



(51) International Patent Classification:

C07D 213/75 (2006.01) **A61P 27/06** (2006.01)
A61K 31/435 (2006.01) **A61P 11/00** (2006.01)

(21) International Application Number:

PCT/US2010/040014

(22) International Filing Date:

25 June 2010 (25.06.2010)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/221,687 30 June 2009 (30.06.2009) US

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(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, RO, RS, RU, 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, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, 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, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

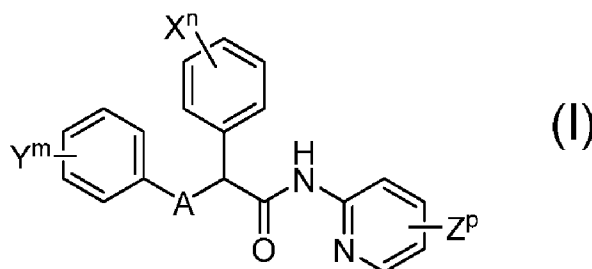
Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) **Title:** OPTIONALLY SUBSTITUTED 2-(ARYLMETHYL, ARYLOXY OR ARYLTHIO) -N- PYRIDIN-2 -YL-ARYL ACETAMIDE OR 2, 2-BIS (ARYL) -N-PYRIDIN-2-YL ACETAMIDE COMPOUNDS AS MEDICAMENTS FOR THE TREATMENT OF EYE DISEASES



(57) **Abstract:** The invention provides compounds represented by the formula (I), each of which compounds may have sphingosine-1-phosphate receptor agonist and or antagonist biological activity: wherein: A, m, n, p, a, X, Y and Z are defined in the specification. These compounds are useful for treating a disease or condition selected from the group consisting of glaucoma, dry eye, angiogenesis and pulmonary edema.

**OPTIONALLY SUBSTITUTED 2-(ARYLMETHYL, ARYLOXY OR ARYLTHIO
-N-PYRIDIN-2-YL-ARYL ACETAMIDE OR 2,2-BIS (ARYL) -N-PYRIDIN-2-YL ACETAMIDE
COMPOUNDS AS MEDICAMENTS FOR THE TREATMENT OF EYE DISEASES**

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By Inventors
Wenkui Ken Fang and Ken Chow

CROSS REFERENCE

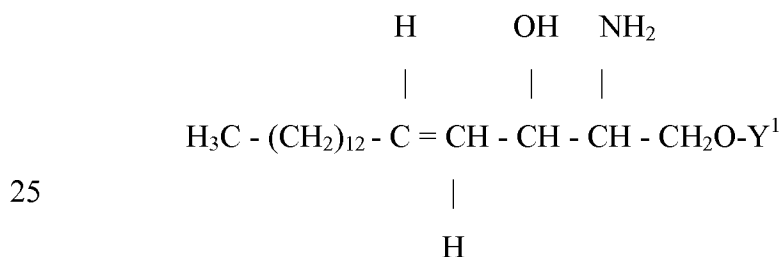
This application claims the benefit of U.S. Provisional Patent Application Serial
10 Number 61/221,687, filed on June 30, 2009, the entire disclosure of which is incorporated
herein by this specific reference.”

FIELD OF THE INVENTION

The present invention relates to derivatives and/or analogues of sphingosine which
15 are useful as drugs for the treatment of eye diseases and conditions selected from the group
consisting of glaucoma, dry eye and angiogenesis and pulmonary edema.

SUMMARY OF ART

Sphingosine is a compound having the chemical structure shown in the general
formula described below, in which Y¹ is hydrogen. It is known that various sphingolipids,
20 having sphingosine as a constituent, are widely distributed in the living body including on
the surface of cell membranes of cells in the nervous system



A sphingolipid is one of the lipids having important roles in the living body. A
disease called lipidosis is caused by accumulation of a specified sphingolipid in the body.
Sphingolipids present on cell membranes function to regulate cell growth; participate in
30 the development and differentiation of cells; function in nerves; are involved in the
infection and malignancy of cells; etc. Many of the physiological roles of sphingolipids
remain to be solved. Recently the possibility that ceramide, a derivative of sphingosine,
has an important role in the mechanism of cell signal transduction has been indicated, and
studies about its effect on apoptosis and cell cycle have been reported

Sphingosine-1-phosphate is an important cellular metabolite, derived from ceramide that is synthesized de novo or as part of the sphingomeyeline cycle (in animals cells). It has also been found in insects, yeasts and plants.

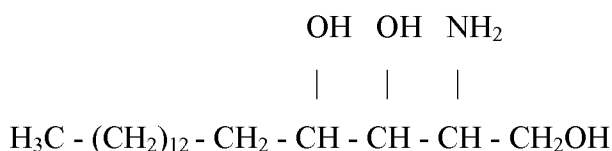
The enzyme, ceramidase, acts upon ceramides to release sphingosine, which is phosphorylated by sphingosine kinase, a ubiquitous enzyme in the cytosol and endoplasmic reticulum, to form sphingosine-1-phosphate. The reverse reaction can occur also by the action of sphingosine phosphatases, and the enzymes act in concert to control the cellular concentrations of the metabolite, which concentrations are always low. In plasma, such concentration can reach 0.2 to 0.9 μM , and the metabolite is found in association with the lipoproteins, especially the HDL. It should also be noted that sphingosine-1-phosphate formation is an essential step in the catabolism of sphingoid bases.

Like its precursors, sphingosine-1-phosphate is a potent messenger molecule that perhaps uniquely operates both intra- and inter-cellularly, but with very different functions from ceramides and sphingosine. The balance between these various sphingolipid metabolites may be important for health. For example, within the cell, sphingosine-1-phosphate promotes cellular division (mitosis) as opposed to cell death (apoptosis), which it inhibits. Intracellularly, it also functions to regulate calcium mobilization and cell growth in response to a variety of extracellular stimuli. Current opinion appears to suggest that the balance between sphingosine-1-phosphate and ceramide and/or sphingosine levels in cells is critical for their viability. In common with the lysophospholipids, especially lysophosphatidic acid, with which it has some structural similarities, sphingosine-1-phosphate exerts many of its extra-cellular effects through interaction with five specific G protein-coupled receptors on cell surfaces. These are important for the growth of new blood vessels, vascular maturation, cardiac development and immunity, and for directed cell movement.

Sphingosine-1 phosphate is stored in relatively high concentrations in human platelets, which lack the enzymes responsible for its catabolism, and it is released into the blood stream upon activation of physiological stimuli, such as growth factors, cytokines, and receptor agonists and antigens. It may also have a critical role in platelet aggregation and thrombosis and could aggravate cardiovascular disease. On the other hand the relatively high concentration of the metabolite in high-density lipoproteins (HDL) may have beneficial implications for atherogenesis. For example, there are recent suggestions that sphingosine-1-phosphate, together with other lysolipids such as sphingosylphosphorylcholine and lysosulfatide, are responsible for the beneficial clinical

effects of HDL by stimulating the production of the potent antiatherogenic signaling molecule nitric oxide by the vascular endothelium. In addition, like lysophosphatidic acid, it is a marker for certain types of cancer, and there is evidence that its role in cell division or proliferation may have an influence on the development of cancers. These are currently
 5 topics that are attracting great interest amongst medical researchers, and the potential for therapeutic intervention in sphingosine-1-phosphate metabolism is under active investigation.

Fungi and plants have sphingolipids and the major sphingosine contained in these organisms has the formula described below. It is known that these lipids have important
 10 roles in the cell growth of fungi and plants, but details of the roles remain to be solved.



Recently it has been known that derivatives of sphingolipids and their related
 15 compounds exhibit a variety of biological activities through inhibition or stimulation of the metabolism pathways. These compounds include inhibitors of protein kinase C, inducers of apoptosis, immuno-suppressive compounds, antifungal compounds, and the like. Substances having these biological activities are expected to be useful compounds for various diseases.

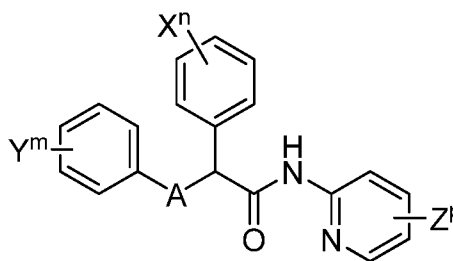
20 Derivatives of sphingosine have been prepared in various patents. For example, see U.S. Patents 4,952,683; 5,110,987; 6,235,912 and 6,239,297 which are hereby incorporated by reference.

Also, compounds which are similar to certain sphingosine derivatives, but which are not reported as being ligands for the sphingosine receptors are reported in various patents
 25 and published patent applications. See for example, U.S. Patents 5,294,722; 5,102,901; 5,403,851, 5,580,878 and U.S. Patent Application Publication No. U.S. 2003/0125371 A2 which are hereby incorporated by reference in their entirety.

SUMMARY OF THE INVENTION

The present invention provides compounds that are able to regulate the functions of
 30 sphingolipid, and pharmaceutical compositions comprising said compounds.

In one aspect of the present invention there is disclosed compounds, having sphingosine-1-phosphate receptor agonist and or antagonist biological activity, represented by the formula I:



wherein:

A is O, S or $(CR_2)_a$ wherein R is selected from the group consisting of H, or lower alkyl;

5 m, n and p are 0 or an integer of from 1 to 5, e.g. 1 or 2;

a is 0 or 1,

wherein when a is 1,

X and Y are independently selected from the group consisting of alkyl, preferably lower alkyl, e.g. methyl, alkyloxy, preferably lower alkyloxy, e.g. methoxy, hydroxyl, halogen, e.g. chloro or bromo, nitrile, trifluoromethyl and carboxy; and

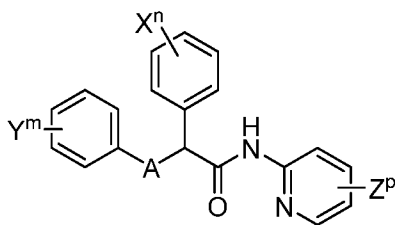
10 Z is selected from the group consisting of alkyl, preferably lower alkyl, e.g. methyl, alkyloxy, preferably lower alkoxy, e.g. methoxy, hydroxyl, halogen, e.g. fluoro, chloro, or bromo, nitrile, trifluoromethyl and carboxy and

when a is 0,

15 X, Y are independently selected from the group consisting of alkyl, preferably lower alkyl, e.g. methyl, alkyloxy, preferably lower alkoxy, e.g. methoxy, hydroxyl, halogen, nitrile, trifluoromethyl, and carboxy; and

Z is selected from the group consisting of alkyl, preferably lower alkyl, e.g. methyl, alkyloxy, preferably lower alkyloxy, e.g. methoxy, hydroxyl, halogen, preferably fluoro, nitrile, trifluoromethyl and carboxy provided however that when a is 0 and the pyridyl ring is (a) 5-chloro pyridyl, then both (i) m and n are not 0 and (ii) X and Y are not chloro or methyl or (b) 5-bromo or iodo pyridyl, then both m and n are not 0, or a pharmaceutically acceptable salt of said compound.

25 In another aspect of this invention, there is disclosed a method of treating or preventing a disease or condition selected from the group consisting of glaucoma, dry eye, angiogenesis and pulmonary edema, which comprises administering to a patient in need thereof a compound represented by the formula II



wherein:

A is O, S or $(CR_2)_a$ wherein R is selected from the group consisting of H, or lower alkyl;

- 5 m, n and p are 0 or an integer of from 1 to 5, e.g. 1 or 2;
 a is 0 or 1,

X and Y are independently selected from the group consisting of alkyl, preferably lower alkyl, e.g. methyl, alkyloxy, preferably lower alkyloxy, e.g. methoxy, hydroxyl, halogen, e.g. chloro or bromo, nitrile, trifluoromethyl and carboxy; and.

- 10 Z is selected from the group consisting of alkyl, preferably lower alkyl, e.g. methyl, alkyloxy, preferably lower alkoxy, e.g. methoxy, hydroxyl, halogen, e.g. fluoro, chloro, or bromo, nitrile, trifluoromethyl and carboxy, or a pharmaceutically acceptable salt of said compound

DETAILED DESCRIPTION OF THE INVENTION

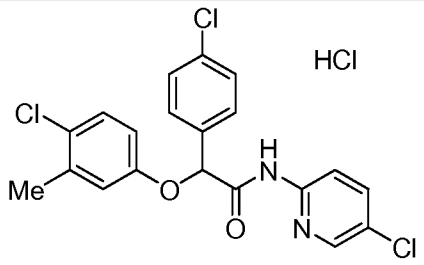
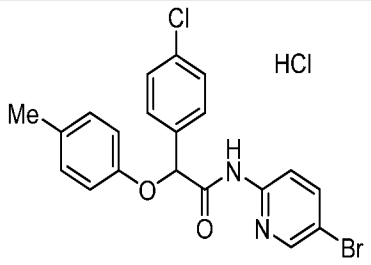
Novel compounds having this general structure were synthesized and tested for sphingosine 1-phosphate receptor (S1P) activity using the FLIPR assay. Cells expressing the receptor of interest (S1P₁, S1P₂ or S1P₃) and a G-protein (Gqi5 or G16) are loaded with fluo-4, a calcium sensitive dye. After removal of excess dye by washing, the cells are placed in the FLIPR TETRA instrument. Baseline fluorescence readings are taken prior to addition the compound to be tested. Agonists will trigger the receptor to interact with the G-protein, leading to an increase in intracellular calcium. The increase in intracellular calcium causes an increase in the fluorescence of the cells, due to the presence of fluo-4.

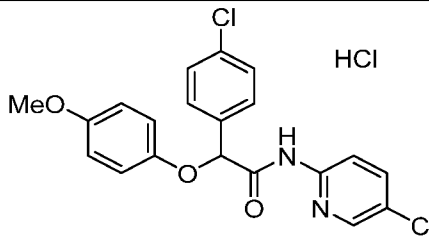
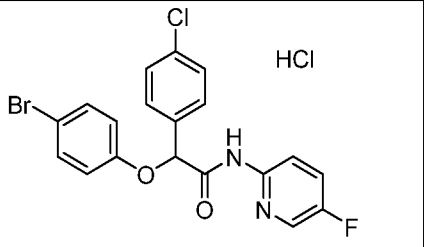
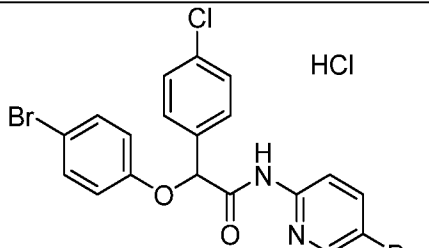
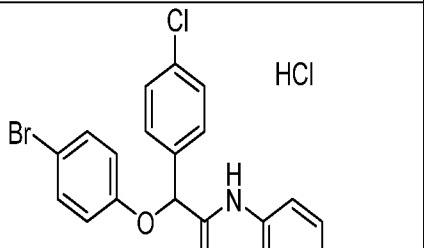
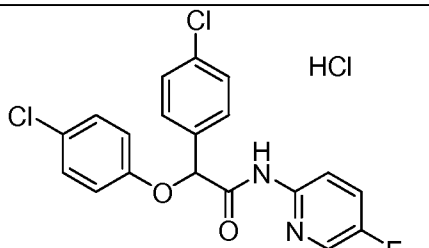
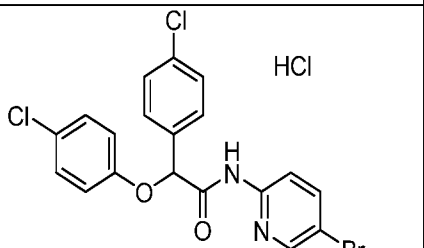
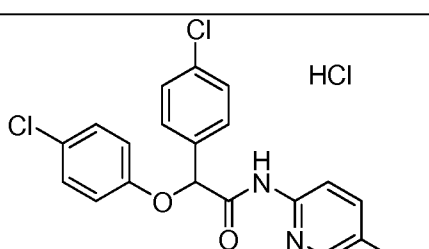
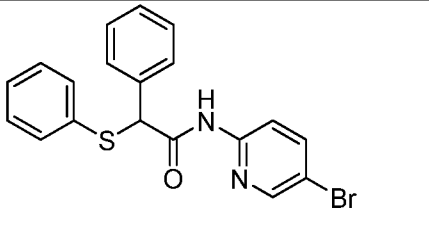
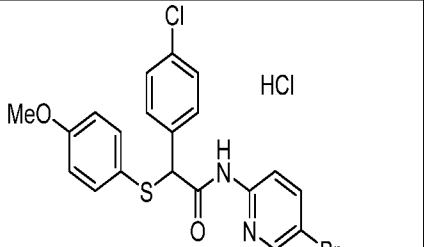
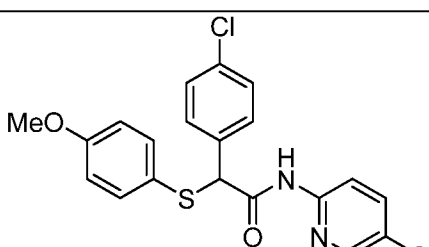
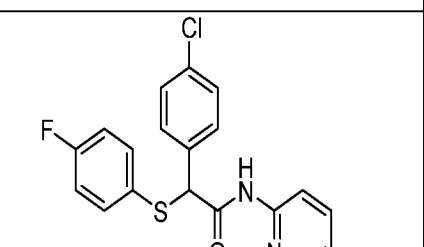
This fluorescence increase is recorded by the FLIPR TETRA. After the calcium transient signal has decreased towards baseline, the standard agonist sphingosine 1-phosphate is added. If the test compound is an antagonist, an initial calcium signal will not be generated and the antagonist will prevent the generation of a calcium signal from sphingosine 1-phosphate. The level of fluorescence is compared to that of sphingosine 1-phosphate, and the EC₅₀ or IC₅₀ of the compound determined by curve fitting.

