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

(19) **World Intellectual Property Organization**
International Bureau

(43) **International Publication Date**
24 January 2013 (24.01.2013)

WIPO | PCT

(10) **International Publication Number**
WO 2013/012844 A1

(51) **International Patent Classification**:
C07D 401/12 (2006.01)
C07D 401/14 (2006.01)
C07D 403/12 (2006.01)
C07D 405/12 (2006.01)
C07D 405/14 (2006.01)
C07D 409/12 (2006.01)
C07D 413/12 (2006.01)
C07D 413/14 (2006.01)
C07D 417/12 (2006.01)
C07D 471/04 (2006.01)
C07D 513/04 (2006.01)
C07D 231/12 (2006.01)
A61K 31/415 (2006.01)
A61K 31/4155 (2006.01)
A61P 9/00 (2006.01)

(21) **International Application Number**:
PCT/US2012/047024

(22) **International Filing Date**:
17 July 2012 (17.07.2012)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
61/509,155 19 July 2011 (19.07.2011) US

(71) **Applicant** *(for all designated States except US)*: **BOEHRINGER INGELHEIM INTERNATIONAL GMBH** [DE/DE]; Binger Strasse 173, 55216 Ingelheim am Rhein (DE).

(72) **Inventors; and**

(75) **Inventors/Applicants** *(for US only)*: **HEIM-RIETHER, Alexander** [DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim am Rhein (DE). **LIANG, Shuang** [CN/US]; Boehringer Ingelheim USA Corp., c/o VP, IP Legal, 900 Ridgebury Rd., P.O. Box 368, Ridgefield, Connecticut 06877-0368 (US). **PADYANA, Anil Kumar** [IN/US]; Boehringer Ingelheim USA Corp., c/o VP, IP Legal, 900 Ridgebury Rd., P.O. Box 368, Ridgefield, Connecticut 06877-0368 (US). **TAYLOR, Steven John** [US/US]; Boehringer Ingelheim USA Corp., c/o VP, IP Legal, 900 Ridgebury Rd., P.O. Box 368, Ridgefield, Connecticut 06877-0368 (US). **ZHANG, Qiang** [CA/US]; Boehringer Ingelheim USA Corp., c/o VP, IP Legal, 900 Ridgebury Rd., P.O. Box 368, Ridgefield, Connecticut 06877-0368 (US).

(74) **Agents**: **MORRIS, Michael, P.** et al.; Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877-0368 (US).

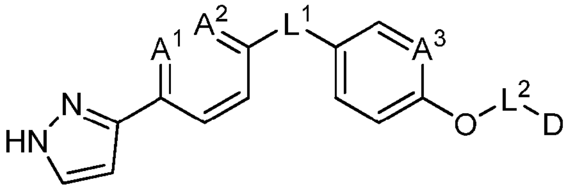
(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE,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

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

[Continued on next page]

(54) **Title**: ARYLPYRAZOLE ETHERS AS INHIBITORS OF LEUKOTRIENE A4 HYDROLASE

(I)



(57) **Abstract**: The present invention relates to compounds of formula I or a pharmaceutically acceptable salt thereof, wherein A^1, A^2, A^3, L^1, L^2 and D are as defined herein. The compounds of formula (I) are useful as inhibitors of leukotriene A_4 hydrolase (LTA4H) and treating LTA4H related disorder. The present invention also relates to pharmaceutical compositions comprising the compounds of formula (I), methods of using these compounds in the treatment of various diseases and disorders, and processes for preparing these compounds.

WO 2013/012844 A1

Published:

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

ARYLPYRAZOLE ETHERS AS INHIBITORS OF LEUKOTRIENE A4 HYDROLASE

Field of the Invention

This invention relates to arylpyrazole ethers that are useful as inhibitors of leukotriene A_4 hydrolase (LTA_4H) and are thus useful for treating a variety of diseases and disorders that are mediated or sustained through the activity of leukotrienes including asthma, allergy and cardiovascular diseases including atherosclerosis, myocardial infarction and stroke. This invention also relates to pharmaceutical compositions comprising these compounds, methods of using these compounds in the treatment of various diseases and disorders, processes for preparing these compounds and intermediates useful in these processes.

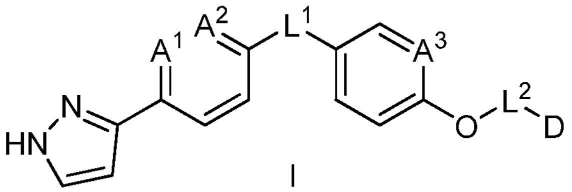
Background of the Invention

Leukotrienes (LT) are oxidized lipids that are produced by several cell types including neutrophils, mast cells, eosinophils, basophils, monocytes and macrophages. The first committed step in the intracellular synthesis of LTs involves oxidation of arachidonic acid by 5-lipoxygenase (5-LO) to leukotriene A_4 (LTA_4), a process requiring the 5-lipoxygenase-activating protein (FLAP). Leukotriene A_4 hydrolase (LTA_4H) catalyzes the hydrolysis of LTA_4 to produce leukotriene B_4 (LTB_4). Through the engagement of the LTB_4 receptors (BLT1, BLT2), LTB_4 stimulates an array of pro-inflammatory responses (leukocyte chemotaxis, cytokine release, etc.). The leukotriene pathway has been implicated in diseases in which inflammation is a critical component of the pathology; these include cancer, asthma, atherosclerosis, colitis, glomerularnephritis, and pain (for a review, see M. Peters-Golden and W.R. Henderson, Jr., M.D., N. Engl. J. Med., 2007, 357, 1841-1854).

Brief Summary of the Invention

The present invention provides novel compounds which inhibit leukotriene A_4 hydrolase (LTA_4H) and are thus useful for treating a variety of diseases and disorders that are mediated or sustained through the activity of leukotrienes, including allergic, pulmonary, fibrotic, inflammatory and cardiovascular diseases and cancer.

In one embodiment, the invention relates to a compound of formula (I):



I

,

or a pharmaceutically acceptable salt thereof, wherein:

A^1, A^2 and A^3 are each independently CH or N;

L^1 is a linker selected from –O- and -CH_2-;

L^2 is absent or a -(C_1-C_6)alkylene- linker; wherein said -(C_1-C_6)alkylene- linker is optionally substituted with one to three groups selected from –OH, halo, -(C_1-C_6)alkyl;

D is a ring selected from

(a) -(C_3-C_7)cycloalkyl, (C_6-C_{10})aryl, and -(5- to 11-membered)heteroaryl;
(b) -(4- to 11-membered)heterocycloalkyl, comprising an O or S ring atom and optionally 1 to 3 additional ring heteroatoms selected from N, O, and S;
(c) 4-8 member monocyclic heterocyclic comprising a N ring atom and 1 to 3 additional ring heteroatoms selected from N, O, and S;
(d) a 6 to 11-membered fused bicyclic, bridged bicyclic or spirocyclic heterocyclic radical comprising a N ring atom and optionally 1 to 3 additional ring heteroatoms selected from N, O, and S; and
(e) a group selected from 2-oxo-pyrrolidin-1-yl, 2-oxo-pyrrolidin-3-yl, 2-oxo-pyrrolidin-5-yl, 1-methyl-2-oxo-pyrrolidin-4-yl, and 2-oxo-piperidin-5-yl

wherein each of said D rings is optionally substituted with one to three R^1 groups; and wherein each of said D rings is further optionally substituted, where possible, by one or two groups independently selected from (=O) and (=S);

each R^1 is independently selected from halo, -OH, -CF_3, -CN, -(C_1-C_6)alkyl, -O(C_1-C_6)alkyl, -C(O)R^2, -C(O)OR^2, -C(O)N(R^2)$_2$, -N(R^2)$_2$, -N(R^2)C(O)R^2, -S(O)$_2$$R^2$, -N($R^2$)-S(O)$_2$-$R^2$, -($C_3$-$C_6$)cycloalkyl, -(5- to 11-membered)heterocycloalkyl, -(C_6-C_{10})aryl, and -(5- to 11-membered)heteroaryl; wherein each of said, -(C_1-C_6)alkyl, -O(C_1-C_6)alkyl, -(C_3-C_6)cycloalkyl, -(5- to 11-membered)heterocycloalkyl, -(C_6-C_{10})aryl, and -(5- to 11-membered)heteroaryl of said R^1 group is optionally substituted with one to three groups selected from halo, -OH, -CF_3, -(C_1-C_6)alkyl, -C(O)OH, -C(O)OC_1-C_6)alkyl, -C(O)(C_1-C_6)alkyl), -NH_2, -NH(C_1-C_6)alkyl, N((C_1-C_6)alkyl)$_2$ and –CN;

each R^2 is independently selected from the group consisting of -H, -(C_1-C_6)alkyl, -(C_3-C_6)cycloalkyl, -(5- to 11-membered)heterocycloalkyl, -(C_6-C_{10})aryl, and -(5- to 11-membered)heteroaryl; wherein each of said, -(C_1-C_6)alkyl, -O(C_1-C_6)alkyl, -(C_3-C_6)cycloalkyl, -(5- to 11-membered)heterocycloalkyl, -(C_6-C_{10})aryl, and -(5- to 11-membered)heteroaryl of said R^2 group is optionally independently substituted by one to three groups selected from halo, -OH, -CF_3, -(C_1-C_6)alkyl, -NH_2, -NH(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$ and -CN.

This invention also relates to pharmaceutical compositions comprising the compounds of formula (I), methods of using these compounds in the treatment of various diseases and disorders, processes for preparing these compounds, and intermediates useful in these preparative processes.

Detailed Description of the Invention

It will be understood that the terms “compounds of formula (I)” and “compounds of the invention” have the same meaning unless indicated otherwise.

In its broadest embodiment (Embodiment 1), the invention relates to compounds of formula (I), and pharmaceutically acceptable salts thereof, as described above in the summary of the invention.

Embodiment 2: In another embodiment, the invention relates to a compound of formula (I) as described in Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein A^1, A^2 and A^3 are each CH.

Embodiment 3: In another embodiment, the invention relates to a compound of formula (I) as described in Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein A^1 and A^3 are each CH, and A^2 is N.

Embodiment 4: In another embodiment, the invention relates to a compound of formula (I) as described in Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein A^1 and A^2 are each CH, and A^3 is N.

Embodiment 5: In another embodiment, the invention relates to a compound of formula (I) as described in Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein A^2 and A^3 are each CH, and A^1 is N.

Embodiment 6: In another embodiment, the invention relates to a compound of formula (I) as described in any of the Embodiments 1-5, or a pharmaceutically acceptable salt thereof, wherein L^1 is -O-.

Embodiment 7: In another embodiment, the invention relates to a compound of formula (I) as described in any of the Embodiments 1-5, or a pharmaceutically acceptable salt thereof, wherein L^1 is $-CH_2-$.

Embodiment 8: In another embodiment, the invention relates to a compound of formula (I) as described in any of the Embodiments 1-7, or a pharmaceutically acceptable salt thereof, wherein L^2 is absent.

Embodiment 9: In another embodiment, the invention relates to a compound of formula (I) as described in any of the Embodiments 1-7, or a pharmaceutically acceptable salt thereof, wherein L^2 is a $-(C_1-C_6)$alkylene- linker; and wherein said $-(C_1-C_6)$alkylene- linker is optionally substituted with one to three groups selected from –OH, halo, $-(C_1-C_6)$alkyl.

Embodiment 10: In another embodiment, the invention relates to a compound of formula (I) as described in any of the Embodiments 1-8, or a pharmaceutically acceptable salt thereof, wherein L^2 is methylene, ethylene, or propylene; and wherein each of said methylene, ethylene and propylene is optionally substituted with methyl.

Embodiment 11: In another embodiment, the invention relates to a compound of formula (I) as described in any of the Embodiments 1-10, or a pharmaceutically acceptable salt thereof, wherein said D is a ring selected from -(C_3-C_7)cycloalkyl, (C_6-C_{10})aryl, and -(5- to 11-membered)heteroaryl; wherein each of said -(C_3-C_7)cycloalkyl, (C_6-C_{10})aryl, and -(5- to 11-membered)heteroaryl is optionally substituted with one to three R^1 groups; and wherein each of said -(C_3-C_7)cycloalkyl, (C_6-C_{10})aryl, and -(5- to 11-membered)heteroaryl is further optionally substituted, where possible, by one or two groups independently selected from (=O) and (=S).

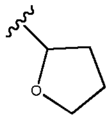
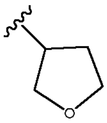
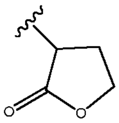
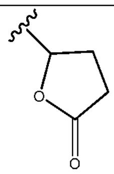
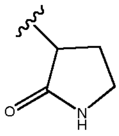
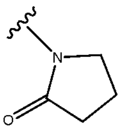
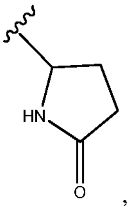
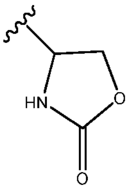
Embodiment 12: In another embodiment, the invention relates to a compound of formula (I) as described in any of the Embodiments 1-10, or a pharmaceutically acceptable salt thereof, wherein said ring D is a -(4- to 11-membered)heterocycloalkyl comprising an O or S ring atom and optionally 1 to 3 additional ring heteroatoms selected from N, O, and S; wherein said -(4- to 11-membered)heterocycloalkyl is optionally substituted with one to three R^1 groups; and wherein said -(4- to 11-membered)heterocycloalkyl is further optionally substituted, where possible, by one or two groups independently selected from (=O) and (=S).

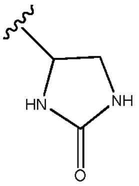
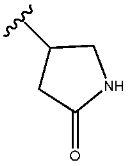
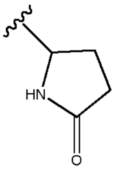
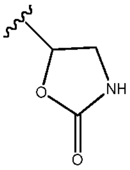
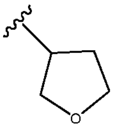
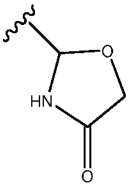
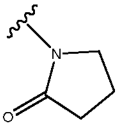
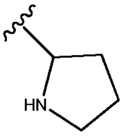
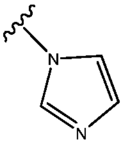
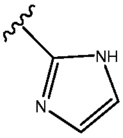
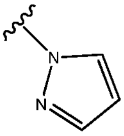
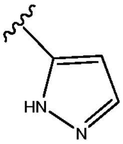
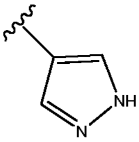
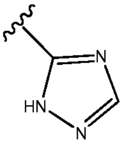
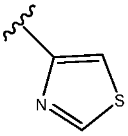
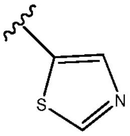
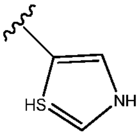
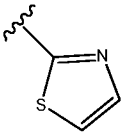
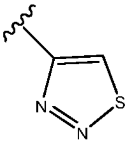
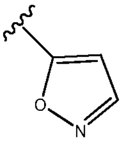
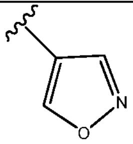
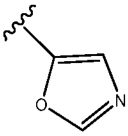
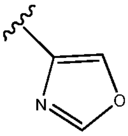
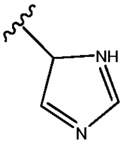
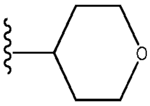
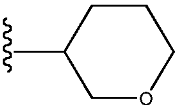
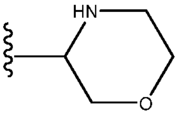
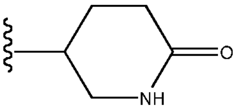
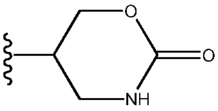
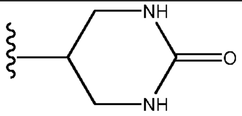
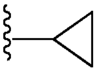
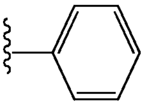
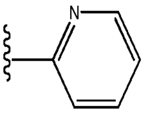
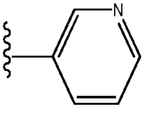
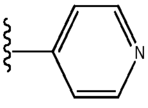
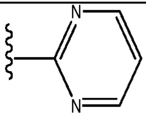
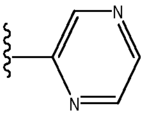
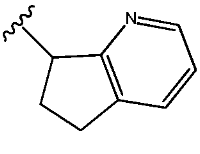
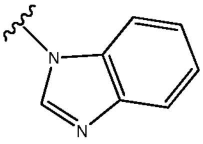
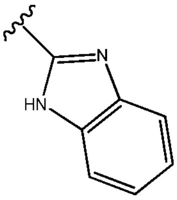
Embodiment 13: In another embodiment, the invention relates to a compound of formula (I) as described in any of the Embodiments 1-10, or a pharmaceutically acceptable salt thereof, wherein said ring D is a 4-8 member monocyclic heterocyclic comprising a N ring atom and 1 to 3 additional ring heteroatoms selected from N, O, and S; wherein said 4-8 member monocyclic heterocyclic is optionally substituted with one to three R^1 groups; and wherein said 4-8 member monocyclic heterocyclic is further optionally substituted, where possible, by one or two groups independently selected from (=O) and (=S).

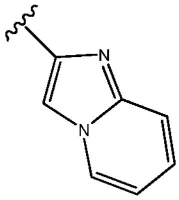
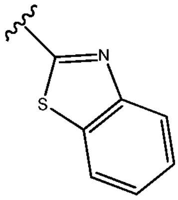
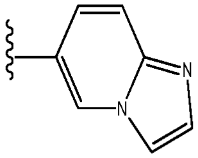
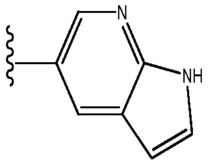
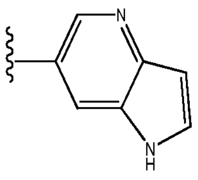
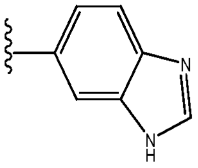
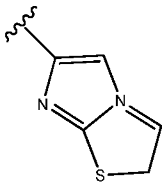
Embodiment 14: In another embodiment, the invention relates to a compound of formula (I) as described in any of the Embodiments 1-10, or a pharmaceutically acceptable salt thereof, wherein said ring D is a 6 to 11-membered fused bicyclic, bridged bicyclic or spirocyclic heterocyclic radical comprising a N ring atom and optionally 1 to 3 additional ring heteroatoms selected from N, O, and S; wherein said 6 to 11-membered fused bicyclic, bridged bicyclic or spirocyclic heterocyclic radical is optionally substituted with one to three R^1 groups; and wherein said 6 to 11-membered fused bicyclic, bridged bicyclic or spirocyclic heterocyclic radical is further optionally substituted, where possible, by one or two groups independently selected from (=O) and (=S).

