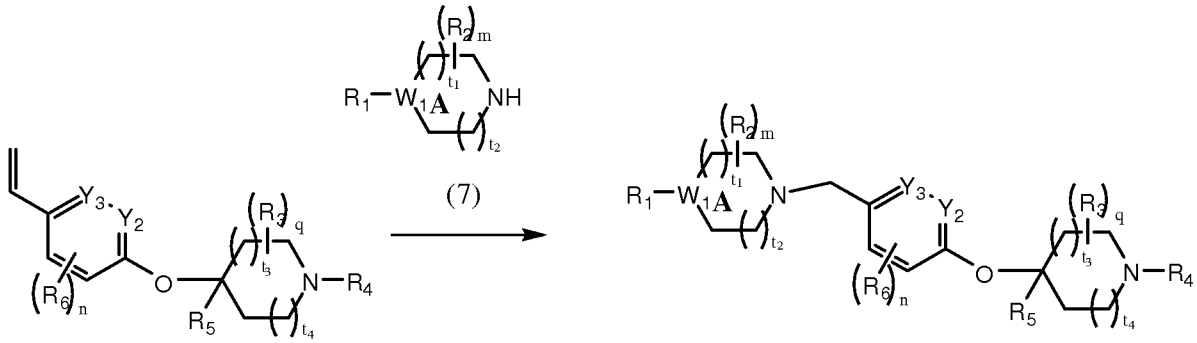
[0088] A compound of Formula I can be prepared by reacting a compound of formula 2 with a compound of formula 3, where Q is a leaving group (for example Cl, Br, OCF_3 and the like) in the presence of a suitable solvent (for example, dimethylacetamide, dimethylformamide, and the like) and a suitable base (for example, potassium carbonate, sodium *t*-butoxide, and the like), optionally in the presence of a palladium catalyst (for example, $Pd_2(dba)_3$, and the like) and a suitable ligand (for example, xantphos, and the like). The reaction proceeds at a temperature of about 0°C to about 200°C and can take up to 24 hours to complete.

Reaction Scheme II



[0089] A compound of Formula I, where Y_1 is oxygen, can be prepared by reacting a compound of formula 4 with a compound of formula 5, where Y is a leaving group (for example OMs, Cl, Br, I and the like), in the presence of a suitable solvent (for example, dimethylformamide, acetonitrile, and the like) and a suitable base (for example, K_2CO_3, Cs_2CO_3, triethylamine and the like). The reaction proceeds at a temperature of about 0°C to about 120°C and can take up to 24 hours to complete.

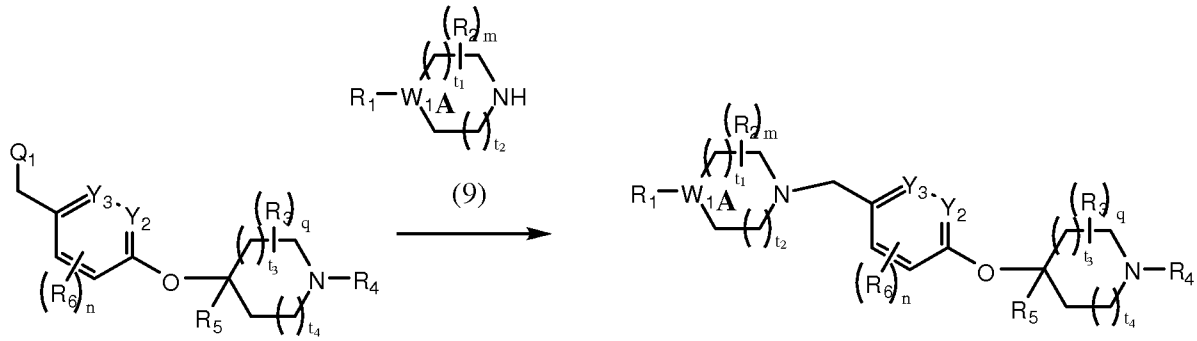
Reaction Scheme III



(6) (7) I

[0090] A compound of Formula I, where Y_4 is CH_2 and W_2 is N, can be prepared by reacting a compound of formula 6 with a compound of formula 7 in the presence of a suitable solvent (for example, dichloroethane, ethanol, and the like) followed by addition of a suitable reducing agent (for example, sodium cyanoborohydride, sodium triacetoxyborohydride, and the like). The reaction proceeds at a temperature of about 0°C to about 120°C and can take up to 24 hours to complete.

Reaction Scheme IV



(8) (9) I

[0091] A compound of Formula I, where Y_4 is CH_2 and W_2 is N, can be prepared by reacting a compound of formula 8 with a compound of formula 9, where Q_1 is a leaving group (for example OMs, Cl, Br, I and the like), in the presence of a suitable solvent (for example, dimethylformamide, acetonitrile, and the like) and a suitable base

(for example, K_2CO_3, Cs_2CO_3, triethylamine and the like). The reaction proceeds at a temperature of about 0°C to about 120°C and can take up to 24 hours to complete.

[0092] Detailed descriptions of the synthesis of compounds of the Invention are given in the Examples, *infra*.

Additional Processes for Making Compounds of the Invention

[0093] 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.

[0094] 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.).

[0095] 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.

[0096] 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).

[0097] 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.

[0098] 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.

[0099] 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.

[00100] In summary, the compounds of Formula I can be made by a process, which involves:

(a) that of reaction schemes I, II, III, IV; 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.

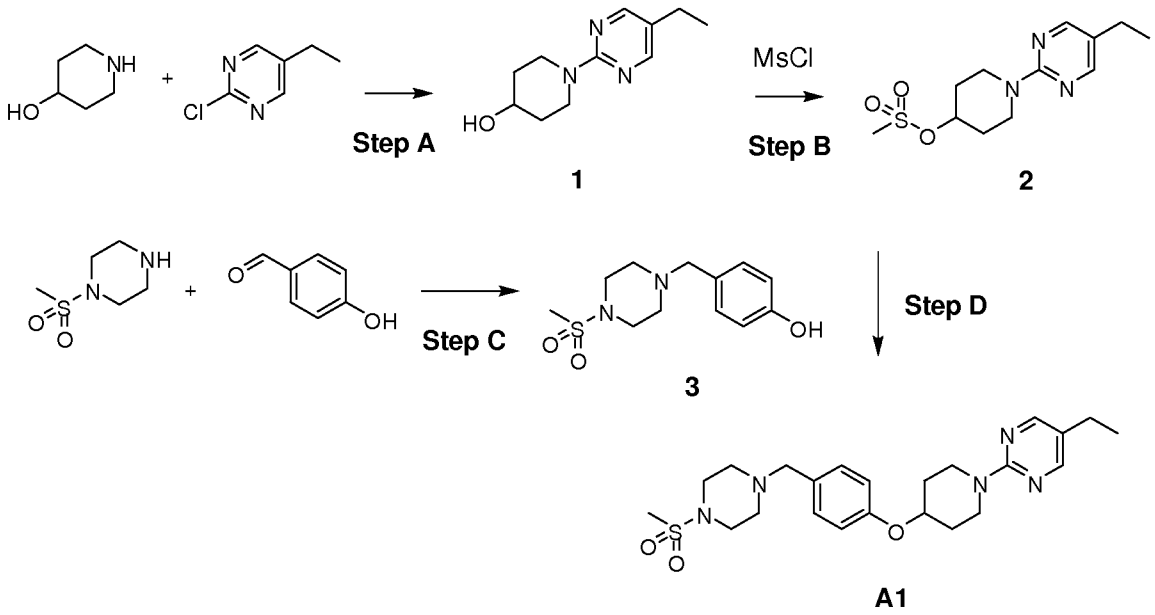
[00101] Insofar as the production of the starting materials is not particularly described, the compounds are known or can be prepared analogously to methods known in the art or as disclosed in the Examples hereinafter.

[00102] 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

[00103] The present invention is further exemplified, but not limited, by the following Examples that illustrate the preparation of compounds of the invention and their intermediates.

Example A1. 5-Ethyl-2-(4-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)-piperidin-1-yl)pyrimidine.



[00104] **Step A:** 4-Hydroxypiperidine (7 g, 70 mmol), 2-chloro-5-ethylpyrimidine (10 g, 70 mmol) and K_2CO_3 (14.5 g, 105 mmol) were dissolved in DMA (50 mL) and stirred at 150°C for 12 h. The reaction mixture was cooled, diluted with H_2O (100 mL) and extracted with EtOAc (3 x 100 mL). The organic layers were combined, washed with H_2O (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and concentrated to provide 1-(5-ethylpyrimidin-2-yl)piperidin-4-ol **1** which was used without purification in Step B: MS *m/z* for $(M+H)^+$ $C_{11}H_{18}N_3O$ calc. 208.1, found 208.2.

[00105] **Step B:** 1-(5-Ethylpyrimidin-2-yl)piperidin-4-ol **1** was dissolved in DCM (200 mL). Diisopropylethylamine (25 mL, 140 mmol) was added, then the mixture was cooled to 0°C. Methanesulfonyl chloride (6.5 mL, 84 mmol) was added dropwise and the mixture was stirred for 1 h at rt. The mixture was poured into H_2O (100 mL) and the organic layer was separated. The organic layer was washed with sat. aq. $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated. The product was recrystallized from EtOAc/hexanes to provide 1-(5-ethylpyrimidin-2-yl)piperidin-4-yl methanesulfonate **2** as an off-white powder: ^1H NMR (400 MHz, $CDCl_3$) δ = 8.20 (s, 2H), 4.99 (m, 1H), 4.21 (m, 2H), 3.61 (m, 2H), 3.07 (s, 3H), 2.49 (q, J = 7.6 Hz, 2H), 2.07 (m, 2H), 1.89 (m, 4H), 1.55 (m, 2H), 1.45 (d, J = 6.8 Hz, 1H), 1.21 (t, J = 7.6 Hz, 3H). MS *m/z* for $(M+H)^+$ $C_{12}H_{20}N_3O_3S$ calc. 286.1, found 286.2.

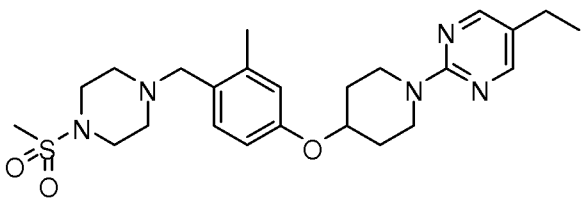
[00106] **Step C:** 4-Hydroxybenzaldehyde (500 mg, 4.09 mmol) and 1-methanesulfonylpiperazine (670 mg, 4.09 mmol) were dissolved in dichloroethane (10 mL). AcOH (50 µL) was added, and the mixture was heated at 80°C for 1 h. Then sodium

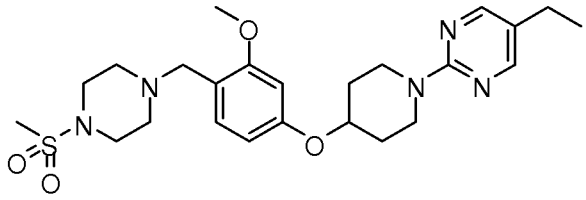
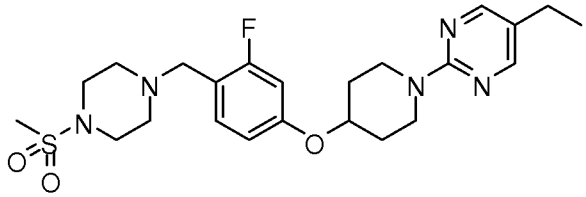
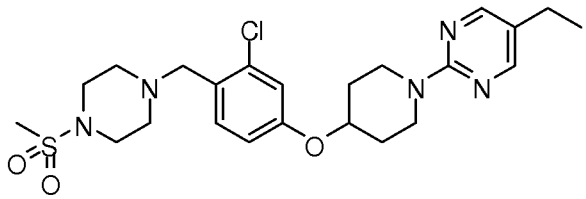
triacetoxyborohydride (1.7 g, 8.2 mmol) was added and the mixture was heated at 80ºC for another 2 h. The reaction was cooled, diluted with sat. aq. $NaHCO_3$ (50 mL), and extracted with DCM (30 mL). The organic layer was washed with brine, dried ($MgSO_4$), filtered, concentrated and purified by flash column chromatography (SiO_2, MeOH/DCM gradient) to give 4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenol **3** as a white powder: ^{1}H NMR (400 MHz, MeOD) δ = 7.15 (d, J = 8.4 Hz, 2H), 6.75 (d, J = 8.4 Hz, 2H), 3.48 (s, 2H), 3.22 (t, J = 4.8 Hz, 4H), 2.83 (s, 3H), 2.54 (t, J = 4.8 Hz, 4H). MS *m/z* for $(M+H)^+$ $C_{12}H_{19}N_2O_3S$ calc. 271.1, found 271.1.

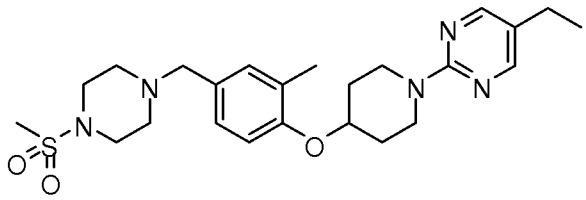
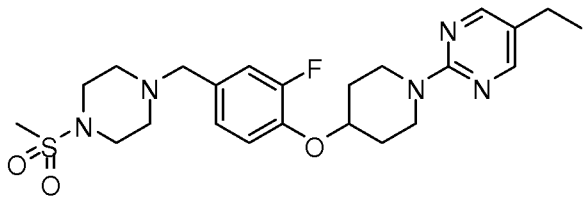
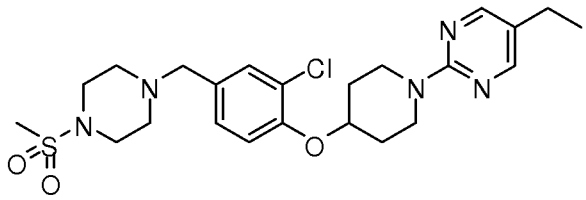
[00107] **Step D:** 1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl methanesulfonate **2** (253 mg, 0.89 mmol), 4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenol **3** (200 mg, 0.74 mmol) and Cs_2CO_3 (482 mg, 1.48 mmol) were heated in AcN (10 mL) at 80ºC for 2 h. The reaction was cooled, filtered, concentrated and purified by flash column chromatography (SiO_2, MeOH/DCM gradient) to give **A1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.11 (s, 2H), 7.14 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H), 4.46 (m, 1H), 4.12 (m, 2H), 3.56 (m, 2H), 3.41 (s, 2H), 3.17 (t, J = 4.8 Hz, 4H), 2.70 (s, 3H), 2.48 (t, J = 4.8 Hz, 4H), 2.39 (q, J = 7.6 Hz, 2H), 1.95 (m, 2H), 1.74 (m, 2H), 1.22 (t, J = 7.6 Hz, 3H). MS *m/z* for $(M+H)^+$ $C_{23}H_{34}N_5O_3S$ calc. 460.2, found 460.2.

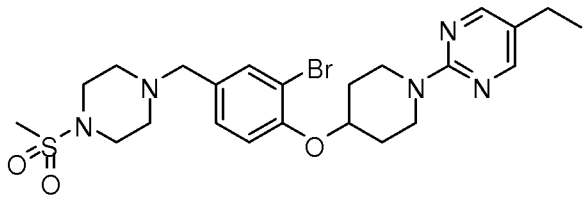
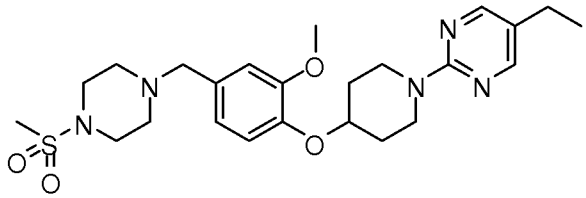
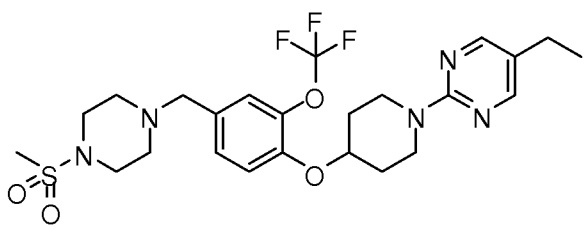
[00108] By repeating the procedure described above, using appropriate starting materials, the following compounds of Formula I, as identified in Table 1, were obtained.

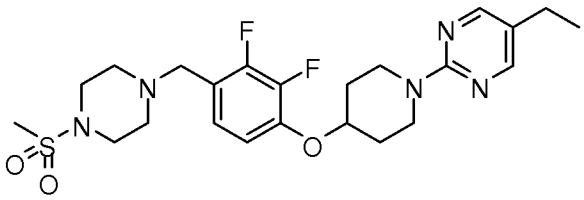
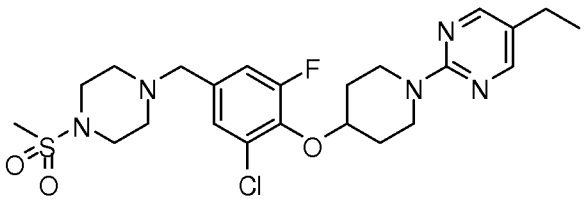
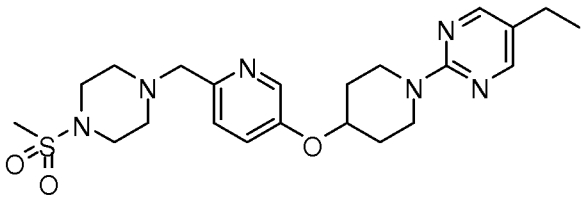
Table 1

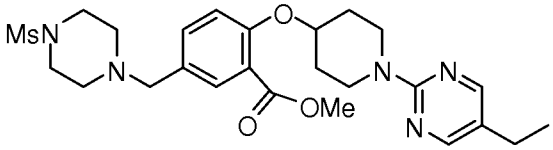
Compound #	Structure	NMR and/or ESMS
A2		^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.37 (s, 2H), 7.37 (d, J = 8.8 Hz, 1H), 6.84 (m, 2H), 4.66 (m, 1H), 4.22 (s, 2H), 4.06 (m, 2H), 3.95 (m, 2H), 2.89 (s, 3H), 2.56 (q, J = 7.6 Hz, 2H), 2.40 (s, 3H), 2.04 (m, 12H), 1.25 (t, J

		= 7.6 Hz, 3H). MS *m/z* for $(M+H)^+$ $C_{24}H_{36}N_5O_3S$ calc. 474.2, found 474.2.
A3		^1H NMR (400 MHz, $CDCl_3$) δ = 8.42 (s, 2H), 7.31 (d, J = 8.4 Hz, 1H), 6.57 (dd, J = 2.4, 8.4 Hz, 1H), 6.53 (d, J = 2.4 Hz, 1H), 4.68 (m, 1H), 4.24 (s, 2H), 4.03 (m, 4H), 3.87 (s, 3H), 3.58 (m, 2H), 3.44 (m, 2H), 2.98 (m, 2H), 2.88 (s, 3H), 2.60 (q, J = 7.6 Hz, 2H), 2.04 (m, 4H), 1.27 (t, J = 7.6 Hz, 3H). MS *m/z* for $(M+H)^+$ $C_{24}H_{36}N_5O_4S$ calc. 490.2, found 490.2.
A4		^1H NMR (400 MHz, $CDCl_3$) δ = 8.43 (s, 2H), 7.42 (t, J = 8.8 Hz, 1H), 6.81 (dd, J = 2.4, 8.8 Hz, 1H), 6.73 (dd, J = 2.4, 12.0 Hz, 1H), 4.66 (m, 1H), 4.25 (s, 2H), 4.06 (m, 4H), 2.88 (s, 3H), 2.59 (q, J = 7.6 Hz, 2H), 2.04 (m, 4H), 1.27 (t, J = 7.6 Hz, 3H). MS *m/z* for $(M+H)^+$ $C_{23}H_{33}FN_5O_3S$ calc. 478.2, found 478.2.
A5		^1H NMR (400 MHz, $CDCl_3$) δ = 8.34 (s, 2H), 7.49 (d, J = 8.4 Hz, 1H), 6.96 (d, J = 2.8 Hz, 1H), 6.85 (dd, J = 2.8, 8.4 Hz, 1H), 4.60 (m, 1H), 4.30 (s, 2H), 3.95 (m, 6H), 2.80 (s, 3H), 2.51 (q, J = 7.6 Hz, 2H), 1.95 (m, 4H),