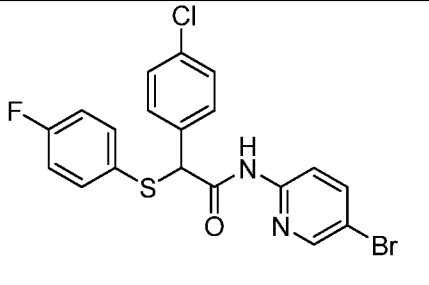
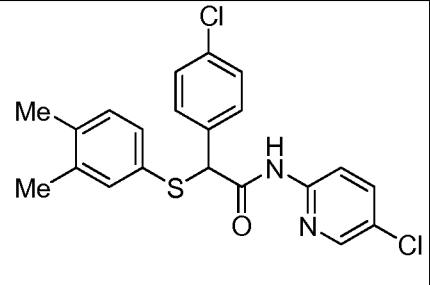
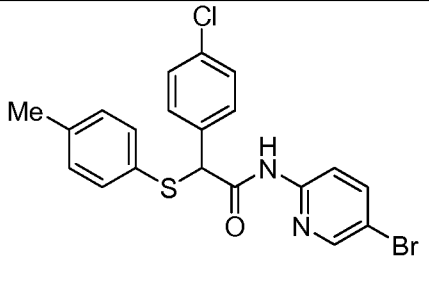
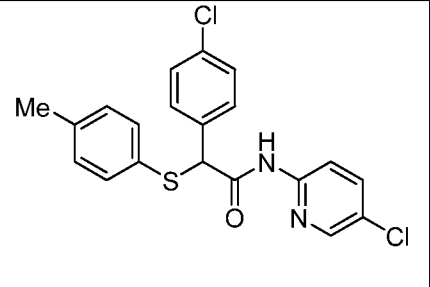
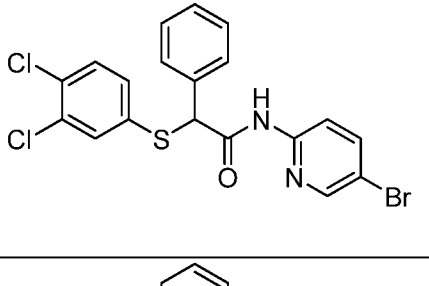
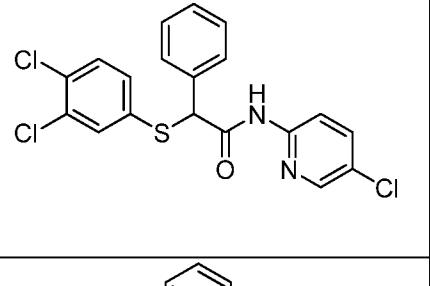
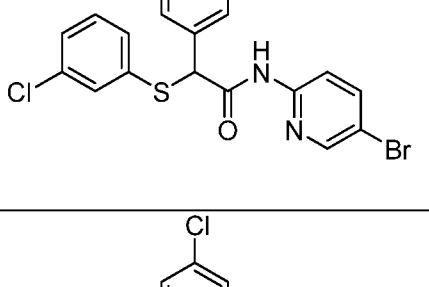
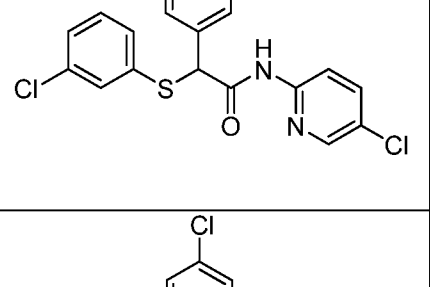
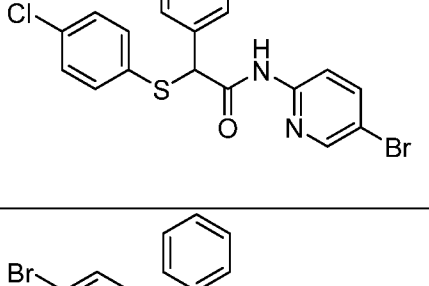
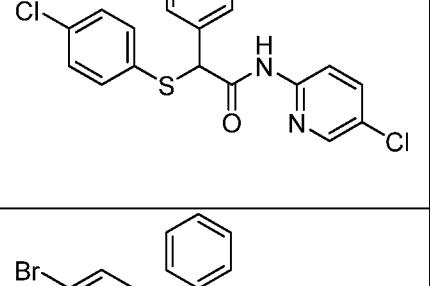
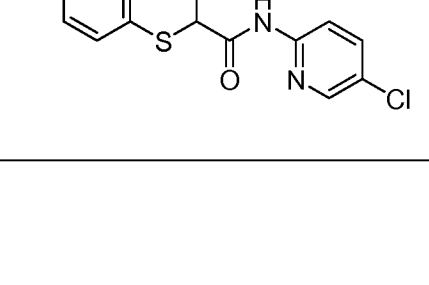
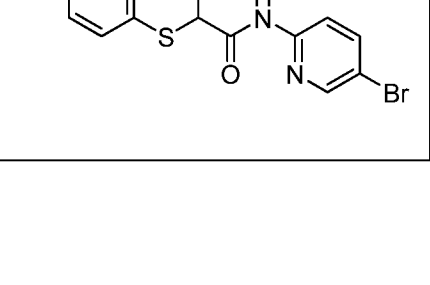
The compounds in this invention will be useful for the treatment of mammals, including humans, for diseases or conditions selected from the group consisting of glaucoma, dry eye and angiogenesis disorders and pulmonary edema.

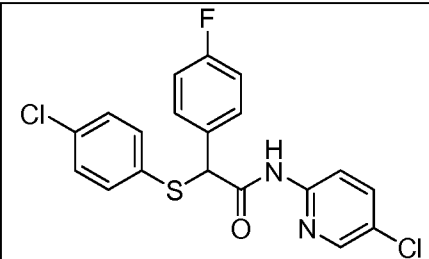
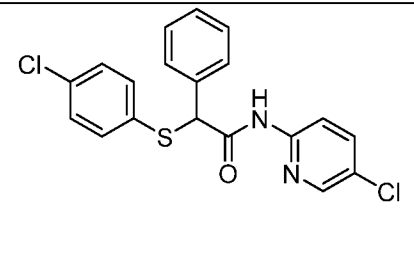
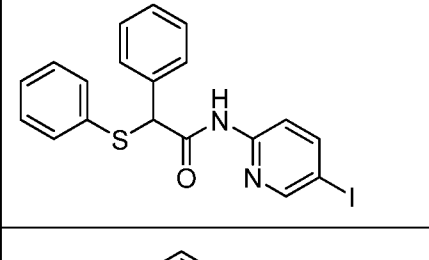
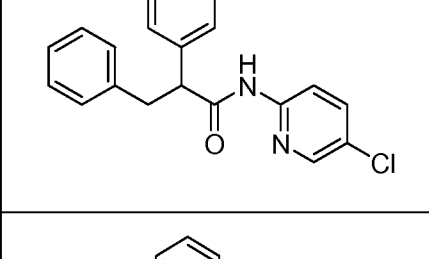
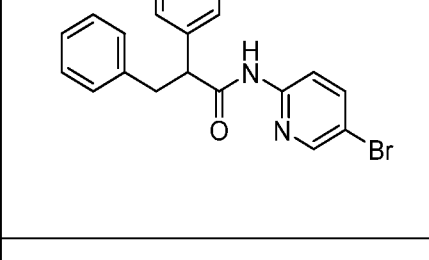
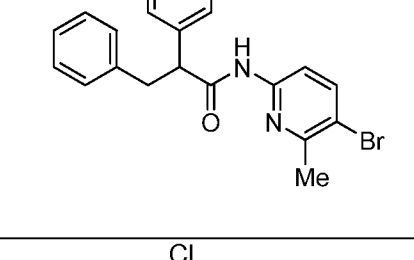
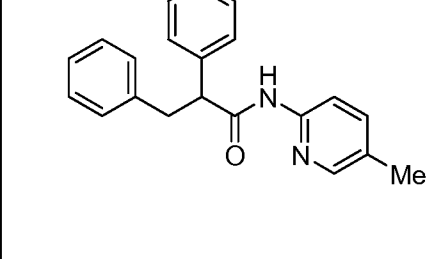
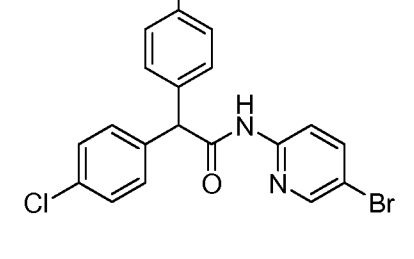
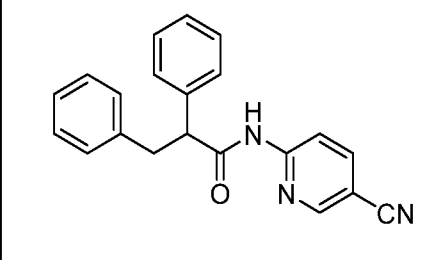
Specific Examples of the compounds of formula I include the compounds of Table 1, below.

TABLE 1

Example Number	Structure	Example Number	Structure
1		2	

3		4	
5		6	
7		8	
9			
10		11	
12		13	

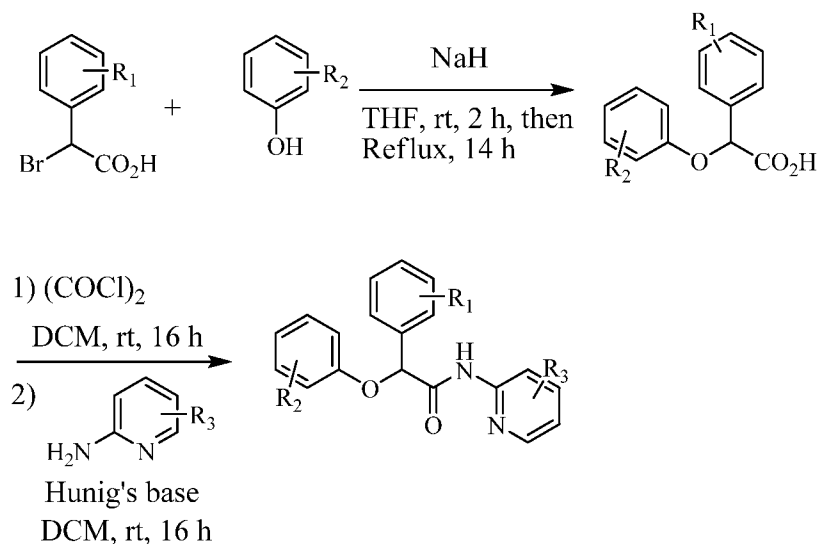
14	 <chem>Fc1ccc(S[C@@H](c2ccc(Cl)cc2)C(=O)Nc3ccc(Br)cn3)cc1</chem>	15	 <chem>Cc1cc(C)c(S[C@@H](c2ccc(Cl)cc2)C(=O)Nc3ccc(Cl)cn3)cc1</chem>
16	 <chem>Cc1ccc(S[C@@H](c2ccc(Cl)cc2)C(=O)Nc3ccc(Br)cn3)cc1</chem>	17	 <chem>Cc1ccc(S[C@@H](c2ccc(Cl)cc2)C(=O)Nc3ccc(Cl)cn3)cc1</chem>
18	 <chem>Clc1cc(Cl)c(S[C@@H](c2ccccc2)C(=O)Nc3ccc(Br)cn3)cc1</chem>	19	 <chem>Clc1cc(Cl)c(S[C@@H](c2ccccc2)C(=O)Nc3ccc(Cl)cn3)cc1</chem>
20	 <chem>Clc1cccc(S[C@@H](c2ccccc2)C(=O)Nc3ccc(Br)cn3)c1</chem>	21	 <chem>Clc1cccc(S[C@@H](c2ccccc2)C(=O)Nc3ccc(Cl)cn3)c1</chem>
22	 <chem>Clc1ccc(S[C@@H](c2ccc(Cl)cc2)C(=O)Nc3ccc(Br)cn3)cc1</chem>	23	 <chem>Clc1ccc(S[C@@H](c2ccc(Cl)cc2)C(=O)Nc3ccc(Cl)cn3)cc1</chem>
24	 <chem>Brc1cccc(S[C@@H](c2ccccc2)C(=O)Nc3ccc(Cl)cn3)c1</chem>	25	 <chem>Brc1ccc(S[C@@H](c2ccccc2)C(=O)Nc3ccc(Br)cn3)cc1</chem>

26	 <chem>Clc1ccc(S[C@@H](C(=O)Nc2cc(Cl)nc2)C(=O)c3cc(F)cc3)cc1</chem>	27	 <chem>Clc1ccc(S[C@@H](C(=O)Nc2cc(Cl)nc2)C(=O)c3cc(Cl)nc3)cc1</chem>
28	 <chem>Ic1cc(NC(=O)[C@@H](SPh)C(=O)c2cc(I)nc2)ccc1</chem>		
29	 <chem>Clc1cc(NC(=O)[C@@H](Sc2ccccc2)C(=O)c3cc(Cl)nc3)ccc1</chem>		
30	 <chem>Brc1cc(NC(=O)[C@@H](Sc2ccccc2)C(=O)c3cc(Br)nc3)ccc1</chem>	31	 <chem>Cc1cc(NC(=O)[C@@H](Sc2ccccc2)C(=O)c3cc(Br)nc3)ccc1</chem>
32	 <chem>Cc1cc(NC(=O)[C@@H](Sc2ccccc2)C(=O)c3cc(C)nc3)ccc1</chem>	33	 <chem>Brc1cc(NC(=O)[C@@H](Sc2cc(Cl)cc2)C(=O)c3cc(Cl)cc3)ccc1</chem>
34	 <chem>N#Cc1cc(NC(=O)[C@@H](Sc2ccccc2)C(=O)c3cc(C#N)nc3)ccc1</chem>		

Some compounds within the scope of the invention may be prepared as depicted in the procedures described below, wherein $R_1 = X$, $R_2 = Y$ and $R_3 = Z$.

The invention is further illustrated by the following examples which are illustrative of a specific mode of practicing the invention and are not intended as limiting the scope of the claims.

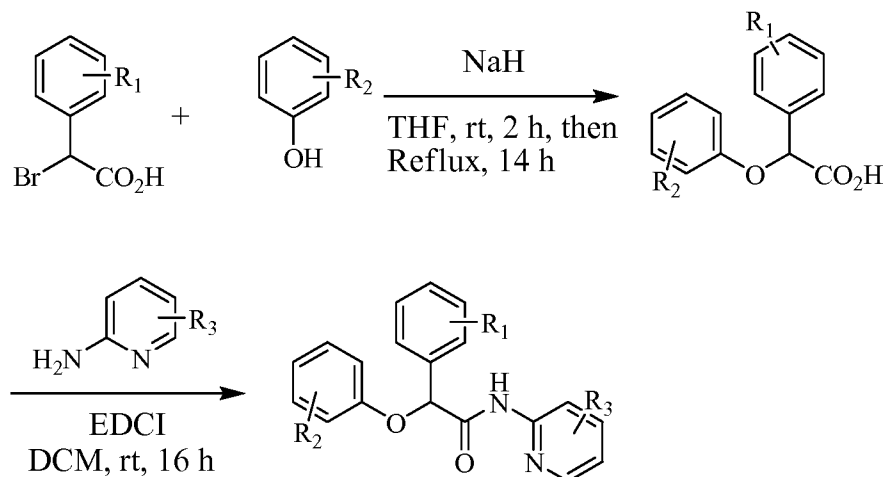
General Procedure A for the Synthesis of 2-(Substituted Phenoxy)-2-(substituted phenyl)-N-(substituted pyridin-2-yl)acetamide Hydrochloride:



The intermediate 2-(substituted phenoxy)-2-(substituted phenyl)acetic acid is obtained from the appropriate substituted α -bromophenylacetic acid (1 eq), substituted phenol (1 eq) and sodium hydride (2-3 eq) according to the synthetic protocol published in William T. Brady, Yun Seng F. Giang, Alan P. Marchand, An Hsiang Wu *J. Org. Chem.*; 1987; 52(15); 3457-3461, (hereinafter Brady et al.).