Embodiment 15: In another embodiment, the invention relates to a compound of formula (I) as described in any of the Embodiments 1-10, wherein said ring D is selected from 2-oxo-pyrrolidin-1-yl, 2-oxo-pyrrolidin-3-yl, 2-oxo-pyrrolidin-5-yl, 1-methyl-2-oxo-pyrrolidin-4-yl, and 2-oxo-piperidin-5-yl; wherein each of said 2-oxo-pyrrolidin-1-yl, 2-oxo-pyrrolidin-3-yl, 2-oxo-pyrrolidin-5-yl, 1-methyl-2-oxo-pyrrolidin-4-yl, and 2-oxo-piperidin-5-yl is optionally substituted with one to three R^1 groups; and wherein each of said selected from 2-oxo-pyrrolidin-1-yl, 2-oxo-pyrrolidin-3-yl, 2-oxo-pyrrolidin-5-yl, 1-methyl-2-oxo-pyrrolidin-4-yl, and 2-oxo-piperidin-5-yl is further optionally substituted, where possible, by one or two groups independently selected from (=O) and (=S).

Embodiment 16: In another embodiment, the invention relates to a compound of formula (I) as described in any of the Embodiments 1-10, or a pharmaceutically acceptable salt thereof, wherein said ring D is selected from:

 ,	 ,	 ,	 ,
 ,	 ,	 ,	 ,

 ,	 ,	 ,	 ,
 ,	 ,	 ,	 ,
 ,	 ,	 ,	 ,
 ,	 ,	 ,	 ,
 ,	 ,	 ,	 ,
 ,	 ,	 ,	 ,
 ,	 ,	 ,	 ,
 ,	 ,	 ,	 ,
	 ,	 ,	 ,
 ,	 ,	 ,	 ,

,	,	,	,
,	,	and .	

wherein each of the aforementioned D rings is optionally substituted by one to three R^1 groups.

Embodiment 17: In another embodiment, the invention relates to a compound of formula (I) as described in any of the Embodiments 1-4, or a pharmaceutically acceptable salt thereof, wherein L^2 and D taken together represent a group selected from:

(1-methyl-pyrrolidin-2-on-4-yl)methyl;
(pyrrolidin-2-on-3yl)oxy;
(pyrrolidin-2-on-5-yl)methyloxy;
2-(pyrrolidin-2-on-1-yl)ethyloxy;
3-(pyrrolidin-2-on-1-yl)propyloxy;
(tetrahydrofuran-3-yl)oxy;
(tetrahydrofuran-2-yl)methyloxy;
(tetrahydrofuran-3-yl)methyloxy;(piperidin-2-on-5-yl)oxy;
(1,3-oxazolidin-2-on-4-yl)methyloxy;
(1,3-oxazolidin-2-on-5-yl)methyloxy;
(morpholin-3-yl)methyloxy;
(morpholin-4-yl)ethyloxy;
1H-pyrazol-5-yl;
(1H-pyrazol-5-yl)methyloxy;
(1H-pyrazol-3-yl)methyloxy;
(1-methyl-1H-pyrazol-3-yl)methyloxy;

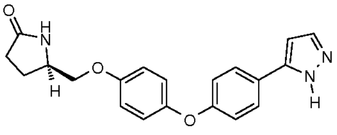
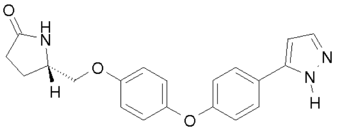
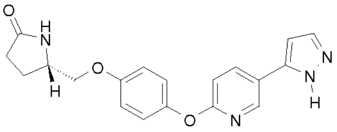
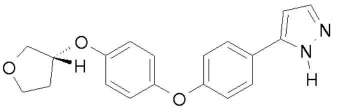
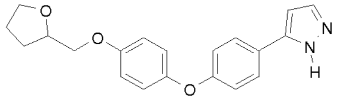
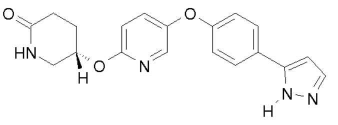
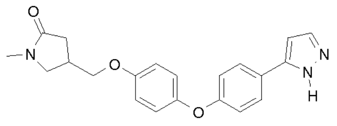
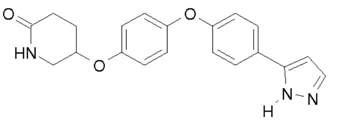
(1-methyl-1H-pyrazol-5-yl)methyloxy;
(1-methyl-2-(2-furyl)-pyrazol-5-yl)methyloxy;
3-(1H-pyrazol-1-yl)-ethyloxy;
2-(1H-pyrazol-4-yl)-ethyloxy;
3-(1H-pyrazol-1-yl)-3-methylpropyloxy;
(furan-2-yl)methyloxy;
(furan-3-yl)methyloxy;
(dihydrofuran-2(3H)-on-3-yl)oxy;
(dihydrofuran-2(3H)-on-5-yl)methyloxy;
(pyridin-3-yl)methyloxy;
(pyridin-4-yl)methyloxy;
(2-(1H-pyrazol-1-yl)- pyridin-5-yl)methyloxy;
1-(pyridin2-yl)-ethyloxy;
2-(pyridin-2-yl)ethyloxy;
2-(pyridin-3-yl)ethyloxy;
2-(pyridin-4-yl)-ethyloxy;
(pyrimidin-2-yl)methyloxy;
(thien-3-yl)methyloxy;
2-(thien-2-yl)ethyloxy;
(tetrahydro-2H-pyran-3-yl)oxy;
(tetrahydro-2H-pyran-4-yl)oxy);
(tetrahydro-2H-pyran-2-yl)methyloxy;
(tetrahydro-2H-pyran-3-yl)methyloxy;
(tetrahydro-2H-pyran-4-yl)methyloxy;
2-(tetrahydro-2H-pyran-2-yl)ethyloxy;
2-(tetrahydro-2H-pyran-4-yl)ethyloxy;
(2-methyl-1H-imidazol-1-yl)ethyloxy;
(pyrazin-2-yl)methyloxy;
benzyloxy;
(4-(methylsulfonyl)benzyl)oxy;
(1,3-thiazol-2-yl)methyloxy;

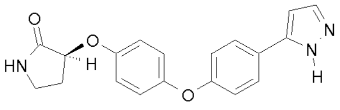
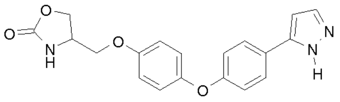
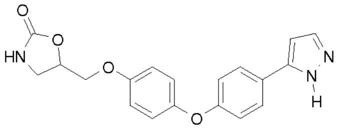
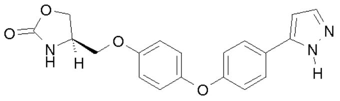
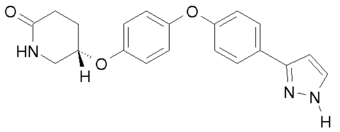
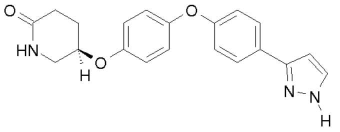
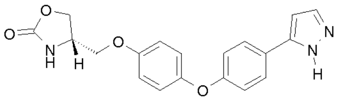
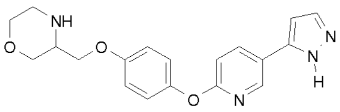
(1,3-thiazol-5-yl)methyloxy;
2-(1,3-thiazol-5-yl)ethyloxy;
(4-methyl-1,2,3-thiadiazol-5-yl)methyloxy;
(isoxazol-5-yl)methyloxy;
2-(isoxazol-4-yl)ethyloxy;
(1-methyl-1,2,4-triazol-5-yl)methyloxy;
(1,3-oxazol-4-yl)methyloxy;
(1,3-oxazol-5-yl)methyloxy;
(2-methyl-1,3-oxazol-4-yl)methyloxy;
(4-methyl-1,3-oxazol-5-yl)methyloxy;
(1H-benzimidazol-2-yl)methyloxy;
(1H-benzimidazol-5-yl)methyloxy;
(1H-benzimidazol-1-yl)ethyloxy;
(1H-benzimidazol-2-yl)ethyloxy;
2-((1H-benzimidazol-2-yl)-amino)ethyloxy;
(imidazo[2,1-b][1,3]thiazol-2-yl)methyloxy;
(1H-pyrrolo[2,3-b]pyridin-5-yl)methyloxy;
(6,7-dihydro-5H-cyclopenta[b]pyridin-7-yl)oxy;
2-(1H-pyrrolo[3,2-b]pyridin-6-yl)-ethyloxy;
(imidazo[1,2-a]pyridin-2-yl)methyloxy;
(1,3-benzothiazol-2-yl)methyloxy; and
(imidazo[1,2-a]pyridin-6-yl)methyloxy.

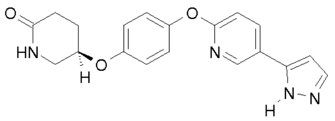
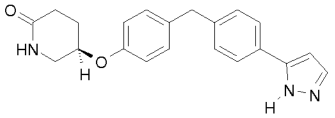
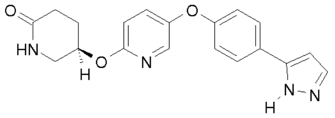
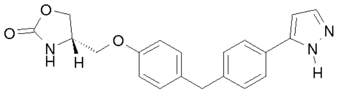
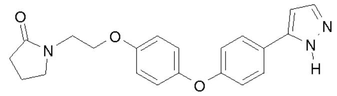
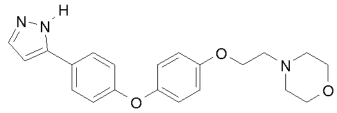
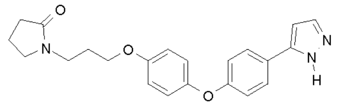
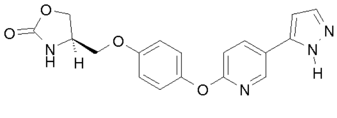
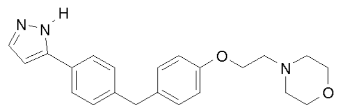
The following are exemplary compounds of the invention which can be made by the general synthetic schemes and examples described below, and methods known in the art.

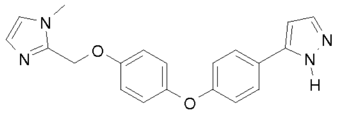
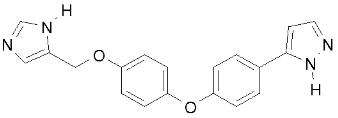
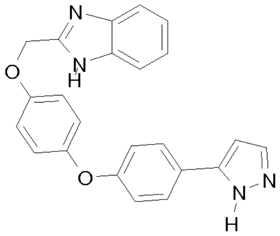
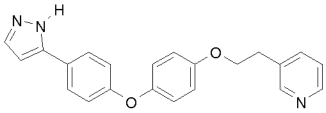
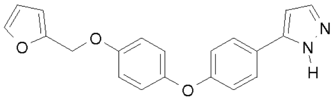
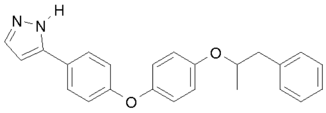
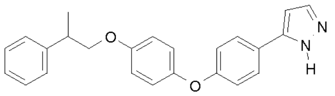
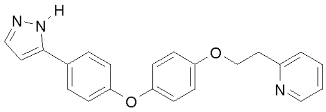
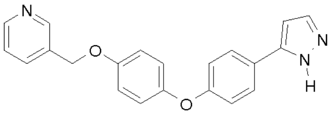
Table 1. Exemplary compounds of the invention.

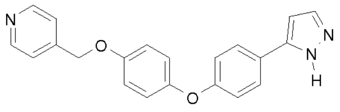
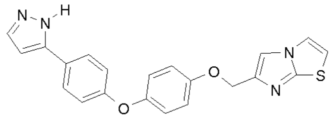
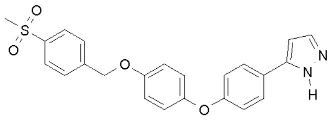
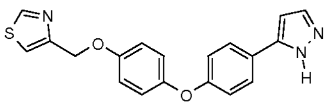
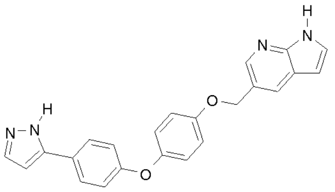
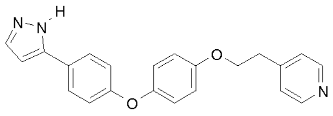
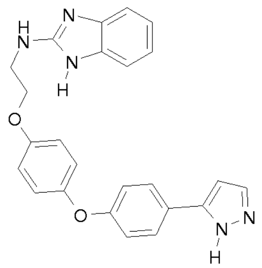
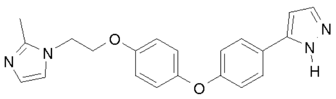
Ex. No.	Structure	Name

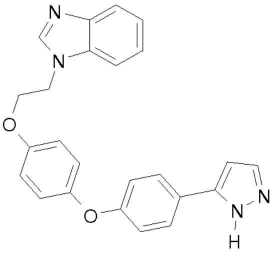
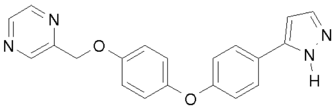
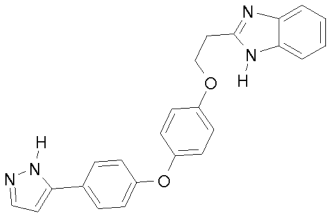
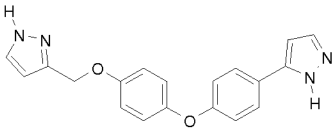
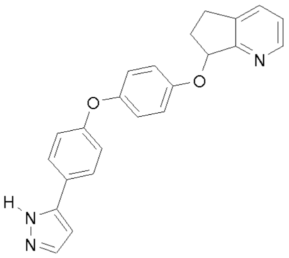
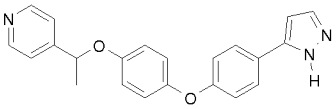
1		(5R)-5-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)pyrrolidin-2-one
2		(5S)-5-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)pyrrolidin-2-one
3		(5S)-5-[(4-{[5-(1H-pyrazol-5-yl)pyridin-2-yl]oxy}phenoxy)methyl]pyrrolidin-2-one
4		5-(4-{4-[(3R)-tetrahydrofuran-3-yloxy]phenoxy}phenyl)-1H-pyrazole
5		5-{4-[4-(tetrahydrofuran-2-ylmethoxy)phenoxy]phenyl}-1H-pyrazole
6		(5S)-5-({5-[4-(1H-pyrazol-5-yl)phenoxy]pyridin-2-yl}oxy)piperidin-2-one
7		1-methyl-4-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)pyrrolidin-2-one
8		5-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}piperidin-2-one

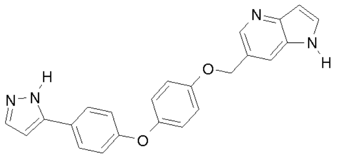
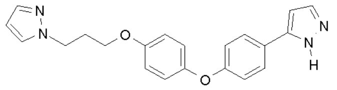
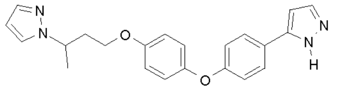
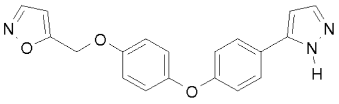
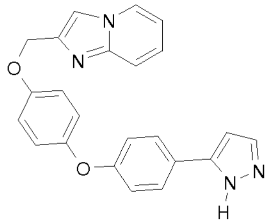
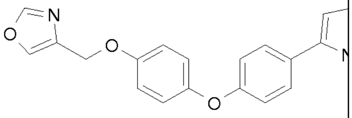
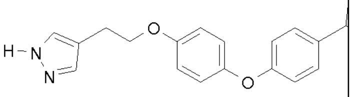
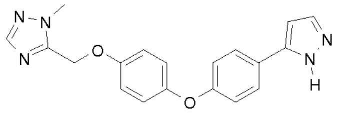
9		(3S)-3-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}pyrrolidin-2-one
10		4-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1,3-oxazolidin-2-one
11		5-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1,3-oxazolidin-2-one
12		(4R)-4-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1,3-oxazolidin-2-one
13		(5S)-5-{4-[4-(1H-pyrazol-3-yl)phenoxy]phenoxy}piperidin-2-one
14		(5R)-5-{4-[4-(1H-pyrazol-3-yl)phenoxy]phenoxy}piperidin-2-one
15		(4S)-4-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1,3-oxazolidin-2-one
16		3-[(4-{[5-(1H-pyrazol-5-yl)pyridin-2-yl]oxy}phenoxy)methyl]morpholine

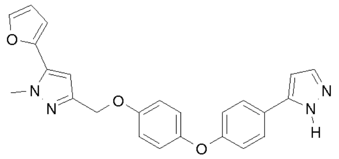
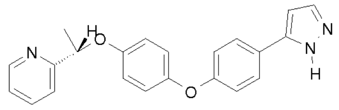
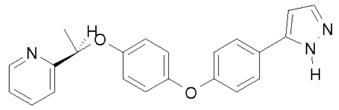
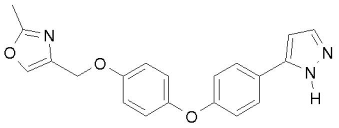
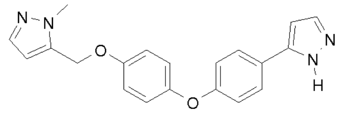
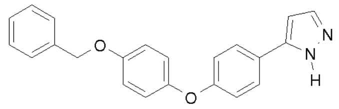
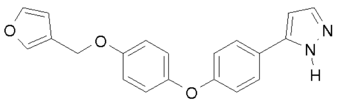
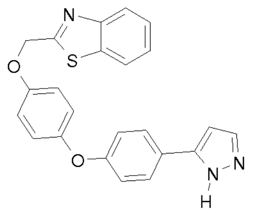
17		(5R)-5-(4-{[5-(1H-pyrazol-5-yl)pyridin-2-yl]oxy}phenoxy)piperidin-2-one
18		(5R)-5-{4-[4-(1H-pyrazol-5-yl)benzyl]phenoxy}piperidin-2-one
19		(5R)-5-({5-[4-(1H-pyrazol-5-yl)phenoxy]pyridin-2-yl}oxy)piperidin-2-one
20		(4S)-4-({4-[4-(1H-pyrazol-5-yl)benzyl]phenoxy}methyl)-1,3-oxazolidin-2-one
21		1-(2-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}ethyl)pyrrolidin-2-one
22		4-(2-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}ethyl)morpholine
23		1-(3-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}propyl)pyrrolidin-2-one
24		(4R)-4-[(4-{[5-(1H-pyrazol-5-yl)pyridin-2-yl]oxy}phenoxy)methyl]-1,3-oxazolidin-2-one
25		4-(2-{4-[4-(1H-pyrazol-5-yl)benzyl]phenoxy}ethyl)morpholine