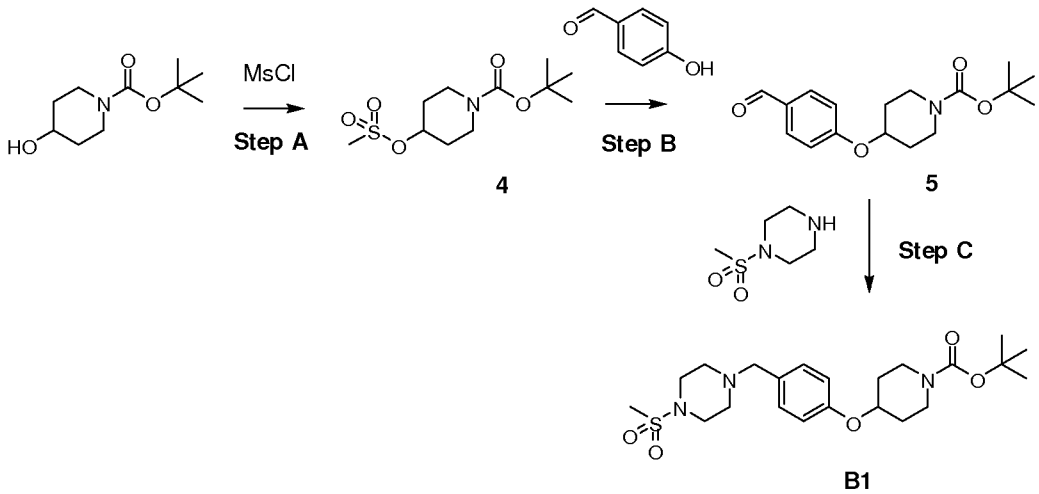
		1.18 (t, J = 7.6 Hz, 3H). MS *m/z* for $(M+H)^+$ $C_{23}H_{33}ClN_5O_3S$ calc. 494.2, found 494.2.
A5		^1H NMR (400 MHz, $CDCl_3$) δ = = 8.44 (s, 2H), 7.21 (s, 1H), 7.20 (d, J = 8.8 Hz, 1H), 6.88 (d, J = 9.2 Hz, 1H), 4.74 (m, 1H), 4.17 (m, 2H), 4.14 (s, 2H), 3.94 (m, 2H), 3.59 (br. s, 2H), 3.47 (br. s, 2H), 2.89 (s, 3H), 2.60 (q, J = 7.6 Hz, 2H), 2.25 (s, 3H), 2.06 (m, 4H), 1.27 (t, J = 7.6 Hz, 3H). MS *m/z* for $(M+H)^+$ $C_{24}H_{36}N_5O_3S$ calc. 474.2, found 474.2.
A6		^1H NMR (400 MHz, MeOD) δ = = 8.39 (s, 2H), 7.35 (m, 3H), 4.82 (m, 1H), 4.36 (s, 2H), 4.10 (m, 2H), 3.85 (m, 2H), 2.95 (s, 3H), 2.59 (q, J = 7.6 Hz, 2H), 2.11 (m, 2H), 1.91 (m, 2H), 1.24 (t, J = 7.6 Hz, 3H). MS *m/z* for $(M+H)^+$ $C_{23}H_{33}FN_5O_3S$ calc. 478.2, found 478.2.
A7		^1H NMR (400 MHz, $CDCl_3$) δ = 8.44 (s, 2H), 7.45 (d, J = 2.0 Hz, 1H), 7.35 (dd, J = 2.4, 8.4 Hz, 1H), 7.03 (d, J = 8.8 Hz), 4.80 (m, 1H), 4.24 (m, 2H), 4.15 (s, 2H), 3.94 (m, 2H), 2.90 (s, 3H), 2.59 (q, J = 7.6 Hz, 2H), 2.07 (m, 4H), 1.27 (t, J = 7.6 Hz, 3H).

		MS *m/z* for $(M+H)^+$ $C_{23}H_{33}ClN_5O_3S$ calc. 494.2, found 494.2.
A8		^1H NMR (400 MHz, MeOD) δ = 8.36 (s, 2H), 7.80 (d, J = 2.4 Hz, 1H), 7.50 (dd, J = 2.4, 8.8 Hz, 1H), 7.26 (d, J = 8.8 Hz), 4.90 (m, 1H), 4.35 (s, 2H), 3.99 (m, 4H), 2.96 (s, 3H), 2.58 (q, J = 7.6 Hz, 2H), 2.07 (m, 2H), 1.94 (m, 2H), 1.24 (t, J = 7.6 Hz, 3H). MS *m/z* for $(M+H)^+$ $C_{23}H_{32}BrN_5O_3S$ calc. 538.1, found 538.2.
A9		^1H NMR (400 MHz, MeOD) δ = 8.40 (s, 2H), 7.19 (d, J = 2.0 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 7.06 (dd, J = 2.0, 8.4 Hz, 1H), 4.72 (m, 1H), 4.35 (s, 2H), 4.10 (m, 2H), 3.88 (s, 3H), 3.84 (m, 2H), 2.95 (s, 3H), 2.59 (q, J = 7.6 Hz, 2H), 2.06 (m, 2H), 1.91 (m, 2H), 1.25 (t, J = 7.6 Hz, 3H). MS *m/z* for $(M+H)^+$ $C_{24}H_{36}N_5O_4S$ calc. 490.2, found 490.2.
A10		^1H NMR (400 MHz, MeOD) δ = 8.38 (s, 2H), 7.55 (d, J = 2.0 Hz, 1H), 7.51 (dd, J = 2.0, 8.4 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 4.39 (s, 2H), 4.04 (m, 2H), 3.90 (s, 2H), 2.96 (s, 3H), 2.59 (q, J = 7.6 Hz, 2H), 2.11 (m, 2H),

		1.91 (m, 2H), 1.25 (t, J = 7.6 Hz, 3H). MS *m/z* for $(M+H)^+$ $C_{24}H_{33}F_3N_5O_4S$ calc. 544.2, found 544.2.
A11		^1H NMR (400 MHz, MeOD) δ = 8.43 (s, 2H), 7.25 (t, J = 9.2 Hz, 1H), 6.90 (t, J = 8.8 Hz, 1H), 4.75 (m, 1H), 4.27 (s, 2H), 4.08 (m, 4H), 2.88 (s, 3H), 2.59 (q, J = 7.6 Hz, 2H), 2.07 (m, 4H), 1.27 (t, J = 7.6 Hz, 3H). MS *m/z* for $(M+H)^+$ $C_{23}H_{32}F_2N_5O_3S$ calc. 496.2, found 496.2.
A12		^1H NMR (400 MHz, MeOD) δ = 8.33 (s, 2H), 7.50 (t, J = 2.0 Hz, 1H), 7.39 (dd, J = 2.0, 11.2 Hz, 1H), 4.66 (m, 1H), 4.34 (s, 2H), 4.19 (m, 2H), 3.73 (m, 2H), 3.39 (m, 4H), 2.96 (s, 3H), 2.56 (q, J = 7.6 Hz, 2H), 2.05 (m, 2H), 1.92 (m, 2H), 1.23 (t, J = 7.6 Hz, 3H). MS *m/z* for $(M+H)^+$ $C_{23}H_{32}ClFN_5O_3S$ calc. 512.2, found 512.2.
A13		^1H NMR (400 MHz, $CDCl_3$) δ = 8.42 (s, 2H), 7.36 (d, J = 2.8 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.34 (dd, J = 2.8, 8.4 Hz, 1H), 4.74 (m, 1H), 4.30 (s, 2H), 4.04 (m, 4H), 3.64 (m, 4H), 3.39 (m, 4H), 2.88 (s, 3H), 2.59 (q, J = 7.6 Hz, 2H), 2.10

		(m, 2H), 2.01 (m, 2H), 1.27 (t, J = 7.6 Hz, 3H). MS *m/z* for $(M+H)^+$ $C_{22}H_{33}N_6O_3S$ calc. 461.2, found 461.2.
A14		^1H NMR (400 MHz, $CDCl_3$) δ = 8.25 (s, 2H), 7.58 (d, J = 2.0 Hz, 1H), 7.43 (dd, J = 2.0, 8.8 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 4.77 (m, 1H), 3.89 (m, 2H), 3.77 (m, 4H), 3.47 (s, 2H), 3.33 (s, 3H), 3.09 (m, 4H), 2.86 (s, 3H), 2.44 (m, 6H), 1.87 (m, 2H), 1.66 (m, 2H), 1.13 (t, J = 7.6 Hz, 3H). MS *m/z* for $(M+H)^+$ $C_{25}H_{36}N_5O_5S$ calc. 518.2, found 518.2

Example B1: N-*tert*-Butyl 4-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidine-1-carboxylate.



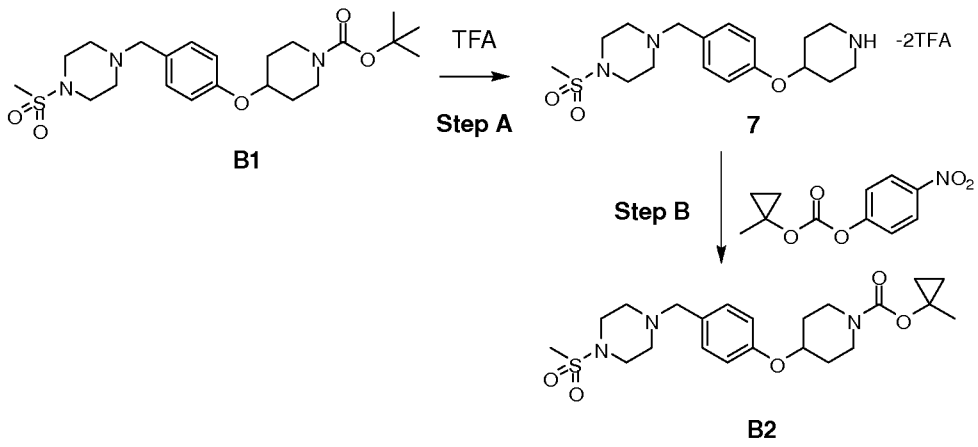
[00109] **Step A:** N-*tert*-Butyl 4-hydroxypiperidine-1-carboxylate (2 g, 9.94 mmol) was dissolved in DCM (20 mL). Diisopropylethylamine (3.4 mL, 19.8 mmol) was added and the mixture was cooled to 0ºC, then methanesulfonyl chloride (0.92 mL, 11.93 mmol) was added dropwise and the mixture was stirred for 1 h at rt. The mixture was diluted with H_2O

(20 mL) and separated. The organic layer was washed with sat. aq. $NaHCO_3$, dried ($MgSO_4$), filtered, concentrated and purified by flash column chromatography (SiO_2, MeOH/DCM gradient) to give N-*tert*-butyl 4-(methylsulfonyloxy)piperidine-1-carboxylate **4**: ^1H NMR (400 MHz, $CDCl_3$) δ = 5.00 (m, 1H), 3.82 (m, 2H), 3.42 (m, 2H), 3.16 (s, 3H), 2.08 (m, 2H), 1.94 (m, 2H), 1.58 (s, 9H). MS *m/z* for (M-C_4H_{11}+H^+ fragment) $C_7H_{14}NO_5S$ calc. 224.0, found 224.1.

[00110] **Step B:** N-*tert*-Butyl 4-(methylsulfonyloxy)piperidine-1-carboxylate **4** (500 mg, 1.79 mmol), 4-hydroxybenzaldehyde (218 mg, 1.79 mmol) and Cs_2CO_3 (1.1 g, 3.58 mmol) were heated in DMF (10 mL) at 80ºC for 2 h. The reaction was cooled, diluted with H_2O (20 mL) and extracted with EtOAc (2 x 20 mL). The organic layers were combined, washed with H_2O (20 mL) then brine (10 mL), dried ($MgSO_4$), filtered, concentrated and purified by flash column chromatography (SiO_2, EtOAc/Hexanes gradient) to give N-*tert*-butyl 4-(4-formylphenoxy)piperidine-1-carboxylate **5**: ^1H NMR (400 MHz, $CDCl_3$) δ = 7.77 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 4.54 (m, 1H), 3.63 (m, 2H), 3.32 (m, 2H), 1.89 (m, 2H), 1.73 (m, 2H), 1.39 (s, 9H). MS *m/z* for (M-C_4H_{11}+H^+ fragment) $C_{13}H_{16}NO_4$ calc. 250.1, found 250.1.

[00111] **Step C:** N-*tert*-Butyl 4-(4-formylphenoxy)piperidine-1-carboxylate **5** (273 mg, 0.89 mmol) and 1-methanesulfonylpiperazine (176 mg, 1.07 mmol) were dissolved in dichloroethane (10 mL). AcOH (50 µL) was added, and the mixture was heated at 90ºC for 1 h, then sodium triacetoxyborohydride (725 mg, 3.42 mmol) was added and the mixture was heated at 90ºC for 2 h. The reaction was cooled, diluted with sat. aq. $NaHCO_3$ (50 mL), and extracted with DCM (30 mL). The organic layer was washed with brine, dried ($MgSO_4$), filtered, concentrated and purified by flash column chromatography (SiO_2, MeOH/DCM gradient) to give the title compound **B1** as a white powder: ^1H NMR (400 MHz, MeOD) δ = 7.22 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 4.47 (m, 1H), 3.72 (m, 2H), 3.50 (s, 2H), 3.25 (m, 4H), 2.79 (s, 3H), 2.56 (m, 4H), 1.92 (m, 2H), 1.76 (m, 2H), 1.49 (s, 9H). MS *m/z* for $(M+H)^+$ $C_{22}H_{36}N_3O_5S$ calc. 454.2, found 454.2.

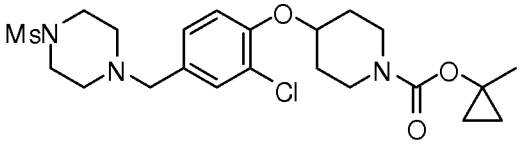
Example B2: 1-Methylcyclopropyl 4-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidine-1-carboxylate.



[00112] **Step A:** N-*tert*-Butyl 4-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidine-1-carboxylate **B1** (340 mg, 0.75 mmol) was dissolved in TFA (20 mL) and stirred at rt for 1 h. The mixture was concentrated *in vacuo* and the residue was dissolved in MeOH and concentrated (2x) to provide the TFA salt of 1-(methylsulfonyl)-4-(4-(piperidin-4-yloxy)benzyl)piperazine **7** (563 mg), which was used directly in Step B without further purification. MS *m/z* for (M-C_4H_{11}+H^+ fragment) $C_{17}H_{28}N_3O_3S$ calc. 354.2, found 354.2.

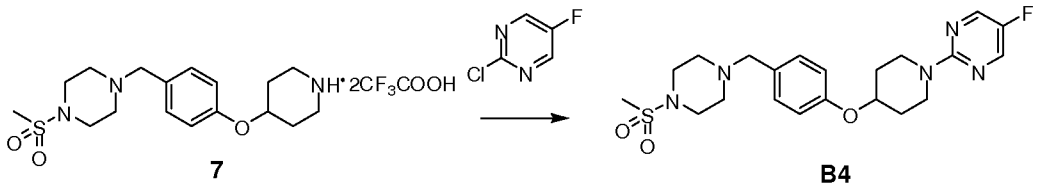
[00113] **Step B:** 1-(Methylsulfonyl)-4-(4-(piperidin-4-yloxy)benzyl)piperazine **7** (36 mg, 0.06 mmol) and 1-methylcyclopropyl 4-nitrophenyl carbonate (22 mg, 0.09 mmol) were dissolved in DCM (5 mL). Triethylamine (60 μL, 0.43 mmol) was added and the mixture was stirred at rt for 2 h. The mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, EtOAc/Hexane gradient) to give the title compound **B2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.13 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 8.4 Hz, 2H), 4.38 (m, 1H), 3.60 (m, 2H), 3.40 (s, 2H), 3.29 (m, 2H), 3.16 (m, 4H), 2.70 (s, 3H), 2.47 (m, 4H), 1.82 (m, 2H), 1.69 (m, 2H), 1.48 (s, 3H), 1.19 (m, 1H), 0.80 (m, 2H), 0.56 (m, 2H). MS *m/z* for $(M+H)^+$ $C_{22}H_{34}N_3O_5S$ calc. 452.2, found 452.2.

Example B3: 1-Methylcyclopropyl 4-(2-chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidine-1-carboxylate.



[00114] By following the same procedures as **B1** except using 3-chloro-4-hydroxybenzaldehyde as the phenol, the title compound **B3** was obtained; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 2.4 Hz, 1H), 7.32 (dd, J = 2.4, 8.4 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 4.63 (m, 1H), 4.15 (s, 2H), 3.59 (m, 4H), 2.88 (s, 3H), 1.87 (m, 4H), 1.56 (s, 3H), 0.89 (t, J = 2.4 Hz, 2H), 0.65 (t, J = 2.4 Hz, 2H); MS *m/z* for $(M+H)^+$ $C_{22}H_{33}ClN_3O_5S$ calc. 486.2, found 486.1.

Example B4: 5-Fluoro-2-(4-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine.

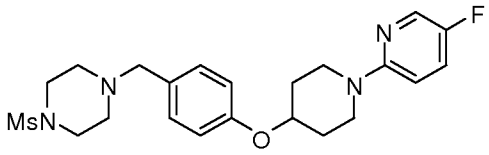
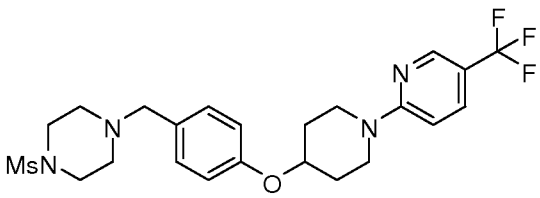
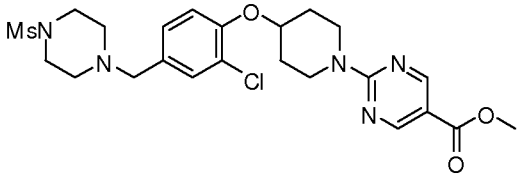
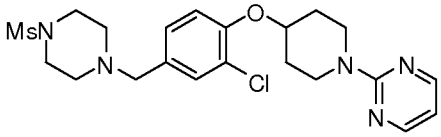


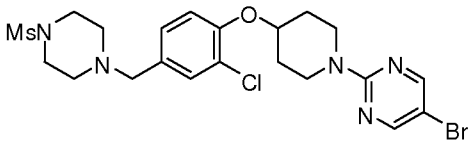
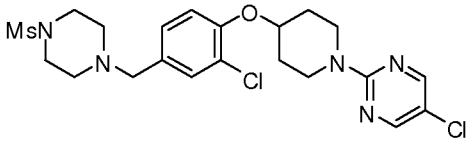
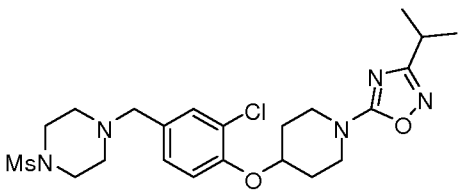
[00115] 1-(Methylsulfonyl)-4-(4-(piperidin-4-yloxy)benzyl) piperazine **7** (30 mg, 0.05 mmol), 2-chloro-5-fluoro-pyrimidine (7 μL, 0.06 mmol) and K_2CO_3 (24 mg, 0.17 mmol) were dissolved in DMA (1 mL) and subjected to microwave irradiation (180ºC, 5 min). The reaction was cooled, diluted with H_2O (10 mL) and extracted with EtOAc (10 mL). The organic layer was washed with H_2O (10 mL) and brine (10 mL), then dried ($MgSO_4$), filtered, concentrated and purified by reverse-phase HPLC (H_2O/AcN gradient) to afford the title compound **B4** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.52 (s, 2H), 7.31 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.4 Hz, 2H), 4.52 (m, 1H), 4.08 (s, 2H), 4.03 (m, 2H), 3.79 (m, 2H) 3.63 (m, 2H), 3.48 (m, 4H), 2.80 (s, 3H), 1.95 (m, 2H), 1.76 (m, 2H). MS *m/z* for $(M+H)^+$ $C_{21}H_{29}FN_5O_3S$ calc. 450.2, found 450.2.