This carboxylic acid is then converted into the corresponding acid chloride by the method published in Martin Newcomb, Michael T. Burchill, Thomas M. Deeb *J. Am. Chem. Soc.*; 1988; 110(19); 6528-6535 (hereinafter Newcomb et al.). The acid chloride (1 eq) and an appropriate substituted 2-aminopyridine (1.5-2.0 eq) are dissolved in 50 ml of dichloromethane at room temperature. Hunig's base (3.50 mL) is added, and the resulting reaction mixture is stirred at room temperature for 14 hours. The reaction mixture is then concentrated and diluted with ethyl acetate. The organic phase is washed sequentially with water and brine, then dried with sodium sulfate and concentrated. Flash chromatography (30 % EtOAc/hexanes) gives the desired free base, which is mixed with HCl in MeOH. Concentration and recrystallization from ether gives the final desired product in HCl salt form.

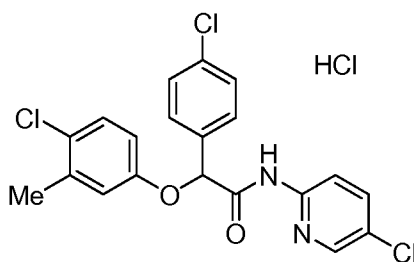
General Procedure B for the Synthesis of 2-(Substituted phenoxy)-2-(substituted phenyl)-N-(substituted pyridin-2-yl)acetamide Hydrochloride:



The intermediate 2-(substituted phenoxy)-2-(substituted phenyl)acetic acid is
 5 obtained from the appropriate substituted α -bromophenylacetic acid (1 eq), substituted phenol (1 eq) and sodium hydride (2-3 eq) according to the synthetic protocol published in William T. Brady, Yun Seng F. Giang, Alan P. Marchand, An Hsiang Wu *J. Org. Chem.*; 1987; 52(15); 3457-3461. This carboxylic acid is then mixed with an appropriate substituted 2-aminopyridine (1.2-1.5 eq) in 50ml of dichloromethane at room temperature.
 10 EDCI (1.5 to 2 eq) is added, followed by a catalytic amount of DMAP (30 mg). The resulting reaction mixture is stirred at room temperature for 14 hours. The reaction mixture is then concentrated and chromatographed (30 % EtOAc/hexanes) to give the desired free base, which is mixed with HCl in MeOH. Concentration and recrystallization from ether gives the final desired product in HCl salt form.

15

EXAMPLE 1



Synthesis of 2-(4-chloro-3-methylphenoxy)-2-(4-chlorophenyl)-N-(5-chloropyridin-2-yl)acetamide hydrochloride:

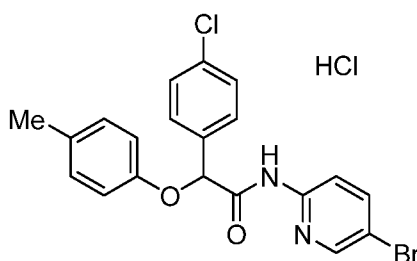
The title compound was generated from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid, 4-chloro-3-methylphenol and 5-chloropyridin-2-amine according
 20

to General procedure B described above. The intermediate 2-(4-chloro-3-methylphenoxy)-2-(4-chlorophenyl)acetic acid was used in the subsequent synthetic transformation without further purification.

2-(4-Chloro-3-methylphenoxy)-2-(4-chlorophenyl)acetic acid: The title compound was obtained from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid (12.00 g, 48.10 mmol), 4-chloro-3-methylphenol (5.90 g, 41.38 mmol) and sodium hydride (60% oil dispersion, 5.50 g, 137.50 mmol) according to the protocols as outlined in general procedure B above. This acid was used in the next synthetic step without further purification.

2-(4-Chloro-3-methylphenoxy)-2-(4-chlorophenyl)-N-(5-chloropyridin-2-yl)acetamide hydrochloride: The title compound was obtained from 2-(4-chloro-3-methylphenoxy)-2-(4-chlorophenyl)acetic acid (taken from the previous step, crude, 3.00 g, 9.64 mmol), 5-chloropyridin-2-amine (1.50 g, 11.67 mmol) and EDCI (3.50 g, 18.25 mmol) according to the protocols as outlined in general procedure B above. Spectroscopic Data: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.23 (s, 3 H), 6.21 (s, 1 H), 6.85 (dd, *J* = 8.80, 2.93 Hz, 1 H), 7.04 (d, *J* = 2.69 Hz, 1 H), 7.29 (d, *J* = 8.56 Hz, 1 H), 7.46 (d, *J* = 8.56 Hz, 2 H), 7.67 (d, *J* = 8.56 Hz, 2 H), 7.85 (dd, *J* = 8.93, 2.57 Hz, 1 H), 7.97 (d, *J* = 8.80 Hz, 1 H), 8.36 (d, *J* = 2.44 Hz, 1 H), 11.28 (s, 1 H), 11.43 - 11.93 (br s, 1 H).

EXAMPLE 2



Synthesis of *N*-(5-bromopyridin-2-yl)-2-(4-chlorophenyl)-2-(p-tolyloxy)acetamide hydrochloride:

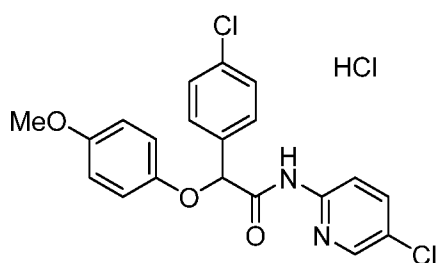
The title compound was generated from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid, *p*-cresol and 5-bromopyridin-2-amine according to General procedure B described above. The intermediate 2-(4-chlorophenyl)-2-(p-tolyloxy)acetic acid was used in the subsequent synthetic transformation without further purification.

2-(4-Chloro-phenyl)-2-(p-tolyloxy)acetic acid: The title compound was obtained from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid (12.00 g, 48.10 mmol), *p*-cresol (5.20 g, 48.09 mmol) and sodium hydride (60% oil dispersion, 5.50 g,

137.50 mmol) according to the protocols as outlined in general procedure B above. This acid was used in the next synthetic step without further purification.

N-(5-Bromopyridin-2-yl)-2-(4-chlorophenyl)-2-(*p*-tolxyloxy)acetamide hydrochloride: The title compound was obtained from 2-(4-chloro-phenyl)-2-(*p*-tolxyloxy)acetic acid (taken from the previous step, crude, 2.70 g, 9.76 mmol), 5-bromopyridin-2-amine (1.90 g, 10.98 mmol) and EDCI (3.50 g, 18.25 mmol) according to the protocols as outlined in general procedure B above. Spectroscopic Data: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.18 (s, 3 H), 6.09 (s, 1 H), 6.89 (d, *J* = 8.56 Hz, 2 H), 7.07 (d, *J* = 8.80 Hz, 2 H), 7.47 (d, *J* = 8.56 Hz, 2 H), 7.66 (d, *J* = 8.56 Hz, 2 H), 7.90 - 7.95 (m, 1 H), 7.96 - 8.01 (m, 1 H), 8.05 (br s, 1 H) 8.45 (d, *J* = 2.45 Hz, 1 H), 11.17 (s, 1 H).

EXAMPLE 3



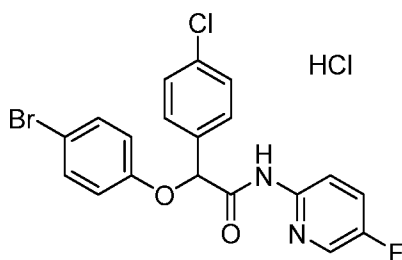
Synthesis of 2-(4-chlorophenyl)-*N*-(5-chloropyridin-2-yl)-2-(4-methoxyphenoxy)acetamide hydrochloride:

15 The title compound was generated from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid, 4-methoxyphenol and 5-chloropyridin-2-amine according to General procedure B described above. The intermediate 2-(4-chlorophenyl)-2-(4-methoxyphenoxy)acetic acid was used in the subsequent synthetic transformation without further purification.

20 *2*-(4-Chlorophenyl)-2-(4-methoxyphenoxy)acetic acid: The title compound was obtained from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid (12.00 g, 48.10 mmol), 4-methoxyphenol (6.00 g, 48.33 mmol) and sodium hydride (60% oil dispersion, 5.50 g, 137.50 mmol) according to the protocols as outlined in general procedure B above. This acid was used in the next synthetic step without further purification.

25 *2*-(4-Chlorophenyl)-*N*-(5-chloropyridin-2-yl)-2-(4-methoxyphenoxy)acetamide hydrochloride: The title compound was obtained from 2-(4-chlorophenyl)-2-(4-methoxyphenoxy)acetic acid (taken from the previous step, crude, 2.90 g, 9.91 mmol), 5-

chloropyridin-2-amine (1.50 g, 11.67 mmol) and EDCI (3.80 g, 19.82 mmol) according to the protocols as outlined in general procedure B above. Spectroscopic Data: ^1H NMR (500 MHz, DMSO- d_6) δ ppm 3.65 (s, 3 H), 6.06 (s, 1 H), 6.76 - 6.88 (m, 2 H), 6.89 - 7.03 (m, 2 H), 7.38 - 7.53 (m, 2 H), 7.66 (d, J = 8.56 Hz, 2 H), 7.87 (dd, J = 8.93, 2.57 Hz, 1 H), 7.99 (d, J = 9.05 Hz, 1 H), 8.38 (d, J = 2.69 Hz, 1 H), 10.60 (br s, 1 H), 11.16 (s, 1 H).

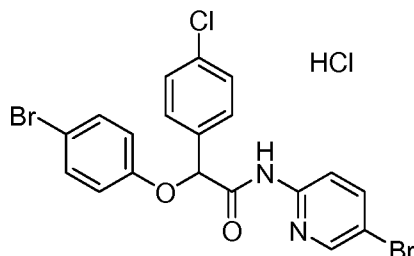
EXAMPLE 4

Synthesis of 2-(4-bromophenoxy)-2-(4-chlorophenyl)-N-(5-fluoropyridin-2-yl)acetamide hydrochloride:

The title compound was generated from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid, 4-bromophenol and 5-fluoropyridin-2-amine according to General procedure B described above. The intermediate 2-(4-bromophenoxy)-2-(4-chlorophenyl)acetic acid was used in the subsequent synthetic transformation without further purification.

2-(4-Bromophenoxy)-2-(4-chlorophenyl)acetic acid: The title compound was obtained from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid (12.00 g, 48.10 mmol), 4-bromophenol (8.30 g, 47.97 mmol) and sodium hydride (60% oil dispersion, 5.50 g, 137.50 mmol) according to the protocols as outlined in general procedure B above. This acid was used in the next synthetic step without further purification.

2-(4-Bromophenoxy)-2-(4-chlorophenyl)-N-(5-fluoropyridin-2-yl)acetamide hydrochloride: The title compound was obtained from 2-(4-bromophenoxy)-2-(4-chlorophenyl)acetic acid (taken from the previous step, crude, 3.40 g, 9.95 mmol), 5-fluoropyridin-2-amine (1.10 g, 9.81 mmol) and EDCI (3.50 g, 18.26 mmol) according to the protocols as outlined in general procedure B above. Spectroscopic Data: ^1H NMR (500 MHz, DMSO- d_6) δ ppm 6.22 (s, 1 H), 6.81 - 7.15 (m, 2 H), 7.45 (t, J = 9.05 Hz, 4 H), 7.68 (d, J = 8.56 Hz, 3 H), 7.98 (dd, J = 9.05, 4.16 Hz, 1 H), 8.32 (d, J = 2.93 Hz, 1 H), 10.88 - 11.21 (br s, 1 H), 11.25 (s, 1 H).

EXAMPLE 5

Synthesis of 2-(4-bromophenoxy)-N-(5-bromopyridin-2-yl)-2-(4-chlorophenyl)acetamide hydrochloride:

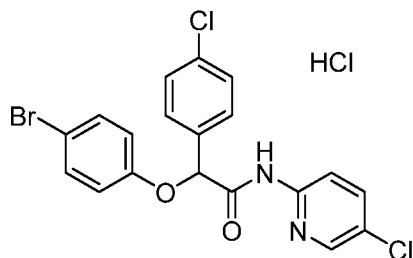
5 The title compound was generated from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid, 4-bromophenol and 5-bromopyridin-2-amine according to General procedure B described above. The intermediate 2-(4-bromophenoxy)-2-(4-chlorophenyl)acetic acid was used in the subsequent synthetic transformation without further purification.

10 *2-(4-Bromophenoxy)-2-(4-chlorophenyl)acetic acid:* The title compound was obtained from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid (12.00 g, 48.10 mmol), 4-bromophenol (8.30 g, 47.97 mmol) and sodium hydride (60% oil dispersion, 5.50 g, 137.50 mmol) according to the protocols as outlined in general procedure B above. This acid was used in the next synthetic step without further

15 purification.

2-(4-Bromophenoxy)-N-(5-bromopyridin-2-yl)-2-(4-chlorophenyl)acetamide hydrochloride:

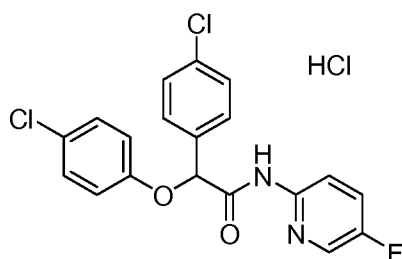
20 The title compound was obtained from 2-(4-bromophenoxy)-2-(4-chlorophenyl)acetic acid (taken from the previous step, crude, 3.40 g, 9.95 mmol), 5-bromopyridin-2-amine (1.90 g, 10.98 mmol) and EDCI (3.50 g, 18.26 mmol) according to the protocols as outlined in general procedure B above. Spectroscopic Data: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 6.22 (s, 1 H), 6.97 (q, *J* = 5.62 Hz, 2 H), 7.45 (dd, *J* = 10.51, 8.80 Hz, 4 H), 7.67 (d, *J* = 8.56 Hz, 2 H), 7.84 - 8.06 (m, 2 H), 8.43 (d, *J* = 2.45 Hz, 1 H), 11.31 (s, 1 H), 11.59 (br s, 1 H).

EXAMPLE 6**Synthesis of 2-(4-bromophenoxy)-2-(4-chlorophenyl)-N-(5-chloropyridin-2-yl)acetamide hydrochloride:**

5 The title compound was generated from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid, 4-bromophenol and 5-chloropyridin-2-amine according to General procedure B described above. The intermediate 2-(4-bromophenoxy)-2-(4-chlorophenyl)acetic acid was used in the subsequent synthetic transformation without further purification.

10 *2-(4-Bromophenoxy)-2-(4-chlorophenyl)acetic acid:* The title compound was obtained from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid (12.00 g, 48.10 mmol), 4-bromophenol (8.30 g, 47.97 mmol) and sodium hydride (60% oil dispersion, 5.50 g, 137.50 mmol) according to the protocols as outlined in general procedure B above. This acid was used in the next synthetic step without further
15 purification.

2-(4-Bromophenoxy)-2-(4-chlorophenyl)-N-(5-chloropyridin-2-yl)acetamide hydrochloride: The title compound was obtained from 2-(4-bromophenoxy)-2-(4-chlorophenyl)acetic acid (taken from the previous step, crude, 3.40 g, 9.95 mmol), 5-chloropyridin-2-amine (1.50 g, 11.67 mmol) and EDCI (3.80 g, 19.82 mmol) according to
20 the protocols as outlined in general procedure B above. Spectroscopic Data: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 6.22 (s, 1 H), 6.97 (d, *J* = 9.05 Hz, 2 H), 7.46 (dd, *J* = 9.78, 8.80 Hz, 4 H), 7.67 (d, *J* = 8.56 Hz, 2 H), 7.85 (dd, *J* = 9.05, 2.69 Hz, 1 H), 7.97 (d, *J* = 9.05 Hz, 1 H), 8.36 (d, *J* = 2.69 Hz, 1 H), 10.07 (br s, 1 H), 11.31 (s, 1 H).

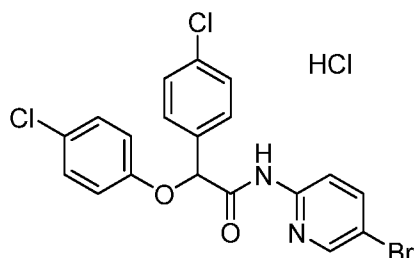
EXAMPLE 7

Synthesis of 2-(4-chlorophenoxy)-2-(4-chlorophenyl)-N-(5-fluoropyridin-2-yl)acetamide hydrochloride:

5 The title compound was generated from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid, 4-chlorophenol, oxalyl chloride and 5-fluoropyridin-2-amine according to General procedure A described above. The intermediate 2-(4-chlorophenoxy)-2-(4-chlorophenyl)acetyl chloride was used in the subsequent synthetic transformation without further purification.

10 *2-(4-Chlorophenoxy)-2-(4-chlorophenyl)acetyl chloride:* The title compound was obtained from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid (12.26 g, 49.14 mmol), 4-chlorophenol (6.30 g, 49.00 mmol), sodium hydride (60% oil dispersion, 5.50 g, 137.50 mmol) and oxalyl chloride (2 M in dichloromethane, 50.00 mL, 100.00 mmol) according to the protocols as outlined in general procedure A above. This acid
15 chloride was used in the next synthetic step without further purification.