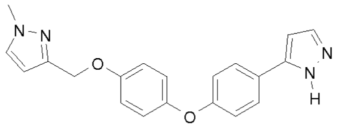
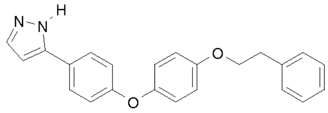
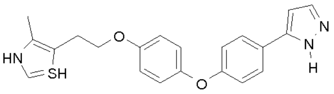
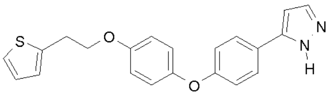
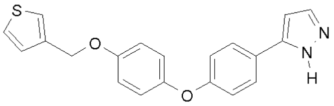
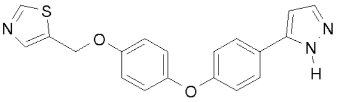
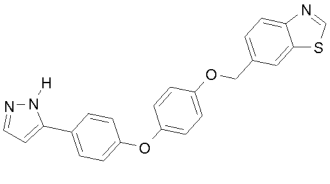
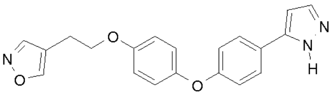
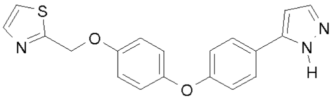
26		5-(4-{4-[(1-methyl-1H-imidazol-2-yl)methoxy]phenoxy}phenyl)-1H-pyrazole
27		5-{4-[4-(1H-imidazol-5-ylmethoxy)phenoxy]phenyl}-1H-pyrazole
28		2-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1H-benzimidazole
29		3-(2-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}ethyl)pyridine
30		5-{4-[4-(2-furylmethoxy)phenoxy]phenyl}-1H-pyrazole
31		5-{4-[4-(1-methyl-2-phenylethoxy)phenoxy]phenyl}-1H-pyrazole
32		5-{4-[4-(2-phenylpropoxy)phenoxy]phenyl}-1H-pyrazole
33		2-(2-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}ethyl)pyridine
34		3-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)pyridine

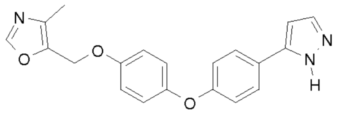
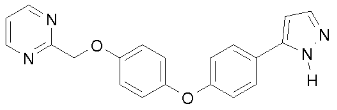
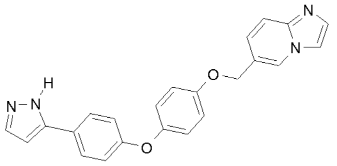
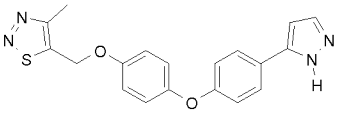
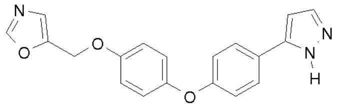
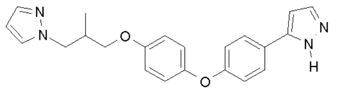
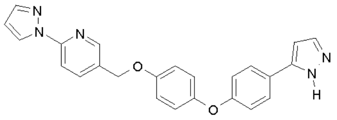
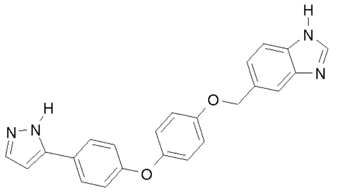
35		4-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)pyridine
36		6-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)imidazo[2,1-b][1,3]thiazole
37		5-[4-(4-{[4-(methylsulfonyl)benzyl]oxy}phenoxy)phenyl]-1H-pyrazole
38		4-{4-[4-(2H-Pyrazol-3-yl)-phenoxy]-phenoxymethyl}-thiazole
39		5-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1H-pyrrolo[2,3-b]pyridine
40		4-(2-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}ethyl)pyridine
41		N-(2-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}ethyl)-1H-benzimidazol-2-amine
42		5-(4-{4-[2-(2-methyl-1H-imidazol-1-yl)ethoxy]phenoxy}phenyl)-1H-pyrazole

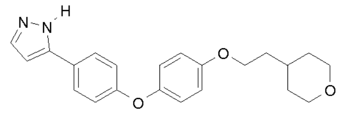
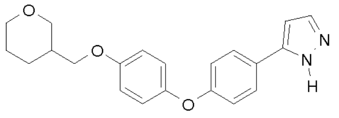
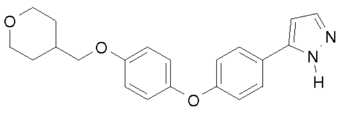
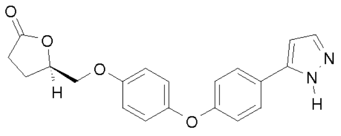
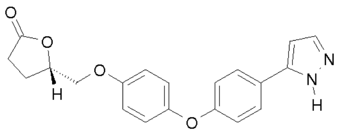
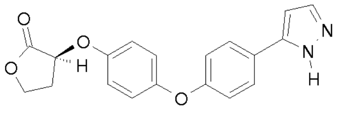
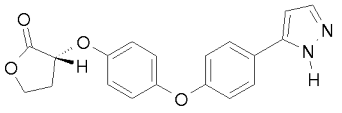
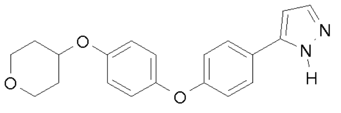
43		1-(2-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}ethyl)-1H-benzimidazole
44		2-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)pyrazine
45		2-(2-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}ethyl)-1H-benzimidazole
46		3-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1H-pyrazole
47		7-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}-6,7-dihydro-5H-cyclopenta[b]pyridine
48		4-(1-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}ethyl)pyridine

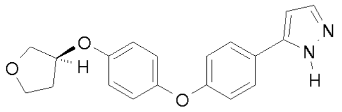
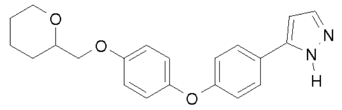
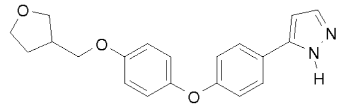
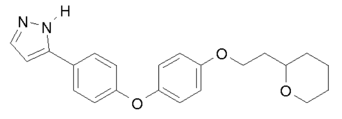
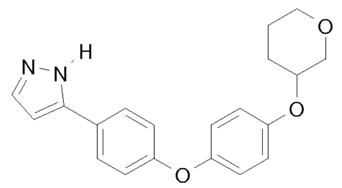
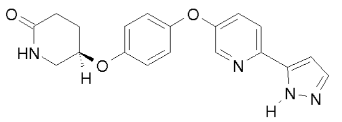
49		6-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1H-pyrrolo[3,2-b]pyridine
50		1-(3-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}propyl)-1H-pyrazole
51		1-(1-methyl-3-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}propyl)-1H-pyrazole
52		5-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)isoxazole
53		2-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)imidazo[1,2-a]pyridine
54		4-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1,3-oxazole
55		4-(2-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}ethyl)-1H-pyrazole
56		1-methyl-5-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1H-1,2,4-triazole

57		5-(2-furyl)-1-methyl-3-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1H-pyrazole
58		2-[(1S)-1-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}ethyl]pyridine
59		2-[(1R)-1-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}ethyl]pyridine
60		2-methyl-4-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1,3-oxazole
61		1-methyl-5-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1H-pyrazole
62		5-{4-[4-(benzyloxy)phenoxy]phenyl}-1H-pyrazole
63		5-{4-[4-(3-furylmethoxy)phenoxy]phenyl}-1H-pyrazole
64		2-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1,3-benzothiazole

65		1-methyl-3-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1H-pyrazole
66		5-{4-[4-(2-phenylethoxy)phenoxy]phenyl}-1H-pyrazole
67		4-Methyl-5-(2-{4-[4-(2H-pyrazol-3-yl)-phenoxy]-phenoxy}-ethyl)-thiazole
68		5-(4-{4-[2-(2-thienyl)ethoxy]phenoxy}phenyl)-1H-pyrazole
69		5-{4-[4-(3-thienylmethoxy)phenoxy]phenyl}-1H-pyrazole
70		5-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1,3-thiazole
71		6-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1,3-benzothiazole
72		4-(2-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}ethyl)isoxazole
73		2-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1,3-thiazole

74		4-methyl-5-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1,3-oxazole
75		2-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)pyrimidine
76		6-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)imidazo[1,2-a]pyridine
77		4-Methyl-5-{4-[4-(2H-pyrazol-3-yl)-phenoxy]-phenoxymethyl}-[1,2,3]thiadiazole
78		5-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1,3-oxazole
79		1-(2-methyl-3-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}propyl)-1H-pyrazole
80		2-(1H-pyrazol-1-yl)-5-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)pyridine
81		5-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1H-benzimidazole

82		5-(4-{4-[2-(tetrahydro-2H-pyran-4-yl)ethoxy]phenoxy}phenyl)-1H-pyrazole
83		5-{4-[4-(tetrahydro-2H-pyran-3-ylmethoxy)phenoxy]phenyl}-1H-pyrazole
84		5-{4-[4-(tetrahydro-2H-pyran-4-ylmethoxy)phenoxy]phenyl}-1H-pyrazole
85		(5R)-5-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)dihydrofuran-2(3H)-one
86		(5S)-5-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)dihydrofuran-2(3H)-one
87		(3S)-3-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}dihydrofuran-2(3H)-one
88		(3R)-3-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}dihydrofuran-2(3H)-one
89		5-{4-[4-(tetrahydro-2H-pyran-4-yloxy)phenoxy]phenyl}-1H-pyrazole

90		5-(4-{4-[(3S)-tetrahydrofuran-3-yloxy]phenoxy}phenyl)-1H-pyrazole
91		5-{4-[4-(tetrahydro-2H-pyran-2-ylmethoxy)phenoxy]phenyl}-1H-pyrazole
92		5-{4-[4-(tetrahydrofuran-3-ylmethoxy)phenoxy]phenyl}-1H-pyrazole
93		5-(4-{4-[2-(tetrahydro-2H-pyran-2-yl)ethoxy]phenoxy}phenyl)-1H-pyrazole
94		5-{4-[4-(tetrahydro-2H-pyran-3-yloxy)phenoxy]phenyl}-1H-pyrazole
95		(5R)-5-(4-{[6-(1H-pyrazol-5-yl)pyridin-3-yl]oxy}phenoxy)piperidin-2-one

In one embodiment, the invention relates to any of the compounds depicted in Table 1, mixtures thereof, and pharmaceutically acceptable salts thereof.

In another embodiment, the invention relates to a compound selected from the group consisting of:

(4R)-4-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1,3-oxazolidin-2-one;

(5R)-5-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)pyrrolidin-2-one;

(5S)-5-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)pyrrolidin-2-one;
(5S)-5-[(4-{[5-(1H-pyrazol-5-yl)pyridin-2-yl]oxy}phenoxy)methyl]pyrrolidin-2-one;
4-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1,3-oxazolidin-2-one;
3-[(4-{[5-(1H-pyrazol-5-yl)pyridin-2-yl]oxy}phenoxy)methyl]morpholine;
4-(2-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}ethyl)morpholine;
(4R)-4-[(4-{[5-(1H-pyrazol-5-yl)pyridin-2-yl]oxy}phenoxy)methyl]-1,3-oxazolidin-2-one;
N-(2-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}ethyl)-1H-benzimidazol-2-amine;
(5R)-5-{4-[4-(1H-pyrazol-3-yl)phenoxy]phenoxy}piperidin-2-one;
(4S)-4-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1,3-oxazolidin-2-one;
5-(4-{4-[2-(2-methyl-1H-imidazol-1-yl)ethoxy]phenoxy}phenyl)-1H-pyrazole;
1-methyl-4-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)pyrrolidin-2-one;
5-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}piperidin-2-one;
(5S)-5-{4-[4-(1H-pyrazol-3-yl)phenoxy]phenoxy}piperidin-2-one;
4-(2-{4-[4-(1H-pyrazol-5-yl)benzyl]phenoxy}ethyl)morpholine;
(4S)-4-({4-[4-(1H-pyrazol-5-yl)benzyl]phenoxy}methyl)-1,3-oxazolidin-2-one;
1-methyl-5-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1H-1,2,4-triazole;
1-(2-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}ethyl)pyrrolidin-2-one;
1-(3-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}propyl)pyrrolidin-2-one;
(5R)-5-{4-[4-(1H-pyrazol-5-yl)benzyl]phenoxy}piperidin-2-one;
mixtures thereof, and pharmaceutically acceptable salts thereof.

In another embodiment, the invention relates to a compound selected from the group consisting of:
3-[(4-{[5-(1H-pyrazol-5-yl)pyridin-2-yl]oxy}phenoxy)methyl]morpholine;
(4R)-4-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1,3-oxazolidin-2-one;

(4R)-4-[(4-{[5-(1H-pyrazol-5-yl)pyridin-2-yl]oxy}phenoxy)methyl]-1,3-oxazolidin-2-one;
4-(2-{4-[4-(1H-pyrazol-5-yl)benzyl]phenoxy}ethyl)morpholine;
4-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1,3-oxazolidin-2-one;
(5S)-5-[(4-{[5-(1H-pyrazol-5-yl)pyridin-2-yl]oxy}phenoxy)methyl]pyrrolidin-2-one;
(4S)-4-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1,3-oxazolidin-2-one;
(5S)-5-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)pyrrolidin-2-one;
5-(4-{4-[2-(2-methyl-1H-imidazol-1-yl)ethoxy]phenoxy}phenyl)-1H-pyrazole;
(5R)-5-{4-[4-(1H-pyrazol-3-yl)phenoxy]phenoxy}piperidin-2-one;
4-(2-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}ethyl)morpholine;
(5S)-5-{4-[4-(1H-pyrazol-3-yl)phenoxy]phenoxy}piperidin-2-one;
5-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}piperidin-2-one;
(4S)-4-({4-[4-(1H-pyrazol-5-yl)benzyl]phenoxy}methyl)-1,3-oxazolidin-2-one;
(5R)-5-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)pyrrolidin-2-one;
1-methyl-4-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)pyrrolidin-2-one;
(5R)-5-(4-{[6-(1H-pyrazol-5-yl)pyridin-3-yl]oxy}phenoxy)piperidin-2-one;
(5R)-5-(4-{[5-(1H-pyrazol-5-yl)pyridin-2-yl]oxy}phenoxy)piperidin-2-one;
1-(3-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}propyl)pyrrolidin-2-one;
(5R)-5-({5-[4-(1H-pyrazol-5-yl)phenoxy]pyridin-2-yl}oxy)piperidin-2-one;
5-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1,3-oxazolidin-2-one;
(5R)-5-{4-[4-(1H-pyrazol-5-yl)benzyl]phenoxy}piperidin-2-one;
N-(2-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}ethyl)-1H-benzimidazol-2-amine;
2-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)pyrazine;
5-(4-{4-[(3S)-tetrahydrofuran-3-yloxy]phenoxy}phenyl)-1H-pyrazole;
1-(2-{4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}ethyl)pyrrolidin-2-one;
5-(4-{4-[(3R)-tetrahydrofuran-3-yloxy]phenoxy}phenyl)-1H-pyrazole;
(5S)-5-({5-[4-(1H-pyrazol-5-yl)phenoxy]pyridin-2-yl}oxy)piperidin-2-one;
1-methyl-5-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1H-pyrazole;
5-{4-[4-(tetrahydrofuran-3-ylmethoxy)phenoxy]phenyl}-1H-pyrazole;
5-{4-[4-(tetrahydrofuran-2-ylmethoxy)phenoxy]phenyl}-1H-pyrazole;

6-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)imidazo[1,2-a]pyridine;
5-{4-[4-(tetrahydro-2H-pyran-4-ylmethoxy)phenoxy]phenyl}-1H-pyrazole;
2-(1H-pyrazol-1-yl)-5-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)pyridine;
5-({4-[4-(1H-pyrazol-5-yl)phenoxy]phenoxy}methyl)-1,3-oxazole; and
mixtures thereof, and pharmaceutically acceptable salts thereof.

In another embodiment, the invention relates to pharmaceutical compositions comprising one or more compounds of formula (I) as defined in any of the embodiment above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

Unless otherwise stated, all terms as used herein in this specification shall be understood to have their ordinary meaning as known in the art. Other more specific definitions are as follows:

The term “(C_1-C_6)alkyl” refers to branched and unbranched alkyl groups having from 1 to 6 carbon atoms. Examples of -(C_1-C_6)alkyls include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentane, iso-pentyl, neopentyl, n-hexane, iso-hexanes (e.g., 2-methylpentyl, 3-methylpentyl, 2,3-dimethylbutyl, and 2,2-dimethylbutyl). It will be understood that any chemically feasible carbon atom of the (C_1-C_6)alkyl group can be the point of attachment to another group or moiety.

The term “-(C_1-C_6)alkylene-” refers to branched and unbranched alkyl linkers having from 1 to 6 carbon atoms. Examples of -(C_1-C_6)alkylene -include methylene, ethylene, propylene, butylene, pentylene, and hexalene.

The term “(C_3-C_6)cycloalkyl” refers to a nonaromatic 3- to 6-membered monocyclic carbocyclic radical. Examples of “(C_3-C_6)cycloalkyls” include cyclopropyl, cyclobutyl, cyclohexyl, cyclopentyl and cyclohexyl.

As used herein, the term "(C_6-C_{10})aryl" refers to an aromatic hydrocarbon rings containing from six to ten carbon ring and includes monocyclic rings and bicyclic rings where at least one of the rings is aromatic. Non-limiting examples of C_{6-10} aryls include phenyl, indanyl, indenyl, benzocyclobutanyl, dihydronaphthyl, tetrahydronaphthyl, naphthyl, benzocycloheptanyl and benzocycloheptenyl.