[00116] By repeating the procedures described above, using appropriate starting materials, the following compounds of Formula I, as identified in Table 2, were obtained.

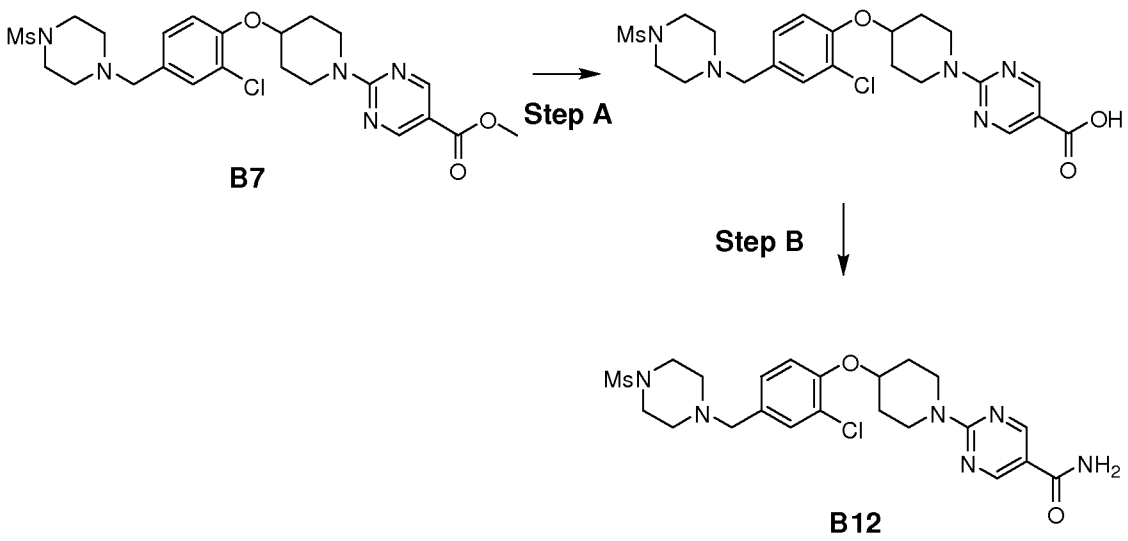
Table 2

Compound #	Structure	NMR and/or ESMS

B5		^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08 (t, J = 2.4 Hz, 1H), 7.60 (m, 1H), 7.33 (d, J = 8.4 Hz, 2H), 6.95 (dd, J = 3.6, 10 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 4.62 (s, 1H), 4.10 (s, 2H), 3.73 (m, 8H), 3.48 (m, 4H), 2.85 (m, 2H), 2.81 (s, 3H), 2.05 (m, 4H). MS *m/z* for $(M+H)^+$ $C_{22}H_{30}FN_4O_3S$ calc. 449.2, found 449.2.
B6		^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.46 (s, 1H), 7.79 (dd, J = 2.0, 9.2 Hz, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 9.6 Hz, 1H), 4.70 (m, 1H), 4.19 (s, 2H), 3.92 (m, 6H), 3.48 (m, 4H), 2.95 (m, 2H), 2.90 (s, 3H), 2.05 (m, 4H). MS *m/z* for $(M+H)^+$ $C_{23}H_{30}F_3N_4O_3S$ calc. 499.2, found 499.2.
B7		^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.77 (s, 2H), 7.30 (d, J = 2.0 Hz, 1H), 7.06 (dd, J = 2.0, 8.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 4.58 (m, 1H), 4.02 (m, 4H), 3.80 (s, 3H), 3.40 (s, 2H), 3.18 (m, 4H), 2.72 (s, 3H), 2.48 (m, 4H), 1.90 (m, 4H). MS *m/z* for $(M+H)^+$ $C_{23}H_{31}ClN_5O_5S$ calc. 524.2, found 524.1.
B8		^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.25 (s, 1H), 8.24 (s, 1H), 7.29 (d, J = 2.4 Hz, 1H), 7.05 (dd, J = 2.0, 8.4 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.41 (t, J = 7.2 Hz, 1H), 4.54 (m, 1H), 4.03 (m, 2H), 3.78 (m, 2H), 3.40 (s, 2H), 3.18 (m, 4H), 2.71 (s, 3H), 2.48 (m, 4H), 1.88 (m, 4H). MS *m/z* for $(M+H)^+$ $C_{21}H_{29}ClN_5O_3S$ calc. 466.2, found 466.1.

B9		^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.31 (s, 2H), 7.38 (d, J = 2.0 Hz, 1H), 7.14 (dd, J = 2.4, 8.4 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 4.63 (m, 1H), 4.03 (m, 2H), 3.88 (m, 2H), 3.48 (s, 2H), 3.27 (m, 4H), 2.80 (s, 3H), 2.57 (m, 4H), 1.96 (m, 4H). MS *m/z* for $(M+H)^+$ $C_{21}H_{28}BrClN_5O_3S$ calc. 544.1, found 544.1.
B10		^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.16 (s, 2H), 7.29 (d, J = 2.0 Hz, 1H), 7.05 (dd, J = 2.0, 8.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 4.55 (m, 1H), 3.93 (m, 2H), 3.80 (m, 2H), 3.40 (s, 2H), 3.18 (m, 4H), 2.72 (s, 3H), 2.49 (m, 4H), 1.87 (m, 4H). MS *m/z* for $(M+H)^+$ $C_{21}H_{28}Cl_2N_5O_3S$ calc. 500.1, found 500.2.
B11		^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 (d, J = 2.4 Hz, 1H), 7.23 (dd, J = 2.4, 8.0 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 4.65 (m, 1H), 4.02 (s, 3H), 3.70 (m, 5H), 3.60 (m, 3H), 2.82 (q, J = 7.2 Hz, 2H), 2.81 (s, 3H), 1.94 (m, 4H), 1.23 (s, 3H), 1.21 (s, 3H). MS *m/z* for $(M+H)^+$ $C_{22}H_{33}ClN_5O_4S$ calc. 498.2, found 498.1.

Example B12: 2-(4-(2-Chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine-5-carboxamide.

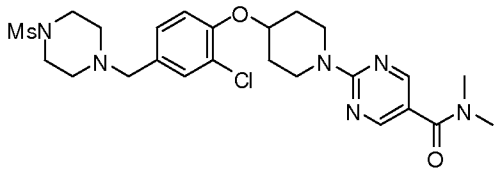
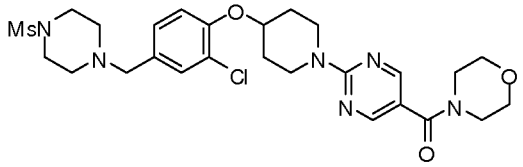


[00117] **Step A:** Methyl 2-(4-(2-chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine-5-carboxylate **B7** (216 mg, 0.41 mmol) was dissolved in THF (5 mL) and LiOH (165 μL of 5M, 0.824 mmol) was added. The mixture was heated at 80ºC for 3h, then cooled and concentrated to give crude 2-(4-(2-chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine-5-carboxylic acid, which was used in the next step without further purification. MS *m/z* for $(M^+ + H^+)$ $C_{22}H_{29}ClN_5O_5S$ calc. 510.2, found 510.1.

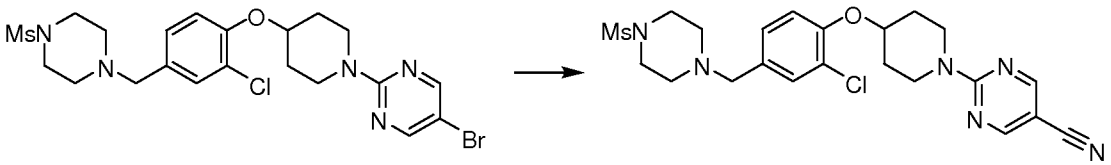
[00118] **Step B:** 2-(4-(2-Chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine-5-carboxylic acid (21 mg, 0.41 mmol) was dissolved in a mixture of DCM (5 mL) and THF (5 mL). Oxalyl chloride (40 μL, 0.45 mmol) was added and the mixture was stirred at rt for 2h, then ammonium hydroxide (100 μL of a 30% solution in H_2O) was added and the mixture was stirred at rt for 12h. The mixture was concentrated and purified by reverse-phase HPLC (H_2O/AcN gradient) to afford the title compound **B12** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.65 (s, 2H), 7.30 (d, J = 2.0 Hz, 1H), 7.07 (dd, J = 2.0, 8.4 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 4.59 (m, 1H), 4.05 (m, 4H), 3.41 (m, 2H), 3.19 (m, 4H), 2.72 (s, 3H), 2.50 (m, 4H), 1.90 (m, 4H). MS *m/z* for $(M+H)^+$ $C_{22}H_{30}ClN_6O_4S$ calc. 509.2, found 509.2.

[00119] By repeating the procedures described above, using appropriate starting materials, the following compounds of Formula I, as identified in Table 3, were obtained.

Table 3

B13		^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.40 (s, 2H), 7.30 (d, J = 2.0 Hz, 1H), 7.06 (dd, J = 2.0, 8.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 4.57 (m, 1H), 3.97 (m, 4H), 3.40 (s, 2H), 3.18 (m, 4H), 3.03 (s, 6H), 2.71(s, 3H), 2.48 (m, 4H), 1.90 (m, 4H). MS *m/z* for $(M+H)^+$ $C_{24}H_{34}ClN_6O_4S$ calc. 537.2, found 537.1.
B14		^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.37 (s, 2H), 7.30 (d, J = 2.0 Hz, 1H), 7.06 (dd, J = 2.0, 8.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 4.57 (m, 1H), 3.97 (m, 4H), 3.65 (m, 4H), 3.59 (m, 4H), 3.40 (s, 2H), 3.18 (m, 4H), 2.72 (s, 3H), 2.48 (m, 4H), 1.89 (m, 4H). MS *m/z* for $(M+H)^+$ $C_{26}H_{36}ClN_6O_5S$ calc. 579.2, found 579.1.

Example B15: 2-(4-(2-Chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine-5-carbonitrile.

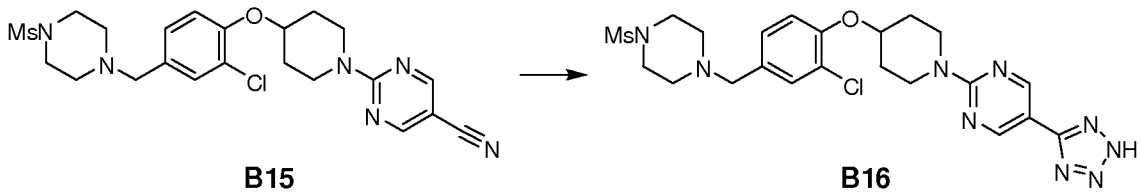


B9 **B15**

[00120] 5-Bromo-2-(4-(2-chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine **B9** (30 mg, 0.055 mmol) was dissolved in DMF (1 mL). $Zn(CN)_2$ (6.5 mg, 0.055 mmol) and $Pd(PPh_3)_4$ (13 mg, 0.011 mmol) were added, and the mixture was degassed with argon for 20 min, then heated at 65ºC for 12h. The mixture was cooled, filtered and purified by reverse-phase HPLC (H_2O/AcN gradient) to

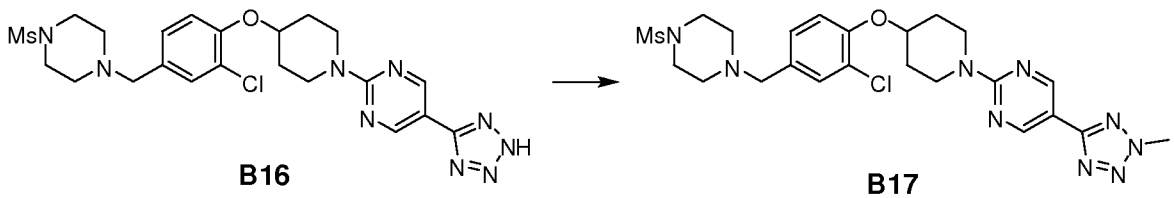
afford the title compound **B15** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.28 (s, 2H), 7.16 (d, J = 2.0 Hz, 1H), 6.93 (dd, J = 1.6, 8.4 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 4.46 (m, 1H), 3.95 (m, 2H), 3.77 (m, 2H), 3.30 (s, 2H), 3.06 (m, 4H), 2.58 (s, 3H), 2.37 (m, 4H), 1.76 (m, 4H). MS *m/z* for $(M+H)^+$ $C_{22}H_{28}ClN_6O_3S$ calc. 491.2, found 491.2.

Example B16: 2-(4-(2-Chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-(2H-tetrazol-5-yl)pyrimidine.



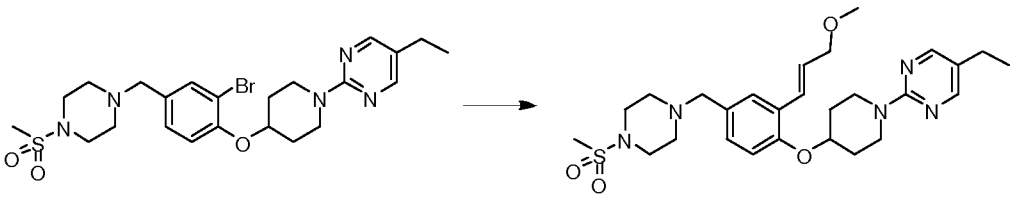
[00121] 2-(4-(2-Chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine-5-carbonitrile **B15** (100 mg, 0.20 mmol) was dissolved in DMF (3 mL). NaN_3 (53 mg, 0.81 mmol) and NH_4Cl (55 mg, 1.02 mmol) were added, and the mixture was heated at 90ºC for 12h. The mixture was diluted with H_2O (10 mL), extracted with EtOAc (10 mL), washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and purified by reverse-phase HPLC (H_2O/AcN gradient) to afford the title compound **B16** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.93 (s, 2H), 7.53 (d, J = 2.0 Hz, 1H), 7.35 (dd, J = 2.0, 8.4 Hz, 1H), 7.19 (d, J = 8.4 Hz, 1H), 4.81 (m, 1H), 4.18 (m, 2H), 3.92 (m, 4H), 3.42 (m, 4H), 3.03 (m, 4H), 2.85 (s, 3H), 2.06 (m, 2H), 1.85 (m, 2H). MS *m/z* for $(M+H)^+$ $C_{22}H_{29}ClN_9O_3S$ calc. 534.2, found 534.2.

Example B17: 2-(4-(2-Chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-(2-methyl-2H-tetrazol-5-yl)pyrimidine.



[00122] 2-(4-(2-Chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-(2H-tetrazol-5-yl)pyrimidine **B16** (28 mg, 0.052 mmol) was dissolved in DMF (2 mL). K_2CO_3 (40 mg, 0.29 mmol) and MeI (4 μL, 0.06 mmol) were added and the mixture was stirred at rt for 2h. The mixture was diluted with H_2O (10 mL), extracted with EtOAc (10 mL), washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and purified by reverse-phase HPLC (H_2O/AcN gradient) to afford the title compound **B17** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.92 (s, 2H), 7.30 (d, J = 2.0 Hz, 1H), 7.06 (dd, J = 2.0, 8.4 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 4.58 (m, 1H), 4.32 (s, 3H), 4.04 (m, 2H), 3.96 (m, 2H), 3.40 (s, 2H), 3.18 (m, 4H), 2.72 (s, 3H), 2.48 (m, 4H), 1.91 (m, 4H). MS *m/z* for $(M+H)^+$ $C_{23}H_{31}ClN_9O_3S$ calc. 548.2, found 548.2.

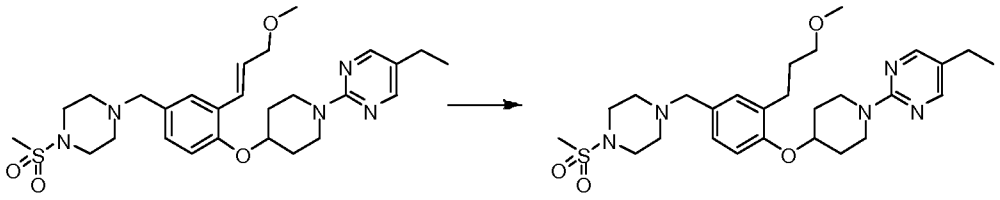
Example C1: (E)-5-Ethyl-2-(4-(2-(3-methoxyprop-1-enyl)-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine.



[00123] 2-(4-(2-bromo-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine **A8** (60 mg, 0.11 mmol), (E)-2-(3-methoxy-1-propenyl)-4,4,5,5-tetramethyl-1,3,2-dioxoborolane (35 μL, 0.16 mmol), Na_2CO_3 (35 mg, 0.33 mmol) and $Pd(PPh_3)_4$ (13 mg, 0.011 mmol) were dissolved in a mixture of dimethoxyethane (360 μL), H_2O (240 μL) and EtOH (180 μL) and subjected to microwave irradiation (170°C, 5 min). The mixture was cooled, diluted with H_2O (10 mL) and extracted with EtOAc (20 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated and purified by reverse-phase HPLC (H_2O/AcN gradient) to afford the title compound **C1** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.43 (s, 2H), 7.54 (d, J = 2.0 Hz, 1H), 7.26 (dd, J = 2.4, 8.8 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 6.88 (d, J = 16 Hz, 1H), 6.32 (dt, J = 7.6, 16 Hz, 1H), 4.73 (m, 1H), 4.16 (m, 2H), 4.10 (m, 2H), 4.02 (m, 3H), 3.40 (s, 3H), 2.89 (s, 3H),

2.68 (m, 7H), 2.59 (q, J = 7.6 Hz, 2H), 2.06 (m, 4H), 1.26 (t, J = 7.6 Hz, 3H); MS *m/z* for $(M+H)^+$ $C_{27}H_{40}N_5O_4S$ calc. 530.3, found 530.2.

Example C2: 3-(2-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yloxy)-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenyl)propan-1-ol.