2-(4-Chlorophenoxy)-2-(4-chlorophenyl)-N-(5-fluoropyridin-2-yl)acetamide hydrochloride: The title compound was obtained from 2-(4-chlorophenoxy)-2-(4-chlorophenyl)acetic acid (taken from the previous step, crude, 2.00 g, 6.34 mmol), 5-fluoropyridin-2-amine (1.20 g, 10.70 mmol) and Hünig's base (3.50 mL, 20.09 mmol)
20 according to the protocols as outlined in general procedure A above. Spectroscopic Data: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 6.17 (s, 1 H), 7.03 (d, *J* = 8.80 Hz, 2 H), 7.07 (dd, *J* = 9.90, 4.52 Hz, 1 H), 7.32 - 7.37 (m, 1 H), 7.48 (d, *J* = 8.56 Hz, 2 H), 7.67 (d, *J* = 8.31 Hz, 2 H), 7.71 (td, *J* = 8.68, 2.93 Hz, 1 H), 8.00 (td, *J* = 10.03, 7.34 Hz, 1 H), 8.19 (t, *J* = 3.06 Hz, 1 H), 8.34 (d, *J* = 3.18 Hz, 1 H), 11.20 (s, 1 H).

EXAMPLE 8

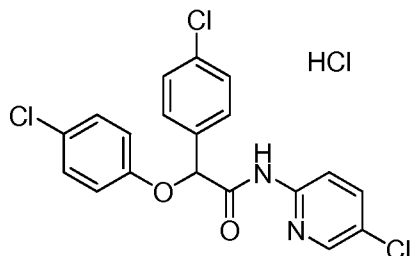
Synthesis of *N*-(5-bromopyridin-2-yl)-2-(4-chlorophenoxy)-2-(4-chlorophenyl)acetamide hydrochloride:

5 The title compound was generated from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid, 4-chlorophenol, oxalyl chloride and 5-bromopyridin-2-amine according to General procedure A described above. The intermediate 2-(4-chlorophenoxy)-2-(4-chlorophenyl)acetyl chloride was used in the subsequent synthetic transformation without further purification.

10 *2-(4-Chlorophenoxy)-2-(4-chlorophenyl)acetyl chloride:* The title compound was obtained from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid (12.26 g, 49.14 mmol), 4-chlorophenol (6.30 g, 49.00 mmol), sodium hydride (60% oil dispersion, 5.50 g, 137.50 mmol) and oxalyl chloride (2 M in dichloromethane, 50.00 mL, 100.00 mmol) according to the protocols as outlined in general procedure A above. This acid
15 chloride was used in the next synthetic step without further purification.

N-(5-Bromopyridin-2-yl)-2-(4-chlorophenoxy)-2-(4-chlorophenyl)acetamide
hydrochloride: The title compound was obtained from 2-(4-chlorophenoxy)-2-(4-chlorophenyl)acetic acid (taken from the previous step, crude, 3.15 g, 9.98 mmol), 5-bromopyridin-2-amine (1.80 g, 10.40 mmol) and Hünig's base (5.00 mL, 28.66 mmol)
20 according to the protocols as outlined in general procedure A above. Spectroscopic Data:
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 6.16 (s, 1 H), 7.02 (d, *J* = 9.05 Hz, 2 H), 7.34 (d, *J* = 9.05 Hz, 2 H), 7.48 (d, *J* = 8.56 Hz, 2 H), 7.66 (d, *J* = 8.56 Hz, 2 H), 7.89 - 7.95 (m, 1 H), 7.96 - 8.03 (m, 1 H), 8.45 (d, *J* = 2.69 Hz, 1 H), 10.03 - 10.47 (br s, 1 H), 11.25 (s, 1 H).

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EXAMPLE 9

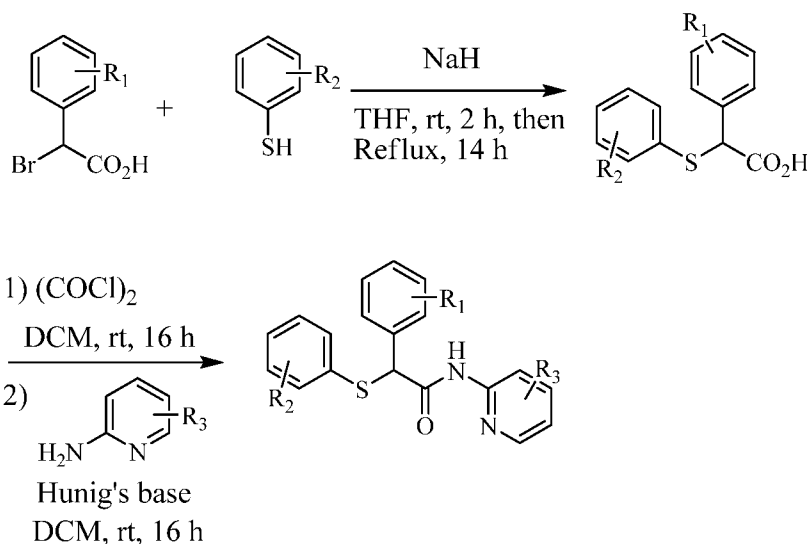
Synthesis of 2-(4-chlorophenoxy)-2-(4-chlorophenyl)-N-(5-chloropyridin-2-yl)acetamide hydrochloride:

5 The title compound was generated from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid, 4-chlorophenol, oxalyl chloride and 5-chloropyridin-2-amine according to General procedure A described above. The intermediate 2-(4-chlorophenoxy)-2-(4-chlorophenyl)acetyl chloride was used in the subsequent synthetic transformation without further purification.

10 *2-(4-Chlorophenoxy)-2-(4-chlorophenyl)acetyl chloride:* The title compound was obtained from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid (12.26 g, 49.14 mmol), 4-chlorophenol (6.30 g, 49.00 mmol), sodium hydride (60% oil dispersion, 5.50 g, 137.50 mmol) and oxalyl chloride (2 M in dichloromethane, 50.00 mL, 100.00 mmol) according to the protocols as outlined in general procedure A above. This acid chloride was used in the next synthetic step without further purification.

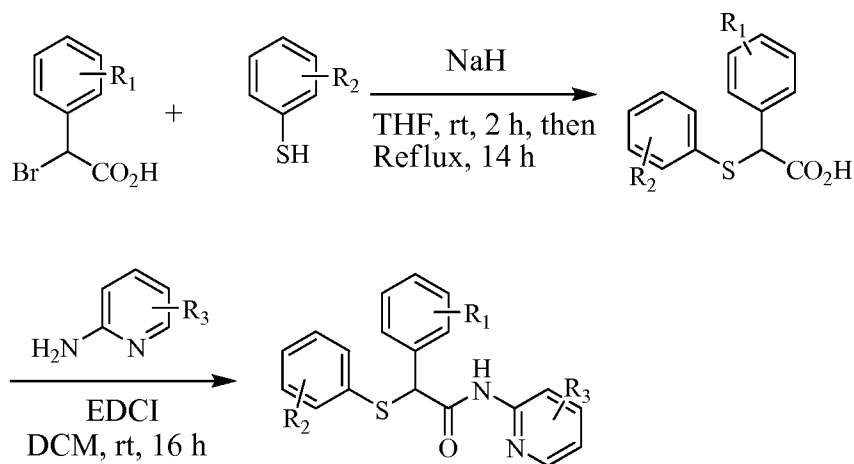
15 *2-(4-Chlorophenoxy)-2-(4-chlorophenyl)-N-(5-chloropyridin-2-yl)acetamide hydrochloride:* The title compound was obtained from 2-(4-chlorophenoxy)-2-(4-chlorophenyl)acetic acid (taken from the previous step, crude, 3.15 g, 9.98 mmol), 5-chloropyridin-2-amine (1.30 g, 10.11 mmol) and Hünig's base (5.00 mL, 28.66 mmol) according to the protocols as outlined in general procedure A above. Spectroscopic Data: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 6.18 (s, 1 H), 7.02 (d, *J* = 9.05 Hz, 2 H), 7.34 (d, *J* = 9.05 Hz, 2 H), 7.48 (d, *J* = 8.31 Hz, 2 H), 7.67 (d, *J* = 8.56 Hz, 2 H), 7.87 (dd, *J* = 9.05, 2.69 Hz, 1 H), 7.98 (d, *J* = 9.05 Hz, 1 H), 8.38 (d, *J* = 2.69 Hz, 1 H), 10.75 (br s, 1 H), 11.28 (s, 1 H).

25 **General Procedure A for the Synthesis of 2-(Substituted Phenylthio)-2-(substituted phenyl)-N-(substituted pyridin-2-yl)acetamide Hydrochloride:**



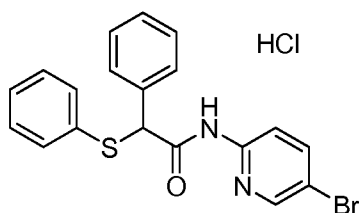
The intermediate 2-(substituted phenylthio)-2-(substituted phenyl)acetic acid was obtained from the appropriately substituted -bromophenylacetic acid (1 eq), substituted thiophenol (1 eq) and sodium hydride (2-3 eq) according to the synthetic protocol published in Brady et al.. This carboxylic acid was then converted into the corresponding acid chloride by the method published in Newcomb et al.. The acid chloride (1 eq) and an appropriately substituted 2-aminopyridine (1.5-2.0 eq) were dissolved in 50ml of dichloromethane at room temperature. Hünig's base (3.50 mL) was added, and the resulting reaction mixture was stirred at room temperature for 14 hours. The reaction mixture was then concentrated and diluted with ethyl acetate. The organic phase was washed sequentially with water and brine, then dried with sodium sulfate and concentrated. Flash chromatography (30 % EtOAc/hexanes) gave the desired free base, which was mixed with HCl in MeOH. Concentration and recrystallization from ether gave the final desired product in HCl salt form.

General Procedure B for the Synthesis of 2-(Substituted phenylthio)-2-(substituted phenyl)-N-(substituted pyridin-2-yl)acetamide Hydrochloride:



The intermediate 2-(substituted phenylthio)-2-(substituted phenyl)acetic acid was obtained from the appropriately substituted α -bromophenylacetic acid (1 eq), substituted thiophenol (1 eq) and sodium hydride (2-3 eq) according to the synthetic protocol published in Brady et al. This carboxylic acid was then mixed with an appropriately substituted 2-aminopyridine (1.2-1.5 eq) in 50ml of dichloromethane at room temperature. EDCI (1.5 to 2 eq) was added, followed by a catalytic amount of DMAP (30 mg). The resulting reaction mixture was stirred at room temperature for 14 hours. The reaction mixture was then concentrated and chromatographed (30 % EtOAc/hexanes) to give the desired free base, which was mixed with HCl in MeOH. Concentration and recrystallization from ether gave the final desired product in HCl salt form.

EXAMPLE 10



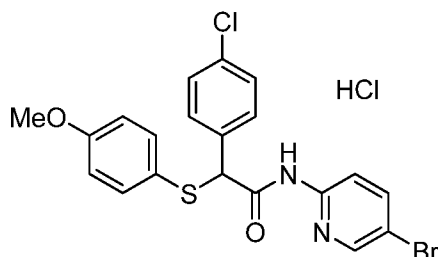
Synthesis of *N*-(5-bromopyridin-2-yl)-2-phenyl-2-(phenylthio)acetamide hydrochloride:

The title compound was generated from commercially available 2-phenyl-2-(phenylthio)acetic acid, oxalyl chloride and 5-chloropyridin-2-amine according to General procedure A described above.

N-(5-Bromopyridin-2-yl)-2-phenyl-2-(phenylthio)acetamide hydrochloride: The title compound was obtained from 2-phenyl-2-(phenylthio)acetic acid (commercially available from VWR), 5-bromopyridin-2-amine (1.60 g, 9.25 mmol) according to the

protocols as outlined in general procedure A above. Spectroscopic Data: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 5.62 (s, 1 H), 7.17 - 7.23 (m, 1 H), 7.28 (t, $J=7.58$ Hz, 3 H), 7.31 - 7.37 (m, 4 H), 7.54 (d, $J=7.09$ Hz, 2 H), 7.97 (d, $J=1.47$ Hz, 2 H), 8.41 (t, $J=1.59$ Hz, 1 H), 11.17 (s, 1 H).

5 **EXAMPLE 11**

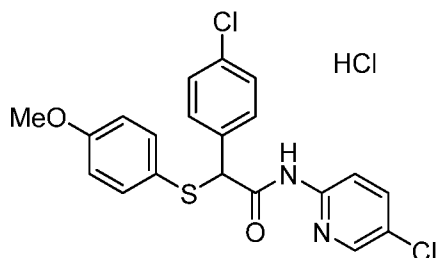


Synthesis of *N*-(5-bromopyridin-2-yl)-2-(4-chlorophenyl)-2-(4-methoxyphenylthio)acetamide hydrochloride:

The title compound was generated from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid, 4-methoxybenzenethiol and 5-bromopyridin-2-amine according to general procedure B described above. The intermediate 2-(4-chlorophenyl)-2-(4-methoxyphenylthio)acetic acid was used in the subsequent synthetic transformation without further purification.

2-(4-Chlorophenyl)-2-(4-methoxyphenylthio)acetic acid: The title compound was obtained from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid (10.61 g, 42.53 mmol), 4-methoxybenzenethiol (6.30 g, 44.94 mmol) and sodium hydride (60% oil dispersion, 5.50 g, 137.50 mmol) according to the protocols as outlined in general procedure B above. This acid was used in the next synthetic step without further purification.

N-(5-Bromopyridin-2-yl)-2-(4-chlorophenyl)-2-(4-methoxyphenylthio)acetamide hydrochloride: The title compound was obtained from 2-(4-chlorophenyl)-2-(4-methoxyphenylthio)acetic acid (taken from the previous step, crude, 3.00 g, 9.72 mmol), 5-bromopyridin-2-amine (1.90 g, 10.98 mmol) and EDCI (3.50 g, 18.25 mmol) according to the protocols as outlined in general procedure B above. Spectroscopic Data: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 3.69 (s, 3 H), 5.37 (s, 1 H), 6.85 (q, $J=5.22$ Hz, 2 H), 7.29 (d, $J=8.80$ Hz, 2 H), 7.36 - 7.43 (m, 2 H), 7.45 - 7.51 (m, 2 H), 7.98 (d, $J=1.47$ Hz, 2 H), 8.41 (t, $J=1.59$ Hz, 1 H), 9.67 (br. s., 1 H), 11.08 (s, 1 H).

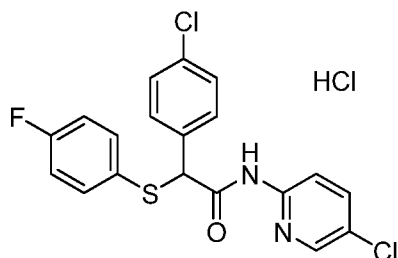
EXAMPLE 12

Synthesis of 2-(4-chlorophenyl)-N-(5-chloropyridin-2-yl)-2-(4-methoxyphenylthio)acetamide hydrochloride:

5 The title compound was generated from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid, 4-methoxybenzenethiol and 5-chloropyridin-2-amine according to general procedure B described above. The intermediate 2-(4-chlorophenyl)-2-(4-methoxyphenylthio)acetic acid was used in the subsequent synthetic transformation without further purification.

10 *2-(4-Chlorophenyl)-2-(4-methoxyphenylthio)acetic acid:* The title compound was obtained from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid (10.61 g, 42.53 mmol), 4-methoxybenzenethiol (6.30 g, 44.94 mmol) and sodium hydride (60% oil dispersion, 5.50 g, 137.50 mmol) according to the protocols as outlined in general procedure B above. This acid was used in the next synthetic step without further
15 purification

2-(4-Chlorophenyl)-N-(5-chloropyridin-2-yl)-2-(4-methoxyphenylthio)acetamide hydrochloride: The title compound was obtained from 2-(4-chlorophenyl)-2-(4-methoxyphenylthio)acetic acid (taken from the previous step, crude, 3.00 g, 9.72 mmol), 5-chloropyridin-2-amine (1.50 g, 11.67 mmol) and EDCI (3.50 g, 18.25 mmol) according
20 to the protocols as outlined in general procedure B above. Spectroscopic Data: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 3.69 (s, 3 H), 5.37 (s, 1 H), 6.86 (q, *J*=5.30 Hz, 2 H), 7.29 (q, *J*=5.14 Hz, 2 H), 7.39 (q, *J*=4.40 Hz, 2 H), 7.43 - 7.53 (m, 2 H), 7.88 (dd, *J*=9.05, 2.69 Hz, 1 H), 8.03 (d, *J*=8.80 Hz, 1 H), 8.34 (d, *J*=2.69 Hz, 1 H), 9.12 (br. s., 1 H), 11.09 (s, 1 H).

EXAMPLE 13

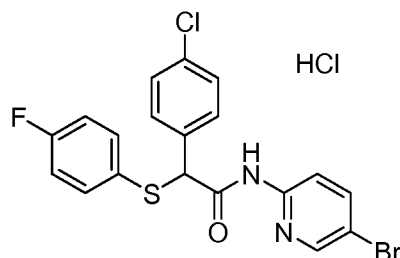
Synthesis of 2-(4-chlorophenyl)-N-(5-chloropyridin-2-yl)-2-(4-fluorophenylthio)acetamide hydrochloride:

5 The title compound was generated from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid, 4-fluorobenzenethiol and 5-chloropyridin-2-amine according to general procedure B described above. The intermediate 2-(4-chlorophenyl)-2-(4-fluorophenylthio)acetic acid was used in the subsequent synthetic transformation without further purification.