As used herein, the term "4 to 11-membered heterocycle" includes stable nonaromatic 4-8 member monocyclic heterocyclic radical or a stable nonaromatic 6 to 11-membered fused bicyclic, bridged bicyclic or spirocyclic heterocyclic radical. The 4 to 11-membered heterocycle consists of carbon atoms and one or more, preferably from one to four heteroatoms chosen from nitrogen, oxygen and sulfur. The heterocycle may be either saturated or partially unsaturated. Non-limiting examples of nonaromatic 4-8 member monocyclic heterocyclic radicals include tetrahydrofuranyl, azetidinyl, pyrrolidinyl, pyranyl, tetrahydropyranyl, dioxanyl, thiomorpholinyl, 1,1-dioxo-1λ^6-thiomorpholinyl, morpholinyl, piperidinyl, piperazinyl, and azepinyl. Non-limiting examples of nonaromatic 6 to 11-membered fused bicyclic radicals include octahydroindolyl, octahydrobenzofuranyl, and octahydrobenzothiophenyl. Non-limiting examples of nonaromatic 6 to 11-membered bridged bicyclic radicals include 2-azabicyclo[2.2.1]heptanyl, 3-azabicyclo[3.1.0]hexanyl, and 3-azabicyclo[3.2.1]octanyl. Non-limiting examples of nonaromatic 6 to 11-membered spirocyclic heterocyclic radicals include 7-aza-spiro[3,3]heptanyl, 7-spiro[3,4]octanyl, and 7-aza-spiro[3,4]octanyl.
As used herein, the term "5 to 11-membered heteroaryl" includes aromatic 5 to 6-membered monocyclic heteroaryls and aromatic 7 to 11-membered heteroaryl bicyclic rings where at least one of the rings is aromatic, wherein the heteroaryl ring contains 1-4 heteroatoms such as N, O and S. Non-limiting examples of 5 to 6-membered monocyclic heteroaryl rings include furanyl, oxazolyl, isoxazolyl, oxadiazolyl, pyranyl, thiazolyl, pyrazolyl, pyrrolyl, imidazolyl, tetrazolyl, triazolyl, thienyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, and purinyl. Non-limiting examples of 7 to 11-membered heteroaryl bicyclic rings include benzimidazolyl, 1,3-dihydrobenzoimidazol-2-one, quinolinyl, dihydro-2*H*-quinolinyl, isoquinolinyl, quinazolinyl, indazolyl, thieno[2,3-d]pyrimidinyl, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzofuranyl,

benzopyranyl, benzodioxolyl, benzoxazolyl , benzothiazolyl, pyrrolo[2,3-b]pyridinyl, and imidazo[4,5-b]pyridinyl.

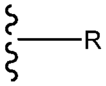
It will be understood that when a heterocyclyl or heteroaryl contains a S ring atom, such S ring atom can be present in the ring in its divalent, tetravalent, or hexavalent form, i.e., –S-, -S(O)- or –S(O)$_2$-.

Each aryl or heteroaryl unless otherwise specified includes it's partially or fully hydrogenated derivatives. For example, quinolinyl may include decahydroquinolinyl and tetrahydroquinolinyl, naphthyl may include its hydrogenated derivatives such as tetrahydranaphthyl. Other partially or fully hydrogenated derivatives of the aryl and heteroaryl compounds described herein will be apparent to one of ordinary skill in the art.

The term "heteroatom" as used herein shall be understood to mean atoms other than carbon such as O, N, and S.

The term "halo" or "halogen" refers to fluoro, chloro, bromo or iodo.

The symbol



means point of attachment of a group R to a moiety.

In all alkyl groups or carbon chains one or more carbon atoms can be optionally replaced by heteroatoms O, S or N. It shall be understood that if N is not substituted then it is NH, it shall also be understood that the heteroatoms may replace either terminal carbon atoms or internal carbon atoms within a branched or unbranched carbon chain. Such groups can be substituted as herein above described by groups such as oxo to result in definitions such as but not limited to: alkoxycarbonyl, acyl, amido and thioxo.

For all compounds disclosed in this application, in the event the nomenclature is in conflict with the structure, it shall be understood that the compound is defined by the structure.

The invention also relates to pharmaceutical preparations, containing as active substance one or more compounds of the invention, or the pharmaceutically acceptable derivatives thereof, optionally combined with conventional excipients and/or carriers.

Compounds of the invention also include their isotopically-labelled forms. An isotopically-labelled form of an active agent of a combination of the present invention is identical to said active agent but for the fact that one or more atoms of said active agent have been replaced by an atom or atoms having an atomic mass or mass number different from the atomic mass or mass number of said atom which is usually found in nature. Examples of isotopes which are readily available commercially and which can be incorporated into an active agent of a combination of the present invention in accordance with well established procedures, include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, *e.g.*, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. An active agent of a combination of the present invention, a prodrug thereof, or a pharmaceutically acceptable salt of either which contains one or more of the above-mentioned isotopes and/or other isotopes of other atoms is contemplated to be within the scope of the present invention.

The compounds of the invention may contain one or more asymmetric carbon atoms and, therefore, may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Isomers shall be defined as being enantiomers and diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be in the R or S configuration, or a combination of configurations.

Some of the compounds of the invention can exist in more than one tautomeric form. The invention includes methods using all such tautomers.

The compounds of the invention are only those which are contemplated to be “chemically stable” as will be appreciated by those skilled in the art. For example, a compound which would have a “dangling valency” or a “carbanion” is not a compound contemplated by the inventive methods disclosed herein.

The invention includes pharmaceutically acceptable derivatives of compounds of formula (I). A "pharmaceutically acceptable derivative" refers to any pharmaceutically acceptable salt or ester, or any other compound which, upon administration to a patient, is capable of providing (directly or indirectly) a compound useful for the invention, or a pharmacologically active metabolite or pharmacologically active residue thereof. A pharmacologically active metabolite shall be understood to mean any compound of the invention capable of being metabolized enzymatically or chemically. This includes, for example, hydroxylated or oxidized derivative compounds of the invention.

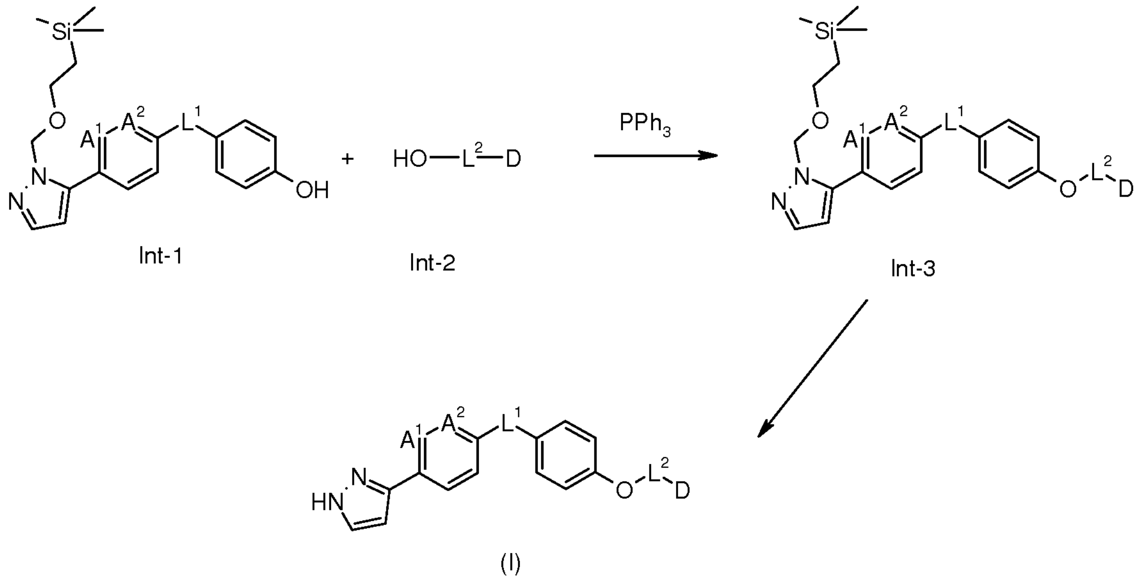
Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfuric, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfuric and benzenesulfonic acids. Other acids, such as oxalic acid, while not themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (*e.g.*, sodium), alkaline earth metal (*e.g.*, magnesium), ammonium and $N(C_1\text{-}C_4\ \text{alkyl})^{4+}$ salts.

In addition, within the scope of the invention is use of prodrugs of compounds of the invention. Prodrugs include those compounds that, upon simple chemical transformation, are modified to produce compounds of the invention. Simple chemical transformations include hydrolysis, oxidation and reduction. Specifically, when a prodrug is administered to a patient, the prodrug may be transformed into a compound disclosed hereinabove, thereby imparting the desired pharmacological effect.

GENERAL SYNTHETIC METHODS

The compounds of the invention may be prepared by the methods described below in Schemes 1 and 2, where the groups A^1-A^3, L^1, L^2 and D are as defined above for the compound of formula (I) unless noted otherwise. Optimum reaction conditions and reaction times may vary depending on the particular reactants used. Unless otherwise specified, solvents, temperatures, pressures and other reaction conditions may be readily selected by one of ordinary skill in the art. Specific procedures are provided in the Synthetic Examples section.

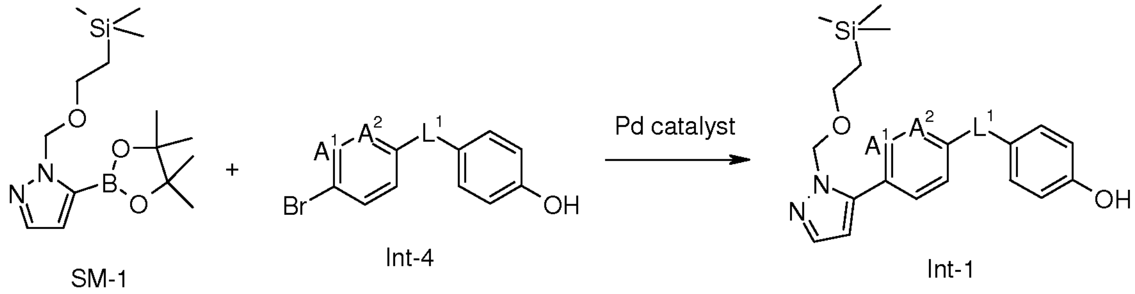
Scheme 1 depicts a general synthetic procedure for making the compounds of formula (I) where A^3 is CH.



As depicted in Scheme 1, compound Int-1 is allowed to react with compound Int-2 in etheral solvent (e.g., THF) and in the presence of a triarylphosphine (e.g., triphenylphospine or resin-supported triphenylphospine) to provide Int-3. Int-3 is then hydrolyzed to provide the compound of formula (I).

Compound Int-1 can be prepared according to the method depicted in Scheme 2.

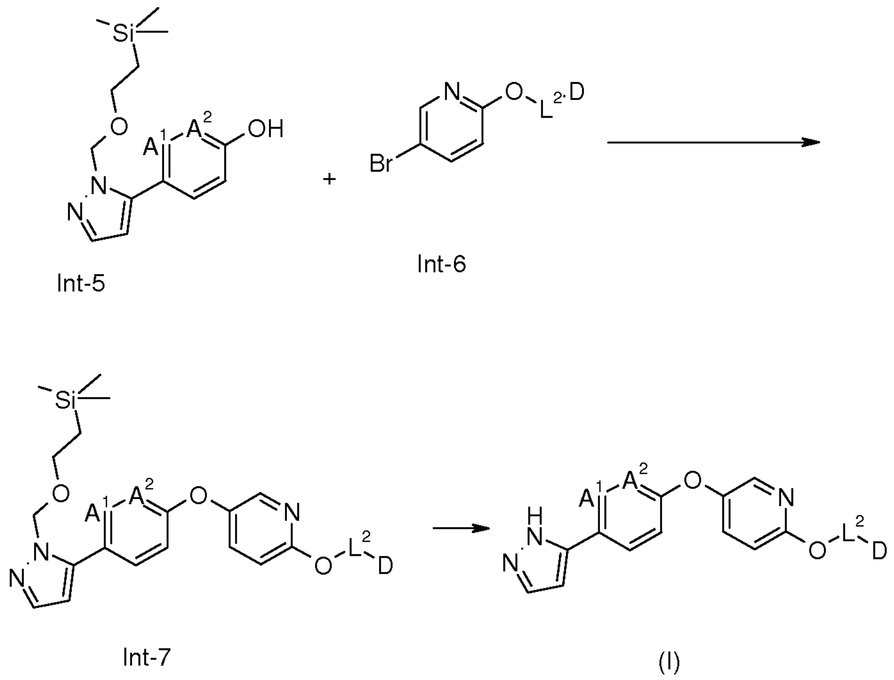
Scheme 2



As depicted in Scheme 2, compound Int-4 is allowed to react with 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrazole (SM-1) in a suitable solvent (e.g., an aqueous/etheral solvent such as DME/water) and in the presence of a transition metal catalyst (e.g., tetrakis(triphenylphosphine)palladium) to provide the compound Int-1. Alternatively, the compound Int-1 can also be prepared according to the method depicted in Scheme 1 where 1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrazole-5-boronic acid (SM-2, not shown) is used instead of compound SM-1. Compound SM-1 and SM-2 can be prepared by known methods. Compounds of formula Int-4 are commercially available or can be made by known methods of methods described in the Examples Section below.

A method of making compounds of formula (I) where A^3 is N is depicted in Scheme 3 below.

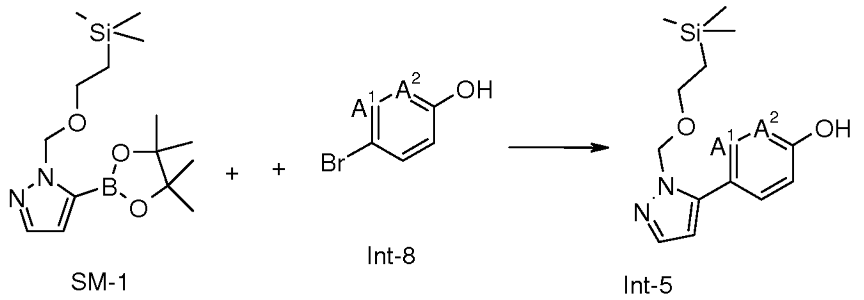
Scheme 3



As depicted in Scheme 3, compound Int-5 is allowed to react with compound Int-6 in the presence of a transition metal catalyst (e.g., copper iodide) to provide compound Int-7 which is hydrolyzed to provide the compound of formula (I).

Compounds of formula Int-5 can be made by the method described in Scheme 4.

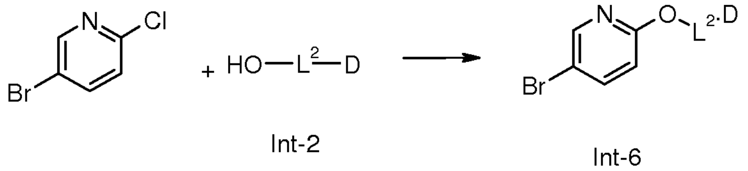
Scheme 4



As depicted in Scheme 4, SM-1 is allowed to react with a compound of formula Int-8 in a suitable solvent (e.g., an aqueous/etheral solvent such as DME/water) and in the presence of a transition metal catalyst (e.g., tetrakis(triphenylphosphine)palladium) to provide the compound of formula Int-5. Compounds of formula Int-8 are commercially available or can be made by known methods.

Compounds of formula Int-6 can be made by the method depicted in Scheme 5 below.

Scheme 5



As depicted in Scheme5, 5-bromo-2-chloropyridine and the compound Int-2 are allowed to react in the presence of base (e.g., sodium tert-butoxide) to provide the compound for formula Int-6.

The examples which follow are illustrative and particular reagents or conditions could be modified as needed for individual compounds without undue experimentation as recognized by one skilled in the art. Starting materials and reagents are either commercially available or may be prepared by one skilled in the art using methods described in the chemical literature and in the Synthetic Examples section below.

SYNTHETIC EXAMPLES

General Methods: Unless noted otherwise, all reactions are run at room temperature (about 25°C), under inert atmosphere (e.g., Argon, N_2), and under anhydrous conditions. All compounds are characterized by at least one of the following methods: ^{1}H NMR, HPLC, HPLC-MS, and/or melting point.

Typically, reaction progress is monitored by thin layer chromatography (TLC) or HPLC-MS. Intermediates and products are purified using at least one of the following methods:

Flash chromatography on silica gel,

Recrystallization,

Chiral HPLC using a 20 x 500 mm Chiralpak AD-H column, or 20 x 500 mm Chiralpak OD-H column, and eluting with an isocratic mixture of isopropanol in heptanes with 0.1% diethylamine (DEA) at 7.5 mL/min,

20 x 250 mm Chiralcel OD-H column, and eluting with an isocratic mixture of isopropanol in heptanes at 7.5 mL/min,

Super Critical Fluid (SCF) Chiral HPLC using a 3.0 x 25.0 cm RegisPack column, eluting with an isocratic mixture of MeOH, isopropylamine (IPA), and super critical carbon dioxide at 125 bar; 80 mL/min, and/or

Reversed phase HPLC using a C18 semi-preparative column eluting with a gradient of MeCN+0.1% TFA /H_2O+0.1% TFA, or MeCN+0.1% formic acid /H_2O+0.1% formic acid.

The reported MS data is for observed $[M+H]^+$. For bromine containing compounds, the $[M+H]^+$ is either reported for one or both of the bromine isotopes (i.e., ^{79}Br and ^{81}Br).

LC/MS methods used to characterize the compounds of the invention are described in Tables 2a and 2b below.

Table 2a. LC/MS Methods and retention times (RT).