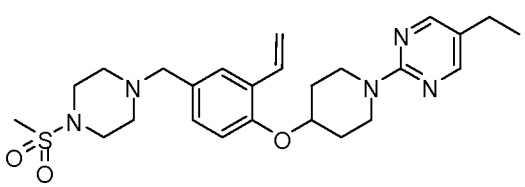


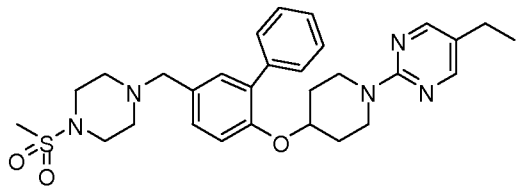
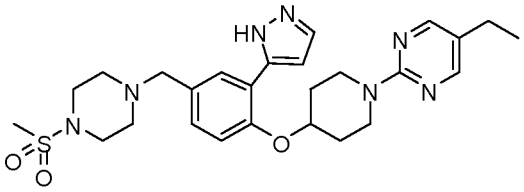
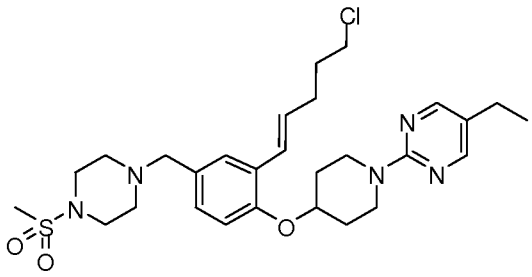
C1 C2

[00124] (E)-5-Ethyl-2-(4-(2-(3-methoxyprop-1-enyl)-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine **C2** (55 mg, 0.104 mmol) and Pd/C (~ 20 mg of 10%, wet) was suspended in a flask with EtOH (10 mL) and the mixture was shaken under H_2 on a Parr shaker (55 psi) for 1h. The mixture was filtered through celite, concentrated, and purified by reverse-phase HPLC (H_2O/AcN gradient) to afford the title compound **C2** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12 (s, 2H), 7.03 (d, J = 2.0 Hz, 1H), 7.00 (dd, J = 2.0, 8.4 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 4.51 (m, 1H), 3.97 (m, 2H), 3.71 (m, 2H), 3.40 (s, 2H), 3.31 (t, J = 6.8 Hz, 2H), 3.25 (s, 3H), 3.17 (s, 3H), 2.71 (s, 3H), 2.60 (m, 1H), 2.48 (s, 3H), 2.40 (q, J = 7.6 Hz, 2H), 1.93 (m, 2H), 1.79 (m, 4H), 1.13 (t, J = 7.6 Hz, 3H); MS *m/z* for $(M+H)^+$ $C_{27}H_{42}N_5O_4S$ calc. 532.3, found 532.0.

[00125] By repeating the procedures described above, using appropriate starting materials, the following compounds of Formula I, as identified in Table 4, were obtained.

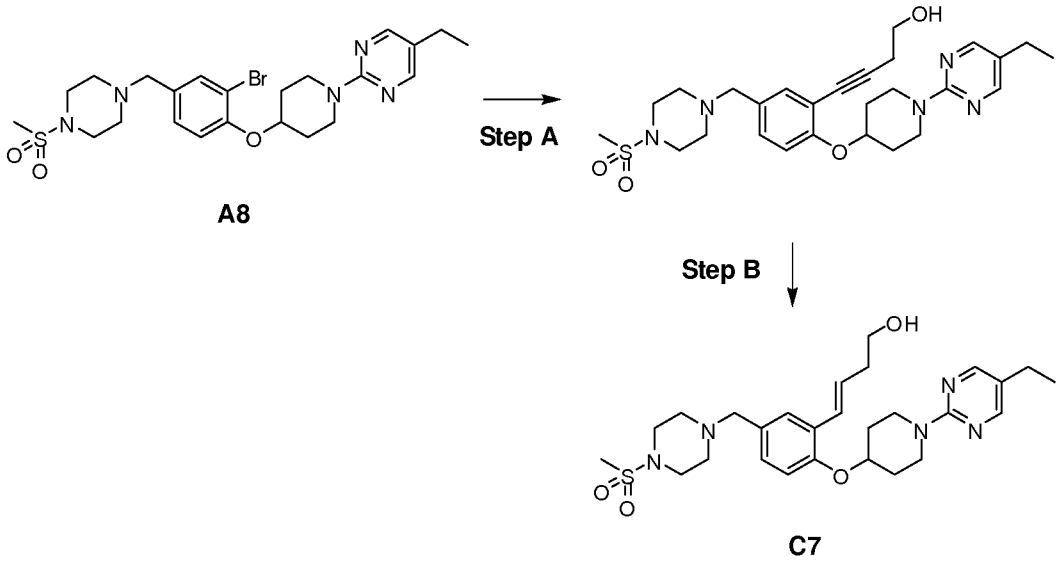
Table 4

C3		^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.45 (s, 2H), 7.55 (d, J = 2.4 Hz, 1H), 7.28 (m, 1H), 7.01 (dd, J = 11.2, 17.6 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 5.77 (dd, J = 0.8, 17.6 Hz, 1H), 5.37 (dd, J = 1.2, 11.2 Hz, 1H), 4.77 (m, 1H), 4.17 (m,

		4H), 3.95 (m, 2H), 3.62, (m, 2H), 3.46 (m, 2H), 2.89 (s, 3H), 2.61 (q, J = 7.6 Hz, 2H), 2.08 (m, 4H), 1.28 (t, J = 7.6 Hz, 3H); MS *m/z* for $(M+H)^+$ $C_{25}H_{36}N_5O_3S$ calc. 486.2, found 486.2.
C4		^1H NMR (400 MHz, $CDCl_3$) δ = 8.38 (s, 2H), 7.51 (m, 2H), 7.37 (m, 5H), 7.06 (d, J = 8.0 Hz, 1H), 4.73 (m, 1H), 4.22 (s, 2H), 4.07 (m, 2H), 3.60 (m, 3H), 2.88 (s, 3H), 2.56 (q, J = 7.6 Hz, 2H), 1.95 (m, 4H), 1.24 (t, J = 7.6 Hz, 3H); MS *m/z* for $(M+H)^+$ $C_{29}H_{38}N_5O_3S$ calc. 536.3, found 536.2.
C5		^1H NMR (400 MHz, $CDCl_3$) δ = 8.34 (s, 1H), 8.32 (s, 1H), 7.83 (d, J = 2.0 Hz, 0.5H), 7.68 (d, J = 2.0 Hz, 0.5H), 7.37 (dd, J = 2.0, 8.8 Hz, 0.5H), 7.24 (d, J = 8.8 Hz, 1H), 7.07 (d, J = 8.8 Hz, 0.5H), 6.90 (dd, J = 2.0, 6.8 Hz, 1H), 6.79 (d, J = 2.4 Hz, 0.5H), 4.79 (m, 0.5H), 4.61 (m, 0.5H), 4.15 (m, 2H), 4.08 (m, 2H), 3.95 (m, 3H), 3.69 (m, 2H), 2.81 (s, 1.5H), 2.80 (s, 1.5H), 2.50 (q, J = 7.6 Hz, 2H), 2.00 (m, 4H), 1.18 (t, J = 7.6 Hz, 3H); MS *m/z* for $(M+H)^+$ $C_{26}H_{36}N_7O_3S$ calc. 526.3, found 526.2.
C6		^1H NMR (400 MHz, $CDCl_3$) δ = 8.32 (s, 2H), 7.54 (d, J = 2.4 Hz, 1H), 7.19 (dd, J = 2.0, 8.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 6.74 (d, J = 16 Hz, 1H), 6.20 (dt, J = 8.8, 16 Hz, 1H), 4.67 (m, 1H), 4.14 (s, 2H), 4.04 (m, 2H), 3.94 (m, 3H), 3.59 (t, J= 6.4 Hz,

		2H), 2.89 (s, 3H), 2.54 (m, 2H), 2.40 (m, 2H), 2.04 (m, 2H), 1.96 (m, 4H), 1.24 (t, J = 7.6 Hz, 3H); MS *m/z* for $(M+H)^+$ $C_{28}H_{41}ClN_5O_3S$ calc. 562.3, found 562.2.

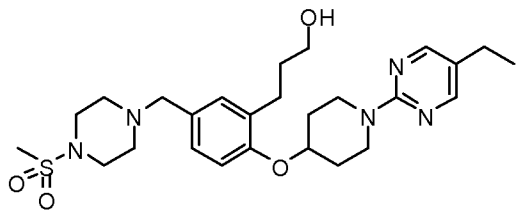
Example C7: (E)-4-(2-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yloxy)-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenyl)but-3-en-1-ol.



[00126] **Step A:** 2-(4-(2-Bromo-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine **A8** (60 mg, 0.11 mmol), but-3-yn-1-ol (182 μL, 3.12 mmol), CuBr (33 mg, 0.23 mmol) and $Pd(PPh_3)_4$ (25 mg, 0.022 mmol) were dissolved in triethylamine (750 μL), degassed for 20 min with argon, then heated at 90ºC for 3h. The mixture was cooled, diluted with H_2O (10 mL) and extracted with EtOAc (20 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated and purified by flash column chromatography (SiO_2, EtOAc/Hexane gradient) to give 4-(2-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenyl)but-3-yn-1-ol as a white powder: ^1H NMR (400 MHz, $CDCl_3$) δ = 8.11 (s, 2H), 7.27 (d, J = 2.4 Hz, 1H), 7.10 (dd, J = 2.4, 8.4 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 4.54 (m, 1H), 4.07 (m, 2H), 3.66 (m, 4H), 3.38 (s, 2H), 3.17 (m, 4H), 2.71 (s, 3H), 2.63 (t, J = 6.0 Hz, 2H), 2.47 (m, 4H), 2.40 (q, J = 7.6 Hz, 2H), 1.94 (m, 4H), 1.82 (m, 2H), 1.53 (m, 2H), 1.12 (t, J = 7.6 Hz, 3H); MS *m/z* for $(M+H)^+$ $C_{27}H_{38}N_5O_4S$ calc. 528.3, found 528.2.

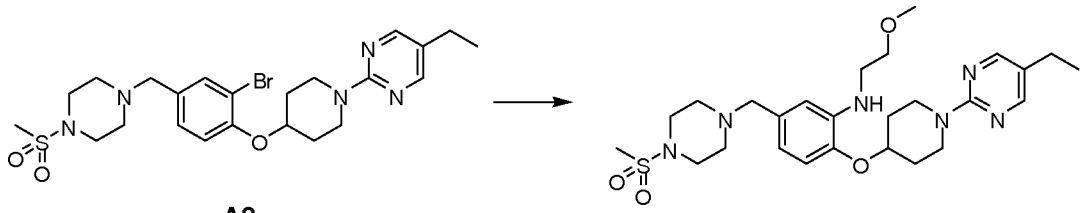
[00127] **Step B:** 4-(2-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yloxy)-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenyl)but-3-yn-1-ol (50 mg, 0.095 mmol) and cyclohexadiene (100 μL) were dissolved in EtOH (2 mL). Pd/C (20 mg of 10%, wet) was added and the mixture was heated at 80°C overnight, then it was cooled and filtered through an 0.2 μm syringe filter. The mixture was concentrated and purified by reverse-phase HPLC (H_2O/AcN gradient) to afford the title compound **C7** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12 (s, 2H), 7.31 (d, J = 2.4 Hz, 1H), 7.04 (dd, J = 2.4, 8.4 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.75 (d, J = 16 Hz, 1H), 6.15 (dt, J = 7.2, 16 Hz, 1H), 4.49 (m, 1H), 4.06 (m, 2H), 3.64 (m, 4H), 3.40 (s, 2H), 3.17 (m, 4H), 2.71 (s, 3H), 2.48 (m, 4H), 2.40 (m, 4H), 1.95 (m, 4H), 1.79 (m, 2H), 1.53 (m, 2H), 1.12 (t, J = 7.6 Hz, 3H); MS *m/z* for $(M+H)^+$ $C_{27}H_{40}N_5O_4S$ calc. 530.3, found 530.2.

Example C8: 3-(2-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yloxy)-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenyl)propan-1-ol.



[00128] By following the same procedure as in **C7** except using prop-2-yn-1-ol as the alkyne, the title compound **C8** was obtained; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.11 (s, 2H), 7.04 (d, J = 2.0 Hz, 1H), 7.01 (dd, J = 2.0, 8.4 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 4.51 (m, 1H), 4.07 (m, 2H), 3.61 (m, 2H), 3.53 (m, 2H), 3.40 (s, 2H), 3.17 (m, 4H), 2.71 (s, 3H), 2.65 (m, 2H), 2.48 (m, 4H), 2.40 (q, J = 7.6 Hz, 2H), 1.97 (m, 3H), 1.77 (m, 4H), 1.52 (m, 2H), 1.13 (t, J = 7.6 Hz, 3H); MS *m/z* for $(M+H)^+$ $C_{26}H_{40}N_5O_4S$ calc. 518.3, found 518.2.

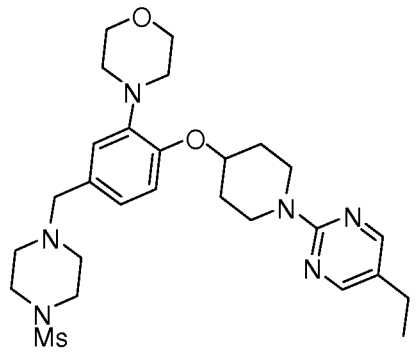
Example C9: 2-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yloxy)-N-(2-methoxyethyl)-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)aniline.



A8 C9

[00129] 2-(4-(2-Bromo-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine **A8** (50 mg, 0.093 mmol), 2-methoxyethylamine (9.6 μL, 0.11 mmol), Xantphos (5.4 mg, 0.0093 mmol), sodium *tert*-butoxide (26 mg, 0.28 mmol) and $Pd_2(dba)_3$ (4 mg, 0.0046 mmol) were dissolved in dioxane (1 mL) and degassed for 20 min with argon. Then the reaction vessel was sealed and heated at 120ºC for 12h. The mixture was cooled, filtered, concentrated and purified by reverse-phase HPLC (H_2O/AcN gradient) to afford the title compound **C9** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.11 (s, 2H), 6.69 (d, J = 8.0 Hz, 1H), 6.53 (d, J = 1.6 Hz, 1H), 6.49 (dd, J = 2.0, 8.0 Hz, 1H), 4.45 (m, 1H), 4.10 (m, 2H), 3.55 (m, 4H), 3.41 (s, 2H), 3.29 (s, 3H), 3.22 (m, 6H), 2.71 (s, 3H), 2.51 (m, 4H), 2.39 (q, J = 7.6 Hz, 2H), 1.97 (m, 4H), 1.76 (m, 2H), 1.12 (t, J = 7.6 Hz, 3H); MS *m/z* for $(M+H)^+$ $C_{26}H_{41}N_6O_4S$ calc. 533.3, found 533.2.

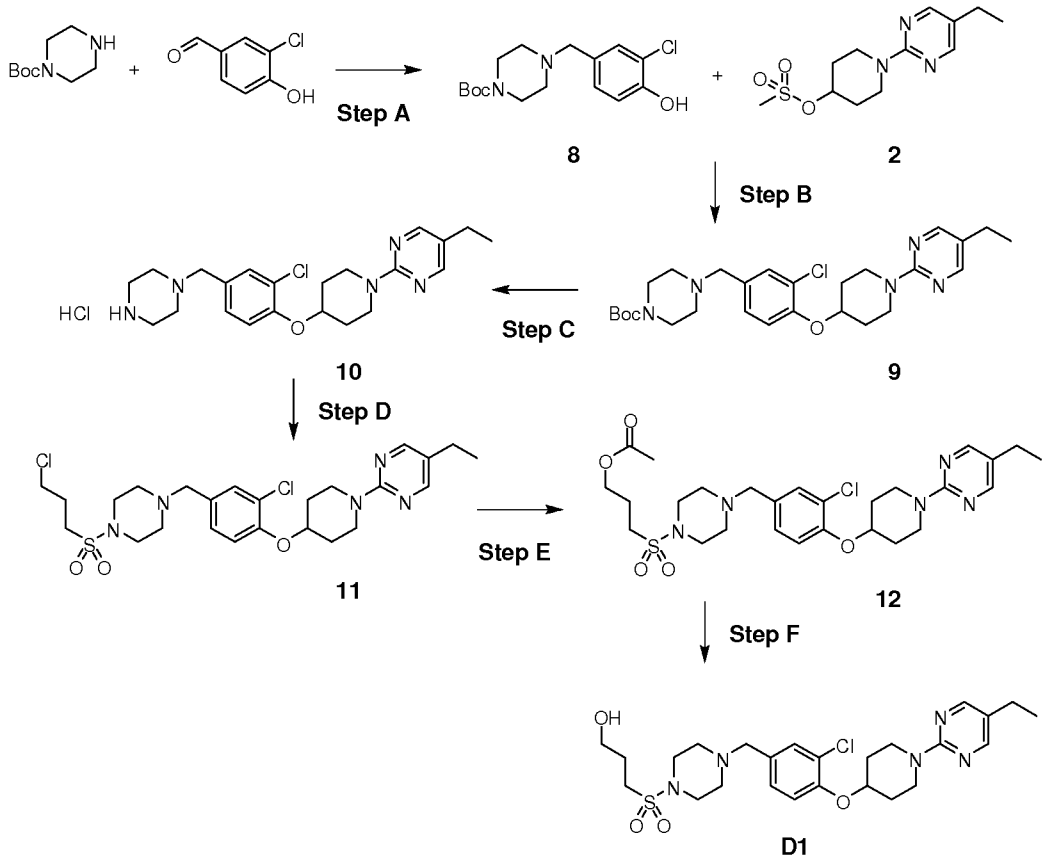
Example C10: 4-(2-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yloxy)-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenyl)morpholine.



[00130] By following the same procedure as in **C9** except using morpholine as the amine, the title compound **C10** was obtained; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12 (s, 2H), 6.82 (m, 3H), 4.55 (m, 1H), 4.03 (m, 2H), 3.77 (m, 4H), 3.65 (m, 2H), 3.22 (m, 4H),

3.03 (m, 4H), 2.73 (m, 4H), 2.40 (q, J = 7.6 Hz, 2H), 1.95 (m, 3H), 1.78 (m, 3H), 1.12 (t, J = 7.6 Hz, 3H); MS *m/z* for $(M+H)^+$ $C_{27}H_{41}N_6O_4S$ calc. 545.3, found 545.2.

Example D1: 3-(4-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)piperazin-1-ylsulfonyl)propan-1-ol.



[00131] **Step A:** 3-Chloro-4-hydroxybenzaldehyde (500 mg, 3.19 mmol) and N-*tert*-butyl piperazine-1-carboxylate (595 mg, 3.19 mmol) were dissolved in dichloroethane (20 mL). AcOH (50 µL) was added, and the mixture was heated at 80ºC for 1 h. Sodium triacetoxyborohydride (1.35 g, 6.38 mmol) was added and the mixture was heated at 80ºC for 2 h. The reaction was cooled, diluted with sat. aq. $NaHCO_3$ (50 mL), and extracted with DCM (30 mL). The organic layer was washed with brine, dried ($MgSO_4$), filtered, concentrated and purified by flash column chromatography (SiO_2, MeOH/DCM gradient) to give N-*tert*-butyl 4-(3-chloro-4-hydroxybenzyl)piperazine-1-carboxylate **8** as a white powder: ^1H NMR (400 MHz, $CDCl_3$) δ = 7.29 (d, J = 2.0, 1H), 7.11 (dd, J = 2.0, 8.0 Hz, 1H),

6.95 (d, J = 8.0 Hz, 1H), 3.44 (m, 6H), 2.39 (m, 4H), 1.47 (s, 9H). MS *m/z* for $(M+H)^+$ $C_{16}H_{24}ClN_2O_3$ calc. 327.1, found 327.2.