10 *2-(4-Chlorophenyl)-2-(4-fluorophenylthio)acetic acid:* The title compound was obtained from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid (10.45 g, 41.89 mmol), 4-fluorobenzenethiol (5.50 g, 42.91 mmol) and sodium hydride (60% oil dispersion, 5.50 g, 137.50 mmol) according to the protocols as outlined in general procedure B above. This acid was used in the next synthetic step without further
15 purification.

2-(4-Chlorophenyl)-N-(5-chloropyridin-2-yl)-2-(4-fluorophenylthio)acetamide hydrochloride: The title compound was obtained from 2-(4-chlorophenyl)-2-(4-fluorophenylthio)acetic acid (taken from the previous step, crude, 3.00 g, 9.65 mmol), 5-chloropyridin-2-amine (1.50 g, 11.67 mmol) and EDCI (3.50 g, 18.26 mmol) according to
20 the protocols as outlined in general procedure B above. Spectroscopic Data: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 5.48 (s, 1 H), 7.15 (t, *J*=8.80 Hz, 2 H), 7.36 - 7.45 (m, 4 H), 7.50 (d, *J*=8.31 Hz, 2 H), 7.88 (dd, *J*=8.93, 2.57 Hz, 1 H), 8.02 (d, *J*=8.80 Hz, 1 H), 8.35 (d, *J*=2.45 Hz, 1 H), 11.14 (s, 1 H).

EXAMPLE 14

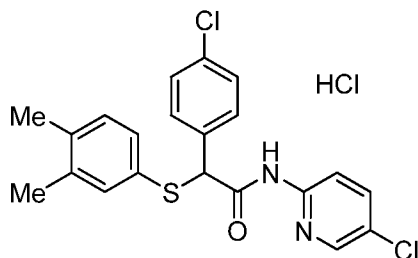


Synthesis of *N*-(5-bromopyridin-2-yl)-2-(4-chlorophenyl)-2-(4-fluorophenylthio)acetamide hydrochloride:

5 The title compound was generated from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid, 4-fluorobenzenethiol and 5-bromopyridin-2-amine according to general procedure B described above. The intermediate 2-(4-chlorophenyl)-2-(4-fluorophenylthio)acetic acid was used in the subsequent synthetic transformation without further purification.

10 *2-(4-Chlorophenyl)-2-(4-fluorophenylthio)acetic acid:* The title compound was obtained from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid (10.45 g, 41.89 mmol), 4-fluorobenzenethiol (5.50 g, 42.91 mmol) and sodium hydride (60% oil dispersion, 5.50 g, 137.50 mmol) according to the protocols as outlined in general procedure B above. This acid was used in the next synthetic step without further
15 purification.

N-(5-Bromopyridin-2-yl)-2-(4-chlorophenyl)-2-(4-fluorophenylthio)acetamide hydrochloride: The title compound was obtained from 2-(4-chlorophenyl)-2-(4-fluorophenylthio)acetic acid (taken from the previous step, crude, 3.00 g, 9.65 mmol), 5-bromopyridin-2-amine (2.00 g, 11.56 mmol) and EDCI (3.50 g, 18.26 mmol) according to
20 the protocols as outlined in general procedure B above. Spectroscopic Data: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 5.56 (s, 1 H), 7.14 (t, 2 H), 7.35 - 7.44 (m, 4 H), 7.51 (d, *J*=8.31 Hz, 2 H), 7.97 (s, 2 H), 8.40 (t, *J*=1.59 Hz, 1 H), 10.66 (br. s., 1 H), 11.20 (s, 1 H).

EXAMPLE 15

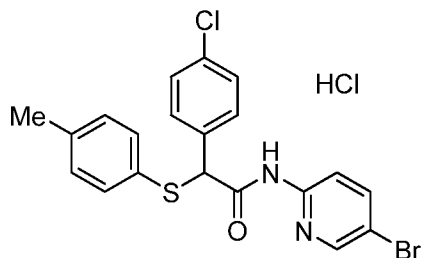
Synthesis of 2-(4-chlorophenyl)-N-(5-chloropyridin-2-yl)-2-(3,4-dimethylphenylthio)acetamide hydrochloride:

5 The title compound was generated from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid, 3,4-dimethylbenzenethiol and 5-chloropyridin-2-amine according to general procedure B described above. The intermediate 2-(4-chlorophenyl)-2-(3,4-dimethylphenylthio)acetic acid was used in the subsequent synthetic transformation without further purification.

10 *2-(4-Chlorophenyl)-2-(3,4-dimethylphenylthio)acetic acid:* The title compound was obtained from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid (11.47 g, 45.97 mmol), 3,4-dimethylbenzenethiol (6.50 g, 47.02 mmol) and sodium hydride (60% oil dispersion, 5.50 g, 137.50 mmol) according to the protocols as outlined in general procedure B above. This acid was used in the next synthetic step without further
15 purification.

2-(4-Chlorophenyl)-N-(5-chloropyridin-2-yl)-2-(3,4-dimethylphenylthio)acetamide hydrochloride: The title compound was obtained from 2-(4-bromophenoxy)-2-(4-chlorophenyl)acetic acid (taken from the previous step, crude, 3.00 g, 9.78 mmol), 5-chloropyridin-2-amine (1.50 g, 11.67 mmol) and EDCI (3.50 g, 18.26 mmol) according to
20 the protocols as outlined in general procedure B above. Spectroscopic Data: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.11 (s, 3 H), 2.11 (s, 3 H), 5.55 (s, 1 H), 6.97 - 7.04 (m, 1 H), 7.04 - 7.09 (m, 1 H), 7.15 (s, 1 H), 7.32 - 7.44 (m, 2 H), 7.46 - 7.61 (m, 2 H), 7.86 (dd, *J*=8.93, 2.57 Hz, 1 H), 8.02 (d, *J*=8.80 Hz, 1 H), 8.34 (d, *J*=2.45 Hz, 1 H), 8.70 (br. s., 2 H), 11.17 (s, 1 H).

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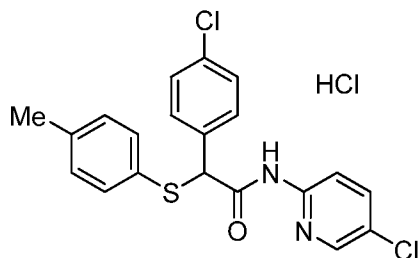
EXAMPLE 16

Synthesis of N-(5-bromopyridin-2-yl)-2-(4-chlorophenyl)-2-(p-tolylthio)acetamide hydrochloride:

5 The title compound was generated from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid, 4-methylbenzenethiol and 5-bromopyridin-2-amine according to General procedure B described above. The intermediate 2-(4-chlorophenyl)-2-(p-tolylthio)acetic acid was used in the subsequent synthetic transformation without further purification.

10 *2-(4-Chlorophenyl)-2-(p-tolylthio)acetic acid:* The title compound was obtained from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid (10.67 g, 42.77 mmol), 4-methylbenzenethiol (5.60 g, 45.09 mmol) and sodium hydride (60% oil dispersion, 5.50 g, 137.50 mmol) according to the protocols as outlined in general procedure B above. This acid was used in the next synthetic step without further
15 purification.

2-(4-N-(5-Bromopyridin-2-yl)-2-(4-chlorophenyl)-2-(p-tolylthio)acetamide hydrochloride: The title compound was obtained from 2-(4-chlorophenyl)-2-(p-tolylthio)acetic acid (taken from the previous step, crude, 3.00 g, 10.25 mmol), 5-bromopyridin-2-amine (2.00 g, 11.56 mmol) and EDCI (3.50 g, 18.26 mmol) according to
20 the protocols as outlined in general procedure B above. Spectroscopic Data: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.22 (s, 3 H), 5.51 (s, 1 H), 7.10 (d, *J*=8.07 Hz, 2 H), 7.24 (d, *J*=8.07 Hz, 2 H), 7.35 (dd, *J*=16.87, 6.36 Hz, 1 H), 7.38 - 7.44 (m, 2 H), 7.51 (d, *J*=8.56 Hz, 2 H), 7.90 - 8.01 (m, 1 H), 8.42 (dd, *J*=2.08, 1.10 Hz, 1 H), 11.15 (s, 1 H).

EXAMPLE 17

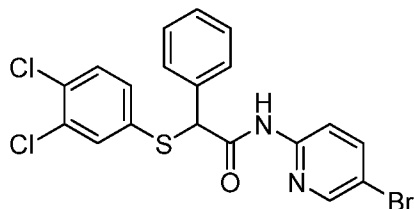
Synthesis of 2-(4-chlorophenyl)-N-(5-chloropyridin-2-yl)-2-(p-tolylthio)acetamide hydrochloride:

5 The title compound was generated from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid, 4-methylbenzenethiol and 5-chloropyridin-2-amine according to general procedure B described above. The intermediate 2-(4-chlorophenyl)-2-(p-tolylthio)acetic acid was used in the subsequent synthetic transformation without further purification.

10 *2-(4-Chlorophenyl)-2-(p-tolylthio)acetic acid:* The title compound was obtained from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid (10.67 g, 42.77 mmol), 4-methylbenzenethiol (5.60 g, 45.09 mmol) and sodium hydride (60% oil dispersion, 5.50 g, 137.50 mmol) according to the protocols as outlined in general procedure B above. This acid was used in the next synthetic step without further
15 purification

2-(4-Chlorophenyl)-N-(5-chloropyridin-2-yl)-2-(p-tolylthio)acetamide hydrochloride: The title compound was obtained from 2-(4-chlorophenyl)-2-(p-tolylthio)acetic acid (taken from the previous step, crude, 3.00 g, 10.25 mmol), 5-chloropyridin-2-amine (1.50 g, 11.67 mmol) and EDCI (3.50 g, 18.26 mmol) according to
20 the protocols as outlined in general procedure B above. Spectroscopic Data: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.20 (s, 3 H), 5.58 (s, 1 H), 7.07 (d, *J*=7.82 Hz, 2 H), 7.24 (d, *J*=8.07 Hz, 2 H), 7.38 (d, *J*=8.56 Hz, 2 H), 7.53 (d, *J*=8.56 Hz, 2 H), 7.85 (dd, *J*=8.93, 2.57 Hz, 1 H), 8.02 (d, *J*=9.05 Hz, 1 H), 8.33 (d, *J*=2.69 Hz, 1 H), 10.42 (br. s., 1 H), 11.22 (s, 1 H).

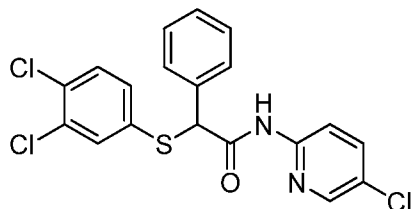
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EXAMPLE 18**Synthesis of *N*-(5-bromopyridin-2-yl)-2-(3,4-dichlorophenylthio)-2-phenylacetamide:**

5 The title compound was generated from commercially available 2-bromo-2-phenylacetic acid, 3,4-dichlorobenzenethiol, oxalyl chloride and 5-bromopyridin-2-amine according to general procedure A described above. The intermediate 2-(3,4-dichlorophenylthio)-2-phenylacetyl chloride was used in the subsequent synthetic transformation without further purification.

10 *2-(3,4-Dichlorophenylthio)-2-phenylacetyl chloride:* The title compound was obtained from commercially available 2-bromo-2-phenylacetic acid (12.00 g, 55.80 mmol), 3,4-dichlorobenzenethiol (10.00 g, 55.84 mmol), sodium hydride (60% oil dispersion, 5.00 g, 125.00 mmol) and oxalyl chloride (2 M in dichloromethane, 50.00 mL, 100.00 mmol) according to the protocols as outlined in general procedure A above. This
15 acid chloride was used in the next synthetic step without further purification.

N-(5-Bromopyridin-2-yl)-2-(3,4-dichlorophenylthio)-2-phenylacetamide: The title compound was obtained from 2-(3,4-dichlorophenylthio)-2-phenylacetyl chloride (taken from the previous step, crude, 3.31 g, 10.00 mmol), 5-bromopyridin-2-amine (1.90 g, 10.98 mmol) and Hünig's base (4.00 mL, 22.93 mmol) according to the protocols as
20 outlined in general procedure A above. Free base was obtained. Spectroscopic Data: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 5.60 (s, 1 H), 7.31 (t, *J*=7.21 Hz, 2 H), 7.36 (t, *J*=7.34 Hz, 2 H), 7.46 - 7.67 (m, 4 H), 7.87 - 8.10 (m, 2 H), 8.43 (s, 1 H), 11.15 (s, 1 H).

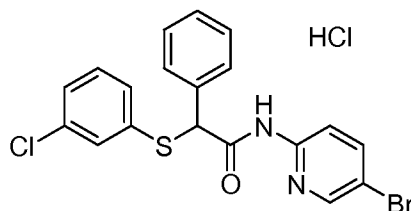
EXAMPLE 19

Synthesis of *N*-(5-chloropyridin-2-yl)-2-(3,4-dichlorophenylthio)-2-phenylacetamide:

5 The title compound was generated from commercially available 2-bromo-2-phenylacetic acid, 3,4-dichlorobenzenethiol, oxalyl chloride and 5-chloropyridin-2-amine according to general procedure A described above. The intermediate 2-(3,4-dichlorophenylthio)-2-phenylacetyl chloride was used in the subsequent synthetic transformation without further purification.

10 *2-(3,4-Dichlorophenylthio)-2-phenylacetyl chloride:* The title compound was obtained from commercially available 2-bromo-2-phenylacetic acid (12.00 g, 55.80 mmol), 3,4-dichlorobenzenethiol (10.00 g, 55.84 mmol), sodium hydride (60% oil dispersion, 5.00 g, 125.00 mmol) and oxalyl chloride (2 M in dichloromethane, 50.00 mL, 100.00 mmol) according to the protocols as outlined in general procedure A above. This
15 acid chloride was used in the next synthetic step without further purification.

N-(5-Chloropyridin-2-yl)-2-(3,4-dichlorophenylthio)-2-phenylacetamide: The title compound was obtained from 2-(3,4-dichlorophenylthio)-2-phenylacetyl chloride (taken from the previous step, crude, 3.31 g, 10.00 mmol), 5-chloropyridin-2-amine (1.50 g, 11.67 mmol) and Hünig's base (4.00 mL, 22.93 mmol) according to the protocols as
20 outlined in general procedure A above. Free base was obtained. Spectroscopic Data: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 5.61 (s, 1 H), 7.31 (t, *J*=6.97 Hz, 2 H), 7.36 (t, *J*=7.34 Hz, 2 H), 7.47 - 7.63 (m, 4 H), 7.88 (dd, *J*=8.93, 2.32 Hz, 1 H), 8.02 (d, *J*=9.05 Hz, 1 H), 8.36 (d, *J*=2.20 Hz, 1 H), 11.15 (s, 1 H).

EXAMPLE 20

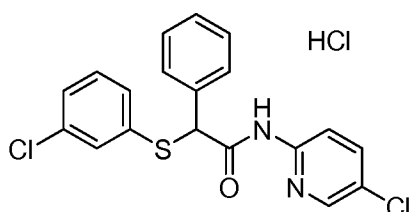
Synthesis of *N*-(5-bromopyridin-2-yl)-2-(3-chlorophenylthio)-2-phenylacetamide hydrochloride:

The title compound was generated from commercially available 2-bromo-2-phenylacetic acid, 3-chlorobenzenethiol, oxalyl chloride and 5-bromopyridin-2-amine according to general procedure A described above. The intermediate 2-(3-chlorophenylthio)-2-phenylacetyl chloride was used in the subsequent synthetic transformation without further purification.

2-(3-Chlorophenylthio)-2-phenylacetyl chloride: The title compound was obtained from commercially available 2-bromo-2-phenylacetic acid (12.00 g, 55.80 mmol), 3-chlorobenzenethiol (8.07 g, 55.80 mmol), sodium hydride (60% oil dispersion, 5.50 g, 137.50 mmol) and oxalyl chloride (2 M in dichloromethane, 50.00 mL, 100.00 mmol) according to the protocols as outlined in general procedure A above. This acid chloride was used in the next synthetic step without further purification.

N-(5-Bromopyridin-2-yl)-2-(3-chlorophenylthio)-2-phenylacetamide hydrochloride: The title compound was obtained from 2-(3-chlorophenylthio)-2-phenylacetyl chloride (taken from the previous step, crude, 2.80 g, 9.42 mmol), 5-bromopyridin-2-amine (1.90 g, 10.98 mmol) and Hünig's base (4.00 mL, 22.93 mmol) according to the protocols as outlined in general procedure A above. Spectroscopic Data: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 5.71 (s, 1 H), 7.20 - 7.32 (m, 3 H), 7.35 (t, *J*=7.46 Hz, 2 H), 7.39 - 7.43 (m, 1 H), 7.55 (d, *J*=7.09 Hz, 1 H), 7.92 - 8.01 (m, 2 H), 8.42 (t, 1 H), 8.97 (br. s., 1 H), 11.22 (s, 1 H).