HPLC Method	Time (min)	Mobile Phase		Flow (mL/min)	Column
		H_2O (0.1%FA)	CH_3CN (0.1%FA)		
1	0	95	5	2.5	Agilent Zorbax C18 SB 3.5um 4.6x30mm cartridge
	1.7	5	95	2.5	
	2	5	95	2.5	
	2.1	95	5	2.5	
	2.3	95	5	2.5	
2	0	95	5	1.5	Agilent Zorbax Eclipse XDB-C8 5um 4.6x150mm
	7	5	95	1.5	
	9	5	95	1.5	

	9.3	95	5	1.5	
	10	95	5	1.5	
3	0	90	10	0.5	Thermo Scientific, Aquasil C18, 50 x 2.1 mm column.
	0.5	90	10	0.5	
	1.5	1	99	0.5	
	2.5	1	99	0.5	
	3.0	90	10	0.5	
	4.0	90	10	0.5	

HPLC Method	**Time (min)**	**Mobile Phase**		**Flow (mL/min)**	**Column**
		95% H_2O + 5% CH_3CN (0.05%Formic Acid)	**CH_3CN (0.05% Formic Acid)**		
4	0	90	10	0.8	BEH 2.1x50mm C18, 1.7um particle diameter
	1.19	5	95	0.8	
	1.7	5	95	0.8	
5	0	95	5	0.6	Waters HSS T3 2.1X100mm 18 um column
	4.45	0	100	0.6	
	5	0	100	0.6	

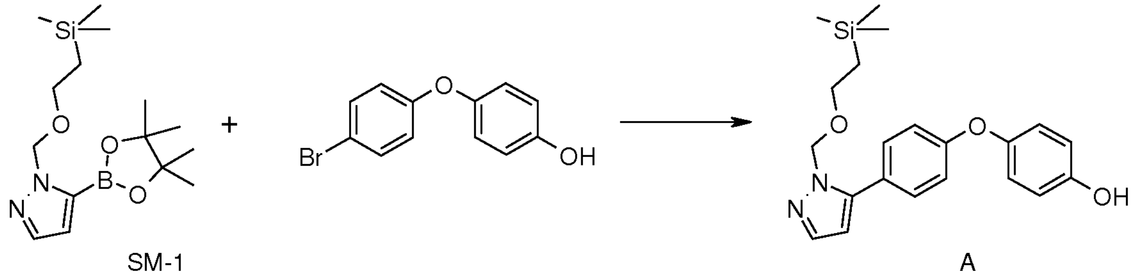
List of Abbreviations:

DCE = dichloroethane
DCM = dichloromethane
DME = dimethoxyethane
DMF = dimethylformamide
DMSO = dimethylsulfoxide
EtOAc = ethyl acetate
EtOH = ethanol
IPA = isopropyl alcohol
MeCN = acetonitrile
MeOH = methanol
TEA = triethylamine
TFA = trifluoroacetic acid

THF = tetrahydrofuran

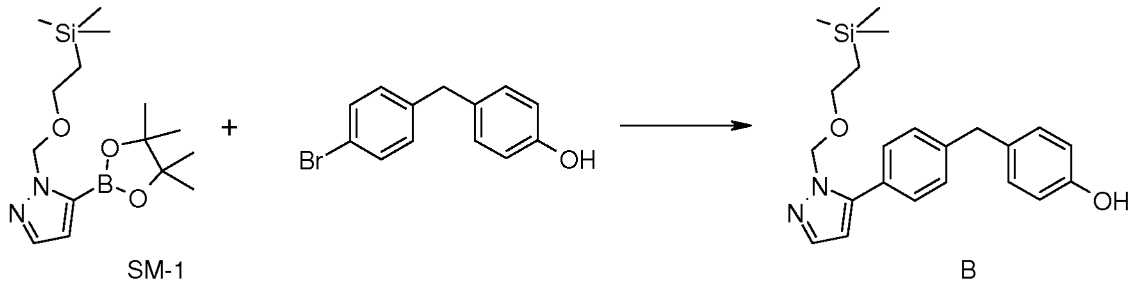
SYNTHESIS OF INTERMEDIATES

Preparation of 4-{4-[2-(2-Trimethylsilanyl-ethoxymethyl)-2H-pyrazol-3-yl]-phenoxy}-phenol (A)



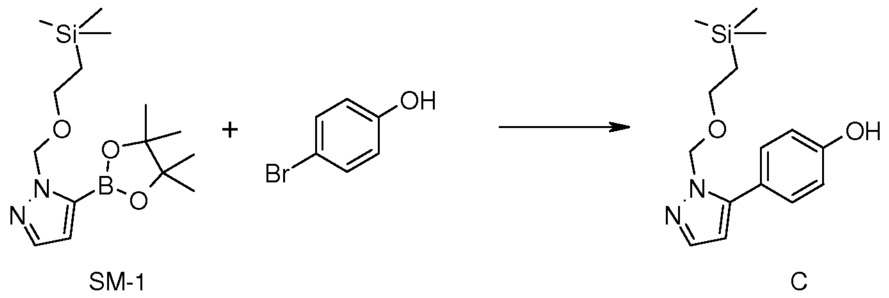
A suspension of 4-(4-Bromo-phenoxy)-phenol (7.0 g, 26 mmol), and 5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrazole (9.4 g, 39 mmol) in a mixture of DME (120 mL) and 2N aqueous Na_2CO_3 (33 mL) is sparged with Argon for 30 minutes. Tetrakis(triphenylphosphine)palladium(0) (1.5 g, 1.3 mmol) is added to the mixture, and the mixture is heated to 100° C. After 16 hours, the mixture is cooled to room temperature and poured into water/ EtOAc. The organic layer is collected, and the aqueous layer is extracted twice with EtOAc. The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue is purified on SiO2 (EtOAc/ heptanes) to provide Intermediate A.

Preparation of 4-{4-[2-(2-Trimethylsilanyl-ethoxymethyl)-2H-pyrazol-3-yl]-benzyl}-phenol (B)



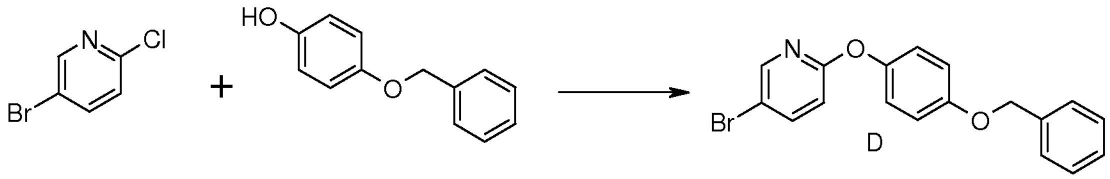
A suspension of 4-(4-Bromo-benzyl)-phenol (2.0 g, 7.6 mmol), compound SM-1 (2.9 g, 9.1 mmol) and tetrakis(triphenylphosphine)palladium(0) (880 mg, 0.76 mmol) in a mixture of DME (20 mL) and 2N aqueous Na_2CO_3 (9.5 mL) is heated to 130 °C for 1 hour. The mixture is cooled to room temperature, diluted with water, and extracted with ethyl acetate. The organic layer is washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue is purified on SiO_2 (methanol/dichloromethane) to provide Intermediate B.

Preparation of (3E,5E)-6-[2-(2-Trimethylsilanyl-ethoxymethyl)-2H-pyrazol-3-yl]-hepta-1,3,5-trien-3-ol (C)



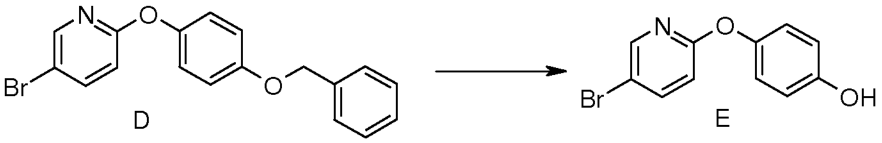
A suspension of 4-bromophenol (2.5 g, 14 mmol), SM-1 (5.6 g, 17 mmol) and tetrakis(triphenylphosphine)palladium(0) (1.6 g, 1.4 mmol) in a mixture of DME (75 mL) and 2N aqueous Na_2CO_3 (22 mL) is evacuated, and purged thrice with argon, and heated to 100°C for 16 hours. The reaction is cooled to room temperature, diluted with EtOAc, and washed with water followed by brine. The organic fraction is collected, dried over Na_2SO_4, filtered, and concentrated. The resulting residue is purified on SiO_2 (EtOAc/ heptane) to provide Intermediate C.

Preparation of 2-(4-benzyloxy-phenoxy)-5-bromo-pyridine (D)



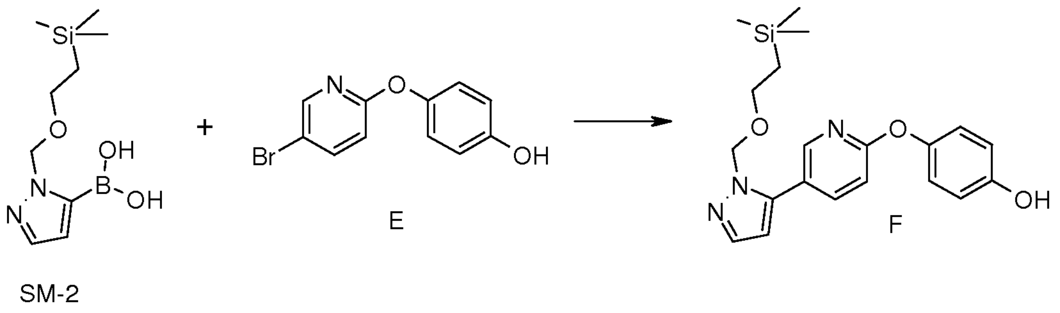
Potassium tert-butoxide (7g, 62 mmol) is added to a solution of 5-bromo-2-chloro-pyridine (10g, 52 mmol) and 4-benzyloxy-phenol (10.4g, 52 mmol) in DMF (104 mL). The mixture is heated to 110°C for 3.5 hours then cooled. The solution is then poured into water /ethyl acetate, and the organic layer is collected. The aqueous layer is extracted twice with EtOAc, and the combined organic layers are washed with brine. The organic layer is then dried over Na_2SO_4, filtered and concentrated. The resulting residue is purified on SiO_2 (EtOAc /heptanes) to provide Intermediate D.

Preparation of 4-(5-Bromo-pyridin-2-yloxy)-phenol (E)



A mixture of Intermediate D (9.5g, 27 mmol), pentamethyl benzene (8g, 54 mmol), and triflouroacetic acid (57 mL, 750 mmol) is stirred at room temperature for 2.5 hours. The mixture is concentrated and the resulting residue is dissolved in EtOAc. The organic layer is washed with saturated sodium bicarbonate followed by brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue is purified on SiO_2 (EtOAc/ heptanes) to provide Intermediate D.

Preparation of 4-{5-[2-(2-trimethylsilanyl-ethoxymethyl)-2H-pyrazol-3-yl]- pyridin-2-yloxy}-phenol (F)



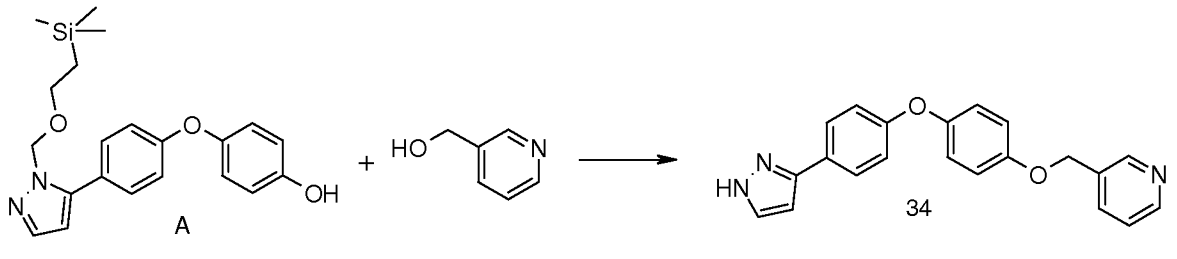
A suspension of Intermediate E (6.0 g, 23 mmol) and 1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrazole-5-boronic acid (SM-2) (6.6g, 27 mmol) in a mixture of DME (60 mL) and 2N aqueous Na_2CO_3 (33 mL) is sparged with Argon for 30 minutes. The mixture is treated with tetrakis(triphenylphosphine)palladium(0) (2.6 g, 2 mmol) and heated to 100°C for 16 hours. The solution is cooled, poured into water/EtOAc, and the organic layer is collected. The aqueous layer is extracted twice with EtOAc, and the combined organic layers are washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue is purified on SiO_2 (EtOAc/heptanes) to provide **F**.

Synthesis of Compounds of Formula I

General Method A through E (protocols for Mitsunobu coupling).

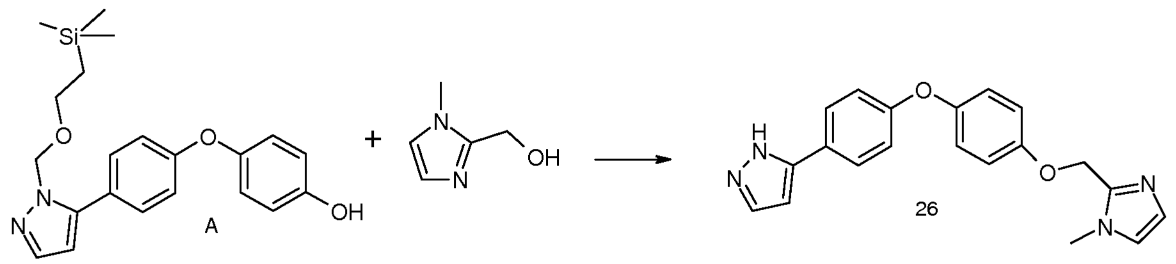
Example of General Method A:

Preparation of 3-{4-[4-(1H-Pyrazol-3-yl)-phenoxy]-phenoxymethyl}-pyridine (Example 34)



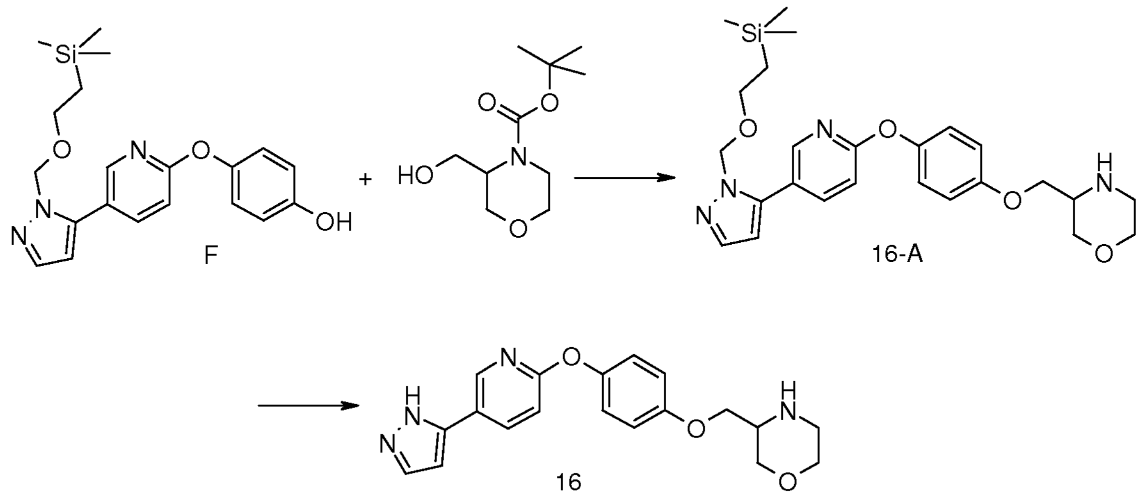
PS-PPh_3 resin (97 mg, 0.3 mmol) is added to a solution of pyridin-3-yl-methanol (21 mg, 0.2 mmol) and Intermediate A (40 mg, 0.1 mmol) in THF (1 mL). Di-tert-butyl azodicarboxylate (34 mg, 0.15 mmol) and THF (0.5 mL) are then added, and the mixture is shaken at room temperature. After 16 hours, additional di-tert-butyl azodicarboxylate (34 mg, 0.15 mmol) and THF (0.5 mL) are added and the reaction is stirred for 16 hours. The mixture is filtered, and the resin is washed with THF, DCE, THF, DCE, and THF (0.5 mL each). The combined filtrates are concentrated, and the resulting residue is dissolved in DCE (1 mL) and 10% citric acid (0.5 mL). The layers are separated using phase separating cartridges, and the product extracted 3 times with 0.5 mL of DCE, and evaporated in vacuo to provide the crude product. The material is dissolved in DCE (1 mL), treated with 4N HCl (125 μL), and shaken. After 16 hours, the mixture is concentrated, and the crude is purified by reversed phase HPLC to provide **34**.

Example of General Method B:
5-{4-[4-(1-Methyl-1H-imidazol-2-ylmethoxy)-phenoxy]-phenyl}-1H-pyrazole (Example 26)



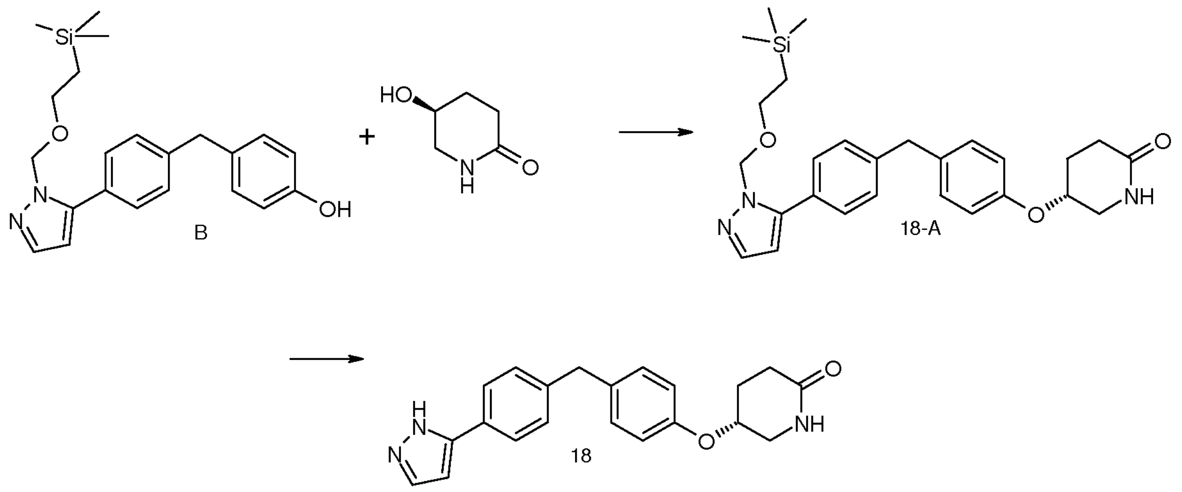
A solution of Intermediate A (124 mg, 0.32 mmol), (1-methyl-1H-imidazol-2-yl)-methanol (55mg, 0.48 mmol), and triphenylphosphine (140 mg, 0.52 mmol) in THF (1.5 mL) is purged with nitrogen and treated with diisopropyldiazodiacarboxylate (75 uL, 0.52 mmol). The mixture is stirred for 16 hours. Additional triphenylphosphine (140 mg, 0.52 mmol) and diisopropyldiazodiacarboxylate (75 uL, 0.52 mmol) are added and stirring is continued. After 48 hours, 4N HCl (2 mL) is added and the solution stirred overnight. The mixture is concentrated, and the residue is purified on reversed phase HPLC to provide **26**.