[00132] **Step B:** 4-(3-Chloro-4-hydroxybenzyl)piperazine-1-carboxylate **8** (940 mg, 2.87 mmol), 1-(5-ethylpyrimidin-2-yl)piperidin-4-yl methanesulfonate **2** (1.23 g, 4.31 mmol) and Cs_2CO_3 (1.8 g, 5.74 mmol) were heated in AcN (5 mL) at 60ºC for 12 h. The reaction was cooled, filtered, concentrated and purified by flash column chromatography (SiO_2, EtOAc/Hexane gradient) to give N-*tert*-butyl 4-(3-chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)piperazine-1-carboxylate **9**: MS *m/z* for $(M+H)^+$ $C_{27}H_{39}ClN_5O_3$ calc. 516.3, found 516.3.

[00133] **Step C:** N-*tert*-Butyl 4-(3-chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)piperazine-1-carboxylate **9** (345 mg, 0.67 mmol) was dissolved in TFA (4 mL) and stirred at rt for 1h. The mixture was basified with sat. aq. $NaHCO_3$ (20 mL) and extracted with DCM (20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give 2-(4-(2-chloro-4-(piperazin-1-ylmethyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine **10**, which was used directly in Step D without further purification: MS *m/z* for $(M+H)^+$ $C_{17}H_{28}N_3O_3S$ calc. 416.2, found 416.2.

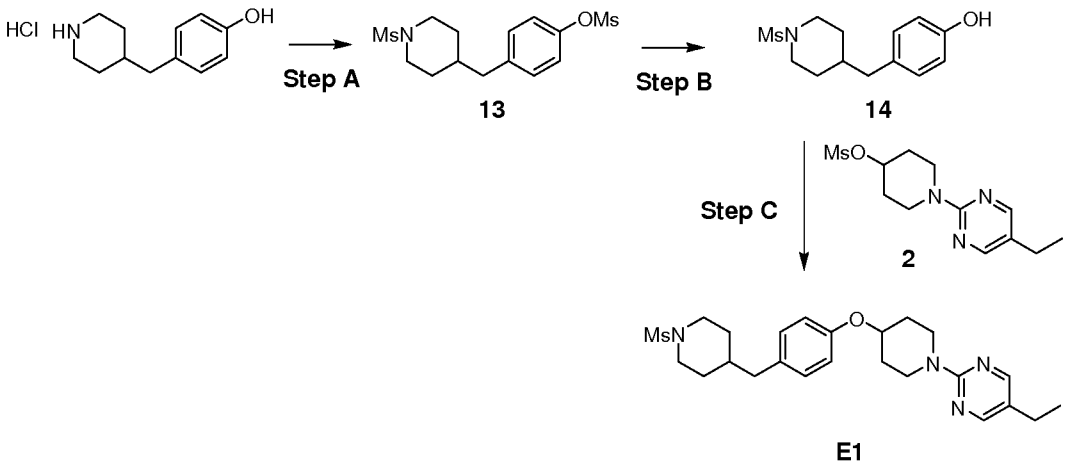
[00134] **Step D:** 2-(4-(2-Chloro-4-(piperazin-1-ylmethyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine **10** (163 mg, 0.39 mmol) was dissolved in DCM (5 mL). Triethylamine (60 µL, 0.43 mmol) was added and the mixture was cooled to 0ºC. 3-Chloropropanesulfonyl chloride (52 µL, 0.43 mmol) was added and the mixture was stirred at rt for 1 h, then was diluted with H_2O (10 mL) extracted with DCM. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give crude 2-(4-(2-chloro-4-((4-(3-chloropropylsulfonyl)piperazin-1-yl)methyl)phenoxy)-piperidin-1-yl)-5-ethylpyrimidine **11**, which was used directly in Step E without further purification: MS *m/z* for $(M+H)^+$ $C_{25}H_{36}Cl_2N_5O_3S$ calc. 556.2, found 556.1.

[00135] **Step E:** 2-(4-(2-Chloro-4-((4-(3-chloropropylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine **11** (0.39 mmol), NaI (60 mg, 0.395 mmol) and NaOAc (96 mg, 1.17 mmol) were dissolved in DMF (2 mL) and heated at 120ºC for 2 h. The mixture was cooled, diluted with H_2O (10 mL) and extracted with EtOAc (20 mL). The organic layer was washed with H_2O(10 mL) and brine (10 mL), then dried ($MgSO_4$), filtered and concentrated to provide 3-(4-(3-chloro-4-(1-(5-ethylpyrimidin-2-

yl)piperidin-4-yloxy)benzyl)piperazin-1-ylsulfonyl)propyl acetate **12** which was used directly in Step F without further purification: MS *m/z* for $(M+H)^+$ $C_{27}H_{39}ClN_5O_5S$ calc. 580.2, found 580.1.

[00136] **Step F:** 3-(4-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)piperazin-1-ylsulfonyl)propyl acetate **12** (0.39 mmol) and $LiOH-H_2O$ (50 mg, 1.19 mmol) were dissolved in THF (3 mL) and H_2O (25 μL) and heated at 60°C for 2 h. The reaction was concentrated and purified by flash column chromatography (SiO2, EtOAc/Hexane gradient) to provide the title compound **D1** as a white powder: ^1H NMR (400 MHz, $CDCl_3$) δ = 8.11 (s, 2H), 7.28 (d, J = 2.0, 1H), 7.05 (dd, J = 2.0, 8.0 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 4.51 (m, 1H), 4.02 (m, 2H), 3.69 (m, 2H), 3.62 (t, J = 6.0 Hz, 2H), 3.39 (s, 2H), 3.25 (m, 4H), 3.01 (m, 2H), 2.46 (m, 4H), 2.39 (q, J = 7.2 Hz, 2H), 2.23 (m, 2H), 1.92 (m, 2H), 1.82 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H). MS *m/z* for $(M+H)^+$ $C_{25}H_{37}ClN_5O_4S$ calc. 538.2, found 538.2.

Example E1: 5-Ethyl-2-(4-(4-((1-(methylsulfonyl)piperidin-4-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine.



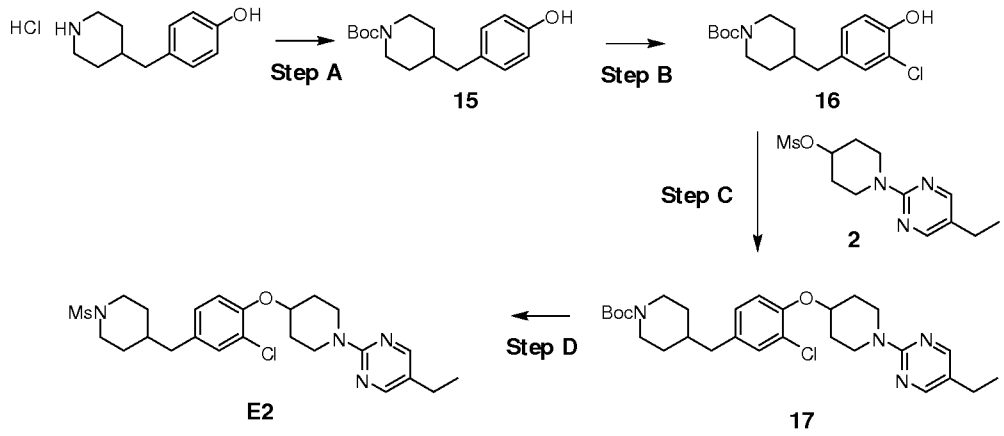
[00137] **Step A:** 4-(Piperidin-4-ylmethyl)phenol hydrochloride (500 mg, 2.19 mmol) was dissolved in DCM (20 mL), then diisopropylethylamine (1.15 mL, 6.58 mmol) and methanesulfonyl chloride (0.34 mL, 4.38 mmol) were added and stirred at rt for 2 h. The mixture was basified with sat. aq. $NaHCO_3$ (20 mL) and separated. The organic layer was

washed with 1N HCl (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to provide 4-((1-(methylsulfonyl)piperidin-4-yl)methyl)phenyl methanesulfonate **13** which was used in Step B without further purification: MS *m/z* for $(M+H)^+$ $C_{14}H_{22}NO_5S_2$ calc. 348.1, found 348.2.

[00138] **Step B:** 4-((1-(Methylsulfonyl)piperidin-4-yl)methyl)phenyl methanesulfonate **13** (2.19 mmol) was dissolved in MeOH (3 mL), then 10% NaOH (2 mL) was added and the mixture was heated at 80ºC for 1 h. The reaction was cooled, quenched with 1N HCl (10 mL) and extracted with EtOAc (20 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (SiO2, EtOAc/Hexane gradient) to provide 4-((1-(methylsulfonyl)piperidin-4-yl)methyl)phenol **14** as a white powder: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.92 (d, J = 8.4 Hz, 2H), 6.69 (d, J = 8.4 Hz, 2H), 3.70 (m, 2H), 2.68 (s, 3H), 2.51 (dt, J = 2.4, 8.0 Hz, 2H), 2.43 (d, J = 7.2 Hz, 2H), 1.67 (m, 2H), 1.49 (m, 1H), 1.26 (m, 2H). MS *m/z* for $(M+H)^+$ $C_{13}H_{20}NO_3S$ calc. 270.1, found 270.1.

[00139] **Step C:** 4-((1-(Methylsulfonyl)piperidin-4-yl)methyl)phenol **14** (50 mg, 0.19 mmol), 1-(5-ethylpyrimidin-2-yl)piperidin-4-yl methanesulfonate **2** (79 mg, 0.28 mmol) and Cs_2CO_3 (121 mg, 0.37 mmol) were heated in AcN (5 mL) at 60ºC for 12 h. The reaction was cooled, filtered, concentrated and purified by flash column chromatography (SiO2, EtOAc/Hexane gradient) to give the title compound **E1** as a white powder: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.31 (s, 2H), 7.07 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 4.56 (m, 1H), 4.13 (m, 2H), 3.81 (m, 4H), 2.77 (s, 3H), 2.61 (m, 2H), 2.53 (m, 4H), 2.02 (m, 2H), 1.90 (m, 2H), 1.78 (m, 2H), 1.61 (m, 1H), 1.36 (m, 2H), 1.23 (t, J = 7.6 Hz, 3H). MS *m/z* for $(M+H)^+$ $C_{24}H_{35}N_4O_3S$ calc. 459.2, found 459.2.

Example E2: 2-(4-(2-Chloro-4-((1-(methylsulfonyl)piperidin-4-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine.



[00140] **Step A:** 4-(Piperidin-4-ylmethyl)phenol hydrochloride (380 mg, 1.67 mmol), Boc_2O (400 mg, 1.83 mmol), and sodium bicarbonate (1.4 g, 16.7 mmol) were dissolved in H_2O (10 mL), and dioxane (10 mL) and stirred at rt for 2h. Then the mixture was extracted with EtOAc (20 mL), washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to provide 4-((1-(methylsulfonyl)piperidin-4-yl)methyl)phenyl methanesulfonate **15** which was used in Step B without further purification: MS *m/z* for $(M\text{-}C_4H_9+H)^+$ $C_{13}H_{18}NO_3$ calc. 236.1, found 236.1.

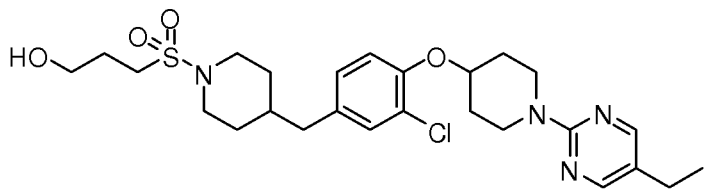
[00141] **Step B:** **N-***tert*-Butyl 4-(4-hydroxybenzyl)piperidine-1-carboxylate **15** (236 mg, 0.811 mmol) was dissolved in DCM (3 mL), then sulfuryl chloride (33 µL, 0.40 mmol) was added and the mixture was stirred at rt for 1h. The reaction was diluted with water (10 mL) and extracted with DCM (20 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (SiO2, EtOAc/Hexane gradient) to provide N-*tert*-butyl 4-(3-chloro-4-hydroxybenzyl)piperidine-1-carboxylate **16** as a white powder. MS *m/z* for $(M\text{-}C_4H_9+H)^+$ $C_{13}H_{17}ClNO_3$ calc. 270.1, found 270.1.

[00142] **Step C:** Following the same procedure as in **D1 Step C** except using N-*tert*-butyl 4-(3-chloro-4-hydroxybenzyl)piperidine-1-carboxylate **16** as the phenol, N-*tert*-butyl 4-(3-chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)piperidine-1-carboxylate **17** was obtained. MS *m/z* for $(M+H)^+$ $C_{28}H_{40}ClN_4O_3$ calc. 515.3, found 514.9.

[00143] **Step D: :** N-*tert*-Butyl 4-(3-chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)piperidine-1-carboxylate **17** (345 mg, 0.67 mmol) was dissolved in TFA (4 mL) and stirred at rt for 1h. The mixture was basified with sat. aq. $NaHCO_3$ (20 mL) and extracted with DCM (20 mL). The organic layer was dried ($MgSO_4$), filtered, and

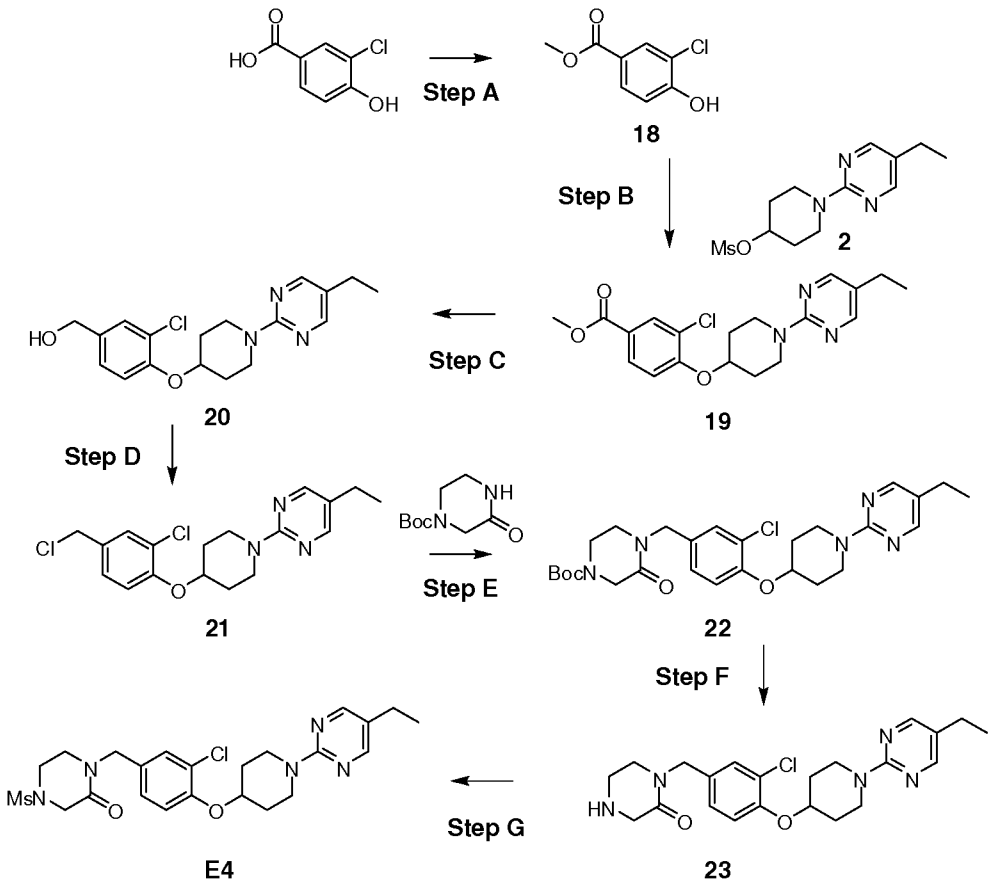
concentrated. The remainder was dissolved in DCM (3 mL) and treated with diisopropylethylamine (34 μL, 0.19 mmol) and methanesulfonyl chloride (8 μL, 0.10 mmol). The mixture was stirred at rt for 1h, then it was concentrated and purified by reverse-phase HPLC (H_2O/AcN gradient) to afford the title compound **E2** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.20 (s, 2H), 7.18 (d, J = 2.0 Hz, 1H), 6.98 (dd, J = 2.0, 8.0 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 4.57 (m, 1H), 4.13 (m, 2H), 3.77 (m, 4H), 2.78 (s, 3H), 2.62 (td, J = 2.4, 12.0 Hz, 2H), 2.50 (m, 4H), 1.99 (m, 2H), 1.90 (m, 2H), 1.77 (m, 2H), 1.62 (m, 2H), 1.34 (m, 2H), 1.12 (t, J = 7.6 Hz, 3H); MS *m/z* for $(M+H)^+$ $C_{24}H_{34}ClN_4O_3S$ calc. 493.2, found 493.2.

Example E3: 3-(4-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)piperidin-1-ylsulfonyl)propan-1-ol.



[00144] By following the same procedures as **D1** except using N-*tert*-Butyl 4-(3-chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)piperidine-1-carboxylate **17**, the title compound **E3** was obtained; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02 (s, 2H), 6.99 (d, J = 2.0 Hz, 1H), 6.79 (dd, J = 2.0, 8.4 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 4.39 (m, 1H), 3.94 (m, 2H), 3.59 (m, 6H), 2.87 (m, 2H), 2.55 (td, J = 2.4, 12.0 Hz, 2H), 2.32 (m, 4H), 1.86 (m, 4H), 1.74 (m, 2H), 1.56 (m, 3H), 1.46 (m, 2H), 1.14 (m, 3H), 1.03 (t, J = 7.6 Hz, 3H); MS *m/z* for $(M+H)^+$ $C_{26}H_{38}ClN_4O_4S$ calc. 537.2, found 537.1.

Example E4: 1-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)-4-(methylsulfonyl)piperazin-2-one.



[00145] **Step A:** 3-Chloro-4-hydroxybenzoic acid (1 g, 5.79 mmol) was dissolved in MeOH (5 mL), then conc. H_2SO_4 (250 µL) was added and the mixture was heated at reflux for 3 h. The reaction was cooled, basified with sat. aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (2 x 20 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated to give methyl 3-chloro-4-hydroxybenzoate **18**: MS *m/z* for $(M+H)^+$ $C_8H_8ClO_3$ calc. 187.0, found 187.1.

[00146] **Step B:** 1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl methanesulfonate **2** (458 mg, 1.61 mmol), 3-chloro-4-hydroxybenzoate **18** (200 mg, 1.07 mmol) and Cs_2CO_3 (697 mg, 2.14 mmol) were dissolved in AcN (3 mL) and subjected to microwave irradiation (180ºC, 3 min). The reaction was cooled, filtered, concentrated and purified by flash column chromatography (SiO2, EtOAc/Hexane gradient) to give methyl 3-chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzoate **19**: ^1H NMR (400 MHz, $CDCl_3$) δ = 8.21 (s, 2H), 8.09 (d, J = 2.0 Hz, 1H), 7.93 (dd, J = 2.0, 8.8 Hz, 1H), 7.01 (d, J = 8.8 Hz, 1H), 4.76 (m, 1H), 4.06 (m, 2H), 3.92 (s, 3H), 3.87 (m, 2H), 2.48 (q, J = 7.6 Hz, 2H), 2.04 (m, 2H),

1.94 (m, 2H), 1.22 (t, J = 7.6 Hz, 3H). MS *m/z* for $(M+H)^+$ $C_{19}H_{23}ClN_3O_3$ calc. 376.1, found 376.1.

[00147] **Step C:** Methyl 3-chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzoate **19** (536 mg, 1.53 mmol) was dissolved in dry THF (10 mL) and cooled to 0ºC, then a 1 M solution of $LiAlH_4$ was added and the mixture was stirred at 0ºC for 10 min. The reaction was quenched by slow dropwise addition of H_2O, then was extracted with EtOAc (30 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (10 mL), H_2O (10 mL), and brine (10 mL), then was dried ($MgSO_4$), filtered and concentrated to give crude (3-chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)phenyl)methanol **20**, which was used in Step D without further purification. MS *m/z* for $(M+H)^+$ $C_{18}H_{23}ClN_3O_2$ calc. 348.1, found 348.1.