EXAMPLE 21



Synthesis of 2-(3-chlorophenylthio)-*N*-(5-chloropyridin-2-yl)-2-phenylacetamide hydrochloride:

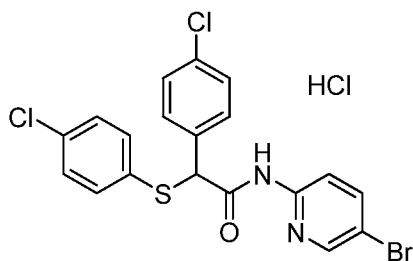
The title compound was generated from commercially available 2-bromo-2-phenylacetic acid, 3-chlorobenzenethiol, oxalyl chloride and 5-chloropyridin-2-amine according to general procedure A described above. The intermediate 2-(3-

chlorophenylthio)-2-phenylacetyl chloride was used in the subsequent synthetic transformation without further purification.

2-(3-Chlorophenylthio)-2-phenylacetyl chloride: The title compound was obtained from commercially available 2-bromo-2-phenylacetic acid (12.00 g, 55.80 mmol), 3-chlorobenzenethiol (8.07 g, 55.80 mmol), sodium hydride (60% oil dispersion, 5.50 g, 137.50 mmol) and oxalyl chloride (2 M in dichloromethane, 50.00 mL, 100.00 mmol) according to the protocols as outlined in general procedure A above. This acid chloride was used in the next synthetic step without further purification.

2-(3-Chlorophenylthio)-N-(5-chloropyridin-2-yl)-2-phenylacetamide hydrochloride: The title compound was obtained from 2-(3-chlorophenylthio)-2-phenylacetyl chloride (taken from the previous step, crude, 2.80 g, 9.42 mmol), 5-chloropyridin-2-amine (1.50 g, 11.67 mmol) and Hünig's base (4.00 mL, 22.93 mmol) according to the protocols as outlined in general procedure A above. Spectroscopic Data: ¹H NMR (500 MHz, DMSO-*d*₆) 1H NMR (500 MHz, <dms>) δ ppm 5.67 (s, 1 H), 6.00 (br. s., 1 H), 7.24 - 7.32 (m, 3 H), 7.36 (t, *J*=7.34 Hz, 2 H), 7.39 - 7.43 (m, 1 H), 7.55 (d, *J*=7.09 Hz, 2 H), 7.88 (dd, *J*=9.05, 2.69 Hz, 1 H), 8.02 (d, *J*=9.05 Hz, 1 H), 8.36 (d, *J*=2.69 Hz, 1 H), 11.20 (s, 1 H).

EXAMPLE 22



20 **Synthesis of N-(5-bromopyridin-2-yl)-2-(4-chlorophenyl)-2-(4-chlorophenylthio)acetamide hydrochloride:**

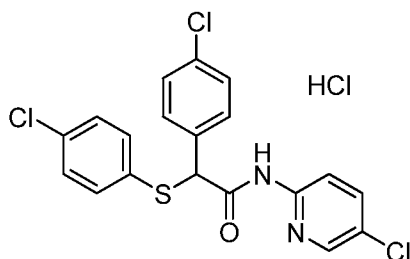
The title compound was generated from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid, 4-chlorobenzenethiol, oxalyl chloride and 5-bromopyridin-2-amine according to general procedure A described above. The intermediate 2-(4-chlorophenyl)-2-(4-chlorophenylthio)acetyl chloride was used in the subsequent synthetic transformation without further purification.

2-(4-Chlorophenyl)-2-(4-chlorophenylthio)acetyl chloride: The title compound was obtained from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid (12.00

g, 48.10 mmol), 4-chlorobenzenethiol (6.96 g, 48.13 mmol), sodium hydride (60% oil dispersion, 5.50 g, 137.50 mmol) and oxalyl chloride (2 M in dichloromethane, 50.00 mL, 100.00 mmol) according to the protocols as outlined in general procedure A above. This acid chloride was used in the next synthetic step without further purification.

- 5 *N*-(5-Bromopyridin-2-yl)-2-(4-chlorophenyl)-2-(4-chlorophenylthio)acetamide hydrochloride: The title compound was obtained from 2-(4-chlorophenyl)-2-(4-chlorophenylthio)acetyl chloride (taken from the previous step, crude, 3.30 g, 9.95 mmol), 5-bromopyridin-2-amine (1.90 g, 10.98 mmol) and Hünig's base (4.00 mL, 22.93 mmol) according to the protocols as outlined in general procedure A above. Spectroscopic Data:
- 10 ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 5.63 (s, 1 H), 6.47 (br. s., 1 H), 7.35 (s, 4 H), 7.39 - 7.42 (m, 1 H), 7.53 (d, *J*=8.56 Hz, 2 H), 7.93 - 7.97 (m, 1 H), 7.97 - 8.01 (m, 1 H), 8.42 (d, *J*=3.18 Hz, 1 H), 11.22 (s, 1 H).

EXAMPLE 23



- 15 **Synthesis of 2-(4-chlorophenyl)-2-(4-chlorophenylthio)-*N*-(5-chloropyridin-2-yl)acetamide hydrochloride:**

The title compound was generated from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid, 4-chlorobenzenethiol, oxalyl chloride and 5-chloropyridin-2-amine according to general procedure A described above. The intermediate 2-(4-chlorophenyl)-2-(4-chlorophenylthio)acetyl chloride was used in the subsequent synthetic transformation without further purification.

20

- 25 *2-(4-Chlorophenyl)-2-(4-chlorophenylthio)acetyl chloride:* The title compound was obtained from commercially available 2-bromo-2-(4-chlorophenyl)acetic acid (12.00 g, 48.10 mmol), 4-chlorobenzenethiol (6.96 g, 48.13 mmol), sodium hydride (60% oil dispersion, 5.50 g, 137.50 mmol) and oxalyl chloride (2 M in dichloromethane, 50.00 mL, 100.00 mmol) according to the protocols as outlined in general procedure A above. This acid chloride was used in the next synthetic step without further purification.

2-(4-Chlorophenyl)-2-(4-chlorophenylthio)-N-(5-chloropyridin-2-yl)acetamide hydrochloride: The title compound was obtained from 2-(4-chlorophenyl)-2-(4-

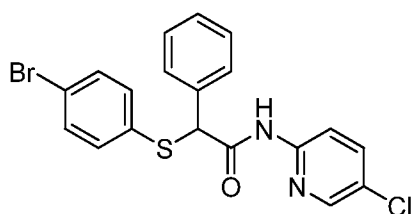
chlorophenylthio)acetyl chloride (taken from the previous step, crude, 3.30 g, 9.95 mmol),

5-chloropyridin-2-amine (1.50 g, 11.67 mmol) and Hünig's base (4.00 mL, 22.93 mmol)

5 according to the protocols as outlined in general procedure A above. Spectroscopic Data:

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 5.61 (s, 1 H), 6.94 (br. s., 1 H), 7.33 - 7.38 (m, 4 H), 7.41 (d, *J*=8.31 Hz, 2 H), 7.53 (d, *J*=8.56 Hz, 2 H), 7.88 (dd, *J*=8.93, 2.57 Hz, 1 H), 8.01 (d, *J*=8.80 Hz, 1 H), 8.35 (d, *J*=2.45 Hz, 1 H), 11.22 (s, 1 H).

EXAMPLE 24



10

Synthesis of 2-(4-bromophenylthio)-N-(5-chloropyridin-2-yl)-2-phenylacetamide:

The title compound was generated from commercially available 2-bromo-2-phenylacetic acid, 4-bromobenzenethiol, oxalyl chloride and 5-chloropyridin-2-amine

15 according to general procedure A described above. The intermediate 2-(4-bromophenylthio)-2-phenylacetyl chloride was used in the subsequent synthetic transformation without further purification.

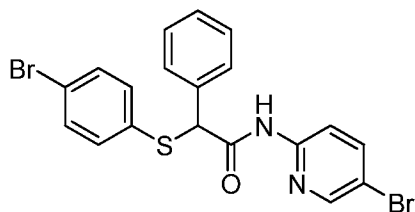
2-(4-Bromophenylthio)-2-phenylacetyl chloride: The title compound was obtained from commercially available 2-bromo-2-phenylacetic acid (10.00 g, 46.50 mmol), 4-bromobenzenethiol (8.80 g, 46.56 mmol), sodium hydride (60% oil dispersion, 5.50 g, 137.50 mmol) and oxalyl chloride (2 M in dichloromethane, 60.00 mL, 120.00 mmol) according to the protocols as outlined in general procedure A above. This acid chloride was used in the next synthetic step without further purification.

2-(4-Bromophenylthio)-N-(5-chloropyridin-2-yl)-2-phenylacetamide: The title compound was obtained from 2-(4-bromophenylthio)-2-phenylacetyl chloride (taken from the previous step, crude, 3.40 g, 9.95 mmol), 5-chloropyridin-2-amine (1.28 g, 9.96 mmol) and Hünig's base (5.00 mL, 28.66 mmol) according to the protocols as outlined in general procedure A above. Free base was obtained. Spectroscopic Data: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 5.58 (s, 1 H), 7.31 (d, *J*=8.56 Hz, 3 H), 7.38 (t, *J*=7.34 Hz, 2 H), 7.52 (d,

25

$J=8.56$ Hz, 2 H), 7.56 (d, $J=7.34$ Hz, 2 H), 7.90 (dd, $J=8.93$, 2.57 Hz, 1 H), 8.06 (d, $J=8.80$ Hz, 1 H), 8.38 (d, $J=2.45$ Hz, 1 H), 11.19 (s, 1 H).

EXAMPLE 25

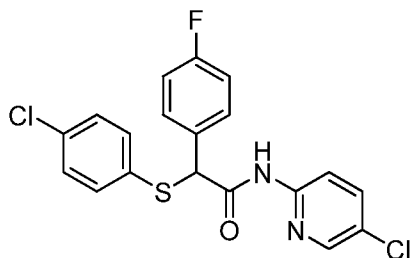


5 **Synthesis of 2-(4-bromophenylthio)-N-(5-bromopyridin-2-yl)-2-phenylacetamide:**

The title compound was generated from commercially available 2-bromo-2-phenylacetic acid, 4-bromobenzenethiol, oxalyl chloride and 5-bromopyridin-2-amine according to general procedure A described above. The intermediate 2-(4-bromophenylthio)-2-phenylacetyl chloride was used in the subsequent synthetic transformation without further purification.

2-(4-Bromophenylthio)-2-phenylacetyl chloride: The title compound was obtained from commercially available 2-bromo-2-phenylacetic acid (10.00 g, 46.50 mmol), 4-bromobenzenethiol (8.80 g, 46.56 mmol), sodium hydride (60% oil dispersion, 5.50 g, 137.50 mmol) and oxalyl chloride (2 M in dichloromethane, 60.00 mL, 120.00 mmol) according to the protocols as outlined in general procedure A above. This acid chloride was used in the next synthetic step without further purification.

2-(4-Bromophenylthio)-N-(5-bromopyridin-2-yl)-2-phenylacetamide: The title compound was obtained from 2-(4-bromophenylthio)-2-phenylacetyl chloride (taken from the previous step, crude, 3.40 g, 9.95 mmol), 5-bromopyridin-2-amine (1.73 g, 10.00 mmol) and Hünig's base (5.00 mL, 28.66 mmol) according to the protocols as outlined in general procedure A above. Free base was obtained. Spectroscopic Data: ^1H NMR (500 MHz, DMSO- d_6) δ ppm 5.57 (s, 1 H), 7.24 - 7.34 (m, 2 H), 7.37 (t, $J=7.34$ Hz, 2 H), 7.53 (dd, $J=13.94$, 7.83 Hz, 4 H), 8.00 (s, 2 H), 8.45 (s, 1 H), 11.18 (s, 1 H).

EXAMPLE 26

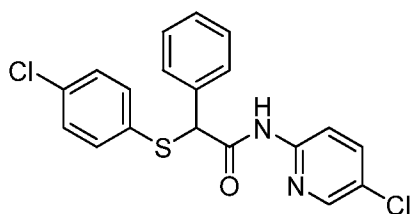
Synthesis of 2-(4-chlorophenylthio)-N-(5-chloropyridin-2-yl)-2-(4-fluorophenyl)acetamide:

5 The title compound was generated from commercially available 2-bromo-2-(4-fluorophenyl)acetic acid, 4-chlorobenzenethiol, oxalyl chloride and 5-chloropyridin-2-amine according to general procedure A described above. The intermediate 2-(4-chlorophenylthio)-2-(4-fluorophenyl)acetyl chloride was used in the subsequent synthetic transformation without further purification.

10 *2-(4-Chlorophenylthio)-2-(4-fluorophenyl)acetyl chloride:* The title compound was obtained from commercially available 2-bromo-2-phenylacetic acid (12.80 g, 54.94 mmol), 4-chlorobenzenethiol (8.00 g, 55.32 mmol), sodium hydride (60% oil dispersion, 5.30 g, 132.50 mmol) and oxalyl chloride (2 M in dichloromethane, 60.00 mL, 120.00 mmol) according to the protocols as outlined in general procedure A above. This acid
15 chloride was used in the next synthetic step without further purification.

2-(4-Chlorophenylthio)-N-(5-chloropyridin-2-yl)-2-(4-fluorophenyl)acetamide:
The title compound was obtained from 2-(4-chlorophenylthio)-2-(4-fluorophenyl)acetyl chloride (taken from the previous step, crude, 3.15 g, 10.00 mmol), 5-chloropyridin-2-amine (1.28 g, 10.00 mmol) and Hünig's base (5.00 mL, 28.66 mmol) according to the
20 protocols as outlined in general procedure A above. Free base was obtained.

Spectroscopic Data: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 5.56 (s, 1 H), 7.21 (t, $J=8.80$ Hz, 2 H), 7.38 (dd, $J=19.07$, 2.45 Hz, 4 H), 7.57 (dd, $J=8.44$, 5.50 Hz, 2 H), 7.90 (dd, $J=9.05$, 2.45 Hz, 1 H), 8.06 (d, $J=8.80$ Hz, 1 H), 8.38 (d, $J=2.20$ Hz, 1 H), 11.17 (s, 1 H).

EXAMPLE 27

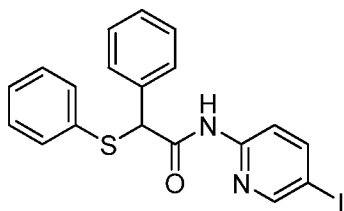
Synthesis of 2-(4-chlorophenylthio)-N-(5-chloropyridin-2-yl)-2-phenylacetamide:

The title compound was generated from commercially available 2-bromo-2-phenylacetic acid, 4-chlorobenzenethiol, oxalyl chloride and 5-chloropyridin-2-amine according to general procedure A described above. The intermediate 2-(4-chlorophenylthio)-2-phenylacetyl chloride was used in the subsequent synthetic transformation without further purification.

2-(4-Chlorophenylthio)-2-phenylacetyl chloride: The title compound was obtained from commercially available 2-bromo-2-phenylacetic acid (12.00 g, 55.81 mmol), 4-chlorobenzenethiol (8.00 g, 55.32 mmol), sodium hydride (60% oil dispersion, 5.00 g, 125.00 mmol) and oxalyl chloride (2 M in dichloromethane, 60.00 mL, 120.00 mmol) according to the protocols as outlined in general procedure A above. This acid chloride was used in the next synthetic step without further purification.

2-(4-Chlorophenylthio)-N-(5-chloropyridin-2-yl)-2-phenylacetamide: The title compound was obtained from 2-(4-chlorophenylthio)-2-phenylacetyl chloride (taken from the previous step, crude, 3.00 g, 10.09 mmol), 5-chloropyridin-2-amine (1.28 g, 9.96 mmol) and Hünig's base (5.00 mL, 28.66 mmol) according to the protocols as outlined in general procedure A above. Free base was obtained. Spectroscopic Data: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 5.57 (br. s., 1 H), 7.26 - 7.46 (m, 7 H), 7.55 (d, *J*=7.34 Hz, 2 H), 7.90 (d, *J*=1.22 Hz, 1 H), 8.06 (d, *J*=8.80 Hz, 1 H), 8.37 (br. s., 1 H), 11.16 (br. s., 1 H).

EXAMPLE 28



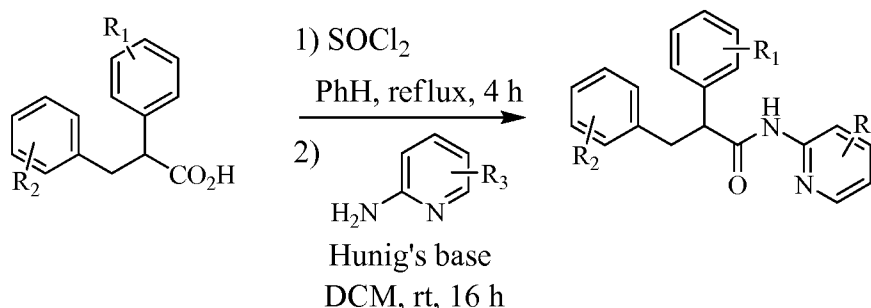
Synthesis of N-(5-iodopyridin-2-yl)-2-phenyl-2-(phenylthio)acetamide:

The title compound was generated from commercially available 2-phenyl-2-(phenylthio)acetic acid, oxalyl chloride and 5-iodopyridin-2-amine according to general procedure A described above. The intermediate 2-phenyl-2-(phenylthio)acetyl chloride was used in the subsequent synthetic transformation without further purification.