Example of General Method C: Preparation of (±) 3-{4-[5-(2H-Pyrazol-3-yl)-pyridin-2-yloxy]-phenoxymethyl}-morpholine (Example 16):



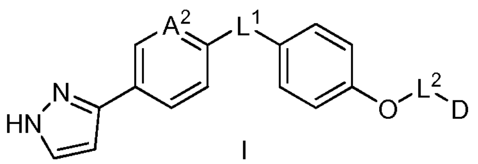
PS-PPh$_3$ resin (175 mg, 0.52 mmol) is added to a solution of Intermediate F (100 mg, 0.26 mmol), and 3-hydroxymethyl-morpholine-4-carboxylic acid tert-butyl ester (102 mg, 0.47 mmol) in THF (3 mL). The mixture is stirred for 10 minutes, treated with di tert-butydiazodicarboxylate (120 mg, 0.52 mmol), and heated to 60 °C. After 16 hours, the mixture is treated with water, and the product extracted with EtOAc. The organic layer is concentrated, and the resulting residue is purified on SiO$_2$ (heptanes/EtOAc) to provide 16-A. Intermediate 16-A is taken up in 4N HCl in dioxane (1 mL) and heated to 45°C. After 15 minutes, the mixture is treated with diisopropylamine (1mL) and concentrated. The resulting residue is purified on SiO$_2$ (DCM/MeOH/NH$_4$OH) to provide **16**.

Example of General Method D: Preparation of (R)-5-{4-[4-(2H-Pyrazol-3-yl)-benzyl]-phenoxy}-piperidin-2-one (Example 18):



PS-PPh_3 resin (810 mg, 0.52 mmol) and di tert-butydiazodicarboxylate (372 mg, 1.6 mmol) are added to solution of Intermediate B (307 mg, 0.81 mmol) and (S)-5-Hydroxy-piperidin-2-one (190 mg, 1.6 mmol) in THF (8 mL). The mixture is stirred for 16 hours, filtered, diluted with EtOAc, and washed with water. The organic layer is collected and concentrated. The resulting residue is purified on SiO_2 (heptanes/EtOAc) to provide 18-A. Intermediate 18-A is taken up in 4N HCl in dioxane (3mL) and heated to 45° C. After 1 hour, the mixture is partitioned between EtOAc and saturated $NaHCO_3$. The organic layer is collected, dried over Na_2SO_4, filtered, and concentrated. The resulting residue is purified on SiO_2 (DCM/MeOH) to provide **18**.

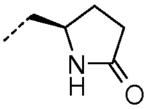
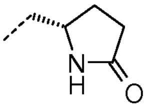
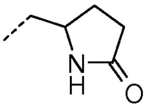
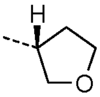
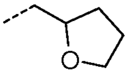
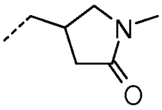
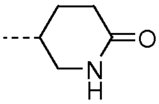
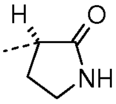
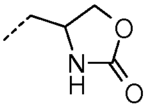
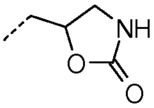
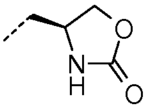
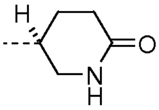
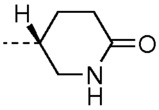
Table 3 provides a summary of the key reagents used to prepare Examples 1-95 according to general methods A, B, C, D, E, or F.

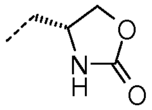
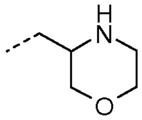
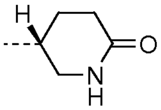
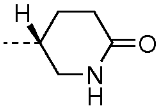
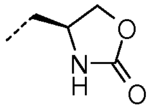
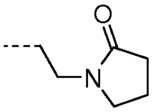
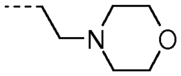
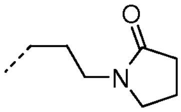
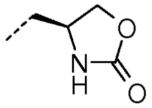
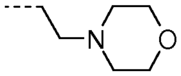
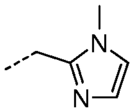
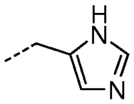
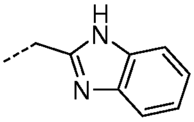


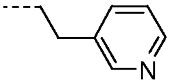
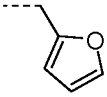
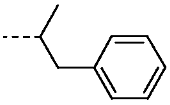
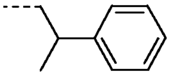
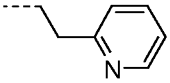
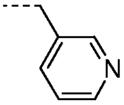
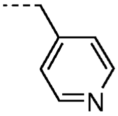
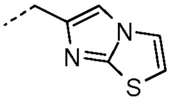
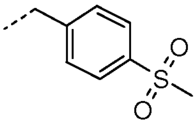
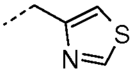
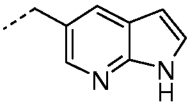
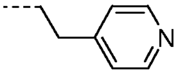
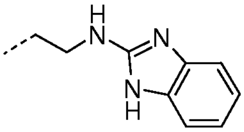
I

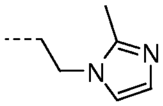
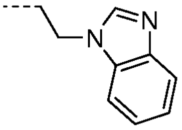
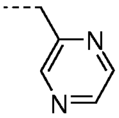
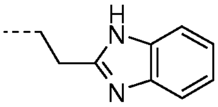
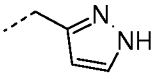
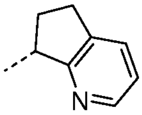
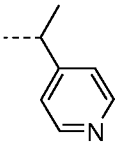
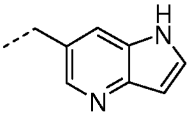
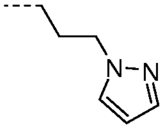
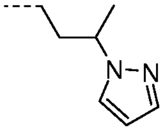
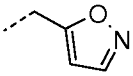
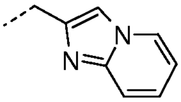
Table 3: Examples synthesized by General Method A, B, C, D, E, or F

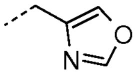
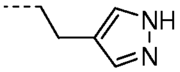
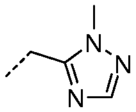
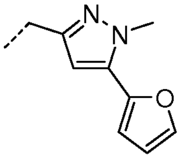
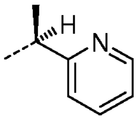
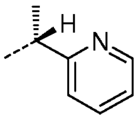
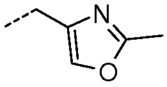
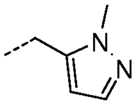
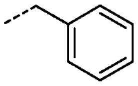
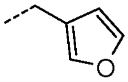
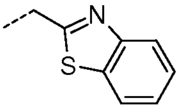
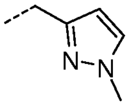
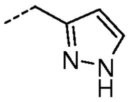
Ex #	A^2	L^1	-L^2-D	Synthesis	MS	Rt	$[M+H]^+$

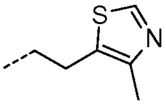
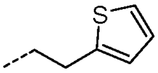
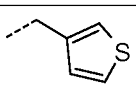
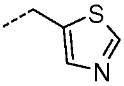
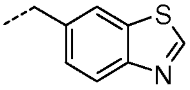
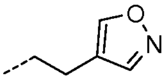
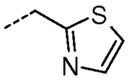
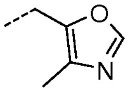
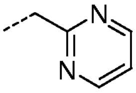
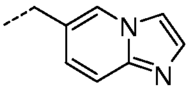
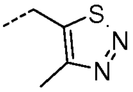
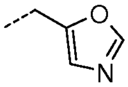
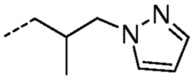
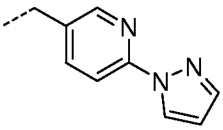
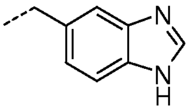
				Method	Method	(min)	
1	C	O		A	4	0.78	350.0
2	C	O		A	4	0.77	350.2
3	N	O		C	3	2.95	345.3
4	C	O		A	4	0.88	323
5	C	O		A	4	0.95	336.8
7	C	O		A	4	0.79	364.2
8	C	O		A	4	0.71	350.9
9	C	O		A	4	0.71	336.1
10	C	O		A	4	0.73	352
11	C	O		A	4	0.71	352.1
12	C	O		B	1	1.37	352.2
13	C	O		B	2	4.94	350.1
14	C	O		B	2	4.95	350.2

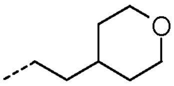
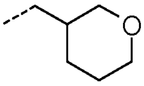
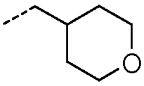
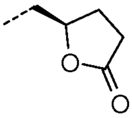
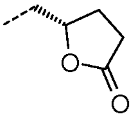
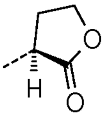
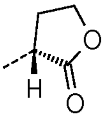
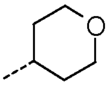
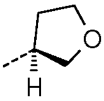
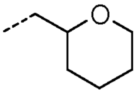
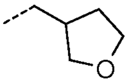
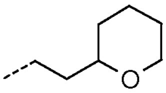
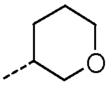
15	C	O		B	1	1.37	352.2
16	N	O		C	2	3.56	353.2
17	N	O		C	2	0.61	353.2
18	C	C		D	4	0.73	348.2
20	C	C		D	3	2.77	350.3
21	C	O		A	4	0.83	364.5
22	C	O		A	4	0.51	366.2
23	C	O		A	4	0.82	378.4
24	N	O		C	1	1.26	353.27
25	C	C		D	3	2.6	364.4
26	C	O		B	2	0.72	347.1
27	C	O		B	2	0.61	333.5
28	C	O		B	2	1.1	383.6

29	C	O		A	4	0.69	358.2
30	C	O		A	4	1.03	333.1
31	C	O		A	4	1.24	371.1
32	C	O		A	4	1.25	371.3
33	C	O		A	4	0.72	358.2
34	C	O		A	4	0.76	344.2
35	C	O		A	4	0.7	344.1
36	C	O		A	4	0.81	389.1
37	C	O		A	4	0.94	421.2
38	C	O		A	4	0.94	350.1
39	C	O		A	4	0.92	383.2
40	C	O		A	4	0.68	358.2
41	C	O		A	4	0.68	412.2

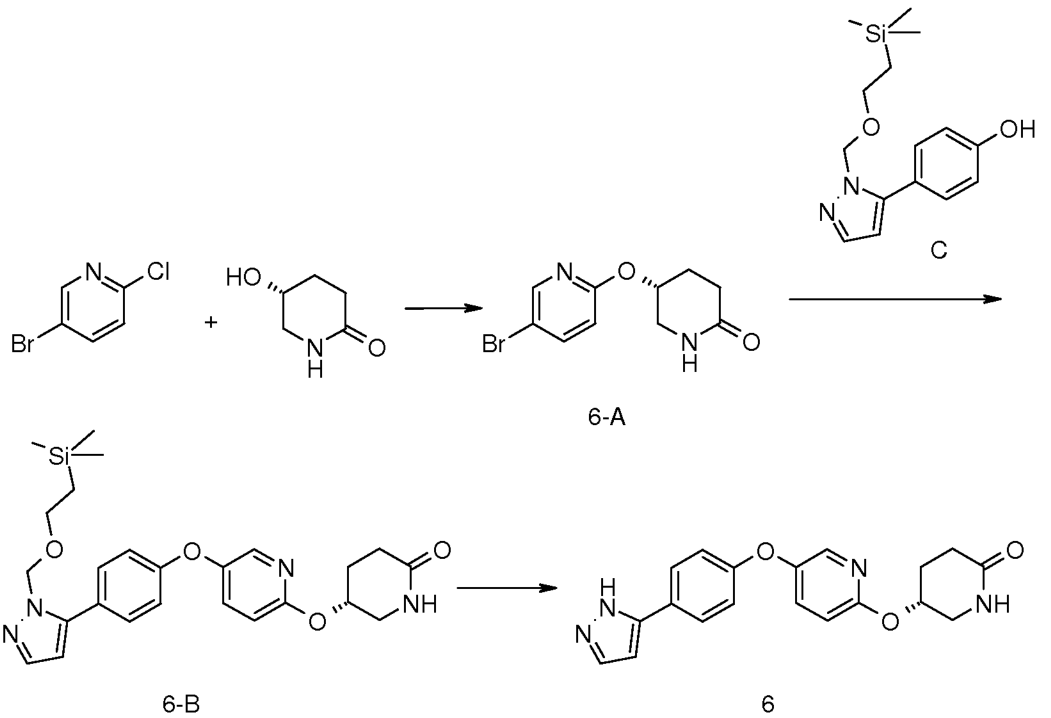
42	C	O		A	4	0.62	361.2
43	C	O		A	4	0.73	397.2
44	C	O		A	4	0.89	345.2
45	C	O		A	4	0.68	397.2
46	C	O		A	3	2.9	333.3
47	C	O		A	4	0.9	370.2
48	C	O		A	4	0.7	358.2
49	C	O		A	4	0.58	383.2
50	C	O		A	4	0.91	361.2
51	C	O		A	4	0.96	375.2
52	C	O		A	4	0.89	334.2
53	C	O		A	4	0.59	383.2

54	C	O		A	4	0.84	334.2
55	C	O		A	4	0.82	347.2
56	C	O		A	4	0.75	348.2
57	C	O		A	4	1.02	413.3
58	C	O		A	4	0.9	358.2
59	C	O		A	4	0.9	358.2
60	C	O		A	4	0.88	348.2
61	C	O		A	4	0.86	347.2
62	C	O		A	4	1.12	343.2
63	C	O		A	4	1.01	333.1
64	C	O		A	4	1.1	400.1
65	C	O		A	4	0.85	347
66	C	O		A	4	1.16	356.9

67	C	O		A	4	0.93	378.1
68	C	O		A	4	1.13	363.2
69	C	O		A	4	1.08	349.1
70	C	O		A	4	0.87	350.3
71	C	O		A	4	1.01	400.1
72	C	O		A	4	0.92	348.2
73	C	O		A	4	0.92	350.9
74	C	O		A	4	0.87	348.9
75	C	O		A	4	0.77	345.1
76	C	O		A	4	0.58	383.1
77	C	O		A	4	0.94	366.1
78	C	O		A	4	0.83	333.9
79	C	O		A	4	0.98	375.1
80	C	O		A	4	1.05	410.2
81	C	O		A	3	2.7	383.4

82	C	O		A	4	1.03	365.9
83	C	O		A	4	1.01	351.9
84	C	O		A	4	0.98	351.4
85	C	O		A	4	0.82	351.1
86	C	O		A	3	2.76	351.3
87	C	O		A	4	0.82	337.1
88	C	O		A	4	0.82	337.1
89	C	O		A	4	0.92	337.5
90	C	O		A	4	0.88	323.2
91	C	O		A	4	1.03	351.1
92	C	O		A	4	0.93	337.9
93	C	O		A	4	1.12	366.3
94	C	O		A	4	0.95	337

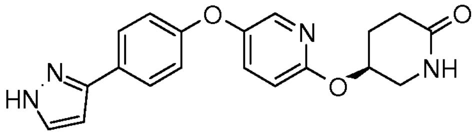
Example 6: Preparation of (R)-5-{5-[4-(2H-Pyrazol-3-yl)-phenoxy]-pyridin-2-yloxy}-piperidin-2-one (6)



Sodium tert-butoxide (439 mg, 4.6 mmol) is added to a solution of (R)-5-hydroxy-piperidin-2-one (287 mg, 2.5 mmol) in DMF (12 mL) at 0°C, and the mixture is warmed to room temperature. After 30 min, 5-bromo-2-cholo-pyridine (400 mg, 2.1 mmol) is added, and the mixture is heated to 100°C for 30 min. Upon cooling, the solution is poured into water/ EtOAc, and phases are separated. The aqueous layer is extracted twice with EtOAc. The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue is purified on reversed phase HPLC to provide Intermediate 6-A. A suspension of Intermediate C (278 mg, 0.96 mmol), Intermediate 6-A (315 mg, 1.20 mmol), potassium phosphate (763 mg, 3.60 mmol), and 2-picolinic acid (30 mg, 0.24 mmol) in DMSO (10 mL) is sparged with Argon for 10 minutes. Copper iodide (23 mg, 0.12 mmol) is added and the mixture is heated to 120° C for 2 hours in a microwave reactor. Upon cooling, the solution is diluted with EtOAc (10 mL) and filtered through a pad of Diatomaceous earth. The filtrate is washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue is purified by reverse phase HPLC to provide the Intermediate 6-B. 4N HCl in dioxane (2mL) is added to a solution of

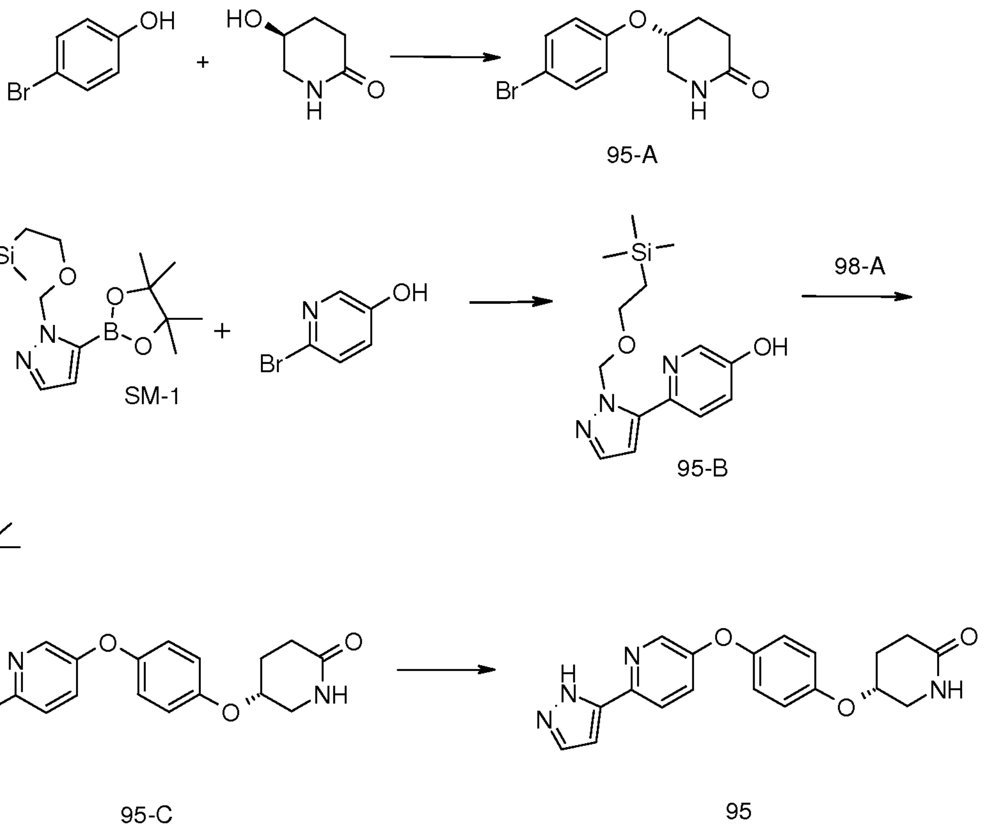
Intermediate 6-B (120 mg, 0.25 mmol) in 1,4-dioxane (1 mL), and the resulting solution is stirred at 45°C for 30 min. during which time a precipitate forms. The solids are isolated by filtration, and purified by reverse phase HPLC to provide an oil. The oil is then dissolved in MeOH (2mL), and passed through PL-HCO_3 MP-resin. The resin is washed with MeOH (2mL), and the combined extracts are concentrated to provide **6**. LC/MS Method 3: Rt = 2.79 min; ES+ m/z $[M+H]^+$ = 351.3.