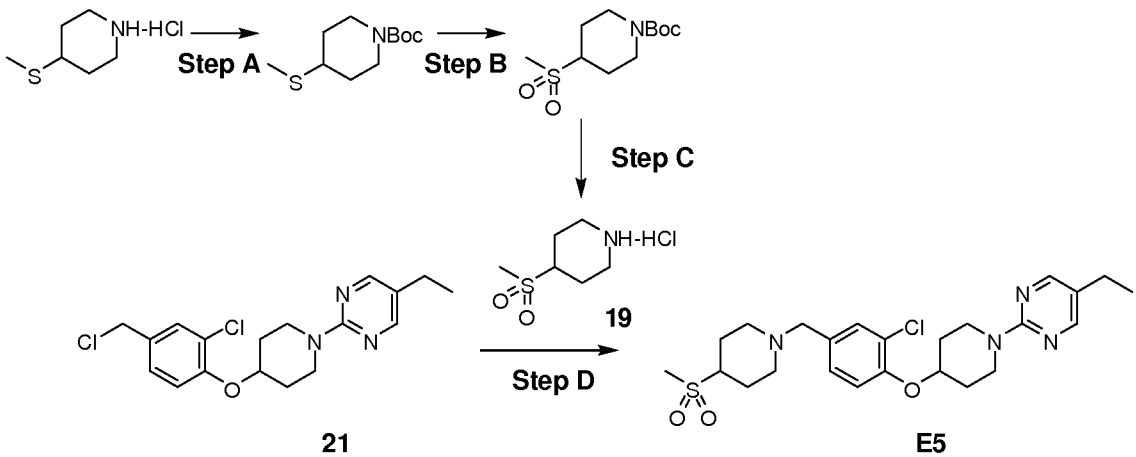
[00148] **Step D:** (3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)phenyl)methanol **20** (1.53 mmol) was dissolved in DCM (20 mL). Diisopropylethylamine (535 µL, 3.07 mmol) was added, followed by methanesulfonyl chloride (130 µL, 1.68 mmol) and the mixture was stirred at rt for 2 h. The mixture was concentrated and purified by flash column chromatography (SiO2, EtOAc/Hexane gradient)to give 2-(4-(2-chloro-4-(chloromethyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine **21**: ^1H NMR (400 MHz, $CDCl_3$) δ = 8.11 (s, 2H), 7.36 (d, J = 2.4 Hz, 1H), 7.16 (dd, J = 2.4, 8.4 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 4.55 (m, 1H), 4.45 (m, 2H), 4.00 (m, 2H), 3.72 (m, 2H), 2.40 (q, J = 7.6 Hz, 2H), 1.91 (m, 2H), 1.83 (m, 2H), 1.12 (t, J = 7.6 Hz, 3H). MS *m/z* for $(M+H)^+$ $C_{18}H_{22}Cl_2N_3O$ calc. 366.1, found 366.1.

[00149] **Step E:** N-Boc-oxopiperazine (40 mg, 0.20 mmol) was dissolved in DMF (5 mL). Sodium hydride (12 mg, 0.3 mmol) was added and the mixture was heated at 60ºC for 1 h, then 2-(4-(2-Chloro-4-(chloromethyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine **21** (76 mg, 0.20 mmol) was added and the mixture was stirred at rt for 12 h. The mixture was quenched with H_2O (20 mL) and extracted with EtOAc (20 mL). The organic layer was washed with H_2O (20 mL) and brine (10 mL), then dried ($MgSO_4$), filtered, concentrated and purified by flash column chromatography (SiO2, EtOAc/Hexane gradient) to give N-*tert*-butyl 4-(3-chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)-3-oxopiperazine-1-carboxylate **22**: MS *m/z* for $(M+H)^+$ $C_{27}H_{37}ClN_5O_4$ calc. 530.2, found 366.1.

[00150] **Step F:** N-*tert*-Butyl 4-(3-chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)-3-oxopiperazine-1-carboxylate **22** (79 mg, 0.15 mmol) was dissolved in a mixture of DCM (2 mL) and a 4 N solution of HCl in dioxane (3 mL) and stirred at rt for 1 h. The mixture was basified with sat. aq. $NaHCO_3$ (40 mL) and extracted with DCM (20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give 1-(3-chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)piperazin-2-one **23**, which was used directly in Step G without further purification: MS *m/z* for $(M+H)^+$ $C_{22}H_{29}ClN_5O_2$ calc. 430.2, found 430.1.

[00151] **Step G:** 1-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)piperazin-2-one **23** (20 mg, 0.04 mmol) was dissolved in DCM (3 mL), then diisopropylethylamine (22 µL, 0.13 mmol) and methanesulfonyl chloride (4 µL, 0.05 mmol) were added and stirred at rt for 2 h. The mixture was basified with sat. aq. $NaHCO_3$ solution (10 mL), and extracted with DCM (10 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated and purified by flash column chromatography (SiO2, EtOAc/Hexane gradient) to give the title compound **E4**: ^1H NMR (400 MHz, $CDCl_3$) δ = 8.36 (s, 2H), 7.25 (d, J = 2.4 Hz, 1H), 7.08 (dd, J = 2.4, 8.4 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 4.66 (m, 1H), 4.48 (s, 2H), 4.17 (m, 2H), 3.94 (s, 2H) 3.86 (m, 2H), 3.42 (m, 2H), 3.33 (m, 2H), 2.80 (s, 3H), 2.52 (q, J = 7.6 Hz, 2H), 1.95 (m, 4H), 1.19 (t, J = 7.6 Hz, 3H). MS m/z for $(M+H)^+$ $C_{23}H_{31}ClN_5O_4S$ calc. 508.2, found 508.1.

Example E5: 2-(4-(2-chloro-4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine.



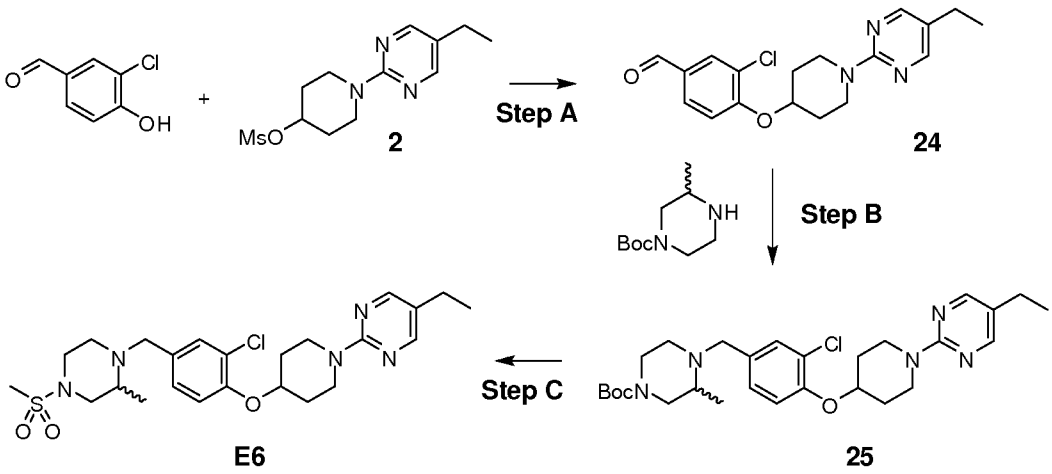
[00152] Step A: By following the same procedure as in in E2 Step A except using 4-methylthiopiperidine hydrochloride as the starting material, N-tert-butyl 4-(methylthio)piperidine-1-carboxylate was obtained.

[00153] **Step B:** N-*tert*-Butyl 4-(methylthio)piperidine-1-carboxylate (1.11 g, 4.8 mmol) and sodium periodate (5 g, 24 mmol) were dissolved in AcN (20 mL) and H_2O (8 mL) and heated at 100ºC for 2h. The mixture was cooled, diluted with water (20 mL) and extracted with EtOAc (20 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated to provide N-*tert*-butyl 4-(methylsulfonyl)piperidine-1-carboxylate: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.32 (s, 2H), 2.99 (tt, J = 3.6, 12.4 Hz, 1H), 2.86 (s, 3H), 2.77 (m, 2H), 2.14 (d, J = 14.0 Hz, 2H), 1.73 (m, 2H), 1.48 (s, 9H). MS m/z for $(M-C_3H_9+H)^+$ $C_7H_{14}NO_4S$ calc. 208.1, found 208.1.

[00154] **Step C:** N-*tert*-Butyl 4-(methylsulfonyl)piperidine-1-carboxylate (0.77 g, 2.91 mmol) was dissolved in HCl (10 mL of 4N in dioxane) and stirred at rt for 2h. The reaction was concentrated to provide 4-(methylsulfonyl)piperidine hydrochloride **19**, which was used directly in Step D without further purification. MS m/z for $(M+H)^+$ $C_6H_{14}NO_2S$ calc. 164.1, found 164.1.

[00155] **Step D:** 4-Methylthiopiperidine hydrochloride (19 mg, 0.09 mmol), 2-(4-(2-chloro-4-(chloromethyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine **21** (23 mg, 0.06 mmol) and Cs_2CO_3 were heated at 60ºC in AcN for 12h. The mixture was cooled, filtered, concentrated and purified by reverse-phase HPLC (H_2O/AcN gradient) to afford the title compound **E5** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.11 (s, 2H), 7.27 (d, J = 2.0 Hz, 1H), 7.10 (dd, J = 2.0, 8.4 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 4.53 (m, 1H), 4.02 (m, 2H), 3.70 (m, 2H), 3.46 (m, 2H), 3.07 (m, 2H), 2.78 (m, 4H), 2.39 (q, J = 7.6 Hz, 2H), 1.94 (s, 3H), 1.93 (m, 2H), 1.84 (m, 2H), 1.12 (t, J = 7.6 Hz, 3H); MS *m/z* for $(M+H)^+$ $C_{24}H_{34}ClN_4O_3S$ calc. 493.2, found 493.2.

Example E6: 2-(4-(2-Chloro-4-((2-methyl-4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine.

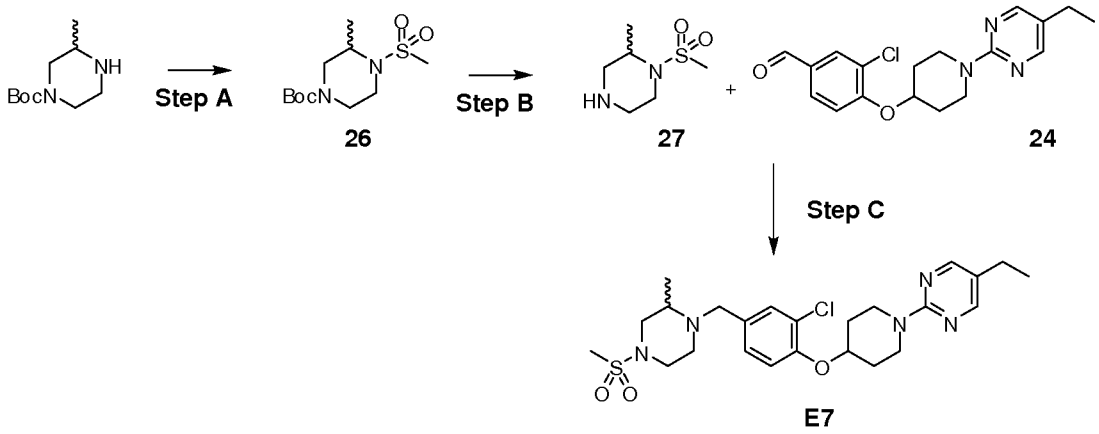


[00156] **Step A:** By following the same procedure as in **A1 Step D** except using 3-chloro-4-hydroxybenzaldehyde as the phenol, 3-chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzaldehyde **24** was obtained. MS m/z for $(M+H)^+$ $C_{18}H_{21}ClN_3O_2$ calc. 346.1, found 346.1.

[00157] **Step B:** By following the same procedure as in **A1 Step C** except using (±)N-4-boc-2-methylpiperazine as the amine and 3-chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzaldehyde **24** as the aldehyde, N-*tert*-butyl 4-(3-chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)-3-methylpiperazine-1-carboxylate **25** was obtained. MS m/z for $(M+H)^+$ $C_{28}H_{41}ClN_5O_3$ calc. 530.3, found 530.0.

[00158] **Step C:** By following the same procedure as in **E2 Step D** the title compound **E6** was obtained: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.20 (s, 2H), 7.38 (d, J = 2.0 Hz, 1H), 7.15 (dd, J = 2.0, 8.0 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 4.61 (m, 1H), 4.11 (m, 2H), 3.79 (m, 2H), 3.46 (m, 2H), 2.79 (s, 3H), 2.48 (q, J = 7.6 Hz, 2H), 1.99 (m, 2H), 1.91 (m, 2H), 1.24 (m, 6H), 0.09 (m, 1H); MS m/z for $(M+H)^+$ $C_{24}H_{35}ClN_5O_3S$ calc. 508.2, found 508.1.

Example E7: 2-(4-(2-Chloro-4-((2-methyl-4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine.

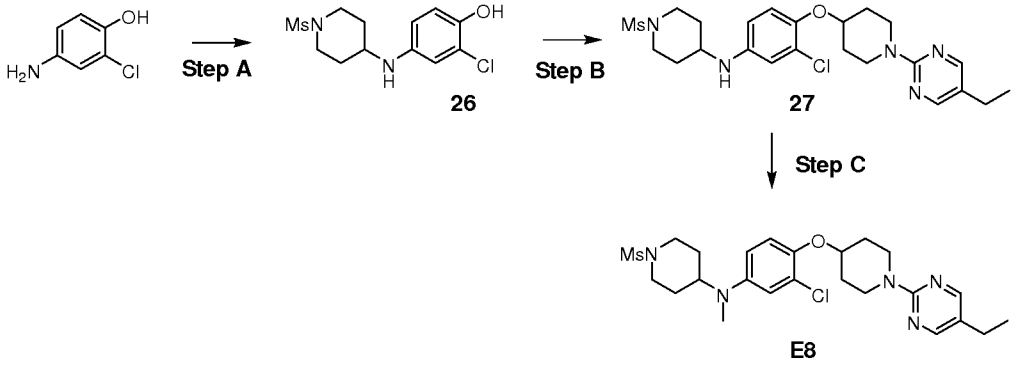


[00159] **Step A:** By following the same procedure as in **E4 Step G** except using (±)N-4-boc-2-methylpiperazine as the starting material, compound **26** was obtained. MS m/z for $(M\text{-}C_3H_9+H)^+$ $C_7H_{15}N_2O_4S$ calc. 223.1, found 223.1.

[00160] **Step B:** By following the same procedure as in **E4 Step F** except using **26** as the starting material, compound **27** was obtained. MS m/z for $(M+H)^+$ $C_6H_{15}N_2O_2S$ calc. 179.1, found 179.1.

[00161] **Step C:** By following the same procedure as in **E6 Step C** except using **27** as the starting material, the title compound **E7** was obtained: ^1H NMR (400 MHz, $CDCl_3$) δ = 8.11 (s, 2H), 7.28 (d, J = 2.0 Hz, 1H), 7.07 (dd, J = 2.0, 8.4 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 4.52 (m, 1H), 4.02 (m, 3H), 3.70 (m, 2H), 3.37 (m, 4H), 2.79 (s, 3H), 2.39 (q, J = 7.6 Hz, 2H), 1.92 (m, 2H), 1.93 (m, 2H), 1.31 (s, 1.5H), 1.30 (s. 1.5H), 1.12 (t, J = 7.6 Hz, 3H), 0.80 (m, 1H); MS m/z for $(M+H)^+$ $C_{24}H_{35}ClN_5O_3S$ calc. 508.2, found 507.9.

Example E8: N-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)phenyl)-N-methyl-1-(methylsulfonyl)piperidin-4-amine.

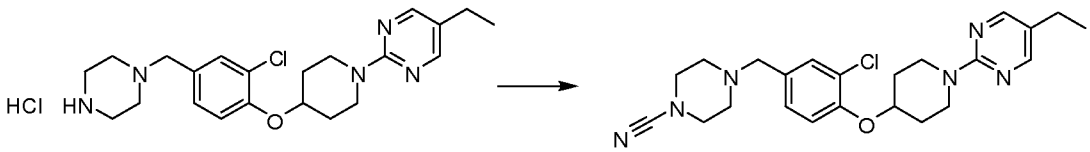


[00162] **Step A:** 4-Amino-2-chlorophenol (200 mg, 1.39 mmol) and 1-methanesulfonyl-4-piperidinone (247 mg, 1.39 mmol) were dissolved in 5% AcOH/EtOH (5 mL) and heated at 60ºC for 1h. The mixture was cooled, then $NaBH_3CN$ (175 mg, 2.78 mmol) was added and the mixture was stirred for 2h at rt. The reaction mixture was diluted with saturated $NaHCO_3$ (10 mL) and extracted with EtOAc (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to provide 2-chloro-4-(1-(methylsulfonyl)piperidin-4-ylamino)phenol **26** which was used in the next step without further purification. MS m/z for $(M+H)^+$ $C_{12}H_{18}ClN_2O_3S$ calc. 305.1, found 305.1.

[00163] **Step B:** By following the same procedure as in **A1 Step D** except using 2-chloro-4-(1-(methylsulfonyl)piperidin-4-ylamino)phenol **26** as the phenol, N-(3-chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)phenyl)-1-(methylsulfonyl)piperidin-4-amine **27** was obtained: ^1H NMR (400 MHz, $CDCl_3$) δ = 8.43 (s, 2H), 7.25 (d, J = 2.8 Hz, 1H), 7.11 (dd, J = 2.8, 8.8 Hz, 1H), 6.98 (d, J = 8.8 Hz, 1H), 4.72 (m, 1H), 4.22 (m, 2H), 3.95 (m, 2H), 3.82 (m, 2H), 3.40 (m, 1H), 2.83 (m, 5H), 2.63 (q, J = 7.6 Hz, 2H), 2.05 (m, 6H), 1.77 (m, 2H), 1.29 (t, J = 7.6 Hz, 3H); MS m/z for $(M+H)^+$ $C_{23}H_{33}ClN_5O_3S$ calc. 494.2, found 494.1.

[00164] **Step C:** N-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)phenyl)-1-(methylsulfonyl)piperidin-4-amine **27** (20 mg, 0.0405 mmol) and paraformaldehyde (50 mg) were dissolved in 5% AcOH/EtOH (5 mL) and heated to 80ºC for 1h. The mixture was cooled, then $NaBH_3CN$ (60 mg, 0.95 mmol) was added and the mixture was stirred for 2h at rt. The mixture was diluted with saturated $NaHCO_3$ (10 mL) and extracted with EtOAc (20 mL). The organic layer was washed with brine (10 mL), dried ($MgSO_4$), filtered, concentrated and purified by reverse-phase HPLC (H_2O/AcN gradient) to afford the title compound **E8** as a white solid: ^1H NMR (400 MHz, $CDCl_3$) δ = 8.44 (s, 2H), 7.19 (d, J = 2.8 Hz, 1H), 7.10 (dd, J = 2.8, 8.8 Hz, 1H), 7.00 (d, J = 8.8 Hz, 1H), 4.66 (m, 1H), 4.18 (m, 2H), 3.98 (m, 4H), 3.61 (m, 1H), 2.98 (s, 3H), 2.84 (s, 3H), 2.80 (td, J = 2.0, 12.0 Hz, 2H), 2.60 (q, J = 7.6 Hz, 2H), 2.05 (m, 6H), 1.83 (m, 2H), 1.27 (t, J = 7.6 Hz, 3H); MS m/z for $(M+H)^+$ $C_{24}H_{35}ClN_5O_3S$ calc. 508.2, found 508.1.