2-Phenyl-2-(phenylthio)acetyl chloride: The title compound was obtained from commercially available 2-phenyl-2-(phenylthio)acetic acid (25.00 g, 102.33 mmol) and oxalyl chloride (2 M in dichloromethane, 100.00 mL, 200.00 mmol) according to the protocols as outlined in general procedure A above. This acid chloride was used in the next synthetic step without further purification.

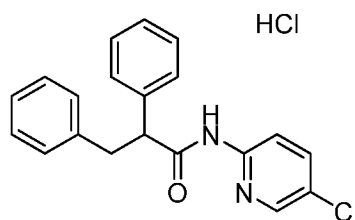
N-(5-Iodopyridin-2-yl)-2-phenyl-2-(phenylthio)acetamide: The title compound was obtained from 2-phenyl-2-(phenylthio)acetic acid (taken from the previous step, crude, 2.62 g, 10.72 mmol), 5-iodopyridin-2-amine (2.00 g, 9.09 mmol) and Hünig's base (4.00 mL, 22.93 mmol) according to the protocols as outlined in general procedure A above. Free base was obtained. Spectroscopic Data: ^1H NMR (500 MHz, DMSO- d_6) δ ppm 5.61 (s, 1 H), 7.23 (d, $J=7.34$ Hz, 1 H), 7.30 (t, $J=7.70$ Hz, 3 H), 7.33 - 7.40 (m, 4 H), 7.56 (d, $J=7.09$ Hz, 2 H), 7.89 (d, $J=8.56$ Hz, 1 H), 8.10 (dd, $J=8.80, 2.20$ Hz, 1 H), 8.53 (d, $J=2.44$ Hz, 1 H), 11.13 (s, 1 H).

General procedure for the Synthesis of 2-(Substituted Phenyl)-3-(substituted phenyl)-*N*-(substituted pyridin-2-yl)acetamide Hydrochloride:



An appropriately substituted carboxylic acid was converted into the corresponding acid chloride by the method published in Newcomb et al.. The acid chloride (1 eq) and an appropriately substituted 2-aminopyridine (1.5-2.0 eq) were dissolved in 50ml of dichloromethane at room temperature. Hünig's base (3.50 mL) was added, and the resulting reaction mixture was stirred at room temperature for 14 hours. The reaction mixture was then concentrated and diluted with ethyl acetate. The organic phase was washed sequentially with water and brine, then dried with sodium sulfate and concentrated. Flash chromatography (30 % EtOAc/hexanes) gave the desired free base, which was mixed with HCl in MeOH. Concentration and recrystallization from ether gave the final desired product in HCl salt form.

EXAMPLE 29



Synthesis of *N*-(5-chloropyridin-2-yl)-2,3-diphenylpropanamide hydrochloride:

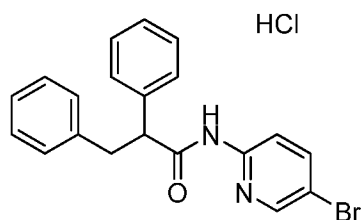
5 The title compound was generated from commercially available 2,3-diphenylpropanoic acid, thionyl chloride and 5-chlororopyridin-2-amine according to the general procedure described above. The intermediate 2,3-diphenylpropanoic acid chloride was used in the subsequent synthetic transformation without further purification.

10 *2,3-Diphenylpropanoic acid chloride:* The title compound was obtained from commercially available 2,3-diphenylpropanoic acid (25.00 g, 110.49 mmol) and thionyl chloride (20.00 mL, 274.19 mmol) according to the protocols as outlined in the general procedure above. This acid chloride was used in the next synthetic step without further purification.

15 *N*-(5-Chloropyridin-2-yl)-2,3-diphenylpropanamide hydrochloride: The title compound was obtained from 2,3-diphenylpropanoic acid chloride (taken from the previous step, crude, 2.50 g, 10.22 mmol), 5-chloropyridin-2-amine (1.28 g, 10.00 mmol) and Hünig's base (3.50 mL, 20.09 mmol) according to the protocols as outlined in the general procedure above. Spectroscopic Data: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.95 (dd, *J*=13.69, 6.11 Hz, 1 H), 3.40 (dd, *J*=13.57, 9.17 Hz, 1 H), 4.26 (dd, *J*=9.17, 6.24 Hz, 1 H), 7.16 - 7.25 (m, 5 H), 7.30 (t, *J*=7.58 Hz, 3 H), 7.43 (d, *J*=7.09 Hz, 2 H), 7.83 (dd, *J*=9.05, 2.69 Hz, 1 H), 8.06 (d, *J*=9.05 Hz, 1 H), 8.29 (d, *J*=2.20 Hz, 1 H), 10.82 (s, 1 H).

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EXAMPLE 30



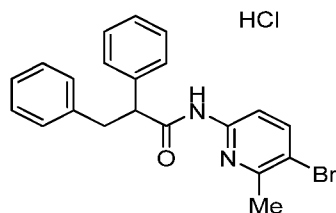
Synthesis of *N*-(5-bromopyridin-2-yl)-2,3-diphenylpropanamide hydrochloride:

5 The title compound was generated from commercially available 2,3-diphenylpropanoic acid, thionyl chloride and 5-bromopyridin-2-amine according to the general procedure described above. The intermediate 2,3-diphenylpropanoic acid chloride was used in the subsequent synthetic transformation without further purification.

10 *2,3-Diphenylpropanoic acid chloride:* The title compound was obtained from commercially available 2,3-diphenylpropanoic acid (25.00 g, 110.49 mmol) and thionyl chloride (20.00 mL, 274.19 mmol) according to the protocols as outlined in the general procedure above. This acid chloride was used in the next synthetic step without further purification.

15 *N*-(5-Bromopyridin-2-yl)-2,3-diphenylpropanamide hydrochloride: The title compound was obtained from 2,3-diphenylpropanoic acid chloride (taken from the previous step, crude, 2.50 g, 10.22 mmol), 5-bromopyridin-2-amine (1.63 g, 9.42 mmol) and Hünig's base (3.50 mL, 20.09 mmol) according to the protocols as outlined in the general procedure above. Spectroscopic Data: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.95 (dd, *J*=13.69, 6.11 Hz, 1 H), 3.40 (dd, *J*=13.69, 9.29 Hz, 1 H), 4.26 (dd, *J*=9.17, 6.24 Hz, 1 H), 7.17 - 7.24 (m, 5 H), 7.30 (t, *J*=7.58 Hz, 3 H), 7.43 (d, *J*=7.09 Hz, 2 H), 7.91 - 7.96 (m, 1 H), 7.98 - 8.06 (m, 1 H), 8.36 (d, *J*=2.45 Hz, 1 H), 10.82 (s, 1 H).

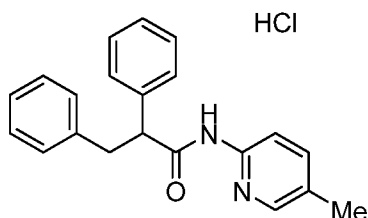
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EXAMPLE 31**Synthesis of *N*-(5-bromo-6-methylpyridin-2-yl)-2,3-diphenylpropanamide hydrochloride:**

5 The title compound was generated from commercially available 2,3-diphenylpropanoic acid, thionyl chloride and 5-bromo-6-methylpyridin-2-amine according to the general procedure described above. The intermediate 2,3-diphenylpropanoic acid chloride was used in the subsequent synthetic transformation without further purification.

10 *2,3-Diphenylpropanoic acid chloride:* The title compound was obtained from commercially available 2,3-diphenylpropanoic acid (25.00 g, 110.49 mmol) and thionyl chloride (20.00 mL, 274.19 mmol) according to the protocols as outlined in the general procedure above. This acid chloride was used in the next synthetic step without further purification.

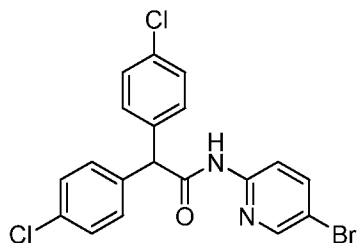
15 *N*-(5-Bromo-6-methylpyridin-2-yl)-2,3-diphenylpropanamide hydrochloride: The title compound was obtained from 2,3-diphenylpropanoic acid chloride (taken from the previous step, crude, 2.50 g, 10.22 mmol), 5-bromo-6-methylpyridin-2-amine (1.87 g, 10.00 mmol) and Hünig's base (3.00 mL, 17.22 mmol) according to the protocols as outlined in the general procedure above. Spectroscopic Data: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.43 (s, 3 H), 2.93 (dd, *J*=13.69, 6.11 Hz, 1 H), 3.39 (dd, *J*=13.69, 9.54
20 Hz, 1 H), 4.27 (dd, 1 H), 6.61 (br. s., 1 H), 7.08 - 7.14 (m, 1 H), 7.16 - 7.24 (m, 5 H), 7.29 (t, *J*=7.58 Hz, 2 H), 7.43 (d, *J*=7.34 Hz, 2 H), 7.78 - 7.84 (m, 1 H), 7.85 - 7.90 (m, 1 H), 10.73 (s, 1 H).

EXAMPLE 32**Synthesis of *N*-(5-methylpyridin-2-yl)-2,3-diphenylpropanamide****5 hydrochloride:**

The title compound was generated from commercially available 2,3-diphenylpropanoic acid, thionyl chloride and 5-methylpyridin-2-amine according to the general procedure described above. The intermediate 2,3-diphenylpropanoic acid chloride was used in the subsequent synthetic transformation without further purification.

10 *2,3-Diphenylpropanoic acid chloride*: The title compound was obtained from commercially available 2,3-diphenylpropanoic acid (25.00 g, 110.49 mmol) and thionyl chloride (20.00 mL, 274.19 mmol) according to the protocols as outlined in the general procedure above. This acid chloride was used in the next synthetic step without further purification.

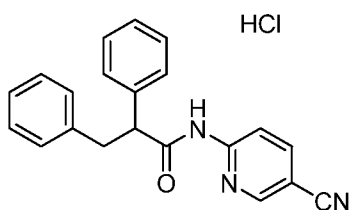
15 *N*-(5-Methylpyridin-2-yl)-2,3-diphenylpropanamide hydrochloride: The title compound was obtained from 2,3-diphenylpropanoic acid chloride (taken from the previous step, crude, 2.50 g, 10.22 mmol), 5-methylpyridin-2-amine (1.08 g, 10.00 mmol) and Hünig's base (3.50 mL, 20.09 mmol) according to the protocols as outlined in the general procedure above. Spectroscopic Data: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.26
20 (s, 3 H), 3.04 (dd, *J*=13.82, 6.72 Hz, 1 H), 3.45 (dd, *J*=13.82, 8.68 Hz, 1 H), 4.46 (t, *J*=7.70 Hz, 1 H), 6.28 (br s, 1 H), 7.10-7.15 (m, 1 H), 7.17 - 7.26 (m, 5 H), 7.27 - 7.34 (m, 2 H), 7.50 (d, *J*=7.34 Hz, 2 H), 7.84 (d, *J*=8.80 Hz, 1 H), 8.00 (d, *J*=8.56 Hz, 1 H), 8.15 (s, 1 H), 12.51 (br. s., 1 H).

EXAMPLE 33**Synthesis of *N*-(5-bromopyridin-2-yl)-2,2-bis(4-chlorophenyl)acetamide:**

- 5 The title compound was generated from commercially available 2,3-diphenylpropanoic acid, thionyl chloride and 5-cyanopyridin-2-amine according to the general procedure described above. The intermediate 2,3-diphenylpropanoic acid chloride was used in the subsequent synthetic transformation without further purification.

- 10 *2,2-bis(4-Chlorophenyl)acetic acid chloride:* The title compound was obtained from commercially available 2,2-bis(4-chlorophenyl)acetic acid (10.00 g, 35.57 mmol) and thionyl chloride (20.00 mL, 274.19 mmol) according to the protocols as outlined in the general procedure above. This acid chloride was used in the next synthetic step without further purification.

- 15 *N*-(5-Bromopyridin-2-yl)-2,2-bis(4-chlorophenyl)acetamide: The title compound was obtained from 2,2-bis(4-chlorophenyl)acetic acid chloride (taken from the previous step, crude, 3.00 g, 10.01 mmol), 5-bromopyridin-2-amine (1.90 g, 10.98 mmol) and Hünig's base (3.00 mL, 17.22 mmol) according to the protocols as outlined in the general procedure above. Spectroscopic Data: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 5.39 (s, 1 H), 7.27 - 7.36 (m, 4 H), 7.37 - 7.46 (m, 4 H), 7.95 - 8.03 (m, 1 H), 8.04 - 8.11 (m, 1 H),
20 8.43 (d, *J*=2.45 Hz, 1 H), 11.17 (s, 1 H).

EXAMPLE 34**Synthesis of *N*-(5-cyanopyridin-2-yl)-2,3-diphenylpropanamide hydrochloride:**

The title compound was generated from commercially available 2,3-diphenylpropanoic acid, thionyl chloride and 5-cyanopyridin-2-amine according to the general procedure described above. The intermediate 2,3-diphenylpropanoic acid chloride was used in the subsequent synthetic transformation without further purification.

5 *2,3-Diphenylpropanoic acid chloride*: The title compound was obtained from commercially available 2,3-diphenylpropanoic acid (25.00 g, 110.49 mmol) and thionyl chloride (20.00 mL, 274.19 mmol) according to the protocols as outlined in the general procedure above. This acid chloride was used in the next synthetic step without further purification.

10 *N-(5-Cyanopyridin-2-yl)-2,3-diphenylpropanamide hydrochloride*: The title compound was obtained from 2,3-diphenylpropanoic acid chloride (taken from the previous step, crude, 3.00 g, 12.26 mmol), 5-cyanopyridin-2-amine (2.00 g, 16.79 mmol) and Hünig's base (3.50 mL, 20.09 mmol) according to the protocols as outlined in the general procedure above. Spectroscopic Data: ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 2.96
15 (dd, *J*=13.69, 6.11 Hz, 1 H), 3.41 (dd, *J*=13.69, 9.29 Hz, 1 H), 4.29 (dd, *J*=9.05, 6.36 Hz, 1 H), 5.58 - 5.75 (m, 1 H), 7.07 - 7.15 (m, 1 H), 7.16 - 7.26 (m, 5 H), 7.31 (t, *J*=7.58 Hz, 3 H), 7.44 (d, *J*=7.34 Hz, 2 H), 8.07 (d, *J*=8.80 Hz, 1 H), 8.17 (dd, *J*=8.80, 2.45 Hz, 1 H), 8.73 (d, *J*=1.96 Hz, 1 H), 10.94 (s, 1 H).

20 Unless otherwise indicated, the following terms as used throughout this specification have the following meanings:

DCM refers to dichloromethane,

DMSO refers to dimethyl sulfoxide,

EDCI refers to 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide,

THF refers to tetrahydrofuran,

25 EtOAc refers to ethylacetate,

"Me" refers to methyl.,

"Ph" refers to phenyl.,

30 "Pharmaceutically acceptable salt" refers to those salts which retain the biological effectiveness and properties of the free bases and which are obtained by reaction with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid,

phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

"Alkyl" refers to a straight-chain, branched or cyclic saturated aliphatic hydrocarbon. Preferably, the alkyl group has 1 to 12 carbons. More preferably, it is a lower alkyl of from 1 to 7 carbons, most preferably 1 to 4 carbons. Typical alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl and the like. The alkyl group may be optionally substituted with one or more substituents selected from the group consisting of hydroxyl, cyano, alkoxy, =O, =S, NO₂, halogen, dimethyl amino and SH.

"Alkenyl" refers to a straight-chain, branched or cyclic unsaturated hydrocarbon group containing at least one carbon--carbon double bond. Preferably, the alkenyl group has 2 to 12 carbons. More preferably it is a lower alkenyl of from 2 to 7 carbons, most preferably 2 to 4 carbons. The alkenyl group may be optionally substituted with one or more substituents selected from the group consisting of hydroxyl, cyano, alkoxy, O, S, NO₂, halogen, dimethyl amino and SH.

"Alkynyl" refers to a straight-chain, branched or cyclic unsaturated hydrocarbon containing at least one carbon--carbon triple bond. Preferably, the alkynyl group has 2 to 12 carbons. More preferably it is a lower alkynyl of from 2 to 7 carbons, most preferably 2 to 4 carbons. The alkynyl group may be optionally substituted with one or more substituents selected from the group consisting of hydroxyl, cyano, alkoxy, O, S, NO₂, halogen, dimethyl amino and SH.

"Alkoxy" refers to an "O-alkyl" group.