Example 7: Preparation of (S)-5-{5-[4-(2H-Pyrazol-3-yl)-phenoxy]-pyridin-2-yloxy}-piperidin-2-one (7)



Compound **7** is prepared according to the procedure described above for the synthesis of Compound **6.** LC/MS Method 3: Rt = 2.79 min; ES+ m/z [M+H]+ = 351.3.

Example 95: Preparation of (R)-5-{4-[6-(2H-pyrazol-3-yl)-pyridin-3-yloxy]-phenoxy}-piperidin-2-one (95)



PS-PPh$_3$ resin (3 mmol/g; 1.93 g, 5.8 mmol) is added to a solution of 4-bromo-phenol (500 mg, 2.9 mmol) and (S)-5-hydroxy-piperidin-2-one (665 mg, 5.8 mmol) in THF (20 mL) . The suspension is heated to 65°C and treated with di-tert-butylazo-dicarboxylate (1.33 g, 5.8 mmol). The resulting mixture is stirred at 65°C for 16 hours then cooled to room temperature. The mixture is filtered through Diatomaceous earth and washed with THF (30 mL). The filtrate is concentrated, and the resulting residue is purified on SiO$_2$ (EtOAc/heptane, then MeOH/DCM) to provide Intermediate 95-A.

6-Bromo-pyridin-2-ol (200 m g, 1.15 mmol) and tetrakis(triphenylphosphine)palladium(0) (66 mg, 0.06 mmol) are suspended in DME (5 mL). After 10min, SM-1 (410 mg, 1.26 mmol) and 2N aqueous Na$_2$CO$_3$ (1.7 mL) are added. The reaction is then purged twice with argon and heated to 100 °C for 20 minutes in a microwave reactor. Upon cooling the reaction is diluted with EtOAc, washed with water and brine, dried over Na$_2$SO$_4$, filtered, and concentrated. The resulting residue is purified on SiO$_2$ (EtOAc/ heptane) to provide Intermediate 95-B.

A suspension of Intermediate 95-B (200 mg, 0.68 mmol), Intermediate 95-A (370 mg, 1.37mmol), cesium carbonate (447 mg, 1.37 mmol), and N,N-dimethylglycine hydrochloride (48 mg, 0.34 mmol) in DMSO (5 mL) is sparged with Argon for 10 minutes. Copper iodide (26 mg, 0.14 mmol) is added to and the mixture is heated to 140° C for 2 hours in a microwave reactor. Upon cooling, the solution is poured into water/EtOAc, and phases are separated. The aqueous layer is then extracted twice with EtOAc. The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue is purified on SiO_2 (EtOAc/ heptanes, then MeOH/ DCM) to provide Intermediate 95-C.

4N HCl in dioxane (1mL) is added to a solution of Intermediate 95-C (82 mg, 0.17 mmol) in 1, 4-dioxane (1 mL). The resulting solution is stirred at 45°C for 30 minutes during which time a precipitate forms. The resulting solid are filtered and purified on reversed phase HPLC to provide an oil. The oil is then dissolved in MeOH (2mL) and filtered through PL-HCO_3 MP-resin. The resulting resin is washed with MeOH (2mL) and the combined solvents are concentrated to provide **95**. LC/MS Method 3: Rt = 2.66 min.; ES+ m/z $[M+H]^+$ = 351.3.

Assessment of Biological Properties

Compounds are assessed for the ability to interact with human LTA_4 hydrolase in an enzymatic assay that measures the ability of the enzyme to cleave the peptide bond of arginyl-aminomethylcoumarin (Arg-AMC). LTA4H Enzyme (1nM final), Arg-AMC substrate (50 μM final), and compound are combined in a reaction buffer (50 mM Tris-HCl (pH 7.5), 100 mM KCl, 0.5% bovine serum albumin) at room temperature for 1h. The formation of product is assessed by measuring the fluorescence of aminomethylcoumarin product (excitation wavelength 380nm/emission wavelength 460nm).

In general, the preferred potency range (IC_{50}) of compounds in the above assay is between 0.1 nM to 10,000 nM, the more preferred potency range is 0.1 nM to 100 nM, and the most preferred potency range is 0.1 nM to 10 nM. The potencies of representative compounds of the invention in the enzyme assay are shown in Table 4 below.

Table 4. IC50 values of LTA4H Enzyme assay.

Example	IC$_{50}$ (nM)	Example	IC$_{50}$ (nM)	Example	IC$_{50}$ (nM)	Example	IC$_{50}$5 (nM)
1	0.2	26	1.2	51	4	76	0.9
2	0.2	27	2.2	52	4.1	77	1
3	0.2	28	1.4	53	3.7	78	2.8
4	3.9	29	4.9	54	4.2	79	2.7
5	6.8	30	65.6	55	7	80	1.9
6	3.5	31	900	56	0.6	81	14.2
7	0.5	32	360	57	11	82	7.9
8	0.5	33	5.2	58	44	83	2.9
9	76.7	34	1.5	59	42.7	84	4.6
10	0.2	35	3.9	60	3.9	85	0.8
11	1.3	36	6	61	1.4	86	0.8
12	0.1	37	3.5	62	142.3	87	23.1
13	0.5	38	3.3	63	52.9	88	16.4
14	0.3	39	7.6	64	44.2	89	4.8
15	0.3	40	3.2	65	12.9	90	2.4
16	0.2	41	0.2	66	959.2	91	10.7
17	1.5	42	0.3	67	11.2	92	3.3
18	0.8	43	1.3	68	820	93	26.9
19	1.9	44	1.1	69	65.3	94	14.1
20	0.6	45	1.7	70	4.9	95	1.6
21	0.7	46	6.1	71	59.5		
22	0.2	47	82.4	72	6.1		
23	0.7	48	16.9	73	10.4		
24	0.2	49	1.2	74	17.9		
25	0.5	50	1.2	75	6.6		

Compounds of the invention are additionally tested in a human whole blood assay to determine their ability to inhibit the synthesis of LTB$_4$ in a cellular system. Compounds are combined with heparinized human whole blood and incubated for 15 minutes at 37°C. Calcimycin (20µM final, prepared in phosphate-buffered saline, pH 7.4) is then added and the mixture is incubated for another 30 minutes at 37°C. The samples are centrifuged for 5 min at low speed (1500 x g) and the plasma layer is removed. Plasma LTB_4 concentrations are then measured using an antibody-based homogenous time-resolved fluorescence method (CisBio, Bedford, MA).

In general, the preferred potency range (IC_{50}) of compounds in the above assay is between 10 nM to 10,000 nM, the more preferred potency range is 10 nM to 1000 nM, and the most preferred potency range is 10 nM to 100 nM. The potencies of representative compounds of the invention in the WHB assays are shown in Table 5.

Table 5. IC_{50} values of LTB_4 production inhibition assay in human whole blood.

Ex. No.	IC_{50} (nM)	Example	IC_{50} (nM)	Example	IC_{50} (nM)	Example	IC_{50} (nM)
1	246	26	2106	51	3111	76	1415
2	163	27	1838	52	2600	77	492
3	142	28	5000	53	5000	78	1652
4	1037	29	2281	54	5000	79	2107
5	1347	30	5000	55	2500	80	1646
6	1079	31	5000	56	5000	81	5000
7	280	32	5000	57	5000	82	2672
8	222	33	3362	58	5000	83	1738
9	5000	34	2537	59	5000	84	1455
10	126	35	1783	60	5000	85	5000
11	573	36	4500	61	1117	86	4499
12	104	37	2090	62	5000	87	5000
13	214	38	5000	63	5000	88	5000
14	178	39	5000	64	5000	89	1769
15	150	40	3118	65	5000	90	777
16	52	41	673	66	5000	91	5000
17	425	42	172	67	5000	92	1199
18	581	43	1909	68	5000	93	4600
19	554	44	766	69	5000	94	1997

Ex. No.	IC_{50} (nM)	Example	IC_{50} (nM)	Example	IC_{50} (nM)	Example	IC_{50} (nM)
20	229	45	5000	70	2392	95	367
21	813	46	4900	71	5000		
22	179	47	5000	72	2546		
23	529	48	3924	73	4099		
24	123	49	3137	74	2551		
25	123	50	2106	75	2837		

METHOD OF USE

The compounds of the invention are effective inhibitors of leukotriene A_4 hydrolase (LTA4H) and thus inhibit leukotriene production. Therefore, in one embodiment of the invention, there is provided a method of treating leukotriene-mediated disorders using compounds of the invention. In another embodiment, there is provided a method of treating cardiovascular, inflammatory, allergic, pulmonary and fibrotic diseases, renal diseases and cancer using compounds of the invention.

In one embodiment, the invention relates to the use of a compound of the invention for the preparation of a medicament for the treatment leukotriene-mediated disorders. In another embodiment, the invention relates to the use of a compound of the invention, for the preparation of a medicament for treating cardiovascular, inflammatory, allergic, pulmonary and fibrotic diseases, renal diseases and cancer.

In one embodiment, the invention relates to a compound of the invention for use as a medicament for the treatment leukotriene-mediated disorders. In another embodiment, the invention relates to a compound of the invention for use in a method of treating cardiovascular, inflammatory, allergic, pulmonary and fibrotic diseases, renal diseases and cancer.

Without wishing to be bound by theory, by inhibiting the activity of LTA4H, the compounds of the invention block the production of LTB_4 resulting from the oxidation of arachidonic acid by 5-LO and subsequent metabolism. Thus, the inhibition of LTA4H activity is an attractive means for preventing and treating a variety of diseases mediated by LTB_4. These include:

Cardiovascular diseases including atherosclerosis, myocardial infarction, stroke, aortic aneurysm, sickle cell crisis, ischemia-reperfusion injury, pulmonary arterial hypertension and sepsis;

Allergic diseases including asthma, allergic rhinitis, rhinosinusitis, atopic dermatitis and urticaria;

Fibrotic diseases including airway remodeling in asthma, idiopathic pulmonary fibrosis, scleroderma, asbestosis;

Pulmonary syndromes including adult respiratory distress syndrome, viral bronchiolitis, obstructive sleep apnea, chronic obstructive pulmonary disease, cystic fibrosis, and bronchopulmonary dysplasia;

Inflammatory diseases including rheumatoid arthritis, osteoarthritis, gout, glomerulonephritis, interstitial cystitis, psoriasis, inflammatory bowel disease systemic lupus erythematosus, transplant rejection, inflammatory and allergic ocular diseases;

Cancer including solid tumors, leukemias and lymphomas; and Renal diseases such as glomerulonephritis.

In one embodiment, the invention relates to a method of treating a leukotriene-mediated disorder comprising administering to a be patient in need thereof one or more of the compounds of the invention, or a pharmaceutically acceptable salt thereof.

In another embodiment, the invention relates to a method of treating a cardiovascular disease comprising administering to a be patient in need thereof one or more of the compounds of the invention, or a pharmaceutically acceptable salt thereof.

In another embodiment, the invention relates to a method of treating a cardiovascular disease comprising administering to a be patient in need thereof one or more of the compounds of the invention, or a pharmaceutically acceptable salt thereof, wherein the cardiovascular disease is selected from atherosclerosis, myocardial infarction, stroke, aortic aneurysm, sickle cell crisis, ischemia-reperfusion injury, pulmonary arterial hypertension and sepsis.

In another embodiment, the invention relates to a method of treating atherosclerosis comprising administering to a be patient in need thereof one or more of the compounds of the invention, or a pharmaceutically acceptable salt thereof.

For treatment of the above-described diseases and conditions, a therapeutically effective dose will generally be in the range from about 0.01 mg to about 100 mg/kg of body weight per dosage of a compound of the invention; preferably, from about 0.1 mg to about 20 mg/kg of body weight per dosage. For example, for administration to a 70 kg person, the dosage range would be from about 0.7 mg to about 7000 mg per dosage of a compound of the invention, preferably from about 7.0 mg to about 1400 mg per dosage. Some degree of routine dose optimization may be required to determine an optimal dosing level and pattern. The active ingredient may be administered from 1 to 6 times a day.

General Administration and Pharmaceutical Compositions

When used as pharmaceuticals, the compounds of the invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared using procedures well known in the pharmaceutical art and comprise at least one compound of the invention. The compounds of the invention may also be administered alone or in combination with adjuvants that enhance stability of the compounds of the invention, facilitate administration of pharmaceutical compositions containing them in certain embodiments, provide increased dissolution or dispersion, increased antagonist activity, provide adjunct therapy, and the like. The compounds according to the invention may be used on their own or in conjunction with other active substances according to the invention, optionally also in conjunction with other pharmacologically active substances. In general, the compounds of this invention are administered in a therapeutically or pharmaceutically effective amount, but may be administered in lower amounts for diagnostic or other purposes.

Administration of the compounds of the invention, in pure form or in an appropriate pharmaceutical composition, can be carried out using any of the accepted modes of administration of pharmaceutical compositions. Thus, administration can be, for example, orally, buccally (e.g., sublingually), nasally, parenterally, topically, transdermally, vaginally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as, for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. The pharmaceutical compositions will generally include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, diluents, vehicles, or combinations thereof. Such pharmaceutically acceptable excipients, carriers, or additives as well as methods of making pharmaceutical compositions for various modes or administration are well-known to those of skill in the art. The state of the art is evidenced, e.g., by *Remington: The Science and Practice of Pharmacy*, 20th Edition, A. Gennaro (ed.), Lippincott Williams & Wilkins, 2000; *Handbook of Pharmaceutical Additives*, Michael & Irene Ash (eds.), Gower, 1995; *Handbook of Pharmaceutical Excipients*, A.H. Kibbe (ed.), American Pharmaceutical Ass'n, 2000; H.C. Ansel and N.G. Popovish, *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 5th ed., Lea and Febiger, 1990; each of which is incorporated herein by reference in their entireties to better describe the state of the art.

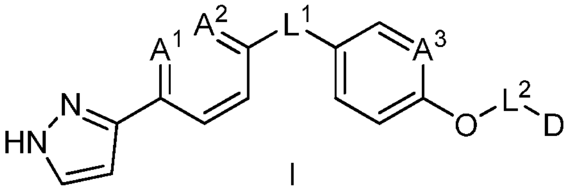
In one embodiment, the invention relates to a pharmaceutical composition comprising a pharmaceutically effective amount of a compound of one or more compounds of the invention, or a pharmaceutically acceptable salt thereof, and an excipient.

As one of skill in the art would expect, the forms of the compounds of the invention utilized in a particular pharmaceutical formulation will be selected (e.g., salts) that possess suitable physical characteristics (e.g., water solubility) that are required for the formulation to be efficacious.

Claims

What is claimed is:

1. A compound of formula (I):



I

,

or a pharmaceutically acceptable salt thereof,

wherein:

A^1, A^2 and A^3 are each independently CH or N;

L^1 is a linker selected from –O- and -CH_2-;

L^2 is absent or a -(C_1-C_6)alkylene- linker; wherein said -(C_1-C_6)alkylene- linker is optionally substituted with one to three groups selected from –OH, halo, -(C_1-C_6)alkyl;

D is a ring selected from

(a) -(C_3-C_7)cycloalkyl, (C_6-C_{10})aryl, and -(5- to 11-membered)heteroaryl;

(b) -(4- to 11-membered)heterocycloalkyl, comprising an O or S ring atom and optionally 1 to 3 additional ring heteroatoms selected from N, O, and S;

(c) 4-8 member monocyclic heterocyclic comprising a N ring atom and 1 to 3 additional ring heteroatoms selected from N, O, and S;

(d) a 6 to 11-membered fused bicyclic, bridged bicyclic or spirocyclic heterocyclic radical comprising a N ring atom and optionally 1 to 3 additional ring heteroatoms selected from N, O, and S; and

(e) a group selected from 2-oxo-pyrrolidin-1-yl, 2-oxo-pyrrolidin-3-yl, 2-oxo-pyrrolidin-5-yl, 1-methyl-2-oxo-pyrrolidin-4-yl, and 2-oxo-piperidin-5-yl

wherein each of said D rings is optionally substituted with one to three R^1 groups; and wherein each of said D rings is further optionally substituted, where possible, by one or two groups independently selected from (=O) and (=S);

each R^1 is independently selected from halo, -OH, -CF_3, -CN, -(C_1-C_6)alkyl, -O(C_1-C_6)alkyl, -C(O)R^2, -C(O)OR^2, -C(O)N(R^2)$_2$, -N(R^2)$_2$, -N(R^2)C(O)R^2, -S(O)$_2R^2$, -N(R^2)-S(O)$_2$-R^2, -(C_3-C_6)cycloalkyl, -(5- to 11-membered)heterocycloalkyl, -(C_6-C_{10})aryl, and -(5- to 11-membered)heteroaryl; wherein each of said, -(C_1-C_6)alkyl, -O(C_1-C_6)alkyl, -(C_3-C_6)cycloalkyl, -(5- to 11-membered)heterocycloalkyl, -(C_6-C_{10})aryl, and -(5- to 11-membered)heteroaryl of said R^1 group is optionally substituted with one to three groups selected from halo, -OH, -CF_3, -(C_1-C_6)alkyl, -C(O)OH, -C(O)OC_1-C_6)alkyl, -C(O)(C_1-C_6)alkyl), -NH_2, -NH(C_1-C_6)alkyl, N((C_1-C_6)alkyl)$_2$ and –CN;

each R^2 is independently selected from the group consisting of -H, -(C_1-C_6)alkyl, -(C_3-C_6)cycloalkyl, -(5- to 11-membered)heterocycloalkyl, -(C_6-C_{10})aryl, and -(5- to 11-membered)heteroaryl; wherein each of said, -(C_1-C_6)alkyl, -O(C_1-C_6)alkyl, -(C_3-C_6)cycloalkyl, -(5- to 11-membered)heterocycloalkyl, -(C_6-C_{10})aryl, and -(5- to 11-membered)heteroaryl of said R^2 group is optionally independently substituted by one to three groups selected from halo, -OH, -CF_3, -(C_1-C_6)alkyl, -NH_2, -NH(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$ and -CN.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A^1, A^2 and A^3 are each CH.