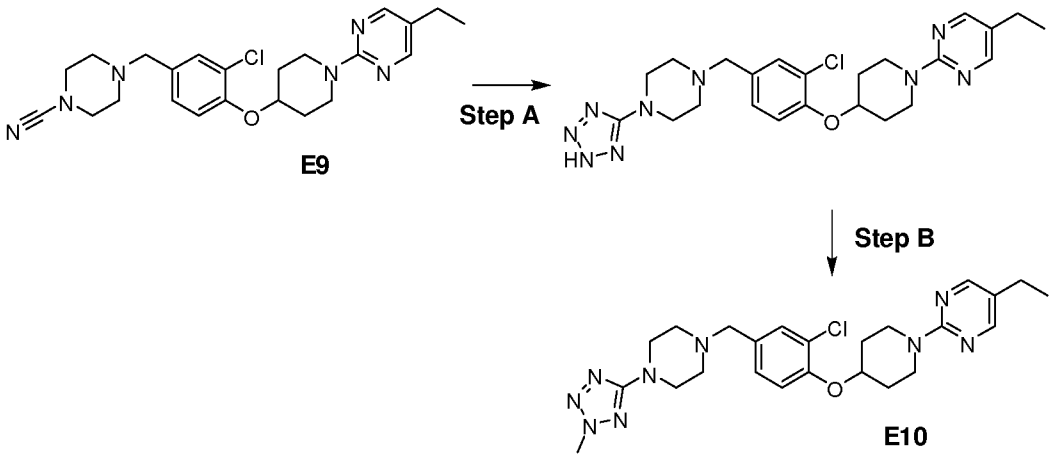
Example E9: 4-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)piperazine-1-carbonitrile.



10 E9

[00165] 2-(4-(2-Chloro-4-(piperazin-1-ylmethyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine hydrochloride **10** (100 mg, 0.22 mmol), cyanogen bromide (26 mg, 0.24 mmol) and K_2CO_3 (66 mg, 0.48 mmol) were dissolved in a 1:1 mixture of H_2O and DCM (8 mL) and stirred at rt for 12h. The mixture was extracted with DCM (5 mL) and the organic layer was dried ($MgSO_4$), filtered, concentrated and purified by reverse-phase HPLC (H_2O/AcN gradient) to provide the title compound **E9** as a white solid. MS m/z for $(M+H)^+$ $C_{23}H_{30}ClN_6O$ calc. 441.2, found 441.1.

Example E10: 2-(4-(2-Chloro-4-((4-(2-methyl-2H-tetrazol-5-yl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine.



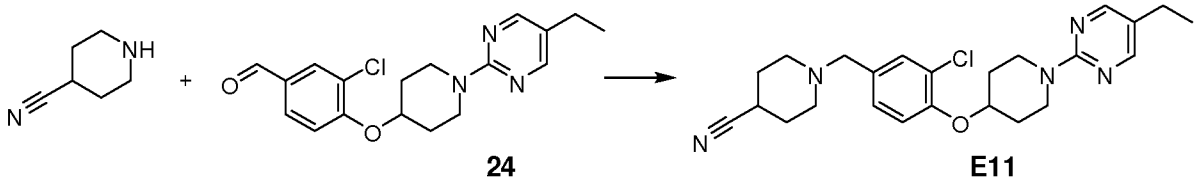
E9 Step A Step B E10

[00166] **Step A:** 4-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)piperazine-1-carbonitrile **E9** (97 mg, 0.22 mmol), sodium azide (38 mg, 0.59 mmol) and NH_4Cl (39 mg, 0.73 mmol) were dissolved in DMF (2 mL) and heated at 90°C for 12h. The mixture was cooled, diluted with H_2O (10 mL) and extracted with EtOAc (20 mL). The organic layer was washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, concentrated and purified by reverse-phase HPLC (H_2O/AcN gradient) to provide 2-(4-(4-((4-(2H-tetrazol-5-yl)piperazin-1-yl)methyl)-2-

chlorophenoxy)piperidin-1-yl)-5-ethylpyrimidine as a white solid: MS m/z for $(M+H)^+$ $C_{23}H_{31}ClN_9O$ calc. 484.2, found 484.1.

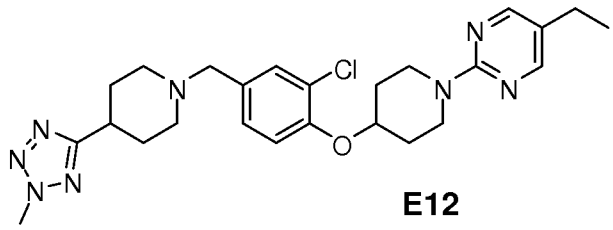
[00167] **Step B:** 2-(4-(4-((4-(2H-Tetrazol-5-yl)piperazin-1-yl)methyl)-2-chlorophenoxy)piperidin-1-yl)-5-ethylpyrimidine (23 mg, 0.047 mmol), K_2CO_3 (50 mg), and iodomethane (3.5 μL, 0.056 mmol) were dissolved in acetone (2 mL) and stirred at rt for 3h. The mixture was filtered, concentrated, and purified by reverse-phase HPLC (H_2O/AcN gradient) to provide the title compound **E10** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.45 (s, 2H), 7.43 (d, J = 2.0 Hz, 1H), 7.37 (dd, J = 2.4, 8.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 4.81 (m, 1H), 4.26 (m, 2H), 4.20 (m, 4H), 3.93 (m, 3H), 2.61 (q, J = 7.6 Hz, 2H), 2.07 (m, 4H), 1.28 (t, J = 7.6 Hz, 3H); MS m/z for $(M+H)^+$ $C_{24}H_{33}ClN_9O$ calc. 498.2, found 498.1.

Example E11: 1-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)piperidine-4-carbonitrile.



[00168] 4-Cyanopiperidine (100 mg, 0.90 mmol), and 3-chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzaldehyde **24** (210 mg, 0.61 mmol) were dissolved in 5% AcOH/EtOH (5 mL) and heated to 60°C for 1h. The mixture was cooled, then $NaBH_3CN$ (60 mg, 0.95 mmol) was added and the mixture was stirred for 2h at rt. The mixture was diluted with saturated $NaHCO_3$ (10 mL) and extracted with EtOAc (20 mL). The organic layer was washed with brine (10 mL), dried ($MgSO_4$), filtered, concentrated and purified by flash column chromatography (SiO_2, MeOH/DCM gradient) to afford the title compound **E11** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.11 (s, 2H), 7.26 (d, J = 2.0 Hz, 1H), 7.04 (dd, J = 2.0, 8.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 4.50 (m, 1H), 4.03 (m, 2H), 3.69 (m, 2H), 3.34 (s, 2H), 2.57 (m, 3H), 2.39 (q, J = 7.6 Hz, 2H), 2.24 (m, 2H), 1.87 (m, 8H), 1.12 (t, J = 7.6 Hz, 3H); MS m/z for $(M+H)^+$ $C_{24}H_{31}ClN_5O$ calc. 440.2, found 440.1.

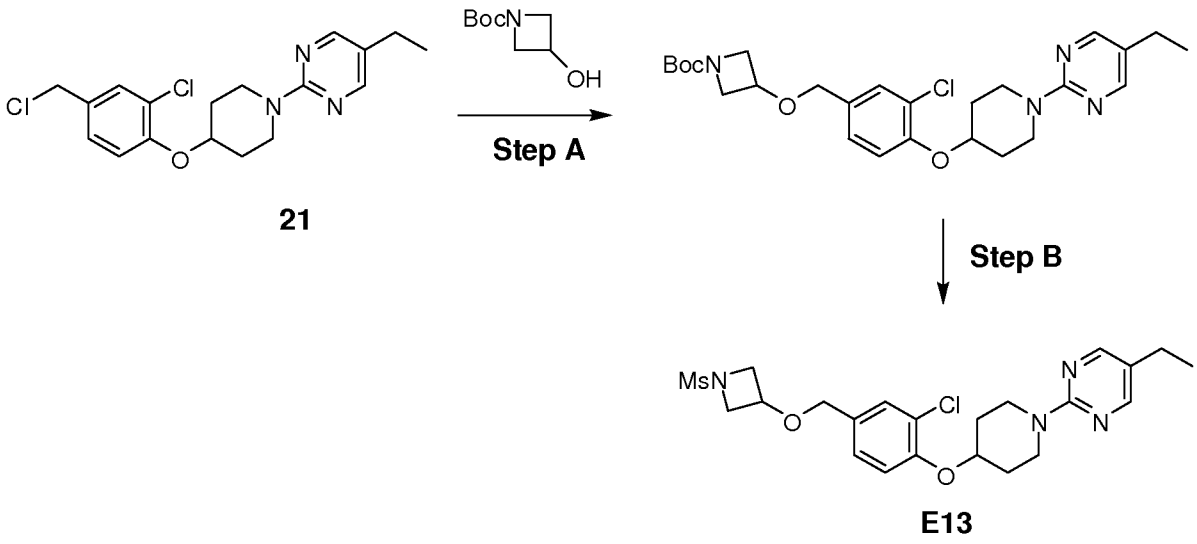
Example E12: 2-(4-(2-chloro-4-((4-(2-methyl-2H-tetrazol-5-yl)piperidin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine.



E12

[00169] By following the same procedures as **E10** except using 1-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)piperidine-4-carbonitrile **E11** as the nitrile, the title compound **E12** was obtained: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.11 (s, 2H), 7.30 (d, J = 2.4 Hz, 1H), 7.09 (dd, J = 2.0, 8.4 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 4.51 (m, 1H), 4.23 (s, 3H), 4.02 (m, 2H), 3.68 (m, 2H), 3.38 (s, 2H), 2.86 (m, 3H), 2.39 (q, J = 7.6 Hz, 2H), 1.85 (m, 10H), 1.12 (t, J = 7.6 Hz, 3H); MS m/z for $(M+H)^+$ $C_{25}H_{34}ClN_8O$ calc. 497.2, found 497.2.

Example E13: 2-(4-(2-Chloro-4-((1-(methylsulfonyl)azetidin-3-yloxy)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine.



21

Step A

Step B

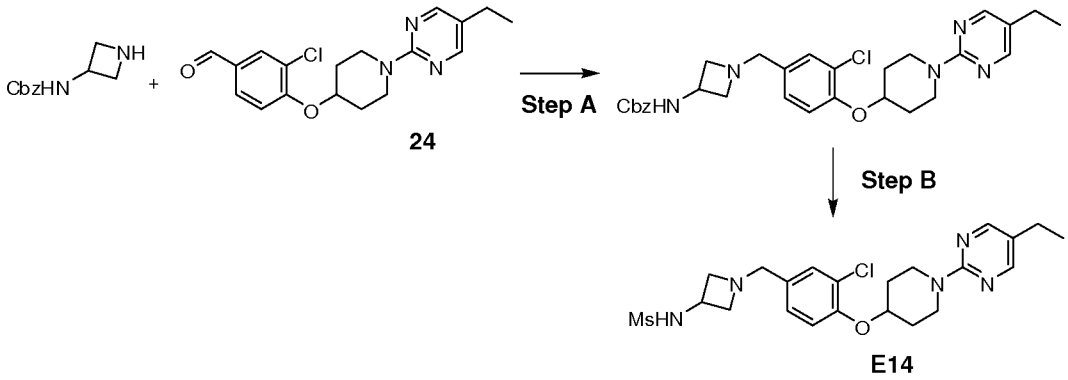
E13

[00170] **Step A:** 2-(4-(2-Chloro-4-(chloromethyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine **21** (66 mg, 0.18 mmol), 1-boc-3-hydroxyazetidine (38 mg, 0.22 mmol)

and Cs_2CO_3 (118 mg, 0.36 mmol) were dissolved in AcN (5 mL) and heated at 60°C for 2h. The mixture was cooled, filtered and concentrated to provide N-*tert*-butyl 3-(3-chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyloxy)azetidine-1-carboxylate, which was used without further purification in the next step. MS m/z for $(M+H)^+$ $C_{26}H_{36}ClN_4O_4$ calc. 503.2, found 503.1.

[00171] **Step B:** By following the same procedure as in **E2 Step D** the title compound **E13** was obtained: ^1H NMR (400 MHz, $CDCl_3$) δ = 8.21 (s, 2H), 7.28 (d, J = 2.0 Hz, 1H), 7.09 (dd, J = 2.0, 8.4 Hz, 1H), 6.90 (d, J = 8.8 Hz, 1H), 4.59 (m, 1H), 4.31 (s, 2H), 4.26 (m, 1H), 3.97 (m, 4H), 3.90 (m, 2H), 3.78 (m, 2H), 2.81 (s, 3H), 2.44 (q, J = 7.6 Hz, 2H), 1.92 (m, 5H), 1.24 (t, J = 7.6 Hz, 3H); MS m/z for $(M+H)^+$ $C_{22}H_{30}ClN_4O_4S$ calc. 481.2, found 481.1.

Example E14: 2-(4-(2-Chloro-4-((1-(methylsulfonyl)azetidin-3-yloxy)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine.

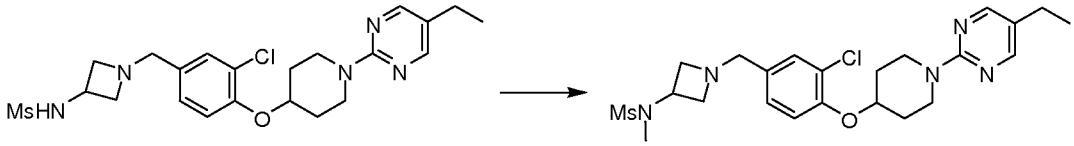


[00172] **Step A:** By following the same procedure as in **A1 Step C** except using benzyl azetidin-3-ylcarbamate as the amine and 3-chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzaldehyde **24** as the aldehyde, benzyl 1-(3-chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)azetidin-3-ylcarbamate was obtained. MS m/z for $(M+H)^+$ $C_{29}H_{35}ClN_5O_3$ calc. 536.3, found 536.3.

[00173] **Step B:** Benzyl 1-(3-chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)azetidin-3-ylcarbamate (82 mg, 0.15 mmol) was dissolved in a 1:1 mixture of EtOH and EtOAc (5 mL). Pd/C (10 mg of 10%, wet) was added and the mixture was stirred under H_2 (1 atm) for 12h. The mixture was filtered through a 0.2 μm syringe filter and

concentrated. The residue was dissolved in THF (2 mL), NEt_3 (42 μL, 0.30 mmol) was added and this mixture was added dropwise to a solution of methanesulfonyl chloride (13 μL, 0.16 mmol) in THF (2 mL) and stirred at rt for 2h. The mixture was concentrated and purified by reverse-phase HPLC (H_2O/AcN gradient) to provide the title compound **E14** as a white powder: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.20 (s, 2H), 7.30 (d, J = 2.4 Hz, 1H), 7.11 (dd, J = 2.4, 8.4 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 4.60 (m, 1H), 4.11 (s, 3H), 3.79 (m, 2H), 3.71 (m, 2H), 3.56 (s, 2H), 3.05 (m, 2H), 2.96 (s, 3H), 2.48 (q, J = 7.6 Hz, 2H), 2.01 (m, 3H), 1.91 (m, 2H), 1.21 (t, J = 7.6 Hz, 3H); MS m/z for $(M+H)^+$ $C_{22}H_{31}ClN_5O_3S$ calc. 480.2, found 480.1.

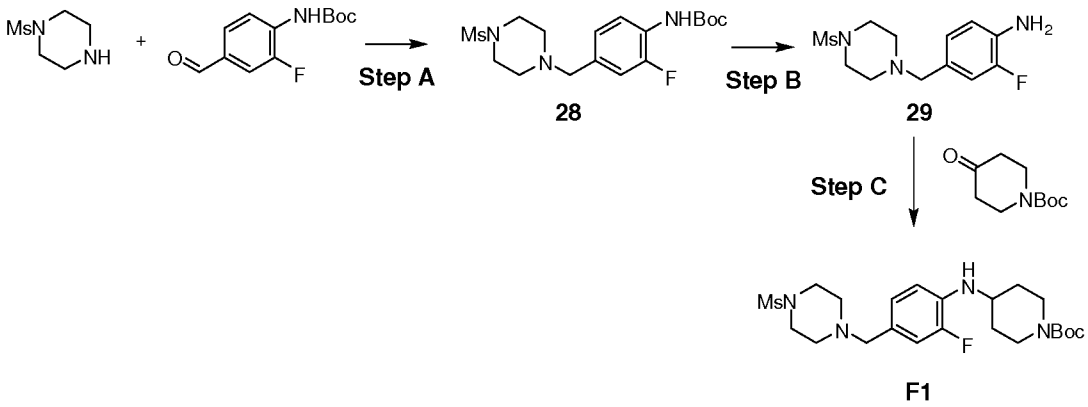
Example E15: N-(1-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)azetidin-3-yl)-N-methylmethanesulfonamide.



E14 **E15**

[00174] 2-(4-(2-Chloro-4-((1-(methylsulfonyl)azetidin-3-yloxy)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine (18 mg, 0.038 mmol) was dissolved in THF (2 mL). NaH (2 mg, 0.046 mmol) was added and the mixture was heated at 60°C for 1h. The mixture was cooled, then iodomethane (4.7 μL, 0.076 mmol) was added and the mixture was stirred at 60°C for 12h. The reaction was quenched with H_2O (5 mL), and the mixture was extracted with EtOAc (10 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated and purified by reverse-phase HPLC (H_2O/AcN gradient) to provide the title compound **E15** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.11 (s, 2H), 7.23 (d, J = 2.0 Hz, 1H), 7.02 (dd, J = 2.4, 8.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 4.51 (m, 1H), 4.14 (m, 1H), 4.03 (m, 2H), 3.69 (m, 2H), 3.48 (m, 3H), 3.09 (m, 2H), 2.80 (s, 3H), 2.68 (s, 3H), 2.39 (q, J = 7.6 Hz, 2H), 1.90 (m, 3H), 1.83 (m, 2H), 1.12 (t, J = 7.6 Hz, 3H); MS m/z for $(M+H)^+$ $C_{23}H_{33}ClN_5O_3S$ calc. 494.2, found 494.1.

Example F1: N-*tert*-Butyl 4-(2-fluoro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenylamino)-piperidine-1-carboxylate.



[00175] **Step A:** N-*tert*-Butyl 2-fluoro-4-formylphenylcarbamate (767 mg, 3.2 mmol) and 1-methanesulfonylpiperazine (580 mg, 3.53 mmol) were dissolved in 5% AcOH/95% EtOH (20 mL) and the mixture was heated at 60°C for 1 h. The reaction was cooled, then $NaBH_3CN$ (603 mg, 9.60 mmol) was added and the mixture was stirred at rt for 2h. The reaction was cooled, diluted with sat. aq. $NaHCO_3$ (50 mL), and extracted with EtOAc (50 mL). The organic layer was washed with brine, dried ($MgSO_4$), filtered, concentrated and purified by flash column chromatography (SiO_2, EtOAc/Hexane gradient) to give N-*tert*-butyl 2-fluoro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenylcarbamate **28** as a white powder: ^1H NMR (400 MHz, $CDCl_3$) δ = 8.03 (m, 1H), 7.06 (m, 2H), 6.70 (s, 1H), 3.49 (s, 2H), 3.26 (m, 4H), 2.80 (s, 3H), 2.55 (m, 4H), 1.55 (s, 9H). MS *m/z* for $(M+H)^+$ $C_{17}H_{27}FN_3O_4S$ calc. 388.2, found 388.2.