"Aryl" refers to an aromatic group which has at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl and biaryl groups. The aryl group may be optionally substituted with one or more substituents selected from the group consisting of halogen, trihalomethyl, hydroxyl, SH, OH, NO₂, amine, thioether, cyano, alkoxy, alkyl, and amino.

"Alkaryl" refers to an alkyl that is covalently joined to an aryl group. Preferably, the alkyl is a lower alkyl.

"Aryloxy" refers to an "O-aryl" group.

"Arylalkyloxy" refers to an "O-alkaryl" group.

"Carbocyclic" refers to cyclic saturated or unsaturated aliphatic hydrocarbon and aryl hydrocarbon groups wherein the ring atoms are exclusively carbons, and comprises from 6 to 20 carbon atoms, including said ring atoms.

"Carbocyclic aryl" refers to an aryl group wherein the ring atoms are carbon.

- 5 "Heterocyclic" refers to cyclic groups wherein the ring atoms comprise carbon atoms and at least one oxygen, nitrogen, and/or sulfur atom and may be saturated, unsaturated, i.e. have one or more double bonds, or aryl, and comprises up to 20 carbon atoms and from 1 to 5 of the above heteroatoms.

- 10 "Heterocyclic aryl" refers to an aryl group having from 1 to 3 heteroatoms as ring atoms, the remainder of the ring atoms being carbon. Heteroatoms include oxygen, sulfur, and nitrogen.

"Hydrocarbyl" refers to a hydrocarbon radical having only carbon and hydrogen atoms. Preferably, the hydrocarbyl radical has from 1 to 20 carbon atoms, more preferably from 1 to 12 carbon atoms and most preferably from 1 to 7 carbon atoms.

- 15 "Substituted hydrocarbyl" refers to a hydrocarbyl radical wherein one or more, but not all, of the hydrogen and/or the carbon atoms are replaced by a halogen, nitrogen, oxygen, sulfur or phosphorus atom or a radical including a halogen, nitrogen, oxygen, sulfur or phosphorus atom, e.g. fluoro, chloro, cyano, nitro, hydroxyl, phosphate, thiol, etc.

"Amide" refers to $--C(O)--NH--R'$, wherein R' is alkyl, aryl, alkylaryl or hydrogen.

- 20 "Ester" refers to $--C(O)--O--R'$, wherein R' is alkyl, aryl or alkylaryl.

"Thioamide" refers to $--C(S)--NH--R'$, wherein R' is alkyl, aryl, alkylaryl or hydrogen.

"Thiol ester" refers to $--C(O)--S--R'$, wherein R' is alkyl, aryl, alkylaryl or hydrogen.

- 25 "Amine" refers to a $--N(R'')R'''$ group, wherein R'' and R''' are independently selected from the group consisting of alkyl, aryl, and alkylaryl.

"Thioether" refers to $--S--R''$, wherein R'' is alkyl, aryl, or alkylaryl.

"Sulfonyl" refers to $--S(O)_2--R''''$, where R'''' is aryl, $C(CN)=C$ -aryl, CH_2CN , alkylaryl, sulfonamide, NH -alkyl, NH -alkylaryl, or NH -aryl.

Also, alternatively the substituent on the phenyl moiety may be referred to as an o, m or p substituent or a 2, 3 or 4 substituent, respectively. (Obviously, the 5 substituent is also a m substituent and the 6 substituent is an o substituent.)

The above compounds are evaluated for S1P3 activity according to the above
5 assay: The results are reported in TABLE 2, below.

TABLE 2

Example No.	FLIPR EC50 (nM) / (% Antagonism)		
	S1P ₁	S1P ₂	S1P ₃
1	>8300	>8300	128 (99)
2	>8300	>8300	185 (100)
3	>8300	>8300	166 (98)
4	>8300	>8300	325 (97)
5	>8300	>8300	90 (97)
6	>8300	>8300	103 (97)
7	>8300	>8300	316 (97)
8	>8300	>8300	15 (97)
9	>8300	>8300	27 (97)
10	>8300	>8300	256 (100)
11	>8300	>8300	361 (100)
12	>8300	>8300	376 (99)
13	>8300	>8300	198 (99)
14	>8300	>8300	127 (99)
15	>8300	>8300	240 (98)
16	>8300	>8300	256 (100)
17	>8300	>8300	322 (99)

18	>8300	>8300	133 (97)
19	>8300	>8300	106 (97)
20	>8300	>8300	166 (97)
21	>8300	>8300	208 (97)
22	>8300	>8300	104 (97)
23	>8300	>8300	173 (97)
24	>8300	>8300	230 (99)
25	>8300	>8300	286 (99)
26	>8300	>8300	166 (102)
27	>8300	>8300	160 (101)
28	>8300	>8300	310 (101)
29	>8300	>8300	198 (101)
30	>8300	>8300	162 (100)
31	>8300	>8300	201 (100)
32	>8300	>8300	725 (99)
33	>8300	>8300	1720 (94)
34	>8300	>8300	1502 (52)

As a result of the above activity of the compounds utilized in the method of the present invention, it is clear that such compounds may be used in treating and/or preventing the following diseases and conditions of the eye as well as other diseases and conditions discussed below. (It should be noted that “treating” means ameliorating and/or modulating a disease or disorder that exists in a subject (whether the subject is aware of the disease or disorder or not) or delaying the onset of the disease or disorder and “preventing” means preventing the recurrence, onset or development of one or more

symptoms of a disease or disorder in a subject by administering one or more compounds of the invention.)

Glaucoma

- 5 S1P3 subtypes are expressed in primary human trabecular meshwork cells and S1P decreases outflow facility >30% in perfused porcine eyes (See IOVS 45, 2263; 2004) by altering paracellular permeability.

Dry Eye/Immunology

Induces lymphocyte sequestration without affecting T cell proliferation.

Angiogenesis disorders

- 10 S1P3 receptor subtype is expressed in vascular endothelial cells and siRNA knockdown of S1P1 and S1P3 inhibits angiogenesis. S1P also promotes vascular endothelial cell migration and promotes barrier assembly and integrity.

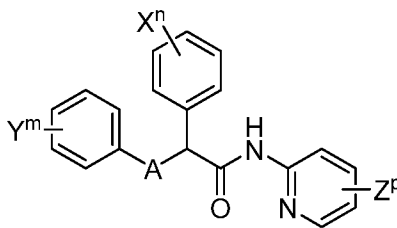
Cardiovascular (S1P3)

S1P3 "knock out" mice lack S1P induced pulmonary edema.

- 15 The foregoing description details specific methods and compositions that can be employed to practice the present invention, and represents the best mode contemplated. Thus, however detailed the foregoing may appear in text, it should not be construed as limiting the overall scope hereof; rather, the ambit of the present invention was to be governed only by the lawful construction of the appended claims. In particular, the present
20 invention includes, as novel compounds, having subtype-selective modulating activity of sphingosine-1-phosphate-3 (SIP₃) receptors, compounds selected from the group consisting of 2-(substituted)(arylmethyl, aryloxy, and arylthio)-N-(substituted pyridin-2-yl)-2-(substituted aryl) compounds, wherein said aryl is a carbocyclic aryl or a heterocyclic aryl, which is substituted with one or more radicals selected from the group consisting of
25 alkyl, alkenyl, alkynyl, alkaryl, alkyloxy, aryloxy, arylalkyloxy, amine, amide, hydroxyl, halogen, nitrile, nitro, trifluoromethyl, carboxy, ester, thiolester, thioether and sulfonyl.

WHAT IS CLAIMED IS:

1. Compounds represented by the formula I having sphingosine-1-phosphate receptor antagonist biological activity:



wherein:

A is O, S or (CR₂)_a wherein R is selected from the group consisting of H, or lower alkyl;

m, n, p are 0 or an integer of from 1 to 5;

a is 0 or 1,

wherein when a is 1,

X and Y are independently selected from the group consisting of alkyl, alkyloxy, hydroxyl, halogen, nitrile, trifluoromethyl and carboxy;

Z is selected from the group consisting of alkyl, alkyloxy, hydroxyl, halogen, nitrile, trifluoromethyl and carboxy, and

when a is 0,

X, Y are independently selected from the group consisting of alkyl, alkyloxy, hydroxyl, halogen, nitrile, trifluoromethyl, and carboxy;

Z is selected from the group consisting of alkyl, alkyloxy, hydroxyl, halogen, nitrile, trifluoromethyl, and carboxy,

provided however that when a is 0 and when the pyridyl ring is (a) 5-chloro pyridyl, then both (i) m and n are not 0 and (ii) X and Y are not chloro or methyl or (b) 5-bromo or iodo pyridyl, than both m and n are not 0, or a pharmaceutically acceptable salt of said compound.

2. The compound of claim 1 wherein m, n, and p are 0 or an integer of 1 or 2.

3. The compound of claim 2 wherein X and Y are independently selected from the group consisting of lower alkyl, lower alkyloxy, hydroxyl, chloro, bromo, nitrile, trifluoromethyl and carboxy; and

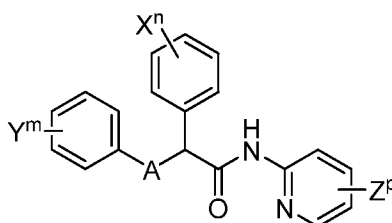
Z is selected from the group consisting of lower alkyl, lower alkoxy, hydroxyl, fluoro, chloro, bromo, nitrile, trifluoromethyl, and carboxy.

4. The compound of claim 3 wherein A is $(CR_2)_a$ and a is 1.
5. The compound of claim 4 wherein m and n are 0 and Z is selected from the group consisting of fluoro, chloro, bromo, and methyl.
6. The compound of claim 2 wherein A is $(CR_2)_a$ and a is 0.
- 5 7. The compound of claim 6 wherein Z is fluoro.
9. The compound of claim 2 wherein A is S.
10. The compound of claim 9 wherein m and n are 0.
11. The compound of claim 10 wherein Z is selected from the group consisting of chloro and bromo.
- 10 12. The compound of claim 2 wherein A is O.
13. The compound of claim 12 wherein X and Y are independently selected from the group consisting of lower alkyl, lower alkyloxy, hydroxyl, chloro, bromo, nitrile, trifluoromethyl, and carboxy; and
Z is selected from the group consisting of lower alkyl, lower alkoxy, hydroxyl,
15 fluoro, chloro, bromo, nitrile, trifluoromethyl, and carboxy.
14. The compound of claim 13 wherein X and Y are independently selected from the group consisting of methyl, methyloxy, chloro and bromo; and Z is selected from the group consisting of fluoro, chloro, bromo and methyl.
15. The compound of claim 2 selected from the group consisting of:
20 2-(4-chloro-3-methylphenoxy)-2-(4-chlorophenyl)-N-(5-chloropyridin-2-yl)acetamide hydrochloride,
N-(5-bromopyridin-2-yl)-2-(4-chlorophenyl)-2-(p-tolyloxy)acetamide hydrochloride,
2-(4-chlorophenyl)-N-(5-chloropyridin-2-yl)-2-(4-methoxyphenoxy)acetamide
25 hydrochloride,
2-(4-bromophenoxy)-2-(4-chlorophenyl)-N-(5-fluoropyridin-2-yl)acetamide hydrochloride,

- 2-(4-bromophenoxy)-*N*-(5-bromopyridin-2-yl)-2-(4-chlorophenyl)acetamide hydrochloride,
2-(4-bromophenoxy)-2-(4-chlorophenyl)-*N*-(5-chloropyridin-2-yl)acetamide hydrochloride,
5 2-(4-chlorophenoxy)-2-(4-chlorophenyl)-*N*-(5-fluoropyridin-2-yl)acetamide hydrochloride,
N-(5-bromopyridin-2-yl)-2-(4-chlorophenoxy)-2-(4-chlorophenyl)acetamide hydrochloride, and
2-(4-chlorophenoxy)-2-(4-chlorophenyl)-*N*-(5-chloropyridin-2-yl)acetamide
10 hydrochloride.
16. The compound of claim 2 selected from the group consisting of:
N-(5-bromopyridin-2-yl)-2-phenyl-2-(phenylthio)acetamide hydrochloride,
N-(5-bromopyridin-2-yl)-2-(4-chlorophenyl)-2-(4-methoxyphenylthio)acetamide hydrochloride,
15 2-(4-chlorophenyl)-*N*-(5-chloropyridin-2-yl)-2-(4-methoxyphenylthio)acetamide hydrochloride,
2-(4-chlorophenyl)-*N*-(5-chloropyridin-2-yl)-2-(4-fluorophenylthio)acetamide hydrochloride,
N-(5-bromopyridin-2-yl)-2-(4-chlorophenyl)-2-(4-fluorophenylthio)acetamide
20 hydrochloride,
2-(4-chlorophenyl)-*N*-(5-chloropyridin-2-yl)-2-(3, 4-dimethylphenylthio)acetamide hydrochloride,
N-(5-bromopyridin-2-yl)-2-(4-chlorophenyl)-2-(*p*-tolylthio)acetamide hydrochloride,
25 2-(4-chlorophenyl)-*N*-(5-chloropyridin-2-yl)-2-(*p*-tolylthio)acetamide hydrochloride,
N-(5-bromopyridin-2-yl)-2-(3, 4-dichlorophenylthio)-2-phenylacetamide,
N-(5-chloropyridin-2-yl)-2-(3, 4-dichlorophenylthio)-2-phenylacetamide,
N-(5-bromopyridin-2-yl)-2-(3-chlorophenylthio)-2-phenylacetamide hydrochloride,
30 2-(3-chlorophenylthio)-*N*-(5-chloropyridin-2-yl)-2-phenylacetamide hydrochloride,
N-(5-bromopyridin-2-yl)-2-(4-chlorophenyl)-2-(4-chlorophenylthio)acetamide hydrochloride,
2-(4-chlorophenyl)-2-(4-chlorophenylthio)-*N*-(5-chloropyridin-2-yl)acetamide hydrochloride,

- 2-(4-bromophenylthio)-*N*-(5-chloropyridin-2-yl)-2-phenylacetamide,
 2-(4-bromophenylthio)-*N*-(5-bromopyridin-2-yl)-2-phenylacetamide,
 2-(4-chlorophenylthio)-*N*-(5-chloropyridin-2-yl)-2-(4-fluorophenyl)acetamide,
 2-(4-chlorophenylthio)-*N*-(5-chloropyridin-2-yl)-2-phenylacetamide, and
 5 *N*-(5-iodopyridin-2-yl)-2-phenyl-2-(phenylthio)acetamide.

17. The compound of claim 2 selected from the group consisting of:
N-(5-chloropyridin-2-yl)-2, 3-diphenylpropanamide hydrochloride,
N-(5-bromopyridin-2-yl)-2, 3-diphenylpropanamide hydrochloride
 10 *N*-(5-bromo-6-methylpyridin-2-yl)-2, 3-diphenylpropanamide hydrochloride, and
N-(5-methylpyridin-2-yl)-2, 3-diphenylpropanamide hydrochloride.
18. A novel compound that is a compound selected from the group consisting of 2-(substituted)(arylmethyl, aryloxy, and arylthio)-*N*-(substituted pyridin-2-yl)-2-(substituted aryl) compounds.
- 15 19. A method of treating or preventing diseases and conditions of the eye selected from the group consisting of glaucoma, dry eye and angiogenesis disorders and pulmonary edema which comprises administering to an animal in need thereof a compound according to claim 1.
20. A method of treating or preventing diseases and conditions of the eye selected from
 20 the group consisting of glaucoma, dry eye and angiogenesis disorders and pulmonary edema which comprises administering to an animal in need thereof a compound according to claim 18.
21. A method of treating an eye disease of a mammal selected from the group consisting of glaucoma, dry eye and angiogenesis disorders and pulmonary edema which
 25 comprises administering to a patient in need thereof a compound having sphingosine-1-phosphate receptor agonist and or antagonist biological activity represented by the general formula II:



wherein:

A is O, S or $(CR_2)_a$ wherein R is selected from the group consisting of H, or lower alkyl;

m, n, p are 0 or an integer of from 1 to 5;

5 a is 0 or 1,

X and Y are independently selected from the group consisting of alkyl, alkyloxy, hydroxyl, halogen, nitrile, trifluoromethyl and carboxy; and

Z is selected from the group consisting of alkyl, alkyloxy, hydroxyl, halogen, nitrile, trifluoromethyl, or a pharmaceutically acceptable salt of said compound.

10

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2010/040014

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D213/75 A61K31/435 A61P27/06 A61P11/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

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

EPO-Internal, 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	WO 03/055482 A1 (NOVO NORDISK AS [DK]) 10 July 2003 (2003-07-10) page 1, lines 3-5 page 16; compound (I) page 27, lines 5-13 examples 31,33,35,38,39,41,44,48,50,106-108,111-113 -----	1-16
A	WO 2007/095561 A2 (ALLERGAN INC [US]; BEARD RICHARD L [US]; DONELLO JOHN E [US]; YUAN HAI) 23 August 2007 (2007-08-23) page 1 - paragraph 1 page 5; compound 1 tables 1,2 page 34, paragraph 2-6 -----	1-20



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

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

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Date of the actual completion of the international search

28 October 2010

Date of mailing of the international search report

05/11/2010

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2010/040014

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