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A^1 and A^3 are each CH, and A^2 is N.

4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A^1 and A^2 are each CH, and A^3 is N.

5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A^2 and A^3 are each CH, and A^1 is N.

6. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein L^1 is -O-.

7. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein L^1 is $-CH_2-$.

8. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein L^2 is absent.

9. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein L^2 is a -(C_1-C_6)alkylene- linker; and wherein said -(C_1-C_6)alkylene- linker is optionally substituted with one to three groups selected from –OH, halo, -(C_1-C_6)alkyl.

10. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein L^2 is methylene, ethylene, or propylene; and wherein each of said methylene, ethylene and propylene is optionally substituted with methyl.

11. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein said D is a ring selected from -(C_3-C_7)cycloalkyl, (C_6-C_{10})aryl, and -(5- to 11-membered)heteroaryl; wherein each of said -(C_3-C_7)cycloalkyl, (C_6-C_{10})aryl, and -(5- to 11-membered)heteroaryl is optionally substituted with one to three R^1 groups; and wherein each of said -(C_3-C_7)cycloalkyl, (C_6-C_{10})aryl, and -(5- to 11-membered)heteroaryl is further optionally substituted, where possible, by one or two groups independently selected from (=O) and (=S).

12. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein said ring D is a -(4- to 11-membered)heterocycloalkyl comprising an O or S ring atom and optionally 1 to 3 additional ring heteroatoms selected from N, O, and S; wherein said -(4- to 11-membered)heterocycloalkyl is optionally substituted with one to three R^1 groups; and wherein said -(4- to 11-membered)heterocycloalkyl is further

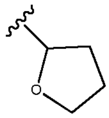
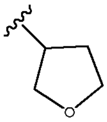
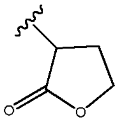
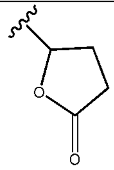
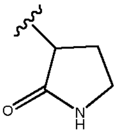
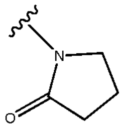
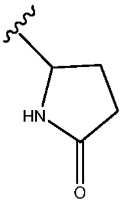
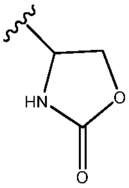
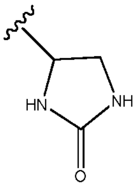
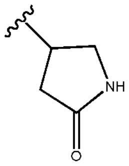
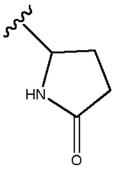
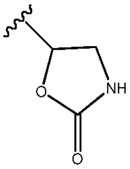
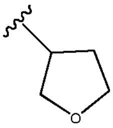
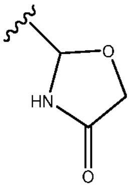
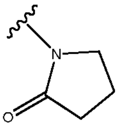
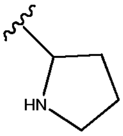
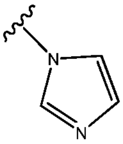
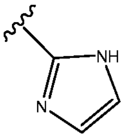
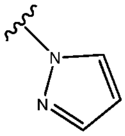
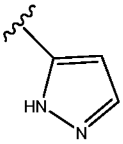
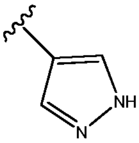
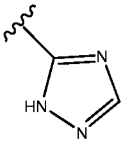
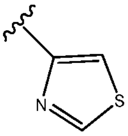
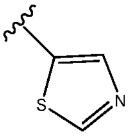
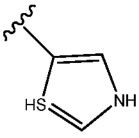
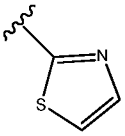
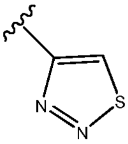
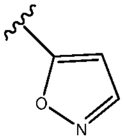
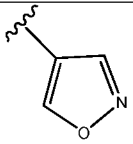
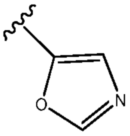
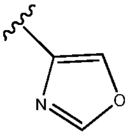
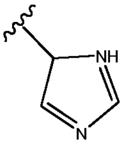
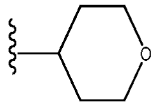
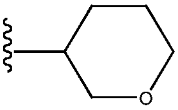
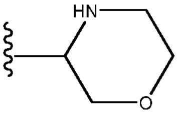
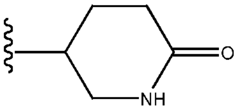
optionally substituted, where possible, by one or two groups independently selected from (=O) and (=S).

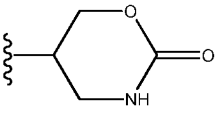
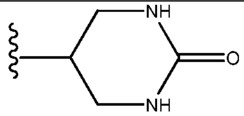
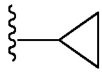
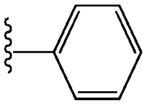
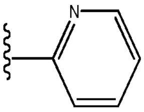
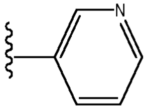
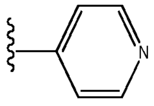
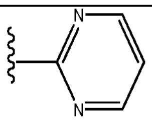
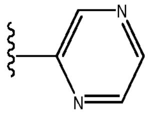
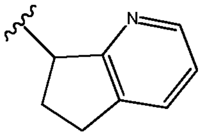
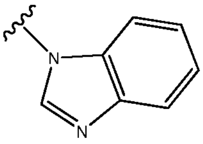
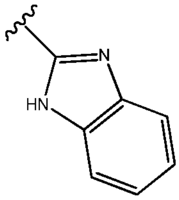
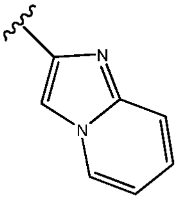
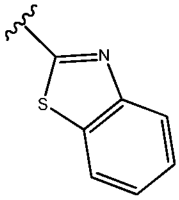
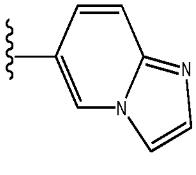
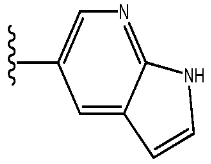
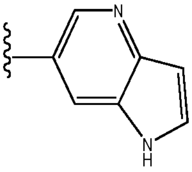
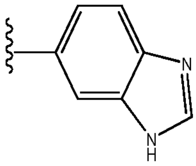
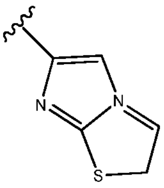
13. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein said ring D is a 4-8 member monocyclic heterocyclic comprising a N ring atom and 1 to 3 additional ring heteroatoms selected from N, O, and S; wherein said 4-8 member monocyclic heterocyclic is optionally substituted with one to three R^1 groups; and wherein said 4-8 member monocyclic heterocyclic is further optionally substituted, where possible, by one or two groups independently selected from (=O) and (=S).

14. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein said ring D is a 6 to 11-membered fused bicyclic, bridged bicyclic or spirocyclic heterocyclic radical comprising a N ring atom and optionally 1 to 3 additional ring heteroatoms selected from N, O, and S; wherein said 6 to 11-membered fused bicyclic, bridged bicyclic or spirocyclic heterocyclic radical is optionally substituted with one to three R^1 groups; and wherein said 6 to 11-membered fused bicyclic, bridged bicyclic or spirocyclic heterocyclic radical is further optionally substituted, where possible, by one or two groups independently selected from (=O) and (=S).

15. The compound of any one of claims 1 to 10, wherein said ring D is selected from 2-oxo-pyrrolidin-1-yl, 2-oxo-pyrrolidin-3-yl, 2-oxo-pyrrolidin-5-yl, 1-methyl-2-oxo-pyrrolidin-4-yl, and 2-oxo-piperidin-5-yl; wherein each of said 2-oxo-pyrrolidin-1-yl, 2-oxo-pyrrolidin-3-yl, 2-oxo-pyrrolidin-5-yl, 1-methyl-2-oxo-pyrrolidin-4-yl, and 2-oxo-piperidin-5-yl is optionally substituted with one to three R^1 groups; and wherein each of said selected from 2-oxo-pyrrolidin-1-yl, 2-oxo-pyrrolidin-3-yl, 2-oxo-pyrrolidin-5-yl, 1-methyl-2-oxo-pyrrolidin-4-yl, and 2-oxo-piperidin-5-yl is further optionally substituted, where possible, by one or two groups independently selected from (=O) and (=S).

16. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein said ring D is selected from:

 ,	 ,	 ,	 ,
 ,	 ,	 ,	 ,
 ,	 ,	 ,	 ,
 ,	 ,	 ,	 ,
 ,	 ,	 ,	 ,
 ,	 ,	 ,	 ,
 ,	 ,	 ,	 ,
 ,	 ,	 ,	 ,
 ,	 ,	 ,	 ,

 ,	 ,	 ,	 ,
	 ,	 ,	 ,
 ,	 ,	 ,	 ,
 ,	 ,	 ,	 ,
 ,	 ,	and  .	

wherein each of the aforementioned D rings is optionally substituted by one to three R^1 groups.

17. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein L^2 and D taken together represent a group selected from:

(1-methyl-pyrrolidin-2-on-4-yl)methyl;

(pyrrolidin-2-on-3yl)oxy;

(pyrrolidin-2-on-5-yl)methyloxy;

2-(pyrrolidin-2-on-1-yl)ethyloxy;

3-(pyrrolidin-2-on-1-yl)propyloxy;

(tetrahydrofuran-3-yl)oxy;

(tetrahydrofuran-2-yl)methyloxy;

(tetrahydrofuran-3-yl)methyloxy;(piperidin-2-on-5-yl)oxy;

(1,3-oxazolidin-2-on-4-yl)methyloxy;
(1,3-oxazolidin-2-on-5-yl)methyloxy;
(morpholin-3-yl)methyloxy;
(morpholin-4-yl)ethyloxy;
1H-pyrazol-5-yl;
(1H-pyrazol-5-yl)methyloxy;
(1H-pyrazol-3-yl)methyloxy;
(1-methyl-1H-pyrazol-3-yl)methyloxy;
(1-methyl-1H-pyrazol-5-yl)methyloxy;
(1-methyl-2-(2-furyl)-pyrazol-5-yl)methyloxy;
3-(1H-pyrazol-1-yl)-ethyloxy;
2-(1H-pyrazol-4-yl)-ethyloxy;
3-(1H-pyrazol-1-yl)-3-methylpropyloxy;
(furan-2-yl)methyloxy;
(furan-3-yl)methyloxy;
(dihydrofuran-2(3H)-on-3-yl)oxy;
(dihydrofuran-2(3H)-on-5-yl)methyloxy;
(pyridin-3-yl)methyloxy;
(pyridin-4-yl)methyloxy;
(2-(1H-pyrazol-1-yl)- pyridin-5-yl)methyloxy;
1-(pyridin2-yl)-ethyloxy;
2-(pyridin-2-yl)ethyloxy;
2-(pyridin-3-yl)ethyloxy;
2-(pyridin-4-yl)-ethyloxy;
(pyrimidin-2-yl)methyloxy;
(thien-3-yl)methyloxy;
2-(thien-2-yl)ethyloxy;
(tetrahydro-2H-pyran-3-yl)oxy;
(tetrahydro-2H-pyran-4-yl)oxy);
(tetrahydro-2H-pyran-2-yl)methyloxy;
(tetrahydro-2H-pyran-3-yl)methyloxy;

(tetrahydro-2H-pyran-4-yl)methyloxy;
2-(tetrahydro-2H-pyran-2-yl)ethyloxy;
2-(tetrahydro-2H-pyran-4-yl)ethyloxy;
(2-methyl-1H-imidazol-1-yl)ethyloxy;
(pyrazin-2-yl)methyloxy;
benzyloxy;
(4-(methylsulfonyl)benzyl)oxy;
(1,3-thiazol-2-yl)methyloxy;
(1,3-thiazol-5-yl)methyloxy;
2-(1,3-thiazol-5-yl)ethyloxy;
(4-methyl-1,2,3-thiadiazol-5-yl)methyloxy;
(isoxazol-5-yl)methyloxy;
2-(isoxazol-4-yl)ethyloxy;
(1-methyl-1,2,4-triazol-5-yl)methyloxy;
(1,3-oxazol-4-yl)methyloxy;
(1,3-oxazol-5-yl)methyloxy;
(2-methyl-1,3-oxazol-4-yl)methyloxy;
(4-methyl-1,3-oxazol-5-yl)methyloxy;
(1H-benzimidazol-2-yl)methyloxy;
(1H-benzimidazol-5-yl)methyloxy;
(1H-benzimidazol-1-yl)ethyloxy;
(1H-benzimidazol-2-yl)ethyloxy;
2-((1H-benzimidazol-2-yl)-amino)ethyloxy;
(imidazo[2,1-b][1,3]thiazol-2-yl)methyloxy;
(1H-pyrrolo[2,3-b]pyridin-5-yl)methyloxy;
(6,7-dihydro-5H-cyclopenta[b]pyridin-7-yl)oxy;
2-(1H-pyrrolo[3,2-b]pyridin-6-yl)-ethyloxy;
(imidazo[1,2-a]pyridin-2-yl)methyloxy;
(1,3-benzothiazol-2-yl)methyloxy; and
(imidazo[1,2-a]pyridin-6-yl)methyloxy.

18. A pharmaceutical composition comprising the compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

19. A method of treating a cardiovascular disease comprising administering to a compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, to a patient in need thereof

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/047024

A. CLASSIFICATION OF SUBJECT MATTER

INV.	C07D401/12	C07D401/14	C07D403/12	C07D405/12	C07D405/14
	C07D409/12	C07D413/12	C07D413/14	C07D417/12	C07D471/04
	C07D513/04	C07D231/12	A61K31/415	A61K31/4155	A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/132822 A1 (NOE MARK C [US] ET AL) 19 September 2002 (2002-09-19) paragraph [0188] claims 1, 10, 11	1,2,6,8, 11,13, 18,19
X	US 2007/066820 A1 (SANDANAYAKA VINCENT [US] ET AL) 22 March 2007 (2007-03-22) examples 133, 134 claims 1,29,32	1-7, 9-13, 15-19

-/--

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 12 September 2012	Date of mailing of the international search report 20/09/2012
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Brandstetter, T

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SANDANAYAKA V ET AL: "Discovery of novel leukotriene A4 hydrolase inhibitors based on piperidine and piperazine scaffolds", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 20, no. 9, 1 May 2010 (2010-05-01), pages 2851-2854, XP027012848, ISSN: 0960-894X [retrieved on 2010-04-16] the whole document -----	1-19
A	SUNDARAPANDIAN THANGAPANDIAN ET AL: "Molecular Docking and Pharmacophore Filtering in the Discovery of Dual-Inhibitors for Human Leukotriene A4 Hydrolase and Leukotriene C4 Synthase", JOURNAL OF CHEMICAL INFORMATION AND MODELING, vol. 51, no. 1, 24 January 2011 (2011-01-24), pages 33-44, XP55037798, ISSN: 1549-9596, DOI: 10.1021/ci1002813 the whole document -----	1-19
A	DOUGLAS R. DAVIES ET AL: "Discovery of Leukotriene A4 Hydrolase Inhibitors Using Metabolomics Biased Fragment Crystallography +", JOURNAL OF MEDICINAL CHEMISTRY, vol. 52, no. 15, 13 August 2009 (2009-08-13), pages 4694-4715, XP55037803, ISSN: 0022-2623, DOI: 10.1021/jm900259h the whole document -----	1-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2012/047024

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002132822 A1	19-09-2002	AR 035362 A1	12-05-2004
		AU 1080002 A	06-05-2002
		BG 107651 A	31-12-2003
		BR 0114917 A	01-07-2003
		CA 2425280 A1	02-05-2002
		CN 1714084 A	28-12-2005
		CR 6939 A	25-11-2003
		CZ 20031069 A3	12-05-2004
		EC SP034568 A	25-06-2003
		EE 200300195 A	15-10-2003
		EP 1332136 A2	06-08-2003
		HR P20030331 A2	30-06-2003
		HU 0302337 A2	28-10-2003
		IS 6749 A	17-03-2003
		JP 2004512327 A	22-04-2004
		MA 26956 A1	20-12-2004
		MX PA03003734 A	28-07-2003
		NO 20031852 A	23-06-2003
		NZ 524774 A	24-09-2004
		OA 12528 A	02-06-2006
		PA 8531501 A1	30-06-2003
		PE 05852002 A1	06-07-2002
		PL 362919 A1	02-11-2004
		SK 4872003 A3	03-08-2004
		SV 2003000704 A	13-01-2003
		US 2002132822 A1	19-09-2002
		UY 26981 A1	20-06-2002
		WO 0234726 A2	02-05-2002
		ZA 200302192 A	05-05-2004
US 2007066820 A1	22-03-2007	AU 2006297798 A1	12-04-2007
		BR PI0616187 A2	14-06-2011
		CA 2623348 A1	12-04-2007
		CN 101312948 A	26-11-2008
		EA 200800865 A1	30-12-2008
		EP 1926708 A1	04-06-2008
		JP 2009508949 A	05-03-2009
		KR 20080050500 A	05-06-2008
		SG 166769 A1	29-12-2010
		US 2007066820 A1	22-03-2007
		US 2007078263 A1	05-04-2007
		US 2009163462 A1	25-06-2009
		WO 2007040681 A1	12-04-2007
		WO 2007040682 A1	12-04-2007