[00176] **Step B:** N-*tert*-Butyl 2-fluoro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenylcarbamate **28** (742 mg, 1.91 mmol) was dissolved in a mixture of DCM (5 mL) and a 4 N solution of HCl in dioxane (5 mL) and stirred at rt for 1 h. The mixture was basified with sat. aq. $NaHCO_3$ (40 mL) and extracted with DCM (20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give 2-fluoro-4-((4-(methylsulfonyl)-piperazin-1-yl)methyl)aniline **29** (481 mg, 88%), which was used directly in Step B without further purification: MS *m/z* for $(M+H)^+$ $C_{12}H_{19}FN_3O_2S$ calc. 288.1, found 288.1.

[00177] **Step C:** 2-Fluoro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)aniline **29** (481 mg, 1.67 mmol) and 4-*oxo*-1-Boc-piperidine (367 mg, 1.84 mmol) were dissolved in 5%

AcOH/EtOH (10 mL) and the mixture was heated at 60°C for 1h. The reaction was cooled, then $NaBH_3CN$ (314 mg, 5.01 mmol) was added and the mixture was stirred at rt for 2 h. The reaction was cooled, diluted with sat. aq. $NaHCO_3$ (50 mL), and extracted with EtOAc (50 mL). The organic layer was washed with brine, dried ($MgSO_4$), filtered, concentrated and purified by flash column chromatography (SiO_2, MeOH/DCM gradient) to give the title compound **E1** as a white powder: ^1H NMR (400 MHz, $CDCl_3$) δ = 7.03 (m, 2H), 6.71 (t, J = 8.4 Hz, 1H), 4.07 (m, 4H), 3.48 (m, 2H), 2.97 (m, 2H), 2.88 (s, 3H), 2.05 (m, 2H), 1.49 (s, 9H), 1.42 (m, 2H). MS *m/z* for $(M+Na)^+$ $C_{22}H_{36}FN_4O_4SNa$ calc. 493.2, found 493.1.

Biological Assays

[00178] Generation of Stable Cell Line

[00179] 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 2mM L-glutamine. The cells are transfected with a DNA mixture containing human GPR119 in pcDNA5/FRT vector and the pOG44 vector (1:9) using Fugene6 (Roche), according to the manufacturer's instruction. After 48 hours, the medium is changed to medium supplemented with 400μg/ml hygromycin B to initiate the selection of stably transfected cells.

[00180] Cyclic AMP Assay in Stable Cell Line

[00181] To test the activity of compounds of the invention, Flp-In-CHO-hGPR119 cells are harvested and resuspended in DMEM plus 3% lipid-depleted fetal bovine serum. Forth μl of cells are plated in 384 well plates at a density of 15,000 cells/well. IBMX (3-isobutyl-1-methyl-xanthine) is added to the cells to a final concentration of 1mM, followed by the addition of 500nl of the compound to be tested. The cells are incubated at 37°C for 30 minutes. Equal volume (20μl) of the HTRF reagents, anti-cAMP-Cryptate and cAMP-XL665, are added to the cells. The plates are incubated at room temperature for 1 hour and read on a HTRF reader according to the manufacturer's instruction.

[00182] Compounds of Formula I, in free form or in pharmaceutically acceptable salt form, produced a concentration-dependent increase in intracellular cAMP level. Compound 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. For example, the following tables show some EC_{50} data for a representative sample of compounds of the invention:

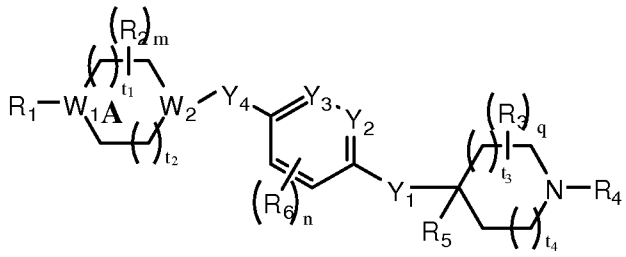
Table of Biological Activity

Example	CHO-GPR119-HTRF (3158) μM
A1	0.056
A2	0.203
A6	0.020
A8	0.005
A13	0.867
A14	0.313
B2	0.127
B3	0.022
B6	0.220
B11	0.013
B13	0.465
B17	0.009
C2	0.187
C5	0.044
C9	0.136
D1	0.008
E2	0.003
E4	0.812
E12	2.68
E15	0.114

[00183] 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:

A can have up to 2 ring $-CH_2-$ group substituted with $-C(O)-$ and can be partially unsaturated with up to 2 double bonds;

m and n are independently 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 hydrogen, cyano, $-X_1S(O)_{0-2}X_2R_{6a}$, $-X_1N(S(O)_{0-2}X_2R_{6a})R_{6a}$, $-X_1S(O)_{0-2}X_2OR_{6a}$, $-X_1S(O)_{0-2}X_2C(O)R_{6a}$, $-X_1C(O)OR_{6a}$, $-X_1R_{6a}$, $-X_1S(O)_{0-2}X_2C(O)OR_{6a}$ 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, C_{1-6}alkyl, C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-8}heterocycloalkyl and C_{1-8}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, 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_2 and R_3 are independently selected from 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, $-C(O)R_8$, and $-C(O)OR_8$; wherein R_8 is selected from hydrogen and C_{1-6}alkyl;

R_4 is selected from R_9 and $-C(O)OR_9$; wherein R_9 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_9 is optionally substituted with 1 to 3 radicals independently selected from halo, cyano, 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, halo-substituted-C_{1-6}alkoxy and $-C(O)OR_{17}$, $-C(O)R_{19}$ and $-C(O)NR_{17}R_{18}$; wherein R_{17} and R_{18} are independently selected from hydrogen and C_{1-6}alkyl; or R_{17} and R_{18} together with the nitrogen atom to which R_{17} and R_{18} are attached form C_{3-8}heterocycloalkyl; R_{19} is selected from C_{1-6}alkyl and C_{3-8}heterocycloalkyl; wherein said cycloalkyl or heterocycloalkyl substituents of R_9 are optionally further substituted with 1 to 3 C_{1-6}alkyl radicals;

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;

R_6 is selected from hydroxy, nitro, cyano, halo, C_{1-6}alkyl, C_{2-6}alkenyl, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{2-6}alkenyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-8}heterocycloalkyl, C_{3-8}cycloalkyl and $-X_3OR_{20}$, $-NR_{20}X_3OR_{21}$, $-C(O)OR_{20}$; wherein X_3 is selected from a bond, C_{1-4}alkylene and C_{2-4}alkenylene; R_{20} and R_{21} are independently selected from hydrogen and C_{1-6}alkyl;

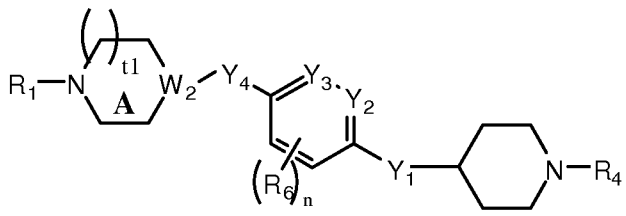
W_1 and W_2 are independently selected from CR_{10} and N; wherein R_{10} is selected from hydrogen and C_{1-6}alkyl;

Y_1 is selected from NR_{11}, O and S; wherein R_{11} is selected from hydrogen and C_{1-6}alkyl;

Y_2 and Y_3 are independently selected from CH and N;

Y_4 is selected from CH_2, OCH_2 and NR_{15}; wherein R_{15} is selected from hydrogen and C_{1-6}alkyl; or the pharmaceutically acceptable salts thereof.

2. The compound of claim 1 of Formula Ia:



Ia

in which:

A can have a ring $-CH_2-$ group substituted with $-C(O)-$;

t1 is selected from 0 and 1;

R_1 is selected from hydrogen, cyano, $-X_1S(O)_{0-2}X_2R_{6a}$, $-X_1S(O)_{0-2}X_2OR_{6a}$, $-X_1C(O)OR_{6a}$, $-X_1S(O)_{0-2}X_2C(O)R_{6a}$, $-X_1N(S(O)_{0-2}X_2R_{6a})R_{6a}$, $-X_1R_{6a}$, $-X_1S(O)_{0-2}X_2C(O)OR_{6a}$ 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, C_{1-6}alkyl, C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-8}heterocycloalkyl and C_{1-8}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, 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_4 is selected from R_9 and $-C(O)OR_9$; wherein R_9 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_9 is optionally substituted with 1 to 3 radicals independently selected from halo, cyano, 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, halo-substituted-C_{1-6}alkoxy and $-C(O)OR_{17}$, $-C(O)R_{19}$ and $-C(O)NR_{17}R_{18}$; wherein R_{17} and R_{18} are independently selected from hydrogen and C_{1-6}alkyl; or R_{17} and R_{18} together with the nitrogen atom to which R_{17} and R_{18} are attached form C_{3-8}heterocycloalkyl; R_{19} is selected from C_{1-6}alkyl and C_{3-8}heterocycloalkyl; wherein said cycloalkyl or heterocycloalkyl substituents of R_9 are optionally further substituted with 1 to 3 C_{1-6}alkyl radicals;

R_6 is selected from hydroxy, nitro, cyano, halo, C_{1-6}alkyl, C_{2-6}alkenyl, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{2-6}alkenyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-8}heterocycloalkyl, C_{3-8}cycloalkyl and $-X_3OR_{20}$, $-NR_{20}X_3OR_{21}$, $-C(O)OR_{20}$; wherein X_3 is selected from a bond, C_{1-4}alkylene and C_{2-4}alkenylene; R_{20} and R_{21} are independently selected from hydrogen and C_{1-6}alkyl;

W_2 is selected from CR_{10} and N; wherein R_{10} is selected from hydrogen and C_{1-6}alkyl;

Y_1 is selected from NH, O and S; and

Y_2 and Y_3 are independently selected from CH and N;

Y_4 is selected from CH_2, OCH_2 and NR_{15}; wherein R_{15} is selected from hydrogen and C_{1-6}alkyl.

3. The compound of claim 2 in which: A can have a ring $-CH_2-$ group substituted with –C(O)–; t1 is selected from 0 and 1; and R_1 is selected from hydrogen, cyano, $-S(O)_{0-2}X_2R_{6a}$, $-X_1N(S(O)_{0-2}X_2R_{6a})R_{6a}$, $-X_1R_{6a}$, $-X_1C(O)OR_{6a}$ and $-S(O)_{0-2}X_2OR_{6a}$; wherein X_1 is selected from a bond and C_{1-4}alkylene; X_2 is selected from a bond and C_{1-4}alkylene; R_{6a} is selected from hydrogen, C_{1-6}alkyl and C_{1-10}heteroaryl optionally substituted with C_{1-6}alkyl.

4. The compound of claim 3 in which: R_4 is selected from R_9 and $-C(O)OR_9$; wherein R_9 is selected from *tert*-butyl, pyridinyl, pyrimidinyl, 1,2,4-oxadiazol-5-yl, tetrazolyl and cyclopropyl; wherein said pyridinyl, pyrimidinyl, 1,2,4-oxadiazol-5-yl, tetrazolyl or cyclopropyl of R_9 is optionally substituted with a radical selected from halo, cyano, trifluoromethyl, isopropyl, methyl, ethyl, methoxy-carbonyl, dimethyl-amino-carbonyl, amino-carbonyl and morpholino-carbonyl.

5. The compound of claim 4 in which R_6 is selected from fluoro, chloro, bromo, trifluoromethoxy, methyl, methoxy, methoxy-carbonyl, 3-methoxyprop-1-enyl, methoxy-propyl, vinyl, phenyl, pyrazolyl, 5-chloropent-1-enyl, hydroxy-propyl, methoxy-ethyl-amino and morpholino; W_2 is selected from CH and N; Y_1 is selected from NH, O and S; and Y_2 and Y_3 are independently selected from CH and N; Y_4 is selected from CH_2, OCH_2 and NCH_3.

6. The compound of claim 5 selected from: 5-Ethyl-2-(4-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine; 5-ethyl-2-(4-(3-methyl-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine; 5-ethyl-2-(4-(3-methoxy-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine; 5-ethyl-2-(4-(3-fluoro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine; 2-(4-(3-chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; 5-ethyl-2-(4-(2-methyl-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine; 5-ethyl-2-(4-(2-

fluoro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine; 2-(4-(2-chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; 2-(4-(2-bromo-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; 5-ethyl-2-(4-(2-methoxy-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine; 5-ethyl-2-(4-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)-2-(trifluoromethoxy)phenoxy)piperidin-1-yl)pyrimidine; 2-(4-(2,3-difluoro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; 2-(4-(2-chloro-6-fluoro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; 5-ethyl-2-(4-(6-((4-(methylsulfonyl)piperazin-1-yl)methyl)pyridin-3-yloxy)piperidin-1-yl)pyrimidine; 5-ethyl-2-(4-(5-((4-(methylsulfonyl)piperazin-1-yl)methyl)pyridin-2-yloxy)piperidin-1-yl)pyrimidine; *tert*-Butyl 4-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidine-1-carboxylate; 1-methylcyclopropyl 4-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidine-1-carboxylate; 5-Fluoro-2-(4-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine; 1-(4-(1-(5-fluoropyridin-2-yl)piperidin-4-yloxy)benzyl)-4-(methylsulfonyl)piperazine; 1-(methylsulfonyl)-4-(4-(1-(5-(trifluoromethyl)pyridin-2-yl)piperidin-4-yloxy)benzyl)piperazine; 5-(4-(2-chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole; 3-(4-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)piperazin-1-ylsulfonyl)propan-1-ol; 5-Ethyl-2-(4-(4-((1-(methylsulfonyl)piperidin-4-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine; *tert*-Butyl 4-(2-fluoro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenylamino) piperidine-1-carboxylate; 1-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)-4-(methylsulfonyl)piperazin-2-one, methyl 2-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)benzoate; 1-methylcyclopropyl 4-(2-chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidine-1-carboxylate; methyl 2-(4-(2-chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine-5-carboxylate; 2-(4-(2-chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine; 5-bromo-2-(4-(2-chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)-phenoxy)piperidin-1-yl)pyrimidine; 5-chloro-2-(4-(2-chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine; 2-(4-(2-Chloro-4-((4-(methylsulfonyl)-piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine-5-carboxamide; 2-(4-(2-chloro-4-((4-

(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-N,N-dimethylpyrimidine-5-carboxamide; (2-(4-(2-chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidin-5-yl)(morpholino)methanone; 2-(4-(2-Chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine-5-carbonitrile; 2-(4-(2-Chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-(2H-tetrazol-5-yl)pyrimidine; 2-(4-(2-Chloro-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-(2-methyl-2H-tetrazol-5-yl)pyrimidine; (E)-5-Ethyl-2-(4-(2-(3-methoxyprop-1-enyl)-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)pyrimidine; 3-(2-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yloxy)-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenyl)propan-1-ol; 5-ethyl-2-(4-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)-2-vinylphenoxy)piperidin-1-yl)pyrimidine; 5-ethyl-2-(4-(5-((4-(methylsulfonyl)piperazin-1-yl)methyl)biphenyl-2-yloxy)piperidin-1-yl)pyrimidine; 5-ethyl-2-(4-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)-2-(1H-pyrazol-5-yl)phenoxy)piperidin-1-yl)pyrimidine; (E)-2-(4-(2-(5-chloropent-1-enyl)-4-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; (E)-4-(2-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yloxy)-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenyl)but-3-en-1-ol; 3-(2-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yloxy)-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenyl)propan-1-ol; 2-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yloxy)-N-(2-methoxyethyl)-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)aniline; 4-(2-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yloxy)-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenyl)morpholino; 2-(4-(2-Chloro-4-((1-(methylsulfonyl)piperidin-4-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; 3-(4-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)piperidin-1-ylsulfonyl)propan-1-ol; 2-(4-(2-chloro-4-((4-(methylsulfonyl)piperidin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; 2-(4-(2-Chloro-4-((2-methyl-4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; 2-(4-(2-Chloro-4-((2-methyl-4-(methylsulfonyl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; N-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)phenyl)-N-methyl-1-(methylsulfonyl)piperidin-4-amine; 4-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)piperazine-1-carbonitrile; 2-(4-(2-Chloro-4-((4-(2-methyl-2H-tetrazol-5-yl)piperazin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; 1-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)piperidine-4-carbonitrile; 2-(4-(2-chloro-4-((4-(2-

methyl-2H-tetrazol-5-yl)piperidin-1-yl)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; 2-(4-(2-Chloro-4-((1-(methylsulfonyl)azetidin-3-yloxy)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; 2-(4-(2-Chloro-4-((1-(methylsulfonyl)azetidin-3-yloxy)methyl)phenoxy)piperidin-1-yl)-5-ethylpyrimidine; and N-(1-(3-Chloro-4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yloxy)benzyl)azetidin-3-yl)-N-methylmethanesulfonamide.

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

8. 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.

9. The method of claim 8, wherein the compound of claim 1 directly contacts GPR119.

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

11. 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.

12. The method of claim 11, 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.

13. The method of claim 11, 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/US2009/039506

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D211/44 C07D401/04 C07D401/14 A61P3/04 A61P3/10
A61K31/497

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 A61P A61K

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/12190 A (ORTHO MCNEIL PHARM INC [US]) 14 February 2002 (2002-02-14) page 8, line 32 - page 9, line 3; claim 51; examples 9,20,25,28-32,54,56,67,72,50,59,62	1-3,7-13
X	DVORAK C A ET AL: "4-Phenoxypiperidines: Potent, Conformationally Restricted, Non-Imidazole Histamine H3 Antagonists" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 48, no. 6, 1 January 2005 (2005-01-01), pages 2229-2238, XP002470382 ISSN: 0022-2623 page 2232; examples 13d-13j,13n-13q; table 2	1-3

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[X] Further documents are listed in the continuation of Box C. [X] 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)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 June 2009	30/06/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Lange, Tim

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/039506

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007/167435 A1 (MUTAHI MWANGI W [KE] ET AL) 19 July 2007 (2007-07-19) page 46; examples 26,Step,2 pages 46,59; examples 73A,100A,101A	1-3,7-13
X	NARKHEDE, SACHIN S.; DEGANI, MARIAM S.: "Pharmacophore Refinement and 3D-QSAR Studies of Histamine H3 Antagonists" QSAR & COMBINATORIAL SCIENCE, vol. 26, no. 6, 2007, pages 744-753, XP002532155 medical use: page 744, left column, line 3 page 748; examples 91-93,95,101,102,104; table 1F	1-3,7-13
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; compound with CAS registry number 906743-38-2 ISHII, TAKAHIRO ET AL: "Preparation of pyridyl non-aromatic nitrogenated heterocyclic-1-carboxylate ester derivatives as FAAH inhibitors" XP002532214 retrieved from STN Database accession no. 2006:844745 abstract -& WO 2006/088075 A1 (ASTELLAS PHARMA INC., JAPAN) 24 August 2006 (2006-08-24)	1-4, 7-11,13
X	WO 2004/035556 A (GLAXO GROUP LTD [GB]; ANCLIFF RACHAEL [GB]; ELDRED COLIN DAVID [GB]; F) 29 April 2004 (2004-04-29) medical use: Page 4, line 42 page 20; example D6	1-4,7-13

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1

Novelty overflow for claim 1:
The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim 1 may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, the search was performed taking into consideration the non-compliance in determining the extent of the search of claim 1.

Lack of support of claim 1:
Furthermore, the present claim 1 relates to an extremely large number of possible compounds. Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the compounds claimed, see pages 26-67 of the description of the present application. The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of claim 1 (PCT Guidelines 9.19 and 9.23).

Therefore, the search of claim1-13 was restricted to: Compounds of structural formula Ia (claim 2), their generalization by the variables as given in claim 1, pharmaceutical composition with them (claim 7) and their alleged biological effect as defined by claims 8-13.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/039506

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/039506

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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